

Production of mass separated ^{11}C beams for PET-aided hadron therapy

Simon Stegemann

Supervisor:
Prof. dr. Thomas Elias Cocolios

Dissertation presented in partial
fulfillment of the requirements for the
degree of Doctor of Science (PhD):
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Simon Stegemann

Examination committee:

Prof. dr. Lino Pereira, chair

Prof. dr. Thomas Elias Cocolios, supervisor

Prof. dr. Piet Van Duppen

Prof. dr. Riccardo Raabe

Prof. dr. ir. Jozef Vleugels

Dr. João Pedro Ramos

(SCK CEN, Belgium)

Dr. Claus-Stefan Schmitzer

(MedAustron, Austria)

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Uitgegeven in eigen beheer, Simon Stegemann, Celestijnenlaan 200D box 2418, B-3001 Leuven (Belgium)

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Acknowledgements

Before I begin to elaborate on ^{11}C , its importance and production, allow me to go a step back. A bit more than four years back in time to be precise. I remember quite vividly how I was faced with the question of what I should do after my undergraduate studies. Funnily enough, I told my friends and family with certainty that I did not want to do a PhD. Now, how did we end up here with my PhD manuscript? While fundamental nuclear physics research, which I performed and enjoyed during my Master's studies, is truly fascinating, I realized towards the end that I was missing something. Namely, a clear motivation and a link to everyday life. In other words, my interest had shifted from fundamental research to more applied physics or applications. By sheer luck I got in touch with the project subject of this thesis, which determined my professional and personal development in so many ways. However, beginning this journey was not an easy decision to make. I did what I suppose many researchers would do, I researched what it is like doing a PhD. What I found was: a PhD is a long journey with many ups and downs, dealing with failures is a common practice, work is mostly done independently and feedback on progress and success is scarce. In fact, I read that PhD students must learn how to reward themselves and that without a strong motivation it is not encouraged to pursue a PhD.

As I am recapitulating over the previous four years, I realize that there is some truth in all of these aspects. However, while I certainly learned to work independently, I received plentiful support from various sources and in different ways, which allowed me to be where I am today, and for which I am very grateful. I would like to use this opportunity to express my gratitude to all of you who contributed to this important milestone in my life.

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Moving to a new country always brings changes, unknowns and challenges. I am very glad that I have found so many great friends here in Leuven who made me feel at home, when being apart from my friends and family in my home town. I am thankful to be part of the 'Love Boat' crew, whose name origin is a funny story itself. Thank you Tiago, Greg, Koen, Leendert and Ivan for our fun trips, oude markt sessions and game nights.

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Many, if not most of my studies lead me to CERN in Geneva, which was truly an amazing experience. No matter for how long I stayed, time was always a valuable and scarce good, which made it clear to me what working under pressure really means. While time was rare, I usually had plenty of problems. I assume that I went pretty much every day down to the workshop announcing 'I have a problem', which resulted sometimes in sarcastic looks. Therefore, I am very grateful for the substantial support for my studies which I received from the locals. Thank you Bernard and Ermanno from the workshop who always found solutions for my problems. Thank you Andrés, Annie, Beatriz, Bernard, Camilo, Carlos, Cristina, Ermanno, James, Joachim, Jochen, João Pedro, Julien, Laura, Mike, Nhât-Tân, Paul, Richard, Sebastian, Simon Se., Stefano, Stu, Thierry and Vincent for including me into the local group, for opening up your laboratories to me, for your help, and for all the activities and drinks we had together.

Once more I recognize while sitting here recapitulating over the past four years, how things changed, how I changed and developed, and I realize the importance of constants which remain the same throughout this never-ending process. Therefore, I am extremely grateful for my family and best friends at home, who always stood by my side.

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Abstract

Ever since the first discovery of an artificially-generated radionuclide, the production of radioisotopes and radioactive ion beams has been an essential tool in nuclear physics research for the study of the atomic nucleus and its properties. Furthermore, the very same discovery is considered as one of the cornerstones in nuclear medicine, where radioisotopes are exploited for the diagnosis and therapy of cancer. This thesis liaises these two fields by utilizing the concept of radioactive ion beam production for the development of a ^{11}C based hadron therapy protocol. Hadron therapy, and particularly ^{12}C therapy is a promising treatment modality for non-metastatic cancers, which uses energetic ion beams to irradiate the tumor, and which allows to distribute the dose to the cancerous tissue while sparing the surrounding healthy tissue. One of the main obstacles in the success of hadron therapy is the correct prediction of the ion beam's range, which in practice suffers from significant uncertainties. *In vivo* range verification based on PET-imaging techniques is considered as a promising method to overcome this hurdle. This thesis is dedicated to such an approach where the stable ^{12}C beam is replaced by its β^+ -emitting radioisotope ^{11}C , which thus allows to combine hadron therapy with on-line PET-imaging. The main difficulty in this respect is the production of a sufficiently intense ^{11}C radioactive ion beam, since effective treatments require $\sim 4 \cdot 10^8$ ions per second delivered to the patient. To date, no radioactive ion beam production system exists that can be implemented into existing treatment facilities and which meets the aforementioned beam intensity requirement with appropriate beam properties. It was therefore the objective to develop such a system.

For this purpose, the isotope separation on-line method was selected, specifically for the production of intense mass separated $^{11}\text{CO}^+$ beams. A target-ion source unit tailored for $^{11}\text{CO}^+$ production was developed, which comprises a porous boron nitride target, operated with a controlled oxygen leak, and an electron cyclotron ion source. The main focus of this thesis was the fabrication and systematic characterization of the porous boron nitride target with a controlled microstructure for enhanced ^{11}C release efficiency. Spark plasma sintering was

employed as processing route, yielding a rigid pre-sintered powder compact with 21% open porosity and an average grain size of $1.7\ \mu\text{m}$. The porous BN target was characterized with respect to its operational limitations in high temperatures and controlled oxidizing atmospheres, where the applicability of temperatures up to $1500\ ^\circ\text{C}$ and oxygen potentials below $-300\ \text{kJ mol}^{-1}$ was proven. A 10% release efficiency of ^{11}C from the BN target operated at the aforementioned conditions was extrapolated from an off-line fractional release study performed at CERN MEDICIS, by exploiting the aforementioned microstructural properties obtained from systematic target characterization studies. A conceptual study, examining possible implementation scenarios of the developed $^{11}\text{CO}^+$ production system into existing hadron therapy centers, demonstrated its feasibility of producing sufficiently intense $^{11}\text{CO}^+$ radioactive ion beams, which as a result ensure the delivery of the required beam intensity to the patient room after beam manipulation and post-acceleration.

Beknopte samenvatting

Sinds de eerste radionucliden kunstmatig kunnen aangemaakt worden, is de productie van radio-isotopen en radioactieve ionenbundels een essentieel hulpmiddel geworden in kernfysisch onderzoek om de atomaire kern en zijn eigenschappen te onderzoeken. Daarenboven wordt deze ontdekking beschouwd als één van de pijlers in nucleaire geneeskunde waar radio-isotopen benut worden voor de diagnose en behandeling van kanker. Deze thesis verbindt de hierboven vermelde twee velden door gebruik te maken van het radioactieve ionenbundelproductie concept voor de ontwikkeling van een ^{11}C gebaseerd hadrontherapie-protocol. Hadrontherapie, en in het bijzonder ^{12}C therapie, is een veelbelovende behandelingsmethode voor niet-gemetastaseerde kanker die gebruik maakt van energetische ionenbundels om de tumor te bestralen. Bovendien laat deze methode toe de dosis te verdelen over het kankerweefsel zodat het omliggende gezonde weefsel gespaard blijft. Eén van de grootste obstakels in het succes van hadrontherapie is de juiste voorspelling van het ionenbundelbereik, welke in de praktijk onderhevig is aan significante onzekerheden. *In vivo* bereikverificatie gebaseerd op PET beeldvormingstechnieken wordt beschouwd als een veelbelovende methode om deze hindernis te overwinnen. Deze thesis is gewijd aan een aanpak waar de stabiele ^{12}C bundel wordt vervangen door zijn β^+ -stralend radio-isotoop ^{11}C . Dit isotoop laat toe hadrontherapie te combineren met online PET beeldvorming. De grootste moeilijkheid hier is de productie van een voldoende intense ^{11}C radioactieve ionenbundel, aangezien het voor doeltreffende behandelingen nodig is $\sim 4 \cdot 10^8$ ionen per seconde toe te dienen aan de patiënt. Tot op heden bestaat er geen productiesysteem voor radioactieve ionenbundels dat enerzijds geïmplementeerd kan worden in de bestaande behandelingsfaciliteiten en anderzijds de bovengenoemde vereiste bundelintensiteit met de geschikte bundeleigenschappen bezit. Het was daarom de doelstelling om een dergelijk systeem te ontwikkelen.

Met dit als doel werd de isotope separation on-line methode geselecteerd, in het bijzonder voor de productie van intense massa gescheiden $^{11}\text{CO}^+$

bundels. Een ionenbrondoelwit, afgestemd op de productie van $^{11}\text{CO}^+$, werd ontwikkeld, bestaande uit een poreus boornitride doelwit, bediend met een gecontroleerd zuurstoflek en een elektronencyclotron ionenbron. De voornaamste focus van deze thesis was de productie en systematische karakterisatie van het poreuze boornitride doelwit met een gecontroleerde microstructuur voor een verbeterde ^{11}C vrijgave-efficiëntie. Vonkplasma-sintering werd gebruikt als verwerkingsroute om een stijf voorgesinterd poedercompact op te leveren met 21% open porositeit en een gemiddelde korrelgrootte van $1.7\ \mu\text{m}$. Het poreuze BN doelwit werd gekarakteriseerd op het gebied van zijn operationele limieten bij hoge temperaturen en gecontroleerde oxiderende atmosferen. De toepasbaarheid van temperaturen tot $1500\ ^\circ\text{C}$ en zuurstof potentialen onder $-300\ \text{kJ mol}^{-1}$ werd bewezen. Een vrijgave-efficiëntie van 10% voor ^{11}C werd geëxtrapoleerd van een offline gedeeltelijke vrijgave studie uitgevoerd bij CERN MEDICIS. Een conceptuele studie, waarbij verschillende mogelijkheden voor het implementeren van het ontwikkelde $^{11}\text{CO}^+$ productiesysteem in bestaande hadrontherapiecentra werden onderzocht, toonde de haalbaarheid aan van het produceren van voldoende intense $^{11}\text{CO}^+$ radioactieve ionenbundels waardoor, na manipulatie van de bundel en post-acceleratie, de vereiste bundelintensiteit aan de patiënt gegarandeerd wordt.

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List of Abbreviations

AAPM	American Association of Physics in Medicine. 12
ARIEL	Advanced Rare IsotopE Laboratory. 54
ASPIC	Apparatus for Surface Physics and Interfaces at CERN. 187
BET	Brunauer-Emmet-Teller. 93
BGO	Bismuth Germanate scintillator. 16
BIF	Biomedical Isotope Facility. 48
BJH	Barrett-Joyner-Halenda. 93
BN	Boron Nitride. 63
BN-C	Carbon-doped Boron Nitride. 111
BNA	Boron Nitride powder provided by Asbury. 80
BNCT	Boron Neutron-Capture Therapy. 7
BNG	Boron Nitride powder provided by Goodfellow. 80
BNM	Boron Nitride powder provided by Momenive. 80
BNNT	Boron Nitride Nanotube. 163
CERN	Conseil Européen pour la Recherche Nucléaire. 51
CGS	Chromatography Gas Separation. 45
CMPS	^{11}C Molecule Production/Separation System. 56

CNAO	Fondazione Centro Nazionale Adroterapia Oncologica. 26
CRC	Centre de Recherche du Cyclotron. 49
CT	Computed Tomography. 13
cw	Constant Wave. 32
dc	Direct Current. 32
DFT	Density Functional Theory. 163
EBIS	Electron Beam Ion Source. 32
EBRT	External Beam Radiation Therapy. 7
ECR	Electron Cyclotron Resonance ion sources. 31
EOB	End-Of-Beam. 160
ESIS	Electron String Ion Source. 57
FAST	Field-Assisted Sintering Technique. 75
GANIL	Grand Accélérateur National d'Ions Lourds. 53
GPS	General Purpose Separator. 51
HDPE	High-Density Polyethylene. 156
HIMAC	Heavy Ion Medical Accelerator in Chiba. 20
HIP	Hot-Isostatic Pressing. 64
HIT	Heidelberg Ion Therapy. 22
HP	Hot-Pressing. 64
HRS	High Resolution Separator. 51
HT	Heat Treated. 131
IP	Ionization Potential. 31
ISAC	Isotope Separator and Accelerator. 54
ISOL	Isotope Separation On-Line. 28
ISOLDE	Isotope Separator On-Line DEvice. 51

LEBT	Low Energy Beam Transfer. 171
LET	Linear Energy Transfer. 10
linac	Linear Accelerator. 7
LOR	Line Of Response. 17
MEDICIS	Medical Isotopes Collected from ISOLDE. 59
MEDICIS-Promed	MEDICIS-Produced radioisotope beams for medicine. 59
MIP	Mercury Intrusion Porosimetry. 95
NIRS	National Institute of Radiological Sciences. 20
PET	Positron Emission Tomography. 16
PSB	Proton Synchrotron Booster. 51
PSD	Pore Size Distribution. 91
QMS	Quadrupole Mass Spectrometer. 109
RFQ	Radio-Frequency Quadrupole. 55
RGAs	Residual Gas Analysis. 118
RIB	Radioactive Ion Beam. 19
RIBO	Radioactive Ion Beam Optimizer. 153
SEM	Scanning Electron Microscope. 94
SOBP	Spread-Out Bragg Peak. 10
SPS	Spark Plasma Sintering. 74
SSA	Specific Surface Area. 91
TDR	Technical Design Report. 44
TGA	Thermogravimetric Analysis. 111
TGA-MS	Thermogravimetric Analysis coupled with Mass Spectrometry. 112
XRD	X-Ray Diffraction. 80

List of Symbols

ε	Total efficiency
$\varepsilon_{\text{accel}}$	Acceleration efficiency
$\varepsilon_{\text{breeding}}$	Charge breeding efficiency
$\varepsilon_{\text{cool-bunch}}$	Cooling and bunching efficiency
$\varepsilon_{\text{diff}}$	Diffusion efficiency
ε_{eff}	Effusion efficiency
$\varepsilon_{\text{form}}$	Molecule formation efficiency
$\varepsilon_{\text{int-eff}}$	Inter-grain effusion efficiency
ε_{ion}	Ionization efficiency
ε_{ν}	Release efficiency governed by effusion
ε_{μ}	Release efficiency governed by diffusion
ε_{rel}	Release efficiency
ε_{sep}	Separation efficiency
$\varepsilon_{\text{sep}}^{\text{CGS, BN}}$	Total CGS-type separation efficiency for the production of neutral, mass separated $^x\text{CO}_2$ using a BN target
$\varepsilon_{\text{sep}}^{\text{CGS, N}_2}$	Total CGS-type separation efficiency for the production of neutral, mass separated $^x\text{CO}_2$ using a N_2 target

$\varepsilon_{\text{sep}}^{\text{ISOL}}$	Total ISOL-type separation efficiency for the production of neutral, mass separated ^{11}CO
$\varepsilon_{\text{trans}}$	Transport efficiency
$\varepsilon_{\text{trap}}$	Trapping efficiency of cold traps or molecular sieve traps
γ_{S}	Specific surface energy
λ	Decay constant
μ	Diffusion delay parameter
μ_{O_2}	Oxygen potential
ν	Effusion delay parameter
Φ	Porosity
Φ_{closed}	Closed porosity
Φ_{open}	Open porosity
Φ_{total}	Total porosity
ρ	Density
$\frac{d\rho}{dt}$	Densification rate
ρ_{air}	Air density
ρ_{apparent}	Apparent density
ρ_{bulk}	Bulk density
ρ_{fl}	Fluid density
ρ_{l}	Density of the lacquer used to coat the samples for density determination using the Archimedes' principle
ρ_{r}	Relative density
ρ_{th}	Theoretical density
σ	Nuclear reaction cross section

σ_t	Total reaction cross section
τ_{delay}	Total delay due to effusion
τ_{mft}	Mean free time in-between two wall collisions
τ_s	Sticking time or sojourn time
A	Activity
A	Atomic mass number
A^*	Specific activity
A/q	Mass-over-charge ratio
c	Speed of light
D	Diffusion constant or diffusivity
$D_{v,50}^{\text{Extrus.}}$	Median pore diameter deduced from mercury intrusion porosimetry using the extrusion curve
$D_{v,50}^{\text{Intrus.}}$	Median pore diameter deduced from mercury intrusion porosimetry using the intrusion curve
$D_{v,50}^{\text{N}_2\text{PI}}$	Median pore diameter deduced from nitrogen physisorption isotherms
E	Energy
e	Electron charge
E_A	Activation energy
E_A^{Gg}	Grain growth activation energy
E_b	Bond dissociation energy
E_{ea}	Electron affinity
E_S	Surface free energy
F_μ	Fractional release of a diffusion-dominated release mechanism
F_ν	Fractional release of an effusion-dominated release mechanism

G	Grain size
$\overline{G}_{\text{BET}}$	Average particle or grain cluster size estimated from nitrogen physisorption data, employing the BET method
$\frac{dG}{dt}$	Grain growth rate
G_{E}	Gibbs free energy
H	Reaction enthalpy
ΔH_{ads}	Adsorption enthalpy
$\overline{I}$	Mean ionization potential of the stopping medium's orbital electrons
I	Beam intensity
k_{ox}	Oxidation-rate increase due to external O_2 supply to a BN target during ISOL-target operation
M	Molar mass
N_{A}	Avogadro's number
n_{c}	Number of wall collisions
N_{t}	Target nuclei per unit area
P	Pressure
$p(t)$	Delay function of the release mechanism
$p_{\mu}(t)$	Delay function of a diffusion-dominated release mechanism
$p_{\nu}(t)$	Delay function of an effusion-dominated release mechanism
P_{dep}	Power deposition
P_{ex}	External pressure applied during pressure-assisted sintering
Q	Reaction Q -value that defines whether a reaction is exothermic or endothermic
q	Ion's charge state

Q_{ads}	Heat of adsorption
R	Mean range of a charged particle in a stopping medium
R_{p}	(Radio-)isotope production rate
S	Entropy
S	Stopping power
S_{A}	Total surface area
T	Temperature
$T_{1/2}$	Half-life
t_{dwell}	Dwell-time used in a spark plasma sintering (SPS) cycle
T_{max}	Maximum temperature used in a spark plasma sintering (SPS) cycle
V_{C}	Coulomb barrier
V_{m}	Molar (or molecular) volume
Y	Production yield
y	Thick in-target production yield
Y_{phys}	Physical thick in-target production yield
Y_{rel}	Production yield of isotopes released from the target matrix
Y_{sat}	Saturation yield
y_{sat}	Thick in-target saturation yield
Z	Atomic number

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Chapter 1

Introduction

Nuclear physics, particularly the process of radioactive decay, plays an important role in nuclear medicine for the diagnosis and therapy of cancers. Cancer is one of the leading causes of death and is therefore a hot topic in research. Many different types of cancer exist, which are treated with a variety of therapies. Most often, patients receive either surgery, chemotherapy or radiotherapy, or a combination of these treatment modalities. Surgery is usually the preferred form of therapy for localized and non-metastasized cancers. However, as cancer therapy most importantly aims to destroy all tumor cells to prevent tumor recurrence, chemotherapy or radiotherapy is often prescribed in parallel. Chemotherapy employs so-called anti-cancer drugs, which often are cell-cycle specific and are therefore most active against fast growing cells [1]. This implies on the one hand that non-proliferating tumor cells are more difficult to kill and therefore likely to recover from the induced damage. On the other hand, healthy fast growing cells such as blood, hair and skin cells are targeted as well, resulting in pronounced side effects on the entire body.

In radiotherapy (radiation therapy) ionization radiation is exploited for tumor cell killing, and is, unlike chemotherapy, capable to target tumor cells specifically and allows homogeneous radiation dose distribution to the entire tumor volume. The curative potential of radiotherapy was very soon explored after Wilhelm Röntgen's discovery of X-rays in 1895. For instance, their therapeutic potential was examined for limited-stage malignancies of the skin [1], and are ever since an important element in nuclear medicine. In this context, Figure 1.1 shows an impressive graphical comparison between the aforementioned types of therapy, in terms of their modeled difference in quantitative tumor cell destruction versus time course of the treatment [1]. It is remarkable how fractionated radiotherapy is able to kill all cells of a macroscopic tumor (≥ 5 mm; $\geq 10^7$ cells) in a

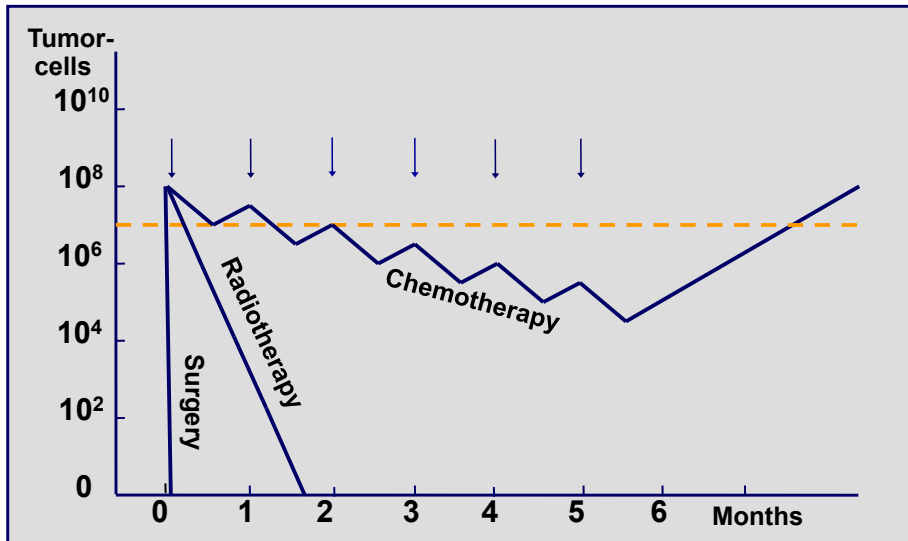


Figure 1.1: Differences between surgery, chemotherapy and radiotherapy in quantitative cell kill versus time course of the treatment. The dashed line segregates between macroscopic (≥ 5 mm; $\geq 10^7$ cells) and microscopic tumors. Six sessions of chemotherapy, indicated by the arrows, are less efficient compared to radiotherapy and surgery. The illustrated effect of different treatment modalities on the number of tumor cells is based on models [2–4]. This plot has been adapted from [1].

considerably shorter time period, compared to chemotherapy, which remains less efficient after six sessions. Moreover, the staggering trend of chemotherapy curve indicates a temporary tumor shrinkage followed by regrowth from residual tumor cells that could not be killed.

In general, radiotherapy can be divided into three main categories: brachytherapy, radionuclide therapy and external beam radiation therapy (EBRT). The former two employ radioisotopes that are delivered internally to the tumor region, and which decay is associated with the emission of a charged particle such as electrons or α -particles. Since these particles deposit their energy on length scales ranging between μm to mm, cell damage is locally restricted and can be thus applied to specific targets by ensuring delivery to the tumor region. In external beam radiation therapy, patients are irradiated with an external beam of particles, which transfer their energy on their trajectory within the human tissue. This feature is exploited for tumor cell killing by tuning the beam energy such that, ideally, the majority of the beam energy is deposited in

the cancerous tissue. EBRT can be divided into two main groups, i.e. photon therapy and charged particle therapy, which differ significantly in terms of their energy distribution profile. Photon therapy, either from high-energy X-rays or from γ -rays, is the most often applied form of EBRT, which however deposits a considerable amount of primary beam energy in the entrance region, i.e. healthy tissue. On the other hand, charged particle therapy exploits electrons or hadrons, e.g. protons or heavy-charged particles such as ^{12}C ions, where especially hadrons can in principle deliver the majority of their energy to the tumor. Crucial in that regard are the definition of the target volume and the correct tuning of the particle beam range. Both of these aspects are far from being trivial, where especially the prediction of the correct beam range is associated with significant uncertainties, which is considered one of the main obstacles in the success of hadron therapy. As a result, *in vivo* verification techniques are desired that allow determination of the charged particles' actual range during treatment. Neutrons may also be used for cancer therapy though their nature as uncharged hadron leads them to form their own category. It is a very exotic type of therapy that is even more exotic than charged hadron therapy.

Different modalities of *in vivo* range verification are currently explored, e.g. by utilizing prompt γ -ray emission or positron emission tomography (PET) [5]. PET-imaging is a standard functional imaging technique, employed in nuclear medicine for the diagnosis and therapy of diseases, which exploits the decay characteristics of radioactive, in detail, positron emitting radionuclides. A possible utilization of PET-imaging for *in vivo* range verification in hadron therapy, is the replacement of the primary stable charged particle beam with a positron emitting radioactive ion beam (RIB). Such RIBs possess comparable efficacy in terms of tumor cell killing capability, compared to their stable counterpart, while enabling monitoring of the actual beam range during treatment by means of PET-image acquisition. ^{11}C is mostly considered as possible therapeutic RIB, because of its relatively accessible implementation into existing ^{12}C based hadron therapy centers and because of its interesting half-life ($T_{1/2} = 20.4$ min) with respect to PET-imaging modalities.

Currently, one of the main difficulties of implementing a ^{11}C based hadron therapy protocol, concerns the delivery of sufficiently intense ^{11}C ion beams ($\sim 4 \cdot 10^8 \text{ s}^{-1}$) with appropriate beam characteristics to the patient. ^{11}C does not occur in nature and thus must be first produced and subsequently formed into an ion beam. The production of RIBs is an essential tool in nuclear physics for the study of atomic nuclei and their properties. While more than 1000 of the known isotopes have been produced as ion beams, no production system exists, capable of delivering the desired ^{11}C intensity with suitable beam properties to the patient room. Generally, two complimentary RIB production methods

exist: in-flight separation and isotope separation on-line (ISOL). The former technique exploits that an energetic heavy-ion beam upon collision with a thin target is fragmented into several (radioactive-)ion beams of similar energy. To the contrary, RIB production via the ISOL method uses primary particle beams to irradiate a usually thick target, generating the (radio-)isotope of interest within the target, which is subsequently extracted from the material and formed into an ion beam. Key component in an ISOL-system is the so-called target-ion source unit.

This thesis aims to develop an ISOL-type RIB production system tailored for ^{11}C that fulfills the aforementioned requirements, particularly in terms of achievable beam intensity, and which can be implemented into existing hadron therapy facilities. The core development with respect to this objective is a suitable target-ion source unit, with focus on an optimized ISOL-target. For this purpose, in a first part of Chapter 2, the general concept of hadron therapy and range uncertainties is further elucidated, as well as the possible advantage of replacing the stable ^{12}C beam with its radioactive counterpart ^{11}C . The second part, provides an overview of the ISOL and in-flight separation methods, and a review of past results concerning ^{11}C RIB production. In the final part of Chapter 2, the gathered knowledge is utilized to define the main challenges and overall strategy with respect to the accomplishment of a suitable production system. Chapter 3 reports on the development phase, including the necessary theoretical background and target fabrication process, as well as its microstructural characterization. In Chapter 4 and 5 the target is systematically characterized in terms of its operational constraints, which is afterwards used to estimate the expected performance of the developed production system in realistic circumstances. The corresponding results are employed in Chapter 6 in a conceptual study that discusses conceivable implementation scenarios of the developed ^{11}C RIB production system into existing hadron therapy centers. Finally, Chapter 7 summarizes the development and characterization phases, and concludes with an evaluation of the developed ISOL-type RIB production system's feasibility of producing sufficiently intense ^{11}C for the development of a ^{11}C based hadron therapy protocol.

The following manuscripts have been included into this thesis in order to highlight the relevance of the following studies and contributions made to their respective areas. These contributions were either peer-reviewed (I), sent for peer-review (II) or provided to a technical design report concerning the realization of a ^{11}C based hadron therapy facility (III):

I Production of intense mass separated ^{11}C beams for PET-aided hadron therapy.

S. Stegemann, T.E. Cocolios, K. Dockx, G. Leinders, L. Popescu, J.P. Ramos, K. Rijpstra, T. Stora, M. Verwerft, J. Vleugels.

Nuclear Instruments and Methods in Physics Research B: Beam Interactions with Materials and Atoms **463** (2020) 403-407.

II ^{11}C release from a porous boron nitride target.

S. Stegemann, J. Ballof, T.E. Cocolios, J.-G. Correia, K. Dockx, O. Poleshchuk, J.P. Ramos, J. Schell, T. Stora, J. Vleugels.

Submitted to: Journal of the European Ceramic Society.

III Technical Design Report for a Carbon-11 Treatment Facility.

L. Penescu.

Contributors list: R.S. Augusto, T.E. Cocolios, E. Fiorina, A. Mairani, K. Parodi, L. Penescu, J. Pitters, M. Pullia, C. Schmitzer, **S. Stegemann**, T. Stora, F. Wenander.

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Chapter 2

Context

2.1 Range uncertainties in particle therapy and PET-aided hadron therapy

2.1.1 Hadron therapy

Hadron therapy, or particle therapy, uses intense and energetic beams of neutrons, protons or heavy charged particles, such as carbon ions, to irradiate and treat cancer, and thus, belongs to *External Beam Radiation Therapy* (EBRT). The basic principle utilized in EBRT, is that external, energetic beams, upon entering the medium, transfer their energy to the tissue. This energy transfer is governed by interactions with the surrounding matter, and the absorbed energy results in tumor cell destruction. In that regard, the average energy absorbed per mass unit is denoted as dose. EBRT is differentiated into two main categories: photon therapy (mostly X-ray therapy) and charged particle therapy. Neutrons are used for exotic treatments such as *Boron Neutron-Capture Therapy* (BNCT), which requires to seed the tumor with boron prior to treatment. This hybrid form of EBRT and targeted therapy will not be discussed further in this manuscript.

Conventional photon therapy is the most often applied form of EBRT, where fast electrons generated using a *linear accelerator* (linac) are rapidly slowed down, producing energetic X-rays, which are subsequently send to the patient. In tissue, high-energy photons present a very spread out dose-depth profile, where most of the dose is deposited in the entrance channel, i.e. the volume before the target region (Fig. 2.1). This absorbed dose, predominately, originates from forward scattered Compton electrons [6]. As a result, a significant dose is always distributed to healthy tissue during treatment. This implies to irradiate the

tumor from many different angles (entry ports), to increase the ratio between cancerous and normal tissue damage [7]. However, this entails that a large volume of healthy tissue receives dose. Note that in conventional photon therapy, irradiation does not result in immediate cell kill [8]. Therefore, therapy is carried out by distributing the prescribed dose over several sessions, which are denoted as treatment fractions. Combining different entry points with fractionation aims to reduce the dose distribution to healthy tissue, and facilitates cell repair of damaged normal tissue. Typically, doses of 1.8 – 2 Gy are given per fraction over the duration of five to seven weeks. However, altered types of fractionation exist: in accelerated fractionation, the prescribed dose and fractions are given in a shorter duration, i.e. more frequently. Other approaches, either deliver the same dose using an increased number of fractions with decreased doses per individual session (hyperfractionation), or apply the contrary, a reduced number of fractions with higher dose per session (hypofractionation) [8].

Charged particle therapy employs electrons or hadrons as therapeutic beam, where this thesis focuses on the latter type. Thus, hereafter the term hadron therapy refers to charged hadrons. The major advantage of hadron therapy over conventional photon therapy is illustrated in Figure 2.1. Hadrons show a very different dose-depth profile, where the majority of the energy is deposited in a very sharp peak at the end of the particle's trajectory (Fig. 2.1a). This feature is the so-called Bragg peak, and results from the interaction from heavy charged particles with matter. These particles lose their energy mostly via inelastic collisions due to Coulomb interactions with orbital electrons, ionizing or exciting these atoms. The mean energy loss per unit path length is described by the Bethe formula (stopping power) [9]:

$$S = -\frac{dE}{dx} = \left(\frac{e^2}{4\pi\epsilon_0}\right)^2 \frac{4\pi Z_p^2}{m_e c^2 \beta^2} \frac{N_A Z_T \rho}{A_T} \left[\ln\left(\frac{2m_e c^2 \beta^2 \gamma^2}{\bar{I}}\right) - \beta^2 - \frac{\delta}{2} \right], \quad (2.1)$$

with the electron charge e , the electron rest mass m_e and the vacuum permittivity ϵ_0 . Z_p and $\beta = v/c$ are the projectile's atomic number and velocity, respectively. The influences of the absorber material are given by its atomic number Z_T , mass number A_T , density ρ and mean ionization potential $\bar{I}$ of its atoms. γ and δ are correction factors for relativistic and density effects. Note that this is a rather general description of the Bethe equation, for which several further correction factors exist. However, since these are not essential for the context of this work, the reader is referred to more comprehensive reviews [7, 9]. High-energy hadrons, such as protons and carbon ions, upon entering a medium transfer very little energy in the entrance channel. However, due to the $1/\beta^2$ factor in Eq. (2.1), the energy transfer increases with decreasing beam energy, which ultimately results in a very rapid absorption of the remaining energy towards the end of the particles' trajectory (Bragg peak). This feature is the essential characteristic which is exploited in hadron therapy. By tuning the beam energy

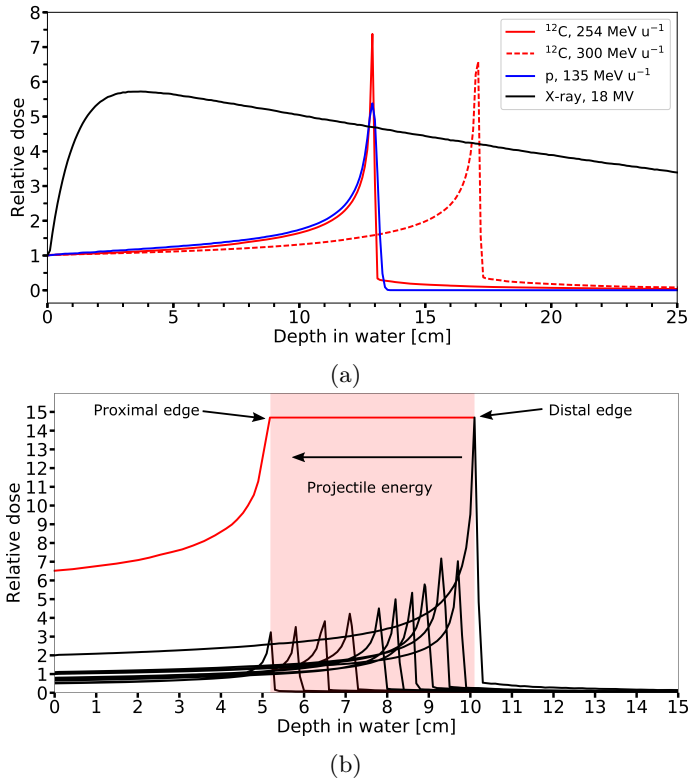


Figure 2.1: (a) Qualitative dose-depth profile for photons from an 18 MV electron linac (black), 135 MeV protons (blue), 254 and 300 MeV u^{-1} ^{12}C ions (red, solid and dashed lines, respectively). The advantage of particle therapy is evidenced as follows: hadrons demonstrate a peak-like structure where most of the energy is deposited in a narrow region at the end of the beam trajectory (Bragg peak), while in conventional photon (X-ray) therapy most of the dose is deposited in the entrance channel. Moreover, at equal ranges, carbon ions present a narrower Bragg peak, due to the mitigated lateral straggling of heavier ion beams. (b) Illustration how a homogeneous dose plateau, i.e. spread-out Bragg peak (SOBP), can be applied by superimposing beams of different beam energy (range). The profiles are reproduced from [7].

such that the particles' range lies within the tumor region, most of the dose is deposited in the cancerous tissue, sparing the healthy tissue in the entrance channel, contrary to X-ray therapy. The total path length, i.e. the mean range

R of hadrons in matter can be deduced from the stopping power by:

$$R = \int_{E_i}^0 dE \frac{1}{dE/dx}. \quad (2.2)$$

Note that the projected range (projected onto the initial beam axis x) is slightly shorter due to scattering. To cover the entire volume of the three dimensional tumor volume, the range of the particle beam can be adjusted by changing the initial beam energy E_i . Superimposing beams of different energy and irradiating from different entry angles allows to distribute the dose homogeneously across the tumor. This is denoted as *Spread-Out Bragg Peak (SOBP)*, and is illustrated in Figure 2.1b. As a result, fewer irradiations from different entry ports, fewer fractions and less overall treatment time are possible, without enhancing toxicity to healthy tissue while ensuring tumor cell kill, compared to conventional photon therapy [6, 7].

Carbon therapy

Employing beams of higher mass in hadron therapy, where most commonly carbon is used, offers in principle a variety of advantages. Comparing the red curve for carbon to the blue curve for protons in Fig. 2.1, shows that the Bragg peak of heavier ions is narrower at the same range. Consequently, carbon therapy allows to further reduce the dose distribution to healthy tissue. While according to Equation (2.1) the Bragg peak should be very sharp, statistical fluctuations in energy loss, also known as longitudinal straggling, and density inhomogeneities of the penetrated tissue result in a broadening of the Bragg peak [6, 7]. The broadening due to energy-loss straggling is described by an asymmetrical Vavilov distribution, which can be approximated by a Gaussian function in the limit of many collisions:

$$f(\Delta E) = \frac{1}{\sqrt{2\pi\sigma^2}} \cdot e^{-\frac{(\Delta E - \overline{\Delta E})^2}{2\sigma^2}}.$$

The energy-loss variance σ^2 is related to the variance of the range straggling σ_R^2 , which is proportional to the mass of the projectile by $\frac{\sigma_R}{R} \propto M^{-1/2}$. As a consequence, range straggling from protons is approximately 3.5 times larger compared to carbon ions.

One of the main advantages of carbon therapy is the higher *Linear Energy Transfer (LET)*, which results in a higher biological effectiveness, and explains why carbon therapy is preferably applied for treatments of radio-resistant tumors. The LET refers to the energy deposition due to the slowing down of a particle in a stopping medium and thus, is related to the stopping power S . The LET depends quadratically on the projectile's atomic number Z_p ,

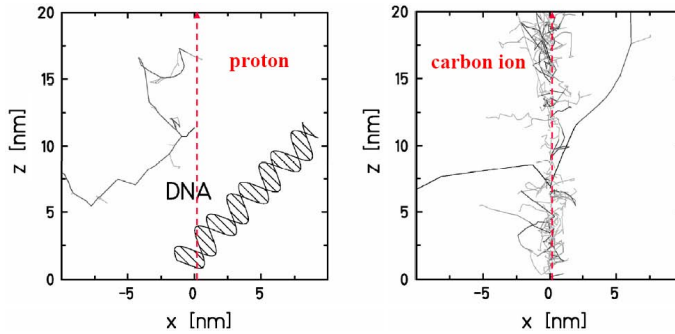


Figure 2.2: Simulated track structure of 1 MeV u^{-1} protons (left) and carbon ions (right) on a nanometer scale. The black lines represent the trajectories of secondary electrons produced by the primary ion beam. A schematic illustration of a DNA molecule to scale is superimposed in the left graph. In the case of carbon ions, the higher density of secondary electrons that cause further ionizations, results in a more clustered DNA damage which is therefore more likely to generate double strand breaks of the DNA, which have a higher chance to lead to cell kill. Taken from [10].

which is reflected in the height of the Bragg peak. High-LET particles possess a high ionization density, especially at the end of the projectile's trajectory, which is the tumor region. These ionizations damage the tumor DNA, and are therefore the essential cause for tumor cell kill. Figure 2.2 shows the difference in ionization density originating from protons and carbon ions. The black tracks are secondary electrons that result from the ionization of the heavy charged particles. It is apparent that carbon ions produce a much higher density of these electrons, which cause further DNA damage. The scale of a DNA strand is schematically illustrated in the left graph. Since carbon ions generate highly clustered ionizations on a nanoscale, double strand breaks of the tumor DNA are more likely to occur. More severe DNA damage, reduces the cell's repair capabilities and therefore has higher chances to result in cell kill. In that manner, carbon therapy is more effective for radio-resistant tumors.

In summary, hadron therapy and especially carbon therapy, allows to maximize the dose distribution to cancerous tissue while reducing dose delivery to healthy tissue in the entrance channel. Heavy charged particles with high-LET values in the tumor region, generate more severe DNA damage, which is more likely to result in cell kill, and thus possesses a higher biological effectiveness. In Figure 2.3 the former advantage of carbon therapy over conventional photon therapy is visualized. In detail, treatment plans using X-rays (left) and carbon ions (right) for a lung cancer are displayed. While X-rays deposit significant dose in

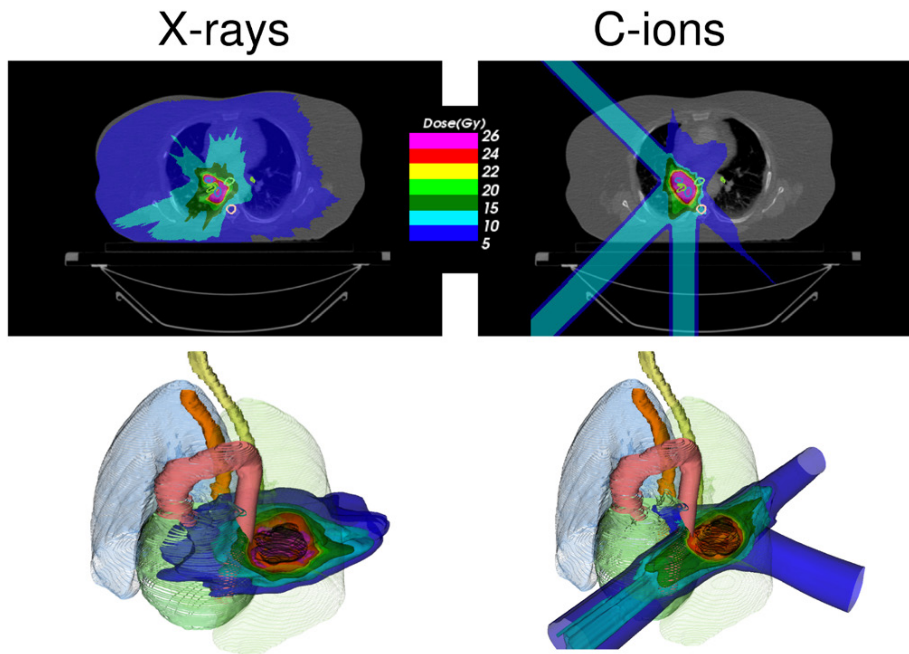


Figure 2.3: Treatment plans of a lung cancer using conventional photon (X-ray) therapy (left) and using carbon ions (right). The plans are made such that only a single high-dose fraction is applied. In carbon therapy, only three beam entry ports (or angles) are required to deliver the prescribed dose to the target volume. Taken from [7].

the surrounding tissue, the carbon treatment plan enables to deliver the same dose to the target region, using only three beams from different entry ports. However, discussing treatment planning will expose the major complication and obstacle in hadron therapy, which shall be illustrated in the following section.

2.1.2 Range uncertainties

Two third of all cancer patients are treated with radiotherapy: 80% receive X-ray therapy, and only 0.8% receive hadron therapy. The remaining patients receive specialized treatment modalities, e.g. brachytherapy and gamma knife. When the delegates of the *American Association of Physics in Medicine* (AAPM) were asked in 2012, what they consider as the main obstacle in hadron therapy, 50% referred to range uncertainties and the other half to the unproven benefit of a reduced integral dose (lack of clinical trials). Furthermore, 20% believed that hadron therapy would never replace conventional photon therapy [7].

As previously stated, the substantial feature of hadron therapy is the ability of tuning the beam range such that the Bragg peak is located in the tumor region, where the energy deposition is maximized. The prescribed range should therefore correspond to the actual range, to fully exploit this modality. Unfortunately, the range estimation is accompanied with significant uncertainties. Table 2.1 lists some of the sources of range uncertainty and their estimated amount in the case of proton therapy. The extent of this list and the magnitude of the total uncertainty are indeed alarming, considering the impact of potentially wrong dose delivery to the patient. In practice, to ensure dose delivery to the tumor, a significant range is added onto the prescribed range. This range margin can be of the order of 3.5% in proton therapy, for therapies where a SOBP is applied [11].

In that regard, for each treatment fraction in hadron therapy, a treatment plan is generated which defines the dose delivery to the tumor, to maximize the SOBP plateau-to-entrance channel dose ratio and the overall exposition of surrounding healthy tissue. These treatment plans are either based on analytical models that calculate the range using the stopping power S (Eqs. (2.1), (2.2)), or are measured in water phantoms for each treatment. For this purpose, firstly, the target volume needs to be defined. Three-dimensional images are recorded from *X-ray Computed Tomography* (CT), which provides the photon attenuation relative to water (CT number) [6]. These CT numbers are given in Hounsfield units:

$$\text{CT number}(\vec{x}) = 1000 \cdot \frac{\mu(\vec{x}) - \mu_w}{\mu_w},$$

with the X-ray absorption coefficients $\mu(\vec{x})$ in tissue at position $\vec{x}$, and in water μ_w . The second step in treatment planning is to relate the CT number to the stopping power, for which no simple functional relationship exist.

Personalized dose calculation predict the dose distribution based on material (tissue) composition and mass densities, where typical target tissues are composed of several hundred CT numbers. Correlations between CT number and material composition are not unique. Identical CT numbers may have the same material properties in terms of composition and ionization potential, but may differ in mass density, which directly impacts the dose calculation [7]. It is thus conceivable that an accurate treatment planning based on CT images that translates tissues into maps of stopping powers (i.e. electron densities, atomic mass numbers, ionization potentials, etc.) is extremely challenging.

In fact, the mean ionization potential $\bar{I}$ is the stopping power's most prominent source of inaccuracy that immediately reflects into range uncertainty. In that regard, even the ionization potential of water is debatable. The ICRU recommends a standard value of 75 ± 3 eV [12]. However, M. Durante and H. Paganetti discuss in their review that experimental values were found in

Source of range uncertainty in the patient	Range uncertainty [% or mm]
Independent of dose calculation:	
Measurement uncertainty in water for commissioning	± 0.3 mm
Compensator design	± 0.2 mm
Beam reproducibility	± 0.2 mm
Patient setup	± 0.7 mm
Dose calculation:	
Biology (always positive)	$+ \sim 0.8\%$
CT imaging and calibration	$\pm 0.5\%$
CT conversion to tissue (excl. I -values)	$\pm 0.5\%$
CT grid size	$\pm 0.3\%$
Mean excitation energy (I -values) in tissue	$\pm 1.5\%$
Range degradation; complex inhomogeneities (negative)	-0.7%
Range degradation; local lateral inhomogeneities	$\pm 2.5\%$
Total (excl. biology and lateral inhomogeneities)	$2.7\% + 1.2$ mm
Total (excluding biology)	$4.6\% + 1.2$ mm

Table 2.1: Sources of range uncertainties and their estimated magnitude for proton therapy. Range uncertainties can be grouped into those due to shortcoming in dose calculations and into those that are not related to this. Originally published by H. Pagnetti [11], modified by M. Durante [7], and in this work. Note that these numbers are estimations based on findings from other works. The corresponding references can be found in [7, 11]

literature to fluctuate between 74.6-81.8 eV [7]. P. Andrea studied, among other things, the impact of varying the mean ionization potential of water in hadron therapy [13]. Figure 2.4 shows Bragg peaks in water, assuming a mean ionization potential $\bar{I} = 67, 74$ and 80 eV for 122 MeV protons (Fig. 2.4a) and 430 MeV $\text{u}^{-1} {}^{12}\text{C}$ ions (Fig. 2.4b). The variations in $\bar{I}$, result in a Bragg peak-drift across a region of $\sim 0.3 \text{ g cm}^{-2}$ (≈ 0.3 cm) for 122 MeV protons, and $\sim 0.6 \text{ g cm}^{-2}$ (≈ 0.6 cm) for 430 MeV $\text{u}^{-1} {}^{12}\text{C}$ ions. This elucidates the difficulty to ensure a correct treatment planning, and is however only one example from the list in Table 2.1. It is thus apparent that an accurate translation from

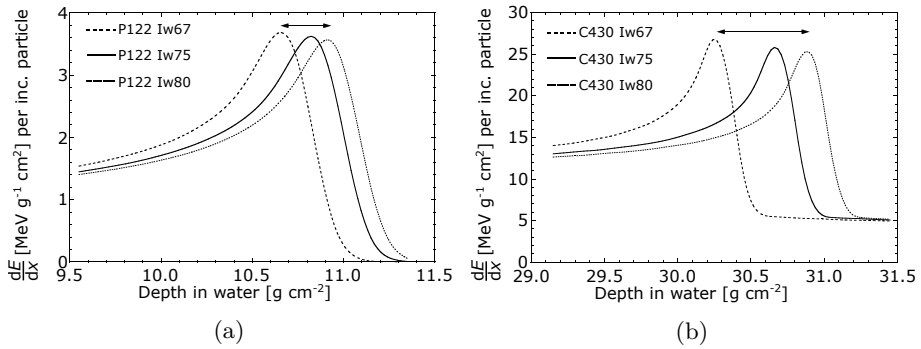


Figure 2.4: Energy loss of 122 MeV protons (a) and 430 MeV u^{-1} ^{12}C ions (b) in water, for mean ionization potential of water $\bar{I} = 67, 75$ and 80 eV. The variation in $\bar{I}$ results in a drift of the Bragg peak over a region of $\sim 0.3 \text{ g cm}^{-2}$ ($\approx 0.3 \text{ cm}$) (a) and $\sim 0.6 \text{ g cm}^{-2}$ ($\approx 0.6 \text{ cm}$) (b). Adapted from [13].

CT images into maps of stopping power is very complicated and will certainly degrade the correctness of the treatment planning.

Using heavy charged particles in particle therapy includes yet another source of uncertainty which has not been mentioned so far, and which does not apply for proton therapy. Consulting the dose-depth profiles of proton and carbon therapy, one notices that heavy charged particles present a dose tail beyond the Bragg peak. This originates from beam fragmentation in which the projectile collides with a target nucleus upon which lighter beam fragments are produced in a nuclear reaction. These lower- Z fragments are emitted predominantly in forward direction with the same velocity. Lighter particles have larger scattering angles in elastic Coulomb interactions with target nuclei and thus, contribute to the lateral beam spread. Since the range of secondary particles scales according to [7]:

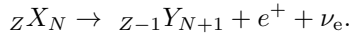
$$\frac{R_f}{R_i} = \frac{M_f}{M_i} \frac{Z_i^2}{Z_f^2}, \quad (2.3)$$

fragments with lower atomic number will exceed the projectile's range, which yields the aforementioned longitudinal dose tail. In the case of ^{12}C , approximately 50% of the primary beam reach the Bragg peak, and mostly hydrogen and helium fragments contribute to the dose tail, while heavier fragments such as $^{9,10,11}\text{C}$, $^{8,10,11}\text{B}$ are stopped in the Bragg peak's vicinity. The main uncertainty in that context, is the lack of double-differential cross sections of the nuclear interactions, which prevents an accurate modeling of the fragmentation process [7].

In summary, while the essential feature of hadron therapy is the ability of tuning the beam energy such that the particle stop within the tumor region, where consequently the majority of the beam energy is deposited, the prediction of the exact range is accompanied by considerable uncertainties due to dose calculation, imaging, beam delivery and patient setup. It is conceived that this is one of the main hurdles in particle therapy and thus, *in vivo* range verification techniques are desired. There are a few potential methods, for example by means of prompt γ -ray emission or positron emission tomography [5]. These methods exploit the detection of decay products resulting from excited tissue nuclei or radioactive isotopes, to trace back their origin, which is correlated with the range. The next section will introduce the application of positron emission tomography for *in vivo* range verification, which is the motivation of this thesis.

2.1.3 *In vivo* range verification based on PET

Positron Emission Tomography (PET) is a standard functional imaging technique in nuclear medicine for the diagnosis of diseases that express an increased metabolic activity, or can be targeted by means of disease-specific receptors. It exploits the decay characteristics of β^+ -emitters to trace back the origin of the decaying nucleus. Radionuclides that decay via the β^+ -decay, convert a bound proton into a neutron and emit a positron e^+ with an electron-neutrino ν_e :



Consequently, in comparison to the mother nucleus X , the daughter nucleus Y reduces its atomic number by one, while increasing its number of neutrons by one. Positrons that transit in matter, are very quickly slowed down, e.g. with a Q -value of ~ 1 MeV for ${}^{11}\text{C}$, the positrons may travel up to 4 mm in water before they slowed down sufficiently to annihilate with an electron. The $e^+ - e^-$ annihilation generates two characteristic γ -rays of 511 keV that travel back-to-back, i.e. with an angle of 180° . This feature is used in PET-imaging, where a PET-radiopharmaceutical, i.e. a pharmaceutical drug labeled with a β^+ -emitter is injected into the patient. For instance, PET-radiopharmaceuticals are chemical compounds (or biomolecules), where one or more stable elements are replaced by a radioisotope, which are denoted as radiotracer. Alternatively, the radioisotope is incorporated into a chelator (small molecule) that is linked to a marker molecule. In both cases, radiotracer or marker are chosen such that the compound presents an increased uptake by the target volume, e.g. a tumor. As a result, the two 511 keV annihilation photons have their origin within the tumor volume. They possess sufficient energy to exit the human body and can be detected by a PET scanner, which is a ring-array of scintillation detectors, such as *Bismuth Germanate* (BGO) detectors. A true annihilation event, originating from the β^+ -decay, is detected in two, opposed detectors in coincidence, where

the line between these two detectors is called *Line Of Response* (LOR). The LOR is not restricted to a single plane, unlike when employing SPECT scanners, which therefore allows to obtain a 3D distribution of the decay origin. However, this requires complex reconstruction algorithms that translate the coincidence data into dose maps containing the spatial information [14].

The idea of using positron emitters for *in vivo* range verification was first discussed [15] and investigated [16–18] at the Lawrence Berkeley National Laboratory in California (USA). In general, two methods exist that exploit the detection of annihilation photons resulting from the β^+ -decay with PET-scanners: autoactivation and external activation.

In vivo range verification by means of autoactivation uses positron emitters which are generated from nuclear interactions between the stable heavy ion beam with the target nuclei of the human tissue. It was discussed in the previous section that high-energy carbon ions undergo beam fragmentation in matter, resulting in lower- Z fragments. Some of these products are in fact positron emitters, where $^{10,11}\text{C}$ and ^{15}O are most abundantly generated, and have applicable/interesting half-lives ($T_{1/2} \approx 19$ s, 20 min and 2 min, respectively) with respect to PET-imaging for beam monitoring. Especially ^{11}C is of interest, due to its half-life and since its distribution presents a peak-like structure, well correlated with the Bragg peak of the incident ^{12}C beam [19]. However, it does not reflect the Bragg peak exactly (Fig. 2.5), and the overall production yield is rather small. Only a few % of the primary beam is fragmented into ^{11}C , which consequently yields a low β^+ -activity that is associated with limited counting statistics, and therefore results in a noisy PET-image.

The autoactivation approach was first implemented in 1997 at the GSI Helmholzzentrum für Schwerionenforschung (Center for heavy ion research), Darmstadt (Germany). Three different implementation techniques (off-line, in-room and in-beam) were studied with respect to their incorporation feasibility into existing therapy schemes [20]. They were evaluated with respect to their integration costs, workflow disturbance (i.e. additional time needed for PET-image acquisition) and the image quality with respect to its explanatory significance.

Off-line PET denotes the application of a conventional PET/CT scanner outside the treatment room. While this solution is associated with low integration costs, the workflow is severely delayed (~ 30 min). Since the PET measurement starts the earliest ten minutes after irradiation, the limited counting statistics issue is enhanced, due to the decay of the relatively short-lived positron emitters. Furthermore, the generated β^+ -activity diffuses away from the region of interest, via the blood flow, which is referred to as *biological wash-out*. Both of these features result in a degraded image quality. However, the main disadvantage is the fact that the PET-image is only recorded after the treatment fraction

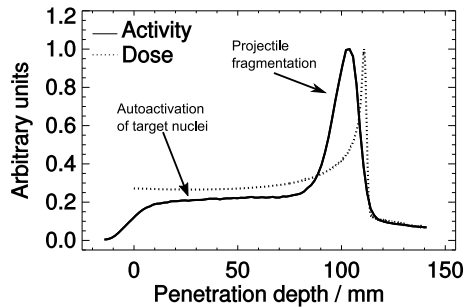


Figure 2.5: Measured β^+ -activity distribution profile resulting from irradiating a PMMA (Poly(methyl methacrylate)) target with 259.5 MeV u^{-1} stable ^{12}C ions. The dotted line illustrates the corresponding relative dose-depth profile of the ion beam. Note that the peak structure results from projectile fragmentation of the primary ^{12}C beam, whereas the plateau originates from autoactivation of the target nuclei. Adapted from [22].

and thus, presents a superposition of different β^+ -activities, originating from different irradiation fields.

In-room PET stands for measurements that are carried out immediately after irradiation in the treatment room itself, where special scanner designs are required that allow implementation into existing facilities, and that do not interfere with the actual treatment [7]. The effect on the facility's workflow is only minor ($\sim 4 - 5 \text{ min}$). Images can be acquired $1 - 2.5$ minutes after irradiation [20, 21], which significantly improves the acquired image quality, by means of mitigated biological wash-out and reduced counting statistic loss due to the decay. To reduce uncertainties due to patient repositioning, mobile stand-alone PET-scanners exist, which can easily be transported to the patient couch.

In-beam PET was declared as the best solution. Images are acquired simultaneously with the treatment, i.e. on-line, using a double-head PET-scanner which is fully integrated into the beam delivery system. While the image quality is moderately inferior compared to the in-room solution, which is mainly caused by the detector design, in-beam PET features the strongest reduction in signal degradation due to decay and biological wash-out. Most important, this method allows best to verify the correctness of the treatment plan, in terms of range uncertainty. Drawback of this concept are the very high integration costs, which originate from the necessity of a custom made PET-scanner and the demanding technical realization [20, 21]. Until 2008, more than 400 patients, mostly suffering from head-and-neck cancer, received treatments that were monitored using in-beam PET-imaging at GSI [20].

However, the produced β^+ -activity distribution does not directly reflect the actual Bragg peak position, which as a result requires correlation modalities. K. Parodi measured the positron emitter dose-depth profile (Fig. 2.5), resulting from irradiating a PMMA (Poly(methyl methacrylate)) target with $259.5 \text{ MeV u}^{-1} \text{ }^{12}\text{C}$ ions [22]. The graph shows a peak-like structure which originates from the ^{12}C beam fragmentation, and the flat region is produced by autoactivation of the target nuclei. Typically, range verification, is performed by comparing the measured spectrum to a β^+ -activity distribution obtained from Monte Carlo simulations [7]. Several methods and algorithms have been reported that conduct *in vivo* range verification via this modality [23], whereas the majority relies on, either, quantitative and automated models, or visual analysis of the activity distal fall-off [24–27]. Nevertheless, the limited counting statistics available in this approach remain a fundamental issue that requires optimizations with respect to detector and identification developments [28, 29].

^{11}C based hadron therapy

The second approach exploiting β^+ -emitters for *in vivo* range verification uses positron emitting radionuclides directly as therapeutic beam in heavy ion therapy [16–18], which was earlier referred to as external activation. This offers a variety of advantages, e.g. higher coincidence statistics and better correlation between dose profile and measured β^+ distribution, but introduces the challenge of producing a sufficiently intense *Radioactive Ion Beam* (RIB).

The possibility of applying positron emitting radionuclides as primary, therapeutic heavy ion beam was first studied experimentally at the Lawrence Berkeley National Laboratory using ^{11}C and ^{19}Ne ions in the 1980s [17, 18]. As the primary beam is composed of positron emitters, the majority of the β^+ -activity directly correlates with the Bragg peak (or SOBP). Thus, on-line or off-line acquired PET-images, can be applied more directly for range verification. Note that the primary RIB likewise generates secondary β^+ -emitters via target and projectile fragmentation.

Similar to the autoactivation case, interesting radioisotopes are $^{10,11}\text{C}$ and ^{15}O , where ^{11}C is the most promising candidate. While ^{10}C offers in principle a better image quality due to its shorter half-life, which means that PET-scans are less deteriorated from biological wash-out, its large Q -value of $\sim 2.6 \text{ MeV}$ mitigates this supremacy to some extent. As the positrons possess more kinetic energy they can travel up to $1.3 - 1.4 \text{ cm}$ in water, resulting in a larger spread of the $e^+ - e^-$ annihilation origin, thus, deteriorating the image quality. Moreover, production and acceleration of sufficient ^{10}C beam intensity for effective treatments and adequate γ statistics are extremely challenging. ^{15}O presents higher biological effectiveness and a shorter half-life. However, beam fragmentation is also enhanced, which means that fewer particles reach the end-

of-range. Furthermore, stable ^{12}C ion therapy is already successfully carried out in treatment facilities and thus, allows easier implementation of a ^{11}C treatment protocol.

Recently, ^{11}C based hadron therapy has gained renewed interest when imaging studies in rabbits were performed at the National Institute of Radiological Sciences (NIRS) in Chiba (Japan). Wash-out rates of $^{10,11}\text{C}$ [30, 31] and ^{15}O [32] were studied in dead and live rabbit brains and thigh muscles. It was reported that approximately one third of the initial ^{11}C inventory could be used for imaging ten minutes after implantation. Furthermore, significantly higher wash-out rates were observed for ^{15}O . The respective RIBs were produced at the Heavy Ion Medical Accelerator in Chiba (HIMAC) via in-flight projectile fragmentation of primary stable ^{12}C and ^{16}O beams on thin beryllium or polyethylene targets. RIB production techniques such as in-flight projectile fragmentation will be discussed in the following section.

Meanwhile, the benefit with respect to PET-imaging capabilities for *in vivo* range verification of ^{11}C based carbon therapy compared to PET-imaging of secondary produced positron emitters from nuclear interactions of a stable carbon beam, was investigated using Monte Carlo simulation tools [33–35], in detail FLUKA was employed [36, 37]. Moreover, experimental data, obtained at the HIMAC in Chiba (Japan), was compared to corresponding predictions from the aforementioned simulations tools, to benchmark their dosimetry and PET-imaging performance [38]. Such simulations provide a very expressive way of demonstrating the advantages of RIB based hadron therapy over stable heavy ion beams, with respect to their imaging capacity for range verification.

The top graphs in Fig. 2.6 show the absorbed dose-depth distribution for 1 Gy SOBPs centered in 10 cm water depth, with a 3 cm dose plateau, for stable ^{12}C and radioactive ^{11}C beams. The very identical dose maps of these cases, illustrate that replacing the stable ion beam with its radioactive counterpart, does not alter the biological effectiveness of the treatment. In other words, changing ^{12}C to ^{11}C has no significant effect on the tumour cell killing capability of the ion beam. On the other hand, the bottom graphs of Fig. 2.6 show, qualitatively, the annihilation events at rest¹ for the aforementioned irradiation scenario. The ^{11}C ion beam presents a considerable gain in the magnitude of annihilation events throughout the 3 cm SOBP plateau, and a more direct correspondence with the range of the carbon beam. In detail, a factor 4.9 is gained at the proximal rise edge, and a factor larger than 30 is gained at the distal edge of the SOBP dose fall-off [35].

¹Annihilation events at rest denotes those decays that occur after the particle has stopped in the medium.

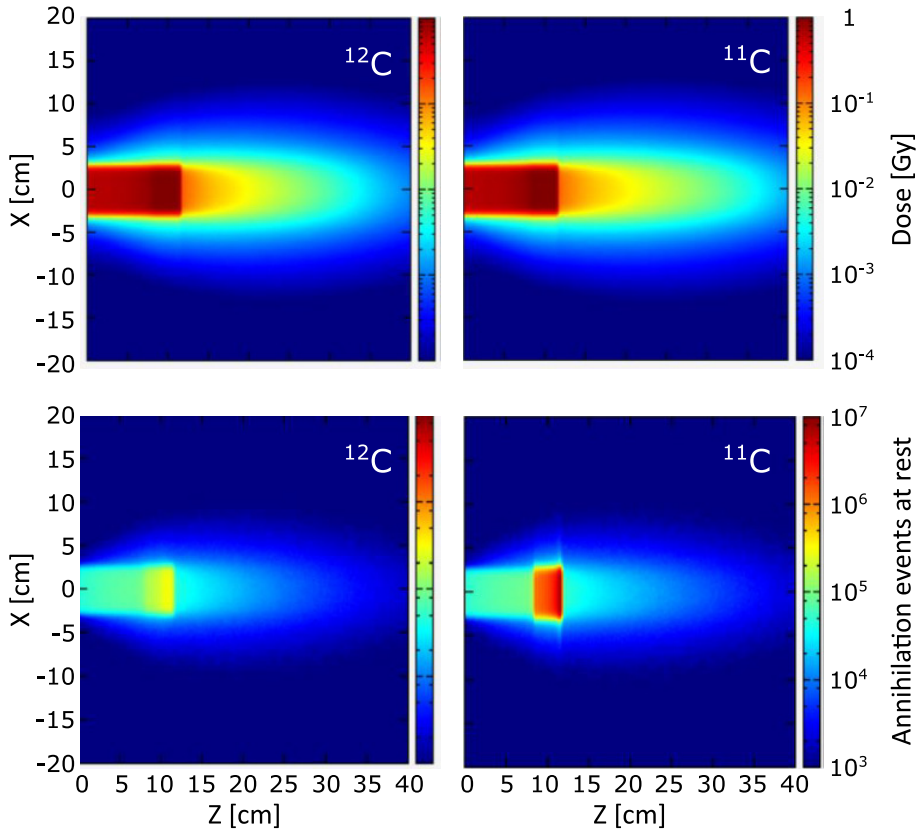


Figure 2.6: Comparison of the absorbed dose distribution for 1 Gy SOBPs centered in 10 cm water depth, and a 3 cm dose plateau, for a primary ^{12}C and ^{11}C beam (top), and the corresponding annihilation events at rest 2D maps, integrated over time (bottom). Adapted from [35]. The simulations were performed using the FLUKA Monte Carlo code.

The same benefit of using ^{11}C as primary beam is depicted quantitatively in Fig. 2.7. The graphs show some of the simulation results of recently developed FLUKA PET TOOLS [34]. These tools aim to provide to the medical community, dedicated simulation packages for clinical applications that feature PET-scanner models, and which can reproduce PET acquisitions in time, mimicking actual hadron therapy scenarios, with respect to beam time structure and PET-scan time. Moreover, the tools feature reconstruction routines for the translation from LOR and coincidence timing window information into a coincidence list data representation.

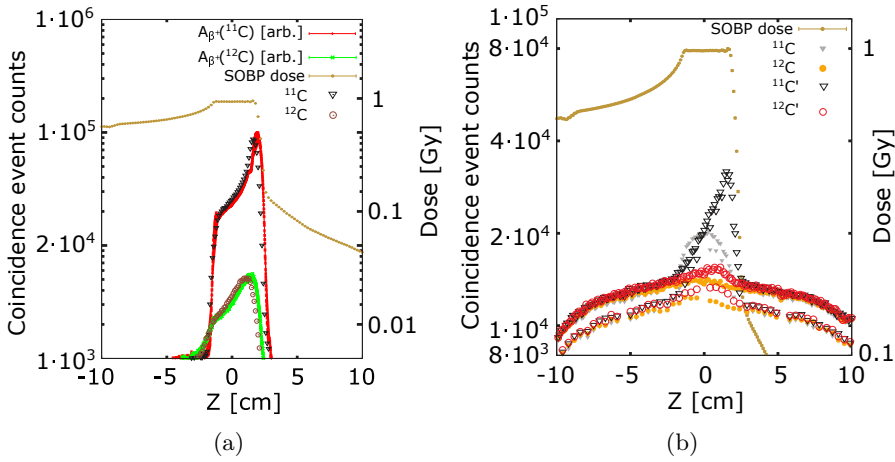


Figure 2.7: Comparison between the estimated coincidence event counts for a 1 Gy SOBP irradiation in an anthropomorphic voxelized head geometry, centered in 10 cm depth, using primary ^{12}C and ^{11}C beams. (a) Off-line PET acquisition, started 5 min after irradiation for a duration of 25 min. The SOBP was applied starting from lowest to highest energy. + and x denote the total annihilation events at rest simulated during the respective acquisition time for ^{11}C and ^{12}C , respectively. ▽ and ○ represent the reconstructed coincidence events using specialized FLUKA PET TOOLS. (b) On-line PET acquisition, showing the reconstructed coincidence counts for ^{11}C and ^{12}C applying the SOBP from lowest to highest energy (▼ and ●, respectively), and in reversed order ($^{11}\text{C}'$: ▽, $^{12}\text{C}'$: ○). In both acquisition cases, the dose profile is superimposed onto the annihilation events at rest (●), and the Z origin is set at 10 cm depth of the patient's head. Adapted from [34].

In this context, the dosimetry and imaging characteristics of stable ^{12}C and radioactive ^{11}C beams were simulated and PET acquisitions were compared in an off-line and on-line (in-beam) scenario [34]. Again, 1 Gy SOBPs, distributed over a 3 cm long dose plateau, were simulated in an anthropomorphic head *voxel* structure, employing a *Siemens Biograph mCT* (TrueV version) PET-scanner and ion beam delivery characteristics similar to the Heidelberg Ion Therapy (HIT) center in Germany. The SOBP irradiations were carried out in 16 spills during 130 s, with 4 s pauses between the spills. Off-line PET acquisitions were simulated 5 min after irradiation for a duration of 25 min, where the scans were recorded in the same room (i.e. in-room PET). The on-line acquisition took place during the entire 130 s of irradiation, including the 4 s pauses [34].

Figure 2.7a shows the result for the off-line acquisition scenario, where

+ and × represent the total annihilation events at rest simulated during the aforementioned acquisition time, for ^{11}C and ^{12}C , respectively. The reconstructed coincidence counts, obtained from the FLUKA PET TOOLS are displayed as ▽ and ○, and the SOBP dose profile is superimposed (●). This comparison demonstrates the supremacy of ^{11}C imaging capabilities, where in detail a ten-fold increase of the β^+ -activity is gained, compared to ^{12}C . Moreover, the 50% distal fall-off of the coincidence counts is less than 1 mm away from the equivalent dose distal fall-off, while for stable ^{12}C the difference is about 3 mm and the coincidence profile is less sharp and less well defined.

The results of the on-line (in-beam) scenario is depicted in Fig. 2.7b, by means of the reconstructed coincidence events, superimposed with the SOBP dose profile (●). Note that in this scheme, the correlation between the total annihilation events at rest (not shown here) and the coincidence counts is, at first, less evidenced (^{11}C : ▽ and ^{12}C : ●). This stems not only from the relatively long half-life of ^{11}C , but also from the beam delivery structure, in which the SOBP was applied from the lowest to highest energy, where the last spill comprised $\sim 30\%$ of the total beam particles. Due to the aforementioned acquisition scheme, the contribution from the last spills are not fully accounted in the coincidence data [35]. However, by applying the same dose in reversed order, i.e. highest to lowest energy (^{11}C : ▽, ^{12}C : ○), the superior correlation between dose profile is demonstrated. Moreover, a signal improvement by a factor two is observed, for the reconstructed coincidences of ^{11}C compared to ^{12}C . Therefore, an easier *in vivo* SOBP range verification is possible by employing a RIB for PET-aided hadron therapy.

These simulations confirm the expected benefits of employing a positron emitting RIB in hadron therapy in regard to their improved PET-imaging quality for *in vivo* range verification. This is especially demonstrated by the much better correlation between the dose profile and the coincidence peak structure for ^{11}C .

To test whether these predictions conform with reality, these simulations were compared to experimental data in terms of ^{11}C dosimetry and PET-imaging capabilities, obtained at the HIMAC in collaboration with the *Imaging Physics Team* of the NIRS [38]. ^{11}C beams, produced by in-flight projectile fragmentation of an initial ^{12}C beam with a beryllium target, were firstly, absorbed in a water container equipped with a moving cross ionization chamber (dosimetry), and secondly implanted in a PMMA phantom and a openPET scanner prototype was used in an in-room PET scenario (PET-imaging performance).

Regarding the dosimetry, Bragg peak profiles were measured for $^{11,12}\text{C}$ beams in water, where some of the results of this comparison are shown in Figure 2.8. In detail, to benchmark the dosimetry performance of the FLUKA Monte Carlo code, dose-depth profiles in water of $210 \text{ MeV u}^{-1} \text{ }^{11}\text{C}$ and $290 \text{ MeV u}^{-1} \text{ }^{12}\text{C}$ ion

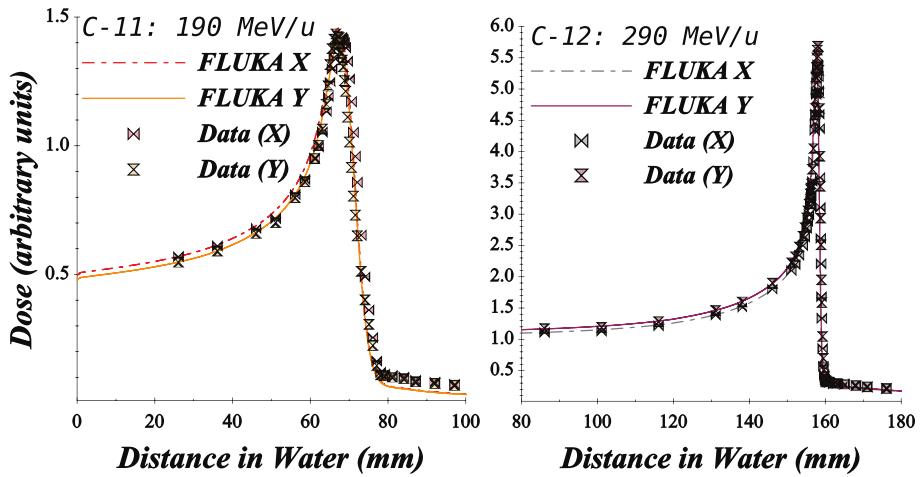


Figure 2.8: Comparison between measured and simulated absorbed dose-depth profiles in water of a radioactive $210 \text{ MeV u}^{-1} {}^{11}\text{C}$ beam (left), and a stable $290 \text{ MeV u}^{-1} {}^{12}\text{C}$ beam (right). In both cases, generally, a good match between simulation and measurement is observed, emphasizing the adequate dosimetry performance of the FLUKA Monte Carlo code. A cross ionization chamber with 64 small ionization chambers in X and Y (horizontal and vertical, respectively) was used for the measurements, and the data was summed both in X and Y , and compared to the simulation's equivalent. Adapted from [38].

beams, measured with the movable cross ionization chamber, were compared to FLUKA simulations of monoenergetic beams adapted to the HIMAC irradiation profile. The result is depicted in Figure 2.8. Overall, the simulations are consistent with the measured profiles. In fact, the beam range discrepancies were within 0.3 mm and 1 mm for stable and radioactive ion beam, respectively. However, an underestimation of the ${}^{11}\text{C}$ fragmentation dose tail beyond the Bragg peak was observed (Fig 2.8 (left)), and was partially attributed to the non-negligible beam impurities.

The PET-imaging performance was assessed by implanting the ${}^{11}\text{C}$ and ${}^{12}\text{C}$ beams in a PMMA phantom in three spills (total $5.4 \cdot 10^7$ particles) and five spills (total $9 \cdot 10^7$ particles), respectively, whereas the spills were distributed with a 3.3 s period and pauses of 1.9 s. PET-images were acquired between the accelerator spills and after irradiation for a continuous measurement time of 23 min. In Figure 2.9, the corresponding FLUKA simulated annihilation events at rest (left) are compared to the reconstructed PET signal (right), measured with the openPET scanner (in-room). An iterative reconstruction algorithm was employed, which lacked an absolute activity calibration [38].

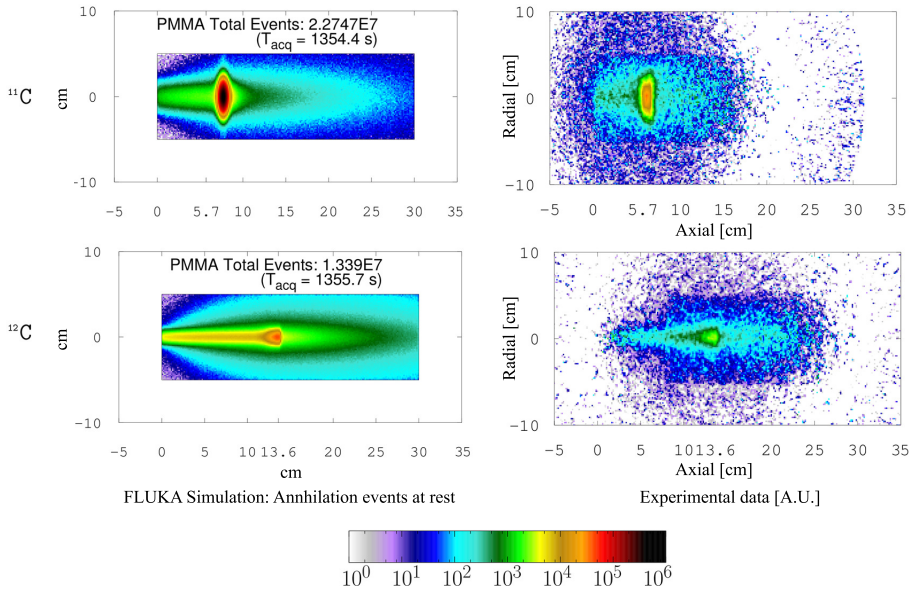


Figure 2.9: Comparison between predicted annihilation events at rest throughout the entire acquisition time, simulated with FLUKA (left), and the reconstructed PET-signal measured with the openPET scanner (right). FLUKA results were normalized to the number of beam particles, and since no calibration was performed on the PET scanner, only a relative scale is available for a qualitative comparison. Adapted from [38].

Thus, only a qualitative analysis was possible. Nevertheless, the simulations reflect the measured annihilation event distributions, where the ^{11}C beam displays a significantly improved signal density and shape in the vicinity of the Bragg peak, which is favourable for Bragg peak localization. This is especially observed in longitudinal distribution, and it is reported that the definition of the Bragg peak is at least a factor two improved by using a ^{11}C RIB. Moreover, the overall event magnitude is considerably increased when using a positron emitting beam. In fact, in some zones of interest in the Bragg peak region, at least one order of magnitude signal improvement was reported, which can be very beneficial in view of range determination and verification. Note that due to the considerably different beam characteristics (e.g. momentum spread and purity), it was not possible to evaluate the range correlation between Bragg peak and PET-signal [38]. Still, these measurements confirm the predicted advantages of ^{11}C hadron therapy protocol with respect to its PET-imaging capabilities for *in vivo* range verification.

Summary

Hadron therapy, and particularly carbon therapy, is a beneficial form of EBRT which allows to maximize dose distribution in the cancerous target volume, while sparing the healthy tissue in the entrance channel of the beam path. However, one of the main obstacles in particle therapy are range uncertainties in the treatment planning that can extend to several percent of the particle range, and thus, could lead to over-expression of dose delivery to healthy tissue. Therefore, *in vivo* range verification techniques are desired that can prove the treatment plan's correctness. In that regard, PET-aided hadron therapy exploits the detection of annihilation photons originating from the β^+ -decay of positron emitters. There are two possible modalities: firstly, detecting the decay products of secondary produced positron emitters through autoactivation of the tissue. Alternatively, one can replace the stable ^{12}C beam by its radioactive and β^+ -decaying counterpart ^{11}C . In comparison to the former approach, ^{11}C based hadron therapy features a better correlation between PET-signal and the Bragg peak or the distal edge fall-off of the dose-depth plateau, which enables a more straightforward evaluation of the applied dose distribution, and might be advantageous for in-beam or on-line PET-imaging. Moreover, ^{11}C hadron therapy results in higher and sharper β^+ -activity, which could reduce PET acquisition times and therefore, impact less the workflow in treatment centers.

Due to the aforementioned aspects, the objective of this thesis is related to the external activation approach, by means of a ^{11}C based hadron therapy protocol. While the benefit of employing ^{11}C was extensively demonstrated, one of the greatest challenge remains to produce a sufficiently intense, monoenergetic and pure RIB. Treatment centers such as MedAustron in Vienna (Austria) and Fondazione Centro Nazionale Adroterapia Oncologica (CNAO) in Pavia (Italy) request carbon beam intensities of $4 \cdot 10^8$ ions per spill ($\sim 4 \cdot 10^8 \text{ s}^{-1}$) delivered to the patient [33]. To understand why this is very demanding and where exactly the difficulties lie, the next section will discuss radioactive ion beam production routes.

2.2 Radioactive ion beam production

It was introduced in the previous sections that the principle of *radioactivity* is of great interest in nuclear medicine for the diagnosis and therapy of cancers. Moreover, this community recently renewed their interest in the production of radioactive ion beams for medical applications. However, the strongest and most thriving interest in the production and investigation of radioisotopes and RIBs lies naturally in the nuclear physics community. Since Frédéric and Irène Joliot-Curie first artificially-produced ^{30}P by bombarding aluminium with α particles, thousands of (radio-)isotopes have been discovered and produced for

nuclear physics research [40]. In general, (radio-)isotopes originate when adding or removing one or more neutrons to/from the atomic nucleus. Figure 2.10 shows the chart of nuclides, which is a visual illustration of the aforementioned feature. It depicts all known (radio-)nuclides, and is basically the playground for nuclear physicists. On the x- and y-axis the number of neutrons and protons are plotted, respectively. The black line is the so called *valley of stability*, and illustrates all stable isotopes present in nature. Starting from a stable nucleus, when adding or removing too many neutrons, the nucleus becomes unstable which is indicated with a different color, where the color code denotes the main decay mode. Decay is a stochastic process, i.e. one does not know when an unstable atomic nucleus decays. However, one finds for a sufficiently large inventory of initial radioactive nuclei N that:

$$\frac{dN}{dt} = -\lambda N, \quad (2.4)$$

$$\lambda = \frac{\ln(2)}{T_{1/2}}. \quad (2.5)$$

λ is the decay constant, which is the probability that a nucleus decays within a time interval dt , and $T_{1/2}$ is the half-life which expresses after which time half of the initial inventory N has decayed. While isotopes of the same element present

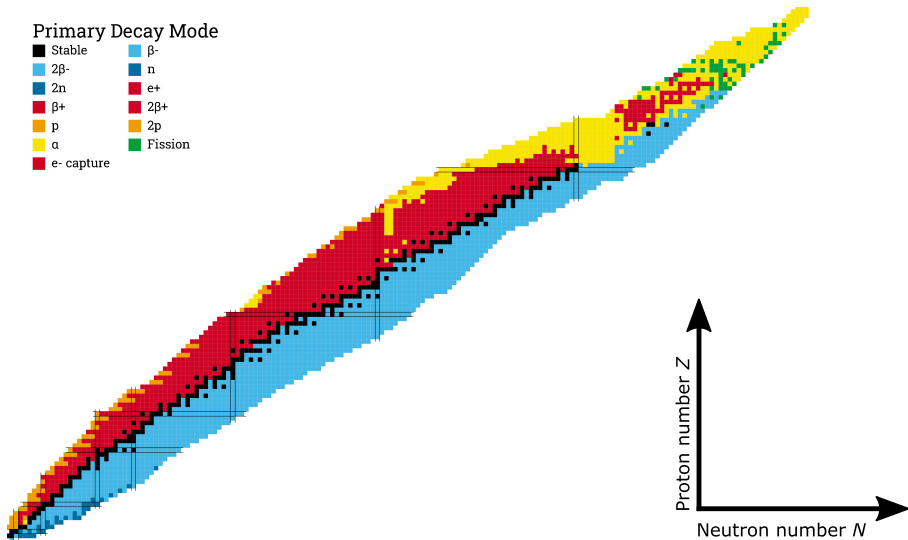


Figure 2.10: Chart of nuclides according to their primary decay mode. Adapted from [39].

the same chemical properties, this does not hold for the nuclear properties. In fact, changing the nuclear configuration by one nucleon, in some cases, has significant impact on certain properties, e.g. the nuclear shape. Other than that, some nuclei have such peculiar properties, which led to the term *exotic nuclei* to discuss such systems. It were essentially discoveries like these and the thrive to understand the physics behind these phenomena that lead to an increasing demand in the production of RIBs.

In general there are two complementary techniques of producing RIBs, namely via the *Isotope Separation On-Line* (ISOL) and the in-flight separation method. In both methods, (radio-)nuclides are produced via nuclear reactions at a production site, by irradiating a target with a primary (stable) particle beam, which is denoted as *driver*. Subsequently, the (radio-)isotopes are carried away for further manipulation and transport to the experimental area. The latter two processes are generally used to purify the RIB, to meet the experiment requirements, before they reach the measurement area. Often RIBs of, sometimes very exotic radionuclides, high intensity, high purity, good beam and timing characteristics, and with energies varying between meV u^{-1} to GeV u^{-1} are desired [41]. One notices that these properties are in fact mostly identical to those requirements for the application in hadron therapy. As a result, RIBs should possess [41]:

1. A high production rate: both techniques require several steps in the production and beam manipulations chain, which are accompanied by (sometimes significant) losses of the originally generated isotopic inventory. Thus, often, a high production rate is necessary to guarantee a sufficiently high beam intensity at the final step.
2. Efficiency: the same motivation in mind as in the previous item, it is required to optimize each step (not only individually) to minimize beam losses. In that regard, efficiency denotes how much of an initial inventory remains after manipulation, and will be a reoccurring theme in this thesis.
3. Fast: since isotopes may have very short half-lives (down to ms), time delay should be minimized to ensure that the radioisotopes reach the experimental area after their production.
4. Selective: the demand of a high purity beam, is hindered by the fact that often the isotope of interest is a minority compared to what is produced in addition via nuclear reactions during target irradiation. Moreover, considerable impurities may originate from the target material itself. Therefore, the separation process needs to filter away contaminants as well as the primary beam.

In view of these properties, the following sections provide a brief overview of the two RIB production methods, including their most relevant features, and a qualitative comparison will be given regarding the feasibility for intense ^{11}C beams for hadron therapy. For more comprehensive summaries, the reader is referred to [40, 41], more in-depth descriptions can be found in [42, 43].

2.2.1 The isotope separation on-line (ISOL) method

The different RIB production and manipulation steps that are comprised in the ISOL method, are illustrated schematically in Figure 2.11. In short, (radio-)isotopes are produced by irradiating a, usually, thick target by a primary particle beam. The isotope of interest is produced, among others, within the target material (*matrix*) via several possible nuclear reactions. By heating the target to high temperatures isotopes are *released* from the target matrix, upon which they *effuse* to an ion source for, most often, $q = 1^+$ ionization. Once they are charged, they are electrostatically extracted and accelerated by an extraction voltage to energies, typically, around 30–50 keV [40]. Electromagnetic separation is performed using a dipole magnet, which magnetic field bends the ions on trajectories according to their mass-over-charge ratio A/q . If required, the relatively pure RIB can be further accelerated by a post-accelerator before sending it to the experimental area. This typically involves a step denoted as *charge breeding*, where the ions are further ionized for more efficient acceleration. In summary, these processes can be grouped into (i) radioisotope production, (ii) ionization, (iii) separation, (iv) charge breeding and (v) post-acceleration:

(i) Radioisotope production

This subject covers all aspects starting from primary irradiation to release (or extraction) from the target material, and is often a bottleneck in RIB production. A target unit comprises the target container that hosts the target material, and which is connected via a transfer line to the ion source. Both container and transfer line are under vacuum, and some containers are equipped with temperature control techniques. During irradiation, isotopes are produced in nuclear reactions, e.g. by fragmentation, fission, spallation or fusion-evaporation. The yield of the reaction is determined by the material composition, the primary beam particle and its energy. The nuclear reaction aspect will be discussed more in-depth in Section 2.2.3. In principle, every conceivable particle may be used as driver beam, however, most often protons or neutrons are applied. Their energy can range between several MeV to GeV, depending on suitability, and most relevant, availability. Such high energies, in some cases coupled to high primary beam intensities, may result in a significant power deposition in the target, typically in the order of kW. It must thus be ensured that the target can withstand not only long operation times at high temperature, but also high temperature gradients. As mentioned, upon production, the isotopes

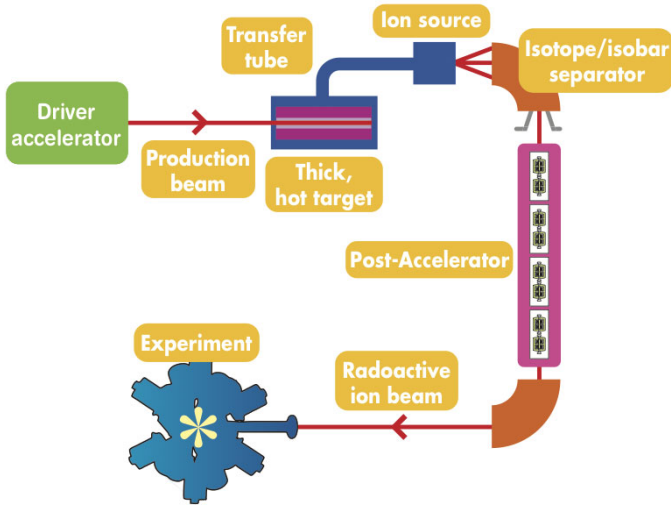


Figure 2.11: Schematic illustration of the processes involved when producing radioactive ion beams with the isotope separation on-line (ISOL) method. The process chain may be divided into two parts: the low-energy part involves all steps starting from primary irradiation until mass separation, and is often used when RIBs of high intensity, purity without requirement in energy are desired. The following beam manipulation steps are needed if experiments with high-energy RIBs are performed. Taken from [40].

must be released from the target matrix. This process is governed by *diffusion* and *effusion* which are both enhanced by high temperatures. The release is in many cases the limiting factor in RIB production, and explains why targets are often operated at temperatures close to their melting point. Generally, slow diffusion will result in longer delay which causes decay losses. An optimized design of the target's microstructure, in terms of grain size and porosity, as well as high-temperature chemistry between isotope and target material are therefore of utmost importance when dealing with refractory elements. The reader may realize that this is a rather extensive matter, which is thus in more detail discussed and described on a more fundamental level in [Article II, Section II](#). Once the isotopes have reached the target surface, they desorb and effuse through a transfer line to the ion source. Transfer lines are often kept at high temperature as well, to reduce long lingering times on the transfer line's surface due to *sorption*. Alternatively, the transfer line can be kept at a lower temperature to provoke increased retention or condensation of unwanted isotopes, which acts as a first separation process. The choice of the ideal driver-target combination is not straightforward. On one hand, one might

select a specific combination to give access to a vast inventory of different (radio-)isotopes, i.e. a target comprising heavy elements (heavy target) and a high-energy primary beam. While one can choose in this way from hundreds of different nuclides using one driver-target combination, yields of specific isotopes might not be maximized or drowned in contaminations from byproducts. On the other hand, one might want to customize this relationship, to avoid increased impurities, and to maximize the yield and final achievable beam intensity. This is by far not an easy task and involves interdisciplinary research in the fields of nuclear physics, high-temperature chemistry, material science and engineering.

(ii) *Ionization*

Isotopes which successfully left the target matrix, effuse in the evacuated target container and through the transfer line to the ion source. In order to allow acceleration and electromagnetic mass separation, the isotopes need to be charged. Therefore, ISOL facilities, usually, possess three types of ion sources from which one can choose, depending on the *Ionization Potential* (IP) of the species to be ionized.

1. *Surface* ion sources: atoms interact with a heated surfaces, through which they can gain or lose one electron. The ionization process depends on the atom's IP and electron affinity E_{ea} , the work function of the material and exponentially on the temperature. Atoms with $\text{IP} < 7$ eV can be positively ionized, and atoms with $E_{\text{ea}} > 1.5$ eV can pick-up an electron from the hot surface.
2. *Laser* ion sources: atoms can be very selectively ionized using resonant laser ionization. In a first step, a chosen atomic state is excited by tuning a primary laser to a wavelength that matches the element-specific excitation energy. The second step, employs a second laser that provides just enough energy to lift the electron from the excited state to the continuum for ionization. Note that also 3-step ionization schemes exist, when very high selectivity is required. Laser ion sources are applicable for atoms with $\text{IP} < 9 - 10$ eV [44].
3. *Plasma* and *electron impact* ion sources: positively charged ions are generated from electron impact ionization, where electrons are accelerated to energies ranging from a few eV to keV [40], thus knocking-out orbital electrons of the injected neutral gas flow resulting from the target. This process is not selective and usually produces $q = 1^+$ ions. However, *Electron Cyclotron Resonance* (ECR) ion sources can produce higher charge states.

Ionization can be used as another separation step, depending on the ion source type that is applied. After ionization, the ions escape the ion source and are

accelerated by a [dc](#) extraction voltage to energies ranging between 30 – 50 keV [\[40\]](#), forming the RIB.

(iii) *Separation*

Electromagnetic mass separation is performed by sending the extracted monoenergetic ion beam into a dipole magnet that bends the ions, due to the Lorentz force, on trajectories according to their A/q ratio. Considering that ionization mostly yields $q = 1^+$, this step selects all ions with the same mass A . Important parameter in that regard is the resolving power $\frac{A}{\Delta A}$ that defines which mass difference ΔA can be resolved. Typical dipole magnets provide resolving powers between a few hundreds and a few thousands, whereas higher values often yield lower transmissions [\[41\]](#). After separation, only isobaric contaminations with the same A remain in the RIB.

(iv) *Charge breeding*

In case that further acceleration of the ion or radioactive ion beam is desired, the charge state is increased for more efficient post-acceleration. The simplest form of charge breeding is the application of a stripper foil, which strips off some of the ions' electrons. The ions are accelerated to energies around 150 keV u⁻¹, to ensure that the ion beam traverses the stripper foil, where often a thin carbon foil is employed. When higher charge states are required, an additional ion source is used instead, typically an *Electron Beam Ion Source* (EBIS) or the already mentioned ECR ion source. Both have their benefits and disadvantages, e.g. an EBIS very quickly reaches high charge states within 20 – 200 ms, but space-charge limitations include an upper limit onto injection capacity. ECR ion sources, on the other hand, provide a constant stable beam background, resulting from the injected buffer gas ionization; moreover, the extracted beam is continuous (constant wave [cw](#)), which, usually, is problematic for the subsequent post-acceleration. More details, and references to a more comprehensive description and comparison can be found in [\[40, 41\]](#).

(v) *Post-acceleration*

To reach energies of 3 – 10 MeV u⁻¹, three types of accelerators are nowadays in use: linacs, cyclotrons or tandem accelerators. The different combinations of charge breeder and post-accelerator result in specific timing characteristics, which can be used for further purification [\[42\]](#).

Efficiency

As stated in Section [2.2](#), the *efficiency* ε is of utmost importance when dealing with RIBs and a high intensity beam requirement. In that regard ε is defined as how much of the initial produced radioactivity is transmitted to the final step, i.e. experiment or, as in the case of hadron therapy, the patient room. Having the aforementioned processes of the ISOL-type RIB production route in mind,

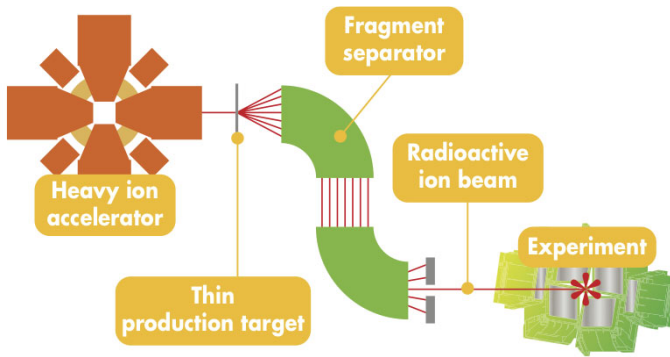


Figure 2.12: Schematic illustration of the in-flight RIB production method. Taken from [40].

one might begin to realize where the difficulty stems from. As a consequence of the descriptions above, ε comprises:

$$\varepsilon = \underbrace{\varepsilon_{\text{rel}} \cdot \varepsilon_{\text{ion}} \cdot \varepsilon_{\text{sep}} \cdot \varepsilon_{\text{trans}}}_{\text{low-E part}} \cdot \underbrace{\varepsilon_{\text{cool-bunch}} \cdot \varepsilon_{\text{breeding}} \cdot \varepsilon_{\text{accel}}}_{\text{post-accel. part}} \quad (2.6)$$

The release from the target matrix depends crucially on the high-temperature chemistry, on the target microstructure and, if isotopes are extracted in a molecular sideband, on the molecule formation efficiency. It is therefore difficult to give a generalized quantification. Typically $\varepsilon_{\text{rel}} \cdot \varepsilon_{\text{ion}} \cdot \varepsilon_{\text{trans}}$ does not exceed a few percent. Mass separation is usually very efficient, and can achieve values up to 90%. If post-acceleration is required, another $\varepsilon_{\text{cool-bunch}} \cdot \varepsilon_{\text{breeding}} \cdot \varepsilon_{\text{accel}} \approx 1\%$ needs to be accounted for.

2.2.2 The in-flight separation method

In contrast to the ISOL method, in-flight separation is based on the acceleration of a stable, primary heavy-ion beam as a driver that is sent onto a thin production target. The primary beam produces the (radio-)isotopes as well by fragmentation, spallation and fission. However, the reaction products traverse the production target, and have approximately the same velocity and direction as the initial beam. Subsequently, separation is performed by a set of dipole magnets and beam optic devices. Generally, less steps are required between production and delivery to the experimental area, as illustrated in Figure 2.12.

(a) Radioisotope production

Regarding the choice of the accelerator, various different types are used: linacs, cyclotrons and synchrotrons. All of these machines are capable to accelerate

stable nuclei up to uranium with high energies and relatively high intensities. Synchrotrons can reach energies above 1 GeV u^{-1} with beam intensities of the order of pnA^2 . On the other hand, cyclotrons and linacs provide beam intensities up to $\text{p}\mu\text{A}$, however, energies are restricted to a few hundreds of MeV u^{-1} . For instance, the RIKEN main cyclotron employs a 345 MeV u^{-1} ^{238}U beam for their RIB research program [45]. Isotope production takes place within a thin, light target, usually beryllium or carbon. One advantage compared to the ISOL method is that the complexity of hot target chemistry is omitted as the reaction products immediately exit the target. Furthermore, the nuclei are completely stripped from their electrons ($q = Z$) which means that no ionization and charge breeding steps are required. Consequently, a much more straightforward relationship between production probability and secondary beam intensity is a feature of this RIB production method. However, since very energetic, intense and highly charged beams bombard the production target, powers up to hundreds of kW are absorbed, which, locally, lead to temperatures above 10^4 K [46], as well as very high temperature gradients that need to be dissipated.

(b) Separation

Separation is performed with the fragment separator which, as mentioned, consists of several dipole magnets, conducting a selection in magnetic rigidity $B\rho$, and higher order magnets (quadrupoles and hexapoles) as beam optic devices. Since the ion beams feature much higher velocities than ISOL beams, the magnets are much larger. In addition, a degrader is often placed in-between the dipoles, to induce Z -dependent energy loss according to the Bethe equation (2.1). This lifts the A/q or $B\rho$ degeneracy and thereby improving the selection of the desired ion beam. However, the separation or beam purity that can be achieved is often not capable to fully, physically separate the individual beam fragments. Thus, fragment identification is rather performed instead of beam purification. Another important parameter is the *acceptance* of the fragment separator, which defines the maximal extent of beam parameters, such as momentum spread, which can be still transmitted through the separator.

Efficiency

One advantage of this method is that beam losses due to release ε_{rel} , ionization ε_{ion} and the post-acceleration $\varepsilon_{\text{accel}}$ are omitted in this method. Transport efficiency $\varepsilon_{\text{trans}}$ depends on the beam optics and kinematics and may reach in optimized configurations values up to 50% [40]. However, production cross

²pnA stands for particle nanoampere, and is used to express beam intensities independent of the charge state. It is given such its value corresponds to the current that would be measured from a singly charged ion beam.

sections are in some cases rather low, not exceeding 1%, and beam characteristic with respect to emittance, beam-spread and purity can be a concern.

ISOL versus in-flight: a comparison

Both ISOL and in-flight separation have their advantages and drawbacks. The ISOL method, generally, is able to provide pure, and relatively intense RIBs with good beam characteristics, in terms of beam emittance and energy spread, because of the beam manipulation steps at low energies. Due to these many steps involved in RIB production, long target ion-source developments are often necessary when exotic beams and high beam intensities are required. This method strongly depends on the chemical interplay between the produced isotopes and the target material, as well as with the surrounding surfaces of target container, transfer line and ion source. As a consequence, very short-lived isotopes are very difficult to produce with sufficient intensities. Moreover, post-acceleration is necessary when high beam energies are needed, which on the other hand, allows better control over the final beam energy.

The in-flight technique requires much less beam manipulation, as no isotope-target material high-temperature chemistry, nor ion source developments are required. Post-acceleration is omitted due to the high-energy driver accelerator, which makes this method much faster and universal, beam energy control is however impeded. This method mostly suffers from low initial production yields, less favorable beam characteristics and often, from poor beam purity. Application of degraders can annihilate A/q degeneracy, which eases control over beam purity. However, this is often accompanied with deteriorated beam properties.

2.2.3 Nuclear reactions

In view of RIB production, the nuclear reaction aspect is one of the first criteria that needs to be addressed. When two nuclei come close together, for instance, by accelerating a particle beam onto a target, a variety of processes may occur, e.g. interactions of electromagnetic or nuclear nature. For instance, an energetic *projectile* a that collides with a static *target nucleus* X , may scatter elastically from the Coulomb potential of the target nucleus. Such a process is called *Rutherford scattering* and was first seen in 1919 and, in fact, lead to the discovery of the atomic nucleus. Furthermore, a projectile can scatter inelastically, thus, exciting the target nucleus which subsequently may decay back to its ground state, e.g. by means of γ -ray emission, or possibly by fission, which sometimes is denoted as Coulomb-induced or Coulex-induced fission [47].

Most important with respect to this thesis is that when a projectile is accelerated onto a target, nuclear reactions may occur, which can lead to the production of

radioisotopes. These radioisotopes are often populated in a very excited state, and the study of such nuclides possesses a central role in nuclear physics and explains the high demand for RIBs. A nuclear reaction can be written as:



where Y and b are the two (or more) reaction products. Y is usually a heavy nucleus, and b is a lighter particle, denoted as *ejectile*. A more compact way of expressing the same formality is:

$$X(a, b)Y. \quad (2.8)$$

Two very important parameters involved in nuclear reactions are the reaction Q -value, and the reaction cross section σ . Q is defined as the mass or binding energy difference between the initial particles and reaction products:

$$\begin{aligned} Q &= (m_{\text{initial}} - m_{\text{final}})c^2 \\ &= (m_X + m_a - m_Y - m_b)c^2 = \begin{cases} > 0 : \text{exothermic} \\ = 0 \\ < 0 : \text{endothermic} \end{cases} \end{aligned}$$

Exothermic reactions can happen spontaneously, i.e. they do not require external energy to occur. The excess in binding energy of the particles is released as kinetic energy of the reaction products. However, this does not include that the reactants need to excess the Coulomb barrier:

$$V_C = \frac{e^2}{4\pi\epsilon_0} \frac{Z_X Z_a}{r}, \quad (2.9)$$

in order to overlap. On the other hand, endothermic reactions require a minimum kinetic energy provided to the system, which is then transformed into nuclear mass or binding energy. The net amount of external energy that must be invested is consequently the sum of the Q -value and the Coulomb barrier. This explains why accelerators are used to induce nuclear reactions of interest.

The reaction cross section σ gives the probability of a given nuclear reaction to occur. It is defined as the reaction events per second divided by the incoming projectiles and target nuclei per unit area:

$$\sigma = \frac{\text{events/s}}{\text{inc. particles/s} \cdot \text{target nuclei/cm}^2} = \frac{R_E}{I \cdot N_t}.$$

As a result, σ has a dimension of area, and is typically expressed in *barn* b, with $1 \text{ b} = 10^{-28} \text{ m}^2$. Note that there are several types of cross sections that provide different information of the occurring reaction. For instance, σ_t is the

total reaction cross section, expressing the probability that any reaction occurs. The doubly differential cross section $\frac{d^2\sigma}{dE_b d\Omega}$ represents the probability of given reaction to occur, with the ejectile being ejected within a solid angle $d\Omega$, and possessing an energy E_b , which provides information in which excited state Y is produced. However, in the context of producing a specific radioisotope for RIB production, one is interested in the reaction cross section σ which provides the overall probability of Y being produced via the selected nuclear reaction, depending on the incoming particle energy. σ is obtained by integrating over all angles and all excited states of Y . In such way, the probability of producing a specific radioisotope, depends on the primary projectile (beam particle), its energy E and the target nucleus X .

In practice, a large variety of nuclear reactions are employed which rely on this feature. In sight of a specific isotope of interest, the choice of the nuclear reaction depends first of all on the location in the chart of nuclides (Fig. 2.10), where certainly, the cross section is the most important parameter. However, physical and chemical properties of the isotope could favor a material with a lower σ , as discussed in the framework of the ISOL method in Section 2.2.1. In general, nuclear reactions may be grouped into *direct* and *compound nucleus* reactions, which are distinct by their time scale. Direct reactions take place on a time scale of the order of 10^{-22} s, whereas the initial beam particle interacts primary with the surface nucleons. Examples are: scattering, knock-out and transfer reactions, such as (p,p') , (p,pn) or (d,p) , respectively. Compound nucleus reactions, on the other hand, take place on a much longer time scale, 10^{-16} to 10^{-18} s and are believed to proceed in a two-step process. In the first step, the projectile enters the nucleus, upon which it interacts with the nucleons, thereby distributing its energy to the nuclear system, i.e. the compound nucleus. The second step is the subsequent decay, which may take place via several different channels [48]. Very important in this modality is that the decay is independent of the formation process of the compound nucleus. This can be imagined as that the bombarded nucleus 'forgets' how it was created. As a consequence, the angular distribution of the decay radiation will be isotropic. It was mentioned that ISOL and in-flight RIB production, most often apply spallation, fragmentation, fission and fusion-evaporation reactions. The former three are in that sense attributed to compound nucleus reactions, whereas fusion-evaporation may be either.

Spallation, fission, fragmentation

Energetic projectiles, such as high-energy protons (500 to 1500 MeV), neutrons (20 – 200 MeV) or heavy-ions ($4 - 100 \text{ MeV u}^{-1}$) that impinge on the target, may enter the nucleus to form the aforementioned compound nucleus [42, 49]. In this intermediate step, the newly formed nucleus possesses a large amount of

excitation energy, which is released by decaying either by spallation, fission or fragmentation. Each of them exhibits different characteristics regarding their decay and decay products. J. Benlliure explained this in an illustrative way, using the example of residual nuclei resulting from bombarding ^{238}U with 1 GeV protons [49]. The consecutive decay forms residual nuclei that can be grouped into regions in the nuclear chart:

Fission

The first group covers a large range of isotopes with neutron excess (right side from the valley of stability) with Z in the range of 23 to 65, and can be attributed to fission products. Fission results mainly from the competition between nuclear and Coulomb forces, and may occur naturally or might be induced by a nuclear reaction [48]. While the nucleus' binding energy increases roughly with A , Coulomb repulsion increases with Z^2 due to the proton's charge. Hence, the average binding energy per nucleon of heavy nuclei would increase when splitting the nucleus into two smaller fragments, where the excess energy is either transformed into kinetic energy of the fragments or is emitted by other decay radiation, such as neutrons. However, very often the Coulomb barrier inhibits the fission process as the fission products need to surpass or tunnel through it.

In cases where the fragments possess sufficient energy to surpass the barrier, natural or *spontaneous fission* occurs. However, most often the energy release of the two fission fragments would not be enough to overcome the barrier, but can be provided by low-energy neutrons (thermal neutrons), photons (*photofission*) or as well by energetic particles as in the context of this thesis. For spontaneous or low-energy induced fission, predominantly symmetric and asymmetric mass distribution of the fission fragments are observed. The latter case, may be explained by the reduced V_C for asymmetric mass distribution, e.g. ^{235}U [48], or possibly by shell structure effects of the fission fragments, as discussed for ^{180}Hg [50]. However, in some cases a mixture of the two distributions has been reported [51].

When an energetic beam particle impinges on a fissile target, forming the energetic compound nucleus, large-scale collective motions of the nucleons can form two separate nuclei drifting apart and reducing the Coulomb barrier. Consequently, these pre-fragments can undergo fission, which is mostly attributed with a more symmetric mass distribution of the fragments [49]. However, peripheral collision of the initial energetic particle beam can lead to small energy transfers, inducing asymmetric fission that produces the observed residual nuclei with the most neutron excess. While fission fragments, generally, preserve the neutron excess and N/Z ratio of the fissile target, compound nuclei which are in a very high excited state, mitigate this excess by means of pre- or

post-fission neutron evaporation, resulting in a broadening of the fragment's mass distribution [49].

Spallation

Spallation residual nuclei form (together with fragmentation) the second group observed in the chart of nuclides. These high- Z residuals are mostly neutron deficient and extend, starting from the target nucleus down to $Z = 65$, forming on average around 20 different nuclides per element [49]. Once the initial energetic beam particle enters the nucleus, it interacts with the nucleons transferring its energy via collisions among them (intra-nuclear cascade [49]). On average they do not possess sufficient energy to leave the nucleus, however, as many collisions take place within the compound nucleus, there is a small probability that some nucleons get sufficient energy due to statistical distributions [48]. Since protons are affected by the Coulomb barrier, neutron emission is more likely, resulting in neutron-deficient residuals.

Fragmentation

When high energy beam particles undergo fragmentation, one can distinguish between two types: projectile fragmentation and target nucleus fragmentation. The former type of reaction is used in the in-flight RIB production technique, whereas in the ISOL method fragments are mainly produced by the latter reaction.

(I) *Projectile fragmentation*

High-energy heavy-ion beams ($> 50 \text{ MeV u}^{-1}$) that collide peripherally with target nuclei may undergo projectile fragmentation, in which some nucleons are removed from the initial projectile. The fragments, mostly, retain the initial velocity and direction of the beam particle, since Coulomb deflections and the nuclear recoil of the ion are small [43]. A macroscopic model that successfully describes observations and is commonly accepted, is the abrasion-ablation model [7, 43, 52], which was developed by J. Bowman et al. in 1973 [53]. When a heavy-ion with relativistic energies so closely passes a target nucleus that their volumes partly overlap, part of the projectile is sheared away ('abrasion') and leaves the remaining fragment in an excited state. Subsequently, the remains of the projectile loses energy in the de-excitation process by emitting one or several particles ('ablation'). The reaction cross sections are relatively constant in the range of 40 MeV u^{-1} to 2 GeV u^{-1} for fragments which have a minor difference in mass with respect to the initial projectile. Moreover, these cross sections are the largest compared to lower- Z fragments, which drop exponentially [43]. Interesting is that for nuclei far away from stability, the region of the nuclear chart which is populated strongly depends on the target [43]. Heavy targets yield very neutron-rich residuals, whereas neutron-deficient nuclides are best produced

from $N \approx Z$ target materials. Important reaction characteristics with respect to the in-flight RIB production method, are the momentum distributions that determine the longitudinal beam emittance. They feature a minor deterioration in velocity and present a nearly Gaussian profile that exceeds the velocity deterioration, and are related to the Fermi momentum of the sheared nucleons [43]:

$$\sigma_{\parallel} [\text{MeV c}^{-1}] = \sigma_0 \cdot \sqrt{\frac{A_f(A_n - A_f)}{A_n - 1}}.$$

$\sigma_{\parallel}$ is the momentum width parallel to the beam direction, σ_0 is the fraction of the mean Fermi momentum of the missing nucleons and $A_{f,n}$ are the mass number of the beam fragment and the nucleons in the beam, respectively. According to electron scattering measurements, the theoretical value of σ_0 corresponds to 100 MeV c^{-1} . However, a slightly lower value of 85 MeV c^{-1} is found in experiments for beams with energies larger than 40 MeV u^{-1} . At high energies, the perpendicular momentum distributions should be identical since contributions from Coulomb scattering are negligible [43].

(II) Target nucleus fragmentation

Target nucleus fragmentation can result from, both heavy-ion beams as discussed above, or from high-energy proton and neutron irradiation. In the latter case, the energetic projectile enters the nucleus, forming the highly excited compound system. In that sense, intermediate-mass fragments could be seen as a very asymmetric fission process [49]. Moreover, the emission of such fragments can evolve at very high excitation energies, to a decay of several fragments, which is denoted as *multi-fragmentation* [49].

Fusion-evaporation

Fusion-evaporation reactions using light- or heavy-ions are a selective tool for neutron-deficient isotope production close to the valley of stability [40, 42]. Instead of producing hundreds of different isotopes, as in the aforementioned reaction channels, fusion-evaporation generally yields a limited number of residuals (~ 10). Light ions, such as protons often have relatively high cross sections ($\sim$ hundreds of mb) and can be applied with high intensities, from a power deposition point of view. As a result, high production yields can be achieved [42]. Heavy-ion beams, however, are typically of the order of 5 MeV u^{-1} and are restricted to much lower intensities ($\sim 1 \mu\text{A}$) and present much lower cross sections.

Resonant reactions

When studying nuclear reaction cross sections as a function of the projectile energy, one may observe peaks for a given configuration, for instance as witnessed

in the $^{14}\text{N}(p,\alpha)^{11}\text{C}$ reaction (Fig. 3.1b). These are resonances in the compound nucleus, which amplitudes can be significantly larger compared to fusion-evaporation cross sections. Resonant reactions occur via the population of discrete, short-lived quasibound states in the compound nucleus, by matching the primary beam energy to that of the resonance state, which subsequently decays, possibly by means of several exit channels, e.g. (in-)elastic scattering, γ -ray or particle emission [48]. As a result, resonances can be utilized for nuclear structure studies, as well as selective (radio-)isotope production, thus, potentially reducing co-production of contaminants. Resonant reactions are especially prominent in light nuclei, as in heavy systems the level density increases rapidly, resulting in narrow state spacing forming a continuum and leading to compound nucleus-type reactions. Nevertheless, resonances can be found in heavy nuclei, where neutron scattering or neutron capture reactions, such as $^{238}\text{U}(n,\gamma)^{239}\text{U}$ [48], belong to the best known examples.

2.2.4 RIB production yield

The previous sections introduced the advantage of using intense ^{11}C beams for PET-aided hadron therapy, which techniques for RIB production exist, and their key features. One of the main challenges in ^{11}C based hadron therapy is the required beam intensity of $\sim 4 \cdot 10^8$ ions s^{-1} which must be delivered to the patient. An important parameter of the two RIB production methods is the *production yield* Y , which expresses the RIB intensity for a given configuration, and is given by:

$$Y = Y_{\text{phys}} \cdot I \cdot \varepsilon,$$

where Y_{phys} denotes the physical production yield, which expresses the amount of nuclei produced per incoming beam particle, and I is the primary particle beam intensity. In case of the in-flight separation method, one can derive:

$$Y^{\text{In-flight}} = Y_{\text{phys}}^{\text{In-flight}} \cdot I \cdot \varepsilon, \quad [\text{s}^{-1}] \quad (2.10)$$

$$= \sigma(E) \cdot N_t \cdot I \cdot \varepsilon_{\text{trans}}, \quad (2.11)$$

where the physical production yield $Y_{\text{phys}}^{\text{In-flight}}$, considering in-flight separation RIB production, is defined. The physical yield of a chosen radionuclide, depends on the reaction cross section σ expressed in cm^2 , the driver beam energy and the target nuclei per cm^2 (N_t). As discussed in Section 2.2.2, Eq. (2.11) illustrates the more direct correlation between production cross section and primary beam intensity I , expressed in particles per second.

In case of ISOL RIB production, the situation is considerably more complex, mostly, due to the different processes involved, and their corresponding

efficiencies:

$$\begin{aligned}
 Y^{\text{ISOL}} &= Y_{\text{phys}}^{\text{ISOL}} \cdot I \cdot \varepsilon, & [\text{s}^{-1}] \\
 &= Y_{\text{phys}}^{\text{ISOL}} \cdot I \cdot \varepsilon_{\text{rel}} \cdot \varepsilon_{\text{ion}} \cdot \varepsilon_{\text{sep}} \cdot \varepsilon_{\text{trans}} \cdot \varepsilon_{\text{cool-bunch}} \cdot \varepsilon_{\text{breeding}} \cdot \varepsilon_{\text{accel}}.
 \end{aligned} \tag{2.12}$$

Note that if isotopes are extracted in a particular molecular sideband, one has to account for the molecule formation, with an efficiency $\varepsilon_{\text{form}}$, which is then included in the release efficiency ε_{rel} . Moreover, one can distinguish between low-energy ISOL RIB production, e.g. employing fusion-evaporation reactions, and configurations using high-energy driver beams. The latter is usually used by the nuclear physics community, since a large inventory of different nuclides can be produced within the target. For instance, CERN ISOLDE uses a primary 1.4 GeV proton beam with I up to $2 \mu\text{A}$ on heavy targets, such as uranium carbide (UC_x). For such cases, the ISOL physical thick in-target production yield is defined similarly as above, since the extremely energetic initial particles do not lose a substantial amount of energy within the target matrix:

$$Y^{\text{ISOL}} = Y_{\text{phys}}^{\text{ISOL}} \cdot I \cdot \varepsilon = \sigma(E) \cdot N_t \cdot I \cdot \varepsilon. \tag{2.13}$$

Note that the equation above is given at saturation level, as ISOLDE targets are irradiated for sufficiently long time periods, typically ranging from several days up to weeks. The saturation aspect will be elucidated on the next page.

If however a specific RIB is requested, as in this thesis concerning ^{11}C , a tailored ISOL system may be used that operates better at low-energies. For such cases, the driver beam loses energy inside the target material, due to Equation (2.1), which must be taken into account. As a result, the beam possesses an energy distribution within the target, which impacts the reaction cross section $\sigma(E)$, and needs to be considered in the physical production yield:

$$Y_{\text{phys}}^{\text{ISOL}} = \frac{N_A}{M} \int_{E_f}^{E_i} dE \frac{\sigma(E)}{S(E)}, \tag{2.14}$$

which expresses how many nuclei are produced per incoming particle. $S(E)$ is the stopping power expressed in $\text{MeV cm}^2 \text{g}^{-1}$ and M is the molar mass of the target material in g mol^{-1} . Note that the above written equation is true for target materials consisting of a single element. For composite materials one has to account for the stoichiometry and, if applicable, for the different cross sections of the constituent isotopes.

Considering a possible implementation of an ISOL-type RIB production system into a hadron therapy center, it may be of interest to evaluate the time dependency of the production process. Note that since the following description holds for ISOL-type radioisotope production, henceforth the 'ISOL'

sub- and superscripts are omitted: $Y^{\text{ISOL}} \equiv Y$, $Y_{\text{phys}}^{\text{ISOL}} \equiv Y_{\text{phys}}$, etc. Upon target irradiation, radioisotope production is initiated with a production rate $R_p = Y_{\text{phys}} \cdot I$, expressed in nuclei per second. However, decay and isotope release occur simultaneously. As a consequence, one finds for the rate of nuclei N produced in or disappearing from the target:

$$\frac{dN(t)}{dt} = R_p - \lambda N(t) - \tilde{\lambda} N(t). \quad (2.15)$$

λN is the rate of decaying nuclei and $\tilde{\lambda} N$ denotes the rate of nuclei that are released from the target, which corresponds to the yield $Y(t)$. It must be mentioned that the representation of the release rate by means of a 'release constant' $\tilde{\lambda}$ is a very simplified description. In reality, a time-dependent density probability function $p(t)$, sometimes referred to as delay function, is used. By using such an idealized description, it is intended to illustrate the relation between in-target production, isotope release and the observed yield. By solving Eq. (2.15) it can be shown:

$$N(t) = \frac{R_p}{\lambda + \tilde{\lambda}} \left(1 - e^{-(\lambda + \tilde{\lambda})t} \right), \quad (2.16)$$

$$Y(t) = N(t) \cdot \tilde{\lambda} = \frac{R_p \cdot \tilde{\lambda}}{\lambda + \tilde{\lambda}} \left(1 - e^{-(\lambda + \tilde{\lambda})t} \right). \quad (2.17)$$

The release efficiency ε_{rel} , which expresses how much of the in-target production can be extracted, can be obtained from:

$$\varepsilon_{\text{rel}} = \frac{\int_0^\infty dt \tilde{\lambda} \cdot N(t)}{\int_0^\infty dt R_p} = \frac{\tilde{\lambda}}{\lambda + \tilde{\lambda}}. \quad (2.18)$$

Combining Equation (2.17) and (2.18) one finds for the time dependence of the ISOL yield:

$$Y(t) = \varepsilon_{\text{rel}} \cdot R_p \left(1 - e^{-\left(\lambda + \frac{\varepsilon_{\text{rel}} \lambda}{1 - \varepsilon_{\text{rel}}}\right)t} \right). \quad (2.19)$$

The term in-between the brackets is called the *saturation factor*. For sufficiently long irradiation times, the saturation factor approaches unity, which defines the saturation yield Y_{sat} :

$$Y_{\text{sat}} = Y(t \rightarrow \infty) = R_p \cdot \varepsilon_{\text{rel}} = Y_{\text{phys}} \cdot I \cdot \varepsilon_{\text{rel}}. \quad (2.20)$$

If one wishes to consider next to the release aspect, the subsequent ISOL stages as well, their corresponding efficiencies have to be multiplied to the equation above. As a consequence, one obtains the ISOL yield as defined in Equation (2.12).

In other cases, it may be relevant to discuss besides the ISOL yield, also the thick in-target production yield y , which expresses how many nuclei are produced within the target without being released. As the isotope release is enhanced at high temperatures, in practice this is achieved by irradiating a cold target such that this mechanism is very inefficient. In essence, the determination of y is analog to the derivation above, whereas the isotope release is excluded from Eq. (2.15), thus:

$$y(t) = R_p \cdot I (1 - e^{-\lambda t}), \quad (2.21)$$

$$y_{\text{sat}} = R_p \cdot I = Y_{\text{phys}} \cdot I. \quad (2.22)$$

The yields which have been introduced so far, are expressed in atoms (ions) per second. Often, yields are reported in a notation which is normalized to the primary beam current I , expressed in μA . In such representations, the yield is typically given in units of $[\text{Bq } \mu\text{A}^{-1}]$, e.g. for thick in-target production yields, or in $[\mu\text{C}^{-1}]$ for physical production and ISOL yields.

2.3 Common ^{11}C production and past produced ^{11}C beams

The previous sections presented what RIB production techniques are available, and summarized their key parameters. In that sense, one must acknowledge that ^{11}C is no exotic radionuclide. In fact, it is well-studied and has a relatively long half-life of 20.4 minutes, which mitigates the time constraint aspect in view of production and beam manipulation processes. Moreover, a well-established production mechanism for PET-radiopharmaceutical synthesis exists. Typical ^{11}C radiolabeled radiopharmaceuticals are: $[^{11}\text{C}\text{-methyl}]\text{Methionine}$, $\text{N}\text{-}[^{11}\text{C}\text{-methyl}]\text{Flumazenil}$, $[^{11}\text{C}\text{-methoxy}]\text{Raclopride}$ and $[1\text{-}^{11}\text{C}]\text{Sodium Acetate}$ [54]. Their production is carried out *in situ*, i.e. in the hospital, using compact PET-cyclotrons providing proton beams of about 20 MeV and beam intensities up to several hundred μA , and high-pressure N_2 gas targets. Furthermore, ^{11}C beams have been produced in the past at different facilities for research purposes.

This section aims to provide the reader an overview over these production mechanisms. In that regard, Section 2.3.1 discusses ^{11}C production using N_2 gas targets, and Section 2.3.2 is a review of past results concerning ^{11}C RIB production³. Both sections are the author's contribution to the *Technical Design Report* (TDR) introduced in Chapter 1.

³Chapter 3 of the TDR.

2.3.1 Nitrogen gas targets for ^{11}C production

This paragraph is an excerpt of Section 4.2 of the aforementioned TDR, presented in Chapter 6 of this thesis, which was contributed by the author of this thesis. It briefly describes common ^{11}C production for the synthesis of PET-radiopharmaceuticals. Note that the TDR version has been edited and is therefore not a verbatim copy.

High-pressure N_2 targets (several bar) are commonly used for the production and synthesis of ^{11}C based radiopharmaceuticals for PET-imaging. The gas cells are irradiated with a low-energy proton beam for a duration of several minutes. Subsequently, ^{11}C is separated from the gas mixture by purging it through a *Chromatography Gas Separation (CGS)* system. Usually, ^{11}C is extracted in molecular form. i.e. CO_2 or CH_4 . Two examples of typical gas target systems are shown in Fig. 2.13. It consists of a water-cooled conical cylinder holding the target gas and a tube system for the gas transport (Fig. 2.13a). The target chamber is filled with high purity N_2 gas to pressures usually greater than 10 bar. Oxygen or hydrogen is mixed in percentage amounts into the target gas to produce $^{11}\text{CO}_2$ or $^{11}\text{CH}_4$, respectively. Typical gas separation systems (Fig. 2.13b) use cryogenic traps, i.e. stainless steel tube/coil immersed in liquid nitrogen, which traps CO_2 by means of condensation, whereas target gas residuals are not retained and are therefore separated from $^{11}\text{CO}_2$. Increasing the trap temperature will vaporize and thus release the trapped gas. Alternatively, chromatography columns (CH_4) or molecular sieve (CO_2) traps may be used. Chromatography columns, such as Porapak Q columns, separate CH_4 from other species based on differential adsorption times on the column's material, which result in different flow rates [55]. Molecular sieve traps are pre-activated columns of a selected microporous material, usually measured in ångström. Advantage of such traps is that they can trap CO_2 at room temperature, and release the captured molecule by heating the material to 100–200 °C [55, 56]. A general disadvantage of gaseous N_2 targets is that ^{11}C production is carried out in batch mode. As a result, to ensure a continuous operation, an automatized target loading/unloading system has to be established. To give the reader an idea, such a system was used in the BEARS project in Berkeley [57].

2.3.2 Production of ^{11}C beams - Overview of past results

The possible advantages of using radioactive ion beams for PET-aided hadron therapy already have a long history [18, 60, 61]. Worldwide, several facilities have attempted to produce ^{11}C beams using different techniques:

- Lawrence Berkeley National Laboratory
- Centre de Recherche du Cyclotron

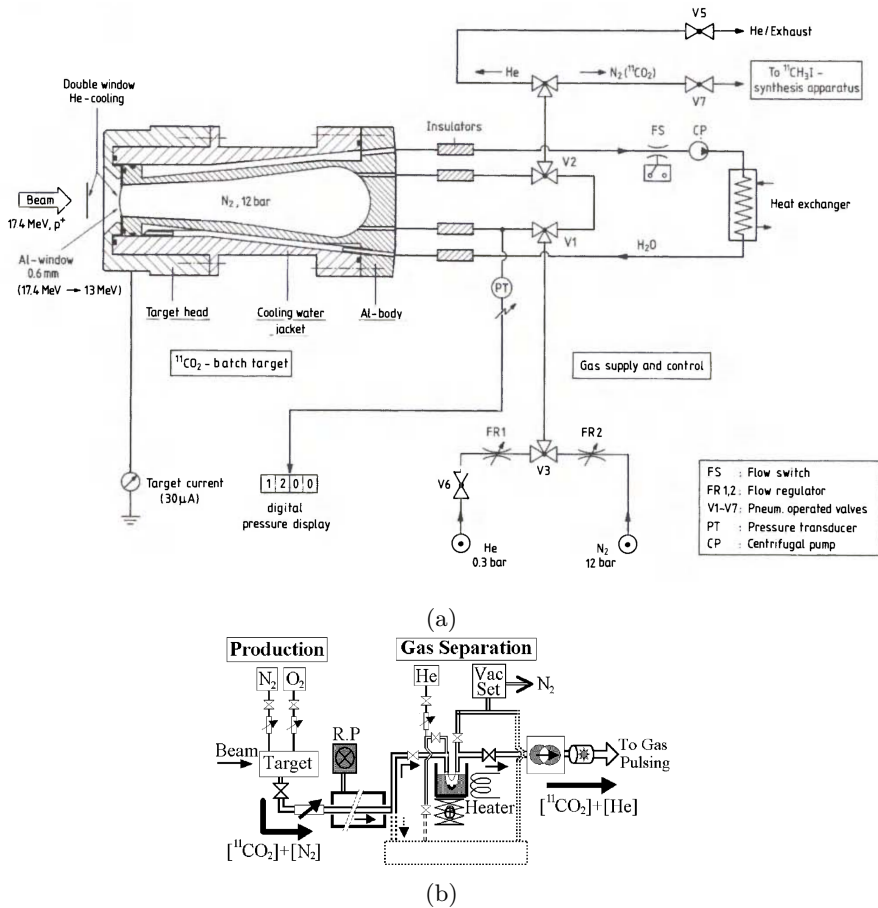


Figure 2.13: Examples for a typical N_2 gas target system (a) and for a chromatography gas separation system (b) using a cryogenic trap [58, 59].

- CERN ISOLDE
- SPIRAL1/GANIL
- ISAC/TRIUMF
- HIMAC/NIRS

This chapter aims to provide an overview of how those facilities produced ^{11}C beams, their properties and particularities, and the developments with respect to high intensity ^{11}C beam production.

Lawrence Berkeley National Laboratory

The Bevalac (Fig. 2.14) at the Lawrence Berkeley National Laboratory facility was an accelerator complex, established in 1974 when coupling the SuperHILAC linear accelerator (8.5 MeV u^{-1}) and the Bevatron proton synchrotron of 6.2 GeV energy [63, 64]. The Bevalac was used for the production of heavy ion beams for both research and radiation therapy and is credited as one of the pioneering facilities for accelerated radioactive ion beams [41]. Between 1977 and 1992, 433 patients were treated, where most of the treatments were performed with a 670 MeV u^{-1} neon beam [65]. Before its decommission in 1993, ^{11}C beams were produced by projectile fragmentation using different initial beams and thin targets. A beam of $2 \cdot 10^7$ ions per pulse was produced by bombarding a 7.8 cm thick Be target with a primary $1.5 \cdot 10^{10}$ ions per pulse ^{12}C beam with an average energy of 350 MeV u^{-1} . This corresponds to a total efficiency of one

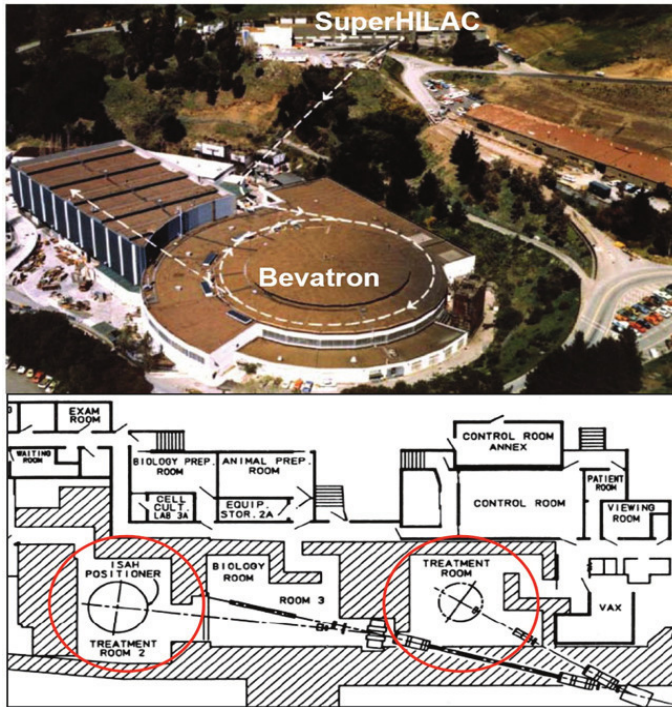


Figure 2.14: The Bevatron of the Lawrence Berkeley National Laboratory facility in Berkeley Hills (California, USA) [62]. (top) bird's eye view of the facilities, with medical treatment rooms in the building on the left of the picture. (bottom) layout of the medical treatment complex.

ion per 750 primaries. It was reported that the primary beam was expected to suffer from 100 MeV u^{-1} energy loss after reaction, yielding a ^{11}C beam with angular spread $\Delta\Theta$ of approximately $\pm 10 \text{ mrad}$ and a momentum spread of $\pm 1\%$ ($\Delta\Theta = 12 \text{ mrad}$, $\Delta p = 2\%$, considering multiple scattering in the target). It was further reported that an excellent separation from the primary beam was achieved using a magnet with 500 resolving power [66]. Besides that, a ^{11}C beam was produced by bombarding a 1" (2.5 cm) Be target with ^{18}O beam of 800 MeV u^{-1} energy, and the production cross section of ^{11}C from a $375 \text{ MeV u}^{-1} \text{ Ne}^{10+}$ beam hitting in a polystyrene target consisting of two discs with 3" (7.6 cm) diameter and 0.25" (0.64 cm) thickness was measured [67, 68].

In 1998, the BEARS initiative was launched at Lawrence Berkeley National Laboratory, which aimed to expand the radioactive ion beam (RIB) capability [70]. For this purpose, a 350 m transfer line was built between the 11 MeV PET-cyclotron at the Biomedical Isotope Facility (BIF) and the 88" ($\sim 224 \text{ cm}$) cyclotron of the Nuclear Science Division (Fig. 2.15). ^{11}C was produced by irradiating a 13 ml (80 mm deep) N_2 gas target filled to 22 atm for five minutes with 10 MeV protons and $\sim 30 \mu\text{A}$ intensity of the medical cyclotron⁴ [57]. 0.2% O_2 was mixed into the gas target to produce $^{11}\text{CO}_2$ to allow gaseous transport and cryogenic separation. The concentration of O_2 was chosen to have sufficient



Figure 2.15: Illustration of the coupling of the Berkeley Isotope Facility and the Nuclear Science Division for the BEARS project [69].

⁴Maximum N_2 thick in-target production yield approximately $10^{11} \text{ atoms s}^{-1}$ for $40 \mu\text{A}$ proton beam intensities.

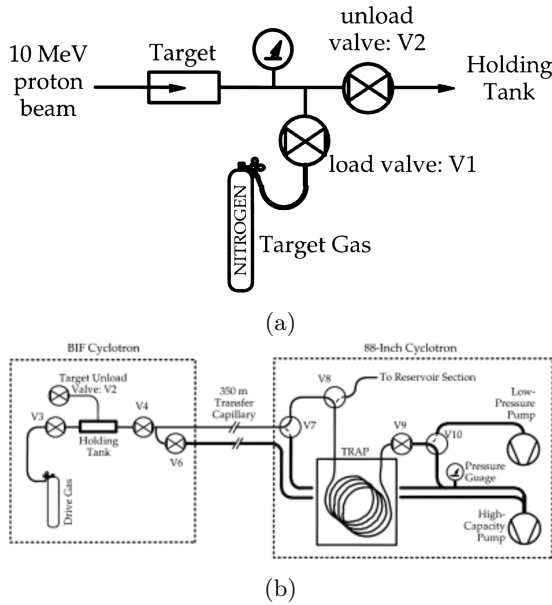


Figure 2.16: The production system of the Biomedical Isotope Facility (a) and the transport system to the 88" (~ 224 cm) cyclotron of the Nuclear Science Division (b) that were used at BEARS to produce ^{11}C beams [57].

oxygen available for $^{11}\text{CO}_2$ formation while avoiding overloading the ion source with non-radioactive chemical species formed during irradiation. Figure 2.16 shows the system that was used to transport the gas mixture to the cryogenic trap for separation and subsequent injection into the AECL-U ECR ion source. It was found that the cryogenic trap was a crucial feature for the performance of the ion source. The AECL-U is a two-frequency ($14 + 10$ GHz) ECR ion source that provided an ionization efficiency distribution of: $3^+ = 4\%$, $4^+ = 11\%$, $5^+ = 4\%$, $6^+ = 2\%$ [57]. The ion source was operated at pressures of the order $\sim 10^{-7}$ mbar, and the 6^+ charge state was selected using a stripper foil to erase boron contaminations. The entire system was operated by a fully automatized control system, handling the loading of the target, the irradiation and the unloading. Using a five minute cycle, a final beam intensity of $1 \cdot 10^8$ ions per second with an energy of 120 MeV u^{-1} was achieved [57].

Centre de Recherche du Cyclotron

The RIB facility at the Centre de Recherche du Cyclotron (CRC) in Louvain-la-Neuve, established in 1989 and in operation until 2009, was the first facility that

coupled an ISOL-type RIB production system to a post-accelerator, therefore, providing the first post-accelerated RIBs [71, 72]. Figure 2.17 shows the accelerator complex with its three accelerators. CYCLONE30 is a 30 MeV proton accelerator with beam intensities up to $300\ \mu\text{A}$ developed for medical purposes [71]. Both CYCLONE44 ($K = 40$) and CYCLONE110 ($K = 110$) are cyclotrons for the post-acceleration of nuclei produced with CYCLONE30. Two types of ion sources were in operation: firstly, sputtering ion sources, consisting of a biased electrode containing the material to ionize [73]. Secondly, a 6 GHz ECR ion source was developed for fast, low charge state ionization. Offline measurements using calibrated CO_2 leaks yielded a $\text{C}^+ = 15\%$ ionization efficiency at an in-source pressure of 10^{-5} mbar [73]. For the production of ^{11}C , two boron based powder targets were tested, boron nitride (BN) and boron oxide (B_2O_3) [74, 75]. For both materials a release study was performed. B_2O_3 melts at $450\ ^\circ\text{C}$, but vitrifies to a glass-like substance after cooling. With the initial melting, a strong outgassing and the formation of bubbles was observed, causing the material to expand. However, once vitrified, the material showed normal melting behavior. Hence, prior to irradiation, the material was vitrified by carefully pre-heating to $800\ ^\circ\text{C}$ and cooling subsequently. The release study of B_2O_3 showed a higher release efficiency at lower temperatures. However, only one cycle could be observed due to the escaping of the powder from the target container. In the case of BN, 6 g of powder was compressed to $0.8\ \text{g cm}^{-3}$ into a graphite cavity and outgassed prior to irradiation. The release of ^{11}C was rather limited at lower temperatures, however, an efficiency of 10% could be obtained at $1000\ ^\circ\text{C}$ in several different runs. It was observed that this characteristic resulted from the lack of free O_2 available for the formation of carbon oxides. Therefore, an oxygen leak was added providing a partial pressure

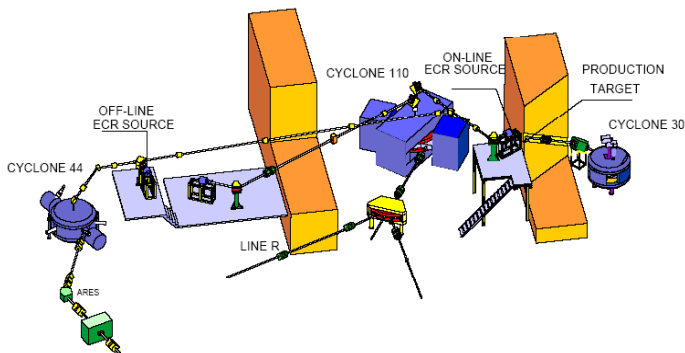


Figure 2.17: Layout of the radioactive ion beam facility at CRC in Louvain-la-Neuve (Belgium) [71]. The RIB project was established in 1989, and was in operation until 2009.

of approximately 10^{-2} mbar. However, no improvement was observed, which was probably due to an unpractical placement of the O_2 leak and the oxygen strongly reacting with the surrounding carbon of the hot graphite cavity. It was later reported elsewhere that an on-line experiment using a BN target operated with an oxygen leak of $0.1 \text{ cm}^3 \text{ h}^{-1}$ resulted in a ^{11}C beam of 10^7 ions s^{-1} [76].

CERN ISOLDE

Since 50 years, CERN ISOLDE (Isotope Separator On-Line DEvice) [77] produces various radioactive ion beams from the chart of nuclides. ISOLDE receives 1.4 GeV protons from the *Proton Synchrotron Booster* (PSB) of the CERN accelerator chain with intensities up to $2 \mu\text{A}$. Three different types of ion sources are available for 1^+ charge state ionization: surface ion source, plasma ion sources and laser ion sources.

At ISOLDE, many target-ion source combinations have been developed over the years, allowing to produce radioisotopes from more than 70 different elements. For mass separation, two separators are available that are operated with independent target-ion source units. The *General Purpose Separator* (GPS), equipped with one bending magnet and an electrostatic switchyard, allows to extract three mass separated beams simultaneously. For higher resolving power (> 5000), the *High Resolution Separator* (HRS) is available, consisting of two bending magnets. The experimental hall of ISOLDE (see Fig. 2.18) hosts many different experiments that can receive the beam from either GPS or HRS.

Several mass separated ^{11}C beams have been produced from different target-ion source units, as can be seen in Table 2.2. They were predominately produced as

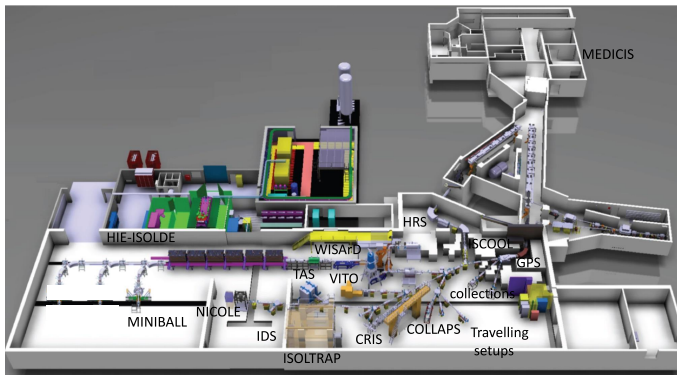


Figure 2.18: Layout of the ISOLDE facility at CERN in Geneva (Switzerland) [78].

oxides, since atomic release is limited because of carbon’s refractory nature and its high reactivity. CO was the prevailing molecular sideband, due to shortage of oxygen supply and molecular breakup of CO₂ in the ion source, yielding CO⁺/CO₂⁺ ratios of 10 – 100 for the oxide targets [79]. The NaF:LiF molten salt target, lacking *in situ* oxygen, provided so far the highest absolute yield, where CO⁺ was 30 times stronger than CO₂⁺ [80]. The presence of oxygen was unexpected and hypothesized to stem from water vapor traces or structural materials in the system.

Besides that, extensive research has been performed for the production and extraction of short-lived carbon beams [79, 83]. Adsorption enthalpies of CO and CO₂ have been measured for several materials: MgO, Al₂O₃, SiO₂, CaO, TiO₂, ZrO₂, HfO₂ and Y₂O₃. High adsorption enthalpies result in longer retention/sticking times of CO or CO₂ on such surfaces, and therefore, reduce the yields. SiO₂ and Al₂O₃ were investigated as coating materials for transfer lines and ion sources. It was found that for CO the retention times are for both materials negligible, but for CO₂ retention on Al₂O₃ becomes more evident at temperatures below 400 °C [83]. Diffusion studies of ¹¹C in MgO, TiO₂ and HfO₂ as pressed powder and pressed fiber pellets showed that diffusion in fiber pellets is faster than in pressed powder pellets. It was furthermore concluded that limitations on the extraction and transport of short-lived carbon isotopes as carbon oxides mainly result from a shortage of oxygen supply, losses on hot tantalum surfaces (> 1000 °C) of the target unit and retention due to the adsorption on hot molybdenum surfaces in the ion source delaying the extraction [79].

Target	Yield [μC^{-1}]	Ion source	Molecular sideband	Ref
HfO ₂ fibers	$4.4 \cdot 10^4$	Plasma-Helicon*		[81]
TiO _x fibers	$6.2 \cdot 10^6$	Plasma-Cold-MK7	$^{11}\text{C}^{16}\text{O}^+$	[82]
NaF:LiF salt	$7.7 \cdot 10^8$	Plasma-Cold-VD7	$^{11}\text{C}^{16}\text{O}^+$	[80]
MgO	$2.1 \cdot 10^5$	Plasma-Cold-MK7	$^{11}\text{C}^{16}\text{O}^+$	[82]
CeO _x fibers	$4.8 \cdot 10^6$	Plasma-Cold-MK7	$^{11}\text{C}^{16}\text{O}^+$	[82]
CaO nanostructured powder	$2.7 \cdot 10^6$	Plasma-Helicon*	$^{11}\text{C}^{16}\text{O}^+$	[81]

*Prototype ion source with low efficiency

Table 2.2: Produced ¹¹C beams at CERN ISOLDE.

SPIRAL1/GANIL

Since 2001 SPIRAL1 at GANIL (see Fig. 2.19) produces radioactive ion beams via the ISOL method [85]. The facility hosts five different cyclotrons for the production and acceleration of RIBs [84]. The two low-energy cyclotrons C01 and C02 send beams to the irradiation beam line IRRSUD ($< 1 \text{ MeV u}^{-1}$). CSS1 ($4 - 13 \text{ MeV u}^{-1}$) and CSS2 in series post-accelerate stable beams up to 95 MeV u^{-1} , which are then send on a graphite target for radioisotope production. The produced radioisotopes effuse to a Nanogan-3 ECR ion source for multi-charge ionization [84]. After mass separation (250 resolving power), the beam can either be send into the low-energy beam line LIRAT, or can be injected into the CIME cyclotron ($K = 265$) for post-acceleration ($1.7 - 25 \text{ MeV u}^{-1}$). Two projects are currently ongoing aiming to expand GANIL's RIB inventory: firstly, the SPIRAL1 upgrade is being finalized, containing new target-ion source systems for more 1^+ RIBs. Furthermore, a Phoenix type charge booster is being installed for 1^+ to n^+ charge breeding [85]. Secondly, the SPIRAL2 project will provide beams produced via the ISOL and the in-flight technique [86].

Although, no ^{11}C beam has been produced yet at SPIRAL1, studies on CO and CO_2 ionization and charge breeding efficiency have been performed [83, 87]. In collaboration with PANTECHNIK, a 2.45 GHz ECR ion source for efficient 1^+ ionization was developed (MONO 1000). Based on this design, a compact version was developed and tested in an off-line study at ISOLDE, where a 14% CO^+ ionization efficiency was determined.

ISAC/TRIUMF

TRIUMF in Vancouver (Canada) is a national laboratory for nuclear and particle physics. Their main accelerator is a sector-focused cyclotron with four independent beam extraction lines that accelerates H^- ions with a total

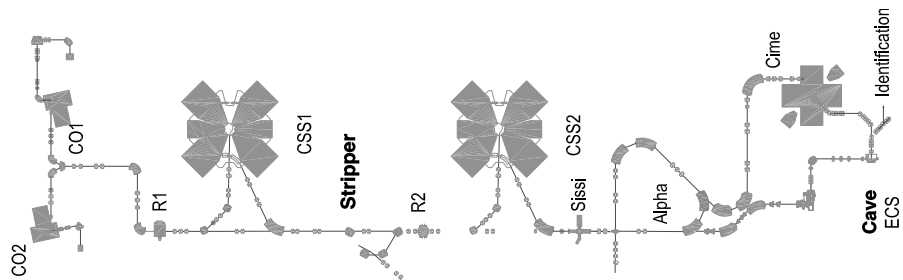


Figure 2.19: Layout of the SPIRAL1 facility at GANIL in Caen (France) [84].

beam current of $300\ \mu\text{A}$ to energies ranging from 70 to 520 MeV [88]. One of these extraction lines enters the ISAC facility, providing proton beams of 500 MeV with up to $100\ \mu\text{A}$ beam intensity for radioactive ion beam production. ISAC comprises one target station with three types of ion sources: surface ion source, resonant laser ion source, plasma ion source (FEBIAD). A separator consisting of two magnets in series separates the ions extracted from the ion source. Currently, a new laboratory is under construction, which will add two more target stations to the inventory of ISAC. In detail, this is the Advanced Rare IsotopE Laboratory (ARIEL) project, which will add another 500 MeV, $100\ \mu\text{A}$ proton beam line and a 50 MeV, 500 kW electron beam line [88].

Up to now, many radioactive ion beams have been produced from numerous targets [89]. For the production of radioactive ^{11}C beams, a composite NiO/Ni target was developed and tested on-line in 2012 and 2013 [90]. The target was operated at a maximum temperature of $1100\ ^\circ\text{C}$ to prevent high vapor pressures overloading the FEBIAD ion source, which would reduce the ionization efficiency. A high power target container was used to dissipate the deposited beam power of the 500 MeV proton beam with a maximum intensity of $16\ \mu\text{A}$. Throughout several runs, a maximum yield of $10^7\ ^{11}\text{CO}^+\ \text{s}^{-1}$ was observed. It is worth mentioning that a ratio $\frac{\text{CO}^+}{\text{C}^+} \approx 10$ was observed, where the C^+ beam is presumably originating from molecular breakup in the ion source [88].

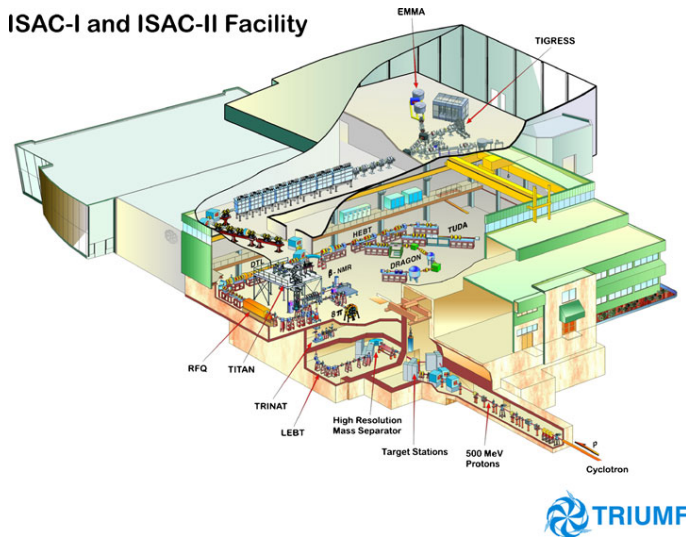


Figure 2.20: Schematic layout of the ISAC-I and ISAC-II ISOL facility in TRIUMF in Vancouver (Canada) [88].

HIMAC/NIRS

Since the National Institute for Radiological Sciences (NIRS) completed in 1994 the construction of the Heavy Ion Medical Accelerator (HIMAC) in Chiba (Japan), more than 10000 cancer patients have been treated using high-energy carbon beams [91]. The original accelerator complex consisted of three ion sources, a RFQ cavity, an Alvarez type Drift-Tube-linac, a pair of synchrotron rings and beam transport lines. The HIMAC can accelerate heavy-ions from protons to xenon up to 800 MeV u^{-1} for a charge-over-mass ratio greater than 0.5 [91]. In 2010 a new treatment facility was added next to HIMAC, comprising a superconducting rotating-gantry and 3D raster-scanning irradiation techniques. NIRS has a strong R&D programme since 2004 and designed a compact accelerator facility for more cost-effective and size-reduced treatment centers.

At first, ^{11}C beam production was studied using the in-flight projectile fragmentation technique [92]. ^{11}C was obtained by sending a primary 430 MeV u^{-1} ^{12}C beam onto a Be target. A set of two bending magnets was used for separation and final focusing was achieved by a triplet of quadrupole magnets. This study showed that the yield strongly depends on the target thickness, degrader thickness (when used) and the angular acceptance. Remarkable is that increasing the degrader thickness from 0 to 10.6 mm, the beam purity is

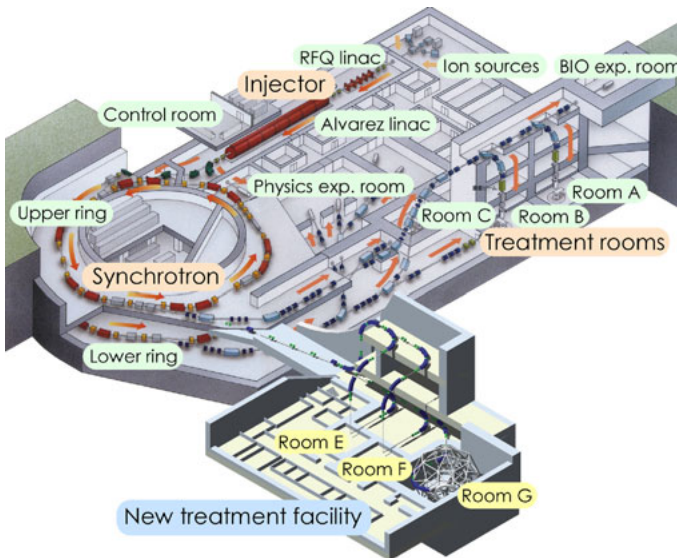


Figure 2.21: Layout of the HIMAC facility in Chiba (Japan) [91].

increased from 93 to 99%, however, decreasing the yield from 0.97 to 0.76%. For most of the tests, no degrader was used, resulting in a relatively poor beam purity of 93% with contaminations of ^{12}C and ^7Be . It was pointed out, that these yield dependencies made the end cut of the depth dose distribution vague and not desirable [92]. Finally, using a $1.8 \cdot 10^9$ pps ^{12}C beam, $7.2 \cdot 10^6$ pps of ^{11}C were delivered using spot scanning, which is insufficient in respect of dose delivery. Furthermore, large momentum spread and emittance resulted in undesirable beam characteristics. More recently, studies on producing ^{11}C beams using the PET-isotope production scheme from N_2 gas targets and using the ISOL method were performed [59, 94]. The first route, via the $^{14}\text{N}(\text{p},\alpha)^{11}\text{C}$ reaction from N_2 gas targets, was a theoretical calculation starting with a 18 MeV proton cyclotron from the NIRS-Cyclotron-Facility. The study included the radioisotope production, gas separation, gas compression, gas pulsing, ionization in an ECR ion source and injection into the HIMAC synchrotron. It was estimated that with the developments discussed in that work, a $^{11}\text{C}^{6+}$ beam with $\sim 10^8$ ppp intensity could be extracted from the HIMAC [59]. However, in subsequent publications [94–96] production via the $^{14}\text{N}(\text{p},\alpha)^{11}\text{C}$ reaction and N_2 gas targets was discarded due to high N_2 impurities ($\sim 10^{22}$ for a 0.1 l target) overloading the ion source. Most recently, NIRS investigates ^{11}C beam production via the ISOL method using solid boron-based targets [94, 96]. Figure 2.22 shows the proposed ISOL-type ^{11}C beam production system, comprising a solid NaBH_4 target, a driver cyclotron providing 20 MeV protons, a ^{11}C Molecule Production/Separation System (CMPS), a 1^+ ion source, a mass separator and an EBIS/ESIS ion source for charge breeding. Since the HIMAC has an acceleration efficiency of 10% (from linac injection to the treatment room) [94], and $\sim 10^9 - 10^{10}$ ^{11}C ions are required for treatment, the ISOL system must be able to provide $\sim 10^{10}$ ions extracted from the ion source system. Three boron-based targets have been tested [94, 97], using 18 MeV protons, a beam intensity of $18 \mu\text{A}$ for 20 minutes and an isotope extraction in form of

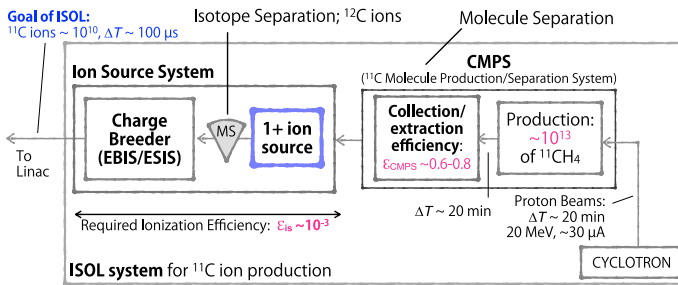


Figure 2.22: Possible ISOL-type ^{11}C beam production system, proposed by NIRS [93].

$^{11}\text{CH}_4$. Elemental boron showed highest in-target production yield, however, only 0.2% could be trapped as $^{11}\text{CH}_4$. From a B_2O_3 target more than 76% could be collected as $^{11}\text{CO}_2$, but they report that the carbon oxide separation is too difficult [97]. Finally, it was claimed that a NaBH_4 target suited best their requirements with $5 \cdot 10^{12}$ collected $^{11}\text{CH}_4$ molecules, which corresponds to more than 29% of the in-target production yield. It was projected that this yield can be increased to the order of 10^{13} by increasing the proton beam intensity to 30 μA . One major concern of this approach is the low melting point of $\sim 400^\circ\text{C}$ and the fact that the target thickness is chosen to absorb the entire proton beam. Consequently, serious complications with respect to heat damage and target endurance should be taken into account. However, based on these findings, the CMPS was developed, comprising two cryogenic traps, which separate the molecular species according to their difference in vapor pressure. Depending on the impurity concentration, a collection/extraction efficiency of 60-80% is reported [98]. As a result, the ion source system depicted in Fig. 2.22 has to reach a total efficiency of 0.1% for the proposed 1^+ to n^+ ionization scheme. Currently, a singly charged ion source based on electron impact ionization is under development [93]. Considering an average C^{4+} ionization efficiency of approximately 10% that was observed in an *Electron String Ion Source (ESIS)* [99, 100], the 1^+ ion source is designed to provide the required 1% ionization efficiency. However, it must be mentioned that the referred charge breeding efficiency was determined using stable, neutral CH_4 gas which was frozen in a cryogenic cell. By heating the cell, the methane was evaporated and part of it was injected into the ion source. A recent study, performed at CERN, yielded that the EBIS charge breeding efficiency using ion beam injection is considerably lower [101]. Since an ESIS ion source is basically a modified EBIS, it is consequently questionable whether this ion source system (Fig. 2.22) will accomplish the desired 0.1% overall ionization efficiency.

Overview

Facility	Production route	Target	^{11}C beam intensity	Form
Berkeley	Projectile fragmentation	Be	$2 \cdot 10^7$ [ppp]	N/A (Prob. C^{6+})
Berkeley	PET-isotope production	N_2	10^8 [pps]	C^{6+}
CRC	ISOL	BN	10^7 [pps]	C^+
ISOLDE	ISOL	$\text{NaF}:\text{LiF}$	$7.7 \cdot 10^8$ [μC^{-1}]	CO^+
TRIUMF	ISOL	NiO/Ni	10^7 [pps]	CO^+
NIRS	Projectile fragmentation	Be	$7.2 \cdot 10^6$ [pps]	N/A (Prob. C^{6+})
NIRS	PET-isotope production	N_2	N/A	N/A
NIRS	ISOL	NaBH_4	N/A	N/A

Table 2.3: Overview of the in the past produced ^{11}C beams at different facilities.

2.4 Goal of this thesis: a tailored ^{11}C RIB production system

Reviewing the past results on produced ^{11}C radioactive ion beams (Sec. 2.3) with respect to their feasibility of delivering an intense ($\sim 4 \cdot 10^8$ ions s^{-1}) and pure beam to the patient, it seems that the projectile fragmentation and in-flight separation of initial ^{12}C beams is not applicable. Low production cross section and undesirable beam characteristics, e.g. purity, large momentum spread and large emittance prevent this method for its medical application in hadron therapy. Instead, an approach is proposed in which existing carbon therapy centers, such as MedAustron and CNAO, are upgraded in the sense that the stable ^{12}C injector of the synchrotron-accelerator based facilities is replaced by a ^{11}C injector [23]. In detail, this includes the supplementation of the present accelerator complex with a radioisotope production-post-acceleration RIB system. The ^{11}C injector comprises in that context ^{11}C production, separation and charge breeding, and must be able to inject into the synchrotron with its given time structure and with a sufficiently high beam intensity. In that context, the European Marie Skłodowska-Curie Actions, innovative training network [MEDICIS-Promed](#) ([MEDICIS](#)⁵-produced radioisotope beams for medicine), was launched in April 2015, in which framework one research pillar was the development of such a ^{11}C based hadron therapy upgrade.

Figure 2.23 presents the possible implementation scenarios that were identified by MEDICIS-Promed. The radioisotope production (I) and separation methods (II), are subject of this thesis, where different driver accelerator-target combinations as well as subsequent separation modalities are investigated. A detailed discussion and feasibility study of these scenarios will be presented in Chapter 6. The complementary parts of these scenarios were investigated by other members of MEDICIS-Promed [101, 103].

Core of this thesis is the development of an ISOL-type RIB production system tailored for ^{11}C , which produces sufficiently intense ^{11}C beams to guarantee the delivery of $\sim 4 \cdot 10^8$ post-accelerated ions to the patient room. Moreover, this system is required to allow implementation into existing hadron therapy centers, e.g. constraints in footprint and regulatory framework, with respect to applicability in a medical environment.

It was discussed in Section 2.2.1 that the bottleneck of the ISOL method is usually attributed to the radioisotope production process, covering all aspects from primary irradiation until injection into the ion source. ^{11}C is not exotic, concerning its half-life and nuclear properties, which relaxes to some extent the

⁵MEDICIS stands for *Medical Isotopes Collected from ISOLDE*, and is a CERN facility dedicated to the production of medical radioisotopes and new accelerator technologies for medical application [102].

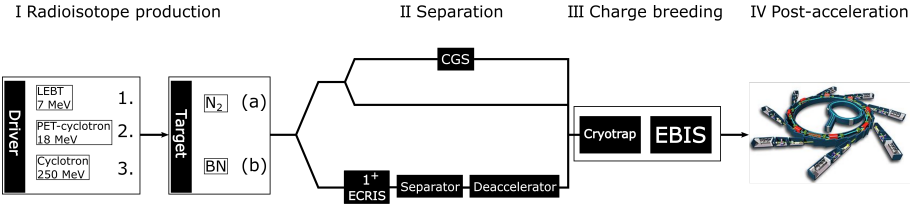


Figure 2.23: Component diagram showing the different accelerator chain options considered within MEDICIS-Promed and within the *Technical Design Report for a Carbon-11 Treatment Facility* [23] for the development of a ^{11}C based hadron therapy protocol. In this thesis the radioisotope production (I) and separation (II) aspects are investigated, with the focus on the development of a solid ISOL-target for singly ionized and mass separated ^{11}C beams.

time constraints with respect to decay losses. However, carbon is very refractory and reactive, i.e. it possesses a low vapor pressure and easily forms strong bonds with hot metal surfaces. It was therefore concluded that a tailored target-ion source unit is required to accomplish the goal of this thesis, with main focus on the development of an ISOL target, optimized for ^{11}C production and release. In that regard, Chapter 3 describes the target material development process, and the underlying fundamental physics which are involved. In detail, this comprises material selection in consideration of the production yield, and the sintering of powder ceramics. In this context it is worth mentioning that in material science, most often, one strives for fully dense powder compacts, i.e. minimization of porosity, whereas ISOL targets with high porosity (especially open porosity) are desired, because of their superior isotope release properties. Hence a new research line was formed for the manufacturing of a porous powder compact for ISOL targetry. In Chapter 4, the developed target is characterized and examined with respect to its operational limitations. Chapter 5 provides a detailed description of the isotope release process, its most important parameters and presents a release study for the determination of carbon's release properties from the developed target. Based on these findings, a conceptual study is performed, examining possible implementation scenarios of the developed target and ^{11}C RIB production system into existing hadron therapy accelerator complexes (Chapter 6). Moreover, the system is evaluated concerning its suitability for producing sufficiently intense ^{11}C beams to accomplish the thesis' objective. Figure 2.23 shows a graphic illustration of the different routes that are investigated, where the developed target (BN) is compared to conventional N₂ gas targets, employed for the production of ^{11}C based radiopharmaceuticals.

Chapter 3

Target development

An important aspect regarding the development of an ISOL-type ^{11}C RIB production system, is the choice of the target material and the primary production accelerator. In this chapter, the target material selection, target fabrication and relevant background theory, as well as the target's microstructural characterization will be discussed.

Several promising targets have been discussed in the review in Section 2.3. The highest production yield was achieved at CERN ISOLDE, employing the NaF:LiF molten salt target. However, drawbacks of this target are its complexity and difficulty in operation, and the high-energy driver accelerator that would be required for production.

Since ^{11}C is considered a light nuclide in terms of radioisotope production, high production yields can be achieved from light targets and low-energy particle beams, exploiting nuclear fusion-evaporation reactions. This is certainly a more favorable condition than heavy targets and high-energy beams, which not only would generate an undesirably large nuclear inventory, possibly introducing beam contamination issues, but also complicating the implementation into existing facilities, due to the large driver accelerator footprint and construction costs.

3.1 Target material

Boron and nitrogen have both relatively high cross sections for the production of ^{11}C , with maximum values around 6 – 8 MeV, which are considered as low energies. Figure 3.1 shows the measured σ for the $^{11}\text{B}(\text{p},\text{n})^{11}\text{C}$ and $^{14}\text{N}(\text{p},\alpha)^{11}\text{C}$

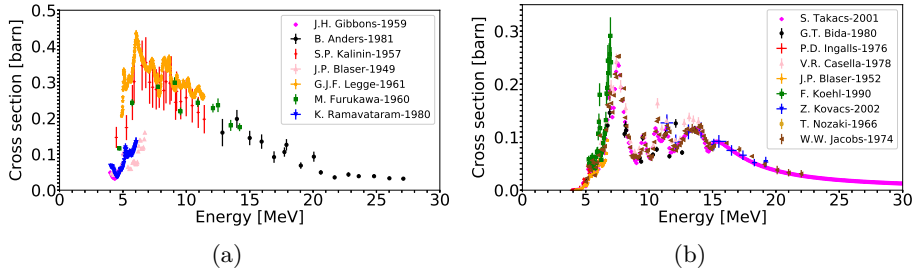


Figure 3.1: Collection of measured cross sections for the $^{11}\text{B}(p,n)^{11}\text{C}$ (a) and $^{14}\text{N}(p,\alpha)^{11}\text{C}$ reactions (b). The data were gathered from the EXFOR database [104].

reactions, respectively. It was introduced in the previous chapter that high-pressure nitrogen gas targets are commonly used in hospitals to generate ^{11}C for the synthesis of PET-radiopharmaceuticals. However, production is carried out in batch mode as the target gas needs to be separated from the reaction product by using cryogenic traps. Hence, the application of a solid target is preferred, to ensure a continuous production of ^{11}C .

Based on the cross sections shown in Fig. 3.1, a natural (or enriched) boron target would be the logical choice for maximized in-target ^{11}C production. The high-temperature chemistry between the radioisotope and target material however prevents a successful ISOL application of such a target, due to the formation of boron carbide (B_4C). Figure 3.2a shows a chemical equilibrium calculation of carbon and boron. Such calculations are based on Gibbs free energy G_E minimization, which indicates whether a chemical reaction at constant temperature and pressure, is thermodynamically favored or not:

$$\Delta G_E = \Delta H - T\Delta S = \begin{cases} > 0, & \text{disfavored} \\ = 0, & \text{equilibrium} \\ < 0, & \text{favored.} \end{cases}$$

H and S are the reaction enthalpy and entropy, respectively, with:

$$\begin{aligned} \Delta H &= \sum H^{\text{products}} - \sum H^{\text{reactants}}, \\ \Delta S &= \sum S^{\text{products}} - \sum S^{\text{reactants}}. \end{aligned}$$

Reactions with negative Gibbs free energy change, proceed in forward direction towards the products, while positive ΔG_E indicates backward direction towards the reactants. If two reactions are competing against each other, the reaction

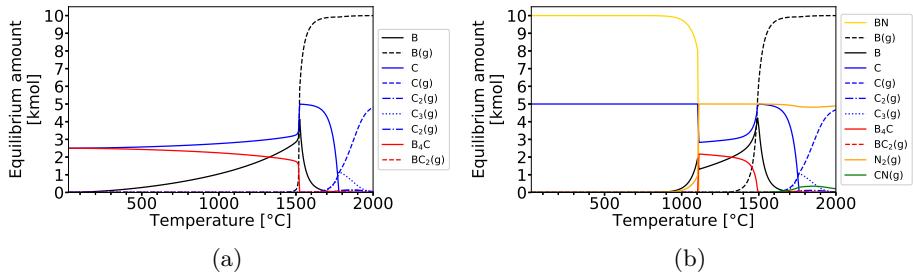


Figure 3.2: Chemical equilibrium calculation at $P = 10^{-6}$ mbar of carbon with boron (a), and carbon in boron nitride (BN) (b). While in the former case boron carbide is formed across the entire temperature range, carbon remains in its atomic form when in contact with BN. Boron and carbon phase transitions, such as glassy boron B(GL) were not considered for this illustration. The calculations were performed using HSC 7 [105].

with the more negative Gibbs free energy change is stable at equilibrium conditions.

In case of carbon in boron, B_4C is thermodynamically favorable across the entire temperature range until boron vaporization occurs. In such a configuration, the release of ^{11}C would be drastically hindered. Therefore, a boron comprising target where carbide formation is not favored is believed to be a better solution.

Boron Nitride (BN) was identified as a promising target material candidate, for three reasons: firstly, BN offers both of the aforementioned reaction channels (Fig. 3.1) for ^{11}C production, and thus, offers next to elemental boron the highest physical in-target production yield. Secondly, previous studies at CRC in Lovain-la-Neuve (see Sec. 2.3) with pristine BN powder yielded first promising results. Thirdly, BN possesses good material properties with respect to an ISOL application, e.g. thermal properties and chemical inertness.

BN exists mainly in three crystalline forms: hexagonal (Fig. 3.3), cubic and wurtzite. Hexagonal boron nitride (h-BN) resembles graphite, and is the most stable form. Cubic boron nitride (c-BN) presents a crystal structure analogous to that of diamond, and is metastable under standard conditions. c-BN is obtained under high-temperatures and high-pressure treatments [106]. Due to its excellent thermal and mechanical properties, a wide variety of powders or compacted forms of h-BN are commercially available. It is often applied as high-temperature lubricant. It possesses a high thermal conductivity ($0.627 \text{ W cm}^{-1} \text{ K}^{-1}$ along the a- and b-axis, and $0.015 \text{ W cm}^{-1} \text{ K}^{-1}$ along the c-axis, Fig. 3.3), low thermal expansion, and a good thermal-shock resistance [106, 107]. Moreover, h-BN is chemically inert, a good insulator, and is reported

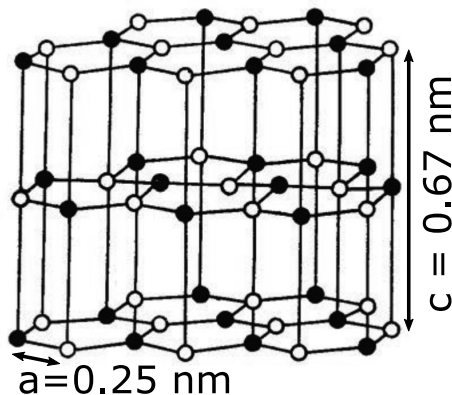


Figure 3.3: Crystal structure of hexagonal boron nitride (h-BN), with ● boron atoms and ○ nitrogen atoms. Adapted from [108], with lattice parameters obtained from [106].

to be applicable in air up to 1000 °C, in vacuum until 2200 °C and in inert atmosphere up to 2800 °C [107, 108]. Compact and dense shapes of BN are manufactured from *Hot-Pressing* (HP) or *Hot-Isostatic Pressing* (HIP), where boric acid is usually added as a binder [107].

These material properties and the chemical equilibrium calculation of carbon in contact with BN (Fig. 3.2b) suggest together with the experimental results measured at CRC in Louvain-la-Neuve that h-BN is an appropriate target material for maximized ^{11}C production. In Fig. 3.2b it is shown that carbon does not react with BN until decomposition around $T \sim 1100$ °C starts. Upon decomposition, N_2 is vaporized and elemental B remains, which in turn can react with the carbon content to form B_4C . In fact, the issue of decomposition is of great importance for the target operation at high temperatures and low pressures such as 10^{-6} mbar, and will be examined in Chapter 4. Instead of using a pristine powder target as it was done in the study at CRC, processing routes that yield a rigid powder compact are investigated in this thesis. Such an ISOL target eases handling and waste management, which is especially relevant in the clinical context of this project. Moreover, a rigid target eliminates the risk of powder escaping from the target container during high intensity proton beam irradiation.

However, from experience at ISOLDE, the production of carbon RIBs is known to be difficult, which can be seen from the rather low reported yields [109]. Ionization is usually not a limiting factor, thus one can conclude that the release from the target material is inefficient. Since carbon is very refractory, i.e. it

possesses a high melting point, the low efficiency most likely stems from slow diffusion within the bulk of the target grains and poor desorption from the material's surface, due to the low vapor pressure. Both of these characteristics are ominous for radioactive ion beam production. Furthermore, carbon is very reactive and forms strong bonds with hot metal surfaces, which are usually present in target containers, transfer lines and/or in the ion source. This may lead to severe lingering times on surrounding materials, and will potentially result in strong losses due to decay. As a result, it was identified that the release and transport from the target matrix is probably the bottleneck of intense ^{11}C RIB production, which requires thoughtful optimization.

In that regard, two measures can be taken: firstly, as stated in Section 2.2.1, small grain sizes for fast diffusion and high open porosity for fast inter-grain effusion are beneficial target properties, which enhance the isotope release from the target matrix. A more fundamental explanation of these processes will be given in Chapter 5, which will clarify why high open porosity and small grain sizes are enhancing the release process. Commercial BN products, manufactured by HP or HIP, are designed to reach the material's theoretical density, thereby, minimizing the porosity. Consequently, the following section will discuss the sintering theory in the framework of obtaining a porous powder compact with small grain sizes.

The second measure is to extract carbon as an oxide molecule. Carbon easily reacts with oxygen, forming the carbon monoxide or carbon dioxide molecular sideband, which are both more volatile and less reactive and thus, can be transported more efficiently to the ion source for 1^+ ionization and subsequent beam manipulation. For this purpose, it is foreseen to operate the target with a controlled oxygen leak, which promotes the oxidation of the generated carbon content without risking excessive target material oxidation. This modality will be further discussed in Chapter 4.

3.2 Sintering

As stated in the previous section, the goal of this thesis is to obtain a rigid BN powder compact, with small grain sizes and large (open) porosity. These material properties ensure fast diffusion and effusion processes of the produced ^{11}C within the target, enhancing the release from the target matrix. The consolidation of a metal or ceramic powder, such as BN, to a density-controlled body, is achieved by *sintering*. Sintering is defined as a processing technique, yielding such density-controlled materials or components by applying thermal energy [110]. In general, sintering aims for the fabrication of reproducible materials, with a designed microstructure through the control of sintering parameters. In that regard, microstructural control refers to the control of

grain size, final sintered-density (i.e. porosity) and the size and distribution of pores, which is precisely what is desired for the manufacturing of a porous BN target [110]. However, most cases applying sintering techniques strive for fully dense powder compacts, which shall be denoted as *conventional application of sintering*, and is certainly in contrast to what is desired for the BN target. Hence, a brief overview over the mechanisms, powder properties and sintering variables influencing the final material, will be given in the following.

3.2.1 Basics of sintering

In general, sintering can be grouped into two main categories: solid state sintering and liquid phase sintering. The latter includes a liquid phase present during the thermal treatment, while in the former type consolidation occurs exclusively in a solid state of the powder compact. In line with the objective of this thesis, henceforth, the focus is set on the former type of sintering. The underlying phenomena involved during the sintering process are densification and grain growth [110]. Thermal energy is applied to a starting powder compact, transforming it into a monolith, whose particles are turned into grains. The driving force of this process is the reduction of the free energy, or total interfacial energy of the system [110, 111]. Three main driving forces exist: (i) the curvature of the particle surfaces, (ii) an externally applied pressure, and (iii) a chemical reaction [111]. These driving forces may act individually or superimposed as basis for the sintering process.

(i) Curvature of the particle surfaces as driving force

In the absence of the latter two, the surface curvature and its surface free energy E_S , governs the sintering process [111]:

$$E_S = \gamma_S S_A = \gamma_S \frac{3V_m}{r}. \quad (3.1)$$

γ_S is the specific surface (interface) energy expressed in $[\text{J m}^{-2}]$, S_A $[\text{m}^2]$ is the system's total surface area and V_m $[\text{m}^3]$ and r $[\text{m}]$ are the molar volume and radius of the particle, respectively. On a 'global' level, the reduction of E_S drives sintering, which according to Eq. (3.1) is achieved by decreasing γ_S or S_A . In that regard, change in the interfacial energy $\Delta\gamma_S$ is attributed to densification, while ΔS_A is due to coarsening (i.e. grain growth) [110–112]. Figure 3.4a shows a schematic illustration of the 'global' driving force of sintering.

However, without a 'local' driving force no sintering can occur [112]. Sintering requires the transport of matter, for which diffusion is the most important mechanism [110, 111], which refers to the movement of atoms driven by gradients, e.g. gradients in vacancy concentration. The flux of diffusing atoms $\vec{\varphi}$ is proportional to the concentration gradient ∇C :

$$\vec{\varphi} = -D\nabla C, \quad (3.2)$$

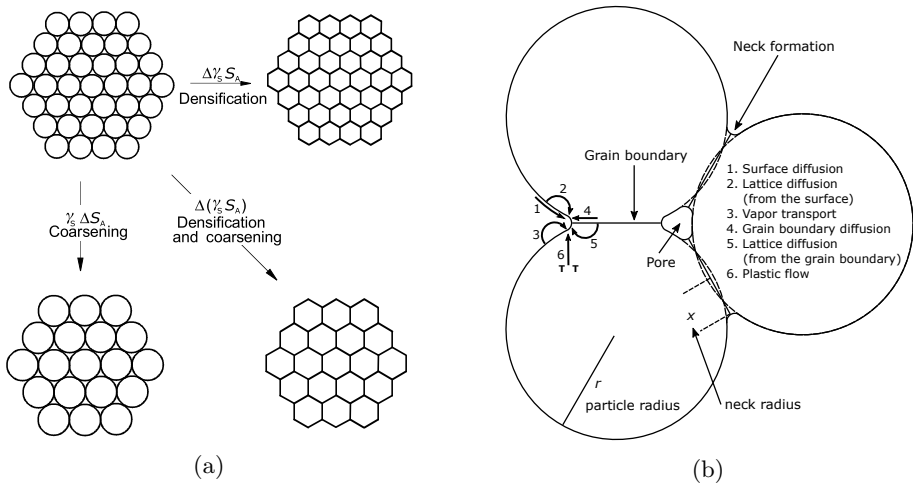


Figure 3.4: (a) Schematic illustration of the basic phenomena occurring during sintering: densification and grain growth. (b) Depiction of the two-particle geometrical model, and the main mechanisms involved in the sintering process. Modified from [110, 111].

where D , the constant of proportionality, is called the *diffusion coefficient* or *diffusivity* in $[\text{m}^2 \text{s}^{-1}]$ or $[\text{cm}^2 \text{s}^{-1}]$. Equation (3.2) is Fick's first law of diffusion [113]. Diffusion is largely influenced by defects, i.e. imperfections in crystalline structures, which allow diffusional mass transport, for instance due to vacancy migration [111]. Since defects control the rate at which matter is transported, they also control the rates of sintering, as well as grain growth [111]. The main diffusion mechanisms involved during the sintering process are illustrated in Fig. 3.4b.

(ii) Pressure-assisted sintering

The application of external pressure during a significant part of the powder compact's thermal treatment is normally the largest contribution to the driving force, assuming no contribution from any chemical reaction [111]. The surface curvature (i) is still adding to the net driving force, however, its contribution is considerably smaller. Since the driving force is increased due to the application of external pressure, the densification rate $\frac{d\rho}{dt}$ is increased as well. On the other hand, grain growth $\frac{dG}{dt}$ is not affected, which makes this form of sintering very effective for systems where $\frac{dG}{dt}$ is high relative to $\frac{d\rho}{dt}$. There are two main types of pressure-assisted sintering, hot-pressing (HP) and hot-isostatic pressing (HIP), which were mentioned discussing commercially available fully dense BN products.

Material variables	<u>Powder:</u> shape, size, size distribution, agglomeration, powder-blend homogeneity, ... <u>Chemistry:</u> composition, impurity, non-stoichiometry
Sintering condition related variables	temperature, time, pressure, heating and cooling rate, atmosphere, ...

Table 3.1: Variables influencing the sinterability and microstructure of a powder compact. Reproduced from [110]

(iii) Reactive sintering

If a chemical reaction is involved during the sintering process, the free energy reduction can be significantly greater compared to the other driving forces. However, in practice this form of sintering is rarely used, as microstructural control becomes extremely difficult [111].

Sintering is complex, and there are various variables or parameters that influence and determine the sinterability and the microstructure of the powder compact. In general, these variables can be divided into two categories: material-related one's and those related to the conditions during sintering. Table 3.1 gives an overview over the most important parameters in that regard. For instance, starting from the raw material, powder size and size distribution affect the densification and grain growth. Interesting in that respect is that powders with an adequate size distribution were found with a more uniform densification after sintering compared to a mono-sized powder [110]. Such results indicate the importance of narrow particle size distributions of starting powders to foster homogeneous densification of the powder compact. During the sintering process itself, parameters such as the applied temperature, time and pressure decisively impact the properties of the final product. The understanding of how these variables impact the sintered body and how they contribute to the mechanisms and sintering kinetics, has been studied extensively since the 1940s [110].

To evaluate the effect of the aforementioned parameters, and to evaluate the densification process, different models depending on the progress of sintering have been developed. In that regard, solid state sintering is usually divided into three consecutive stages, which are simply called: initial-, intermediate- and final stage of sintering. In the following, a brief overview over these stages will be given.

3.2.2 Stages of solid state sintering

The progress of the sintering degree over time, is commonly believed to occur in the aforementioned three sequential stages. Each stage is characterized by a density interval over which the powder compact's microstructure is reasonably well defined [111]. A schematic illustration of a powder compact's typical densification curve throughout these stages is shown in Figure 3.5. The relative density $\rho_r = \frac{\rho}{\rho_{th}}$ denotes the compact's density ρ normalized to the theoretical density ρ_{th} of the powder. The term *green body* refers to the shaped powder compact before thermal treatment, which is often denoted as *firing* [111]. Various different shaping techniques exist, where in its simplest form the mass of a fine powder is consolidated or compressed in a die applying external pressure. Table 3.2 provides an overview of the relative density intervals, microstructural features and common models that are associated with the corresponding stages of sintering. These analytical models, usually, assume a starting powder comprising spherical particles of the same size and uniformly packed [111]. Given that the porosity Φ is defined as:

$$\Phi = 1 - \frac{\rho}{\rho_{th}} = 1 - \rho_r,$$

one can conclude from Fig. 3.5 and Tab. 3.2 that the BN ISOL-type target should remain in the initial or intermediate stage. The final stage is associated with considerably low porosity and, very important, with disconnected pores (i.e. closed porosity).

Within the ISOL method, the release of isotope-target combinations is preferably dominated by diffusion, i.e. avoiding long lingering times of the isotope due to adsorption on the target material inside the pore network. This matter will be discussed in more detail in Chapter 5. Due to carbon's refractory nature,

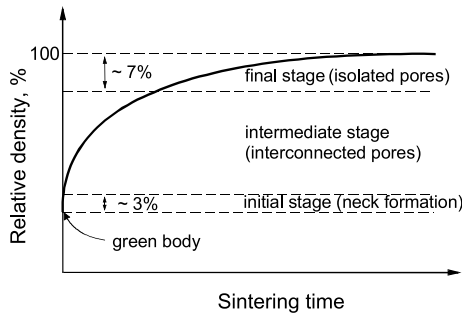


Figure 3.5: Schematic depiction of a powder compact's densification curve as a function of the sintering time. Adapted from [110].

diffusion is expected to be slow and thus, the limiting factor of the release process. A rigid BN powder compact which is in the final stage of sintering would suffer from significant delays due to the diffusion process, leading to poor release efficiencies due to the isotope’s decay. Moreover, isotopes that reach the pore volume have to re-diffuse into the grains as the pores are isolated and not connected to the target’s surface.

Initial stage

The main characterization of the initial stage is relatively rapid neck formation and neck growth between the powder particles by diffusion, vapor transport, plastic or viscous flow. The linear shrinkage (or densification) is limited to 3 – 5%. Prior firing, green bodies typically present relative densities about $\rho_r \approx 0.5 - 0.6$, which limits the increase of densification to $\rho_r \sim 0.65$ [111]. The sintering kinetics of the initial stage are usually modeled by a geometrical model, assuming two spherical particles of radius r that are in contact. As mentioned, upon heat treatment, neck formation and neck growth occurs. The necks are considered to be circular with a radius x . These geometrical features are illustrated in Figure 3.4b. Based on these geometrical assumptions, the neck growth $\frac{x}{r}$ and linear shrinkage $\frac{\Delta l}{l_0}$ (densification) can be derived for the

Stage	Typical microstructural feature	Relative density range	Idealized model
Initial	Rapid inter-particle neck growth	Up to ~ 0.65	Two monosize spheres in contact
Inter-mediate	Equilibrium pore shape with continuous porosity	$\sim 0.65 - 0.90$	Tetrakai-decahedron with cylindrical pores of the same radius along the edges
Final	Equilibrium pore shape with isolated porosity	$> \sim 0.90$	Tetrakai-decahedron with spherical monosize pores at the corners

Table 3.2: Overview of microstructural features, relative density ranges and typically models associated with the sintering stages. Reproduced from [111].

different sintering mechanisms summarized in Fig. 3.4b [111]:

$$\left(\frac{x}{r}\right)^m = \frac{H}{r^n}t, \quad (3.3)$$

$$\left(\frac{\Delta l}{l_0}\right)^{\frac{m}{2}} = -\frac{H}{2^m r^n}t, \quad (3.4)$$

H is a function including the geometric and material parameters of the powder, and m , n are exponents that depend on the sintering mechanism [111]. A variation of different values for m , n and H is found, depending on the assumptions made within the aforementioned sintering mechanisms, where $m \in [2, 7]$ and $n \in [1, 4]$. For instance, in the case of grain boundary diffusion it can be derived:

$$\left(\frac{x}{r}\right)^6 = \frac{96D_{\text{Gb}}\delta_{\text{Gb}}\gamma_{\text{S}}V_{\text{m}}}{k_{\text{B}}T r^4}t,$$

$$\left(\frac{\Delta l}{l_0}\right)^3 = \frac{3D_{\text{Gb}}\delta_{\text{Gb}}\gamma_{\text{S}}V_{\text{m}}}{2k_{\text{B}}T r^4}t,$$

with D_{Gb} the coefficient of grain boundary diffusion, δ_{Gb} the constant thickness over which it occurs and k_{B} the Boltzmann constant. These equations show that neck growth relative to the grain radius occurs with $t^{1/6}$, linear shrinkage happens with $t^{1/3}$ and both are more excessive for small initial particle sizes. Note that the diffusion coefficient's temperature dependence is given by an Arrhenius-type equation:

$$D_{\Delta} = D_0 \cdot e^{-\frac{E_{\Delta}^{\Delta}}{k_{\text{B}}T}}. \quad (3.5)$$

D_{Δ} denotes the diffusion coefficient of the dominating densification mechanism (e.g. Δ = grain boundary diffusion, surface diffusion,...), D_0 is a pre-exponential factor and E_{Δ}^{Δ} is the activation energy of corresponding diffusion mechanism.

Intermediate stage

The intermediate stage of sintering covers the largest interval of the sintering progress. Within this stage, relative densities up to 0.9 are achieved. In general, the model describing this stage differs for polycrystalline and amorphous powders. Since boron nitride is polycrystalline, the focus is set on the former type. Coble proposed a geometrical model within which the powder is idealized by space-filling, bcc-packed tetrakaidecahedral grains, each having an equal size [114]. The pores are considered to be cylindrical, with their axis located on the edges of the grains, and extending along the entire edge. Densification is considered to occur through equal, radial pore shrinkage until it becomes unstable and

begins to isolate. The densification rate which is usually used to express the sintering kinetics, relates to the pore shrinkage via $\frac{d\Phi}{dt} = -\frac{d\rho_r}{dt}$, and it can be derived for lattice and grain boundary diffusion [110, 111]:

$$\frac{1}{\rho_r} \frac{d\rho_r}{dt} \propto \begin{cases} \frac{D_L}{G^3 T}, & \text{lattice diffusion,} \\ \frac{D_{Gb}}{\Phi^{1/2} G^4 T}, & \text{grain boundary diffusion.} \end{cases} \quad (3.6)$$

Note that the models used for the derivation, assume a constant grain size during the sintering progress. In reality, grains may grow during the thermal treatment, which then needs to be considered in the derivation of the equations above. Equation (3.6) elucidates that the relative densification rate depends drastically on the grain size.

Final stage

As stated earlier, the final stage of sintering begins when the pores disconnect from each other and become isolated. Pore shrinkage continues until all of the porosity disappears, resulting in a fully dense body. The final stage of sintering is characterized by relative densities exceeding 0.90, and the microstructural development can occur via several modalities [111]. However, since it is not the objective of this thesis to obtain a rigid powder compact in the final stage of sintering, the reader is referred for more information to comprehensive descriptions [110–112].

3.2.3 Grain growth

It was introduced that the fundamental phenomena during sintering are densification and grain growth. However, the aforementioned mechanisms described the sintering process assuming a constant grain size throughout the densification curve. In reality, the densification of polycrystalline powder compacts occurs with simultaneous coarsening of the microstructure. Both phenomena are very complex and difficult to model, which makes a combined theoretical description very difficult. R. M. German summarized some phenomenological observations of combined densification and grain growth (or coarsening), where the most relevant in the context of this thesis are [115]:

1. Grain growth accelerates with increasing ρ_r ($\frac{dG}{dt}$ is slow up to 0.7 ρ_r);
2. Coalescence, i.e. merging of two grains actively contributes to coarsening;
3. Smaller initial G have a higher contribution to grain growth;
4. Wide initial particle size distributions with a large fraction of small particles have faster grain growth;

5. Second phases, including pores, mitigate grain growth;
6. Pore growth occurs late during the sintering progress;
7. Smaller grain sizes are observed when more porosity or second phase is present.

Grain growth occurs in both dense and porous polycrystalline solids, and generally, it can be divided into two groups: *normal* and *abnormal* grain growth. [110, 111]. The former type is characterized by an average increase in grain size, but sizes and shapes remain in a relatively narrow range, whereas abnormal growth is typically outlined by the development of a few large grains which grow fast by consuming smaller neighboring grains. Generally, grain growth is driven by the reduction of free energy, following the reduction of the total grain boundary area [111, 112], which is in fact identical to the driving force of sintering, assuming no external pressure and no reactive sintering.

The considerations for porous powder compacts differ to some extent compared to fully dense bodies, since both grains and pores increase at the expense of their quantity with prolonged annealing time. Moreover, pore and grain boundaries interact with each other, resulting in pore migration during the coarsening process [111]. As this thesis deals with the processing of a porous ceramic, the following description is limited to such cases.

Grain growth in porous solids

Grain growth in the initial stage of sintering is limited, and becomes very prominent towards the end of the intermediate and during the final stage. However, it can occur during the early stage, mainly due to surface diffusion and vapor transport, and these early changes in the powder compact's microstructure have significant impact on the consecutive microstructural evolution [111]. Porous solids present grains that are interpenetrated by a (possibly complex) pore network, which is very difficult to model. So far, no detailed analysis of the coarsening process has been established. The kinetics (or thermodynamics) are thus examined on a more qualitative level, assuming an idealized microstructure comprising almost spherical pores on an isolated grain boundary [111]. Depending on the mechanisms (e.g. pore mobility, surface diffusion, grain boundary diffusion, etc.) the rate of grain growth $\frac{dG}{dt}$ follows [110, 111, 115]:

$$\frac{dG}{dt} = \frac{K}{TG^\alpha}, \quad (3.7)$$

where α is a mechanism-dependent exponent ranging between 2 and 4, and K is the grain growth rate parameter:

$$K = K_0 \cdot e^{-\frac{E_A^{Gg}}{k_B T}}, \quad (3.8)$$

with K_0 the pre-exponential frequency factor, comprising the atomic vibration frequency and other parameters such as diffusivity, molar volume, etc. E_{Gg} is the grain growth's activation energy.

Conclusion

With the information that was presented in Section 3.2, it is possible to draw conclusions regarding the fabrication of a rigid, porous BN powder compact with controlled microstructure. As outlined above, it is not desired to obtain a fully dense body, i.e. a powder compact that entered the final stage of its densification curve (Fig. 3.5). Hence, very high sintering temperature and long annealing times should be avoided (refer to Eqs. (3.3) and (3.4)). While small G are certainly desired with respect to short ^{11}C diffusion times, very small initial particle sizes are not necessarily beneficial, as densification and grain growth rate are likewise enhanced (see Eq. (3.7)). Instead, since the densification's driving force is considerably increased when applying an external pressure:

$$\frac{d\rho_t}{dt} \propto (\Sigma + P_{\text{ex}}),$$

whereas the grain growth rate remains unaffected: $\frac{dG}{dt} \approx \dot{G}_s$, pressure-assisted sintering is a possibility to ensure quickly a certain degree of densification, while minimizing grain growth. Σ denotes the *sintering stress*, which is proportional to the driving force of solid state sintering without external pressure P_{ex} , which originates from the reduction of the free surface energy E_S due to the curvature of the particle surfaces. $\dot{G}_s$ is the grain growth rate due to such a sintering modality, which, in fact, originates likewise from the surface free energy reduction. Furthermore, Equation (3.5) and (3.8) illustrate that in conditions where the activation energy of densification is higher than that of grain growth, fast heating, short annealing times and rapid cooling can mitigate grain growth at lower temperatures during powder processing.

All these characteristics can be achieved by spark plasma sintering, which therefore will be briefly introduced in the following.

3.3 Spark plasma sintering

Spark Plasma Sintering (SPS) is a field- and pressure-assisted sintering technique, using high dc currents and low voltages for the thermal treatment and fabrication of powder compacts. SPS is similar to HP, in the sense that they both can provide an uniaxial external pressure for densification rate enhancement, where the powder is stored and confined in a punch/die system (see Fig. 3.6). However, they differ fundamentally concerning the heat production and transmission to

the powder [112, 116]. High pulsed dc currents, typically ranging between 1 and 10 kA, are generated and transmitted through the punch/die system to the sintering material. Very high heating and cooling rates of $1000\text{ }^{\circ}\text{C min}^{-1}$ and $400\text{ }^{\circ}\text{C min}^{-1}$, respectively, can be achieved, enabling fast firing sintering cycles [116]. This is especially beneficial for systems where the dominant densification mechanism (e.g. grain boundary and lattice diffusion, refer to previous sections) has a higher activation energy compared to the coarsening mechanism (e.g. surface diffusion). The rapid heating reduces possible grain growth at lower temperatures, and reduces the overall sintering time at high temperatures, retarding coarsening. As stated earlier in this chapter, external pressure enhances densifying mechanisms, such as grain boundary and lattice diffusion while not affecting the coarsening mechanisms. Thus, only the densification rate is enhanced, and the time spent at maximum temperature is reduced, retarding grain growth [112, 116].

Figure 3.6 shows a schematic illustration of a SPS apparatus. The powder is loaded in a punch/die system, which is placed between two pistons that uniaxially provide the pressure, with maximal loads ranging between 50 to 250 kN, to the sintering material. The whole system is sealed in a water cooled vacuum chamber, which can provide low pressure ($10^{-1} - 10^{-2}$ mbar), inert (Ar, N₂) and reducing (H₂-mixtures) atmospheres. The current is generated by the electrodes and is transmitted by the conducting tooling materials to the powder [116]. Since temperature control is essential in this technique, thermocouples and/or pyrometers are used for monitoring. Pyrometers usually measure temperatures exceeding $450 - 600\text{ }^{\circ}\text{C}$, which is why often both types are used. Temperature monitoring is best performed, by focusing the pyrometer above the sample center (axial measurement), and placing a thermocouple in a radial hole within the die (Fig. 3.6).

The concept of using a dc pulsed current for heating, stems from a proposal claiming that a plasma is generated, which leads to the destruction of surface films, local temperature gradients, vaporization and sputtering phenomena. However, so far, the presence of a spark or plasma under typical SPS conditions was never detected [112, 116]. Thus, alternative notations, such as *Field-Assisted Sintering Technique* (FAST), are sometimes preferably used in literature. In fact, the field may have various effects on the sintering process, for instance by Joule heating (conductive powders) and electromigration which affect the mass transport (e.g. enhanced diffusivity, increased rates of phase formation and enhanced defect mobility) [112]. However, some of these effects require strong electric fields, which cannot be provided by the very low voltages used in SPS [116]. Moreover, one has to differentiate between conducting and non-conducting powders. The effects above mostly apply for the former type, as the current is (usually) not passing through the sintering material itself for

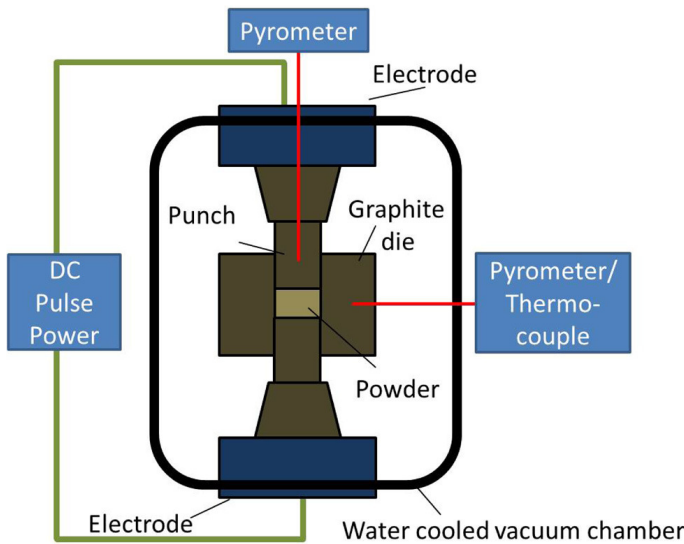


Figure 3.6: Schematic illustration of a typical SPS apparatus.

non-conductive materials. The exact influence of the electrical field is not yet fully understood. Since boron nitride is a very good electrical insulator, none of these effects are expected to play a role in the sintering process. For additional information the reader is therefore referred to more comprehensive descriptions in [112, 116].

3.4 Manufacturing of a porous BN target

The previous sections gave an overview of the fundamental mechanisms involved in solid state sintering. We can now utilize this knowledge for the fabrication of a porous BN powder compact with controlled microstructure. It is apparent that in the conventional application of sintering, fully dense bodies with small grain sizes are desired. While the latter is certainly likewise required for the BN ISOL-target, advanced progress with respect to BN's densification curve (Fig. 3.5) needs to be avoided. It was therefore necessary to explore the sintering behavior of BN in a different modality as it is usually performed and reported in literature. For this purpose, three h-BN powders from different suppliers and concomitant particle size distributions were obtained. Table 3.3 lists these powders and some of their properties. SPS was chosen as sintering technique due to its advantages with respect to microstructural control, as stated in Section 3.3. To find the most suitable sintered BN target, in consideration with its

ID	BNM	BNA	BNG
Supplier	Momentive Grade HCP	Asbury BTBN5003	Goodfellow
Particle size ^(a) [μm]	8.3 (d_{50})	2.5 (d_{50})	10 (max)
Surface area ^(a) [$\text{m}^2 \text{g}^{-1}$]	13	17	n/a
Purity [%]	~ 99.5	99	n/a
Impurities [%]	O: 0.456 ^(a) , C: 0.03, and others	O: 0.8, C: 0.02, and others	n/a
^(a) Measured by the supplier			

Table 3.3: Overview of the boron nitride powders, and some of their properties, used for the fabrication of porous BN SPS pre-sintered powder compacts.

application in this thesis, several sintering cycles were explored. Note that since this thesis' definition of 'sintered' differs from the conventional application of sintering, as from now, the final product is referred to as *pre-sintered* BN.

As a starting point, the work of C. Steinborn et al. was consulted, who studied the microstructure, densification and electrical properties of different BN products, including a commercial h-BN powder, processed by SPS [117]. In detail, SPS cycles with T_{max} and P_{ex} ranging between 1500 – 1900 °C and 10 – 50 MPa, respectively, were tested. The highest reported porosity was around 25%.

In this work, the effect of varying maximum temperature $T_{\text{max}} = 1600, 1700, 1800$ and 1900 °C, dwell-time $t_{\text{dwell}} = 5$ and 15 min at T_{max} , and the starting powder were investigated. Other parameters such as atmosphere (~ 2 mbar air pressure), external pressure ($P_{\text{ex}} = 25$ MPa), heating rate (100 °C min^{-1}) and cooling rate (~ 400 °C min^{-1}) were not altered. Since excessive densification must be avoided, P_{ex} is only applied during t_{dwell} at T_{max} . Figure 3.7 shows a schematic illustration of the SPS cycles that were investigated. The pre-sintered powder compacts were evaluated after firing by their rigidity, porosity and reproducibility. The following section will provide a brief description of the fabrication procedure.

3.4.1 Fabrication procedure

For the fabrication of the pre-sintered BN powder compacts, first, the raw powder of approximately 2.7 g was loaded into the punch/die system, which is displayed in Fig. 3.8a. This system comprised one cylindrical die with a 30 mm

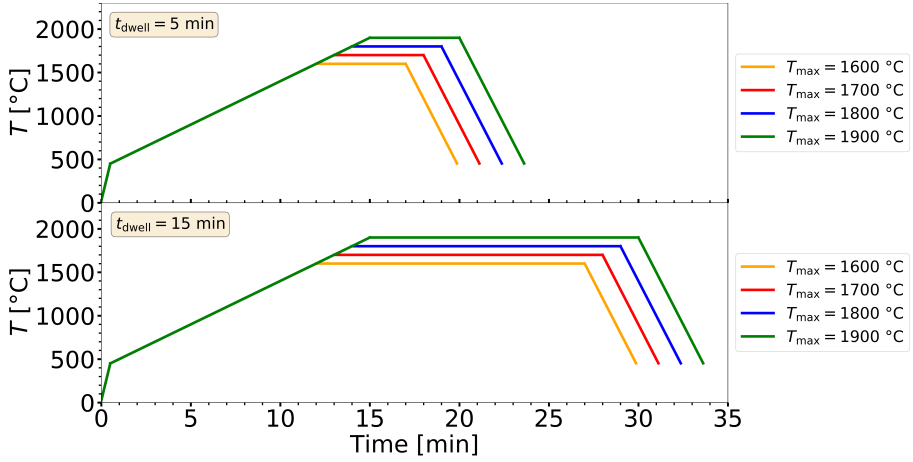


Figure 3.7: Schematic representation of the different sintering cycles tested for the fabrication of a porous SPS pre-sintered BN powder compact. Other parameters, such as heating rate ($100\text{ }^{\circ}\text{C min}^{-1}$), cooling rate ($\sim 400\text{ }^{\circ}\text{C min}^{-1}$), $P_{\text{ex}} = 25\text{ MPa}$ and atmosphere ($\sim 2\text{ mbar}$ air pressure) were not altered. Note that the external pressure was only applied during the dwell-time at maximum temperature.

extrusion, and two punches of equivalent diameter. Both shapes were made from graphite. To prevent sticking of the powder to the graphite assembly during firing, a thin graphite coating was placed between the walls of the die and on top of the punches. Subsequently, the powder was compressed using a hydraulic press, yielding a green body (Fig. 3.8c) with $\rho_{\text{green}} = 1.241(22)\text{ g cm}^{-3}$, $\rho_r = 0.577(21)$ and $\Phi = 0.423(21)$ ¹, determined from mass and geometry. Prior firing, a 'heat jacket' made from graphite foam (3.8b (right)) is put around the assembled system to reduce temperature mitigation due to radiative cooling. Subsequently, the system is placed in between the two pistons of the SPS apparatus, as shown in Figure 3.8e. Two thermocouples provide temperature readout for $T < 450\text{ }^{\circ}\text{C}$, since the pyrometer used in this machine is only able to measure temperatures above this limit. The three different BN powders, summarized in Table 3.3, were pre-sintered using the aforementioned sintering parameters that are schematically presented in Figure 3.7. Once the 'active' cooling ($t \sim 3\text{ min}$) was completed, the assembly was still at temperatures between $500 - 600\text{ }^{\circ}\text{C}$. The remaining heat was reduced via radiative cooling, before the sample could be accessed. After the temperature treatment it was observed that a thin layer of the pre-sintered powder compact had turned

¹Determined for the BNM powder, with $\rho_{\text{th}} = 2.15(7)$ provided by the supplier.

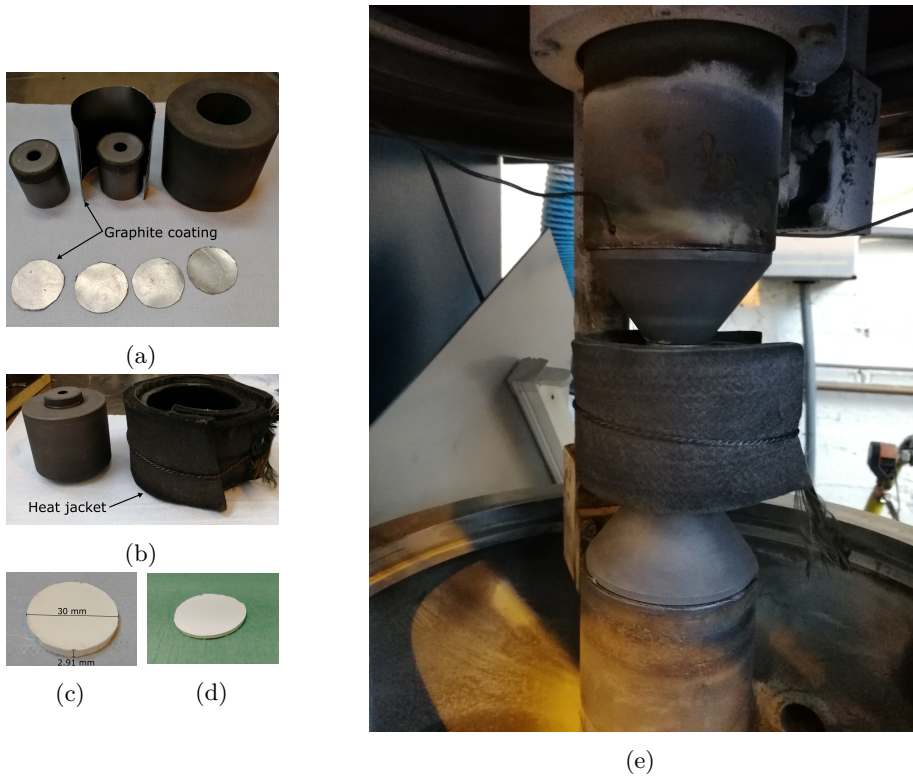


Figure 3.8: (a) Punch/die system into which the BN powder is loaded. (b) Punch/die system containing the compressed powder and compressed prior sintering. The graphite foam which is shown on the right side of the picture is used to shield the assembly from radiation cooling during the sintering process. (c) Momentive BN powder green body. (d) Image of a SPS pre-sintered BN powder compact after dry grinding. (e) SPS apparatus used for the fabrication of pre-sintered BN targets.

greyish, indicating carbon diffusion into the sample. This layer was removed by dry grinding, resulting in a white monolith (see Fig. 3.8d).

3.4.2 BN sintering cycle selection and microstructural characterization

The cycle probing $T_{\max} = 1600$ °C did not show satisfactory results in terms of rigidity and reproducibility for any of the tested dwell-times t_{dwell} , and is therefore excluded. All other cycles yielded acceptable pre-sintered BN powder

compacts in terms of these two categories, whereas the Momenive powder seemed to have the best reproducibility. Note that hereupon the Momenive, Asbury and Goodfellow powders are referred to as **BNM**, **BNA** and **BNG**, respectively. The BNG samples presented in some trials, especially at the higher sintering temperatures, a yellowish color, which origin was not determined.

X-ray diffraction - BN structure

To identify whether the sintered targets present macroscopic impurities after the fabrication process, and to prove their hexagonal crystalline structure, *X-Ray Diffraction* (XRD) patterns were recorded for further evaluation of the investigated sintering cycles (refer to Fig. 3.7). Figure 3.9 shows the recorded XRD scans of the individual BNM cycles ($T_{\max} = 1800\text{ }^{\circ}\text{C}$, $t_{\text{dwell}} = 15\text{ min}$ is missing). From these graphs we can extract that the polycrystalline crystal structure of h-BN is retained, and that no macroscopic impurity is present after sintering. Moreover, maximum sintering temperature and dwell-time seem not to have an effect on the product's structure. The most probable impurity one would expect is graphite, which diffused into the material's bulk from the punch/die system during the fabrication process (see Sec. 3.4). However, boron

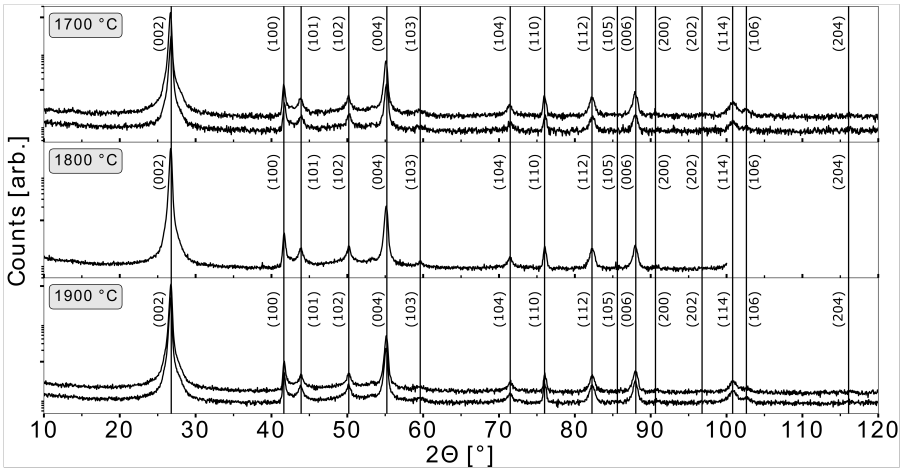


Figure 3.9: XRD scans of pre-sintered BN powder compacts obtained from various BNM sintering cycles. In each subfigure, the lower and upper curve correspond to $t_{\text{dwell}} = 5, 15\text{ min}$, respectively. Note that for $T_{\max} = 1800\text{ }^{\circ}\text{C}$ only $t_{\text{dwell}} = 5\text{ min}$ was recorded. The vertical lines represent the Miller indices for h-BN (PDF 34-0421), consulted from the International Centre for Diffraction Data [118].

nitride and graphite have the same crystal structure – BN is sometimes referred to as ‘white’ graphite – which is why the diffraction angles of the most intense peaks are almost identical². It is therefore impossible to resolve a potential graphite contamination by XRD measurements. Nevertheless, imagining that carbon diffused into the sample’s bulk, one can conclude that B_4C is not formed during the heat treatment ($2\Theta(B_4C) = 37.85^\circ$), which, as discussed in Section 3.1, would prevent ^{11}C to be released from the target. The XRD patterns for the BNA and BNG samples look very similar, and since no additional information can be extracted from the XRD patterns which are relevant for the objective of this thesis, the remaining scans are not presented henceforth.

It was previously stated that the different sintering cycles and starting powders were evaluated by their rigidity, porosity and reproducibility. This section reports on the porosity determination of the corresponding SPS pre-sintered BN powder compacts, the selection of the most suitable SPS cycle for the development of a porous BN target, as well as its microstructural characterization.

These aspects are comprised in Article II, which was sent for peer-review, and which will be presented in Chapter 5. The remaining part of this section is an extended version of the corresponding excerpt of Article II, i.e. Section III.1, with expanded descriptions of measuring techniques and their results. To ensure an appropriate integration into this chapter, some paragraphs required adjustment. The following section is therefore not a verbatim copy.

Article II: III.1. Boron nitride target characterization

III.1.1 Porosity determination

Porosity, i.e. the ratio between the void space and the total volume (bulk volume), relates to a material’s *bulk density* ρ_{bulk} and *theoretical density* ρ_{th} :

$$\Phi_{\text{total}} = \frac{V_{\text{void}}}{V} = 1 - \frac{\rho_{\text{bulk}}}{\rho_{\text{th}}} = 1 - \rho_r. \quad (3.9)$$

As introduced in Section 3.2, neck growth and densification, which occur during sintering, can result in the isolation of pores, which are therefore not connected to the bulk surface. Such pores are called closed pores and their corresponding volume relates to the *closed porosity* Φ_{closed} . Analogous, pores that are connected to the surface are related to the *open porosity* Φ_{open} . These parameters correlate via the equation:

$$\Phi_{\text{total}} = \Phi_{\text{open}} + \Phi_{\text{closed}}. \quad (3.10)$$

²The most intense peaks are at $2\Theta(\text{BN}) = 26.79^\circ$ and $2\Theta(\text{C}_2) = 26.40^\circ$, respectively.

A high total porosity comprising as much open pores as possible is beneficial when discussing the release process of an isotope that is produced in a nuclear reaction during target irradiation. This will be further discussed in Chapter 5.

Archimedes' principle - total porosity

To assess the total porosity of the pre-sintered compacts, it was necessary to determine the sample's bulk density ρ_{bulk} . For this purpose, the Archimedes' principle was applied, measuring the weight of the displaced fluid $m_{\text{fl}}^{\text{displ}}$ of known density ρ_{fl} , when immersing a sample of mass m_{s} . In this way, the bulk density can be calculated using:

$$\frac{\rho_{\text{bulk}}}{\rho_{\text{fl}}} = \frac{m_{\text{s}}}{m_{\text{fl}}^{\text{displ}}} = \frac{m_{\text{s}}}{m_{\text{s}} - m_{\text{s}}^{\text{fl}}},$$

since $m_{\text{fl}}^{\text{displ}}$ multiplied with the gravitational acceleration, equals the buoyancy force. m_{s}^{fl} is the measured weight of the sample, when immersed in the fluid. To account for additional buoyancy effects when weighed in air, the above written equation becomes to:

$$\rho_{\text{bulk}} = \frac{m_{\text{s}} \cdot (\rho_{\text{fl}} - \rho_{\text{air}})}{C(m_{\text{s}} - m_{\text{s}}^{\text{fl}})} + \rho_{\text{air}}. \quad (3.11)$$

C is a correction factor that accounts buoyancy effects of parts of the measuring apparatus, which are likewise immersed in the fluid. Typically, water or ethanol are used for this principle, however, since BN reacts with both substances, an additional step had to be included, which ensured that the BN samples are not in contact with the fluid. For this purpose, the samples were coated in a lacquer (Enthone - Enplate Stop-off No. 1) with density ρ_{l} . As a consequence, one could calculate the sample's density using:

$$\rho_{\text{s}} = \frac{m_{\text{s}}}{\frac{m_{\text{s}+1}}{\rho_{\text{s}+1}} - \frac{m_{\text{l}}}{\rho_{\text{l}}}}, \quad (3.12)$$

$$\rho_{\text{s}+1} = \frac{m_{\text{s}+1}(\rho_{\text{fl}} - \rho_{\text{air}})}{C(m_{\text{s}+1} - m_{\text{s}+1}^{\text{fl}})} + \rho_{\text{air}}, \quad (3.13)$$

with $m_{\text{s}+1}$, $\rho_{\text{s}+1}$ and $m_{\text{s}+1}^{\text{fl}}$ the mass, density and measured mass of the coated sample immersed in the fluid, respectively. m_{l} is the mass of the coated lacquer. To ensure the highest possible accuracy, the lacquer's density needed to be measured before measuring the BN samples' densities. This was achieved by applying the same approach, however, replacing the BN sample by an object of known density. In this case, a brass-piece was used, which density could be measured by the original Archimedes' principle (Eq. (3.11)). Three brass-pieces

were coated with the lacquer and dried for 24 h in air. The Archimedes' principle was applied and the density ρ_l was calculated using Eqs. (3.12) and (3.13), where one has to substitute the BN sample's contributions (ρ_{s+l} , ρ_s , m_s) with the brass' parameters (ρ_{b+l} , ρ_b , m_b). In this way, the corresponding densities $\rho_b = 8.398(7) \text{ g cm}^{-3}$ and $\rho_l = 1.313(19) \text{ g cm}^{-3}$ were obtained for brass and lacquer, respectively. With known ρ_l , the bulk densities of the sintering cycles illustrated in Figure 3.7 can be determined. The measurement values used for this derivation can be found in Table A.3 in Appendix A.2.

Helium-gas pycnometry - open porosity

According to Equation (3.10) the open porosity can be determined by measuring the closed porosity, which corresponds to:

$$\Phi_{\text{closed}} = 1 - \frac{\rho_{\text{apparent}}}{\rho_{\text{th}}}. \quad (3.14)$$

ρ_{apparent} is the *apparent density*, which correlates to the material's skeleton volume plus closed pore volume. The apparent density was measured by helium-gas pycnometry (*Multipycnometer*, *Quantachrome*), which measures the apparent volume employing the Archimedes' principle and Boyle's law of gas expansion. This technique uses the pressure difference that results from allowing the gas from a pressurized reference cell with known volume V_R to expand into the sample cell holder V_C , whose volume is known as well. Assuming ideal gas

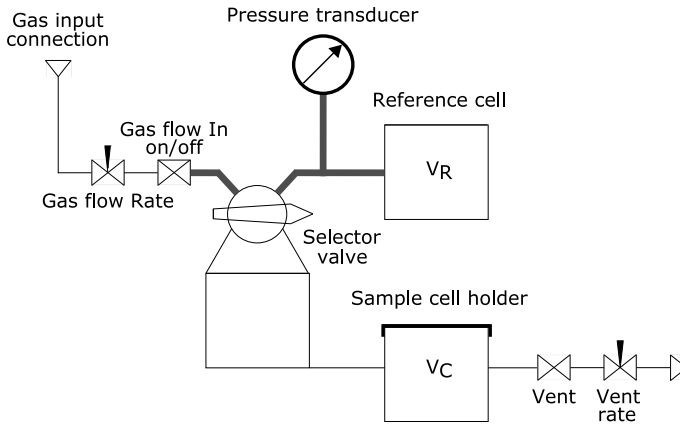


Figure 3.10: Schematic representation of the He-gas Quantachrome multipycnometer used to measure the apparent density ρ_{apparent} of the SPS pre-sintered BN powder compacts.

conditions, one can show:

$$V_S = V_C - V_R \left[\frac{P_i}{P_f} - 1 \right],$$

where P_i and P_f are the recorded pressure of the initially filled reference cell and after the gas is allowed to expand into the cell housing the sample, respectively. The gas which is pressurized above ambient pressure is able to penetrate the open pores of the sample, thus probing the sample's apparent volume. To ensure high accuracy, gases with small atomic volume are typically used, such that infiltration of very fine pores is possible. Thus, often helium is employed, as it was the case in this thesis. Figure 3.10 shows a schematic illustration of the multipycnometer used in this case.

Results

The results of the pre-sintered BNM, BNA and BNG bulk density ρ_{bulk} measurements, assessed by the Archimedes' principle, are presented in Table 3.4. The complete data set, comprising the measured variables (refer to Eqs. (3.12) and (3.13)), and uncertainty calculation are presented in Appendix A.2 and A.1. Using ρ_{bulk} , the relative density ρ_r and porosity Φ can be calculated (Eq. (3.10)). These results are shown in Table 3.5 and visualized in Figs. 3.11 and 3.12. Note that for completeness, the measured ρ_{bulk} of the individual runs are plotted in Figs. 3.11b and 3.12b, which were used to calculate the average bulk density, and based on that ρ_r and Φ .

First, the influence of $t_{\text{dwell}} = 5$ and 15 min was investigated by pre-sintering two to three BNG samples for each T_{max} . The results indicate that longer holding time during maximum sintering temperature, results in an increased densification. This is in agreement with the expectations of the sintering theory (refer to Eqs. (3.3), (3.4) and (3.6)), which predicts that densification scales with sintering time. The determined ρ_r indicate that the densification progress of the pre-sintered samples was interrupted sometime between the initial and

T_{max} [°C]		1700	1800	1900
	t_{dwell} [min]	ρ_{bulk} [g cm ⁻³]		
BNG	15	1.598(18)	1.521(18)	1.462(22)
BNG	5	1.516(21)	1.462(20)	1.414(23)
BNM	5	1.290(50)	1.395(16)	1.397(25)
BNA	5	1.319(20)	1.330(70)	1.320(90)

Table 3.4: Bulk densities ρ_{bulk} of pre-sintered BN powder compacts, processed by different SPS cycles, and measured using the Archimedes' principle.

$T_{\max}$ [°C]	t_{dwell} [min]	1700			1800			1900		
		ρ_r	Φ	ρ_r	Φ	ρ_r	Φ	ρ_r	Φ	ρ_r
BNG	15	0.743(26)	0.257(26)	0.707(24)	0.293(24)	0.680(24)	0.320(24)	0.680(24)	0.320(24)	0.680(24)
BNG	5	0.705(25)	0.295(25)	0.680(24)	0.320(24)	0.658(24)	0.342(24)	0.658(24)	0.342(24)	0.658(24)
BNM	5	0.600(30)	0.400(30)	0.649(22)	0.351(22)	0.650(24)	0.350(24)	0.650(24)	0.350(24)	0.650(24)
BNA	5	0.614(22)	0.386(22)	0.620(40)	0.380(40)	0.610(50)	0.390(50)	0.610(50)	0.390(50)	0.610(50)

Table 3.5: Relative densities ρ_r and total porosities Φ of pre-sintered BN powder compacts, processed by different SPS cycles, and determined from the measured bulk density ρ_{bulk} (refer to Tab. 3.4)

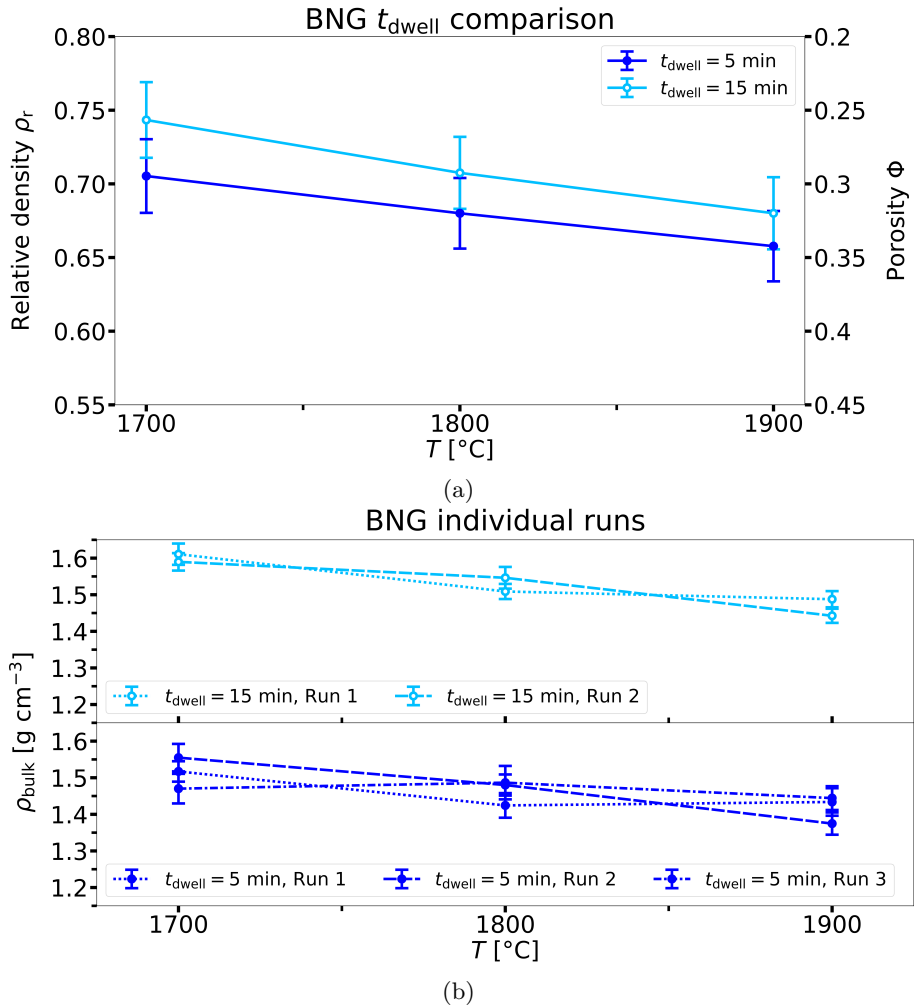


Figure 3.11: (a) Comparison of the dwell-time's t_{dwell} effect on the relative density ρ_r and porosity Φ of BNG SPS pre-sintered powder compacts. The values were calculated from the averaged bulk density ρ_{bulk} , determined from density measurements using the Archimedes' principle (b).

early start of the intermediate stage, which is precisely what was engaged. In the case of BNG, one observes a decrease of ρ_r when T_{max} is increased. This might be at first surprising, as the diffusion coefficients involved in the sintering process depend exponentially on the temperature (see Eq. (3.5)).

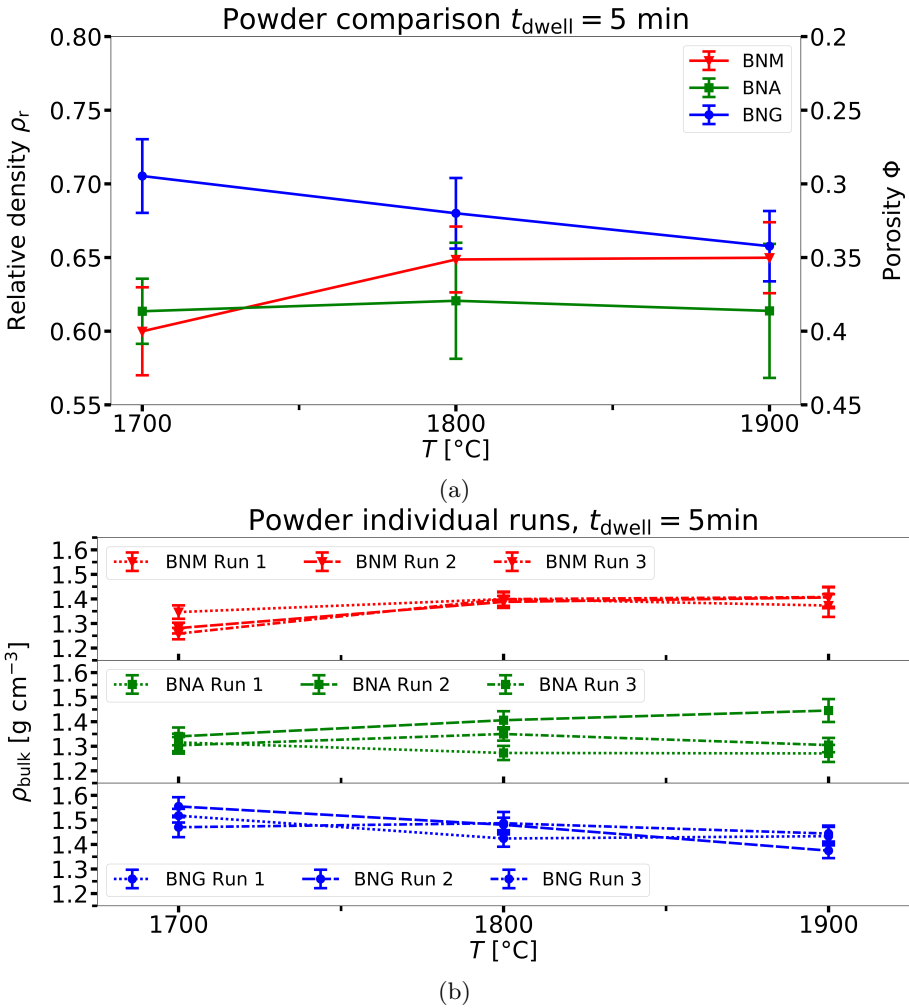


Figure 3.12: Comparison of the starting powder's effect (BNG, BNM, BNA) on the relative density ρ_r and porosity Φ of SPS pre-sintered powder compacts, employing a dwell-time $t_{\text{dwell}} = 5 \text{ min}$. The values were calculated from the averaged bulk density ρ_{bulk} , determined from density measurements using the Archimedes' principle (b).

Consequently, with higher T_{max} the densification rate should be enhanced. On the other hand, the aforementioned equations show that the sintering progress is inversely proportional to the temperature. Consequently, the activation

energy's magnitude of the dominant diffusion mechanism would determine whether increasing sintering temperature rather results in an increasing or decreasing densification. However, the measurement uncertainty hinders to draw a definite conclusion. Moreover, the relative density of BNA and BNM as a function of $T_{\max}$ do not show the same trend (Fig. 3.12). Nevertheless, we can conclude that $t_{\text{dwell}} = 5$ min is favorable compared to $t_{\text{dwell}} = 15$ min as the total porosity is higher in the former case.

Comparing the effect of the employed starting powders and $T_{\max}$ on the final porosity, it seems that BNG yields less favorable results. Although, at higher temperatures, this feature is less prominent due to the measurement uncertainties. Considering that much less information regarding particle size and purity is present, BNG is excluded. With the given measurement uncertainties, no clear trend or advantage of BNM and BNA can be identified. BNA seems to have a larger uncertainty spread, whereas Φ remains relatively constant across the investigated temperature range. However, since diffusion and grain growth $\frac{dG}{dt}$ (Eq. (3.8)) are both strongly enhanced by higher temperatures, the lowest $T_{\max}$ is favored, to reduce possible graphite diffusion of the SPS tools (graphite-die, punch and coating) into the bulk target, as well as potential grain coarsening. Since BNM seemed to yield a slightly better result regarding overall rigidity and reproducibility, the following sintering cycle was selected: BNM, $t_{\text{dwell}} = 5$ min, $T_{\max} = 1700$ °C, $P_{\text{ex}} = 25$ MPa during dwell-time, sintering atmosphere of ~ 2 mbar air pressure and a heating and cooling rate of 100 °C min^{-1} and ~ 400 °C min^{-1} , respectively.

Figure 3.13 shows the measured temperature profile (red), absolute piston travel (green) and applied force (blue) of the aforementioned selected SPS cycle. The temperature profile is constant until point A is reached, as temperatures with $T < 450$ °C cannot be measured by the pyrometer. During rapid heating, one observes a negative piston travel (point B), which is attributed to the thermal expansion of the SPS tools (die, punch, etc.), and possibly of the sample. After $T_{\max}$ is reached, the applied pressure is quickly increased from the base load (5 kN) to 17 kN, which corresponds to $P_{\text{ex}} = 25$ MPa (point C). During the dwell-time (point D), densification occurs, visible by the positive piston travel. The extent of the piston travel in that interval is only moderate, which is in agreement with the low density increase from $\rho_{\text{green}} = 1.241(22)$ g cm^{-3} to $\rho_{\text{bulk}} = 1.290(50)$ g cm^{-3} after sintering. Although, with the given measurement uncertainties it is possible that no densification occurs, and only neck growth is taking place.

Finally, the selected SPS pre-sintered BN powder compact was characterized regarding its open porosity Φ_{open} , employing a series of He-gas pycnometry measurements, yielding $\rho_{\text{apparent}} = 1.74(8)$ g cm^{-3} . The measured data set used to determine ρ_{apparent} can be found in Appendix

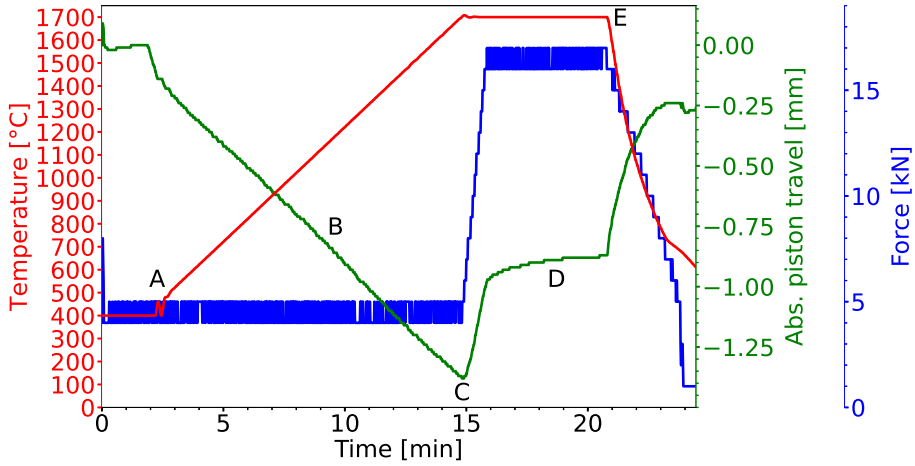


Figure 3.13: Measured temperature profile (red), piston travel (green) and applied pressure (blue) recorded during SPS pre-sintering a BNM powder compact. Point A: initiation of $100\text{ }^{\circ}\text{C min}^{-1}$ heating rate ($T = 450\text{ }^{\circ}\text{C}$); point B: negative piston travel due to thermal expansion of the SPS tools; point C: applying of pressure load P_{ex} ; point D: piston travel due to densification of BN during dwell-time; point E: initiation of $\sim 400\text{ }^{\circ}\text{C min}^{-1}$ cooling.

A.2. Applying the result of the measured bulk density, Equation (3.14) to correlate the apparent density to the closed porosity and Equation (3.10), we identify the following characteristics of the developed BN target:

$$\begin{aligned}\rho_{\text{bulk}} &= 1.30(10)\text{ g cm}^{-3}, & \Phi_{\text{total}} &= 0.40(5), \\ \rho_{\text{apparent}} &= 1.74(8)\text{ g cm}^{-3}, & \Phi_{\text{closed}} &= 0.19(5), \\ & & \Phi_{\text{open}} &= 0.21(7).\end{aligned}$$

Note that the uncertainty of the bulk density was rounded to the following digit to account for potential inaccuracies due to the coating procedure in the Archimedes' principle, which, for instance, could be deteriorated by embedded air reservoirs.

As the most suitable SPS cycle was identified, the target fabrication phase of the development process is completed. From this point forward, when addressing the developed BN target, it is thus referred to the respective SPS cycle, which was summarized on the previous page. While first BN target characterizations

with respect to its total and open porosity were conducted at this stage, a substantial understanding of the microstructural properties is essential for the examination of the isotope release mechanism. Hence, further characterizations concerning the average grain size and pore size of the developed porous SPS pre-sintered BN powder compact were performed and are presented henceforth.

III.1.2 Grain and pore size determination

Knowledge and control over the grain size during target operation are essential parameters influencing the release efficiency ε_{rel} . It can be shown that ε_{rel} is inversely proportional to the target's grain size, for isotope-target combinations where the release is governed by diffusion [119–121]. Thus, if the grain size G is increased by a factor of ten, the efficiency is reduced accordingly. As pointed out before, ISOL targets are operated at high temperatures to enhance diffusion and effusion processes, and thus the isotope release. Therefore, targets should desirably not present high grain growth rates at high temperatures, which otherwise would deteriorate the release efficiency.

Laser diffraction - BN powder particle size

Figure 3.14 shows the particle size distribution of the unprocessed BN powder, in the form obtained from the supplier, measured by laser diffraction using a *Beckman Coulter LS 13 320* particle sizing analyzer. The powder presents an arithmetic mean d_v and median particle diameter of $d_{v,50}$ ³:

$$d_v = \left[\frac{\sum_i v_i \cdot d_i^p}{\sum_j v_j \cdot d_j^q} \right]^{\frac{1}{p-q}} \quad \begin{matrix} p=1 \\ q=0 \\ \hline \end{matrix} 6.1 \mu\text{m},$$

$$d_{v,50} = \quad \quad \quad = 4.8 \mu\text{m},$$

where $v_{i,j}$ denotes the differential volume percentage of channel i or j . Note that particle size measurements by means of laser diffraction assume isolated (and spherical) particles, which is difficult to guarantee from a practical point of view. Thus, these results may rather indicate an agglomerate size, instead of a true particle size of the BN starting powder.

There are different techniques available to determine the particle or grain size of materials. To estimate the grain size in the pre-sintered BN powder pellet, nitrogen physisorption isotherms were applied, which are a powerful tool for material characterization and will be briefly introduced.

³The median of a particle size distribution is defined as the size where 50% of the particles present a larger and smaller diameter.

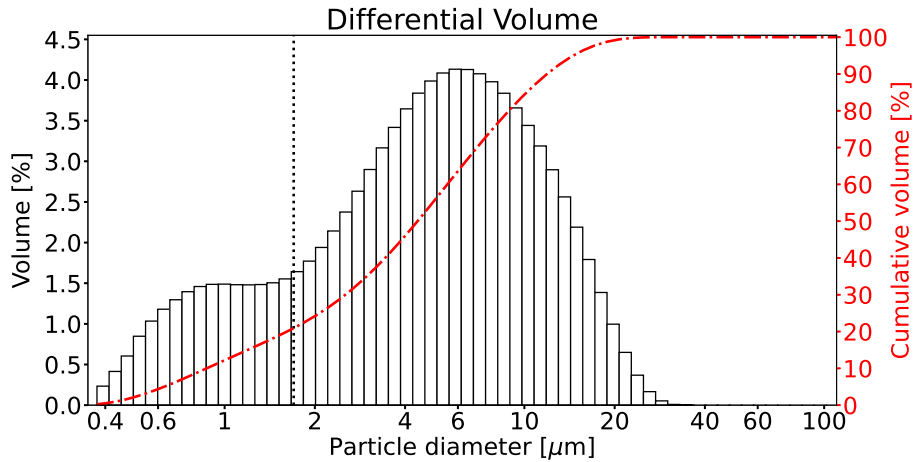


Figure 3.14: Particle size distribution of the dry boron nitride starting powder, as measured by laser diffraction. The vertical dotted line indicates the average particle or grain cluster size $\bar{G}_{\text{BET}} = 1.7(1) \mu\text{m}$, estimated from N_2 physisorption isotherms (Sec. III.1.2.1).

III.1.2.1 Nitrogen physisorption isotherms

Adsorption is a powerful experimental technique to probe material properties, for instance, the *Specific Surface Area* (SSA). Adsorption is the adhesion of an atom or molecule on a surface, at a pressure P [Pa] below the adsorbate's saturated vapor pressure P_0 [Pa]. In this context, an *adsorption isotherm* is defined as the amount of an adsorbate on a surface, at constant temperature and as a function of the relative pressure P/P_0 [122]. Usually, such adsorption isotherms feature characteristic shapes, for which a classification system was developed by J. H. de Boer and numbered by S. Brunauer et al. [123]. These classifications are commonly used in literature, and possess common interpretations [122]. Adsorption is a reversible process, i.e. a desorption isotherm can be recorded in the same manner. Adsorption-desorption isotherms typically exhibit characteristic shapes as well, where a hysteresis is often observed. Some characteristic hysteresis loop shapes are often found and therefore have been grouped into four types H1-H4 [124]. However, interpretation of these hysteresis loops should be considered with caution, as there is still ongoing research regarding the origin and the mechanisms involved in their creation [122]. Principally, isotherm data can provide information regarding pore size, pore shape and *Pore Size Distribution* (PSD), as there are several analytical techniques to interpret adsorption-desorption isotherms. In that regard, pore sizes are commonly classified by IUPAC into three groups [125]:

1. Micropores: pores with diameters smaller than 2 nm;
2. Mesopores: pores with diameters larger than 2 nm and smaller than 50 nm;
3. Macropores: pores with diameters larger than 50 nm.

However, isotherms can only provide information regarding micro- and mesoporosity, and is basically by definition unsusceptible to macroporosity, since pressures very close to P_0 would be required for pore filling, which cannot be measured reliably. In other words, systems that measure adsorption-desorption isotherms cannot distinguish between open surface adsorption and macroporosity.

For a better understanding regarding the pore structure of SPS pre-sintered BN powder compacts, adsorption isotherms using nitrogen as adsorbate at liquid nitrogen temperature ($T = 77.2$ K) were measured. This is a well established technique that allows to record the full adsorption-desorption isotherm. For this purpose, a high speed sorption analyzer *Quantachrome eNOVA2200* was used, which possesses two measuring cells. Prior to the analysis, samples were outgassed for at least 24 h at 300 °C, and the adsorption and desorption isotherms were recorded, using 34 and 26 measuring points, respectively. The

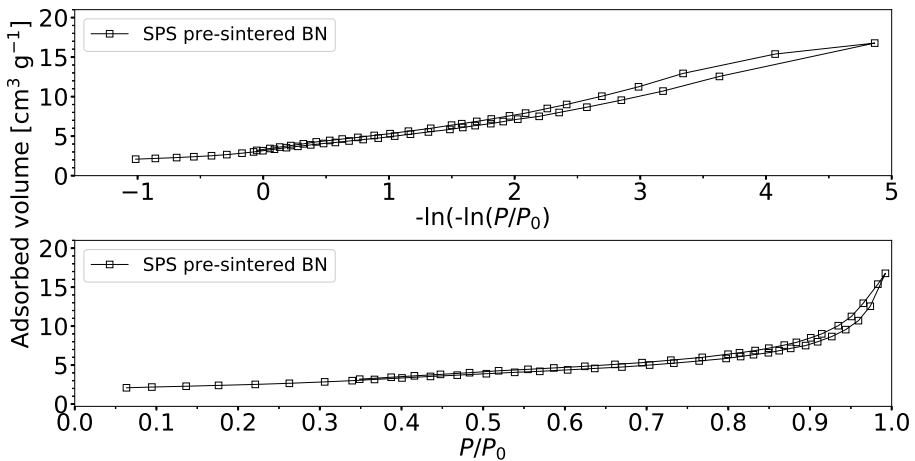


Figure 3.15: Nitrogen adsorption-desorption isotherm of a SPS pre-sintered BN powder compact, plotted as a function of the relative pressure P/P_0 (bottom), and shown in the standard curve representation, i.e. χ plot (top) [122]. The curves indicate a type II adsorption isotherm and a type H3 hysteresis loop, characteristic for non-porous, or macroporous materials with slit-like pores.

measurements were carried out in high precision mode (0.05 torr pressure tolerance and 180 s equilibration time [126]). To ensure higher precision, P_0 was measured simultaneously in the second cell, for every third measurement point. Figure 3.15 shows a measured isotherm of a SPS pre-sintered BN powder compact, as a function of the relative pressure P/P_0 (bottom) and in the so-called standard curve representation or χ plot, which is recommended to use for the isotherm classification [122]. The curve indicates a type II adsorption isotherm with type H3 hysteresis loop, which are believed to be the result of non-porous, or macroporous materials with slit-like pores.

From the isotherm data, the SSA was determined using the *Brunauer-Emmet-Teller* (BET) method, and information regarding the PSD and pore volume was deduced from the desorption isotherm using the *Barrett-Joyner-Halenda* (BJH) technique, which is sensitive to mesoporosity. For a detailed description of these methods we refer to [122, 126]. First, the PSD and total pore volume, determined by the BJH method, shall be discussed. Fig. 3.16 indicates an apparent total pore volume $V_p^{\text{tot}}/m_{\text{sample}} = 0.024 \text{ cm}^3 \text{ g}^{-1}$ in the micropore and mesopore regions, and the PSD shows that mesoporosity is declining with a $1/x$ behavior over the meso-region. From the porosity measurements which are described in Section III.1.1, one can calculate the total pore volume $V_{\text{open}}/m_{\text{sample}} = \frac{\Phi_{\text{open}}}{\rho_{\text{bulk}}} = 0.162(55) \text{ cm}^3 \text{ g}^{-1}$ that is accessible to nitrogen physisorption isotherms. Thus, we can conclude from these findings that only 15% of the open pore volume comprises micro and mesopores, and the remaining 85% are composed of macropores. Moreover, a median pore size of $D_{V,50}^{\text{N}_2\text{PI}} = 26 \text{ nm}$ can be deduced from the cumulative pore volume, which however, may not be representative since the majority of the pore volume is expected in the macroporous region.

The analysis of the isotherm data using the BET method yielded a $\text{SSA} = 8.3(4) \text{ m}^2 \text{ g}^{-1}$, which is close to the $\text{SSA} = 13 \text{ m}^2 \text{ g}^{-1}$ of the BN starting powder, as provided by the supplier. Any degree of sintering will result in a decreasing SSA, since the initial stage is accompanied by neck formation between the material grains, which consequently reduces the SSA. A model which relates a powder's SSA to its average particle size was developed by R. M. German to estimate the number of particles in agglomerates [127], and was employed to estimate the average particle or grain cluster size in SPS pre-sintered BN:

$$\bar{G}_{\text{BET}} = \frac{K}{\text{SSA} \cdot \rho_{\text{th}}}. \quad (3.15)$$

K is a geometrical factor which derives from the surface area to volume ratio, SSA denotes the specific surface area measured using the BET method and ρ_{th} is the material's theoretical density. Note that this model assumes fully dense, isolated particles, such that the N_2 gas can assess most of the available surface

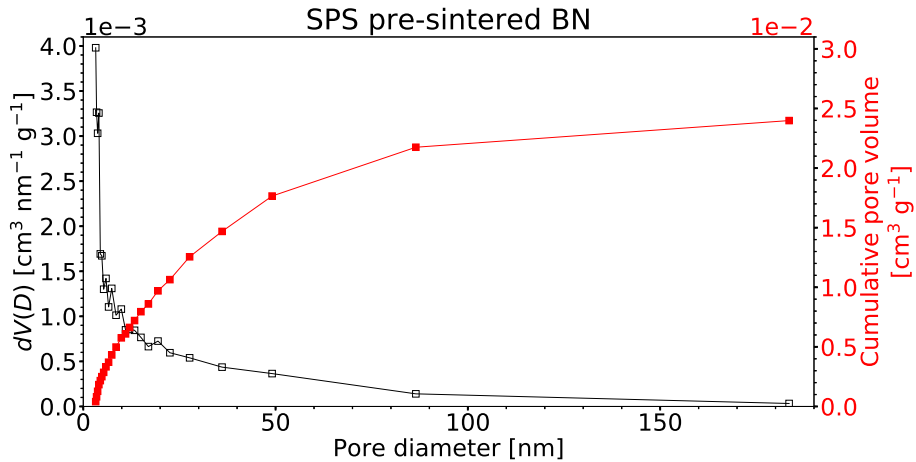


Figure 3.16: Pore size distribution (PSD) $dV(D)$ ($\square$) and cumulative pore volume ($\blacksquare$) of a SPS pre-sintered BN powder compact, obtained from a nitrogen desorption isotherm, using the BJH method.

area [127]. The porosity measurements (refer to Sec. III.1.1) show that the BN's sintering process was interrupted at an early stage, as the green body's density increased by less than 5%. As a result, it is likely that only moderate neck formation occurred, transforming the starting powder's particles into grains, which is considered to be reasonably compliant with the above written assumptions. However, the porosity measurements also indicate a relatively large closed porosity, i.e. isolated volume. Therefore, we replace ρ_{th} in Eq. (3.15) with the apparent density $\rho_{\text{apparent}} = 1.74(8) \text{ g cm}^{-3}$ to exclude the inaccessible pore volume.

Figure 3.17 shows *Scanning Electron Microscope* (SEM) images of the SPS pre-sintered BN's surface (Fig. 3.17a) and fractured region when breaking the sample (Fig. 3.17b), and illustrates that boron nitride particles possess a flake-like geometry, very similar to graphite. According to R. M. German [127] such particle shapes correspond to a geometry factor $K = 24$. Thus, one obtains $\bar{G}_{\text{BET}} = 1.7(1) \mu\text{m}$, which is considered as a rough approximation of the target's average particle or grain cluster size. This result deviates to some extent from the particle size distribution of the BN starting powder (Fig. 3.14), measured by laser diffraction, with larger particle diameters. However, the SEM images of the porous BN target (Fig. 3.17) present grain sizes ranging from submicrometers to several micrometers, supporting the average particle size obtained from SSA measurements using the BET method. Moreover, slit-like pores in the macroporous region can be identified, which is in agreement with

the interpretation of the N_2 adsorption-desorption isotherm shape. It is thus likely that the particle size measurement (Fig. 3.14) of the pristine BN powder, as discussed, rather provides an agglomerate size distribution.



(a)



(b)

Figure 3.17: SEM images of SPS pre-sintered BN powder pellets, showing the material surface (a) and a fracture region (b).

III.1.2.2 Mercury intrusion porosimetry

As previously stated, N_2 physisorption isotherms (N_2 PI) do not provide reliable information regarding pore sizes exceeding 50 nm. Hence, a complimentary study was performed by means of *Mercury Intrusion Porosimetry* (MIP)

(*Micromeritics AutoPore IV*). MIP assesses porous compounds by impregnating their voids with mercury, and is capable to examine porous structures over a range from 5 nm to 500 μm [128]. Mercury is a non-wetting liquid, consequently, it does not penetrate the pore opening unless an external force is applied. In practice, this is achieved by applying pressure, which results in a specific pore intrusion dV . The applied pressure relates inversely to the pore size, which is described in the Washburn equation [128], assuming, similarly to the BJH method in N_2PI , cylindrical pore shapes. Moreover, it is assumed that all pores are either connected from larger pores or from the surface. Next to the intruded volume, the extruded volume is monitored during pressure reduction. Thereby, pore size distribution and cumulative intrusion and extrusion volume are measured, which is in fact similar to the adsorption-desorption isotherm of N_2 physisorption.

Figure 3.18 shows the differential mercury intrusion ($\square$) and extrusion ($\blacksquare$) as a function of the pore diameter ($dV(D)$), employing a contact angle of 130° , superimposed with the PSD of the N_2 desorption isotherm ($\circ$), which was discussed in the previous section. The corresponding cumulative volumes of mercury intrusion and extrusion versus the applied pressure, and accordingly versus the pore diameter, are illustrated in Figure 3.19.

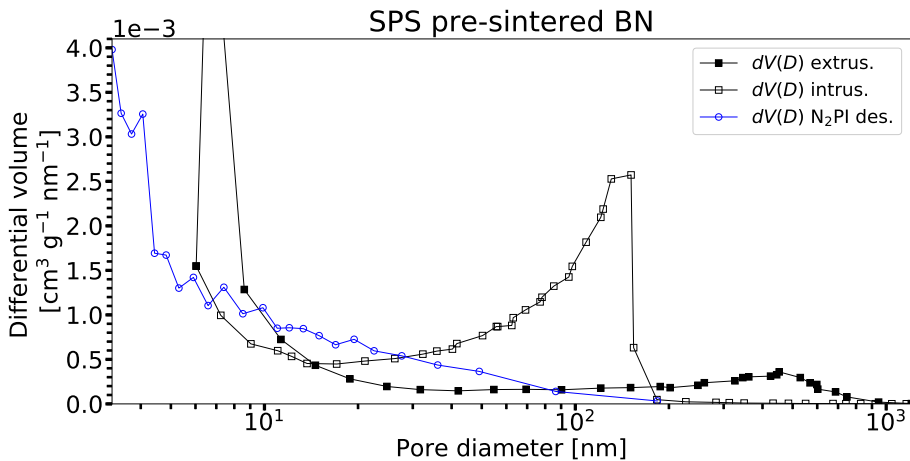


Figure 3.18: Mercury intrusion porosimetry (MIP) measurement of SPS pre-sintered BN, showing the differential intrusion ($\square$) and extrusion volume ($\blacksquare$) as a function of the pore diameter. For comparison, the complimentary results obtained from N_2 physisorption isotherms (N_2PI), reported in Section III.1.2.1, are superimposed ($\circ$).

First, the PSD of the intrusion process will be discussed. For pore diameters smaller than 40 nm a reasonably good agreement between MIP and N_2 physisorption PSD is observed. Beyond this limit, a peak centered around 130 nm is measured with MIP, whereas the PSD of N_2 PI continues to decrease. This supports the interpretation of the results presented in the previous section, indicating that 85% of the pore volume comprises macropores. From the cumulative intrusion volume ($\square$ in Fig. 3.19), we can deduce a median pore diameter of $D_{v,50}^{\text{Intrus.}} = 120$ nm, and for diameters larger 200 nm no significant increase is observed. Compared to the N_2 PI (refer to Fig. 3.16), a poor agreement is observed regarding the cumulative intrusion volume, with $D_{v,50}^{N_2\text{PI}} = 26$ nm, which is expected due to the unreliability of the N_2 PI technique within the macroporous region. Hence, the results obtained from MIP are considered as the more reliable source concerning the actual PSD of the SPS pre-sintered BN powder compact.

The mercury extrusion shows a considerably different PSD compared to the intrusion process. While a good agreement for small pore diameters is observed, mercury extrusion exhibits a significantly broader distribution centered around a median pore diameter $D_{v,50}^{\text{Extrus.}} = 470$ nm. Moreover, comparing the measured intrusion and extrusion volume illustrated in Figure 3.19, a hysteresis is observed. The latter is a common characteristic of MIP, and may be attributed to the actual pore shape, which does not match the modeled cylindrical geometry and assumption that all pores are accessed through larger entrances. The sudden increase around 120 nm during the intrusion process indicates a pore shape

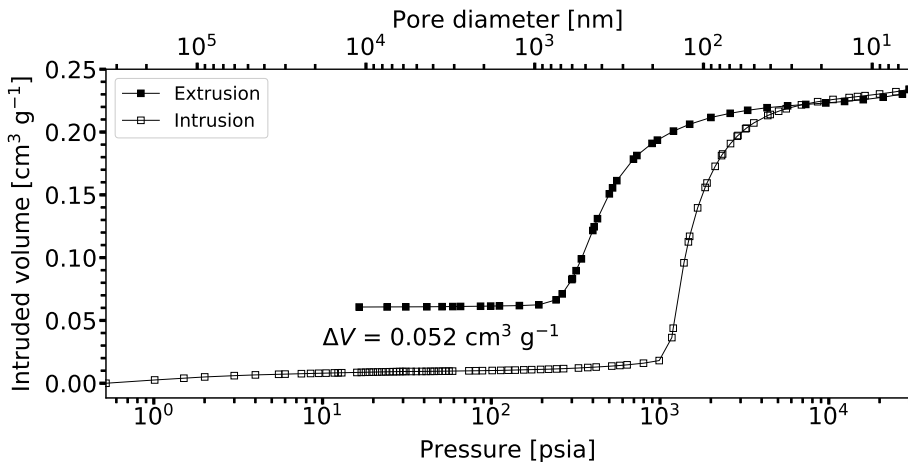


Figure 3.19: Cumulative mercury intrusion ($\square$) and extrusion ($\blacksquare$) curves of SPS pre-sintered BN.

with small throats and large pore cavities, so-called 'ink-bottle' shapes [128]. Such geometries prevent pore filling of the larger cavities at lower pressures, since higher pressures are required to enter through the smaller throats. Upon pressure reduction, mercury is entrapped within the pore network, which may be explained by pore networks with cavity-to-throat size ratios exceeding one, together with the dynamic character of the extrusion process. Eventually, $\sim 25\%$ of the total cumulative intrusion volume remains within the material. It is thus conceivable that $D_{v,50}^{\text{Intrus.}}$ rather represents the pore's throat size, whereas $D_{50}^{\text{Extrus.}}$ is more likely to be correlated with the cavity size. However, evaluation of the extrusion data should be performed with caution as high pressures may result in material compression and/or destruction. Both phenomena measure a false (open) pore volume, whereas in the latter case the microstructure is permanently damaged, giving access to closed porosity.

It is noteworthy that the measured total intrusion volume of approximately $0.23 \text{ cm}^3 \text{ g}^{-1}$, which corresponds to the open pore volume $V_p^{\text{MIP}}/m_{\text{sample}}$, deviates by more than 1σ from $V_p/m_{\text{sample}} = 0.162(55) \text{ cm}^3 \text{ g}^{-1}$, determined from He-gas pycnometry (refer to Secs. III.1.1 and III.1.2.1). To some extent, this deviation could be explained by possible fluctuations of ρ_{th} , which is used for the derivation of Φ_{tot} and consequently, for V_p/m_{sample} . However, the aforementioned discrepancy is too pronounced to be solely attributed to such fluctuations. Nonetheless, the open pore volume determination by means of He-gas pycnometry measurements is the more reliable measurement technique, since helium can penetrate the smallest pores due to its size. Thus, it is likely that some material compression and/or destruction occurred during the MIP measurement, giving access to false and/or closed pore volume. Unfortunately, it is not possible to conclude from MIP data whether material compression, damage or a combination of both resulted in the observed deviation. Consequently, we consider an average pore size around $D_{v,50}^{\text{Intrus.}} = 120 \text{ nm}$ to $D_{v,50}^{\text{Extrus.}} = 470 \text{ nm}$ as a reasonable approximation for the developed SPS pre-sintered BN powder compact.

3.5 Summary

This chapter described the material selection, target fabrication and microstructural characterization of an ISOL-type target tailored for ^{11}C RIB production. Boron nitride was identified as promising target material candidate due to its high physical in-target production yield and high-temperature stability. To enhance the ^{11}C release efficiency, spark plasma sintering was applied, to obtain a porous powder compact with controlled microstructure. Several processing routes, differing in BN starting powder and sintering parameters were investigated, where the SPS cycle associated with the most suitable results

in terms of porosity, rigidity and reproducibility was selected as ISOL target: BNM, $t_{\text{dwell}} = 5$ min, $T_{\text{max}} = 1700$ °C, $P_{\text{ex}} = 25$ MPa during dwell-time, sintering atmosphere of ~ 2 mbar air pressure and a heating and cooling rate of 100 °C min $^{-1}$ and ~ 400 °C min $^{-1}$, respectively.

The developed porous SPS pre-sintered BN powder compact was characterized with respect to its microstructural properties, exploiting several experimental techniques. A total and open porosity of 40(5)% and 21(7)%, respectively, were determined using the Archimedes' principle and He-gas pycnometry, which corresponds to a densification of less than 5%, compared to the green body before firing. From nitrogen physisorption isotherms, the specific surface area $\text{SSA} = 8.3(4)$ m 2 g $^{-1}$ was deduced employing the BET method, and was utilized to estimate the average particle or grain cluster size $\bar{G}_{\text{BET}} = 1.7(1)$ μm , which is however a rough approximation. The N $_2$ physisorption isotherm measurements showed that more than 85% of the open pore volume comprises pores with diameters exceeding 50 nm. A complimentary study exploiting mercury intrusion porosimetry, reassured this observation and enabled to estimate the average pore size regime of 120 – 470 nm.

Chapter 4

Cold characterization of operational limits

The previous chapter discussed the target material selection and fabrication aspects regarding the development of a porous BN ISOL target with controlled microstructure for enhanced isotope release properties. In addition, to foster examination of the release mechanism, the microstructural properties were characterized exploiting several different experimental techniques. In this chapter, the feasibility of the developed BN target is investigated, with respect to its application in an ISOL-type RIB production system, tailored for the production of intense ^{11}C beams. This comprises mainly two aspects: stability at high temperatures and low pressures, and stability in controlled oxidizing atmospheres at high temperatures. As previously stated, ISOL targets are often operated at temperatures close to their melting point, since diffusion and effusion processes increase exponentially with temperature. However, it was pointed out in the preceding chapter that chemical equilibrium calculations suggest BN dissociation at intermediate temperatures $T \approx 1000 - 1100\text{ }^{\circ}\text{C}$ (refer to Fig. 3.2b), which would be a strong limiting factor, and therefore requires examination. Concerning the second aspect, the reader is reminded that target operation in controlled oxidizing atmospheres is foreseen to promote the formation of carbon oxides, in particular carbon monoxide, since carbon is very refractory and reactive. Thus, both release and transport efficiency are expected to be significantly enhanced by producing ^{11}C in the CO molecular sideband. However, it is well reported in the literature that BN oxidizes at high temperatures ($T > 900\text{ }^{\circ}\text{C}$) and oxygen-rich atmospheres. Therefore, it must be ensured that no excessive oxidation occurs at the typical ISOL-target operational conditions, combined with a controlled, externally-provided oxygen

supply. The following article will discuss these aspects, and first investigations regarding the operational feasibility in the aforementioned conditions will be presented. In Section 4.2, supplementary material, in-depth discussions and supplementary experimental studies will be given.

4.1 Article I: Production of intense mass separated ^{11}C beams for PET-aided hadron therapy

Note that the following article was slightly adapted from the on-line version, in order to fit the style of this thesis. This concerns mostly font styles and references which were not online at the time of publication.

Production of intense mass separated ^{11}C beams for PET-aided hadron therapy

S. Stegemann^{a,*}, T.E. Cocolios^a, K. Dockx^a, G. Leinders^b, L. Popescu^c, J.P. Ramos^{a,d}, K. Rijpstra^c, T. Stora^d, M. Verwerft^b, J. Vleugels^e

^a KU Leuven, Institute for Nuclear and Radiation Physics, Celestijnenlaan 200d, 3001 Heverlee, Belgium

^b Belgian Nuclear Research Centre SCK CEN, Institute for Nuclear Materials Science, Boeretang 200, 2400 Mol, Belgium

^c Belgian Nuclear Research Centre SCK CEN, Institute for Advanced Nuclear Systems, Boeretang 200, 2400 Mol, Belgium

^d CERN, EN-STI, Geneva 23 CH-1211, Switzerland

^e KU Leuven, Department of Materials Engineering, Kasteelpark Arenberg 44, 3001 Heverlee, Belgium

Abstract

A novel production system based on the isotope separation on-line (ISOL) method is being developed to produce intense mass separated ^{11}C beams for PET-aided hadron therapy. In this work, we present a systematic study of the target that was developed for optimized ^{11}C beam production. A solid boron nitride target (BN) with approximately 21% open porosity was manufactured by spark plasma sintering to provide maximized in-target production yield with enhanced isotope release properties. Operational limitations with respect to high temperatures and oxidizing atmospheres were studied, revealing that the BN target can withstand temperatures up to 1500 °C and can be operated with a controlled O₂ leak, providing O₂ potentials up to -300 kJ mol^{-1} , measured at 1000 °C.

Keywords: Radioactive ion beam production, ^{11}C production, target material

*Corresponding author

Email address: simon.stegemann@kuleuven.be (S. Stegemann)

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I Introduction

Cancer is one of the major causes of death. In 2014 more than 1 in 4 deaths were caused by cancer in the European Union, which corresponds to a total number of almost $1/3^{\text{rd}}$ million deaths [129]. Radiation therapy plays an important role in the treatment of cancers. Hadron therapy, and particularly carbon therapy, is a very precise treatment for localized tumors where the tumor is irradiated with a pure, monoenergetic and high intensity particle beam [10]. Carbon therapy significantly reduces the dose exposure to healthy tissue compared to conventional photon therapy. This is the direct result of the energy loss of heavy charged particles in matter. Such particles have a sharp peak at the end of the particle's trajectory (Bragg peak), where most of the energy is deposited. Treatments are performed according to complex treatment planning systems that simulate the beam trajectory through the human body, and thus, calculate the dose distribution of the particle beam to the human body and to the target cells. However, these treatment planning systems suffer from range uncertainties, which originate for instance from anatomical changes throughout the treatment fractions. Consequently, the verification of the actual dose distribution in the tissue is an important feature which remains difficult. Current attempts involve PET-imaging (positron emission tomography imaging) with secondary β^+ -emitters, such as $^{10,11}\text{C}$ or ^{15}O , which are produced by the primary ^{12}C beam interacting with water contained in human tissue [33, 130]. Studies on off-line and in-beam PET-imaging of these secondary β^+ -emitters showed promising results [29, 131]. However, limiting statistics and the washing out of the β^+ -emitter distribution remain fundamental issues in such an approach [28, 131]. The subject of this work is an alternative approach, in which the stable ^{12}C beam is entirely replaced with its radioactive isotope ^{11}C ($T_{1/2} = 20.4$ min). By using the β^+ -emitter directly as therapeutic beam, treatment can be combined with on-line PET-imaging. The PET-images, acquired during treatment, provide 3D dose distribution maps of the irradiation field, which allow to validate the correctness of the treatment planning [33].

The challenge remains to produce a radioactive particle beam of sufficient intensity. Effective treatments require $4 \cdot 10^8$ ions s^{-1} delivered to the patient [33]. As radioisotope beam production is a multi-step process (see Fig. 4.1), with inevitable beam losses at each step, optimization of each individual process is essential. This work focuses on the production system (highlighted in red, in Fig. 4.1) tailored for high intensity ^{11}CO beams.

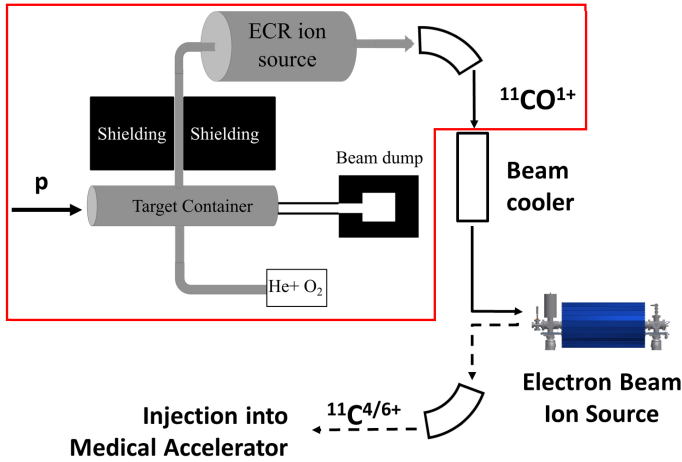


Figure 4.1: Schematic layout of a ^{11}C based hadron facility, as it is proposed within the MEDICIS-Promed network [132]. The highlighted part shows the production system discussed in this paper. The beam cooling [133] and charge breeding [103] are further research projects within MEDICIS-Promed. The different parts are not to scale.

In nuclear medicine ^{11}C is a well-known radioisotope, commonly used for PET-imaging. The production is usually done in the hospital by irradiating a nitrogen gas target with a low-energy proton beam [58, 59]. Once a sufficient quantity is being produced, the gas cell is dismantled from the target station for further chemical separation and the labelling to the carrier molecule. However, for radioactive ion beam (RIB) production this method is unpractical since such gas targets are under much higher pressures and therefore cannot be directly coupled to the ion source [33]. Furthermore, while it is in principle possible to produce a sufficient activity with one gas cell to deliver enough ions per spill to treat one patient, it remains unpractical with respect to a continuous treatment of several patients per day. Another technique to produce radioactive ion beams is projectile fragmentation. However, such beams suffer from low production cross sections and poor quality [66]. Hence, we propose a production system based on the isotope separation on-line method (ISOL), which allows to produce intense, continuous and pure radioactive ion beams. In detail, a thick, usually solid target is mounted in a target chamber which is connected to the ion source. Protons are impinging on the target, producing various (radio-)isotopes via different nuclear reactions. The isotopes are diffusing to the surface of the material, from where they vaporize. Once the isotopes are released, they effuse to the ion source where they are ionized to the 1^+ charge state before they

can be accelerated by a low extraction voltage, followed by mass separation with a dipole magnet. High temperatures enhance the diffusion and effusion processes. In this way, radioactive ion beams for physics research have been produced for more than 50 years at CERN-ISOLDE (Isotope Separator On-Line DEvice) [77], which serves as an example for the ^{11}C beam production. The ISOL type production unit, schematically illustrated in the highlighted part of Fig. 4.1 will consist of a solid boron nitride (BN) target, an electron cyclotron resonance (ECR) ion source and a controlled oxygen leak for molecular isotope extraction. This target-ion source unit is chosen to maximize the C^+ yield to meet the requirements for effective cancer treatments and will be discussed in the following. In detail, a systematic study on the feasibility of the target material is presented, by investigating operational limitations with respect to high-temperatures and oxidizing atmospheres.

II Materials and methods

II.1 Target development

BN has been identified as a promising target material, due to its two reaction channels with high cross sections for ^{11}C production ($^{11}\text{B}(\text{p},\text{n})^{11}\text{C}$ and $^{14}\text{N}(\text{p},\alpha)^{11}\text{C}$) [104]. Both cross sections reach their maximum around $E = 6 - 8$ MeV, which are low-energy and will result in high energy deposition in the target material. Low-energy beams have a higher stopping power and therefore lose more energy in comparison to high-energy beams. To optimize the isotope production versus energy deposition, the proton beam energy and target thickness are chosen so that the beam energy is in the interval $E \in [5, 15]$ MeV. Such proton beams can be provided by compact cyclotrons, routinely used in hospitals for PET-isotope production. The corresponding physical in-target production yield can be expressed as:

$$Y_{\text{phys}} = \frac{N_{\text{A}}}{M} \int_{E_{\text{f}}=5}^{E_{\text{i}}=15} \frac{f_{\text{b}} \cdot \sigma_{^{11}\text{B}}(E) + f_{\text{n}} \cdot \sigma_{^{14}\text{N}}(E)}{S(E)} dE, \quad (4.1)$$

with N_{A} the Avogadro's number, M the molar mass, $S(E)$ the stopping power expressed in $\text{MeV cm}^2 \text{g}^{-1}$, σ_i the cross sections in millibarn and $f_{\text{b}, \text{n}}$ the fractional isotopic abundances. Previous studies by M. Loiselet et al. in the Centre de Recherche du Cyclotron (CRC) at Louvain-la-Neuve with BN, yielded already a 10^7 pps ^{11}C beam [134]. However, BN was used as powder [74, 75], which introduces limitations on beam energy and intensity to prevent the powder from escaping the target chamber. To overcome this, and furthermore, to facilitate target handling and waste management, a BN powder compact is investigated in this work.

II.1.1 Target preparation

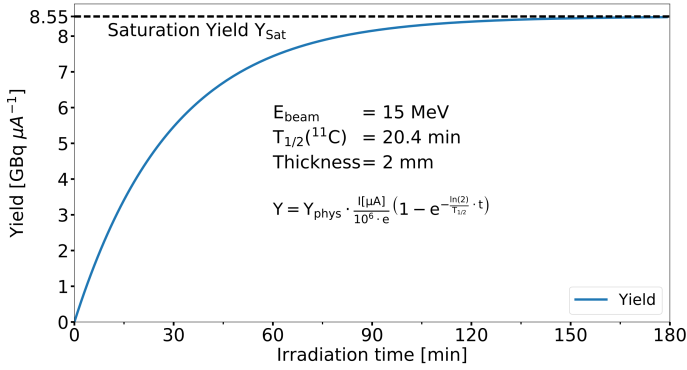


Figure 4.2: In-target production yield resulting from irradiating a 2 mm thick SPS pre-sintered BN target having 40% porosity with a 15 MeV proton beam. The target thickness is chosen to optimize the isotope production versus energy deposition.

One possible way to obtain a rigid target is by sintering of a powder compact. Sintering is a complex process, in which parameters such as temperature, pressure and time have a strong impact on the material properties and densification of the powder compact [110, 135]. In that respect, the isotope release properties are essential, as they are often considered as a bottleneck in RIB production [136, 137]. Generally, small grain sizes for short diffusion times in combination with large pore sizes and high open porosity for fast effusion, enhance the isotope release [137, 138]. Therefore, it is desirable to process a powder compact that is not fully densified, i.e., sintering does not reach the theoretical density, and which microstructure is stable at typical ISOL target operational conditions [135]. To obtain such a powder compact, hexagonal BN (h-BN) targets were manufactured by spark plasma sintering (SPS), often also denoted as field-assisted sintering technique (FAST) [116]. This technique sends high dc currents through a punch/die system in which the powder is compacted to rapidly heat up the material. High heating/cooling rates up to $1000 \text{ }^\circ\text{C min}^{-1}$ and $400 \text{ }^\circ\text{C min}^{-1}$, respectively, can be applied, reducing grain coarsening at lower temperatures. We explored three h-BN powders from different suppliers and concomitant particle size distributions¹, and optimized the SPS sintering cycle's temperature, dwell-time and pressure. The following parameters were used: Momentive HCP powder, a SPS cycle under 2 mbar air pressure, $100 \text{ }^\circ\text{C min}^{-1}$ heating rate, $T_{\text{final}} = 1700 \text{ }^\circ\text{C}$ and a sintering-pressure of 25 MPa with

¹Momentive: Grade HCP, $d_{50} = 8.3 \text{ } \mu\text{m}$, purity 99.5%. Asbury: BTBN5003 $d_{50} = 2.5 \text{ } \mu\text{m}$, purity 99%. Goodfellow: max. particle size $10 \text{ } \mu\text{m}$, purity 99.5%

5 minutes dwell-time. In this way, a BN powder pellet with bulk density of 1.3 g cm^{-3} corresponding to a total porosity of 40% was manufactured². With respect to isotope release, open porosity is an important property, which was determined to be 21% by He-gas pycnometry. Based on these results, the target thickness to absorb 10 MeV of the initial proton beam can be calculated and corresponds to 2 mm. Fig. 4.2 shows the expected in-target production yield as a function of irradiation time. Note that the $8.55 \text{ GBq } \mu\text{A}^{-1}$ saturation yield is proportional to the applied beam current, which will depend on the maximum applicable target temperature and the cooling efficiency.

II.1.2 Heat management

Using low-energy beams for ^{11}C production from BN results in high power deposition and consequently, rapid heating of the target material. Hence, heat management has to be considered. Generally, ISOL targets are operated at pressures $P = 10^{-6} - 10^{-4} \text{ mbar}$ and at temperatures just below their melting point since high temperatures enhance diffusion. An equilibrium calculation of h-BN at a pressure of 10^{-6} mbar , performed with HSC7 [105], suggests that BN dissociation: $2\text{BN} \rightarrow 2\text{B} + \text{N}_2(\text{g})$ starts already at $T \approx 1000 \text{ }^\circ\text{C}$ (see Fig. 4.3). This phenomenon is especially important as the target container will

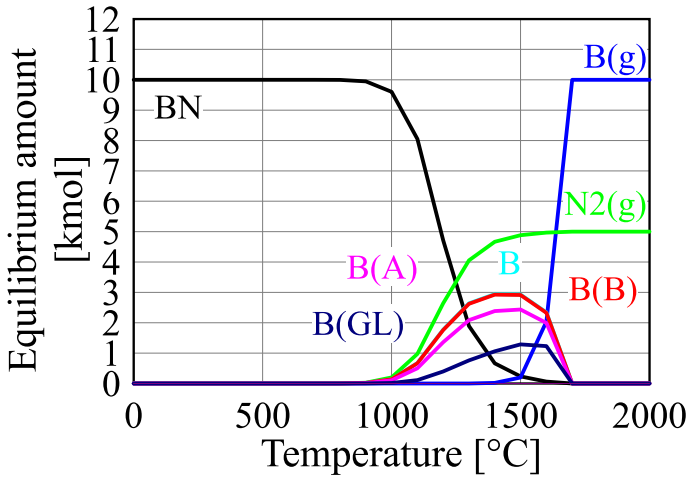


Figure 4.3: Equilibrium calculation of h-BN at a pressure of $P = 10^{-6} \text{ mbar}$ showing that BN dissociation is starting at $T \approx 1000 \text{ }^\circ\text{C}$. Note that B(g), B(A), B(GL), B(B) denote different phases of boron: gas, amorphous, glass, β -rhombohedral. The calculation was carried out with HSC7 [105].

²The theoretical density of h-BN powder corresponds to $2.1 - 2.2 \text{ g cm}^{-3}$ at $23 \text{ }^\circ\text{C}$

be coupled with a short transfer line to the ECR ion source, whose efficiency depends crucially on the injected gas load [139]. To study the extent of BN dissociation at high temperatures and low pressures, a heat test was performed using an experimental setup which was used in another study to assess TiC mass losses and phase dynamics [140]. The aim of this study was to determine the maximum temperature at which the target can be operated to prevent overloading the ion source. The experimental setup consisted of an Al_2O_3 tube inserted in a furnace that could be heated up to 1500 °C with a rate of 8 °C min⁻¹. A vacuum system with two turbo pumps and two evacuation

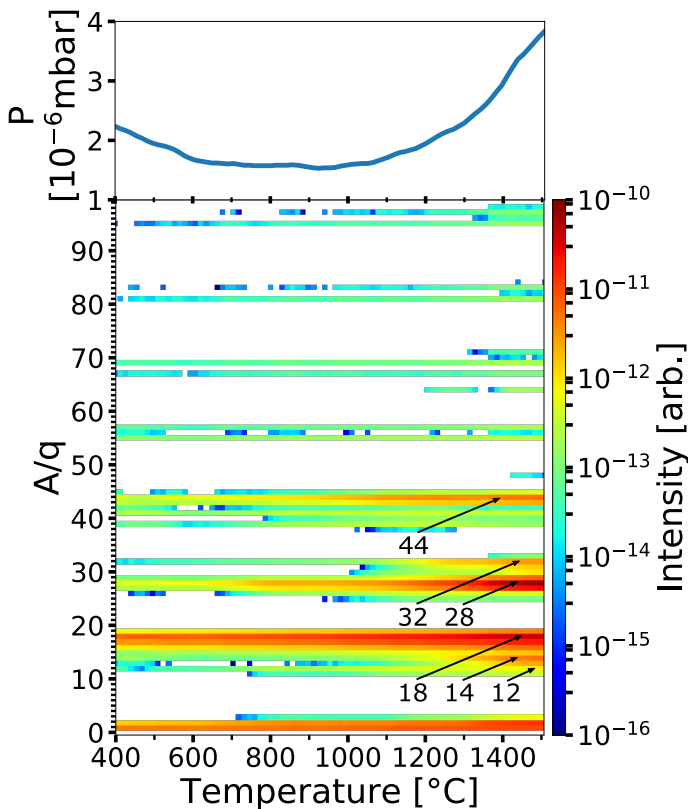


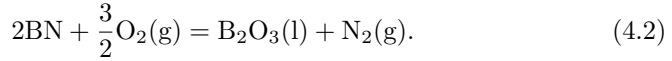
Figure 4.4: Heat treatment up to 1500 °C of SPS pre-sintered BN in an evacuated furnace. (Top) Relative pressure and (bottom) mass spectrum detected during the heating cycle. At high temperatures, a modest pressure increase and enhanced mass signals $A/q = 14$ (N), 28 (N_2 , CO) are observed. Signals at $A/q = 12$ (C), 18 (H_2O), 32 (O_2), 44 (CO_2) probably result from contaminations in the Al_2O_3 tube.

lines allowed to evacuate the tube to a base pressure of 10^{-6} mbar, and to measure residual gases and the relative pressure change with a *Quadrupole Mass Spectrometer* (QMS) and a full-range gauge. The results are shown in Fig. 4.4. The detected mass-over-charge (A/q) signals were corrected for background residuals by measuring one full cycle with the empty Al_2O_3 boat. The relative pressure change (top) illustrates only a moderate pressure increase for $T > 1000$ °C. Although the measured pressure does not correspond to the actual vapor pressure we can conclude from experience with this setup that the observed pressure increase indicates slow dissociation kinetics, allowing to operate the BN target at 1500 °C. This is supported by the total mass loss of the samples after heat treatment, which is below 1%. The mass spectrum presents an increased $A/q = 14$ (N), 28 (N_2 , CO) signal, which corresponds to the evaporation of N_2 from the dissociation of BN and, to some extent, to CO. Furthermore, increased signals of $A/q = 12$ (C), 32 (O_2), 44 (CO_2) are observed at high temperatures, and a strong $A/q = 18$ (H_2O) is detected throughout the whole measurement. These may result from corresponding contaminations in the Al_2O_3 tube, as the H_2O signal decreased in subsequent measurements and the blank measurement was taken in the end. Besides that, high masses are detected, which were not present in the background spectrum. The origin of these signals is not clear, however, a pattern of $A/q = 12, 14$ indicates a formation of clusters binding an additional nitrogen or carbon atom.

II.1.3 Molecular isotope extraction

For high intensity beam production, molecular isotope extraction and beam formation are considered for two reasons: firstly, carbon is very refractory, resulting in poor release efficiency from the target material, where carbon monoxide is more volatile and is expected to increase the release efficiency; secondly, carbon is very reactive and easily forms refractory carbides with hot metal surfaces. Since carbon monoxide is less reactive, retention times on the surrounding material are reduced, increasing the transport efficiency. Thus, as indicated in Fig. 4.1, a controlled O_2 leak is foreseen in the production system, to extract ^{11}CO from the target matrix. Introducing O_2 into the system includes the risk of target oxidation. To find operational conditions where BN oxidation is not favorable, Ellingham diagrams can be consulted. They show the thermodynamic stability (standard Gibbs free energy) of metal/metal-oxide couples as a function of temperature. In equilibrium, and assuming negligible reactant and product vapor pressure, the standard Gibbs free energy of such couples corresponds to $RT \cdot \ln(P_{\text{O}_2})$, which is commonly denoted as the O_2 potential μ_{O_2} . One can obtain from this plot equilibrium conditions where BN oxidation is not thermodynamically favored. In Fig. 4.5, the BN/ B_2O_3 -line corresponds to the line of stability for BN, where the oxidation can be described

by:



Potentials above this line will result in the oxidation of BN, whereas below this line the BN-state is thermodynamically favored, and conditions may be found where O_2 oxidizes the C-content in the BN target matrix to CO or CO_2 . It must be mentioned here that Ellingham diagrams, usually, depict standard state conditions, e.g. all partial pressures equal to one. In such cases, volatile species do not contribute to the Gibbs free energy, due to its logarithmic partial pressure dependency.

However, this is here not reasonable, as C will only be produced in trace amounts and the N_2 partial pressure P_{N_2} resulting from the BN oxidation and dissociation has to be considered. It is however not clear how to evaluate these partial pressures at equilibrium. As a starting point, an initial N_2 partial pressure of 100 ppm leaking into the thermal analysis tool, which remains unaltered in equilibrium, was assumed for the calculation. Leaks of this magnitude have been measured in the exhaust gas of the experimental setup that was used in this study. Assuming the same partial pressure for P_{CO} and P_{CO_2} yields the

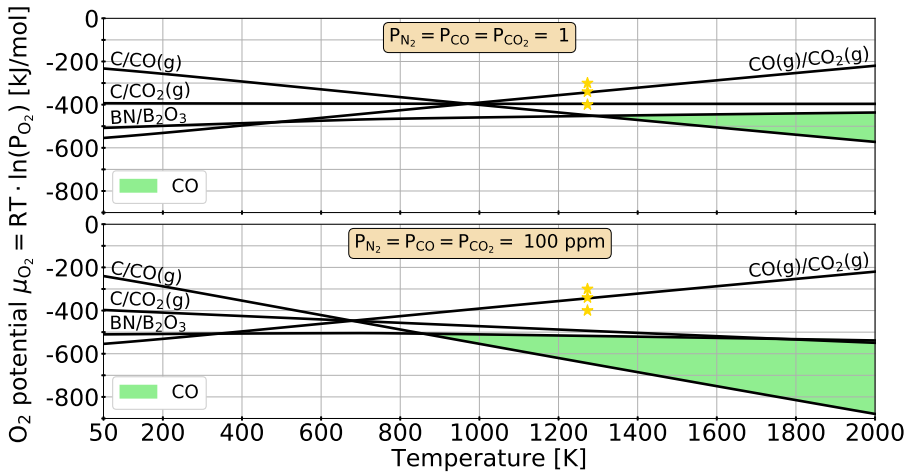


Figure 4.5: Ellingham diagram for BN exposed to O_2 , showing the O_2 potential $\mu_{\text{O}_2} = RT \cdot \ln(P_{\text{O}_2})$ as a function of the temperature for standard state condition (top) and for $P_{\text{N}_2} = P_{\text{CO}} = P_{\text{CO}_2} = 100 \text{ ppm}$ (bottom). The solid $\text{BN}/\text{B}_2\text{O}_3$ -line corresponds to the line of stability for BN, and the green-shaded area mark conditions where C oxidation is favored, forming CO. The stars illustrate the conditions that were investigated by thermogravimetric analysis that is explained in the text.

diagram shown in Fig. 4.5 (bottom). The standard state case is shown as a reference in Fig. 4.5 (top). The green-shaded area marks conditions where oxidation of C to CO is thermodynamically favored, and BN does not oxidize. While it seems that at 1000 °C desirable conditions exist, such low μ_{O_2} are difficult to probe experimentally. However, the comparison of the top and bottom graph in Fig. 4.5 shows that the area of interest is increasing when decreasing the partial pressures, which is favorable for selective carbon oxidation. Since it is not clear how to evaluate the partial pressures at equilibrium, as a starting point, *Thermogravimetric Analysis* (TGA) of pure BN and carbon-doped SPS pre-sintered BN (BN-C, with $[\text{C}] = 0.01, 0.1, 1, 5 \text{ wt.}\%$) were performed at 1000 °C for O_2 potentials $\mu_{\text{O}_2} = -400, -340$ and -300 kJ mol^{-1} (indicated at stars in Fig. 4.5). At the time of the measurements, 1000 °C was still expected to be the maximum applicable temperature, and the O_2 potentials were chosen with respect to CO and CO_2 formation. From the results one can examine, firstly, the high-temperature oxidation kinetics of SPS pre-sintered BN in controlled atmospheres. This is important since the calculations contain no information on the kinetics, which are relevant for target operation. Secondly, conclusions on the release properties of C from BN may be drawn, by measuring the carbon-doped BN material.

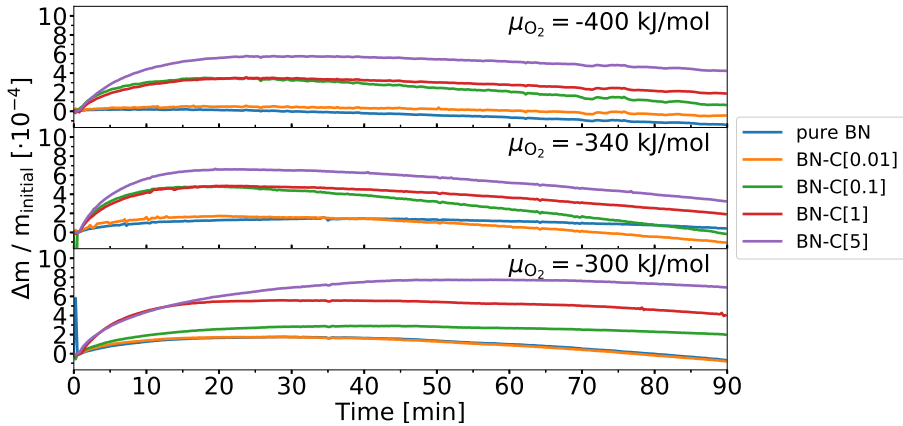


Figure 4.6: TG measurement of BN and BN-C (with $[\text{C}] = 0.01, 0.1, 1, 5 \text{ wt.}\%$) for $\mu_{\text{O}_2} = -400, -340, -300 \text{ kJ mol}^{-1}$. Note that $t = 0$ denotes the time when the gas composition is changed to the O_2 active mixture. The graphs show that both, an increased O_2 potential and increased C-content are enhancing the mass gain by O_2 uptake.³

³Since there was a minor mistake in the data processing and in the figure's label, it is slightly modified compared to the original publication in the corresponding article. However, the discussion and conclusion of this figure remain unaffected.

For the measurements, the samples were prepared in an Al_2O_3 crucible, standing on a thermocouple. This assembly was mounted on a precision balance and the assembly was surrounded by a Rh furnace, equipped with a leak-tight fit and controlled gas in- and outlets. The whole system was coupled to a quadrupole mass spectrometer (QMS), allowing to measure the mass change over time and the mass-over-charge ratio (A/q) of the evaporated gases simultaneously (TGA-MS). A gas control system could vary between different atmospheres: (1) Inert (Ar , N_2), (2) reducing (H_2/Ar), (3) oxidizing ($0.01 - 21$ vol.% O_2) and (4) vacuum ($> 10^{-5}$ mbar). The samples were heated in Ar-atmosphere up to 1000°C with a heating rate of $20^\circ\text{C min}^{-1}$. To stabilize the TG signal, the sample was kept for 30 minutes at 1000°C . Subsequently, the atmosphere was changed to an oxidizing atmosphere of chosen O_2 potential by mixing gas-flows of 5% H_2/Ar gas with an O_2 gas mixture and the TGA-MS signals were recorded for 1.5 h. For each O_2 potential, a full blank measuring cycle was recorded to correct for buoyancy-effects on the sample holder. Additionally, the mass spectrum was recorded to correct for background signals. The result of this study can be seen in Figures 4.6-4.8, where the mass spectra in Figures 4.7, 4.8, unfortunately, fail to yield conclusive information. First, the pure BN case

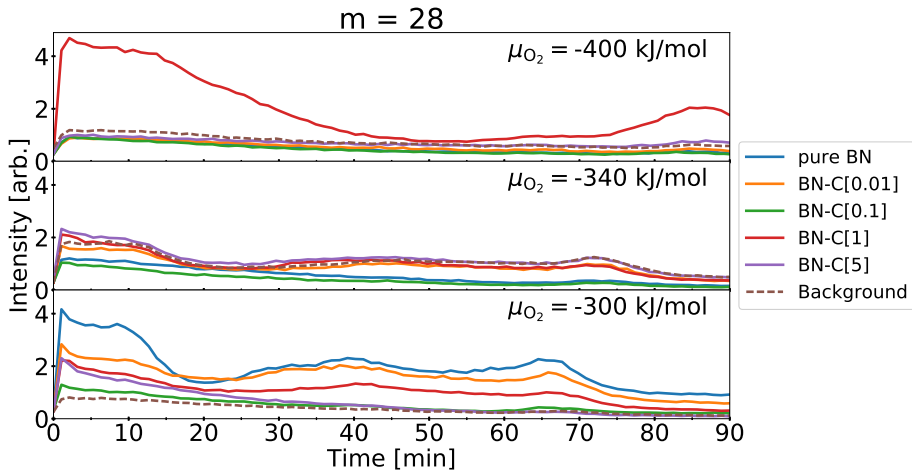


Figure 4.7: $A/q = 28$ MS measurement of BN and BN-C (with $[\text{C}] = 0.01, 0.1, 1, 5$ wt.%) for $\mu_{\text{O}_2} = -400, -340, -300 \text{ kJ mol}^{-1}$. Note that $t = 0$ denotes the time when the gas composition is changed to the O_2 active mixture. Only at $\mu_{\text{O}_2} = -300 \text{ kJ mol}^{-1}$, in comparison to the background signal, a prominent N_2 signal is observed. The enhanced signal of BN-C[1] at $\mu_{\text{O}_2} = -400 \text{ kJ mol}^{-1}$ (top) is in strong contrast to the rest of the series, and is therefore more likely the result of a leak into the setup.

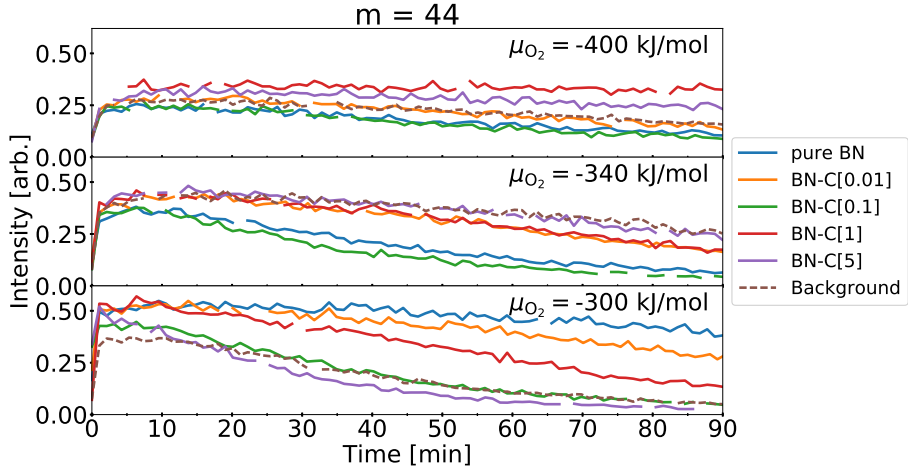


Figure 4.8: $A/q = 44$ MS measurement of BN and BN-C (with $[C] = 0.01, 0.1, 1, 5$ wt.%) for $\mu_{\text{O}_2} = -400, -340, -300$ kJ mol $^{-1}$. Note that $t = 0$ denotes the time when the gas composition is changed to the O_2 active mixture.

shall be discussed. Fig. 4.6 shows that BN follows parabolic oxidation kinetics. A similar behavior was reported by N. Jacobson et al. [141] who studied the high-temperature oxidation of hot-pressed, high-density CVD (chemical vapor deposition) and low-density CVD BN. The parabolic behavior results from a parabolic weight gain and simultaneous linear weight loss [142, 143]. According to Eq. (4.2), the weight gain should correspond to the uptake of O_2 , while, according to N. Jacobson et al. [141], the weight loss results from the volatilization reaction: $\text{B}_2\text{O}_3(\text{l}) + \text{H}_2\text{O}(\text{g}) = 2\text{HBO}_2(\text{g})$. However, BN shows no oxidation at $\mu_{\text{O}_2} = -400$ kJ mol $^{-1}$, while still showing significant weight loss, dismissing the volatilization reaction from above. Only at $\mu_{\text{O}_2} = -340$ or -300 kJ mol $^{-1}$ moderate parabolic oxidation kinetics with a maximum weight gain of less than 0.1% are observed, where only at $\mu_{\text{O}_2} = -300$ kJ mol $^{-1}$, in comparison to the background signal, a prominent N_2 signal can be observed in the mass spectrum (blue line in Fig. 4.7 (bottom)). It is however not clear whether the mass loss can be assigned to the evaporation of HBO_2 . While an increased $A/q = 44$ (HBO_2) signal is detected (blue line in Fig. 4.8 (bottom)), we observed a similar trend for the Ar-signal (not shown here), which is unaffected by the oxidation reaction. Therefore, the increased $A/q = 44$ signal is more likely a result of overall fluctuations.

From the TGA-MS measurements of the BN-C samples, unfortunately, no conclusive information regarding the C-extraction properties could be obtained.

The BN-C samples seem to follow parabolic oxidation kinetics as well, where an increased C concentration results in an increased mass gain (see Fig. 4.6), indicating the formation of carbon oxides. However, a qualitative interpretation of the mass spectra (Fig. 4.7 and 4.8) is impossible as signals that originate from the detected carbon are expected at $A/q = 28, 44$ (CO and CO₂, respectively), which cannot be distinguished from N₂ and potential HBO₂ signals. Furthermore, considerable background signals are present, making weak signals indistinguishable from the background.

Nevertheless, we can conclude from this study that BN can be thermally treated under small O₂ potential without risking excessive material oxidation, and that carbon has an effect on the oxidation behavior. Future prospects are to investigate the effect of the N₂ partial pressure as it might be beneficiary with respect to selective C oxidation.

III Summary & conclusion

An ISOL type production unit for mass separated ¹¹C beams, comprising a solid BN target and an ECR ion source, is currently under development. BN is a promising target material for high intensity ¹¹C beam production via the ISOL method. To enhance the release properties, BN powder pellets with approximately 21% open porosity were manufactured by spark plasma sintering. From this result, we expect a 8.55 GBq μA^{-1} saturation yield by irradiating a 2 mm thick target with 15 MeV protons. In this context it was experimentally proven that the BN target can withstand temperatures of at least 1500 °C in typical ISOL operational conditions. The feasibility of ¹¹CO isotope extraction via a controlled O₂ leak was investigated by measuring the high-temperature oxidation kinetics of BN and BN-C materials. Operating BN in controlled oxidizing atmospheres imposes no limitations on the material itself, whereas no conclusive information on the carbon release characteristics by studying BN-C systems could be made. Consequently, a study with activated pellets from which ¹¹C can be studied is essential to determine the release properties of the material. Such a program is ongoing at the CERN MEDICIS facility [102].

IV Outlook

It was mentioned that an ECR ion source is foreseen to be used for the ¹¹C beam production unit (Fig. 4.1). The advantage of such plasma ion sources is their absence of hot metal surfaces, which may retain CO. At GANIL, in collaboration with PANTECHNIK, a 2.45 GHz ECR ion source for efficient 1⁺ ionization was developed (MONO 1000). Based on that, a compact source was developed and tested in an off-line study at ISOLDE. Promising 14% ionization

efficiency was achieved [83]. For the study presented in this work, further ionization efficiency measurements of commercial PANTECHNIK ECR ion sources are being prepared.

Acknowledgments

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4.2 Addendum: operational limitations at high temperatures and controlled oxidizing atmospheres

This section will expand the previously reported studies regarding the developed BN target's feasibility at high temperatures and controlled oxidizing atmospheres. Supplementary descriptions and data of the preceding experimental studies, as well as complementary research will be presented.

4.2.1 Driver accelerator selection

Firstly, the choice of the primary production accelerator, as outlined in Section II.1, shall be discussed in more detail. It was suggested, in order to optimize the thick in-target production yield versus energy deposition, to employ a compact 15 MeV proton accelerator, whereas the target thickness is chosen such that the proton beam traverses the target with an excess energy of 5 MeV. This was motivated by the reaction cross sections for ^{11}C production shown in Fig. 3.1, which both reach their maximum around 6 – 8 MeV, and decrease significantly for $E_i < 5$ and $E_i > 15$ MeV. As discussed in Section II.1, such low-energy beams result in a significant energy deposition, which needs to be considered since both yield and power deposition $P_{\text{dep}} [\text{W}] = E_{\text{dep}} [\text{MeV}] \cdot I [\mu\text{A}]$ scale linearly with the applied initial beam intensity (current). In other words, a higher primary beam energy may increase the production yield moderately, while P_{dep} increases more drastically, which would result in rapid and excessive target heating. This modality is illustrated graphically in Figure 4.9, by means of E_{dep} . In detail, the physical thick in-target production yield Y_{phys} simulated with FLUKA (•) and calculated from tabulated cross section data (□) is plotted

as a function of the initial proton beam energy. The target thickness is chosen such that the proton beam retains approximately 5 MeV of its initial energy when exiting the target matrix. The deposited energy ($\bullet$), obtained from the FLUKA simulation is plotted accordingly. Note that the target thickness is adjusted with an accuracy of 1 mm, to account for mechanical feasibility of the fabrication process. One can identify that at lower energies, where the cross sections are large, Y_{phys} increases linearly. For energies exceeding 15 MeV, Y_{phys} starts to saturate due to the decreasing cross sections. As a result, the thick in-target saturation yield $y_{\text{sat}} = y(t \rightarrow \infty)$ (refer to Sec. 2.2.4), exhibits merely a modest increase, for increasing primary proton energy E_i .

While an increasing primary energy, together with increasing target thickness, always results in higher production yields, the generated activity, as well as the deposited energy, are not distributed uniformly across the target material. Let us consider the proposed 2 mm thick BN target employed with a 15 MeV proton beam at target entry. When increasing the incident energy E_i , the thickness must be increased as well by adding stacks of 1 mm thick BN target material in front of the target. The protons of higher energy, slow down within these stacks, generating additional ^{11}C activity, which is however less efficient due to the lower cross sections at higher energies. Since the aforementioned excess

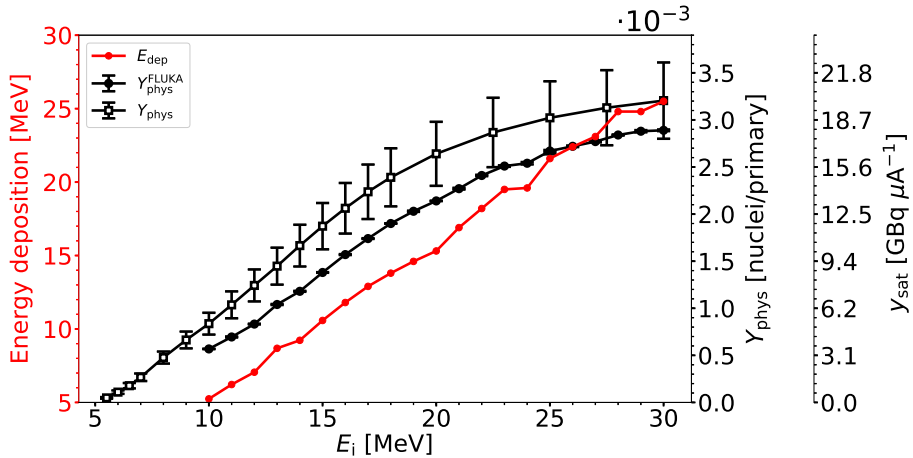


Figure 4.9: Deposited energy E_{dep} ($\bullet$), FLUKA simulated physical thick in-target production yield $Y_{\text{phys}}^{\text{FLUKA}}$ ($\bullet$) and physical thick in-target production yield Y_{phys} ($\square$) obtained from measured cross sections as a function of the primary proton beam energy E_i when irradiating a BN target. Note that the target thickness is chosen such that the proton beam traverses the target retaining 5 MeV of its initial energy.

energy of 5 MeV shall be maintained, E_i and the number of stacks is adjusted accordingly, such that the protons hold approximately 15 MeV after traversing the stack's material and entering the proposed 2 mm thick BN target. As a result, both ^{11}C density and deposited energy are the highest in this area.

On the other hand, the production of other radionuclides besides ^{11}C , may not decrease accordingly within the stack volume, as their cross sections could be less affected by higher proton energies. In fact, supplementary reaction channels may become possible, giving rise to additional contaminations. This feature is illustrated quantitatively in Table 4.1 by means of the *specific activity* $A^* = \frac{A(^{11}\text{C})}{A_{\text{tot}}}$, which normalizes the produced ^{11}C activity to the total activity within the corresponding volume. The upper part of Table 4.1 presents the expected specific activity of the suggested 2 mm thick BN target irradiated with 15 MeV protons. The lower part shows A^* within the individual stacks, the required primary energy E_i and the cumulative specific activity $A^*_{\text{cumul.}}$, when applying the BN target with the corresponding numbers of stacks.

It is apparent that compared to the BN target, A^* decreases considerably within the stack volume, indicated that the majority of ^{11}C is produced within the target volume (top). As a result, $A^*_{\text{cumul.}}$ is decreasing with increasing number of stacks. It is therefore arguable whether a thicker target operated with higher proton energies would result in more beneficial conditions. Considering that the gain compared to the overall target activation is rather low, the originally suggested 2 mm thick target is conceived as an appropriate approach.

d [mm]	E_i [MeV]	A^* [GBq μA^{-1}]	$A^*_{\text{cumul.}}$ [GBq μA^{-1}]
2	15	0.789(3)	0.789(3)
Stack nr.	E_i [MeV]	A^* [GBq μA^{-1}]	$A^*_{\text{cumul.}}$ [GBq μA^{-1}]
1	18	0.576(6)	0.712(3)
2	21	0.434(4)	0.645(2)
3	24	0.358(4)	0.598(2)
4	26	0.294(4)	0.562(2)
5	29	0.267(6)	0.533(2)
6	30	0.254(4)	0.519(2)

Table 4.1: FLUKA simulated specific ^{11}C activity $A^* = \frac{A(^{11}\text{C})}{A_{\text{tot}}}$ and cumulative specific activity $A^*_{\text{cumul.}}$ resulting from adding BN stacks of 1 mm thickness (bottom) to the proposed 2 mm BN target (top). E_i is the primary proton beam energy at target entry, such that 5 MeV is retained by the proton beam exiting the target matrix. Note that A^* denotes the specific ^{11}C activity produced in the corresponding stack, and that the activities are given at saturation level.

It was not yet discussed that Figure 4.9 shows a comparison between the physical thick in-target production yield obtained from FLUKA simulations and from measured cross sections. FLUKA is a Monte Carlo particle physics transport code that is routinely applied at CERN for the simulation of particle generation and transport. However, it is most often used for high-energy experimental physics. Therefore, to validate its applicability at low-energies, the physical thick in-target production yield was calculated from measured cross sections, by fitting the tabulated cross section data (refer to Fig. A.1). The discrepancy factor between Y_{phys} obtained from tabulated cross section data and from FLUKA simulations is less than 1.50(20), which is a remarkably good agreement, considering the difficulty in fitting the cross section data. It is thus confirmed that FLUKA is able to provide reasonable estimations regarding the expected production yields, and justifies its application. The performed fits and further explanations regarding the yield calculation is reported in Appendix A.3.

4.2.2 Thermogravimetric analysis of BN and BN-C compounds at 1000 °C

In Section II.1.3, the high-temperature oxidation behavior of BN and carbon-doped BN samples was investigated using TGA-MS measurements. In detail, the mass change over time (TG-signal, Fig. 4.6) and the simultaneously detected A/q signals of the expected N_2 (Fig. 4.7) and CO evaporation products (Fig. 4.8), were illustrated for pure and carbon-doped BN-C[0.01, 0.1, 1, 5] samples. Regarding the BN-C study, it was pointed out that an increasing carbon concentration seems to result in an increased mass gain, indicating O_2 uptake due to the oxidation of the carbon content. In that regard, it was briefly mentioned that a qualitative evaluation of this modality was impossible, due to the entanglement of corresponding A/q signals and considerable background contributions. However, no detailed discussion concerning BN-C oxidation, and no illustration of the complications due to overlapping signals were presented. Therefore, this sections aims to elucidate the complexity of studying the carbon release properties using carbon-doped BN samples, which reinforces the necessity of investigating this modality from activated targets.

Figure 4.10 and 4.11 show the *Residual Gas Analysis* (RGA) of pure BN and BN-C[5] samples, respectively. In the BN case, the mass spectra of $\mu_{\text{O}_2} = -400$ and -340 kJ mol^{-1} present no significant A/q signals above background (Figs. 4.10a and 4.10b), which conforms with the negligible mass change in the TG spectra. On the other hand, $\mu_{\text{O}_2} = -300 \text{ kJ mol}^{-1}$ has a pronounced nitrogen signal, which can be associated with the detected mass change, as it does not correlate with the overall fluctuations.

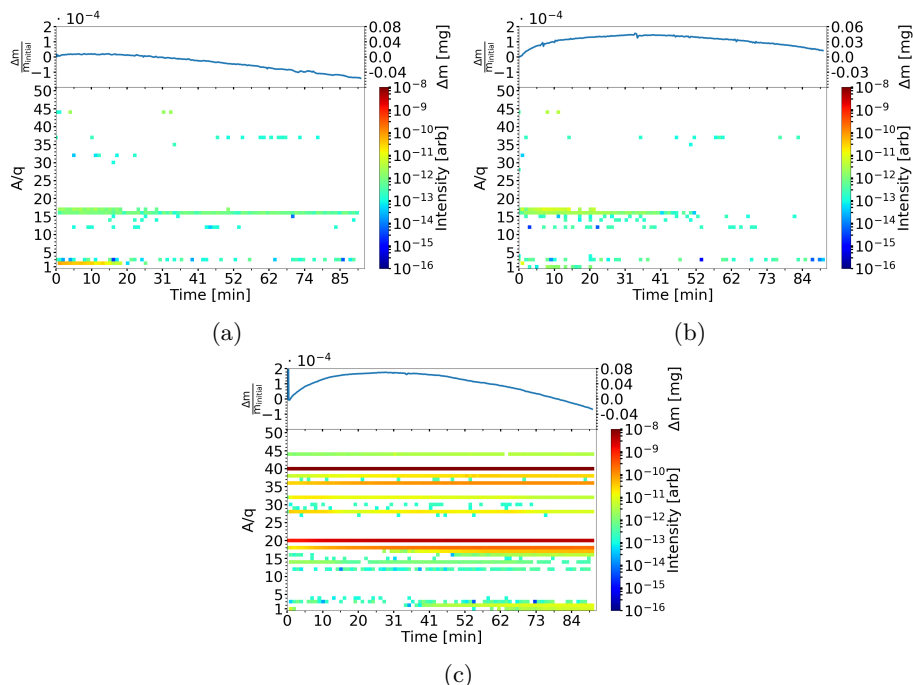


Figure 4.10: TGA-MS measurements of pure BN samples evaluated at different oxygen potentials: $\mu_{\text{O}_2} = -400 \text{ kJ mol}^{-1}$ (a), $\mu_{\text{O}_2} = -340 \text{ kJ mol}^{-1}$ (b) and $\mu_{\text{O}_2} = -300 \text{ kJ mol}^{-1}$ (c). A description of the experimental setup used to generate this plot is presented in Section II.1.3.

Consulting the impact of the pre-doped carbon on the oxidation kinetics, it seems that increasing carbon concentration mitigates the $A/q = 28$ signal (Fig. 4.7 (bottom)), whereas the mass gain increases (Fig. 4.6). A possible explanation could be that oxygen preferably binds to the carbon content in the BN-C matrix without being vaporized, instead of oxidizing BN which would release N_2 . It is however not possible to associate the $A/q = 28$ signal to either CO or N_2 , as there are no prominent signals at $A/q = 29$ or 30 , which would ease identification via the natural isotopic abundances of carbon and nitrogen. To illustrate this issue, the RGA data of BN-C[5] for $\mu_{\text{O}_2} = -400$, -340 and -300 kJ mol^{-1} is plotted in Figure 4.11. For some of the oxygen potentials, signals above background are recorded. However, the overall fluctuations of the MS data prevent us to draw definite conclusions. This characteristic is graphically expressed by the BN and BN-C samples' argon signal fluctuations, displayed in Fig. 4.12, when compared to the background contribution. In cases where an elevated A/q

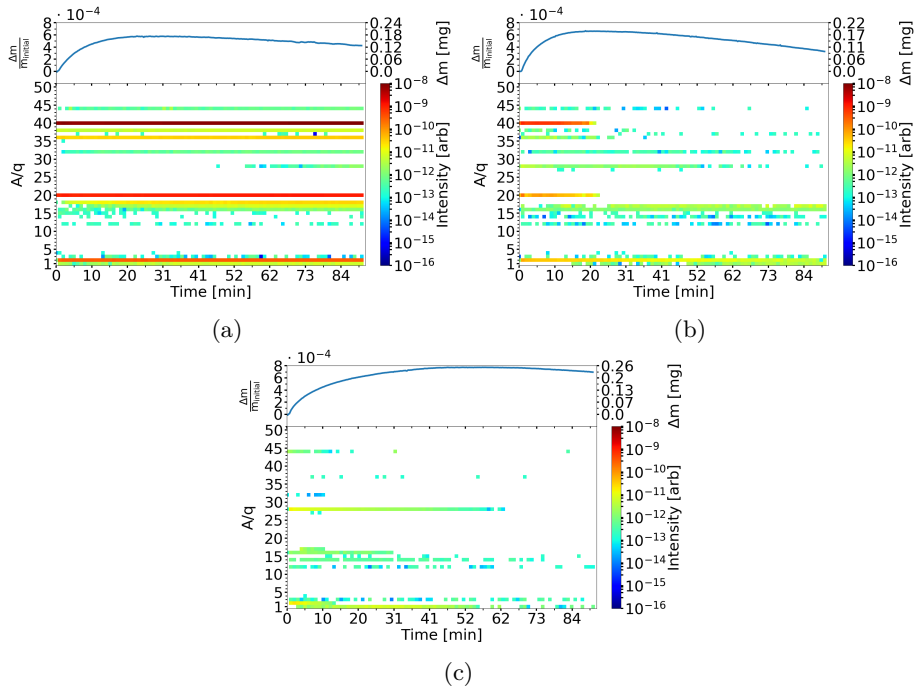


Figure 4.11: TGA-MS measurements of BN-C[5] samples evaluated at different oxygen potentials: $\mu_{\text{O}_2} = -400 \text{ kJ mol}^{-1}$ (a), $\mu_{\text{O}_2} = -340 \text{ kJ mol}^{-1}$ (b) and $\mu_{\text{O}_2} = -300 \text{ kJ mol}^{-1}$ (c). A description of the experimental setup used to generate this plot is presented in Section II.1.3.

signal is recorded (refer to Figs. 4.7 and 4.8), the argon signal is enhanced as well. Since the argon signal is not affected by the possibly occurring oxidation reaction, an increased $A/q = 40$ signal indicates overall fluctuations of the examined gas composition.

Besides the A/q signal's entanglement issue, it is possible that vaporized carbon oxides condensed in the gas transfer line before they reached the QMS. Although this might be conceived as rather unlikely, it is nonetheless an uncertainty factor, contributing to the overall ambiguity.

Summarized, it is not possible to conclude on possible carbon monoxide vaporization from the target, which would indicate beneficial circumstances for the carbon release, or whether oxygen binds to the carbon content but is not vaporized. Note that since the other carbon-doped TGA-MS measurements show the same features and do not contribute any additional information for the above

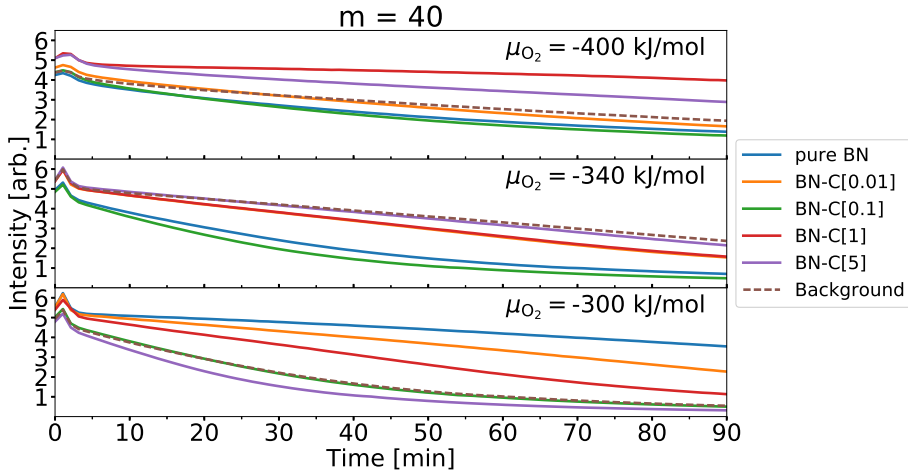


Figure 4.12: Recorded $A/q = 40$ (Ar) signal of TGA-MS measurements for pure and carbon-doped BN targets for different oxygen potentials $\mu_{O_2} = -400, -340, -300 \text{ kJ mol}^{-1}$ and varying C concentrations of the carbon-doped SPS pre-sintered BN powder compacts. A description of the experimental setup used to generate this plot is presented in Section II.1.3.

written discussion, they are not shown henceforth. In essence, studying pre-doped BN samples, using stable carbon as dopant, demonstrates the requirement of investigating carbon's release characteristics from the developed SPS pre-sintered BN target, by performing a dedicated release study from activated targets.

4.2.3 Thermal stability of BN and BN-C compounds up to 1500 °C

In Section II.1.2 the high-temperature stability of the developed SPS pre-sintered BN target was investigated by performing heat treatments up to 1500 °C in an evacuated furnace. It was observed that the dissociation rate is only moderate within this temperature region, which demonstrates that there are no operational limitations up to $T = 1500 \text{ °C}$, with respect to an ISOL application of this material. However, it was not reported in Article I that the release properties of carbon from BN were tested by pre-doping BN samples with stable carbon in the same modality as it was performed for the high-temperature oxidation kinetic's investigations.

In this section, the aforementioned high-temperature study of carbon-doped BN (BN-C) is discussed, which employed the experimental setup described in

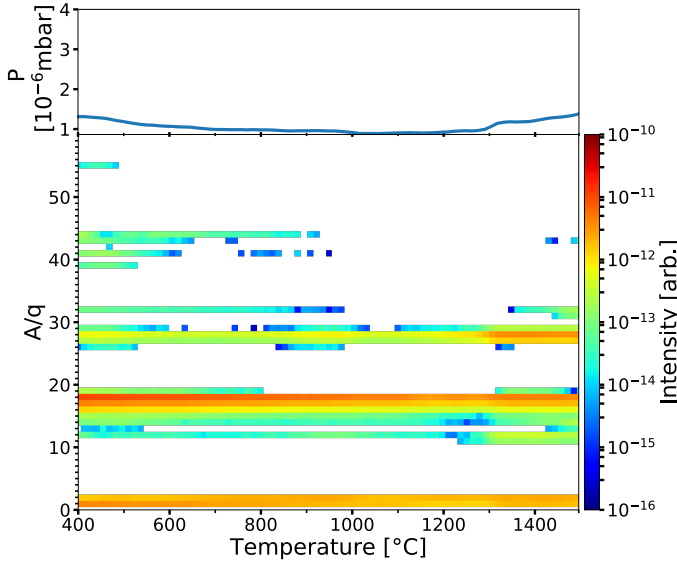


Figure 4.13: Heat treatment up to 1500 °C of SPS pre-sintered BN-C[5] in an evacuated furnace. (Top) Relative pressure and (bottom) mass spectrum detected during the heating cycle. A description of the experimental setup that was used to generate this plot is presented in Section II.1.2.

Section II.1.2. This comprises thermal treatments with simultaneous RGA of BN-C samples with carbon concentrations $[C] = 0.01, 0.1, 1$ and 5 wt.%. Note that the measurement order was: BN, BN-C[0.01], BN-C[0.1], BN-C[1], BN-C[5] and followed by a background measurement.

The RGA spectra indicate a gradual outgassing of the experimental setup during the course of the measurement campaign, expressed by a progressive reduction of the detected A/q signals. For clarification, the RGA of BN-C[5] is shown in Figure 4.13, which is significantly cleaner compared to BN's RGA (see. Fig. 4.4). Note that since the BN-C[0.01, 0.1, 1] runs, do not provide additional information for this discussion, they are not shown henceforth.

Figure 4.14 compares the detected $A/q = 12$ (C), 28 (N_2 , CO) and 29 (CO) signals of BN and BN-C[0.01, 0.1, 1, 5] samples depending on the temperature. At first, it seems that increasing carbon concentration stabilizes the system, as the nitrogen signal decreases (center). Note that a relative pressure reduction was likewise observed. However, due to the gradual outgassing, it is difficult to confirm this observation. The total mass loss of the heat treatment (see Tab. 4.2) seems to support the hypothesis of carbon stabilizing the system. However,

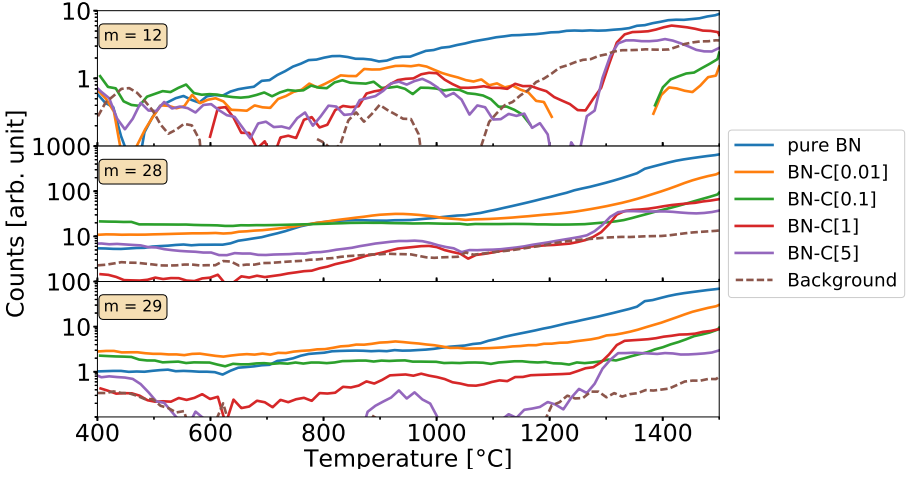


Figure 4.14: Comparison of different $A/q = 12$ (C), 28 (N_2 , CO) and 29 (CO) signals, recorded during thermal treatments of SPS pre-sintered BN and BN-C powder compacts with varying C concentrations. A description of the experimental setup used to generate this plot is presented in Section II.1.2.

with the given measurement uncertainties, it remains difficult to conclude. A potential carbon oxide evaporation can be assessed by comparing the detected $A/q = 12$ (C), 28 (N_2 , CO) and 29 (CO) signals, as depicted in Fig. 4.14. Analog to the previously reported high-temperature oxidation study, the identification of potential carbon oxide signals is complicated due to too large background contributions and overlapping signals. A sudden increase around $T \sim 1300$ °C is observed, which however cannot be associated to CO, as the isotopic abundance ratio $A/q(T > 1300 \text{ °C}) = \frac{29}{28} \approx 0.13$ is considerably larger than the expected 0.0112. Unfortunately, $A/q = 30$ which could have been associated with carbon monoxide, is not detected.

As a result, due to the system’s impurity level and due to the entanglement

	Pure BN	BN-C[0.01]	BN-C[0.1]	BN-C[1]	BN-C[5]
m_i [mg]	358.1(2)	340.1(2)	365.5(2)	348.4(2)	229.3(2)
m_f [mg]	356.3(2)	339.4(2)	364.6(2)	347.6(2)	228.9(2)
Loss [%]	0.51(6)	0.23(6)	0.21(6)	0.25(6)	0.32(8)

Table 4.2: Mass loss of BN and BN-C samples due to the heat treatments discussed in Section II.1.2.

of the $A/q = 28$ signals, it is not possible to conclude on the influence of the pre-doped, stable carbon within the SPS pre-sintered BN-C target matrix. This reassures the necessity to study the release properties from activated targets.

4.2.4 Thermal stability and oxidation kinetics of BN at 1500 °C during ISOL-target operation

The thermal studies that were described in [Article I](#) and in the previous two sections, provided first results regarding the operational limitations at high temperatures and controlled oxidizing atmospheres. In detail, these studies demonstrated that calibrated oxygen leaks, generating oxygen potentials up to $\mu_{O_2} = -300 \text{ kJ mol}^{-1}$, as well as temperatures up to 1500 °C impose no constraints on target operation. However, especially regarding the high-temperature stability studies, significant impurity levels of the experimental setup prevented to draw quantitative conclusions with respect to the dissociation kinetics of the developed BN target. For this purpose, complementary high-temperature studies were performed with improved experimental design. These studies aimed to provide more quantitative results regarding the time scale for which the target can be kept at such operational conditions.

Typically, ISOL targets are continuously irradiated and operated for several days, sometimes up to weeks, for physics experiments. In the BN target's case, which shall be applied in a cancer treatment facility for PET-aided hadron therapy, at least 16 h of continuous and reliable target operation are required. This time scale is motivated by the fact that the hadron facilities' accelerator complex is usually started during the night, to ensure steady patient treatment during the day.

The following experimental campaign deals with the investigation of operational limitations for such scenarios. In detail, high-temperature RGA was performed at $T = 1500 \text{ °C}$ for $t = 8$ and 16 h in vacuum, and controlled oxidizing atmospheres. Moreover, since reliable target operation is crucial concerning the medical requirements, it is important that the release properties remain constant throughout this time scale. Reviewing the sintering theory which was addressed in [Section 3.2](#), it is apparent that extended time periods at elevated temperatures, potentially, initiate further target sintering, i.e. densification and grain growth, which directly affect the isotope release process. To exclude this possibility, the microstructural stability was investigated by measuring the specific surface area (SSA) before and after the aforementioned heat treatments.

Experimental layout

The technical realization of an improved experimental setup was challenging, especially concerning the controlled oxygen supply. Since this aspect is relevant

for the mechanical development of a target container and target-ion source unit, the following paragraph will briefly discuss this modality, and a more detailed description is given in Appendix B. Figure B.1 shows a typical ISOLDE target testing unit, comprising a tantalum based cylindrical container into which the target material is loaded. Copper blocks hold the target container and allow high currents (typically 300 – 600 A) to flow through the assembly, thereby generating temperatures possibly exceeding 2000 °C via resistive heating. Thin tantalum sheets (~ 1 mm) are wrapped around the container, and serve as a heat screen, to mitigate radiative cooling effects. The target is closed with a stainless steel lid, which can be seen in the background of the picture, thus allowing to evacuate the entire system⁴. The experimental test bench used in this study (ISOLDE pump stand), connects such a heating unit to the required

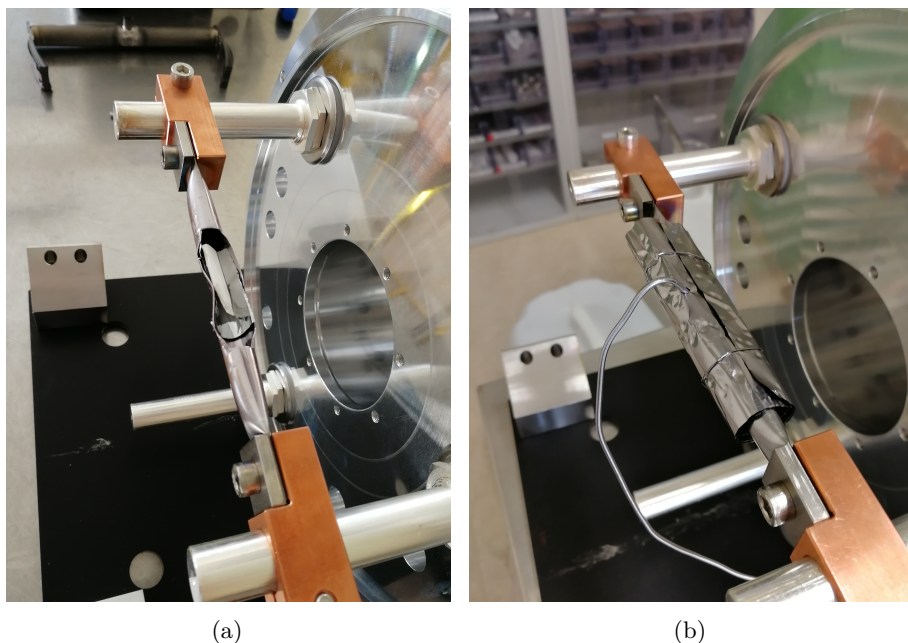


Figure 4.15: New ISOLDE heating unit comprising a carved Ta tube lined with a thin Re foil (a). A Ta sheet was wrapped around the sample bed and served as a heat screen (b). A Ta tube connected to a gas inlet was meant to provide a calibrated leak of $\sim 10^{-5}$ mbar 1 s^{-1} to the sample. However, it did not succeed concerning the O_2 supply, which will be outlined later in this section.

⁴Note that conventional ISOLDE targets are equipped with a transfer line which emerges radially out of cylindrical target container and guides the released atoms through molecular flow to the ion source for consecutive ionization.

power supply and a vacuum system, equipped with a pressure gauge and a QMS for simultaneous pressure read-out and residual gas analysis (RGA). The heating unit displayed in Figure B.1 was in fact tested in this study. However, it was excessively contaminated from previous studies, which resulted in very pronounced background signals (e.g. CO). Moreover, tantalum reacts with BN and therefore requires a protective layer to prevent direct contact. As a result, a new heating unit was built with new materials and a slightly simplified design (Fig. 4.15).

A plain tantalum tube was clenched between the copper blocks and an opening was cut which was used to load the sample. The entire ensemble was conductive, enabling resistive heating. Direct contact between Ta and the BN sample was prevented by placing a rhenium sheet inside the tantalum tube (Fig. 4.15a). Subsequently, a Ta sheet was wrapped around the system to diminish radiative cooling. For the high-temperature studies in regulated oxidizing atmospheres, a calibrated O₂ leak ($\sim 10^{-5}$ mbar l s⁻¹, using a 90/10 vol.% Ar/O₂ gas mixture) was guided from a gas inlet via a Ta tube to the sample (Fig. 4.15b). Generally, this setup demonstrated significantly cleaner conditions and yielded satisfactory results regarding the high-temperature treatments, which will be discussed first in the following section. However, it did not suffice regarding the high-temperature studies in controlled oxidizing atmospheres, as the metal-based gas feedthrough (within the target) failed to provide O₂ to the sample. This modality will be discussed later in this section.

Results: thermal stability of BN at 1500 °C in vacuum

Figure 4.16 shows an excerpt of the RGA of the 16 h heat treatment at 1500 °C, where $t = 0$ min denotes the time when the final temperature is reached, plus ten additional minutes to ensure that the assembly is in thermodynamical equilibrium. A blank background thermal treatment was performed to account for background signals, which was subtracted from the displayed data. Similar to the previous high-temperature RGA (refer to Sec. II.1.2), the most prominent signals are the common air constituents and other common species: H ($A/q = 1$), H₂O ($A/q = 18$), N₂ ($A/q = 28$), O₂ ($A/q = 32$), Ar ($A/q = 40$) and CO₂ ($A/q = 44$).

Since BN's dissociation is solely accompanied by the evaporation of N₂: $2\text{BN} \rightarrow 2\text{B} + \text{N}_2$, the time evolution of $A/q = 28$ is presented in Figure 4.17 (red, bottom). The recorded background contribution (green, bottom), as well as overall base pressure (top) are shown for comparison. One observes that upon heating ($t = 0$), the signal diminishes, where a sudden outburst occurs at $t \approx 30$ min ($T \approx 700\text{--}800$ °C), which most likely corresponds to the vaporization of condensed CO or N₂ residuals in the experimental setup. Subsequently, it decreases gradually over time. At first, it seems that in comparison to the background, an enhanced

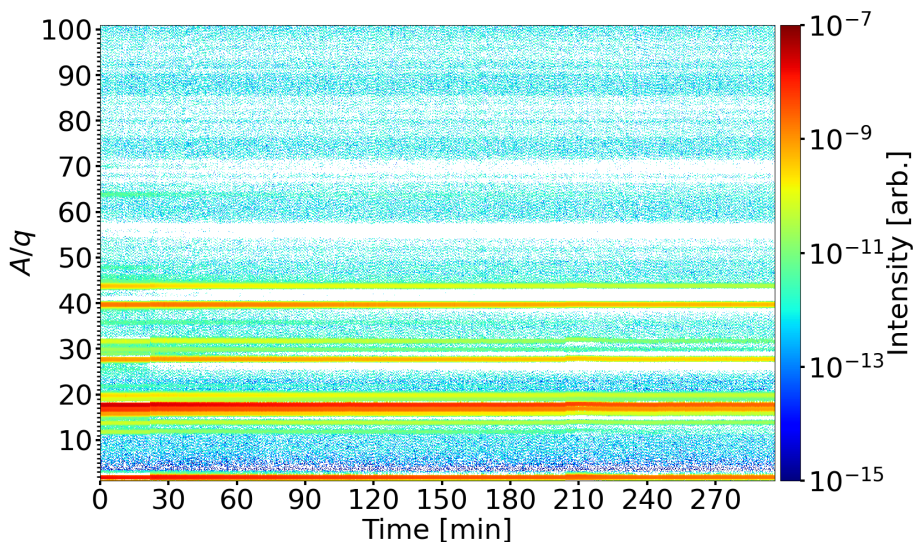


Figure 4.16: Excerpt of a 16 h RGA at $T = 1500\text{ }^{\circ}\text{C}$, probing a SPS pre-sintered BN target. $t = 0$ denotes the moment in time the system reached thermal equilibrium at the tested temperature. The displayed A/q signals have been corrected for background contributions.

N_2 evaporation is present. However, the aforementioned atmospheric and other common contributions to the mass spectrum, follow an equivalent trend, which resembles the time evolution of the overall pressure (top). Assuming an increased N_2 concentration in the residual gas, resulting from BN dissociation, one should observe an enhanced ratio when normalized to the vacuum's base pressure. However, this could not be confirmed from such a normalized representation. Consequently, the enhanced N_2 signal shown in Fig. 4.17 is rather the result of the increased base pressure and fluctuations. On the other hand, it is chemically conceivable that vaporized nitrogen reacts with the surrounding tantalum of the sample container and heat screens, forming TaN , which therefore circumvents detection in the QMS. However, a SEM-EDX⁵ analysis of the used heat screens could not confirm this possibility. Finally, the samples presented no significant weight loss for $t = 8$ and 16 h thermal treatments at $1500\text{ }^{\circ}\text{C}$.

Since the BN target seems to be thermodynamically very stable at the previously examined maximum temperature, and since the temperature control accuracy of the employed experimental setup may vary up to $50\text{ }^{\circ}\text{C}$, due to radiative

⁵Scanning Electron Microscope (SEM) uses electron beams probing a material's surface on a nanoscale. Energy-Dispersive X-ray (EDX) is an analytical tool which can be employed to determine the atomic composition of the material.

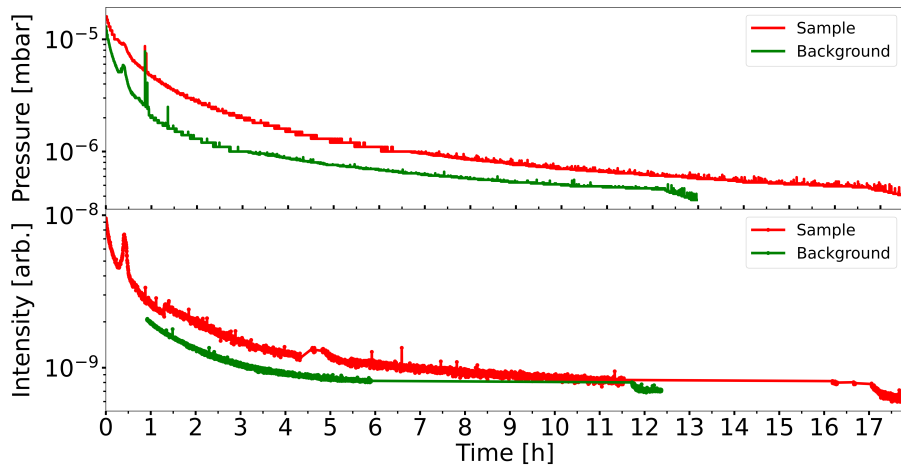


Figure 4.17: $A/q = 28$ signal of a 16 RGA at $T = 1500$ °C (bottom) and the recorded overall base pressure (top), probing a SPS pre-sintered BN target (red). Heating was initiated at $t = 0$ and thermal equilibrium at final temperature was reached around $t = 1$ h. The equivalent A/q signal of a blank background measurement is shown for comparison (green). Note that the flat lines resulted from network connection issues of the QMS with the data acquisition system, and that the background's A/q signal during heating was not recorded.

cooling and non-reproducibility of the exact heat screen assembly, the impact of temperatures exceeding 1500 °C was studied. For this purpose, a SPS pre-sintered BN sample was heat treated, whereas the temperature was step-wise increased in 50 °C intervals, spanning from 1500 to ~ 1950 °C. To ensure thermodynamic equilibrium, the system was kept constant for ten minutes, before proceeding to the following temperature value. During this treatment, the base pressure and gas composition was monitored, in order to perform a residual gas analysis (RGA). Prior to this experiment, the sample was kept at 1500 °C for approximately five hours, to outgas the system and to stabilize the A/q signals. Moreover, a blank measurement was performed to correct the recorded spectrum for background contributions.

The result is shown in Fig. 4.18, where one can clearly observe a gradual increase of the nitrogen signals ($A/q = 14, 28$ and 29). Other constituents, such as hydrogen, carbon and carbon dioxide ($A/q = 1, 12$ and 44, respectively), present a very similar increase pattern. It is thus conceivable that the $A/q = 28$ comprises CO to some extent. Moreover, each temperature step demonstrates a sudden increase, followed by a moderate signal attenuation. This could indicate that the signal increase rather results from an outgassing of the system, instead

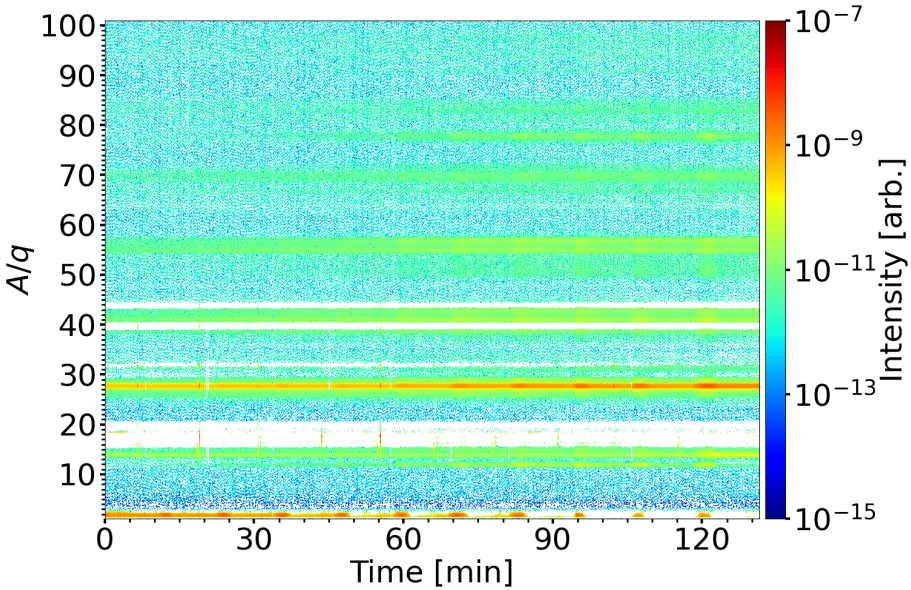


Figure 4.18: RGA of a SPS pre-sintered BN target where the temperature is increased in ~ 50 $^{\circ}\text{C}$ steps. For each temperature step, the A/q signals were recorded for ten minutes after the system reached thermal equilibrium, and corrected for background contributions. Prior step-wise temperature increase, the loaded setup was kept for five hours at 1500 $^{\circ}\text{C}$ to stabilize the system.

of the dissociation of boron nitride. This aspect can however be better assessed by examining the time evolution of the $A/q = 28$ signal compared to the background (bottom) and overall pressure (top), shown in Figure 4.19. Note that the indexes A to K denote the different temperature regions, which are specified in the figure's caption. Firstly, one observes that nitrogen's mass-over-charge signal exceeds the background signal across the entire time-temperature evolution, whereas the base pressure is lower, but approaches the background level towards $T \approx 1950$ $^{\circ}\text{C}$. The signal's profile clearly resembles the step-wise temperature increase, which was already indicated in the RGA (Fig. 4.18), where for temperatures exceeding 1700 $^{\circ}\text{C}$, the increase seems to be more pronounced. However, the aforementioned signal attenuation after temperature and signal increase, likewise enhances for higher temperatures. Comparing the sample's time-temperature evolution to the background, the profiles exhibit a very similar pattern. However, above 1700 $^{\circ}\text{C}$, the sample-to-background ratio (S-to-B) seems to increase slightly, indicating enhanced BN dissociation kinetics. On the other hand, consulting the actual ratios with given measurement uncertainties, deduced from the RGA data (Tab. 4.3), it is not possible to verify

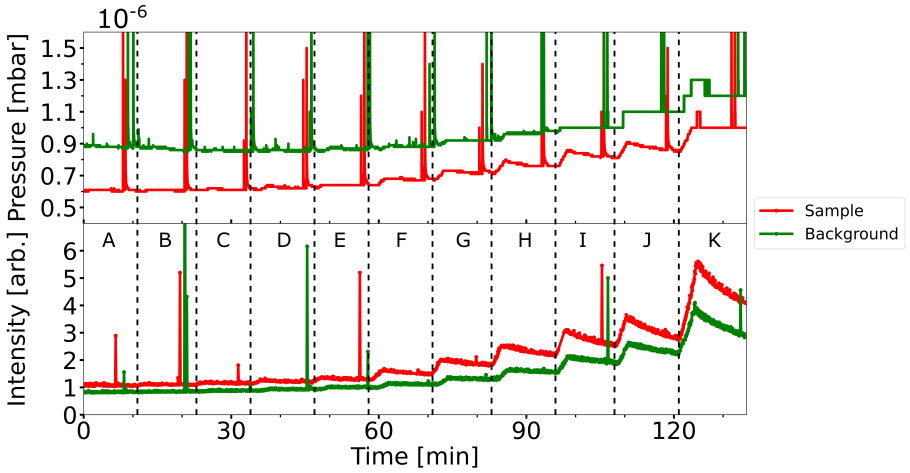


Figure 4.19: Recorded $A/q = 28$ signal (bottom) of a thermal treatment where the T is increased in $\sim 50^\circ$ steps, probing a SPS pre-sintered BN target (red) and an equivalent background measurement (green). The overall base pressure (top) was recorded simultaneously. Each T was recorded for ten minutes at thermal equilibrium, with: A ≈ 1500 , B ≈ 1550 , C ≈ 1600 , D – E ≈ 1650 , F ≈ 1700 , G ≈ 1750 , H ≈ 1800 , I – J ≈ 1850 , K $\approx 1950^\circ\text{C}$. Prior step-wise T increase, the loaded setup was kept for five hours at 1500°C to stabilize the system.

this observation.

Note that the five hour heat treatment at 1500°C , followed by the time-temperature profile illustrated in Figure 4.19, resulted in a total mass loss of approximately $0.11(4)\%$, which is surprisingly low. Furthermore, the high-temperature treatment of SPS pre-sintered BN targets at 1500°C for 8 and 16 h, essentially, showed no mass loss with the given measurement uncertainties. This

	A	B	C	D	E	F
S-to-B	1.32(23)	1.30(3)	1.33(11)	1.30(12)	1.40(50)	1.37(3)
	G	H	I	J	K	
S-to-B	1.42(4)	1.43(4)	1.35(18)	1.233(31)	1.37(11)	

Table 4.3: Sample-to-Background ratio (S-to-B) deduced from RGA data, recorded when heat treating a BN target with temperatures between 1500 and $\sim 1950^\circ\text{C}$ (refer to Fig. 4.19).

is on the one hand, very beneficial in the context of ISOL-type target operation, but on the other hand opposing to some extent the previous findings of high-temperature studies reported in [Article I](#) (Sec. 4.1), indicating slightly enhanced mass losses. A possible explanation could be a chemical reaction between boron nitride and alumina for temperatures exceeding $T \approx 1200 - 1300$ °C, resulting in the dissociation of BN. The studies reported in Sec. 4.1 and 4.2.2 employed Al_2O_3 in the experimental setup, whereas the assembly used for the advanced high-temperature dissociation study was solely metal based. This feature was postulated by G.D. Alton et al. consulting chemical equilibrium calculations [144]. However, similar calculations conducted with HSC, which is used in this work for qualitative indication of the thermochemical interplay between different materials, could not reproduce these results. Furthermore, such calculations should be treated with caution, and rather be used as a first indication for experimental studies, as for instance BN’s high-temperature stability was assessed being problematic in vacuum at temperatures around $T \approx 1100^\circ\text{C}$ (refer to Fig. 4.3), which was experimentally contradicted in this thesis.

To assess whether long thermal treatments affect the target’s microstructure, the specific surface area (SSA) of the fabricated SPS pre-sintered BN powder compact was evaluated before and after heat treatment. The SSA is an observable which indicates whether densification and grain growth occurred, as these processes reduce the material’s accessible surface area. For this purpose, nitrogen physisorption isotherms were recorded, which were introduced in Section 3.4.2.

Table 4.4 shows the measured SSA of pristine BN powder, SPS pre-sintered BN and different *Heat Treated* (HT) samples, which were kept for varying duration at 1500 °C. Note that the assessed pre-sintered BN target is associated with a larger uncertainty, which stems from measurements of two different samples, therefore, accounting for the additional statistical uncertainty. The other measurements result from a single analysis, which consequently indicates that their systematic error is underestimated. With the given measurement uncertainties, it seems that the high-temperature treatments do not affect the

Sample	Powder	Target	16 h HT	8 h HT	HT*
SSA [$\text{m}^2 \text{g}^{-1}$]	8.590(80)	8.33(37)	8.272(29)	8.523(19)	8.636(26)

Table 4.4: Specific surface area (SSA) of pristine BN powder, SPS pre-sintered BN and different heat treated (HT) samples. HT* refers to the heat treatment with step-wise temperature increase up to ~ 1950 °C, presented in Fig. 4.18 and 4.19, recorded after 5 h signal stabilization at 1500 °C.

SSA. In other words, no further degree of sintering occurs due to the thermal treatments, demonstrating that grain size and porosity remain stable throughout target operation. Interesting is that the pristine powder used for the fabrication of the BN target possesses essentially the same SSA before sintering. The supplier provided a slightly higher average value of $13 \text{ m}^2 \text{ g}^{-1}$, whereas $8 \text{ m}^2 \text{ g}^{-1}$ was reported as the minimal value of a given distribution. It was however difficult in this experimental campaign to measure the pristine powder's SSA, as the powder could not be mounted easily into the measuring apparatus. Nonetheless, these results confirm the findings of the porosity measurements of the SPS pre-sintered target, reported in Sec. 3.4.2, which demonstrated that the fabrication process is not accompanied with significant densification. In addition, the SSA measurements indicate that no significant grain growth occurs during thermal treatments.

Results: oxidation kinetics of BN in controlled oxidizing atmospheres at 1500 °C

Next to the dissociation characteristics at high temperatures, it was intended to study the oxidation behavior at the foreseen operational conditions. However, the delivery of a sufficient O_2 flow to the target material is remarkably complicated. Since this is relevant from a practical point of view, when producing a dedicated BN based target-ion source unit for the production of ^{11}C beams for PET-aided hadron therapy, this aspect will be discussed briefly in the following, and in more detail in Appendix B.

While the tantalum based heating unit shown in Fig. 4.15 functioned very well for the high-temperature studies in vacuum, it was not possible to provide oxygen to the sample, using the calibrated leak displayed in Fig. 4.15b. As stated previously, a 90/10 vol.% Ar/O_2 gas mixture was employed with a $\sim 10^{-5} \text{ mbar l s}^{-1}$ calibrated leak. While the Ar contribution could be detected with the QMS, no O_2 could be observed. This stems from the tantalum parts, and especially from the tantalum tube guiding the gas mixture from the gas inlet to the sample. At elevated temperatures, Ta strongly reacts with O_2 , therefore consuming the low amount present in the gas mixture. This issue is in fact of concern for other metals, such as molybdenum, tungsten and graphite, commonly used for the fabrication of target containers, vessels and transfer lines. These parts are either purposely kept at higher temperatures to enhance diffusion within the target matrix and to diminish retention times due to adsorption, or are indirectly heated from the deposited power of the primary particle beam employed for isotope production. It was therefore decided to replace most of the metal parts with ceramic materials, firstly, to ensure O_2 supply to the sample, and secondly, to guarantee that evaporated gases of interest (N_2) reach the QMS for RGA, instead of, potentially, reacting with surrounding hot metal

surfaces. Figure B.2 shows the developed technical solution, mostly comprising alumina ceramics (Al_2O_3). Note that a direct contact between Al_2O_3 and BN was avoided, using a thin ($\sim \text{mm}$) Re sheet as lining.

To investigate the high-temperature oxidation behavior at $T \sim 1500^\circ\text{C}$ and oxidizing atmospheres with oxygen potentials $\mu_{\text{O}_2} \leq -300 \text{ kJ mol}^{-1}$, three measurements were taken in the following order: (i) background measurement where the gas leak is opened at final temperature, (ii) an equivalent measurement with a SPS pre-sintered BN sample and (iii) a measurement probing the BN target in this assembly without applying the calibrated oxygen leak.

Figure 4.20 shows the recorded residual gases' time evolution during dwell-time at $T \sim 1500^\circ\text{C}$, represented by the detected mass-over-charge ratio as a function of time. These plots illustrate the major complication in the analysis, which are the considerable background gases present in the experimental setup. One observes that the experimental setup outgassed gradually during the measurement campaign. The background spectrum (i) shown in Fig. 4.20a, clearly presents the most polluted RGA, which unfortunately, implies its impracticability to serve as a correction medium for the following measurements. The BN sample, heat treated applying the calibrated O_2 leak (ii) (Fig. 4.20b) features considerable atmospheric background signals, such as water ($A/q = 18$) and carbon dioxide ($A/q = 44$), which are however fading throughout the measurement. Unfortunately, only the measurements taken without external oxygen supply (iii) shows a reasonably clean spectrum.

Signals of interest, with respect to the oxidation behavior of BN in typical ISOL-target conditions, are unfortunately only N_2 and its isotopic abundances. As previously discussed, nitrogen evaporation results from both target dissociation and oxidation (refer to Eq. (4.2)), where it was shown in the previously reported advanced high-temperature study, as well as in Secs. II.1.2 and 4.2.3 that the dissociation rate of the developed BN target at given environmental conditions is either negligible or not detectable. Figure 4.21 shows the time evolution of the N_2 signal ($A/q = 28$) compared to the background measurement, as well as several other selected residual gases (H_2O , O_2 , Ar and CO_2). In detail, Fig. 4.21a shows the entire thermal cycle, including heating and cooling (bottom) and the simultaneously measured base pressure (top). As mentioned in the previous paragraph, one observes gradual outgassing over time, whereas the N_2 (red, bottom) decrease is noticeably slower compared to the background measurement (dotted red). Moreover, other residuals, such as water (blue) and CO_2 (orange) decrease much more rapidly, and the overall base pressure (black, top) is slightly higher compared to the background measurement (dotted black, top), which was however, in general, more polluted (see Fig. 4.20).

A possible explanation for this observation could be an equilibrium amount

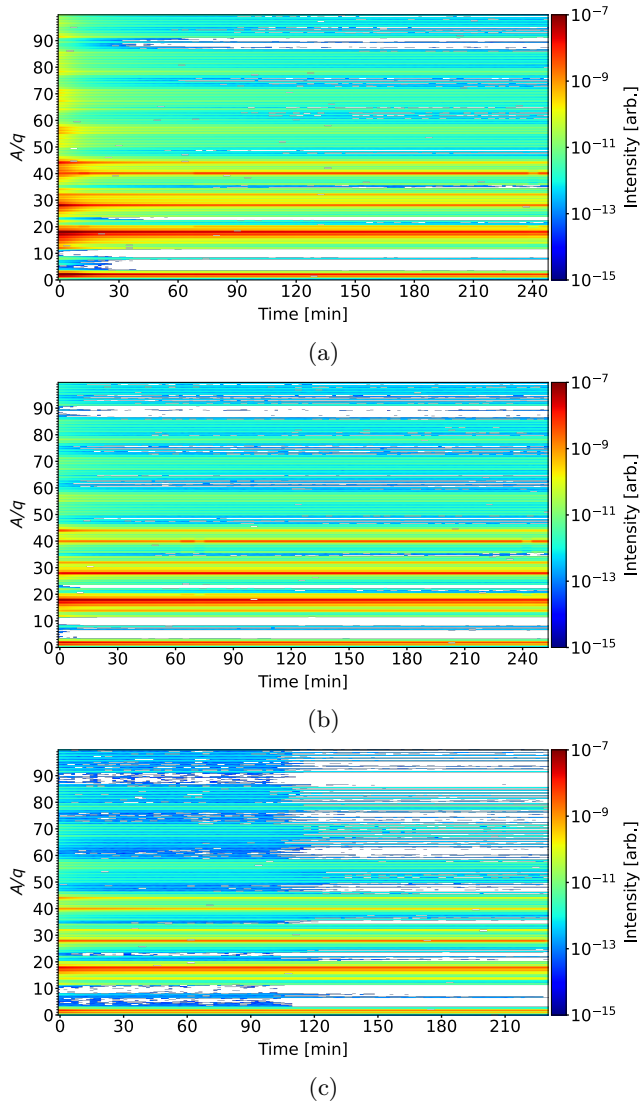


Figure 4.20: RGA of SPS pre-sintered BN targets at high-temperatures (~ 1500 °C) and controlled oxidizing atmospheres (O_2 leak: $1.6 \cdot 10^{-5}$ mbar $l\ s^{-1}$). (a) background measurement, (b) BN sample with O_2 leak open and (c) BN sample with O_2 leak closed.

of free oxygen inside the alumina tube (refer to Fig. B.2), which originates

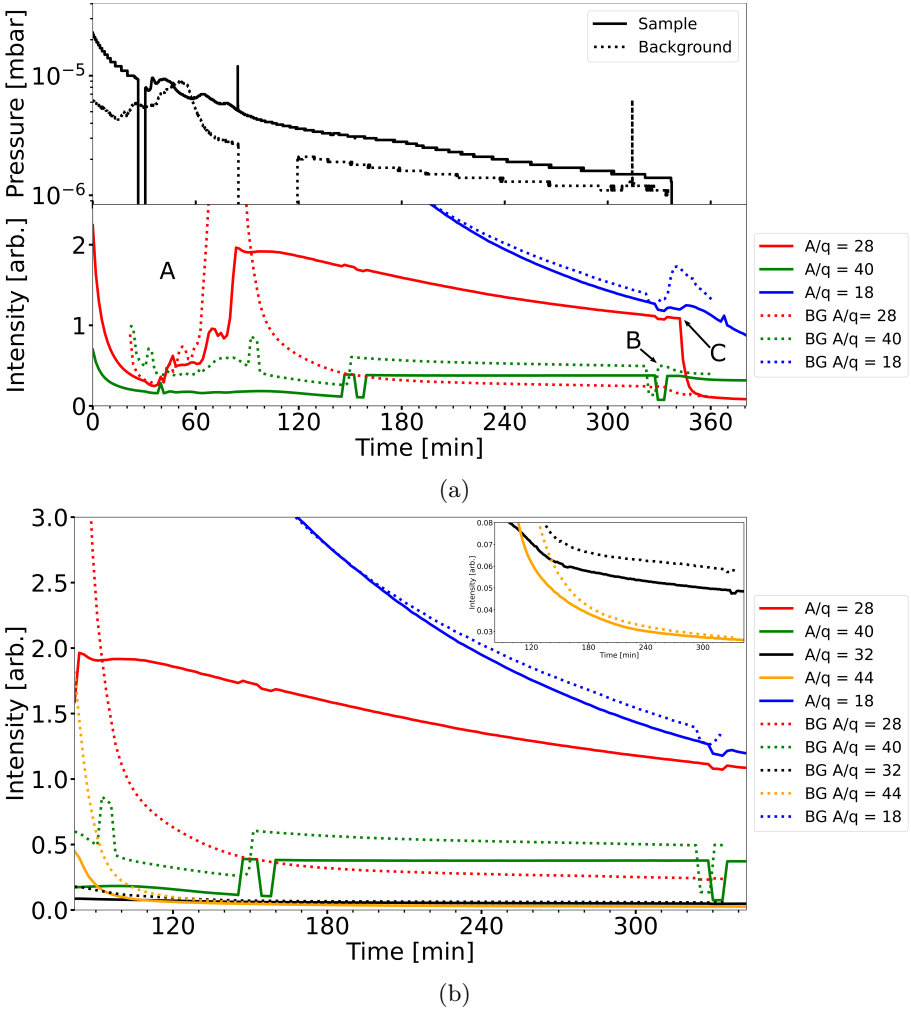


Figure 4.21: (a) Detected A/q signals during heating (A), dwell-time at $\sim 1500^\circ\text{C}$ and cooling (B and C for background and sample cooling, respectively), probing a SPS pre-sintered BN sample applying a 90/10 vol.% Ar/O₂ calibrated leak of $1.6 \cdot 10^{-5} \text{ mbar l s}^{-1}$. Corresponding background signals are shown for comparison, which were measured beforehand (bottom). Simultaneously recorded base pressure (top). (b) Detected A/q signals solely during dwell-time at final temperature.

from the dissociation of Al₂O₃ at the tested temperature. Consequently, this

free oxygen could oxidize the target material, resulting in the less steep slope of the N_2 signal during dwell-time. This process is however mitigating over time, as the subsequent measurement without external O_2 supply (Fig. 4.22) exhibits very constant N_2 and O_2 signals (see Fig. 4.22b). This hypothesis is supported by three observations: firstly, in both measurements probing BN, the N_2 signal drops abruptly upon cooling, whereas the background's N_2 signal, as well as the other residual gases, feature considerably slower decreases. This aspect is indicated by points (B) and (C) in Figs. 4.21a and 4.22a. Alumina is stable up to 1500 °C in vacuum, which corresponds to the temperature that was examined in the sample's spacial region. However, due to the Boltzmann distribution, a certain amount of molecules possess higher thermal energies, which therefore thermodynamically favor Al_2O_3 dissociation. This effect diminishes exponentially with decreasing temperature, resulting in less free oxygen and thus, less BN oxidation. The second observation, supporting the aforementioned hypothesis, is the samples' mass loss due to these thermal treatments. Mass losses of 0.791(60)% and 0.516(61)% were measured, for applied and not applied O_2 leak, respectively. This is reasonably higher compared to the mass loss of the high-temperature treatments reported in Sec. 4.2.3, which were performed for considerably longer duration and, in one case, higher temperatures. Thirdly, a grey layer was found on the alumina tube after the thermal treatments, which unfortunately, was as well observed on the samples' surfaces. This thin layer probably originates from aluminium deposition, which source is discussed in Appendix B.

Assuming that the atmosphere surrounding the BN sample is more oxygen-rich, as motivated above, one can nonetheless identify in Figure 4.21 that external oxygen supply via the calibrated leak has an effect on the detected residual gases. During the approximately 250 min dwell-time at $T \sim 1500$ °C (Fig. 4.21b), the calibrated leak was sequentially opened and closed around $t = 150$ and 330 min. This is observed best by examining the $A/q = 40$ signal, which corresponds to argon and accounts for $\sim 90\%$ of the calibrated leak. Upon opening and closing the calibrated leak, one can clearly identify the effect on the H_2O , N_2 , O_2 and Ar signal. Moreover, in the background case, minor changes in the N_2 signal are likewise detected, indicating that the gas feedthrough possessed traces of residual water and nitrogen vapors.

To quantify whether the application of the calibrated leak, significantly influences the target oxidation behavior, the absolute signal change $\Delta(A/q)$ was deduced from the RGA data and is reported in Table 4.5. The impact on the nitrogen signal is clearly enhanced when a BN sample is employed, which in theory should also impact the oxygen signal. However, given that the O_2 signal was generally very low and the fact that it is consumed in chemical reactions whenever it contacts a hot metal surface (e.g. heating elements), this feature cannot be

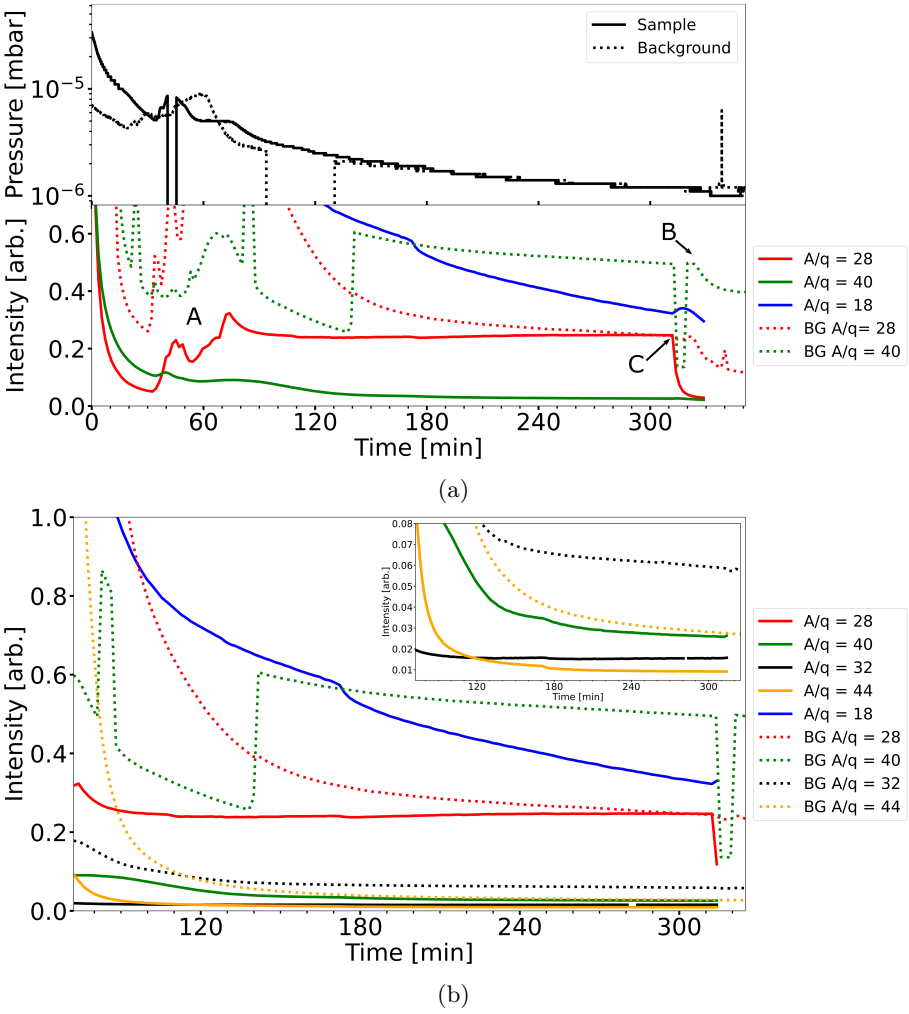


Figure 4.22: (a) Detected A/q signals during heating (A), dwell-time at $\sim 1500^\circ\text{C}$ and cooling (B and C for background and sample cooling, respectively), probing a SPS pre-sintered BN sample without additional external O_2 supply. Corresponding background signals are shown for comparison, which were measured beforehand (bottom). Simultaneously recorded base pressure (top). Note that the BG $A/q = 18$ signal is not shown as it lies outside the displayed detection limits. (b) Detected A/q signals solely during dwell-time at final temperature.

A/q	18 (H ₂ O)	28 (N ₂)	32 (O ₂)	40 (Ar)
Sample	7(4)	2.85(82)	0.008(6)	28.4(13)
Background	9(3)	0.826(84)	0.008(5)	36.0(26)

Table 4.5: Signal change $\Delta(A/q)$ [arb.] due to opening and closing a calibrated leak ($1.6 \cdot 10^{-5}$ mbar l s⁻¹ using a 90/10 vol.% Ar/O₂ gas mixture) during a BN heat treatment. Deduced from a RGA, visualized in Fig. 4.21.

deduced from the RGA data.

Consulting the $\Delta(A/q) = 40$ change, it can be seen that the impact on the target oxidation is possibly higher as indicated by comparing the sample's and background's $\Delta(A/q)$. One has to keep in mind that the external part of the gas feedthrough of the calibrated leak gas system is filled with the gas mixture above ambient pressure. This process was however manually regulated, i.e. it is possible that, compared to each other, the gas feedthrough was unequally pressurized, which would influence, to some extent, the actual gas volume seeping through the calibrated leak into the target unit. During the experiment deviations of $\lesssim 0.02$ bar were observed. Assuming that such deviations result in a measurable signal fluctuation, the $\Delta(A/q) = 40$ difference between sample and background measurement indicate that in the latter case the absolute gas flow seeping through the calibrated leak was enhanced. As a consequence, the actual N₂ signal's enhancement, which correlates with BN oxidation rate's enhancement, originating from the external oxidation supply, might be larger than indicated by the values reported in Tab. 4.5.

The determination of the oxidation-rate increase due to the external O₂ supply is difficult, and principally requires a measurement deducing the N₂ ionization efficiency of the QMS. Without its knowledge, meaningful estimation regarding the oxidation modality can only be extracted by studying ratios. For this purpose, it is assumed that the background's $\Delta(A/q) = 28$ signal change, originating from residual nitrogen traces in the gas feedthrough, is equally present during the sample's measurement. Moreover, it is assumed that the constant oxidation rate due to free O₂ in the atmosphere resulting from the alumina tube, corresponds to the measured signal shown in Figure 4.21b, where no calibrated leak was applied. Employing these assumption, one can find for the oxidation-rate increase Δk_{ox} due to external oxygen supply:

$$\Delta k_{\text{ox}} = \frac{\Delta(A/q)^{\text{S}} - \Delta(A/q)^{\text{BG}}}{(A/q)^{\text{S}^*}} = 8.2(3.4)\%.$$

$\Delta(A/q)^{\text{S}, \text{BG}}$ denote nitrogen's signal change due to opening and closing the calibrated leak for the sample and background measurement, respectively

(refer to Tab. 4.5). $(A/q)^{S^*}$ represents the averaged N_2 signal resulting from background contributions and oxidation due to O_2 originating from the Al_2O_3 tube (refer to Fig. 4.21b). Considering the overall measurement uncertainties, pollution of the experimental setup during the earlier measurements and the assumptions required for this estimation, instead of declaring an absolute value, it is reasonable to declare an upper limit:

$$\Delta k_{ox} < 12\%.$$

4.3 Summary & conclusion

In this chapter, the operational limitations of the developed SPS pre-sintered BN target were investigated with respect to its application in typical ISOL-target conditions, i.e. high temperatures and low pressures ($\sim 10^{-6}$ mbar). Moreover, limitations due to target oxidation at such conditions was examined, since $^{11}CO^+$ beam production is considered to enhance isotope release and transport efficiencies.

Since the ^{11}C production is maximized, employing a low energy primary proton beam with high intensity, pronounced target heating is expected from target irradiation. To optimize the thick in-target production yield versus energy deposition, calculations and simulations based on tabulated cross section data and using the Monte Carlo particle transport code FLUKA have been performed (refer to Secs. II.1 and 4.2.1). A primary proton accelerator providing energies of 15 MeV and a 2 mm thick target, such that 10 MeV are deposited within the target matrix were found to be a reasonable compromise, yielding a physical and saturation in-target production yield of $Y_{phys} = 1.37(1) \cdot 10^{-3}$ nuclei per primary and $Y_{sat} = 8.55(6)$ Gbq μA^{-1} , respectively.

The developed BN target was reported to be thermodynamically stable at temperatures around 1500 °C (principally, even up to 2000 °C), for expected operational durations of 8 to 16 hours. The total mass loss was negligible for the aforementioned scenarios (Secs. II.1.2, 4.2.3 and 4.2.4). In addition, the target's microstructure (grain size) was discovered to be stable for such thermal treatments, by measuring the change in specific surface area (SSA). No further degree of sintering could be determined considering given measurement uncertainties, indicating no significant microstructural deterioration (refer to Sec. 4.2.4).

The impact of applying a controlled oxygen supply to the target during operation, to promote molecular ^{11}C extraction in the CO sideband, was examined via different modalities.

TGA-MS measurements probing the BN target at $T = 1000$ °C and oxygen potentials $\mu_{O_2} = -400, -340$ and -300 kJ mol $^{-1}$ revealed that no or very

moderate oxidation occurs (refer to Sec. II.1.3). As a result, no limitations are expected by operating the target in controlled oxidizing atmospheres with $\mu_{\text{O}_2} \leq -300 \text{ kJ mol}^{-1}$.

Supplementary studies at 1500 °C in a typical ISOL-target unit and low base pressures ($\sim 10^{-6}$ mbar) revealed two important aspects: The application of a calibrated leak ($\sim 10^{-5}$ mbar l s⁻¹ using a 90/10 vol.% Ar/O₂ gas mixture) to promote ¹¹CO formation is feasible and imposes no operational limitations. The oxidation rate's enhancement, due to the external O₂ supply was discovered to be less than 12%, whereas the overall target oxidation was moderate, as suggested by the mass loss of less than 1%.

The second aspect that was discovered during these studies was that the technical realization of a target unit for such experimental studies is extremely challenging. Hot metal parts consume the externally provided oxygen unless the target design is carefully optimized. This difficulty directly translates to the mechanical aspect concerning the development of a tailored target-ion source unit for ¹¹CO⁺ RIB production and therefore, needs to be addressed for the production of intense mass separated ¹¹C beams for PET-aided hadron therapy. A more detailed description of the encountered issues and of the experimental layout used for the aforementioned studies can be found in Appendix B.

It is noteworthy that, probably, the aforementioned impact of the calibrated leak on the oxidation rate was observed on top of a 'background' oxidation, due to oxygen originating from partial dissociation of ceramic parts used for the fabrication of the heating unit. While the application of the calibrated leak had a measurable impact on the oxidation rate, as discussed, its contribution to the overall moderate oxidation was at most 12%. It may therefore be more practical to employ the partial dissociating of oxygen-comprising ceramic tools as passive O₂ supply feature, instead of incorporating a calibrated leak into the target-ion source unit. Such a technical solution is certainly easier to accomplish, and may suffice as the required oxygen supply to promote ¹¹CO formation. However, it must be ensured that this process occurs in a controlled modality.

During the high-temperature studies reported in Secs. II.1.2 and II.1.3, it was attempted to study carbon's release characteristics from the developed BN target, by examining carbon-doped samples at high-temperatures and controlled oxidizing atmospheres. For this purpose, stable carbon was added to the BN powder, prior to the SPS pre-sintering fabrication process. Unfortunately, no conclusive results could be obtained. The major challenges in that regard were large background contributions and overlapping A/q signals which could therefore not be associated to either target dissociation, oxidation or evaporated carbon oxide species. It was therefore concluded that carbon's release properties from the developed BN target can only be deduced from activated target studies

(refer to [Article I](#)). Such a study was performed and will be discussed in the following chapter.

Chapter 5

Hot target characterization

The previous chapter addressed the expected thick in-target production yield and operational constraints of the SPS pre-sintered BN powder compact. A proper understanding of the latter aspect is an essential step before a newly developed ISOL-target can be considered for on-line application. The reported studies identified that target operation at temperatures up to $T = 1500\text{ }^{\circ}\text{C}$ and controlled oxidizing atmospheres of $\mu\text{O}_2 \leq -300\text{ kJ mol}^{-1}$ with overall low pressures is feasible. These frame conditions are consequently applied for all subsequent considerations and experimental investigations.

With respect to the accomplishment of a ^{11}C RIB production system that meets the high beam intensity requirements ($4 \cdot 10^8$ ions per spill) and can be implemented into existing hadron therapy centers, the release efficiency must be known in order to approximate the RIB production yield. The assessment of carbon's release properties from the developed BN target by means of pre-doped targets using stable carbon, is inapplicable, as reported in the previous chapter. It was therefore concluded that this modality can only be determined from activated target studies, i.e. hot target characterization. Such studies are ideally performed directly at ISOL facilities in dedicated on-line experiments [138, 145–147]. However, beam time is limited. The following article presents an alternative approach, where the release properties are extrapolated from an off-line experiment, utilizing the knowledge of the target's microstructure, obtained from systematic cold characterizations.

5.1 Article II: ^{11}C release from a porous boron nitride target

Note that the following article has been extended compared to the version which was submitted for peer-review. While these extensions merely correspond to supplementary descriptions of fundamental phenomena and explanations of employed experimental techniques, some paragraphs needed to be adjusted accordingly. This section is therefore not a verbatim copy of the corresponding article, but is more appropriate for a thesis format.

^{11}C release from a porous boron nitride target

S. Stegemann^{a,*}, J. Ballof^b, T.E. Cocolios^a, J.-G. Correia^{c,d}, K. Dockx^a, O. Poleshchuk^a, J.P. Ramos^{a,b,**}, J. Schell^{c,e}, T. Stora^b, J. Vleugels^f

^a KU Leuven, Institute for Nuclear and Radiation Physics, Department of Physics and Astronomy, Heverlee, Belgium

^b CERN, EN-STI, Geneva, Switzerland

^c CERN, EP-UIS, Geneva, Switzerland

^d Centro de Ciências e Tecnologias Nucleares, Instituto Superior Técnico, Universidade de Lisboa, Bobadela LRS, Portugal

^e Institute for Materials Science and Center for Nanointegration Duisburg-Essen (CENIDE), University of Duisburg-Essen, Essen, Germany

^f KU Leuven, Department of Materials Engineering, Kasteelpark Arenberg 44, 3001 Heverlee, Belgium

Abstract

A porous pre-sintered boron nitride target was recently developed for the production of intense ^{11}C beams for positron emission tomography-aided (PET) hadron therapy. This target material presents beneficial properties, such as high in-target production yield, thermal stability and chemical inertness. In a previous study, this target has been characterized with respect to its operational limitations. In this work, we report on a dedicated fractional release study from activated targets. Release fractions are a powerful technique to gain insight into on-line release properties from off-line measurements, if sufficient knowledge regarding the target's microstructure is available. A release fraction of $F_\mu(t = 300 \text{ s}) = 0.045(7)$ of ^{11}C from a porous boron nitride target was measured by performing a short heat treatment at 1500°C in an oxidizing atmosphere. The target was characterized in view of its grain size, porosity and pore structure, which enabled to translate F_μ into an on-line release efficiency of approximately 10%. Moreover, this study allowed to estimate the order of magnitude of carbon's diffusion coefficient $D(1500^\circ\text{C}) = 10^{-15} - 10^{-14} \text{ cm}^2 \text{ s}^{-1}$ in a porous boron nitride target.

Keywords: Radioactive ion beam production, ^{11}C release, boron nitride target, release fractions, release efficiency

*Corresponding author

Email address: simon.stegemann@kuleuven.be (S. Stegemann)

**Present address:

Belgian Nuclear Research Centre SCK CEN, Institute for Advanced Nuclear Systems, Mol, Belgium

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I Introduction

The advantage of using light ions and PET-isotopes such as ^{11}C for radiotherapy has been subject of many discussions and studies. In that regard, pioneer work was performed at the BEARS facility at LBNL [41, 67, 68]. The exploitation of ^{11}C as a therapeutic beam has re-gained increased attention after pilot-studies at NIRS, Chiba, where low-intensity ^{11}C beams have been produced by projectile fragmentation for pre-clinical imaging studies [31, 59, 92]. Since ^{11}C is a β^+ -emitter (half-life, $T_{1/2} = 20.4$ min), therapy can be combined with on-line PET-imaging techniques when using it for hadron therapy [33]. While this isotope is routinely produced in hospitals for the radiosynthesis of diagnostic radiopharmaceuticals, no production-post-acceleration system has been developed which delivers sufficiently intense ^{11}C radioactive ion beams (RIBs) to the patient ($4 \cdot 10^8$ ions/spill [33]). Within MEDICIS-Promed [148], new accelerator systems based on the isotope separation on-line (ISOL) method are being developed, tailored for ^{11}C beam production [149], manipulation and post-acceleration [103, 133]. To meet the requirements for effective treatments, i.e. intense and pure RIBs, and furthermore, to implement a ^{11}C based protocol into existing facilities, optimization along the accelerator chain is essential. Regarding the production of intense mass separated ^{11}C beams, a porous boron nitride (BN) ISOL-type target has been developed for this purpose [149]. BN was chosen as target material due to its high in-target production yield exploiting the nuclear reactions $^{11}\text{B}(p,n)^{11}\text{C}$ and $^{14}\text{N}(p,\alpha)^{11}\text{C}$ with high cross sections, and due to BN's thermal stability. To enhance ^{11}C release efficiency, two approaches were taken: firstly, the target was manufactured to provide a controlled microstructure, i.e. small grain sizes and high open porosity, for fast diffusion and effusion processes; secondly, molecular isotope extraction in the form of ^{11}CO is considered due to higher volatility and reduced reactivity with surrounding surfaces. While this target has been characterized and tested with respect to its high-temperature stability and high-temperature oxidation behavior, previous attempts to gain insight into the ^{11}C release characteristics by

doping BN powder with stable carbon prior pre-sintering, yielded no conclusive results [149]. Consequently, we report in this work the results of a carbon release study from activated BN pellets that was performed at CERN MEDICIS [102]. In detail, release fractions of ^{11}C were measured off-line, at a new experimental test bench in MEDICIS. By using the knowledge regarding properties of the target's microstructure, the estimated on-line release efficiency of the porous BN target was determined, which is one of the most crucial parameters in RIB production via the ISOL method. In that regard, Section II briefly introduces the ISOL method and discusses the fundamental diffusion and inter-grain effusion processes which govern the isotope release. Moreover, influences of the target's microstructure on the release process, such as grain size and porosity, will be explained. Section III summarizes these properties and how they were determined in the case of the porous BN target. In addition, the test bench, experimental setup and layout that were developed and used for the release study will be described. The results of the fractional release measurement, and its translation into an on-line release efficiency are presented in Section IV. Furthermore, it was possible to estimate the order of magnitude of carbon's diffusion coefficient in BN.

II Isotope release from solid targets

While RIBs produced by the ISOL method generally provide desirable beam characteristics with respect to its application in hadron therapy, e.g. beam purity and beam emittance, the challenge remains to produce sufficiently high beam intensities. ISOL beams are generated in a multi-step process, which naturally are accompanied with beam losses at each step. To maximize the production, this technique is best applied by bombarding a thick, usually solid target with a primary particle beam to produce (radio-)isotopes from various nuclear reactions. The isotopes are released from the target matrix, by heating the target to high temperatures. The released isotopes effuse to an ion source, where they are ionized, typically, to the 1^+ charge state. Subsequently, they can be electrostatically extracted and mass separated by sending them through the magnetic field of a dipole magnet that bends the ions' trajectories according to their mass-over-charge ratio. This sequential character of ISOL RIB production, with its associated beam losses, can be expressed in the production yield Y [s^{-1}]:

$$\begin{aligned}
 Y &= Y_{\text{phys}} \cdot I \cdot (1 - e^{-\lambda t}) \cdot \varepsilon, \\
 \varepsilon &= \varepsilon_{\text{rel}} \cdot \varepsilon_{\text{ion}} \cdot \varepsilon_{\text{sep}} \cdot \varepsilon_{\text{trans}}, \\
 \varepsilon_{\text{rel}} &= \varepsilon_{\text{diff}} \cdot \varepsilon_{\text{form}} \cdot \varepsilon_{\text{int-eff}} \cdot \varepsilon_{\text{eff}}.
 \end{aligned}
 \tag{5.1}$$

Y_{phys} is the physical production yield, which expresses how many nuclei are produced per incoming beam particle. Y_{phys} defines together with the primary beam current I [particles s^{-1}] and the saturation factor displayed in-between the brackets, the thick in-target production yield. The saturation factor is radioisotope specific and depends on its decay constant $\lambda = \frac{\ln(2)}{T_{1/2}}$. The total efficiency ε of the RIB production process accounts for the aforementioned beam losses of the corresponding mechanisms. Within the ISOL process-chain, the isotope release (ε_{rel}) is often considered as one of the bottlenecks in RIB production [136, 137]. Generally, three processes are involved when isotopes are released from the target matrix:

- Step 1. The isotopes that are produced within the bulk of the target material's grains have to diffuse to the grain surface from which they are vaporized, or desorbed ($\varepsilon_{\text{diff}}$).
- Step 2. The desorbed isotopes reach the pore volume, through which they effuse to the target surface ($\varepsilon_{\text{int-eff}}$).
- Step 3. Upon desorption from the target's surface, isotopes effuse out of the target container and through a transfer line to the ion source (ε_{eff}).

As indicated, the latter two processes are governed by effusion, whereas they differ regarding the length scale on which they occur. Effusion within the pore network takes place in-between the target grains, with characteristic effusion lengths around nm to μm before they collide with another surface. On the other hand, effusion within the target container and transfer line is associated with lengths of the order of mm to cm. Hence, in order to distinguish among these two mechanisms, step 2 is denoted as *inter-grain effusion* ($\varepsilon_{\text{int-eff}}$), whereas step 3 is simply referred to as *effusion* (ε_{eff}). Note that since ^{11}C production using the CO molecular sideband is considered, in principle, one has to account for the molecule formation process, with an efficiency $\varepsilon_{\text{form}}$ (see Eq. (5.1)), and the required time scale. However, compared to the other parameters that time scale is considered to be negligible.

Since this work did not involve the ionization step when discussing the release properties of ^{11}C from the BN target, only the former two mechanisms (step 1 and 2) will be discussed in the following. Moreover, when addressing the isotope release, henceforth, we solely refer to those isotopes that have been physically separated as ^{11}CO from the target matrix, by desorbing from the target's surface. The subsequent effusion is therefore neglected.

II.1 Diffusion-dominated formalism

In this section, the release mechanism is examined by solely considering the diffusion process (step 1), i.e. once the isotopes entered the pore volume they

are considered as released. Such an approach is applicable when diffusion is significantly slower than inter-grain effusion, which consequently dominates the release process. Diffusion is governed by Fick's laws [113, 150], which phenomenologically describe the flux of diffusing particles $\vec{\varphi}$ as proportional to a concentration gradient ∇C :

$$\vec{\varphi} = -D\nabla C, \quad (5.2)$$

where D is the *diffusion coefficient* or *diffusivity* in $[\text{m}^2 \text{ s}^{-1}]$ or $[\text{cm}^2 \text{ s}^{-1}]$. Equation (5.2) is Fick's first law, which yields, when combining with the continuity equation $-\nabla \cdot \vec{\varphi} = \frac{\partial C}{\partial t}$, Fick's second law:

$$\frac{\partial C}{\partial t} = \nabla \cdot (D\nabla C). \quad (5.3)$$

For tracer-host combinations (i.e. isotope-target) where the release process is dominated by diffusion, D is governing the time scale of the diffusion process. M. N. Rahaman [111] described the diffusion process at an atomic level, where diffusion of atoms may be illustrated as the periodic jumping of atoms from one lattice site to another. For each jump, the energy barrier E_A has to be exceeded, which is called the *activation energy* for diffusion, usually expressed in [eV]. Using the probability $p = e^{-\frac{E_A}{k_B T}}$ that atoms have sufficient energy to exceed the energy barrier, M. N. Rahaman shows that the net flux of atoms from one site to another follows [111]:

$$\varphi = -\frac{\nu a^2}{6} \cdot e^{-\frac{E_A}{k_B T}} \cdot \frac{\partial C}{\partial x}, \quad (5.4)$$

which corresponds to Fick's first law in one dimension. As a result, one obtains for the diffusion coefficient:

$$D = \frac{\nu a^2}{6} \cdot e^{-\frac{E_A}{k_B T}} = D_0 \cdot e^{-\frac{E_A}{k_B T}}, \quad (5.5)$$

and with $E_A = \Delta H - T\Delta S$,

$$D = \frac{\nu a^2}{6} e^{\frac{\Delta S}{k_B}} \cdot e^{-\frac{\Delta H}{k_B T}}. \quad (5.6)$$

k_B is the Boltzmann constant in $[\text{eV K}^{-1}]$, ν is the vibration frequency of the atoms about their mean position, a is the crystal lattice parameter, D_0 is called the pre-exponential factor and ΔS , ΔH are the entropy and enthalpy of atomic diffusion, respectively. The above written relation (5.5) is known as the *Arrhenius equation* of diffusion, and is often referred to when discussing

ISOL targetry. It shows that the diffusion coefficient depends exponentially on the target temperature, which explains why ISOL targets are often operated at temperatures close to their melting point. Typically, when discussing diffusion in solids, D is of the order $10^{-12} - 10^{-8} \text{ cm}^2 \text{ s}^{-1}$ for temperatures in the range of $1600 - 1800 \text{ }^\circ\text{C}$ [151]. However, as it will be discussed in Section IV.2, D can be of significantly lower magnitude when dealing with diffusion of refractory elements in refractory host materials. Since we are discussing the diffusion of radioactive isotopes, the time scale of the diffusion process is of utmost importance for the production of radioactive ion beams. Fick's second law (Eq. (5.3)) has been analytically solved for different boundary conditions [150, 152, 153]. For instance, it can be shown that for diffusion in a sphere of radius G , or in a thin foil of thickness L , assuming a homogeneous initial concentration C_0 and constant surface concentration C_S , the concentration corresponds to:

$$\frac{C(r, t') - C_S}{C_S - C_0} = \frac{2G}{\pi} \sum_{n=1}^{\infty} \frac{(-1)^n}{n} \sin\left(\frac{n\pi}{G} r\right) \cdot e^{-\frac{Dn^2\pi^2}{G^2} t'} \quad (5.7)$$

$$\frac{C(x, t') - C_S}{C_0 - C_S} = \frac{4}{\pi} \sum_{n=0}^{\infty} \frac{1}{(2n+1)} \sin\left(\frac{(2n+1)\pi}{L} x\right) \cdot e^{-\frac{D(2n+1)^2\pi^2}{L^2} t'} \quad (5.8)$$

The fraction F_μ that is released in a time period t can be calculated by:

$$\frac{M(t)}{M(\infty)} = \frac{-\int_0^t dt' D \left(\frac{\partial C}{\partial x} \right)_{r=G}}{-\int_0^\infty dt' D \left(\frac{\partial C}{\partial x} \right)_{r=G}} \equiv F_\mu, \quad (5.9)$$

$$\frac{M(t)}{M(\infty)} = \frac{-\int_0^t dt' D \left[\left(\frac{\partial C}{\partial x} \right)_{x=0} - \left(\frac{\partial C}{\partial x} \right)_{x=L} \right]}{-\int_0^\infty dt' D \left[\left(\frac{\partial C}{\partial x} \right)_{x=0} - \left(\frac{\partial C}{\partial x} \right)_{x=L} \right]} \equiv F_\mu, \quad (5.10)$$

where $M(t)$ and $M(\infty)$ denote the diffusant's quantity that has left the sphere or foil in time t and at infinite time, respectively. Inserting the Equations (5.7) and (5.8) in Equations (5.9) and (5.10), respectively, yields:

$$F_\mu(t) = \int_{t'=0}^t dt' p_\mu(t') = \begin{cases} p_\mu = \frac{6\mu}{\pi^2} \sum_{n=1}^{\infty} e^{-\mu n^2 t'}, & \text{sphere} \\ p_\mu = \frac{8\mu}{\pi^2} \sum_{n=0}^{\infty} e^{-\mu(2n+1)^2 t'}, & \text{foil} \end{cases} \quad (5.11)$$

where we introduced the diffusion delay parameter:

$$\mu = \frac{\pi^2 D^1}{G^2}. \quad (5.12)$$

Eq. (5.11) is a very useful relation that shows that by measuring the fractional release $F_\mu(t)$ from the target matrix, in principle, one can determine the delay function $p_\mu(t)$, the diffusion delay parameter μ and the diffusion coefficient D . Note that in reality, target grains may have a variety of different shapes, and may not necessarily be uniform in size. For practical reasons, it is therefore often assumed that G (or L) denotes a simplified representation of the actual target grains. The determination of release fractions has been subject for many measurement campaigns investigating release characteristics and diffusion coefficients of different isotope-target combinations. Some examples can be found in [119–121, 154–162]. Moreover, with knowledge of the delay function $p_\mu(t)$, one can estimate the on-line release efficiency $\varepsilon_\mu(T_{1/2})$ governed by diffusion:

$$\varepsilon_\mu(T_{1/2}) = \int_0^\infty dt p_\mu(t) \cdot e^{-\lambda t}, \quad (5.13)$$

with the decay constant λ , which comprises $T_{1/2}$. In essence, $\varepsilon_\mu(T_{1/2})$ estimates how much of an initial inventory of isotopes can be extracted from the target matrix before it decays.

II.2 Inter-grain effusion-dominated formalism

The diffusion-dominated approach (step 1), described in the previous section, considers an isotope that diffused out of the grain and desorbed from its surface as instantaneously released from the target. This is however only a simplified description of the actual process and it overestimates the release efficiency. As mentioned, atoms that desorb from the target grains, enter the pore volume within the target matrix (step 2). This pore volume can be imagined as a network of tubes or channels that, ideally, are connected to the surface of the target (open porosity). Atoms that enter the closed porosity volume have to re-enter and diffuse through the bulk to reach the open porosity volume to be released from the target. It is conceivable that such a process is very time consuming, which is why such isotopes are usually considered to decay before they can be released from the target matrix. Therefore, let us assume that each pore is connected to the target surface. Atoms that enter this volume effuse through the pore network, whereas re-diffusion into the grains is omitted. While the pure diffusion (step 1) is globally well understood and modeled, this does not hold for the inter-grain effusion (step 2), for which the *sticking time* or *sojourn time* τ_s is the most relevant characteristic. Once the atoms are

¹Note that one has to replace G by L , when discussing the foil solution.

located within the pore volume, they travel via molecular flow towards the target surface. During this process they collide with the grain surface where they are adsorbed for a certain time period, which is governed by the Frenkel equation:

$$\tau_s = \tau_0 \cdot e^{-\frac{\Delta H_{\text{ads}}}{RT}}. \quad (5.14)$$

The above written equation is of an Arrhenius-type form with a pre-exponential factor τ_0 , which corresponds to the period of the oscillation of the adsorbed molecule perpendicular to the material's surface [163–165] and its order of magnitude is often approximated by 10^{-13} s [166, 167]. The *adsorption enthalpy* ΔH_{ads} is the dominating physical property in the adsorption process. Adsorption may be illustrated in the following way: When an atom or molecule collides with a surface, instead of scattering elastically, it remains stuck for a period of time, defined by Eq. (5.14). Generally, two processes may result in the adsorption of an adsorbate onto a specific surface (adsorbent): physical adsorption (physisorption) or chemical adsorption (chemisorption).

In the former case, predominantly weak van der Waals forces yield to a retention of the adsorbate on a surface. The atoms or molecules approaching the surface, experience first an attractive force until a certain distance is reached, where a strong repulsive force is present, resulting in an equilibrium where the net force is zero. The potential energy at this distance is at its minimum. No transfer or sharing of electrons is involved in this interaction, i.e. no chemical bond is generated. The adsorbent possesses also kinetic energy, resulting in oscillations which can lead to bond breakage. Physisorption is an exothermic, reversible interaction with rather low adsorption enthalpies $\Delta H_{\text{ads}} > -80$ kJ mol $^{-1}$.

Chemisorption on the other hand, involves strong (usually covalent) chemical bonds that lead to the adsorption of an atom or molecule onto a given surface. Generally, chemisorption is classified into two cases: activated and non-activated chemisorption. The former is essentially a two-step process, in which the adsorbate is first physically adsorbed, and only after a certain minimum energy U_a is provided, chemisorption occurs. In that regard, U_a is denoted as the *activation energy* of adsorption. According to that, non-activated chemical adsorption takes place if no such energy barrier has to be overcome. The overall process is exothermic, i.e. after U_a is provided to the system, heat Q_{ads} is released. However, chemisorbed molecules may dissociate, leading to atomic chemisorption which in some cases may be endothermic as well [168, 169]. Note that in literature, terms like adsorption enthalpy, heat of adsorption, activation energy or adsorption energy are not clearly defined. It seems that by convention, when discussing the energy released during the adsorption process, i.e. the heat of adsorption Q_{ads} , this quantity is chosen to be positive, hence $Q_{\text{ads}} = -\Delta H_{\text{ads}}$. Furthermore, while it is evidenced that physisorption is considerably weaker than chemisorption, and thus, features noticeably lower heats of adsorption

Q_{ads} , there is no exact boundary between these two. Hence, often very low or very high heats of adsorption are used to distinguish between these two processes [170]. Usually, physisorption is characterized with heats of adsorption $Q_{\text{ads}}^{\text{phys}} < 80 \text{ kJ mol}^{-1}$, whereas typical values for chemisorption are in the region of 200 kJ mol^{-1} , and may be even much higher for metals. Since the sojourn time τ_s decisively influences the delay during the isotope release, if one considers an inter-grain effusion dominated mechanism, it is apparent that ΔH_{ads} is of great importance. If the adsorption enthalpy for the corresponding adsorbate-adsorbent pair is unknown, rough estimates can be done, mostly for metals, by a semi-empirical model developed by B. Eichler et al. [171–173].

In contrast to step 1 and 3, the inter-grain effusion is by far less deliberated in literature. However, it is worth mentioning some studies in that regard. L. Carraz et al. discussed in 1978 both the diffusion and inter-grain effusion mechanisms (step 1 and 2 in this work) [120]. It was pointed out that isotope-target combinations where the release mechanism is dominated by inter-grain effusion is less favorable for RIB production, since isotopes which feature long sticking times on the target matrix material will experience a significant lingering time within the complex pore structure of the target material, and therefore, are expected to exhibit very poor release efficiencies. R. Kirchner studied the release and ionization efficiency in ISOL systems, and extensively discussed, next to the grain diffusion mechanism (step 1) as summarized in this work, the effusion from the target container to the ion source of the target-ion source unit (step 3) [121]. These two mechanisms were discussed, first individually, and later on, in a combined model forming the basis for subsequent studies. R. Kirchner described the delay caused by effusion analog to the volume flow through an orifice, by an exponential time dependence, governed by a delay parameter ν :

$$p_\nu(t) = \nu \cdot e^{-\nu t}, \quad (5.15)$$

$$\nu = \frac{1}{\tau_{\text{delay}}} = \frac{1}{n_c(\tau_s + \tau_{\text{mft}})}. \quad (5.16)$$

$p_\nu(t)$ is the delay function for the effusion through an orifice, governed by the effusion delay parameter ν . τ_{delay} is the total delay an isotope experiences due to the molecular flow through this orifice and physical adsorption on surrounding surfaces. n_c are the number of collisions, τ_s is the sojourn time as written in Eq. (5.14) and τ_{mft} is the mean free time in-between two consecutive wall collisions. With this, a fractional release $F_\nu(t)$ and release efficiency for isotope release dominated by effusion can be calculated using Equation (5.11) and

(5.13), respectively:

$$F_\nu(t) = \int_{t'=0}^t dt' p_\nu(t'), \quad (5.17)$$

$$\varepsilon_\nu(T_{1/2}) = \int_0^\infty dt p_\nu(t) \cdot e^{-\lambda t}. \quad (5.18)$$

The combined model which treats the diffusion through the target grains in the time interval $[0, \tilde{t}]$, followed by the molecular effusion to the ion source $[\tilde{t}, t]$, is obtained by the convolution of the individual delay functions:

$$p_{\mu,\nu}(t) = \int_{\tilde{t}=0}^t d\tilde{t} p_\mu(\tilde{t}) p_\nu(t - \tilde{t}) \quad (5.19)$$

$$= \begin{cases} \frac{6\mu\nu}{\pi^2} \sum_{n=1}^{\infty} \frac{e^{-\nu t} - e^{-\mu n^2 t}}{\mu n^2 - \nu}, & \text{sphere} \\ \frac{8\mu\nu}{\pi^2} \sum_{n=0}^{\infty} \frac{e^{-\nu t} - e^{-\mu(2n+1)^2 t}}{\mu(2n+1)^2 - \nu}. & \text{foil} \end{cases} \quad (5.20)$$

To better match this delay curve with observed release profiles at CERN ISOLDE, E. Bouquerel modified p_ν by a double exponential function to better parametrize the slower observed release, due to thick targets and the transfer line between the target unit and the ion source [174]. This modified model was applied in [154, 175]. M. S. Leitner developed a Monte Carlo code *Radioactive Ion Beam Optimizer* (RIBO) to simulate and fit release profiles, where the diffusion, effusion and ionization processes were modeled [176]. The inter-grain effusion phenomenon is simulated for powder and fiber targets, where the mean free flight path between two consecutive collisions and the average sojourn time on the grain surfaces τ_s are decisive input parameters. The atoms that are desorbed into the pore volume effuse to the target surface, conducting a random walk that is governed by the cosine law, applied on a surface randomly oriented in 2π . The velocity of the effusing species is either attributed after each collision from the Maxwell-Boltzmann distribution, or to reduce computation time, is attributed by the mean velocity of the Maxwell-Boltzmann distribution throughout the effusion process. This code was used in a study for the SPES direct target [177]. O. Alyakrinskiy et al. discussed another approach based on Knudsen diffusion, i.e. the effusion at low pressures in media where the representative scale length (for instance, the pore diameter) is smaller or of similar magnitude than the mean free path [178]. Moreover, the influence of grain size and porosity on the inter-grain effusion release efficiency were calculated, assuming a material microstructure of randomly packed or partially overlapping spheres with a fixed diameter, and pores uniformly distributed with

100% open porosity. The final release efficiency was obtained by multiplying the diffusion efficiency with the inter-grain effusion efficiency.

In summary, the isotope release is, preferably, governed by diffusion in the target grains, where large diffusion coefficients D and small grain sizes G and high operational temperatures result in high release efficiencies. Strong contributions of inter-grain effusion, in the sense of long sticking times τ_s , should be avoided, as it may result in significant lingering times within the pore structure, ominous for the production yield Y of short-lived radioisotopes. Important in that aspect is the chemical interplay of the isotope-target combination (low heats of adsorption), and the pore structure, i.e. large pore sizes and high open porosity. As a result, ISOL targets should be characterized in terms of:

- high-temperature stability;
- high-temperature chemistry, i.e. target reactivity with isotopes and, if provided, the surrounding atmosphere;
- target microstructure, i.e. grain size, porosity, pore size.

III Materials and methods

III.1 Boron nitride target characterization

Section II demonstrated the importance of controlling the target's microstructure, with respect to enhanced isotope release properties. For the production of intense ^{11}C beams, a porous BN target with 21(7)% open porosity was manufactured by spark plasma sintering (SPS), and was recently characterized with respect to its stability at high temperatures and in oxidizing atmospheres [149]. Since then, investigations regarding the target's microstructure were performed using different experimental techniques, as discussed below. Note that hereafter this target is referred to as SPS pre-sintered BN powder compact.

As an extended version of this section was incorporated into Chapter 3 of this thesis, the BN target characterizations are not repeated. The reader is thus referred to Section 3.4.2.

III.2 Experimental release fractions

The main goal of this work was to determine the release properties of carbon from the BN target. Previous attempts, testing carbon pre-doped SPS pre-sintered BN targets yielded no conclusive results. These samples were prepared by generating a homogeneous blend of carbon black and boron nitride powders of different concentrations prior sintering. It was therefore concluded that a study with activated BN targets is necessary to obtain the desired properties of this

material. For this purpose, a dedicated experimental test bench was developed and installed at CERN MEDICIS, which offered the ideal infrastructure and resources for such an experiment. The general layout of the release study comprised five steps:

- (A) target irradiation to generate an inventory of ^{11}C within the target matrix;
- (B) retrieval of the active material and transport to the measurement setup;
- (C) determination of the initial ^{11}C activity, A_i ;
- (D) release of ^{11}C , by performing a heat treatment in a controlled oxidizing atmosphere for a time period $[t' = 0, t]$;
- (E) determination of the remaining ^{11}C activity, A_f .

By comparing the initial and remaining activity, the released fraction in the time interval $[t' = 0, t]$ is determined by:

$$F_\mu(t) = 1 - \frac{A_f(t_0)}{A_i(t_0)}, \quad (5.21)$$

with $A_i(t_0)$ and $A_f(t_0)$, the ^{11}C activity before and after the heat treatment reevaluated to a reference time t_0 . In the following, a more detailed description of the experimental steps (A) – (E) will be given, considering the special requirements mainly given by the relatively short half-life of ^{11}C ($T_{1/2} = 20.4$ min).

(A) Target irradiation at MEDICIS

MEDICIS is located at CERN behind the ISOLDE RIB facility, and is dedicated to the production and collection of medically relevant radioisotopes [102]. It recycles 1.4 GeV protons from the proton synchrotron booster (PSB), with intensities up to $2\ \mu\text{A}$, after they have traveled through the ISOLDE target. For its activation, the MEDICIS target is transferred to its irradiation position in ISOLDE, where it recycles approximately 66% of the original 1.4 GeV protons with $\sim 85\%$ of the initial energy after traversing the ISOLDE target. Once a sufficient activity of the isotope of interest is generated, the target is transferred to an off-line separator where a RIB is produced exploiting the ISOL principle. In view of the release study, subject of this work, the striking feature of the MEDICIS facility's infrastructure, is the capability to transfer and retrieve a target within 15 minutes, using a railway system (MONTRAC).

A BN target, comprising four ~ 2 mm thick pellets of 6 mm diameter was irradiated with $2.1 \cdot 10^{15}$ protons on target in five minutes ($\bar{I} \approx 1.1\ \mu\text{A}$). The number was chosen in order to produce sufficient ^{11}C activity without substantially activating the target material and the target unit, as it would

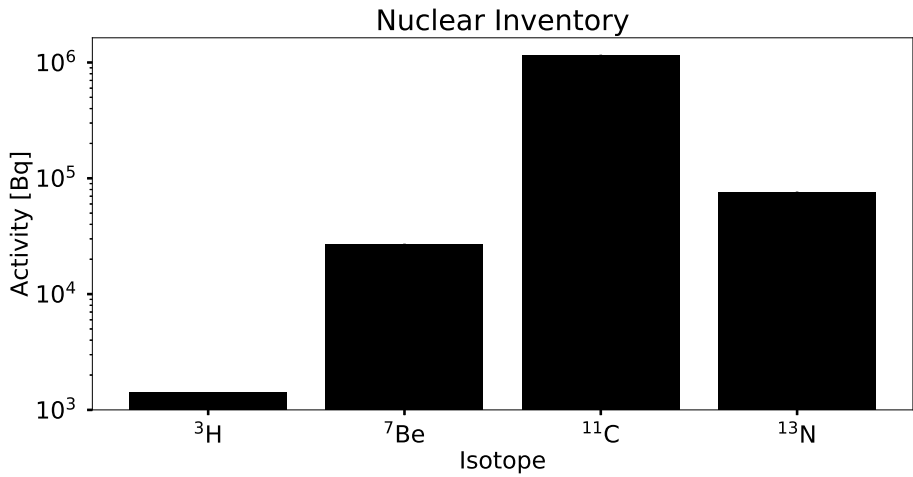


Figure 5.1: Activities arising from the estimated nuclear inventory after irradiating four BN pellets with $2.1 \cdot 10^{15}$ protons and two hours cooling time. The activities have been calculated using the Monte Carlo code FLUKA [36, 37].

introduce difficulties with manual target manipulations. Moreover, the proton beam was sent directly onto the BN target with 1.4 GeV, by directing it below the ISOLDE target to avoid scattering on the dense target container. In this way, broadening of the proton beam due to interactions with the ISOLDE target was almost fully omitted, allowing to further reduce activation of the target unit. A cooling time of approximately two hours was necessary to meet radio protection regulations. Fig. 5.1 shows the activity in the BN pellets arising from the expected nuclear inventory for the aforementioned scenario.

(B) Target retrieval and transport

This step comprised the retrieval of the activated target pellets from the MONTRAC system, transport to the experimental area and mounting into the experimental setup, which was used to measure the release fractions. In this context, it was essential to minimize the exposure time to any activated material, e.g. target frame and target container, housing the BN target pellets. Figure 5.2 shows the irradiation apparatus that was employed in this study. The target frame design is compatible with the MEDICIS infrastructure (robotic arm and MONTRAC) and ensures very fast pickup and transfer of the target container to the experimental setup. The container was manufactured from *High-Density PolyEthylene* (HDPE), which is a radiation hard polymer, and its design allowed very fast retrieval of the active target material. The target frame

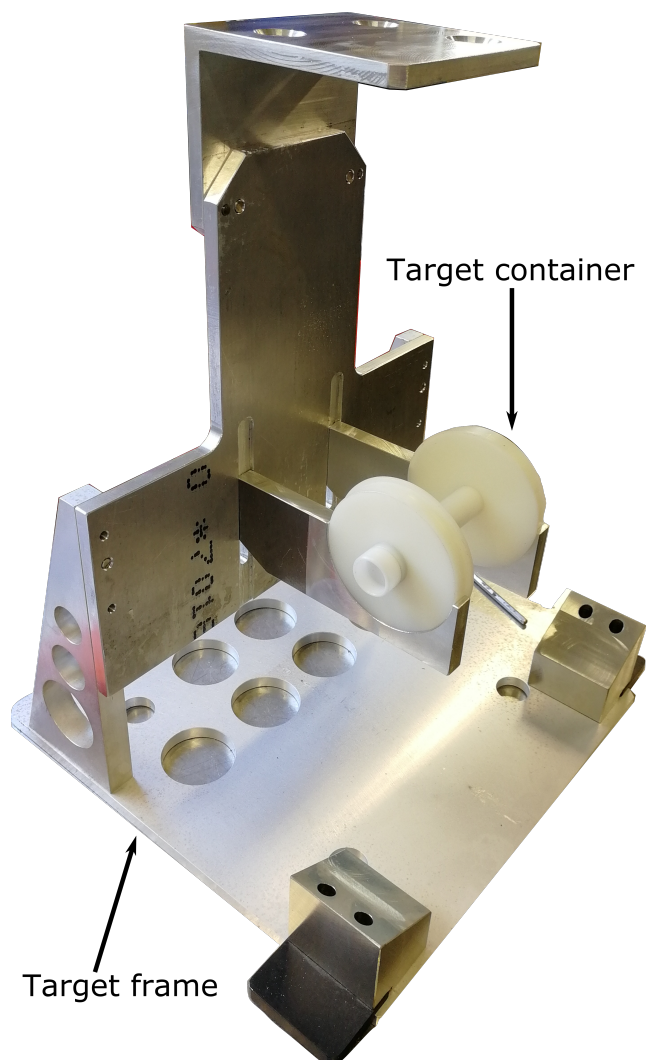


Figure 5.2: Irradiation apparatus that was used to irradiate a BN target at CERN MEDICIS. The target frame is made of Al and holds a HDPE container.

and respective HDPE container were built and slightly modified according to an analog system that was developed for TiC irradiations and used later for PbBi studies [179].

(C, E) ^{11}C activity determination

To determine the fraction of the ^{11}C inventory that was released during the heat treatment, the target activity was measured before and after the heat treatment. ^{11}C is a β^+ -emitter that features no characteristic γ -line besides the 511 keV annihilation photons, which are a prominent background across CERN, and especially at the MEDICIS and ISOLDE facilities. Moreover, Fig. 5.1 indicates that ^{13}N ($T_{1/2} = 9.97$ min) is produced alongside ^{11}C , which is another β^+ -emitter. Consequently, it was necessary to measure the 511 keV $\gamma - \gamma$ coincidences to minimize background γ -rays. Event-by-event data was collected in order to extract the activity's time behavior and disentangle ^{11}C from ^{13}N according to their respective half-lives. Two CeBr₃ scintillation detectors, with cubic $48 \cdot 48 \cdot 48$ mm³ crystals and integrated scintillation read out with associated electronics were used. An energy resolution of 5.19(2)% and 5.63(2)% at 511 keV were achieved in channel 0 and 1, respectively. Note that no energy resolution optimization was crucial, as only the intensity of the 511 keV peak is used for the release study. Two measurement configurations, differing in the distance between the two detectors were employed during the experiment. A larger distance before the heat treatment provided a higher coincidence angle accuracy, whereas a shorter distance after heat treatment ensured enough statistics for the analysis. The corresponding 511 keV $\gamma - \gamma$ coincidence efficiencies were determined to be 0.0805(25)% and 0.2140(60)%, respectively, using a 20 nanosecond coincidence time window, and a FWHM energy window on the 511 keV peak.

(D) Heat treatment

The high-temperature stability and high-temperature oxidation behavior of the BN target were characterized in [149], where it was demonstrated that temperatures up to 1500 °C and oxygen potentials up to $\mu_{\text{O}_2} = -300$ kJ mol⁻¹ can be applied. Hence, the release study was performed at aforementioned temperature and with a controlled oxygen leak of 10^{-5} mbar l s⁻¹, which corresponds to $\mu_{\text{O}_2} \approx -350$ kJ mol⁻¹ using an Ar/O₂ mixture (90/10 vol.%), and a turbo vacuum pump with 1400 l min⁻¹. The heat treatment was conducted for five minutes. When designing the experimental setup for this experiment, two main requirements needed to be fulfilled: firstly, maximized heating and cooling rates were essential, as otherwise the end result would be falsified by isotopes that are released along the heating or cooling process. Secondly, the design must assure a quick activity determination ((C), (E)) before and after the heat treatment, to minimize delays in view of the relatively short ^{11}C half-life. In practice, the former was achieved by rapidly inserting the target material into a pre-heated furnace at 1500 °C, thereby heating the BN pellets in ~ 6 min to this temperature. The latter was ensured, by placing the

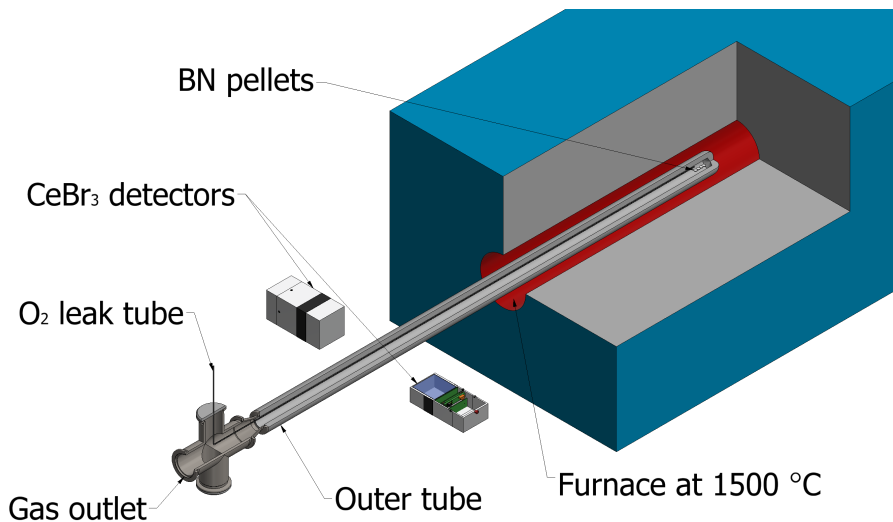


Figure 5.3: Sketch of the experimental setup that was used to perform the heat treatment of activated BN pellets. These pellets were mounted into the outer tube, which when mounted onto the full assembly could be evacuated by a vacuum pump. A controlled O_2 leak was applied through the inner tube which was coupled to a Pfeiffer leak valve.

detectors for the $\gamma - \gamma$ coincidence measurement close to the furnace. Fig. 5.3 shows a sketch of the experimental setup, which permitted these requirements, and that was used in this release study. Upon target material retrieval (B), the activated BN pellets were placed into an *outer tube*, which was then mounted onto a vacuum cross, and the whole system was evacuated. An inner *leak tube*, coupled to a Pfeiffer leak valve, provided a controlled oxygen supply to the target material during heat treatment. Both outer and leak tube were made of alumina. The initial ^{11}C activity of the BN pellets was measured by placing the aforementioned tube system between the two scintillation detectors, followed by insertion of the tube system into the furnace to heat treat the BN target and to release ^{11}C . Subsequently, the tube system was removed from the furnace and the remaining activity was measured.

IV Results

Figure 5.4 shows the γ -ray singles spectra of the activated target material before the heat treatment, measured in both detectors and normalized to the acquisition time. For comparison, a background measurement is presented as

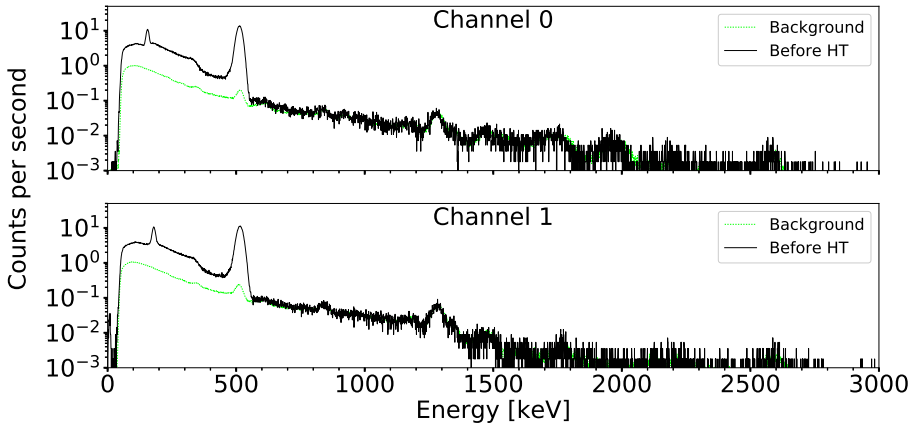


Figure 5.4: γ -ray singles spectra measured in both detectors and normalized to the acquisition time, with: activated target material before heat treatment (solid black line, measured for 9.3 min) and a background measurement (dotted green line, measured for 188 min).

well. We see that besides the 511 keV peak, resulting from the ^{11}C decay, no other transition is clearly apparent above background (excluding the X-ray peak at low-energies). The expected 478 keV transition, originating from the ^7Be decay is buried in the shoulder of the 511 keV peak. The presence of the 511 keV line in the background spectra endorses the necessity of applying a $\gamma - \gamma$ coincidence algorithm to the measured data. Figure 5.5 presents decay-time spectra, using a 20 nanosecond coincidence time window, and a FWHM energy window on the 511 keV peak. Note that altering the energy window did not affect the result. To obtain the ^{11}C activity before and after the heat treatment, first, a doubly exponential function was fitted to the data, in order to account for ^{13}N , which is expected to be produced next to ^{11}C (see Fig. 5.1), and which would contribute to the 511 keV $\gamma - \gamma$ coincidences. However, the fit result showed no indication of ^{13}N , which stems from the more than two hours that have passed after *End-Of-Beam* (EOB) and the measurement, corresponding to more than 12 half-lives of ^{13}N . It was hence justified to neglect any contribution of this isotope to the decay curve, by fitting an exponential function of the form:

$$A(t) = A_0 \cdot e^{-\frac{\ln(2)}{T_{1/2}} t}, \quad (5.22)$$

to the experimental data. Applying the fit results

$$A_0^i = A_i = 7.838(69) \cdot 10^4 \text{ s}^{-1},$$

$$A_0^f = A_f = 2.612(14) \cdot 10^4 \text{ s}^{-1},$$

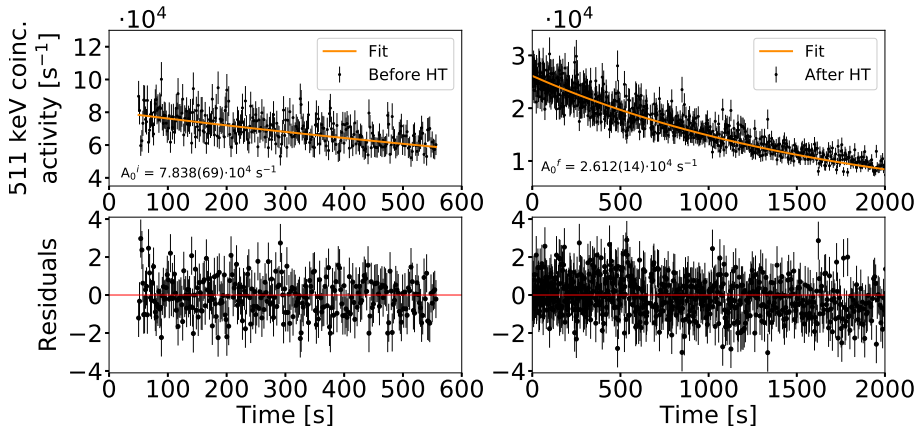


Figure 5.5: Decay-time spectra associated with 511 keV coincidences, before (left) and after (right) the five minute heat treatment at 1500 °C and with a O_2 leak of 10^{-5} mbar l s^{-1} , using an Ar/O_2 (90/10 vol.%) mixture. An exponential function was fitted to the data, with the pre-exponential factor as the only variable.

to Equation (5.21) and correcting for decay losses², yields a fractional release of

$$F_\mu(t = 300 \text{ s}) = 0.045(7). \quad (5.23)$$

It is worth comparing the measured ^{11}C activity $A(\text{EOB}) = 50(3)$ MBq, extrapolated back in time to when the proton irradiation stopped (EOB), with the predicted ^{11}C activity $A = 68(1)$ ³ MBq, using the FLUKA Monte Carlo simulation tool. The simulation result is close to the measured value, however, it does not coincide within the error bars of the experimentally determined result. Most likely, this stems from deviations of the actual beam size compared to the beam size employed for the FLUKA simulation, and from the unknown reaction cross section at the high energy used in this experiment.

IV.1 Carbon release properties

The main goal of this study is to determine release properties of carbon from the porous BN target that was developed exclusively for this purpose. We have discussed in Section II that fractional release data enables deep insight into these properties, if sufficient knowledge regarding the target microstructure is present. In that regard, it is first necessary to discuss whether the carbon release

²The time-lapse between the two measurements was approximately 31 minutes.

³The FLUKA simulation uncertainty stems solely from statistical errors.

process may be classified as being dominated by grain diffusion or inter-grain effusion. As discussed in Section II, in this work ^{11}C is considered as released when it reached the grain surface via bulk diffusion, followed by ^{11}C oxidation, desorption from the grain surface and inter-grain effusion through the open pore volume out of the target matrix (or target envelope). The subsequent effusion to the ion source is not discussed, i.e. neglected. ^{11}C oxidation is predicted to occur predominantly in the CO sideband, as indicated by chemical equilibrium calculations [149], and past results on $^{11}\text{CO}_{x=1,2}$ RIB production, summarized in [23], where CO/CO₂ ratios between 10 – 100 were observed. It was mentioned that, in principle, one has to address the molecule formation process of the isotopes that reached the grain surface by diffusion. However, it is impossible to account for the amount of ^{11}C isotopes that reached the grain surface, but did not oxidize. Such carbon isotopes are considered as not released, as atomic evaporation from BN is drastically impeded by carbon's low vapor pressure. Moreover, inter-grain effusion is most likely very slow, due to long sticking times on the target material. Therefore, we assume that the measured released fraction occurred in the CO sideband, with a negligible time required for the oxidation process. It is not possible to address the molecule formation efficiency $\varepsilon_{\text{form}}$, which is already included in the measured release fraction. As a result, only bulk diffusion and inter-grain effusion are assumed to contribute to the release mechanism.

In terms of diffusion, the carbon and boron nitride isotope-target combination represents the diffusion of a refractory element within a refractory host material. It would therefore be reasonable to assume that the release process is diffusion dominated. The BN target of this work was obtained by pre-sintering boron nitride powder using spark plasma sintering. The target was manufactured such that a rigid powder compact was obtained, while avoiding severe densification. It is thus legitimate to treat the BN target as a powder target, i.e. as spherical particles, in view of the release study. However, the SEM images displayed in Fig. 3.17 illustrate that the target grains present a flake-like shape, which may be viewed as somewhat similar to a foil geometry. We have therefore concluded to calculate the delay function p_μ , and accordingly the diffusion delay parameter μ for both, a foil and powder target. By inserting the measured $F_\mu(t = 300 \text{ s})$ into Eq. (5.11), we can calculate the diffusion delay parameter under the assumption that the release process is governed solely by diffusion:

$$\mu = \begin{cases} 6.2(19) \cdot 10^{-6} \text{ s}^{-1}, & \text{powder (spherical)} \\ 13.0(40) \cdot 10^{-6} \text{ s}^{-1}. & \text{foil} \end{cases} \quad (5.24)$$

To evaluate whether the hypothesis of a diffusion-dominated release mechanism is justified, i.e. step 2 is negligible, it is necessary to assess the inter-grain

effusion aspect. Note that the following evaluation is exploratory, aiming for a rough order of magnitude approximation.

The inter-grain effusion mechanism is treated similar to the macroscopic effusion outside the target envelop as described by R. Kirchner (refer to Eq. (5.16) and [121]). For this purpose, the complex pore network, which can be illustrated by a series of interconnected pores, is approximated by a cylindrical tube which is connected to the target surface. As a result, isotopes which entered the pore volume in the form of ^{11}CO , due to the external oxygen supply, are delayed via molecular flow within a straight tube, superimposed with a mean sojourn time τ_s on the tube's surface, for each collision. Since this is a very simplified model of the actual microscopic structure, it provides a rough estimation of the delay caused by inter-grain effusion. The sojourn time of CO on BN is described by $\tau_s = \tau_0 \cdot e^{-\frac{\Delta H_{\text{ads}}}{RT}}$ (refer to Eq. (5.14)). The pre-exponential factor τ_0 , often approximated by 10^{-13} s, may be estimated by the time of vibration of the atoms of the adsorbent [165], which is described by the Lindemann equation [180]:

$$\frac{1}{\tau_0} = f = 2.06 \cdot 10^{12} \sqrt{\frac{T_m}{MV_m^{2/3}}}.$$

The equation above relates the vibration eigenfrequency f of the atoms within a crystal to its melting point T_m , where M is the molecular mass and V_m is the molecular volume in cm^3 . Using this equation to estimate τ_0 for the CO-BN adsorbate-adsorbent combination, yields $\tau_0 = 9.6 \cdot 10^{-14}$ s, supporting the aforementioned approximation. Subsequently, to determine the sticking time of CO on BN, the adsorption enthalpy ΔH_{ads} must be known. Some studies were carried out, where the adsorption of CO was investigated, numerically, for different boron nitride structures [181–185]. These studies performed *Density Functional Theory* (DFT) calculations regarding carbon monoxide adsorption properties on pristine and doped *Boron Nitride Nanotube* (BNNT) systems, and on hexagonal BN sheets. While ΔH_{ads} certainly depends strongly on the actual material properties and therefore should be measured for an accurate description of the adsorption process, all of the aforementioned CO-BN studies suggest that CO undergoes weak physisorption on BN systems, which is compatible with the chemical inertness of boron nitride. Therefore, we take the upper limit of physisorption $\Delta H_{\text{ads}} > -80 \text{ kJ mol}^{-1}$, as discussed in Section II, to estimate the sticking time, which yields:

$$\tau_s \approx 2.3 \cdot 10^{-11} \text{ s}.$$

Approximations for the total number of wall collisions n_c and the mean flight time between each collision τ_{mft} can be deduced from the pore structure of the material:

$$\tau_{\text{mft}} = \frac{\lambda_{\text{mdt}}}{\bar{v}}. \quad (5.25)$$

λ_{mdt} is the mean distance travelled between these collisions, and $\bar{v}$ the average speed of the CO molecules, derived from the Maxwell-Boltzmann distribution. Note that particle-particle collisions within the void of the target matrix are neglected, as their mean free path is much larger than the pore dimensions. Thus, λ_{mdt} can be estimated by the average travel path of a CO molecule that is desorbed from the surface of a tube, randomly in an area of π , and traveling in a straight path to the opposite surface. The tube's diameter was associated with the mean pore diameter determined from MIP measurements, discussed in Section III.1.2.2. These measurements indicated that a large fraction of the pore volume consists of pores with narrow throats with $D_{\text{v},50}^{\text{Intrus.}} = 120$ nm and larger pore cavities $D_{\text{v},50}^{\text{Extrus.}} = 470$ nm. Applying these diameters and a cylindrical pore shape in Equation (5.25), yields:

$$\tau_{\text{mft}} \approx \begin{cases} 7 \cdot 10^{-10} \text{ s}, & D_{\text{v},50}^{\text{Intrus.}} \\ 3 \cdot 10^{-9} \text{ s}. & D_{\text{v},50}^{\text{Extrus.}} \end{cases}$$

The number of wall collisions n_c before carbon reaches the surface of the target matrix, can be estimated by the actual travel length $L = t_{\text{mean}} \cdot \bar{v}$. A desorbed molecule, randomly leaves the surface into an area of 2π , which therefore might lead to significant longer distances, compared to the geometrical dimensions of the solid target. The mean travel time or time constant of a molecule that travels via molecular flow through a volume V with a conductance C , corresponds to [186, 187]:

$$t_{\text{mean}} = \frac{4}{\pi^2} \frac{V}{C},$$

where C is the system's total conductance. Since the inter-grain effusion of ^{11}CO is considered as the molecular flow through a pore with diameter D and length l , where the molecule eventually leaves the target matrix, one has to account for the flow through the orifice at the tube's end. This may be illustrated as two conductances in series, C_V and C_O , respectively. From vacuum theory one finds for the conductance of an orifice with surface area A , $C_O = 0.25 \cdot \bar{v}A$ [188]. For systems where the tube's length is much greater than its cross section, the conductance corresponds to [189]:

$$C_V = \frac{8}{3\sqrt{\pi}} \frac{A^2}{Ul} \sqrt{\frac{2RT}{M}},$$

where U denotes the periphery of the cross section and R is the gas constant. The total conductance C is obtained by adding C_V and C_O inversely, analog to the electrical counterpart. As a result, one obtains for a cylindrical tube, with $A = \pi(D/2)^2$ and $U = \pi D$:

$$L = 12l^2 \frac{1 + \frac{4D}{3l}}{\pi^2 D}. \quad (5.26)$$

Note that such an approach to estimate the actual travel length was employed in similar studies and models [174, 187]. The tube's length l was approximated by a pore that is located in the geometrical center of a 2 mm thick and 6 mm diameter target pellet, which connects with a straight line to the surface. A mean value was determined by averaging over an area 2π , and thus:

$$n_c = \frac{L}{\lambda_{\text{mdt}}} \approx \begin{cases} 4 \cdot 10^7, & D_{\text{v},50}^{\text{Intrus.}} \\ 2 \cdot 10^6, & D_{\text{v},50}^{\text{Extrus.}} \end{cases}$$

Finally, applying τ_s , τ_{mft} and n_c into Equation (5.16), the inter-grain effusion delay parameter for the given case is of the order:

$$\nu = \frac{1}{n_c(\tau_s + \tau_{\text{mft}})} \approx \begin{cases} 35 \text{ s}^{-1}, & D_{\text{v},50}^{\text{Intrus.}} \\ 165 \text{ s}^{-1}, & D_{\text{v},50}^{\text{Extrus.}} \end{cases}$$

It should be mentioned that in this simplified model, as well as in MIP and N_2 physisorption isotherms, the commonly assumed cylindrical pore shape, seems to oppose to some extent the experimental evidence presented in this work. For instance, not only the topological microstructure presented by the SEM images in Fig. 3.17, but also the N_2 adsorption-desorption isotherm, indicate a slit-like pore shape. Therefore, an equivalent derivation was performed using a rectangular cuboid as pore volume, with a 10:1 ratio for the cross section sides and the same length l as motivated above. For such a geometry, one finds for the estimated travel length, $L = \frac{4}{\pi^2} \left[\frac{3}{4} l^2 \left(\frac{2}{x} + \frac{2}{y} \right) + 4l \right]$, where x and y denote the lengths of the cross section sides. Performing corresponding derivations regarding λ_{mdt} , τ_{mft} and n_c , yields an inter-grain effusion delay parameter $\nu \approx 20 \text{ s}^{-1}$ and $\nu \approx 80 \text{ s}^{-1}$, considering $D_{\text{v},50}^{\text{Intrus.}} = 120 \text{ nm}$ and $D_{\text{v},50}^{\text{Extrus.}} = 470 \text{ nm}$, respectively. Thus, the approximated tube geometry scarcely affects ν , considering the order of magnitude approximation from above.

This result verifies the assumption that the release process is dominated by the diffusion mechanism, since $\nu \gg \mu$. It is therefore legitimate to neglect any inter-grain effusion contribution to the delay function $p(t)$, which enables us to draw conclusions regarding the diffusion coefficient D and the expected on-line release efficiency ε_{rel} , assuming that the effusion to the ion source ε_{eff} is negligible.

Inserting the diffusion delay parameter (see Eq. (5.24)) into Equation (5.13) yields for the on-line release efficiency:

$$\varepsilon_\mu = \varepsilon_{\text{rel}}(T_{1/2} = 20.4 \text{ min}) = \begin{cases} 0.097(14), & \text{powder (spherical)} \\ 0.096(15), & \text{foil} \end{cases} \quad (5.27)$$

This result is in agreement with release efficiency measurements of pristine BN powder that were carried out at the RIB facility at the Centre de Recherche du Cyclotron (CRC) in Louvain-la-Neuve [74]. Release efficiencies around 10% were observed at 1000 °C. While one would expect higher efficiencies applying higher temperatures, as done in this study, one would also expect lower efficiencies from a pre-sintered target compared to a pristine powder target. Therefore, it is conceivable that the on-line release efficiency ε_{rel} (Eq. (5.27)) determined in this study is of a reasonable magnitude. The advantage of a rigid pre-sintered powder compact as ISOL target is that it avoids limitations on beam current and energy, to prevent the powder from escaping the target container. Furthermore, such targets ease target handling and waste management which are all important aspects, since it is foreseen to be implemented into a medical environment for the production of intense ^{11}C beams for PET-aided hadron therapy.

IV.2 Diffusion coefficient

Since this study allowed to determine the diffusion delay parameter μ , one can, in principle, derive the diffusion coefficient of carbon in boron nitride at $T = 1500$ °C (Eq. (5.12)). Therefore, the particle or grain-cluster size G is required. Applying the estimation obtained from the SSA measurements using the BET method, $\bar{G}_{\text{BET}}$ (Sec. III.1.2.1), yields:

$$D(1500 \text{ °C}) = \begin{cases} \frac{\mu \bar{G}_{\text{BET}}^2}{4\pi^2} = 4.5(15) \cdot 10^{-15} \text{ cm}^2 \text{ s}^{-1}, & \text{powder} \\ \frac{\mu \bar{G}_{\text{BET}}^2}{\pi^2} = 3.9(13) \cdot 10^{-14} \text{ cm}^2 \text{ s}^{-1}. & \text{foil} \end{cases} \quad (5.28)$$

Depending on whether we employ the solution of Fick's second law, considering a powder target (spherical target grains), or a foil target, the diffusion coefficient is of the order $D \approx 10^{-15} - 10^{-14} \text{ cm}^2 \text{ s}^{-1}$. As there was only one measurement performed at $T = 1500$ °C we believe that the result should rather be interpreted as an order of magnitude, since dedicated diffusion studies involve measurements at several different temperatures to generate so-called Arrhenius plots which show the temperature dependence of the diffusivity D , and allow to extract the pre-exponential factor D_0 and activation energy E_A of diffusion (refer to Eq. (5.5)). Unfortunately, it was not possible to investigate D at different temperatures in this study. Moreover, an accurate determination of the mean particle or grain cluster size G is difficult and associated with a considerable uncertainty, due to the relatively rough approximation deduced from SSA measurements using the BET method (refer to Sec. III.1.2.1).

However, the order of magnitude of carbon diffusion in boron nitride obtained in this work is considered reasonable, since it is comparable to the order of magnitude of carbon self-diffusion and boron diffusion in graphite (Fig. 5.6)

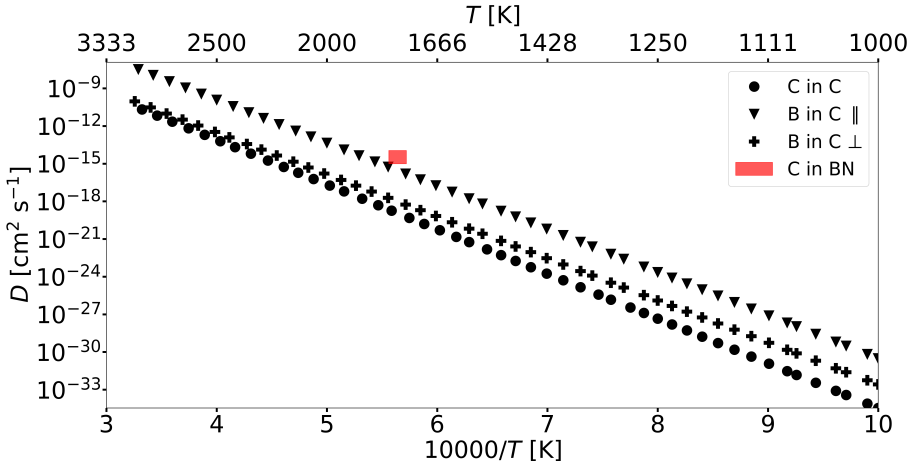


Figure 5.6: Arrhenius plots showing diffusion coefficients as a function of temperature for self-diffusion of carbon ($\bullet$) and for diffusion of boron in graphite, parallel ($\blacktriangledown$) and perpendicular ($+$) to the layer planes of graphite. The colored area indicates the diffusion coefficient $D(1500\text{ }^\circ\text{C}) \approx 10^{-15} - 10^{-14} \text{ cm}^2 \text{ s}^{-1}$ of carbon in boron nitride that was determined in this work. The data to generate these plots were taken from [161, 162].

[161, 162]. Carbon self-diffusion can be considered as a lower limit, which is indeed several orders of magnitude lower. Boron diffusion in graphite represents a mirrored tracer-host circumstance, where a good agreement for diffusion parallel to the layer planes is observed. The developed porous BN target was manufactured using hexagonal BN, which possesses an identical layer structure as graphite. Since the developed BN target is a bulk material, in principle, several mechanisms contribute to the measured diffusivity, e.g. bulk diffusion, diffusion parallel and perpendicular to the basal planes and grain boundary diffusion. Nonetheless, the comparison shown in Figure 5.6 suggests that carbon diffuses predominantly parallel to the layer planes of boron nitride.

V Summary

A pre-sintered boron nitride target, manufactured by spark plasma sintering, was developed especially for the production of intense ^{11}C beams. In past studies, this target was characterized with respect to its operational limitations, regarding its high temperature and high-temperature oxidation stability. A release study by means of measuring release fractions from activated targets was performed at CERN MEDICIS to complete these studies. The target's

microstructure was investigated by a series of different measuring techniques, testing properties such as porosity, specific surface area, grain size, and pore structure. A dedicated experimental test bench was developed and installed at CERN MEDICIS, utilizing this facility's unique infrastructure. The new test bench allowed, firstly, to measure the release fractions of the relatively short-lived ^{11}C . Secondly, measurements could be performed under controlled atmospheres, where an oxidizing atmosphere was applied, to promote ^{11}C release in the form of carbon monoxide. Finally, measurements could be performed off-line, which is a striking advantage when developing new ISOL targets.

^{11}C was released from the porous BN target by performing a five minute heat treatment at 1500 °C under oxidizing atmosphere, by supplying a 10^{-5} mbar l s^{-1} oxygen leak, using an Ar/O_2 (90/10 vol.%) gas mixture. The released fraction $F_\mu(t = 300 \text{ s}) = 0.045(7)$ was determined by measuring the 511 keV $\gamma - \gamma$ coincidences, originating from the β^+ -decay. Combining the measured release fraction with the identified microstructural properties of the SPS pre-sintered BN target, enabled to determine the on-line release efficiency assuming two possible target geometries, and neglecting effusion from the target container to the ion source:

$$\varepsilon_{\text{rel}}(T_{1/2} = 20.4 \text{ min}) = \begin{cases} 0.097(14), & \text{powder (spherical)} \\ 0.096(15), & \text{foil} \end{cases}$$

In addition, since the release process was classified as purely driven by diffusion, the magnitude of the diffusion coefficient $D(1500 \text{ °C}) = 10^{-15} - 10^{-14} \text{ cm}^2 \text{ s}^{-1}$ could be determined.

Acknowledgments

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Chapter 6

Implementation strategies into existing hadron therapy centers

The previous three chapters examined the microstructural properties (Chapter 3), operational limitations (Chapter 4) and carbon release characteristics (Chapter 5) of the developed porous BN target. In detail, the feasibility of operating the target at $T = 1500\text{ }^{\circ}\text{C}$ with oxygen potentials $\mu_{\text{O}_2} \leq -300\text{ kJ mol}^{-1}$ was demonstrated, and a ^{11}C release efficiency of $\varepsilon_{\text{rel}}(T_{1/2} = 20.4\text{ min}) = 10\%$ was extrapolated from an off-line release study. Target characterization is thus complete, and it is possible to utilize the obtained knowledge to study possible implementation concepts of a ^{11}C RIB production system into existing carbon therapy centers, which meet the high beam intensity requirements of $4 \cdot 10^8$ post-accelerated ions per spill delivered to the patient room. In that regard, a conceptual study of different ^{11}C production and separation modalities was performed, and contributed by the author of this thesis to the *Technical design report for a Carbon-11 Treatment Facility*, which was introduced in Chapter 1.

The following section is the corresponding excerpt of the aforementioned TDR¹. Note that the TDR version was edited and is thus not a verbatim copy.

¹Section 4.2 of the TDR.

6.1 ¹¹C production and separation

The realization or implementation of a ¹¹C production system into existing hadron therapy centers such as CNAO and MedAustron faces several challenges. The accomplishment of the required high ion beam intensity ($4 \cdot 10^8$ ions per spill) delivered to the patient room is considered as one of the main difficulties and is therefore discussed henceforth. The production of such intense radioactive ion beams (RIBs) demands optimization of individual steps along the process-chain. Reviewing the past results on the production of post-accelerated ¹¹C ion beams (Sec. 2.3), it is apparent that production via the projectile fragmentation method cannot be considered. Low production cross section and undesirable beam characteristics such as large momentum spread, large emittance and beam purity prevent the applicability of this method. Consequently, this report discusses the isotope production and post-acceleration approach. In this method, a chosen target is irradiated by a primary light particle beam (driver), followed by isotope extraction, separation, ionization/charge breeding and injection into the synchrotron for post-acceleration. Figure 6.1 presents an overview of possible implementation scenarios which are evaluated in this work. Goal of this discussion is to identify and discuss these scenarios in consideration of their feasibility to achieve delivery of the required beam intensity, and which allow implementation into existing facilities. In this chapter we will discuss the ¹¹C production and separation (Fig. 6.1I and 6.1II). In detail, different target-driver options, their expected yields and different separation techniques required for the injection into the electron beam ion source (EBIS) will be discussed.

6.1.1 ¹¹C production

The target

The choice of the target is an essential criterion for the accelerator chain. In principle, many choices of beam-energy-target combinations are possible, however, mostly two types of beam-target combinations are conceivable

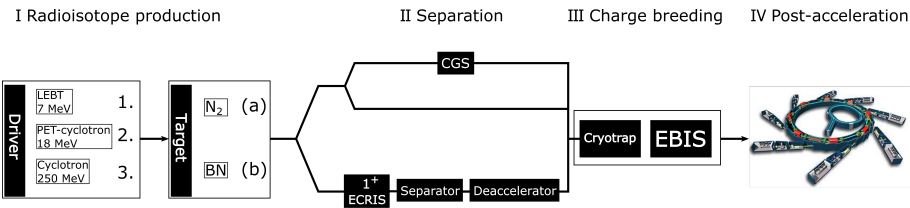


Figure 6.1: Component diagram showing different accelerator chain scenarios. Note that ECRIS denotes ECR ion source.

with respect to the production of high intensity post-accelerated ^{11}C beams: commercial nitrogen gas targets or a thick boron comprising target, both operated with a proton driver.

The following paragraph of TDR section 4.2 is omitted, as it describes conventional N_2 gas targets that are commonly operated with a chromatography gas separation (CGS) system and a brief description of the developed BN target, which both were already introduced in this thesis. Concerning the former target type, the reader is thus referred to Section 2.3.1, which is the corresponding excerpt of the TDR.

While the BN target was developed as an ISOL-type target, it is however conceivable in respect to the continuing accelerator chain (Fig. 6.1), to operate the target with a CGS system in order to deliver 'neutral beams'. Vice versa, N_2 gas targets can be operated with an ISOL-type separation system, i.e. 1^+ ionization and electromagnetic mass separation.

The primary proton driver

We introduced in the previous section two possible target materials that mostly will be discussed in this report, i.e. a N_2 gas target and a solid BN target. With respect to their corresponding ^{11}C production yields, the choice of the primary proton accelerator (driver) needs to be discussed. There are in principle three options:

- firstly, within the accelerator chain of CNAO and MedAustron, 7 MeV protons with intensities up to $7\text{ }\mu\text{A}$ can be extracted from the linac of the *Low Energy Beam Transfer* line (LEBT);
- secondly, a compact cyclotron used for industrial production of radioisotopes. There are several products commercially available. For instance, IBA's 18 MeV proton cyclotron CYCLONE®**KIUBE**, available in several editions that differ in beam intensity. Furthermore, IBA offers commercial N_2 gas target solutions, as well as solid target stations [190];
- thirdly, one could consider a more energetic, but compact proton therapy cyclotron to also extend the treatment facility's capacity. Such a cyclotron could be used, on the one hand, for the production of ^{11}C for PET-aided hadron therapy. On the other hand, it may be used for conventional proton therapy. Consequently, such an approach would increase the throughput of the treatment facility. Such cyclotrons are commercially available, for instance the VARIAN ProBeam™ 250 MeV, $0.8\text{ }\mu\text{A}$ superconducting cyclotron. However, consulting the reaction cross sections for ^{11}C production, shown in Fig. 3.1, it is evidenced that maximized

production yield is achieved at low-energies. Consequently, considerably more target material has to be irradiated to slow down the beam.

Isotope production

Energetic particles that impinge on a target may produce (radio-)isotopes by means of nuclear reactions. The physical thick in-target production yield Y_{phys} denotes the amount of nuclei produced per incoming beam particle for a given nuclear reaction, and can be expressed as:

$$Y_{\text{phys}} = \frac{N_A}{M} \int_{E_f}^{E_i} \frac{\sigma(E)}{S(E)} dE, \quad \left[\frac{\text{nuclei}}{\text{primary}} \right], \quad (6.1)$$

with N_A the Avogadro's number, M the molar mass, $S(E)$ the stopping power expressed in $\text{MeV cm}^2 \text{ g}^{-1}$, σ the cross section in cm^2 . E_i and E_f are the initial and final beam energy after passing through the target material. Applying Eq. (6.1) to the BN and N_2 targets provides the following physical thick in-target ^{11}C production yields:

$$Y_{\text{phys}}^{\text{BN}} = \frac{N_A}{M_{\text{BN}}} \int_{E_f}^{E_i} \frac{f_b \cdot \sigma_{^{11}\text{B}}(E) + f_n \cdot \sigma_{^{14}\text{N}}(E)}{S(E)} dE, \quad (6.2)$$

$$Y_{\text{phys}}^{\text{N}_2} = \frac{N_A}{M_{\text{N}_2}} \int_{E_f}^{E_i} \frac{2 \cdot f_n \cdot \sigma_{^{14}\text{N}}(E)}{S(E)} dE, \quad (6.3)$$

where $f_{b, n}$ denote the fractional isotopic abundances.

Considering continuous proton beam irradiation with intensity I , the in-target production yield of radioisotopes as a function of irradiation time is given by:

$$y(t) = Y_{\text{phys}} \cdot \frac{I[\mu\text{A}]}{10^6 \cdot e \cdot z} \left(1 - e^{-\frac{\ln(2)}{T_{1/2}} \cdot t} \right), \quad \left[\frac{\text{Bq}}{\mu\text{A}} \right], \quad (6.4)$$

with electric charge e and charge number z , which equals unity for protons. Equation (6.4) illustrates that during target irradiation, isotopes are permanently being produced, while decaying at the same time. However, after a sufficiently long irradiation time (usually 4-5 half-lives), an equilibrium is reached, which is commonly denoted as the saturation yield:

$$y_{\text{sat}} = y(t \rightarrow \infty) = Y_{\text{phys}} \cdot \frac{I[\mu\text{A}]}{10^6 \cdot e \cdot z}. \quad (6.5)$$

On the other hand, stable isotopes do not decay and are therefore continuously produced with a production rate $R_p = Y_{\text{phys}} \cdot I$.

ISOL-type target operation

Equation (6.4) and (6.5) are applicable concerning in-target production yields, e.g. by irradiating a N_2 gas target or cold target. If however isotopes are extracted from the target during irradiation, the formalism needs to be adapted to account for the released isotopes. This is the case concerning ISOL-type RIB production and can be expressed in the differential equation:

$$\frac{dN(t)}{dt} = R_p - \lambda N - f(p(t), N(t)).$$

N are the nuclei of a given isotope in the target, R_p is the corresponding production rate, $\lambda = \frac{\ln(2)}{T_{1/2}}$ is the decay constant of the possibly radioactive isotope and $f(p(t), N(t))$ is a function describing the release from the target. An important parameter in this context is the delay function $p(t)$, which expresses the probability of an isotope produced at $t = 0$ to be released at time t . With knowledge of the delay function and production rate, one can derive the ISOL release efficiency $\varepsilon_{\text{rel}}(T_{1/2})$ and the yield Y_{rel} of produced isotopes that are released from the target:

$$\begin{aligned} \varepsilon_{\text{rel}}(T_{1/2}) &= \int_0^\infty dt \, p(t) \cdot e^{-\frac{\ln(2)}{T_{1/2}} \cdot t}, \\ Y_{\text{rel}}(t, T_{1/2}) &= R_p \int_0^t dt' \, p(t') \cdot e^{-\frac{\ln(2)}{T_{1/2}} \cdot t'}. \end{aligned} \tag{6.6}$$

Similar to thick in-target production, one can denote a saturation yield for sufficiently long irradiation times: $Y_{\text{rel}}^{\text{sat}}(t \rightarrow \infty, T_{1/2}) = R_p \cdot \varepsilon_{\text{rel}}(T_{1/2})$.

Based on these equations, the expected in-target production yields and ISOL-yields for released isotopes can be calculated for the different target-driver combinations. For this purpose, simulations were performed with the particle physics Monte Carlo code FLUKA [36, 37].

In-target production yield simulations

At this point we shall briefly discuss the target geometry that is used as an input for the simulations. In the case of the N_2 gas target, a geometry based on the commercial IBA target was applied [191]. In detail, this comprises a 40 cm^3 , conical target container filled with a 20 bar N_2/O_2 (99/1 vol.%) gas mixture. For the simulation, a conical geometry with a length of 11.3 cm and front and back radii $r_1 = 0.75 \text{ cm}$, $r_2 = 1.35 \text{ cm}$, respectively were employed. Moreover, a $600 \text{ }\mu\text{m}$ thick aluminum entrance window was assumed, which is important to address as the proton beam will lose energy in this window. In the case of the solid BN target, a cylindrical target pellet was used, with a diameter of 3 cm and surface area $S = 7.1 \text{ cm}^2$. The target thickness is varied depending on the

primary proton beam energy, such that the proton beam exits the target pellet with a remaining energy of 4 – 5 MeV. With such a configuration, the deposited power can be reduced, while the in-target production yield is only marginally decreased. This can be understood by studying Fig. 3.1, which shows that both cross sections significantly drop for energies lower than 5 MeV.

Table 6.1 compares the expected ^{11}C in-target production yields for the different driver-target scenarios. Note that in case of the produced in-target yield it has to be distinguished between BN and N_2 gas target. The latter is produced in batch mode, consequently, we can define an end-of-beam (EOB) yield according to Equation (6.4). Furthermore, IBA quotes yields for their N_2 target in combination with the CYCLONE[®]KIUBE 18 MeV cyclotron [190]. These yields are shown in brackets. However, for consistency, additional simulations were performed for this scenario. Comparing these yields, exhibits deviations of a factor < 2 . IBA offers another N_2 solution, where ^{11}C is produced in the CH_4 molecular sideband. For this purpose, the target mixture contains 5-10% H_2 instead of O_2 . However, the yield is considerably lower, due to more complicated hot atom chemistry [191] and therefore is not displayed here. The solid BN target, in principle, will be operated on-line (cw). To allow comparison of respective in-target production yields between the N_2 and BN target, the release aspect is not yet included in Table 6.1. As production is carried out continuously, the specified BN in-target yield is given at saturation level (Eq. (6.5)), which is reached after approximately 1.5 h.

Table 6.1 shows that the N_2 gas target generally offers lower yields compared to the BN target, which mainly can be attributed to the higher cross sections when exploiting the (p,n) reaction channel on boron. The discrepancy between these two targets is more pronounced for the 7 MeV linac and 250 MeV cyclotron as the commercial gas targets are not designed for these energies and consequently do not utilize the nitrogen ^{11}C production cross section adequately. In detail, the 7 MeV linac loses up to 6 MeV within the aluminium entrance window, which implies that it is arguable whether any ^{11}C is produced at all, as the cut-off energy of the $^{14}\text{N}(\text{p}, \alpha)^{11}\text{C}$ reaction is around 3 MeV. The FLUKA simulated yields of the LEBT-linac- N_2 gas target combination should be therefore treated with caution. The 250 MeV cyclotron on the other hand, deposits merely 1 MeV within the N_2 target gas, which explains the low yields. Both 7 MeV linac and 250 MeV cyclotron would benefit from an optimization of the N_2 gas target design.

Considering the BN target, the 250 MeV VARIAN ProBeamTM-BN combination offers the highest saturation yield y_{sat} , when normalized to the primary proton beam current, since a stack of many target pellets is required to slow down the proton beam below 5 MeV (~ 34 cm). However, the CYCLONE[®]KIUBE cyclotron driver option presents the highest achievable in-target yield due to the

Accelerator	LEBT-Linac		CYCLONE [®] KIUBE	
Particle	proton		proton	
Energy [MeV]	7		18	
Intensity [μ A]	7		50	
Pulse structure	pulsed		cw / pulsed	
Beam cross section [mm^2]	Gaussian; FWHM 8.24 ²		Gaussian; FWHM 8.24 ²	
Batch/extraction time [min] / cw	cw 30 + 4 + 1		cw 30 + 4 + 1	
Target size, geometry	cylindrical 40 cm ³ , conical		cylindrical 40 cm ³ , conical	
$S[\text{cm}^2] \cdot L[\text{cm}] / r_1, r_2, L[\text{cm}]$	7.1·0.2 0.75, 1.35, 11.3		7.1 · 0.29 0.75, 1.35, 11.3	
Target material	BN		BN	
Density [g cm^{-3}]	1.3		1.3	
Deposited beam power [W]	49		700	
Target temperature [°C]	1500		1500	
$y_{\text{sat}}[\text{GBq } \mu\text{A}^{-1}]$	1.7		11.9	
In-target yield	12		593	
EOB / saturation [GBq]	10		80	
Release efficiency [%]	CO		CO	
Molecular sideband	N ₂ , Ar, O ₂		N ₂ , Ar, O ₂	
Impurities	O ₂		NO _x	

Table 6.1: Comparison of in-target production yields for different driver-target combinations. The yields are calculated using the FLUKA code [36, 37]. In case of the N₂ target in combination with the CYCLONE[®]KIUBE cyclotron, yields are quoted from IBA as well [190], and are displayed in brackets. The in-target production yields are expressed as End-Of-Beam (EOB) yields and as saturation yield for N₂ batch mode and BN ISOL-type operation, respectively. The release efficiency $\varepsilon_{\text{rel}}(T_{1/2} = 20.4 \text{ min}) = 10\%$ of the BN target was experimentally determined [192], whereas the efficiency for the N₂ target refers to the trapping efficiency $\varepsilon_{\text{trap}}(T_{1/2} = 20.4 \text{ min})$ (Eq. (6.7)) which will be explained in the following section. The listed impurities are only the ones originating from the target material itself and its operation. In the BN case, Ar refers to the carrier gas used with the controlled O₂ leak.

Accelerator	VARIAN ProBeam TM	
Particle	proton	
Energy [MeV]	250	
Intensity [μ A]	0.8	
Pulse structure	cw / pulsed	
Beam cross section [mm ²]	Gaussian; FWHM 8.24 ²	
Batch/extraction time [min] / cw	cw	30 + 4 + 1
Target size, geometry	cylindrical	40 cm ³ , conical
$S[\text{cm}^2] \cdot L[\text{cm}] / r_1, r_2, L [\text{cm}]$	7.1-34.2	0.75, 1.35, 11.3
Target material	BN	N ₂
Density [g cm ⁻³]	1.3	0.02332
Deposited beam power [W]	148	0.7
Target temperature [°C]	1500	n/a
y_{sat} [GBq μ A ⁻¹]	79	0.7
In-target yield	63	0.35
EOB / saturation [GBq]		
Release efficiency [%]	10	80
Molecular sideband	CO	CO ₂
Impurities	N ₂ , Ar, O ₂	N ₂ , O ₂ , NO _x

Table 6.1 (Continued)

much higher proton beam intensity. In standard edition, beam currents up to 150 μ A are possible [191]. Eq. (6.4) shows that the produced yield scales linearly with the proton current. The selection of the primary proton current I should be handled with caution, as power deposition into the target matrix scales linearly with I , which as a result may lead to rapid heating of the target material. It was mentioned previously that generally ISOL-type targets are operated at high temperatures, to enhance diffusion and effusion processes. Previous studies [149] investigated the high-temperature stability of the BN target in typical ISOL operational conditions. In this respect, BN dissociation was expected at temperatures above 1000 °C. When using an ISOL-type separation technique, i.e. 1⁺ ionization and electromagnetic mass separation, the extent of target dissociation is however of great importance since the ECR ion source ionization efficiency depends crucially on the injected gas load. High-temperature studies, probing the developed BN target at temperatures up to 1500 °C demonstrated its applicability in such conditions [149]. Eventually, the maximum applicable beam current for the BN target will depend on how efficient the target can be cooled. The commercial IBA N₂ target is in practice operated with a 50

μA beam current. In the case of BN, such a beam current would correspond to a power deposition of 700 W. We assume at this point that target cooling techniques are able to prevent the target to exceed the 1500 °C maximum temperature.

6.1.2 Isotope separation

The separation of ^{11}C from impurities depends on the target-driver combination, the molecular side band in which ^{11}C is produced, the impurities' species and their quantities. The appropriate separation modality is strongly influenced by the EBIS, which can only operate with reasonable ^{11}C charge breeding efficiency, if the injected ^{11}C is not surpassed by orders of magnitude from impurities. As illustrated in Figure 6.1II, there are in principle three different possibilities:

- (i) direct coupling to the EBIS, i.e. no separation is required, such that a neutral gas is injected and directly ionized to a high charge state;
- (ii) application of a CGS system to isolate CO_x from other species;
- (iii) ISOL-type separation, using a $q = 1^+$ ECR ion source, electromagnetic mass separation and a deaccelerator.

Direct target coupling and injection into the EBIS (i), i.e. no separation is required, would of course be the favorable route, as it would not require further components. If however the amount of impurities is considerably larger, chemical separation, e.g. CO_2 from N_2 , by means of a cryogenic or molecular sieve trap (CGS system (ii)) may be applicable. On the other hand, electromagnetic mass separation (iii), enables isotopic separation due to the A/q selectivity. For a brief descriptions of these separation modalities, the reader is referred to Sec. 2.3.1 and 2.2.1, respectively.

N_2 gas target

Nitrogen gas targets are filled to 20 bar, which will further increase during irradiation, therefore it is not possible to directly couple to the EBIS charge breeder (i) or to an ECR ion source (iii). For both sources, the operation efficiency depends crucially on the injected gas load. Consequently, some sort of trapping needs to be implemented, to separate the macroscopic quantities of N_2 and O_2 from the active target gas. It is therefore reasonable to use a CGS system to separate $^{11}\text{CO}_2$ from these impurities. Since ^{11}C is produced in the CO_2 molecular sideband, a cold trap or molecular sieve trap may be used, whereas the commercially available N_2 gas target is usually equipped with the former type [191]. The trapping efficiency of cold traps depends on the surface area of the coil that is immersed in liquid nitrogen. Usually trapping efficiencies greater than 95% are achievable [193]. The trapping of CO_2 is carried out over

a duration of approximately four minutes, followed by one minute of heating to release the trapped molecules. Hence, one batch of ^{11}C is produced and purified in $30 + 4 + 1$ minutes, as indicated in Tab. 6.1. By considering the decay during trapping, one obtains an isotope specific separation efficiency $\varepsilon_{\text{sep}}^{\text{CGS}, \text{N}_2}$:

$$\begin{aligned}\varepsilon_{\text{sep}}^{\text{CGS}, \text{N}_2} &= \varepsilon_{\text{trap}} \cdot \varepsilon_{\text{trans}}, \\ \varepsilon_{\text{trap}}(T_{1/2}) &= 0.95 \cdot e^{-\frac{\ln(2)}{T_{1/2}} \cdot 300}.\end{aligned}\tag{6.7}$$

For instance, considering the decay of ^{11}C with $T_{1/2} = 20.4$ minutes, approximately $\varepsilon_{\text{trap}} = 80\%$ of the produced ^{11}C can be recovered as $^{11}\text{CO}_2$. Once this separation process is finished, the molecules can be injected into the EBIS. Assuming a transport efficiency of 50%, an overall efficiency of $\varepsilon_{\text{sep}}^{\text{CGS}, \text{N}_2} = \varepsilon_{\text{trap}} \cdot \varepsilon_{\text{trans}} = 0.8 \cdot 0.5 = 0.4$ can be achieved for ^{11}C . One drawback of such a cold trap is that N_2 , O_2 , NO_x and CO are trapped to some extent as well [56, 193]. Using liquid argon instead of liquid nitrogen resolves the trapping of N_2 [193]. Alternatively, when using a molecular carbon sieve trap, equal efficiencies can be achieved, while O_2 , CO , or NO are probably not retained [56]. As a consequence, a molecular sieve trap might be better suited, since it is not clear how much N_2 , O_2 and NO_x is trapped together with $^{11}\text{CO}_2$ in the CGS system. As mentioned earlier, if these species exceed the quantity of $^{11}\text{CO}_2$ by an order of magnitude or more, this will be problematic for the charge breeding in the EBIS.

Besides the contamination resulting from the target material itself (N_2 and O_2), other (radio-)isotopes are produced during irradiation, which must be taken into account. Figure 6.2d-6.2f show the simulated physical thick in-target production yields, expressed in nuclei per μC , for an IBA-type N_2 target in combination with the different driver options. Minor contaminations are expected for 7 MeV LEBT-linac (Fig. 6.2d) due to the low driver beam energy. When employing the more energetic 18 MeV or 250 MeV cyclotrons (Figs. 6.2e and 6.2f, respectively), considerably more elemental byproducts are generating during irradiation, which may form molecules such as NO_2F , FNO and H_2O . These molecules should easily be removed from $^{11}\text{CO}_2$ using a cold or molecular sieve trap. However, among ^{11}C , other carbon isotopes are produced as well, which cannot be separated by a CGS system due to their identical chemical properties. Depending on their quantity, further separation may be required before injecting into the EBIS. Table 6.2 provides an overview of the expected gas output per batch of a N_2 target after CGS-type separation, depending on the proton driver.

When using the 7 MeV LEBT-linac or the 18 MeV CYCLONE®**KIUBE** cyclotron, the number of produced carbon impurities is either lower or of the same order of magnitude. It is therefore feasible to directly inject into the

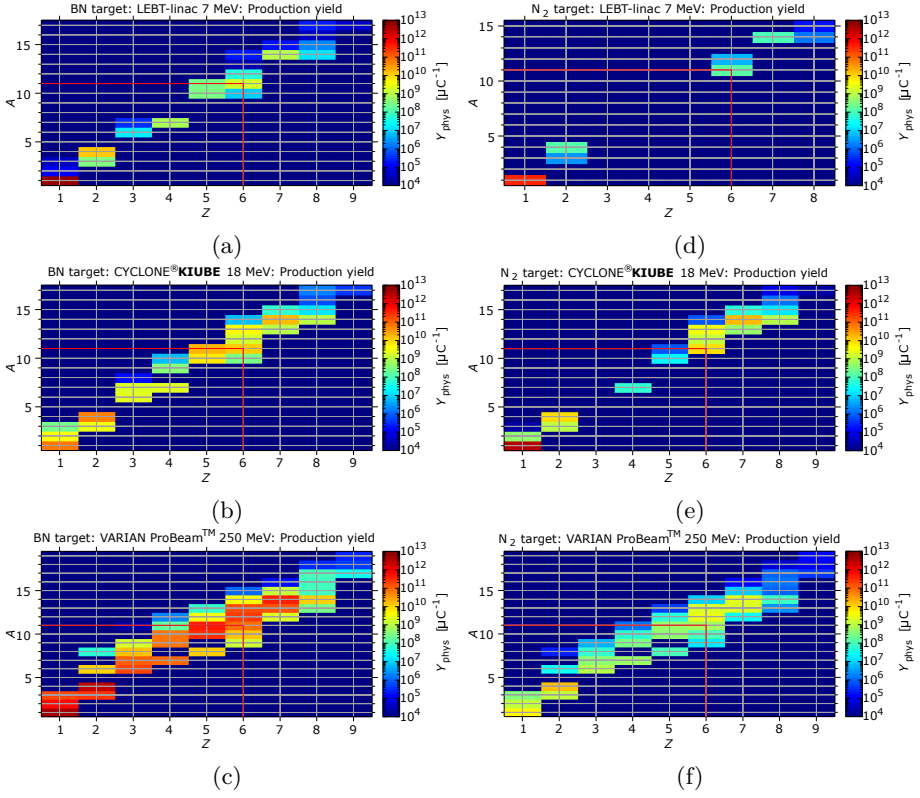


Figure 6.2: FLUKA simulated physical thick in-target production yields of a BN and N_2 target for the different accelerator options, as discussed in the body of this manuscript. Details regarding the target geometry and beam profile can be found in Table 6.1. Note that the yield is expressed in nuclei per μC .

EBIS, provided that potential trapping of target gas residuals (N_2 , O_2 and NO_x) is limited. However, when using the 250 MeV VARIAN ProBeamTM cyclotron for isotope production, Table 6.2 suggests that $^{12,13}\text{C}$ are exceeding ^{11}C production by one order of magnitude, which is perceived as inadmissible if no further separation modality is applied.

	LEBT-Linac	CYCLONE® KIUBE	VARIAN ProBeam™
$^{10}\text{CO}_2$	-	-	$2 \cdot 10^4$
$^{11}\text{CO}_2$	$5 \cdot 10^{11}$	$2 \cdot 10^{14}$ ($1 \cdot 10^{14}$)	$2 \cdot 10^{11}$
$^{12}\text{CO}_2$	$3 \cdot 10^{10}$	$5 \cdot 10^{13}$	$2 \cdot 10^{12}$
$^{13}\text{CO}_2$	-	$1 \cdot 10^{14}$	$1 \cdot 10^{12}$
$^{14}\text{CO}_2$	-	$3 \cdot 10^{10}$	$7 \cdot 10^9$
$\text{N}_2, \text{O}_2,$ NO_x	unknown	unknown	unknown

Table 6.2: Expected gas output expressed in molecules per batch from a N_2/O_2 (99/1 vol.%) target employed with a CGS system. (top) Recovered carbon isotopes after 30 minutes of irradiation, followed by four minutes of trapping and one minute of release in the CGS system. The separation efficiency was calculated isotope-specific using Eq. (6.7). The number in parenthesis refers to the expected yield derived from the recovered activity as provided by IBA [190]. (bottom) Residual impurities originating from the target gas, which are possibly trapped to some extent.

BN target

Considering a possible application of the solid BN target, one has to acknowledge that its operation differs in several ways. Firstly, target irradiation is performed in constant wave (cw) mode, as indicated in Tab. 6.1; secondly, ISOL-type targets are usually operated at pressures $10^{-6} - 10^{-4}$ mbar to prevent discharges in the ion source; thirdly, as mentioned earlier, high temperatures and a controlled oxygen leak are applied to enhance the isotope release from the target matrix. As a result, (radio-)isotopes are continuously produced and evaporated from the target, resulting in a steady gas flow effusing towards the EBIS.

The BN target was specifically developed for ^{11}C RIB production, and has been characterized with respect to its operational limitations [149] and release properties [192]². These studies concluded that target operation at $T = 1500$ °C and controlled oxidizing atmospheres with oxygen potentials $\mu_{\text{O}_2} \leq -300$ kJ mol⁻¹ is feasible, and is therefore applied for the following considerations. In practice, such O_2 potentials are accomplished by calibrated leaks of the order of 10^{-5} mbar l s⁻¹ using an Ar/ O_2 (90/10 vol.%) gas mixture. Note that an Ar comprising gas mixture instead of pure O_2 was necessary due to safety regulations. A release efficiency $\varepsilon_{\text{rel}}(T_{1/2} = 20.4 \text{ min}) = 10\%$ was estimated for ^{11}C in such operational conditions. Moreover, the release study enabled approximation of the delay function $p(t)$ (refer to Eq. 6.6), which allows calculation of the carbon isotope specific yield $Y_{\text{rel}}(t, T_{1/2})$ as a function of time

²Chapter 4 and 5 of this thesis, respectively.

t , or at saturation level $t \rightarrow \infty$ for short-lived radioisotopes. Note that it was not possible to determine the molecular sideband distribution in which ^{11}C and other carbon isotopes are released. Chemical equilibrium calculations predict a predominant CO sideband, which is supported by the past results of Chapter 2³, where the CO/CO₂ ratio is usually between 10 – 100. Hence, ^{11}C release is assumed to occur in the CO sideband, where it is however not possible to account for the molecule formation process and its corresponding efficiency. In the case of ^{11}CO , the formation efficiency is included in the experimentally determined release efficiency [192], whereas for other carbon isotopes it is not possible to address this feature, which is thus neglected.

As mentioned above, such target operation will result in a continuous gas flow originating from the target. To evaluate whether direct injection of this gas output into the EBIS (i) is feasible, one needs to estimate the ^{11}CO yield, as well as the amount of impurities that are comprised in this gas flow. The aforementioned target operation is associated with impurities from three different sources: (radio-)isotopes generated during target irradiation which are evaporated from the target next to ^{11}CO , vapor pressure of the target material due to the 1500 °C target temperature, and the applied gas leak of 10^{-5} mbar l s^{-1} using an Ar/O₂ (90/10 vol.%) gas mixture.

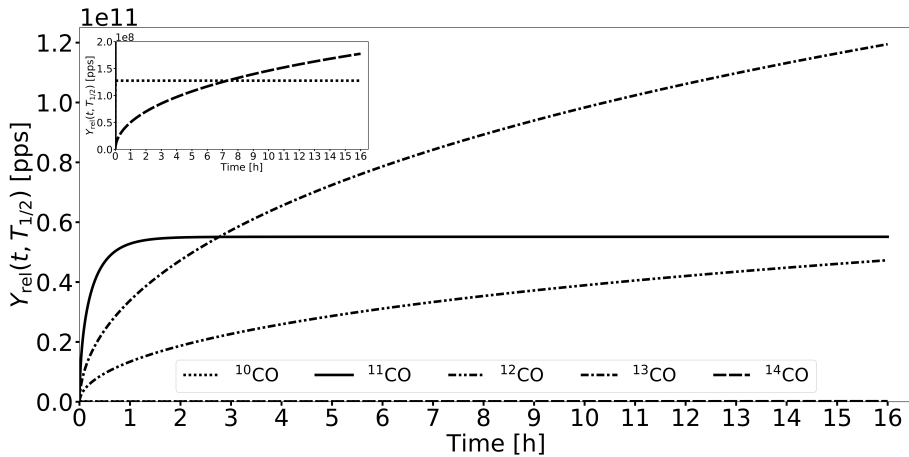


Figure 6.3: Released carbon yields $Y_{\text{rel}}(T_{1/2})$ (Eq. (6.6)) of the BN target employed with a 18 MeV, 50 μA proton cyclotron. While radioisotopes saturate after ~ 1.5 h due to their half-life, stable carbon isotope do not reach saturation after 16 h of continuous irradiation.

³Chapter 2 refers to the TDR version. The mentioned past studies were presented in Section 2.3 of this thesis.

We first discuss the expected ^{11}C yield and former impurity source, i.e. (radio-)isotopes produced during irradiation which are evaporated from the target. Figure 6.2a-6.2c show the FLUKA simulated physical thick in-target production yields, expressed in nuclei per μC , considering the BN target employed with the different production driver. The released ^{11}C and ^{12}C isotopic impurities are calculated using Equation (6.6), with a release efficiency $\varepsilon_{\text{rel}}(T_{1/2} = 20.4 \text{ min}) = 10\%$ for ^{11}C , thus, assuming that saturation is reached ($\sim 1.5 \text{ h}$). Concerning the ^{12}C impurities, a delay function $p(t)$:

$$p(t) = \frac{6\mu}{\pi^2} \sum_{n=1}^{\infty} e^{-\mu n^2 t},$$

$$\mu = 6.2(19) \cdot 10^{-6} \text{ s}^{-1},$$

was employed, where the yields of short-lived carbon radioisotopes is given at saturation, reached after approximately 1.5 h. On the contrary, saturation of stable carbon isotopes will require significantly more time, as no decay is occurring. This feature is illustrated in Figure 6.3 showing the released ^{12}C molecules when using the BN target with the 18 MeV CYCLONE[®]KIUBE cyclotron. Therefore, to be able to compare, the expected yields of stable and long-lived carbon radioisotopes are calculated assuming $t = 16 \text{ h}$ of irradiation. This duration is chosen, considering that in practice the synchrotron is started during the night for beam commissioning and accounting for a full day of operation for therapy. Note that the carbon release study yielded two slightly different $p(t)$ approximations depending on microstructural features of the target material. Since merely an order of magnitude evaluation of ^{12}C yields is discussed here, and no considerable difference in yields between these two delay function was calculated, we restrict the following discussion to the delay function which is shown above. The reader is referred for more information to the corresponding release study [192]⁴.

The results of the aforementioned derivation for the expected gas output of the BN target due to evaporated (radio-)isotopes are shown in the top part of Table 6.3. In conclusion, the 7 MeV LEPT-linac produces ^{12}C impurities of comparable magnitude, whereas the 18 MeV CYCLONE[®]KIUBE and the 250 MeV VARIAN ProBeamTM cyclotron, generate isotopic contaminants that exceed ^{11}C by one or two orders of magnitude. In the former case, it has to be investigated whether such a load degrades the EBIS performance to an inadmissible degree, whereas the latter case most likely prevents direct injection into the EBIS (i). Besides carbon, other, volatile, isotopes are produced inside the target (see Fig. 6.2a-6.2c) that are expected to be released very efficiently. Isotopic nitrogen and oxygen will only be traces compared to the impurities

⁴Chapter 5 of this thesis.

	LEBT-linac	CYCLONE® KIUBE	VARIAN ProBeam™
^9CO	-	-	$7 \cdot 10^5$
^{10}CO	$6 \cdot 10^5$	$1 \cdot 10^8$	$1 \cdot 10^8$
^{11}CO	$1 \cdot 10^9$	$6 \cdot 10^{10}$	$6 \cdot 10^9$
^{12}CO	$2 \cdot 10^8$	$5 \cdot 10^{10}$	$1 \cdot 10^{11}$
^{13}CO	$1 \cdot 10^5$	$1 \cdot 10^{11}$	$7 \cdot 10^{10}$
^{14}CO	$8 \cdot 10^5$	$2 \cdot 10^8$	$2 \cdot 10^9$
^{15}CO	-	-	$2 \cdot 10^3$
He	$\sim 9 \cdot 10^{10}$	$\sim 3 \cdot 10^{12}$	$\sim 2 \cdot 10^{12}$
N ₂	$< 2 \cdot 10^{14}$	$< 2 \cdot 10^{14}$	$< 2 \cdot 10^{14}$
O ₂	$\sim 2 \cdot 10^{13}$	$\sim 2 \cdot 10^{13}$	$\sim 2 \cdot 10^{13}$
Ar	$\sim 2 \cdot 10^{14}$	$\sim 2 \cdot 10^{14}$	$\sim 2 \cdot 10^{14}$

Table 6.3: Expected gas output expressed in $[\text{s}^{-1}]$ from operating the BN target at 1500 °C with a 10^{-5} mbar l s^{-1} Ar/O₂ (90/10 vol.%) gas leak for the different driver beams. (top) Released carbon monoxide yields calculated using Eq. (6.6), assuming saturation for short-lived radioisotopes and 16 h of target operation for long-lived and stable isotopes. (bottom) Gas output resulting from target operation, and vaporized He generated in nuclear reactions, assuming 100% release efficiency.

resulting from target operation, which will be discussed henceforth. However, hydrogen and helium isotopes are produced in significant amounts, which will most likely be a limiting factor for the EBIS performance. The release of hydrogen is difficult to evaluate as it may form chemical compounds such as HBO. Helium on the other hand should be simply released, where the bottom part of Table 6.3 indicates the maximum extent by assuming a 100% release efficiency.

The second source of impurities stems from target operation at $T = 1500$ °C and is attributed to the vaporization of N₂ due to BN dissociation: $2\text{BN} \rightarrow 2\text{B} + \text{N}_2(\text{g})$. This feature was investigated in dedicated high temperature stability studies at the ISOLDE off-line laboratories, which showed that no N₂ evaporation is detectable at a base pressure of $\sim 5 \cdot 10^{-7}$ mbar. Assuming ideal gas conditions, room temperature in the gas transfer line and using the 300 l s^{-1} throughput of the employed turbo vacuum pump, less than $3 \cdot 10^{15}$ particles per second are vaporized from the target. A residual gas analysis showed that N₂ accounts for approximately 7% of the total residual gas composition, which corresponds to $\sim 2 \cdot 10^{14}$ N₂ molecules per second. This is significantly exceeding the expected ^{11}CO yield for all possible proton driver, therefore eliminating direction coupling of the BN target to the EBIS charge breeder (i).

Nonetheless one should address the third source of impurities, which originates from the application of the 10^{-5} mbar l s^{-1} calibrated gas leak using an Ar/O_2 (90/10 vol.%) gas mixture. Such a controlled gas supply contributes twofold to the impurities: firstly, a net gas flow of $\sim 2 \cdot 10^{14}$ molecules per second is associated to the corresponding leak, assuming ideal gas conditions and room temperature in the gas transfer line. It is worth emphasizing that an Ar/O_2 gas mixture is employed due to safety regulations, preventing injection of pure O_2 , which could reduce the gas leak by one order of magnitude while maintaining the same oxygen potential. Moreover, argon could be replaced by helium, considering the charge space limitation of the EBIS charge breeder. Secondly, BN is sensitive to oxidation at high temperatures, resulting in further N_2 evaporation: $2\text{BN} + \frac{3}{2}\text{O}_2(\text{g}) = \text{B}_2\text{O}_3(\text{l}) + \text{N}_2(\text{g})$. A quantitative analysis of the oxidation kinetics of such target operation indicated that the external O_2 supply results in less than 12% enhanced N_2 evaporation, which is insignificant considering the order of magnitude estimation that is discussed at this stage.

In summary, Table 6.3 shows the expected continuous gas output that originates from the BN target, where the top part refers to the released ^{11}CO and isotopic carbon contaminants produced from target irradiation. The bottom part displays the approximated impurities resulting from target operation. As the impurities are exceeding the ^{11}CO flow significantly for all of the discussed proton driver, it is necessary to incorporate a separation modality prior EBIS injection. In that regard, separation may be based on chromatography gas separation (CGS) (ii) or on an ISOL-type electromagnetic separation system (iii).

BN target with CGS-type separation

^{11}CO isolation using a CGS system is challenging as the main impurities are N_2 , O_2 and the carrier gas (Ar) of the oxygen leak. CO and N_2 have very similar boiling points (81.6 and 77.4 K, respectively) which complicate the separation process. The typical cold traps and molecular sieve traps described earlier are not suited for efficient CO trapping, since CO is, at most, only partly captured [56]. There exists a variety of other systems or materials [194] that are used to purify CO-containing gas mixtures. However, often they work under high pressures or they trap significant amounts of N_2 and O_2 as well, while CO is only trapped to 2 – 3%. Alternatively, one could oxidize ^{11}CO to $^{11}\text{CO}_2$ for which the CGS systems described earlier can be applied. Studies on high-temperature CO oxidation suggest that high conversion efficiencies can be achieved in short times [195]. In the aforementioned study, hot inert (N_2) carrier gas was sent through a cylindrical quartz duct in which CO and water were rapidly mixed. Best results were obtained at temperatures ~ 1100 °C with a water mole fraction of 0.0248. Conversion efficiencies close to 100% were found in a time span less than one second. If we consider such an approach

for CO oxidation, this prevents the subsequent application of a cold trap for CO₂ separation as water will condense as well. However, carbon molecular sieve traps have a low affinity for water and therefore are a suitable option [56]. One drawback of such a separation route is again the fact that trapping results in a batched injection. Furthermore, oxidizing CO to CO₂ is not desirable for the EBIS operation, since the additional oxygen atom occupies the available charge space.

To calculate the amount of recovered isotopes when employing the BN target with such a modified CGS system, one has to account for the accumulation and simultaneous decay of radioisotopes. Although considering the application of a molecular sieve trap instead of a cold trap, due to their similar working principle, we can apply the same trapping mechanism as discussed for the cold traps, i.e. trapping and release time of four and one minute, respectively with a trapping efficiency larger than 95%. The accumulation of radioisotopes during trapping, can be described by the same formalism as thick in-target radioisotope production: $\dot{n}(t) = \tilde{y} - \lambda \cdot n(t)$, with n the number of a specific radioisotope in the trap and $\tilde{y}$ the rate with which it is vaporized from the target (Tab. 6.3). As a result, Equation (6.4) can be applied to calculate the entrapped activity, where the production rate, $Y_{\text{phys}} \cdot I$ is replaced by $\tilde{y}$. Finally, one obtains for the amount of injected molecules by accounting for the decay of the specific radioisotope during the release from the trap:

$$n(t = 4 \text{ min}) = \frac{\tilde{y}}{\lambda} (1 - e^{-\lambda \cdot 240}) e^{-\lambda \cdot 60} \cdot 0.95 \cdot 0.5, \quad (6.8)$$

where a transport efficiency of 50% was incorporated. Note that the radioisotope-dependency is given by the decay constant $\lambda = \frac{\ln(2)}{T_{1/2}}$. Based on Equation (6.8) one can define the total separation efficiency $\varepsilon_{\text{sep}}^{\text{CGS, BN}}$ for the BN target applied with a CGS system:

$$\varepsilon_{\text{sep}}^{\text{CGS, BN}}(T_{1/2}) = \frac{n(t = 4 \text{ min})}{\tilde{y}} \cdot \lambda(T_{1/2}). \quad (6.9)$$

As a result, an overall efficiency of approximately 6% is found for $^{11}\text{CO}_2$. Note that Eqs. (6.8) and (6.9) are only valid for radioactive species. Stable carbon contaminants resulting from the BN target will not decay during the four minutes of accumulation, and will be subsequently injected into the EBIS with an efficiency of $\varepsilon = 0.95 \cdot 0.5 \approx 50\%$. As a result, a deterioration of the $^{11}\text{CO}_2$ -to-carbon impurity ratio will occur. This feature should be addressed when considering the possible application of a CGS system combined with the BN target, as the impurity level should not exceed the amount of $^{11}\text{CO}_2$ molecules significantly. The expected load of the BN target-CGS system combination is shown in Table 6.5.

BN target with ISOL-type separation

As mentioned earlier, an ISOL-type electromagnetic mass separation system (iii) may be used to isolate ^{11}CO from other impurities, since BN was developed as an ISOL target. In particular, this comprises the use of a suitable ion source for efficient 1^+ ionization and a dipole magnet. ISOL facilities, such as ISOLDE, routinely use three types of ion sources, i.e. surface ion sources, laser ion sources and plasma ion sources. The first two are not applicable in this case due to the high ionization potential of CO. Many types of plasma ion sources exist [196], in particular electron cyclotron resonance (ECR) ion sources are promising due to their absence of hot metal surfaces, which may chemically react with CO causing delay due to retention, or break-up the bond due to dissociative chemisorption. ECR ion sources generate the e^- -plasma by injecting a buffer-gas and RF wave into a metallic cavity that is kept at room temperature. The plasma, which ionizes the atoms by impact ionization, is confined by a magnetic field [197]. Several types of ECR ion sources exist, however, most ECR ion sources are manufactured to provide high extraction currents, whereas the ionization efficiency is most important for RIB production. As pointed out in [149], a 2.45 GHz ECR ion source for efficient 1^+ ionization (MONO 1000) was developed at GANIL in collaboration with PANTECHNIK. Based on that, a compact source was developed and tested in an off-line study at ISOLDE. Promising ionization efficiencies of $\varepsilon_{\text{ion}}(\text{CO}) = 14\%$ and $\varepsilon_{\text{ion}}(\text{CO}_2) = 4\%$ were achieved [83], which are used as reference values henceforth. The electromagnetic mass separation is performed by using a dipole magnet that bends the ions exiting the ion source on trajectories according to their mass-over-charge ratio. Dipole magnets, tailored for the A/q of interest typically have separation efficiencies of $\sim 90\%$. Possible residual beam impurities are $^{13}\text{N}^{14}\text{N}$ since it shares the same A/q ratio when ionized to the $q = 1^+$ charge state.

As indicated in Fig. 6.1III, after EM mass separation, the ion beam must be decelerated before it can be injected into the EBIS. This feature results from the fact that the EBIS charge breeding is most efficient when neutral $^{11}\text{CO}_x$ is trapped in a cold trap inside the EBIS charge breeder, followed by a controlled release. Note that this cold trap does not serve as a separation instrument and is not correlated with the CGS system discussed previously. The operation of the EBIS charge breeder will be explained in more detail in the next chapter⁵. Neutralization of the $^{11}\text{CO}^+$ molecular ion beam is achieved by collisions with the beam line, whereas deceleration is required to prevent implantation and molecular break-up. The energy to which the molecular beam has to be decelerated depends on the bond dissociation energy, which corresponds to $E_b = 8.33$ eV in case of CO^+ [199]. $^{11}\text{CO}^+$ molecules

⁵This statement refers to the TDR, where the charge breeding aspect is discussed.

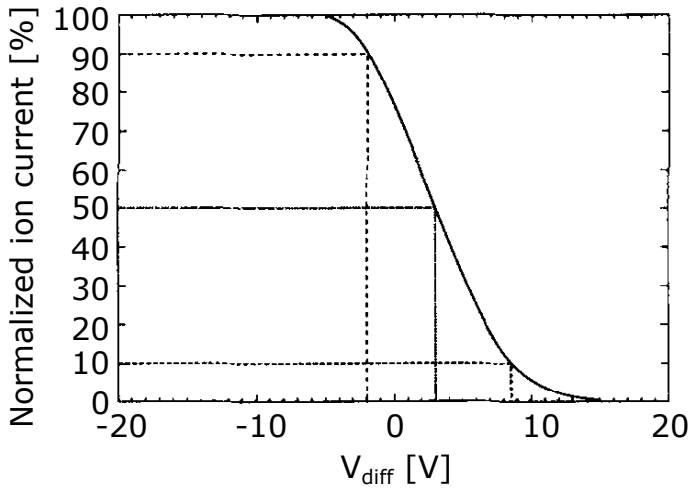


Figure 6.4: Measured transmission of a ^{113}In ion current, decelerated to 1 eV with a setup described in [198]. Note that the figure has been modified.

with energies $E > E_b$ that collide with the beam line for neutralization will consequently break up their bond, and are therefore lost.

There are currently three major deceleration techniques used in physics research, denoted as *soft-landing* of RIBs onto prepared surfaces [200], whereof two of them employ a mass separator and RIB production: firstly, the *Apparatus for Surface Physics and Interfaces at CERN ISOLDE* (ASPIC), incorporated in the VITO beam line. RIBs with a 1^+ charge state and 60 keV beam energy are implanted on a Mo catcher foil. Subsequently, the foil is placed over a transport foil and by means of heating, the isotopes diffuse from the catcher onto the transport foil. As a last step, the transport foil is moved over the sample surface and by resistively heating (with lower temperature) the isotopes are soft-landing onto the samples' surface [200]. The second, and more favorable approach, employs electrostatic techniques to decelerate RIBs to 5 eV [198, 201]. A detailed description of the deceleration setup can be found in [198]. In summary, it consists of five cylindrical electrostatic lenses with a length of 6 mm and 38 mm diameter. The lenses are biased in relation to the target which high voltage is derived from the source section to make the deposition energy sensitive to fluctuations of the acceleration/extraction voltage. It is reported that in principle very high transmissions efficiencies ($\sim 100\%$) are achievable. However, the efficiency is very sensitive to the potential difference between the ion source and the target of the deceleration apparatus (see Fig. 6.4). While in such way, in principle, deceleration can be very efficient, the

energy spread of the molecular ion beam that exits the ECR ion source will have significant impact on the overall efficiency. This can be understood in the following way: If the ion beam originating from the ECR ion source, features a large energy distribution, some ions with lower energies will be reflected into the beam line, and ions with higher energies will not be decelerated below 8.33 eV, and consequently, break-up. It is therefore important to adjust the deceleration apparatus according to the ECR ion source output. Consulting literature [202, 203], it seems that the ion energy spread depends on the plasma potential, voltage stability of the extraction voltage power supply, energy coupling to the ions from electron-ion scattering and scales with the ion charge state. As a result, energy spreads for singly charged ions can be as low as a few eV. For comparison, in [203], the energy spread of Ar-beams from an ECR ion source was determined to be 8 – 20 eV, where the lowest energy spread was achieved for singly charged ions. However, it is necessary to determine the exact value of the corresponding ECR ion source to optimize the deaccelerator. To account for voltage fluctuations, we take a transmission efficiency of 80% within a 10 V region, as indicated in Fig. 6.4. After the beam is decelerated, it can be neutralized via collisions with the beam line, followed by injection into the EBIS. As a result, an ISOL-type mass separation method, including deceleration and neutralization and a 50% transport efficiency of the neutral molecule flow, a total efficiency of $\varepsilon_{\text{sep}}^{\text{ISOL}} = \varepsilon_{\text{ion}} \cdot \varepsilon_{\text{sep}} \cdot \varepsilon_{\text{dec}} \cdot \varepsilon_{\text{trans}} = 0.14 \cdot 0.9 \cdot 0.8 \cdot 0.5 \approx 0.05$ can be achieved.

6.1.3 Summary

The discussions in the previous sections demonstrated that it is unfortunately neither for the N₂ gas target, nor for the solid ISOL-type BN target possible to directly inject into the EBIS charge breeder for high charge state ionization. Given the current available data, it seems that in both cases the amount of impurities prevents this route.

Since the N₂ gas target is filled to high pressures, a CGS separation system needs to be applied. Separation can either be conducted employing a cold trap or molecular sieve trap, where the commercially available N₂ is typically equipped with the former type and was therefore considered in this discussion. However, carbon sieve traps seem to offer the advantage of not trapping any nitrogen or oxygen from the target gas. With respect to impurities produced from nuclear reactions, it seems that no further separation technique must be applied when employing the LEBT-linac or CYCLONE®KIUBE compact 18 MeV cyclotron, since the expected impurities do not exceed ¹¹CO₂ by orders of magnitude. To the contrary, the 250 MeV VARIAN ProBeamTM proton therapy cyclotron is expected to generate an impurity level that exceeds ¹¹CO₂ considerably. Table 6.4 shows the number of ¹¹CO₂ molecules that can be injected from one batch.

It should be highlighted that these values correspond to the yield that can be expected when using a commercial N₂ gas target as offered by IBA. Such a target is however not optimized for 7 MeV or 250 MeV beams. Optimization of the target design, e.g. thinner entrance window for low-energy beams or larger volume for high-energy beams, could increase, to some extent, the in-target production yield.

The BN ISOL target, developed specifically for ¹¹C RIB production, offers the highest in-target production yields, and is operated continuously, unlike the N₂ target. Impurities originating from target operation are exceeding the expected ¹¹CO yield significantly, enforcing separation prior to EBIS injection. In principle, both CGS-type or ISOL-type electromagnetic separation may be applied. In the former case, the ¹¹CO gas originating from the target needs to be oxidized to CO₂ as chromatography gas separation systems cannot efficiently trap and separate CO from other species. CGS-type separation will result in batched injection into the EBIS, where one batch requires approximately five minutes. However, modified trapping times are in principle possible, and a semi-continuous injection could be achieved by employing several traps. It should be emphasized that while the oxidation seems to be a very efficient process, experimental validation should be performed. Table 6.5 shows the expected number of molecules that can be injected for one separated batch (*CGS* columns). Note that in this method isotopic impurities cannot be separated from ¹¹C which is of concern when using the 250 MeV cyclotron for isotope production, and which might be problematic for the 18 MeV CYCLONE®**KIUBE** accelerator as well. On the other hand, when using an ISOL-type separation method, a continuous injection into the EBIS is possible. In general, RIB production via the ISOL method is well established. However, in this case, the deceleration process and particularly the energy spread of the ion beam exiting the ECR ion source require further investigation. The *ISOL* columns in Table 6.5 present the ¹¹CO yields that can be expected for the different accelerators. While the ISOL method allows to separate all of the impurities associated to target operation and most impurities generated during target irradiation, contaminations that share the same A/q (¹¹CO = 27) ratio will be injected as well. In that regard, ¹³N¹⁴N can be expected to be an occurring impurity. Consulting the ¹³N production yields in Figures 6.2a-6.2c, and considering a similar ionization efficiency [83], the ¹³N¹⁴N currents are: LEBT-linac < 2 · 10³ s⁻¹, CYCLONE®**KIUBE** < 2 · 10⁹ s⁻¹ and VARIAN ProBeamTM < 6 · 10⁹ s⁻¹. While the bond dissociation energy of N₂⁺ = 8.7076(10) eV is comparable to that of CO⁺ (8.33 eV) [204], we report here only upper limits as it is not clear how to evaluate the release efficiency of ¹³N, which is expected to be rather low, since it is the same chemical element as the target. However, even when assuming a 100% release efficiency, the low-energy accelerators produce manageable quantities with respect to injection into the EBIS. Regarding the 250 MeV cyclotron, a

quantitative analysis seems to be required.

It should be addressed that while the primary proton currents of the 7 MeV LEBT-linac and 250 MeV VARIAN ProBeamTM cyclotron are fixed, the compact 18 MeV CYCLONE[®]**KIUBE** cyclotron can in principle deliver much higher intensities as the employed 50 μA . Concerning the application of the BN target, the applied beam current is dictated by the operational target temperature and by how efficiently this target temperature can be kept by means of cooling techniques. In this study $T = 1500\text{ }^{\circ}\text{C}$ was used as operational target temperature, as its feasibility was experimentally proven [149]. However, recent studies indicated that in principle higher temperatures up to 2000°C are possible, which probably enhance the release efficiency, and thus the yield. Taking these two aspects into account, it could be possible to increase the expected yield of the BN target applied with the 18 MeV cyclotron, if increased beam currents and/or higher target temperatures are feasible.

Accelerator	LEBT-linac	CYCLONE® KIUBE	VARIAN ProBeam™
Particle	proton	proton	proton
Energy [MeV]	7	18	250
Intensity [μ A]	7	50	0.8
Pulse structure	pulsed	cw / pulsed	cw / pulsed
Beam cross section [mm^2]	Gaussian; FWHM 8.24 ²	Gaussian; FWHM 8.24 ²	Gaussian; FWHM 8.24 ²
Batch/extraction time [min]	30 + 4 + 1	30 + 4 + 1	30 + 4 + 1
Target size, geometry	40 cm ³	40 cm ³	40 cm ³
r_1 , r_2 , L [cm]	0.75, 1.35, 11.3	0.75, 1.35, 11.3	0.75, 1.35, 11.3
Target material	N ₂	N ₂	N ₂
In-target yield	0.7	262 (176)	0.35
EOB [GBq]			
Separation technique	CGS	CGS	CGS
Separation efficiency [%]	40	40	40
Molecular sideband	CO ₂	CO ₂	CO ₂
Injection EBIS [molecules]	$5 \cdot 10^{11}$	$2 \cdot 10^{14}$ ($1 \cdot 10^{14}$)	$2 \cdot 10^{11}$
Residual impurities: $\times \text{CO}_2$ [molecules]	$3 \cdot 10^{10}$	$\sim 2 \cdot 10^{14}$	$\sim 3 \cdot 10^{12}$
N ₂ , O ₂ , NO _x [molecules]	unknown	unknown	unknown

Table 6.4: Expected ¹¹C load per batch for the EBIS charge breeder, considering different N₂ target-accelerator combinations. The in-target yields are calculated using the FLUKA code [36, 37]. In case of the N₂ target in combination with the CYCLONE®**KIUBE** cyclotron, yields are quoted from IBA as well [190], and are displayed in brackets. The in-target production yields are expressed as End-Of-Beam (EOB). Regarding the batch/extraction time, the value represent: irradiation- + trapping- + release-time as explained in the text, which is attributed with an overall separation efficiency $\varepsilon_{\text{sep}}^{\text{CGS}, \text{N}_2} = \varepsilon_{\text{trap}}(T_{1/2} = 20.4 \text{ min}) \cdot 0.5 = 0.4$ (Eq. (6.7)).

Accelerator	LEBT-linac	CYCLONE® KIUBE	VARIAN ProBeam™
Particle	proton	proton	proton
Energy [MeV]	7	18	250
Intensity [μ A]	7	50	0.8
Pulse structure	pulsed	cw / pulsed	cw / pulsed
Beam cross section	Gaussian; FWHM	Gaussian; FWHM	Gaussian; FWHM
Beam mm^2	8.24 ²	8.24 ²	8.24 ²
Batch/extraction time			
[min] / cw	cw	cw	cw
Target size, geometry	cylindrical	cylindrical	cylindrical
$S[\text{cm}^2] \cdot L[\text{cm}]$	7.1.0.2	7.1.0.29	7.1.34.2
Target material	BN	BN	BN
In-target yield			
EOB [GBq]	12	593	63.4
Release efficiency [%]	10	10	10
Technique	ISOL	ISOL	ISOL
Separation efficiency [%]	5	5	5
Molecular sideband	CO	CO	CO
Injection EBIS	$6 \cdot 10^7$	$3 \cdot 10^9$	$3 \cdot 10^8$
	$[\text{s}^{-1}]$	$[\text{s}^{-1}]$	$[\text{s}^{-1}]$
Residual impurities:			
$^{13}\text{N}^{14}\text{N}$ $[\text{s}^{-1}]$	$< 2 \cdot 10^3$	$< 2 \cdot 10^9$	$< 6 \cdot 10^9$
$\times \text{CO}_2$ [molecules]	-	$\sim 2 \cdot 10^{10}$	-
		$\sim 2 \cdot 10^{13}$	$\sim 2 \cdot 10^{13}$

Table 6.5: Expected ^{11}C load for the EBIS charge breeder, considering different BN target-accelerator combinations. The in-target yields are calculated using the FLUKA code [36, 37]. The in-target production yields are given at target saturation. The release efficiency refers to the ^{11}CO extraction by applying a controlled O_2 leak at 1500 °C (Eq. (6.6)). The separation efficiency is accounted by $\epsilon_{\text{sep}}^{\text{ISOL}} = \epsilon_{\text{ion}} \cdot \epsilon_{\text{sep}} \cdot \epsilon_{\text{dec}} \cdot \epsilon_{\text{trans}} = 0.14 \cdot 0.9 \cdot 0.8 \cdot 0.5 \approx 0.05$ for ISOL-type separation. CGS-type separation with an separation efficiency $\epsilon_{\text{sep}}^{\text{CGS}}$, BN ($T_{1/2}$) (refer to Eq. (6.7)), results in a batched EBIS injection (5 min).

Other conceivable targets

The previous sections focused on the oxygen-doped N_2 gas targets and BN as a solid boron comprising target. There are however other potential targets worth mentioning.

Commercial nitrogen gas targets are also available from IBA with hydrogen-doping to produce ^{11}C as $^{11}\text{CH}_4$. This molecular sideband would be favorable for the EBIS charge breeder, as H occupies less charge space compared to O, thereby increasing the ^{11}C capacity which can be ionized efficiently. The expected in-target production yield, on the other hand, is significantly lower due to more complex hot atom chemistry [191]. Considering a N_2 gas target with hydrogen-doping in combination with the 18 MeV CYCLONE®**KIUBE** accelerator, 50 μA proton beam current and 30 minutes irradiation time, an in-target production yield and recovered activity of 2.2 GBq μA^{-1} and 37 GBq, respectively [190]. Isotope purification can be carried out with chromatography columns such as Porapak Q. Considering a 50% transport efficiency, $3 \cdot 10^{13}$ $^{11}\text{CH}_4$ molecules can be injected from one batch. To validate whether this is a feasible possibility, one should study the impurities and their quantity in relation to $^{11}\text{CH}_4$.

Regarding a solid boron comprising target, B_2O_3 could be a promising alternative to BN. Due to the *in situ* availability of O_2 , ^{11}C is produced as oxide, where $^{11}\text{CO}_2$ is the expected predominating molecular sideband, thereby omitting the necessity of a calibrated O_2 leak to the target. Consequently, easier target operation and higher release efficiencies can be expected at lower temperatures. The major drawback of this material in comparison to BN is its very low melting point of 450 $^\circ\text{C}$, complicating target operation. This introduces limitations on the primary proton beam current which directly correlates with the production yield. B_2O_3 has been studied as a target material in different works [74, 97, 205]. For instance, in the Centre de Recherche du Cyclotron, M. Gaelens et al. investigated the ^{11}C release efficiency from boron oxide powder targets and observed 10% release efficiency at low temperatures as 300 $^\circ\text{C}$. However, problems of the powder escaping the target chamber were encountered. A powder compact such as the BN target discussed in this report, could solve this issue. A research program aiming for the fabrication of such a rigid B_2O_3 target has been carried out at KU Leuven, Belgium [206]. Figure 6.5 shows the physical thick in-target production yields for the different production accelerators, expressed in nuclei per μC . To conclude whether one of this B_2O_3 target-driver combination allows to deliver sufficient $^{11}\text{CO}_2$ to the EBIS, a series of aspects need to be addressed:

- material properties after powder processing;
- temperature boundary;

- ^{11}C release efficiency;
- residual gas analysis of target in operation;
- molecular side band distribution.

Based on the results of the studies listed above, analog investigations concerning possible production and separation scenarios can be conducted to estimate the possible injections into the EBIS charger breeder. Preliminary studies indicate however that this material is very difficult to process and that it might not be suitable as a rigid powder compact ISOL target [206].

When using a more energetic proton cyclotron, such as the VARIAN ProBeamTM 250 MeV cyclotron, it is conceivable to use the molten salt target that has been used at CERN ISOLDE and marks the most intensive $^{11}\text{CO}^+$ beam produced up to now [80]. While this target was designed to produce different RIBs, surprisingly high $^{11}\text{CO}^+$ yields of $7.7 \cdot 10^8 \mu\text{C}^{-1}$ were observed, which was partly attributed to a remarkably high release and ionization efficiency of $\varepsilon = \varepsilon_{\text{rel}} \cdot \varepsilon_{\text{ion}} = 5\%$ [130]. On top of that, this efficiency can still be improved since

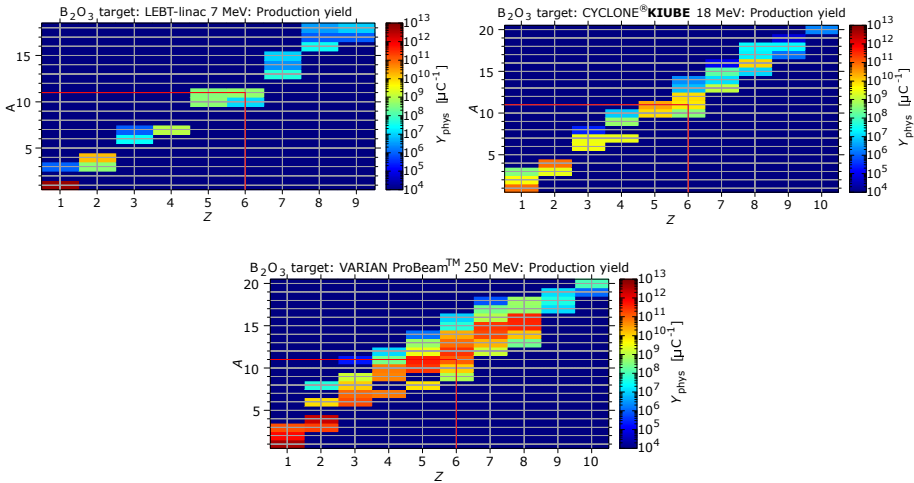


Figure 6.5: FLUKA simulated physical thick in-target production yields of a B_2O_3 target for different production accelerators. When using the LEBT-linac the target thickness was chosen to absorb the entire beam (a), whereas for the higher beam energies (b) and (c) the thickness was chosen such that the primary beam traverses the target retaining 4 – 5 MeV of its original energy. The beam profile was identical as reported in Tab. 6.1. Note that the yield is expressed in nuclei per μC .

a VADIS (Plasma-Cold-VD7) ion source was used, which is not very efficient for CO ionization. To investigate whether this target could produce sufficient ^{11}C yields for the purpose of this work, the physical thick in-target production yield was calculated using FLUKA, and by means of Eq. (6.1). In the latter case, the cross sections for ^{11}C production were calculated using the Talys1.8 code [207] and the stopping power was derived from SRIM [208]. The corresponding physical thick in-target production yields were determined as $1.5 \cdot 10^{10} \mu\text{C}^{-1}$ and $2.0 \cdot 10^{10} \mu\text{C}^{-1}$, respectively. The discrepancy may be attributed to the target geometry which was employed for the FLUKA simulations, according to the target specifications described in [80]. When considering the geometry, protons can escape the target, therefore, not contributing to the ^{11}C yield. The estimated load which can be injected into the EBIS, can be calculated using the physical thick in-target production yield, a $0.8 \mu\text{A}$ beam current of the 250 MeV proton driver and the total efficiency $\varepsilon = \varepsilon_{\text{rel}} \cdot \varepsilon_{\text{ion}} \cdot \varepsilon_{\text{sep}} \cdot \varepsilon_{\text{dec}} \cdot \varepsilon_{\text{trans}}$, where $\varepsilon_{\text{rel}} \cdot \varepsilon_{\text{ion}} = 0.05$ as reported in [130], and $\varepsilon = \varepsilon_{\text{sep}} \cdot \varepsilon_{\text{dec}} \cdot \varepsilon_{\text{trans}} = 0.9 \cdot 0.8 \cdot 0.5 = 0.36$ as approximated in this work. As a result, one obtains $2 \cdot 10^8$ (FLUKA) or $3 \cdot 10^8$ (Talus) ^{11}CO molecules per second injected into the EBIS. Note that this yield most likely can be increased using an ECR source for 1^+ ionization.

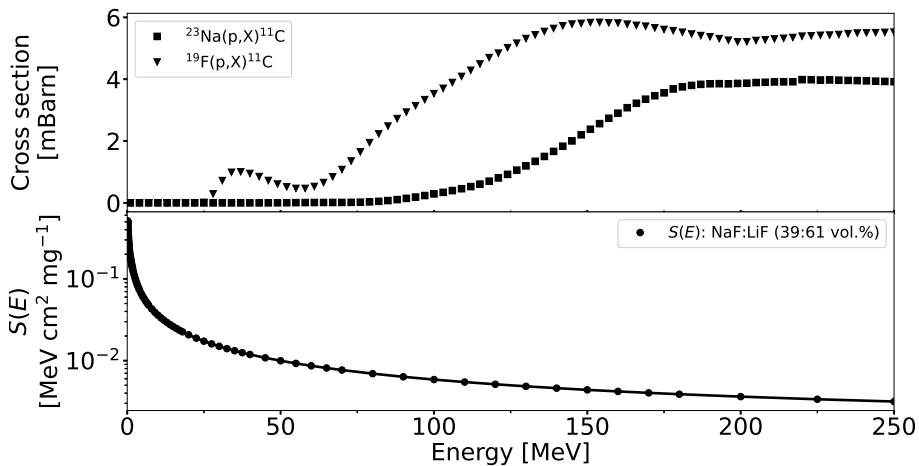


Figure 6.6: (Top) Cross sections for the production of ^{11}C using a NaF:LiF (39:61 vol.%) molten salt target. The cross section were calculated using the Talys 1.8 code [207]. (Bottom) Stopping power for a NaF:LiF (39:61 vol.%) molten salt target, calculated with SRIM [208].

6.2 Discussion

To evaluate the discussed production and separation modalities of the BN and N₂ targets with respect to their capability of producing sufficient ¹¹C to ensure the requested $4 \cdot 10^8$ post-accelerated ions to the patient room, it is necessary to assess the charge breeding and post-acceleration stages, which have been examined in dedicated studies [101], and is summarized in the TDR [23]. Figure 6.7 summarizes the constraints of MedAustron's and CNAO's accelerator complexes, which require approximately $5 \cdot 10^9$ ¹¹C^{4+,6+} ions extracted from the EBIS charge breeder within a pulse length of 10 – 60 μs [23]. The charge breeding aspect is far from being trivial, as the EBIS which is currently employed at CERN ISOLDE is not designed for such high currents. It was concluded that such an EBIS output can only be guaranteed when neutral ¹¹C is injected, as it was discussed in the previous section, and preferably in the CO or CH₄ molecular sideband, due to space charge limitations. Moreover, continuous injection was found significantly less efficient, which led to the proposal of employing accumulation in a cryotrap within the EBIS itself for pulsed release and injection into the electron beam. It is not the goal of this thesis to discuss the EBIS working principle and constraints in detail. The reader is thus referred for an in-depth assessment to dedicated descriptions reported in [23, 101].

In summary it was concluded that 10^{10} ¹¹CO molecules must be trapped in the cryotrap inside the EBIS charge breeder, which are subsequently released in a short time period (~ ms) into the electron beam, where ¹¹CO is rapidly broken up and ionized to the $q = 4^+$ or $q = 6^+$ charge state. Thereby, a pulse of $\sim 5 \cdot 10^9$ ions can be extracted with the requested 10 – 60 μs pulse length, which matches the time structure of the hadron therapy center's accelerator complex and is therefore injected into the synchrotron. Within the synchrotron the pulse is post-accelerated, bunched, extracted and subsequently guided to the patient room over a duration of 0.1 to 10 s. This extraction time span is used to accumulate the next pulse in the EBIS charge breeder. In other words, to ensure the delivery of $4 \cdot 10^8$ post-accelerated ¹¹C^{4+,6+} ions to the patient room, the production and separation stage, discussed in this thesis, must inject $\sim 10^{10}$ neutral ¹¹CO molecules within a time span shorter than ten seconds. Reviewing the estimated yields of the N₂ and BN target production and separation concepts (Tab. 6.4 and 6.5, respectively), discussed in Section 6.1.2, this seems challenging, however, possible.

Considering the application of the BN target in the preferred ISOL-type cw operation mode, one can exclude the 7 MeV LEBT-linac and 250 MeV VARIAN ProBeamTM proton therapy cyclotron as their estimated yields are too low to accumulate the required load in the EBIS. The 18 MeV CYCLONE®**KIUBE** compact PET-cyclotron on the other hand, allows injection of $3 \cdot 10^9$ s⁻¹, with

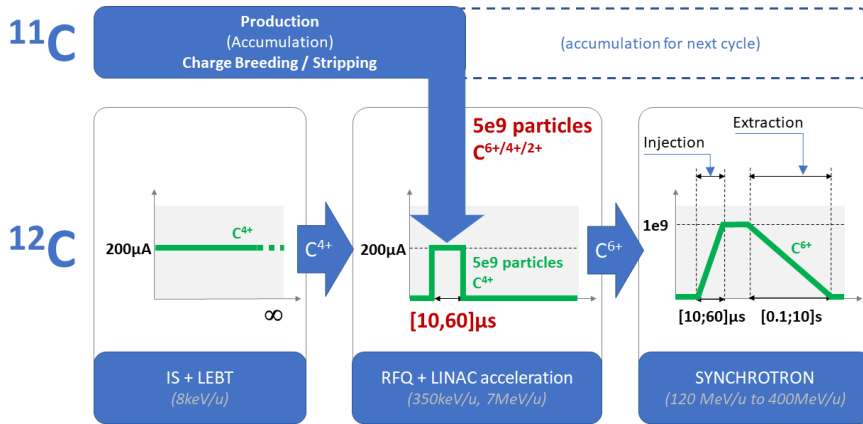


Figure 6.7: Summary of the main constraints for ^{11}C RIB injection into MedAustron's accelerator complex. To meet the requested $4 \cdot 10^8$ post-accelerated $^{11}\text{C}^{4+,6+}$ ions in the patient room, approximately $5 \cdot 10^9$ $^{11}\text{C}^{4+,6+}$ ions must be extracted from the EBIS charge breeder within a pulse length of 10 – 60 μs [23]. Courtesy of L. Penescu.

an admissible impurities level ($< 2 \cdot 10^9 \text{ s}^{-1}$) in worst case conditions. It is thus feasible to accumulate more than 10^{10} ^{11}CO molecules within ten seconds.

The CGS-type separation target operation is generally more difficult to evaluate, since it results in a batched injection scheme. Moreover, as ^{11}C is injected in the CO_2 molecular sideband, EBIS charge breeding will be less efficient due to the charge space occupied by the additional oxygen atom per molecule. Moreover, isotopic impurities ($^{12}\text{CO}_2$) cannot be separated from $^{11}\text{CO}_2$, therefore occupying the available charge space and thus further reducing the charge breeding efficiency.

The BN target operated with CGS-type separation provides a batch within five minutes, which however could be increased. Since the BN target gas output is occurring continuously, it is conceivable to design a separation modality consisting of several traps which therefore ensures a semi-continuous filling of the EBIS charge breeder. Note that this scenario requires the oxidation of the ^{11}CO target output, and a molecular sieve trap (Sec. 6.1.2). Considering that charge breeding will be less efficient, it is arguable whether the $1 \cdot 10^{11}$ $^{11}\text{CO}_2$ molecules provided by one batch when employing the 7 MeV LEBT-linac is sufficient. Longer trapping could increase the amount of ^{11}C per batch, however

stable contaminants are more efficiently accumulated which in turn reduces the charge breeding performance. The 18 MeV cyclotron provides $6 \cdot 10^{12}$ $^{11}\text{CO}_2$ molecules with an impurity level of approximately $2 \cdot 10^{13}$ $^x\text{CO}_2$ molecules, which will further degrade the EBIS charge breeding efficiency. Assuming that the charge breeding efficiency is not reduced by orders of magnitude this implementation scenario seems feasible. The 250 MeV cyclotron on the other hand, is attributed with an impurity level surpassing the $^{11}\text{CO}_2$ load by almost two orders of magnitude and is therefore inadmissible.

Considering the N_2 gas target with CGS-type separation, the situation is similar as discussed above, however, a considerable longer batch time of 35 minutes needs to be accounted. It is therefore more difficult to design an automatized irradiation and separation protocol that allows semi-continuous filling of the EBIS charge breeder. Moreover, if the CGS system comprises a cryogenic trap, as it is usually the case in commercial solutions, the potential trapping of N_2 , O_2 , NO_x target gas residuals needs to be addressed, as it may increase the residual contaminations to an inadmissible degree. Alternatively, one may employ a molecular sieve trap, which seems to be better suited, as the aforementioned target gas constituents should not be retained. The 7 MeV linac is associated with approximately $5 \cdot 10^{11}$ $^{11}\text{CO}_2$ molecules per batch with $3 \cdot 10^{10}$ $^x\text{CO}_2$ impurities, which at first appears as feasible. However, it has to be kept in mind that typical N_2 gas target container are not designed for such low-energy proton beams, therefore absorbing the majority of the primary beam energy in the aluminium entrance window ($\sim 600 \mu\text{m}$), which as a result makes the estimated yield arguable to some extent. The 18 MeV CYCLONE[®]KIUBE cyclotron provides $\sim 2 \cdot 10^{14}$ $^{11}\text{CO}_2$ molecules per batch with an identical impurity contribution, which seems appropriate. The more energetic 250 MeV cyclotron is associated with considerably lower yields, $2 \cdot 10^{11}$ $^{11}\text{CO}_2$ molecules per batch, which is again significantly surpassed by impurities $\sim 3 \cdot 10^{12}$ and is therefore not applicable.

In conclusion, it seems that the BN target in ISOL-type separation mode, operated with a compact 18 MeV cyclotron, is the most promising solution as it facilitates continuous injection of the preferred CO molecular sideband with acceptable impurity levels. The expected yield of $3 \cdot 10^9 \text{ s}^{-1}$ ^{11}CO molecules injected into the EBIS charge breeder allows accumulation of the required $\sim 10^{10}$ ^{11}CO molecules within a time span of less than ten seconds. Alternatively, one may replace the ISOL-type separation system with a modified CGS system (Sec. 6.1.2), considering the same accelerator-target combination. However, a layout comprising several traps is required to guarantee a semi-continuous filling of the EBIS. On the other hand, one may substitute the BN target with a commercial N_2 gas target operated with a 18 MeV proton cyclotron. In such a configuration, the potential trapping of target gas in the CGS system must be

addressed, which may require to replace the commonly equipped cold trap with a molecular sieve trap. Moreover, an automatized target loading-, extraction- and separation systems needs to be designed to allow semi-continuous injection of batches into the EBIS charge breeder. For instance, such a system was employed in previous works [57].

Chapter 7

Summary & conclusion

The goal of this thesis was to develop a ^{11}C RIB production system that can be implemented into existing hadron therapy centers, and which meets the challenging beam intensity requirement of $4 \cdot 10^8$ ions per spill delivered to the patient. The ISOL method was identified as the favorable RIB production method, due to its better beam characteristics in terms of purity, momentum spread and emittance, compared to in-flight projectile fragmentation. Key component in an ISOL-type RIB production system is the target-ion source unit. Due to the high beam intensity requirement, development of a deliberate ^{11}C RIB production system is needed, to ensure sufficiently high ^{11}C ion beam yields, to guarantee the desired intensity in the patient room after beam manipulation and post-acceleration. The main objective of this thesis was therefore the development and characterization of an ISOL target optimized for $^{11}\text{CO}^+$ production. This chapter summarizes the systematic study that was performed in order to accomplish the goal of this thesis, and is structured according to the approach that was employed in this work:

- material selection, target fabrication and microstructural characterization;
- cold target characterization;
- hot target characterization;
- implementation strategies of the developed production system into existing facilities.

It is not the intention to repeat previous discussions within the corresponding chapters. It is rather foreseen to discuss the aforementioned items and their implications in a broader context.

7.1 Material selection, target fabrication and microstructural characterization

This aspect is certainly one of the essential phases in the development process of a tailored target-ion source unit. Since RIB production via the ISOL method evolves in a sequential modality, the choice of the appropriate target material sets the cornerstone for the subsequent stages. However, this does not entail that a material which offers the highest cross section for (radio-)isotope production is automatically the best choice. A variety of different parameters will impact the final production yield and therefore should be addressed when initiating the development process. For instance, a certain material that offers the highest production yield may also generate a higher impurity level, which may impose limitations at a later stage where these impurities need to be separated from the desired beam. In other circumstances, a given target material may be superior concerning the physical thick in-target production yield, but results in lower yields due to primary proton beam limitations originating from power deposition and target temperature constraints.

In the context of large scale ^{11}C production, boron offers in principle the highest cross section for maximized in-target production yields. However, considering the high-temperature chemistry between target material and the isotope of interest, a natural or enriched boron target is not an applicable choice. The formation of B_4C would drastically hinder the release from the target material, therefore, resulting in low production yields. The isotope release and efficiency are in fact the overall tone of this thesis. Generally, it is considered as one of the major bottlenecks in RIB production via the ISOL method. Due to the refractory nature of carbon, this was certainly expected to be a limiting factor that must be considered during the development process. In this respect, three different measures were taken: firstly, instead of developing a boron target which is likely to be unsuccessful due to the aforementioned formation of B_4C , a boron comprising target was identified as a more appropriate approach. In detail, boron nitride was identified as promising candidate; secondly, carbon desorption from the target material's surface is likely to be very inefficient in atomic form, due to its high sublimation point ($\sim 3000\text{ }^\circ\text{C}$). As a result, molecular isotope extraction by means of the carbon monoxide molecular sideband was implemented into the production system. The results of this approach will be discussed in the next section; thirdly, since the release process is decisively determined by the microstructural properties of the solid target, a fabrication process was employed that allows control of the pre-sintered target's microstructure, in terms of densification and grain growth. The latter aspect was examined in Chapter 3 and is discussed henceforth.

Spark plasma sintering (SPS) was chosen as powder processing route, as it allows

to mitigate possible grain growth at lower temperatures. Starting powders from different suppliers and concomitant particle size distributions were processed by a selection of SPS cycles, where the impact of sintering temperature and time was studied. The respective parameters were chosen such that no excessive densification would occur, i.e. interrupting the sintering progress at an early stage. The pre-sintered BN powder compacts were subsequently evaluated by means of their stability, reproducibility and total porosity. The latter characteristic is motivated by the enhanced release properties of porous targets. The former two aspects are chosen from a practical point of view. During ISOL target operation, the target material should be rigid and retain its form and shape to prevent target material escaping the target container. Moreover, a constant and reproducible performance must be guaranteed considering its application in a medical environment.

The results of the evaluated SPS cycles were conform with expectations from the sintering theory. Prolonged sintering times yielded less porous bodies, justifying the selection of a cycle with shorter dwell-times at maximum temperature. The effect of higher temperatures was less pronounced and not consistent between varying starting powders. BNA powders indicated rather constant porosities, while BNM showed a modest increase. On the other hand, BNG targets were attributed with increasing porosities for increasing maximum sintering temperature. However, the generally large measurement uncertainties prevented to draw definite conclusion regarding the impact of the sintering temperature. Since higher temperatures enhance diffusion, the lowest sintering temperature was chosen, to diminish possible carbon diffusion from the sintering apparatus' tools into the bulk of the powder compact.

The SPS cycle that was associated with the most satisfactory results concerning the evaluation criteria was selected as ISOL target: BNM, $t_{\text{dwell}} = 5$ min, $T_{\text{max}} = 1700$ °C, $P_{\text{ex}} = 25$ MPa during dwell-time, sintering atmosphere of ~ 2 mbar air pressure and a heating and cooling rate of 100 °C min⁻¹ and ~ 400 °C min⁻¹, respectively. The respective BN target possesses a total and open porosity of approximately 40(5)% and 21(7)%, respectively. A densification of less than 5% occurred, compared to the green body before firing, which demonstrates interruption of the sintering progress around the initial and early intermediate stage (refer to Tab. 3.2).

At this point one should acknowledge that powder processing by means of SPS is next to hot-pressing the predominantly applied sintering technique for the fabrication of BN powder compacts. However, there are other more elaborate processing routes reported in literature, which in some cases feature higher total porosities. Such approaches usually include primary BN powder synthesis and/or different sintering techniques. For instance, porosities up 70 – 80% have been reported in [209, 210].

Microstructural characterization

Besides the porosity determination via the Archimedes' principle and He-gas pycnometry, characterization of the BN target's microstructure has been performed exploiting several experimental techniques (Chapter 3). Nitrogen physisorption isotherms indicated that the majority ($\sim 85\%$) of the accessible pore volume comprises slit-like pores larger than 50 nm. The analysis of the isotherm data employing the BET method allowed determination of the specific surface area (SSA), which on the one hand reassured that the target fabrication via spark plasma sintering merely results in modest densification. On the other hand, it was possible to estimate the average particle or grain cluster size $\bar{G}_{\text{BET}} = 1.7(1) \mu\text{m}$ of the pre-sintered BN powder compact from the SSA, which is an important parameter with respect to the description of the release process. Since nitrogen physisorption isotherms cannot provide reliable information of the macroporous pore volume, a complementary study was performed, using mercury intrusion porosimetry. This study reassured that the majority of the open pore volume is macroporous, and allowed estimation of the average pore size regime 120 – 470 nm. Examination of the surface topology by means of scanning electron microscope (SEM) images, showed target grains with flake-like geometries and sizes ranging from submicrometers to several micrometers, coherent with the approximation obtained from the SSA. Moreover, slit-like pores were observed, as indicated by nitrogen physisorption isotherms.

These target characterizations yielded sufficient information regarding the microstructural properties of the developed BN target, which fostered the evaluation of carbon's release properties. It further allowed to assess that the ^{11}C release from the target would be diffusion limited and not effusion limited.

7.2 Cold target characterization

The fabrication of a novel ISOL target tailored for specific RIB production is merely the first step with respect to its path towards on-line application. A proper understanding of its microstructural properties and operational limitations is an important development phase. In ideal conditions, one can directly examine the target's feasibility at an ISOL facility in on-line experiments. Unfortunately, beam time is usually limited. This thesis demonstrated the power of off-line experiments, if a proper understanding of the target's microstructure is present. In any case, before a target can be considered for on-line application, its operational limitations should have been identified. Therefore, this section will discuss the dedicated studies that were carried out in that regard. This concerns the results presented in Chapter 4.

Operational limitations

The studies concerning the operational limitations of the developed BN target, comprised mostly three aspects: primary beam energy selection, high-temperature stability and stability in controlled oxidizing atmospheres at high temperatures. Concerning the former feature, since this target is best utilized when irradiated with low-energy beams, in principle, one has an additional degree of freedom compared to high-energy facilities such as ISOLDE. This degree of freedom refers to the selection of the employed energy interval. High-energy beams, such as the 1.4 GeV beam at ISOLDE, traverse the target without significant energy loss. This is reflected in the physical production yield $Y_{\text{phys}} = \sigma(E) \cdot N_t$, where the cross section $\sigma(E)$ is constant. On the other hand, low-energy beams slow down during their path within the target matrix and thus, possess an energy distribution as illustration in the physical thick in-target production yield $Y_{\text{phys}} = \frac{N_A}{M} \int_{E_f}^{E_i} dE \frac{\sigma(E)}{S(E)}$. As a result, the aforementioned degree of freedom refers to the selection of the initial energy E_i of the proton beam entering the target, and the final beam energy E_f upon target exit. It is not always clear how to utilize this characteristic best, as it may depend on several factors. For instance, the upper limit is dictated by the available proton driver. However, it may not be ideal to exploit the entire available energy interval, which is adjustable via the target thickness and the correlated energy loss. While an extended energy interval certainly increases the thick in-target production yield, this may occur at the expense of a more significant generation of contaminants, potentially giving rise to separation issues. It is not the intention to go into further detail, however, it should give the reader an impression that this criterion may have considerable impact for specific cases and should therefore be addressed.

In the case of boron nitride, this material is best exploited by energies ranging between 10 to 30 MeV, as indicated by the tabulated cross section data shown in Figure 3.1. In Section 4.2, it was motivated to employ the BN target with an energy interval $E \in [5, 15]$ MeV. The lower limit stems from the relatively small cross sections below 5 MeV, with threshold energies around 3 MeV due to the reaction Q -values, $Q \approx -2.7$ MeV and $Q \approx -2.9$ MeV of the $^{11}\text{B}(\text{p}, \text{n})^{11}\text{C}$ and $^{14}\text{N}(\text{p}, \alpha)^{11}\text{C}$ reactions, respectively. The upper limit of 15 MeV was suggested to increase the specific activity $A^* = A(^{11}\text{C}) / A_{\text{tot}}$, which indicated that higher E_i increase the absolute ^{11}C yields at the cost of much greater total target activation. Furthermore, it was not discussed in Section 4.2 that stable contaminants such as $^{12,13}\text{C}$ exhibit a more enhanced increase in production yields for higher E_i . As discussed in Chapter 6, this is potentially of concern for subsequent beam manipulation steps, e.g. charge breeding. Depending on the applied separation modality, such impurities cannot be separated from ^{11}C , which therefore occupy the available charge space in the EBIS, limiting the

charge breeding efficiency. As a result, the energy interval $E \in [5, 15]$ MeV was considered as a reasonable compromise.

Besides the selection of the proton beam energy interval, the operational limitations have been studied extensively in terms of high-temperature stability and stability in controlled oxidizing atmospheres at high temperatures (Chapter 4). ISOL target operation is usually carried out at high temperatures, e.g. up to $\sim 2200^\circ\text{C}$, to enhance diffusion and effusion properties. However, high vapor pressures originating from the target material are degrading the ionization efficiency of the ion source. It is thus necessary to determine the target's temperature boundaries. As a rule of thumb, a target is best operated at temperatures as high as necessary, in terms of diffusion and release efficiency, but as low as possible. Considering that carbon is very refractory, diffusion and release efficiencies were expected to be low. This assumption was confirmed by the order of magnitude of carbon's diffusion coefficient in BN $D(1500^\circ\text{C}) = 10^{-15} - 10^{-14} \text{ cm}^2 \text{ s}^{-1}$. Therefore, high temperatures are certainly necessary to achieve reasonable release efficiencies.

At an early stage, chemical equilibrium calculations indicated a maximum applicable temperature of $T \sim 1000 - 1100^\circ\text{C}$. However, a variety of high-temperature studies contradicted this prediction, as reported in Chapter 4. Thermal treatments at $T = 1500^\circ\text{C}$ over time periods up to 16 h, demonstrated no enhanced N_2 evaporation rates above background, and negligible weight loss. This temperature was therefore proven as applicable concerning ISOL-type target operation. On top of that, a thermal 'stress' test up to 2000°C indicated that in principle higher temperatures are conceivable. One additional conclusion that one can draw from these results is that chemical equilibrium calculations are in principle a good tool for first qualitative evaluations of the thermodynamic interplay between different species. However, an experimental validation should in many cases be considered.

In this context it was also necessary to evaluate the high-temperature oxidation behavior of the developed BN target in controlled oxidizing atmospheres. To enhance the release and transport efficiencies, isotope extraction in form of carbon monoxide was implemented into the ISOL production system, by means of a calibrated O_2 leak. As literature suggested BN oxidation at higher temperatures, it was necessary to evaluate if target operation in controlled oxidizing atmospheres is feasible (Article I). Chemical equilibrium calculations suggested that there are no realistic operational conditions in which carbon oxidation is thermodynamically favored over target oxidation (Fig. 4.5). However, as stated above, experimental validation of such equilibrium calculations was necessary. Moreover, such calculations do not address the kinetic character of chemical reactions. It is thus possible that despite being thermodynamically favored, oxidation occurs extremely slow, or extremely

rapid for that matter. To examine this feature, thermogravimetric analysis of the BN target at ambient pressure was performed ([Article I](#)). Target oxidation was observed to occur merely modest for oxygen potentials below $\mu_{\text{O}_2} = -300 \text{ kJ mol}^{-1}$, which was therefore taken as an applicable operational limit.

A complementary study evaluated the high-temperature oxidation kinetics at typical ISOL conditions, i.e. high temperature in combination with low pressures ($\sim 10^{-6}$ mbar) (Sec. 4.2.3). Despite the difficulty of developing a suitable experimental setup that ensures external O_2 supply to the target, these studies reassured the feasibility of operating the BN target with a controlled O_2 supply. Thermal treatments at $T = 1500 \text{ }^\circ\text{C}$ with a calibrated leak of $1.6 \cdot 10^{-5} \text{ mbar l s}^{-1}$, using an Ar/ O_2 gas mixture (90/10 vol.%), were applied for time periods up to six hours, where no excessive oxidation and weight change could be observed. It was thus guaranteed that the operational limitations of the developed BN target have been addressed sufficiently. Thermal treatments at $1500 \text{ }^\circ\text{C}$ and oxidizing atmospheres with $\mu_{\text{O}_2} < -300 \text{ kJ mol}^{-1}$ for time periods up to 16 h were proven feasible.

It is however relevant to stress the extremely challenging technical realization of ensured external O_2 to the BN target. Because of the typically applied form of target heating and hot metal parts which are therefore present in ISOL target containers, it was observed that oxygen was consumed before it could reach the target. The newly developed ceramic-based testing unit could solve this issue. However, a more oxygen-rich atmosphere was observed, which most likely resulted from partial decomposition of the ceramic (Al_2O_3) tools. This feature could potentially be utilized to supply O_2 , instead of implementing a calibrated oxygen leak into the ^{11}C production system. However, it must be guaranteed that this process occurs in a controlled modality. Alternatively, one could explore other target materials which offer *in situ* oxygen for the formation of carbon monoxide or carbon dioxide. Boron suboxide (B_6O) seems a promising candidate, unlike B_2O_3 , because of its higher thermal stability, e.g. decomposition is believed to occur above $1760 \text{ }^\circ\text{C}$ [211]. However, it seems that the properties of this material have not yet been sufficiently characterized. Moreover, it must be evidenced that $^{11}\text{CO}_{x=1,2}$ formation is thermodynamically favored over B_4C formation.

7.3 Hot target characterization

Since the isotope release was identified as a limiting factor in ^{11}C RIB production, the evaluation of the release process by means of determining the release efficiency of carbon, was the core of this thesis. It was mentioned that this modality is best studied in dedicated on-line experiments at an ISOL facility.

As beam time is however limited, respective studies are preferably conducted off-line, if possible. An approach, employing cold studies with pre-doped BN targets using stable carbon, was reported as inapplicable (Chapter 4). Instead, this thesis examined the release process from activated targets, i.e. hot characterization, by performing a fractional release study (Chapter 5). Measuring release fractions, i.e. determining how much of an initial inventory could be extracted from the target material in a short time span, is a powerful tool with respect to the estimation of the on-line release characteristics, if sufficient knowledge regarding the target's microstructure is present.

For this purpose, a new experimental test bench was developed and installed at CERN MEDICIS (Chapter 5), where the BN target was activated. The general layout of typical off-line fractional release studies is in principle simple: (1) target activation; (2) determination of the initial radioisotope inventory; (3) isotope release by means of a short heat treatment; (4) determination of the remaining radioisotope inventory. However, due to the relatively short half-life of ^{11}C concerning such experiments, and due to the lack of a specific γ transition besides the characteristics 511 keV γ -rays resulting from the positron annihilation, the aforementioned phases needed to be planned accordingly (Chapter 5). In that regard, it is noteworthy that MEDICIS offers an ideal infrastructure for fractional release studies, as it is possible to transport and retrieve a target within ~ 15 minutes to and from the irradiation point. In total, the nuclear physics experiments at ISOLDE, were interrupted for merely ~ 30 minutes, which was sufficient to measure carbon's release fraction $F_\mu(t = 300 \text{ s}) = 0.045(7)$ from the developed BN target.

It was demonstrated in Chapter 5 that with a proper understanding of the material's microstructural properties, together with a good understanding of the underlying physical processes involved during the release process, it is possible to extrapolate release fractions to an approximation of the on-line release efficiency. In that regard, key parameters were the average particle or grain cluster size and average pore size, which allowed to estimate the release efficiency $\varepsilon_{\text{rel}}(T_{1/2} = 20.4 \text{ min}) = 10\%$ of ^{11}C from the BN target. This result is in good agreement with release efficiency measurements of ^{11}C from pristine BN powder. Moreover, this study allowed to derive an approximation for the delay function $p(t)$, which expresses the probability of an isotope to be released in a certain time period, and is therefore an important parameter with respect to the modeling of the release process.

It should be addressed that these results rely on the classification of the release process to be solely driven by diffusion. The contributions of inter-grain effusion in-between the target grains and effusion from the target container to a potential ion source, to the delay function $p(t)$ were motivated to be negligible. The applied model for that motivation, relied mostly on the obtained information

concerning the target's pore structure. However, other decisive input parameters were the adsorption enthalpy ΔH_{ads} and the pre-exponential factor τ_0 which govern the sojourn time of CO onto the target grains (refer to Eq. (5.14)). These parameters were not measured in this thesis. An experimental determination could therefore improve the quality of the employed model. However, no considerable impact is expected on the final assumption that inter-grain effusion in-between the target grains and effusion from the target to the ion source are negligible.

7.4 Implementation strategies into existing hadron therapy centers

The systematic characterization of the developed SPS pre-sintered BN target with respect to its operational boundaries, microstructural features and most important, release properties allowed to study possible implementation scenarios of the developed ^{11}C radioactive ion beam (RIB) system into existing hadron therapy treatment facilities (Chapter 6). This study was part of a collaborative project which investigated the design of a ^{11}C based carbon therapy facility, where in detail the production (I), separation (II), charge breeding (III) and post-acceleration stages (IV) were discussed, as illustrated in Figure 6.1, and constitutes the goal of the associated Work Package within MEDICIS-Promed. In that regard, this thesis examined the former two stages, i.e. production and separation for neutral gas injection into the EBIS charge breeder. The charge breeding stage comprises molecular break-up and 4^+ or 6^+ ionization of ^{11}C for post-acceleration, which was unfortunately reported to be very challenging, due to the high current requirement of $5 \cdot 10^9$ $^{11}\text{C}^{4+,6+}$ ions extracted from the EBIS within a pulse length of $10 - 60 \mu\text{s}$. This enforced the development of a ^{11}CO production scheme that allows neutral injection into the EBIS, and accumulation of $\sim 10^{10}$ molecules in a time span shorter than ten seconds.

For this purpose, the BN target was compared to commercially available N_2 gas targets, designed for the production of $^{11}\text{CO}_2$. Three possible primary proton accelerators, differing in energy and beam intensity, as well as two separation modalities were considered. It was difficult to compare the BN target with the N_2 target, due to their very different modes of operation. Nonetheless, it was concluded that the BN target is generally favorable as it facilitates continuous injection into the EBIS charge breeder. Moreover, ^{11}C is produced in the CO molecular sideband, when the ISOL-type separation technique is applied that was proposed in this thesis, which allows more efficient charge breeding compared to the CO_2 molecular sideband that is associated to CGS-type separation.

	LEBT-Linac	CYCLONE [®] KIUBE	VARIAN ProBeam TM
Energy [MeV]	7	18	250
Intensity [μ A]	7	50	0.8
Injection EBIS:			
ISOL [s^{-1}]	$6 \cdot 10^7$	$3 \cdot 10^9$	$3 \cdot 10^8$
CGS [molecules]	$1 \cdot 10^{11}$	$6 \cdot 10^{12}$	$7 \cdot 10^{11}$
Residual impurities:			
ISOL [s^{-1}]	$< 2 \cdot 10^3$	$< 2 \cdot 10^9$	$< 6 \cdot 10^9$
CGS [molecules]	$2 \cdot 10^{10}$	$\sim 2 \cdot 10^{13}$	$\sim 2 \cdot 10^{13}$

Table 7.1: Expected $^{11}\text{CO}_{x=1,2}$ injection into the EBIS charge breeder of the BN target depending on the proton driver and separation system, where the molecular sideband is ^{11}CO and $^{11}\text{CO}_2$ for ISOL-type and CGS-type separation, respectively. More detailed information are displayed in Table 6.5.

Table 7.1 summarizes the results of the studied implementation concepts of the BN target into the accelerator complex of existing facilities, such as MedAustron and CNAO. The most promising scheme was concluded as the BN target operated with a compact 18 MeV proton driver, which provides the necessary energy to cover the interval of $E \in [5, 15]$ MeV that was suggested for optimized target operation (Sec. 7.2). As indicated above, electromagnetic mass separation (ISOL-type) by means of a compact ECR ion source and dipole magnet is believed as best solution, as it allows to inject ^{11}CO continuously, instead of $^{11}\text{CO}_2$ in batch mode. While this corresponds to the tailored ^{11}C RIB production system that was developed in this thesis, the conceptual implementation study revealed that a neutralization step must be incorporated into the production scheme, due to the above mentioned EBIS charge breeder limitations. In practice, neutralization may be achieved by decelerating the RIB to energies below 8.33 eV, followed by collisions with the beam line. In this way, an intensity of $3 \cdot 10^9$ ^{11}C molecules per second was estimated, which allows accumulation of $\sim 10^{10}$ molecules within the EBIS charge breeder in a time period shorter than ten seconds.

As a result, this study demonstrated that the developed ^{11}C RIB production system, comprising the porous SPS pre-sintered BN target operated with a controlled oxygen leak and a compact ECR ion source for 1^+ ionization, is capable of producing sufficiently intense $^{11}\text{CO}^+$ RIBs, enabling the delivery of $4 \cdot 10^8$ post-accelerated $^{11}\text{C}^{4+,6+}$ into the patient room. The goal of this thesis was thereby accomplished.

Nonetheless, it might be of interest to discuss that the CYCLONE[®]KIUBE

cyclotron, in principle, can deliver much higher primary proton beam intensities as the applied $I = 50 \mu\text{A}$, which could increase the yield, if needed, due to its linear dependency on I . For this purpose, it is necessary to study target cooling possibilities that allow to keep the BN target at $T = 1500^\circ\text{C}$ for increased beam currents, resulting in large deposited power densities. The expected yield could possibly be further improved by heating the target to higher temperatures as the suggested 1500°C . The cold target characterization discussed in Section 7.2 indicated that in principle target temperatures up to 2000°C might be applicable. On one hand, this relates directly to the previous argument of increasing the proton beam intensity. On the other hand, increased target temperature, probably increases the release efficiency and thus the yield. The reader may argue that throughout this thesis it was stressed that high temperatures enhance exponentially the diffusion rate, which should therefore definitely, instead of 'probably', increase the release efficiency. However, one needs to consider that B_4C formation in BN may become thermodynamically favorable at higher temperatures, which in turn would impede carbon release, and therefore should be examined.

While it was demonstrated that the developed ^{11}C RIB production system is in principle applicable, and allows the development of a ^{11}C based hadron therapy protocol, there are still several aspects that require further examination. It was not possible to investigate the proposed ionization and mass separation stages within the ISOL process-chain. Therefore, dedicated studies should be performed, examining the performance of the suggested BN-ECR ion source unit, where the neutralization step is experimentally tested as well. This should ideally lead to on-line studies, proving the estimated ^{11}CO yield. This study has been proposed in collaboration between MedAustron, CERN and KU Leuven within the PRISMAP project, currently under evaluation by the European Commission.

Appendix A

Supplementary calculations and data

A.1 Treatment of uncertainties

In this section, the uncertainty calculation of observables is reported, which uncertainty cannot be associated, solely, from error propagation or from statistical error determination. Note that the following approach is adapted from [212].

For a given observable $y(x_1, x_2, \dots, x_k) \equiv y$, e.g. obtained through a certain measurement technique, the error is denoted as δy . This uncertainty may derive from error propagation due to the input parameters $x_1, x_2, \dots, x_k$, or be of statistical origin. A series of n independent measurements yields a data set:

$$\{y_i\}_{i \in [1, n]}, \quad \{\delta y_i\}_{i \in [1, n]}.$$

The average $\bar{y}$ of this data set and its corresponding uncertainty $\Delta \bar{y}$, is calculated employing the standard weighted least-squares procedure:

$$\bar{y} \pm \Delta \bar{y} = \frac{\sum_{i=1}^n \omega_i \cdot y_i}{\sum_{i=1}^n \omega_i} \pm \left(\sum_{i=1}^n \omega_i \right)^{-1/2}. \quad (\text{A.1})$$

where ω_i denote the weights:

$$\omega_i = \frac{1}{(\delta y_i)^2}.$$

However, in some cases, the uncertainty resulting from Equation (A.1) seems inadequate compared to the spread or deviation of the determined average $\bar{y}$ from the measured data set. Likely, this results from an underestimation of some of the errors, contributing into the determination of y . In statistics, the discrepancy of $\bar{y}$ from the individual observations y_i , often referred to as *goodness*, is assessed by the reduced chi square χ_{red}^2 :

$$\chi_{\text{red}}^2 = \frac{\chi^2}{n-1},$$

$$\chi^2 = \sum_{i=1}^n \omega_i (\bar{y} - y_i)^2.$$

Cases which demonstrate a spread around the median value, where the uncertainty $\Delta\bar{y}$ does not account for this spread adequately, χ_{red}^2 will be exceeding one. Since it is often not clear which of the parameters' errors were underestimated, the reduced chi square is applied as a *scaling factor* S :

$$S = \begin{cases} \text{(a)} & 1, & \chi_{\text{red}}^2 \leq 1, \\ \text{(b)} & \sqrt{\chi_{\text{red}}^2}, & 1 < \chi_{\text{red}}^2 \leq 3, \\ \text{(c)} & 2 \cdot \sqrt{\chi_{\text{red}}^2}, & \chi_{\text{red}}^2 > 3, \end{cases} \quad (\text{A.2})$$

such that Equation (A.1) becomes to:

$$\bar{y} \pm \Delta\bar{y} = \frac{\sum_{i=0}^n \omega_i \cdot y_i}{\sum_{i=1}^n \omega_i} \pm S \cdot \left(\sum_{i=1}^n \omega_i \right)^{-1/2}. \quad (\text{A.3})$$

For scenarios, where the calculated weighted mean is representative for the corresponding data set $\{y_i\}_{i \in [1,n]}$, i.e. case (a), the original uncertainty is 'accepted', thus, $S = 1$. On the other hand, if $\bar{y}$, moderately, deviates from the data set such that $\Delta\bar{y}$ is not representative for the data sets' spread around its average, considering the individual δy_i (case (b)), $\Delta\bar{y}$ is artificially enhanced by multiplying $\sqrt{\chi_{\text{red}}^2}$. Note that a reduced chi square larger than one and smaller than or equal to three is considered as a moderate discrepancy. If however the deviation is more pronounced, i.e. case (c) a more robust enhancement of $\Delta\bar{y}$ is conducted as indicated in Eq. (A.2).

A.2 Supplementary data

m_b [mg]	m_b^{fl} [mg]	m_{b+l} [mg]	m_{b+l}^{fl} [mg]
6435.1	5834.2	6978.2	6053.9
5181.2	4696.7	5730.1	4921.0
5793.9	5251.7	6458.7	5514.6
10066.8	9126.2		
4218.4	3823.6		

Table A.1: Measured variables for the determination of the copper brass’ $\rho_b = 8.398(7) \text{ g cm}^{-3}$ and lacquer’s $\rho_l = 1.313(19) \text{ g cm}^{-3}$ bulk density via the Archimedes’ principle (refer to Sec. 3.4.2). The former was determined applying Eq. (3.11), and the latter by coating the brass pieces with a lacquer (Enthone - Enplate Stop-off No. 1), and by using Eqs. (3.12) and (3.13). Note that all measured masses are associated with a systematic error $\delta m = 0.5 \text{ mg}$, $C = 0.99983$, $\rho_{\text{fl}} = 0.78606(10)$ and $\rho_{\text{air}} = 0.0012 \text{ g cm}^{-3}$.

m_s [mg]	ρ_{apparent} [g cm ^{−3}]
451.0(5)	1.860(50)
375.9(5)	1.680(60)
527.8(5)	1.870(40)
641.1(5)	1.800(40)
491.8(5)	1.750(40)
385.4(5)	1.620(40)
410.1(5)	1.600(40)

Table A.2: Measured variables for the determination of $\rho_{\text{apparent}} = 1.74(8) \text{ g cm}^{-3}$ of SPS pre-sintered BN samples by means of He-gas pycnometry (*Multipycnometer Quantachrome*). Refer to Section 3.4.2.

Powder	T [°C]	t_{dwell} [min]	m_s [mg]	m_{s+1} [mg]	m_{s+1}^{fl} [mg]
BNG	1700	15	573.7	1330	518.6
BNG	1700	15	910.4	1657.3	760.6
BNG	1700	5	695.8	1430.6	630.7
BNG	1700	5	668.5	1576.7	695.6
BNG	1700	5	421.8	1112.3	473.8
BNM	1700	5	504.9	1168.1	476.7
BNM	1700	5	523.1	1129.7	446.0
BNM	1700	5	763.5	1737.2	678.1
BNA	1700	5	677.9	1902.5	765.0
BNA	1700	5	646.7	1787.9	726.0
BNA	1700	5	591.1	1622.2	649.1
BNG	1800	15	583.2	1040.1	463.1
BNG	1800	15	544.0	1131.9	503.8
BNG	1800	5	583.6	1429.2	601.4
BNG	1800	5	728.8	1566.8	678.6
BNG	1800	5	357.1	1002.6	427.7
BNM	1800	5	630.5	1402.6	586.7
BNM	1800	5	644.0	1357.3	566.0
BNM	1800	5	616.8	1455.5	607.4
BNA	1800	5	412.0	1050.4	414.1
BNA	1800	5	565.3	1481.8	617.6
BNA	1800	5	602.8	1385.5	566.4
BNG	1900	15	498.4	929.0	408.2
BNG	1900	15	866.0	1565.4	675.2
BNG	1900	5	632.6	1645.8	693.0
BNG	1900	5	465.8	1119.0	462.0
BNG	1900	5	617.3	1458.1	619.3
BNM	1900	5	261.3	821.4	336.8
BNM	1900	5	633.5	1861.5	772.8
BNM	1900	5	566.4	1555.9	647.8
BNA	1900	5	555.9	1604.4	633.4
BNA	1900	5	545.5	1613.6	678.1
BNA	1900	5	635.1	1586.1	634.7

Table A.3: Measured variables for the determination of the bulk density ρ_{bulk} via the Archimedes' principle, probing SPS pre-sintered BN samples', coated with a lacquer with density $\rho_l = 1.313(19)$ g cm $^{-3}$ (refer to Sec. 3.4.2 and Eqs. (3.12) and (3.13)). Note that all measured masses are associated with a systematic error $\delta m = 0.5$ mg, $C = 0.99983$, $\rho_{\text{fl}} = 0.78606(10)$ and $\rho_{\text{air}} = 0.0012$ g cm $^{-3}$.

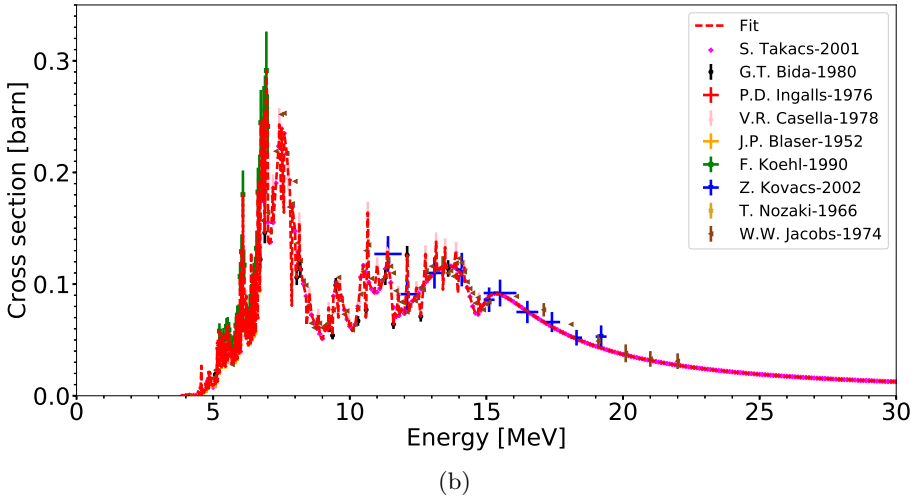
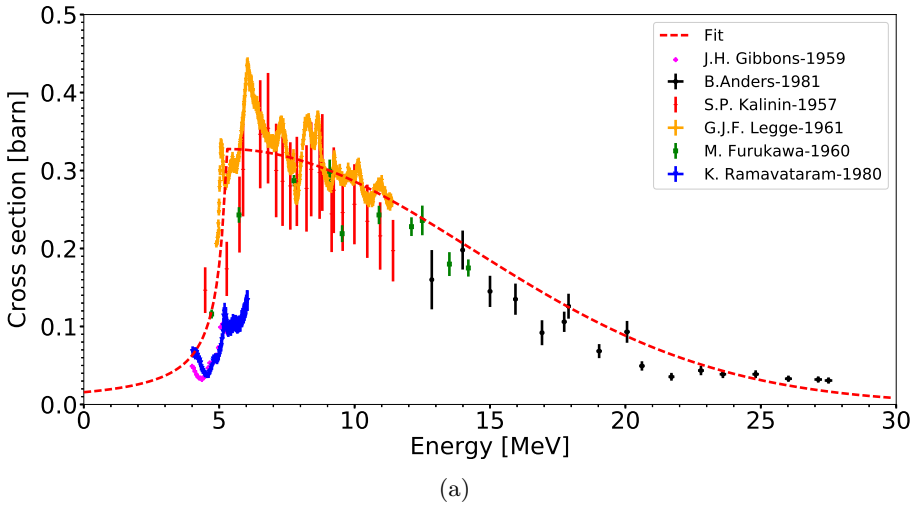


Figure A.1: Fitted tabulated cross section data of the nuclear reactions: (a) $^{11}\text{B}(p,n)^{11}\text{C}$ and (b) $^{14}\text{N}(p,\alpha)^{11}\text{C}$. A Crystal Ball and spline function were fitted to the data, respectively.

A.3 Calculated thick in-target production yield of BN

To calculate the physical thick in-target production yield of the SPS pre-sintered BN target, the tabulated cross section data (Fig. A.1) was fitted using a Crystal

Ball and spline function for the nuclear reaction channels: (a) $^{11}\text{B}(\text{p},\text{n})^{11}\text{C}$ and (b) $^{14}\text{N}(\text{p},\alpha)^{11}\text{C}$. From these fits, the cross sections' energy dependence $\sigma_{^{11}\text{B}}(E)$ and $\sigma_{^{14}\text{N}}(E)$ was obtained. The stopping power $S(E)$ was calculated using SRIM [208], where the measured density $\rho = 1.3 \text{ g cm}^{-3}$ of the BN target was employed. Using these results, BN's physical thick in-target production yield $Y_{\text{phys}}(E_i)$, with $E \in [5, E_i]$ MeV, was determined using Equation (4.1). A graphical illustration of $Y_{\text{phys}}(E_i)$ is shown in Fig. 4.9 in Section 4.2. In detail, one finds for the suggested energy interval $E \in [5, 15]$ MeV:

$$Y_{\text{phys}} = 1.86(23) \cdot 10^{-3} \frac{\text{nuclei}}{\text{primary}},$$

which is in reasonably good agreement with the results obtained from FLUKA simulations:

$$Y_{\text{phys}}^{\text{FLUKA}} = 1.38(1) \cdot 10^{-3} \frac{\text{nuclei}}{\text{primary}}.$$

These findings confirm the applicability of FLUKA, for discussing the estimated ^{11}C production yield of the developed BN target, employing low-energy proton beams.

Appendix B

Experimental heating units



Figure B.1: Formerly applied ISOLDE heating unit, comprising a cylindrical Ta target container, Ta heat screen and copper blocks holding the assembly.

The technical or mechanical realization of a dedicated experimental setup that allows examination of BN's high-temperature dissociation and oxidation behavior in typical ISOL-target conditions was discovered to be very challenging.

Especially concerning to capability of providing a calibrated oxygen leak to the sample, and the capability to detect generated gaseous species relevant for the experimental study.

Since nitrogen is essentially the only product that demonstrably correlates with target dissociation and oxidation, the experimental setup is required to be very clean. An existing, standard ISOL-target heating unit, as shown in Fig. B.1, did not yield satisfactory results. As outlined in Section 4.2.4, pronounced contamination issues originating from previous studies employing this unit, prevented the application of this setup. However, this enclosed tantalum tube design imposed further complications, since Ta reacts with BN, forming TaN. Hence, initially, an alumina boat was applied to carry the BN sample and to prevent direct contact to Ta.

In former studies, alumina showed good compatibility with BN (refer to Article I). However, alumina chemically reduces when in contact with tantalum, which was attempted to be avoided by using rhenium strips as protective layer. Nevertheless, when applied in such modality with the setup shown in Fig. B.1, the entire boat turned grey. Moreover, grey deposits were also observed on the BN sample's surface. There are three different possible explanations for these occurrences: firstly, Ta and Al_2O_3 reacted with each other, either due to partial contact which was not properly avoided or due to minimal vaporization of these materials. This is supported by Al and TaO deposits on the inside of the tantalum container, as well as Al on the alumina boat, measured by SEM-EDX. Secondly, BN could have reacted with Al_2O_3 as proposed by G.D. Alton et al. [144] and briefly discussed in Section 4.2.4. The grey layer which was observed on the heated BN sample's surface was indeed identified as aluminium using SEM-EDX. However, it was mostly seen on the surfaces facing away from the alumina boat. Thirdly, as discussed in Section 4.2.4, while Al_2O_3 is in vacuum stable up to the investigated temperature $T = 1500\text{ }^\circ\text{C}$, due to the Boltzmann distribution, molecules can possess higher thermal energies which therefore thermodynamically favor dissociation. The latter hypothesis could explain Al deposits on BN's surface and the TaO and Al deposits on the inner part of the Ta tube. However, it is not possible to determine which mechanism was resulting in the reported observations. Moreover, it is conceivable that all three processes occurred.

Due to these observations and the contamination issues from previous experiments, the heating unit shown in Fig. B.1 was replaced by a improved design as displayed in Fig. 4.15 and discussed in Sec. 4.2.4. The application of an alumina boat was omitted and the tantalum tube design was simplified. A rhenium sheet prevented direct contact of BN to Ta. This solution performed well and yielded satisfactory results for the high-temperature studies in vacuum (Sec. 4.2.4).

However, it failed concerning the oxidation studies in controlled oxidizing atmospheres at high temperatures. The used gas mixture was guided from a calibrated leak and gas inlet implemented in the target unit via a Ta tube through the Ta heat screen to the sample. This configuration however entailed passive heating of the leak tube, which as a result consumed the entire O_2 content of the gas mixture. Unfortunately, it is from a technical point of view very complicated to replace metal parts in ISOL target containers and target units. Generally, high temperatures are accomplished through resistive heating, employing high currents (typically 300 – 600 A) passing through the corresponding metals. It is therefore technically challenging to establish a system that allows oxygen to enter the target without being consumed beforehand in chemical reactions with these hot metal surfaces. Note that this issue is not only of concern for the high-temperature oxidation studies reported in this thesis, but also for the mechanical development of a target-ion source unit tailored for ^{11}C RIB production. It is hence interesting to report on the solutions that have been employed in this study.

Metal parts and tools were, if possible, omitted and replaced by ceramics. Figure B.2 shows the developed ceramic based heating unit. The sample was placed nearby the front-end of a 20 cm long tube, which was closed at the rear-end. Note that a thin rhenium sheet was used as lining, to prevent direct contact of BN with the ceramic tube. Heating was accomplished by a tantalum coil centered above the sample location (Fig. B.2a). Such heating is rather inefficient, implying the application of molybdenum heat screens to mitigate radiative cooling (Fig. B.2b). The calibrated oxygen leak is provided through a stainless steel pipe from the gas-inlet to the rear-end of the ceramic tube, which length is chosen such that as low temperatures as possible are present at the junction between stainless steel tube and the ceramic. In addition, the copper block holding the ceramic tube acts as a heat sink, since it is contrary to a ceramic a very good thermal conductor. A temperature calibration was conducted, using a thermocouple, to determine the required current to reach ~ 1500 °C in the sample's proximity, and a second thermocouple monitored the temperature at the leak entrance. In this way, maximum temperatures around 300 °C were measured at the tube's rear-end.

Since the applicability of alumina had become questionable during previous high-temperature studies, it was initially attempted to apply yttria-stabilized zirconia (Y_2O_3 - ZrO_2) tubes instead. This material is reported to be very refractory and to possess a superior high-temperature stability compared to Al_2O_3 . However, upon first heat treatments it seemed that excessive decomposition occurred. High oxygen levels were observed in the RGA and the tube turned dark-grey around the hot zone, which was not only found on the tube's surface, but also in the material's bulk. A XRD measurement showed next to the expected peaks

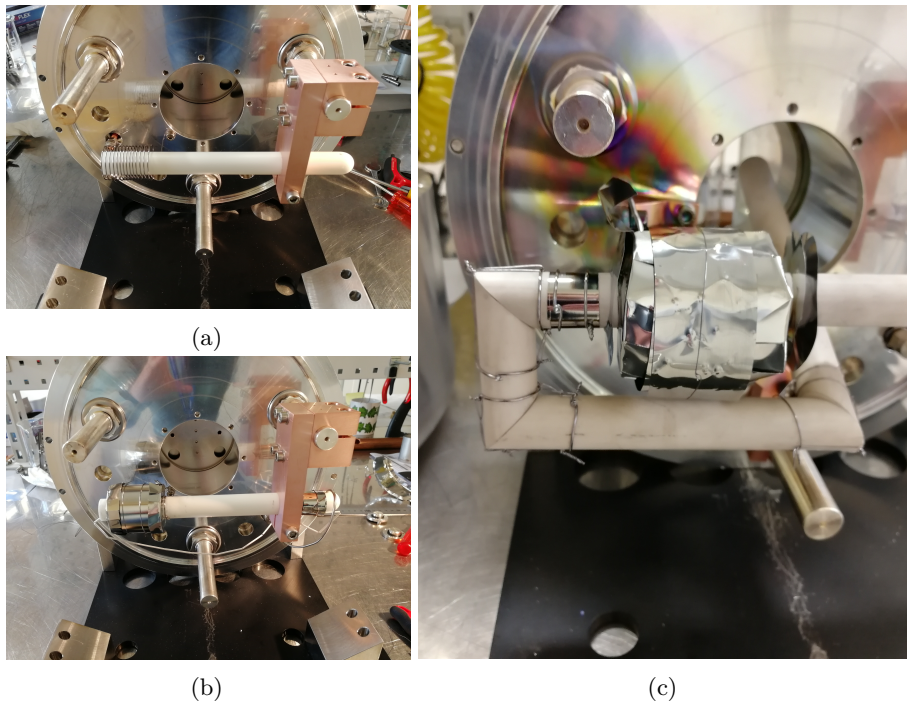


Figure B.2: Ceramic-based heating unit that was developed for high-temperature studies in oxidizing atmospheres. The sample is mounted into an alumina pipe which is closed at one end. Heating is conducted through resistive heating employing a Ta coil (a). Mo heat screens mitigate radiative cooling, and the oxidizing gas mixture is connected from the gas inlet via a stainless steel tube that punches through a hole in the rear-end of the ceramic tube (b). A guidance system, manufactured from alumina tubes, directs the gas after it passed the sample to the vacuum system (c). Thereby, it is ensured that the majority of the oxidizing gas mixture bypasses hot metal parts which otherwise could consume the O_2 .

of Y_2O_3 - ZrO_2 only one additional peak, which could not be assigned to Zr or Y, and remains unresolved. Nevertheless, this material did not meet the necessary requirements and was therefore replaced by a geometrically equivalent alumina tube.

While the setup that is described so far allowed to direct the oxygen flow to the sample, it was not yet possible to prove this experimentally as the gas bypassed hot metal surfaces of the heating and shielding elements before reaching the

QMS for RGA. Thus, a guidance system, comprising further alumina tubes, was installed to direct the gas immediately to the vacuum system, thereby minimizing the exposure to hot metals. Figure B.2c shows the complete experimental setup which was applied for the advanced high-temperature studies in controlled oxidizing atmospheres (refer to Sec. 4.2.4). While this technical solution performed reasonably well concerning the external oxygen supply to the sample and detection of oxygen and secondary products from the oxidation reaction (N_2), grey deposits were observed on the inner walls of the tube and on the target material's surface (refer to Sec. 4.2.4). These deposits likely correspond to aluminium which was vaporized after partial thermodynamic dissociation of the alumina tube, as it was discussed above, for previously observed depositions employing the typical ISOLDE heating unit shown in Figure B.1. However, an XRD analysis of the corresponding BN sample could not associate the secondary observed peaks clearly to Al or AlN.

It was discussed in Section 4.3 that the application of ceramic parts in the technical realization of a target-ion source unit tailored for $^{11}CO^+$ RIB production, which exhibit a controlled dissociation behavior at 1500 °C, may be a more practical solution to provide oxygen to the target. However, the condensation of vaporized metals origination from the oxide's chemical reduction, as it was the probably case in the employed alumina based heating unit, must be addressed and avoided.

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FACULTY OF SCIENCE
DEPARTMENT OF PHYSICS AND ASTRONOMY
INTERDISCIPLINARY RESEARCH
Celestijnenlaan 200D box 2418
B-3001 Leuven
simon.stegemann@kuleuven.be
<https://fys.kuleuven.be/iks/interdisciplinary-research>

