Contribution aux exercices de prospective nationale 2020-2030

Accélérateurs et instrumentation associée

PRODUCTION, FORMATION AND STUDIES OF HIGH-QUALITY RADIOACTIVE ION BEAMS FOR RADIOTHERAPY

PRODUCTION, FORMATION ET ETUDES DE FAISCEAUX D'IONS RADIOACTIFS DE HAUTE QUALITE POUR LA RADIOTHERAPIE

Auteur principal

Nom : Traykov Emil

Affiliation : IPHC/IN2P3/CNRS

Email et coordonnées : emil.traykov@iphc.cnrs.fr
Institut Pluridisciplinaire Hubert Curien
Equipe Instrumentation Accélérateurs
23 Rue du Loess BP 28
67037 STRASBOURG CEDEX 2
FRANCE

Co-auteurs

BOUQUEREL Elian (EIA/IPHC), ROUSSEAU Marc (DRHIM/IPHC)

Contribution à rédiger en français ou en anglais et à envoyer à PROSP2020-GT07-COPIL-L@IN2P3.FR avant le ***1er novembre 2019***

1. Informations générales

Titre :

Production, formation and studies of high-quality Radioactive Ion Beams for radiotherapy

Production, formation et étude de faisceaux d'ions radioactifs de haute qualité pour la radiothérapie

Acronyme : *(optionnel)*

Résumé *(max. 600 caractères espaces compris)*

We propose the use of Radioactive Ion Beams (RIB) for radiotherapy due to major advantages compared to stable ion beams. The main RIB of interest are short-lived beta-decaying isotopes with delayed alpha emissions from the daughter nucleus allowing increasing the dose locally but preserving healthy tissue. The broad spectrum of the alphas can reduce the beam energy steps necessary for achieving uniform dose distribution. Another advantage in using short-lived RIB for irradiation is the possibility of live monitoring of the stopping distribution and the dose deposition by PET/SPECT techniques.

Préciser le domaine de recherche *(plusieurs choix possibles)*

- o ***Physique des accélérateurs (nouveaux concepts machines, optique et dynamique des faisceaux…)***
- o ***Sources de particules (****électrons, positrons, muons, protons, ions lourds stables,* ***ions radioactifs…) et cibles associées***
- o *Supraconductivité accélérateur (aimants fort champ, cavités SRF…)*
- o *Accélération plasma (électrons, ions…) et interaction lasers/faisceaux*
- o *Technologies RF innovantes (structures haut gradients, alimentations RF…)*
- o ***Diagnostics faisceau, instrumentation et contrôle intelligent***
- o ***Développement durable de la discipline (infrastructures technologiques, efficacité énergétique, fiabilité…)***
- o *Autre R&D spécifique : (préciser)*

Préciser la motivation principale visée par la contribution :

- o *Accélérateurs pour la physique nucléaire*
- o *Accélérateurs pour la physique des particules*
- o *Accélérateurs pour les sources de lumière ou de neutrons*
- o ***Accélérateurs pour les applications sociétales (santé, énergie, industrie…)***
- o *Autre : (préciser)*

2. Description des objectifs scientifiques et techniques *(2 pages max incl. figures)*

Décrire les objectifs scientifiques et/ou techniques de la contribution proposée en en précisant les motivations.
Préciser comment ces objectifs se situent par rapport à l'état de l'art et au contexte international (ex : est-ce une contribution visant un développement théorique ou expérimental ? Est-elle dans la continuité de concepts ou technologies actuelles, ou bien est-ce une nouvelle approche conceptuelle ?)
Préciser les liens éventuels avec d'autres projets nationaux ou internationaux existants ou envisagés.

The are several known advantages of accelerated particle beams over X-rays for radiotherapy, such as precise dose delivery due to finite range, higher biological effectiveness (increasing with the mass of the ion) and reduced damage to the surrounding healthy tissue [Dur17]. Moreover, heavier beams, such as carbon, have an additional advantage over protons for treatment of radio-resistant cancers [Uhl14]. The present contribution aims to increase even further the advantages of stable ion beams by their substitution with short-lived Radioactive Ion Beams (RIB) leading to several important enhancements:

- For RIB, the principle for dose deposition during slowing is the same as for stable ion beams, i.e. the use of the Bragg peak for the dose distribution. However, RIB have an additional localized energy transfer by the decay products of the stopped nuclei causing **enhanced dose deposition in situ (DDIS)**.
- The broad energy distribution of the decay products allows **decreasing the number of energy steps necessary for achieving uniform dose along the depth of the tumor**.
- Online detection of either 511 keV annihilation gammas (PET) or characteristic gammas from excited states of the decay products (SPECT) could allow **live monitoring of the dose distribution**.

The delivery of high-energy, high-quality RIB for cancer treatment is associated with design and construction of dedicated accelerator facilities, which require detailed R&D on several specific topics and related techniques:

1. Identification and comparison of short-lived isotopes for RIB radiotherapy

There are two types of isotopes suitable for RIB radiotherapy. The first type are isotopes the decay of which is accompanied with energetic secondary ionizing particles, e.g. delayed alpha emission, increasing the local dose deposition inside the tumor. The second type are positron or gamma emitting isotopes, which allow rate counting with either PET or SPECT techniques [Cze13, Isr19], thus allowing monitoring of dose position distribution. A preliminary list of suitable isotopes is shown in the table.

RIB	Half-life	Decay mode	*E* [MeV/u] *(15 cm H_2O)*	Production mode	notes
^{8}Li	839.9 ms	β^-, ^{8}Be→α+α	157	ISOL, In-flight	Increased DDIS
^{8}B	770 ms	β^+, ^{8}Be→α+α	280	ISOL, In-flight	Increased DDIS
^{9}Li	178.3 ms	β^-, **^{9}Be** /49.2% B.R. β^-, n+(^{8}Be→α+α) /50.8% B.R.	147	ISOL, In-flight	Increased DDIS
^{9}C	126.5 ms	β^+, p+(^{8}Be→α+α) /61.6% β^+, α+(^{5}Li→p+α) /38.4% B.R.	327	In-flight	Increased DDIS
^{11}C	20.364 min	β^+, **^{11}B** /99.8% B.R., E_0 = 960.5 keV	289	ISOL, In-flight	Dose monitoring
^{13}N	9.965 min	β^+, **^{12}C**, E_0 = 1198.5 keV	318	ISOL, In-flight	Dose monitoring
^{15}O	122.24 min	β^+, **^{15}N**, E_0 = 1732.0 keV	343	ISOL, In-flight	Dose monitoring
^{18}F	109.74 min	β^+, **^{18}O**/96.9% B.R., E_0 = 633.9 keV	354	ISOL, In-flight	Dose monitoring

Light short-lived isotopes suitable for future RIB radiotherapy. Beam energy necessary for 15 cm range in water.

Detailed studies are necessary to compare the possible isotopes and select the most suitable choices. These studies require both simulations and experiments for determination of the energy transfer distributions of the secondary particles and for achieving uniform dose distributions in combination with spread-out Bragg peaks.

2. Choice of preferable production scheme for different RIB

There are two main methods for RIB formation [Blu14] - *Isotope Separation On-Line (ISOL)* and *In-flight* production/separation (Fig. 1).

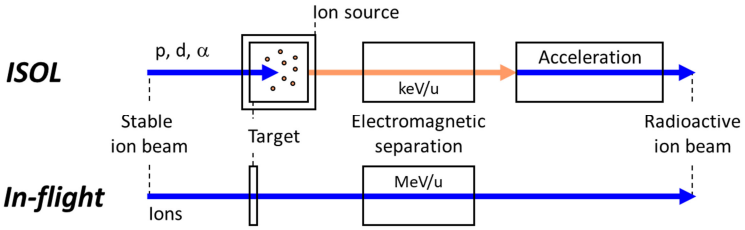

Figure 1. Schematic description of ISOL and In-flight RIB production schemes [Blu14].

The *ISOL* method allows higher production rates in general but, unlike the *In-flight* method, is highly element dependent due to the times and efficiencies associated with the processes inside the target/ion source, such as diffusion, effusion and ionization. An advantage of the *ISOL* method is related to the possible inclusion of a low-energy RIB production section (e.g. for lithium isotopes) at the injection lines of existing or planned carbon

therapy centers, such as HIT, MIT, CNAO and MedAustron [Dos18]. Alternatively, *In-flight* production may be preferred for certain elements and more exotic isotopes with low production cross sections, e.g. ^{9}C and ^{8}B.
The RIB intensity, I_{RIB} in both production schemes (ISOL and In Flight) can be expressed by:

$$I_{RIB} = I_{beam}\sigma d\varepsilon_1\varepsilon_2\varepsilon_3 \dots \varepsilon_n,$$

where I_{beam} is the primary beam intensity, σ is the production cross section, d is the target thickness, and ε_1, ε_2, …, ε_n are efficiencies related to the RIB decays and to various losses during the final RIB formation and selection.
In order to reach RIB quality and intensities necessary for therapy, for each of the isotopes one has to evaluate and search for the optimal combination of parameters involved. Besides defining the optimal production scheme, one has to evaluate practical aspects of building a RIB facility for radiotherapy, such as feasibility, cost, reliability, radiation safety, etc. The following lines summarize various preliminary R&D necessary for applying RIB in radiotherapy.

A. RIB production by Isotope Separation On-Line (ISOL)

- **Primary beams, production targets, cross-sections**

ISOL production is typically based on high-intensity light primary beams (protons, deuterons, helium) and thick production targets [Dom08]. The primary beam energy and the target thickness are matched. Energy dependent integrated cross-sections are used for the evaluation of the optimal combination of target material and thickness.

- **Diffusion, effusion and ionization of short-lived isotopes**

The radioactive isotopes are produced inside the production target, which requires subsequent diffusion through the solid target material, effusion within the target container, ionization near the exit aperture and electrostatic extraction forming low-energy RIB. There is a large database [Ten05] available for comparing diffusion, effusion and ionization related efficiencies and delays. Missing data should obtained by dedicated measurements.

- **Charge breeding and selection**

Low energy RIB are extracted typically as 1^{+} ions. In order to prepare them for post-acceleration a higher *q/m* ratio is desired which is achieved by injection into either ECRIS or EBIS charge breeders [Del16]. After obtaining the desired *q/m*, the RIB may require separation from unwanted radioactive beam impurities. This can be achieved in *q/m* filters, such as Quadrupole Mass Filters (QMF) or Magnetic Sectors (MS).

- **Post-acceleration**

Post-acceleration is necessary for reaching the desired energies for tumor irradiation. The RIB acceleration can be implemented either at existing/future carbon radiotherapy centers [Dos18] or at dedicated accelerator facilities designed to match the specific properties of the selected RIB.

B. RIB production by In-flight separation

- **Primary beams, production targets, cross-sections**

In-flight production uses high-intensity heavy ion beams and thin production targets resulting in forward-focused products. The energies of the primary beam and the desired radioactive isotope are similar and should be sufficient for the reaching desired ranges of RIB for irradiation. At these high energies, up to few 100 MeV/u, the cross sections for compound nuclear reactions are small and it is usually beneficial to use beam fragmentation instead. Production in inverse kinematics and at high beam energies leads to momentum distributions of the products being similar to the ones of the primary beam [Tra07]. This reduces losses related to the angular and energy distributions of the RIB.

- **Beam quality selection by collimation**

Angular distributions of the produced radioactive isotopes are usually larger than the ones necessary for radiotherapy. In order to improve the RIB quality a collimation system may be necessary for defining the beam.

- **High-energy RIB separation**

A fragment magnetic separator with a high momentum acceptance, e.g. as the ones compared in [Mor03], may be necessary for separation of the desired RIB from the primary beam and other unwanted reaction products without significant losses of the RIB of interest.

3. Développements associés, calendrier et budget indicatifs *(1 page max. incl. figures)*

Préciser les travaux envisagés pour mener à bien les objectifs décrits (étude conceptuelle, expérience, prototypage, construction…) ainsi que les résultats espérés et leur échéance, en précisant si possible les partenaires potentiels.
Si possible, évaluer grossièrement l'ordre de grandeur du financement nécessaire pour mener le développement envisagé (coût complet, en distinguant équipements, consommables et ressources humaines).

The work necessary for reaching the described objectives can be ordered the following way:

1. Identification and comparison of short-lived isotopes for RIB radiotherapy

- Simulations for stopping distributions, energy transfers and dose deposition from the primary RIB and secondary particle emission.
- Experimental verification of the results from the simulations.
- Definition of desired RIB properties for radiotherapy, e.g. intensity, energy, emittances, etc.

2. Comparison and choice of preferable production schemes for different RIB

- Comparison of *ISOL* and *In-flight* production rates for desired RIB based on existing experimental data on cross-sections, diffusion and effusion times, ionization efficiencies, etc.
- Analysis of the present limits and state-of-the-art for each of the involved stages: primary beam acceleration, beam intensities, target thickness, delays of various stages (for *ISOL*), beam formation and separation techniques. Definition of further R&D necessary for obtaining missing data.

3. Design studies and comparison of different approaches for RIB accelerators

- *ISOL* production stage for coupling to the injection of existing or future carbon irradiation centers.
- *In flight* RIB production at existing carbon accelerators with a production target and a separator section at the back end. Feasibility studies of combining Gantries with a Fragment separator for RIB selection.
- RIB production with dedicated novel accelerators, defined by the specifics of the desired RIB.

The possibility of using RIB for cancer therapy is an emerging idea. The implementation of RIB for cancer therapy requires many preliminary steps; therefore, presently it is difficult to make reliable estimates for the cost and necessary work force. Once the preliminary studies have been completed, the cost for implementation of RIB as an addition to stable ion beams is expected to be a small fraction compared to the total cost of existing hadrontherapy accelerator facilities.

4. Impact
(0.5 page max.)

Décrire les retombées espérées pour le développement de futures installations de recherche basées sur des accélérateurs ou pour d'autres applications sociétales.
Le cas échéant, préciser les partenariats industriels envisageables.

If proved feasible, cancer treatment with radioactive ion beams will be superior to all existing hadron therapies based on stable light ion beams. The expected advantages include either an increased dose deposition inside the tumor for the same dose in the healthy tissue or online dose monitoring, which is especially useful in cases where the tumor is close to a sensitive or vital tissue.
Production of RIB for radiotherapy should be easy to implement as an upgrade to existing and planned carbon irradiation centers. The costs of such upgrades should be low compared to the total price of a carbon therapy center.
Possible collaborations should be envisaged at existing and future hadrontherapy centers and with research groups working on hadrontherapy.

Références

[Dur17] Charged-particle therapy in cancer: clinical uses and future perspectives, M. Durante, R. Orecchia & J. S. Loeffler, Nature Reviews Clinical Oncology Vol. 14 (2017) 483-495

[Uhl14] Comparing the Use of Protons and Carbon Ions for Treatment, M. Uhl, K. Herfarth, and J. Debus
The Cancer Journal. 20(6): (2014) 433-439

[Cze13] PET/CT in Oncology: Current Status and Perspectives, J. Czernin, M. Allen-Auerbach, D. Nathanson, and K. Herrmann, Curr. Radiol. Rep. 1(3), (2013) 177-190

[Isr19] Two decades of SPECT/CT – the coming of age of a technology: An updated review of literature evidence, O. Israel et al, Euro. J. Nuc. Med. Molec. Imaging, Vol. 46(10), (2019) 1990-2012

[Blu14] Facilities and methods for radioactive ion beam production, Y. Blumenfeld, T. Nilsson and P. Van Duppen, Physica Scripta (2013) T152

[Dos18] ENLIGHT: European network for Light ion hadron therapy, M. Dosanjh, U. Amaldi, R. Mayer and R. Poetter, Radiotherapy and Oncology, 128(1), (2018) 76-82

[Dom08] High intensity targets for ISOL, historical and practical perspectives, M. Dombsky and P.Bricault
Nucl. Instr. and Meth. B, Vol. 266 (19–20), (2008) 4240-4246

[Del16] Optimizing charge breeding techniques for ISOL facilities in Europe: Conclusions from the EMILIE project, P. Delahaye *et al*, Rev. Sci. Instrum. 87 (2016) no.2, 02B510

[Ten05] TARGISOL: An ISOL-database on the web, O. Tengblad, M. Turrion and L. M. Fraile, Eur. Phys. J. A (2005) 25: 763-764

[Tra07] Production of radioactive nuclides in inverse reaction kinematics, E. Traykov *et al,* Nucl. Instr. and Meth. A, Vol. 572(2), (2007) 580-584

[Mor03] Commissioning the A1900 projectile fragment separator, D.J. Morrissey *et al,* Nucl. Instr. and Meth. B, 204 (2003) 90–96