COMPACT MEDICAL CYCLOTRONS AND THEIR USE FOR RADIOISOTOPE PRODUCTION AND MULTI-DISCIPLINARY RESEARCH

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Abstract

Compact medical cyclotrons are conceived for radioisotope production in a hospital-based environment. Their design in terms of field shape, stability and radio-frequency (RF) is aimed at obtaining high intensity (>150 μA) beams at kinetic energies of the order of 20 MeV. To guarantee high performances, an optimization procedure during the commissioning phase is crucial as well as a regular preventive maintenance. Beyond radioisotope production, these accelerators can be the heart of a multi-disciplinary research facility once access to the beam area and beams down to the pA range are possible. The first requirement can be achieved by means of an external beam transport line, which leads the beam to a second bunker with independent access. Currents down to the pA range can be obtained by specific ion source, RF and magnetic field tuning procedures, opening the way to nuclear and detector physics, radiation protection, radiation bio-physics and ion beam analysis developments. On the basis of the experience gained with the cyclotron at the Bern University Hospital, the accelerator physics aspects of compact medical cyclotrons are discussed together with their scientific potential.

INTRODUCTION

Cyclotrons are fundamental tools in modern medicine. They are employed to treat cancer by particle teletherapy [1, 2] and to produce radiolabelled compounds for diagnostic imaging and metabolic therapy [3, 4].

In the last years, a remarkable scientific and technological progress led to the development of several commercial medical cyclotrons. They presently represent reliable and affordable solutions to fulfill the needs of research laboratories, radio-pharmaceutical companies and healthcare institutions. In this process, the interplay among academia and industry has been crucial and the majority of the cyclotrons and of the related equipment on the market is the result of spin-off endeavors.

Medical cyclotrons can be schematically classified in five categories on the basis of their main characteristics: the energy and the intensity of the accelerated beams. As reported in Table 1, proton therapy cyclotrons feature the largest energy and the lowest intensity. They can be based on conventional or on superconducting technology. Their problematics are different with respect to the machines designed for radioisotope production [2] and will not be discussed here. Some research laboratories have recently installed 70 MeV cyclotrons which can be used for the production of specific radioisotopes (ex. ^{82}Sr for ^{82}Rb generators) and for research activities. These accelerators can provide beams of different energy and accelerate also alphas or deuterons. Along this line, 30 MeV cyclotrons are installed in research laboratories or in radiopharmaceutical companies producing Single Photon Emission Tomography (SPECT) radioisotopes (^{131}I in particular). Both 70 and 30 MeV cyclotrons require a large infrastructure and are therefore quite rare. The most common medical cyclotrons feature a beam energy in the range 15-25 MeV and are excellent tools to produce ^{18}F ($T_{1/2}$=110 minutes), the most common and requested radioisotope for Positron Emission Tomography (PET). These accelerators are compact, cost effective and can be installed in a hospital-based facility. There are more than 300 cyclotrons of this kind in operation and their number is continuously increasing [3]. For simplicity, I will refer to them as compact medical cyclotrons and they will be discussed in detail throughout this paper. Other commercial medical cyclotrons feature smaller beam energies and are often devoted to the production of only one PET radioisotope in limited quantities. They will not be further discussed.

Compact medical cyclotrons usually run during the night or early in the morning to produce short-lived radioisotopes for PET imaging. They are available during daytime and their beams could in principle be used for multi-disciplinary research. To exploit their valuable science potential, specific conditions must be fulfilled. Since daily radioisotope production induces high residual radioactivity, the cyclotron bunker is accessible only for very short periods which are

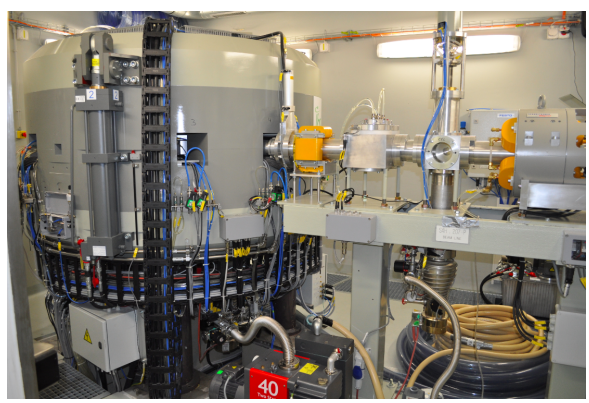

Figure 1: The compact medical PET cyclotron and its research beam line installed at the Bern University Hospital.

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Table 1: Schematic Classification of Commercial Cyclotrons*

	Main Use	Typical User	Max. Proton Energy (MeV)	Max. Beam Current (μA)
A	Proton therapy	Hospital	200-250	10^{-3}
B	Radioisotope production / research	Research laboratory	70	500-700
C	SPECT radioisotope production	Research lab. / industry	30	500-1000
D	**PET radioisotope production**	**Hospital / industry**	**15-25**	**100-400**
E	PET radioisotope production	Hospital	10-12	50

* Compact medical cyclotrons are highlighted in bold.

not suitable for research activities. A beam transfer line is therefore needed not only to shape the beams but also to lead the accelerated particles to a separate research area with independent access. Furthermore, beams in the picoampere and nanoampere range are mandatory for developments in nuclear and detector physics, material science, radiation biophysics, and radiation-protection. These intensities are 5 to 8 orders of magnitude lower with respect to the design ones and specific studies and optimizations of the accelerator are mandatory to obtain stable research beams.

One compact medical cyclotron is installed at the Bern University Hospital (Inselspital) [5, 6]. It is shown in Figure 1 and serves daily for the production of ^{18}F used for the synthesis of PET radio tracers with full Good Manufacturing Practice (GMP) industrial standards. Thanks to its beam transfer line, a rich multi-disciplinary scientific program is ongoing in complete synergy with industrial radioisotope production. On the basis of the experience gained with this facility, the accelerator physics aspects of compact medical cyclotrons are discussed and their scientific potential highlighted.

COMPACT MEDICAL CYCLOTRONS

Compact medical cyclotrons are commercial accelerators designed and optimized for the production of PET radioisotopes. Their main characteristics are determined by the physics of the concerned nuclear reactions. In particular, the process ^{18}O(p,n)^{18}F has a cross section of 100-700 mb in the range 4-16 MeV with the maximum around 6 MeV. This sets the value of the extracted beam energy. The beam current is determined by the amount of activity to be produced, which in turn depends on the cross section. As an example, about 500 GBq of ^{18}F can be produced in 120 minutes by bombarding two targets simultaneously with a total current of about 150 μA. After the synthesis, this corresponds to about 200-250 GBq of FDG, the most common PET radiotracer. Being the typical injected dose for one examination 400-500 MBq, a single cyclotron can serve several PET centers.

The main compact medical cyclotrons presently available on the market are reported in Table 2. Their typical weight is 22-24 tons and their dimensions less than 2×2×2 m^3. Being so compact, they well match the needs of a hospital-based facility. They are usually shielded by a bunker with about 2 m thick concrete walls. Local target shielding is sometimes used to match specific space needs. Compactness, high-performance, reliability and cost effectiveness are crucial and research is moving in this direction, as shown by the evolution of the cyclotrons produced by the Belgian company IBA (Figure 2). Due to the large currents, the considerable neutron fluxes and the high produced and induced activities, radiation protection is a critical issue to be taken into account in the design either of the accelerator or of the whole facility.

Some selected features of these accelerators are discussed in the next subsections, ideally following the trajectory of the accelerated ions from their source to the target.

Ion Source

All compact medical cyclotrons in Table 2 accelerate H$^-$ ions and, often as an option, D$^-$. These ions are produced in a plasma generated by an ion source fed by a gas bottle. Hydrogen purity is a key feature and maximum care has to be payed in the design and construction of the gas transfer lines. In particular, the presence of oxygen has a strong influence in the amount of produced ions and on the long term performance of the source. Cyclotrons are equipped with one or two sources. The main design choice is between external or internal ion sources. Cusp type external sources have the advantage of providing larger currents and to be accessible for maintenance without venting and opening the cyclotron. On the other hand, the design of the central region is more complex since a specific low energy (~25 keV) injection line (ex. one quadrupole doublet and a tilted spiral inflector) is needed. As a consequence, this solution is more expensive.

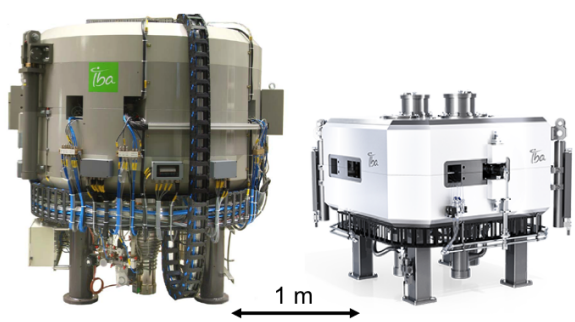

Figure 2: Comparison between the Cyclone 18/9 (total weight 24 tons, first design 1986) and the new KIUBE (17 tons, launched in 2016). (Courtesy IBA)

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Table 2: Main Compact Medical Cyclotrons*

Manufacturer	Model	Particles	Energy (MeV)	Max. Beam Current (μA)	Source	Extracted Beams
ACSI	TR19	H^- (D^-)	14-19 (9)	>300 (100)	Ext. Cusp	2
ACSI	TR24	H^-	15-24	>300	Ext. Cusp	2
Best	15p	H^-	15	400	Ext. Cusp	2
Best	25p	H^-	25	400	Ext. Cusp	2
GE	PETtrace	H^- / D^-	16.5 / 8.4	>80 / 60	Int. PIG	6
IBA	Cyclone 18/9	H^- (D^-)	18 (9)	>100 (65)	Int. PIG	8
IBA	KIUBE	H^-	18	200	Int. PIG adjustable	8
Sumitomo	HM-18	H^- / D^-	18 (10)	>90 / 50	Int. PIG	2

* Presently available on the market, and as indicated by row D in Table 1.

Internal Penning ion gauge (PIG) sources allow for an easier design and are cost effective. The ions are extracted by a puller directly connected to the RF of the cyclotron. The distance between the chimney and the puller is critical and has to be carefully adjusted during maintenance. To perform this operation, the accelerator has to be vented and opened. To be able to optimize the source at any time, a remotely controlled motorized system has been realized for the IBA KIUBE cyclotron. Two H^- sources can be installed in the same machine, as in the case of the Bern cyclotron. Since the sources can be swapped in about one minute, this is an important feature to enhance production reliability. Internal sources emit positive ions into the vacuum chamber with a negative impact on the vacuum. A much stronger pumping system is therefore needed. Furthermore, the worse vacuum conditions translate into an enhancement of H^- ions undergoing stripping before extraction. Up to about 50% of the H^- ions extracted from the source are transformed into the so called neutral beam (H^0) which produces activation of the vacuum chamber. A regular check and maintenance (typically 3 or 4 times a year) of the ion source(s) is very important to keep high performances (Figure 3).

Central Region

The central region is one of the most critical issues in cyclotron design since even tiny variations of the magnetic field have a large influence on the beam due to its low energy (below ~1 MeV, corresponding to a radius of less than ~10 cm). To minimize beam losses, the extracted current and the stability of the beams have to be optimized during commissioning by fine-tuning the magnetic filed. This is done by means of a shimming procedure that needs high currents and cannot be performed at the factory due to induced activation. In the case of the Bern cyclotron, 10 cm diameter 100 μm thick discs were inserted in the central region to locally tune the magnetic field. Although time consuming, this procedure is important not only to allow high performance for radioisotope production but also to obtain stable low currents beams for research activities.

Magnet, Vacuum and RF System

Compact medical cyclotrons are room-temperature sector-focused machines, usually featuring two dees and four sectors. Superconducting cyclotrons for radioisotope production are under study although this technology brings complications in a hospital-based environment.

The main coil is used to generate the magnetic field that shapes the trajectory of the particles. Vertical focusing is realized via the hill-valley structure of the poles. High accuracy of the magnetic field is of paramount importance and is assured by an iterative construction process performed by the manufacturer in which the field is mapped and, on the basis of trajectory calculations, the poles are mechanically modified. This procedure is repeated till when the required precision is reached. To optimize the beam in case of dual beam extraction, secondary re-centering coils are used to locally modify the magnetic field. This feature is machine dependent and its optimization needs care. In Bern, stable dual asymmetric beams have been also obtained (ex. 100 μA on one target and 50 μA on the other), opening the possibility of the production of two different radioisotopes at the same time. Most of the cyclotrons accelerate particles in the horizontal plane. The vertical acceleration plane (as in the case of the the GE PETtrace) has the advantage of a more comfortable opening and an easier access to the internal parts during maintenance.

The vacuum system must be powerful, especially for cyclotrons equipped with internal ion sources. A vacuum level of better than 10^{-5} mbar is needed during irradiations. This is realized using oil diffusion pumps (ODP) always kept in operation and connected in correspondence of the valleys.

A fixed frequency RF system is chosen mostly to limit the costs. This implies a careful tuning during the commissioning phase aimed at minimizing the reflected power. In the case of the IBA 18/9 cyclotron, the frequency of 42 MHz is used which corresponds to the second harmonic for protons and to the fourth for deuterons. To correct for the effects due to the mass defect of the deuterons, the magnetic field is slightly modified by moving the so called flaps inside the valleys of the magnet. The RF peak voltage typically ranges

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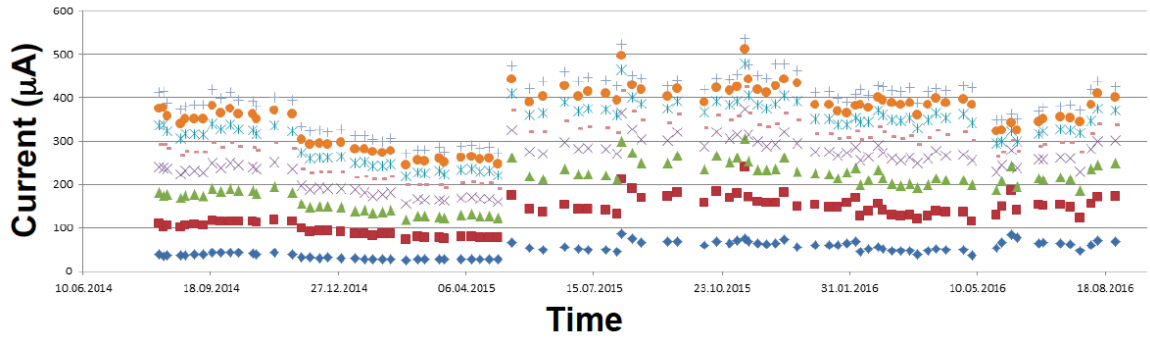

Figure 3: The beam current measured with a probe located in the central region is checked weekly to monitor the performance of the ion sources. The effects of maintenance are clearly visible. Different colors correspond to different settings of the arc current of the PIG ion source of the Bern cyclotron.

between 25 and 50 kV. It determines the number of turns and influences the transverse beam emittance.

Extraction

Extraction is obtained by stripping the negative ions. This method is simpler and more cost effective with respect to magnetic septa used in positive ion cyclotrons. About ~5 µm thick pyrolytic carbon foils are used as strippers. Their efficiency is about 100%. When inserted in the beam, they have to stand temperatures of about 1500° C or more due to the power released by the protons and, mainly, by the stripped electrons. For this reason, they may get damaged during operation and they have to be carefully inspected and possibly changed during maintenance. It is important to remark that the development of efficient and reliable strippers significantly contributed to the success of negative ion medical cyclotrons. The radial position of the stripper determines the extraction energy. Several foils (usually 2 or 3) are mounted on a rotating carrousel to allow for a quick substitution without opening the cyclotron. The angle of the stripper with respect to the beam can be adjusted to optimize extraction. In some machines, the extraction energy can be varied by moving the stripper radially inside the vacuum chamber. All the cyclotrons of Table 2 allow bombarding two targets at the same time. This is the so called dual beam mode. It is realized by inserting two strippers located approximately at an angular distance of about 180°. On the other hand, the number of the extracted beams may vary. Some manufacturers opted for the extraction in only 2 points where the beam dimensions are optimized for target bombardment. This solution has the drawback of the need of a multiple target holder if, as it is usual, more than two targets are used. Other manufacturers chose a different design in which the beam is extracted in 6 or 8 out-ports where targets can be mounted. Since the beam envelope varies all along the turns, the beam characteristics are not the same on all the ports.

RADIOISOTOPE PRODUCTION

Besides ^{18}F, other relevant PET isotopes are: ^{11}C (20 min.), ^{13}N (10 min.) and ^{15}O (122 sec.). Being characterized by much shorter half-lives, they have necessarily to be used within the centre where they are produced. For this reason, they are interesting more for scientific than for industrial purposes. In the last years, research concentrated on the development of methods for the production of standard as well as novel radioisotopes for PET imaging. A short summary follows with emphasis on the accelerator physics aspects. More details can be found in References [7, 8].

Targets

Targets can be classified in three categories according to the state of the bombarded material: gas, liquid and solid. They are mounted directly on the out-port of the cyclotron. Gas and liquid targets consist of a water cooled irradiation chamber of a few cubic centimeters volume which is filled with a specific material (ex. $H_2{}^{18}O$ water for ^{18}F production). The beam enters the chamber through a thin window which faces a second window in contact with the vacuum chamber of the accelerator. The few millimeter gap between the two windows is used to flow helium for cooling. Aluminum or havar alloy is used for the windows while the target body is usually made of aluminum or niobium. The choice of the materials depends on the produced radioisotope and its chemistry since even tiny impurities may have severe negative implications on the yield of the synthesis and on the purity of the final product. During bombardment, the beam should be as stable as possible either in shape or in intensity. Beam hot spots have to be avoided. Since no focusing elements are usually present between the stripper and the target, the operator has to optimize the beam by means of the stripper angle, the main and the re-centering coils as well as the RF peak voltage. Solid target stations are the main tool to produce novel PET radioisotopes. The target material is usually electroplated on an aluminum or platinum disk. The use of compressed powder target materials is presently under study. After irradiation, the disk is released and brought out of the cyclotron bunker via a manual or a remotely controlled (mechanic or pneumatic) system.

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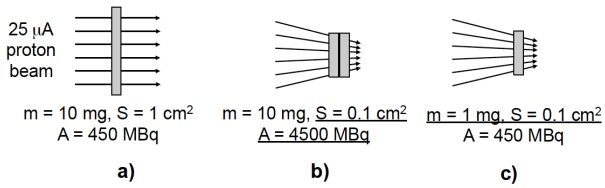

Figure 4: Different scenarios for the production of ^{43}Sc using a solid target station. Standard beam (a); highly focused beams (b and c).

Non-standard Radioisotopes

Non-standard radioisotopes (ex. ^{64}Cu, ^{66}Ga, ^{76}Br, ^{86}Y, ^{89}Zr, ^{124}I for PET; ^{67}Ga, ^{123}I, ^{111}In for SPECT; ^{165}Er for therapy) can be produced by irradiation of very rare and expensive highly enriched materials by means of solid target stations. Their production in quantity and quality suitable for clinical applications presents several challenges, including crucial accelerator physics issues. As a sound example, let's consider the production of scandium, a novel isotope for theranostics (^{44}Sc and ^{43}Sc for PET and ^{47}Sc for metabolic therapy) under study in Bern. In particular, ^{43}Sc can be produced with compact proton cyclotrons via the reactions ^{43}Ca(p,n)^{43}Sc and ^{46}Ti(p,α)^{43}Sc. As shown in Figure 4, only a few mg of enriched material can be used and the beam current is limited to about 25 μA in commercial solid target stations. Furthermore, the beam extracted from the cyclotron has a cross section S of about 1 cm^2 or more. These constraints severely limit the amount of produced activity (case a). If the beam could be focussed on a surface of 0.1 cm^2, a factor 10 could be gained (case b) or, alternatively, the same activity could be obtained with one tenth of the material (case c). To reach this goal, a focussing system is needed together with beam monitoring detectors able to control on-line the position and the shape during irradiation. The beam energy is also a crucial parameter. In particular, ^{43}Sc and ^{44}Sc are produced at the same time and their ratio is strongly energy dependent.

MULTI-DISCIPLINARY RESEARCH

The science potential of compact medical cyclotrons extends far beyond novel radioisotopes for medical applications. With an infrastructure encompassing a beam transfer line, a second bunker and an optimized cyclotron able to provide currents down to the pA range, considerable beam time can be devoted to multi-disciplinary research without any interference with industrial routine production. This is the case of the Bern cyclotron laboratory, where nuclear physics (ex. scandium production cross sections), novel particle detector and radiation protection (ex. radioactivity induced in air by proton and neutron beams [9]) studies are on-going. Furthermore, radiation hardness of materials and electronic components is investigated for the ATLAS experiment at CERN and for the JUICE mission of ESA. Ion beam analysis and radiation biophysics studies are also possible. All these activities are based on specific accelerator and detector physics developments.

Low Currents

Compact medical cyclotrons are designed to produce beams larger than 100 μA. To obtain stable beams down to the pA range, specific procedures have to be developed based on ion source, main coil and RF tuning [10]. Collimators can also be employed. The arc current of the ion source has to be set at the minimum allowing a stable plasma. This is usually enough to reduce the extracted current to about 1 μA. The main coil and the RF peak voltage can then be tuned to vary the intensity outside the isochronous condition. Stable beams down to 1 pA have been obtained for several hours with the Bern cyclotron. This procedure requires care and a continuous adjusting is necessary to compensate effects mostly due to the warm-up of the main coil.

Beam Monitoring Detectors

Good knowledge of the beam is essential to set-up and monitor its characteristics according to specific needs. Compact medical cyclotrons are usually equipped with general purpose beam monitoring devices sensitive only above ~1 μA and with a limited spatial resolution. The beam position if often controlled only by reading the current on collimators. Specific beam monitoring devices (such as Faraday cups or secondary emission detectors (SEM)) have to be developed for low current research applications. Along this line, a novel compact profile monitor detector (named UniBEaM [11]) was designed and constructed by the AEC-LHEP group to measure, control and use low- (pA, nA) as well as high-intensity (μA) beams. Its spatial resolution is below 100 μm. It is based on specific Ce and Sb doped scintillating fibres moved through the beam. The produced light is collected to measure the beam profile. The industrialization of this instrument is licensed to the Canadian company D-Pace.

Beam Transfer Lines

The optimization of the injection of the beam extracted from a medical cyclotron into a long (~6 m) transfer line requires care. In particular, the beam must be centered in position and angle with an accuracy better than 1 mm and 1 mrad, respectively. This could require the adjustment of the radial position of the strippers [12]. For this reason, the measurement of the exit position and angle of the beam with

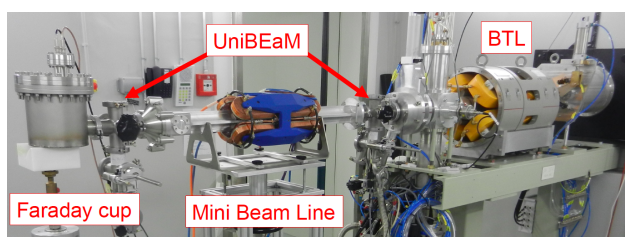

Figure 5: The mini beam line under test at the end of the beam transfer line (BTL) at the Bern cyclotron laboratory.

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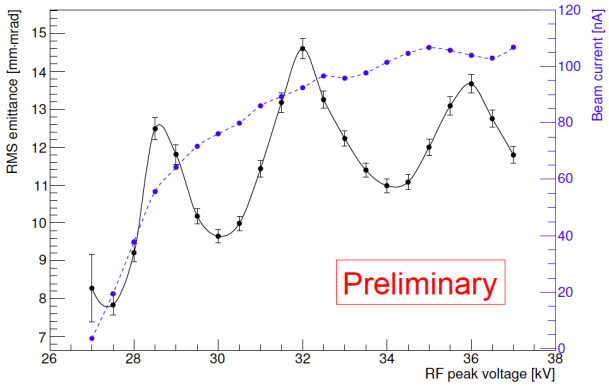

Figure 6: The horizontal transverse beam emittance and the beam current versus the RF peak voltage.

respect to the vacuum chamber is recommended as the first step of the commissioning.

Aiming at enhancing radioisotope production capabilities, compact focusing and steering elements to be installed between the exit port of the cyclotron and the target would be highly beneficial, especially in the case of solid target stations. For this purpose, D-Pace developed a 40 cm long compact mini beam line [13]. It consists of a quadruple doublet and a horizontal-vertical steering system embedded in a single light magnet. Its full characterization is in progress in Bern by means of UniBEaM detectors located before and after this novel device (Figure 5).

Transverse Beam Emittance and Simulation

A predictive simulation is a fundamental tool to study the set-up of a beam transfer line according to specific needs. The main input is represented by the transverse beam emittance and by the Twiss parameters, which are poorly known for compact medical cyclotrons. Furthermore, these parameters are machine dependent and vary according to conditions such as the status of the ion source or the type of strippers. Their measurement is usually performed by means of the quadrupole variation method, which requires a precise knowledge of the field gradient in the quadrupoles and is time consuming. To obtain an on line measurement of both the Twiss parameters and the transverse beam emittance, a method was developed based on four UniBEaM detectors [14]. This procedure does not require any knowledge of the focusing elements of the beam line. Based on the measurements of four profiles and a best fit procedure, the transverse beam emittance can be studied as a function of the main parameters of the cyclotron. The horizontal beam emittance as a function of the RF peak voltage is shown in Figure 6, where the influence of RF on the betatron motion is visible.

CONCLUSIONS AND OUTLOOK

Compact medical cyclotrons are the tool of choice for the production of radioisotopes for PET imaging. Designed to fulfill the needs of hospital-based facilities, they are characterized by a high science potential that started to be exploited only in the last years. A growing multi-disciplinary scientific community [15] is clustering around these particle accelerators for the benefit of science and society.

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