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Review

Particle accelerators for PET radionuclides

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Abstract

The requirements set for particle accelerators for production of radioactive isotopes for PET can easily be derived from first principles. The simple general need is for proton beams with energy in the region 10–20 MeV and current 20–100 microAmps. This is most reliably and cost-effectively achieved by the well proven technology of the compact medical cyclotron, presently available from several companies. The main features of these cyclotrons are essential similar: resistive, sector focused iron magnets, internal negative ion sources and stripping extraction. The remaining differences between different manufacturers will be discussed the light of what is actually needed for a given PET site operation.

Alternatives to the conventional cyclotron have been proposed and tested but have at present very limited use. These alternatives will be discussed, as well as the future possibilities of supplying point of demand tracer production with very small cyclotrons of energy well below 10 MeV.

The authors best advice at present for new PET sites is to negotiate for conventional cyclotron solutions from experienced manufacturers. It is the combined performance of cyclotron and target in terms of available activity output and the specific activity that is the real figures of merit and it is recommended that cyclotron solutions are weighted according to this and that acceptance tests are set up to realistically evaluate the routine availability of this output.

Key words: cyclotron, target, PET, isotope production

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Introduction: what energies and particles are needed

Radionuclides suitable for use in PET imaging will always be found close to the line of stability in the chart of nuclides. The requirements of suitable half-life and almost pure positron emission lead to a few dozen widely used isotopes that all decay to stable nuclei. The positron emission process by which the imaging information is created is the result of a conversion of a neutron to a proton inside the nucleus. Correspondingly, all currently used PET isotopes can be made by (p,n) reactions from a stable target isotope. Only in the two special cases of production of C-11 and N-13 the (p,alpha) process is normally preferred, but this simply because the chemical availability of the product isotope in these cases is better from the target element one number above instead of one number below the product. The third exception to the general rule of (p,n) preference is the production of O-15. It can be made in plentiful activity from (p,n) on isotopically enriched N-15 gas, but the corresponding deuteron process N-14(d,n) O-15 gives the same result but from much cheaper and readily available natural nitrogen. The production of O-15 is the single justification for having deuteron beams in pet isotope production, and can only be justified in installations having scanners near to the cyclotron and planning research with O-15.

The (p,n) process is inherently a low energy process with surprisingly constant onset below 9 MeV across the range of target elements. In order to reach practical activity outputs somewhat higher energies are needed. Four requirements sets the need for the maximum energy of a PET cyclotron:

— the possibility for running robust targets and target windows at high pressures (mandated mainly in clinical F-18 and high specific activity C-11 production);
— the need for very high production rates and correspondingly high steady state activity. This can be reached by having particles hitting a thick target at energies well above the energy of maximum cross section giving a large useful range spanning the entire region of high cross section;
— the capability of getting high output from the (p,alpha) routes to C-11 and especially N-13. The threshold energy of the (p,alpha) reactions is higher than for (p,n).

Cyclotrons with proton energies 11 to 19 MeV are in wide spread use to day for both routine and research applications. While higher energies do give incrementally larger isotope outputs for sufficiently thick targets, the yield over target power ratio drops significantly at energies above the relevant excitation

maximum. As most targets are cooling limited below the maximum beam power available from the cyclotron, the highest activity output from such targets is achieved at lower energies.

If deuterons are deemed necessary because of routine O-15 need, it should be remembered that even very low deuteron energy (around 4 MeV) is enough to make the O-15 output of a simple target saturate the count rate capability of a modern 3D PET scanner. In dual particle cyclotrons, the deuterons are always run in the second harmonic of the proton frequency, giving deuteron energies equal half the proton energy. For this reason, any practical proton/deuteron PET cyclotron will have enough deuterons for the O-15 production.

There is no need for alpha particles in the production of presently used PET radionuclides. In-110m can be made by an alpha beam, but this isotope as never found any practical use. Alpha capable cyclotrons are often presented as high end solutions to advanced isotope production centers, but it should be remembered that the main justification of alpha particles is in the generation of the therapeutic nuclides Cu-67 and At-211 that are not relevant for PET.

Is there a need for higher energy proton cyclotrons for the combined production of Tc-99m and PET radionuclides?

Based on recent short episodes of worldwide Tc-99m generator shortage and some widely publicised worst case scenarios for the long term availability of fission-based Mo-99, a direct cyclotron production of Tc-99m from Mo-100(p,2n)Tc-99m has been demonstrated and marketed. In order to satisfy even fractionally the present day Tc-99m needs, this requires cyclotrons of energy in the 16–24 MeV range with high beam current and capability of long uninterrupted runs. In principle such cyclotrons could also source a PET isotope program. This will however need much attention to both practical scheduling and site construction considerations as well as more demanding radiation safety requirements. If cyclotron produced Tc-99m should ever become a real and widespread need, separate cyclotrons for PET and for Tc-99m will probably be the optimal solution. In the opinion of the present author the higher costs of buying and running a 20+ MeV cyclotron for PET operations can not be expected to be paid back by any foreseeable Tc-99m market. It is an international experience that most attempts to foster both PET and SPECT isotope routine production on the same 30 MeV cyclotron have proved impractical, most often leading to the installation of second, dedicated PET cyclotron on the same site when PET operations reach routine levels.

Guidance on the choice of cyclotron and initial site planning considerations

The initial choice of cyclotron can have long term influence on the development and success of any given PET centre operation. Cyclotrons together with the required shielding and utility supplies are heavy, costly, space requiring and often difficult, expensive or even impossible to move or change. Cyclotrons have a much longer expected lifetime of service than most other medical equipment. It is highly warranted to plan as carefully as possible the projected short and long term needs for a given cyclotron before any tender or buying decision is made and before detailed site planning is performed. The IAEA has issued an extensive guideline on the initial analysis of cyclotron dimensioning and planning [1]. Equally important guidelines are available in ref. [2] and [3] on the principles and practice of radionuclide production with cyclotrons with production details for individual isotopes in ref. [3].

How much beam current is needed?

In principle, the activity output for any possible isotope product can be increased by raising the beam current on target. Most modern cyclotrons are negative ion machines with built in possibilities of simultaneously extraction of beam on two beam ports. At the same time the target developments especially for solid and water targets have extended the safe operation level into the kW power range. This all justifies demand for the highest possible current available out of given cyclotron, potentially divided on 2–3 beam ports. It should however be remembered that there are important limits to cyclotron beam currents:

— higher beam current inevitably leads to higher neutron output from both targets and collimators, this requiring more neutron shielding;
— higher beam currents leads to more activation and radiation damage to cyclotron components, thereby making service more demanding and costly;
— higher beam currents and multiple beam runs require higher levels of operation skills and increase the radiation dose afflicted and the time consumed in recovery from faults in operation.

Modern commercial compact cyclotrons all have the capability of delivering at least 50–100 microampere on any target. This level is easily obtainable even with internal ion source. The expensive option of external ion source make operation in the region 100–500 microampere possible, but it should be remembered that practically no PET isotope target can withstand these beam currents. Planning for a cyclotron with more than 150 microampere capability should be carefully argued against realistic production needs. While high beam currents in principle opens for regional distribution of the produced PET radiopharmaceuticals with two or more targets operating in shifts or in tandem, simple transport logistics may easily limit the supply area and thus the need. It should also be remembered that regional supply inevitably leads to higher demands on site planning and GMP compliance. While the external ion sources are in principle more easily accessible and open for service without interruption of main cyclotron vacuum, the service skills, alignment and condition of an external ion source is more demanding than for an internal source. Internal ion source lifetimes of more than 6 months of daily operation have been achieved. External ion source cyclotrons need more shielding, and are outside the reach of self shielding capability — at least in the case where the full power of the external ion source is used.

The output of the important PET isotopes C-11, N-13 and F-18 as function of available energy and beam current is readily available from the database in ref. [4]. While the thick target yields in this database are theoretical values computed from the best available selection of excitation function data, practical values at well commissioned and maintained cyclotrons are near these theoretical limits. (Remember, however that the yield from O-18(p,n)F18

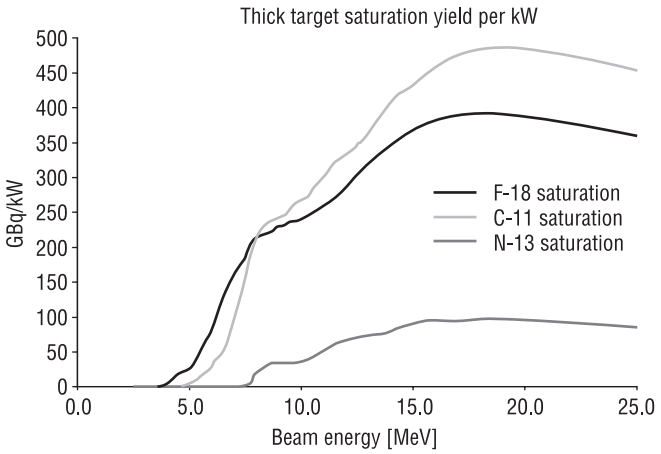

Figure 1. Thick target yields per power unit deposited in target

is given for a pure molecular O-18 oxygen target. When shooting on highly enriched O-18 water the yield is at least 10% lower).

As can be seen from the database, the yield of a given reaction can be increased both by raising beam energy and beam current. As most targets are limited in beam power capability by cooling requirements, there is however reason to look at the yield per power unit deposited in the target. Such graphs are depicted in Figure 1, computed on the basis of yields in ref. [4].

The figure shows that yields per kW injected into target levels off for all reactions above about 15 MeV. Beyond this point beam energy and beam current can be traded against each other as long as the limit is the deposited power allowed in target. This is most important today for high output F-18 targets. Higher energy protons (in the range of 11-19 MeV) can be justified in terms of more robust target windows (allowing higher target pressure), thicker targets and higher yields, but the technological evolution of high current, low energy targets has lead to very good performances even at 11 MeV. At the lower energy of 11 MeV, thin foils are needed. Such foils can only survive when supported by so called grids in front of the target. The grids have less than 100% beam transmittance and when comparing cyclotron and target data across manufacturers it is important to discriminate between beam out of cyclotron and beam into the target material. With proper designed and aligned grids it is possible to achieve multi-Curie outputs for C-11 and F-18 even from 11 MeV cyclotrons.

Vacuum technology and cooling

While poor vacuum conditions, pumping speed limitations and leaks were often the beam limiting factors in early cyclotrons, modern vacuum technology has completely changed this picture. Negative ions do need baseline tank pressures about a decade lower than for positive ions; this is easily obtainable with any of the 3 available pumping solutions: Diffusion pumps, Turbo pumps or cryopumps. The various cyclotron manufacturers have different preferences, but no clear overall preference can be extracted from existing operational data. For all 3 solutions the performance of an internal ion source cyclotron is limited by the pressure in the central region in the presence of the ion source gas load (2–6 cm^3 hydrogen per minute) and with RF heating of surfaces. Proper maintenance of the vacuum system, prevention of oil backstreaming and good cooling is the key to high output and reliability. Poor vacuum in negative ion machines leads to large beam losses due to gas stripping, even at high radius, resulting in activation build-up and radiation dose to service staff.

The cooling to the cyclotron and the associated power supplies is normally provided by external cooling water supplied to a dedicated heat exchanger in the cyclotron cooling loop. The internal cooling water loop of a cyclotron is maintained at much cleaner standards and with very low conductivity in the water. Some of the serious and long lasting cyclotron errors and lifetime limiting events have been related to poorly designed or poorly maintained cooling systems, leading to pipe corrosions, partial blockage of cooling circuits and hot-spot build ups. Careful design and control of the external cooling circuit and the year round availability of the necessary cooling is a key to reliability in cyclotron operations. In this context the air conditioning and temperature control of rooms with the electronics and the power supplies should not be forgotten. Even modern electronics do age at accelerated pace when run outside the design temperatures.

Maintenance, spare parts and serviceability

The commercial cyclotrons from the main manufacturers are all very reliable and easily serviced, provided that they are carefully installed and commissioned and that regular service is performed by skilled technicians. For reliable routine operation, it is strongly recommended that planned preventive maintenance periods (2–4 days annually or biannually) are respected. Cyclotrons with heavy production load will be radioactive, and the need for unplanned maintenance in the middle of a busy operation schedule will inevitably lead to high radiation doses to the service technicians. It is important that spare parts are available on very short notice. It is expensive and often impossible to have local stocks of all spare parts, and only the obvious "consumables" (foils, ion source components, o-rings and vacuum parts) really deserve local stock. For new or inexperienced cyclotron groups a service contract should be negotiated with the cyclotron manufacturer if cyclotron up-time is of importance. Given careful service, modern cyclotrons have more than 20 years of lifetime.

Commercial cyclotrons

Although the basic design of the compact cyclotrons is essentially universal, several "flavours" of commercial cyclotrons are available. Overviews of the existing suppliers and the various machines offered can be found in the references [1] and [5]. Such listings will quickly become outdated, and the listings are only given as introduction. Manufacturers should always be contacted for updated specifications and configurations. It is strongly recommended that key operational characteristics (that is: available activity outputs, uptime etc) are included in the acceptance tests. Careful planning and construction of a site and the orderly installation, commissioning and operator training is a key to success. The present author often says: "there are no bad cyclotrons, only badly installed or maintained cyclotrons", but of course this is a proverb with limitations. Well proven manufacturers and cyclotron

designs should be preferred unless a PET group has very strong technical competence and good reasons to explore alternatives.

Alternative designs

Although various types of linear accelerators (electrostatic, Alvarez-type and RFQs) have been developed and successfully used for PET, they have never demonstrated superior performance or lower cost when weighted against the activity outputs of the universally accepted isotope production accelerator: the cyclotron. Even the cyclotron itself is under development, and the introduction of superconducting magnets has been done for a few machines. It is perfectly possible to produce large quantities of PET isotopes with such alternative accelerators, but it then becomes a technical operation itself. As said above, such groups should have independent accelerator competence, and this paper is not written with such groups in the scope. PET isotope manufacturing technology can still be improved, and completely new methods can possibly be introduced (laser driven acceleration, dielectric wall devices etc.) but this development is far from mature, and you ask for trouble when trying to base a demanding routine PET operation on the basis of unproven technology. It is, after all, the isotope and radiopharmaceutical output that is our endpoint, not the accelerator technology.

The energy range and the intensities needed for PET radionuclide production are extremely well covered by modern compact (also called medical) cyclotrons. Although the basic principle of the cyclotron is now more than 80 years old (Lawrence, 1932), many developments during the last 30 years have made the cyclotrons much more reliable instruments. They are powerful in terms of isotope output, they are user friendly and easily serviced and with reasonably small requirements for space, power and cooling. Little reason remains to decide for anything else than cyclotron for PET radionuclide production, whether it is for routine clinical use or for research. However, there remain a lot detailed choices, not only on maximum beam energy between handfuls of well established commercial manufacturers, but also between different sizes and installations of the cyclotron: bunker versus self-shield, possible beam lines for solid targets or target multiplexing directly on the cyclotron tank. These choices should be analyzed on the basis of local possibilities (space and money) and requirements (tracer need).

The Atomic Energy Agency (IAEA) has issued a number of useful guidelines [1–4] to assist the right size of cyclotron and the design and operation of a PET radioisotope facility. These texts will guide the reader also to the very important interplay between the accelerator itself and the targets, the radiochemistry, the pharmaceutical and regulatory issues and the operational costs.

Bedside and table-top cyclotrons

There are some very promising current developments in terms of very compact "bed side" PET tracer delivery systems based on highly integrated small cyclotron systems. The advent of such platforms might once again change the way that we think and operate PET facilities in the future. ABT and GE are actively pursuing such machines, but reliable routine operation and regulatory compliance are still to be demonstrated. Much of the evolution in PET has been driven by developments by the community of cyclotron engineers and target wizards and this new technology is again such an example. The very small machines are only made possible by advances in cyclotron technology, target materials, radiochemistry systems and in software control and may well end making a much wider range of PET tracers clinically available on a broader scale and in larger numbers than previously believed possible. But wait and see! In the meantime, stay with the conventional cyclotron.

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