Production of Isotopes

2

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The rapid development and increasing interest in the use of metabolic imaging techniques has created a steady demand for on-site or regional production of radioisotopes. This chapter presents some basic concepts associated with radioisotope production, in particular, those aspects related to cyclotron production of positron-emitting radionuclide.

Concepts

Nuclear Reactions

The force experienced between two charged particles is expressed by Coulomb's law according to the relation (we have omitted some constant factors from the equations to simplify their expression):

$$F(r) = Q_1 Q_2 / r^2 \tag{2.1}$$

The potential associated with Coulomb's force described in Eq. 2.1 is

$$V(r) = Q_1 / r \tag{2.2}$$

where Q_1 and Q_2 are the electric charges of particles 1 and 2, respectively, and r is the distance between them. In the case of atomic nuclei this potential barrier can be represented as in Fig. 2.1, where the potential energy of the particles inside the nucleus (radius R) U_0, is assumed to be much lower than the barrier height B, that is $U_0 \ll B$. Experimental evidence strongly supports this assumption.

In a simplified picture to describe a nuclear reaction, an incoming positively charged projectile (proton or deuteron) needs to surmount this repulsive positively charged barrier presented by the target nucleus. In other words, the projectile must approach the target nucleus at a minimum distance of the order of the nuclear radius for a nuclear reaction to occur. This minimum energy is therefore

$$E_B = Z_1 Z_2 e^2 / R \tag{2.3}$$

with $Q_1 = Z_1 e$, $Q_2 = Z_2 e$, and where Z_1 and Z_2 are the atomic number of projectile and target, respectively, e is the electron charge, and R is the nuclear radius. For protons incident on carbon this value is $E_B = 2.3$ MeV, and for aluminum $E_B = 4.4$ MeV. From Eq. 2.3, a higher projectile energy is needed to penetrate the nucleus of a heavier target to produce a nuclear reaction.

The so-called compound nucleus model for nuclear reactions was first proposed by Bohr in 1936. It assumes that when a target T is bombarded by an incident nuclear particle i, the two may combine to form a compound nucleus $(T+i)$. This new compound nucleus possesses an excitation energy directly related to the incident

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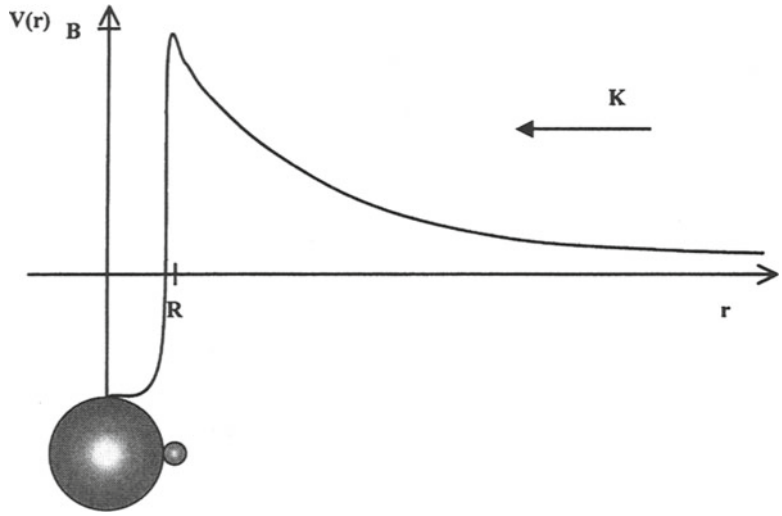
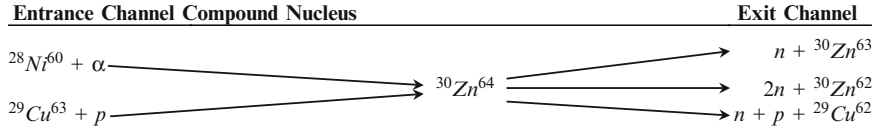


Fig. 2.1 Coulomb potential $V(r)$ between two charged nuclides as a function of their distance r. The barrier height B represents the minimum energy that the projectile has to carry to penetrate the target when it reaches the target outer radius R. A projectile with kinetic energy K as shown would not be able to penetrate the target nucleus

projectile energy. The identity of the incoming particle is lost, and the total energy of the excited compound nucleus is shared in a complicated manner by all the nucleons. The same compound nucleus in the same excited state can also be formed starting from a different combination of projectile/target; that is, it is possible to have $(T+i)=(T'+i')$. The properties of the compound nucleus are independent of the reaction. As an example, the compound nucleus $^{30}Zn^{64}$ can be formed according to the following scheme:



the cross section for production of the compound nucleus is nonzero even for incident projectile energies lower than the Coulomb barrier. Figures 2.2, 2.3, 2.4, and 2.5 present experimental cross sections for the production of some short-lived radioisotopes (^{11}C, ^{13}N, ^{15}O, ^{18}F).

Cross Section for Nuclear Reactions

The cross section for production of a certain final nuclear product reaction channel can be expressed as the probability of formation of the compound nucleus (intermediate state) times the probability of decaying into that channel. It is expressed in units of area (1 mbarn = 10^{-3} b = 10^{-27} cm^2). It can be interpreted as the *effective surface per nucleus presented by the target to the incoming projectile.* Due to quantum mechanical effects,

Particle Accelerators

The force experienced by a particle with electric charge q in the presence of an electromagnetic field is described by the Lorentz force according to

$$\vec{F} = q(\vec{E} + \vec{v} \times \vec{B}) \tag{2.4}$$

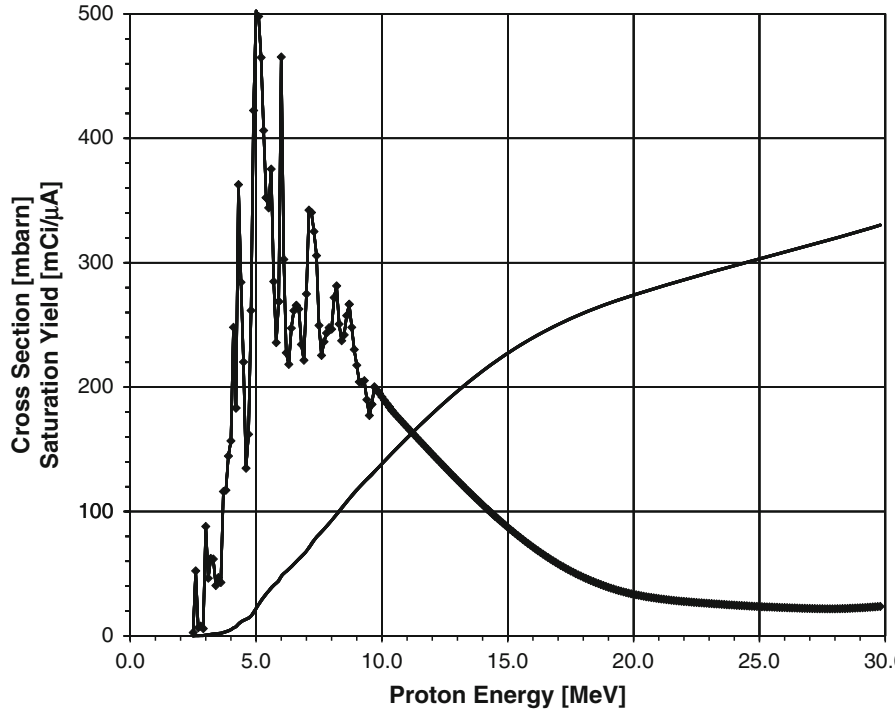


Fig. 2.2 Experimental cross section and theoretical saturation activity shown as a continuous line (Eq. 2.19) for the reaction $^{18}O(p,n)^{18}F$

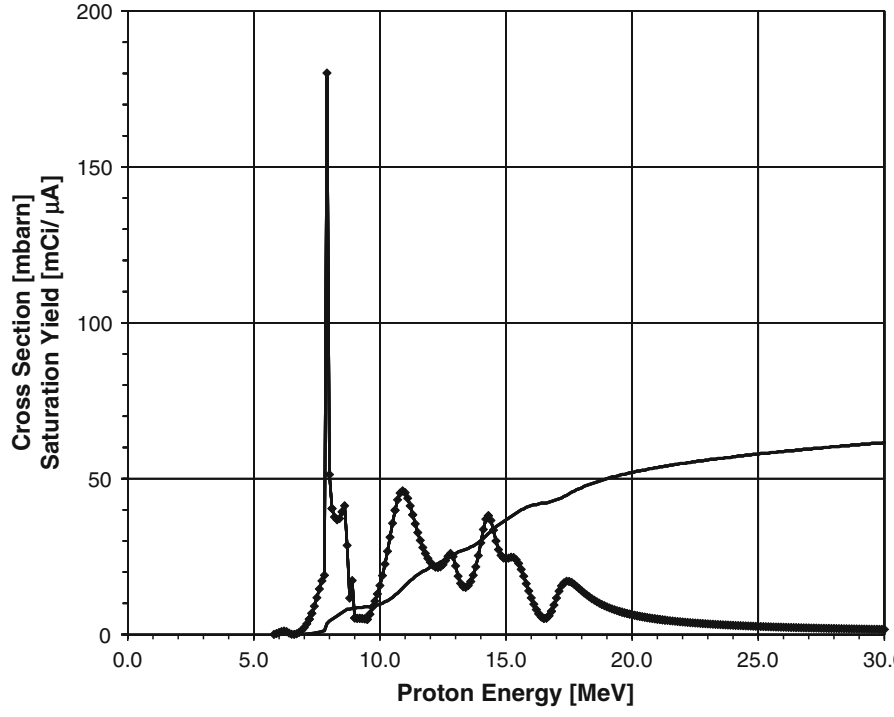


Fig. 2.3 Experimental cross section and theoretical saturation activity shown as a continuous line (Eq. 2.19) for the reaction $^{16}O(p,\alpha)^{13}N$

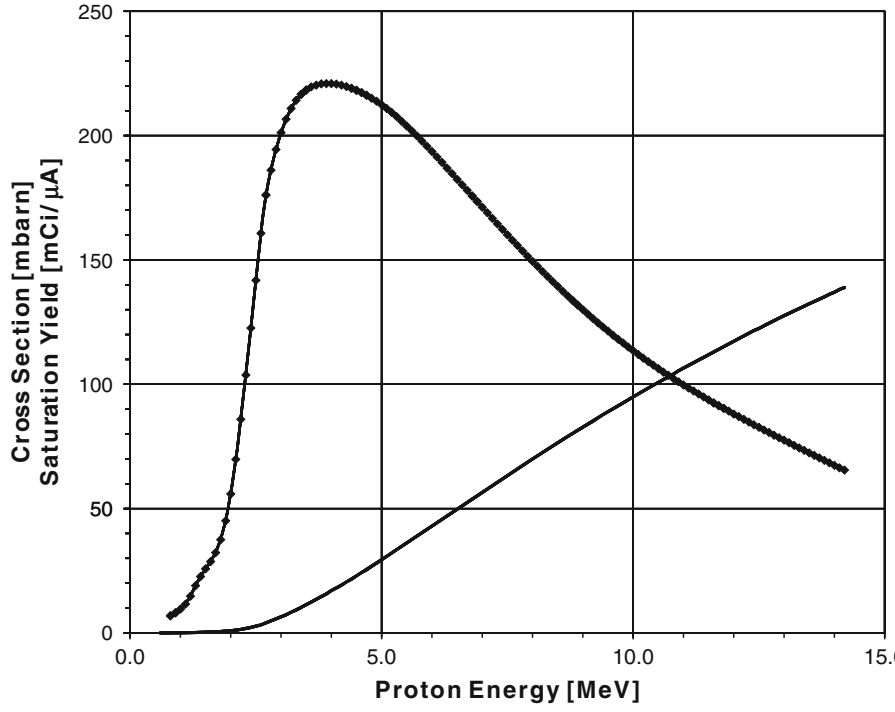


Fig. 2.4 Experimental cross section and theoretical saturation activity shown as a continuous line (Eq. 2.19) for the $^{14}N(d,n)^{15}O$ reaction

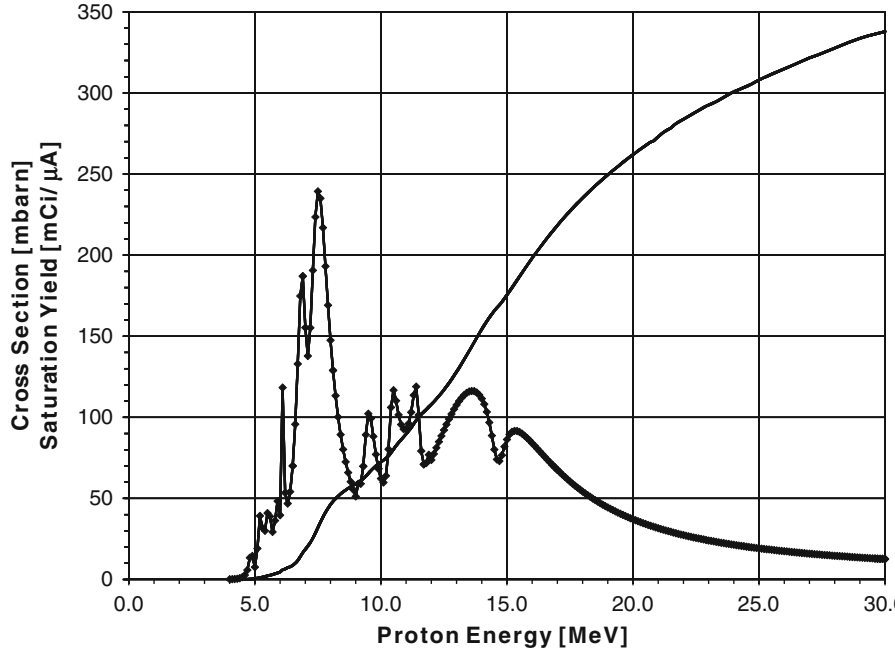


Fig. 2.5 Experimental cross section arid theoretical saturation activity shown as a continuous line (Eq. 2.19) for the $^{14}N(p,\alpha)^{11}C$ reaction

Where $\vec{E}$ is the electric field, $\vec{B}$ is the magnetic field, and $\vec{v}$ is the particle velocity. The vectorial nature of Eq. 2.4 requires intensity and spatial orientation to be considered for the magnitudes involved. The second term within the parentheses, defined as $\vec{v}\times\vec{B} = |v||B|\sin(v\angle B)$, shows that the magnetic field affects only the velocity component perpendicular to it. The electric field $\vec{E}$ is described as the difference in electric potential V per unit distance (gradient).

In the absence of magnetic fields, a particle exposed to a potential difference V will be accelerated to a final energy given by

$$E = E_0 + qV \tag{2.5}$$

where E_0 is the initial energy (not to be confused with electric field E). Equation 2.5 represents the basic accelerating mechanism behind any particle accelerator.

Static and alternating electric fields, from a few volts up to tens of megavolts (MV), are currently used for charged particle acceleration. For example, on an early Van de Graaff accelerator, an ion source is located inside a high-voltage terminal. Ions produced at this high voltage potential are accelerated toward ground potential, where the target is located. The acceleration takes place in an evacuated tube to avoid collisions between the ions and the air molecules. Maximum attainable voltage at the terminal is limited by practical considerations, and is close to 25 MV for state-of-the-art, large installations.

From Eq. 2.4 it follows that an alternative method to increase the ion's final energy, for a given potential difference, is to increase the ion's charge state (higher q). To take advantage of this mechanism, Van de Graaff accelerators have been modified to operate in tandem geometry. In this mode, the high-voltage terminal (dome) is kept at a positive potential respect to ground. Negative ions are produced instead, at the ion source outside the accelerator, and injected into the accelerator tube. The negative ions are attracted, and hence accelerated by the positive dome. After acceleration toward the positive dome, electrons are stripped off the negative ions by collisions with gas molecules or a micron-thin carbon foil. Projectiles thus converted into positive ions are accelerated by repulsion again toward ground potential (target). This configuration is very effective in achieving higher energies, especially for heavy ions, because the final energy is a function of the ion final charge state. For protons, the maximum attainable energy can be only twice the value of the dome potential. Another limitation of the tandem configuration is that not all species can be produced as negative ions in usable amounts.

Alternating electric fields are also utilized for charged particle acceleration. In this way, extremely high energies have been achieved. Again, positive ions are produced and accelerated toward a series of electrodes where an alternating electric field is applied. When the ions exit the first electrode, the electric field has already changed polarity, further accelerating the ions. Bunches of ions are then accelerated in this fashion. These linear structures, commonly known as linear accelerators, which are up to several kilometers in length, have successfully been used to accelerate ions to velocities approaching the speed of light. The applied electric fields amount to several hundred kilovolts at frequencies from tens of Hz to GHz.

The Cyclotron

First conceived by Lawrence in 1929, and successfully demonstrated in 1930 with important contributions from Livingston, the cyclotron was and still is one of the primary sources for medical radioisotope production. According to Eq. 2.4, in the presence of a magnetic field the total force experienced by the charged particle will have an additional component perpendicular to the plane defined by the particle velocity and magnetic field, thereby restraining the moving particles into circular orbits. These types of accelerators are known as *circular accelerators* (betatron, cyclotron, synchrotron), due to the approximately circular orbits described by the particles.

The introduction of negative ion cyclotrons over the past two decades has significantly improved exit projectile flux, which increases the

amount of radioisotope produced. The main components of the cyclotron are the following:

1. Vacuum chamber: To minimize collisions between ions and air molecules and thus minimize beam loss, the acceleration process takes place in areas where air density has been reduced to approximately 10^{-9} times that of atmospheric pressure. A short aluminum cylinder provides an airtight seal between the magnet polar pieces. Vacuum pumps remove the air from this chamber.
2. Ion source: Positive ions are typically produced by collisions between gas molecules (hydrogen in the case of protons) and accelerated electrons emitted from a cathode. Source geometry and applied electric fields facilitate the extraction of produced ions into the main accelerating field. Negative ions are created by exposing desired gas molecules to an intense plasma discharge and again using favorable geometries and electric and magnetic fields to extract hydrogen (or deuterium) atoms that have an extra electron attached.
3. Magnet: A strong (~1.5 T) magnetic field is applied across the magnet pole pieces defining the vacuum region. The effect of the magnetic field on the ion trajectories is to maintain them in circular orbits and to constrain the orbits near a plane perpendicular to the applied magnetic field as determined by Eq. 2.4.
4. Radiofrequency field: Ions are extracted from the source and injected into the vacuum chamber by a high-voltage alternating electric field applied to the accelerating structures, also known as *dees* because of the original shape proposed by Lawrence. While inside these hollow structures, ions continue to travel in an approximately circular orbit. When the ions reach the transition region between dees, the electric field has reversed polarity so that the distal dee has a higher potential than the proximal dee to accelerate the particles in the transitional gap. The particles are not accelerated inside the dees. Tens of kiloelectron volts (keV) are gained during each transition. As the ion energy increases, its orbital radius becomes larger. Near the outer radius, where the magnetic field sharply decreases, ions have reached their maximum energy.
5. Extraction: When the ions reach the outer region of the vacuum chamber, the extraction mechanism varies depending on the polarity of the ions as injected from the ion source. In the case of positive ions, a negative voltage is applied to a plate placed around the outer radius, pulling the positive ions from the trapping magnetic field and directing them to proper targets or through a beam line for further transport. During this process, between 10% and 50% of the beam is lost. When negatively charged ions are accelerated, a thin foil, typically a few micrometers-thick carbon, is placed on the ions' path. At several million electron volt (MeV) energies, the beam will traverse the foil with insignificant energy loss. Electrons from the negative ions are lost by interaction (stripping) with the solid foil, thereby converting them into positive ions. This sudden reversal of charge polarity reverses the Lorentz force direction (see Eq. 2.4) and the ions are pushed out of the machine by the same magnetic field that was keeping them inside. Extraction efficiencies close to 100% are currently achieved using this mechanism.
6. Targets: Although the main purpose of the cyclotron is to accelerate a particle beam to fairly high energies, targets for radioisotope production should be considered an integral part of the machine. Liquid, gas, or solid targets for production of radioisotopes need to be tailored to the particular characteristics of a given cyclotron to optimize use of beam energy, intensity, and profile. They can be located in close proximity to the cyclotron, or the beam can be transported through evacuated tubes (beam lines) under the guidance of focusing magnets (quadrupoles) to a distal location or a different room.

Cyclotrons for medical radioisotope production are commercially available from several manufacturers (Table 2.1). Typical beam energies ranging from 8 or 9 MeV up to 30 MeV are considered standard. Single-energy proton-only machines are widely used for production of positron emission tomography (PET) tracers. The energy range

Table 2.1 Commercially available cyclotrons

Manufacturer	Model	Energy	Standard features	Options
CTI molecular imaging Knoxville, TN (www.ctimi.com)	RDS 111	11-MeV protons	50-μA beam single port	RDS Eclipse; higher beam current and higher yield; 18 F targets
			40-μA per target in dual-port mode (80-μA total); self-shielded	
EBCO technologies Richmond, BC, Canada (www.ebcotech.com)	TR13-19	13–19-MeV protons	100-μA protons; dual-port irradiations; fix energy or field upgradable to 19 MeV	Vault or self-shielded; 9-MeV deuterons on TR-19; 300-μA protons; multiple beam lines on one or both ports
GE medical systems (www.gemedicalsystems.com)	PETtrace MINItrace	16.5-MeV protons 8.4-MeV deuterons; 9.6-MeV protons	75-μA protons; six ports for targets Self-shielded	Vault or self-shielded Dual-port irradiations
IBA Louvain-la-Neuve, Belgium (www.iba.be)	CYCLONE 10/5	10-MeV protons 5-MeV deuterons	60-μA protons 35-μA deuterons 80-μA protons	Dual-port irradiations standard on both models; multiple beam lines on one or both ports
	CYCLONE 18/9	18-MeV protons; 5-MeV deuterons	35-μA deuterons	

Stated machine characteristics were extracted from brochures and/or Web sites provided by manufacturers. For latest features, contact cyclotron manufacturers

between 8 and 19 MeV can supply most PET radioisotopes. Cyclotrons with energies of 30 MeV and higher can also be used for production of single photon emission computed tomography (SPECT) tracers (Tl 201, Ga 67, In 111, etc.). The other parameter defining radioisotope production rate is the available beam current from the machine. The higher the beam current tolerated by the target, the higher the amount of isotope that can be expected from a production run.

Production of PET Isotopes

Radioisotopes for PET

The physical properties of the four radioisotopes most widely used for PET studies are given in Table 2.2. These "organic" radioisotopes are particularly well suited for labeling biomolecules. Their short half-life provides the benefit of fast clearing from the patient's body, but it requires the on-site or nearby production of the radioisotope. Another important advantage of these radioisotopes is their high branching ratio for positron emission. The number of potentially useful positron emitters is certainly not limited to those included in Table 2.2. Several others have been successfully used for PET studies. Depending on the desired radioisotope, a combination of highly enriched target material or higher cyclotron energy or both may be necessary.

Production Cross Section

The concept of *cross section* for some event (σ_A) can be defined as the effective area per target atom presented to the projectile. Consider a target with area S, thickness Δx (small), and containing N atoms per unit volume. The probability (P_A) for a projectile to interact with a target atom producing an event (A) is given by the ratio of effective to total area:

$$P_A = n\sigma_A / S = N\Delta x\sigma_A \tag{2.6}$$

where $n = NS\Delta x$ is the total number of target atoms.

If the beam has a current density $J = I / S$, where I is the beam current, the average number of events (A) per unit time is given by

$$JSP_A = Jn\sigma_A \tag{2.7}$$

Equation 2.7 is valid only for single charged projectiles. Because we are dealing with a number of events, the important quantity is the actual number of incident projectiles and not their charge state. For projectiles with charge state different from unity, for example; α particles, Eq. 2.7 needs to be divided by the projectile charge state.

Radioactive Decay

The total number of atoms $A(t)$ at time t remaining from the radioactive decay of A_0 atoms at time to, is

$$A(t) = A_0 e^{-\lambda(t-to)} \tag{2.8}$$

where λ is the radioactive decay rate and $T = \ln 2/\lambda = 0.693/\lambda$ is the half-life of the radionuclide.

The total radioactive decay rate at any time is equal to the product of the total number of atoms A times the probability for radioactive decay λ_A, i.e., $A\lambda_A$.

Differential Equation for a Daughter Product

The radioactive decay of a nuclide A into a nuclide B, which is also radioactive, can be represented by

$$A \xrightarrow{\lambda_A} B \xrightarrow{\lambda_B} C$$

At any time, the activity of A is $A\lambda_A$ and of B is $B\lambda_B$. The rate of change dB/dt in the number of atoms of type B is then equal to the balance between supply as a result of the decay of A minus the rate of loss of B through its own decay:

$$\frac{dB}{dt} = A\lambda_A - B\lambda_B \tag{2.9}$$

Table 2.2 Characteristics of commonly used PET isotopes

Isotope	Half-life (min)	Mode of decay (%)	End-point energy of β^+ groups (keV)	Maximum β^+ range in water (mm)	Principal nuclear reactions (energy range MeV)
^{11}C	20.3	β^+ (99.8), EC (0.2)	960	4.1	^{14}N(p,α)^{11}C (15–4)
^{13}N	9.96	β^+ (100)	1,190	5.1	^{16}O(p,α)^{13}N (20–5)
^{15}O	2.03	β^+ (99.9), EC (0.1)	1,723	7.3	^{14}N(d,n)^{15}O (6–0)
					^{15}N(p,n)^{15}O (15–5)
^{18}F	109.7	β^+ (96.9), EC (3.1)	635	2.4	^{18}O(p,n)^{18}F (18–3)
					^{20}Ne(d,α)^{18}F (30–0)

EC electron capture

Replacing the number of atoms of type A at any given time using Eq. 2.9, we have

$$\frac{dB}{dt} = A_0\lambda_A e^{-\lambda_A t} - B\lambda_B \tag{2.10}$$

and solving the differential equation we obtain

$$B = A_0 \frac{\lambda_A}{\lambda_B - \lambda_A}\left(e^{-\lambda_A t} - e^{-\lambda_B t}\right) \tag{2.11}$$

The activity of B is $B\lambda_B$ or

$$B\lambda_B = A_0\lambda_A \frac{\lambda_B}{\lambda_B - \lambda_A}\left(e^{-\lambda_A t} - e^{-\lambda_B t}\right) \tag{2.12}$$

and since the activity of A at time t is $A\lambda_A = A_0\lambda_A e^{-\lambda_A t}$, we can replace into Eq. 2.12 to obtain

$$B\lambda_B = (A\lambda_A)\frac{\lambda_B}{\lambda_B - \lambda_A}\left(1 - e^{-(\lambda_B - \lambda_A)t}\right) \tag{2.13}$$

Production Yield

The process of radioisotope production by nuclear bombardment is mathematically analogous to the process of radioactive decay into a daughter product. The number of target atoms that are exposed to the beam during irradiation can be called A_0. The probability of transforming one of the atoms into nuclei B per unit of time can be called λ_A. Then, $A_0\lambda_A$ is the rate at which new atoms of B are produced. The target is equivalent to a radionuclide with activity $A_0\lambda_A$ producing the radioactive substance B. The probability λ_A is very small, but the product $A_0\lambda_A$ can be significant because A_0 is very large and can be taken as constant during irradiation $(A \equiv A_0)$. Assuming that $\lambda_A << \lambda_B$, Eq. 2.13 can be approximated by

$$B\lambda_B = A\lambda_A(1 - e^{-\lambda_B t}) \tag{2.14}$$

The net activity accumulated during time t is therefore

$$B\lambda_B = A_0\lambda_A(1 - e^{-\lambda_B t}) \tag{2.15}$$

The interaction rate per unit of time λ_A can be calculated as the product of the current I of incident projectiles and the cross section, summed over the projectile trajectory, that is,

$$\lambda_A = I\int_{x_1}^{x_2}\sigma(x)dx \tag{2.16}$$

and by replacing $dx = \dfrac{dE}{(dE/dX)}$ and $\sigma(x) \equiv \sigma(E)$ we obtain

$$\lambda_A = I\int_{E_i}^{E_{Th}}\frac{\sigma(E)}{(dE/dX)}dE \tag{2.17}$$

where E_i is the incident projectile energy, E_{Th} is the threshold energy for the given nuclear reaction, $\sigma(E)$ is the cross section, and dE/dx is the projectile energy loss per unit of path length. Both magnitudes, $\sigma(E)$ and dE/dx, are experimentally obtained and readily available from the literature.

Rewriting Eq. 2.16 in a more practical way, we obtain

$$B\lambda_B = \frac{N_A\rho}{M}I(1 - e^{-\lambda_B t})\int_{E_i}^{E_{Th}}\frac{\sigma(E)}{(dE/dX)}dE \tag{2.18}$$

with $A_0 = \frac{N_A \rho}{M}$, and N_A the Avogadro's number, M the atomic mass, and ρ the target density.

Equation 2.18 contains all of the information necessary to calculate production yield for a given radioisotope. The number of new radioactive atoms being produced is proportional to the integral term, while the buildup of activity is described by the term inside the parentheses, which is a function of decay rate as well as the duration of irradiation. The exponential nature of the term within parentheses shows that 50% of the maximum attainable activity is produced in one half-life of the isotope. Extending irradiation through another half-life produces only an extra 25%.

The terms in Eq. 2.18 that are independent of beam current and irradiation time describe a quantity commonly known as *saturation activity:*

$$S_a = \frac{N_A \rho}{M} \cdot \int_{E_i}^{E_{Th}} \frac{\sigma(E)}{(dE/dX)} dE \qquad (2.19)$$

This magnitude is a function of projectile incident energy and is usually expressed in units of [mCi/μA]. It includes all of the necessary information to calculate production yields for any given projectile/target combination. Another commonly used magnitude that describes the production process is the *yield (Y),* representing the slope at the origin from Eq. 2.18 and is defined as

$$Y = S_a \cdot \lambda_B \qquad (2.20)$$

Production of Radiopharmaceuticals

The higher resolution and sensitivity provided by PET as compared to SPECT as a consequence of the collinearity of the two 511-keV photons after an annihilation event are not the only advantageous characteristics of the technique. The short half-life of the radioisotopes being used results in lower overall radiation doses to the patient. Simultaneously, it allows the use of labeled drugs in concentrations so small so as not to overwhelm the biologic systems or compete with the normal metabolic function while remaining well below any toxic levels. As an example, a typical 15-mCi dose of ^{13}N-labeled ammonia routinely used for myocardial perfusion studies represents 13 pg of product, many orders of magnitude below what is considered a permissible safety level.

Since the introduction of PET as a research and clinical tool, ^{18}F has been the radioisotope most widely used because of its practical half-life of nearly 2 hours as compared to other tracers with half-lives of just a few minutes. The reaction of choice for the production of ^{18}F during the early stages of development was ^{20}Ne(d,α)^{18}F. After the introduction of the no-carrier added synthesis for 2-[^{18}F]-Fluoro-2-Deoxy-D-Glucose (FDG) in the mid 1980s by Hamacher et al. [1] , the production of ^{18}F using the reaction ^{18}O(p,n)^{18}F with highly enriched ^{18}O-water targets became the method of choice. Furthermore, it permitted proton-only machines with energies as low as 10 MeV to produce considerable amounts of ^{18}F. This rapid and highly efficient conversion method motivated equipment manufacturers to offer remote and automated equipment for the synthesis of FDG. Second- or even third-generation synthesis boxes can produce single, double, or up to four batches of FDG with a single setup. Decay-corrected radiochemical yields (conversion efficiency from ^{18}F into FDG) as high as 75–80% are routinely achieved. Preventive maintenance programs combined with proper personnel training have improved equipment reliability to better than 98%. Some FDG production equipment permits, through software reconfiguration, modification of the system to process other compounds.

^{15}O demands that the location of the camera facility be not more than a few hundred meters from the production facility. Proton-only machines require use of the enriched isotope ^{15}N as target material through the ^{15}N(p,n)^{15}O reaction. Given the high cost of the starting material, provisions to recover the enriched isotope should be implemented, if not supplied, by the cyclotron manufacturer. Facilities where deuterons are available can take advantage of the ^{14}N(d,n)^{15}O reaction without recycling the target. Rapid processing of the radioisotope

transforms the target product into ^{15}O-water, $^{15}O\text{-}O_2$, or $C^{15}O$ depending on the application.

Production of ^{13}N and simultaneous conversion to ^{13}N-ammonia is commonly achieved inside the target followed by a quick and efficient purification step through a disposable cartridge to remove potential contaminants (mainly traces of ^{18}F and metal ions from the target foil). Use of this tracer is limited to in-house production or distribution from a production facility within a relatively short distance.

Large amounts of C11 can be produced even with modest energy cyclotrons through the $^{14}N(p,\alpha)^{11}C$ reaction. Several commercial units permit rapid and efficient methylation of the target product (typically in the form of $^{11}CO_2$) as the precursor step for the radiolabeling of any number of compounds.

In general, a good number of other PET tracers can also be produced using enriched target materials at the low-energy end of commercial cyclotrons, with the option of in some cases using natural targets as the cyclotron energy is increased or when deuterons are available. Depending on the specific program requirements for one or several radioisotopes, a detailed analysis of different production routes, cost analysis of recovery processes in the case of enriched target materials, and an analysis of potential by-product impurities should be conducted prior to deciding on a particular cyclotron.

Facility Design

During planning and design of a particular facility, local and federal regulations for production of radiopharmaceuticals should be considered to ensure compliance and also to minimize the risk of potentially expensive upgrades or retrofit of the facility at a later time. Furthermore, current Good Manufacturing Practice guidelines and regulations should be firmly implemented together with a strong training and enforcement program to assure product safety and quality as well as adherence to the ALARA (as low as reasonably achievable) concept to minimize radiation exposure to production personnel and the public in general. Cyclotron manufacturers provide assistance with facility design and planning, but their responsibility is typically limited to issues related to machine installation and commissioning. In the case of self-shielded cyclotrons, radiation levels outside the shields and within some distance as promised by the manufacturer should be incorporated as part of the machine acceptance criteria. This acceptance test should be conducted at maximum machine output during irradiation conditions that maximize production of γ-rays and neutrons.

A health or medical physicist or other qualified professional should be consulted during design stages to address whether (or not) to install the cyclotron in a vault to evaluate the overall radiation shielding issues of fire and air conditioning, ventilation, air flow patterns, and exhaust monitoring. Personnel access and circulation through restricted areas should also be considered. Most facilities have adopted the criteria of keeping the vault or room where the cyclotron is located at negative pressure relative to the room where radioisotope processing occurs. The isotope production room, where the hot cells are typically installed, is also kept at negative pressure from the surrounding area for radiation safety reasons.

Reference

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