Cyclotrons & Radiochemistry

David Stout PhD

Topics

- **Cyclotrons:** How to accelerate protons
- **Cyclotrons:** Targetry, making radioactive atoms
- **Radiochemistry:** Half-life limitations, Chemistry in a box
- **Safety:** Radioactive, chemical, electrical, mechanical issues
- **Operational Consideration:** logs, stack monitoring, usage, transfer records, access & personnel
- **Visual Tour:** Installation & systems

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- **Cyclotrons:** How to accelerate protons
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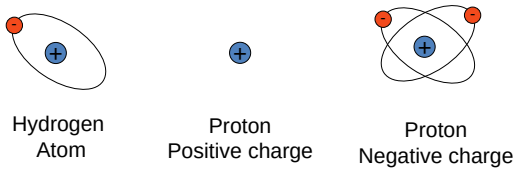
Cyclotrons: General Info

- Cyclotrons accelerate ionized particles to high speed (energy) and bombard target materials to add or remove protons and/or neutrons to create radioactive isotopes from stable non-radioactive atoms.
- Accelerated particles can be protons or combinations of protons and neutrons, essentially the nucleus of various atoms. Must have a charge to accelerate.
- Our Crump cyclotron is a Siemens RDS (Radiochemistry Delivery System) Eclipse RD (RDS 111 or Deep Valley), which accelerates only negative ion protons.

Cyclotrons: General Info

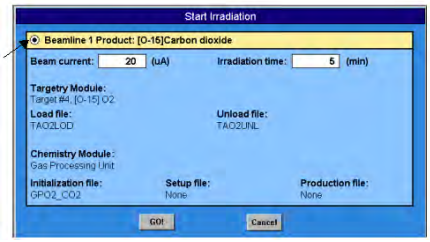


- Most but not all cyclotrons are used to accelerate protons.
- Both positive ion p+ protons or negative ion p- protons, consisting of a plasma gas where two electrons associate with each proton, can be accelerated.
- Must have a charged ion to accelerate in a magnetic field

Cyclotrons: General Info

- Positive ion cyclotrons
  - Easy to make p+ ions, easy to steer
  - Extract beam using a septum that deflects protons, which becomes highly activated. Harder to control beam extraction
  - Many parts become highly radioactive
- Negative ion machines
  - Harder to create negative ion protons
  - Easy to destroy ions, requires good vacuum
  - Fewer and lower level activation of internal parts, reducing dose to personnel servicing the systems

Cyclotrons: General Info



- Modern cyclotrons are highly computer controlled. Software controls all operations, including power, cooling, loading and unloading targets.
- Cyclotrons require considerable electrical power, chilled water, ventilation, drainage and skilled personnel to operate.
- Equipment is dangerous and has electrical, radioactive and mechanical safety hazards.

Cyclotrons: General Info

Four systems are necessary to create a proton beam capable of creating radioactive atoms:

- **Vacuum**: Required to allow high radio frequency power without arcing, keep ions from hitting other particles, keep beam focused
- **Ion Source**: Produces protons for acceleration
- **Acceleration Force**: Alternating Radio Frequency (RF) used to pull/push ions to higher velocities within a magnetic field that contains the ions
- **Beam Control**: Required to focus, steer and deliver the ions to a designated target

Cyclotrons: Vacuum

- Particles can only be accelerated inside a relatively high vacuum.
- Vacuum units we use are Torr, for the Italian scientist Torriceli. Room pressure is ~760 Torr, which equated to 760 mm of Hg (mercury)
- A mechanical vacuum pump brings the cyclotron tank from room pressure (1 Torr) to ~1x10-3 Torr.
- High vacuum diffusion pumps (DPs) bring the vacuum down to ~10-7 or 10-8. These pumps operate at ~220C, thus are very hot. They require chilled water to cool the outside and precipitate molecules entrained in a stream of recirculation hot oil.
- The mechanical pump runs continuously to evacuate the DP exhaust.

Cyclotrons: Rough Vacuum

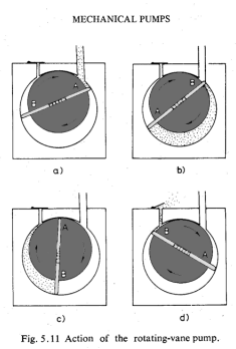


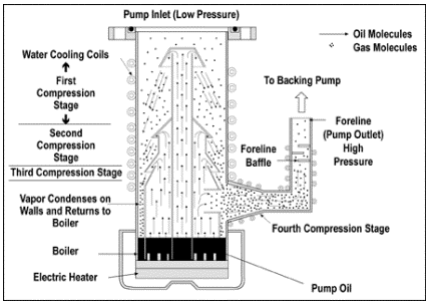
Fig. 5.11 Action of the rotating-vane pump.

- Our cyclotron has two mechanical or roughing (low) vacuum pumps: a main roughing pump that runs continuously and a small pump used occasionally for evacuating targets and the helium cooling system.
- These pumps must be checked at least weekly for oil level. They are located inside the shields and under the main cyclotron tank. A small mirror on a stick is useful to see the oil level window, as the pumps are heavy and hard to move.

Cyclotrons: High Vacuum

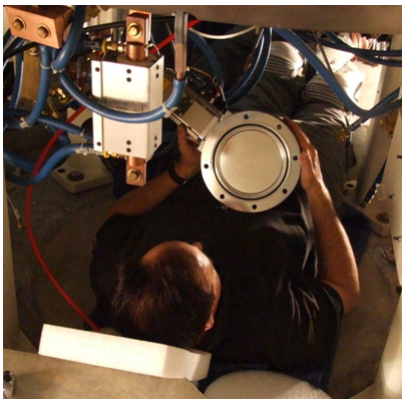
- High vacuum is necessary to prevent negative ion protons from hitting or interacting with other atoms. This would diffuse the beam, make parts more radioactive and reduce the performance.
- Required to enable radio frequency oscillation at high voltages without arcing, known as crowbarring.
- Entire tank and all components must be sealed without leaks. Even a small leak will cause considerable problems and parts may prematurely burn up.
- Materials cannot outgas or emit contaminants.
- Water, oils, grease and solvents will cause poor vacuum and can lead to excessive arcing and sparking.

Cyclotrons: High Vacuum



The RDS has 3 diffusion pumps to create high vacuum. They are run continuously and require about 3 gallons/min of chilled water to keep cool enough for operation. Loss of chilled water will close an interlock and turn off the pumps.

Cyclotrons: High Vacuum



Butterfly valves are located between the DPs and the main tank, allowing the tank to be isolated for servicing while the DPs remain operational. This saves ~2 hours to recover vacuum after opening the tank. Also keeps things from falling into the DPs when servicing.

Cyclotrons: High Vacuum

Display on electrical cabinet showing ion gauge vacuum meter and schematic for the vacuum system. All lights should be green for operations, with 10-7 for main tank vacuum and 10-3 for foreline DP pressure. When ion source gas is on, pressure goes up to 10-6.

Cyclotrons: Chilled Water

- Chilled water is required to cool the DPs, magnet, ion source and power supplies.
- When on shutdown with only DPs running, our building supply of 3 GPM is sufficient.
- For operation, we must turn on the booster pump and raise the flow to 10 GPM. Flow must be verified before operation.
- Air hammer arrestor is essential to prevent blowing out seals and breaking hoses and housings.

Cyclotrons: Chilled Water

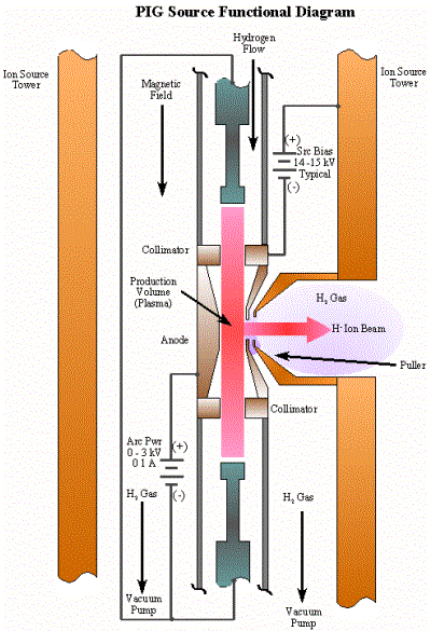
- The building supplied chilled water cools a secondary recirculating deionized chilled water system that runs inside the electronics cabinets, ion source, main magnet and DPs.
- The chilled water systems are located on the right side of the cyclotron. Consists primarily of a pump, make-up water tank and deionization filter.

Cyclotrons: Ion Source

- The RDS cyclotrons use a Penning Ion Gauge source, known as a PIG, that sits vertically into the top of the main tank
- Ion source creates the negatively charged protons.
- Source sits in a very specific location since the ions must be emitted in a precise location for acceleration
- Source can be steered automatically by software using motors to align the beam
- One DP is located directly underneath to remove the hydrogen gas
- Must be cleaned and rebuilt on a routine basis, thus designed for easy insertion and removal

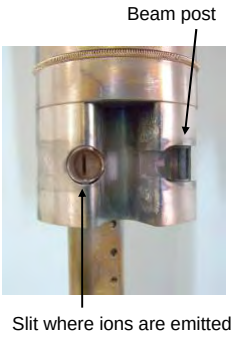
Cyclotrons: Ion Source

- A stream of hydrogen gas flows across an energized anode, creating a plasma (red).
- The ion source bias voltage pulls out negatively charged ions, where they enter the magnetic field and radio frequency to be accelerated (purple cloud).
- Control over beam current is primarily modulated by bias power, though gas flow and IS power can also be regulated.

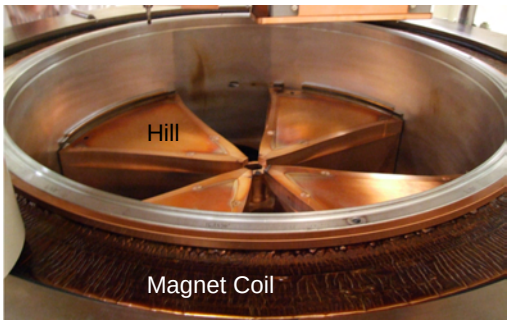


Cyclotrons: Ion Source

- Beam intensity is measured in Amps. Our Eclipse RD (Research Design) system can operate up to 40 microAmps (uA) on target. This is primarily determined by target cooling, since the ion source can produce well over 80 uA.
- A similar RDS cyclotron, Eclipse HP, is designed for high production and can operate up to 60 uA or higher. It uses larger targets, different target cooling and has more shielding.
- Our cyclotron is a RD, but has the HP shields, thus we have more radiation protection and could upgrade to HP in the future.

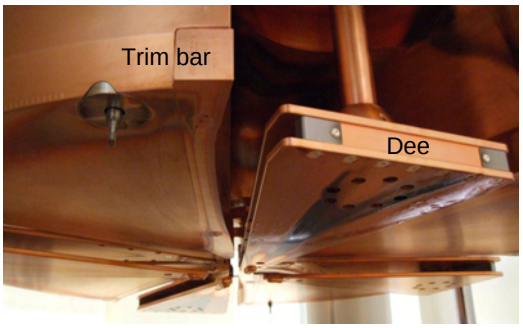


Cyclotron Tank



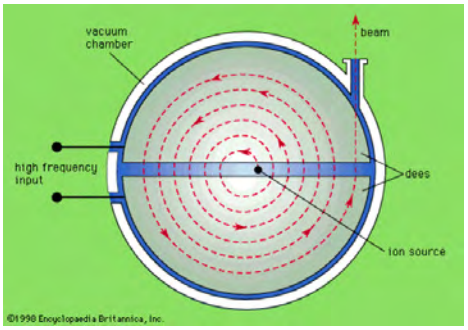
- The main vacuum tank is surrounded by a water cooled electromagnet that pushes the ions inwards as they orbit.
- Inside are a series of 4 pie shaped wedges and gaps, called hills and valleys. Older cyclotrons had only two, which looked like the capital letter D. From this shape, the term Dees originated and is still used today.
- Tank is maintained at high vacuum continuously. Performance is best when the tank is closed and under high vacuum.
- Two seals are used on the tank, one for RF, another for vacuum.

Cyclotron Tank



- Dees are located between the hills and are pulsed with radio frequency to accelerate the ions. Acceleration occurs between the hill and Dee (pulling), and again on the backside between the Dee and hill (pushing). With 4 Dees, the beam is accelerated 8 times per orbit.
- Special trim bars are located on the leading and trailing edge of each Dee and are very critically aligned. These bars help focus the beam and keep the particles moving together.

Cyclotron Tank

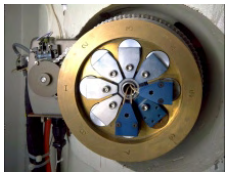


- Negative ions are accelerated as they exit the ion source, and are bent counterclockwise by the magnetic field. They spiral outwards with each revolution.
- RF causes the ions to bunch up into packets. Since the RF is pulsed and is present everywhere in the tank, the ions all travel together like spokes on the wheel of a bicycle. This is called isochronous motion.
- Since the time is the same for each orbit, but the distance increases as the ions move away from the source, the ions gain energy. At the outside orbit, they are traveling close to 18% of the speed of light .

Cyclotron Energy

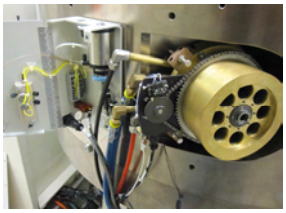
- The energy of the protons is determined by the number of orbits, thus the size of the tank, magnetic field and RF are all factors.
- RDS systems orbit ~80 times before extracting the beam and has a final energy of 11 MeV (11 million electron volts).
- The amount of power placed on target is up to 440 Watts (11 MeV times 40 uA). For HP systems, this goes up to 660 Watts.
- Radioactive field inside is over 500 REM, which is lethal. Shielding is essential and should not be bypassed.
- Older cyclotrons had 2 RF oscillators as opposed to 1, so they were called RDS 112 (11 MeV, dual oscillator) versus the current systems that are formerly called RDS 111.

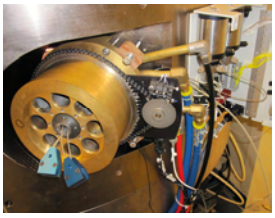
Cyclotron Beam Extraction



- Beam is extracted by passing through a graphite stripper foil. This removes the electrons, changing the polarity of the ion from negative to positive (bare proton).
- Since the magnetic field remains, reversing the polarity cause the proton to arc clockwise, thus outwards away from the tank.
- A beam port is located where the ions pass outside the tank, through a vacuum foil, helium cooling plenum, target foil and into the target material.
- Outside the beam port, a target carousel is located that can hold up to 6 targets. It rotates like a revolver to beam one target at a time.

Cyclotron Dual Beam Extraction





- RDS cyclotrons usually have two beam ports, thus it is possible to have 2 target carousels and up to 12 targets.
- The extraction foils need to be carefully controlled to enable splitting the beam, so both carousels can be irradiated at the same time. This is known as dual beam.
- Each extraction carousel has 4 positions, 3 with foils and one for bypass
- Dual beam operations require more time to get beam stable on target (~15 min), since the software must tune the beam on each target.

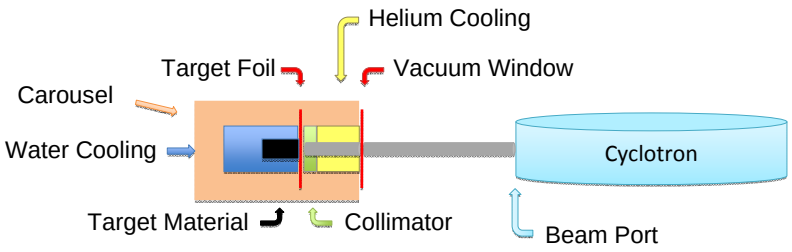
Cyclotron Beam Control

- The ions in the tank must be carefully controlled to properly accelerate them and keep them from hitting the internal components.
- The amount of ions can be controlled by the ion source bias.
- The speed of their orbit is controlled by both the magnetic field and RF.
- The extraction onto the target is controlled by stepper motor control of the extraction foils, which can be fine tuned during bombardment.
- Foils are nominally at 90, 180 and 270 degrees, with 0 is the pass position

Cyclotron Beam Control

- When coming from the tank, the beam passes through a water cooled collimator. This minimizes the power placed into the target body and keeps the beam centered on the target.
- The collimator and target carousel are electrically isolated, so that the current generated by the beam can be measured.
- The ratio of current on collimator versus target is the transmission percentage, which should be in the 75-85% range.
- Too high a transmission means the beam is tightly focused and could cause localized foil overheating , leading to rupture, called 'blowing the foil'.

Schematic of Beam Line



Topics

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Unshielded TSU

Target Support Unit located outside the cyclotron shields on the electrical cabinet

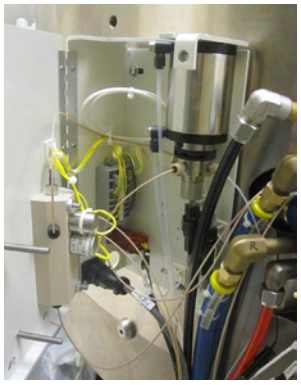
Consists of valves, pumps, target materials

Shielded TSU

A second set of Target Support Units (TSU) are located under the cyclotron on the support post for the tank

Primarily valves and circuit wiring needed to load and unload targets

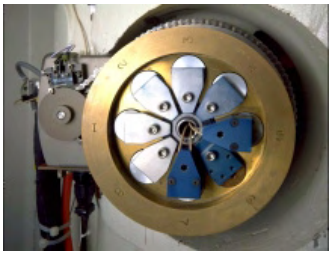
F-18 Shielded TSU



For making F-18 using O-18 water, the TSU is located very close to the target to minimize the tubing length. The unit is primarily a set of valves for both liquid filling and unloading and for gas pressurization and delivery.

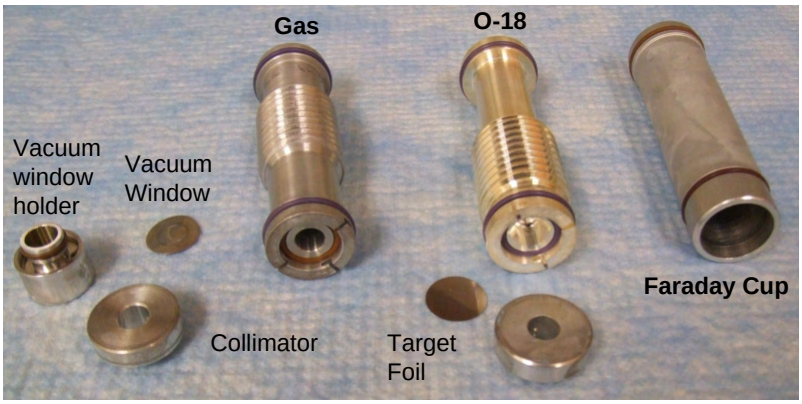
Target Carousel

- Holds up to 6 targets
- At least 2 spaces for faraday cups
- Rotates up to 315°
- Fill/Delivery lines feed through center
- Chilled water flows around target inserts



Target carousel

Target Types



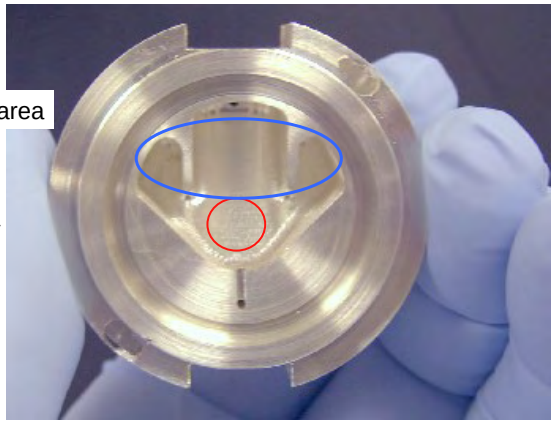
We have 3 target options; gas, O-18 and Faraday cups. The cup is used to fill unneeded target locations in the carousel and as a location where beam testing can be done without damaging gas or O-18 targets.

High Power Target Body

Argon gas for pressurizing and delivery push gas added through top port

Gas expansion area

Beam strike area



Target filled and emptied through bottom port

Atomic Numbering

Nucleus is composed of two particles (nucleons)

- Proton – positively charged
- Neutron – not charged

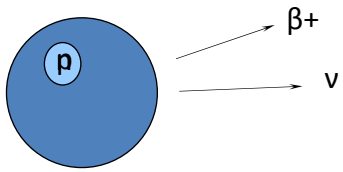
The number of protons determines the element

The total of neutrons and protons determines the mass

Name	Number of protons	Number of neutrons	Total number of nucleons
F-19	9	10	19
O-18	8	10	18
F-18	9	9	18

Positron Emitting Isotopes

- β+ (positron) emission
  - A proton in the nucleus is converted into a neutron, a positron (antimatter electron) and a neutrino
  - F-18 (9 protons, 9 neutrons) decays to O-18 (8 protons, 10 neutrons)
  - Also written ^{18}F



Isotope Decay Units

- The units of decay rate are Curies or Becquerels
- One Curie is 3.7×10^{10} decays per second
- The Becquerel is one decay per second
- One Curie is 37 Giga-Becquerels
- This is the typical way that radioactivity is quantified
- **Note that this is the rate of decay, which is different from the total number of activated nuclei**

Half Life Decay

- There is a fixed probability of decay for each nucleus
- This results in a fixed fraction of the population decaying in a given time period (exponential decay)
- The time it takes for the decay rate to drop to half its value is called the *half-life*
- The decay rate at a given period of time can be calculated by

$$A(t) = A_0 \cdot e^{-0.693 \cdot t / t_{1/2}}$$

where:

- A_0 = decay rate at t = 0
- $t_{1/2}$ = half life (in same units as t)
- t = time since A_0 was measured (same units as $t_{1/2}$)

Common PET Isotopes

- Each radioisotope has a unique half-life.
- The four commonly used isotopes in PET and their half lives are:

Name	Half life
F-18	109.8 minutes
C-11	20.2 minutes
N-13	9.96 minutes
O-15	122 seconds

Isotope Production Nomenclature

Activation

- Stable nuclei can be bombarded with nucleons (neutrons or protons) or other nuclei to form activated nuclei
- This process is referred to as a *nuclear reaction*
- The nomenclature for nuclear reactions is

target nucleus (bombarding particle, recoiling particle) product nucleus

For example

$$^{18}O(p,n)^{18}F$$

means ^{18}O bombarded by protons, results in ^{18}F and a neutron

Production Yield

Production Limit

- As nuclear reactions takes place, the number of activated nuclei grows, as does the number undergoing decay
- The saturation activity is when the production rate equals decay
- Knowing the saturation activity one can calculate the expected activity at any time using the following equation:

$$A(t) = A_{sat}\left(1 - e^{-0.693 \times t/t_{1/2}}\right)$$

where:

- A_{sat} = Activity at saturation
- $t_{1/2}$ = half life (in same units as t)
- t = time since beginning of production (same units as $t_{1/2}$)

Number of Atoms

Total number of F-18 nuclei in 1 Ci:

$$A_0 \frac{t_{1/2}}{0.693} = 3.7e10 \text{ sec}^{-1} \frac{109.8 \text{ min} \times 60 \text{ sec}/\text{min}}{0.693}$$

= 3.5 x10^**14** atoms **352 trillion nuclei!**

Proton Generation Rate

Proton bombardment

- Protons have elemental charge = 1.6 x 10^{-19} Coulombs
- You can work out how many protons you have per microamp of beam current

$$amp = \frac{coulomb}{second}$$

$$1\mu amp = 10^{-6} \frac{coulomb}{second}$$

$$1\mu amp = 10^{-6} \frac{coulomb}{second} \cdot \frac{proton}{1.6 \times 10^{-19} coulomb}$$

$$= 6.25 \times 10^{12} \frac{proton}{second}$$

Number of Protons per F-18 Atom

Exercise: calculate total number of protons required to produce one F-18 nucleus

- Get number of F-18 nuclei produced per second from one microamp
- A good saturation activity for F-18 is 100 mCi/μA
- At saturation, decay and production are equal, so this is also an indication of production rate

$$100\frac{mCi}{\mu A}\cdot\frac{3.7\times10^{7}\,sec^{-1}}{mCi}=3.7\times10^{9}\,\frac{^{18}F}{second}$$

- We know number of protons per second in 1 microamp from previous slide

$$\frac{6.25\times10^{12}\,\frac{proton}{second}}{3.7\times10^{9}\,\frac{^{18}F}{second}}=1689\frac{proton}{^{18}F}$$

Other Reactions

During Bombardment

-**Nuclear reactions** (already looked at)

-**Ionization heating**

- Primary proton energy loss mechanism
- Secondary effects on material are the primary cause of stress to targets
  - Thermal expansion
  - Pressure increases
  - Temperature increases

-**Hot atom chemistry**

- Determines chemical form of the resulting nucleus and chemical environment of the target

Stopping Power: Bethe Equation

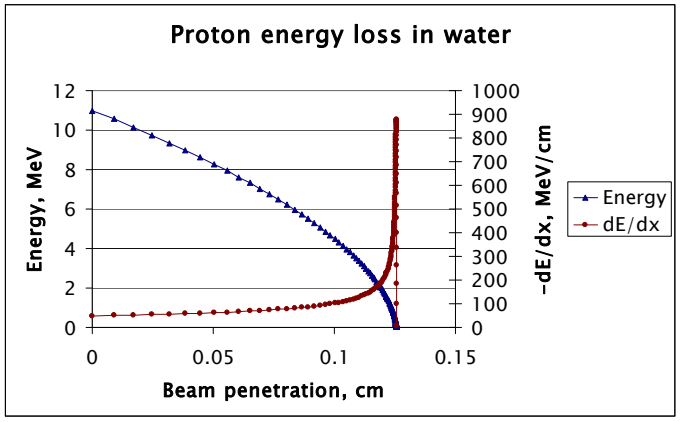
Bethe Stopping Power equation

$$-\frac{dE}{dx} = \frac{4 \cdot \pi \cdot e^4 \cdot z^2}{m_e \cdot v^2} \cdot N \cdot Z \cdot \ln\left(\frac{2 \cdot m_e \cdot v^2}{I}\right)$$

Where:

- N = number density of target atoms
- Z = average atomic number of target material
- z = charge of projectile
- m_e = electron mass
- v = projectile velocity

Stopping Power: Bethe Equation



Most protons stopped at 1.3 mm
Some go further since vapor bubbles form during bombardment

Heat Deposition

How much heat is being deposited in the target?

- Total heat deposited is current times energy (μA* MeV)
- Example: 11 MeV * 40 μA = 440 watts
- Maximum heat density (in the Bragg peak)
- Heat causes thermal expansion and pressure increase

$$850\ \frac{MeV}{cm} \cdot \frac{40\ \mu A}{0.5\ cm^2} = 68{,}000\ \frac{Watts}{cm^3}$$

Energetic Atoms

Hot atom chemistry

- The nuclear reaction must conserve momentum and energy
- Product radionuclide will have high energy (on the order of a few MeV) after the reaction, moving rapidly through the target medium, and will be highly ionized
- The medium will also be highly ionized
- The final chemical form of the product radionuclide is sensitive to:
  - Small contaminants
  - Wall materials
  - Dose rate (eV/molecule - minute)
  - Dose (eV/molecule)

Target Design Constraints

- Temperature
- Pressure
- Medium and phase (liquid water or hot gas)
- Chemistry
- Volume
- Lifetime
- Energy/yield

Targetry Support

Support equipment

- Small volumes, high pressures and low contamination
- Much of the equipment comes from HPLC
  - Capillary tubing
  - Chromatography valves (up to 1000 psig)
  - Pressure transducers
  - Syringe pumps
  - Diaphragm pumps
  - HPLC pumps

Fluoride Ion Production

Isotope: ^{18}F

Reaction: $^{18}O(p,n)^{18}F$

Chemical form: Fluoride ion (F-)

Target material: ^{18}O enriched water (argon overpressure)

Target volume: RD: 1.1 ml
HP: 2.3 ml

Target body: 99.99% pure silver or tantalum

Target window: .001" thick Havar (high strength Nickel-Cobalt alloy)

Typical pressure: RD: 650 psig beam off, ~800 psig beam on
HP: 340 –350 psig beam off, ~600 psig beam on

Carbon-11 Production

Isotope: ^{11}C

Reaction: $^{14}N(p,\alpha)^{11}C$

Chemical form: Carbon dioxide gas (CO_2) in Nitrogen gas (N_2)

Target material: unenriched Nitrogen gas with 2.5% O_2

Target volume: RD: 7 ml (120 std. cc)
HP: 9.5ml (~200 std. cc gas)

Target body: Aluminum

Target window: .001" thick Havar (high strength Nickel-Cobalt alloy)

Typical pressure: RD: 280 psig beam off, 900 psig beam on

HP ~ 300 psig load pressure

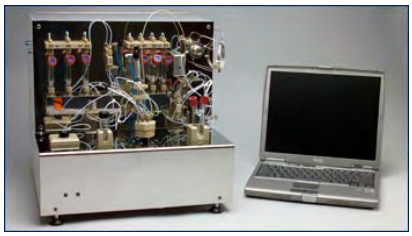
Topics

- **Cyclotrons:** How to accelerate protons
- **Cyclotrons:** Targetry, making radioactive atoms
- **Radiochemistry:** Half-life limitations, remote operations
- **Safety:** Radioactive, chemical, electrical, mechanical issues
- **Operational Consideration:** logs, stack monitoring, usage, transfer records, access & personnel
- **Visual Tour:** Installation & systems

Topics to cover

- O-18 recovery, QMA, volume
- Drying, precursors, reagent additions
- Remote operations
- Short reaction times, half life limitation
- Automated vs. manual
- Safety concerns; show how we design protection
- QC, HPLC, sterility, pyrogenicity, radiochem purity
- Handling radiation, measuring, dose calibrator
- GC/MS, analytical HPLC, TLC

Radiochemistry



Radiochemistry is a difficult task. Synthesis must be done typically in less than 2 hours or 3 half lives, whichever is shorter.

Automated, semi-automated and manual methods. For animals, small volumes with high specific activity are required.

Common Radioisotopes

radio-nuclide	decay mode	half-life	principal emission	production	application
^{3}H	β–	12.3 y	β–	reactor	autoradiography
^{11}C	β+	20.2 m	511 keV γ	cyclotron	PET
^{14}C	β–	5730 y	β–	reactor	autoradiography
^{18}F	β+	110 m	511 keV γ	cyclotron	PET
^{32}P	β–	14.3 d	β–	reactor	in situ hybridization
^{35}S	β–	87.9 d	β–	reactor	in situ hybridization
^{99m}Tc	I.T.	6 h	140 keV γ	generator	SPECT
^{111}In	E.C.	2.8 d	172/247 keV γ	cyclotron	SPECT
^{123}I	E.C.	13 h	159 keV γ	cyclotron	SPECT
^{125}I	E.C.	60.2 d	~30keV x-rays	reactor	SPECT
^{131}I	β–	8.1 d	364 keV γ	reactor	SPECT

The most common isotopes used in nuclear medicine are produced by reactors, generators or cyclotrons. These isotopes have a wide range of half lives and energies. Beta (-) emitters with short ranges are suited to autoradiography or in situ work. Beta (+) positron emitters are used in PET, while gamma emitters are most commonly used with SPECT imaging.

Positron Emitting Isotopes

Isotope	Half-life	β+ fraction	Max. Energy	Positron Range
C-11	20.4 min	0.99	0.96 MeV	0.4 mm
N-13	9.96 min	1.00	1.20 MeV	0.7 mm
O-15	123 sec	1.00	1.74 MeV	1.1 mm
F-18	110 min	0.97	0.63 MeV	0.3 mm
Na-22	2.6 years	0.90	0.55 MeV	0.3 mm
Cu-62	9.74 min	0.98	2.93 MeV	2.7 mm
Cu-64	12.7 hours	0.19	0.65 MeV	0.3 mm
Ga-68	68.3 min	0.88	1.90 MeV	1.2 mm
Rb-82	78 sec	0.96	3.15 MeV	2.8 mm
I-124	4.18 days	0.22	3.16 MeV	2.8 mm
Zr-89	3.27 days	0.23	0.90 MeV	1.2 mm

The most widely used isotopes for PET imaging are F-18, C-11, O-15 and N-13. These are produced in cyclotrons and used on-site or nearby due to the short half-life. Longer lived isotopes, such as I-124, Cu-64 and Na-22, are produced in reactors. Short lived isotopes like Rb-82 and Ga-68 are made using generators and must be used on site due to the very short half life.

UCLA Preclinical work uses mainly F-18, I-124, Cu-64, Zr-89 and Ga-68

Isotope Production

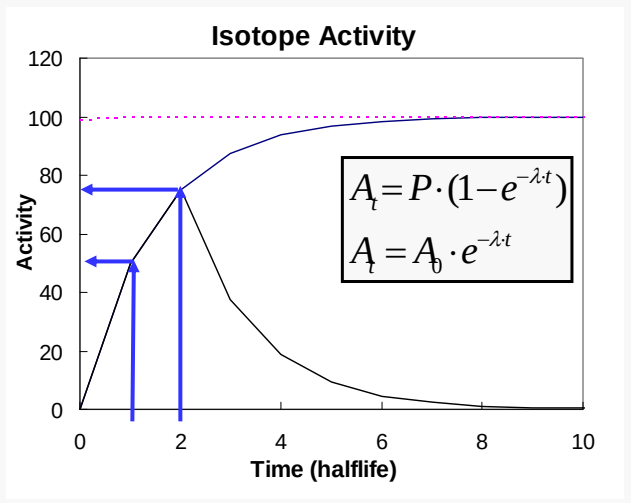
Because the most commonly used PET isotopes decay quickly, they need to be produced on demand using a cyclotron.

Production of the isotope is related to the half life, with decay starting at the moment of creation (t0), limiting the amount that can be produced

$$\frac{dN_2}{dt} = P - \lambda_2 \cdot N_2$$

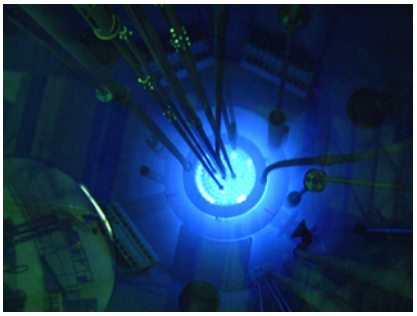
P: Isotope production rate (atoms/sec)
λ: Isotope decay constant (sec^{-1}) = ln(2)/half life
N: Number of isotope atoms present

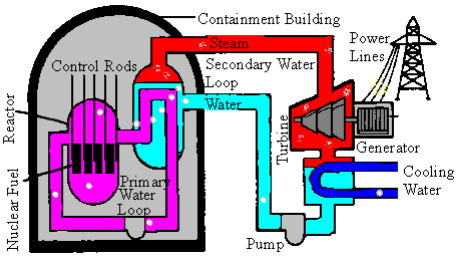
Isotope Buildup



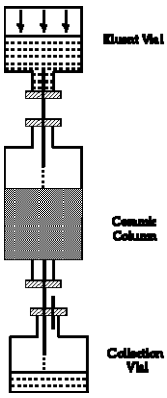
The activity at any given time, A_t, is a function of the number of atoms produced, P, and the decay rate, which is related to the half life. Production of the isotope falls off with the half life, as the newly produces atoms begin to decay. Once the cyclotron is turned off, production stops and decay follows exponential decay.

Reactors

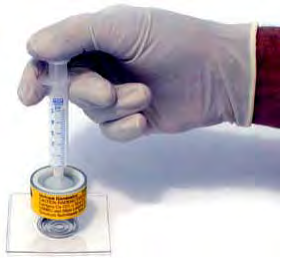




Nuclear reactors can be used to bombard target materials to create long lived isotopes that require higher energies than a cyclotron can produce. The target material often needs processing to remove the desired element from the non-radioactive materials. Isotopes such as tritium, C-14 and P-32 are produced using this method. These isotopes are often attached to specific molecules used for imaging research or may be locally combined to create imaging probes. A wide range of labeled compounds are available for purchase and shipment from several companies.



Generators



Generators operate by having a long lived isotope encapsulated in a solid matrix material. The daughter isotope has a shorter half life and is removed by flushing a solvent over the parent isotope. Common isotopes used in nuclear medicine produced this way include Tc-99 and Ga-68. Technetium is a common SPECT imaging isotope and many different reagent kits are available to create specific imaging probes using the generator.

Hot Cells & Radiochem Labs

Radioisotopes in either gas or liquid form are delivered from the cyclotron to a shielded hot cell in a radiochemistry lab through small bore plastic delivery lines. These lines are usually buried under concrete and shielded with lead to reduce exposure. The hot cells have ~7 cm of lead to shield the radiochemist from the gamma radiation. Prior to delivering the radioactivity, the chemistry synthesis box or apparatus are configured, reagents loaded, HPLC systems set up and the final product vial put in location for easy removal.

There are two standard types of hot cells commonly used for radiochemistry. The standard version is about 8-9' high and has a moveable shielded door to allow access for setting up synthesis equipment. The doors often have leaded glass windows for observing the interior of the cell. The smaller minicell design are often stacked with one above another and have a hinged door that opens outward and a tray the slides out for accessing the synthesis equipment. The minicells are usually used with automated radiochemistry synthesis boxes for routine productions, where access or visibility is not needed during a run.

At the end of the synthesis, there is a small side door on the standard units for retrieving the final product vial, or the door is cracked open on the minicells to retrieve the product vial. The activity is assayed and then sent to the imaging center or for shipping.

Radiochemistry Time Constraint

Radioisotope decay starts immediately after turning off the cyclotron bombardment, milking the generator or removing the product from the reactor, thus isotope creation to injection time should be minimized. The general rule of thumb is that the radiochemistry process should take no longer than 3 half lives. The table below gives these values for the most common PET isotopes.

Isotope	Half life	3x half life
F-18	109 min	5 hours
C-11	20 min	1 hour
N-13	10 min	30 min
O-15	2 min	6 min

The half life constraint is a challenge for O-15 and N-13. For simple methylations or other quick chemistry methods, C-11 can be used; however, it is not suitable for chemistry that requires long reaction times or purification steps. F-18 can be used for longer chemistry runs of several hours. The likely limitation for F-18 chemistry is not so much half life as one of throughput, since it may be necessary to use the personnel or equipment to make more than one product per day.

The production time includes the time to unload the cyclotron target, conduct the chemistry, purify the product into an injectable sterile solution, assay the activity and deliver the product to the site of usage.

Radioisotope Preparation

After all the steps (including chemistry), the isotope can be present in the following forms:

Carrier Free:

Only the radioactive form of the isotope is present, without the corresponding non-radioactive isotope

Carrier Added:

The non-radioactive isotope is added or present during the preparation

*Stable forms of the isotope are ***Carrier***

Carrier free reactions with F-18 are fairly simple, since the highly reactive fluorine atoms capable of chemical reactions (unbound) are not normally present in any significant quantity. Reactions with oxygen, nitrogen and carbon present a greater challenge, since reactive forms of these atoms are often present in quantity in the normal atmosphere. Special care and cleaning are required for carrier free work with these isotopes, particularly methylation reactions where radioactive CO_2 is used.

Specific Activity

Specific Activity (SA):

The activity concentration (in Bq/mol) of the isotope

A measure of the amount of radioactivity corresponding to the number of molecules

Example:

Carrier Free Specific Activity (CFSA) of ^{18}F

$$\frac{dN}{dt} = \lambda \cdot N(decays/\sec), \lambda = \frac{\ln 2}{t_{1/2}}(\sec^{-1})$$

$$6.023 \cdot 10^{23} atoms/mol$$

$$CFSA_{F-18} = \frac{\ln 2}{t_{1/2}} \cdot 6.023 \cdot 10^{23}(atoms/s/mol) = 0.634 \cdot 10^{20} Bq/mol$$

Specific Activity

In practice, typical values of specific activity at the end of chemistry are lower than CFSA:

FDG ~ 10^{17} Bq/mol (~3.3kCi/mmol)

FHBG ~ $5 \cdot 10^{16}$ Bq/mol (~1.4kCi/mmol)

What would be the specific activity at the end of a day (8hrs later)?

Since specific activity is related to the amount of radiation present, it goes down with time as the product decays. The shorter the half life, the faster the SA goes down with time. For this reason, C-11 can present some problems for multiple studies of neuroreceptors, where the amount of compound is important to the experimental conditions given the low number of neuroreceptors in vivo.

Specific Activity

For ^{18}F, the Specific Activity (SA) for FHBG 8 hrs after production is:

1.8 hr half life, 8 hours => 4.75% remaining
SA = 1.4kCi/mmol * 0.0475 = 66Ci/mmol

We typically require 0.2mCi for imaging, therefore we inject about 2nmol of FHBG in the whole mouse

For longer lived isotopes such as F-18, the SA decrease over time can still be substantial, but is less of a factor. In most cases, the amount of mass (number of molecules) is very small, since only small amounts of radiation are needed to follow in vivo processes.

To make effective use of time and resources, often it makes senses to use a production run to image as many subjects as possible. The difference in SA with sequential imaging is one reason some investigators image two or more animals at the same time. Where target locations are few, such as neuroreceptors, SA differences may create significant and unwanted differences in measurements. The choice of imaging two or more animals at once must be balanced against additional production run costs, available time, higher scatter and attenuation and the logistics of handling two separate animals at once.

Preparation Volume

The volume of preparation can be quite significant. In general it is only safe to inject less than 10% of the blood volume to prevent causing edema or other hemodynamic changes (250 uL in mice).

Typical FDG volume at end of chemistry 20cc, 800 mCi
Typical FHBG volume at end of chemistry 2cc, 20 mCi

Injection volume can be a more significant issue than specific activity when chemistry yields are low or too dilute.

What is the injected volume at the end of the day for 0.2mCi FHBG?

Noon concentration: 20mCi/2cc (10mCi/cc) = 20 uL
Evening, (8hrs later): (0.9mCi/cc) = 210 uL

A low radiochemistry yield can easily result in large volumes to maintain a specific radioactivity injection amount

Tracer concept

Definition:

"Compound whose concentration is so low that it does not disturb the measured system"

Typically much less than 10% of occupied receptors or endogenous competitive compound

Example: Total glucose in human body

C*V = 5mmol/L*70L = 350mmol = 70g

Tracer concentration: Less than 7g of sugar, or ~35 mmol

10mCi FDG = 10^{-7}M or 100 nmol

Tracer concept

Definition:

"Compound whose concentration is so low that it does not disturb the measured system"

Typically much less than 10% of occupied receptors or endogenous competitive compound

Example: Total glucose in human body

C*V = 5mmol/L*70L = 350mmol = 70g

Tracer concentration: Less than 7g of sugar, or ~35 mmol

10mCi FDG = 10^{-7}M or 100 nmol

A single can of soda contains ~39 grams of sugar

Tracer concept: Mouse

Definition:

"Compound whose concentration is so low that it does not disturb the measured system"

Typically much less than 10% of occupied receptors or endogenous competitive compound

Example: Total glucose in body

C*V = 5mmol/L*70L= 350mmol = 70g

in mice: 5 mmol/L*0.03L = 150 nmol = 150 mg

Tracer concentration: Less than 15 mg, or ~15 nmol

0.2mCi FDG = $2x10^{-9}$M or 2 nmol

Variety of Imaging Probes

A wide range of imaging probes have been developed for imaging with PET, including:

- **Fluoride Ion** for bone
- **FDG** glucose metabolism
- **FLT** DNA synthesis
- **NH3** Ammonia blood flow
- **FHBG** Gene Therapy marker
- Thymidine Kinase Inhibitors
- Numerous dopamine ligands; FESP, FDOPA
- Numerous other neurotransmitter ligands
- C-11 Acetate Prostate cancer
- Thousands more

Sterility & Pyrogenicity

Injections into humans and other research subjects need to be sterile and pyrogen free, otherwise they can cause adverse reactions and might alter the metabolic process under review.

Pyrogens are substances that cause an elevated temperature or fever. Temperature regulation is controlled by many substances, including cytokines (protein messengers) and tumor necrosis factors such as interleukins. Since these factors may be present in research animals as part of the process under investigation, thus it is important not to introduce additional factors that might change temperature and result in alterations of probe biodistribution and metabolism.

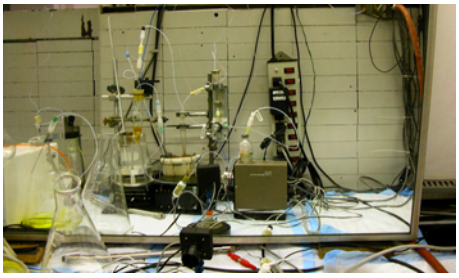
Sterility presents more of a long term problem. There may not be observable acute effects, however the imaging sessions conducted at later times, perhaps days or weeks later, might be adversely effected by unwanted infections and pathogens. This is a particular problem for immunocompromised animals commonly used to study human diseases.

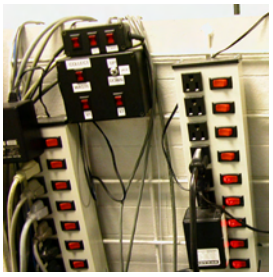
Careful design of the chemistry, so as not to introduce pyrogens in the final product, and passing the final product through a sterilizing filter are simple effective ways to control these two factors.

Radiochemistry Methods: Automated

Radiochemistry can be roughly grouped into three methods; automated, semi-automated and manual methods. Automated radiochemistry synthesis boxes, as shown above, are becoming increasingly prevalent and are now available from many companies. These boxes are suitable for fast, reproducible and routine productions. In most cases, they can also be programmed to explore research chemistry methods for new imaging probe production. Typically these boxes are set up in a dedicated location within a shielded hot cell and are not frequently moved.

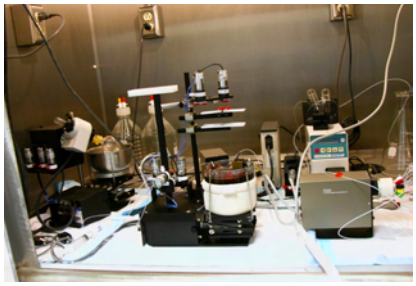
Radiochemistry Methods: Manual





A common method for experimenting with new radiochemistry techniques is to use manual movements of fluids and gasses. This is accomplished by using syringes to push or pull reactants and by turning on and off power switches to heating and cooling apparatus. Tongs and other remote manual handling devices might be used to transfer liquid transfer lines from waste to collection vials. This method is quite flexible and parts can be reconfigured and moved around to use with other synthesis experiments.

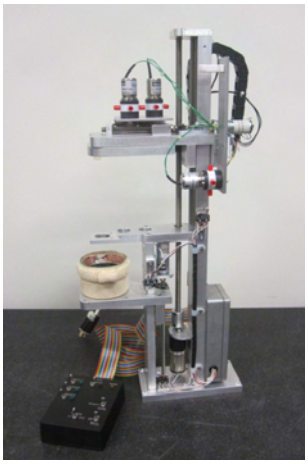
Radiochemistry Methods: Semi-Automated



For radiochemistry runs that are more routine or share parts in common with other synthesis runs, often semi-automated controls for reactions are created. These can include electrical switches to control values to deliver reactants, direct gas or liquid gas flows, control temperature. Computer monitoring of valve states and radioactivity locations, HPLC traces and controls to direct fluid flows might also be incorporated.

Often these semi-automated set-ups are dedicated to the production of a specific radiolabeled probe and are not frequently moved around.

Crump Radiochemistry System



- Semi-automated radiochemistry synthesis device
- Controlled via remote manual switches
- 3 Towers together used for FAC or other 3 pot synthesis
- Used in radiochemistry hot cells
- Designed and built in-house
- Reagent additions and transfers by syringe lines running outside hot cell

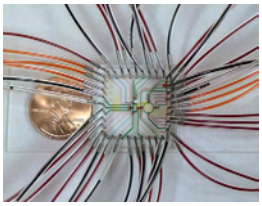
ELYXIS

- Disposable cartridge based radiochemistry system
- Wireless control via computer, iPad, etc.
- Heating, cooling, 3 pot synthesis
- Radiation sensors
- Hands-off automated system
- For use in radiochemistry hot cells

Delivery Methods

Once created, radiolabeled probes must be delivered to the site of use. Longer lived products, including F-18, can be placed in lead or tungsten shipping containers for transport to locations anywhere within 1-2 half lives (2-4 hours for F-18). For local in-house delivery and on-site use of short half live products, dollies for shipping containers or dose transport 'pigs' are often used. In some places, pneumatic tube systems are used to send small tubes (rabbits) containing unshielded activity in vials to nearby hot labs located within imaging centers. The tubes travel very quickly (~50 km/hr) and are a safe, fast and effective way to transport activity with little exposure to personnel or public. In rare cases, gas lines of small bore tubing may be run from the cyclotron or hot lab directly to the imaging center for on-site delivery of short half life isotopes produced in furnaces, such as CO2, O2 or carbon monoxide.

Radiochemistry of the Future



20 min?

Considerable effort is underway to reduce the demands on the radiochemists and open up new possibilities to produce radiolabeled probes quickly on site. At present, most radiochemistry is done on a fixed schedule due to the need to plan out production for multiple uses, arrange staffing times and for precursor synthesis and purification steps necessary right before synthesis. The goal is to move more towards probe synthesis and imaging on demand, to closer meet the needs of the biological community to image at the optimal times for the process.

Recent work in nanofludics has been promising, with synthesis times of 10-15 minutes and yields suitable for imaging several rodents with one run. The system shown above is about 2 cm square and is designed to be used with F-18 for producing FDG. Eventually the goal is to have several chip types with computer controlled synthesis to make a wide range of compounds as needed. This approach would require centralized F-18 production and delivery, but decentralized and site-specific synthesis of any compound desired.