

## Chapter 11

# POSITRON EMISSION TOMOGRAPHY (PET)

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## 11.1 INTRODUCTION

The Positron Emission Tomography (PET) nuclear technique (Fig.1) has wide-ranging research and clinical potential. The advantages over traditional nuclear medicine techniques are the biological aspects of the radioactive pharmaceuticals, which allow imaging of function in-vivo, as well as the increased sensitivity and accurate attenuation correction provided by the PET imaging modality.

In hospital settings, a cyclotron (Fig.2) is used to produce positron-emitting radioactive materials which, because of their short half-life, cannot be obtained from commercial sources. Of particular interest are the radioactive forms of biologically important elements such as oxygen, nitrogen, carbon and fluorine, which can be used to label a wide range of biochemicals.



Figure 1. Positron Emission Tomography (PET) scanner, Aberdeen University.

When the new radioactive biochemical is administered to a patient, the radiation emitted can be detected by a PET imager or positron camera (Fig. 3) to produce a three dimensional image of the distribution of the biochemical in the body.



Figure 2. Cyclotron for the production of the isotopes used in PET scanning.



Figure 3. Positron Camera at the University of Birmingham, UK.

## 11.2 THE PHYSICS OF PET

The concept of using radiolabelled pharmaceuticals for medical imaging is not new, and has been used in nuclear medicine departments for many years. The difference between PET and conventional nuclear medicine techniques lies in the type of radiation emitted.

In conventional nuclear medicine imaging, the radioactive substances used emit single gamma-rays. These are detected by a special camera with a heavy lead collimator attached. The collimator stops the camera detecting photons which are not perpendicular to the camera's face, so that those gamma-rays which are detected have a known direction. If the gamma-ray directions are known, images of the body can be built up.

In PET, the radioactive substances used emit positrons. A positron is the anti-matter equivalent of the electron, and will undergo an annihilation reaction with an electron after traveling just 1-2 mm in the body. In this type of annihilation reaction, two gamma-rays traveling in opposite directions are released.

The basis of PET is the detection of the gamma photons emitted when a positron, produced by the beta decay of an unstable nucleus tracer such as  $F^{18}$ ,  $C^{11}$ ,  $N^{13}$ , or  $O^{15}$ , annihilates with an electron. This annihilation occurs when the positron is essentially at rest, and conservation of energy and momentum then require that two 0.511 MeV photons are emitted back-to-back. Simultaneously detecting both photons defines a line, and the annihilation is assumed to have occurred somewhere along this line. In PET it is necessary to detect a large number of events from which the spatial distribution of the tracer can be inferred.

Positrons are emitted in the beta decay of nuclei which are proton rich. One proton is converted into a neutron, and a positron and a neutrino are emitted. Because of the three body nature of the decay, the emitted positrons have a range of kinetic energies. The energy distributions are shown below for the four radio nuclides most commonly used in PET.

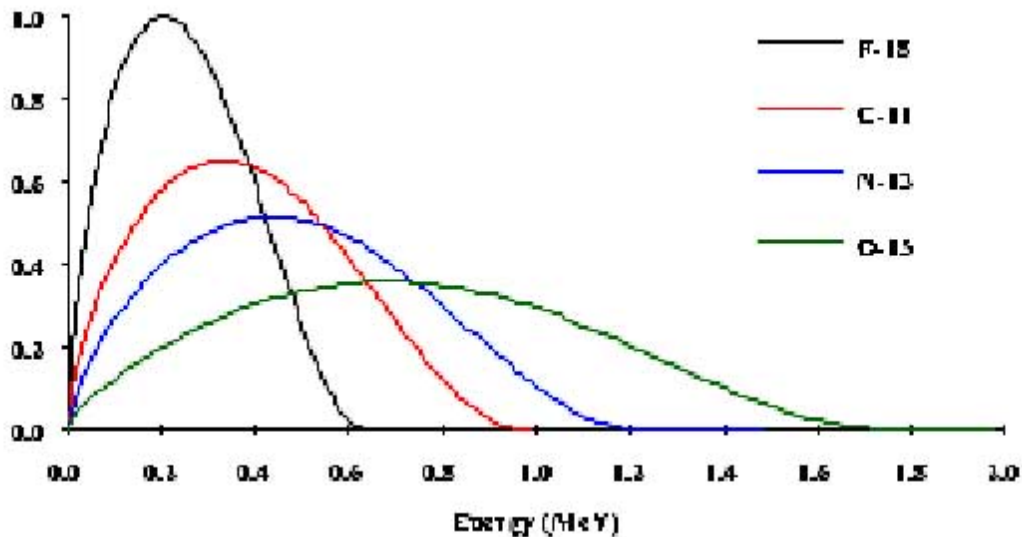


Figure 4. Normalized Energy Distribution of Positrons from Fluorine<sup>18</sup>, Carbon<sup>11</sup>, Nitrogen<sup>13</sup> and O<sup>15</sup>.

In a condensed medium such as a solid or a liquid, the emitted positron slows down to thermal energies in a few picoseconds ( $1 \text{ ps} = 10^{-12} \text{ sec}$ ), traveling up to 1mm and even less in a very dense medium. After a period in thermal equilibrium the positron

will annihilate with an electron usually into two 0.511 MeV gamma photons. The average lifetime for this is 100-500 ps dependent on the material characteristics.

Alternatively, in a molecular medium, the bound state of an electron and positron (positronium), may be formed during the slowing down process, in which case one would expect the decay to produce either two or three photons depending on the angular momentum of the bound state. However, the two gamma lifetime for the singlet parapositronium is 125 ps while the triplet orthopositronium has a three gamma lifetime of 142 ns, so that in practice most orthopositronium states convert to parapositronium and decay by two photon emission.

The kinetic energy of the annihilating electron positron pair, in practice that of the electron as the positron has slowed to thermal energies, leads to an acollinearity of the emitted photons in the laboratory frame of  $<1^\circ$ .

The resolution achievable by any PET imaging system is ultimately limited by the finite range of the positron prior to annihilation and the effect of the slight acollinearity of the two photons. If a pair of detectors separated by 50cm is used to detect the photons then the uncertainty in location arising from this acollinearity is around 1mm, comparable to the range of the emitted positrons. In practice, detector systems never achieve this level of precision. For PET, the best resolution achievable is around 5-8 mm.

PET scanning relies on the coincident detection of photons in two detectors. Pulses are considered to be coincident if they occur in two detectors within a specified resolving time  $t$  of each other. Because of this finite resolving time there is the possibility of two independent pulses occurring by chance so as to produce a *random coincidence*. The rate of random coincidences is given by:

$$R = 2t.R_1.R_2 \quad (1)$$

where  $R_1$  and  $R_2$  are the singles count rates in the individual detectors.

Thus the randoms rate is proportional to the square of the activity, and this may limit the activity which may usefully be imaged. For a point source mounted centrally between two identical detectors:

$$R = \frac{2\tau}{\varepsilon^2} (\text{Real Coincidences})^2 \quad (2)$$

where  $\varepsilon$  is the efficiency of each detector for detecting 511 keV photons.

As the real coincidence count rate increases, the proportion of randoms increases and eventually becomes unacceptable, and this is particularly serious when the efficiency of the detectors is low.

In principle it is possible to detect just the random coincidences by introducing a delay into one arm of the coincidence circuit, and these can then be subtracted from the full data. In many commercial PET systems randoms measurement is done in parallel with the normal data logging. Although in principle this enables an exact correction to be made for the presence of randoms, in practice because of limited statistics the quality of the data deteriorates dramatically once the number of random coincidences exceeds the number of real coincidences. The resolving time  $t$  is 7.5-12.5 ns. This is coupled with an efficiency of 7-23 percent.

Two other types of unwanted event may interfere with the data. Firstly, photons may be scattered prior to detection and hence arrive at the wrong point. Also, some positron emitting radionuclides such as  $\text{Na}^{22}$  and  $\text{I}^{124}$  emit gamma-rays in association with the beta decay, giving the possibility of detecting *associated gamma-ray coincidences* in which a gamma-ray is detected in coincidence with an annihilation photon (or another gamma-ray). Some PET systems employ collimating septa which block photons incident at large angles in an attempt to discriminate against unwanted coincidences.

### 11.3 POSITRON CAMERA

A PET camera consists of rings of detectors, which are electronically linked. If two of the detectors detect gamma rays at the same time, it is a good indication that an annihilation reaction took place somewhere on the line joining those two detectors. In this way directional information can be obtained without the need of a lead collimator, and gamma rays traveling in a whole range of directions can be used to build up the image. This makes PET many times more sensitive than conventional nuclear medicine techniques.

A Positron Camera is shown in Fig. 3 as a Forte dual-headed gamma camera manufactured by Adac Laboratories (California). It consists of two heads on a motorized gantry which permits rotation about a horizontal axis, and adjustment of the face-to-face separation of the detectors from 250 to 800mm.

Each head contains a single crystal of Sodium Iodide  $\text{NaI(Tl)}$  scintillator,  $500 \times 400 \text{mm}^2$  and 16mm thick, optically coupled to an array of 55 photomultiplier tubes (49 76mm tubes and 6 50mm tubes).

Whereas in a conventional gamma camera the photomultipliers are all interconnected via a network of resistors or capacitors to generate the positional signals, in this system each photomultiplier is connected to a separate ADC and a single board computer in the head controls the 55 ADC channels. When scintillation occurs in the crystal its centroid is determined via software; this is more flexible than an analogue circuit, resulting, for example, in less distortion near the edge of the crystal. The main benefit, however, is in count rate, since very fast pulses can be used and signals from different regions of the crystal can to some extent be processed in parallel, with the result that the dead-time per pulse is approximately 170ns and each head can operate at a singles rate of over 2M cps.

The detectors have an energy resolution of better than 15% (FWHM of the 511keV photopeak), sufficient to discriminate against photons scattered by more than  $30^\circ$ . The quantum efficiency of each head for detecting 511keV photons is approximately 23% (full spectrum) or 16% using just photopeak pulses, while the coincidence resolving time is 7.5ns. With a central point source, useful count rates of over 100k events/s can be achieved.

The spatial resolution of the camera (FWHM of the back projected image of a point source) is approximately 6mm. The data are recorded event by event on computer for subsequent processing.

### 11.4 RADIOCHEMISTRY

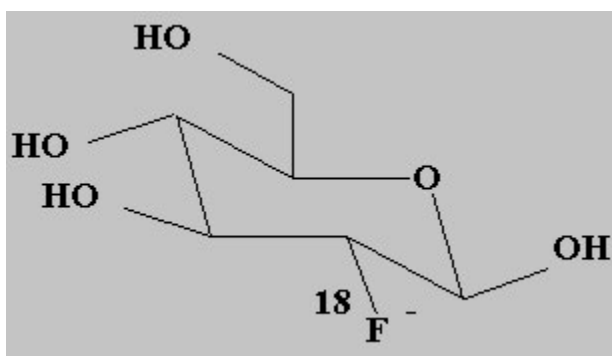
The positron-emitting substances most frequently used in PET are isotopes of carbon, nitrogen, oxygen and fluorine, which can be used to make chemicals similar to those naturally occurring in the human body. These radionuclides are all very short-lived, with half-lives ranging from approximately 2 minutes to 2 hours, and must be made in a cyclotron which generates the isotopes and make the radio-labelled pharmaceuticals needed.

The accelerator nuclear reaction using protons to produce the  $F^{18}$  isotope is:



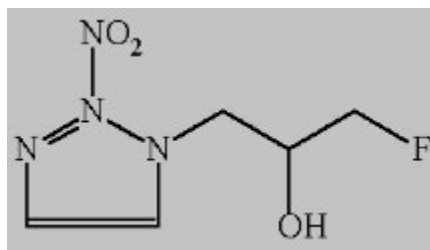
Radionuclide production In PET is oriented toward the safe production of tracers for routine clinical use. A high pressure water target for  $F^{18}$  production at an operating pressure of approximately 500 psi is normally used. The part of the Radioisotope Delivery System (RDS) is used with the chemical processing units help synthesize the following tracers.

### 2- $F^{18}$ Fluoro-2-deoxy-D-glucose (FDG)



$F^{18}$  fluorodeoxyglucose (FDG) is a glucose metabolism tracer. This is the most common tracer used at PET centers. The principle of nucleophilic substitution is used to synthesize the FDG, a process mediated by an aminopolyether. Enough FDG is normally produced to carry out approximately 6-7 patient scans per day.

### $F^{18}$ -Fluoromisonidazole



$F^{18}$ -Fluoromisonidazole (F-Miso) is a hypoxic agent which is metabolically trapped by viable cells according to their degree of hypoxia. The chemistry is mediated

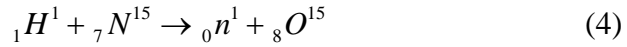
by Kryptofix 222 in a similar manner as that for FDG and involves nucleophilic substitution of the appropriate precursor.

### **F<sup>18</sup> Fluorine**

F<sup>18</sup> Fluoride is used for bone scanning studies. This is produced by direct bombardment of high purity O<sup>18</sup> water in a fluoride target and is produced in aqueous form.

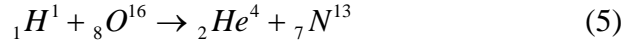
### **O<sup>15</sup> Water**

O<sup>15</sup> is used in blood flow studies. O<sup>15</sup> water is produced via the protons bombardment of N<sup>15</sup> gas; the O<sup>15</sup> gas is reduced, over a palladium catalyst, to the final product. The nuclear reaction is:

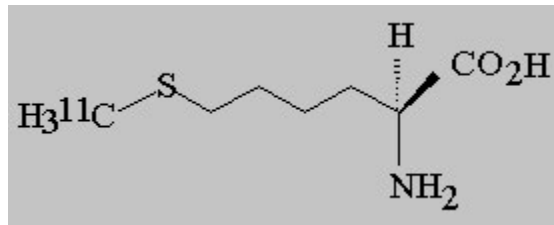


### **N<sup>13</sup> Ammonia**

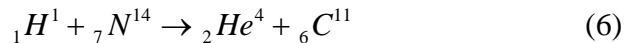
N<sup>13</sup> Ammonia is used in cardiac blood flow studies. This is produced by direct bombardment of O<sup>16</sup> water using a small amount of ethanol to scavenge for oxidizing radicals. The relevant nuclear reaction is:



### **[S-methyl-C<sup>11</sup>]-Methionine**

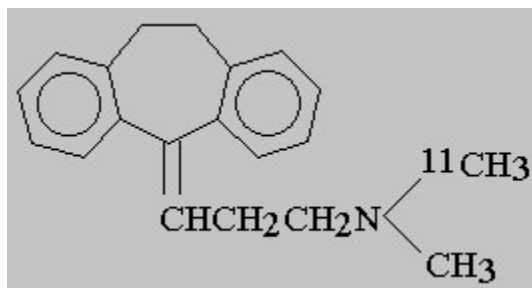


C<sup>11</sup>-Methionine an amino acid is being used to view protein synthesis in tumors. The synthesis takes place in a dedicated hot cell for C<sup>11</sup> tracer synthesis. C<sup>11</sup> carbon dioxide is produced by direct bombardment of N<sup>14</sup> gas according to the nuclear reaction:



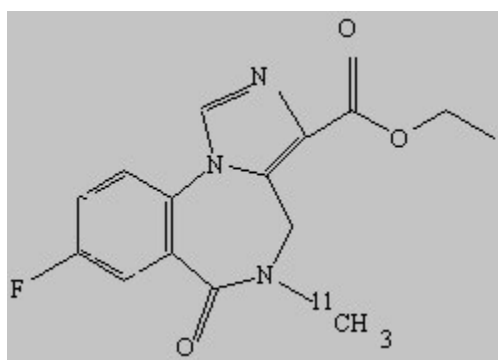
This is reduced to methyl iodide by reduction with lithium aluminum hydride and subsequent reaction with hydroiodic acid. Synthesis follows via reaction with the precursor L-homocysteine thiolactone and purification using preparative HPLC. The synthesis time including purification is 25 minutes resulting in [11C]-Methionine with a radiochemical purity > 99%.

### **C<sup>11</sup>-Amitriptyline**



C<sup>11</sup>-Amitriptyline is a tricyclic antidepressant. The synthesis takes place in a dedicated hot cell for C<sup>11</sup> tracer synthesis. C<sup>11</sup> carbon dioxide is produced by direct bombardment of N<sup>14</sup> gas; this is reduced to methyl iodide by reduction with lithium aluminum hydride and subsequent reaction with hydroiodic acid. Synthesis follows via reaction with the precursor nortriptyline hydrochloride and purification using preparative HPLC. The synthesis time including purification is 45 minutes resulting in C<sup>11</sup>-Amitriptyline with a radiochemical purity > 99% and average specific activity of 1Ci/mmol.

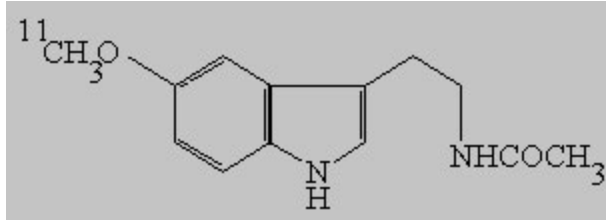
### **C<sup>11</sup>-Flumazenil**



C<sup>11</sup>-Flumazenil is a benzodiazepine receptor antagonist and is being used clinically to locate epileptic foci. The synthesis takes place in a dedicated hot cell for C<sup>11</sup> tracer synthesis. C<sup>11</sup> carbon dioxide is produced by direct bombardment of N<sup>14</sup> gas; this is reduced to methyl iodide by reduction with lithium aluminum hydride and subsequent reaction with hydroiodic acid. Synthesis follows via reaction with the precursor R0 15-5528 and purification using preparative HPLC. The synthesis time including purification is 45 minutes resulting in C<sup>11</sup>-Flumazenil with a radiochemical purity > 99% and average specific activity of 0.8 Ci/mmol.

### **C<sup>11</sup>-Melatonin**





Melatonin is a neurohormone secreted by the pineal gland. It is labeled with  $C^{11}$  for potential use *in vivo* using PET. The synthesis takes place in a dedicated hot cell for  $C^{11}$  tracer synthesis.  $C^{11}$  carbon dioxide is produced by direct bombardment of  $N^{14}$  gas; this is reduced to methyl iodide by reduction with lithium aluminum hydride and subsequent reaction with hydroiodic acid. The synthesis involves O-methylation of the precursor N-acetyl5hydroxytryptamine with  $C^{11}$ -Methyl iodide and purification using preparative HPLC. The synthesis time including purification is 25 minutes resulting in  $^{11}C$ -Melatonin with a radiochemical purity > 99% and average specific activity of 1.5 Ci/mmol.

## APPENDIX

### DECAY SCHEMES OF POSITRON EMITTERS

Parent state:

G.S.

Half life:

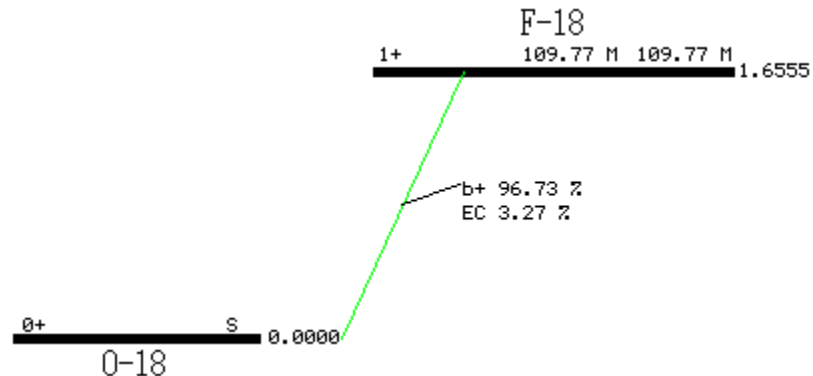
109.77 M(5)

Q(gs):

1655.50(63) keV

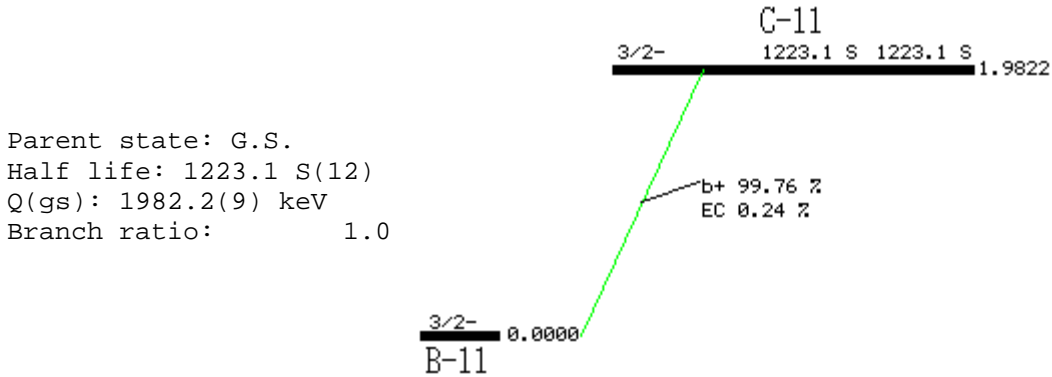
Branch ratio:

1



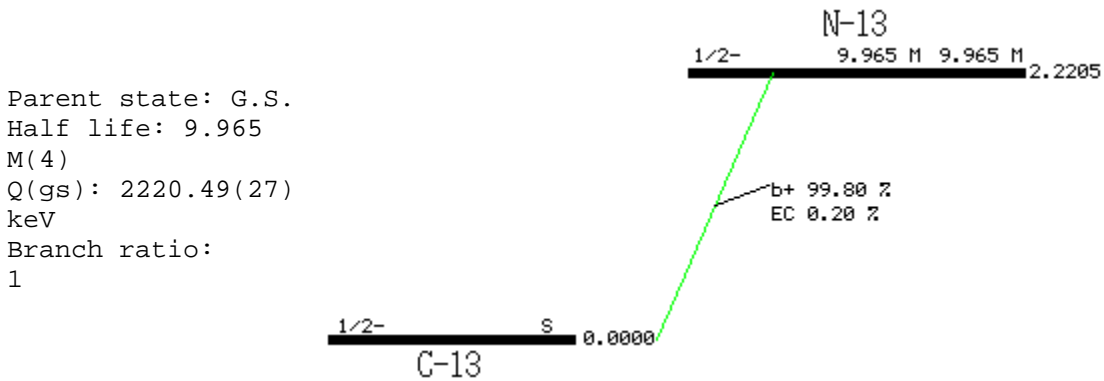
**Beta+ ray:** total intensity =96.7

Max.E(keV)	Avg.E(keV)	Intensity(rel)	Spin	
633.5( -)	249.8( 3)	96.73( 4)	1+	1+
			0+	0+



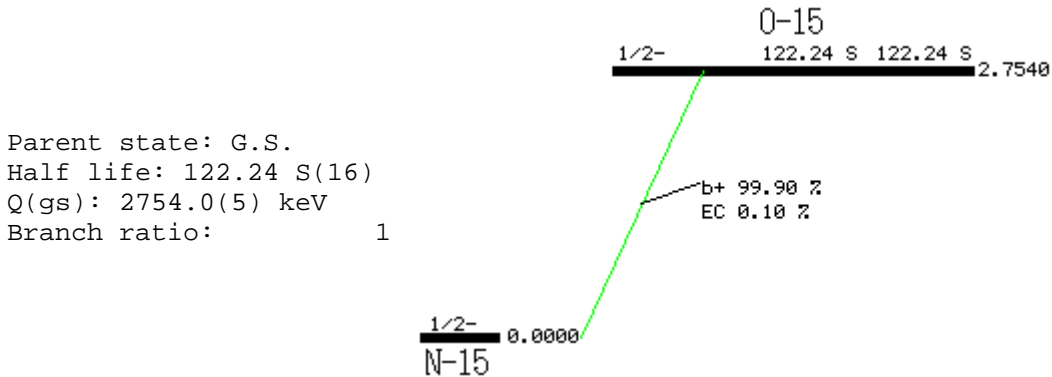
**Beta+ ray:** total intensity =99.8

Max.E(keV)	Avg.E(keV)	Intensity(rel)	Spin
960.2( -)	385.6( 4)	99.759(15)	3/2-
			3/2-



**Beta+ ray:** total intensity =99.8

Max.E(keV)	Avg.E(keV)	Intensity(rel)	Spin
1198.5( -)	491.82(12)	99.8036(20)	1/2-
			1/2-



**Beta+ ray:** total intensity =99.9

Max.E(keV)	Avg.E(keV)	Intensity(rel)	Spin
1732.0( -)	735.28(23)	99.9003(10)	1/2-
			1/2-

EC: total intensity = 1.0e-01

### 22NA B+ DECAY

Parent state:

G.S.

Half life:

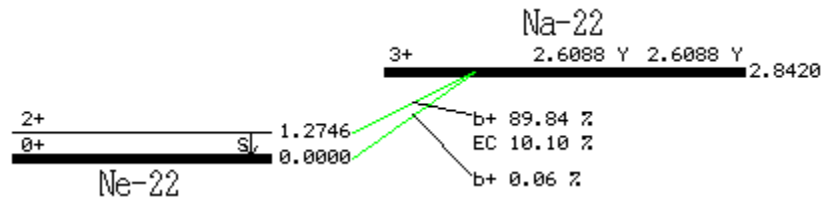
2.6088 Y(14)

Q(gs):

2842.0(5) keV

Branch ratio:

1.0



**Beta+ ray:** total intensity =89.9

Max.E(keV)	Avg.E(keV)	Intensity(rel)	Spin	
1820.0( -)	835.00(23)	0.056(14)		3+
545.4( -)	215.54(21)	89.84(10)		0+
				2+

**Gamma ray:**

Energy(keV)	Intensity(rel)
1274.53( 2)	99.944(14)