An Introduction to Positron Emission Tomography (PET)

LECTURE 1
Principles & Applications

Alan C. Spivey
a.c.spivey@imperial.ac.uk

Imperial College London

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Format & scope of lecture 1

• What is PET & what features does it have?
• Overview of the process of PET radiolabelling
• Generating the radioisotopes
• Incorporation of the radioisotope into the tracer - radiochemistry
  – Use of PET in drug development
• Decay of the tracer in the body and data collection
• Image generation and interpretation
  – Case study – [¹⁸F] FDG
What is PET imaging? - overview

- A very powerful medical imaging technique
- While magnetic resonance imaging (MRI) provides detailed information about anatomical changes, PET can image biological processes and the binding of drugs to targets
- PET can therefore detect biological abnormalities before there are anatomical defects, and has been very useful for the early diagnosis of disorders such as dementia
PET imaging – type of application

- **PET enables study of how the body uses substances such as glucose, ammonia, water and oxygen**
- **Can observe biochemical processes (physiology, unlike MRI), brain activity, blood flow in the heart**
- **Patient is injected with a radiolabelled bioactive compound, picomoles of tracer, providing 5 to 10 millicuries**
- **Proceeds to its site of action (receptor, membrane, enzyme)**
- **Binds to sites of action as an endogenous compound would**

![Chemical structures]

- **[¹¹C] methylspiperone**
- **[¹⁸F] FDG**
PET Imaging – unique features

- Use of $^{11}$C allows direct observation of target molecule
- High sensitivity ($10^{-10}$ – $10^{-12}$ M) – only nanograms / low micrograms of tracer required
- Possibility to rapidly translate from models to humans
- Imaging is quantitative, which helps with interpretation of image data

Hooker, Harvard Chem 156 course [URL]
**PET imaging – typical image output**

**$^{11}$C Labelling experiment** - Tracer is [$^{11}$C] methylPPEP which attaches to cannabinoid receptor 1 (CB1), a G coupled protein. Cannabinoid signalling in CNS not well understood but has a role in cognitive function.

*Human:* Barras *NeuroImage* 2014, 97, 151 [DOI]

*Monkey:* Yasuno *Neuropsychopharmacology* 2008, 33, 259 [DOI]
PET imaging - *importance in healthcare*

1. *Improves the treatment and diagnosis of disease*
2. *Accelerates the development of new drugs*
   - Micro-dosing allows fate of new drug candidates during development to be followed in early trials on humans (see later)

Consequently, there is demand from the market…

<table>
<thead>
<tr>
<th>Year</th>
<th>Number of procedures</th>
</tr>
</thead>
<tbody>
<tr>
<td>2001</td>
<td>280,000</td>
</tr>
<tr>
<td>2002</td>
<td>430,000</td>
</tr>
<tr>
<td>2003</td>
<td>666,000</td>
</tr>
<tr>
<td>2004</td>
<td>1 million</td>
</tr>
<tr>
<td>2010</td>
<td>3.2 million</td>
</tr>
</tbody>
</table>

**Sales of [¹⁸F] FDG**
- 2003 $ 202 million
- 2004 $ 240 million
- 2010 $ 795 million

![[¹⁸F] FDG](image)
PET imaging - logistics

The process of obtaining a PET image involves FOUR stages:

1. **Generation of a radioisotope (often using a cyclotron)**

2. **Use of rapid synthetic chemistry to incorporate radioisotope into a radiotracer molecule and then purification of the tracer molecule**

3. **Administration of the tracer molecule into the patient**

4. **Image collection and data analysis of location and concentration of the tracer**

\[ 1-2 \ t_{\frac{1}{2}} \quad <2 \ t_{\frac{1}{2}} \quad \text{fast!} \quad <4 \ t_{\frac{1}{2}} \]
PET imaging - logistics
PET imaging – *race against time!*

- **PET radioisotopes have short half-lives due to their radioactive decay**

Yields and levels of activity are ‘decay corrected’

Typical checkpoints include:

**End of bombardment (EOB)**
when generation of isotope is complete

**End of synthesis (EOS)**
when radioactive product is isolated

**Time of injection (TOI)**
when scanning starts
PET imaging – radiochemical calculations

• The activity of a radioisotope \( A \) after a time \( t \) is given by the equation:

\[
A(t) = A_0 e^{-\lambda t}
\]

• Where the decay constant \( \lambda \) is obtained from:

\[
\lambda = \ln 2 / t_{1/2}
\]

• Where \( t_{1/2} \) is the half-life of the radioisotope in question.

• So, if 1.65 GBq of an \([^{18}F] \) compound is prepared EOS, the amount of radioactivity present 3.5 hours after synthesis can be readily calculated:

\[
t_{1/2} \text{ for } ^{18}F = 110 \text{ (min)} \\
\lambda = \ln 2 / 110 = 6.301 \times 10^{-3} \\
A(t) = 1.65 \ e^{-6.301 \times 10^{-3} \times 210} \\
A(t) = 0.44 \text{ GBq or } 440 \text{ MBq}
\]
Overview of the PET technique

• When a radioactive isotope has an excess of protons in its nucleus – this causes instability, which leads to a spontaneous nuclear reaction involving release of a positively charged electron (a positron, $\beta^+$)

• A radiotracer labelled with a positron emitter is injected into the patient

• The radiotracer emits a positron which travels around 3 mm through tissue

• The positron annihilates with electrons in neighbouring atoms

• Two anti parallel gamma rays are produced which travel through tissue, exit the body and are picked up by the detector array which surrounds the patient

• The data is processed to regenerate a 3D ‘map’ of the origin of each annihilation event

Generating the radioisotope
Which radioisotopes emit positrons?

- Radioisotopes that spontaneously decay by loss of positrons are proton rich:

<table>
<thead>
<tr>
<th>Radionuclide</th>
<th>Half-life</th>
<th>Mode of decay</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{14}$C</td>
<td>6000 yr</td>
<td>$\beta^-$</td>
</tr>
<tr>
<td>$^3$H</td>
<td>12 yr</td>
<td>$\beta^-$</td>
</tr>
<tr>
<td>$^{32}$P</td>
<td>14 days</td>
<td>$\beta^-$</td>
</tr>
<tr>
<td>$^{90}$Y</td>
<td>64 hr</td>
<td>$\beta^-$</td>
</tr>
<tr>
<td>$^{67}$Cu</td>
<td>62 hr</td>
<td>$\beta^-, \gamma$</td>
</tr>
<tr>
<td>$^{47}$Sc</td>
<td>82 hr</td>
<td>$\beta^-, \gamma$</td>
</tr>
<tr>
<td>$^{188}$Re</td>
<td>17 hr</td>
<td>$\beta^-, \gamma$</td>
</tr>
<tr>
<td>$^{123}$I</td>
<td>13 hr</td>
<td>$\gamma$</td>
</tr>
<tr>
<td>$^{99m}$Tc</td>
<td>6 hr</td>
<td>$\gamma$</td>
</tr>
<tr>
<td>$^{11}$C</td>
<td>20 min</td>
<td>$\beta^+$</td>
</tr>
<tr>
<td>$^{13}$N</td>
<td>10 min</td>
<td>$\beta^+$</td>
</tr>
<tr>
<td>$^{15}$O</td>
<td>2 min</td>
<td>$\beta^+$</td>
</tr>
<tr>
<td>$^{19}$F</td>
<td>110 min</td>
<td>$\beta^+$</td>
</tr>
</tbody>
</table>

How do we generate radioisotopes? – *the cyclotron*

- **Invented by physicist Ernest Lawrence (University of California, Berkeley) in 1932**
- **Nobel Prize for Physics in 1939**
- **A circular-shaped particle accelerator that typically accelerates protons \( (_1^1H^+) \) but can also accelerate deuterons \( (_2^1H^+) \) and \( \alpha \)-particles \( (_4^2He^{2+}) \) and even hydride \( (_1^1H^-) \) and deuteride \( (_2^1H^-) \)**

The high energy protons are fired into a ‘target’ containing stable isotope precursor atoms, initiating a nuclear reaction to form the radioisotope and the concomitant ejection of a by-product particle (typically a neutron or \( \alpha \)-particle):

\[
_{18}O + p \rightarrow _{18}F + n
\]

is written in compact notation as \( _{18}O(p,n)_{18}F \)
The cyclotron – *the instrument*

1932 – Berkeley, California

Modern hospital cyclotron
\(^{18}\text{F}\) production via the \(^{18}\text{O}(p,n)^{18}\text{F}\) reaction

\[
^{18}\text{O} + \text{proton} \rightarrow \text{8 protons, 10 neutrons} \\
^{18}\text{F} + \text{neutron} \rightarrow \text{9 protons, 9 neutrons, 1 neutron}
\]
Characteristics of commonly used positron-emitters

<table>
<thead>
<tr>
<th>Radionuclide</th>
<th>Half-life</th>
<th>Chemical Form</th>
<th>Nuclear Reaction(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{11}\text{C}$</td>
<td>20 min</td>
<td>$^{11}\text{CO}_2 / ^{11}\text{CH}_4$</td>
<td>$^{14}\text{N(p,α)}^{11}\text{C}$</td>
</tr>
<tr>
<td>$^{13}\text{N}$</td>
<td>10 min</td>
<td>$^{13}\text{NH}_4^+ / ^{13}\text{NO}_x$</td>
<td>$^{16}\text{O(p,α)}^{13}\text{N}$</td>
</tr>
<tr>
<td>$^{15}\text{O}$</td>
<td>2 min</td>
<td>$^{15}\text{O}_2$</td>
<td>$^{15}\text{N(p,n)}^{15}\text{O}$</td>
</tr>
<tr>
<td>$^{18}\text{F}$</td>
<td>110 min</td>
<td>$^{18}\text{F}^- \text{ or } ^{18}\text{F}_2$</td>
<td>$^{18}\text{O(p,n)}^{18}\text{F}$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>$^{20}\text{Ne(d,α)}^{18}\text{F}$</td>
</tr>
</tbody>
</table>
Incorporating the isotope into a tracer (synthesis – see next lecture!)
Process of Isotopic Labelling for PET
'Chemistry’ vs ‘PET radiochemistry’

<table>
<thead>
<tr>
<th>Yield</th>
</tr>
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<tbody>
<tr>
<td>Purity</td>
</tr>
<tr>
<td>Chemical</td>
</tr>
<tr>
<td>Stereochemical</td>
</tr>
<tr>
<td>&gt; Millimolar scale</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Radiochemical Yield</th>
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</thead>
<tbody>
<tr>
<td>Purity</td>
</tr>
<tr>
<td>Chemical</td>
</tr>
<tr>
<td>Stereochemical</td>
</tr>
<tr>
<td>Radionuclidic</td>
</tr>
<tr>
<td>Radiochemical</td>
</tr>
<tr>
<td>Sub-micromolar scale</td>
</tr>
<tr>
<td>Time</td>
</tr>
<tr>
<td>Pharmaceutical quality</td>
</tr>
<tr>
<td>Radiation</td>
</tr>
</tbody>
</table>

NB. **radionuclidic purity** - the proportion of the total radioactivity that is present as a specific radionuclide.  
**radiochemical purity** - the proportion of the total activity of a specific radionuclide in a specific chemical form.
Dealing with radioactivity

How do you carry out a chemical reaction if your reactants and products are radioactive?

• **Rule 1.** don’t use your hands!

• **Rule 2.** use a robot – or automated system

• **Rule 3.** do it behind a lead shield to minimise radiation exposure

• **Rule 4.** work fast! Short-lived isotopes don’t hang around for long, so introduce PET isotope in the last synthetic step
Radiochemistry terms

1. Radiochemical yield (RCY):
   - A function of the chemical yield and the rate of decay
   - Radiochemists want to maximise RCY

2. Carrier added and no-carrier added:
   - The carrier is the stable isotope – this dilutes the radioactivity
   - The amount of carrier affects the ‘specific activity’
   - Generally, for a true tracer method we want high specific activity

3. Specific activity:
   - Radioactivity per unit mass (MBq μmol⁻¹)
The need for speed!

Chemical yield (fast reaction)
max. RCY (fast reaction)

Chemical yield (slow reaction)
Max. RCY (slow reaction)

RCY
Radioactive decay

Time
t1
t2
Drug development

- **High failure rate in developing new drugs**
  - Due to inappropriate metabolism and pharmacokinetics
  - Costs of $800-1000 million!
  - 10–12 years required to develop drug

- **What is needed?**
  - Faster identification of the best candidate molecules for clinical trials

- **Benefits to society – better drugs brought to market faster**
How can PET help in ‘smarter’ drug development?

Allow earlier trials on humans
- Ultra sensitivity PET, micro-dosing (~ 100 μg) studies
- Sub-pharmacological dose is administered (no efficacy or safety data are obtained)
- This will have no toxicological effects

The Drug Development Process:

Many models must be used to predict the way a potential drug will be absorbed and metabolised in vivo.

PET can follow the action of a potential drug in a human body with a small enough dose to eliminate pharmacological effect.

Potential drug candidates can be directly screened for activity in humans, allowing much earlier identification of suitable drug candidates.
Decay of the tracer in the body & data collection
Overview of the PET workflow
Positron emission - *annihilation*

- *Proton-rich isotopes may decay via positron emission, in which a proton in the nucleus decays to a neutron, a positron and a neutrino. The daughter isotope has an atomic number one less than the parent.*
- *As positrons travel through human tissue they give up their kinetic energy principally by Coulomb interactions with electrons. They follow a tortuous path through the tissue as they give up their kinetic energy before annihilation.*
- *When the positrons reach thermal energies, they start to interact with electrons typically by annihilation, which produces two 511 keV photons which are anti-parallel.*

For $^{18}$F the process is:

$$^{18}\text{F} \rightarrow ^{18}\text{O} + \beta^+ + \nu$$

(9 protons, 9 neutrons)

Where $\beta^+ = \text{positron}$

$\nu = \text{neutrino}$
• **The average distance travelled by the positron depends on its energy – this is determined by the radioisotope being used**
  – The lower the energy the shorter the distance travelled and so the higher the potential imaging resolution

Hooker, *Harvard Chem 156 course* [URL]
Image generation & interpretation
PET Imaging instruments
Coincidence detection

- In a PET camera, each detector generates a timed pulse when it registers an incident photon (γ ray). These pulses are then combined in coincidence circuitry, and if the pulses fall within a short time-window, they are deemed to be coincident.
- Subsequent electronic collimation and then tomography are used to generate a 3D image of the annihilation event locations.

http://depts.washington.edu/nucmed/IRL/pet_intro/intro_src/section2.html
Visualising 3D data in 2D

The 4^{th} dimension is (time) is referred to as a frame…
Case study – $[^{18}F]$ FDG

- **2-deoxy-2-$[^{18}F]$-fluoro-D-glucose**
  - Most widely used PET tracer in clinical use - ~23 min synthesis time
  - Visualises glucose metabolism in e.g. heart, lungs, brain…
  - Cancer cells have high metabolic activity and so ‘light-up’ with $[^{18}F]$ FDG
    - use for e.g. lung, colorectal, lymphoma, melanoma, head & neck cancer imaging
PET scan of a healthy patient

This is an $^{18}$F FDG scan of a healthy 70-year old patient.

The scan looks typical for the age with a good cortical signal (i.e. the outer rim of this transverse section through the brain).

http://www.insidestory.iop.org
Alzheimer’s disease (AD) is a condition where the brain gradually deteriorates, leading to changes in a person’s behaviour, as well as short term memory loss and cognitive impairment.

Brain imaging using PET can confirm a diagnosis as patient with AD will typically show a reduction in glucose use in the cerebral cortex – the thin, outermost layer of the brain responsible for complex brain functions e.g. memory, language and consciousness.
PET scan of a patient with a brain tumour

Brain tumours are areas of tissue where the cells have mutated and are replicating uncontrollably. Mutation can occur as a result of normal brain cells coming into contact with radiation or harmful chemicals, which damage the DNA of the cells.

PET scans can identify tumours because they use up more energy, and therefore glucose, than normal tissue. The FDG tracer occurs in higher quantities at the tumour site and this shows up as a bright area on the PET image.

http://www.insidestory.iop.org