CH4102/CH4107

Introduction to Medical Imaging

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Course Outline

Dates

- 8 lectures (2.3., 8.3., 9.3., 15.3., 16.3.)
- 1 tutorial (20.3.)

Assessment

- Exam paper: Chose 3 out of 4 questions (100 marks each)
- Example questions will be provided throughout the lectures and tutorial
Course Overview

1 Introduction
   1.1 Definition of Medical Imaging
   1.2 Radiation for Medical Imaging
   1.3 Definition of Imaging Terms

2 X-Ray
   2.1 X-Ray CT (CAT scans)
   2.2 Basic Physical Principles of X-Ray CT
   2.3 Interpreting X-Ray Radiographs
   2.4 Case studies

3 Nuclear Imaging
   3.1 Basic Principles of Nuclear Imaging
   3.2 SPECT
   3.3 PET
   3.4 Synthesis of Radiotracers

4 MRI
   4.1 Recap: Physical Principles of NMR
   4.3 MRI Contrast Agents
Teaching Material

All examinable material is covered in lectures and students are not required to acquire specialised text books.

The course is largely based on:


The Sprawls Resources for study, review, reference and teaching: physics and technology for effective and safe medical imaging; [www.sprawls.org/resources](http://www.sprawls.org/resources)

A full list of references is included at the end of the lecture slides.
1 Introduction

1.1 Definition of Medical Imaging

**Medical Imaging**: interaction of energy (radiation) with matter (patient) in non-invasive, painless technologies to view the interior of the human body in order to diagnose, monitor or treat medical conditions

**Classical Imaging**: direct manifestation of the interaction of radiation with tissue (qualitative)

**Modern Imaging**: reconstruction of the interaction of radiation with tissue, using mathematical and computational tools (quantitative)

Artist’s view of the future of medical imaging
source: https://www.brother.co.uk/business-solutions/healthcare/future-of-hospital-technology
### Classical Imaging

1895  Discovery of **X-Rays** by Wilhelm Conrad Roentgen

1901  1st Nobel Prize in Physics “in recognition of the extraordinary services he has rendered by the discovery of the remarkable rays subsequently named after him”

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**Braun cathode ray tube**


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1896 first medical X-ray by W. C. Roentgen: hand of his wife Anna Bertha Ludwig

Source: commons.wikimedia.org

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W. C. Roentgen

Source: nobelprize.org
Modern Imaging

1971  Sir Godfrey Newbold Hounsfield (EMI) develops first X-ray CT device, based on mathematical methods developed by Allan McLeod Cormack

1979  Joint Nobel Prize in Physiology/Medicine “for the development of computer assisted tomography”

G. N. Hounsfield
Source: nobelprize.org

A. M. Cormack
Source: nobelprize.org

CT image of a brain
Source: commons.wikimedia.org
1.2 Radiation for Imaging

Requirements
- sufficient energy to escape the human body
- easily detected
- low risk

Ionising radiation
- X-ray, gamma photons, electrons
- energy absorbed/attenuated

Energy source
- low
- high

Radiation for imaging
Source: Cho, Foundations of Medical Imaging
1.3 Definition of Imaging Terms

**Radiation** is the transfer of energy.

Requirements for imaging: correct energy, easily detected, low risk

**Ionising radiation** (high energy photons) is capable of removing an orbital electron from the atom with which it interacts.

Planck’s equation

\[ E = hf = h \frac{c}{\lambda} \]

\[ E = m c^2 \]

- \( E \) = photon energy
- \( f \) = frequency
- \( h \) = Planck’s constant
- \( c \) = speed of light
- \( \lambda \) = wavelength

\[ \text{interaction of ionising radiation with matter} \]

source: Ignatavicius and Workman, 2002
**Ionising radiation levels and their effect**

<table>
<thead>
<tr>
<th>Radiation Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1 mSv</td>
<td>chest X-ray</td>
</tr>
<tr>
<td>2.4 mSv/yr</td>
<td>typical background radiation experienced by everyone (of which medical: ca. 15%)</td>
</tr>
<tr>
<td>6 mSv</td>
<td>full-body FDG PET scan (ca. 60 mSv in bladder due to final accumulation/excretion)</td>
</tr>
<tr>
<td>9 mSv/yr</td>
<td>exposure of airline crew flying New York – Tokyo route</td>
</tr>
<tr>
<td>10 mSv</td>
<td>full-body CT scan</td>
</tr>
<tr>
<td>20 mSv/yr</td>
<td>maximum permissible dose to radiation workers</td>
</tr>
<tr>
<td>100 mSv/yr</td>
<td>lowest annual level at which cancer risk is evident</td>
</tr>
<tr>
<td>1,000 mSv</td>
<td>single dose causes temporary radiation sickness (nausea, lower white blood cell count), not fatal; accumulated dose estimated to cause fatal cancer many years later in ca. 5% of people</td>
</tr>
<tr>
<td>2,500 mSv</td>
<td>typical, localised daily chemotherapeutic dose</td>
</tr>
<tr>
<td>5,000 mSv</td>
<td>single dose could kill half of those exposed to it within a month</td>
</tr>
<tr>
<td>10,000 mSv</td>
<td>fatal within weeks</td>
</tr>
</tbody>
</table>

Health risks are small but cumulative; repeated exposure to ionising radiation increases the risk of cancer.

Source: World Nuclear Association
**Question 1**: What is medical imaging?

**Question 2**: Summarise the requirements for the radiation used in medical imaging.

**Question 3**: What is ionising radiation and what are its health risks to the patient?
**Question 1:** What is medical imaging?
- The interaction of radiation with matter (patient).
- A technology that allows physicians to view the interior of the human body without the need for invasive procedures (non-invasive, painless) to diagnose and monitor medical conditions.
- We distinguish between classical imaging which gives qualitative images and modern imaging which allows for quantitative imaging through the use of computational reconstruction.

**Question 2:** Summarise the requirements for the radiation used in medical imaging.
- Correct energy (sufficient energy to escape the body)
- Easily detected
- Low risk (safe)

**Question 3:** What is ionising radiation and what are its health risks to the patient?
- Radiation is the transfer of energy \( E = hf = \frac{hc}{\lambda} \).
- Ionising radiation consists of high-energy photons that are capable of removing an orbital electron from the atom with which they interact.
- Health risks are small but cumulative; repeated exposure to ionising radiation increases the risk of cancer.
Definition of imaging terms related to image quality

**Spatial Resolution** describes the smallest feature that can still be visualised = how “sharp” the image looks; low spatial resolution = unable to differentiate between two objects/tissues that are relatively close together

Example:
(a) MRI showing two small white-matter lesions (arrows).
(b) Corresponding image acquired with 4x poorer spatial resolution.

**Definition of imaging terms related to image quality**

**Signal-to-noise ratio (SNR)** = the ratio of the signal to the standard deviation of the noise.

**Noise** refers to any signal that is recorded, but which is unrelated to the actual signal of interest. The recorded signal must be as large as possible to get the highest signal-to-noise ratio.

The effect of noise on image quality:
As the noise level increases, features within the image become indistinguishable, reducing the diagnostic value of the MR image.

Definition of imaging terms related to image quality

**Contrast-to-noise ratio (CNR):** Contrast describes how easy it is to distinguish between adjacent structures/tissues in the image.

*Example:*
(a) MRI showing two small white-matter lesions (arrows).
(b) Corresponding image acquired with reduced CNR between the lesions and the surrounding healthy tissue.

Definition of imaging terms related to image quality and diagnosis

Sensitivity = the fraction of original energy/radiation that contributes to the image
Artifact = structure/appearance that is not natural, but due to technical or processing errors
Accuracy of clinical diagnoses = the number of correct diagnoses divided by the total number of diagnoses; depends critically upon image quality

Artifacts caused by non-uniform attenuation of X-ray beams

source: Perry Sprawls, Emory University, www.sprawls.org/resources
2 X-Ray

X-rays passing through a body are **attenuated at different rates** by different tissue density. The attenuated X-rays are collected by detectors and converted to **2D image**.

**Advantages**
- fast, portable

**Disadvantages**
- low resolution, few details
- 2D images of 3D body can be difficult to interpret

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Source: Mikael Häggström, Blausen Medical Annotations

A: Chest X-ray; B: CT scan

Source: *J. Bras. Pneumol.* 2013, 39, 108
2.1 X-Ray CT

*Computed Tomography* (CT) or *Computerised Axial Tomography* (CAT): Greek *tomos* = a cut/slice/section, *graphein* = to write/record

Combines X-ray technology with advanced computer signal processing: each image created during a CT procedure shows the organs, bones, and other tissues in a thin “slice” of the body (2D). The sum of these images makes up a *cross-sectional display of the whole body* (3D).

Cardiac imaging with the Revolution CT scanner

source: www.ge.com

X-Ray CT scanner

source: commons.wikimedia.com

Basic set-up for X-ray CT

Source: Cho, *Foundations of Medical Imaging*; www.fda.gov
Question: What is the difference between a classic X-ray scan, and a CAT (X-ray CT) scan? (3 main points)
**Question**: What is the difference between a classic X-ray scan, and a CAT (X-ray CT) scan? (3 main points)

**Planar X-ray**:
- Narrow beam of radiation and single detector
- Qualitative, 2D image of attenuated X-rays (similar to a shadow on a wall)
- Low spatial resolution, few details.

**X-ray CT**
- Multiple detectors in a circular arrangement around the patient and a moving X-ray source allow for a large number of images (“slices”) to be taken.
- Digital image processing provides a quantitative, 3D reconstruction of the patient’s body.
- Good spatial resolution.
2.2 Basic Physical Principles of X-Ray CT

Recap: X-Ray Generation

X-rays are generated by heating a filament wire, electrons are accelerated by an electric current, and suddenly decelerated upon impact with a metal target (W, Mo, Rb)

99% of their energy is converted to heat, and 1% is converted to X-ray photons by two possible pathways:

(1) Characteristic Radiation

The accelerated electron ejects an electron in the metal atom’s inner shell: K-shell ionisation

→ an outer-shell electron fills this “core hole”, emitting a quantised photon as characteristic X-ray radiation
Recap: X-Ray Generation

(2) Bremsstrahlung Radiation
(German for: deceleration radiation)
The accelerated electron is decelerated by interaction with electrons in the metal nucleus → kinetic energy loss is emitted as Bremsstrahlung radiation X-ray photon

Bremsstrahlung radiation

\[ E = E_1 - E_2 \]

incoming projectile electron \( (E_1) \)
outgoing projectile electron \( (E_2) \)
X-Ray Generation

X-ray beams generated by these sources are not monoenergetic → **Beam Hardening**: X-rays of different energies undergo different amounts of attenuation (visible artifacts in reconstructed image)

→ requires post-processing or “pre-hardening” of the beam by passing through Al or Cu filter to reduce the range of X-ray photon energies

![General form of an X-ray emission spectrum: X-ray photons have wide range of energies](source: radiologykey.com)

![Effect of “pre-hardening” on X-ray emission spectrum: (A) Al filter, (B) Sn + Al filters, (C) Sn + Cu + Al filters](source: radiologykey.com)

CT scans: left: beam-hardening artifacts; right: corrected image

**Attenuation** = Transmission loss = **Measure of tissue density**

Recap: X-ray images are produced by X-ray photons being **attenuated at different rates** by different tissue density.

Photon density $I$ that emerges when a narrow beam of monoenergetic photons with energy $E_0$ and intensity $I_0$ passes through a homogeneous absorber of thickness $x$:

$$I = I_0 e^{-\mu(\rho, Z, E_0) x}$$

- $\mu$ linear attenuation coefficient
- $\rho$ density of the absorber
- $Z$ atomic number

Two dominant types of interactions:
- **Photoelectric absorption** (X-ray photon completely absorbed by transferring its energy to an electron)
- **Compton scattering** (directional and energy change)
**Attenuation** = Transmission loss = **Measure of tissue density**

Two dominant types of interactions:

- **Photoelectric absorption** (X-ray photon completely absorbed by transferring its energy to an electron)
- **Compton scattering** (directional and energy change)

![Diagram of Compton scattering]

### Compton Scattering:

\[
\lambda_f - \lambda_i = \Delta \lambda = (1 - \cos \theta) \frac{h}{m_e c}
\]

- \( h \) Planck’s constant
- \( m_e \) electron rest mass
- \( c \) speed of light

**Contribution of each interaction to the total linear attenuation coefficient of X-rays in water**

*Source: Cho, Foundations of Medical Imaging*
2.3 Interpreting X-Ray Radiographs

*What does a planar X-ray image look like?*

**Qualitative Characteristics of X-Ray Radiographs**

The ability of tissues to attenuate X-rays passing through them is called **radiopacity**. The higher the radiopacity of an object, the whiter it appears on the CT image.

Radiopacity depends on:

- **Atomic number** (e.g. lead is highly radiopaque, effectively shields X-rays)
- **Physical opacity** (e.g. air and liquid have approx. the same atomic number, but air has very low physical opacity and appears black on the radiograph)
- **Thickness** (the thicker the tissue, the greater the attenuation – appears whiter)

\[ I = I_0 e^{-\mu(\rho, Z, E_0) x} \]

- \( \mu \) linear attenuation coefficient
- \( \rho \) density of the absorber
- \( Z \) atomic number
Qualitative Characteristics of X-Ray Radiographs

Basic tissue radiopacities

• **Bone**: composed mainly of calcium and phosphorus → high radiopacity (diseased bone may appear darker)
• **Soft tissue** and **fluid** have the same radiopacity and can thus be difficult to distinguish, variations in volume and thickness create a pattern of different densities on the radiogram (*e.g.* organs)
• **Gas**: very radiolucent, appears black → sometimes used as negative contrast agent in CT (*e.g.* air, CO₂)
• **Heavy atoms** (*e.g.* iodine, barium) are used as positive contrast agents (appear white)
**Question**: Qualitatively describe how X-ray images are produced and what they look like.
**Question**: Qualitatively describe how X-ray images are produced and what they look like.

**Answer**: X-ray photons are **attenuated at different rates** by different tissues. The higher the **radiopacity** of an object (*i.e.* its ability to attenuate X-rays), the whiter it appears on the CT image.

Bone has a high radiopacity and thus appears very bright on X-ray radiographs. Soft tissue and fluid appear lighter (greyish). Gas (*e.g.* air) has a high radiopacity and appears black.

Diseased tissue can be detected due to changes from its expected behaviour, *e.g.* diseased (less dense) bone may appear darker than healthy bone; calcification (formation of small calcium crystals) appears brighter than surrounding soft tissue.

![Aggressive bone tumour lesion](source: www.radiologyassistant.nl)

![Calcification can be a sign of breast cancer; biopsy is required to confirm malignancy](source: www.radiologyassistant.nl)
Quantitative Characteristics of X-Ray Radiographs

Spatial Resolution

Spatial resolution in (planar) X-ray radiography is determined by:

(1) The distance between the X-ray tube and the patient / the detector

\[ P \text{ ("penumbra") is the "geometric unsharpness"} \]

\[ P = \frac{f (S_1 - S_0)}{N!} \]

- \( f \) X-ray focal spot
- \( S_0 \) tube – patient distance
- \( S_1 \) tube – detector distance

(2) The properties of the X-ray detector.

→ For good spatial resolution, the patient should be placed as close to the detector and as far from the X-ray source as possible.

→ Smith, Webb, Introduction to Medical Imaging
Quantitative Characteristics of X-Ray Radiographs

**Signal-to-noise ratio** \( SNR \propto \sqrt{N} \)

Even with no patient present, the number of X-rays striking each part of the detector varies slightly – this introduces a statistical fluctuation of the signal intensity of each pixel (noise)

\[
P(N) = \frac{\mu^N e^{-\mu}}{N!}
\]

\(P(N)\) is the probability that \(N\) X-rays strike the detector plate per unit area:

\[
\sigma = \sqrt{\mu}
\]

The statistical uncertainty in this number is represented by the standard deviation \(\sigma\):

\[
SNR = \frac{N}{\sigma} \propto \sqrt{N}
\]

→ Doubling the image SNR requires four times the number of X-rays to be detected, increasing the radiation dose by a factor of four.

Poisson distribution of the probability \(P(N)\) of a certain number of X-rays striking a unit area of the detector

source: Smith, Webb, Introduction to Medical Imaging
Quantitative Characteristics of X-Ray Radiographs

Contrast-to-noise ratio

CNR in (planar) X-ray radiography is determined by:

1. SNR (higher SNR gives better contrast)
2. Spatial resolution (good spatial resolution gives better contrast)
3. Compton scattering (the higher the contribution of Compton scattered X-rays, the lower the CNR)
   - Compton scattering is predominant for high energy X-rays, photoelectric effect dominates for low energy X-rays giving good contrast (but requiring higher dose)
   - The thicker the body part that is being imaged, the larger the contribution of Compton scattered X-rays, reducing the contrast.
   - Anti-scatter grids can be used to reduce Compton scattering, but these also reduce the SNR.
Improving Image Contrast: Contrast Agents

= chemical substances administered during imaging to enhance natural contrast and/or obtain dynamic information

Recap: Radiopacities

- **Gas**: very radiolucent, appears black → sometimes used as negative contrast agent in CT (e.g. air, CO₂)
- **Heavy atoms** (e.g. iodine, barium) are used as positive contrast agents (appear white)
**Contrast Agents: Iodine-based contrast agents**

- Iodine very efficiently absorbs X-rays: appears white in radiograph
- Iodine-based contrast agents are administered intravenously
- Major concern: safety → the contrast agent must be as effective as possible at the lowest dose and side-effects must be minimised
- Generic structure of iodinated contrast agents:

  ![Generic structure](image)

  - 3 iodines on each benzene ring: reduces the required dose.
  - Non-ionic, low osmolarity → low risk of side-effects.
  - Excreted through urine within 24 hours.

**Digital subtraction angiography:**

- Investigates clotting of arteries/veins, irregularities in systemic blood flow
- Left image: blood vessels without iodinated contrast agent
- Right image: digital image subtraction of left image and an image of blood vessels with iodinated contrast agent → the fine vessels containing iodinated contrast agent are clearly shown as dark areas in the subtraction images.
**Question:** Explain what contrast agents are and why they are used in imaging.
**Question**: Explain what contrast agents are and why they are used in imaging.

**Answer**: Contrast agents are **chemical substances** administered during imaging (usually orally or intravenously) to **enhance low contrast**. (*E.g.* soft tissue and fluid have the same radiopacity – imaging of organs can be difficult.)

Example: Barium sulphate (BaSO$_4$) is a contrast agent that is administered orally as a thick suspension in water for X-ray imaging of the upper GI tract. Barium very efficiently absorbs X-rays, thus appearing white on the radiograph (positive contrast agent). Areas in which it is absent – *e.g.* lesions and tumours – are visible as areas of low X-ray absorption (dark areas).

![Barium sulphate enhanced X-ray image of the colon. White arrows show an adenocarcinoma (tumour).](source: Smith, Webb, Introduction to Medical Imaging)
2.4 Case Studies

Example 1: CT in archaeological studies

- Advantage of X-ray CT: **non-invasive, non-destructive**, important for preservation of valuable art and archaeological artefacts
- Often used in the **study of mummies**: spatial contrast and resolution often better than in living patients (less fluid content, less scattering, no movement artifacts)
- Current research at the University of Granada revealed the first known case of breast cancer in an Egyptian mummy from 2,000 B.C.

Mummy CT scan carried out at the Aswan University hospital (above); and images obtain from the scan (left)  
source: www.ugr.es

source: Prof. Miguel Cecilio Botella López, Universidad da Granada
Example 2: Imaging of the brain

- **Challenge:** soft brain tissue and cerebrospinal fluid have very similar radiopacities, making it very difficult to image the brain by X-ray/CT
- First solution (early 1900s): draining cerebrospinal fluid, replacing it with air (high risk of haemorrhage, infection)
- 1927 Egas Moniz pioneered the use of contrast agents for X-ray imaging of blood vessels in the brain (cerebral angiography)
- The development of CT enabled more detailed anatomic images of the brain to be obtained
- Today, MRI provides more sensitive images of the brain without the risk of ionising radiation

![Head X-ray](image1.png)

![Cerebral angiogram with iodinated contrast](image2.png)

![CT (left) and MRI (right) images](image3.png)
Recap: X-Ray CT

Radiation:
• X-rays (ionising)

Applications
• **Anatomic** information
• Bones, teeth, joints
• Organ structure, blood vessels

Advantages
• Short scanning times
• Good spatial resolution (CT)

Disadvantages
• Exposure to ionising radiation may increase cancer risk
• No real-time information
• Low resolution where soft tissue contrast is low
(contrast agents offer improvement)
3  Nuclear Imaging

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1903</td>
<td>Nobel Prize in Physics: Antoine Henri Becquerel for “his discovery of spontaneous radioactivity”; Pierre Curie, Marie Curie for “their joint researches on the [...] radiation phenomena”</td>
</tr>
<tr>
<td>1901</td>
<td>Advent of nuclear medicine (initially radiotherapeutics, later radioimaging)</td>
</tr>
<tr>
<td>1945</td>
<td>Nobel Prize in Chemistry: George de Hevesy “for his work on the use of isotopes as tracers in the study of chemical processes”</td>
</tr>
</tbody>
</table>

De Hevesy’s *Tracer Principle* introduces a radioactive atom to a molecule under study, making it easily identifiable.

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**X-Ray/CT Imaging:** *structural data* (anatomic)

**Nuclear Imaging:** *functional data* (physiological or metabolic)
3.1 Basic Principles of Nuclear Imaging

3.1.1 Procedural Principles

radiotracer synthesis → administration of radiotracer → radioactive decay, detection of radiation → signal processing → image: biodistribution of radiotracer in body
3.1.2 Physical Principles

Types of Ionising Radiation

A radioactive isotope is one which undergoes a spontaneous change in the composition of the nucleus, termed a disintegration, resulting in emission of energy (radiation).

<table>
<thead>
<tr>
<th>Type</th>
<th>Composition</th>
<th>Rest Mass (u)</th>
<th>Charge</th>
<th>Penetration</th>
</tr>
</thead>
<tbody>
<tr>
<td>X-Ray</td>
<td>photon (shell electrons)</td>
<td>0</td>
<td>0</td>
<td>strongly penetrating</td>
</tr>
<tr>
<td>Alpha (α)</td>
<td>He(^{2+}) (2 protons, 2 neutrons)</td>
<td>4.002</td>
<td>+2</td>
<td>short distance (stopped by skin/air)</td>
</tr>
<tr>
<td>Beta (β)</td>
<td>electron (e(^{-})) or positron (e(^{+}))</td>
<td>5.486 \times 10^{-4}</td>
<td>±1</td>
<td>Short/medium distance (stopped by thin layer of Al)</td>
</tr>
<tr>
<td>Gamma (γ)</td>
<td>photon (nucleus)</td>
<td>0</td>
<td>0</td>
<td>non-penetrating</td>
</tr>
</tbody>
</table>

RECAP: Requirements for radiation used in imaging: sufficient energy to escape the human body, easily detected, good half-life, low risk

→ Radiopharmaceuticals for diagnostic purposes are generally labelled with γ emitters (SPECT) or β\(^{+}\) emitting radionuclides (PET).
**Radioactive decay**: release of energy and/or particles from unstable nuclei (radionuclides) to achieve greater stability

First-order kinetics:

<table>
<thead>
<tr>
<th>Rate of decay</th>
<th>( \frac{dN}{dt} = -\lambda N )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( N(t) = N_0 , e^{-\lambda t} )</td>
<td></td>
</tr>
</tbody>
</table>

Physical half-life \( T_{1/2} = \frac{\ln 2}{\lambda} \)

- \( N \)  number of atoms
- \( N_0 \) number of atoms at \( t = 0 \)
- \( t \)  time
- \( \lambda \) decay constant \([s^{-1}]\)

The **half-life** is the time required for the radioactivity to drop to half its value. In nuclear medicine scans, the total **radioactive dose** experienced by the patient is calculated from the physical and the biological half-life of the radiotracer.

The **amount of radioactive substance** is quantified by its rate of decay or **activity**:

- 1 Bq (Becquerel) = 1 disintegration per second
- 1 Ci (Curie) = \( 3.7 \times 10^{10} \) disintegrations per second

\( 1 \text{ Ci} = 37 \text{ GBq} \)
Properties of ideal tracers for nuclear imaging

- Radioactive **half-life** needs to be short enough to produce significant radioactivity without requiring a large initial dose, but long enough that the tracer can clear the blood and distribute in the relevant organs.
- **Mono-energetic decay** (e.g. clean $\gamma$-emission only) improves contrast and decreases the radioactive dose.
- The emitted radiation should have a high enough **energy** to travel through the patient and reach the detector (for $\gamma$-emission ca. 100 keV).
- Tracer **uptake** should be high in the organ(s) of interest, but low in the rest of the body (non-specific uptake).
3.2 Single Photon Emission Computed Tomography (SPECT)

**Planar Scintigraphy**
- planar (2D) imaging of $\gamma$ radiation
- *cf.* planar X-ray scan
- mainly used for whole-body scans of tumours
- radiation detected by a scintillation camera

**Principle components of a Scintillation Camera:**
- **Collimator** (lead or tungsten plate): mechanically aligns photons
- Photons hit $\text{NaI(Tl)}$ *scintillation crystal*, conversion into visible light photons ($E \approx 3$ eV)
- Light is converted to electrons in *photomultiplier tubes*: determine position of scintillation event
- Output (z signal) is filtered (energy window) to reduce noise from Compton scattering
Single Photon Emission Computed Tomography (SPECT)

• Combines planar imaging (scintigraphy) with a rotating gamma camera to acquire a large set of projections and provide an in vivo quantitative measure of gamma emitting radionuclides in three dimensions (3D).

• cf. 3D X-ray CT scan

• Collimation occurs by restricting the acceptance angle of radiation (only ca. 0.015% of emitted radiation transmitted) → low photon-collection efficiency, low sensitivity (single most important factor limiting the performance of SPECT)
Resolution ($R$) \[ R^2 = R_i^2 + R_c^2 \]

Intrinsic Resolution $R_i$
= ability of the camera to locate where the incoming photon interacts with the scintillation crystal (affected by crystal thickness, photon energy, scatter in crystal, number of photomultiplier tubes): intrinsic resolution ca. 3 – 5 mm

Collimator Resolution $R_c$ (larger factor)
= contribution to the resolution from the collimator (depends on collimator design, distance from radiation source): collimator resolution ca. 1 cm (for $x = 10$ cm)

\[ R_c = \frac{d (l + x)}{l} \]
Example 1: SPECT imaging of the brain

Nuclear brain imaging

- challenge: hydrophilic radiotracers cannot cross blood-brain barrier (BBB)
- lipophilic tracers cross BBB: uptake proportional to regional blood flow
- indications: cerebrovascular disease, epilepsy, dementia, Parkinson’s disease, brain death, etc.
- disadvantage: poor specificity (i.e. the same SPECT pattern may be encountered in different pathologies)
- During its infancy (early 1960s), SPECT was the only non-invasive test capable of imaging pathology inside the brain.
- common radionuclides used for brain SPECT:
  - $^{133}$Xe (diffusible gas, regional cerebral blood-flow imaging rCBF)
  - $^{123}$I (rCBF, dopamine/serotonin transporter, $\beta$-amyloid plaque imaging)
  - $^{99m}$Tc (rCBF, brain death, dopamine transporter imaging)
**Confirmation of Brain Death by Nuclear Imaging**

**Diagnosis of brain death**: irreversible cessation of all function of the cerebrum and brain stem

**Procedure**: $^{99m}$Tc-tracer uptake correlates with brain blood flow, which is assessed by
- flow and static scintigraphy
- SPECT (patients who are unstable and on life support equipment cannot undergo SPECT imaging)

$[^{99m}$Tc]$^{-}$DTPA flow and static scintigraphy scans:
- left: brain death confirmed (no tracer in brain tissue); right: negative brain death scan (tracer in brain tissue); both: tracer in arteries (confirms: correct dose)

$[^{99m}$Tc]$^{-}$HMPAO SPECT scan: no tracer uptake in brain – brain death confirmed

Example 2: SPECT in Cardiology

Nuclear imaging of the heart
- SPECT tracer uptake correlates with myocardial blood flow
- myocardial perfusion is measured at rest and after exercise or pharmacologic stress: under stress, diseased heart tissue receives less blood flow than normal heart tissue
- indications: coronary blockages, scarring (previous heart attack), function of heart muscle (prediction of future events), etc.

Illustrations of healthy heart (top) and SPECT scans from similar angles (bottom)
source: P. J. Lynch, Yale University

99mTc-tetrofosmin SPECT images of heart after pharmacologic stress (top) and at rest (bottom): arrows show ischemia in the lower heart wall
source: P. A. Kaufmann, O. Gämperli, Uni. Hospital Zurich
3.3 Positron Emission Tomography (PET)

- Nuclear imaging techniques that uses positron (beta) emitting radiotracers
- Principles of a PET scanner:
  - proton in the radiotracer decays to neutron, emitting positron and neutrino, e.g. $^{18}_{9}F_{9} \rightarrow ^{18}_{8}O_{10} + \beta^+ + \nu$
  - positron combines with an electron in the body (annihilation): creates two collinear photons
  - both photons are detected simultaneously by a ring of detectors

\[ E = m_{e}c^2 = 511 \text{ keV} \]

Simplified diagram of a PET scanner

Source: commons.wikimedia.org
**Why is the SNR and resolution in PET so much better than in SPECT?**

- 100 – 1,000 SNR and significantly better spatial resolution than SPECT
- Both photons are detected simultaneously by a complete ring of detectors: no *collimation* necessary → highest resolution and sensitivity imaging
- Higher energy $\gamma$-photons (511 keV instead of ca. 140 keV): reduced attenuation in tissue

**Resolution limits**

- angular uncertainty: photons not *exactly* collinear ($180^\circ \pm 0.25^\circ$)
- uncertainty in annihilation position (positron range depends on kinetic energy of emitted positron)
- total uncertainty ca. 2–3 mm fwhm
# PET vs. SPECT

<table>
<thead>
<tr>
<th>Radionuclides</th>
<th>PET</th>
<th>SPECT</th>
</tr>
</thead>
<tbody>
<tr>
<td>e.g.</td>
<td>$^{11}$C, $^{13}$N, $^{15}$O, $^{18}$F, $^{82}$Ru</td>
<td>$^{99m}$Tc, $^{123}$I, $^{131}$I, $^{67}$Ga, $^{111}$In, $^{201}$Tl</td>
</tr>
<tr>
<td>Detection</td>
<td>Two annihilation photons</td>
<td>Single gamma photons</td>
</tr>
<tr>
<td>Advantages</td>
<td>Short scan times (30 min); Higher resolution (5–7 mm);* Fewer artifacts, better contrast; Radionuclides closely related to human metabolic processes</td>
<td>Long tracer half-life; Cheaper, more widely available</td>
</tr>
<tr>
<td>Disadvantages</td>
<td>Expensive; Short tracer half-life: facility must be close to cyclotron</td>
<td>Long scan times (&gt;2h); Low resolution (12–15 mm);* Prone to artifacts</td>
</tr>
<tr>
<td>Most common diagnostic use</td>
<td>Oncology</td>
<td>Cardiology</td>
</tr>
</tbody>
</table>

* values for 2013, in cardiac imaging
**Question**: What are the advantages and disadvantages of PET imaging?
**Question**: What are the advantages and disadvantages of PET imaging?

**Advantages**

- Functional/metabolic information
- Highly accurate and specific
- Good tissue-specific contrast

**Disadvantages**

- Ionising radiation (health risk to patients)
- Short tracer half-life
- High cost
**[¹⁸F]-FDG PET**

**[¹⁸F]-Fluorodeoxyglucose (FDG)**

- standard radiotracer used for PET neuroimaging and cancer patient management (>90% of oncologic PET scans use FDG)
- glucose analogue: FDG is taken up by cells with high glucose metabolism, and accumulates in cells as it is metabolically stable
- *increased glucose metabolism of tumor cells*: FDG uptake substantially increased

---

**FDG uptake by cells and metabolic trapping**

GLUT = glucose transporter
G6Pase = glucose-6-phosphatase
GPI = glucose-6-phosphate isomerase
**[¹⁸F]-Fluorodeoxyglucose (FDG)**

*beta*-decay of [¹⁸F]-FDG allows for PET imaging of cancer

**Advantages**
- highest resolution and sensitivity
- fast results (reconstructed images available ca. 3 min after end of scan)
- specific functional and metabolic information
- fast excretion of radiotracers through urine (disadvantage: strong signal in kidneys, urinary tract, bladder)

**Disadvantages**
- background uptake in cells with high physiological function (e.g. brain, liver, ...)
- poor anatomic detail

Physiological distribution of [¹⁸F]-FDG in male patients

**Dual-Modality PET/CT**

- **combination of functional imaging** (PET, SPECT) **with anatomic imaging** (CT, MRI)
- software fusion of different images with high accuracy is difficult
- hardware fusion: highly accurate dual-modality scanners
- requirements for hardware fusion
  - small temporal difference between scans
  - patient bed must move through both fields with minimal downward deflection
  - minimise claustrophobic effect
- advantages of dual-modality PET/CT
  - better anatomic detail
  - **differentiate background tracer uptake from abnormal uptake**
- >90% of all studies: oncology

Dual-modality PET/CT scanner

Example 1: PET/CT for diagnosis and treatment monitoring of cancer

- initial $^{18}$F-FDG PET/CT scan shows tumour on the right femur (no metastases)
- treatment: chemotherapy; if unsuccessful: amputation
- follow-up PET/CT scan after initial chemotherapy: great decrease in radiotracer uptake in the primary tumor, suggesting excellent response to chemotherapy; no amputation necessary

source: www.petscaninfo.com Childhood Cancer Case Study 1
Example 2: PET/CT for the diagnosis of Alzheimer’s disease (AD)

**[18F]FDG-PET imaging:**
- characteristic patterns of glucose metabolism can help to differentiate AD from other causes of dementia
- AD: decreased glucose metabolism in lateral parietal cortex

**Amyloid PET imaging:**
- accumulation of β-amyloid plaques (Aβ) has been implicated in AD pathogenesis
- PET amyloid imaging agents bind to insoluble fibrillar Aβ40 and Aβ42
- does not establish diagnosis of AD, but may be used to monitor treatment
**Example 3: SPECT/CT**

- first dual-modality system, gained in popularity after the establishment of PET/CT: allows for precise anatomic location of tumours/tissues
- mainly used for tissues outside the brain

Diagnosis of pheochromocytoma with $^{99m}$Tc-MIBG SPECT/CT:
(A) Planar scintigraphy: mildly intense focal lesion on left
(B/E): SPECT, (C/F): CT, (D/G): SPECT/CT images show uptake in (enlarged) left AND right adrenal glands → TWO pheochromocytomas


meta-iodobenzylguanidine (MIBG)
Iobenguane
**Example 4: PET/MRI**

- Newest dual-modality system, mainly used for pre-clinical research
- Comparison with PET/CT: **advantages of PET/MRI**
  - Lower radiation dose (especially significant when imaging children)
  - Simultaneous data acquisition possible
  - Better soft-tissue contrast and contrast in functional imaging
  - Very good at detecting metastatic and recurring tumours
- Comparison with PET/CT: **disadvantages of PET/MRI**
  - No imaging of lung and bones
  - More expensive, longer acquisition time
  - Limited field of vision, relies on bones for anatomic location of signal

![Siemens Biograph mMR](image-url)
3.4 Radiosynthesis of PET and SPECT tracers

**PET**: $^{11}$C, $^{15}$O, $^{13}$N, $^{18}$F

**SPECT**: $^{123}$I, $^{99m}$Tc

"Bench-to-beside" tracer synthesis: workflow
- Production of radioisotope in cyclotron and delivery to radiolaboratory
- Automated synthesis and purification (HPLC) in lead-lined hot cell
- Quality control and delivery of tracer to hospital
- Administration to patient

University of Michigan PET centre  
Image © Prof. Peter Scott

"Bench-to-bedside" radiosynthesis of PET tracers  
**General Considerations for Radiosynthesis**

- *fast* reactions: **three isotope half-lives** for isotope production, synthesis, purification, analysis
- short half-life of radioisotopes: **late-stage radiolabelling** (incorporation of radionuclide as one of the last steps in the synthesis)
- **safety**: handling radioactive material
- **easy** reactions: ideally to be carried out by (synthetically) untrained personnel
- **challenges**: very small amounts of material, radionuclide in sub-stoichiometric amounts

GE Healthcare FASTlab for cassette-based “plug-and-play” PET tracer synthesis

*source: gehealthcare.co.uk*
**Characterisation**

- HPLC, TLC, GC; purity must be very high for clinical use

- **Radiochemical Yield (RCY):** a function of both the chemical yield and half-life of the radioisotope, expressed as a fraction of the radioactivity originally present in the sample following a radiochemical separation (decay-corrected: mathematically adjusted to take into account radioactive decay; or non-decay-corrected); measured by radio-TLC

- **Specific Activity (SA):** radioactivity per unit mass of labelled compound (theoretical max. values never reached because of unavoidable isotopic dilution by the naturally occurring stable isotope)

![radio-TLC scanner (Raytest)](image)

*analysis of radio-TLCs*

**Question 1**: What are the challenges associated with radiotracer synthesis compared to the synthesis of ‘cold’ molecules?

- Fast reactions: 3 isotope half-lives for entire process from isotope production to tracer analysis
- Increased safety risk: handling of radioactive material
- Reactions should be easy enough to be carried out in the clinic by synthetically untrained personnel
- Very small amounts of material
- Stoichiometry changes to ‘cold’ reactions: radionuclide becomes limiting reagent
- Short half-life of radioisotopes: incorporation of radionuclide needs to happen as late in the synthesis as possible, to obtain maximum specific activity of tracer
3.4.1 Radiolabelling with Carbon-11

**Production of carbon-11**

\[ ^{14}\text{N} \ (p,\alpha)^{11}\text{C} \]

Proton bombardment of nitrogen-14 results in release of an \( \alpha \) particle to give carbon-11; decays to 99.8% by *positron emission* and 0.2% by electron capture to \(^{11}\text{B} \)

\[
\begin{align*}
\text{N}_2 + \text{O}_2 & \rightarrow ^{11}\text{CO}_2 \\
\text{N}_2 + \text{H}_2 & \rightarrow ^{11}\text{CH}_4
\end{align*}
\]

two key carbon-11 precursors are \(^{11}\text{CO}_2 \) and \(^{11}\text{CH}_4 \)

\[ ^{11}\text{C} \text{ half-life } t_{1/2} = 20.4 \text{ min} \]

Rule-of-thumb: 3 isotope half-lives for radiotracer synthesis \( \rightarrow \) for \(^{11}\text{C} \): ca. 60 min.

**Advantage of labelling with carbon-11**

- no change in chemical and biological properties

**Disadvantages**

- short half-life
- limited number of \(^{11}\text{C} \)-labelled precursors
Synthesis of $^{11}$C precursors

$[^{11}\text{C}]\text{CH}_2\text{O} \leftrightarrow [^{11}\text{C}]\text{CH}_3\text{OH} \rightarrow [^{11}\text{C}]\text{CH}_3\text{I} \rightarrow [^{11}\text{C}]\text{CH}_3\text{OTf}$

$[^{11}\text{C}]\text{CO} \leftrightarrow [^{11}\text{C}]\text{CO}_2 \rightarrow [^{11}\text{C}]\text{CH}_4 \rightarrow [^{11}\text{C}]\text{CCl}_4$

$[^{11}\text{C}]\text{RCOCl} \leftrightarrow [^{11}\text{C}]\text{RCO}_2\text{MX} \rightarrow [^{11}\text{C}]\text{HCN} \rightarrow [^{11}\text{C}]\text{COCl}_2$

phosgene

$[^{11}\text{C}]\text{RCH}_2\text{X} \leftrightarrow [^{11}\text{C}]\text{RCH}_2\text{OH}$
**Incorporation of $^{11}$C by nucleophilic substitution**

Most commonly used reagents: $[^{11}$C]$\text{CH}_3$I and $[^{11}$C]$\text{CH}_3$OTf

![Chemical reaction diagram]

$S_N2$ substitution nucleophilic bimolecular (inversion of stereochemistry)

**Synthesis of $[^{11}$C]$\text{CH}_3$I**

*Solution phase synthesis:*

$$^{11}\text{CO}_2 \xrightarrow{\text{LiAlH}_4} ^{11}\text{CH}_3\text{OH} \xrightarrow{\text{HI}} ^{11}\text{CH}_3\text{I}$$

*Gas phase synthesis: typically gives $^{11}\text{CH}_3\text{I}$ in higher specific activities*

$$^{11}\text{CO}_2 \xrightarrow{\text{H}_2/\text{Ni}, 400 \degree\text{C}} ^{11}\text{CH}_3\text{OH} \xrightarrow{\text{I}_2, 700 \degree\text{C}} ^{11}\text{CH}_3\text{I}$$

**Synthesis of $[^{11}$C]$\text{CH}_3$OTf**

$$^{11}\text{CH}_3\text{I} \xrightarrow{\text{AgOTf, 200 \degree\text{C}}} ^{11}\text{CH}_3\text{OTf}$$

Triflate is a stronger electrophile → faster reactions, milder conditions
These reagents allow for the **methylation** of any **nucleophilic atom**

\[ \text{[}^{11}\text{C}]\text{-PIB} \]

β-amyloid agent for PET imaging of Alzheimer's disease


\[ \text{[}^{11}\text{C]flumazanil} \]

PET imaging agent for central benzodiazepine receptors


\[ J. \text{ Org. Chem.} \text{ **2006**, 71, 210} \]
**Question:** Where can the following molecules be carbon-11 labelled using $[^{11}\text{C}]\text{CH}_3\text{I}$?
Incorporation of $^{11}$C by palladium catalysed cross-coupling

**Suzuki Coupling**

\[
\text{Pd(dppf)Cl}_2, K_2\text{PO}_4, \text{DMF, microwave, 90 s}
\]

\[
\begin{align*}
\text{boronic acid} & \quad \xrightarrow{^{11}\text{CH}_3} \quad \text{Pd(dppf)Cl}_2, K_2\text{PO}_4, \text{DMF, microwave, 90 s} \\
\text{NC} & \quad \leftarrow \quad \text{H}_3^{11}\text{C} \\
(\text{HO})_2\text{B} & \quad \rightarrow \quad \text{H}_3^{11}\text{C} \\
\end{align*}
\]

$^{[11]}$C-M-MTEB

PET imaging agent of metabotronic glutamate receptor (mGluR5)

*Synapse* **2005**, *56*, 205

**Stille Coupling**

\[
\text{Pd}_2(\text{dba})_3, \text{P(o-tol)}_3, \text{DMF, 130 °C, 5 min}
\]

\[
\begin{align*}
\text{organostannane} & \quad \xrightarrow{^{11}\text{CH}_3} \quad \text{Pd}_2(\text{dba})_3, \text{P(o-tol)}_3, \text{DMF, 130 °C, 5 min} \\
\text{H}_3^{11}\text{C} & \quad \leftarrow \quad \text{OH} \\
\text{HO} & \quad \rightarrow \quad \text{HO} \\
\end{align*}
\]

$^{[11]}$C-FMAU

PET imaging agent for cell proliferation


**Compare with S$_{N}$2 approach:**

\[
\text{THPO} \quad \xrightarrow{\text{t-BuLi (2 eq)}} \quad \text{HPTO} \quad \xrightarrow{\text{H}_3^{11}\text{C}^-} \quad \text{THPO} \\
\text{THP = Tetrahydropyranyl protecting group}
\]

THP deprotection


10-50% R CY
Palladium catalysed cross-coupling mechanism

Factors that influence Pd mediated cross-couplings:
- choice of Pd pre-catalyst: Pd(II) or Pd(0)
- selection of phosphine ligand, steric and electronic properties will affect oxidative addition and transmetalation
- organostannanes are toxic and produce toxic by products, however, reactions are typically more general than boronic acids

This example: ArX + $^{11}$CH$_3$I
$^{11}$CH$_3$X + ArI also possible
Methyl transfer reagents $^{11}\text{CH}_3X$ in palladium cross-coupling

Chem Comm. 2005, 97

J. Labelled Compd. Radiopharm. 2004, 47, 71
**Question 1:** Which of the following reagents could be used to radiolabel X with $^{11}$C?

- A $^{11}$CH$_3$OTf
- B $^{11}$CH$_3$I
- C $^{11}$CH$_3$SnR$_3$

**Question 2:** Which of the precursors Y can be radiolabelled with $^{11}$CH$_3$I?

- A X = H
- B X = SiMe$_3$
- C X = OTf
- D X = B(pin)$_2$

Ar-B(pin)$_2$ =
Incorporation of $^{11}$C with $[^{11}\text{C}]-\text{phosgene}$

**Synthesis of $[^{11}\text{C}]\text{COCl}_2$**  

\[ ^{14}\text{N}(p,\alpha)^{11}\text{C} \xrightarrow{\text{O}_2} [^{11}\text{C}]\text{CO}_2 \xrightarrow{\text{Zn}} [^{11}\text{C}]\text{CO} \xrightarrow{\text{PtCl}_4, 380 \degree \text{C}} [^{11}\text{C}]\text{COCl}_2 \]

\[ ^{14}\text{N}(p,\alpha)^{11}\text{C} \xrightarrow{\text{H}_2} [^{11}\text{C}]\text{CH}_4 \xrightarrow{\text{Cl}_2, \text{CuCl}, 380 \degree \text{C}} [^{11}\text{C}]\text{CCl}_4 \xrightarrow{\text{O}_2, \text{Fe}, 300 \degree \text{C}} [^{11}\text{C}]\text{COCl}_2 \]

20 minutes  
low specific activity: 14 GBq/μmol  
10-12 minutes  
specific activity: 26 GBq/μmol

**Use in radiotracer synthesis**

\[ [^{11}\text{C}]\text{CGP 12177} \]
radioligand for β-adrenergic receptors  

\[ [^{11}\text{C}]\text{GI181771 (10\% RCY)} \]  
selective CCK-A agonist  
**Incorporation of $^{11}$C with $[^{11}\text{C}]\text{HCN}$**

**Synthesis of $[^{11}\text{C}]\text{HCN}$** 

\[
\begin{align*}
^{14}\text{N}(\rho, \alpha)^{11}\text{C} & \xrightarrow{\text{H}_2} \ [^{11}\text{C}]\text{CH}_4 \xrightarrow{\text{NH}_3, \text{Pt}, 1000 \degree \text{C}} [^{11}\text{C}]\text{HCN} \\
^{14}\text{N}(\rho, \alpha)^{11}\text{C} & \xrightarrow{\text{O}_2} \ [^{11}\text{C}]{\text{CO}_2} \xrightarrow{\text{H}_2, \text{Ni}, 400 \degree \text{C}} [^{11}\text{C}]\text{CH}_4 \xrightarrow{\text{NH}_3, \text{Pt}, 1000 \degree \text{C}} [^{11}\text{C}]\text{HCN}
\end{align*}
\]

**Reactions with $[^{11}\text{C}]\text{HCN}$**

- Michael addition
- Reissert-Kaufmann reaction

**Reactions with $[^{11}\text{C}]\text{CuCN}$**

\[
[^{11}\text{C}]\text{HCN} \xrightarrow{\text{CuSO}_4, \text{NaIO}_4, 80 \degree \text{C}, 2 \text{ min}} [^{11}\text{C}]\text{CuCN}
\]

- Rosenmund-von-Braun reaction

*J. Label Comp Radioph. 2006, 49, 829*
Incorporation of $^{11}$C with $[^{11}\text{C}]\text{CO}$

Synthesis of $[^{11}\text{C}]\text{CO}$  

$^{14}\text{N}(\rho,\alpha)^{11}\text{C} \xrightarrow{\text{O}_2} [^{11}\text{C}]\text{CO}_2 \xrightarrow{\text{Zn or Mo}} 400{^\circ}\text{C} [^{11}\text{C}]\text{CO}$

Palladium mediated carbonylation with $[^{11}\text{C}]\text{CO}$

![Chemical reactions diagram](image_url)

- **Nitrogen nucleophiles**: R = aryl, alkyl or (CH$_2$)NH$_2$
- **Organoboranes**: R = aryl or alkyl

\[ R' - \text{aryl or alkyl} \]

\[ X = \text{OTf, I, Br} \]
Palladium mediated carbonylation with $[^{11}\text{C}]\text{CO}$ - Mechanism

**Mechanism with nitrogen nucleophiles:**

1. **Reductive elimination**
   - $\text{Ar-}^{-\text{H}} \rightarrow \text{Pd}^{\text{II}} \rightarrow \text{Ar-}^{-}\text{X}$
   - $X = \text{OTf, I, Br}$

2. **Oxidative addition**
   - $\text{Ar-}^{-}\text{Pd}^{\text{II}} \rightarrow \text{Ar-}^{-}\text{Pd}^{\text{III}} \rightarrow \text{Ar-}^{-}\text{Pd}^{\text{II}}$
   - $\text{C}=\text{O}^+$

3. **Ligand exchange**
   - $\text{H}_2\text{N-}^{-}\text{R} \rightarrow \text{Pd}^{\text{II}} \rightarrow \text{Ar-}^{-}\text{Pd}^{\text{II}}$

4. **CO insertion**
   - $\text{Ar-}^{-}\text{Pd}^{\text{II}} \rightarrow \text{Ar-}^{-}\text{Pd}^{\text{II}}$

**Mechanism with organoboranes:**

1. **Reductive elimination**
   - $\text{Ar-}^{-}\text{H} \rightarrow \text{Pd}^{\text{II}} \rightarrow \text{Ar-}^{-}\text{X}$
   - $X = \text{OTf, I, Br}$

2. **Oxidative addition**
   - $\text{Ar-}^{-}\text{Pd}^{\text{II}} \rightarrow \text{Ar-}^{-}\text{Pd}^{\text{III}} \rightarrow \text{Ar-}^{-}\text{Pd}^{\text{II}}$
   - $\text{C}=\text{O}^+$

3. **Transmetallation**
   - $\text{Ar-}^{-}\text{Pd}^{\text{II}} \rightarrow \text{Ar-}^{-}\text{Pd}^{\text{II}}$

4. **CO insertion**
   - $\text{Ar-}^{-}\text{Pd}^{\text{II}} \rightarrow \text{Ar-}^{-}\text{Pd}^{\text{II}}$

Medical Imaging
**Question:** Consider the three functional groups (a, b, c) in molecule X. (Using the necessary protecting groups on other parts of the molecule) which of these positions could be carbon-11 labelled with:

- **A** \(^{11}\text{CH}_3\text{OTf}\) b (Pd cat.), c (S\(_2\)N2)
- **B** \(^{11}\text{CN}\) a (base), b (CuCN)
- **C** \(^{11}\text{CO}\) b (Pd cat. or radical)
Radical carbonylation with $[^{11}\text{C}]\text{CO}$

$$R'\leftarrow\text{I} + ^{11}\text{CO} \xrightarrow{h\nu} R'\text{OH}$$
organic solvent/ $\text{H}_2\text{O}$
6 min
50-70% RCY

$$R'\leftarrow\text{I} + ^{11}\text{CO} \xrightarrow{h\nu} R'\text{OR}$$
organic solvent/ $\text{ROH}$
6 min
up tp 85% RCY

$$R'\leftarrow\text{I} + ^{11}\text{CO} \xrightarrow{h\nu} R'\text{NR}_2$$
organic solvent/ $\text{RNH}_2$
6 min
up tp 85% RCY

Mechanism of radical carbonylation

$$R\leftarrow\text{I} \xrightarrow{h\nu} R: \text{C}=\text{O}: \xrightarrow{R} R: \text{C}=\text{O}^+$$

carboxylic acids
esters
amides
Incorporation of $^{11}$C with $[^{11}\text{C}]\text{CO}_2$

Reaction of $[^{11}\text{C}]\text{CO}_2$ with Grignard reagents

\[
\text{H}_3\text{C} - \text{MgCl} \quad \xrightarrow{\text{O}^{11}\text{C}=\text{O}} \quad \text{O} \quad \xrightarrow{\text{H}_3\text{C} - \text{OH}} \quad \text{[}^{11}\text{C}\text{-acetate}}
\]

\[\text{J. Label. Comp. Radiopharm. 2006, 49, 263}\]

Use of $[^{11}\text{C}]$-acetate

$[^{11}\text{C}]$-acetate: radiotracer which enters the Krebs cycle reflecting cell oxidative metabolism. Now finding applications in oncology (e.g. prostate and liver):

$[^{18}\text{F}]$-FDG PET tracer not ideal for prostate cancer due to the slow growth of tumour cells. Only with $[^{11}\text{C}]$acetate is high uptake observed in PET scan.

Cu catalysed carboxylation of boronic acids with $[^{11}\text{C}]\text{CO}_2$

- good **functional group tolerance** (e.g. aldehydes, bromides, cyanides) – difficult to access using Li or Mg
- **excellent RCYs** (exception: heterocyclic substrates)

\[
\begin{align*}
\text{R-} & \overset{^{11}\text{CO}_2, \text{Cul}}{\xrightarrow{\text{TMEDA, K}_{222}, \text{KF}}} \text{R-} \\
\text{B(OR)\textsubscript{2}} & \overset{\text{DMF, 100 °C, 5 min}}{\xrightarrow{\text{R-COOH}}} \text{B(pin)} \\
\end{align*}
\]

\[
\begin{align*}
\text{Ph-} & \overset{^{11}\text{CO}_2, \text{Cul}}{\xrightarrow{\text{TMEDA, K}_{222}, \text{KF}}} \text{Ph-} \\
\text{B(pin)} & \overset{\text{DMF, 100 °C, 2 min}}{\xrightarrow{\text{1. SOCl\textsubscript{2}, 100 °C, 2 min}}} \\
 & \xrightarrow{\text{2. DMF, 50 °C, 5 min}} \text{Ph-} \overset{\text{Oxytocin receptor ligand}}{\xrightarrow{\text{one-pot synthesis}}} \text{Ph-} \\
\end{align*}
\]

20% RCY, RCP >98%
Cu catalysed carboxylation of boronic acids with $[^{11}\text{C}]\text{CO}_2$ - Mechanism

\[ \begin{align*}
\text{Cu}^{l-} & \rightarrow \text{Cu}^{l-} \quad \text{(transmetallation)} \\
\text{CO}_2 \text{ insertion} & \rightarrow \text{Cu}^{l-} \quad \text{(ligand exchange)} \\
\text{Fr}^{-} & \rightarrow \text{Fr}^{-} \quad \text{(rate complex (boronate))} \\
\text{L} & \rightarrow \text{L} \quad \text{(L = ligand)} \\
\end{align*} \]
Overview: Incorporation of carbon-11

H₃⁰¹ⁱC—I/OTf

Good for S_N2 on nucleophilic sites
Ar—OH \rightarrow Ar—O⁻¹¹CH₃
R₂NH \rightarrow R¹⁻¹¹CH₃

Good for Pd mediated cross-coupling
Ar—B(OH)₂ \rightarrow Ar⁻¹¹CH₃
R—SnMe₃ \rightarrow R⁻¹¹CH₃

Very reactive towards nucleophiles (alcohols, amines) to create carbonyls

Generation of isocyanates (synthetically useful precursor)

Nucleophilic source of CN labels activated aromatic rings

Precursor of CuCN: converts ArI to ArCN

Labelling of carbonyls via Pd mediated carbonylation...

...or radical chemistry

Reacts with Grignard reagents to give carboxylic acid derivatives

O=C=O
**Question:** Which positions in the following molecules are amenable to carbon-11 labelling (without making any changes to the structure shown)?

![Image of two molecules: Raclopride and p38 kinase inhibitor]
3.4.2 Radiolabelling with Oxygen-15

*Production of oxygen-15*

\[ ^{14}\text{N}(d,n)^{15}\text{O} \]

Deuterium bombardment of nitrogen-14 results in release of a neutron to give \(^{15}\text{O} \); decays 99.9\% by positron emission to \(^{15}\text{N} \)

\[ ^{15}\text{O}\text{CO}_2 \xrightarrow{\text{carbon, 400} \, ^\circ\text{C}} \] \[ ^{15}\text{O}\text{O}_2 \xrightarrow{\text{H}_2/\text{Pd or Pt}} \] \[ ^{15}\text{O}\text{H}_2\text{O} \]

\[ ^{15}\text{O}\text{CO} \xrightarrow{\text{carbon, 1025} \, ^\circ\text{C}} \] \[ ^{15}\text{O}\text{n-butanol} \]

Multi-step synthesis is not possible due to short half-life

\[ ^{15}\text{O} \text{ half-life } t_{1/2} = 2.04 \, \text{min} \]

The short half-life prevents the isotope from being transported away from the site of production.
**PET imaging with $[^{15}\text{O}]{\text{H}}_{2}\text{O}$**

- coronary artery disease: major cause of death, identified by evaluating myocardial blood flow (MBF)
- most accurate measurement of MBF: PET
- $[^{15}\text{O}]{\text{H}}_{2}\text{O}$ widely used as freely diffusible PET tracer for MBF

(A) PET/CT image using $[^{15}\text{O}]{\text{H}}_{2}\text{O}$ and (B) MRI image showing myocardial infarction (arrow)

(PTI$_{vb}$: fitted blood volume fractions)

3.4.3 Radiolabelling with Nitrogen-13

Production of nitrogen-13

\[ ^{16}\text{O} (p,\alpha)^{13}\text{N} \]

Proton bombardment of oxygen-16 results in release of an \( \alpha \) particle to give \(^{13}\text{N}\); decays 100% by positron emission to \(^{13}\text{C}\).

\[ ^{16}\text{O} (p,\alpha)^{13}\text{N} \rightarrow [^{13}\text{N}]\text{NO}_2 + \text{NO}_3 \]

DeVarda’s Alloy

Al/Cu/Zn alloy

\[ [^{13}\text{N}]\text{NH}_3 \]

main imaging agent is ammonia and its derivatives, multi-step synthesis is not possible due to short half-life

\[ ^{13}\text{N} \text{ half-life } t_{1/2} = 9.97 \text{ min} \]

The short half-life prevents the isotope from being transported away from the site of production.

PET imaging with \([^{13}\text{N}]\text{NH}_3\)

Like \([^{18}\text{O}]\text{OH}_2\), \([^{13}\text{N}]\text{NH}_3\) is used for myocardial blood flow imaging.
3.4.4 Radiolabelling with Fluorine-18

*Production of fluorine-18*

\[ ^{20}\text{Ne}(d,\alpha)^{18}\text{F} \]
\[ ^{18}\text{O}(p,n)^{18}\text{F} \]

deuteron bombardment of neon-20 results in release of an \( \alpha \) particle to give fluorine-18; proton bombardment of oxygen-18 results in release of a neutron to give fluorine-18; decays to 97% by positron emission and 3% by electron capture to \( ^{18}\text{O} \)

\[
\text{Ne} \quad \xrightarrow{\text{K}_2\text{CO}_3} \quad [^{18}\text{F}]\text{F}_2 \quad \text{for electrophilic } ^{18}\text{F}-\text{labelling}
\]

\[
[^{18}\text{O}]\text{H}_2\text{O} \quad \xrightarrow{\text{K}_2\text{CO}_3} \quad [^{18}\text{F}]\text{KF}_{(aq)} \quad \text{for nucleophilic } ^{18}\text{F}-\text{labelling (higher SA)}
\]

\[ ^{18}\text{F} \text{ half-life } t_{1/2} = 110 \text{ min} \]

rule-of-thumb: 3 isotope half-lives for radiotracer synthesis and transport \( \rightarrow \) for \( ^{18}\text{F} \): ca. 5.5 hours
Advantage of labelling with fluorine-18: most widely used radionuclide in PET

- short positron linear range in tissue (2.3 mm) → highest resolution PET images of all available positron emitters
- $t_{1/2}$ long enough to allow for transportation to sites several hours away, and the imaging of long physiological processes
- fluorine is a good isostere for –H (size) and –OH (polarity) (isosteres = groups or molecules which have chemical and physical similarities, producing broadly similar biological effects)
- metabolic stability of fluorinated biomolecules

Disadvantages

- no naturally fluorinated biomolecules exist: small pool of biologically active targets, unknown effects of introducing an “unnatural” fluorine atom

Radiolabelling strategies

- direct labelling with $^{18}$F$^+$ or $^{18}$F$^-$: late-stage one- or two-step labelling
- indirect labelling with $^{18}$F-fluorinated prosthetic groups: lower SA, but often greater functional-group compatibility than direct labelling
Direct, electrophilic fluorination with $[^{18}\text{F}]^+$

- most traditional $^{18}\text{F}$-labelling technique, not used very much anymore
- disadvantages:
  $[^{18}\text{F}]\text{F}_2$ highly reactive and difficult to handle $\rightarrow$ very unselective, low RCYs
  “cold” $[^{19}\text{F}]\text{F}_2$ added as a carrier gas in production $\rightarrow$ low specific activities, low radiochemical yields (theoretical maximum: 50% RCY)
- less reactive derivatives have been developed to increase RCY and selectivity
Electrophilic $[^{18}F]$-fluorination of alkenes

$[^{18}F]$FDG (8% RCY)
most common PET imaging agent (oncology)
Lab. Comp. Radiopharm. 1978, 14, 175

$[^{18}F]$FDG (40% RCY)
J. Nucl. Med. 1982, 23, 899

$[^{18}F]$EF5
PET hypoxia imaging agent
Electrophilic aromatic substitution with $[^{18}\text{F}]^+$

- low selectivity (various mono- and di-fluorinated products)
- difficult separation/purification

$[^{18}\text{F}]$-RG peptide (Arg-Gly-Asp)
integrin receptors for tumour imaging
Electrophilic demetallation with $[^{18}\text{F}^+]$

\[ \text{M} = \text{SiR}_3, \text{GeR}_3, \text{SnR}_3, \text{Ag}, \text{HgR} \]

very rarely: MgX, Li

Synthesis of $[^{18}\text{F}]$FDOPA: **improved regioselectivity** using organometallic reagents

<table>
<thead>
<tr>
<th>$[^{18}\text{F}^+]$</th>
<th>M</th>
<th>Selectivity 2-:5-:6-$[^{18}\text{F}]$FDOPA</th>
</tr>
</thead>
<tbody>
<tr>
<td>$[^{18}\text{F}]F_2$</td>
<td>H</td>
<td>35 : 5 : 59</td>
</tr>
<tr>
<td>$[^{18}\text{F}]$AcOF</td>
<td>$\text{SnMe}_3$</td>
<td>0 : 0 : 100 (8% RCY)</td>
</tr>
<tr>
<td>$[^{18}\text{F}]$Selectfluor</td>
<td>$\text{SnMe}_3$</td>
<td>0 : 0 : 100 (12% RCY)</td>
</tr>
<tr>
<td>$[^{18}\text{F}]$Selectfluor</td>
<td>Ag</td>
<td>0 : 0 : 100 (19% RCY)</td>
</tr>
</tbody>
</table>
Direct, nucleophilic fluorination with $^{18}\text{F}^-$

- advantages: higher specific activity than $^{18}\text{F}\text{F}_2$, reactivity easier to modulate → most modern radiofluorinations use $^{18}\text{F}^-$

- disadvantages: often requires harsh reaction conditions

- aqueous fluoride is a poor nucleophile (high degree of solvation): $^{18}\text{F}^-(\text{aq})$ is trapped on an ion-exchange column, dehydrated, and eluted with MeCN, $\text{M}_2\text{CO}_3$ and a cryptand source, to afford the more nucleophilic $^{18}\text{F}\text{MF}$ ($\text{M} = \text{K}$ or Cs)

$^{18}\text{O}(p,\gamma)^{18}\text{F}$ $\rightarrow$ $^{18}\text{F}^- + \text{H}_2^{18}\text{O}$ $\xrightarrow{\text{M}_2\text{CO}_3}$ $[^{18}\text{F}\text{MF}]$

$[^{18}\text{F}]\text{KF/K}_{222}$: complexation of potassium by the azacryptand kryptofix-222 ($\text{K}_{222}$), leaving a more exposed, nucleophilic fluoride anion

$[^{18}\text{F}]\text{TBAF}$: alternative $^{18}\text{F}^-$ activation by eluting off ion-exchange column with tetrabutylammonium hydrogen carbonate
Question: Why are nucleophilic radiofluorination methods preferred over electrophilic ones?

- $^{18}\text{F}^-$ is available with higher specific activity than $[^{18}\text{F}]\text{F}_2$.
- Electrophilic fluorinating reagents are highly reactive and difficult to handle. Nucleophilic fluorinating reagents can be safer and their reactivity can be easier to modulate.
- Disadvantage: harsh reaction conditions may be required.
**Direct, aliphatic nucleophilic substitution with \[^{18}F^-\]**

\[
\text{Nu}^- \quad \text{H}_3\text{C} \quad \text{X} \quad \xrightarrow{\delta^- \text{H} \quad \text{H} \quad \delta^-} \quad \text{Nu}^- - \text{CH}_3 \quad \text{X}^- \\
\text{X} = \text{I}, \text{OTf}, ... \\
\]

**S\text{N}_2 substitution nucleophilic bimolecular (inversion of stereochemistry)**

Efficient \(^{18}\text{F}\)-radiolabelling in **one step** (no protecting groups)...

**[^18F]LBT-999**

Dopamine transporter ligand

...or **two steps** (with protecting groups)

1. \[^{18}\text{F}\]TBAF, tBuOH 120 °C, 10 min
2. HCl (deprotection)

[^18F]FLT
Direct, *aliphatic nucleophilic substitution* with $[^{18}\text{F}]^-$

[Chemical reaction diagram]

Fully automated $[^{18}\text{F}]$FDG production:
- RCY 60-70%
- overall synthesis time (cyclotron to purified product) < 26 min

GE Healthcare FASTlab for cassette-based “plug-and-play” PET tracer synthesis
source: gehealthcare.co.uk
Direct nucleophilic aromatic substitution with $[^{18}\text{F}^-]$

- aromatic ring activated by an *ortho-* or *para-* electron-withdrawing group (EWG = NO$_2$, CN, carbonyl)
- $X =$ NO$_2$, NR$_3$, Hal, OMs, OTs, OTf
- high RCY and SA in a simple, one-pot method
- often requires harsh conditions

**Halogen exchange (Halex) reaction**: low specific activity due to isotopic dilution (impossible to separate $^{18}$F/$^{19}$F products)
Radiolabelling of *diaryliodonium salts* with $[^{18}\text{F}]^-$

- **good RCYs in short reaction times**
- **radiolabelling of electron-rich aromatics** possible
- **regiocontrol**: nucleophile preferentially reductively eliminates with
  1. (a) the more electron-rich aromatic,
  2. (b) the less sterically hindered aromatic.
**Indirect $^{18}$F-radiolabelling with prosthetic groups**

**Prosthetic group** = a small, $^{18}$F-labelled molecule that can be added to a wide variety of compounds which are incompatible with direct fluorination (e.g. large, complicated molecules)

**Radiolabelled alkylation agents**

$$
\begin{align*}
& X - Br \\
& \xrightarrow{[^{18}F], K_2CO_3, K_{222}, 18F^- \text{limiting reagent}} 18F - \text{selective mono-fluorination} \\
& \xrightarrow{(S)-(\cdots)-tyrosine, NaOH, NaI, DMSO} [^{18}F]\text{FET}
\end{align*}
$$
Cu-mediated **Click reaction** with radiolabelled alkylating agents

Click chemistry = reactions that are simple, high yielding, wide in scope, stereospecific and create only byproducts that can be removed without chromatography (K. B. Sharpless, 2001); often refers to **1,3-dipolar cycloaddition of azides and alkynes**:
Radiolabelled arylation agents: palladium-catalysed cross-coupling
Overview: Incorporation of fluorine-18

**Direct labelling**
- $[^{18}\text{F}]\text{F}_2$ and its derivatives
  - low SA, low RCYs (max. 50%)
- Traditional labelling of nucleophilic positions
- Electrophilic demetallation: better selectivity

**Indirect labelling: prosthetic groups**
- Can provide more effective labelling for large, complicated molecules

**Mainly $[^{18}\text{F}]\text{KF}$ and $[^{18}\text{F}]\text{TBAF}$**
- higher SA, better selectivity

Good for labelling of electrophilic positions
- Reacts with diarylidenonium salts for the radiofluorination of electron-rich aromatics
3.4.5 Radiolabelling with Iodine-123

**Production of iodine-123**

\[ {^{124}\text{Te}(p,2n)}^{123}\text{I}} \]

Proton bombardment of highly enriched tellurium-124 results in release of two neutrons to give iodine-123; decays to 100% by electron capture to tellurium-123 (principal photon emission energy: 0.16 MeV)

\[
\text{Te} + \text{NaOH} \rightarrow [^{123}\text{I}]\text{NaI} \quad \text{most common}^{123}\text{I}-\text{labelling reagent}
\]

\[^{123}\text{I} \text{ half-life } t_{1/2} = 13.2 \text{ h} \]

**Advantages of \(^{123}\text{I}-\text{labelling**}

- **long half-life**: SPECT tracers more available than PET tracers, longer imaging studies possible (e.g. pharmacokinetics)
- availability of other isotopes (e.g. \(^{125}\text{I}\), a low energy \(\delta\)-emitter used in pre-clinical development; \(^{131}\text{I}\), a \(\gamma\)- and \(\beta\)-emitter used in radiotherapy)
- covalently bound to tracer → easier to incorporate than \(^{99m}\text{Tc}\)

**Disadvantages of \(^{123}\text{I}-\text{labelling**}

- **size** → greater steric perturbation of a molecule than e.g. \(^{18}\text{F}\)
Nucleophilic \(^{123}\text{I}\)-labelling reactions

Halex reaction

\[
\begin{align*}
\text{[^{123}\text{I}]Nal (NH}_4\text{)_2SO}_4} \\
145-150 ^\circ \text{C} \\
30-45 \text{ min}
\end{align*}
\]

\(X = \text{I, Br, Cl}\)

Most common nucleophilic exchange methodology for radioiodination
- \(X = \text{I}\) : low SA, due to isotopic dilution (radiotracer inseparable from “cold” molecule)
- \(X = \text{Br, Cl}\) : harsh conditions required
Electrophilic $^{123}$I-labelling reactions

- more common than nucleophilic approach: mild, fast, selective, higher RCY and SA
- electrophilic $[^{123}\text{I}^+]$ is generated by **oxidation of $[^{123}\text{I}]\text{NaI}$**:

\[
[^{123}\text{I}]\text{NaI} \xrightleftharpoons{\text{oxidant}}[^{123}\text{I}]\text{HOI} \text{ or } [^{123}\text{I}]\text{H}_2\text{OII}
\]

oxidant:

- N-chloro tosylamide
- Chloramine-T
- Iodo-Gen®
- peracetic acid

- $[^{123}\text{I}]$NaI + $[^{123}\text{I}]$NaI

\[
\text{O} \quad \text{Cl} \quad \text{N} \quad \text{N} \quad \text{Cl}
\]

\[
\text{O} \quad \text{Cl} \quad \text{N} \quad \text{N} \quad \text{Cl}
\]

\[
\text{Me} \quad \text{CO} \quad \text{OH}
\]

- chloramine-T

$[^{123}\text{I}]$NaI + $[^{123}\text{I}]$NaI

\[
\text{O} \quad \text{N} \quad \text{H}
\]

\[
\text{SnMe}_3
\]

$[^{123}\text{I}]$NaI + $[^{123}\text{I}]$NaI

\[
\text{O} \quad \text{N} \quad \text{H}
\]

\[
[^{123}\text{I}]
\]

$[^{123}\text{I}]$NaI + $[^{123}\text{I}]$NaI

\[
\text{rt, 5 min}
\]
3.4.5 Radiolabelling with metastable Technetium-99m

**Production of technetium-99m**

\[ ^{235}\text{U}(n,\gamma)^{99}\text{Mo} \]

neutron bombardment of highly enriched uranium-235 results in release of a \(\gamma\) particle to give molybdenum-99 (\(t_{1/2} = 67 \text{ h}\)) which decays to technetium-99m (chemically extracted in a \(^{99m}\text{Tc}\) generator); \(^{99m}\text{Tc}\) decays to 88\% by \(\gamma\)-emission (principal photon emission energy: 0.14 MeV) and to 12\% by internal conversion to \(^{99}\text{Tc}\)

\[ [^{99}\text{Mo}]\text{MoO}_4^{2-} \xrightarrow{\text{NaCl}_{(aq)}} [^{99m}\text{Tc}]\text{TcO}_4^{-} \]

elution of \([^{99m}\text{Tc}]\text{TcO}_4^{-}\) from an alumina column in a \(^{99m}\text{Tc}\) generator

source: *Dalton Trans.* 2011, 40, 6077

\(^{99m}\text{Tc}\) half-life \(t_{1/2} = 6.0 \text{ h}\)

radioactive decay of a **metastable** isomer simply occurs through rearrangement of the nucleons, without transmutation into another element.
Advantages of $^{99m}$Tc-labelling: most widely used radionuclide

- availability: easy production from $^{99}$Mo in commercially available generators, easy radiotracer synthesis from commercially available kits
- $t_{1/2}$ long enough to allow for transportation to sites several hours away, and the imaging of long physiological processes, yet short enough to minimise the absorbed radiation dose to the patient

Disadvantages

- target synthesis requires metal-ligand complex formation: restricts application (e.g. blood-brain-barrier)

Radiolabelling strategy

- complexation of $^{99m}$Tc with chelating ligands, usually by reduction of Tc(VII) (most common reductants: stannanes, NaBH$_4$)
- challenge: formulation of stable, efficient labelling kits
**Question 1:** Why is $^{99m}$Tc one of the most widely used radionuclides? What are its advantages over other isotopes?

- Easily prepared from $^{99}$Mo in commercially available generators.
- Easy radiotracer synthesis in commercially available kits (no need for chemists on site to produce tracers).
- Long half-life allows for transport of tracers and imaging of long physiological processes.
- Half-life not long enough to pose a great radiation risk to patient.

**Question 2:** Why is it necessary to complex $^{99m}$Tc to chelating ligands before administration to patients?

- Like Gd (see section on MRI contrast agents later), Tc has no biological function in the human body and the free metal ions are toxic ($LD_{50}$ in mice 130 mg $^{99}$Tc/kg).
- Complexation with chelating ligands makes the tracer more stable, decreases toxicity (by preventing the metal from interacting with biomolecules in the body) and allows for safe excretion.

1source: Coffey, J. L. Medical and Health Sciences Division Oak Ridge Associated Universities
Complexation of $^{99m}Tc$ with chelating ligands

Synthesis of $[^{99m}Tc]$-HMPAO

$[^{99m}Tc]$-Q12
heart imaging agent

$[^{99m}Tc]$-HMPAO
perfusion radiotracer
**Bifunctional chelating agents** for target-specific $^{99m}$Tc imaging agents bind $^{99m}$Tc securely without dissociating *in vivo*, and link to a biologically active molecule without affecting its integrity.

**Two-step labelling:** $[^{99m}\text{Tc}]\text{Tc(CO)}_3(\text{H}_2\text{O})_3$

\[ [^{99m}\text{Tc}]\text{TcO}_4^- + \text{Na}_2[\text{H}_3\text{BCO}_2] \xrightarrow{100 \, ^\circ\text{C, 20 min}} \text{ligand exchange} \]

$\text{BM} = \text{biomolecule} + \text{linker}$
Bifunctional chelating agents for target-specific $^{99m}$Tc imaging agents

One-step labelling: HYNIC conjugates

hydraxine-nicotinamide (HYNIC) $\xrightarrow{\text{biomolecule-NH}_2}$ e.g. peptide, protein, ...

BM = biomolecule

$[{^{99m}}\text{Tc}]\text{TcO}_4^-$ tricine, PR$_3$

100 °C, 10-20 min
4 Magnetic Resonance Imaging (MRI)

1950 Nobel Prize in Physics for the discovery of NMR: F. Bloch, E. M. Purcell

1971 Raymond V. Damadian hypothesizes that $^1$H NMR relaxation time of water might be used to detect cancer

1973 Paul C. Lauterbur applies gradients to MRI magnetic field strength to gain spatial information on hydrogen nuclei; image acquisition and mathematical construction is greatly improved by Peter Mansfield

2003 Joint Nobel Prize in Physiology/Medicine “for their discoveries concerning magnetic resonance imaging”

Left: R. Damadian (left) and L. Minkoff (right) with “Indomitable”, the first MRI prototype

Right: first MRI scan of a human

sources: ojcpcd.com; www.fonar.com
4.1 Recap: Physical Principles of NMR

\[
\begin{align*}
RF (E = \hbar \omega_0) & \quad E_- = \frac{1}{2} \hbar \omega_0 \quad \text{spin down antiparallel} \\
\Delta E = \hbar \omega_0 & \quad B_0 \quad \text{external magnetic field} \\
FID (E = \hbar \omega_0) & \quad E_+ = -\frac{1}{2} \hbar \omega_0 \quad \text{spin up parallel} \\
\end{align*}
\]

\[
E_m = -m \hbar \gamma B_0 = -m \hbar \omega_0
\]

\(B_0\) = external magnetic field

\(m\) = spin quantum number (for \(^1\text{H}: +\frac{1}{2}, -\frac{1}{2}\))

\(\hbar\) = Planck’s constant

\(\gamma\) = gyromagnetic ratio

\(\omega_0 = \gamma B_0\) = Larmor frequency

MRI is **NMR of water molecules** in the body. To relax, water protons need to encounter fluctuating fields (other protons or contrast agents).

**Relaxation mechanisms**

Longitudinal / spin-lattice relaxation \(T_1\)

Transverse / spin-spin relaxation \(T_2\)
Relaxation mechanisms

Longitudinal / spin-lattice relaxation $T_1$

$T_1$ relaxation describes how the component of the magnetization vector along the direction of the static magnetic field $B_0$ ($M_z$) relaxes to its original value after application of a 90° RF pulse. $T_1$ is defined as the time point at which the magnetization has recovered to 63% of its equilibrium value.

$$M_z = M_0 \left(1 - e^{-t/T_1}\right)$$

$T_1$ relaxation process

Relaxation mechanisms

Transverse / spin-spin relaxation $T_2$

$T_2$ relaxation describes how the proton magnetic moments move out of phase with each other after alignment by a 90° RF pulse, due to spin-spin interactions and due to the random nature of molecular motion, decreasing the transverse magnetisation $M_{xy}$. $T_2$ is defined as the time point at which the magnetization has recovered to 37% of its equilibrium value.

\[ M_{xy} = M_0 (1 - e^{-t/T_2}) \]

$T_2$ relaxation process

MRI Imaging

- differences in water content (proton density) among tissues and organs: **contrast** = the relative difference of the MRI signal intensity between two adjoining tissues
- in many diseases the pathological process causes changes of the water content → **different T\textsubscript{1} and T\textsubscript{2} relaxation times**
- each MRI image consists of a T\textsubscript{1} component and a T\textsubscript{2} component, but it is possible to switch off most of one of either components, creating a T\textsubscript{1} or T\textsubscript{2} weighted image
- Main difference to X-ray and nuclear imaging: **no ionising radiation** required

MRI scanner
source: researchgate.net
**T₁ Weighted MRI**

- Different tissues in the body have different T₁ relaxation times
- Faster T₁ relaxation → higher signal intensity (SI) (e.g. high signal intensity of fat)
- Used mainly to image **anatomy** (e.g. musculoskeletal system)

![Diagram of signal intensity and tissues](image)

- **T₁ weighted MRI of upper legs:** normal anatomy
  
  source: www.startradiology.com/the-basics/mri-technique/

- **Wrist X-ray:** no abnormalities; **T₁ weighted MRI:** fracture, bone edema (fat-containing bone marrow signal decreases)
  
  source: www.startradiology.com/the-basics/mri-technique/
T₂ Weighted MRI
- Different tissues in the body have different T₂ relaxation times
- Faster T₂ relaxation → higher signal intensity (high signal intensity of water)
- Used mainly to image pathology associated with edema/fluid

brain tumour with surrounding edema (high signal intensity in T₂)

source: www.startradiology.com/the-basics/mri-technique/
**Contrast Agents** = substance administered during imaging to enhance natural contrast and/or obtain dynamic information

- Major limitation of MIR: low sensitivity/contrast compared to other imaging modalities (e.g. PET, SPECT), because tissue properties too similar → signals are cancelled by space averaging
- 35% of MRI scans use contrast agents: \( T_1 \) or \( T_2 \) relaxation time of protons that absorb the contrast agent is reduced → improves contrast
- \( T_1 \) weighted MRI: paramagnetic metal ions (e.g. \( \text{Gd}^{3+} \))
- \( T_2 \) weighted MRI: super-paramagnetic nanoparticles (e.g. iron oxides)

Enhancement of tumour visualisation after Gd administration

source: www.startradiology.com/the-basics/mri-technique/
**Gadolinium-based paramagnetic \( T_1 \) contrast agents**

**Mode of Action**

- **paramagnetism**: magnetisation in external magnetic field → unpaired electrons with strong magnetic moment can induce **magnetic relaxation** in nearby nuclei
- direct interaction of \( \text{Gd}^{3+} \) with water molecules through fast exchange on the open coordination site: **inner-sphere relaxation**
- second shell of water-ligand interactions: **outer-sphere relaxation**
- fast \( T_1 \) relaxation results in signal enhancement: **positive contrast** (bright)
- **extracellular** action

<table>
<thead>
<tr>
<th>Ion</th>
<th>Configuration</th>
<th>Magnetic moment</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{Cr}^{3+} )</td>
<td>( 3d^3 )</td>
<td>3.88</td>
</tr>
<tr>
<td>( \text{Mn}^{2+} )</td>
<td>( 3d^5 )</td>
<td>5.92</td>
</tr>
<tr>
<td>( \text{Fe}^{3+} )</td>
<td>( 3d^5 )</td>
<td>5.92</td>
</tr>
<tr>
<td>( \text{Eu}^{3+} )</td>
<td>( 4f^8 )</td>
<td>3.4</td>
</tr>
<tr>
<td>( \text{Gd}^{3+} )</td>
<td>( 4f^7 )</td>
<td>7.94</td>
</tr>
<tr>
<td>( \text{Dy}^{3+} )</td>
<td>( 4f^9 )</td>
<td>10.65</td>
</tr>
</tbody>
</table>

Electronic configuration and magnetic moment of metal ions used in \( T_1 \) contrast agents

*source: Adv. Mater. 2009, 21, 2133*

Representative examples of \( T_1 \) contrast agents

Properties

- paramagnetic: Gd$^{3+}$ easily magnetised at room temperature, strong paramagnet
- electron spin relaxation time of the metal must match proton Larmor frequency
- toxic (strong complexes with biological ligands), slow clearance: complexation with **strong chelating ligands**

Synthesis

\[
\begin{align*}
\text{HO}_2\text{C} & \quad \text{N} & \quad \text{N} & \quad \text{N} & \quad \text{CO}_2\text{H} \\
\text{HO}_2\text{C} & \quad \text{N} & \quad \text{N} & \quad \text{N} & \quad \text{CO}_2\text{H} \\
\text{DTPA} & & & & \\
\text{diethylenetriaminepentacacetate} & & & & \\
\end{align*}
\]

\[
\begin{align*}
\text{HO}_2\text{C} & \quad \text{N} & \quad \text{N} & \quad \text{N} & \quad \text{CO}_2\text{H} \\
\text{HO}_2\text{C} & \quad \text{N} & \quad \text{N} & \quad \text{N} & \quad \text{CO}_2\text{H} \\
\text{DOTA} & & & & \\
1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid & & & & \\
\end{align*}
\]

\[
\begin{align*}
\text{Gd}^{3+} & \quad \text{CO}_2\text{H} \\
\text{Gd}^{3+} & \quad \text{CO}_2\text{H} \\
\end{align*}
\]
Super-paramagnetic iron oxide (SPIO) $T_2$ contrast agents

Properties

- **super-paramagnetism**: small, single-domain magnetic particles $\rightarrow$ strong internal magnetisation in external magnetic field with large field inhomogeneities that cause dephasing of neighbouring protons
- fast $T_2$ relaxation results in signal loss: **negative contrast** (dark)
- most commonly used $T_2$ contrast agents: iron oxide-based **nanoparticles**
- higher magnetic moment than $T_1$ contrast agents $\rightarrow$ no direct chemical exchange between bound and free water molecules required $\rightarrow$ lower dose required
- non-toxic, rapidly cleared
- **intravascular** action ("blood pool contrast agents")

$T_2$ weighted MRI of lymph nodes before (a) and after (b) administration of SPIO  

TEM images of representative $T_2$ nanoparticle contrast agents  
**Example: Brain MRI for the diagnosis and monitoring of Multiple Sclerosis**

MS presents with lesions (demyelation) which can be detected as high intensity (white) signals in Gd-enhanced brain MRI and non-enhanced spinal MRI.

(A) T2 weighted brain MRI showing multifocal regions of high signal intensity; (B) Gd contrast enhanced brain MRI; (C) MRI showing lesions in spinal chord

source: www.medscape.org
## Recap: Overview of medical imaging techniques

<table>
<thead>
<tr>
<th>Technique</th>
<th>Radiation</th>
<th>Applications</th>
<th>Benefits</th>
<th>Disadvantages</th>
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</thead>
<tbody>
<tr>
<td><strong>MRI</strong></td>
<td>radiofrequency + magnetic field</td>
<td>- <strong>anatomic</strong> information&lt;br&gt;brain, spinal chord, veins, abdominal organs tumours, cysts, abnormal tissue&lt;br&gt;- tumours, cysts, abnormal tissue</td>
<td>- non-ionising radiation&lt;br&gt;- high spatial resolution</td>
<td>- low sensitivity&lt;br&gt;- long scanning time&lt;br&gt;- no real-time information&lt;br&gt;- relatively expensive</td>
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<tr>
<td><strong>X-Ray (CT)</strong></td>
<td>X-rays (ionising)</td>
<td>- <strong>anatomic</strong> information&lt;br&gt;bones, teeth, joints organ structure</td>
<td>- short scanning times&lt;br&gt;- good spatial resolution</td>
<td>- exposure to ionising radiation may increase cancer risk&lt;br&gt;- no real-time information&lt;br&gt;- low resolution where soft tissue contrast is low</td>
</tr>
<tr>
<td><strong>Radionuclide Imaging</strong></td>
<td>Beta/Gamma radiation (ionising)</td>
<td>- <strong>functional</strong> information&lt;br&gt;cancer&lt;br&gt;cardiovascular diseases&lt;br&gt;neurological diseases</td>
<td>- highly accurate and specific functional information&lt;br&gt;- good, tissue-specific contrast</td>
<td>- ionising radiation&lt;br&gt;- rel. low spatial resolution (SPECT)&lt;br&gt;- high cost</td>
</tr>
</tbody>
</table>
Books

Papers

Lectures and other resources
The Sprawls Resources for study, review, reference and teaching: physics and technology for effective and safe medical imaging; www.sprawls.org/resources