NUCLEAR PHYSICS FOR MEDICINE

How nuclear research is improving human health
THE RISE OF NUCLEAR MEDICINE AND RADIATION THERAPY

Procedures employing nuclear particles and radiation to understand, diagnose and cure disease are becoming an ever-more important component of critical life-saving healthcare.
Nuclear medicine and radiation therapy encompass several aspects:

- The emissions from radioactive isotopes can be employed as diagnostic tools by creating images of a patient’s tissues and organs to reveal details of both the structure and function. To provide images of target cells or living processes, these isotopes are chemically combined with molecules known to bind to specific biomolecules.
- Radioisotopes are also used as tracers in pharmaceutical research to study the behaviour of drugs in the body.
- Beams of nuclei, as well as emissions from radioisotopes, can be targeted so as to kill cancer cells that are otherwise inaccessible or difficult to destroy by other means.

Using a reconstruction algorithm, a computer can then produce a 3D image from the data. The most commonly used radioisotope is technetium-99m. It accounts for about 80 per cent of medical radioisotope usage today. It is extremely suitable because it has an intermediate half-life of six hours, and the gamma-rays have an energy well suited for imaging. It can also be made available even in remote locations by being generated from a longer-lived isotope (see p.7) made in accelerators or reactors elsewhere. Over the decades, methods have been developed to bind technetium to a variety of inorganic and organic compounds, enabling it to reach many different kinds of target tissues.

Another imaging technique that has gained popularity since 2000 is positron emission tomography, PET. It employs positron-emitting isotopes, which are injected in the same way. The positrons emitted annihilate when they come into contact with ordinary matter to release a pair of gamma-rays that fly off in opposite directions along a so-called line of response (LOR). The pairs can be identified because they reach detectors positioned on opposite sides almost simultaneously; their point of origin can then be ascertained along the LOR. Again, an image can be reconstructed. The positron-emitting isotope most commonly used is fluorine-18 combined with a glucose derivative that is easily distributed in the body. Because it has a short half-life of just under two hours, the radiation dose is low.

**IMAGING**

The most used nuclear imaging technique is single-photon computed tomography, or SPECT, in which the gamma-rays, emitted in all directions by a radioisotope that has been injected into the body, are detected by a special gamma camera. The camera scans the patient, or organ site, from all angles, collecting data on the location of the points of emission.

In hadron therapy, all the energy of an ion beam is delivered to a precise target location – the tumour – without damaging surrounding tissues.

**THERAPY**

A direct spin-off from nuclear physics research is the use of accelerated beams of nuclear particles (hadrons) to treat cancer. Thin pencil-like beams of protons, and more recently carbon-12 nuclei (as ions), are used to selectively irradiate a tumour in the same way as in conventional X-ray ‘teletherapy’. The energetic hadrons break up the DNA strands within the tumour cells so that they die. The advantage of hadron therapy, is that most of the particle energy is deposited within a small volume inside the tumour, thus sparing healthy tissue. This makes it ideal for treating tumours close to organs at risk and those in children, for which exposure to radiation should be minimised. Since its launch in 1954, about 100,000 hadron-therapy procedures have been carried out across the world, of which approximately 10,000 are with carbon ions. It is still quite an undeveloped clinical procedure with considerable potential for expansion.

Another therapeutic approach is to inject radioisotopes chemically attached to molecules that are preferentially taken up by cancer cells. Targeted radionuclide therapy is best used to reach cancer cells that have spread and distributed metastases that cannot be reached with surgery or external radiation therapy.
Hadron therapy has several advantages over X-ray therapy. It can accurately deliver a highly controlled dose of radiation to the tumour, while sparing surrounding healthy tissue. It is more effective at treating highly-resistant tumours. Moreover, the reduced exposure of the normal tissue makes it possible to reduce the number of treatments.

**THE IDEAL PROCEDURE**

A state-of-the-art set-up would consist of a compact accelerator (see p.7), which can deliver highly tuneable beams to a patient lying in front of a gantry that is rotated to accommodate different beam arrangements.

A crucial part of the procedure is the treatment planning. The target tissues are imaged in 3D using X-ray CT scanning, magnetic resonance imaging and/or PET (see opposite). The images are taken in sequential segments to identify the target volume and the position of the organs at risk. Computer simulation is then carried out to determine the energies and orientation of the beams that will achieve the correct level and distribution of the radiation dose, together with the number of treatments needed.

The computed dosage is then delivered by ‘painting’ the beam across the target area at different depths. Tumour tissue is not homogeneous, and dose-painting ideally allows the amount of radiation reaching different parts of the tumour to be modified. This means that doses can be delivered in fewer treatments, which is cheaper and aids patient recovery.

**MOVING TARGETS**

A major issue in any treatment is the fact that tumours and normal organs move, and so compensatory scanning methodologies are being developed that can take account of, for example, breathing or bowel movement. The target can be scanned more than once to average out the motion (re-scanning), or the beam can be stopped and started to coincide with a pre-defined position of the target (‘gating’). Another promising option is to track the motion using simultaneous imaging to guide the beam (tracking). Charged particles generate positron-emitting isotopes in the patient, which can be exploited as a PET imaging agent, both in treatment monitoring and beam guidance. Such techniques will allow clinicians to treat tumours in the lung, the rectum, and in the left breast (without affecting the heart).

**NEW TREATMENTS**

Protons and carbon ions are not the only particles that can be used in therapy. Helium ion beams might offer a lower-dose, better-targeted treatment than protons for young cancer sufferers, because these ions scatter less than protons. Oxygen-16 ion beams are being studied as a more effective alternative for treating hypoxic tumours such as those characterising pancreatic cancer, which are very radiation-resistant and for which the therapeutic outcomes are currently poor.

**COMBINED THERAPIES**

An important part of cancer therapy is to assess the type and range of treatments needed. Particle therapy can not only shrink or kill the main tumour, but also boost an immune response, which can then be amplified by immunotherapy (using target antibodies that attack cancer cells). Such combined treatments would also target metastases, leading to much improved survival prospects for cancer sufferers.

**LOCATION OF THERAPY CENTRES**

Proton therapy is available in 42 centres worldwide with more than 30 being planned. Carbon-ion therapy is carried out in eight centres in Germany, Italy, Japan and China.
SPECT and PET are both capable of visualising the physical functioning of tissues and biomolecular changes by attaching the isotope to a selected molecule. For example, metabolic activity in the brain can be followed with the PET fluorine-18 tracer, fluorodeoxyglucose (FDG). Although SPECT is still better established than PET, interest in the latter is increasing because it offers twice as high spatial resolution – at about 4 mm.

THE NEED FOR HIGHER RESOLUTION

Both imaging techniques are entering a new era, driven by the need for higher resolution and improved molecular specificity. Small-animal imaging is an essential component of biomedical research, in particular in following the uptake of drugs. However, a resolution of better than 1 mm is needed to study the brain of a mouse, for example. More advanced instrumentation is therefore required that is capable of imaging smaller structures. The early diagnosis of disease at the molecular level, radiotherapy planning, and the simultaneous imaging of moving organs to guide treatment (see opposite), also demand the highest resolution possible.

RECENT ADVANCES

Fortunately, nuclear and particle-physics research is providing a range of developments that is benefiting medical imaging.

- New photodetectors based on miniaturised semiconductor chip designs have been developed to enable compact, higher-resolution instruments to be designed for small-animal PET.
- To pair up the back-to-back annihilation gamma-rays in PET requires being able to measure detection times with a precision of half a billionth of a second. Image quality can be improved by narrowing the location of the annihilation. This is achieved by measuring the time difference of arrival at the detectors of the two gamma-rays (each will have travelled different distances and passed through differing tissues). This requires dedicated reconstruction algorithms, which are developed in nuclear physics laboratories.
- A further potential improvement in localisation that is creating great interest could be obtained using a new class of PET isotopes in which a third, additional gamma-ray is emitted by the daughter nucleus of the positron-emitting isotope. This can be detected by a gamma-ray camera, and again, by measuring the time after the annihilation event, its trajectory used to triangulate the point of origin.

In addition, nuclear reactions induced in tissues by a therapeutic hadron beam (such as carbon-12 ions) may generate positron-emitting nuclei (such as carbon-11), which can then be used to generate PET images with a suitable detector.

All these processes require a deep knowledge of nuclear processes, as well as the facility to design ultra-fast position-sensitive detectors, and optimised simulation and reconstruction software.

COMBINATION IMAGING

Today, SPECT or PET are generally combined with X-ray CT scanning in order to provide structural information that renders a more quantitatively accurate image. To obtain even more valuable complementary information, the option of additional magnetic resonance imaging (MRI) would be preferable. However, the high magnetic field associated with MRI presents challenges for traditional PET and SPECT instrumentation – which is being addressed through the development of a new generation of solid-state detectors.
Virtually all radioisotopes have to be produced by the artificial transmutation of stable elements via nuclear reactions first investigated at nuclear physics facilities. During recent decades, more than 3000 radioactive isotopes have been discovered in this way. While many are very short-lived or extremely difficult to produce, several dozen have properties that make them potentially useful for medical applications.

A medical isotope must:

- for imaging, emit long-range, medium-energy radiation so that it can be detected outside the patient’s body;
- not emit (non-beneficial) high-energy radiation that would require excessive radiation shielding or isolation protocols;
- for therapy, emit short-range radiation that deposits the maximum amount of energy in a defined target tissue volume;
- have a half-life long-enough to be delivered, but short enough not to cause unnecessary radiation exposure for the patient or present waste-disposal problems;
- have appropriate chemical properties so that it can, for example, seek out target tissues, or be coupled to molecules that preferentially bind to specific tissues;
- decay or be expelled from the body within a suitable period;
- be produced in large enough amounts for clinical use at an economic cost.

**RECENT SUCCESSES FROM NUCLEAR PHYSICS**

Very short-lived isotopes are accessible in the clinic from the decay of longer-lived ‘generator’ isotopes. The PET isotope, rubidium-82, which is a promising agent for studying the blood flow in heart muscle, has a half-life of only 75 seconds. It is generated from strontium-82, which can be made only in the larger accelerators based in nuclear physics centres. To meet rising demand, new dedicated machines are now coming online. Such machines can also make the long-lived generator isotope, germanium-68. Its decay produces the PET isotope, gallium-68. Via chemical compounds called chelators, it can be attached to a large variety of cancer-specific molecules, such as peptides that bind to certain cell receptors found in neuroendocrine tumours, to produce successful PET scans.

Lutetium-177 can also be attached via chelators to large organic molecules, and its nuclear decay properties (half-life one week, low-energy, short-range beta radiation) make it ideal for the targeted radionuclide therapy of neuroendocrine and other tumours. The side-effects are much milder than for chemo-therapies, so its use is rapidly growing.

Isotopes that emit alpha particles offer a new type of targeted radiotherapy that is now coming to the fore. As in hadron therapy, all the energy is deposited within a short range. The first alpha-emitting radiopharmaceutical based on radium-223 has now been approved and is used to treat otherwise difficult-to-treat bone metastases.

**THERANOSTICS**

The planning of cancer treatments is hampered by the fact that – depending on their cell biochemistry – patients respond differently to chemo- or immunotherapy. Nuclear physics can offer a more personalised approach known as theranostics. Using ‘matched pairs’ of diagnostic and therapeutic isotopes (for example, copper-64 and copper-67, that combine with the same targeting vector), clinicians can tailor the radiation dose needed to maximise success. Just recently, nuclear physicists even identified and produced a matched quartet of terbium isotopes, which provide a set of decay characteristics producing excellent tumour visualisation and therapeutic efficacy. Theranostics is also possible in teletherapy, using high-energy proton beams for simultaneous proton radiography and treatment. Collaborative work is underway to establish economic methods of production.
Nuclear medicine and radiation therapy offer some highly effective strategies for combating disease, but their application is limited by the current availability of dedicated infrastructures to provide radioisotopes or ion beams for therapy. The demand for radioisotopes is increasing rapidly, and there are supply bottlenecks for some well-established radioisotopes, such as the generator of technetium-99m – molybdenum-99, as well as some new isotopes with clinical potential.

The development of hadron therapy is also curtailed by the fact that the accelerators needed to generate the beams are large and expensive. The most serious obstacle, hampering the worldwide spread of hadron-therapy centres, is the high cost. Should it drop enough to match that of X-ray therapy, hadron therapy could become the dominant – if not the sole – radiotherapy offered.

A major challenge for nuclear physicists, therefore, is to develop economic methods of production and delivery. New generations of affordable, more compact accelerators (see opposite) are now being developed that could considerably expand the curative value of nuclear particles and radiation.

The importance of collaboration
Nuclear medical research is extremely interdisciplinary, and nuclear physicists aim to work closely with other specialists:
- chemists and life scientists – in the optimisation of nuclear medical procedures;
- instrument specialists and software engineers – in developing optimised instrumentation such as detectors, electronics and computer programs;
- clinicians – in designing effective treatment strategies;
- and commercial instrument companies – in developing cost-effective treatment systems.

Goals and challenges
The future of nuclear medicine and radiation therapy is extremely promising.

Enabling nuclear technologies for medicine
Many non-invasive diagnostic techniques take advantage of devices and technologies that were originally developed for research in subatomic physics. These include:
- superconducting magnets required for MRI, itself a technique based on nuclear physics;
- X-ray digital detectors called charge-coupled devices;
- a new generation of advanced chips for detecting high-energy radiation;
- computer algorithms for data-processing in nuclear physics, also applied to treatment planning.

Novel accelerator schemes
One of the first accelerators developed was the cyclotron, in which charged particles travel in a spiral controlled by magnetic fields, while being accelerated by a radio-frequency electric field. Small, low-energy cyclotrons are in use today to make medical isotopes on-site, and for proton therapy. However, many isotopes must be made at higher energies, requiring other types of circular and linear machines that are in operation only in central research facilities. The same argument applies to the production of ion beams for therapy. A great deal of work is going into developing novel compact accelerators – which might even be installed directly in a treatment room.

- The fixed field accelerating gradient (FFAG) accelerator
  Work is being undertaken on a compact circular accelerator that is similar to a cyclotron but with an advanced magnetic-field configuration, enabling higher energies to be reached in smaller dimensions.

- The dielectric wall accelerator
  A very compact device, which employs a linear electromagnetic wave travelling down a tube made of insulating material to accelerate particles, is now being developed for proton therapy. The design has the advantage that the energy and intensity of the beam can be modulated to deliver a precise dose to a tumour.

- Laser acceleration
  Another concept that is developing fast, though still far from clinical use, is that of laser-driven acceleration in which a plasma of charged particles rides the wake of an intense table-top laser beam.