Medical isotope production with the IsoDAR cyclotron

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Jose R. Alonso and colleagues describe technical advances that will allow the proposed IsoDAR (isotope decay at rest) cyclotron — being developed for neutrino physics research — to produce many medical isotopes more efficiently than existing cyclotrons can.

A wide variety of clinical isotopes can be produced using cyclotrons[1], by bombarding other atoms with accelerated particles. Example isotopes include ^{19}F used in fluorodeoxyglucose for positron emission tomography (PET) and ^{125}I used for single-photon emission computerized tomography (SPECT) studies. Each application has its own specific biology and chemistry; for each isotope, the beam energy, beam particle and target are also unique. Although the production of many radioisotopes is established, there are avenues for improvement. In particular, the much higher beam current, higher energy and flexibility of beam species puts the proposed IsoDAR (isotope decay at rest) cyclotron in a favourable position to produce important isotopes that are economically difficult to make at present.

The IsoDAR cyclotron, to be deployed at the Kamioka Observatory in Japan, is a compact cyclotron designed primarily for sterile neutrino searches. IsoDAR will deliver 10 mA of 60 MeV protons, a beam current that is an order of magnitude larger than in existing cyclotrons. The IsoDAR experiment[2] places a powerful antineutrino source in close proximity to a large liquid scintillator detector (such as the Kamioka liquid-scintillator antineutrino detector, KamLAND) as a definitive test for the existence of sterile neutrinos. Its 600 kW of protons strike a Be target to produce neutrons that flood a ^{7}Li sleeve generating ^{8}Li, whose decay produces electron antineutrinos with a flux equivalent to that of a 50 kiloCurie (2 petaBecquerel) β-decay source. The cross-section for neutrino interactions is so small that to obtain a statistically meaningful number of observed interactions a very large number of neutrinos must be produced, which in turn requires accelerator technology well beyond today's limits[3]. This dramatic improvement of performance, driven by the requirements of particle physics, can be put to use in opening new possibilities for the production of medical isotopes.

Cyclotron technology

Cyclotrons use radio frequency (RF) electric fields to accelerate charge particles, which are held on spiral trajectories by static magnetic fields. The first cyclotron was built by Ernest Lawrence in 1930 as a tool for nuclear physics research. As the field developed, nuclear physicists — and later, particle physicists — required ever-increasing beam energies for basic physics studies. Because cyclotrons can only produce lower-energy particles, restricting them to megaelectronvolt rather than gigaelectronvolt or teraelectronvolt energies, they were superseded by synchrotrons as the preferred machines for science at the frontiers of high energy. However, the megaelectronvolt energies attainable by a cyclotron are ideal for producing radioisotopes.

Early cyclotrons accelerated protons, the simplest ion. However, the current of a proton beam is limited by the process of extracting the beam from the magnet. This extraction was done using a septum: a thin sheet placed between the last and second-last orbital turns, which allows the establishment of an electric or magnetic field that deflects particles in the last turn out of the magnet and towards the desired target. However, if the pitch of the spiral trajectory is not large enough, some protons strike the septum plate, causing activation and damage. Today's cyclotrons use H⁻ ions, which have the same dynamics as protons (apart from a minus sign) but can be extracted using a very thin stripping foil. This foil removes the two electrons from the ion leaving a proton, which bends the opposite way from the H⁻ and cleanly exits the cyclotron. Although using a stripper foil rather than a septum increases the possible machine current, there are still two important limitations to cyclotron performance. The first is stripper-foil lifetime. Heat deposited in the foil from the passage of ions limits H⁻ currents to a maximum of ~1 mA. The electrons released by the break-up of the H⁻ ion on the foil are bent with very small radii, spiralling repeatedly through the foil until all their energy is lost. Over 90% of the foil heating comes from these electrons. The second important limitation arises because space charge — the repulsive force between like charges — causes the size of the beam to grow. This growth can fill in the spaces between the turns of the spiralling beam, making septum extraction more difficult, and can also lead to loss of beam as it strikes the walls of the vacuum enclosure and

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Table 1 | **Comparison of IsoDAR with IBA cyclotrons**

Parameter	IsoDAR	IBA C-30	IBA C-70
Ion species accelerated	H_2^+	H^-	H^-
Maximum energy (MeV AMU^{-1})	60	30	70
Proton beam current (mA)	10	1.2	0.75
Available beam power (kW)	600	36	52
Pole radius (m)	1.99	0.91	1.24
Outer diameter (m)	6.2	3	4
Iron weight (tonne)	450	50	140
Electric power required (MW)	2.7	0.15	0.5

IsoDAR, isotope decay at rest.

other structures inside the cyclotron. As beam current increases, space charge effects become more serious.

The IsoDAR cyclotron will accelerate H_2^+ instead of H^-, a choice that has several advantages[4]. One advantage is that although septum extraction would be the primary means of taking the beam out of the cyclotron, beam extraction can be aided by stripper foils, even at the higher current levels. The H_2^+ ion passing through a foil generates only one free electron, which is bent away from the magnet centre, and can be intercepted by a catcher before re-entering the foil. Such a catcher cannot be used with H^- because it would need to be on the inner side, and would interfere with inner turns. The now-free proton has a much smaller bending radius, and can be made to spiral around, using the field differences between the higher and lower magnetic field strength regions of the cyclotron, to exit cleanly from the cyclotron[3]. A very narrow stripper foil can be used to shadow the septum plate, intercepting ions that would strike it. The protons emerging from this stripper foil are bent inwards, and avoid the septum. In addition, stripper foils could be used to extract larger portions of the beam directly into production targets, becoming the primary extraction technique. An H_2^+ beam also reduces the effect of space charge in two ways: the H_2^+ ion has two protons for every charge (effectively doubling the proton current) and doubling the ion mass reduces the kinematic growth of the bunch from the electrostatic repulsion forces.

The choice of H_2^+ also means that the cyclotron has the flexibility to accelerate other ions with the same charge-to-mass ratio, such as deuterons, alpha particles or C^{6+} (a carbon nucleus with all 6 electrons removed). This opens up possibilities for generating isotopes not accessible with proton beams.

Beyond accelerating H_2^+, another major innovation of the IsoDAR cyclotron is the use of a RF quadrupole (RFQ) to pre-bunch the beam into the cyclotron, which substantially improves efficiency over other cyclotrons. For example, the injection line in a compact cyclotron brings the continuous beam from the ion source along an axial channel into the centre of the cyclotron, where it is bent into the plane of the magnet. The RF accelerating system (known as dees for cyclotrons) captures ions that are in the correct phase, which is typically only ~10% of the incident beam. 'Traditional' RF bunchers improve

this efficiency to ~20%. This inefficiency requires more powerful ion sources, and the large beam losses in the central region cause heat and erosion damage to the cyclotron. A properly designed RFQ can increase the capture efficiency to 80% or more. However, the RFQ must operate at the cyclotron frequency, of the order of 30 MHz, which is exceptionally low for traditional RFQs. Recent designs, using 4-rod geometries, however, can meet this requirement. The 'front end' of the IsoDAR cyclotron, including an ion source optimized for H_2^+ and the RFQ, is currently under construction[5].

TABLE 1 shows a comparison between IsoDAR and two widely used commercial cyclotrons. IsoDAR is somewhat larger and heavier, because of the higher momentum required to achieve an equivalent energy per proton for the H_2^+ ion, but this is a modest price to pay for the tenfold increase in available current.

Isotope production
We illustrate the possibilities opened up for isotope production with two examples: ^{68}Ge and ^{225}Ac. The ^{68}Ge/^{68}Ga generator is currently receiving a lot of attention in the isotope community, providing an effective means of generating isotopes for PET. The IsoDAR cyclotron could increase the production of ^{68}Ge by as much as a factor of approximately 15 over the IBA C-30 cyclotron. This increase is due to a factor of 8 increase in current, which is supplemented by the higher energy of the beam on target, allowing effective use of both of the naturally occurring isotopes of the Ga target material (abundances: 40% ^{71}Ga and 60% ^{69}Ga). If the target is thick enough, the proton energy decreases as it penetrates the target, passing through energies in which specific reactions are most favoured. In these reactions, the proton is absorbed by the Ga nucleus, forming an excited compound nucleus. The excitation energy is reduced by boiling off neutrons, each neutron taking off approximately 10 MeV. The first reaction of interest is ^{71}Ga + p (50 ± 7 MeV) → ^{68}Ge + 4n, which is inaccessible to a 30 MeV cyclotron. At greater depths in the target, the reaction of interest is ^{69}Ga + p (25 ± 7 MeV) → ^{68}Ge + 2n. The width of each excitation function is ~15 MeV, and the integrated yield over the excitation function of both reactions is about the same, so the higher proton energy effectively doubles the production of ^{68}Ge over that of a 30 MeV cyclotron.

The second example is ^{225}Ac, a promising α-emitter that has shown high effectiveness in therapy applications[6]. Early production techniques employed extremely complex target preparation and chemical separation processes, leading to high costs and limited access. In the USA, Los Alamos National Laboratory (LANL) and Brookhaven National Laboratory (BNL) have developed a technique involving the irradiation of a natural Th target[7]. The yield of ^{225}Ac at 200 MeV is quite good, but even at 60 MeV the yield is still reasonable. The laboratories estimate being able to use their accelerators (Los Alamos Neutron Science Center at LANL and Brookhaven Linac Isotope Producer at BNL) to provide a factor of 60 more ^{225}Ac per year than is currently available. The IsoDAR cyclotron could increase this amount by another factor of 100.

In summary, we believe that the performance break-throughs developed for the IsoDAR cyclotron can have significant benefits for isotope production. These developments are presented in greater detail in a separate publication[3]. One possible challenge for IsoDAR is that the beam power available far exceeds present-day target handling capabilities. However, techniques exist for splitting the beam between many targets; furthermore, the availability of the higher power will surely stimulate the development of targets capable of handling higher powers. Although IsoDAR is larger and hence more expensive than existing cyclotrons, the huge increase in yield of difficult-to-produce isotopes should provide a rationale for the inclusion of one or more of these cyclotrons in major isotope-production centres. The high yield also requires sophisticated target handling and processing equipment not likely found in a hospital, again suggesting that large commercial centres should be the site for these sophisticated accelerators. IsoDAR joins superconducting magnets, the World Wide Web and its high-capacity data-handling systems, and many other technology innovations developed to solve problems in particle physics that are now applied in many diverse fields.

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Competing interests
The authors declare no competing interests.