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Owen, H (University of Manchester) *et al*

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Hywel Owen^a, Randal MacKay^b, Ken Peach^c & Susan Smith^d

^a University of Manchester/Cockcroft Institute, Manchester, UK.

^b Christie NHS Foundation Trust, Manchester, UK.

^c Particle Therapy Cancer Research Institute, University of Oxford, Oxford, UK.

^d Accelerator Science and Technology Centre, Science and Technology Facilities Council, Daresbury, UK.

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Hadron accelerators for radiotherapy

Hywel Owen^{a*}, Randal MacKay^b, Ken Peach^c and Susan Smith^d

^aUniversity of Manchester/Cockcroft Institute, Manchester, UK; ^bChristie NHS Foundation Trust, Manchester, UK; ^cParticle Therapy Cancer Research Institute, University of Oxford, Oxford, UK; ^dAccelerator Science and Technology Centre, Science and Technology Facilities Council, Daresbury, UK

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Over the last twenty years the treatment of cancer with protons and light nuclei such as carbon ions has moved from being the preserve of research laboratories into widespread clinical use. A number of choices now exist for the creation and delivery of these particles, key amongst these being the adoption of pencil beam scanning using a rotating gantry; attention is now being given to what technologies will enable cheaper and more effective treatment in the future. In this article the physics and engineering used in these hadron therapy facilities is presented, and the research areas likely to lead to substantive improvements. The wider use of superconducting magnets is an emerging trend, whilst further ahead novel high-gradient acceleration techniques may enable much smaller treatment systems. Imaging techniques to improve the accuracy of treatment plans must also be developed hand-in-hand with future sources of particles, a notable example of which is proton computed tomography.

Keywords: particle accelerators; oncology; radiotherapy

1. Introduction

During the course of the last century life expectancy has increased dramatically, particularly in the more developed countries of the world. This has in the main been due to the reduction in the number of deaths caused by such things as infectious disease and malnutrition, and the provision of clean water and the introduction of mass vaccination have contributed to a greater length and quality of life for billions of people. As life expectancy has increased, these more-avoidable causes of death have been increasingly replaced by the so-called ‘diseases of old age’, a prominent one being cancer. As an example, of the approximately 493,000 deaths in the United Kingdom in 2010, over 140,000 were due to cancer: some are an intrinsic feature of becoming older (such as prostate cancer) whilst some result from the side-effects of lifestyle choices such as smoking. These numbers are to be compared with the 67,000 deaths from respiratory diseases each year and the even larger 158,000 deaths associated with circulatory disease [1].

Whilst cancer is associated with ageing (about two thirds of cancer occurs in people over the age of 65), it is also an important disease for children and young adults; it is rightly a focus of much research to improve both the cure and the control of this most varied affliction. A remarkable improvement in the curative capability of treatment has occurred over the last thirty years. In the UK for example,

the ten-year survival rate for those patients diagnosed with leukaemia has risen from less than 10% in 1971 to over 30% in 2007, whilst over the same period women diagnosed with breast cancer have seen their likelihood of cure rise from less than 40% to nearly 80%. Unsurprisingly given the very varied nature of the cause, location and development of the disease, there is no single reason why cancer survival rates have risen markedly in this generation; rather it is the combined effect of improved detection from epidemiology and diagnostic methods, coupled to the improved oncology techniques utilised for treatment.

Three principal modalities exist for the treatment of cancer [2,3] – surgery, chemotherapy and radiotherapy – which are supported by a number of diagnostic and imaging methods to maximise their effectiveness. Rather than choosing one modality most clinical treatments utilise several in combination to effect cure and/or control; 40% of those cured of cancer have had radiotherapy as a treatment. In the UK about 1 in 3 people are diagnosed with cancer, and about half of them receive radiotherapy.

The rest of this article explains what radiotherapy is and how it is delivered, and what technical challenges remain today for those wishing to use it to treat cancer. Whilst great strides have been made in the last thirty years, there is still much that needs to be done both to develop a fuller understanding of the nature of cancer, and then to use that

*Corresponding author. Email: hywel.owen@manchester.ac.uk

knowledge to create more effective therapies to deal with it.

2. X-ray radiotherapy

Radiotherapy may be defined as the use of ionising radiation to treat disease, ionising radiation being any particle that – when incident upon a target atom – imparts sufficient energy to cause an ionisation and thereby a biological effect. This was realised very soon after the discovery of x-rays by Willhelm Röntgen in 1895 using a Crookes tube [4]; at the same time as his discovery Röntgen also conceived the ideas both of radiography (by taking a picture of his wife's left hand) and of fluoroscopy. Just a few months later x-rays were used by Freund and Schiff in Vienna to treat diseases of the skin [5–8], and in the following year Emil Grubbé – who ironically first trained as a homeopath – probably carried out the first treatment of cancer (of the breast) in Chicago [9]. These efforts were later aided by the realisation in 1896 by Herbert Jackson that electron focusing could improve the directionality of the x-rays [10]. Each of these early concepts has a counterpart in modern radiotherapy: one requires a suitable source of particles; a method by which they may be delivered accurately; and a manner in which the radiation dose delivered by the particles may be monitored. Also in these early years it was realised that, as well as using external beams (originally called *teletherapy*) to perform treatments, radioactive ‘seeds’ might be used to impart radiation if placed within the body adjacent to an area to be treated. This was originally inadvertently done by Becquerel with a radioactive source in his pocket (giving a so-called ‘Becquerel burn’) but modern variants of this *brachytherapy* approach are now well-developed, although we will not consider them further here. Apart from cancer, radiotherapy is now only rarely used for other conditions such as the treatment of endometriosis or of skin lesions; in the UK at least, only clinical oncologists may prescribe radiotherapy.

It was already realised early on that x-ray photons were hard to direct solely onto a specific desired part of the body, and that dose was delivered to surrounding tissues as well. However, systematic work by Henri Coutard in Paris in the 1920s showed that healthy tissue could survive around a treated volume if the radiation was delivered in a number of small doses, which is today termed *fractionation* [11,12]; the radiobiological justification for fractionation is now often described using the *five R's*: Repair, Repopulation, Redistribution, Re-oxygenation, and Radioresistance [13–15]. Consideration of clinical benefit with respect to x-ray source usage by Ralston Paterson and others led to the rational justification of particular fractionation regimens such as the Manchester hypofractionation system, which remain today as the primary models of treatment [16,17]. Since then great advances have been made in the ability to control and direct x-ray dose, and the modern linacs used for

this purpose – which in a 1–2 m accelerating structure typically deliver 6 to 40 MeV electrons onto a Bremsstrahlung target to generate the x-rays – are able to vary both their beam intensity and the direction of the incident radiation, the latter achieved by mounting the accelerator and target onto a rotating treatment arm. The addition of transverse shaping of an incident x-ray *field* using remotely-movable *multi-leaf collimators* has enabled present-day techniques such as *intensity-modulated radiotherapy* (IMRT). Using sophisticated imaging now available from techniques such as computed x-ray tomography, magnetic resonance imaging, and positron emission tomography [18–20], IMRT is today able to very accurately *conform* a desired dose to a specified *planning target volume* (PTV) determined by clinical requirements and by using computer-aided treatment planning [21–27]. For example, in the UK there are now over 250 clinical linacs delivering more than 130,000 treatments each year, more than half of which treatments are for breast and prostate cancer [3]; virtually all of these machines are capable of IMRT. However, whilst there are not many advances left to be made in the ability to provide tumour conformation, it has proved difficult to control sufficiently the unwanted *out-of-field dose* to *organs at risk* (OAR). So, despite the rather mature (and therefore affordable) technology options for x-ray radiotherapy, there remains a desire to examine alternatives; the principle of these is the use of heavy charged particles such as protons or light nuclei, a method known as *hadron therapy* which is now discussed.

3. Hadron therapy

Robert Wilson was the first to point out, in 1947, that protons could be superior to x-rays for radiotherapy due to their inherently different manner of stopping in matter [28]. X-ray photons primarily deposit their dose either by being absorbed by or scattered from individual atomic electrons which subsequently move to deposit their dose via a Bremsstrahlung shower further downstream from the absorption point; therefore, after a short (around 3 cm) *build-up* distance the beam intensity decreases more-or-less exponentially with depth in a uniform material whilst at the same time laterally spreading due to scattering. Protons are not absorbed; they deposit their kinetic energy gradually and at a rate inversely proportional to that energy (that is, inversely proportional to the velocity squared for non-relativistic particles), so that most of the energy is deposited near to the end of the proton's *range* in a target; this high-dose end is the *Bragg peak*. The Bethe–Bloch equation that describes this varies slightly according to which corrections are used [29–31], but a common formula (from the Particle Data Group [32]) is

$$-\left\langle \frac{dE}{dx} \right\rangle = k_z^2 \frac{Z}{A} \frac{1}{\beta^2} \times \left[\frac{1}{2} \ln \frac{2m_e c^2 \beta^2 \gamma^2 T_{\max}}{I^2} - \beta^2 - \frac{\delta(\beta\gamma)}{2} \right], \quad (1)$$

where Z and A are the atomic number and atomic mass of the absorber, z is the charge of the incident particle, $I \simeq 11.5Z \text{ eV}$ is the mean ionisation potential, $T_{\text{max}} = 2m_e c^2 \beta^2 \gamma^2 / [1 + 2\gamma m_e / M + (m_e / M)^2]$ is the maximum kinetic energy that may be imparted to an electron in a single collision, $k = 4\pi N_A r_e^2 m_e c^2$, and β and γ are the conventional relativistic factors. $\delta(\beta\gamma)$ is a density correction term.

The depth at which most of the dose is deposited may be varied by changing the incident proton energy; ions such as C^{6+} (carbon) slow down in much the same way, but with less multiple scattering of the ions from their original direction which thereby leads to a smaller *penumbra*. Apart from the dose from secondary radiation (produced for example from the products of rarer inelastic collisions during slowing), the result is that the *distal* dose downstream of the Bragg peak is very nearly zero. The difference between proton and ion therapy lies predominantly in their *radiobiological effectiveness* (RBE), which is a measure relating the initial energy of an incident particle and the biological effect it has on a particular part of the body; different tissues respond differently to the same radiation, and RBE varies in principle both with particle type and with the initial energy that particle has.

The *physical absorbed dose* is the quantity used to measure the effect of radiotherapy upon a tumour. Physical absorbed dose is given in grays (Gy), where $1 \text{ Gy} = 1 \text{ J kg}^{-1}$. This quantity is compared to two others for illustration. Firstly, the deposited energy required to raise the temperature of a body of water by 1 K is $\sim 4200 \text{ J kg}^{-1}$; therefore 1 Gy raises that water temperature by a trivial amount of $\sim 0.5 \text{ mK}$. Secondly, for gamma rays (more exactly, 1.3 MeV gamma rays from ^{60}Co decays) the radiobiological effect of 1 Gy of deposited energy is to deliver an *effective* (equivalent) dose of 1 sievert (Sv) ; in other words the RBE of this energy of photons is 1 . 1 Sv is an enormous dose that may be fatal if delivered to the whole body, and should be compared to the normal legal limit of 1 mSv dose to members of the public from artificial sources of radiation. The radiobiological effect of 1 Gy therefore far exceeds the effect from heating, and for protons is brought about by the *linear energy transfer* (LET) of the protons as they slow down. At the high doses used in radiotherapy (the *deterministic* regime above $\sim 0.1 \text{ Gy}$) these DNA breaks cause rapid cell death by disrupting cell replication; at low doses the effects are more subtle (*stochastic* regime), but include effects such as the creation of mutations which may later cause cancerous effects. The RBE of protons is similar to that of x-ray photons, and is presently taken to be 1.1 for the purposes of treatment planning irrespective of proton energy [33,34]. The higher LET inherent in ion stopping results in a greater probability of localised double-strand DNA breaks and thereby a higher RBE; whilst this is a topic of active research, the RBE of for example carbon ions varies between around ~ 2.4 and ~ 3.0 [35,36].

As a side-note, older units may sometimes be encountered. Whilst the gray and sievert are the SI accepted units, the rad is still in common usage. $1 \text{ Gy} = 100 \text{ rad}$ and $1 \text{ Sv} = 100 \text{ rem}$. Since $1 \text{ cGy} = 1 \text{ rad}$, many radiotherapy planning systems (and staff) use the cGy as a convenient unit of measure.

For radiotherapy treatments the protons must of course have sufficient energy to penetrate the body, which in composition and density is often quite similar to water; water therefore constitutes a convenient standard material for calibration. Using ICRU49 data [37,38] the range of a 160 MeV proton is about 17.6 cm in water (a proton loses around 1 MeV per millimeter when water is traversed at these energies); 230 MeV is sufficient for treating adult patients (protons then have a range of 33 cm), which coincidentally is in practice a limit on the extraction energy from conventional cyclotrons as will be seen below. By comparison, the range of 160 MeV protons in air is around 166 m , due to air being around 830 times less dense than water at standard temperature and pressure. Carbon ions have a higher rate of LET so that 33 cm penetration through water requires a C^{6+} ion energy of around 400 MeV/nucleon . This simple fact explains why the majority of hadron therapy utilises protons; they are technologically simpler to use, and whilst their RBE is not particularly superior to x-rays, their dose may be made much more localised so that organs at risk are better avoided.

4. Clinical requirements, dose and current

Radiotherapy utilises a number of regimens of total dose and fractionation determined by the clinical oncologist, but in broad terms a delivered dose typically prescribed to a PTV is measured in tens of grays; for example, a prostate treatment using protons may demand the delivery of 70 Gy delivered in 35 fractions of 2 Gy each, fractions being delivered five days per week over a number of weeks. To minimise both inaccuracies from patient movement and their discomfort, and noting that much of the time (say, 15 min) in the *treatment room* is spent in patient preparation and positioning, a commonly-accepted requirement is that each fraction of 2 Gy should be delivered in around a minute. Although tumours may be smaller, a de-facto standard specification is to specify that this 2 Gy dose is to be delivered in 1 min to a 1 litre PTV ($10 \times 10 \times 10 \text{ cm}$); larger PTVs need more incident particles for the same dose. By comparison, x-ray treatment systems deliver typical dose rates of around 5 Gy min^{-1} .

Unlike x-ray radiotherapy where linacs are almost exclusively utilised today (although there are still some x-ray treatments delivered using cobalt-60 radioactive sources derived from irradiating a cobalt target with neutrons in a nuclear reactor [39]), various types of particle accelerator are used today for hadron therapy; these are discussed later. But from the point of view of the oncologist a particle

accelerator source can be characterised mainly in terms of its ability to produce a desired range of proton energy, its *beam quality* (energy spread and transverse extent or emittance), and in the *beam current* (number of charged particles per second) that it may deliver to the patient to obtain the required *dose rate* of 2 Gy litre min^{-1} . The time structure with which the protons are delivered is a secondary consideration, and is what primarily distinguishes one technology from another.

It is instructive to estimate the source beam current requirements. Although a variety of depths and depth ranges may be encountered, as an example a depth range of 10 cm is taken in which the shallowest depth treated is 10 cm and the deepest is 20 cm; this corresponds very broadly to the more difficult treatments one may encounter in an adult patient. Using the Particle Data Group definition of the Bethe–Bloch slowing formula, a proton with 166 MeV kinetic energy has a range of around 20 cm, whilst a 112 MeV proton has a range of around 10 cm. A 166 MeV proton deposits 26.6 pJ when stopped (i.e. converting its kinetic energy), whilst a 112 MeV proton deposits 17.9 pJ. Using a simple-minded average of these two values, it is seen that protons covering a range of 10 to 20 cm depth will typically deposit around 22 pJ of energy. To deliver 1 J of deposited energy therefore requires around 45 Gp (45 billion protons), so if these protons are spread over our example 1 litre target volume ($10 \times 10 \times 10$ cm) to give 1 Gy and are delivered in 1 min, this corresponds to 750 Mp s^{-1} , or 0.12 nA. It is assumed that around half of this energy will be deposited upstream of the tumour (a reasonable guess which is justified later), so that the current required at the patient surface for 1 Gy min^{-1} is around 0.25 nA. Thus, 2 Gy litre min^{-1} requires around 0.5 nA of proton current, depending somewhat upon the incident proton energy. Whilst treatment obviously requires much more careful dose estimation, this simple estimate is a useful guide to, and a comparator of, accelerator technology. Delivering 0.5 nA at the patient makes different requirements on different types of accelerators, and how this is achieved by them is discussed next. However, this simple consideration allows a rule of thumb to be used, which is that the number of protons required to deliver a 2 Gy fraction to a patient is around ~ 90 Gp, or 16 nC of charge.

4.1. Proton field delivery: scattering and spot scanning

X-ray radiotherapy conforms a delivered dose to a PTV by transversely shaping the broad radiation field from the Bremsstrahlung target using transverse adjustable *multi-leaf collimators* (MLCs) whose (tungsten) leaves may number more than 100 in the most modern therapy machines; IMRT uses multiple such fields (irradiation directions) to deliver a required dose distribution. To make best use of protons their dose must also be conformed both transversely and in depth. Since early proton treatments were often ob-

tained from research proton accelerators which delivered their particles at a fixed energy, it became customary to accomplish the depth conformation using a combination of a range shifter and a modulator. A range shifter is simply a piece of suitable homogenous material – often a Perspex-like

plastic – which introduces energy loss to the incident protons so that their resulting energy is correct for the Bragg peak to lie at the deepest point in the target. A range modulator is an additional variable-thickness absorber that creates a *spread-out Bragg peak* (SOBP) that covers the depth range of the PTV; this already gives a superior dose distribution compared to x-rays, as illustrated in Figure 1. The modulation may be obtained by rotating a suitable propeller whose blades vary in thickness appropriately such that the resulting dose is uniform over the SOBP; uniformity is obtained by varying the proton dose at a given depth [40]. The question then arises as to how finely the depth variations must be graduated to achieve a uniform dose rate over the SOBP. Use is made of the fact that, due to the stochastic nature of the proton scattering as they slow down, there is significant depth *straggling* which to a good approximation is 1.2% of the proton range over the range of energies used in therapy; a monochromatic (single energy) beam of protons thus deposits its dose over a range of depths which is typically 1–2 mm in most PTVs. Dose uniformity is also desired in the transverse direction for present-day treatment plans; again, until around ten years ago this was achieved using a *passive scattering* method using a *double scatterer* arrangement in which the first scatterer introduces an angular spread to the particles whilst the second (called a *bolus*) is contoured in depth to achieve a uniform dose rate across some field size

Figure 1. Illustration comparing photon (x-ray) therapy with proton therapy for the same total dose over a given range of treatment depths. The photon dose builds up a few centimetres from the patient surface and thereafter reduces approximately exponentially. A number of single-energy Bragg peaks, weighted in intensity, are added together to deliver a constant-dose spread-out Bragg peak (SOBP). The proximal dose upstream of the treatment depths is already much reduced, whilst the distal dose is zero with a few millimetres of the distal (deepest) part of the SOBP.

prior to conformation using a patient-specific collimator; the first scatterer can be a simple fixed sheet, or it can be a modulator. Conformation to the *distal edge* of the target volume may be achieved by contouring the range shifter in thickness, but retains an unwanted upstream dose over some parts of the field; an example of a compensator and range modulator is shown in Figure 2. Significant losses are inherent in passive-scattering arrangements: double-scattering systems transmit as little as 40% of the protons that enter them, and the lost protons that encounter high-Z materials such as metal equipment may generate neutrons that impart an additional unwanted out-of-field dose that is difficult to characterise.

To improve on the conformation possible with passive methods, several *spot scanning* methods have been developed which are today in the process of being adopted clinically. As the name suggests, an (unscattered) narrow '*pencil beam*' from the accelerator source is delivered to a large number of discrete locations – termed *voxels* – in the target volume using fast deflection magnets. Whilst in principle either electric or magnetic fields may act upon charged particles such as protons to accelerate or deflect them via the Lorentz force $\mathbf{F} = q(\mathbf{E} + \mathbf{v} \times \mathbf{B})$ only magnetic fields are technically practical for deflection, and may give typical static field strengths up to $\sim 1.8\text{ T}$ if normal-conducting electromagnets are used. Typical scanning rates move the

pencil beam around 1 cm ms^{-1} , taking as little as 2 ms per step [41]; such scanning can address the individual voxels within the target with sizes of a few millimetres or even less, and combined with variation of the dose rate gives rise to the technique of *intensity-modulated proton therapy* (IMPT); this technique is also used with carbon ion beams at facilities such as the Heidelberg Ion Therapy Centre.

The previous section used a crude approximation that around 45 Gp are needed per 1 Gy of dose into a $10 \times 10 \times 10\text{ cm}$ cube water volume whose centre lies 15 cm from the water surface. The irradiation of such a volume with realistic incident spot scanning is now considered, in which the spots are weighted in energy and dose rate such that a uniform dose is deposited within the volume; an example calculation using GEANT4/GATE (a widely-used Monte Carlo code for particle transport [42,43]) is shown in Figure 3 which assumes an incident divergence-free spot size of 8 mm (r.m.s. width). Using these values it is estimated that 90.8 Gp Gy^{-1} are needed, where 43.1% of the dose is deposited in the cube, 0.58% deposited distal to it, 12.5% laterally, and 43.7% proximally (including lateral scattering outside the cube boundaries). In other words, around half the dose is deposited outside of the intended volume, as our earlier approximation assumed. It can be seen from this calculation that lateral scattering – which is caused largely by multiple Coulomb scattering (MCS) within the material – is significant. When compared to a one-dimensional calculation that neglects such scattering, roughly the same proximal dose (43.3%) is observed but a larger dose to the target volume of 56.5% is predicted due to the lack of laterally-lost particles.

The lateral broadening of spots due to MCS – which depends on the chosen depth of the Bragg peak – mean

Figure 2. Compensator (top) and range modulator (bottom) used at Clatterbridge Hospital to provide longitudinal conformation of the 62 MeV protons delivered from their cyclotron to the depth range of the tumour. The modulator wheel is 190 mm in diameter. (Courtesy Prof. Andrzej Kacperek/Clatterbridge Hospital)

Figure 3. GEANT4 simulation showing irradiation from the right of a $10 \times 10 \times 10\text{ cm}$ water volume whose centre lies 15 cm from the water surface, using $\sigma = 8\text{ mm}$ wide proton spots weighted in intensity to obtain a uniform dose within the cube. The shallowest spots inherently give rise to a proximal dose, but the Bragg peak gives a very low distal dose. Calculation courtesy of A. Aitkenhead.

that it is not clinically useful to reduce the incident spot size below some limit, which is usually taken to be around 4 mm. A similar consideration applies due to the intrinsic proton straggling, so that there is little benefit in having an energy spread much less than 0.5% of the incident proton energy. However, determining what the (mean) incident proton energy ought to be for a given depth is much more difficult due to current limitations in converting patient images to proton-relevant density, and this will be discussed later on.

5. Making and accelerating hadrons

The successful clinical delivery of proton therapy makes demands on the particle energy, average beam current, and beam quality which is brought to the patient surface, and the more modern method of spot scanning makes greater demands on that beam quality; clinical facilities use a number of specifications to define the controllability of the supplied particles [44]. Beam quality consists of a number of measures which include the *beam emittance* of the particles, their *energy spread*, their positional (pointing) stability, and related factors such as the stability of those measures and the degree to which the beam current may be varied or maintained [44,45]. Under certain circumstances some of these measures are approximately conserved; for example, the *normalised emittance* $\epsilon_n = \epsilon_x \gamma$ in each plane is conserved in a normal focusing channel. As has already been seen in the case of passive scattering, the beam quality at the patient is the combination of what is produced by the chosen source of particles and the intervening *beam delivery system*, which for particle therapy often includes such things as *energy selection systems* (which includes collimation), *degraders* or *gantries* to modify and select the beam properties and to properly direct the protons onto the patient. Beam measures such as emittance are only conserved in the absence of such things as collimation (which may reduce the emittance by eliminating large-amplitude particles) or scattering (which can increase the emittance). There now follows a discussion of the dominant accelerator technologies that either are in use or are considered for use in particle therapy; a more general introduction to accelerator technology for other applications has previously been presented [46].

5.1. Cyclotrons

The most widespread accelerator type used for proton therapy is the cyclotron, which was the first so-called *cyclic* accelerator as it re-uses the same (small number) of accelerating gaps to give a large energy gain for a small gap voltage per turn. As its inventor Ernest Lawrence realised – and for which he was awarded a Nobel Prize – as low energy protons are accelerated their speed increases with their kinetic energy such that their revolution frequency remains constant [31,47–49]. An alternating voltage applied with constant frequency to the gap between the *dees* enables

the protons to be accelerated when crossing the gap in either direction, the applied frequency f_a being either the same as the revolution frequency f_r or some harmonic of it $h = f_r/f_a$; h is termed the *harmonic number*. Lawrence's key insight was the observation that the bend radius ρ in a given field strength B is proportional to the proton momentum p such that

$$B\rho = p/q,$$

where $q \simeq 1.6 \times 10^{-19}$ C is the particle charge; the product $B\rho$ thus obtained is termed the *beam rigidity*, which determines how the particles may be confined. In a cyclotron ρ changes with p typically over a wide range (from tens of kV from a centrally-placed ion source to several hundred MeV) whilst B is held at a fixed value of several tesla. Ion sources vary greatly in design, but a common layout is a chimney inserted axially through the centre of the cyclotron and into which hydrogen gas is fed from both ends. A discharge voltage induces a plasma confined by a solenoidal field within the chimney, and protons are extracted from a small aperture by applying a voltage; some of these protons are then captured into the bunches defined by the dee voltage cycle. The bunches may be stably accelerated over some range of phases with respect to when the peak field occurs across each dee, and many bunches may be accelerated simultaneously with the higher-energy ones circulating with progressively greater radius until they reach a position where they are extracted; the principle of the cyclotron is shown in Figure 4. To avoid significant losses the *turn separation* of the next-to-last and last turns must be great enough to allow the last turn to cleanly enter the extraction system, typically a small channel that imparts an electrostatic deflection field in addition to the overall bending field from the main cyclotron dipole field. The cyclotron

Figure 4. Illustration showing a classical cyclotron, in which a single pair of dees produce acceleration at each gap if the alternating voltage applied to them is in synchronism with the particle revolution. A single magnet provides a bending field B which may be varied with azimuth by placing *hills* and *valleys* in the *pole pieces* to aid focusing, and which may also be shaped radially.

field is in any case shaped – particularly near the extraction radius – so that it provides stable focusing separately in both the horizontal and vertical planes of particle oscillation; a constant field would give a natural *weak focusing* to the circulating protons in the horizontal plane, but no vertical focusing [45]. The extraction efficiency of a cyclotron is typically somewhere between 25% and 80% depending upon the design, hence the *circulating* current must be higher for a desired extracted current. Therapy cyclotrons typically utilise dees in which the available voltage is around 50 to 120 kV. Given that the harmonic number is typically 1, 2 or 4, the effective acceleration voltage per turn is thus no more than around 0.5 MV.

In most practical implementations the extraction energy of a cyclotron is fixed, so that energy variation at a patient must be achieved by using an *energy selection system* (ESS). The ESS first degrades the energy of the incoming protons by slowing them down in some robust material of variable thickness, for example two back-to-back moveable wedges; this *degrader* – also known as a range shifter, and used to set the largest depth that the particles will penetrate to – has the undesirable side-effect of introducing an increased beam emittance from scattering and an increased energy spread from straggling. Whilst a lower-Z material such as beryllium ($Z = 4$) may be used to minimise such scattering effects for a given energy loss, carbon is easier to work with and therefore widely used [50]. Following the degrader an achromat and collimators are used to define the exit emittance and energy spread. For example, the 250 MeV PROSCAN facility at the Paul Scherrer Institute utilises carbon wedges which – to obtain an always homogenous absorption – must present a minimum thickness to the incoming 250 MeV protons; the thickness variation of 30 to 200 mm results in an output proton energy from around 70 to 238 MeV. A schematic layout of such an ESS is shown in

Figure 5. Schematic layout of a generic cyclotron energy selection system, showing the variable energy degrader that generates a desired mean energy, an emittance collimator to define the transverse extent of the beam (both in size and divergence), and an energy selection achromat incorporating a slit to define the energy range of particles sent to the patient. Quadrupoles, in one of a number of possible optical arrangements, are used to confine the beam envelopes in both transverse planes normal to the beam motion.

Figure 5, which includes both emittance and energy collimation. A dipole is required to disperse the resulting energies from the degrader onto a slit to select a desired energy (in the PROSCAN ESS for example this gives a beam *dispersion* of 37 mm per percent change in particle momentum), with one or more quadrupoles and a second dipole used to make an achromat to recombine the dispersed energies for further transport downstream.

A degrader and ESS introduce significant losses, and result in an increased beam emittance and energy spread. Typical values for the emittance and energy spread after degradation and collimation might be around ~ 2 MeV energy spread and 40π mm mrad, and at these values the total transmission of the ESS is rather low. For example, at the lowest PROSCAN energy of 70 MeV the transmission is only 0.3% and the total current delivered by the cyclotron must be correspondingly larger to achieve the required dose rate at the patient, i.e. at least 100 nA [50]. If the transmission efficiency of a passive scattering system is also taken into account, one sees that the required circulating current in a cyclotron must be many hundreds of nanoamperes, much larger than the ~ 0.25 nA needed at the patient. For example, the IBA C235 cyclotron is stated to achieve an extracted current typically around 300 nA, with an associated extraction efficiency of around 30%. Spot scanning systems have much higher efficiency as might be expected, reducing the required current from the accelerator source.

Extraction and transmission efficiencies are not only important for determining the required accelerator current but also to limit particle loss that may cause component activation and thereby limit access to equipment during repair and maintenance procedures. For example, reducing the extraction efficiency of a cyclotron from 75% to 25% – whilst keeping the same extracted current – increases the losses within the cyclotron by a factor of nine. It is usually the case that most of this loss occurs at the extraction energy, with protons primarily being lost on the boundary walls of the extraction channel.

5.2. Isochronous cyclotrons and synchrocyclotrons

Cyclotrons may be grouped into two classes. Isochronous cyclotrons are designed such that bunches may circulate simultaneously at different energies but with the same revolution period, so that the bunches may all be accelerated by the same fixed radio-frequency (RF) acceleration system. Maintaining this isochronous condition becomes increasingly difficult at higher particle energies due to the onset of relativistic effects. At moderate energies (say, 30 MeV) the magnetic field seen at a given particle radius may be tailored to maintain a sufficiently isochronous condition [51–53]; however, this becomes technically impractical above around 250 MeV. Whilst a few research cyclotrons exist at higher energies [54] no commercial cyclotrons deliver protons above 250 MeV. The alternative approach is

to use a synchrocyclotron, in which the acceleration system frequency is swept upwards to keep synchronism with a single accelerated bunch.

In an isochronous cyclotron particles are continuously generated by an ion source and then captured into the stable radio frequency (RF) phases (*buckets*) defined by the applied dee voltage, and the average current is spread out over bunches that then populate every available bucket; the duty factor (fraction of time the RF is on) is 1, in other words bunches are continually exiting the cyclotron. As an example, the IBA C235 cyclotron has a normal-conducting central magnetic field of 1.7 T and extraction mean field of 2.17 T (achieved by reducing the pole gap as the extraction radius is reached), so that the gyro frequency (cyclotron frequency) has a constant value of 26.5 MHz. A fixed RF frequency of 106 MHz gives a harmonic number $h = 4$ and so bunches are therefore extracted from the cyclotron at this same frequency. Each bunch therefore contains less than 100,000 protons, which means that the mutual Coulomb repulsion between them is not significant at extraction. Another example is the Varian COMET superconducting cyclotron, in which the relevant difference here is the higher central field (around 2.4 T) and the correspondingly higher extraction mean field (3.03 T). The higher average bending field increases the cyclotron frequency to 36.5 MHz, whilst the harmonic number in COMET is $h = 2$ (73 MHz).

To achieve a smaller cyclotron it is obvious that a larger average dipole field must be provided; fields above about 2 T require superconducting technology so that the large currents required to drive the field may be supported with low heat loss [55–61], with the additional benefit that the magnets may be much lighter than their normal-conducting equivalents [30]. A number of commercial providers now offer such cyclotrons [59,62]. However, the use of large fields results in any pole pieces used for shaping being essentially saturated, so that variation of the field with radius can no longer be readily achieved; this means that the cyclotron can no longer be made isochronous over all energies. Hence a synchrocyclotron approach must be used in which the dee acceleration frequency is made to change with the energy of a single accelerated bunch. An example of this is the Orsay 200 MeV proton therapy synchrocyclotron, in which the central field is 1.6 T, and where the RF frequency varies during the acceleration cycle from 19 to 26 MHz [63].

5.3. Synchrotrons

The other widespread accelerator technology in use is the synchrotron [46], as typified by the Loma Linda (LLUMC) facility – the first purpose-built hospital-based proton therapy centre – and by the Hitachi PROBEAT 250 MeV synchrotron design installed by both Hitachi and Mitsubishi [64–73]. In contrast to cyclotrons, synchrotrons

accommodate the change in p during acceleration by increasing the vertical guide field $B_y(t)$ so that ρ may be kept constant. In addition, nearly all synchrotrons have benefited from their use of *strong focusing* – a method invented by Nicholas Christofilos when working as an elevator engineer – which is achieved by interleaving *quadrupole* magnets with the *dipole* magnets to create an appropriate *periodic focusing channel* that confines the range of particle amplitudes and energies to a sufficiently-small envelope [74].

The envelope is characterised by the so-called *Twiss functions* that may be derived from the beam-optical *lattice* arrangement of magnets [45,75]. The most important Twiss functions are the beta functions $\beta_x(s)$ and $\beta_y(s)$ that vary in each plane with distance travelled s ; for example, the beam size in the horizontal plane at any point in the accelerator is obtained for a monochromatic beam ensemble as $\sigma_x(s) \simeq (\epsilon_x \beta_x(s))^{1/2}$, where ϵ_x is the emittance, the emittance being approximately a constant of the motion. Strong focusing may also be achieved using a transverse field gradient $B_y(t) = B_0(t) + g(t)x$ in the dipoles themselves, and the focusing is varied with the guide field so that the Twiss functions are to all intents constant as the particles are accelerated. An important pair of parameters in synchrotrons are the horizontal and vertical *tunes*, which are the number of transverse oscillations in each plane that the particles execute with respect to their average path; as in cyclotrons, the tunes must be kept away from integer values or certain rational fractions to avoid, for example, resonant loss due to magnet imperfections.

Whilst the combination of varying B_y and the use of strong focusing mean that much smaller dipole magnets may be used for a given energy range between particle injection and extraction, particles may only be injected at one point (the minimum) of that B -field cycle. The acceleration rate is in practice limited by the rate at which the dipole fields themselves may be varied, which is determined by induction effects in the electromagnet coils to be presently no more than 50 Hz, and usually much less than that in medical synchrotrons for which the cycling rate is measured in seconds rather than in hertz. An illustration of a synchrotron is shown in Figure 6.

Acceleration is usually achieved in synchrotrons using a number of discrete RF cavities [45,46] such that the harmonic number h is much larger than 1; particles may be placed in any of the RF buckets (but usually only 1) that are created by the varying phase of the accelerating field over the circumference of the synchrotron. These particles are then accelerated over many turns prior to a pulsed extraction. In the Hitachi synchrotron, for example, a single bunch of protons is accelerated using a magnet cycle time of between around 2 and 7 s that may be chosen using a programmed (ramped) current applied to the magnet coils; only one bunch is extracted per magnet cycle, and so it must contain many more protons than the bunches from a cyclotron to provide the same dose rate.

Figure 6. Schematic illustration of a synchrotron (on the left), showing the most important components: dipoles for confinement, quadrupoles for focusing, and RF cavities to provide the accelerating electric field. The particular arrangement of the magnetic components is termed the *accelerator lattice*, which determines the *beam optics* and the associated (varying) values of the Twiss functions and beam dispersion. The particular lattice arrangement is very nearly always periodic, and is designed not only to define the beam envelopes but also to assist in the control of unwanted effects such as beam instabilities, space charge defocusing, and so on. A simplified diagram of an electromagnetic quadrupole (on the right) shows how it consists of four steel poles that generate alternating polarity fields at the pole tips using appropriate current in the coils; the field at the centre of a quadrupole is zero in the absence of errors. A particular quadrupole only focuses particles in one plane of motion (either horizontal or vertical) and so at least two quadrupole types are required for stable focusing in both planes, the second type obtained by swapping North with South poles.

Pulsed extraction at the required energy is obtained typically by a radio-frequency driven or quadrupole-driven resonant method [45], and a feedback loop using the measured extracted intensity is used to achieve a desired rate of extracted protons; this slow, controlled extraction of protons from a stored bunch is called a *spill* [76]. The acceleration time is made as short as possible to maximise the spill time available, and is typically around 0.5 s (i.e. around 10^6 turns in the 23 m circumference Hitachi accelerator). Given that the RF frequency must vary considerably due to the variation in proton velocity – the proton energy varies from around 3 to 7 MeV at injection to 70–250 MeV at extraction – non-resonant structures are used such as induction cells, which deliver around 10 kV of acceleration each. The bunch revolution frequency for a 20 m circumference will vary from about 1 MHz at injection to around 10 MHz at extraction, with the extracted bunches ranging in velocity from around 0.37 c (70 MeV) to 0.6 c (250 MeV). The flat-top duration at the top of the magnet ramp – when the extraction is carried out – may be varied between around 0.5 to 5 s. Extraction efficiency using these resonant methods is typically high ($> 90\%$), so that the injected and extracted bunch charges are essentially the same, and range from around 20 Gp (3.2 nC) in LLUMC to around 100 Gp (16 nC) in the Hitachi synchrotron. To vary the dose rate at the patient the number of ions per spill can be reduced, down to around 0.001 Gp. The maximum bunch charge is much higher than in a cyclotron, which makes up for the much lower extraction pulse rates, but the resulting space charge and other induced effects must be accounted for in the design.

Although a large dose can be obtained from each spill, it will typically occur at a constant energy and therefore deliver to constant treatment depth. Traditionally, dose conformation in synchrotrons was achieved using a range shifter and modulator to create the SOBP over the required depth range together with a double-scatterer. Using this method a number of spills (cycles) are required to deliver 2 Gy to a tumour volume, around 30 for 2 Gy litre in a minute (25×25 cm field size for Hitachi and 13×13 cm in LLUMC); again, a treatment time of 1 min is possible. Spot scanning may also be achieved, by scanning at a particular layer depth (i.e. within one pulse and therefore one spill), possibly using gated control of the spill current to enable delivery of discrete spots.

To improve the precision with which layers may be scanned in energy, the rapid-cycling synchrotron (RCS) has been proposed [77,78]. As the name suggests, the key difference is the much faster acceleration time (< 25 ms) and higher repetition rate (> 20 Hz), achieved using low-inductance magnets. The high cycle rates require single-turn rather than resonant extraction [79,80]. Whilst not yet constructed for particle therapy, the magnet cycling rate required for an RCS has been demonstrated in other accelerators, for example the ISIS and J-PARC synchrotrons with cycle rates of 50 and 25 Hz respectively.

5.4. FFAGs

FFAG (Fixed Field Alternating Gradient) accelerators are a form of cyclotron in which the magnetic field varies both azimuthally and radially; the difference with respect to

conventional cyclotrons is that the variation of field with radius changes in polarity depending on the azimuth [81–83]. In other words, FFAGs contain both horizontally-focusing and vertically-focusing dipoles, giving the same strong focusing as utilised in synchrotrons; however, the fields are fixed in time so that accelerated particles move to larger average radius as they do in a cyclotron. The first FFAGs – constructed at the former Midwestern Universities Research Association in the 1950s to accelerate electrons – were of the so-called *scaling* type for which the field gradient is carefully chosen to give a constant tune during acceleration [81,84].

Neglected for a long period both due to the greater energy reach of synchrotrons and due to the greater complexity in constructing large-aperture FFAG magnets, the first proton FFAGs were eventually first constructed in Japan around 10 years ago in pursuit of more rapid acceleration (for example to accelerate unstable particles such as muons) rather than to achieve the highest energy; 150 MeV proton acceleration has been demonstrated [85]. The changing velocity of protons necessitates the same swept – frequency of RF acceleration used in synchrocyclotrons, with millisecond sweep rates made possible by cavities with low quality factor using modern magnetic alloys. Achieving fast acceleration is not only useful for the acceleration of unstable particles but of course to give an advantage for particle therapy delivery, and the RACCAM (Recherche en ACCélérateurs et Applications Médicales) proposal examined such an approach to deliver 180 MeV protons in a multi-room treatment centre [86].

Whilst scaling FFAGs give a pulse rate advantage over synchrotrons for particle therapy [87,88], their magnets are still larger than ideal. *Non-scaling* designs dispense with the requirement for constant tune which allows smaller magnets. If acceleration is rapid enough then crossing resonances may be tolerable as was demonstrated in EMMA, the first and presently only existing non-scaling FFAG [89]. The slower acceleration probably needed for proton therapy will need careful control of the tune variation, which is possible with complex field shaping to achieve a balance between the competing desirable qualities of small magnet apertures, *isochronicity* with energy such that fixed-frequency acceleration may be used, and constant tune [90,91].

An example of a non-scaling FFAG design for proton therapy is PAMELA, which proposes a 1 kHz cycle rate to allow better voxel repainting during treatment and thereby to average out dose errors caused by patient motion; it also allows lower bunch charges to be used [92]. In the PAMELA inner ring, protons are accelerated from 30 to 250 MeV (beam rigidity 0.811 to 2.432 Tm) in 0.44 ms, during which sweep time the RF frequency varies from 19.2 to 45.6 MHz (harmonic number $h=10$, i.e. revolution frequency from 1.92 to 4.56 MHz); the voltage per turn is around 160 kV over the eight two-gap cavities (10 kV per gap crossing). The minimum revolution time of 220 ns

occurs at the extraction energy, so that the extraction kicker pulse length determines the number of RF buckets that may be filled. In PAMELA an extraction kicker pulse rise time of 100 ns was assumed, allowing the other time fraction of the circumference to be filled with up to five bunches. However, the primary advantage of spreading the required charge over more than one bunch is that intensity variation can be adjusted via bunch filling; that must be set against the greater difficulty in obtaining adequate beam stability control when extracting a train of five bunches, versus the simpler problem of extracting a single bunch. Single-bunch operation is probably the appropriate choice.

5.5. Linacs

Linear accelerators (Linacs) [46] pre-date all cyclic accelerators in their development having first been proposed by Wideroe in the 1920s [93], but were in the past not favoured compared to cyclic accelerators because an insufficient accelerating gradient (a few MV m^{-1}) implies a relatively long linac to achieve therapeutic energies. However, in recent years several developments have been made to achieve high enough gradients to enable use in a hospital setting, for example by the TERA and TOP-IMPART collaborations (greater than 10 MV m^{-1}) [94–98]. In both these cases 3 GHz normal-conducting accelerating structures have been proposed to achieve gradients above 20 MV m^{-1} ; in the case of the TERA LIBO proton linac a side-coupled linac is used [99], and has been chosen by at least one commercial company (Advanced Oncotherapy) as a technology to be integrated for patient treatment [100]. Higher-frequency structures are now being considered to achieve gradients nearer 100 MV m^{-1} , thought to be near the limit for conventional cavity-based acceleration; one such example is the use of high-frequency technology ($> 10 \text{ GHz}$) developed for the Compact Linear Collider. Even higher frequencies have been proposed.

An advantage of linear accelerators is that, whilst their duty factor (the fraction of time the RF pulse is applied to the accelerating structures) is quite small the achieved gradient – and hence the output proton energy – may be varied from pulse to pulse thereby avoiding the need for energy selection. This is similar in principle to synchrotrons except that in linacs the pulse rate may be much higher. Using the TERA LIBO structures as an example, the repetition rate may be as high as 400 Hz (pulses every 2.5 ms) with a gradient of 15.3 MV m^{-1} ; pulse lengths may be supplied up to about $5 \mu\text{s}$ which corresponds to a duty factor of 2×10^{-3} . Within each $5 \mu\text{s}$ pulse about $4.5 \mu\text{s}$ may be filled with beam, giving around 13,500 RF buckets (2998 MHz RF frequency) into which bunches may be placed.

Similar to synchrotrons, and unlike cyclotrons where an ion source may be used to directly inject particles into the accelerator, linacs require a particle source of sufficient energy, say above a few MeV. In other hadron accelerator

applications this is now conventionally done with a *radio-frequency quadrupole* (RFQ); the RFQ is a hybrid device invented in the early 1970s which consists of a scalloped arrangement of vanes within a resonant (cavity-like) structure, such that both sufficient acceleration and focusing are provided to avoid undesirable space charge when high intensity beams are to be accelerated [101]. The bunching of particles achieved in the RFQ is sufficient to avoid significant particle loss in following structures. An alternative approach adopted for TERA is to use a low-energy cyclotron as the injector; the bunches extracted from the cyclotron are much longer ($f \sim 10$ MHz) than the following linac RF buckets ($f \sim 3$ GHz) into which particles are to be captured, but the rather low capture efficiency (typically around 10%) is made up for by the large cyclotron current possible. Cyclotron energies between 30 and 70 MeV have been proposed for this scheme, known as the *cyclinac* [98].

5.6. Dielectric wall accelerators

Dielectric wall accelerators (DWAs) for proton therapy are a progression from technology originally developed for high-intensity linear induction accelerators to conduct flash radiography. The dielectric wall accelerator utilises the fact that some insulators can sustain large electric fields without breaking down if the pulse length of that field is small, e.g. 10 ns. Development of suitable so-called *high-gradient insulators* may sustain electric fields up to as much as 100 MV m^{-1} ; a laser-driven Blumlein switch causes this pulse to travel along a stack of dielectric rings in step with the accelerated particles [102–104]. If achieved in a complete accelerator, such a gradient would allow a complete acceleration system to 250 MeV to be only several metres in length. Sample structures have been demonstrated and a commercial company (CPAC) is offering a solution which may be demonstrated in the next few years.

5.7. Laser proton acceleration

Similar to the argument for using DWAs, the motivation for using laser-driven acceleration is to increase the effective electric field seen by the accelerated particles to minimise the physical space required by the accelerator; present-day conventional radio-frequency cavities are limited to gradients of less than 100 MV m^{-1} . There are a number of possible laser-based schemes which have been recently reviewed by several authors [105–107]; most attention has been paid to demonstrating efficient acceleration of protons. Significant attention is presently being given to the *target normal sheath acceleration* (TNSA) method, whereby protons are accelerated from the rear surface of a thin target illuminated at the front surface by a strong laser pulse [108]. The laser energy is converted via several mechanisms into a reasonably-collimated (around 10 degree opening angle) beam of effectively-free electrons within the target

thickness of density $\sim 10^{20} \text{ cm}^{-3}$ or more, and where the electrons have relativistic energies (a few MeV). As the electrons exit the rear surface of the target foil they may generate a local electric field in excess of 10^{12} V m^{-1} which then accelerates ions from the surface of the foil. Acceleration of protons and ions has been demonstrated up to tens of MeV with reasonable beam quality and energy spread [105,109,110], and simulations indicate that with sufficient incident laser power higher proton energies approaching 250 MeV might be achieved [111].

However, despite the advances which have been made in over the last decade in obtaining high-energy protons there remain a number of challenges. Firstly, whilst improvements have been achieved in beam quality it is still rather poor compared to the more conventional accelerator methods already described; careful energy selection and beam capture is required [112], possibly based on novel compact methods such as pulsed ion optics [113] or Gabor lenses [114,115]. Another challenge is to increase the repetition rate of the produced pulses to obtain clinically-relevant intensities [113] and to utilise the resulting protons. One avenue to reduce the particle energy spread is to use so-called radiation-pressure (‘light sail’) acceleration [116], in which the incident photons themselves impart momentum to the accelerated ions. Whilst the use of laser technology is very promising, it is likely that it will be a few years before clinical experiments are performed to prepare for patient treatment.

6. Delivering particles to the patient

Whilst protons and ions deliver dose near the end of their range and relatively less near the patient surface compared to x-rays, it is still clinically advantageous to be able to vary the orientation of the incident particles [117]. Whilst a single field direction may be preferred for some treatments (for example ocular cancers), for many treatments several fields are utilised wherein particles are directed from a number of directions using a moveable mechanism [118,119]. This system is known as a *gantry*, the principle of which is shown in Figure 7; in typical particle therapy installations a single accelerator source delivers particles to more than one treatment room, each of which may be equipped either with a gantry or with a fixed-direction *beamline*. Most gantries are of the *isocentric* type shown, in which a (supine) patient in an essentially fixed position receives treatment whilst the gantry rotates around them. It can be shown that a normally-incident beam that can rotate 180° about the patient can deliver a full 4π coverage of irradiation angles if used in combination with a patient table that rotates by 360° in the horizontal plane; however, many gantries opt to use a full 360° of gantry rotation which reduces the requirement to rotate the patient and thereby reduces positioning errors. An example of a patient treatment room is shown in Figure 8.

Figure 7. A schematic illustration of a particle therapy installation incorporating an isocentric particle therapy gantry. The gantry plane rotates around an axis that is horizontal and passes through an isocentre that lies within the patient.

Figure 8. The Gantry 2 treatment room at the Paul Scherrer Institute. The rotating gantry is concealed behind a sliding false wall; sufficient distance must be provided between the end of the treatment nozzle and the patient to allow safe rotation. However, the distance from the end of the nozzle to the patient surface should also be minimised as far as practicable to limit scattering in the intervening air. (Courtesy Prof. Tony Lomax/PSI)

Isocentric gantries comprise a number of dipole and quadrupole magnetic elements as well as monitors to measure beam position and profile, particularly in the *treatment nozzle* which shapes the treatment field at the patient. The first nozzles utilised passive scattering, whilst more modern designs may incorporate fast deflection magnets to enable spot scanning. In either case, the outer radius of the gantry – and hence the size of the treatment room – is determined partly by the space required for nozzle and clearance around the patient, and partly by the achievable magnetic field in the final dipole magnet, and for 250 MeV protons is around 4 m [120]. The deflection magnets for spot scanning may lie either downstream of the final dipole or upstream; the difference is that if upstream scanning is combined with a point-to-parallel beam optics then the scanned spot will move normally to the patient surface

rather than in a fan, such that the effective *source-to-axis distance* (SAD) is infinite. Since infinite SAD reduces the dose at the patient surface for a given tumour dose it is to be clinically preferred as it spares the skin of undesired dose, but does require a larger aperture in the final dipole(s) to accommodate the scanned field which may be as large as 30×40 cm in some gantry designs. This larger aperture increases both the size and weight of the overall gantry, and designs must choose a trade-off between SAD and treatment capacity. The concept of upstream scanning is illustrated in Figure 9, and exemplified at the Paul Scherrer Institute's Gantry 2 [122].

Spot scanning is gradually being adopted by newer treatment centres, and the combination of this '*step and shoot*' dose delivery with the variable gantry angle is termed *intensity-modulated proton therapy* (IMPT) in analogy with IMRT. Similarly to x-ray treatment, IMPT also seeks to minimise dose to healthy tissues by improving the conformality of the delivered dose to the target volume over what may be achieved with double scatterers and range modulation. As seen above, to deliver an IMPT fraction within 2 min implies a budget of only around a millisecond for delivery of dose to each voxel; this is typically limited by the speed at which the transverse scanning magnets may respond. Another advantage of IMPT is the elimination of the patient-specific beam-shaping components needed in passively-scattered treatments, which not only saves cost but also reduces the parasitic neutron dose brought about by nuclear interactions when the edges of the proton treatment field are collimated.

A single accelerator supplying several gantries takes advantage of the fact that the actual *beam-on* time for treatment is short (around 2 min as noted above), and that much of the patient time in the treatment room is taken up by patient positioning and other preparations. If the accelerator source has a high capital cost then a multi-room arrangement may be appropriate; if beam switching, verification, treatment time and other issues are taken into consideration, it has been shown that around 3–4 rooms make best

Figure 9. A schematic illustration of an isocentric three-dipole gantry (of the so-called ‘Pavlovic’ design [121]) which incorporates spot scanning magnets upstream of the final (90°) dipole. With appropriate beam optics and entrance and exit edge angles, the *betatron phase advance* of the Twiss functions between the scanning magnets and the isocentre may be made approximately 90°, creating point-to-parallel transport optics that result in an effectively infinite SAD; this thereby gives the parallel scanning at the patient shown. The disadvantage is that the aperture within the final dipole must be sufficient for the intended treatment field size, necessitating a larger dipole *good field region* and hence greater mass and coil excitation current requirements.

Figure 10. Visualisation of the proposed TULIP single-room treatment accelerator that incorporates the linac within the gantry. This design is an example of a cyclinac, in which a cyclotron is used as an *injector* to obtain moderate particle energies prior to the linac structures. (Courtesy Prof. Ugo Amaldi/TERA Foundation)

use of a single accelerator and that more rooms do not translate readily into a greater number of patient treatments [123–125]. The single-accelerator, multi-room scheme is offered by a number of vendors including Hitachi, IBA, Sumitomo and Varian.

The potential disadvantage of a single-accelerator, multi-room centre is that it is susceptible to single points of failure that may disrupt patient treatment. If the capital cost – and size – of the accelerator source can be reduced it can then be preferable to have each gantry utilise a single accelerator similar to the scheme utilised now for x-ray treatment, and ideally to have the accelerator mounted on the gantry itself to minimise floor space requirements [126,127]. This is a scheme recently brought into operation by one manufacturer (Mevion) which has developed a 250 MeV superconducting

synchrocyclotron that is made smaller and lighter (20 tons) by its utilisation of a very high 9 tesla niobium-tin magnet. If other emerging technologies such as high-gradient linacs, dielectric wall acceleration, or laser-based acceleration can be made small enough then gantry mounting would be an attractive option there too. For example, the TERA TULIP (‘TURNing LINac for Protontherapy’) project proposes combining the acceleration as part of the beam gantry (shown in Figure 10), and using a small, low-energy cyclotron as an injector [128]. It is notable in any case that a number of vendors are starting to offer single-room solutions, said partly to be a way of minimising initial costs for smaller treatment centres.

6.1. Carbon treatment

A carbon ion requires acceleration to a higher kinetic energy than a proton to achieve the same treatment depth; 425 MeV/u is a typical specification which allows treatment to around 33 cm in a patient, at which energy the beam rigidity $B\rho$ is 6.57 Tm. This is around three times the beam rigidity of a 250 MeV proton with the same penetrative power, which has so far limited carbon machines to being synchrotrons [72,129–131]. This large rigidity also increases the demands upon gantries, which until recently have been restricted to using normal-conducting magnets. Normal-conducting dipole magnets with apertures suitable for therapy beams are limited to field strengths of 1.8 T, which leads directly to the possible sizes of proton and carbon gantries. Parallel-scanning gantries will typically have heavier magnets due to the larger aperture requirement in the final dipole, and Gantry 2 at the Paul Scherrer Institute has a final magnet weighing around 45 tons [122]. The only existing gantry for carbon treatment is at the Heidelberg Ion Therapy centre [72], where the 3.65 m magnet bending radius set by the carbon ion energy and dipole field result in a total moving steel mass of around 630 tons, 130 of

Figure 11. The Heidelberg carbon-ion gantry, presently the only operating gantry for carbon ion treatment. (Courtesy Prof. Thomas Haberer/Heidelberg Ion Beam Therapy Centre)

Figure 12. Three-dimensional visualisation of the NIRS superconducting rotating gantry for heavy-ion therapy. (Courtesy Dr. Yoshiyuki Iwata/NIRS)

which are the magnetic elements; this gantry is shown in Figure 11. Despite the large size (18 m length and 7 m radius) the *isocentre* accuracy during rotation is still around 1 mm.

Alternative approaches to the isocentric concept have been proposed to reduce the required mass of moving steel. One such approach is the ‘Riesenrad’ (‘Ferris Wheel’) gantry where the patient rotates around the beam (whilst remaining supine), so that only a single rotating dipole magnet is needed at the end of the beam delivery system [132,133]. However, whilst the gantry is lighter, the surrounding building and radiation shielding are larger and require more complex patient-handling systems. But it is not just for carbon treatment where it might be desirable to reduce the gantry diameter. The first treatment gantry at the Paul Scherrer Institute utilised a hybrid ‘eccentric’ gantry where both the patient and gantry magnets rotate about an isocentre, which was used as a method to minimise the overall size of the installation [134,135].

6.2. Recent gantry developments

The use of superconducting (SC) coils at low temperature (typically at around 4 K, i.e. liquid helium temperatures) enables larger magnetic fields and therefore in principle allows gantries to be made smaller; however, unlike most other applications of superconducting technology, SC gantry magnets have to cope with being rotated. This demands the use of fluid-free cryocooler technology [136], but care must still be taken to avoid flexural changes during the rotation of these more sensitive magnets. Despite these greater difficulties, several groups are developing superconducting magnets suitable for carbon beam delivery. For example, NIRS in Japan are prototyping 3.0 T magnets [137] that can change their field on a 200 ms timescale. NIRS [138], ETOILE [139] and Lawrence Berkeley Laboratory [140] envisage gantry designs capable of transporting carbon ions with energies up to about 430 MeV/u, the ETOILE design for example proposing dipole fields up to 3.3 T that reduce the bending radius to around 2 m; the NIRS gantry design is shown schematically in Figure 12. These designs foresee a reduction in the gantry sizes to around 13 m length and 4 m radius and weights of around 200 tons, not too dissimilar to existing normal-conducting proton gantry dimensions. A lack of speed when adjusting the gantry dipole fields may be handled by utilising a range shifter and modulator downstream of the last gantry dipole.

Another way to reduce gantry weight, and possibly size as well, is to utilise FFAG-style optics. The idea here is that the addition of a strong alternating focusing component to a dipole system can reduce the Twiss envelope functions and the aperture required to transport off-energy particles; both these effects reduce the aperture required within the dipoles and thereby can significantly reduce their weight. FFAG gantries may incorporate either normal-conducting or superconducting magnets, the latter allowing a further reduction in gantry size at the expense of cryostat weight [88,141,142]; very light permanent-magnet arrangements have also been proposed. An associated benefit of reducing

the off-energy trajectories (i.e. the *dispersion* of the beam) is that a set of magnet field settings may transport a number of energies; existing gantry designs have a limited energy bandwidth that they can transport, and therefore must adjust their field strengths with beam rigidity for a wider range of treatment depths.

6.3. Imaging with accelerators

Although proton therapy can give a more accurate treatment than x-rays can, a present limitation is knowing how to accurately calculate the slowing in the intervening tissues prior to the target. Present-day imaging utilises techniques such as computed tomography which gives a standardised measure – in *Hounsfield units (HU)* – of the tissue attenuation. Whilst it is possible to convert HUs into approximate proton-relevant *stopping powers* (for example, bone has HU values between about +400 and +2000) [143], the conversion is insufficiently accurate to predict the Bragg peak depth to better than within several millimetres, giving the risk of significant *underdosing* or *overdosing* if the Bragg peak falls outside its intended target [29,144]. This is managed in treatment by prescribing a *margin* around the target volume as is commonly done in radiotherapy for other reasons, and by trying to ensure that the optimised treatment plan is *robust* against density uncertainties [145]. Because of this limitation a number of techniques – some to be used in combination with each other – are being studied to improve the prediction of proton stopping, and include techniques such as magnet resonance imaging (MRI), and monitoring of secondary particles produced during treatment [146–148].

If sufficient proton energy can be provided the Bragg peak will lie beyond the patient, and a measurement of its *residual energy* can measure the energy lost traversing the body. Many such measurements (somewhat less than a billion [149]) of individual proton energy loss with trajectory may be combined to create a *proton computed tomograph* (pCT) [150–154]. To image adult patients requires an entrance energy somewhat higher than the 250 MeV needed for treatment – 330 MeV being a common specification due to the need to measure the residual energy accurately enough in a *calorimeter* – and some accelerator designs (such as for example the ProTom synchrotron design [155]) address the need for these energies. Ganties must of course be able to handle both treatment and imaging if techniques such as pCT are to be taken toward clinical use from the present point of technical demonstration [149]. Hand in hand with improved imaging to support proton therapy must be the development of improved calculation methods, and a rapidly-developing area is the much greater use of Monte Carlo techniques in codes such as GEANT4 [42,156]. These Monte Carlo methods use statistical particle tracking to improve upon traditional dose estimation methods, and rely on the ever-improving availability of cheap computing power

to carry out detailed enough dose predictions. A number of groups are working on algorithmic improvements or tolerable physics simplifications to improve the speed of such calculations [43,157–160].

7. Conclusions

Proton and ion therapy are already mature enough technologies to be widely available commercially, but there are significant advances yet to be made. The established technologies of cyclotrons and synchrotrons presently dominate treatment centres worldwide, but there are emerging technologies which may potentially offer cost and/or size advantages; an overriding concern in a clinical setting though must be the requirement to achieve very high reliability in conjunction with patient throughput, something that established technologies may demonstrate more readily.

The use of superconducting magnets seems likely to play an increasing role in clinical particle accelerators as it is also doing in the traditional application of particle accelerators, in high-energy physics. Superconducting cyclotrons are already in clinical use, and superconducting magnets are likely to see clinical use in proton and carbon gantries in the near future [161]; they also hold out promise for use in future FFAG accelerators and gantries.

The reduction in size of accelerator components enabled for example by superconducting technology is likely to lead to a greater use of single-accelerator, single-room treatment facilities, and there are signs of this change happening. In the longer term, if very small (~ 2 m) proton accelerators become available then it is most probable that they will be used as single-room facilities analogous to the way x-ray therapy is delivered today.

Finally, an important avenue for progress will be the development of improved methods of obtaining patient image data and using it for more accurate treatment. Most widespread in development is proton tomography, but other methods will also find increased use. Coupled to this is the need for systematic improvements to the understanding of the underlying radiobiology that determines the response of tissues to protons and light ions. One such proposal is to utilise the CERN LEIR facility for radiobiology [162], and this and other studies are necessary to maximise the benefit of hadron therapy in the future [34,163,164].

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Notes on contributors

Hywel Owen is a Lecturer in Accelerator Physics at Manchester University, where he previously received his Ph.D. in physics in 1994; he is also a member of the Cockcroft Institute of Accelerator Science and Technology. He worked for a number of years at Daresbury Laboratory (now part of the UK Science and Technology Facilities Council) during which time he co-designed accelerators such as the DIAMOND Light Source. Since 2008 he has worked at Manchester on a number of projects, one of which was the first non-scaling FFAG – EMMA – a testbed for future particle therapy accelerators.

Randal MacKay completed his physics degree at Newcastle University in 1989 and his Ph.D. in physics at UMIST in 1993, after which he trained as a clinical scientist at Nottingham until 1995. For most of his career he has worked at the Christie Hospital in Manchester, and was appointed its director of medical physics and engineering in 2009. He is presently technical lead on the new UK proton therapy centre under construction there, and holds an honorary Senior Lectureship in cancer science at Manchester University. His research interests are in dosimetry and biological modelling, and he sits as joint chair on the New Technology Physics and Quality Assurance workstream within the UK Clinical and Translational Radiotherapy research working group.

Ken Peach studied physics at Edinburgh, receiving a Ph.D. in particle physics in 1972. After several postdoctoral positions he eventually was appointed Professor in 1996. After a brief period at CERN as Deputy Leader of the experiments division, he became director of particle physics and of e-Science at Rutherford Appleton Laboratory (now also part of STFC). In 2005 he was appointed director of the John Adams Institute for Accelerator Science at the University of Oxford, and in 2009 co-director of the Particle Therapy Cancer Research Institute. During his time at Oxford he led the design study for PAMELA, a proposed FFAG for proton and carbon therapy.

A graduate in physics from Glasgow University, Susan Smith began her career in physics at Daresbury Laboratory in 1985, working first on the UK Synchrotron Radiation Source, and then on a number of projects including the DIAMOND Light Source where she led the accelerator design. She then led the implementation of both the ALICE and EMMA accelerators, and after a number of roles at the Laboratory was appointed its director in 2009. She is also currently a visiting Professor at Liverpool University, and is a member of the Cockcroft Institute management team.

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