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Application of Novel Accelerator Research for Particle Therapy

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Abstract

This thesis seeks to review the latest trends in hadron therapy devices, and evaluate the potential of novel, researched accelerator concepts for future application. Although the clinical benefits of hadron therapy over photon therapy is unproven or disputed for many cancer types, there are several cases where hadron therapy presents a superior option. Many governments and medical institutions are planning or already executing development of new hadron treatment facilities. However, the higher associated costs have been a formidable obstacle for hadron therapy endeavors. This may be about to change; recent years have seen the introduction of economic single-room devices, and novel accelerator concepts hold potential to reduce cost further through improved compactness. Single-room gantry-mounted cyclotrons have already entered the market at prices competitive with X-ray facilities, and advanced, compact proton and ion accelerators offering unprecedented treatment could soon be ready for commercialization.

Preface

In Norway, there is a considerable interest for particle therapy. Norway does not currently have any facilities offering hadron therapy, and patients are flown to facilities in other countries for treatment. According to a recent report [1], 11,000 patients received radiation therapy in 2010; most of these received conventional X-ray treatment in Norway. However, it is estimated that 10-15% of patients receiving conventional X-ray treatment could benefit from hadron therapy; if this prognosis is adjusted for demographic developments it is estimated that within a few years about 1,500 Norwegians annually will be affected by cancer relevant for hadron therapy. However, the Norwegian government has expressed interest in establishing hadron therapy facilities; whether this will result in a national combined proton/ion facility or regional proton facilities in major cities such as Oslo, Bergen, Trondheim and Tromsø remains to be seen. (A report [1] recommended the former option, but government interests seem to move towards the latter, to provide service on a more regional level, among other arguments.) Proton and ion facilities have traditionally been highly costly investments, and care must be made when choosing between the many options.

At the Department of Physics, University of Oslo (UiO), a group dedicated to particle accelerator science has recently been established. This master's thesis study was initiated by Assoc. Prof. Erik Adli[1], with the motivation to investigate how research in accelerator science may improve particle therapy in the future, and to increase Norwegian competence within accelerator technology for particle therapy centers.

Stanford University, situated in Silicon Valley, is known for its rich traditions within innovation and outstanding research. It is also the home of the SLAC National Accelerator Laboratory, which has a rich history of groundbreaking physics research. Almost a decade ago, a task force was initiated to evaluate state-of-the-art and novel accelerator concepts for a hadron therapy facility in the San Francisco Bay Area. The task force involved staff and researchers from the Stanford University School of Medicine, the Stanford Department of Physics and SLAC, among others. However, after some time the project was dropped, partly due to difficulties with obtaining funding. The interest for medical applications of accelerator research is still present, not in the least due to the strong focus on innovation and technology transfer ubiquitous in the San Francisco Bay Area, and there is much competence to be found related to radiation therapy. SLAC has therefore presented an ideal environment for this thesis.

As part of my engagement at SLAC, I have had the opportunity to be involved in one of the most exciting research projects on novel accelerator concepts, namely the E-200 experiment investigating beam-driven plasma wakefield acceleration [2]. Although this

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[1]University of Oslo (UiO), SLAC National Accelerator Laboratory

experiment itself has limited direct relevance to radiation therapy, my participation therein has provided valuable insight in accelerator physics and ongoing research. The E-200 experiment is therefore given minor attention in the main body of the thesis.

This thesis aims to be of relevance for (1) actors considering acquirement of a radiation therapy facility, or involved in the process of such, and (2) individuals or groups involved in research on advanced accelerator concepts interested interested in the prospect of application within radiation therapy. It is clear that radical improvements in accelerator technology and/or design is necessary to save hadron therapy from losing too much ground in economic consideration. The focus of this thesis is therefore on state-of-the-art and novel accelerator concepts, within a medical context, for the most part assuming only modest knowledge of physics and medicine in the reader.

Acknowledgements

First and foremost I would like to thank my co-supervisor at SLAC, Erik Adli, for being an amazing mentor. I have indeed been lucky to have such a genuinely enthusiastic supervisor, showing involvement in my project and my personal development far beyond the expected. Thank you for being central in making these seven months awesome.

I would also like to thank my main supervisor, Bo-Sture Skagerstam, for providing good advice regarding the course of my project, as well as valuable feedback on the thesis itself. My sincere gratitude also goes to my co-supervisor at NTNU, Tore Lindmo, who has overseen the biophysical aspects of this thesis.

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Furthermore, I thank the many amazing people I have had the pleasure to encounter at and around SLAC for valuable discussions, in particular: Sami Tantawi, for always finding time to explain concepts of accelerator physics; Dr. Billy Loo at the Stanford Medical Center, for providing valuable insight form a radiation oncologist's perspective; Joel England, for lessons on dielectric laser accelerators; Vinod Bharadwaj, for numerous explanations of accelerator mechanisms; and, not in the least, Dieter Waltz, for lessons in everything from ultramarathons to accelerator physics, and for simply being an awesome person.

Dette er ikke bare avslutningen på en halvårig masteroppgave, men et femårig studium. Det er nesten litt lett glemme. Selveste kronen på verket, rosinen i pølsa.

Takk til fysmat-gjengen for fantastiske studieår. Dere vet hvem dere er. Særlig du, kompis.

Nabla og Nonnegata 8 har også bidratt mye til en fantastisk tid i Trondheim. Anerkjennende nikk i deres retning og tommel opp.

Helt til sist vil jeg takke min familie, som, i tillegg til ære en over middels ålreit gjeng, ved mange anledninger har hjulpet meg gjennom studieperioden. Det kan sies mye med mange ord - eller få. Dere vet.

Åja, og takk til meg selv, som har holdt ut med untertegnede hele veien. Bra jobba!

Contents

Abbreviations

SLAC - Stanford Linear Accelerator Center, now known as SLAC National Accelerator Laboratory

FACET - Facility for Advanced Accelerator Experimental Tests

RT - Radiation Therapy

RF - Radiofrequency

SOBP - Spread-Out Bragg Peak

LET - Linear Energy Transfer

IMRT – Intensity-Modulated Radiation Therapy

VHE(E) - Very High Energy (Electrons)

PTCOG - Particle Therapy Cooperative Group

CLIC - Compact Linear Collider

ILC - International Linear Collider

LCC - Linear Collider Collaboration

FFAG - Fixed-Field Accelerating-Gradient

NLCTA - Next Linear Collider Test Accelerator

LBNL - Lawrence Berkeley National Laboratory

LLUMC - Loma Linda University Medical Center

HIMAC - Heavy Ion Medical Accelerator in Chiba

NIRS - National Institute of Radiological Science

PSI - Paul Scherrer Institute

GSI - Helmholtz Center for Heavy Ion Research (Gesellschaft für Schwerionenforschung)

FWHM - Full Width at Half Maximum

TERA - Italian research Foundation for Oncological Hadrontherapy

Nomenclature

Although photons are in principle particles, the term *particle therapy* is generally reserved for methods using massive particles, thus excluding photon based treatment forms like X-ray therapy. This distinction is also made in this thesis. To clarify: I will be using the term *particle therapy* for all types of radiation therapy excluding photons. *Hadron therapy* [2] describes the use of hadrons, i.e. particles made up of three quarks. Neutrons, protons and all other ion species fall under this category, but I shall, whenever possible and sensible, refer to therapy involving these as *proton*, *neutron* and *ion* therapy [3], respectively. Similar terms are used for electron and photon based treatment. It is also convenient to distinguish between different ions within hadron therapy. Ions with atomic mass equal to or lower than that of neon are called *light*, while *heavy* ions refer to the more massive particles [24, p.4-5]. The term *radiation therapy* still refers to all types of cancer treatment using ionizing radiation, comprising all of the above.

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[2] Both "hadron therapy" and "hadrontherapy" are extensively used. Although some authors argue for the latter [25], I will be using the former, as I think it is more grammatically correct - "radiotherapy" is a contraction, and thus not an equivalent comparison; furthermore, one should show consistency for equivalent terms such as "photon therapy".

[3] In this thesis, the term *ion therapy* does not include protons, but rather refers to ions with atomic number greater than one.

Introduction

Cancer is the second leading cause of death in the western world today; in both the EU [3] and the USA [4]. Treatment of cancer consist of surgery, radiation, chemotherapy, hormone therapy, biological therapy, and targeted therapy. The treatment offered to the patient depends on factors associated with both the cancer type and the patient; often a patient will undergo more than one treatment regimen. Radiation therapy is offered in approximately 50% of all cases involving localized, malignant tumors [5], and about half of these patients receive radiation therapy for curative purposes [6, p.324].

Researchers have always been quick to assess the medical potential of innovations within science. Such was the case for X-rays, which from their early discovery have been applied for medical purposes. Following observations of the physiological effects of radiation on human cells, X-rays were soon used for curative purposes. In fact, only months after their "official" discovery [7], X-rays were used to treat a patient for breast cancer [8]. However, early devices were unable to produce high-energetic, penetrating beams for treatment of deep-seated tumors, and so X-rays before the mid-1900s were generally limited to palliative[4] purposes or to treat superficial cancers. This changed with the development of particle accelerators during the late '20s and '30s. Pioneering work by Rolf Wideroe and Ernest O. Lawrence led to the development of the linac (linear accelerator) and the cyclotron, whose operational principles are fundamental in all successive radiation therapy devices. During the '50s, megavoltage electron linacs became commercially available, facilitating production of devices that could produce the energetic X-rays needed for treatment of deep-seated malignancies [9, p.3-14]. The invention of the betatron in 1940 made direct electron beam treatment a more viable option than before [9], which was particularly advantageous for treating superficial tumors, due to their defined range. Hadrons were presented as a treatment option when Robert R. Wilson suggested the use of protons for medical purposes in 1946 [10], and first trials began in 1954 using the Lawrence cyclotron at the Lawrence Berkeley National Laboratory (LBNL). Soon after, in 1957, cancer patients were treated with protons at the research accelerator in Uppsala, Sweden [9], paving the way for the many European efforts of later years.

Protons are actually just one particle type considered for radiation therapy, but were natural candidates for initial efforts due to their lightness and simplicity [9]. The experiences with protons led to assessment of other heavy, charged particles, such as helium, carbon, nitrogen, neon, silicon and argon [11]. Other particles used for treatment include pions [12] and neutrons [13]. Still, irradiation with protons remained the main focus of research and most common form of radiation therapy. A milestone in hadron therapy was achieved when the first designated proton treatment centered was opened at the Loma Linda University

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[4]Palliative treatment does not have a curative intent, but is used for purposes such as alleviating symptoms.

Medical Center (LLUMC), USA in 1990. Up until this point, patients had been treated using research accelerators typically found at physics institutions; the initiation of this first of many successive so-called "turnkey" facilities represented growing interest for the efficacy of hadron therapy.

In 1994, the first designated facility offering carbon therapy opened with the Heavy Ion Medical Accelerator in Chiba (HIMAC) at the National Institute of Radiological Science (NIRS), Japan. Carbon ions were chosen because preceding research indicated them more favorable from a clinical perspective, for reasons to be outlined later in this section. Although disputed, carbon ions are generally understood as more advantageous than other ion species; clinical experiences have also provided many encouraging results [14]. Therefore, successive ion therapy endeavors have primarily operated with carbon ions as well [12]. In Europe, two research centers contributed to significant advances in the field, namely the Paul Scherrer Institute (PSI), Switzerland and the Helmholtz Center for Heavy Ion Research (GSI), Germany, which began treating patients in 1996 and 1997, respectively. In 2009, the first dual proton/ion [5] opened for treatment at the Heidelberg Ion Therapy center (HIT), Germany. To this day[6], over 100,000 patients have been treated with (non-photon) particle therapy worldwide. Of these, approximately 94,000 have been treated with protons and about 11,000 with carbon ions. Of the 48 hadron therapy centers currently operation, seven offer carbon therapy, of which three are combined proton/ion facilities. [12]

Although hadron therapy holds great interest for hadron therapy, and many believes the clinical properties to be clearly advantageous to conventional photon therapy, the comparison of efficacy and clinical capability between hadron and photon therapy remains somewhat of a controversy [5]. The reason is the lack of phase III clinical trials [15]; these are randomized, controlled trials (RCTs) involving multiple treatment centers and groups of 300-3,000 patients. Such trials are difficult to conduct in radiation therapy for several reasons. One is that it is difficult to conduct a purely randomized trial when the main priority is to heal the patient - from a research perspective, it is desirable to isolate results from other potentially manipulating factors, but it would for example be unethical to deny a patient chemical treatment from a fear of muddling experimental results. Furthermore, there is the ethical problem of executing an RCT when one form of treatment is believed to be clearly better than the other. On one hand, it is argued that the lack of conclusive studies is an argument for equipoise [7] between the two treatment forms, but on the other hand, said lack of RCTs might simply mean that they are too problematic from an ethical point of view, suggesting the lack of equipoise. There are, however, some phase II trials available, and advocates of hadron therapy argue that the results from these are compelling

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[5]The facility predominantly uses carbon as the primary element for ion therapy, but is also able to apply other elements, such as helium or oxygen [16].

[6]As of February 24rd.

[7]In this context, *equipoise* means balance, in the sense that one option cannot be concluded to be better than the other.

enough to conclude that hadron therapy is superior to photon therapy for several cancer types [17, 5]. Especially pediatric malignancies are championed as a clear candidate for hadron therapy, where the young age of the patients is a sound argument for going lengths to ensure optimal treatment with minimum dose delivery to healthy tissue, due to risks to growth, second malignancies and reduced life quality [17].

The investigation of the clinical potential of different particles is far from complete. It also is possible that other particles that have so far eluded scrutiny from a clinical perspective may exhibit advantageous properties we simply have yet to discover, and turn out to be viable candidates. For example, muons [18] and, in later years, even antiparticles [19] have been proposed as possible candidates. It may also be that well-known particles within radiation therapy may expose new properties under new conditions. At the time of writing, an experiment is being conducted at SLAC to evaluate the radiobiological effectiveness for very-high-energy (VHE) electrons [8]. Direct electron beam treatment has traditionally held a limited role within radiation therapy, since the low penetration depths and high scattering associated with electrons in the conventional clinical energy range of 6-20 MeV [9] is unsuitable for treatment of deep-seated tumors. Moving to higher energies both increases the range and reduces the scattering, but the biological effects of such VHE electrons have not yet been established. This is the basis for the current experiment at SLAC, which is described further in Sec- 2.7.

In this thesis, I will first go through the physical mechanisms serving as the basis for radiation therapy. In Sec.2 I outline the history and basic concepts of the different forms of radiation therapy, describing their advantages and weaknesses. The section proceeds with a discussion of the economic aspects, and ends with a summary of the accelerator parameters given by the clinical requirements.

In Sec. 3 I outline the basic premises of conventional, state-of-the-art and novel accelerator technology. This section focuses on the operating principle, albeit in a medical context. The application value of the different concepts is reviewed in Sec. 4. The thesis ends with a conclusion, containing a summary of the most important considerations for medical accelerators and the most promising accelerators for medical purposes, and some closing remarks aimed for the Norwegian efforts.

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[8]Most authors use the abbreviation *VHEE*, but to me it seems more natural to talk about VHE *electrons*. I shall use one form or the other where it seems natural.

[9]The full electron clinical range is 5-50MeV [20]; however, electrons have generally not been used to treat deep-seated tumors (> 10 cm), and have been mainly limited to the energy range 6-20 MeV. [21]

1 Particle-matter interactions and biological effects

1.1 Background

The effects of radiation therapy results from how particles interact with atoms and deposit energy as they travel through tissue, where the nature of the interaction and the effect of the resulting damage depends on the particle in question. Conceptually, the biological effect of radiation therapy arises from the damage done to the DNA molecule in the cell. All cells undergo cell division as part of the cell cycle, and cancer cells are characterized by rapid, disorderly cell division, ultimately causing vital organs to fail if not controlled. The DNA molecule carry the genetic code and acts as a "recipé" during division. If the DNA is sufficiently damaged, the cells are unable to perform a successful cell division, or the resulting new cell becomes unviable. Cells carry extensive repair mechanisms and may restore some of the damage done to the DNA, which is a good thing for healthy cells, but presents an additional challenge when seeking to eliminate malignant cells. Not only do we need to deliver damage to the tumor, but *irrepairable* damage. If both strands comprising the DNA helix are broken (figure 1) it is referred to as a double-strand break; such damage is harder to repair compared to a single-strand break, and is thus desirable to inflict in the tumor from a clinical perspective.

At the heart of the reactions causing the biological effects central in particle therapy are the interactions of charged particles. Although for example photons, as used in conventional radiotherapy, are without charge, the processes in which their energy is deposited rely heavily on charged particles, as will be explained below. In particle therapy, the different particles applied for radiation interact in different ways, resulting in varying effectiveness for cancer treat-
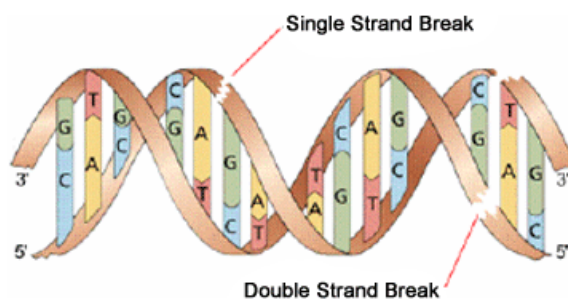
Figure 1: Schematic of single and double strand break in a DNA molecule. *From http://teachnuclear.ca.*

ment. Incident radiation deposit energy not in a single event, but through a series of interactions; a highly energetic particle is slowed down gradually, like a football kicked into a field of straw. Usually, the energy deposition processes of different particles involve the same particle-matter interactions, but of variable composition. Hence I shall first describe the particle interactions, then how these interactions apply for different types of radiation.

1.2 Charged particles

For clarity, a few remarks should be made on some of the basic terms associated with high-energy particles. Particles are said to be relativistic when the Lorentz factor deviates to a non-negligible extent from unity. This occurs when the velocity is about 10% the speed of light, since the Lorentz factor is given by

$$\gamma = \frac{1}{\sqrt{1 - (\frac{v}{c})^2}}. \tag{1}$$

Relativistic particles are usually described using $\beta = v/c$. This is convenient because the beta value has the convenient relation $\beta = \sqrt{1 - 1/\gamma^2}$ with the Lorentz factor in addition to giving the velocity. The term *ultrarelativistic* is used when the rest energy becomes insignificant compared to the kinetic energy, which occurs when the velocity is almost equal to the speed of light, i.e. $\beta > 0.99$. The rest mass or rest energy [10] for electrons, protons and neutrons is 0.511, 938 and 940 MeV, respectively. (As is seen, protons and neutrons are about 2,000 times more massive than electrons.) The total energy of a particle is

$$E^2 = (pc)^2 + (m_0 c^2)^2, \tag{2}$$

where the first and second terms are the kinetic and zero-point energy, respectively. Relativistic effects occur when the kinetic energy is greater than 1% of the rest energy. Particles can generally be said to be ultrarelativistic when the rest energy is less than 1% of the total energy, i.e. around 50 MeV for electrons and 100 GeV for protons.

An important factor in accelerator physics is the charge-over-mass ratio, or q/A ratio (A is the atomic mass number). Because a proton is much more massive, it will gain a smaller increase in velocity over the same electric potential as an electron, which has the same (opposite) charge.

1.2.1 Bremsstrahlung

Bremsstrahlung, or "braking radiation", is radiation emitted by charged particles when decelerated by other particles or, in a broader sense, by an external electromagnetic field. This comprises deflection, since a particle deviating from a linear trajectory (e.g. a particle in circular orbit) experiences acceleration perpendicular and deceleration parallel to the line of motion. Although the term, strictly speaking, covers deflection in an external magnetic

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[10]These terms are often used interchangeably, since the mass is given in units of energy when using natural units.

field, it is generally just used for radiation emitted from particles deflected by other charged particles. Synchrotron and cyclotron radiation are instead used to describe radiation from deflection in an external field.

The origin of braking radiation lies in energy conservation. When an electron with energy E_1 is slowed down by the forces exerted by a nucleus, it emits a photon with energy

$$E_\gamma = E_1 - E_2, \qquad (3)$$

and proceeds with energy E_2, so the total energy is conserved. Here we realize the distinction made between the general usage of breaking radiation and other types of emitted radiation. When a particle gradually changes course in a circular path in an external field, it emits near continuous radiation predominantly tangential to its orbit. This is referred to as synchrotron radiation. Although this, strictly speaking, also falls under the term braking radiation, the latter term is mainly reserved to describe photon emittance as a result of sudden changes in direction due to deflection by atoms in matter.
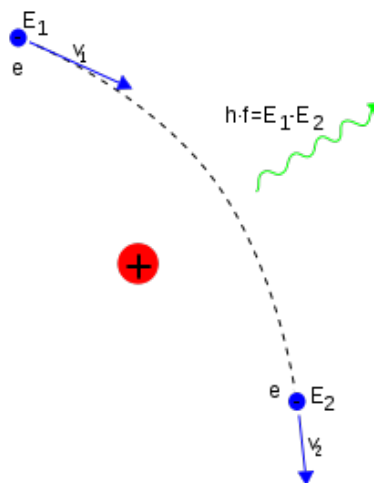

Figure 2: An electron is deflected by an atomic nucleus. A photon (green) is emitted, with energy corresponding to the energy loss of the electron. *From Wikipedia.*

It can be shown that the total radiated power due to braking radiation goes as

$$P = \frac{q^2 \gamma^4}{6\pi\epsilon_0 c^3} \left(\frac{d}{dt}\mathbf{v} + \frac{(\mathbf{v} \cdot \frac{\mathbf{d}}{\mathbf{dt}}\mathbf{v})^2}{1 - (v/c)^2} \right). \qquad (4)$$

As $E = \gamma mc^2$, we see that this scales with m^{-4}. As electrons have a much smaller mass that protons and, even more so, ions, it is obvious that energy loss due to braking radiation will be far more significant for electrons than for heavier particles at the same energies.

1.2.2 Stopping power and linear energy transfer (LET)

As a charged particle travels through the material of some sample, its electric field will interact with the bound electrons of the atoms in the material. These interactions between potentials constitute the *electronic stopping force*. Consequently, it will leave behind a trail of excited and ionized atoms along its path. The impulse transferred in these collisions depends on the charge, energy and angle of the incident particle, but in a head-on collision

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between an ion of mass M and energy E and an electron with mass m initially at rest, the electron will emerge with an energy

$$\Delta E = \frac{4mM}{(m + M)^2} \tag{5}$$

and a speed about twice that of the ion [22]. Since $m \ll M$ we can write $\Delta E \approx E(4m/M)$, and we see that the energy loss from a head-on collision will be small compared to the particle's initial energy E (most collisions will yield a much smaller impulse transfer). In short, such collisions will not hinder the incident ion notably or cause it to deviate much from its trajectory; only after a large number of such collisions will it be brought to a halt. Hence, it will travel along a relatively straight path as all these small deflections even out.

In medical physics, it is common to use the term *linear energy transfer* (LET), which is closely related to the electronic stopping force. Often, one is only interested in the energy deposited along the close vicinity of the primary particle path. A common approximation is then to exclude electrons above a certain energy, as these travel far away before depositing energy due to their low mass and high speed. This is the *restricted* LET. The *unrestricted* LET, where no such approximation is made and absolutely all secondary electrons are taken into account, is identical to the electronic stopping power.

In addition to the electronic stopping power we also have the *nuclear* stopping power. Contrary to what the name might imply, it is not due to nuclear forces, but arises from the repulsive forces in the elastic collisions between the incident ion and the atoms in the sample. These collisions are much rarer than the ion-electron interactions, which usually account for the majority of the energy losses in most cases [22].

Higher LET results in higher ionization density. This means that radiation with a high LET coefficient will cause more clustered, tightly spaced damage to tissue than radiation with a lower coefficient. This is reflected in the Bragg curve (shown for alpha particles Fig. 3), which has a sharper peak and thus more densely clustered energy deposition for particles with higher LET coefficients. The advantages of high LET are of great significance in radiation therapy primarily due to two aspects: first, clustered ionization has a far higher chance of causing critical damage, such as a double-strand break. Second, radiation with high LET is less affected by modifying factors such as cell repair and reoxygenation. Various modification factors and their effects are discussed further in Sec. 2.

1.2.3 The Bethe formula and the Bragg peak

The stopping power can be expressed mathematically through a quantum-mechanical derivation giving an expression known as the Bethe-Bloch formula:

$$-\frac{dE}{dx} = \left(\frac{ze^2}{4\pi\epsilon_0}\right) \frac{4\pi Z\rho N_A}{Am_e\nu} \left[\ln\left(\frac{2m_e\nu^2}{I}\right) - \ln(1-\beta^2) - \beta^2\right]. \tag{6}$$

Here, $\nu = \beta c$ is the ion velocity, ze is the ion total electronic charge, N_A is Avogadro's number, and A, Z and ρ are the atomic mass number, atomic number and density of the stopping material, respectively. I is the mean energy required to ionize an atom in the material, which is often approximated by $I = (10eV) \cdot Z$. This approximation is known as the Bloch correction; when included, Eq. 6 is referred to as the Bethe-Bloch formula.

A few comments are in order. In particle accelerators, ions are stripped of their electrons before acceleration, and so ze can be set equal to the charge of the nucleus. It should be noted that since dE is negative, the expression is positive. For energies between 100 keV and 1 GeV, the $1/v^2$ term in Eq. 6 dominates, and the expression can be approximated as

$$dE/dx = const./E^k, \tag{7}$$

with $k \approx 0.8$. [22, p,130-131] As can be seen from this approximation, the rate of energy loss increases as the total energy is reduced. This means that the stopping power and thus the number of ionization occurrences in the medium will increase along the path of the particle as it is slowed down, until it comes to a halt. Fig. 3 shows this process or alpha particles in air.
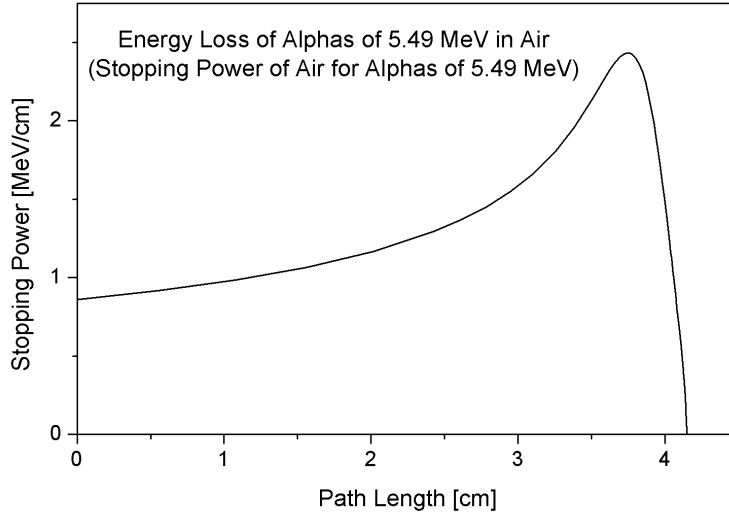
Figure 3: The Bragg-shaped curve of stopping power plotted against penetration depth for an alpha particle in air. *From Wikipedia.*

The characteristic curve and peak shown in Fig. 3 is the *Bragg curve* and *Bragg peak*, respectively. As goes forth from Eq. 6, the stopping power increases with nucleus size. Heavier particles therefore have shorter range and need higher energies to reach the same penetration depths as lighter particles. For example, a 40 MeV alpha particle has four times the stopping power and the same range as a 10 MeV proton [22].

1.3 Photon-matter interactions

There are various ways photons may interact with and transfer energy to matter. In the MeV regime, the mechanisms of importance are the photoelectric effect, Compton scattering and pair production [22]. Electrons are ejected from orbit or created entirely through these processes. As previously mentioned, charged particles are instrumental in the energy deposition of photons, as is also the case here; these secondary electrons account for most of the subsequent energy transfer in the medium.

1.3.1 Photoelectric effect

Electrons are bound to a nucleus with a binding energy described by the electronic work function. If an incident photon have energy exceeding the work function of some bound

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electron, it may eject the electron through photoelectric absorption. The photon is then completely absorbed and converted, giving kinetic energy to the electron according to the laws of mass-energy conservation. It has to be a *bound* electron because the nucleus is actually needed for the process to occur, even though the photon is just absorbed by the electron. During the process, the nucleus acts as a catalyst by acquiring some of the momentum in a recoil (but does not otherwise affect the energy transfer much). The reason the nucleus is needed has to do with momentum conservation of a massless initial particle, and can be realized by moving to the inertial frame of the photon and viewing the event as an inelastic collision.

An electron thus ejected as a free particle through the photoelectric effect is called a *photoelectron*, but we shall use the term *secondary electron* when generally describing an electron emerging as part of a particle-matter interaction, when it is not necessary to specify the exact mechanism behind its origin. The kinetic energy of the ejected electron is given by

$$T = E_\gamma - B_e, \tag{8}$$

with B_e being the work function of the previously bound electron. Photons may only need energies of a few electronvolts for the effect to occur, depending on the medium.

1.3.2 Compton scattering

Instead of being absorbed by the electron, the photon may transfer some of its energy through a collision and continue at a deflected angle. The electron may or may not be ejected from its orbit, depending on the energy and cross section of the incident photon. Usually the process can be regarded as an elastic collision between an energetic photon and an unbound electron at rest, see Fig. 4. This is a valid assumption because at sufficiently low energies, where this is approximation becomes an issue, the photoelectric effect dominates over Compton scattering.

Figure 4: λ and λ' denotes the photon before and after the collision, respectively. The arrow shows the trajectory of the electron from its starting point. *From Wikipedia.*

Due to conservation of momentum we have

$$\mathbf{p}_\gamma = \mathbf{p}'_\gamma + \mathbf{p_e}, \tag{9}$$

where $\mathbf{p}_\gamma$ denotes the photon momentum before the collision, while $\mathbf{p}'_\gamma$ and $\mathbf{p_e}$ are the momentum of the photon and electron after the collision, respectively. From the trigonometry
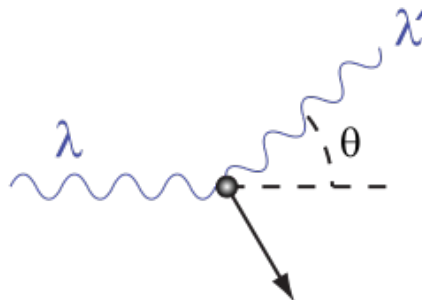
of the collision as shown in Fig. 4, we see that we can express the kinetic energy of the electron as

$$(p_e c)^2 = E_\gamma^2 + E_\gamma'^2 - 2E_\gamma^2 E_\gamma'^2 \cos\theta$$
$$= E^2 - m^2 c^4, \tag{10}$$

using $E_\gamma = p_\gamma c$ and Eq. 2. The energy of the scattered photon is found [22, p.139] to be

$$E_\gamma'^2 = \frac{E_\gamma}{1 + (E_\gamma/mc^2)(1 - \cos\theta)}. \tag{11}$$

The cross section and hence the probability of Compton scattering show a relatively weak dependence on the energy of the incident photon, and a stronger dependence on the factor Z/A [22, p.140]. Thus, Compton scattering plays a role in a broad range of the deceleration process of particles.

1.3.3 Pair production

For energies higher than twice the electron zero-point energy, i.e. above 1.22 MeV, a single photon may spontaneously convert its energy into a particle-antiparticle pair. Conservation of mass-energy, momentum and flavors[11] requires the pair to be exact opposites of each other. In our case, a high-energy photon may turn into a electron-positron pair, which fulfills this criterion as they have identical mass but opposite charge. As explained with photoabsorption above, the process can only happen in the vicinity of a nucleus, which is needed for momentum conservation.

Residual energy above the self energy of the electron-positron pair goes into kinetic energy in the form of velocity, and relativistic mass for the very high-energy range. Also, the probability of pair production increases with photon energy.

1.3.4 Summary

As explained above, photons may eject electrons into free orbit through the photoelectric effect or Compton scattering, or create free electrons through pair production. These secondary electrons may in turn slow down by emitting additional photons. Similarly, high-energy electrons being slowed down through braking radiation will emit photons, which in turn energize or create electrons. It is therefore seen that an incident electron or photon will cause a chain reaction of energy deposition mechanism when slowing down in matter, each mechanism branching out to cause additional events. The result is a shower-like series of events.

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[11]Electric charge is one type of flavor.
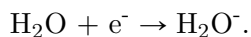
1.4 Free radicals

All of the mechanisms outlined above describes ways atoms may become ionized from incident radiation. Whether it is from collisions or effects such as photoelectric absorption, an electron may be ejected from orbit by an incident particle. With high-energy radiation, many atoms will become ionized as the particle traverses a medium. For example, a photon may eject a high-energy electron through Compton scattering, which in turn will collide with subsequent electrons, ejecting them from their orbits, leading to new interactions. The deflected photon can also eject new electrons through Compton scattering or other photon-matter interactions, further continuing the process. This is illustrated in Fig. 5. It is common to talk about the *ionization density* of radiation. Less scattering and heavier particles with higher LET generally inflict higher ionization density, as the chain of processes occur over a less spread-out area.

In addition, the resulting ions may in turn cause further reactions. How strongly ions interact with other atoms depends on the ion shell structure. Electrically neutral atoms or molecules with an unpaired electron are extremely reactive, and are known in chemistry as *free radicals*.

Two processes creating free radicals are of special importance to us, andoccur by irradiation of water and oxygen molecules. A water molecule ionized by some incident radiation will leave a free electron and an oxidized molecule:

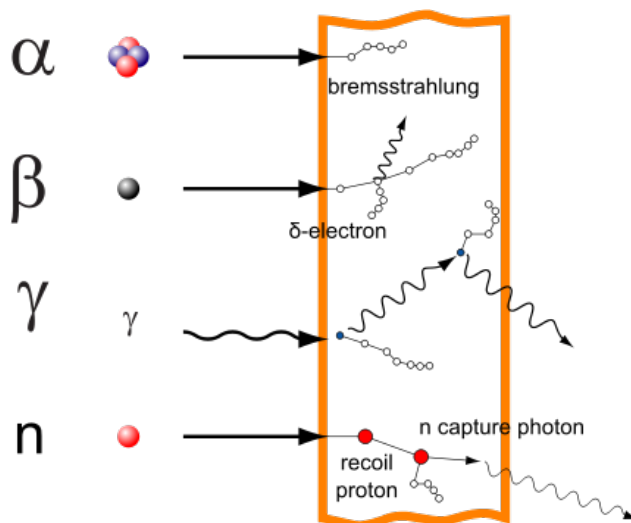Figure 5: Illustration exemplifying how energy is deposited through an interplay of various mechanisms. *From Wikipedia.*

$$H_2O + \text{radiation} \rightarrow H_2O^+ + e^-.$$

This electron may be captured by another water molecule,

$$H_2O + e^- \rightarrow H_2O^-.$$

Both these combinations are unstable, leading to

$$H_2O^+ \rightarrow H^+ + OH^\bullet$$
$$H_2O^- \rightarrow H^\bullet + OH^-,$$

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where the the dot symbol $^\bullet$ denotes that some ion, $X^\bullet$, is a free radical. Now, an organic molecule[12] containing H, which we shall simply denote RH, may react with a radical,

$$RH + OH^\bullet \rightarrow R^\bullet + H_2O$$
$$RH + H^\bullet \rightarrow R^\bullet + H_2,$$
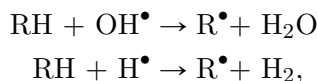
converting it to an organic free radical, $R^\bullet$. Such organic free radicals have a tendency to react strongly with other organic molecules, which may be a vital part of a biological structure such as a chromosome. Such a reaction may cause severe damage leading to the death of the cell, if not repaired. Furthermore, if the tumor cell is situated in an oxygen-rich environment, the following processes may occur:

$$R^\bullet + O_2 \rightarrow RO_2{}^\bullet$$
$$RO_2{}^\bullet + RH \rightarrow RO_2{}^\bullet H + R^\bullet. \tag{12}$$
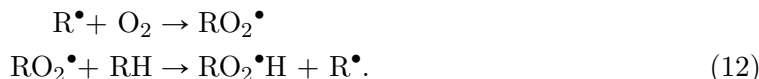
In an oxygen-rich environment, this process could continue in a chain reaction. This significantly increases the effect of the original radiation, and is known as the *oxygen enhancement effect*. The advantages and uses of this effect is discussed further in Section 2.2.2.

1.5 Radiation dose

I have so far outlined how particles transfer energy to other atoms and molecules as they travel through matter, with special notice given to the processes resulting in ionization, which is when an electron is knocked out of orbit from an atom or molecule.

In medicine, one is often primarily concerned with the amount of energy causing harmful impact to cells. One measure of this is the gray, abbreviated Gy, which is defined as the amount of energy from ionizing radiation absorbed per kilogram of matter, or

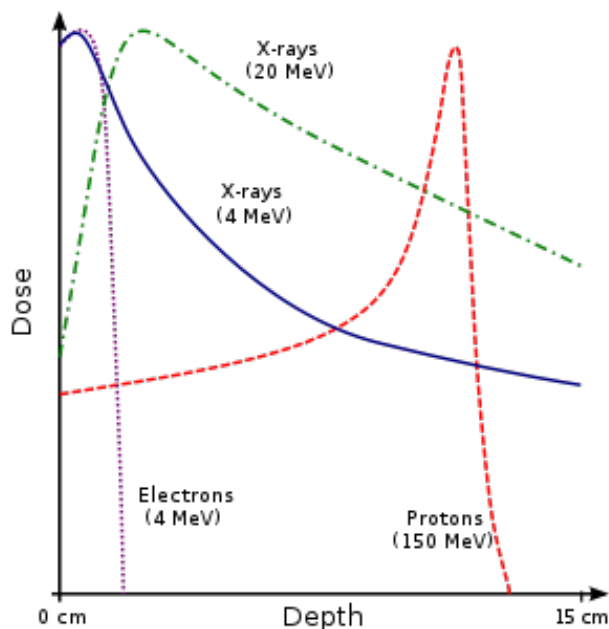
Figure 6: Penetration depths of four types of radiation in human tissue. *From Wikpedia.*

$$1 \text{ Gy} = 1 \, \frac{\text{J}}{\text{kg}}. \tag{13}$$

---

[12]An organic molecule is in a very generalized sense a molecule containing carbon.

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As seen in Sec. 1.2.3, heavy particles exhibit increasing energy deposition with depth, affecting the absorbed dose in a similar way. The dose deposition of charged particles follow a curve with a sharp Bragg peak, as illustrated in Fig. 6.

The depth at which this peak occurs is dependent on the energy of the incident irradiation. Fig. 7 shows the Bragg curve of several proton beams with different energies and intensities. The defined range and increased dose delivery in the Bragg peak are the main reasons why protons and heavy particles are highly suitable for radiation therapy. For a tumor of a given thickness, it is possible to apply a beam with particle energies varying over a range corresponding to a large dose deposition over the tumor volume. By also adjusting the beam intensities accordingly, the resulting superposition of these is a *spread-out Bragg peak* (SOBP), see Fig. 7.

1.6 Radiobiological effectiveness

The different particle-matter interactions inflict damage in fundamentally different ways. This means that the resulting amount of biological damage is likely not equal for two different types of interaction even though the radiological *dose* is the same. The property *radiobiological effectiveness* (RBE) is a widely used and practical way of comparing the actual biological impact between treatment forms of different nature. The RBE is found by comparing the amount of absorbed dose needed to achieve the same biological damage, i.e. kill the same number of cells, with a "benchmark" form of radiation. It is defined as the dose ratio

$$\text{RBE} = \frac{\text{D}_{\text{ref}}}{\text{D}_{\text{particle}}}. \qquad (14)$$

D_{ref} is the reference radiation, which is chosen as 1.2 MeV pho-
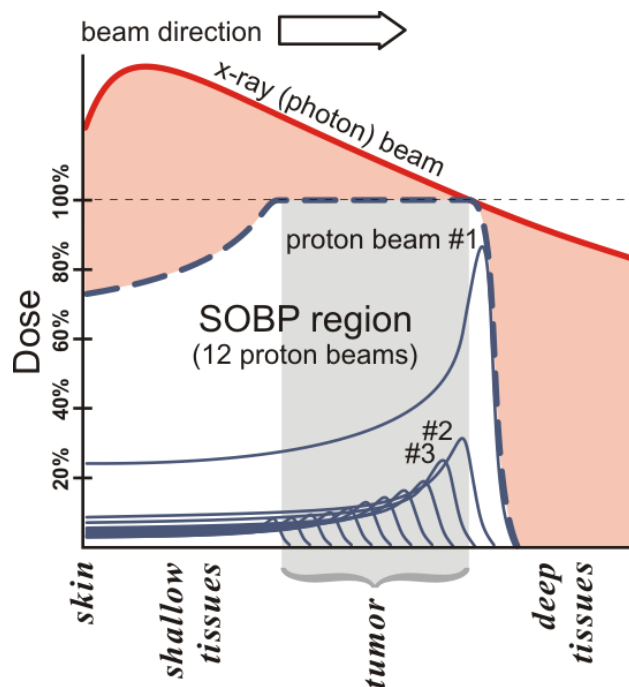

Figure 7: The figure shows how twelve Bragg curves with different energies and intensities combine to form a spread-out Bragg curve. An X-ray beam corresponding to the same dose deposition at the distal edge of the target is included for comparison. The X-ray beam delivers much more dose in the healthy tissue proximal and distal to the tumor. *From Wikipedia.*

22

tons emitted from a ^{60}Co target [23, 24]. As an example, radiation with a RBE of 1.4 will need only $1/1.4 = 71.43\%$ of the reference X-ray dose absorbed to achieve the same biological lethality.

One of the challenges within research on particle therapy is to accurately compare different treatment methods, as mentioned in the introduction. Accurate RBE values make it possible to compare results attained with different types of radiation - at least in principle; although the above formula is extremely simple, actually finding the values in the RBE ratio can be very complicated, as it relies on several factors such as dose, tissue type etc., and the calculation procedure itself is a topic of some controversy [16]. Because the RBE depends upon the LET it also varies with depth. This should be taken into account when determining the energies for the treatment beam, so that one obtains a spread-out Bragg peak for the actual biological damage.

It should be realized that a high RBE is not automatically an advantage *per se*, as a uniformly higher RBE is just similar to an allover larger dose. However, higher RBE may be efficient for radioresistive tumors (Sec. 2). With most particles, the RBE stays more or less constant with penetration depth. This is largely the case for protons, where the RBE only slightly increases near the end range [24]. Carbon ions, however, exhibit a pronounced increase in RBE around the Bragg peak compared with the plateau [14]. This property is highly advantageous, as it further reduces the dose delivered proximal to the tumor compared with the peak region.

2 Radiation therapy

2.1 Beam delivery

The overlying goal in radiation therapy is to maximize the damage inflicted to cancerous cells, while keeping the damage to healthy cells to a minimum. As described in the previous section, particle type and beam energy are very important factors, but so is the transport and delivery of the beam itself. A central principle in radiation therapy is *conformality*, which implies restricting the scanned volume (volume irradiated by the beam) as closely as possible to the tumor. The advantage of hadron therapy is the ability to provide highly conformal scanning by applying a SOBP matching the tumor; considerable effort is therefore given to ensure the optimal delivery of the beam. The transport, focusing, shaping and energy adjustment of the beam is the *beam delivery system* (BDS). We separate between *passive* and *active* scanning, which main principles of these two techniques can be understood quantitatively from Fig. 8 and 9. The former method applies a broad beam to irradiate the whole tumor at a time, while the latter uses a narrow "pencil beam" to scan the target volume with multiple strokes. In passive scanning, the beam is broadened to

cover the target after passing through a single or double scatterer, typically a metal foil. A range modulator then causes a spread in energy, which creates the corresponding SOBP. The beam is then shaped by collimators, which match the projected tumor shape. The shape of the collimator is thus unique to each tumor (and the angle of incidence). Finally, the beam traverses a compensator, which shapes the distal edge of the beam according to the tumor. Because of the sharp drop in dose deposition after the Bragg peak, hadron beams are well-suited to treat tumors in close proximity to sensitive organs. However, shaping the beam to the distal edge of the tumor results in unwanted radiation in the proximal tissue; since the whole beam has similar energy distribution, the compensator only provides a longitudinal displacement of the SOBP.
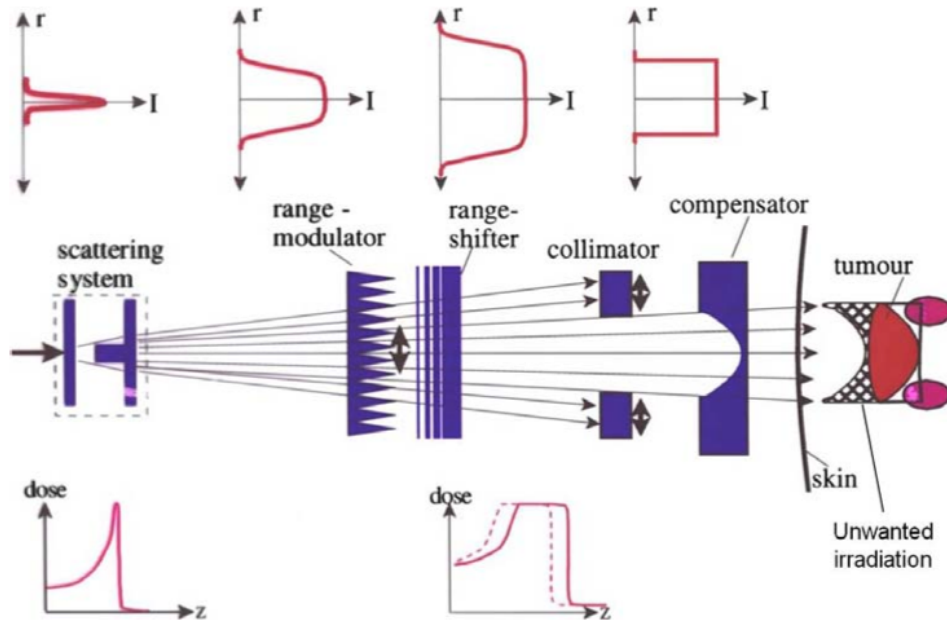
Figure 8: The various stages in passive beam delivery. *From [37].*

Passive scanning is the traditional and by far most common type of beam delivery. The collimator would typically be a solid piece of brass, uniquely crafted for each patient. Apart from the practical impracticality of crafting numerous such rigid collimators, they would also need to be replaced for each new angle of irradiation (see Sec. 2.3) to match the tumor shape. Modern devices instead employ so-called multileaf collimators, where many moveable "leaves" (typically tungsten) may be dynamically adjusted to fit any shape, see Fig. 10. This scheme has great practical advantages, but also adds complexity to the reliability of the device. But it is still a passive scattering system, and any collimator design suffers from scattering and consequential neutron exposure.

Figure 9: In an active scanning system, magnets steer the beam transversally, while longitudinal adjustment is provided by energy modulation. *From Ref. [38].*

Active scanning represent a more modern but elaborate approach, and is only used in a few therapy facilities - only a few percent of patients treated with hadron therapy have received active scanning [25]. Instead of using scatterers to spread the beam over the target area, magnets are employed to steer a narrow beam in the transversal directions, enabling "painting" o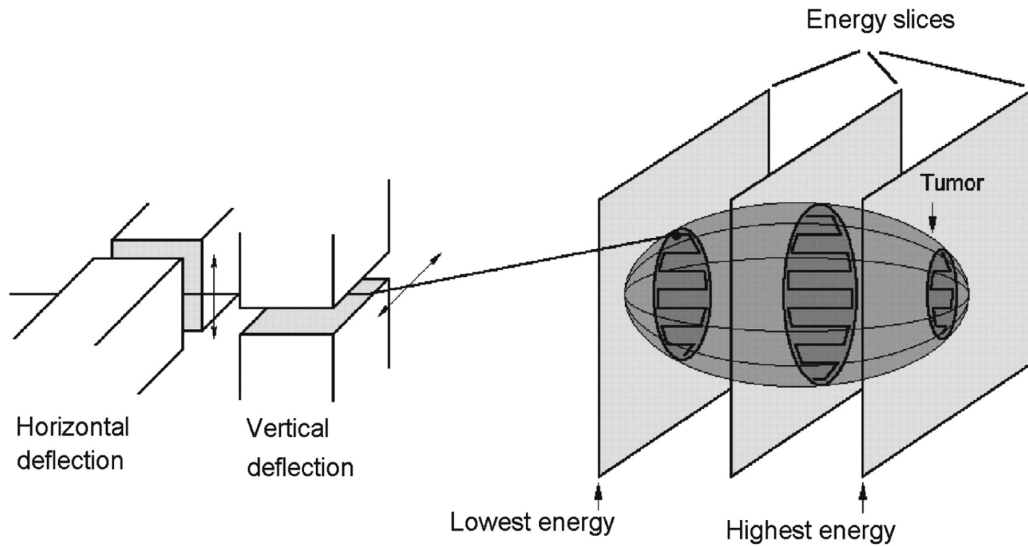f the tumor with many "strokes". With this scheme, it is desirable to keep a highly monoenergetic beam, and adjust the scanning depth by modulating the beam energy. It is thus possible to achieve more conformal scanning since the dose distribution can be controlled in all three dimensions - distal conformality does not cause unwanted proximal dose, as is the case with passive scanning. (Each scanned volumetric element is referred to as a *voxel*, from the combination of the words *volume* and *pixel*.) Two different types of active scanning is raster scanning, involving movement of a continous beam; and spot scanning (or "hold & shoot" scanning), where the beam is delivered in many tiny, pulsed shots.

A challenge with active scanning, however, is sensitivity to tumor and organ motion. A typical treatment session takes 15-20 minutes, and although much care is made to position the patient as stable as possible, respiration and body functions such as heart contractions cause unavoidable organ motions. If such motion should cause the tumor to move during treatment, the narrow pencil beam used in active scanning may miss the target altogether and deliver high dose to healthy tissue. Furthermore, the motion of organs may alter the beam range, as it depends on the density of the matter it traverses. In order to minimize the risk for a "critical miss" where dose is delivered to healthy tissue instead of the target,

one option is to introduce *smearing*, which effectively spreads the beam out over the edge of the tumor. It is not an ideal solution, since this compromise adds to the dose delivered to surrounding healthy tissue. Respiratory *gating* represents a different approach, and consists of timing the dose delivery with the inspiration/expiration cycle. This reduces the uncertainty of tumor position, but increases the duration of treatment.Another technique is to scan the whole tumor multiple times, called *multipainting*. By distributing the total delivered dose in multiple layers, the uncertainty of delivering high dose to healthy tissue is reduced through statistical averaging; the statistical error is reduced with $n^{1/2}$, where n is the number of repaintings [25]. In this way, it is also possible to correct any accidental under- or over-dosage by adjusting the intensity in successive paintings of a given voxel.

Another way to overcome the challenges presented by organ motion is to synchronize active scanning with medical imaging through Image Guided Radiation Therapy (IGRT). The specific methods and operating principles of medical imaging lie beyond the scope of this thesis. However, several practices to perform tracking of tumor movements exist, and if the transverse position and energy of a pencil beam could be modulated sufficiently fast, it may be possible to provide a very precise and highly conformal treatment beam.

The device must be capable of modulating the output energy to produce a SOBP, and to treat tumors of different depths. Some accelerators, like the synchrotron and linac, are capable of doing so within the device itself; others, like the cyclotron, produce a fixed output beam. In the case of the latter, it is necessary to have the beam pass through an energy selection system (ESS). In most cases, the ESS consists of absorbers that can be mechanically adjusted to tune the energy, as shown in Fig. 11. Although mechanical, such absorbers may be adjusted as fast as 50 ms [26]. This is not quite fast enough to be unaffected by organ motion. A more serious challenge, though, is the beam loss and scattering that occurs when the beam traverses such

Figure 10: Modern, dynamic multileaf-collimator. *From www.varian.com.*

absorbers. Beam transmission typically varies between 0.1% and 10% [16], which causes activation. Furthermore, beam energies higher than 10 MeV/u (i.e. all clinical hadron beams) cause neutrons to be scattered from the absorbers [27]. Such secondary neutron radiation may be problematic in some cases, especially for single-room facilities. Usually, the problem is avoided by placing the ESS far from the patient; thus, the neutrons may be dumped in a radiation shielded area while the treatment beam is transported to the patient. On the other hand, single-room facilities aim to achieve high compactness by placing the entire device inside the treatment room. In
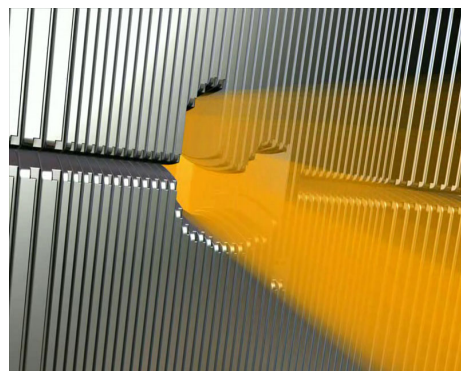
such cases, the scattered neutrons from a mechanical ESS cannot easily be shielded without affecting the beam. Active scanning using electronically adjustable energy modulation overcome this problem, since no absorbers are needed. Although neutron production also occur in the patient, such radiation is more or less negligible [28].

2.2   Fractionation

The main principle behind fractionation is to divide the dose in smaller fractions instead of delivering the whole dose at once. There are multiple reasons for doing this, but the initial motivation was to make use of the self-repair mechanisms of healthy cells. All cells may repair some of the damage done to the DNA, but healthy cells do so much more efficiently than cancerous cells. In healthy cells, minor damages are usually repaired after about six hours. For this reason it is benefi-

Figure 11: By rapid adjustment of the mechanical wedge absorbers, it is possible to attain fast energy modulation. *From Wikipedia.*

cial to deliver the dose in fractions separated by at least this amount of time, allowing healthy cells to recover in between treatments. As cancerous cells recover at a much slower rate, they are significantly weakened and much more prone to suffer critical damage upon subsequent irradiation.

The dose prescribed for a given treatment depends greatly on the tumor type and the patient, but in general, 60-80 Gy is usually needed to obtain local control of a deep-seated (> 10 cm) tumor. For photons, this total dose is typically fractioned into 25-35 subtreatments over equally many days, i.e. 2-3 Gy per fraction. Fewer fractions may be used for particles with high LET, since cells are less able to repair the damage inflicted. For carbon ions, the average number of fractions lies around 13-14 [14].

2.2.1   Cell cycle

All cells continuously undergo a cyclic chain of events in which they grow, replicate DNA and undergo cell division. Over the cell cycle, the cell goes through stages of different levels of radiosensitivity. Somewhat counterintuitively, the most radiosensitive cells are in general those that divide quickly, are well nourished and metabolically active.

Since the degree of radiosensitivity varies over the cell cycle, the tumor cells will, when

irradiated, exhibit varying degree of lethality rates depending on their stage in the cell cycle at the time of irradiation. Therefore, by allowing time to pass in between treatments, the portion of the cells that were previously in a radioresistant state (and survived) will pass into a more radiosensitive state by the time of subsequent irradiation. By iterating this process, it is possible to kill more cells than with no or less fractionation.

2.2.2 Oxygen enhancement

In section 1.4 I discussed how the creation of free radicals may contribute to DNA damage, and in Eq. 12 it was shown that the effects of such radicals is pronounced in an oxygen-rich environment. This is an important phenomenon in radiation therapy, where oxygen is a a central *radiosensitizer*, i.e. an agent that enhances the effects from radiation. The degree of which a certain type of radiation is enhanced by an oxygen-rich environment can be expressed through the oxygen enhancement ratio (OER), defined as

$$OER_{particle} = \frac{D_{anoxic}}{D_{oxic}}. \tag{15}$$

(D_{anoxic} and D_{anoxic} describes the dose needed to obtain tumor control in anoxic and oxic states, respectively.)

As we would expect, this ratio is high for radiation types such as X-rays, where a large fraction of the biological damage occurs through free radicals. The OER ratio is dependent decreasing towards unity with high LET values. Therefore, carbon ions are much less dependent on oxygen than protons and photons.

The oxygen enhancement effect is of much importance for fractionation purposes. The argument goes as follows: a tumor is characterized by rapid and uncontrolled cell division, causing it to often outgrow its blood supply. This leaves the cells in the core of the tumor in a hypoxic state, as oxygen is mostly consumed by the cells near
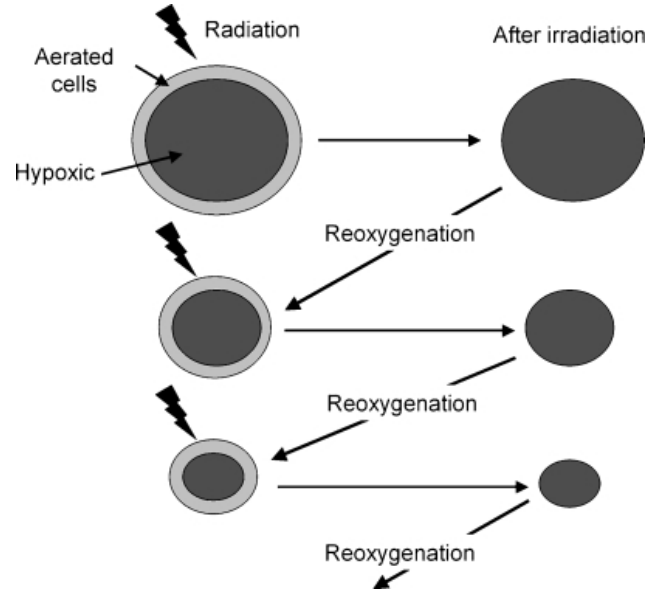

Figure 12: Fractionation is an iterative process of repeated irradiation, making use of the enhanced RBE ratio from reoxygenation. *From [29].*

28

the surface of the tumor. Because of the oxygen enhancement effect, if such a tumor is uniformly irradiated, the biological damage will be greater in the cells near the surface than the cells near the core, effectively reducing the tumor is reduced to the surviving cells mostly found in the former core. A simple sketch is shown in Fig. 12. With the previous outer layer perished, the remaining tumor cells now have a richer supply of oxygen, allowing the cells near the surface of the "new" tumor to oxygenize. Thus, by fractionating the radiation dose, the tumor is allowed to oxygenize between each treatment, which causes its outermost part to become more susceptible for radiobiological damage. For every successive radiation fraction, the tumor is reduced by shredding off the outer layers.

2.2.3   Hypofractionation

Hypofractionation is a collective term for radiation treatments where the total radiation dose is divided in fewer but larger fractions than the conventional. By limiting the number of fractions the total treatment time is reduced, resulting in lower costs and patient inconveniences as well as increased capacity per facility.

As already mentioned, it can be advantageous to portion the treatment in many fractions when cell repair and varying radiosensitivity are factors of significance [49]. However, these mechanisms apply to a far less extent for high-LET radiation, allowing the dose to be delivered in fewer fractions. Studies experimenting with different fractionation regimens have found that hypofractionation can in many cases be just as effective as conventional fractionation [14]; indeed, hypofractionation may in some cases even be clinically advantageous [47]. Over the past two decades, there as been a trend of reduced number of average fractions per treatment for carbon therapy [14]; however, there is no textbook answer to give the "right" number of fractions for a given tumor and patient.

2.3   Multi-angular scanning

Using multiple angles for irradiation has been common practice for may decades. The dose deposition from X-rays generally decreases with depth (Fig. 7), but by irradiating the same target volume from multiple angles it is possible to deliver a higher dose per volume to the tumor than the healthy tissue, even for deep-seated tumors. The surrounding tissue still receives a larger total dose, but spread out over a greater area. This is advantageous in healthy, self-repairing tissue, since larger doses increases the amount of non-repairable damage; such 3D conformal radiation therapy (3D-CRT) has therefore been able to provide a better tumor/tissue dose, at least in terms of cell lethality. The principle of multi-angular scanning extends to therapy of all particle types - it is generally better to distribute the unavoidable dose delivered to healthy tissue over a greater area, since less concentrated

dose is more easily repaired by healthy cells. Again, this applies to a somewhat less extent for high-LET radiation.

The number of portals varies greatly. For hadron therapy, it is often sufficient with a few angles, while IMXT may make use of 10-12 beams [25].

2.4   Photon therapy

X-rays, or, high-energy photons, is by far the most commonly used method of radiation therapy. This fact can be attributed to the low costs, well-known principles of operation and well-documented side effects associated with photon therapy. The clinical energy range is an important factor for dimension requirements within radiation therapy, as will be discussed. Fig. 13 shows a simple schematic of the structure and main components of an X-ray treatment device.
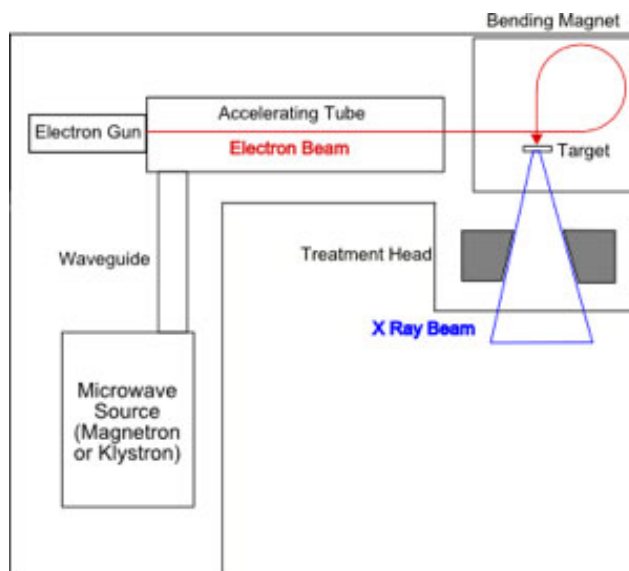
Figure 13: Conceptual outline of an X-ray treatment device. The electrons are bent $270°$ to preserve achromaticity. *From www.radonc.com.*

Free electrons produced from a source (in Fig.13: an electron gun) are accelerated in a linac, which is typically powered by a klystron. The electrons hit a target, for example a ^{60}Co plate, scattering high-energy photons on the opposite side. A collimator blocks photons exceeding the desired beam size, so that it has the appropriate shape when irradiating the tumor. Since photons do not have a pronounced end range, there is no need for scattering and compensator systems such as used for beam delivery in hadron therapy devices (Fig. 8).

Due to the advantages of 3D irradiation, as mentioned under Sec. 2.3, the device must be built such that it can be rotated around the patient. Fig. 14 shows a full setup with a patient undergoing a full 360° scan, with snapshots of the device head at several positions during the cycle.

As the figure shows, the linac needed for X-ray generation can be very compact. For curative purposes, the electron energies needed to produce the desired X-rays lie in the low MeV range, typically between 4 and 25 MeV [21].[13] As conventional linac gradients typically lie around 10-

Figure 14: Figure showing various positioning of treatment head as part of a multi-angular scan. *From www.peninsulacancercenter.com.*

25 MV/m, linacs for high-energy X-ray devices are usually only about one meter long. Thus, it is possible to construct rotating treatment devices as shown in Fig. 14 in a relatively simple and inexpensive way. Hadron therapy need much more expensive and sophisticated devices, which is the main reason why photon therapy dominates the field of radiation oncology today.

However, photon therapy has its limitations. Photons have very low LET, and delivers damage to the DNA molecules in tumor cells primarily through the creation of free radicals, resulting in unclustered, somewhat sporadic ionization. Consequentially, the damage inflicted by photons is unclustered and often repairable. Although the superior repair mechanisms of healthy cells over those of tumor cells can be used to boost the beneficial effects of fractionation, it would be far more advantageous to deliver a precise, irreparable dose to the tumor instead. Because most damage is delivered through free radicals, radiation oncologists cannot rely on the beam alone to obtain satisfactory results. Instead, it is necessary to employ methods such as fractionation. The oxygen effect mainly imposes limitations, since cells in the tumor core have a significantly reduced sensitivity towards low-LET radiation types such as X-rays. The variations in radiosensitivity over the cell cycle is also much more pronounced for photons than for particles with higher LET.

Another challenge associated with photons is the lack of a well-defined range. Photons are highly penetrating, and a beam of X-rays shows relatively little change in energy deposition as it travels through tissue. This is clearly seen in Fig. 6, where electrons and protons have

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[13]Diagnostic X-rays operate at much lower energies, of about 0.1 MeV [21].

a well-defined penetration depth compared to the slowly subseding X-rays. Not only is a considerable dose delivered distal to the tumor; the dose delivered proximal to the target is even larger than in the tumor itself.
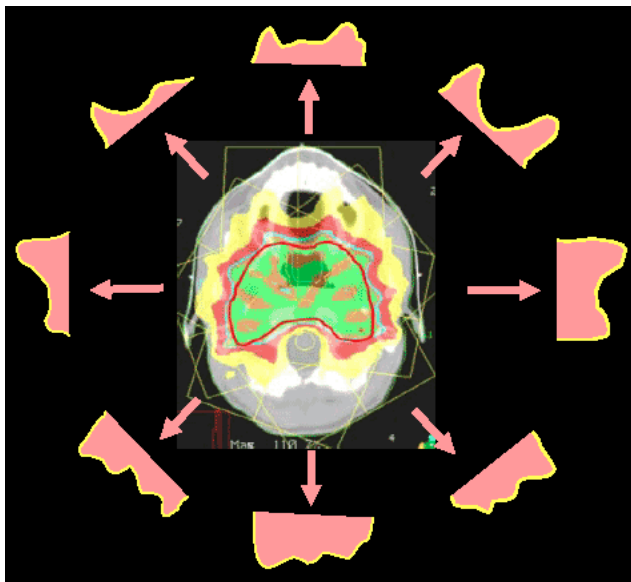

Figure 15: IMRT of a brain tumor. Intensities and collimator shapes are varied in order to deliver as conformal dose as possible, as simulated with a computer program. *From www.biij.org.*

The irradiation of healthy tissue due by X-rays can, however, be improved on with *intensity-modulated radiation therapy* (IMRT). (For clarity: IMRT is often used exclusively for X-rays, but in recent times, intensity-modulated *proton* therapy (IMPT) has gained momentum. Therefore, it makes sense to use the term IMXT when describing intensity-modulated X-ray therapy, and let IMRT be a generalization of the principle for all radiation types.) This is an extension of the 3D principle, but in addition to simply irradiate from multiple angles, the shape and intensity of the beam are varied with the relative position in order to provide a much more conformal scanning. Much due to rapid progress within computing seen over the last two decades, IMXT quickly gained ground as simulations could be efficiently applied to find the combinations of portals (angles of irradiation) and intensities needed to deliver a much more conformal dose than previously achievable. IMXT has become the "gold standard" of photon therapy, and with good reason - there is much dispute concerning whether proton therapy is preferable over IMXT for deep-seated tumors. In recent times, several major U.S. insurance companies have decided to stop covering proton therapy for prostate cancer, the most commonly encountered malignancy in the male population, arguing that the clinical results are either inconclusive or not sufficient to make up for the costs [36].

Although X-ray treatment cannot offer the advantages associated with proton therapy, it still remains the method of choice for radiation oncologists in most cases, due to its availability and inexpensiveness. Not in the least with the improvements on IMXT during later years, most hospitals continue to find the cost/gain-consideration balancing in the favor of photon therapy.

2.5   Proton therapy

Despite the favorable properties of hadron beams, proton therapy suffers from the costs associated with the bulky, sophisticated devices needed reach clinical energies. One particularly desirable attribute of hadrons is the Bragg peak (Fig. 6) in the energy deposition curve. Fig. 7 shows how proton beams of different energies are applied to create a spread-out Bragg peak (SOBP) matching the a given tumor, compared with the dose deposition curve of a corresponding photon beam. Like for X-rays, protons exhibit some amount of irradiation in the area leading up to the tumor, but significantly less. Also, and more importantly, the curve drops to zero almost immediately after the peak area. In other words, not only do protons deliver less radiation to surrounding tissue than photons, but also almost zero dose distal to the tumor, and is thus a superior choice when irradiating a tumor close to a vital organ or sensitive tissue. This is the primary reason why proton beams are so desirable within the field of radiation therapy.

The other important factor is the higher LET of protons. The sharp Bragg peak combined with moderately high LET implies high ionization density near the end of the proton range, but the damage done from such radiation is also qualitatively different from that of low-LET radiation. Protons exhibit a radiobiological effectiveness (RBE) of about 1.1, even slightly higher near the end of the range [24].

However, protons penetrate tissue with much greater effort, and need as a consequence much higher energies than photons in order to reach the same depths. As Fig. 6 shows, 150 MeV protons have a range of 12-13 cm, and the full clinical range of proton treatment devices lies around 70 to 250 MeV. The requirement of higher energies is the reason why proton treatment facilities need cyclotrons or synchrotrons, in contrast to the compact linacs sufficient for X-ray production. In addition, the requirement of 3D scanning (Sec. 2.3) impose the need for large, rotating devices called *gantries*.

2.6   Ion therapy

Heavy ions have many of the same characteristics as protons, but more pronounced: they have higher LET and ionization density, sharper Bragg peak but need even higher energies to penetrate matter. Although heavier ions have sharper Bragg peaks than protons, the energies do not drop all the way to zero after the peak. Instead, a small "elbow" or "tail" is observed after the peak, giving some residual radiation also after passing through the target. The reason is that the beam breaks up through nuclear fragmentation, and carry some energy past the Bragg range. The resulting dose contribution after the peak is very small, but non-negligible, and of significance for tumors close to vital tissue.

As mentioned earlier, the high LET associated with the heavy carbon ions cause ionization

occurrences to increase towards the end range, as shown in Fig. 16. This causes highly clustered damage in the target area, affected to little extent by cell repair and radioresistive phenomena.

[39].
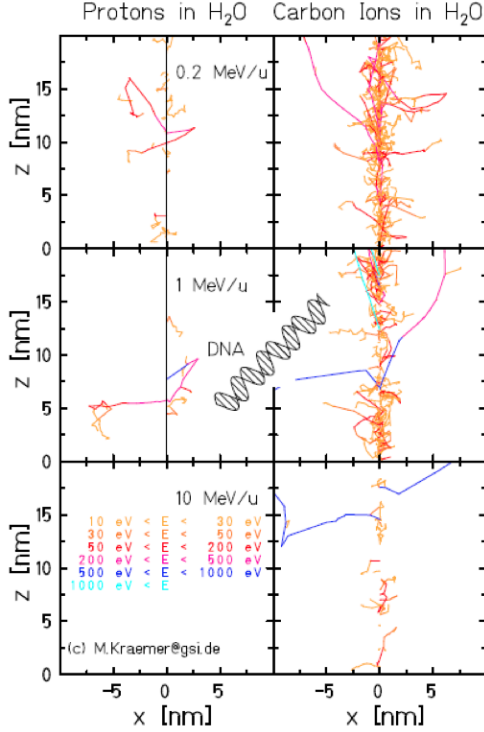
Figure 16: The figure shows the extremely dense ionization trail left by the carbon ion beam near the end range. Protons show similar behavior, but to a much less extent. *From Ref. [50].*

The RBE for heavy ions is therefore even higher than for protons; in some cases reaching values as high as around 3.0, and increasing towards the end range [24]. Carbon ions therefore seem out to be well suited for treating radioresistive tumors.

Because of the larger mass of carbon ions compared to protons, high energies are needed to produce the penetration depths needed to treat deep-seated tumors. Carbon ions therefore present the most costly alternative within radiation therapy, as discussed below.

2.7 Electron therapy

Traditionally, electron therapy has been reserved for treatment of superficial tumors. Electrons in the 2-25 MeV energy range have a penetration depth that scale roughly as 0.5 cm/MeV, and are therefore more suitable than photons for such purposes [21]. This energy range is the same as used for X-ray generation, and the linacs required to accelerate electrons to these energies are compact, common and inexpensive. At these energies, electrons exhibit relatively high lateral spread and short penetration depth.

Recent times has seen an emerging interest for the prospect of applying VHE electrons for radiation therapy [30]. (Some authors use the term for the 50-100 MeV range, others are affiliated with the 150-250 MeV range. In this thesis VHE electrons simply refer to electrons of significantly higher energies than the traditional clinical range, typically between 50 MeV and 250 MeV. [33, 31, 20]) Fig. 17 shows the ionization curves for electrons of four different,

low energies. Electrons in the conventional range of 6-20 MeV for direct treatment (4-25 MeV for production of X-rays) have defined penetration depths, but because they deposit energy more uniformly over the range, exhibit significant lateral spread and lack the sharp cutoff seen in protons, they are less preferable to hadrons. However, VHE electrons have a large penetration depth and thus show an almost flat deposition curve over the clinical range (more on the clinical range in Sec. 2.9). Such a flat dose deposition curve may be advantageous over that of photons, which deliver much dose proximal to the target. Indeed, simulations have shown that a VHE electron beam may provide a dose delivery of equal or better quality than an X-ray beam [32, 33]. Furthermore, since electrons are charged, it is possible to manipulate the beam using magnets, for example enabling active scanning.

Although initial simulations show promise, the usefulness of VHE electrons thus comes down to their actual clinical properties. An experiment is currently conducted at SLAC and the Stanford School of Medicine aiming to investigate the radiobiological efficiency of such energetic electrons. Little is known about the RBE coefficients for electrons at these energies, but if they should prove to be advantageous over those of photons, direct VHE electron therapy could prove to be an inexpensive and well-suited form of treatment. Because the experiment is still being carried out, the outcome is not yet determined; also, I am unfor-

Figure 17: Penetration depths electrons of different energies in water. *From www.photobiology.com.*

tunately unable to describe the experiments in greater detail for confidentiality reasons. However, since radiation therapy using VHE electrons is a hypothetical future feasibility, I will consider some accelerator concepts with potential for acceleration of electrons.
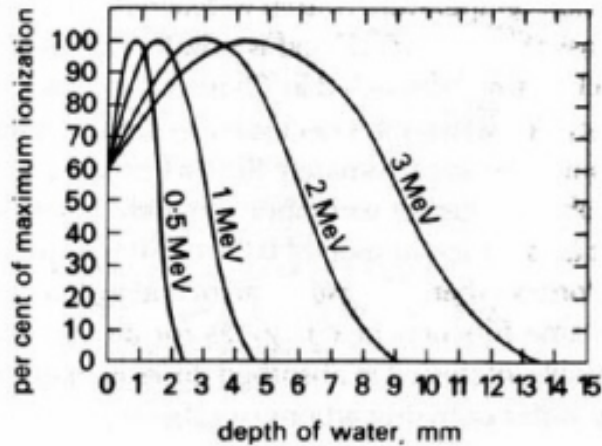
2.8   Economy

"If proton accelerators were small and cheap, no radiation oncologist would use X rays."

[25, p.575]

Because of the Bragg peak and high LET, hadron therapy is generally preferable over photon therapy, if costs are not considered. There is little dispute that hadron therapy is in most cases able to produce a more conformal dose delivery. However, the clinical experiences are in many cases not conclusive. Much of the reason for the disputes is the lack of sufficient RCTs, as discussed in Sec . Although hadron therapy is believed to be advantageous in many cases from a clinical perspective, solutions need to be economically viable if they are to be implemented by hospitals. High cost is the main limiting factor for the availability of hadron therapy today.

The expenses for radiation therapy can be divided in two parts: the initial investment, and the operation costs. Included in the operation costs are expenses associated with maintenance, competent staff, power usage etc. The necessary, or minimum, costs for treatment consist of the operation costs, but also associated expenses like patient housing. Hadron therapy requires in general more sophisticated instruments than photon therapy, with more specialized staff to run and maintain them, which increase the expenses. In addition, hospitals often need to repay the initial investment; this results in an extra *business cost* added to the total treatment price. For hadron therapy, such business costs may comprise more than half of the total expenses [40]. Generally stated, the treatment itself is substantially more expensive with protons than with photons. Numbers vary, but proton therapy tend to cost over two times per fraction than photon therapy. (Since the number of fractions vary with tumor type, strongly affecting the total expenses, it makes sense to compare the costs of each fraction rather that the full treatment, while also keeping in mind that significantly fewer fractions are often used within hadron therapy and specifically ion therapy than within conventional photon therapy.)

As mentioned in Sec. 2.5 and 2.6, heavier particles need higher energies to reach the same penetration depths as lighter particles. Higher energies means more powerful accelerators, which further drive up the costs. Not only are the accelerators themselves expensive; larger facilities are needed to accommodate the device with sufficient radiation shielding, and large gantries are needed to provide multi-angular scanning. These considerations often make the initial investment too discouraging for hospitals considering to offer proton therapy.The accelerator itself typically costs 20 (40) M€ [14] for protons (carbon ions), which usually contributes about 20 to 30% of the total investment cost of the facility. The price of a gantry is typically of the order 10 M€for protons. [25]Gantries for carbon beams are somewhat more costly since more energetic particles require larger dimensions, both in terms of more powerful magnets and larger bending radius. [15] If new accelerator technology can reduce the dimensions of the accelerators, the initial investment may be significantly less. (However, expenses associated with maintenance, power consumption and staff may

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[14]M€ = million euros. Values are not converted into a common currency nor adjusted for inflation in this paper, but presented with their original value.

[15]Very powerful magnets could be employed to reduce the bending radius, but this would increase the emitted synchrotron radiation given in Eq. 4.

be unchanged, or even higher, depending on the design.)
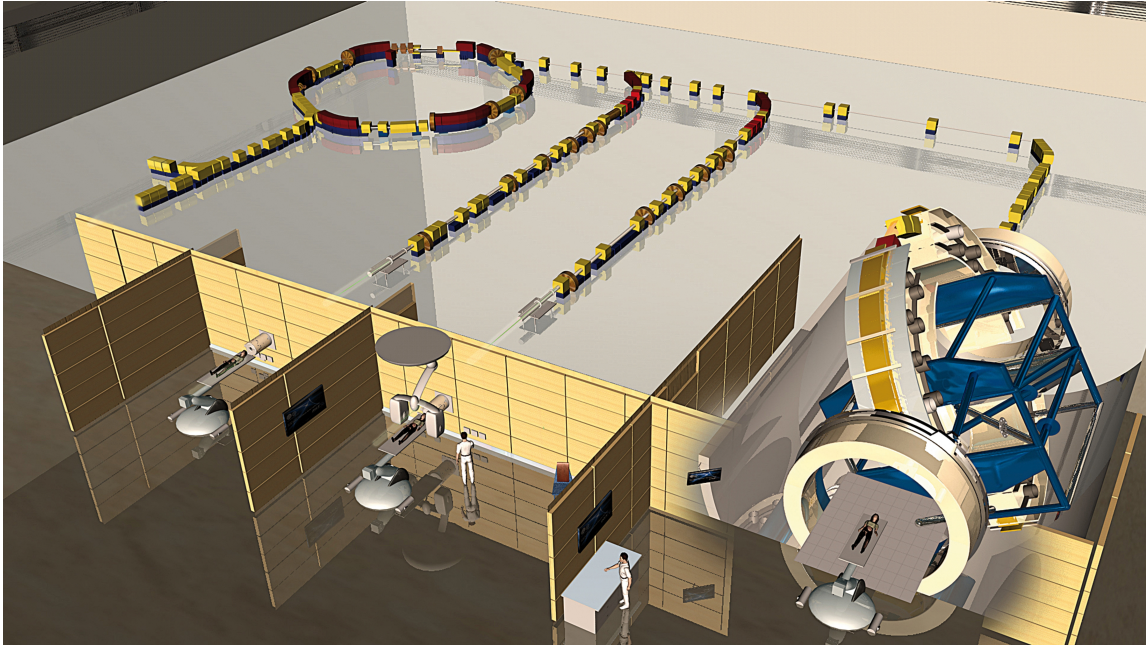
Figure 18: Sketch of the combined dual proton/ion center at HIT, with one gantry and two fixed beamlines. *From http://www.klinikum.uni-heidelberg.de*

As of the time of writing, there are 48 hadron therapy facilities in the world. Most of these are proton facilities; only seven offer heavy ion therapy [12]. Because of the clinical advantages the interest for hadron therapy is huge, but the large difference in costs compared with conventional radiotherapy usually proves too discouraging for hospital and government endeavors. This, however, is changing. According to PTCOG, there are 39 new hadron therapy facilities either almost ready for operation, under construction or planned, worldwide. There are several reasons behind this renewed optimism. Hypofractionation for heavy charged particles is gaining momentum within the field, which would be of great benefit carbon therapy. If a patient can be treated with fewer fractions, the total costs per treatment drops, making such treatments more accessible. Also, reducing the amount of fractions also increases the capability of the facility, since more patients can be treated than with modalities reliant on larger fractionation. [14]

Hadron facilities have traditionally been significantly more expensive than photon facilities. A 2003 study [40] investigating the relative costs of proton and photon therapy found the typical investment cost to be 62.5 M€ for a two-gantry proton facility, and 16.8 M€ for a two-linac X-ray facility. The operation cost wast given per fraction, 1,025 € for protons and 425 € for photons, giving an operation cost ratio of 2.4 ± 0.35 at 85% confidence.

However, these numbers include the business cost, which is added to the cost of treatment to repay the initial investment. The business cost are of particular significance for protons, comprising 42% of the total treatment cost, compared to 28% for photons. If the business cost is dropped, the cost of treatment becomes 370 € and 230 € , for a cost-per-fraction ratio of 1.6. [40].

A more recent study from 2010 [41] performed a similar cost analysis, but also included cost analysis for a combined proton/carbon ion facility. Investment costs where here found to be 138.6 M€ , 94.9 M€ and 23.4 M€ for combined, proton and photon facilities, respectively. The respective treatment cost per fraction were approximately 1128€ , 743€ and 233€ , resulting in a cost ratio of 4.8 for the combined and 3.2 for the proton facility compared to treatment at the X-ray facility. Comparing the expenses between proton and photon therapy (or carbon therapy) is not trivial, though - even the definition of expenses can be problematic, for example regarding studies in the U.S. where variable insurance reimbursement may also taken into account. [42] Still, it is interesting that the relative investment cost for protons compared with photons is higher in the 2010 study than in the previously mentioned 2003 study. In fact, the authors of the previous study estimated that the investment cost for a proton facility was likely to decline as more devices would enter the market, and suggested that a cost reduction of 20% could occur over a 5-10-year period [40]. It seems that more commercial availability and increased use of accelerators conventionally used for hadron therapy cannot alone bring prices down sufficiently. Rather, new innovations in device technology and design are needed to make hadron therapy worthwhile.

Proton therapy is the most commonly used form of particle therapy, thus also the most investigated and debated. Hadron therapy remain a field full of disputes, often centered around the clinical advantages and economic competitiveness of proton versus photon therapy. Studies evaluating the economic aspects have reached different conclusions. So far, there is thus not yet consensus on whether proton therapy is allover cost-effective or not [40, 42]. To clarify: as the numbers from the above mentioned cost analyses show, proton therapy is clearly more expensive "in itself"; that is, when only the investment cost and operation cost are considered. Even if the initial investment is "forgiven", proton facilities still carry higher treatment cost per fraction [40], but reducing the number of fractions may to some extent level the cost differences compared with photon therapy [40, 14]. However, the numbers change when taking additional socioeconomic considerations into account. First of all, hadron therapy may in many cases reduce side effects, extend life expectancy and increase the quality of life - all of which can be "measured" under the term *Quality-Adjusted Life Years* (QALY). The basic premise for this term is quite simple: utility (quality of life) times amount of years equals QALY, where *utility* is a weighting number ranging from 0 (death) to 1 (perfect health). For example, one year of perfect health gives a QUALY of 1. Half a year of perfect health is euqal to a full year with utility 0.5, i.e. $1 \cdot 0.5 = 0.5$. The use of this model is debated [43], in particular because utility is

a relatively intangible term. The value of each QALY gained is also disputed, but typically estimated at \$ 50,000 [44].

Although it is difficult to put a price on longevity or quality of living, the socioeconomic impacts of these factors are more easily compared. A 2003 study [45] evaluating the cost-effectiveness of proton and photon treatment of childhood medulloblastoma, taking said considerations into account, found proton therapy to be clearly favorable, with 23,600€ in cost savings and 0.68 QALY per patient. Analyses showed that reduced development following treatment had significant economical consequences, in particular due to intelligence quotient (IQ) loss and growth hormone deficiency (GHD). A recent study [46] found similar results, with proton therapy being cost-effective in addition to providing higher quality-adjusted life years. This should be of particular interest to countries with socialized healthcare, where the government both provide healthcare and carry the burden for the socioeconomic impacts from reduced health in the population.

Evaluating the relative costs of different forms of radiation therapy is a very complicated affair, far beyond the scope of this thesis. I aim only to present data representable for the market, and outline some of the most important cost mechanisms. A more thorough comparison would also include factors such as number of patients treated per year, sessions per patient etc. [25]

2.9 Summary: clinical requirements

It is highly advantageous if a treatment device can be made as cheap, simple and compact as possible, but any accelerator designed for radiation therapy *must* be able to meet the clinical requirements. Energies are determined by the penetration depths needed to treat different tumors, but the required physical range is not always the same for protons and carbon ions. For example, the lower range for protons is 60-70 MeV which corresponds to 3 cm and is used mainly for treating ocular tumors. On the other hand, the lower range of about 150 MeV for carbon ions corresponds to about 5 cm [16, 67]; because of the fragmentation "tail" after the Bragg peak, carbon ions are not used for treating ocular tumors and thus have a less strict requirement on the lower end of the required penetration depths. Traditionally, a 3-38 cm range has been required for proton devices, while a range of 5-25 cm seems to be applicable for carbon ion treatment [16]. The corresponding energy ranges are shown in the table below.

The accuracy of the dose delivery is determined by the energy spread, which gives a longitudinal distribution, and the lateral beam profile, which determines the transverse distribution. This is primarily of importance for hadron therapy, since the sharp Bragg peak requires small energy spread in order to not cause dose misdelivery. Both energy distribution and spacial distribution of particles are typically Gaussian, and it is common to talk

about the full width at half maximum (FWHM). The transverse distribution of a particle beam is typically Gaussian, but can be shaped more uniformly with a collimator. Still, it is not possible to have perfect lateral "edges", i.e. an instant drop from full to zero intensity. The lateral "edges" of the beam is called the beam *penumbra*, and is typically defined as the part of the beam where the distribution amplitude goes from 80% to 20%.

Reliability is an important concern. The availability (i.e. "uptime") of the entire device should be at least 95%; thus, the availability of the accelerator should exceed 99%. One reason is that radiation stimulation can cause cancer cells to increase growth over a short time; therapy for patients in the third or forth week can in principle not be aborted, as the probability for cancer recurrence increases drastically in this period. [69].]

It is desirable with a low-emittance (see Sec. 3) beam, both because it enables use of magnets with smaller apertures and thus smaller sizes, and because it improves the transverse beam profile. Finally, a device must be able to deliver a dose rate of 2 Gy/min, which imposes requirements on the output current. The current consists of the accelerator repetition rate and charge per bunch. An advantage with high repetition rate is that (active) spot scanning can be performed with enhanced precision, since a given dose can be distributed over more spots and in more layers [26].

A repetition rate of 100-200 Hz is sufficient to apply the multipainting technique, although higher repetition rates allow faster adjustment of the beam. Combined with the bunch charge, higher output current could enable faster treatment. Finally, within active scanning, it should be possible to adjust the beam longitudinally in steps corresponding to 1 mm. [26, 16]

Again, there is no universal textbook answer for the "right" parameters for a medical accelerator. The following table simply describes what is viewed as the current requirements from a clinical perspective.

Parameter	Value	Comment
Min. energy [MeV/u]		
-electrons	5	Conventional
-protons	60-70	Values differ
-C ions	150	
Max energy [MeV/u]		
-electrons	50	Conventional
-protons	250	(∗)
-ions	410	
Energy spread [%]	0.3-0.4	Hadron therapy
Energy modulation step [MeV/u]	1	Active scanning
Repetition rate [Hz]	100-400	Multipainting
Bunch charge at min./max repetition rate [pC]		
-protons	16/4	Multipainting
-C ions	3/1	Multipainting
Availability [%]	99	

(∗) No textbook answer is found. Most medical proton cyclotrons operate at 230 or 250 MeV, while a study [27] estimated 240 MeV to be sufficient for 100/100 patient cases evaluated.

2.10 The challenge

"Future facilities need to become *cheaper*."

The clinical advantages carbon ion and proton therapy hold over conventional X-ray treatment have motivated development of research projects and facilities devoted to hadron therapy worldwide, the present enthusiasm reflected by the 39 proposed facilities either planned or under development to day's date. However, there is not consensus on the extent hadron therapy is more beneficial than photon therapy, due to the lack of clinical evidence. These issues are likely to remain widely debated, because of the difficulties of conducting sufficient trials.

The cost issue remains the main challenge for hadron therapy, and in order to accelerate development and make such treatment more accessible, future facilities need to become *cheaper*. We distinguish between investment and operation costs. The main contributing factors to the investment cost is the treatment device itself, which includes accelerator, beam transport, gantry (if applicable) and BDS (Sec. 2.1), in addition to the construction of the facility. In addition to the price tag of the device itself, the accelerator type also affect the construction cost through requirements on dimensions and radiation shielding. The operation cost is driven by the power usage, staff and maintenance required by the device. These are the main considerations providing the context in which accelerator concepts are reviewed in this thesis.

3 Particle acceleration principles

Among the tens of thousands of particle accelerators existing today, most are small linacs used for applications such as generation of X-rays. Only a few are large-scale accelerators operating beyond the MeV range, the most famous being the Large Hadron Collider (LHC) at CERN. Such powerful colliders allow physicists to extend the frontiers of physics by investigating the various phenomena that occur under the new conditions available at higher energies. A challenge is the huge dimensions needed for such high-energy colliders; the LHC with its circumference of 27 km is outright enormous. There is therefore a desire for more compact accelerators also within the high-energy physics community.

At the time of writing there is a global effort to develop a linear collider for high-energy physics research, capable of reaching TeV energies. There are in essence two projects vying for candidacy, namely the Compact Linear Collider (CLIC) and the International Linear Collider (ILC)[16]. Both of these projects are included in the Linear Collider Collaboration (LCC), an organization dedicated to the realization of a next-generation, big-scale linear collider for high-energy physics research. Through fundamentally different designs, both groups propose a TeV accelerator tens of kilometers long. The interest surrounding this development is a strong motivator for research on high-gradient linear accelerators.

The main accelerator at SLAC National Accelerator Laboratory (formerly known as just SLAC) is still the largest linear accelerator in the world. It became operational in 1962, and has been used extensively for collision experiments. Throughout the years of operation, research at SLAC has produced several Nobel Prizes in Physics; the latest as recent as 2006. At the present time, the three-kilometer linac is divided into two facilities. Two-thirds of the accelerator length is occupied by the Facility for Advanced Accelerator Experimental Tests (FACET), which purpose is primarily novel accelerator research. The other one-third constitutes the SLAC Linac Coherent Light Source (LCLS).

The field of radiation oncology is in dire need of advances within accelerator technology. When evaluating the potential for improved medical accelerator schemes, it is natural to separate between conventional and state-of-the-art accelerators, and accelerators that are not yet operational, but still under research.

3.1 Conventional accelerators

To aid in later discussions on advanced and novel technologies, I will here outline the basic operating principles of the most common existing particle accelerators.

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[16]The ILC group is the result of the merging of three former collaborative groups, namely the Next Linear Collider (NLC), Global Linear Collider (GLC) and Teraelectronvolt Energy Superconducting Linear Accelerator (TESLA) collaborations.

3.1.1 Cyclotrons

The two semicircular areas of the cyclotron in figure lies between magnets of this shape, providing a strong magnetic field bending incident particles in a circular trajectory. One such component is called a *dee*, after the D-shape. In its most basic form, a cyclotron consist of two dees spaced slightly apart, such as shown in Fig. 19. An electric field is applied over the gap, providing a kick to the particles each time they pass from one dee to another. After each pass over the accelerating gap the electrons thus follow a semicircular path with increasing radius, spiraling out as they gain momentum, and are ejected when they reach the radius corresponding to the output energy. Because the velocity increases in accordance with the path length, the periodicity is the same for each successive orbit at non-relativistic energies, making it possible to apply an RF (radiofrequency) field with fixed frequeny. However, at higher energies, it is necessary to compensate for relativistic effects. This is primarily done by either applying a time-modulated RF field, or employ magnets that acts differently at particles of higher energies. The first design, where the RF field is kept in sync while the periodicity varies over time, is called a *synchrocyclotron*. In the latter principle, the magnetic field gradients vary with radius, to be in accordance of particles with higher energies. A cyclotron employing this design is an *isochronous* cyclotron.

The advantages with cyclotron is that they offer high compactness and continuous beam output at relatively high currents. However, the beam is extracted at a fixed energy, raising the need for an ESS if used for medical purposes (Sec. 2.1). It is actually possible to extract beams at a few different energies, by having more than one extraction line. Thus, one may construct a cyclotron delivering both protons and ions, by having one ejection line corresponding to the desired proton energy and one for the desired carbon ion energy.

Conventional cyclotrons typically employ magnets of a few Tesla, measure 4-5 m in diameter and weigh a few hundred tons. Comparably, superconducting cyclotrons are able to achieve close to 10 T, using very compact magnets. A superconducting synchrocyclotron producing a 250 MeV beam could weigh as little as 35 tons with a diameter of about 2 m, making them very attractive from a medical perspective. [65] Such compactness opens up possibilities for a single-room device, which is highly desirable. This is discussed further in Sec. 4.
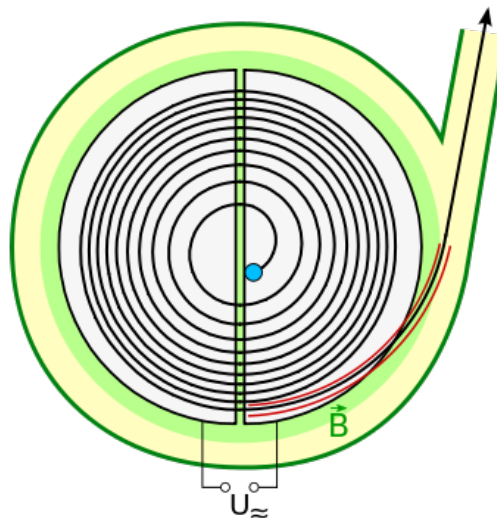

Figure 19: A cyclotron in its simplest form, with a continuous, outward-spiraling beam. The particle receives an accelerating kick each times it passes over the gap between the magnet dees, orbiting with increased radius and energy until ejected through a single extraction line at a fixed output energy. From *Wikipedia*.

3.1.2 Synchrotrons

Synchrotrons accelerate particles in a closed orbit (typically circular), where the acceleration is performed by having the particles traverse one or several accelerating cavities many times. Relativistic effects are compensated for by varying the magnets over time in accordance to the particles' increasing energy. A synchrotron always produced a pulsed beam, since the beam traverse the same cavities successively.

In contrast to the cyclotron, the output energy of a synchrotron can be varied electronically. This is an advantage, since it eliminates the need for mechanical absorbers, which cause neutron scattering, beam profile deterioration (hereunder increased emittance and energy spread) and beam loss. However, it turns out the energy modulation in synchrotron, albeit electronically performed, is quite slow. The reason is the ramp-up time needed when accelerating a beam up to a certain energy. The injection/ejection of particles into/out of the main orbit is fast, being performed by kicker magnets with rise time, of only a few µs, but because there is no good way to decelerate the beam, it is necessary to dump it and accelerate a new one every time the output energy is to be modulated down. Because of the ramp-up time of the guiding magnets, this process takes as long as one to several seconds, making such devices unsuitable for active scanning and IGRT (Sec. 2.1). Slow extraction appears to be a ubiquitous property of synchrotrons, but perhaps this will change in the future. [65]

3.1.3 Linacs

Obviously, circular accelerators have the advantage over linacs that the particles may undergo a large number of revolutions, greatly increasing the maximal energies reached. Linacs have a finite length and are therefore limited by the acceleration gradient, as discussed in the Introduction. Still, there are some cases where linacs are preferable over circular accelerators. As goes forth from Eq. 4, particles with low mass such emit considerable braking radiation at high energies, which, in a medical context, imposes requirements on additional radiation shielding. This problem is avoided when electrons travel along a straight path through a linac.

For medical applications, one very important feature of linacs is the ability to adjust the output energy near-instantaneously. As discussed in Sec. 2.1, it generally takes at least 50 ms to modulate the energy when using mechanical absorbers, which also have the disadvantage of neutron scattering. Although synchrotrons can adjust energy electronically, it takes about a second or more to accelerate a new beam up to the desired energy; this limitation is mainly due to the adjustment time of the guiding magnets.

In addition to avoiding unwanted neutron radiation [28], spot scanning enables use of the multipainting technique, which can provide highly accurate dose delivery. In order to make full use of the spot scanning technique, it should be possible to vary the energy in between each successive "hadron pulse" in the output beam. The spacing of these pulses depend on several factors, but is about 10 (2.5) ms for a 100 (400) Hz linac [26]. As it turns out, only linacs are able to produce sufficiently fast energy modulation; by electronically turning on or off one or a number of the klystrons, it is possible to modulate the beam energy over a very short time period, of the order of 1 ms.

We generally separate between normal-conducting and superconducting accelerators, when discussing both conventional and novel accelerator types. In superconducting accelerators, which have become more available during later years components are cooled to very low temperatures, typically a few kelvins to drive large currents. For magnets, this enables very strong and compact components, which is an important aspect for accelerators. In terms of driving the accelerating field, superconducting accelerators also cost effective, since less input power is needed to drive the currents. Still, normal-conducting accelerators have certain advantages over superconducting ones, based on the different physical principles applied. For state-of-the-art accelerators, one very important aspect is the difference in the physics behind the limitations for the accelerating gradient. Fortunately, this is a major area of interest not only in radiation therapy but also in fundamental physics, and the last two decades has seen large efforts by various resourceful collaborative groups to provide new acceleration schemes, most notably by the CLIC collaboration and what is now known collectively as the ILC collaboration. The main difference between these projects is that the design proposed by the ILC group applies superconductive components, while the CLIC group relies on normal-conducting technology, however with a novel acceleration scheme. Extensive R&D campaigns were launched by both groups to overcome the technical challenges facing the realization of a very large-scale linear collider.

3.1.4 Breakdown

As mentioned earlier, conventional accelerators (whether normal- or superconducting) typically have an accelerating gradient of about 10-25 MV/m. The main limitation lies in various *breakdown* phenomena, which occur when large fields are present within the accelerator cavities. Breakdowns are sudden, stochastic occurrences, and in general the frequency of breakdowns increases with the magnitude of the surface electric field and thus also the accelerating gradient. In normal-conducting accelerators, large cavity fields may result in RF breakdown predominantly due to spontaneous field emissions. The phenomenon still lacks a complete theoretical understanding, but is to some extent explained by experimental observations [51]. In the range 100 MHz to 3 GHz the gradient limit increases as the cubic root of frequency, often referred to as the Kilpatrick limit. This is a somewhat misleading term, because the Kilpatrick limit actually describes an increase in gradient according to the relation

$$f = 0.00164 \, E_k^2 \exp(-8.5/E_k), \tag{16}$$

which is derived from empirical data of spontaneous field emission in vacuum [52]. However, with the ultra-high-vacuum technology available in modern times, these datasets are somewhat outdated, as it is possible to achieve fields many times higher what given by this "limit". Still, the original Kilpatrick limit is being used for benchmarking for historical reasons. It should therefore be kept in mind that the original Kilpatrick limit is not a hard limit for gradients in modern accelerators, but used to refer to a relation between gradient and frequency.

Above the 0.1-3 GHz range, a weaker frequency dependence is seen up to about 11 GHz [54], but no clear dependence is seen in the 20 to 40 GHz range [55]. When RF breakdown occurs, the accelerator is effectively "shortened"; because nearly all of the RF power is absorbed, the beam receives little or no acceleration over the cavity in question.

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Not only does this result in a loss of energy; an RF breakdown also affects the beam physically. High currents are generated during a breakdown, and the magnetic fields from such discharges gives the beam a "kick", i.e. a transverse displacement. A breakdown causes further displacement as result of missing acceleration and angular misalignment. The total resulting transverse displacement may be of tens of μrad and thus even exceed the beam divergence in terms of angular magnitude. [56]
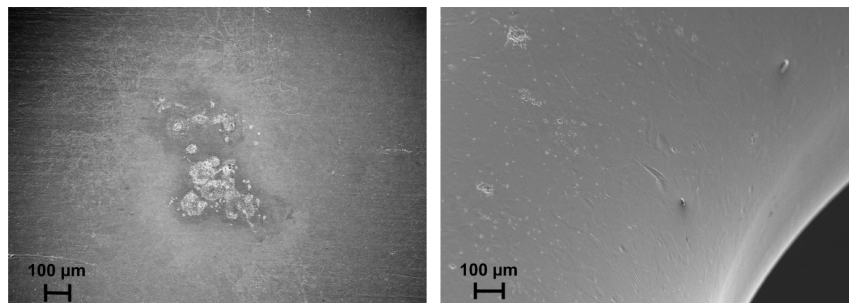

Figure 20: Scanning electron microscope images of the typical surface damage caused by several vacuum arcs during breakdown with a DC field. *From Ref. [90].*

The accelerating gradient of superconducting accelerators have a "hard limit" given by a critical surface field value before the magnetic field is "quenched" in the cavity. For a typical niobium cavity, this limit corresponds to a gradient of about 50 MV/m. In practice, however, other mechanisms impose a much lower limit on the gradient, since the rapidness of breakdown occurrences increases with field strength. Especially thermal breakdown and field emissions severely limits the gradient; although not imposing "hard" constraints, the increasingly large breakdown rates in practice limit present-day superconducting accelerator designs to gradients of around 30 MV/m.

Much progress in overcoming the breakdown challenges has been made in recent years by experimenting with pulse length. It turns out that the breakdown rate BDR in normal-conducting structures is affected by beam pulse length τ as well as the gradient E, following the empirical scaling law [61]:

$$BDR \propto E^{30}\tau^5. \tag{17}$$

In other words, BDR decreases significantly with reduced pulse length, although it has a much stronger field dependence. This new understanding has been crucial in gaining high gradients while simultaneously maintain acceptable breakdown rates.

Both normal-conducting and superconducting accelerators have in common that extreme care must be taken in the production of the cavities to avoid breakdown, as several of these phenomena have occur when there are microscopic surface defects or impurities [57]. It is seen that breakdowns are problematic not only due to the limitation on the gradient, but also because they reduce the reliability of the accelerator. Because the frequency of breakdowns generally increases with field strength, one must find a compromise between maximum gradient and reliability. Both of these aspects are of great significance within radiation therapy, where the accelerating gradient affect the dimensions and thus the costs, and the reliability affects the treatment of the patient itself,

which is of paramount importance. The prospect of accidental dose delivery due to a breakdown occurrence is another point in favor of applying the multipainting technique, which may easily correct misdeliveries given that the breakdowns are not too frequent - a BDR $< 3.6 \cdot 10^{-7}$ should generally be more than sufficient, as it corresponds to one breakdown per eight minutes in a 24 m long 300 Hz linac [66]. One should also consider the effects of transverse kicks from the RF field discharges such as mentioned above from a medical point of view. In the associated CLIC study [56], the discharges could result in a kick angle of several μrad. For a relatively large medical accelerator several meters long, this could also cause a transversal displacement in dose delivery, in addition to the longitudinal displacement due to the loss of energy. Again, the multipainting technique should be able to compensate for this.

3.1.5 State-of-the-art linac

The designs suggested by the CLIC and ILC collaborations for normal- and superconducting linear accelerators, respectively, are representative when evaluating the potential of a state-of-the-art linac. Although both these projects are mainly considered with a multi-kilometer linac, many of the parameters are still relevant for a medical linac a few meters long. The groups have provided much knowledge on aspects like the optimization of gradient, emittance and power efficiency, which are also all important factors for medical purposes. The principles of CLIC and ILC are first outlined, which focuses on the acceleration of electrons. This is relevant for the theorized prospect of using VHE electrons for particle therapy. Subsequently, state-of-the-art acceleration of proton linacs is described.

In June 2013, the ILC collaboration released the ILC Technical Design Report which, after nearly 20 years of R&D, constitutes the design for a state-of-the-art superconducting linear accelerator [58]. The proposed design is complete, and the accelerator is "technically ready to be proposed and built" [59]. The cavities will have differing gradients (because of mass production), with an average value of 31.5 MV/m [58]. Although the gradients may reach higher values, they are ultimately limited by the gradient corresponding to the critical magnetic field where the superconductivity is quenched. Normal-conducting cavities do not suffer from the same limitation; although RF breakdowns provide formidable challenges, it is possible to reach quite high gradients by careful consideration of material and physical parameters such as beam pulse length. At the CLIC Test Facility (CTF3) at CERN, CLIC researchers has successfully demonstrated their target gradient of 100 MV/m while keeping within their designated breakdown rate criteria of $3 \cdot 10^{-7}$, reaching maximum gradients of 150 MV/m [60]. This was done by applying very short pulses, according to Eq. 17. The proposed 100 MV/m concept is designed to run with pulse lengths of just a few hundred ns (156 ns flat-top, 240 ns full length) [62].

Achieving such high gradients means that the accelerator can be of smaller dimensions, which significantly reduces construction costs. Unfortunately, this also leads to higher power requirement, due to increased power loss. Both the field amplitude and the RF frequency affects the RF-to-beam efficiency, but although the high frequencies associates at high gradients contribute positively, the negative contribution form the electric field is stronger. For a cavity of a given length, the power needed to produce a certain field scales as

$$P \propto f^{-1/2} \ [68, p.97]. \tag{18}$$

On the other hand, ohmic wall losses scale with the square of the field, and so the allover efficiency decreases with higher gradients. If the proposed CLIC accelerator were built as a conventional linac, where the accelerating cavities are powered by individual klystrons, it would need tens of thousands of klystrons requiring an enormous amount of power to accelerate the beam to the desired TeV-scale energies. This problem was circumvented through the development of a novel two-beam acceleration scheme, which is briefly described in Sec. A.1

To summarize, it is possible with the present day accelerator technology to achieve gradients of 100 MV/m at acceptable breakdown rates ($BDR < 3 \cdot 10^{-7}$) for *electrons*. Unfortunately, we cannot readily obtain the same gradients when accelerating protons. This is because the proton moves with lower speed than the much lighter electron, through a non-constant field. For example, at 10 MeV, electrons are approaching ultrarelativistic limit with $\beta > 0.99$, while protons are moving at about 14% the speed of light. The longitudinal electric field from a standing wave over an RF gap can be expressed as

$$E = E_0 \sin(\phi_{\mathrm{rf}}(t) + \phi_{\mathrm{s}}), \quad \phi_{\mathrm{rf}} = h\omega_0 t \ \ [64, p.240], \tag{19}$$

where h is an integer called the harmonic number, g is the RF cavity gap width and R_0 is the average radius of the orbiting particle. ϕ_s is the phase between the field and the particle. The energy gain for a particle traversing the RF gap is obtained by integrating the field over the time exposed to the field,

$$\Delta E = eE_0 \beta c \int_{-g/2\beta_0 c}^{g/2\beta_0 c} \sin(h\omega_0 t + \phi_{\mathrm{s}})dt, = eE_0 gT \sin(\phi_{\mathrm{s}}), \tag{20}$$

where T is the transit time factor:

$$T = \frac{\sin(hg/2R_0)}{(hg/2R_0)} \ [64, p.241]. \tag{21}$$

Let us continue with the example of acceleration of 10 MeV. At these "low" energies, the velocity of a proton is about 1/7 that of an electron. This means that the electric field will have varied more by the time the proton pass through the RF gap. While the field does not deviate much from its peak amplitude during the time the electron traverses the gap, the average field experienced by the proton is lower. However, the surface field is unchanged, and so we cannot just increase the field to compensate for the lowered gradient, because of breakdowns (Sec. 3.1.4. Therefore, the attainable gradient is significantly less for particles with a lower q/A ratio (Sec- 1.2) than electrons. With the X-band frequencies used in the CLIC design to achieve gradients of 100 MV/m for electrons, it may be possible to produce a gradient of about 70 MeV for protons.Although not quite as phenomenal as for electrons, it would be a vast improvement over the conventional gradients of 15-25 MeV.

3.2 Novel accelerator concepts

3.2.1 FFAG accelerators

Fixed-Field Alternating-Gradient accelerators (FFAGs) can be said to be something between a cyclotron and a synchrotron, or a compound of the two. On one hand, they apply magnetic fields constant in time, like in a cyclotron; however, the geometry of the magnets are chosen such that the fields vary in a certain way with radius. On the other hand, the particles are constantly focused and defocused along the trajectory, like in a synchrotron. This is done by having the magnets guiding the particles alternate between focusing and defocusing gradients. As the particles traverse through the magnets, they will enter the focusing magnets with a displacement from the center after being deflected by the previous defocusing magnet. Since the focusing force in a magnet is stronger further from the center, this leads to a beneficial net focusing effect, which is referred to as *strong focusing* [69].

Like in a synchrotron, the acceleration occurs in a few accelerating cavities which the particles usually traverse many times, building up energy. Synchrotrons and FFAGs are actually quite similar, especially in recent times as modern synchrotrons usually apply alternating gradients to achieve strong focusing. A distinction is made between scaling (S-) and non-scaling (NS-) FFAGs. In S-FFAGs, the particles follow orbits of identical shape but different size, as the radius increases with gain in momentum. In NS-FFAGs, the gradient is modified further modified to make the particles revolve in smaller orbits (of non-identical shapes). This ables the construction of more compact devices, particularly if superconducting magnets are applied. A challenge with NS-FFAGs is the potential crossing of resonances. A particle pulse may stray out of orbit due to a small perturbation, causing it to receive a different kick from the next magnetic lens due to the displacement from the ideal orbit. This will again cause further misalignment and accumulation of displacement through successive magnets, leading to a resonance effect that ultimately causes the beam to be lost. However, if
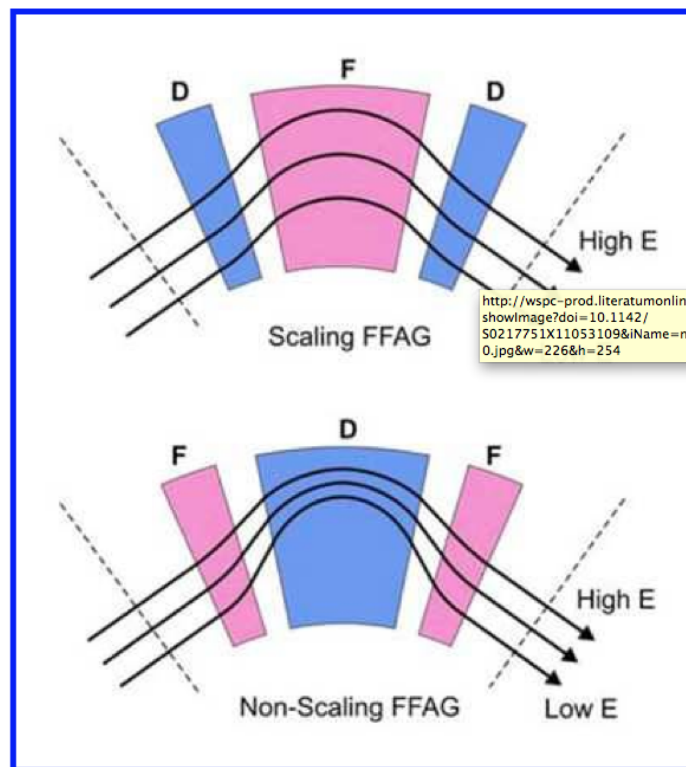
Figure 21: The basic premise for scaling and non-scaling FFAGs. *From [69].*

the acceleration is fast enough (and the resonance small enough) it may pass through even though it crosses resonance. This concept has thus far been in the developing state. At the forefront of this research is EMMA (Electron Model for Many Applications) and PAMELA (Particle Accelerator for MEdicaL Applications), under the British CONFORM (COnstruction of a Non-scaling FFAG for Oncology, Research and Medicine) project. These two devices are proof-of-principle NS-FFAG accelerators for electrons and hadrons, respectively.

Because of the time-constant magnetic fields, FFAGs are able to provide output beams of relatively high currents (up to many mA). Moreover, it is possible to extract the beam at various energies with electric and magnetic reflectors; this is a great advantage for hadron therapy since it eliminates the need for impractical absorbers. Although the concept of FFAGs has been around for decades, technical advances within recent times have sparked renewed interest as new, exciting applications may become possible. Since magnetic fields are static in time, FFAGs have great potential for rapid acceleration, which would make them very promising for applications such as muon factories or mass-producers of other short-lived particles. This has led to considerable attention from fundamental physics communities. Research on NS-FFAGs has also been motivated by medical application value, as compact, high-current accelerators are favorable from a clinical point of view.

The capability of strong focusing is a generally beneficial attribute for almost all accelerator appliances, and has become a standard in modern synchrotrons as well as FFAGs. Using fixed magnetic fields also provides some benefits, such as easy operation and simple and cheap power supplies [69].

FFAGs has received some recognition for the potential of high output currents, which is desirable within the context of other applications. Although relatively high currents are usually advantageous in hadron therapy, particularly for enabling the multipainting technique; however, currents of a few nA are generally more than sufficient.

3.2.2   Dielectric wall accelerat

Dielectric wall accelerators (DWAs) are a type of induction accelerators, building on the same basic design principles but using a dielectric material instead of the impractical magnetic cores found in conventional induction accelerators. The accelerating gradient of conventional induction accelerators is typically of order 1 MV/m; in contrast, DWAs under current development are able to reach gradients of order 100 MV/m, making them very interesting from a medical perspective [73]. The perhaps most impressive feat is that this gradient is not limited to electrons - in theory,
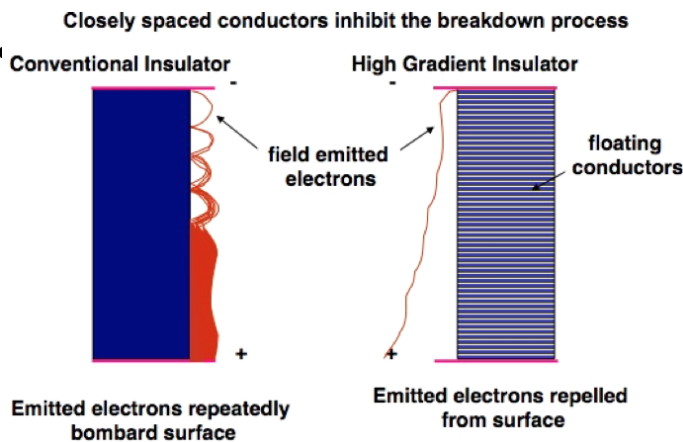

Figure 22: The figure shows the effects of the flashover mechanism for a conventional insulator and a high-gradient insulator. While the emitted electron causes an avalanche of secondary electrons to bombard surface of the conventional insulator, emitted electrons tend to be swept away from the high-gradient insulator surface. *From [73].*

the accelerator should be adjustable to accelerate any gradient, and a design is already proposed for a very compact 100 MV/m accelerator for proton therapy 4.

Because of the challenges with breakdown in conventional accelerators at high fields, recent research has proposed a design in which a so-called high-gradient insulator comprises the internal wall of the accelerator tube. These insulators are less prone to breakdown, especially with short pulses: there is an inverse dependence of the attainable breakdown field strength with pulse width [73]. In one approach, short pulses are produced across the insulator by use of thin chargeable lines called *Blumleins* connected to switches which can be timed with great precision. By arranging stacks of Blumleins along the accelerator tube and timing the opening and closing of the connecting switches, it is possible to create a virtual traveling wave of pulses. Since the timing can be adjusted, it is possible to match the speed of the virtual wave to the acceleration of any charged particle, thereby enabling acceleration of ions as well as protons. The pulses produced may be as short as a few ns, enabling gradients of 100 MV/m to be applied.

The main limiting breakdown mechanism in dielectric materials is avalanche ionization, in a *flashover* event. Like in a conventional accelerator cavity, an electron may be emitted from the surface by the strong imposed field. In a dielectric structure, such an emitted electron is pulled back to the surface where it collides and emits secondary electrons, leading to a chain reaction, as shown in Fig. 22. The consequential surface bombardment desorb gas molecules, which initiates a destructive flashover.

3.2.3   Dielectric Laser Accelerator

At SLAC, the Next Linear Collider Test Accelerator (NLCTA)[17] facility is currently home to pioneering research on a dielectric laser accelerator (DLA). Instead of using radio-band frequencies, a coherent laser beam is used to generate the electric fields for acceleration in the cavities of a dielectric structure. The current research operates in the infrared laser regime, with cavities on the scale of some hundred nm to a few μm. By moving to the optical regime the SLAC group hopes to achieve unprecedented compactness, which could lead to the realization of inexpensive "tabletop" accelerators.

A laser beam is applied perpendicular to the accelerating structure, such that the oscillating electric field is parallel to the beam direction of motion. In order to extract as much energy from the laser beam as possible, the design of the SLAC group [18] uses accelerating cavities of dimensions half the laser wavelength. Thus, a particle "sees" only one electric field that is either accelerating or decelerating. If a particle is to experience net acceleration, it must either pass through more accelerating cavities than decelerating cavities, or experience a stronger accelerating than decelerating field in the cavities. The SLAC design makes use of the latter principle. By extending every second cavity in the transverse direction of the propagating laser beam, the amplitudes are reduced over these cavities,

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[17]The NLCTA facility is not part of the SLAC main linac, like FACET or LCLS, but contains its own linac capable of reaching energies of about 220 MeV.

[18]The group consists of researchers from SLAC, Stanford University and the University of California, Los Angeles. Although somewhat misleading, I refer to the group as "the SLAC group" for simplicity.

]

The peak amplitude in these cavities is thus reduced to, say, $A/2$, where A is the peak amplitude in the cavities with dimensions corresponding to half the laser wavelength. The longitudinal length of the cavities are also that of half the laser beam wavelength, such that during the time it takes a particle traverses a cavity, the gradient changes sign in the following cavity. In this design, the particles are already accelerated to relativistic speeds prior to entering the accelerating structure; thus they maintain near-constant velocity during acceleration [19]. By careful timing, an incident particle will thus traverse the cavities with amplitude A when the field is accelerating, and by the time the gradient changes sign the particle will be in the following cavity with amplitude $A/2$, and so forth. The particle is in this way able to achieve a net acceleration across the structure, which turns out to be quite formidable: gradients of several hundred MV/m have been shown to be achievable in the optical regime, which is an order of magnitude higher than conventional accelerators [71].

For such high gradients we naturally run into the familiar breakdown problems, although dielectric materials show far higher tolerance to high fields than metals [72]. A key issue is to figure out which material, structure composition and structure geometry is best suited to overcome these obstacles. At SLAC, silicon and silicon dioxide were chosen as the materials of choice - although other compounds showed higher damage threshold fluence, these have practical advantages since they are well-known and relatively easy to manufacture.

For proof-of-principle experiments, using electrons is often a natural starting point, as has been the case for the EMMA accelerator under the CONFORM project (3.2.1, [69]). The present research on DLAs at SLAC use electrons as the particles to be accelerated, due to the availability of a low-emittance, compressed beam at the NLCTA facility and the interest for the ongoing LCC project. Also, due to their low mass, electrons are more easily accelerated to relativistic energies, which is a prerequisite for the DLA project at SLAC. However, in a recent paper [75], researchers at the Max Planck Institute of Quantum Optics, Germany, demonstrated a proof-of-principle DLA for nonrelativistic electrons. If DLAs can be used both for injection and further acceleration at the GV/m scale at relativistic energies, it may be possible to design a very compact accelerator; both because of the high gradient and because no space-demanding klystrons would be needed for such an all-optical device.

Joel England, who is a SLAC researcher working on the DLA project, has suggested in a conversation that it is possible to combine these efforts into a complete device with very high compactness, including an electron source, pre-accelerating module and main accelerating structure. One could for example use a small tungsten chip as an electron source, and apply a static electric field to accelerate the electrons to some tens of keV into the pre-accelerating module. There, further acceleration up to relativistic energies can be performed with the principle as described by Breuer and Hommelhoff [75]. For lower energies, where the electron velocity is significantly increasing with acceleration, the modules need to be of increasing length to keep the electron in phase with the incident laser pulse(s). (By engineering these to be corresponding to different harmonics of the same base field, the same laser may be used.) Finally, the electrons are accelerated through a series of

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[19]All particles are limited by the speed of light. Therefore, when a particle already at relativistic velocity undergoes acceleration, it gains diminishing increase in velocity, but increasingly acquires mass. We refer to this as the relativistic or effective mass of the particle.

modules operating with the above outlined DLA scheme, where the number of successive modules determine the final output energy. One laser will likely power several modules, through a laser beam transport system where parts of the beam is diverted at regular intervals to power different parts of the accelerator. Depending on the desired output energy and practical considerations, the whole device may be powered by a single or several lasers.

Just like the energy can be modulated in an RF linac, it should be easy to vary the energy by switching on/off laser modules. England believes an optical DLA would be able to do this on the millisecond scale like with klystrons, or even faster. Such a device should also be able to meet the clinical requirement of 2 Gy/min (Sec. 2.9). A tungsten chip source such as mentioned above have been proven to produce about 2,000 electrons per bunch, which England believes could be done at a repetition rate of 10-100 MHz. Only 1,000 electrons at a repetition rate of 10 MHz would be needed to match the current as indicated in Tab. 2.9.

3.3   Plasma wakefield acceleration

In its broadest sense, plasma wakefield acceleration refers to acceleration of particles through the generation of strong electric fields from charged particle motion in a plasm. We generally separate between beam-driven and laser-driven plasma wakefield acceleration, abbreviated PWFA and LWFA, respectively. The distinction is simply that the former relies on a beam an the other on a laser to create the plasma wakefield. (Laser acceleration of particles from a solid is not included here, but is covered separately in the next section.)

A gas may become ionized if it is exposed to a field of energy high enough to overcome the ionization threshold. Such a configuration where the electrons are free from the nuclei is a plasma, and can be created by either a laser or a particle beam, as long as the energy is sufficiently high. A plasma created in this way is not sustainable, though; as soon as the (laser or particle) beam has passed, the ionizing field vanishes, and the plasma seeks towards its initial configuration. During the short time before its collapses, the plasma exhibit some very special properties which, as it turns out, are highly beneficial for acceleration purposes. In particular, plasmas are known to be able to withstand huge electric fields, several orders of magnitude greater than in conventional accelerators [78].

3.3.1   PWFA

Among the many exciting experiments at SLAC is the E-200 project at FACET, which conducts leading research on PWFA. It should be stated that PWFA does not likely have any immediate relevance for radiation therapy; on the other hand, LWFA holds significant potential for medical application purposes. PWFA is still described because of its connection with LWFA, and because it has received significant attention within the fields of accelerator and high-energy physics. At SLAC, PWFA experiments have produced groundbreaking results [79] which are not only interesting within a high-energy-physics context, but also aids in the understanding of the physical processes in play which are highly relevant for LWFA. This subsection on PWFA serves to describe the main mechanisms of plasma wakefield acceleration similar for both LWFA and PWFA, in addition to describing the PWFA-specific processes. The reader mainly interested in the medical perspective may proceed to the following section on LWFA.

For a beam-driven PWF acceleration process, two electron bunches are sent through the plasma with only a few femtoseconds of separation; one to create the wakefield, and one to ride it. The first bunch is called the *drive* bunch, and the second is called the *witness* bunch. Before entering the ionized gas, the electrons are first pre-accelerated up to about 20.35 GeV by conventional RF acceleration throughout the first two kilometers of the main linac. A strong laser of 10 TW is fired into the oven containing the gas, ionizing a column around the laser beam. Because the plasma is very unstable and will almost immediately reconfigure to form a gas within microseconds, timing is everything - the electron bunches must immediately follow through the body of gas ionized by the laser beam. If the beam density is greater than the plasma density, the free plasma electrons are expelled from the beam path due to the repelling electric forces; the case where *all* electrons are expelled is called the *blowout regime.* The volume left behind the passing bunch then contains a high deficiency of electrons, pulling the repelled electrons back towards center of the beam path. This continuous process of electrons scattering out and converging behind the drive bunch crates a wakefield that is constant along the reference frame of the drive bunch.

The wakefield of free electrons puts up a very strong electric field, following a periodicity given by the plasma oscillation. The trick is to get the witness bunch carefully positioned right behind the drive bunch within a single period of the wakefield, such that it "surfs" the wakefield where it is at its strongest, near the back end of the "bubble" defined by the period. This is challenging, since the length of the wakefield is of order 10-30 µm for plasma densities of $n_c = 10^{18} - 10^{19} cm^{-3}$.

The processes described thus far are applicable for LWFA as well, except that the wakefield is created with a laser rather than a drive bunch. As one might guess, the drive bunch used in PWFA is continuously decelerated as it expels electrons from its path; thus, the plasma wakefield acts as a converting medium for an energy transfer from the drive bunch to the witness bunch. This transfer process occurs as long as the drive bunch is able to create a wakefield, which is limited by the length of the ionization column in the gas. This is primarily an engineering challenge with potential for improvement. Relatively short oven are able to produce very high acceleration anyway; for example was an energy gain of over 42 GeV seen over an 85 cm long oven [79]. The energy transfer efficiency is quite high, around 10-20% [79].

Although PWFA is able to produce ultra-high accelerating gradients, they are not very suitable for medical purposes. The reason is that pre-accelerated, highly relativistic particles are needed for the interactions to take place, with energies higher than what is needed for clinical purposes in the first place. The description of PWFA has therefore been confined to general processes also relevant for LWFA, which, as shall be seen, *does* have potential for radiation therapy

3.3.2   LWFA

As mentioned, the basic premise of LWFA is in several ways similar to that of PFWA, outlined above. What makes LWFA interesting from a medical perspective, however, is the high compactness offered by an all-optical device. No pre-accelerated bunch is required to create the wakefield; in fact, no pre-accelerated witness bunch is needed either, as the electrons to be accelerated are obtained from the laser-plasma interactions. One example of a proposed injection scheme is to create a wakefield with sufficiently high amplitude, with the effect that the wave "breaks" when converging behind the laser pulse, launching some electrons into the bubble formed by the wakefield (referred

to as the *bubble regime*) [80].

Of interest from a medical perspective is the ability to produce moderate- to high-energetic particles over a very short distance. This is where LWFA shows great potential; experiments have been able to produce 100 MeV electrons over distances of a few mm with a defined energy peak. A challenge, however, is to reduce the energy spread, which may be as low as 1% but often around 5-10%. [81, 80] This is an ongoing effort, as an energy spread of much less than 1% is required for some potential applications like free-electron lasers and high-energy accelerators [80]. In radiation therapy, the requirement of low energy spread apply mostly for particles with a defined end range. The great advantage with protons and carbon ions is the sharply defined Bragg peak, which allows precise dose delivery. This is also of importance for low-energy electrons, which have traditionally been used to treat superficial tumors. In the conventional clinical energy range of 6-20 MeV, electrons have a clear range, as shown in Fig. 17. For very high energies, of 50-250 MeV, however, the energy deposition is more or less constant through the whole clinical range. In other words: the relatively large energy spread in LWFA is a challenge for treatment in the 6-20 MeV energy range, but much less so for hypothetical VHE electron treatment.

It is natural to wonder if the principle of LWFA (and PWFA) may be applied for other particles, such as protons. While it is possible to achieve acceleration of protons in a wakefield, it would require injection of a pre-accelerated proton bunch. LWFA is thus primarily suitable for accelerating electrons. Despite not relevant for hadron therapy, LWFA holds great medical relevance. One has to do with the radiation emitted through oscillations in the plasma. Because the plasma electrons all converge towards the center of the beam path, "witness" electrons riding the wake experience a strong radial focusing forces in addition to longitudinal acceleration. This causes them to oscillate, so-called *betatron oscillations*, through which synchrotron radiation is emitted in the form of ultrashort, highly coherent X-rays. A LWFA X-ray device could deliver photon beams of higher quality than currently available, in addition to be of very compact design.

Another field of potential is cancer treatment using a direct beam of VHE electrons. As mentioned, this is a relatively new concept, and simulations and a few experiments have been carried out, relatively little is known about the radiobiological effectiveness of such particles. If VHE electrons should prove suitable for radiation therapy, LWFA should be thoroughly investigated as a candidate for eventual devices. A challenge with LWFA is the need for ultraintense laser pulses; experiments conducted thus far have been using terawatt and petawatt lasers which, in addition to being complex, are not commercially available [80]. These issues would have to be answered if LWFA is considered for application purposes.

3.3.3   Laser-driven ion acceleration

As described in the previous section, lasers can be used to create a plasma wakefield in an ionized gas. Sufficiently powerful lasers can also be used to create accelerating fields within a solid. Recent years have seen a renewed optimism for laser acceleration of ions for radiation therapy, after research over the last decade has made significant progress but also discovered challenges. By applying a strong laser on a slab of material it is possible to eject electrons and ions of moderately high energies over a very short distance. (Accelerating gradients on the TV/m scale is achieved, although this occurs as a near-instantaneous acceleration and is not sustainable over a longer distance, or repeatable.)

Most of the research has centered around what is known as target normal sheath acceleration (TNSA), which up until recently has shown the most promise for laser acceleration of ions. The basic premise is as follows: a strong laser pulse is applied normal on a metallic foil with thickness on the µm scale which we refer to as a thick foil. Electrons are accelerated by the pulse, both coherently by the pulse field and by thermal excitations through collision processes. The electrons are "blown out" on the rear surface, effectively setting up an electric field that tugs on the abundant ions in the material. The result is that the ions are accelerated up to relatively high energies over a very short distance as they are pulled out after the electrons. However, because the slab is of µm thickness, most of the laser pulse is reflected at the front surface. Typically less than 1% of the laser energy is converted into accelerating the ions; research over the last decade has been unable to provide higher energies than about 60 MeV per proton, for acceleration of hydrogen ions [76]. Experimental results of TNSA show that ion energies scale approximately with the square root of the laser intensity [82], which implies that extremely powerful lasers would be needed to reach clinical energies of 250 MeV/u for proton therapy. Another problem is the large energy spread in the accelerated particles. The ejected electrons form a thermal spectrum, and the electric field produced results in a very uneven acceleration of the ions. It is highly desirable from a medical perspective to produce a monoenergetic beam output. For a given pulse in radiation therapy, all particles with energies differing from the clinically desired must be disposed off, which requires bending magnets and shielding. More particles with non-desirable energies requires more beam dump and higher activation.

In order to realize laser-accelerated ions for radiation therapy, research has needed to show substantial improvement to

- reach clinical energies,
- reduce required laser intensity and power, and
- produce a more monoenergetic beam.

Reducing laser power is not only important to avoid high power costs, but also to reduce the complexity of the design, since only the world's most powerful lasers are able to come close to the required intensities through TNSA today. In addition to the mentioned issues are challenges related to the feasibility of a treatment device, such as beam transport and delivery. Significant progress on the above issues is the reason for the renewed optimism of recent years.

With TNSA, ions experience acceleration through sudden jerks by disorganized electrons. If, however, one could achieve *adiabatic* acceleration, both higher energies and a more monoenergetic spectrum could be obtained. This has been the focus of recent efforts. It turns out that by using a thin foil of nm thickness instead of a thick foil, the physics change drastically, making it possible to achieve what is called coherent acceleration of ions with laser (CAIL). One immediate effect is that the laser pulse is not entirely reflected at the front surface of such a thin foil; instead the laser pulse contributes to the further acceleration of electrons as they emerge from the rear surface. Furthermore, the material of the thin foil can be chosen such that the laser pulse has vanishing group velocity; this greatly increases the period of acceleration for the electrons, which are initially at rest.

If a particle moves with more or less the same velocity as the accelerating field, it may be successfully trapped in a separatrix, or "bucket". The somewhat informal term "bucket" describes a range in

phase space where the particle is kept within and by an external field. Consider a particle moving with just about the same speed as an electromagnetic wave, positioned between the peak and zero-value of the accelerating field. The accelerating gradient changes with each half period of the wave, and so the bucket will consist of a range between the peak positive amplitude and somewhere in the negative region: if the particle accelerates into the area of opposite sign, the negative gradient will push it back; similarly, if it slips behind and towards the peak, it will be accelerated towards the point of equilibrium again. (Thus, buckets can also be used to create bunches; if a continuous stream of particles move with an electromagnetic field at appropriate speeds, said effect will automatically compress the particles into bunches of certain intervals.) If the field velocity changes too suddenly, ions may spill out of the bucket. Adiabatic acceleration, on the other hand, may supply a stable enough bucket to provide constant acceleration over a considerable time, until the field provided by the electrons dissipates [20]. By having the laser pulse circularly instead of linearly polarized, it may be possible to further enhance adiabatic acceleration [76].

Even if the ions are not contained in a bucket for the entire duration of the acceleration, it is still beneficial to have a fairly close synchronization between the accelerating field and the particles. If several phases of the accelerating field pass over the particle, it will still receive a net acceleration; because it is moving along the direction of the field, it will be pulled along the accelerating field and spend longer time there than in the decelerating phase, which it is effectively pushed out of.

Research in the CAIL regime has successfully produced ions of moderate energies and a pronounced peak in the energy distribution, using beams of lower intensities than previous TNSA efforts. There is still a large spread in energy and the distribution is at best quasi-monoenergetic [77]; however, producing a Gaussian-like distribution is an important first step to achieving a monoenergetic output. Although a peak around clinical energies has yet to be produced, CAIL results show an improvement of more than a factor of ten in conversion efficiency. Still, these experiments have employed very strong lasers of up to several hundred TW, with intensities on the 10^{19} - 10^{20} scale, to reach these energies.

Although a factor of ten lower than the laser powers needed to produce the same energies through TNSA, these power requirements are still nowhere near the capabilities of commercial-type lasers. For comparison, the world's most powerful laser is currently the Texas Petawatt Laser, which relies on a complex, multi-million-dollar system to produce pulses of 1.1 Petawatts. Significant improvement in energy conversion therefore remains a key challenge for application purposes. [76]

3.4   Remarks

The performance of laser-driven ion acceleration and laser wakefield acceleration is currently limited by the available laser power. There are currently strong ongoing, international efforts to increase the achievable laser peak power, mean power and efficiency, and make TW and PW laser systems cheaper and more compact [86, 87]. It is expected that the improvement of laser technology in the coming decade will make these technologies even more interesting for medical applications.

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[20]After the laser pulse exits the target, the group velocity instantly picks up. Some energetic electrons escape while the rest are pulled back towards surface, leading to the collapse of the electric field pulling the ions. It may be possible to prolong the acceleration by adding a secondary material to the design immediately after the thin foil.

4 Accelerators for future radiation therapy

In this chapter, the various technologies described previously are summarized and compared in terms of efficacy within hadron therapy. For some concepts, there are already designs for treatment devices, which are discussed. Other concepts are less mature, and will be given comments for future outlook.

4.1 Clinical requirements

The main considerations for an accelerator for particle therapy are outlined in Sec. 2. Before proceeding to evaluating different technologies and designs for particle therapy, I will provide some final considerations to be taken into account.

Radiation from scattered neutrons in mechanical absorbers is a significant concern. If an ESS using absorbers is needed, the accelerator should produce an output beam with output energy as close as possible corresponding to the maximum treatment depth. A study [27] evaluated 100 different treatment plans from patients treated with IMRT, and estimated through simulations that a maximum energy of 240 MeV would be needed to treat 100% of the patients with proton therapy. Most proton devices have a maximum output energy of 250 MeV, which means that patients suffer from unnecessary radiation from scattered neutrons if 240 MeV is really sufficient. The same study also estimated that 90% of patients in the treatment plans reviewed could be treated at 198 MeV. Decreasing the energy from 250 MeV to 200 MeV reduces the neutron energy fluence produced by a factor of 2.3. [27] In other words, a 200 MeV device would produce significantly less unwanted radiation through neutron scattering than current devices and still be able to treat 90% of patients.

The energies used in radiation therapy are determined by the clinical requirements on penetration depths. But it may be that not all hospitals should aim to cover the same clinical ranges. E.g. could a portion of hospitals choose an energy range with slightly less maximal energy, and still cover 90-95% of patients [27]. By moving from the "gold standard" of 250 MeV and 230 MeV in proton therapy to, say, 200 MeV, the first consequence is that accelerators could be a little more compact. However, the difference would not be large, so this in itself might not be a sufficient argument to rule out 10% of potential patients. It is mostly for devices reliant on mechanical absorbers for energy modulation this may be an important consideration. Sometimes, the energy selection system may be positioned far from the patient, such that unwanted radiation neutron from the absorbers is made negligible. For a gantry-mounted design, however, this is not possible, and neutron scattering is an issue that cannot be ignored. A less energetic output beam would cause less neutron scattering in the absorbers, and thus provide a more preferable treatment option for the portion of patients that may be treated within the given energy range

It is, however, better if mechanical absorbers are not needed. Active scanning systems hold the promise of optimal treatment because (1) they can deliver a highly conformal dose, (2) no mechanical absorbers are needed, avoiding neutron scattering, and (3) it is possible to compensate for tumor/organ motion, and correct for accidental dose deliveries.

[Are gantries needed? Facilities usually have several treatment rooms per accelerator; typically

there could be 1-2 gantries, and a couple fixed beamlines either for ocular tumors or with rotating tables. This thesis is not concerned with evaluating the need for gantries, but rather situated in the context for which gantries are necessary.]

The idealized, perfect treatment device would deliver all dose to the tumor and none to healthy tissue during a very short time, and fit inside existing hospital treatment rooms. I have thus far outlined various technologies and methods aiming to deliver the most optimal treatment. Still, a perfect device is useless if nobody can afford it. It is sometimes necessary to compromise if anything is to be offered at all; this is definitely true in radiation therapy where economic considerations have been a severe hindrance for availability and development. It seems likely that there is a market for expensive, advanced devices as well as cheaper, simpler devices. Concepts of both types are discussed in this section.

4.2   Superconducting cyclotron

In recent times, a design comprising a gantry-mounted superconducting synchrocyclotron has caused much excitement for companies interested in proton therapy, namely the Mevion S250 developed by Mevion Medical Systems. Although a gantry-mounted 70 MeV superconducting cyclotron actually started operation as early as 1990, it is not until now such an accelerator is able to provide a full clinical beam energy. The first device is already in operation, since December 2013 [88]. The main reason why this represents a breakthrough is because of the strongly reduced costs: the price tag for a facility housing

Figure 23: The gantry-mounted S250 superconducting synchrocyclotron. *From www.dotmed.com.*

such a single-room device is only \$25 M to \$30 M [89], which is a vast improvement. Other medical centers are catching up as well: similar devices are currently being installed in five different locations [88, 12], and several more are planned.
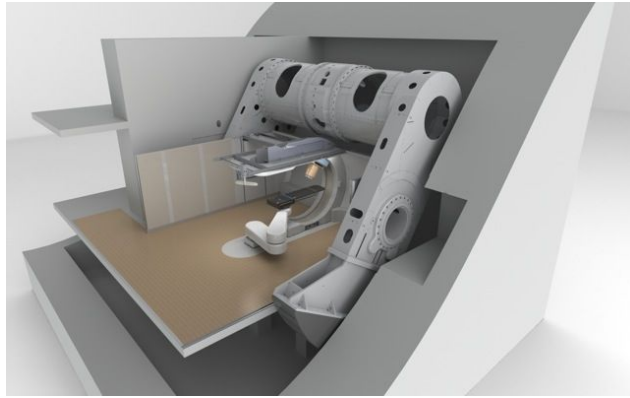
It therefore seems like single-room devices have been proven to cut costs severely, providing a cost-competitive alternative to X-ray facilities. The operation cost is likely higher than for X-ray devices, the extent of which remains to be seen as clinical experiences emerge.

The main drawback with a gantry-mounted cyclotron is that needs a passive scattering system to deliver the clinical energies. This means that (1) the device cannot utilize the advantages associated with active scanning, and (2) the patients are exposed to some radiation following neutron scattering form the mechanical absorbers, since the ESS is mounted directly over the patient along with the accelerator. Thus, the nozzle (section from the accelerator to the patient) is relatively long, since both the ESS and the BDS are contained; further adding to dimensions and gantry

complexity.

However, it must be stated that it constitutes an impressive and exciting design. The market is in dire need for economic solutions, and this is the first turnkey hadron facility able to come close to matching the costs of an X-ray facility.

4.3   Cyclinac and turning linac

The reader may have noticed that although linacs are described in detail in this thesis, they have yet to actually be applied for hadron therapy, except as injectors for cyclotrons or synchrotrons. Given the interest of recent years in active scanning, this may about to change. One interesting concept is the *cyclinac*, proposed and under development by Ugo Amaldi *et al* [**?**, 26] under the TERA (Research foundation for oncological hadrontherapy) foundation. As the name implies, it is a combination of a cyclotron and a linac with the former as an injector to the latter, although the injector could also be another type of accelerator, such as an FFAG accelerator, should it prove practical. For the present time, though, a cyclotron is the preferred option due to its compactness and simplicity. Such a scheme could be used to accelerate any type of ion (including protons), although the current effort focuses on carbon ions, through the CABOTO (CArbon BOoster for Therapy in Oncology) design.
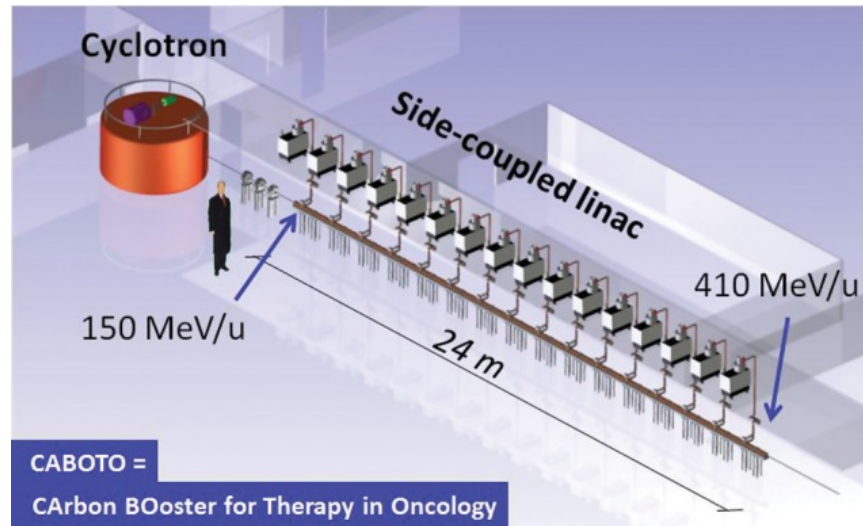

Figure 24: The CABOTO design.In addition to the cyclotron and linac in the figure, a gantry would also be needed. *From [66].*

In the proposed CABOTO cyclinac, carbon ions are first accelerated to 150 MeV in the cyclotron. Although no such cyclotrons are currently commercially available [66], a study [16] specifically investigating the optimal cyclotron for medical cyclinacs found this to be the most desirable injector accelerator, after evaluating both economic and medical considerations. A survey of clinical treatments at HIMAC [67], which shows that the maximum range for 3200 patients over the period

1994-2006 lies between 5 and 25 cm; this was among the considerations for choosing 150 MeV/u as the minimum clinical energy, which corresponds to 5 cm for carbon ions. After initial acceleration by the cyclotron, the CABOTO beam may then be accelerated further in the subsequent linac, up to a maximum output energy of 410 MeV/u, which corresponds to a depth of 28.7 cm in water. (If protons are to be used in the same device, additional energy modulation is necessary - since the clinical energy range in proton therapy lies around 70-250 MeV/u, it would be necessary to decelerate the cyclotron output beam of 150 MeV to reach shallower depths. This could be done with mechanical absorbers, but with the consequence of unwanted scattering. It may also be possible to use the linac as a decelerator; this has been investigated and proposed as a possible solution [16, p.161], but has so far not been presented in the current design [66].)

It was found that an isochronous cyclotron or a synchrocyclotron presented the best alternatives for a cyclinac injector accelerator, and in the end the former was deemed more preferable. One reason was that both designs would be similar in size (yoke diameter around 4.5-5 m); the synchrocyclotron was initially assumed to provide a more compact alternative, which turned out not to be possible mainly due to restrictions on the stray magnetic field outside of the yoke (a limit of 50 mT is imposed to ensure the reliability of surrounding hardware, and thus the reliability of the accelerator itself). Furthermore, the added complexity of the non-constant RF system for the synchrocyclotron as well as injection and ejection systems favor the choice of an isochronous cyclotron. [16]

Among the goals with CABOTO is to provide a design with compactness competitive with existing candidate accelerators for hadron therapy. This imposes requirements on the injector dimensions, but also a need for high-gradient acceleration modules in the linac. To further increase compactness of the whole device, several designs has been proposed for a combined accelerator/gantry, called a TUrning LInac for Particle therapy (TULIP) [83]. The TULIP design aims not to provide full 360° scanning, but rather around ±110°. An advantage of the high conformality possible with hadron therapy is that less fields of different angles are needed to provide the sufficient dose distribution compared with photon treatment. Moving from full 360° to smaller angles could reduce the complexity and thus also the cost of a device, if it can be done without significantly reducing the clinical capability.

A gantry-mounted linac scheme like TULIP would greatly benefit from even higher gradients, since large gantries are expensive and impractical. Over recent years, the proposed CABOTO design has moved from operating with 3 GHz to 5.7 GHz [66]. By moving to higher frequencies, it is possible to achieve higher gradients, as outlined in Sec.3.1.4. The current designs for CABOTO propose a gradient of about 30-35 MV/m [16, 85].

As described in Sec. 3.1.5, the maximum attainable gradient is limited by the q/A ratio of the particle. Although not being able to match the gradients of more than 100 MV/m available for electrons, it is possible to achieve far higher gradients than the conventional for protons. Since protons need energies of "only" about 230 MeV, it is thus possible to envision a very compact design for a proton treatment device. In a recent talk, Amaldi, representing the Italian research Foundation for Oncological Hadrontherapy (TERA), proposes a proton TULIP to use a gradient of about 50 MeV/m [84], thus reducing the length of the mounted linac from about 11 m to 5-6m. This design also relies on C-band klystrons to generate the RF fields, and experiments are still carried out to determine the optimal frequency [66, 85]. The choice of both frequency and gradient is a complicated consideration. Higher gradients provide more compact devices, but with higher power consumption due to increased beam loss. In general, higher frequencies reduce the breakdown
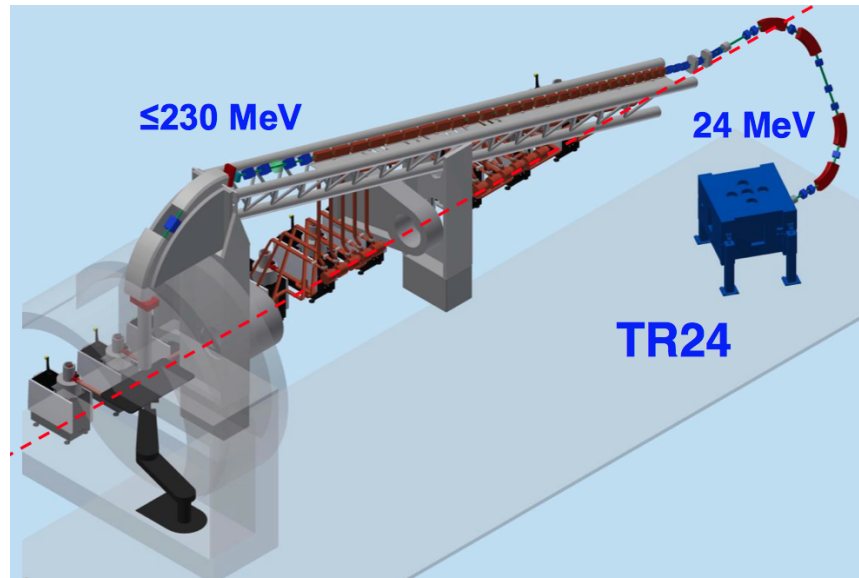
Figure 25: The TULIP design is a combined gantry/linac for proton therapy. The patient table is situated to the left in the figure, and the linac rotates in part arount the patient. Because the linac is 5-11 m long, a fully gantry-mounted design would have been impractical. *From [66].*

rate in addition to reducing the power consumption for a given gradient. One might therefore think that it is advantageous to operate at higher frequencies than the C-band, also for gradients of 30-50 MV/m like proposed for CABOTO and TULIP. Why, then, is not the device designed for X-band frequencies, given the demonstration of very high gradients for electrons with CLIC? One reason is likely the lack of commercially available X-band klystrons, which would be a major obstacle when seeking funding.However, such devices are beginning to appear on the market; if these become available and affordable, they could enable an even more compact TULIP. Although, as mentioned, the gain from increased compactness must be weighed against other factors, like power consumption.

4.4 FFAGs

The CONFORM project has conducted a proof-of-principle experiment for electrons with the EMMA accelerator [91], and experiments with hadrons are ongoing [69]. Recent years have seen renewed interest for FFAGs, which hold potential to provide fast acceleration at high energies and large currents.

Over the last decade, several FFAG designs have been proposed for hadron therapy applications [69]; Fig.26 shows an example of a three-ring system suggested by researchers at LBNL. Between these rings are extraction lines, such that a beam will be transferred from one ring to another to undergo several rounds of acceleration. Using this design, it is possible to achieve a very dense lattice, and the beams could in principle be extracted rapidly at various stages.

A great advantage over the synchrotron is the possibility to eject particles at different energies, without waiting for the magnet ramp-up time. FFAGs represent in many ways the best of both cyclotrons and synchrotrons, and if researchers succeed in producing a highly compact accelerator, a hypothetical gantry-mounted FFAG could be of great interest for proton therapy.

The question is whether FFAGs will be able to provide reliable, compact devices for accelerating ions. Part of the answer may be given in the near future by the proof-of-principle PAMELA accelerator.
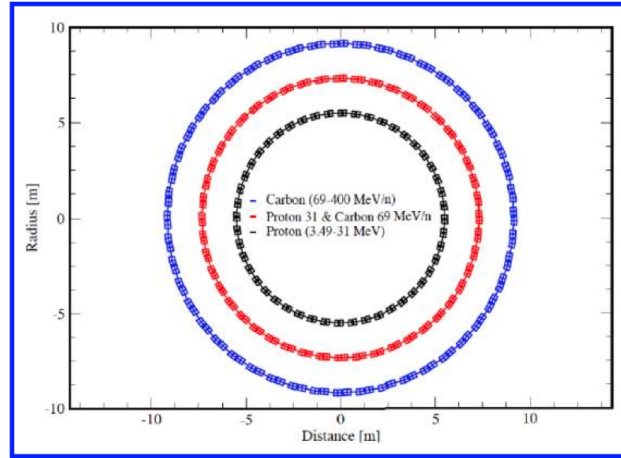

Figure 26: Sketch of three concentric NS-FFAGs for hadron therapy, constituting a very dense lattice. *From [92].*

4.5 Rotating linac for proton therapy

Researchers at LLNL have in collaboration with TomoTherapy Medical Systems already proposed a design for a highly compact, gantry-mounted proton DWA [74], but a proof-of-concept needs to be seen. Fig. 27 shows an artist's rendition of a high-gradient gantry-mounted proton linac. Operating at an unprecedented gradient of 100 MV/m with length 2.5 m, the proposed device would enable construction a single-room facility of groundbreaking compactness, providing clinical energies with a maximum output of 250 MeV. Construction costs would likely be significantly less than the 35-ton gantry-mounted SC synchrocyclotron produced by Mevion (Fig. 23), which is already considered a considerably cheap and compact device. Because energy can be modulated along the linac, there is no need for an ESS system. Consequentially, the nozzle can be made very compact as well, resulting in an allover very modest height requirement for the facility. However, there may be many years before the technology matures significantly to come close to realization.

It also seems of great interest to further investigate the concept of a NC RF-linac, using "CLIC technology". As mentioned, TERA has expressed interest in acceleration of protons using gradients of 50 MV/m for a compact proton [84]. However, this is for a C-band design; it may be possible to obtain higher gradients by moving to the X-band regime. So far, experiments have been carried out on 3.3 GHz and 5.7 GHz [85, 66]. It would be of great interest to see a future proof-of-concept experiment at frequencies > 10 GHz. The TULIP 2.0 design described by Amaldi is only partly gantry-mounted, because the main linac would be 5-6 m long even with accelerating gradients of 50 MV/m. If moving to the X-band regime could enable sustainable gradients for proton acceleration of 70-80 MV/m, it could be possible to realize a fully gantry-mounted single-room device. It may still be that a partly mounted solution is still advantageous, but construction costs would benefit from an even more compact design. There are many considerations at play when striving to find

the optimal design; still, it would be valuable to further investigate the highest attainable gradients for protons as well as electrons.

4.6   Laser-driven accelerators and VHEE devices

LWFA, DLA, and laser acceleration of ions have all received significant attention due to the large gradients they are able to produce over short fields. At the present time, though, the immensely powerful fields needed to produce the required interactions are nowhere near current commercialization. With the realization that this could quickly change with the rapid development of technology today, these concepts maintain a relevance for medical application.

Through laser acceleration using thin foils, it is possible to produce vast fields accelerating ions, which has caused much excitement in the field. However, the main challenge to be overcome, except for the laser requirements, is to manage to produce a monoenergetic spectrum at clinical energies. First of all, the energy spread should be below 0.3-0.4% to ensure precise dose delivery. Second, all non-clinical parts of the distribution must be extracted and dumped, imposing the need for additional magnets and radiation shielding [93]. Third, it is not clear to me whether the foils can still be used for consecutive irradiations. Following conversations with Joel England

Figure 27: Artist's sketch of a rotating 2.5 mDWA, with 100 MV/m gradient. *From www.newswise.com.*

at SLAC, involved in the DLA project, it seems to me they cannot, since the ultrathin foil appear to be physically distorted by the immensely powerful incident laser. A third challenge from an application perspective would be to engineer a practical solution that does not reduce the allover reliability of the system If, however, these challenges are overcome, there would be much reason for excitement over potential medical applications. Laser pulses are easily transported, and thus it could be possible to construct an all-optical gantry. It could perhaps be of similar design and length as Fig. 27, with the laser pulse being be transported up to the top and aimed down towards
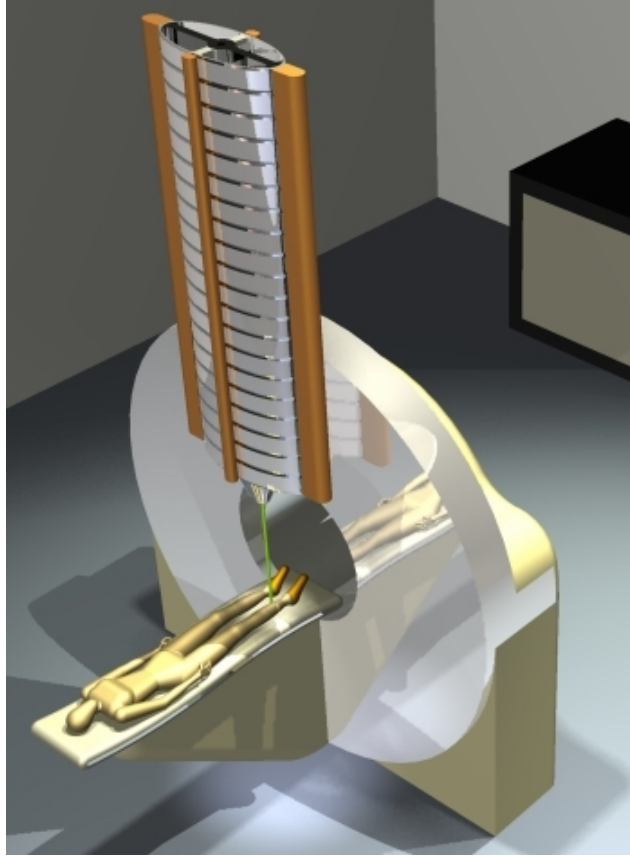
a foiled trained to the target. The remaining length of the structure would be needed for ESS and BDS.

LWFA and DLA have both experimentally produced very large gradient fields. However, both of these concepts are mostly suitable for acceleration of electrons. For LWFA, a proton would most likely have to be pre-accelerated before it could experience sustained acceleration in a plasma wakefield, effectively defeating the purpose. And the DLA concept is, at least for the time being, concerned with a design where the particle quickly reaches relativistic speeds. However, the principle of of accelerating non-relativistic electrons through a DLA [75] could be extended to the case of protons - it would only be significantly less practical and result in a much lower gradient, for reasons discussed in Sec. 3.1.5. It would be interesting to see what gradients are achievable for such a scheme.

LWFA and DLA may not hold any immediate relevance for hadron therapy, but it is not unlikely there may still be an area of application within particle therapy. The ongoing effort at SLAC and Stanford School of Medicine investigating the radiobiological efficiency of VHE electrons is likely to produce results in the relatively near future. They are not the first to look at the radiobiological efficiency of VHE electrons [30], but the results could be of significant impact for the continued interest in the field. If VHEE therapy turn out to be viable, both LWFA and DLA are interesting candidates. Of the two, DLA appears most appealing: although an ultracompact, all-optical device such as proposed by J. England in Sec. 3.2.3 has not been constructed or tested, it may present an accelerator of unprecedented compactness; an "accelerator-on-a-chip", as referred to by England. An accelerator of such small dimensions may also open for new applications, such as for endoscopic treatment or brachytherapy. For VHEE applications, both DLA and LWFA would have to compete with current, state-of-the-art technology, since gradients of > 100 MV/m have already been demonstrated at CTF3.

Even if VHEE therapy should turn out not viable, LWFA still holds potential to produce X-rays of higher quality than available today through synchrotron emissions during betatron oscillations in the plasma. Although fascinating, this concept does not fall within the focus of this thesis.

5 Conclusions

I have in this thesis attempted to gain an understanding of the requirements posed on accelerators for radiation therapy. Although some "truths" exist, the field of radiological oncology is full of uncertainties, areas of improvement and even controversies. In other words: "a document that establishes the medical requirements for hadron therapy accelerators and that is approved by all the hadron therapy community is still missing" [69].

There is currently a strong interest for hadron therapy. Although the clinical differences between hadron, in particular proton, and photon therapy is widely disputed, the numerous facilities under construction and under planning witness of a widespread enthusiasm. This trend is likely to continue, with the continued era of economic single-room facilities.

For ion therapy, the proposed cyclinac may hold great promise for offering high-precision IGRT using the multipainting technique. It also has compactness similar to existing accelerators, or

better. For interested actors, however, it must also be shown to be competitive on price. FFAGs are in an early phase, but could prove suitable for proton and/or ion therapy.

The first line of single-room facilities has very recently entered operation for proton therapy. Although the properties of this device may be somewhat less desirable than what offered by e.g. CABOTO, the Mevion accelerator compensates with a very low price. For a long time, it has been argued that cheaper options must become available if proton facilities are to be build. Now, following the introduction of the first low-cost proton facilities, five more are already under construction [12]. However, such a concept is not yet ready for ion therapy application, as ion cyclotrons would not be compact enough to be mounted on a gantry.

A gantry-mounted rotating proton linac may not be hopelessly far from realization. Apart from the concept involving the rotating DWA, it may be possible to reach very high gradients for protons using "CLIC technology". More research is needed on the acceleration of protons in the X-band regime. For the DWA design, a proof-of-concept would be needed to demonstrate the feasibility of a sustainable 100 MV/m gradient.

The most advanced acceleration technologies under development today, namely laser-driven ion acceleration, DLA, DWA and LWFA, are far from ready for application. Even when the technology matures, A coarse estimate is that applications for particle therapy will be in 10-20 years time at the earliest. However, if these technologies indeed are shown to hold their promise, they will allow even more compact and cost-effective solutions for particle therapy centers than even the most optimized accelerators based on conventional technology.

6 Closing remarks

Norway may consider investing in inexpensive single-room treatment centers in addition to a national combined proton/ion center. With the recent advent of single-room facilities it seems reasonable to not proceed hastily with three or four highly expensive proton centers based on conventional design. Furthermore, new, interesting principles are on the way. It could be argued that future patients cannot afford to wait for additional years of evaluation; if such is the case it may be an idea to begin with a single-room facility in the near future, which is more quickly constructed, then perform new evaluations based on subsequent development in the field before commencing with the other facilities (if several facilities are still to be built).

In Norway, the development of one or more hadron therapy centers may soon be initiated. As of the writing of this thesis, the Norwegian endeavor, which is still in a very early stage, aims towards development of three or four proton facilities as opposed to one national combined proton/ion center, to provide services on a more regional level. If this endeavor commences it should be considered whether these facilities should be identical or not. As exemplified by the case of neutron activation for different output energies, different designs may provide more desirable treatment for certain patient groups. On the other hand, expenses may be reduced by constructing facilities of the same design. Furthermore, if one facility cannot treat all patient groups, some patients would have to undergo treatment in a different region. Transportation and housing of patients during the treatment also contributes to expenses, in addition to being in itself less preferable for the patient. The full consideration is a complex one, but it is important that all factors are evaluated.

A   Appendix

A.1   CLIC two-beam acceleration

Much of the novelty of the CLIC design lies in the proposed two-beam acceleration scheme. If a conventional design were to be used for CLIC, one would need thousands or tens of thousands of klystrons to power the accelerator, with very large energy losses because of the high electric fields used. Instead, much higher efficiency is gained by using a drive beam to power the main linac. The concept is crudely explained thus: a high-current drive beam is accelerated with RF fields of not very high gradients but with high RF-to-beam efficiency (around 98%), providing it with an output energy of 9 GeV. The energy of the drive beam is then converted (with about 84% efficiency) to generate new RF fields through a deceleration process, which is used to exert a high-gradient (100 MV/m) acceleration on another, low-current beam - the main beam. An RF-to-beam efficiency of about 24% is associated with such a high gradient; this relatively low efficiency is compensated for by having a high current drive beam accelerate a low-current beam. [62, p.15-20]
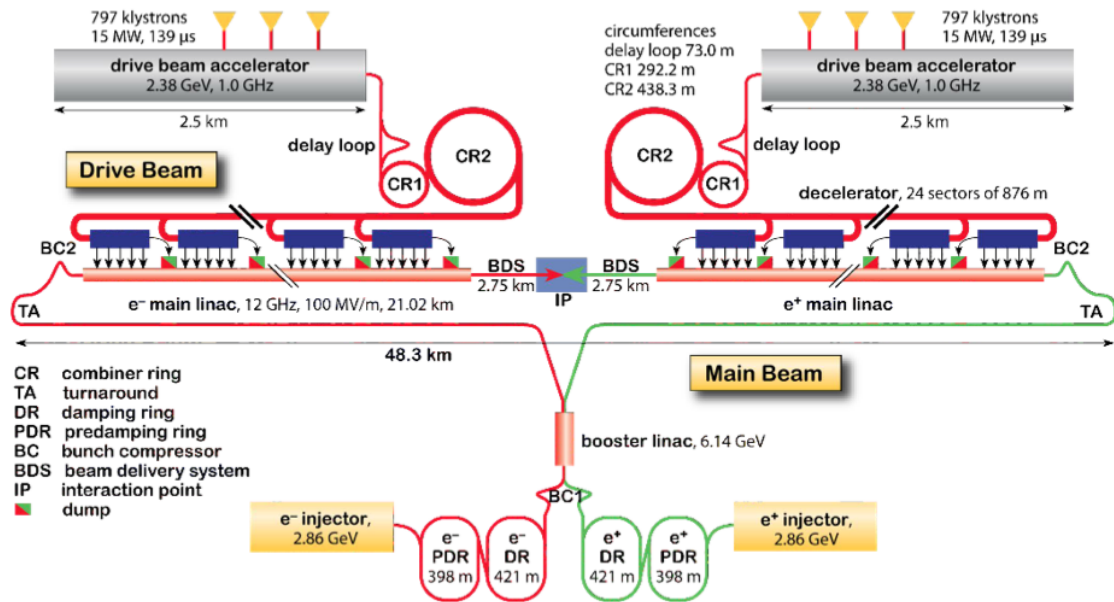

Figure 28: The CLIC design at 3 TeV. *From [62].*

A.2 Plasma wakefield acceleration at SLAC

The main principles of the E-200 experiment is covered in Sec. 3.3.1, but a few more details are briefly given on the part of the experiment the author has been mostly involved in. As mentioned, the plasma wakefield acts as a medium for an energy transfer between the drive bunch and the witness bunch. It is important to find a good and reliable way to measure the energy of the bunches after exiting the oven, in order to describe the magnitude of energy transfer that has taken place. For this purpose, we make use of the Cherenkov radiation emitted for a particle traveling faster than the speed of light in a given medium. After the acceleration/deceleration process in the oven, the bunches exit the vacuum tube and enter the air in the accelerator tunnel. Since we know that the drive bunch in front now carry less energy than the witness bunch, we give both a kick with a magnet, causing a transverse displacement. The displacement is greater for a lower-energy particle; thus, the witness beam and the drive beam enter the air gap with a relative transversal displacement. In the air, the velocity of the electron bunches exceeds that of light, causing optical Cherenkov radiation to be emitted in a radial cone from each of the bunches. Next, the bunches pass through two silicon wafers, both at a $45°$ angle, spaced 5 cm apart. The first wafer blocks all previously generated Cherenkov light. As the bunches traverse the 5 cm air gap, radiation is continuously emitted, all of which is reflected by the second wafer onto a system of mirrors, eventually leading to a camera pre-aligned and focused on the point between the two wafers. The energy of the bunches is calculated by comparing their relative positions (which are given by the last magnet kick, dependent on the energies) with a reference beam with known energy.

Further details on the E-200 experiment can be found in Refs. [2, 79]; the part concerning the Cherenkov setup is described in greater detail in a paper soon to be submitted for a journal (Ref. [94]).

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