

Méthodes pour l'automatisation de la dosimetrie en radiothérapie.

Methods for automatization of radiotherapy dosimetry.

Thèse de doctorat de l'université Paris-Saclay

Spécialité de doctorat: ...

École doctorale n° 573 Interfaces : matériaux, systèmes, usages, ED INTERFACE
Graduate School: Sciences de l'Ingénierie et des Systèmes, SIS

Thèse préparée dans les unités de recherche **Radiothérapie** (Institut Régionale du Cancer de Montpellier), **Advanced Research** (TheraPanacea), et **MICS, Mathématiques et Informatique pour la Complexité et les Systèmes** (Université Paris-Saclay, CentraleSupélec) , sous la direction de **Nikos Paragios**, Professeur, et la co-direction de **Paul-Henry Cournède**, Professeur

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Titre: Méthodes pour l'automatisation de la dosimétrie en radiothérapie.

Mots clés: Mathématiques, Intelligence Artificielle, Radiothérapie

Résumé:

La dosimétrie en radiothérapie est essentielle pour garantir la précision et la sécurité des traitements contre le cancer. La complexité et la variabilité de la planification des traitements nécessitent des méthodologies avancées pour l'automatisation et l'optimisation. Cette thèse présente des approches novatrices visant à automatiser le processus de dosimétrie en radiothérapie.

Cette thèse commence par le développement d'un moteur de dosimétrie et une évaluation approfondie des algorithmes d'optimisation open-source existants pour la planification des traitements. Ensuite, ce manuscrit analyse les relations entre différentes doses. Cette analyse conduit à la proposition d'un cadre novateur pour l'optimisation multi-objectif et la sélection robuste de plans à l'aide de la théorie des graphes.

Afin de réduire davantage le temps nécessaire pour la planification en radiothérapie, la thèse explore l'application de l'apprentissage par renforcement pour l'optimisation des doses. Le système proposé réalise la dosimétrie pour de nouveaux patients en exploitant les données de dose

des patients traités dans le passé. Cette méthode entièrement automatisée peut s'adapter aux pratiques de différentes cliniques, réduisant ainsi le besoin d'ajustements manuels et facilitant son adoption en pratique.

De plus, la thèse examine l'utilisation de l'apprentissage profond pour la prédiction des doses, en proposant une série de modèles guidés par des Histogrammes Dose-Volume (DVH) cibles. Ce guidage orientation permet l'incorporation de directives lors de la génération de doses par les modèles. En outre, cette technique permet d'entraîner un seul modèle capable de s'adapter, plutôt qu'un modèle pour chaque clinique.

Les contributions de cette thèse présentent des avancées dans la dosimétrie en radiothérapie, ouvrant la voie au développement d'un système de planification de traitement entièrement automatisé, s'adaptant aux contraintes cliniques, conçu pour fonctionner avec une e. Ces innovations pourraient améliorer les flux de travail cliniques, en réduisant l'intervention humaine à un minimum, rendant la radiothérapie plus efficiente.

Title: Methods for automatization of radiotherapy dosimetry.

Keywords: Mathematics, Artificial Intelligence, Radiotherapy

Abstract:

Radiotherapy dosimetry is critical in ensuring the precision and safety of cancer treatments. The complexity and variability of treatment planning necessitate advanced methodologies for automation and optimization. This thesis introduces novel approaches aimed at automating the radiotherapy dosimetry process.

The research begins with developing a dosimetry engine, and comprehensively evaluating existing open-source optimization algorithms for treatment plannification. Then, this thesis analyzes the relationships between different treatment plans. This analysis leads to the proposal of a novel framework for multi-objective optimization and robust plan selection using graph theory.

To further reduce the time required for radiotherapy planning, the thesis explores the application of reinforcement learning for dose optimization. The proposed system performs

dosimetry for new patients by leveraging dose data from past patients. This fully automated method can adapt to clinical dependencies, reducing the need for manual fine-tuning and easing its adoption in practice.

In addition, the thesis investigates the use of deep learning for dose prediction, proposing a series of models guided by target Dose Volume Histograms (DVH). This guidance facilitates the incorporation of guidelines into the deep-generated doses. Moreover, it allows a single model to be trained instead of one for each clinic.

The contributions of this thesis represent advancements in radiotherapy dosimetry, paving the way for the development of a fully automated, clinically dependent treatment planning system designed to operate with minimal human intervention. These innovations could enhance clinical workflows, making radiotherapy more efficient.

Acknowledgments

During those three years, I often felt alone, but I eventually realized that I couldn't name people who supported me, not because there were too few, but because there were so many. This section is dedicated to all those who indirectly contributed to this manuscript.

[...]

List of Contributions

- Teaching: *Consistency and Reproducibility of Grades in Higher Education: A Case Study in Deep Learning*
- ArXiV: Radiotherapy Dosimetry: A Review on Open-Source Optimizer
- ESTRO: A Novel Framework for Multi-Objective Optimization and Robust Plan Selection Using Graph Theory
- SFPM: Dose Volume Histograms Guided Deep Dose Predictions
- AIME: Radiotherapy Dose Optimization via Clinical Knowledge Based Reinforcement Learning (conference + full paper)
- ASTRO: Clinically Dependent Fully Automatic Treatment Planning System
- SFRO: Attention Mechanism on Dose-Volume Histograms for Deep Dose Predictions

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Background

Abstract

The background chapter of this PhD provides a comprehensive overview of key concepts in cancer treatment and radiotherapy. If you already know about radiotherapy and multi-leaf collimator, I strongly advise to skip this chapter.

This chapter begins by outlining the nature of cancer, its phases, stages, risk factors, and common types of treatments (with their advantages and disadvantages). Then, the physics of radiotherapy is explored, with a focus on ionizing radiation, and biological effects of radiation. This chapter also presents the patient journey in radiotherapy, from diagnosis and treatment prescription to planning and follow-up. Key technologies used in radiation therapy, such as multi-leaf collimator (MLC) linear accelerator (LINAC) are introduced. Lastly, this chapter covers the irradiation techniques, and details major steps in the dosimetry process: beam orientation optimization (BOO), fluence map optimization (FMO), leaf sequencing (LS), and direct aperture optimization (DAO).

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1.1 Medical context

This PhD thesis is about radiation therapy (RT) for cancer treatment.

1.1.1 About cancer

Cancer is a complex disease that can affect many parts of the body, and is a leading cause of death worldwide. Cancer is characterized by the uncontrolled growth of cells that can invade and destroy surrounding tissues. The World Health Organization (WHO) estimated 20 million new cancer cases in 2022, and 9.6 million deaths linked to cancer in 2022 [1]. Cancer touches about 20% of the population, and is responsible for 1 in 10 deaths.

Cancer markers There are several cancer markers. Cancer cells proliferate uncontrollably. They also reprogram cellular metabolism to support their growth [7]. They can also stop cell growth arrest mechanisms. They usually manage to evade apoptosis (programmed cell death). Cancer cells can escape the immune system, and change their cellular response phenotypic via plasticity. At some point, cancer cells can get the ability to undergo a sufficient number of successive cell cycles of growth and division to generate macroscopic tumors. To support their growth, they create new blood vessels to get nutrients. Finally, they can escape and form metastasis, and will eventually provoke senescence.

Conditions leading to cancer Cancer is a complex disease. First, cancer is caused by mutations in the DNA. These mutations can be inherited or acquired. Second, cancer is embraced by epigenetic reprogramming, i.e., gene expression changes (not caused by changes in the DNA sequence). Third, cancer is often associated with an inflammatory context; inflammation can promote cancer growth and spread. Finally, cancer is often associated with a disruption of the microbiota (the microbial community living in and on the human body). This disruption can promote cancer growth and spread.

Phases of cancer Cancer develops in several phases.

Initiation The first phase is initiation: a normal cell is transformed into a cancer cell. Mutations in the DNA cause this transformation.

Promotion The second phase is promotion or "tumorigenesis". During this phase, the cancer cell grows and divides uncontrollably to form a tumor cluster of cells. This growth is promoted by changes in gene expression and other factors [39]. It may also create new blood vessels to get nutrients and oxygen.

Evolution The final phase is evolution. The tumor will first grow locally, then regionally, invading and damaging surrounding tissues. Finally, the cancer cell will spread to other body parts, forming metastasis. Metastasis is the leading cause of death in cancer patients [32].

Cancer stages Cancer is classified into stages [2].

- Stage 0: 'in situ neoplasm'; it means a group of abnormal cells in an area of the body. The cells may develop into cancer in the future.
- Stage 1: the cancer is small and contained within the organ it started in.
- Stage 2: the tumor is larger than in stage 1, but the cancer hasn't started to spread into the surrounding tissues.
- Stage 3: the cancer is larger; it has started to spread into surrounding tissues and cancer cells in the lymph nodes nearby.
- Stage 4: the cancer has spread from where it started to another body organ. This spread is also called secondary or metastatic cancer.

Doctors use the TNM system to describe the cancer stage [18].

T stands for the size of the Tumour; It can be 1, 2, 3, or 4, with one being small and four being large.

N stands for the number of lymph Nodes affected; It can be between 0 and 3. 0 means no lymph node contains cancer cells; 3 means many lymph nodes contain cancer cells.

M stands for the existence of metastasis in another part of the body. It can be 0 (no spread) or 1 (the cancer has spread).

Most common cancers According to the WHO, the most common cancers are lung, breast, colorectal, prostate, skin, and stomach cancer. This thesis mainly focuses on prostate cancer, which is among the most common ones.

Risk factors Tobacco use, alcohol consumption, unhealthy diet, physical inactivity, and air pollution are risk factors for other cancer types. However, the leading risk factor for prostate cancer is age. Thus, it touches all social populations evenly and is unavoidable.

1.1.2 Treatment types

There are three main types of cancer treatment: surgery, radiation therapy, and chemotherapy. The choice of treatment depends on the type and stage of cancer, the patient's age and general health, and other factors.

1.1.2.1 Surgery

Surgery is the most effective cancer treatment [21]. It involves removing the tumor and surrounding tissue. Surgery is often used to treat early-stage cancer that has not spread to other parts of the body. For surgery to be possible, the tumor must be located in a place the surgeon

can easily access. Surgery can be followed by other treatments, such as radiation therapy or chemotherapy, to kill any remaining cancer cells.

Advantages Surgery is curative, meaning that cancer is completely removed, and the patient can "forget" about it. It is also a local treatment, with limited side effects on the body. Finally, only one session is needed.

Disadvantages Surgery is invasive, and can be painful. However, the main disadvantage, is that it can only be used for localized cancer (with no metastasis) and is accessible to the surgeon.

1.1.2.2 Chemotherapy

Chemotherapy is a treatment that uses drugs to kill cancer cells. It is systemic, meaning it can reach cancer cells anywhere in the body. Therefore, it usually has strong side effects. Chemotherapy is often used to treat cancer that has spread to multiple parts of the body (i.e., metastatic cancer).

Depending on how advanced the cancer is, chemotherapy can be used to cure, control, or relieve symptoms (palliation).

Advantages Chemotherapy can be used to treat cancer that has spread to multiple parts of the body. It can also be used to relieve symptoms and improve quality of life.

Disadvantages Chemotherapy is a heavy treatment, with strong side effects. It can also weaken the immune system, making the patient more susceptible to infections. Finally, newer drugs tend to be very expensive.

1.1.2.3 Radiation therapy

Radiation therapy is a treatment that uses high-energy radiation to kill cancer cells. It is semi-local, meaning that it only affects the tumor, and the tissues traversed by the radiation beams [33]. Radiation therapy is curative most of the time. It can be used alone or in combination with other treatments.

Radiation therapy can be delivered in two ways: external radiation therapy and internal radiation therapy. External radiation therapy uses a machine to deliver radiation to the tumor from outside the body. Internal radiation therapy uses radioactive materials placed directly into or near the tumor. This thesis focuses on external radiation therapy.

Advantages Radiation therapy is a non-invasive treatment, with limited side effects. It is relatively localized, and can be used to treat cancers that are not accessible via surgery.

Disadvantages Radiation therapy still targets healthy cells. Depending on the patient's response, it may cause side effects.

1.1.2.4 Other treatments

Cancer research is very active, and new treatments are constantly being developed. These treatments are often used in combination with others.

Immunotherapy Immunotherapy is a treatment that uses the body's immune system to fight cancer. It can boost or change how the immune system works to find and attack cancer cells. It is a systemic treatment.

Targeted therapy Targeted therapy is a treatment that uses drugs to target specific molecules that are involved in cancer growth. It is a systemic treatment.

Hormone therapy Hormones are proteins or substances the body makes that help control how specific cell types work. Hormone therapy is a treatment that uses drugs to block or lower the amount of hormones in the body that are involved in cancer growth. It is a systemic treatment.

Stem cell transplant A stem cell transplant is a treatment that uses stem cells to replace cells damaged or destroyed by cancer treatment. It is a systemic treatment.

1.2 Physics of Radiotherapy

Radiation therapy uses high-energy radiation to kill cancer cells.

1.2.1 Ionizing radiation

Ionizing radiation has enough energy to remove tightly bound electrons from atoms, creating ions. X-rays and gamma rays are both electromagnetic radiations that are ionizing and high-energy photons. Some particle radiations, such as particles, beta particles, and neutrons, are also ionizing, but radiotherapy uses photon radiations.

X-rays are produced by accelerating electrons to collide with a target material and are used in medical imaging and (external) radiation therapy. In contrast, gamma rays originate from the radioactive decay of specific atomic nuclei and are used in (internal) radiation therapy.

Because ionizing radiation therapy can damage the DNA in cells and lead to cell death, it is used in radiation therapy for treating cancer.

1.2.2 Photon interactions

Photon-matter interactions within an absorbing medium undergo stochastic processes. Four types of interactions (figure 1.1) are possible for photons; their occurrence depends on the atomic number, matter, and the energy of the incident photon [12]. Three of the four interactions generate secondary ionizing particles that deposit energy in the medium.

1.2.2.1 Rayleigh scattering

The Rayleigh scattering (figure 1.1a) does not change the energy of the incident photons and consequently has no direct consequence on the body. Rayleigh scattering predominantly occurs with low-energy photons (typically < 100 keV).

1.2.2.2 Photoelectric absorption

The photoelectric absorption effect (figure 1.1b) is the process by which an atom absorbs a photon, and an electron is ejected from the atom. The photon ceases to exist, and its energy is transferred to the electron. The ejected electron, called a photoelectron, can ionize other atoms, leading to dose deposition. The photoelectric effect is the dominant interaction for low-energy (< 100 keV) photons.

1.2.2.3 Compton scattering

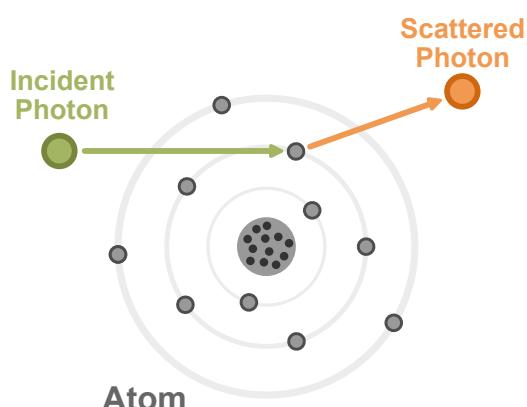
Compton scattering (figure 1.1c) is the process by which an atom scatters a photon, and ejects an electron from the atom. The photon is scattered at an angle, and part of its energy is transferred to the electron. The emitted electron is called a Compton electron, which can ionize other atoms, leading to dose deposition. Compton scattering is the dominant interaction for medium-energy (≈ 0.1 to ≈ 10 MeV) photons.

1.2.2.4 Pair production

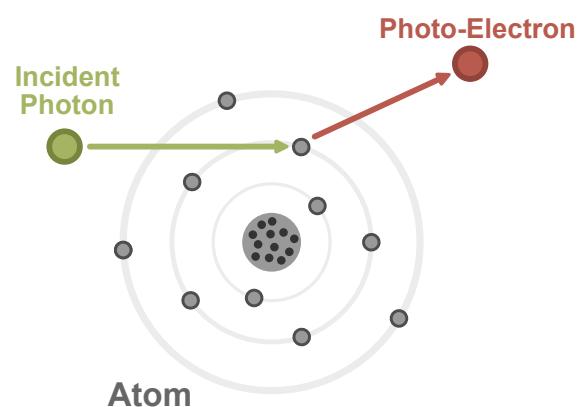
Pair production (figure 1.1d) is when an atomic nucleus absorbs a photon and creates an electron-positron pair. The photon ceases to exist, and its energy is transferred to the electron-positron pair. The positron rapidly interacts with another electron of the matter, producing two photons emitted at 180° from each other. The electron can ionize other atoms, leading to dose deposition. Pair production is the dominant interaction for high-energy (> 10 MeV) photons.

1.2.3 Photon attenuation

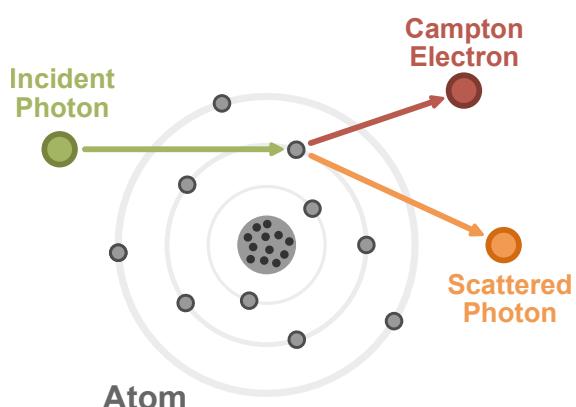
The photon beam will be attenuated as it passes through the medium, and its intensity will decrease. The dose deposition in the medium is proportional to the intensity of the photon beam. The attenuation of the beam follows an exponential law concerning the depth of the



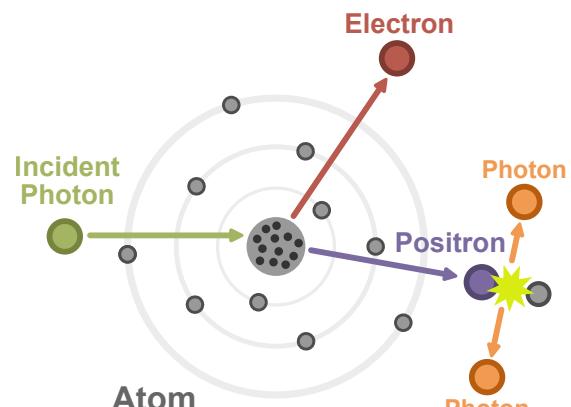
(a) Diagram of Rayleigh Diffusion.



(b) Diagram of Photoelectric Absorption.



(c) Diagram of Compton Scattering.



(d) Diagram of Pair Production.

Figure 1.1: Diagrams of photon interactions with matter observed in the kilo and mega-voltage energy range.

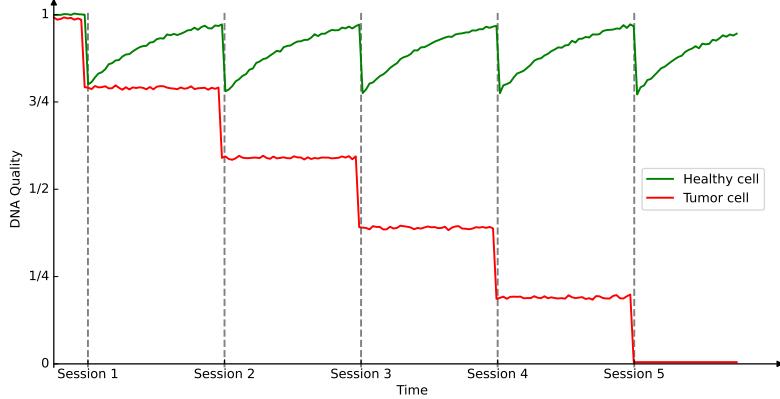


Figure 1.2: Quality of the the DNA in healthy and tumor cell after radiotherapy sessions.

medium traversed (Lambert-Beer law) [5]:

$$I(x) = I_0 \exp(-\mu x)$$

where I is the intensity of the photon beam after passing through a thickness x of the medium, I_0 is the initial intensity of the photon beam, and μ is the attenuation coefficient of the medium.

1.3 Biological effect on cells

Ionizing radiation can damage the cells, leading to cell death in various ways.

1.3.1 Radiation effects on DNA

Ionizing radiation damages the DNA [30] in cells and leads to cell apoptosis, necrosis, or senescence. Radiation induces DNA damage through both direct and indirect mechanisms: Directly, it causes single-strand breaks (SSBs), double-strand breaks (DSBs) [29], DNA crosslinks, and DNA-protein crosslinks [25]. Indirectly, radiation generates reactive oxygen species (ROS) and reactive nitrogen species (RNS), further contributing to DNA damage.

DNA repair Cells have mechanisms to repair DNA damage. There are several types of DNA repair mechanisms, including base excision repair (BER), nucleotide excision repair (NER), mismatch repair (MMR), and double-strand break repair (DSBR). Cancer cells often have defects in DNA repair mechanisms, making them more sensitive to radiation therapy [18]. This repair mechanism being available only for healthy cells leads to cell death only for cancerous cells, when their DNA is too damaged to survive (see figure 1.2).

1.3.2 Radiation affects the plasma membrane

Radiation significantly impacts the biological properties of the plasma membrane by affecting its composition, structural integrity, and functional capabilities. Radiation exposure can alter the fluidity and permeability of the cell membrane, affecting the transport of ions and molecules into and out of the cell. Additionally, radiation causes corrosive damage, and damage to the membrane can initiate signaling events that are important for the apoptotic response [9]. These changes can have cascading effects on various cellular processes, highlighting the critical role of the plasma membrane in maintaining cellular homeostasis under stress conditions.

1.3.3 Radiations and cell organelles performances

Radiation exerts significant detrimental effects on various cellular organelles, impacting their functionality and overall cellular health [31]. One critical target of radiation damage is the endoplasmic reticulum, where radiation can disrupt protein folding and processing, leading to cellular stress and apoptosis. Additionally, ionizing radiation induces alterations in ribosomal structure and function, impairing protein synthesis and compromising cellular homeostasis. Mitochondria, the cell's powerhouses, also exhibit altered behavior following radiation exposure, including disruptions in energy production and initiating apoptotic pathways. Furthermore, lysosomes, essential for cellular waste processing and recycling, suffer damage upon irradiation, potentially accumulating cellular debris and impairing cell function. These collective effects highlight radiation's broad and profound impact on cellular organelle performance [38].

1.3.4 Radiation alters the biological behavior of tumor cells and the immune system

Radiation profoundly influences the biological behavior of tumor cells and the immune system, impacting critical aspects of cancer progression and immune response. It affects tumor cell proliferation, often reducing the ability of cancer cells to multiply by damaging their DNA and cellular structures. Radiation also influences tumor cells' invasion and metastasis potential, either by directly impairing their motility or altering the tumor microenvironment to make it less conducive to cancer spread. Additionally, radiation can modulate cancer-promoting inflammation, either by inducing pro-inflammatory signals that support tumor growth or by disrupting the inflammatory milieu to hinder cancer progression.

1.3.5 Radiation effects when combined with immunotherapy

Radiation may support immunotherapy, making the effect of both treatments more significant than the sum of their impact if used alone.

Ray-Enhanced Anti-CTLA-4 Immunotherapy Radiation therapy can enhance the efficacy of anti-CTLA-4 immunotherapy, a treatment that blocks the CTLA-4 protein in T cells, thus boosting the immune system's response against cancer cells. The combination of radiation

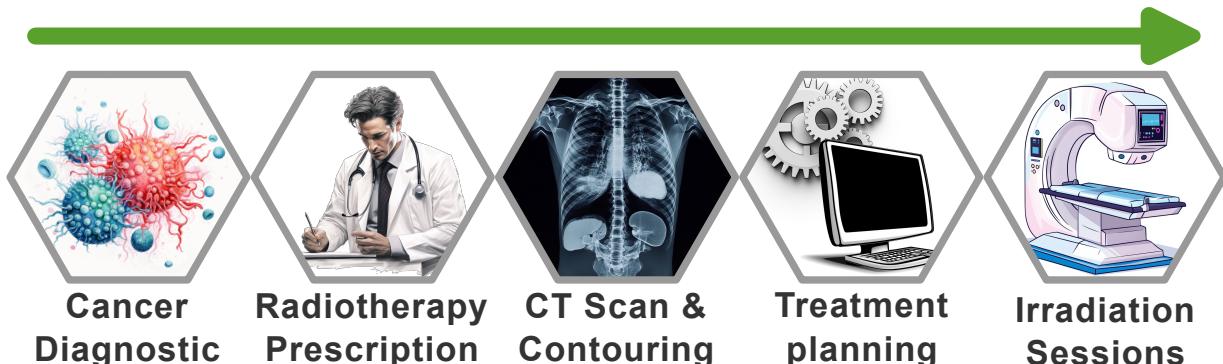


Figure 1.3: Typical radiotherapy patient path.

and anti-CTLA-4 immunotherapy has shown promising results, as radiation-induced tumor cell death releases antigens that can further stimulate the immune system [34]. This synergy can improve tumor control and potentially better clinical outcomes than either treatment alone.

Radiation Combined with Anti-PD-1/PD-L1 Immunotherapy Combining radiation with anti-PD-1/PD-L1 immunotherapy has shown significant success. Anti-PD-1/PD-L1 therapies block the PD-1/PD-L1 pathway, which tumors exploit to evade immune detection. Radiation therapy can augment this effect by increasing the immunogenicity of the tumor, thereby making cancer cells more susceptible to immune attack [15].

TLR-Mediated Immunologic Effects of Radiation Therapy Radiation therapy can also exert immunologic effects through Toll-like receptors (TLRs), a class of proteins involved in pathogen recognition and activation of innate immunity. Radiation can activate TLRs on immune cells, producing cytokines and chemokines that enhance the immune response against tumors. This TLR-mediated effect contributes to the synergy between radiation and immunotherapies, leading to more robust anti-tumor responses [37].

While this thesis does not focus on biological aspects, one should remember that radiation affects cells in various ways, and cancer therapy is complex.

1.4 Patient Path

The radiotherapy patient path encompasses several critical stages, each essential for the effective treatment of cancer. This section outlines the sequential steps of radiotherapy, from initial detection and diagnosis to follow-up care.

1.4.1 Diagnostic

Patients diagnosed with a tumor can go through several paths: surgery, radiotherapy, immunotherapy, chemotherapy, or any combination. Doctors will choose the most appropriate

treatment(s) based on evidence they have (biopsy, radios, et cetera). This manuscript will focus on the radiotherapy path.

1.4.2 Radiotherapy Prescription

Following a confirmed diagnosis and the choice of radiotherapy treatment, the oncologist develops a prescription. This prescription specifies the type, dosage, and frequency of radiation treatment tailored to the patient's specific cancer type, location, and stage. The doctors define minimal tumor irradiation and maximum damage to surrounding healthy tissues. Most of the time, templates are used and fine-tuned to fit specific patients.

1.4.3 CT scan and Contouring

A computed tomography (CT) scan is performed to obtain detailed images of the patient's anatomy. These images are used to delineate the tumor and surrounding organs at risk. The contouring task used to be a manual operation but is now done automatically, thanks to the progress of artificial intelligence on segmentation tasks. The CT scan also provides the spatial information necessary for precise irradiation simulation.

1.4.4 Treatment Planning

The treatment planning process involves developing a detailed plan specifying the patient's radiation dose distribution. Advanced software calculates the optimal arrangement of radiation beams to achieve the desired dose while minimizing exposure to healthy tissues. This thesis registers new advances in the planning step. Plans must be reviewed and approved by doctors.

1.4.5 Irradiation Sessions

Irradiation sessions, or treatment delivery, is the actual irradiation of the patient. Cone Beam Computed Tomography (CBCT) is usually done to reposition the patient with the scan so that all organs align with the planning CT. Nowadays, the tendency is to reduce the number of irradiation sessions (the old typical five weeks of five sessions is now usually two weeks of five sessions).

1.4.6 Follow-up

After the completion of radiotherapy, patients enter the follow-up phase. Regular follow-up appointments are scheduled to monitor the patient's response to treatment, manage any side effects, and detect any signs of recurrence.

1.5 Machines

The discovery of X-rays by German physicist W. C. Roentgen in 1895 marked a pivotal moment in medical science. Only one year later, in 1896, Despeignes began using radiotherapy in France. Victor Despeignes delivered 15-30 minutes with 80 irradiation sessions (so-called "fractions") to relieve the pain of patients with stomach cancer [16].

Since then, machines have become more powerful and more complex. Modern machines can deliver mega-voltage radiation [17], which are sufficiently high to destroy tumors in minutes. However, such high-power treatments will irreversibly damage healthy tissues. Hence, as the machines became more powerful, constructors built more complex modulation mechanisms to preserve organs at risk.

1.5.1 Molds

The first kind of modulation used was molds: their purpose was to stop the irradiation before it reached the body. By strategically obscuring the rays, organs can be spared, as they will receive a small amount of irradiation dose, while the tumor will receive a fatal dose. Molds had significant limitations due to their single-use nature. It was necessary to create a custom mold for each patient as their anatomy differs. Typically, three molds were required for the three irradiation angles. Modern technology avoids single-use molds using motorized blockers to stop the rays and dynamically modulate the radiation beam.

1.5.2 Multi-Leaf Collimator - LINear ACcelerators

Multi-Leaf Collimator (MLC) technology combined with Linear Accelerators (LINAC) was a revolution in the radiotherapy world [4] [40]. They are capable of turning around the patient to deliver irradiation from multiple angles (figure 1.4a). Moreover, an array of motorized leaf pairs can shape the radiation beam with high precision (figure 1.4b). Additionally, MLC systems are sometimes equipped with jaws, which help to shape the beams better. The MLC-LINAC is the most common type of radiation therapy machine used today. This manuscript will focus on the MLC-LINAC system due to its widespread use and versatility in clinical settings.

1.5.3 Tomotherapy

Tomotherapy systems have an irradiation head that rapidly rotates around the patient, equipped with a single layer of binary blockers that can be activated and deactivated almost instantaneously [23]. The tomotherapy machines follow a helical path [19], rotating around the patient while simultaneously moving along their body.

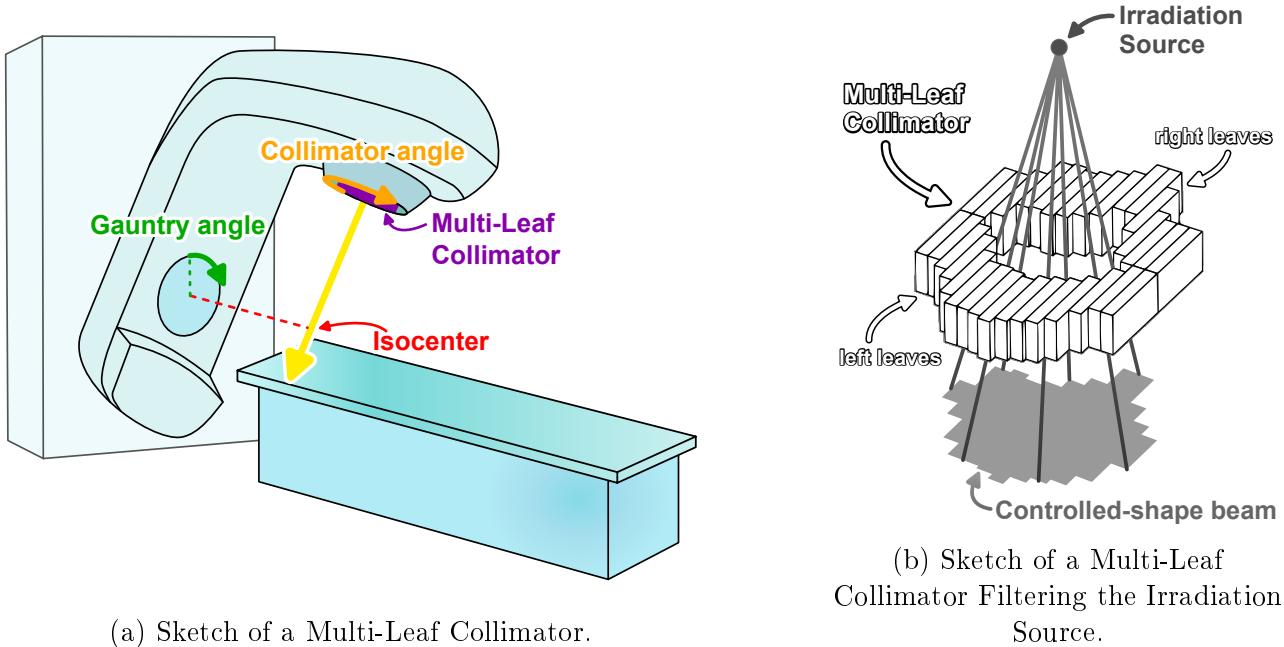


Figure 1.4: MLC-LINAC Machines Irradiation Filtering System.

1.5.4 CyberKnife

CyberKnife systems are another non-invasive alternative to conventional MLC-LINAC radiotherapy machines with higher flexibility [20]. These CyberKnife machines have the irradiation head mounted on a robotic arm, which allows a vast array of motions around the patient. This flexibility enables the delivery of even more complex-shaped doses. CyberKnife technology is particularly beneficial for treating unusual tumors in challenging or sensitive body areas.

1.5.5 Brachytherapy

Brachytherapy involves the placement of a radioactive source directly inside the body of the patient [8]. This technique allows for delivering localized high-dose radiation. Although brachytherapy involves an invasive procedure, it significantly minimizes radiation exposure to surrounding healthy tissues. The localized character of brachytherapy makes it a good treatment option for some types of cancer.

1.6 Irradiations techniques

This section describes the main irradiation techniques that can be used with MLC-LINAC machines. The techniques have evolved over the years of MLC usage. Better irradiation techniques improve tumor targeting while keeping exposure of healthy tissues to a minimum.

1.6.1 3-Dimensional Conformal Radiotherapy

Three-Dimensional Conformal Radiotherapy (3D CRT) shapes radiation beams to closely fit the contours of the tumor. The MLC leaves are positioned to match the tumor's contour projection on a plane perpendicular to the radiation rays, typically using three angles. Such shaping of the beams can be done with mold (which is single-use) or with an MLC. Although 3D CRT targets the Principal Target Volume (PTV) more than Organs At Risk (OARs), modern techniques provide superior sparing of healthy tissues. Consequently, advanced and less naive methods have largely supplanted 3D CRT in contemporary clinical practice.

1.6.2 Intensity Modulated RadioTherapy

Intensity Modulated RadioTherapy (IMRT) represents a significant advancement over 3D CRT by taking better advantage of the MLC capabilities. Instead of delivering radiation with uniform intensity from each angle, IMRT dynamically adjusts the beam intensity to improve patient outcomes [24].

Number of Beams The choice of the number of beams in IMRT is a balance between treatment complexity and effectiveness. Using many beams can evenly spread the unwanted dose across all organs, but adds complexity to treatment planning and prolongs the delivery time, which can increase patient movement and reduce dose precision. Conversely, fewer beams simplify planning and shorten treatment time but may result in less optimal dose distribution. Research indicates that 50 beams are needed for "nearly optimal IMRT" [13]. Beams at exactly 180 degrees from each other tend to have (very) similar influence on the dose distribution on the patient. Therefore, dosimetrists tend to choose an odd number of equispaced beams. In practice, the number of beams used is below 25.

1.6.3 Volumetric Modulated ArcTherapy

Volumetric Modulated Arc Therapy (VMAT) enhances IMRT by allowing the MLC LINAC head to rotate while delivering radiation. Unlike IMRT, which stops the head at specific positions around the patient, VMAT continuously irradiates while rotating. This technique can better distribute the unwanted dose and reduces the irradiation time [14].

However, the mechanical constraints of the machine complicate the optimization problem for VMAT compared to IMRT, making the optimization more computationally intensive. Studies have demonstrated that, IMRT with a Sliding Window and more than 7 angles can achieve equally effective dose distribution [6] [27]. While demonstrated with IMRT Sliding Window, the techniques developed in this manuscript apply to VMAT, given sufficient computational resources.

1.7 Dosimetry steps

Dosimetry aims to design a treatment plan (i.e., machine instructions) that delivers the best possible dose for the patient. The "best" dose is difficult to define, so doctors formulate high-level clinical dose requirements. These requirements are abstract, so transitioning to machine instructions requires a series of sub-steps. For Intensity-Modulated Radiation Therapy (IMRT), three main steps are typically followed: Beam Orientation Optimization (BOO), Fluence Map Optimization (FMO), and Leaf Sequencing (LS).

1.7.1 Beams Orientation Optimization

Beam Orientation Optimization (BOO) is the initial dosimetry step. This step determines the optimal number of radiation beams and their respective angles. The beams' orientation significantly impacts the dose distribution within the patient: beams close to each other tend to have similar effects on the body. In contrast, far-apart beams tend to create doses impacting different tissues in the body. There is one exception to this rule of thumbs: Beams exactly 180° from each other can have a similar biological effect because rays will follow the same line, just entering the body from opposite directions. Despite its importance, the practical benefits of BOO are questionable. Research [28] suggests that an extensive BOO process offers only slight improvement over more straightforward strategies, like using equispaced beam angles. When using equispaced beams, it's common to use an odd number of beams to avoid beams at exactly 180° having the same effect. Employing an odd number of beams is standard practice when utilizing equispaced beam arrangements. This approach avoids beams positioned at precisely 180° from each other, with similar clinical effects (as mentioned before). Therefore, this manuscript will assume the use of an odd number of equispaced beams and no further BOO.

1.7.2 Fluence Map Optimization

Fluence Map Optimization (FMO) is the critical step in the IMRT planning process. FMO aims to create fluence maps, i.e., a two-dimensional radiation intensity distribution on each beam's cross-sectional area. The fluence maps should be optimized to shape the dose distribution according to the treatment plan's objectives. At this stage, the physical constraints of the MLC still need to be considered; the primary focus is on achieving the desired dose distribution within the patient. The output of FMO is a set of idealized fluence maps for each beam.

1.7.3 Leaf Sequencing

Leaf Sequencing (LS) determines the specific positions and movements of the MLC leaves. The objective is to ensure that the delivered fluence map closely approximates the ideal fluence map generated during the Fluence Map Optimization (FMO) step. This approximation must be attained while considering the physical limitations of the treatment machine, such as irradiation

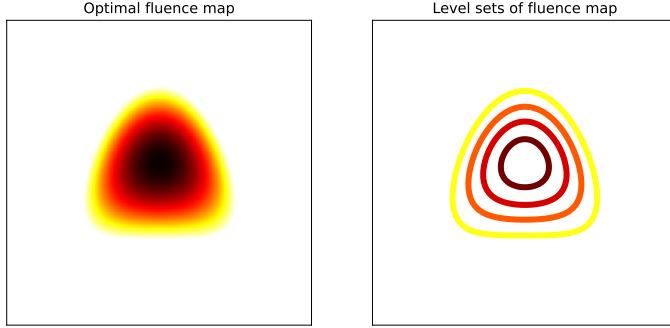


Figure 1.5: Example of a fluence map discretization.

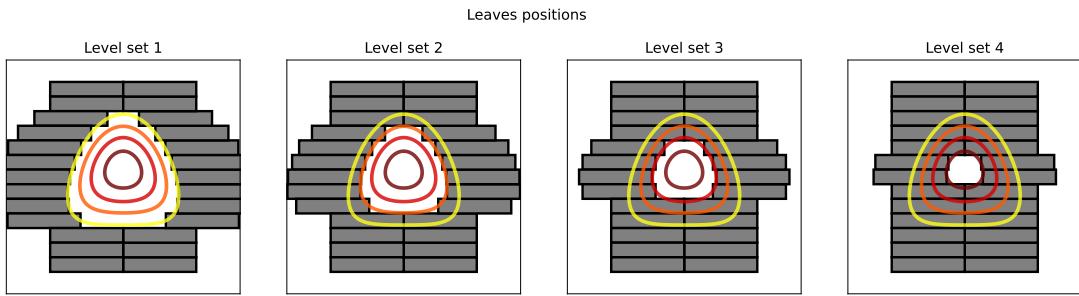


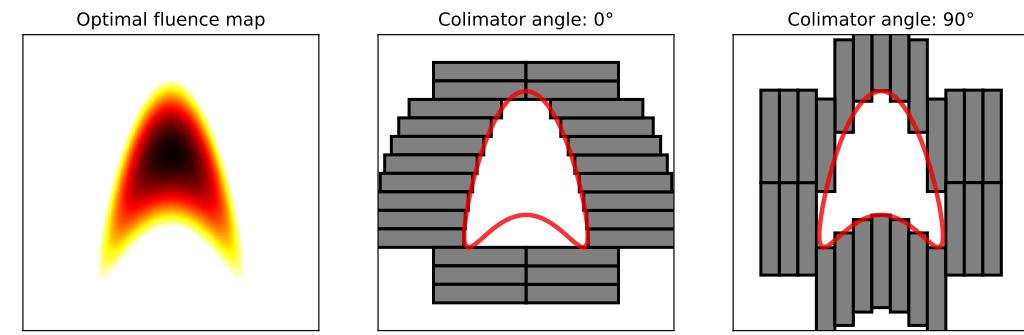
Figure 1.6: Example of level set matching with leaves.

power, leaf speed, or collimator speed, along with a soft constraint on the total treatment duration.

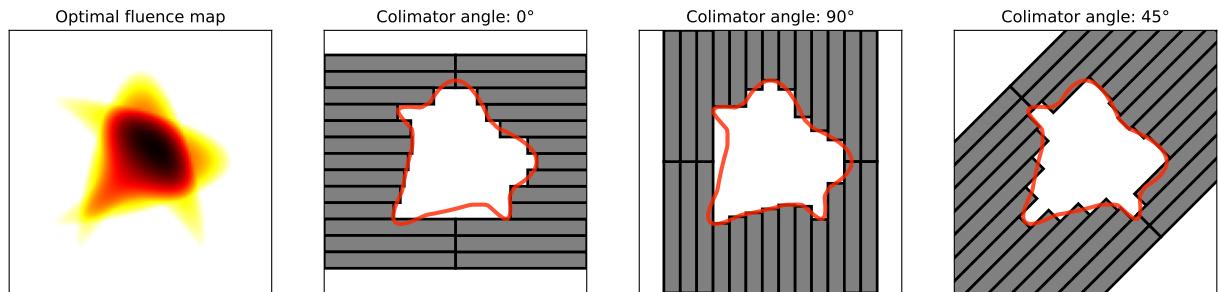
Step and Shoot The "Step and Shoot" technique in IMRT involves sequentially moving the MLC leaves to different positions to deliver varying radiation intensities. This technique for leaf sequencing is relatively simple computationally.

The fluence maps are divided into discrete levels (figure 1.5). Then, the MLC leaves are positioned so that the open area of the irradiation head matches the level set (figure 1.6). Note that convex level sets can all be matched with the MLC leaves; if the level set is concave, changing the collimator angle may allow the leaves to match the level set shape (figures 1.7a, 1.7b, 1.7c). Each level set is delivered as a static beam in sequence. As the level sets are refined, the irradiation time increases Dosimetrists must set a tradeoff between achieving greater accuracy and maintaining an efficient treatment time.

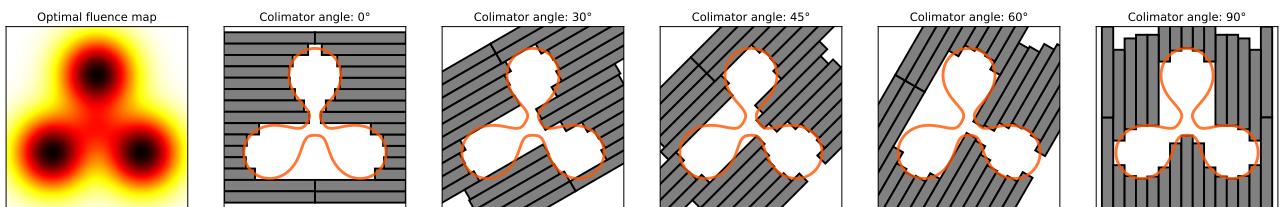
Sliding Window The "Sliding Window" technique employs a continuous sweep motion of the MLC leaves. This approach enables the delivery of any continuous, positively defined fluence within the irradiation window of the MLC-LINAC. In contrast with step and shoot, a sliding window is more computationally intensive: Finding the appropriate leaf motions requires solving a linear programming problem for each pair of leaves (sometimes called "Inverse Sliding



(a) Example of a concave level set matched with leaves.



(b) Example of a more complex concave level set matched with leaves.



(c) Example of a concave level set impossible to match with leaves.

Figure 1.7: MLC leaves can not always be set to shape level sets of fluence functions.

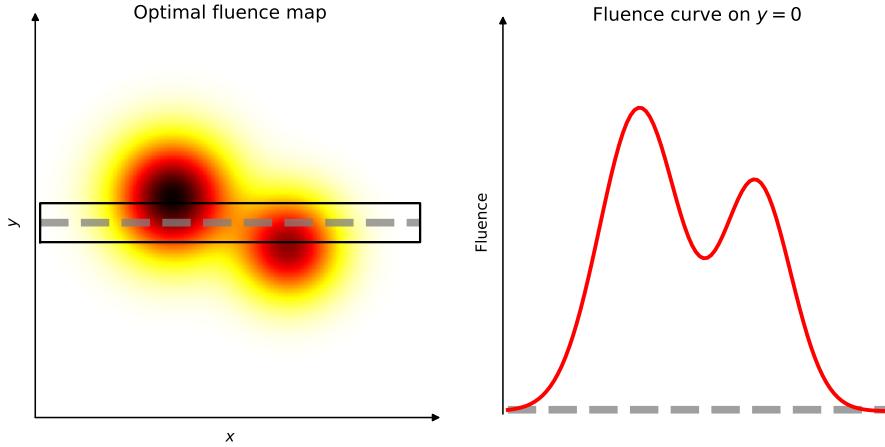


Figure 1.8: Example of a fluence map segmentation along a leaf pair axis.

Window Algorithm").

The fluence is segmented in a one-dimensional fluence curve along each leaf pair axis (see figure 1.8). Suppose the motion of the leaves is from left to right: The difference between the time the right and left leaves pass by a point determines the amount of irradiation delivered at that point. The greater the time difference, the more rays will be sent from that point (in figure 1.9a and 1.9b, the time laps between left and right leaves passing a point is proportional to the fluence delivered at that point). One needs to carefully move the opening (right) and closing (left) leaves to deliver the correct amount of rays at each point of the fluence map. Solving a linear programming problem allows a leaf pair to deliver any fluence within arbitrary approximation in a reasonable amount of time (figure 1.9). A playground to calculate the leaf's motion for an arbitrary fluence is available here: <https://mics-lab.github.io/PresentationJuin2023PRFD/demo>.

The sliding window technique is used most of the time, as delivery time is much (about twice) faster [26]. This manuscript assumes the use of this technique, focusing on optimizing the fluence distribution.

1.7.4 (Optional) Direct Aperture Optimization

Direct Aperture Optimization is mainly used in VMAT and occasionally employed to enhance IMRT plans. Unlike traditional approaches, which separate fluence map optimization from leaf sequencing, DAO directly optimizes the motion of the MLC leaves.

In VMAT, applying conventional leaf sequencing to any arbitrary fluence map is not feasible. Therefore, DAO is essential, as it is the only optimization method capable of generating a VMAT treatment plan.

When applied to IMRT, DAO can refine the treatment plan by directly adjusting the aperture

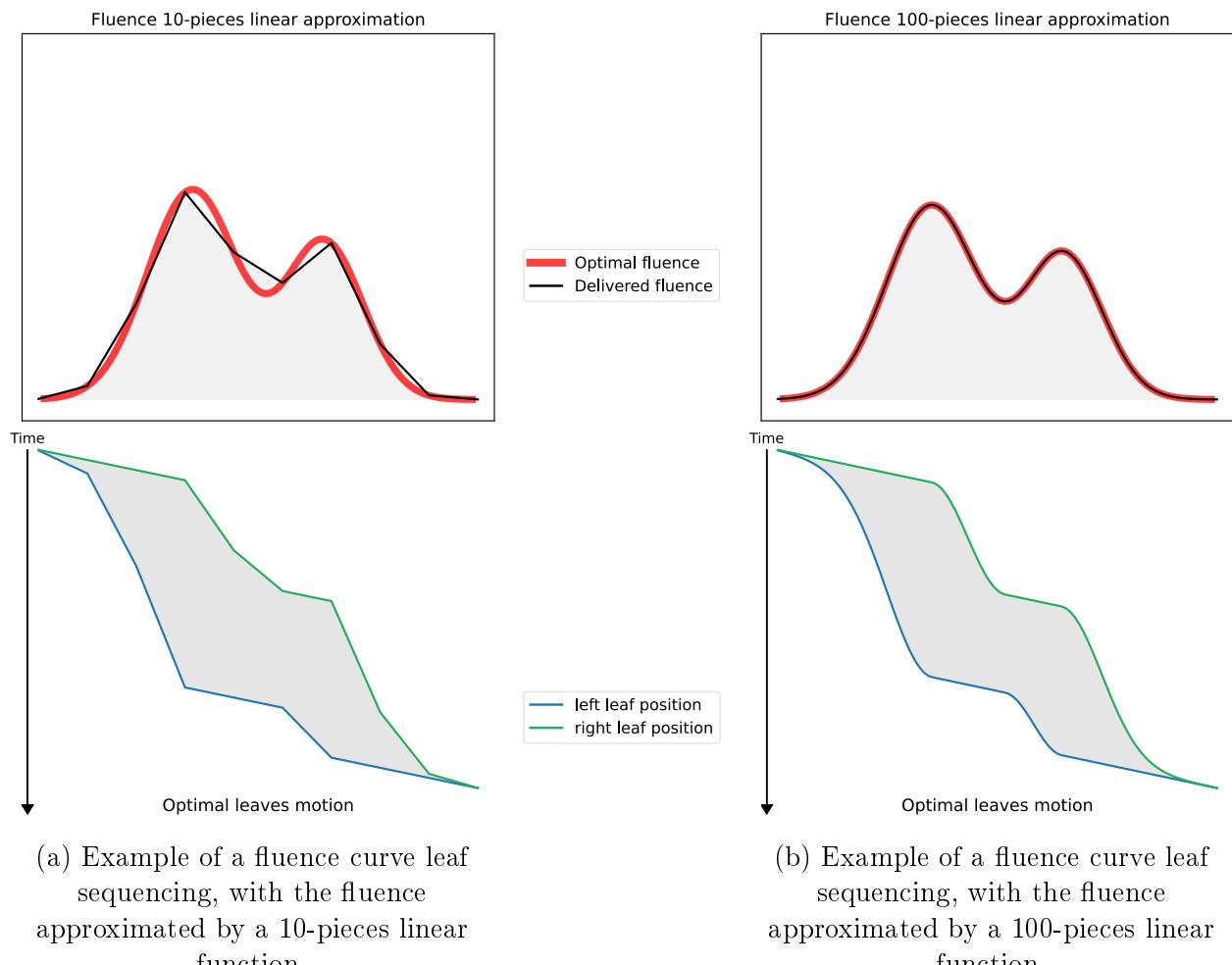


Figure 1.9: Fluence curve can be approximated with arbitrary error.

shapes to better align with the desired dose distribution while accounting for the physical constraints of the treatment machine. However, as this manuscript is not focused on leaf sequencing, it assumes that no additional DAO is applied following conventional leaf sequencing.

1.8 Simulation

Throughout the dosimetry process, several approximations are employed. First, the assumption is that each bixel (beam pixel) operates independently. This approximation fails to account for interactions between adjacent bixels. Additionally, during FMO, ideal fluence maps are generated without considering the physical limitations of the treatment machine, such as the width of the multi-leaf collimator (MLC) leaves (often 5mm). Furthermore, the effects of beam penumbra and the scattering of radiation within the patient's body are often simplified or neglected in the FMO. Given these approximations, re-simulation of the treatment plan is critical to verify that the machine instructions deliver a dose distribution closely aligned with the expected outcomes.

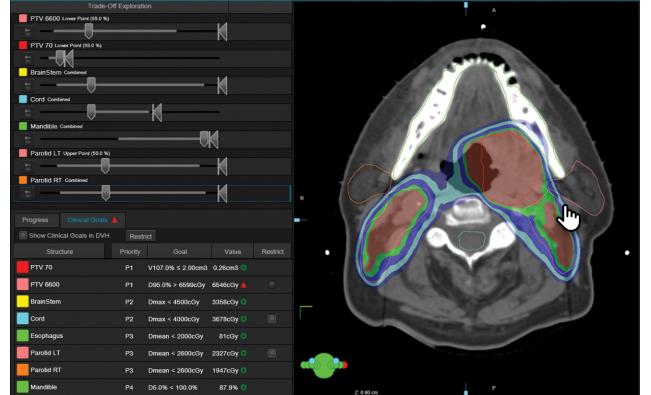
1.9 Treatment Planning Systems

Treatment Planning Systems (TPS) are the crucial tools that calculate the precise machine (MLC) motions according to the dosimetrists priorities and the irradiation technique chosen.

1.9.1 Manufacturer

Eclipse™ (Varian)

Eclipse™ [36], developed by Varian, is one of the most widely used TPS globally. It supports VMAT with one or multiple arcs, and IMRT with any number of beams. Eclipse™ integrates with Varian's suite of treatment machines, and integrates an automatic contouring tool [35].



Advertisement screenshot of Eclipse™ (Varian's TPS).

ONE® | Planning (Elekta)

ONE® | Planning [11] is Elekta's TPS, and is also widely used, supporting IMRT and VMAT. It is renowned for its speed with high-precision dose calculation using the Monte Carlo method.



Advertisement screenshot of
ONE® | Planning (Elekta's TPS).

Precision® (Accuray)

Developed by Accuray, Precision® [3] is the dedicated TPS for CyberKnife and TomoTherapy systems.

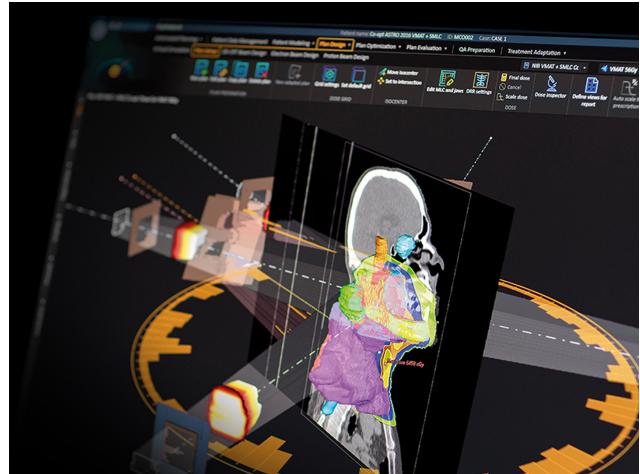


Advertisement screenshot of
Precision® (Accuray's TPS).

1.9.2 Non-manufacturer

RayStation (RaySearch)

RayStation [22], developed by RaySearch Laboratories, is a TPS known for its advanced optimization algorithms. Unlike manufacturer-specific systems, RayStation can output plans for a wide range of linear accelerators and imaging devices. It offers robust support for various treatment techniques, including VMAT, IMRT, 3D-CRT, Cyberknife, and TomoTherapy.



Advertisement screenshot of
RayStation (RaySearch's TPS).

matRad (German Cancer Research Center - DKFZ)

matRad [10] is an open-source TPS developed by the German Cancer Research Center (DKFZ) for research and education. While not intended for clinical use, matRad offers a flexible platform for testing and developing new treatment-planning algorithms.



AutoPlan (TheraPanacea - Unpublished)

AutoPlan is the upcoming TPS from TheraPanacea, designed to incorporate artificial intelligence and machine learning into the treatment planning process.

Introduction

Abstract

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2.1 Context

Cancer; RT; optim to be done

2.2 Problematic

Manual optim is time consuming; need to automate

2.3 State of the Art

2.4 Unsolved problems

2.5 Contribution

Dosimetry Optimization

Abstract

Biological tissues are sensible to radiations in a non-linear manner [?], and slight variations in dose can have significant biological effects. Organs have differing sensibilities to radiation, which increases further the difficulty in formulating the goals to achieve when designing a radiation dose. Some organs can tolerate high cumulative doses if the radiation is well distributed. In contrast, others may withstand high doses at localized points ("hot spots") but cannot handle large doses overall. To address these differences, clinicians impose dose-volume histogram constraints in addition to the prescribed dose. Although the ideal objective is to minimize or eliminate radiation exposure to organs, achieving 0 Gy is impossible. The necessity of finding compromises drives the need for advanced optimization techniques to generate fluence maps that best satisfy the medical constraints. Therefore, various techniques can be used to calculate fluence maps (i.e., performing the critical fluence map optimization step). In this chapter, we explore some fluence map optimization techniques.

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3.1 Discretization

The optimization process starts with transforming the continuous nature of both the radiation field and the human body into discrete elements. This transformation enables computation with modern computers.

3.1.1 Fluence Map Discretization: Bixels

Fluence maps are broken down into discrete elements called "bixels" (**b**eam **e**lements). Bixels represent small and independent beams of radiation.

The width of each bixel is constrained by the width of the multi-leaf collimator leaves. Modern multi-leaf collimator systems typically have a leaf width of 0.5 cm.

The height of a bixel can be selected arbitrarily, as the leaf can move continuously. Nevertheless, square bixels (akin to image pixels) are commonly used and will be employed throughout this manuscript.

Bixels whose beams do not affect the planning target volume are typically excluded from calculations to improve computational efficiency. Activating these bixels could only degrade dose quality by increasing the dose to organs at risk without benefiting the dose distribution within the planning target volume.

3.1.2 Human Body Discretization: Voxels

The human body of the patient is also divided into discrete elements, as it is a three-dimensional object; the elements are "voxels" (**v**olume **e**lements). Each voxel represents a small portion of tissue within the patient's body, and will determine the granularity of the dose computed.

The maximum resolution of the voxel grid is defined by the planning image, which is typically a CT scan. It is common practice to resample the planning image to reduce computational demands. In this manuscript, where new techniques are explored, we have opted to resample the voxel grid to a resolution of 5 mm, ensuring a balance between computational efficiency and accuracy.

Additionally, to further optimize the computational process, only voxels corresponding to the planning target volume (PTV) and organs at risk (OARs) are retained for calculations. This selective approach reduces unnecessary computation.

3.1.3 Dose-Influence Matrix

The Dose-Influence Matrix (or DI-Matrix) links the discretized fluence map (the bixels values) and the discretized dose distribution within the patient (the dose on each voxel). This matrix defines how the radiation from each individual bixel influences the dose delivered to every voxel in the patient's body.

We start by converting the 2D fluence map, composed of individual bixel values, into a column vector b . Similarly, we represent dose distribution in the patient's 3D space as a vector d , where each entry corresponds to the dose in a specific voxel. The DI-Matrix L governs the relationship between these vectors b and d via the matrix-vector multiplication $d = Lb$. This mathematical operation computes the total dose at each voxel by summing the contributions from all active bixels (here, we assume that the effect of bixels is linear).

The DI-Matrix is constructed by simulating the radiation delivered by each individual bixel. For each bixel, the jaws of the multi-leaf collimator are virtually opened to allow only that specific beamlet to go through. A radiation transport model calculates the dose deposited in each voxel, considering the beam's spread and attenuation as it travels through the body. The resulting 3D dose deposition fills one column of the matrix L , corresponding to that bixel's influence on all voxels. Repeating this process for each bixel generates the entire DI-Matrix.

The accuracy of the dose calculation depends on the precision of the DI-Matrix. Simple models like pencil beam approximations, which assume a linear trajectory with minimal scattering, are considered too coarse. In contrast, more advanced simulations, such as Monte Carlo methods, provide a detailed and accurate dose calculation, although at a higher computational cost. In this manuscript, we employ collapsed cone convolution techniques, which balance efficiency and accuracy.

3.2 Naive Optimization Method

A natural starting point in dose optimization is to attempt to directly achieve the delivery of a uniform dose, equal to the prescription, on all voxels within the PTV, and no dose elsewhere. We can attempt to find the bixels values delivering this dose by solving a least squares problem. We attempt to find the fluence map b that minimizes the difference between the actual dose d and the target dose d_{target} , which is set to the prescribed dose within the PTV.

Formally, the optimization problem can be stated as:

$$\min_b \|d_{\text{target}} - Lb\|^2$$

where d_{target} is the target dose vector, defined as follow for a prescription of $p\text{Gy}$:

$$d_{\text{target}} = p \cdot \mathbf{1}_{\text{PTV}}$$

Here, $\mathbf{1}_{\text{PTV}}$ is the indicator vector for PTV that is equal to 1 for voxels within the PTV and 0 elsewhere.

To solve this problem, we perform a least squares minimization to find the optimal fluence map b , where the matrix-vector multiplication Lb yields the dose distribution d across the entire patient volume.

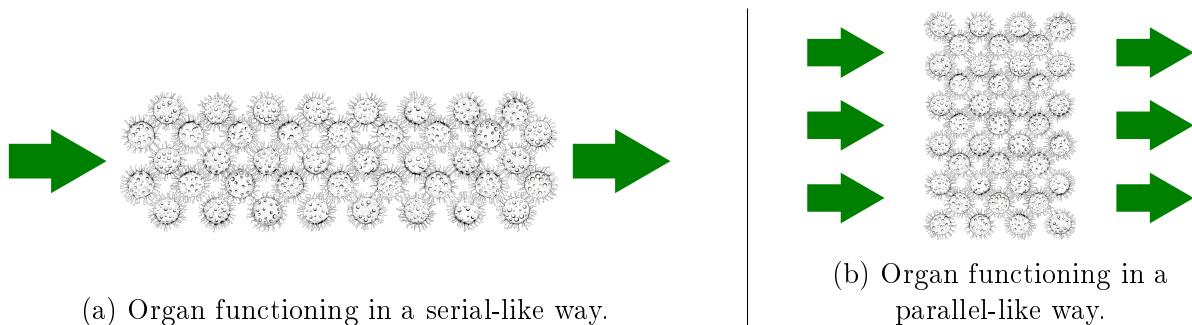


Figure 3.1: Organs functioning types.

However, this method is often inadequate in practice, as it attempts to solve the system based solely on the prescribed dose within the PTV, while neglecting any constraints on doses to the organs at risk (OARs). Since no constraints are imposed on the OAR doses, this naive optimization can result in high doses to critical structures, leading to unacceptable treatment plans. As a result, more sophisticated optimization methods that incorporate dose constraints on OARs and account for dose-volume constraints are necessary to achieve clinically viable treatment plans.

3.3 Constraints and Importance Factors

In order to obtain clinically acceptable doses, we need to incorporate the clinical aims in the optimization.

3.3.1 Constraints Formulation

Different organs exhibit varying sensitivities to radiation, which influence their dose tolerance limits [?] [?]. Normal tissues are categorized as serial, parallel, or mixed, based on the functional organization of their sub-units. This classification determines the appropriate absorbed dose limits for normal tissues.

Serial organs (figure 3.1a), such as the spinal cord or esophagus, are characterized by a functional dependence on the integrity of every sub-unit. Damage to even a tiny region in these tissues can result in the loss of the organ's overall function. In contrast, parallel organs (figure 3.1b), such as the lung or liver, possess a reserve capacity where damage to a portion of the tissue does not necessarily impair overall function, as long as a critical volume remains intact.

For parallel-like structures, dose–volume reporting specifying V_D , the volume receiving at least the absorbed dose D , is commonly used, with D adapted to the specific organ. For instance, [?] demonstrated a correlation between the incidence and severity of lung pneumonitis and $V_{20\text{ Gy}}$, the volume of the lung receiving more than 20 Gy. Additionally, in parallel-like structures, the median absorbed dose ($D_{50\%}$), representing the dose received by at least 50% of the volume,

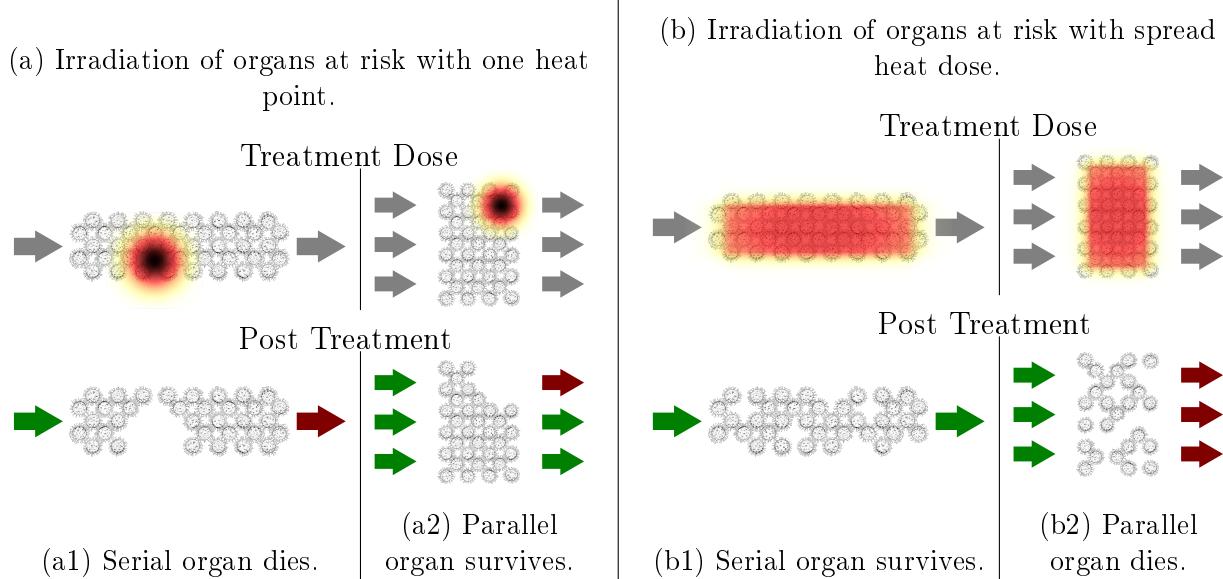


Figure 3.2: Irradiation type survival of organs serial-like and parallel-like.

provides a valuable measure of the total dose delivered to the organ at risk.

For serial-like organs, it is recommended to report $D_{2\%}$ as the maximum absorbed dose, as $D_{0\%}$ is subject to noise.

Finally, for organs with a mixed parallel-serial structure, it is advised to report $D_{50\%}$, $D_{2\%}$, and V_D , with D selected based on the threshold beyond which there is a significant risk of serious complications.

3.3.2 Optimization Problem

Ideal

Practical

3.4 Dose Mimicking

3.5 Optimization Algorithm Review for Dosimetry

3.5.1 Introduction

3.5.2 Methods

3.5.3 Data

3.5.4 Objective function

3.5.5 Open-source Optimizers

(Stochastic) Gradient Descent

Conjugate Gradient

Newton

SLSQP

RMSprop

BFGS-based

Pure BFGS

L-BFGS

Adam-based

Pure Adam

RAdam

NAdam

AdamDelta

Adamax

Rprop

Other optimizers variations

3.5.6 Results

Newton's method

Best Algorithms

LBFGS vs BFGS

3.5.7 Discussion

Doses Relationship

Abstract

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4.1 Distance Between Doses

4.1.1 Introduction

Pre-dose-optimization

Radiotherapy doses

Dose Optimization

Dose-Volume Histograms

Dose Evaluation

Stop Criterion

4.1.2 Method

4.1.2.1 Naive Doses Comparison

4.1.2.2 Doses Samples

4.1.2.3 Distances Between Doses

Comparing Doses Voxel-wise

Comparing Dose Volume Histogram Curves

Discrete DVH Approximation

Fréchet Distance

Hausdorff Distance

Wasserstein Distance

Kolmogorov-Smirnov Distance

Total Variation Distance

4.1.3 Results

4.1.3.1 Dose Distances Comparison

4.1.3.2 Link between Total Variation and Wasserstein

4.1.3.3 Bounding of Total Variation and Voxel Distance

Definitions

Sorting lists

Proof Outline

Conclusion

4.1.3.4 Distances Distribution Comparison

Comparing Total Variation and Voxel-wise

Comparing Total Variation and Wasserstein

4.1.4 Discussion

4.2 Network of Doses

4.2.1 Introduction

4.2.2 Radiotherapy

Dose Optimization Inputs

Dose Simulation

Dose-Volume Histograms

Evaluation of Doses

4.2.3 Methods

4.2.3.1 Radiotherapy Dose Optimization

Simulation & Approximation

Physical Limitations

Mathematical Objective Function

MLC Fluence Discretization

Bixels Smoothness

Convexity

Multiple Plans Generation

Optimizer

4.2.3.2 Data

(Phantom) Patient

Dose normalization

4.2.3.3 Dose Clustering Techniques

Dose Distance

Community Detection

Evaluating Communities Split

4.2.4 Results

4.2.4.1 Doses Network

Graph Plots

DVH Plot

4.2.4.2 Dose Clustering Evaluation

4.2.5 Discussion

4.2.6 Conclusion

**4.3 A Novel Framework for Multi-Objective Optimization
and Robust Plan Selection Using Graph Theory (ESTRO 2024)**

Classical Dosimetry Automation

Abstract

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5.1 Radiotherapy Dose Optimization via Clinical Knowledge Based Reinforcement Learning (AIME 2024)

Abstract

5.1.1 Introduction

5.1.2 Materials and Methods

5.1.2.1 Reinforcement Learning Reward

5.1.2.2 Architecture

5.1.2.3 Avoiding Off-Distribution

5.1.2.4 Quantitative Results

5.1.2.5 Qualitative Results

5.1.3 Discussion

5.1.4 Conclusion

Appendix

Synthetic phantom patients

Clinical dose

Optimization

5.2 Clinically Dependent Fully Automatic Treatment Planning System (ASTRO 2024)

5.2.1 Purpose / Objective

5.2.2 Materials/Methods

5.2.3 Results

5.2.4 Conclusion

Dosimetry Automation via Mimicking

Abstract

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6.1 Dose-Volume Histograms Guided Deep Dose (SFPM 2024)

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6.2 Attention Mechanism on Dose-Volume Histograms for Deep Dose Predictions (SFRO 2024)

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