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Méthodes pour l'automatisation de la dosimetrie pour les traitements radiothérapiques.

Methods for automatization of the dosimetry for radiotherapy treatments.

Thèse de doctorat de l'université Paris-Saclay

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Titre: Méthodes pour l'automatisation de la dosimetrie pour les traitements radiothérapiques.

Mots clés: Mathématiques, Intelligence Artificielle, Radiothérapie

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Title: Methods for automatization of the dosimetry for radiotherapy treatments.

Keywords: Mathematics, Artificial Intelligence, Radiotherapy

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Acknowledgments

A PhD is more than just hard work; it thrives on mentorship, collaboration, and unwavering support. [...]

List of Contributions

- Teaching: *Consistency and Reproducibility of Grades in Higher Education: A Case Study in Deep Learning replace icon*

- 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 (full paper coming soon)
- 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

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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 [?]. 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 [?]. 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., changes in gene expression (that are 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. This transformation is caused by mutations in the DNA.

Promotion The second phase is promotion or "tumorigenesis". During this phase, the cancer cell grows and divides uncontrollably to form a cluster of cells called a tumor. This growth is promoted by changes in gene expression and other factors [?]. 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 [?].

Cancer stages Cancer is classified into stages [?].

- Stage 0: 'in situ neoplasm'; it means a group of abnormal cells in an area of the body. The cells may develop into cancer at some time 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 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 is also called secondary or metastatic cancer.

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

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

N stands for the number of lymph Nodes affected; It can be between 0 and 3. 0 means that there are no lymph nodes containing cancer cells; 3 means many lymph nodes containing 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 focus 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 main risk factor for prostate cancer is age. Thus, it touches all social population evenly and is un-avoidable.

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.

Surgery Surgery is the most effective cancer treatment. 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 that 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, hence having 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.

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, it can be expensive.

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. Radioation 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 a little bit of healthy cells. Depending on the patient's response, it may cause side effects.

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 made by the body 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 that have been 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, as well as in (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 a stochastic processes. Several interactions are possible for photons. Some random interactions generate secondary ionizing particles. It is these secondary particles that deposit the energy in the medium.

1.2.3 Photoelectric effect

The photoelectric effect 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 is called a photoelectron. The photoelectron can ionize other atoms, leading to the creation of secondary electrons. The photoelectric effect is the dominant interaction for low-energy photons.

1.2.4 Compton scattering

Compton scattering is the process by which an atom scatters a photon, and an electron is ejected from the atom. The photon is scattered at an angle, and part of its energy is transferred to the electron. The scattered photon is called a Compton electron. The Compton electron can ionize other atoms, leading to the creation of secondary electrons. Compton scattering is the dominant interaction for medium-energy photons.

1.2.5 Pair production

Pair production is the process by which 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 electron and positron can ionize other atoms, leading to the creation of secondary electrons. Pair production is the dominant interaction for high-energy photons.

1.2.6 Photon attenuation

The photon beam will be attenuated as it passes through the medium, and the intensity of the beam 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 medium traversed (Lambert-Beer law) [**?**]:

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

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 in cells. This 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), DNA crosslinks, and DNA-protein crosslinks. Indirectly, radiation generates reactive oxygen species (ROS) and reactive nitrogen species (RNS), which further contribute 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 [**?**].

1.3.2 Radiation affects the plasma membrane

Radiation significantly impacts the biological properties of the plasma membrane by affecting its composition, influencing its structural integrity, and functional capabilities. Exposure to radiation 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 cause corrosive damage, those damages to the membrane can initiates signaling events that are important for the apoptotic response [**?**]. 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. 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, which can impair protein synthesis and compromise cellular homeostasis. Mitochondria, the powerhouses of the cell, also exhibit altered behavior following radiation exposure, including disruptions in energy production and initiation of apoptotic pathways. Furthermore, lysosomes, which are essential for cellular waste processing and recycling, suffer damage upon irradiation, potentially leading to the accumulation of cellular debris and impaired cell function. These collective effects highlight the broad and profound impact of radiation on cellular organelle performance [**?**].

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 key 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 the invasion and metastasis potential of tumor cells, either by directly impairing their motility or by 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 on T cells, thus boosting the immune system's response against cancer cells. The combination of radiation and anti-CTLA-4 immunotherapy has shown promising results, as radiation-induced tumor cell death releases antigens that can further stimulate the immune system. This synergy can lead to improved tumor control and potentially better clinical outcomes compared to 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 work by blocking 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.

TLR-Mediated Immunologic Effects of Radiation Therapy Radiation therapy can also exert immunologic effects through Toll-like receptors (TLRs), which are a class of proteins involved in pathogen recognition and activation of innate immunity. Radiation can activate TLRs on immune cells, leading to the production of 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.

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 involved in the radiotherapy process, 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 choos 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 progresses of artificial intelligence on segmentations 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 that specifies the radiation dose distribution within the patient. Advanced software is used to calculate the optimal arrangement of radiation beams to achieve the desired dose while minimizing exposure to healthy tissues. This thesis registers new advances on 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

1.5.1 Molds

1.5.2 MLC-LINAC

1.5.3 Tomotherapy

1.5.4 CyberKnife

1.5.5 Brachytherapy

1.6 Irradiations techniques

1.6.1 3D-RT

1.6.2 IMRT

Step and Shoot

Sliding Window

1.6.3 VMAT

1.7 Treatment Planning Systems

1.7.1 Manufacturer

Eclipse (Varian)

ONE | Planning (Elekta)

Precision (Accuray)

1.7.2 Non-manufacturer

RayStation (RaySearch)

matRad (German Cancer Research Center - DKFZ)

AutoPlan (TheraPanacea - coming soon)

1.8 Dosimetry steps

Challenges

1.8.1 BOO

1.8.2 FMO

1.8.3 LF

1.9 Simulation

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

3.1 Optim engine: classic and dose mimicking

3.2 relation between optim doses (distance and network)

3.3 ESTRO (novel approach with graph theory)

Automation: Classical Approach

Abstract

4.1 RL + classic optim algo (AIME / ASTRO)

Automation: Deep Dose

Abstract

5.1 DVH guided deep dose + dose mimicking algo (SFPM / SFRO)

Conclusion

Perspectives