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Heuristics for direct aperture optimization in Intensity modulated radiotherapy treatment: a systematic literature review

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Report presented by Vinicius Jameli to the Institute of Mathematics, Statistics and Scientific Computing as part of the requirements for obtaining credits in the Supervised Project course, under the guidance of Prof. Aurelio Ribeiro Leite de Oliveira.

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Abstract

Teletherapy is a cancer treatment that uses ionising radiation to extinguish tumour cells. These ionising particles are delivered via a linear accelerator, which rotates around the patient and distributes radiation at every feasible angle. The treatment's goal is to use the smallest dose required to eliminate cancerous tissue while sparing healthy organs. To accomplish this, the linear accelerator incorporates a tool called Multileaf Collimator (*MLC*), a set of moving blades that shapes the format of the radiation field to modulate the resultant intensity of each aperture, performing what is called Intensity Modulated Radiation Therapy (*IMRT*). Direct Aperture Optimisation (*DAO*) is an *IMRT* technique that optimises the *MLC* 's apertures and the opening time of each simultaneously. Showing promising results by requiring fewer *MLC* 's segments per angle than other approaches, *DAO* has been broadly used in the last 20 years. This piece of work aims to create a systematic literature review (*SLR*) of *DAO*; focusing on the heuristic methods involved when solving the optimisation problem; analysing studies published between 2000 to 2021, indexed in seven databases (*ACM*, *IEEE Xplore*, *PubMed*, *Science Direct*, *Springer*, *Scopus* and *Web of Science*). Since the project is not yet completed, it is presented a summary of radiotherapy planning and *DAO*, the embraced *SLR* methodology, progress made up to this point, and the authors' current endeavours.

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1 Introduction

A global estimate showed that approximately 18 million new cases of cancer and 9.6 million cancer-related deaths occurred in the world in 2018 (Bray et al. [2018]). According to the National Institute of Cancer (*INCA*), Brazil will have approximately 625,000 new cases for each year of the 2020 to 2022 triennium.[4]

One of humanity's weapons to fight against this malady is the worldwide known cancer treatment called radiotherapy, which emerged from the discovery of the *X-Ray* in 1895, giving rise to the first radiotherapy book, printed in 1904 (Freund [1904]). It comprises the usage of ionizing radiation to extinguish the tumour by making small ruptures in the *DNA* inside tumour cells which prevents their multiplying and leads them to death (Abshire and Lang [2018]). In the external beam radiation therapy context, called teletherapy as well, ionizing particles are delivered by a linear accelerator, an instrument that rotates around the patient distributing a radiation dose at every feasible angle (Almeida [2012]).

Even with the freedom to choose angles, most types of teletherapy do not reach all parts of the body, which means they are not helpful in treating cancer that has spread through the patient. However, more than half of people with cancer are treated with radiation because of its versatility in being used either alone or in combination with other treatments. Nowadays, this procedure has been used to cure or shrink early-stage tumours, prevent tumour recurrence, treat symptoms caused by advanced cases, and treat cancer that has recurred.

But not all that glitters is gold. Radiation is well known to raise the risk of getting cancer, and this is one of the possible side effects that oncologists have to think about when they weigh the benefits and risks for each patient. These risks back in the emergence of teletherapy treatments were incredibly higher than that of contemporary ones.

Their major cause was that older treatment plans often either delivered too little radiation dose to the PTV (Planning Target Volume), too much radiation dose to the PRT (Planning risk volume) or both. Thus, what is at stake as regards treatment plans is the patient's quality of life against the probability of the eradication of their disease (Romeijn et al. [2006]).

A revolution started in the late 1990s, when a brand new type of treatment emerged: the $IMRT$ (Intensity Modulated Radiation Therapy); capable of creating non-uniform fluxes to improve dose distribution (Bortfeld [2012]).

In light of this sophistication, the treatments' planning phase began to draw more attention not just from physicians, medical physicists and radiologists, but also from engineers and mathematicians (Webb [2003]). The planning phase‘s major goal is to decide how the linear accelerator is supposed to deliver radiation at each angle to achieve an optimal dosage distribution. Not coincidentally, "optimal dose distribution" alludes to an optimization problem; which is, of course, what this subject is all about.

In clinical practice, some of the planning tools used by medical physicists are software made by the manufacturers of linear accelerators and the so called *dose delivery problem* is then solved by it, in order to propose a better treatment during the planning phase.

One possible approach to solve the dose delivery problem is Direct Aperture Optimization (DAO); an $IMRT$ technique that optimizes the MLC's apertures and the opening time of each simultaneously. Showing promising results by requiring fewer MLC's segments per angle than other approaches, DAO has been broadly used in the last 20 years. This piece of work aims to conduct, to the best of the authors' knowledge, the first systematic literature review (*SLR*) of DAO in twenty-two years of the topic's existence. Specifically, focusing on the heuristic methods involved when solving the optimization problem.

The selected studies to be revised were published between 2000 to 2021 and indexed in

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[4] Source: `https://www.inca.gov.br/estimativa/introducao`

seven databases (*ACM*, *IEEE Xplore*, *PubMed*, *Science Direct*, *Springer*, *Scopus* and *Web of Science*).

This report is structured as follows: the section 2 offers a background in radiotherapy planning, followed by the methodology used to formulate the systematic literature review in section 3. The section 4 states the current stage of the *SLR* development, and the last one, section 5, summarises what has been discussed.

2 Treatment planning scenario

2.1 Radiation therapy classification

It is surprisingly easy to mix up the different types of radiotherapy. The very first step into this topic is to understand which of them this research is about.

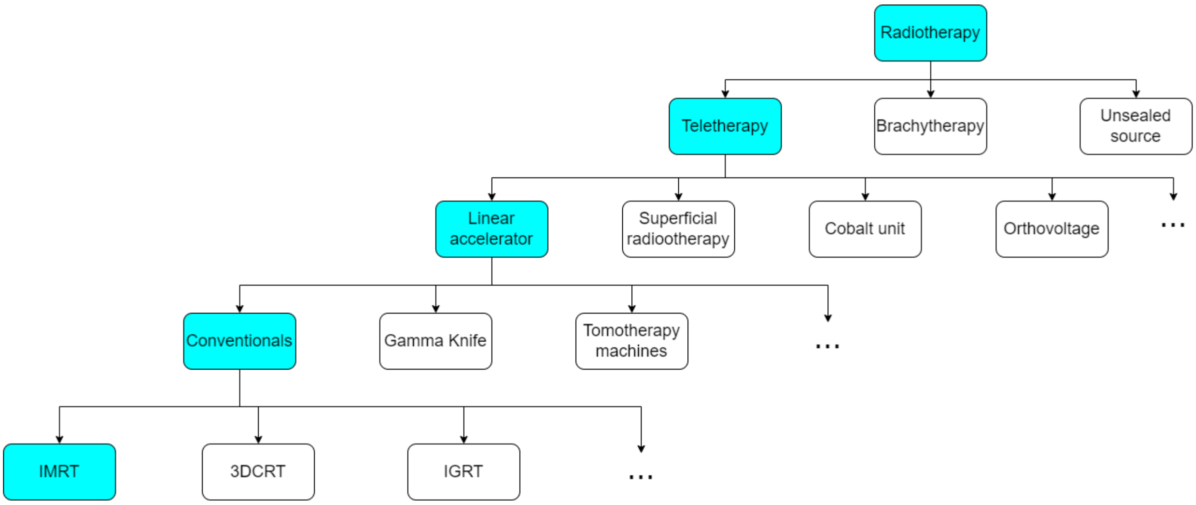


Figure 1: Tree diagram of radiation therapy classifications.

As highlighted in figure 1, this project is concerned with the teletherapy field, where radiation is generated and delivered from the outside of the patient (Almeida [2012]). An example of a different approach is brachytherapy, from the Greek “brachys”, meaning “short distance”, where the source of radiation is encapsulated and inserted in the patient at or near the tumour, temporarily or permanently (Guinot et al. [2017]). In contrast, the unsealed radiation therapy delivers radiation via an injection into the bloodstream, the use of body cavities, or by swallowing it (Volkert and Hoffman [1999]).

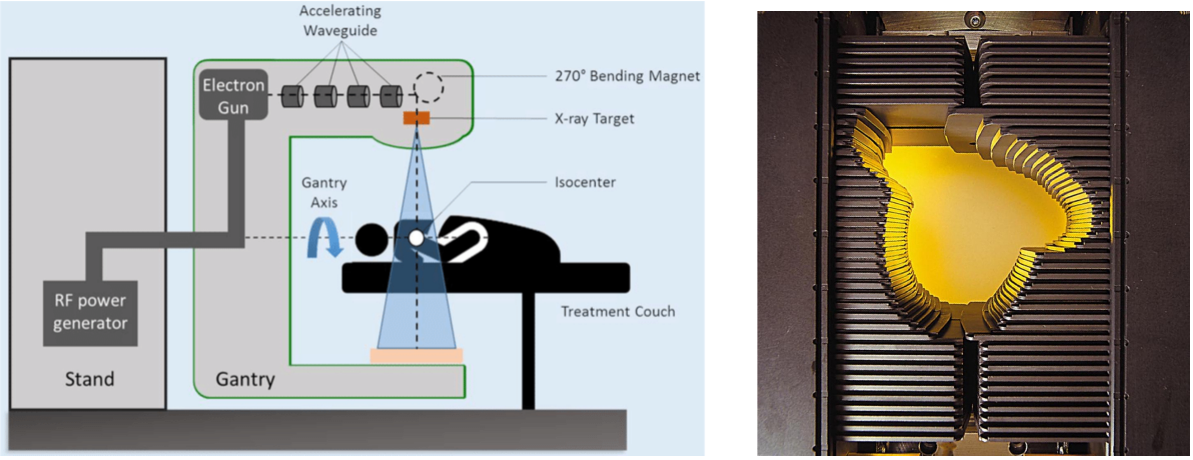
To perform better treatments then, many different machines used in teletherapy were created in the last decades. The one studied in this project, the most popular kind nowadays, is the linear accelerator. However, one can also find in older treatment stations some equipments for superficial radiation therapy that uses low energy *X-rays*, or those for cobalt therapy, which uses cobalt-60 isotopes, among other types of equipment.

Because of its versatility, a linear accelerator may have different shapes and sizes that consequently change its application. For instance, *Gamma Knife* is a very precise robot used in radio surgeries (Lindquist [1995]), and thomotherapy machines are very similar to *CT* scanners albeit with a built-in binary *MLC* (Mackie et al. [1999]). For the sake of the project, the most conventional type is supposed, represented in the next figure.

Finally, given the wide range of ways to deliver the radiation dose to the patient, which will be discussed later in the text, the model in question investigates the *IMRT* approach, as mentioned in the introduction.

2.2 Linear accelerator

The main equipment for most teletherapy treatments is the linear accelerator. Even though there are different brands on the market, its components common to all different types are represented in the schematic figure 2a[5], followed by a brief description.



(a) Components of a typical linear accelerator.

(b) Example of a large *MLC*.

Figure 2: Linear accelerator components and *MLC* example.

This is an isocentric tool; the gantry can make a complete turnaround on its axis, which allows the dose to be irradiated from any direction and to be intercepted at a fixed point in space, the isocenter. The treatment table, or treatment couch, where the patient gets partially immobilized, moves forwards and backwards, away from or towards the gantry, and rotates in the horizontal plane around its vertical axis.

Below the region called "X-ray Target" it is located the collimator, which collimates the beams, changing their format. Today, the most efficient one is the Multileaf Collimator (*MLC*), shown in the figure 2b[6]. Its leaves can move in static (step-and-shoot) or dynamic fashion, in order to establish an ideal field format on each static angle or on the gantry‘s arc of movement; more about it is discussed in section 2.5. As was mentioned earlier, a binary *MLC* can extend a blade completely or not extend it at all. On the other hand, a standard *MLC* can extend its blades for all along its length.

Essentially, *IMRT* is a radiotherapy technique that uses the *MLC* to create non-uniform radiation fluences, which are delivered to the patient from any position of the treatment beam, in order to improve dose distribution.

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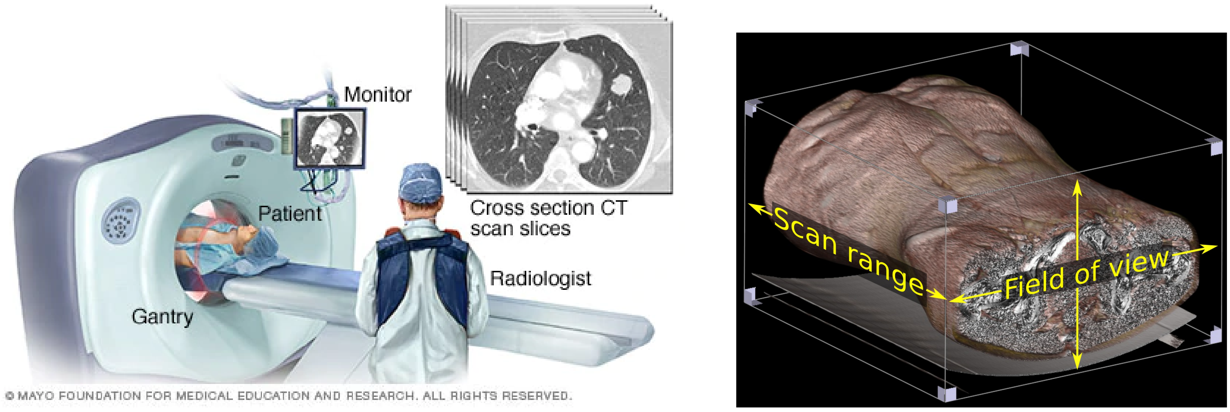
[5] Image taken from the article (Jumeau et al. [2020])

[6] Image taken from the article (Baatar et al. [2018])

2.3 Computational Tomography

Once a patient is diagnosed with cancer and referred for radiotherapy treatment, the oncologist commonly orders a tomography (or a *MRI*), also known as *CT* scan, of the treatment region, in order to prescribe the amount of ionizing radiation dose for each treatment region measured in gray (Gy), where gray is a unit of ionizing radiation dose in the SI. It is defined as the absorption of one joule of radiation energy per kilogram of matter (Bureau international des poids et measures et al. [1977]).

A tomography is nothing more than a collection of radiological images, known as slices, in one of the three possible patient planes; sagittal, coronal and transverse; [7] represented in figure 3a[8], which can later be computationally collected to build a three-dimensional structure of the treatment region, as shown in the figure 3b[9], allowing for a more precise visualization of the organs which enables doctors and medical physicists to make better decisions.



(a) Illustration of a tomography in execution.

(b) Three dimensional reconstruction of an abdomen and pelvis *CT* scan.

Figure 3: Tomography execution and *3D* reconstruction.

2.4 Treatment volumes

With the *CT* scan, oncologists make the delineation of the treatment volumes before prescribing any radiation dose. The classification of these structures is displayed in the figure 4[10], followed by their description.

- ***GTV***, or "Gross tumour Volume": tangible or visible volume of the disease.
- ***CTV***, or "Clinical Target Volume": volume of tissue that contains ***CTV*** or subclinical disease not grossly visible, but with a certain probability of occurrence considered relevant for treatment.
- ***ITV***, or "Internal Target Volume": defined as the ***CTV*** plus a margin that includes uncertainties in the size, shape and position of the ***CTV*** relative to anatomical landmarks (i.e., bladder filling, breathing movements, etc). This is called the inner margin.

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[7] The number of slices can vary as the *CT* scan machine changes.

[8] Image taken from the website: https://www.mayoclinic.org/tests-procedures/ct-scan/multimedia/ct-scan-slices/img-20008348

[9] Image taken from the article (Haggstrom [2014])

[10] Image taken from the book (Almeida [2012])

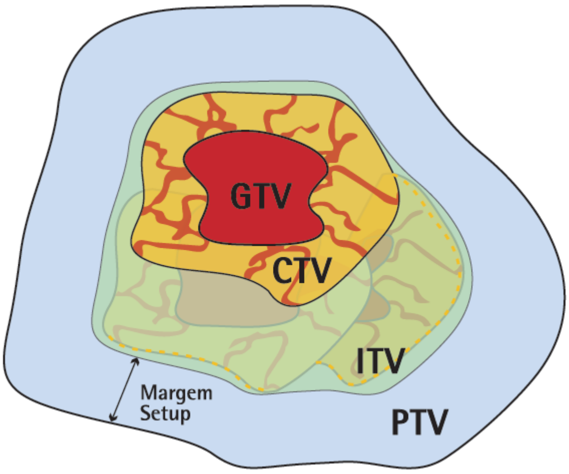

Figure 4: Treatment volumes classification.

- ***PTV***, or "Planning Target Volume": the dose distribution format that must ensure with a clinically acceptable probability that the entire ***CTV*** has received the prescribed dose, considering geometric uncertainties such as organ movement and patient positioning on the table.

- ***PRV***, or "Planning Risk Volume": similar to the previous one, refers to the dose distribution format that must ensure with clinically acceptable probability that all OAR's (Organ At Risk) receive less than the prescribed dose limit, considering the same uncertainties.

Beyond naming the structures, it is also important for an oncologist to separate organs by how they relate to radiation. The two main such categories are:

- *Rope organs*: consist of functional units acting independently of each other. Their functionality is only compromised if a relevant number of functional units is damaged, therefore, damage depends on the radiated volume. Examples: kidney, liver, lungs, parotid, etc.

- *Chain organs*: comprise a chain of functional units, which all must be preserved to ensure tissue functionality. As regards them, the irradiated volume is, theoretically, irrelevant and the damage will depend exclusively on the maximum local dose in the structure. Examples: spinal cord, kidney, liver, gastrointestinal tract, nerves, etc.

A more thorough discussion of rope and chain organs is found in (Withers et al. [1988]).

2.5 Planning

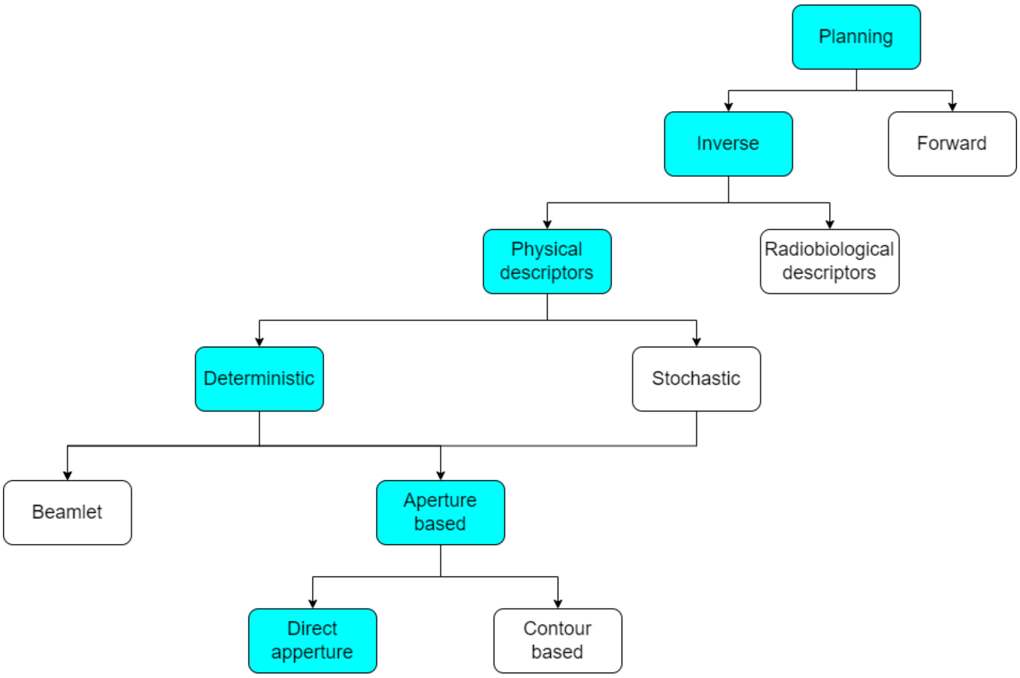

Figure 5: Radiotherapy planning categories.

In light of what has been told, this project is about the planning phase of the teletherapy to which the linear accelerator used must have a *MLC* and its dose delivery based on *IMRT*. It may seem a lot, though it is still not enough to properly define the problem. There is not only one exclusive way to approach the planning phase, and its details are discussed in this section. Figure 5 introduces them.

Inherent to any kind of planning, initially the medical physicist has to decide the gantry and couch angles to be used, the energy of the linear accelerator, the isocenter's spatial location, the patient position on the treatment couch, etc.

The next decision is which of the following approaches should the operator take:

2.5.1 Forward *vs* inverse

- *Forward planning*: This is a manual process of choosing the open field formats based on the Beams's Eye View (*BEV*) (Khan et al. [2021]), and their weights for each previously selected treatment angle. Then, given a first incidence, subfields that radiate part of the target are added in order to decrease hot spots (spots with excessive dose), complement the dose in uncovered regions or protect some *OAR* that is in that direction. These steps are presented in figure 6[11].

- *Inverse planning*: In cases with irregularly shaped ***PTV***, concavities or multiple *OAR*'s, the use of inverse planning is essential. While Forward planning depends entirely on the operator, inverse planning incorporates countless tools that act on the decision-making nature of the problem.

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[11] Image adapted from the book (Almeida [2012])

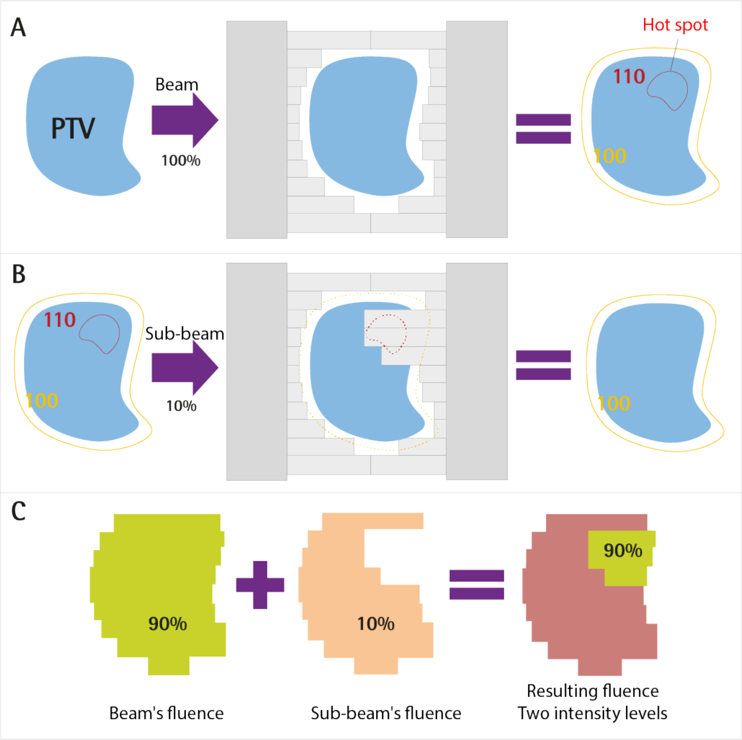

Figure 6: Example of a forward planning approach.

2.5.2 Physical *vs* radiobiological descriptors

When there is a choice for the inverse planning approach, one must decide between using tools that use physical descriptors to help with the dose-delivery problem or tools that use radiobiological descriptors.

Physical descriptors are composed of the dose prescriptions given from the oncologist and the tumour dose uniformity level (Almeida [2012]); explained in section (nao tem mais a section). Radiobiological descriptors, on the other hand, consider how the heterogeneity of each tissue changes the absorbed dose for each plan.

Unfortunately, radiobiologic descriptors are relatively recent and have much less associated research when compared to physical descriptors, which leads this project to stick with physical descriptors.

2.5.3 Deterministic *vs* stochastic

The optimization algorithms used to minimize the objective function can be classified into two broad categories: deterministic and stochastic (Webb [2003]).

Deterministic algorithms include the most famous and used methods to minimize functions. For instance, in non-linear formulations, one can include *Gradient-based* and *Newton's* methods. In contrast, methods like *Simplex* and *interior point* are the major ones for linear formulations.

Stochastic algorithms mention methods like *Simulated annealing*, *Tabu search*, and genetic algorithms, among others. These can deal with more complex objective functions; based on biological objectives or *DVH* constraints; that normally deterministic methods alone fail. [12]

Nevertheless, it has the drawback of a larger amount of iterations to find reasonable solutions. (Boyer et al. [2001], Das et al. [1998]).

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[12] Stochastic methods are mostly used together with deterministic methods in dose-delivery problems.

2.5.4 Beamlet *vs* aperture based optimization

Because inverse planning and physical descriptors were chosen, it is time to select the way in which the radiation beam is optimized. In fact, the goal is to find the best *MLC* arrangement for each treatment angle using optimization models found within the tools previously mentioned.

This "*MLC* arrangement" is commonly called "Ideal fluence", which the optimization models are required to calculate for each treatment angle in order to modulate the dose in the best way possible.

The figure 7[13] summarizes the difference between the two methods of calculating the ideal fluence. In the beamlet approach, the collimator is discretized in "beamlets", and the intensity administered by each of them is determined by the time the respective *MLC* blade allows radiation to pass through. Then, the optimization model must calculate the optimal intensity (or weight) for each beamlet at every treatment angle. This is how this project's model works.

On an opposite construction, when using aperture based optimization, the collimator is not discretized in beamlets. The planning process is based on a small pre-set of apertures (*MLC* configurations) per beam direction. The optimization is then limited to calculating the optimal weights of these pre-defined openings (which can, for example, be derived from the patient's anatomy), or the simultaneous optimization of the shapes and weights of the openings. The former approach is called Contour-Based Aperture Optimization while the latter is called Direct Aperture Optimization (*DAO*). Direct aperture optimization is applied in intensity modulated arc therapy (*IMAT*) and volumetric intensity modulated arc therapy (*VMAT*) (Bortfeld [2012]).

One of the main advantages of aperture optimization compared to beamlet-based optimization is that many problems that are related to blades sequencing can be avoided. Established fields comprise a few segments per beam, which are similar to conventional fields and therefore easier to verify.

2.6 Blades sequencing problem

Moreover, nothing has been said so far about the blade sequencing problem. Once the ideal fluence is calculated for each angle, the linear accelerator has the incumbency of delivering this modulated fluence.

A question follows about how is it possible to deliver an ideal fluence where each beamlet has different intensities using just one aperture, and the answer is it is not possible.

Since the linear accelerator's power is constant during treatment, it is only possible to create influences of constant intensity. Because of that, each ideal fluence is constituted by the sum of many constant fluences. Now, remember that each beamlet intensity or weight is related to the amount of time this beamlet is going to be opened, allowing radiation to pass through. Then, the *MLC* has to create a set of movements that will correspond to the time of exposure of each beamlet. The image 8 represents how this process happens with a simple example. The numbers 5, 10 and 15 represent different intensities for the beamlets painted in yellow, orange, and red, respectively.

Having said that, one must be beware this example. It does not mean that the linear accelerator can only create beams with intensity of value 5. By "constant", the authors only mean that every beamlet of the aperture in question has to have the same intensity. In other words, since the intensity is just related to the amount of time the aperture is going to be opened, the linear accelerator can create constant fluences with different intensities than 5 by just letting it open more or less time. In the same example, to create a constant fluence with

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[13] Image adapted from the book (Almeida [2012])

intensity of value 10 on every beamlet, the machine just needs to let the *MLC* open twice the time it was needed on the constant fluence of value 5.

Also, the set of movements for each ideal fluence is not unique. Given a non-trivial ideal fluence, there are many ways of creating and ordering the *MLC* movements in order to deliver the same total dose, and the figure 8 just represents one possible solution.

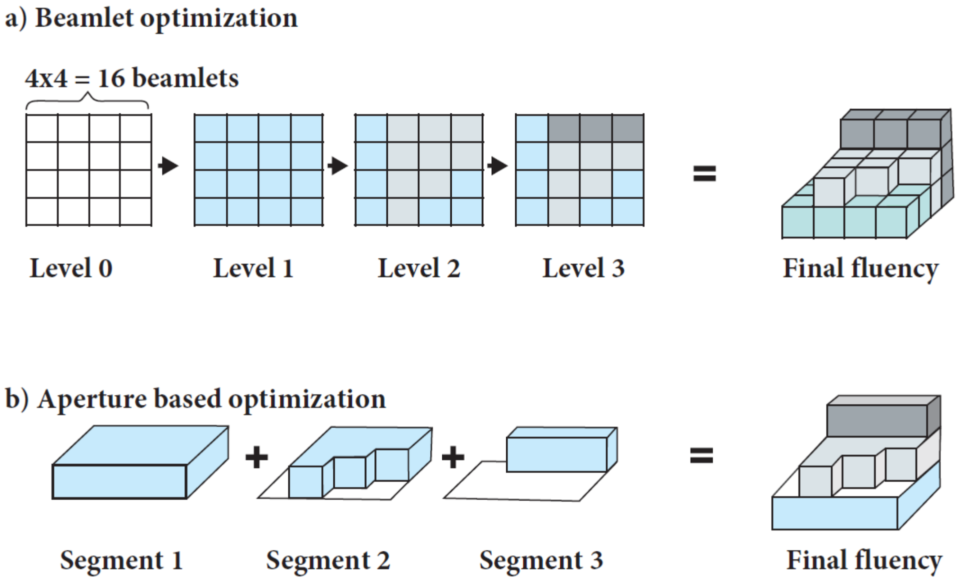

Figure 7: Beamlet *vs* aperture optimization.

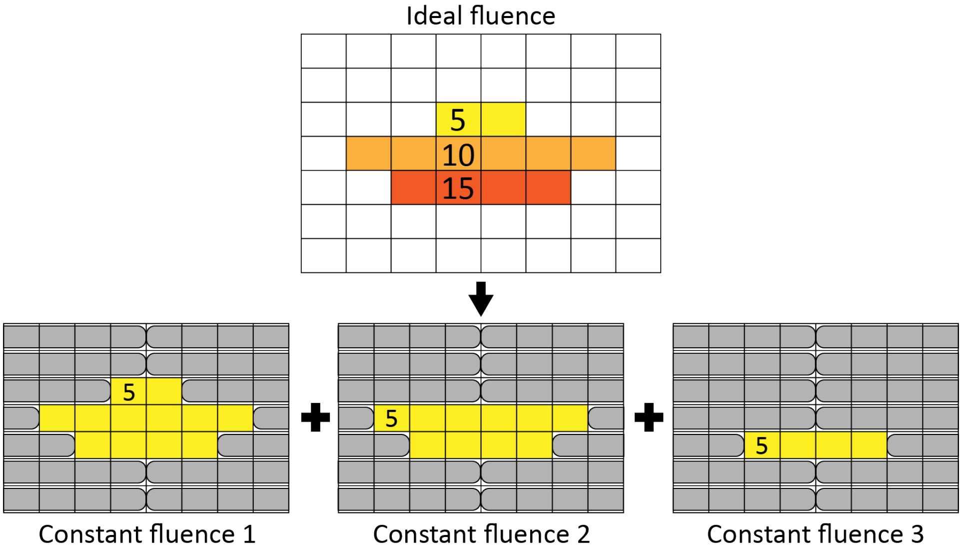

Figure 8: *MLC* sequencing of an ideal fluence example.

2.7 Planning overview

To finish the planning section, an overview of the entire process, supposing a step and shoot philosophy, is given in the figure 9[14], and a list of different methods of *IMRT* is presented in the table 1, adapted from the article (Grégoire and Mackie [2011]).

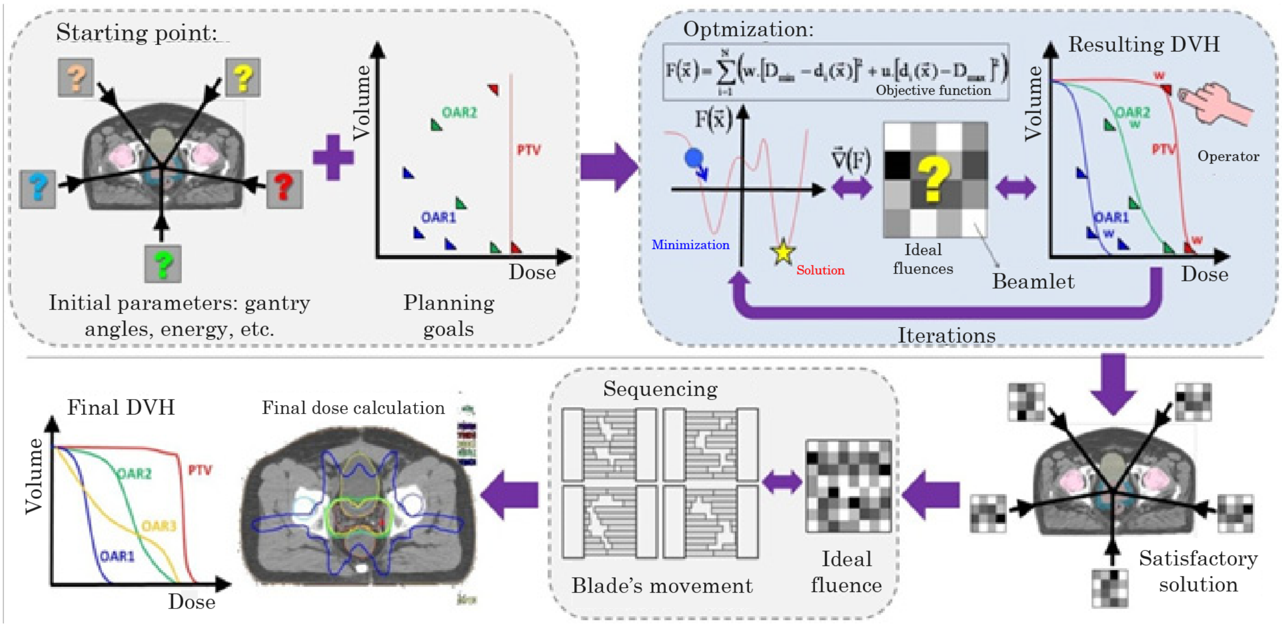

Figure 9: Step and shot planning overview

Type of method	Intensity modulation method	Preferred optimization approach
Compensators blocks	A beam filter designed to provide a patient-specific intensity pattern designed by an optimization procedure	Optimized beamlets
Segmental *MLC* (step and shoot)	Multiple *MLC* segments delivered from each treatment direction	Direct-aperture optimization
Dynamic *MLC* (sliding window)	Blades slide across the field at different rates	Optimized beamlets
Intensity modulated arc therapy (*IMAT*)	Blades slide across the field at different rates	Direct-aperture optimization
Volumetric modulated arc therapy (*VMAT*)	*MLC* blades move while the gantry rotates with variable speed.	Direct-aperture optimization

Table 1: Preferred optimization approaches for each *IMRT* method.

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[14] Image adapted from the book (Almeida [2012])

3 Systematic literature review

The systematic literature review was carried out following the process proposed by Kitchenham (Keele et al. [2007]). The method guarantees that the review's result is verifiable and repeatable by other researchers. Kitchenham highlights three fundamental phases for conducting a literature review:

1. Planning the review, which includes creating the research questions and reviewing the protocol;
2. Conducting the review, which includes the selection and quality of the respective studies, data extraction, and data synthesis;
3. Publicising the results after the review is completed.

To ensure the outcome's quality, the checklist of elements proposed by *PRISMA* methodology (Page et al. [2021]) was incorporated as follows.

3.1 Research questions

In order to keep in track the relevant topics for this *SLR*, five research questions were formulated and presented in table 2 .

ID	Research Question (RQ)
RQ1	What heuristics have been used on aperture shape optimization?
RQ2	What heuristics have been used on aperture weight optimization?
RQ3	What objectives have been identified by region?
RQ4	What types of cancer and databases has DAO been used?
RQ5	Which future investigations are suggested?

Table 2: Research questions for the systematic literature review.

3.2 Data sources and search strategies

To conduct this systematic literature review, the authors searched for scientific papers in seven databases: *ACM Digital Library*, *IEEE Xplore Digital Library*, *PubMed*, *Science Direct*, *Scopus*, *Springer* and *Web of Science*. For these sources, it is considered only documents from journals and conferences. Other more general sources, like *Google Scholar*, were not included because they usually index studies already available in the primary ones.

3.3 Article selection

Once the databases were set, it was time to determine the specific search strings that would be used in the databases' search engine and define the exclusions and inclusions criteria.

3.3.1 Search strings

The search strings were formulated based on the relevant topics to our systematic literature review. It was determined to use two specific keywords in the queries, "Direct Aperture Optimisation" and "Intensity modulated Radiotherapy Treatment". With only these two strings, the resultant articles are satisfactorily close to the desired topic.

ID	Search strings (SS)
SS1	("dao" OR "direct aperture optimization") AND ("imrt" OR "intensity modulated radiotherapy treatment")

Table 3: Search string.

3.3.2 Study selection criteria

In order to refine the search even more, it was defined inclusions and exclusions criteria to select the studies, highlighted in tables 4 and 5.

ID	Inclusion Criteria (IN)
IN1	Published between January 2000 and March 2021
IN2	Journal articles and conference papers
IN3	Related to intensity modulated radiotherapy treatment
IN4	Related to direct aperture optimisation
IN5	Focused in the associated optimization problem

Table 4: Inclusion Criteria.

ID	Exclusion Criteria (EX)
EX1	Focused only in other radiotherapy techniques
EX2	Focused only in medical approach
EX3	Only abstracts
EX4	Does not have computational implementation

Table 5: Exclusion Criteria.

3.3.3 Document selection

The selection process was done in March 2021. By just searching the selected strings on the databases' search engine, the initial set arranged 1623 studies. Then, after checking the titles and authors for duplicates and applying the inclusion and exclusions criterion, the number surprisingly dropped to 108. The figure 10 presents the process in more detail.

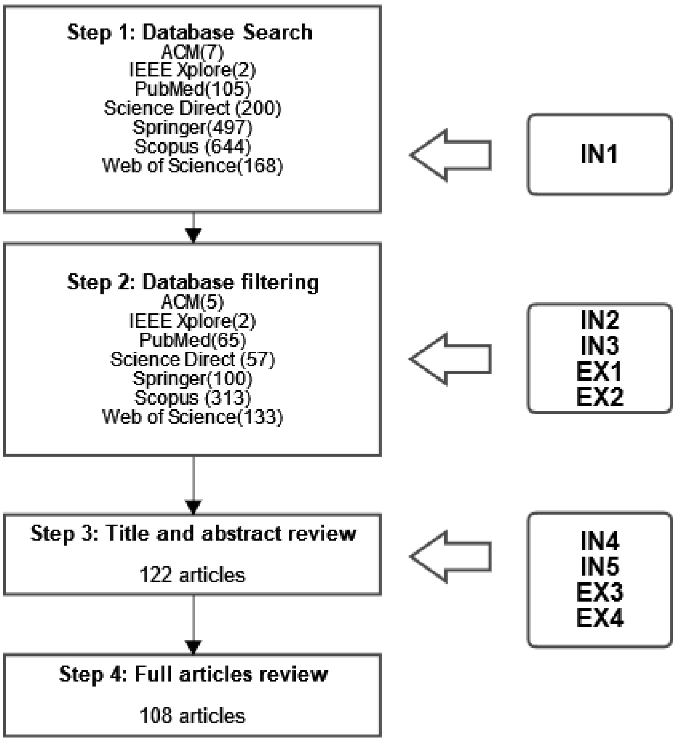

Figure 10: Flowchart with the results of the article selection process.

3.4 Data synthesis

With the search phase complete, the information is extracted from each of the 108 studies, summarizing and tabulating the information based on different metrics, such as the year of publication and document type; detailed below.

3.4.1 Year of publication

It was considered studies published between 2002 and 2020. The figure 11 presents the number of studies found at each year between 2000 and 2020. The studies from 2021 were not included once the article selection was finished in March of the same year. However, many more studies were published in 2021, leading the authors to believe that this number will increase significantly in the following years.

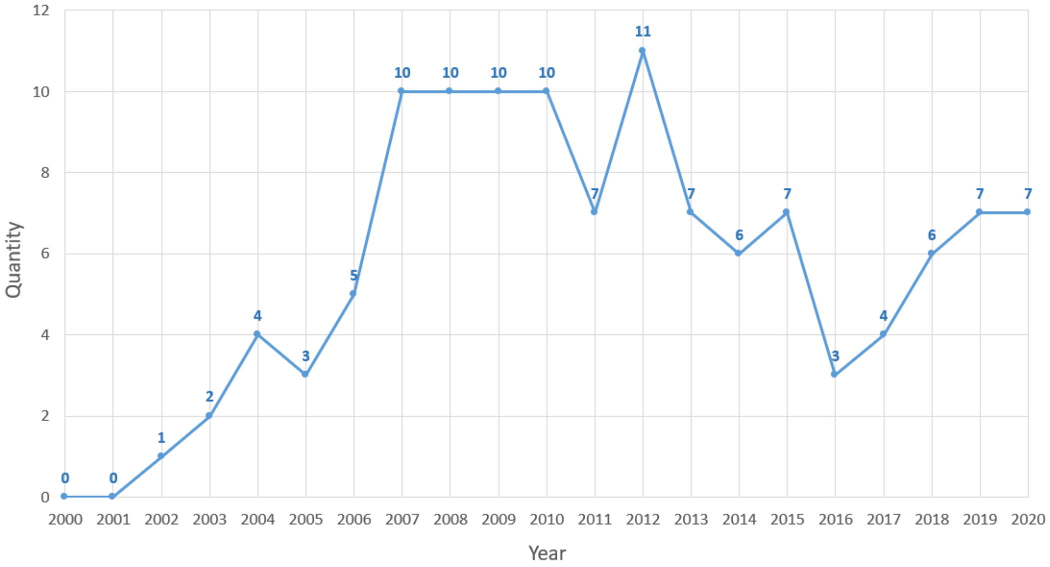

Figure 11: Number of articles found at each year.

3.4.2 Document type

It was analysed the origin of the studies reviewed and determined whether they were conference proceedings or had been submitted to a scientific journal. Figure 12 shows a significant number of papers published in journals with 104 articles.

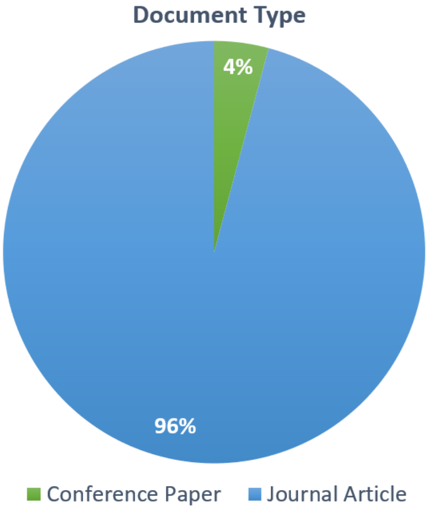

Figure 12: Percentage of journal articles and conference papers.

4 Stage of development

Unfortunately, it is not possible to provide partial results of a literature review, once the answers for the questions showed in the table 2 can only be presented after all the selected articles are analysed. Nevertheless, for the sake of this report, the progress made so far and the goals for the next few months are given below.

From the 108 articles selected so far, 61 were already analysed. The authors aim to finish studying the last 47 by the end of January of 2023, leaving February to revise the information extracted from the 108 articles, and concluding the article by March.

5 Conclusion

It is not the intention of any literature review to condense decades of scientific effort into a single article. The character of a literature review aims only to give the authors' perspective on the evolution of a particular field throughout time.

In fact, It is the author's responsibility to be impartial in the face of the evidences. Although, the intrinsic subjectivity present, for instance, in the article's choice, the the results' interpretation, and even the topics that will be discussed can not be ignored.

Fortunately, once the authors' partiality does not play a big role on their project, the systematic literature review is the most efficient and straightforward tool to establish the state-of-the-art of a study area; giving guidelines for future endeavors to investigate more promising problems.

Ultimately, the goal of this report is to present an introduction to the radiotherapy planning problem, and briefly discuss the methodology used in the *SLR*.

Soon, the authors hope to be able to publish the article in renowned journals, due to its uniqueness and utility for the radiotherapy planning community.

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