Chapter 4

An Enumeration of Radiotherapy Terminologies, Planning and its Optimization

This chapter deals with the explanation of IMRT equipment, planning, and radiotherapy terminologies. The Dose Volume Histogram (DVH) and Digital Imaging Communications in Medicine (DICOM) are described. Linear Programming formulation (LLP) for IMRT optimization is framed and solved to show the application of Operation Research in cancer treatment and finally deals with conclusion and future scope of the paper.

4.1 EXTERNAL BEAM RADIOTHERAPY

4.1.1 IMRT EQUIPMENT AND TREATMENT PLANNING

Intensity Modulated Radiotherapy (IMRT) with Multi-Leaf Collimator (MLC) facilitates a shaped array of 3mm beam lets. It is a specialized, computer-controlled device that has many tungsten fingers, or leaves, within the linear accelerator (LINAC) (Craft, et al, 2014). Multi-Leaf Collimator (MLC) creates a time-varying opening such that a finer shaped distribution of the dose is formed. This avoids any unsustainable damage to the surrounding critical structures (OARs) (Craft, 2007). The main components of LINAC are shown in Figure 4.1.
4.2 IMRT OPTIMIZATION

Optimization Algorithm is necessary to estimate beam weights from a chosen objective function along with its set of constraints. Based on mathematical properties of objective functions i.e. they are framed as

- Convex function
- Non-Convex function

4.2.1 CONVEX FUNCTION

In convex function there is only global minimum, where as in non-convex function, both local and global minimum exists. Therefore for convex objective functions deterministic algorithms search based on gradient approach are applied. Two of the approaches that are commonly applied are
4.2.1.1 STEEPEST DESCENT

Steepest Descent is mainly applied for reaching the global minimum of a convex objective function \( COF(x) \) where \( x \) denotes the set of treatment variables as argument, for the function, that as to be tuned for optimal value. The objective function of \( OF(x) \) for varies values of \( x \) can be plotted as illustrated in Figure 4.2 for a general one dimensional non-convex \( OF(x) \).

![Figure 4.2 One-Dimensional Non-Convex Function](image)

The gradient \( OF(x) \) guides the steepest direction tracing the surface of the \( OF(x) \). Therefore finding the minimum of objective function with respect to \( x \) by iterative method is depending on the strength of \( x \) at every step of the iteration \( i \). The current value of \( x \) from iteration \( i \) to \( i+1 \) for steepest descend gradient approach is as shown in equation 4.1.

\[
x(i+1) = x(i) - \gamma \cdot \Delta OF[x(i)]
\]

(4.1)

From Figure 4.2 the visualization iterative search can be mapped to a ball sliding down hill toward the steepest direction to reach the valley, which is minimum. The constant co-efficient \( \gamma \) in equation is known as Damping Factor. Since this value is fixed for every iteration, the steepest descend suffer with too many small steps. To overcome this problem Newton’s method is applied.
4.2.1.2 NEWTON’S METHOD

Newton’s Method computes 2nd order derivatives of the objective function \( OF(x) \) for calculation of the damping factor (\( \gamma \)). This controls the efficiency of the optimization. Finding the Taylor expansion of objective function \( OF[x(i)] \) till the 2nd order derivatives the new damping factor (\( \gamma \)) for every iteration is to be determined. Generally in radiotherapy optimization the damping factor (\( \gamma \)) is denoted in 2nd order derivative of \( OF(x) \) is known as the Inverse Hessian \( H^{-1} \). Therefore the step size for next iteration is calculated as shown in equation 4.2.

\[
\begin{align*}
    x(i + 1) &= x(i) - H^{-1}[x(i)]\n    x(i + 1) &= x(i) - \gamma_{newton} \n    x(i + 1) &= x(i) - \gamma_{newton} \n\end{align*}
\]

The disadvantage of Newton method is the long computation time of the Inverse Hessian for every step. To overcome this problem for subsequent steps the inverse hessian are approximated and such optimization approach is known as ‘Quasi Newton’ Method.

4.2.2 NON CONVEX FUNCTION

For objective functions that are non-convex approach based stochastic algorithms are applied. Commonly used stochastic algorithms in radiotherapy optimization are

4.2.2.1 SIMULATED ANNEALING

Simulated annealing with the aid of two strategies escapes from being trapped into local minima. They are

- Climbing Hill
- Tunneling
This algorithm continues to allows the probability of exploring in the uphill direction to find the global minimum through the local minimum is reached as shown in Figure 4.3.

![Figure 4.3 Visualization of Tunneling and Hill Climbing Strategies](image)

The process of migrating from a local minimum to a global minimum penetrating through the barrier is known as Tunnelling as shown in Figure 4.3. This process of sampling of distribution function involves both of these strategies. Let $\Delta x(i)$ be the step size for $i^{th}$ iteration derived from the displacement distribution $D[\Delta x(i)]$. The length of this distribution is time dependent and usually shorter when approaching optimal solution. The new step of iteration from current position is decided with the aid of a probability distribution $P(i)$ as shown in equation 4.3.

$$P(i) = \exp\left[\frac{-\Delta OF(i)}{k_B T(i)}\right] \tag{4.3}$$

Where $\Delta OF(i) = OF[x(i) + \Delta x(i)] - OF[x(i)]$
The varying combinations of Probability Distribution $P(i)$ and Displacement Distribution $D[\Delta x(i)]$ determine the various versions of simulated annealing algorithms. The most common types are

- **Boltzmann Annealing** where during the initial stage of iteration temperature is high at $T(0)$ for hill climbing. For subsequent iteration $T(i)$ the temperature reduces gradually satisfying the condition as shown in equation 4.4.

$$T(i) \geq T(0) \cdot \frac{1}{\log(i)} \quad (4.4)$$

Here to compute the step size $\Delta x(i)$ Gaussian distribution is applied as shown in equation 4.5.

$$D_{Boltz}[\Delta x(i)]=\left[2\pi T(i)\right]^{\frac{N}{2}} \cdot \exp\left[-\frac{\Delta x(i)^2}{k_B T(i)}\right] \quad (4.5)$$

- **Fast Simulated Annealing** where the temperature update for each iteration is as shown in equation 4.6.

$$T(i) = \frac{T(0)}{i} \quad (4.6)$$

Here to compute the step size $\Delta x(i)$ Cauchy Distribution is applied as shown in equation 4.7.

$$D_{fast}[\Delta x(i)] = \frac{T(i)}{\left[\Delta x(i)^2 + T(i)^2\right]^{(N+1)/2}} \quad (4.7)$$
4.2.2.2 GENETIC ALGORITHM

Mimic the basic principles of evolution in biology for identifying the ’most probable survivor’ from the large search space. The process of convergence to arrive at an optimal solution is aided by applying genetic principles like Inheritance Cross over mutation and selection method. This generally applied to solve very complex problems having large search space.

The first step in this algorithm is to generate the initial population by the method of encoding for the formulated optimization problem. Considering one-dimensional objective function with the range of solution space is 0-15. Then encoding is done with 4-bit binary representation. For example $A(x=2)$ and $B(x=14)$ are then encoded as $A = \{0010\}$ and $B = \{1110\}$.

The second step is to evaluate the generated initial population based on the fitness function. Here A has higher probability then, since the objective is to converge into global minimum.

In each iteration offspring are generated from the solution population that has passed the fitness function evaluation. The two offspring $C = \{0001\}$ and $D = \{1101\}$ are generated by crossover of A and B at position 2. This process ensures that sufficient number of solutions is available for next iteration.

Apart from crossover, to generate offspring mutation is also used to avoid the convergence in local minimum, instead of global minimum. For example mutations of $C = \{0001\}$ for one bit change. When an expected termination criterion of the algorithm is met, the final solution is decoded back into appropriate treatment parameters for IMRT optimization.

Based on sequential method the solution approach to IMRT treatment planning is as shown in Figure 4.4. In IMRT there in an intensity map for each angle. To satisfy each one of the intensity map a collection of shape matrices are formed as
shown in Figure 4.6. A specific fluence or intensity is created for MLC leaves that operate in step and shoot method by generating a defined aperture and radiation given for fixed time duration (Carlsson, 2008).

4.2.1 BEAM ANGLE OPTIMIZATION

The first step in IMRT optimization is coming into agreement for set of beam angles for radiation dose delivery such that target geometry is covered entirely sparing the normal tissues and critical organs.

Generally in clinical practice angles that differ below 5° have similar effect on treatment. So with a variation of 5° for each angle, the number of combinations that can be generated as search space is $C_7^{72} = 1473109704.0$ or having a 10° variation for each angle the search space generated is $C_7^{36} = 8347680.0$

With these 36 angles using a linear objective function will take around a minute to compute for given set of angles on a conventional computer. In other words 15 years are needed to determine the optimal solution.

Therefore to reduce the time of computation procedures such as heuristics and meta-heuristics are modeled to solve the problem of Beam Angle Optimization (BAO). Heuristics can provide acceptable solutions for solving complex and hard problems of this type within a reasonable period of time.

Generally heuristics are classified into two types namely
• Specific heuristics which are modelled and implemented to solve a specific problem.

• Meta-heuristics are flexible to solve any optimization problem by reducing the size of search space and explore that space intelligently with aid of guiding strategy.

Usually random search methods like simulated annealing, genetic algorithm, particle swarm optimization and tabu search are used to handle the BAO problems.

The formulation of the BAO problem involving geometric and intensity profiles is given as shown in equation 4.8 and 4.9.

\[
\text{min } f(\theta^1, \ldots, \theta^n) \quad (4.8)
\]

\[
\text{s.t. } (\theta^1, \ldots, \theta^n) \in \Theta^n \quad (4.9)
\]

Where \( \Theta \) being the set of all beam angles.

\( f \), denotes the objective function for estimating the fluence to be delivered for the given set of beam angles \( (\theta^1, \ldots, \theta^n) \).

4.2.2 FLUENCE MAP OPTIMIZATION

After BAO the second process is to plan the amount of radiation dose to be delivered. Basically the objective of this problem is to estimate weights for each beamlet that get deposited into discretised volume elements known as voxels.

The X-ray beams are split into array of beamlet, which are received by voxels of the tumour target and its surrounding geometry. Therefore the objective of FMO is to calculate the dose received by a particular voxel from a particular from a particular beamlet. This information is registered as \( i^*j \) Dose matrix \( D \). The each element in the matrix is the combination of beamlet weight and dose delivered by the beamlet \( j \) on voxel \( i \).
Now considering \( N_{\text{vox}} \) denotes the total count of voxels and \( N_{\text{bem}} \) represents the total count of beamlets. With \( n \) fixed number of beam angles generated from BAO problem, the dose deposited to the voxel \( i \) by the beamlet \( j \) is given by the principle of superposition as shown in equation 4.10

\[
\sum_{i=1}^{N_{\text{vox}}} \sum_{j=1}^{N_{\text{bem}}} D_{ij} w_j
\]

(4.10)

Where, \( w_j \) denotes the weight of the beamlet \( j \). Based on the prescription suggested by the physician the following notations are framed to formulate the objective and constraints for the FMO problem as follows.

- \( D_{TD} \) - Total Dose
- \( TA_{PTV} \) - Target Aim prescription for the PTV
- \( D_{PTV} \) - Dose in PTV
- \( UB_{PTV} \) - Upper Bound for the dose in PTV
- \( LB_{PTV} \) - Lower Bound for the dose in PTV
- \( D_{OAR} \) - Dose in OAR
- \( UB_{OAR} \) - Upper Bound for dose in OAR
- \( D_{NT} \) - Dose in Normal Tissues (NT)
- \( UB_{NT} \) - Upper Bound for dose in NT

Therefore the formulation of the problem to kill tumour in PTV and spare the NT and Organ at Risk (OAR) by as much minimal dose as possible is given as shown in equation 4.11.

\[
\min_w \rightarrow f(D_{TD})
\]

\[
s.t. \sum_{i=1}^{N_{\text{vox}}} \sum_{j=1}^{N_{\text{bem}}} D_{ij} w_j
\]
The process of finding the most efficient use of MLC to deliver optimal fluences found from FMO problem is called Leaf Sequencing. The intensity profile to be delivered from a specific angle is denoted by an m*n matrix B. The matrix elements of this matrix B is a combination of beamlet weight and the radiation dose to be delivered by the beamlet jon voxel i as shown in Figure 4.5 that illustrates a tiny fluence map.

\[
\begin{bmatrix} 9.0 & 4.0 \\ 6.0 & 1.0 \end{bmatrix}
\]

**Figure 4.5 Tiny Fluence Map**

The two possible to decompose this matrix into deliverable shape are addressed in two cases.

Case I: The one way of decomposition is as shown in equation 4.12.

\[
\begin{bmatrix} 9.0 & 4.0 \\ 6.0 & 1.0 \end{bmatrix} = 9.0 \begin{bmatrix} 1 & 0 \\ 0 & 0 \end{bmatrix} + 4.0 \begin{bmatrix} 0 & 1 \\ 0 & 0 \end{bmatrix} + 6.0 \begin{bmatrix} 0 & 0 \\ 1 & 0 \end{bmatrix} + 1.0 \begin{bmatrix} 0 & 0 \\ 0 & 1 \end{bmatrix}
\]

(4.12)

Now the time required to deliver radiation doses through the set of deliverable shape as per prescription is defined as beam on time. For the
decomposition matrix in case I, this beam on time is measured as sum of doses of tiny fluence matrix.

Therefore the solution from the four shapes generated from decomposition in case I as total beam on time as shown in equation 4.13

\[ 9.0 + 4.0 + 6.0 + 1.0 = 20.0 \] (4.13)

The beam on time is 20.0 units of time. Now assuming that the IMRT machine requires 15 units of time to switch from one deliverable shape to another, along with 1 unit of relative time between shapes, the total time needed in case I is as shown in equation 4.14

\[ 15.0 \times 4.0 + 20.0 = 80.0 \] (4.14)

Finally to deliver the radiation dose with the matrix decomposition shown in case I require 80.0 units of time. An alternative decomposition is addressed in

Case II: The alternate way of decomposition is as given in equation 4.15

\[
\begin{bmatrix}
9.0 & 4.0 \\
6.0 & 1.0
\end{bmatrix}
= 1.0 \times \begin{bmatrix}
1 & 1 \\
1 & 1
\end{bmatrix} + 5.0 \times \begin{bmatrix}
1 & 0 \\
1 & 0
\end{bmatrix} + 3.0 \times \begin{bmatrix}
1 & 1 \\
0 & 0
\end{bmatrix}
\]

(4.15)

In this case the decomposition matrix has three deliverable shapes when compared to case I which has four deliverable shapes. Therefore total time needed in Case II is as shown in equation 4.16

\[ 15.0 \times 3.0 + 9.0 = 54.0 \] (4.16)

From the equation it is shown that to deliver the radiation dose with the matrix decomposition shown in Case II requires 54.0 units of time which is comparably less with respect to Case I.
Figure 4.6 Creating a Fluence-map using MLC

The rectangular beams from MLC of IMRT equipment are discretized beamlets. The dose deposition algorithm computes the amount of dose absorbed on each voxels of the tumour target.

4.3 DICOM IMAGES AND DVH

4.3.1 DICOM IMAGES

The National Electrical Manufactures Association (NEMA) created a standard to aid distribution and viewing of medical images known as DICOM. This standard is compatible with all latest imaging equipment’s, accessories, networking servers, workstations, printers and picture archiving and communication systems (PACS) which are installed by multiple manufactures. The DICOM standard enables the following capabilities:

- Network Image Transfer enables two devices to communicate by sending images as objects, querying remote devices and retrieval of these objects.
- On-Line Imaging Study management enables network capability for medical devices to integrate with many information systems.

- Network Print management enables printing of images on a networked camera.

- Open Media Interchange enables exchange of objects and related information manually.

MatLab supports DICOM files and is vital tool in processing of DICOM images. The Figure 4.7 shows a file structure of reading metadata and image data of DICOM file.

![Figure 4.7 Metadata and Image Data of DICOM File](image)

From the Figure 4.7 it can be seen that the DICOM requires a 128-byte preamble, followed by letters “DICM”. This is followed by data elements organised in groups. The first column of an data element contains DICOM tag, the second column contains the value representation, the third column represents the value length and the fourth column specifies the official DICOM name of the field.
The DICOM standard assigns specific names for the different DICOM tags. For e.g. (0010, 0010) is the identifier of patient’s name and the content shown in Figure 4.6 is Joe Bloggs. There are two ways to interpret word in a DICOM file, the Little Endian (00) and Big Endian (FF). In Little endian the word read from right to left and vice versa for Big Endian. Few other codes that are to be decoded for human interpretation are patient name (PN), Unique Identification (UID), and Image. From this discussion the importance of header information for real DICOM files is known.

4.3.2 DOSE-VOLUME HISTOGRAM

Dose-Volume histogram is mathematical tool to assess whether a radiation therapy plan meets desired constraints for a volume of interest, within certain limitations.

Dose Volume Histogram (DVH) enables one to determine the radiation dose deposited on each structure. For ideal case the plot of DVH is 100% for entire volume of tumour voxels and falls to zero level immediately. This indicates that tumour volume is treated as per the prescription suggested by the physician. For Organ at Risk (OAR), the plot of OAR is 0%, indicating that critical structures are completely spared from radiation dose as shown in Figure 4.8.

![Figure 4.8 Cumulative DVH for Ideal Case](image-url)
Generally, ideal cumulative DVH is impossible in clinical practice. The relation between differential dose-volume histogram or dDVH and more familiar cumulative dose-volume histogram is as shown in equation (4.17).

\[ cDVH(D) = \sum_{x=D}^{D_{\text{max}}} dDVH(x) \]  

(4.17)

**Figure 4.9** Dose Volume Histogram

A cumulative DVH is represented in Figure 4.9, where each curve is related to different structure or tissues. Therefore the amount of radiation received by each structure is calculated from DVHs.
4.4 LINEAR PROGRAMMING FORMULATION FOR IMRT

4.4.1 PROBLEM STATEMENT

The target is divided into nine voxels, voxel 1 to 9. For simplicity we have considered the two-dimensional approach for the problem. Each beam is divided into three beamlets that make total six beamlets. Also, it is given that 7Gray of radiation is at least required to damage the tumour cells. Also, the spinal tissue cannot tolerate the radiation of more than 5Gray level. The region which is subjected to radiation therapy is divided into 9 voxels where voxel1, voxel3, voxel6 and voxel9 are other healthy tissues, voxel2, voxel4, voxel7 and voxel8 are tumour tissues and voxel5 in the spinal tissue. So, we need to minimize the damage to voxels 1,3,5,6 and 9. The problem statement is transformed into structured input as shown in Figure 4.10.

4.4.2 STRUCTURED INPUT

![Figure 4.10 Beamlet Irradiation on Voxels in 2D](image)

Figure 4.10 Beamlet Irradiation on Voxels in 2D
The target area is discretized into equal size cells known as Voxels. The two beams are split into number of beamlets known as Bixels to incident on voxels. The Multi-Leaf Collimator (MLC) of IMRT machine minimizes the intensity of X-rays on healthy tissues and critical organs and maximizes the intensity to kill the tissues in tumor region.

Let \( x_i \) = Decision variable for \( i^{th} \) beamlet

\[ c_i = \text{Cost co-efficient of } i^{th} \text{ variable} \]

\[ Z = \text{Function to be minimized} \]

Thus for n decision variables the objective function is to minimization is as in equation (4.18).

\[
\text{Minimize} \quad Z = \sum_{i=1}^{n} c_i x_i \quad (4.18)
\]

Let \( a_{ij} \) = co-efficient of the \( j^{th} \) constraint and \( i^{th} \) variable.

\[ b_i = \text{Dose limitation for } i^{th} \text{ constraint.} \]

\[
\sum_{j=1}^{n} a_{ij} x_j \leq b_i \quad \text{For all } i=1, 2 \ldots m
\]

and \( x_j \geq 0 \) for all \( j=1,2,\ldots,m \)

4.4.3 PROBLEM FORMULATION

The problem formulation to minimize total healthy tissue dose is as shown in equation (4.19).

\[
\text{Minimize} \quad Z = 3x_1 + 4.5x_2 + 2.5x_3 + x_4 + 2x_5 + 4x_6 \quad (4.19)
\]
Subject to Constraints:

\[ 2x_1 + x_5 \geq 5 \]
\[ x_2 + 2x_4 \geq 7 \]
\[ 1.5x_3 + x_4 \geq 7 \]
\[ 1.5x_3 + x_5 \geq 7 \]
\[ 2x_3 + 2x_5 \leq 5 \]
\[ x_1, x_2, x_3, x_4, x_5, x_6 \geq 0 \]

Where, \( Z \) is the objective function

\[ x_1, x_2, x_3, x_4, x_5, x_6 \] are decision variables.

Based on given objective function and set of constraints as input the Linprog tool has calculated the Intensities for beamlets 1 to 6. This is shown in Table 4.1 and plotted as shown in Figure 4.10. These six beamlets values are substituted in objective function to calculate the total minimum dose for healthy tissues and critical structures, which is \( Z=22.75\text{Gy} \).

**Table 4.1 Intensity Values**

<table>
<thead>
<tr>
<th>BEAMLET</th>
<th>INTENSITY(Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.25</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>3.5</td>
</tr>
<tr>
<td>5</td>
<td>2.5</td>
</tr>
<tr>
<td>6</td>
<td>0</td>
</tr>
</tbody>
</table>
4.4 CONCLUSION

The IMRT machine and its treatment planning are discussed. Then the need for DICOM standard along with DVH generated using 3D image data sets created from various treatment modalities are explained. Finally the LLP formulation for IMRT optimization are formed and solved by Linprog MatLab tool to illustrate the application of Operations Research for cancer treatment. The future scope of the paper is to analyze the possibility of graph theory, multi objective optimization and Markov models for treatment planning optimization.