Mathematical Optimization in Radiotherapy Treatment Planning

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Outline

1. Treatment Planning Topics
2. Introduction to Photon Therapy
3. Treatment Planning for 3D-conformal Radiotherapy

Topics

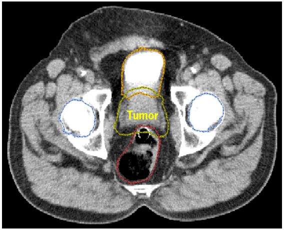
- Introduction to Photon Therapy
- 3D-conformal Radiotherapy (3D-CRT)
- Intensity-modulated Radiotherapy (IMRT)
- Multi-criteria IMRT Treatment Planning
- Temporal Treatment Planning and Fractionation
- Advanced Topics in RT Treatment Plan Optimization

Radiotherapy

- Each year around 1.6 million patients are diagnosed with cancer in the U.S.
  - 50–65% of them benefit from some form of radiotherapy
- Radiotherapy is often used in combination with other treatment modalities
  - e.g., surgery, chemotherapy, etc.
  - to control localized disease

Radiotherapy Goal

- The goal of radiotherapy is to deliver a prescribed radiation dose to the tumor while sparing surrounding healthy tissues to the largest extent possible



Radiation Biology

- Radiation kills cells by damaging their DNA
- Radiation action mechanisms
  - *directly ionizing*
    - charged particles, e.g., electrons, protons, and α-particles
  - *indirectly ionizing*
    - x- and γ- rays

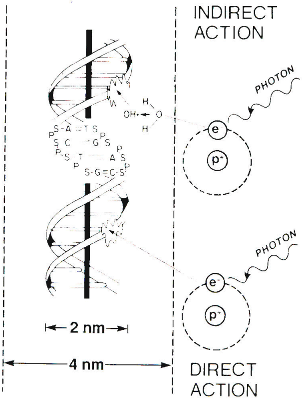


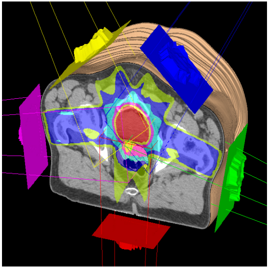
Figure: [Hall and Giaccia, 2006]

Photon Therapy

- Photon therapy uses high-energy photons
  - x-rays (1-25 MV) generated by
    - *linear accelerators* (LINAC)
    - Cobalt units (^{60}Co)
- Radiation source is mounted on a *gantry*

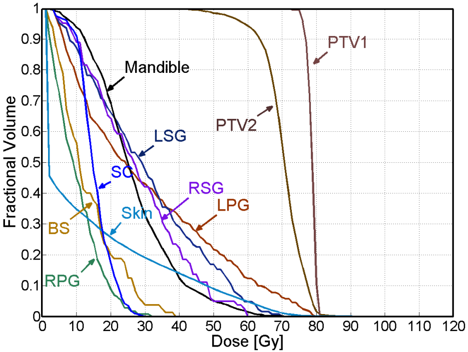
Radiation Dose

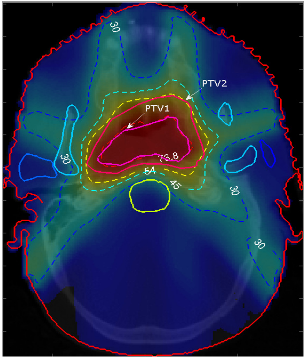
- *Dose* is the measure of energy deposited in medium by ionizing radiation per unit mass
  - *gray* (Gy) $= \frac{\textit{Joule}}{\textit{Kilogram}}$
- Dose deposited in patient is measured using a fine cubical grid
  - cubes are called *voxels*



Dose Distribution Visualization

- Visualizing the dose distribution
  - dose-volume histogram (DVH)
  - isodose lines
  - dose-wash diagram





Dose Volume Histogram (DVH)

- Dose distribution can be characterized similar to a random variable
  - f: dose distribution function
  - F: cumulative dose distribution function
  - DVH: $1 - F$ and differential DVH: f

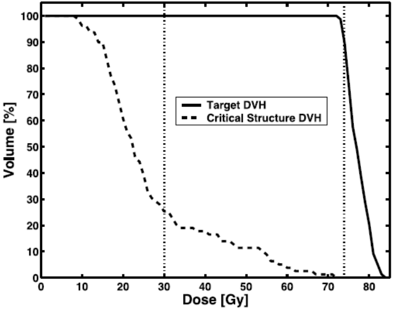


Figure: [Romeijn and Dempsey, 2008]

Dose Evaluation Criteria

- Measuring the dose distribution quality
  - physical criteria
    - penalty functions, excess and shortfall criteria, etc.
  - biologically-motivated criteria
    - *tumor control probability* (TCP), *normal-tissue complication probability* (NTCP), *equivalent uniform dose* (EUD), etc.

Physical Criteria: Penalty Functions

- Voxel-based penalty functions $G : \mathbb{R}^{|I|} \to \mathbb{R}$

$$G(\mathbf{d}) = \|\mathbf{d} - \mathbf{d}^*\|_p$$

$$G(\mathbf{d}) = \sum_{i \in I} \gamma_i^- \max\{d_i - t_i, 0\}^p + \gamma_i^+ \max\{t_i - d_i, 0\}^q$$

- Notation
  - I: set of all voxels in relevant structures
  - $\mathbf{d} = (d_i : i \in I)^\top$: vector of dose distribution
  - t_i: prescribed (threshold) dose in voxel $i \in I$
  - γ_i^-, γ_i^+: relative importance factors for underdosing vs. overdosing in voxel $i \in I$

Physical Criteria: Excess and Shortfall Criteria

- Based on $1-\alpha$ fraction of a structure that receives the maximum (minimum) dose
- Defined using dose distribution functions f, F

$$\alpha\text{-VaR}(\mathbf{d}) = \min_{d \geq 0} \{d : F(d) \geq \alpha\}$$

$$\alpha\text{-CVaR}(\mathbf{d}) = \min_{d \geq 0} \left\{ d + \frac{1}{1-\alpha} \int_d^\infty (z-d) f(z) dz \right\}$$

[Romeijn and Dempsey, 2008]

- Notation
  - $\mathbf{d} = (d_i : i \in I)^\top$: vector of dose distribution

Biological Criteria: Tumor Control Probability

- Measuring the probability that no *clonogenic* cell survives in the target

$$\mathrm{TCP}(\mathbf{d}) = e^{-N\cdot\mu(\mathbf{d})}$$

- Notation
  - N: number of initial clonogenic cells
  - $\mu(\mathbf{d})$: survival fraction of clonogenic cells in the target after receiving dose distribution **d**

Biological Criteria: Equivalent Uniform Dose

- Finding an *equivalent uniform dose* that results in the same biological damage as dose distribution **d** in a given structure

$$\mathrm{EUD}\left(\mathbf{d}\right) = \left(\sum_{i \in I} d_i^{\alpha}\right)^{\frac{1}{\alpha}} \qquad \text{[Niemierko, 1999]}$$

$$\text{tail-EUD}\left(\mathbf{d}\right) = d_0 - \Omega^{-1}\left(\Omega\left(\min\left\{\mathbf{d}, d_0\right\}\right)\right)$$

[Bortfeld et al., 2008]

- Notation
  - for targets $\alpha < 0$
  - for organs-at-risk $\alpha \geq 1$ depending on the organ structure
  - $\Omega\left(\mathbf{d}\right)$: generalized Ω-mean of the dose distribution **d**

Biological Criteria: Normal Tissue Complication Probability

- Measuring the probability of complications in the critical structure

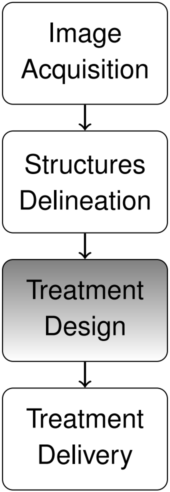
$$\mathrm{NTCP}(\mathbf{d}) = \Phi\left(\frac{\mathrm{EUD}(\mathbf{d}) - TD_{50}}{mTD_{50}}\right)$$

[Lyman, 1985], [Kutcher and Burman, 1989]

- Notation
  - TD_{50}: uniform dose at which the structure exhibits a 50% complication probability
  - m: shape parameter of NTCP curve
  - Φ: c.d.f. of standard normal distribution

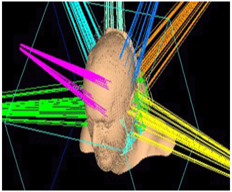
Radiotherapy Treatment Planning

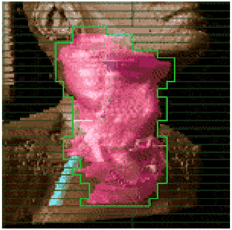
- The process of designing radiotherapy treatment for a cancer patient
  - a joint effort by radiation oncologists, medical physicists, and dosimetrists
- Treatment design is to find optimal radiotherapy machine settings to deliver desired dose distribution
  - these settings are patient specific



3D-conformal Radiotherapy (3D-CRT)

- At a given distance, radiation source provides a rectangular field
- To deliver a *conformal* dose distribution, radiation beam is shaped
  - *beam's eye-view* (BEV) determines projection of patient volume in the radiation beam plane
  - at each beam angle using BEV we determine an *aperture* that conforms to tumor shape





3D-CRT: Aperture Radiation Fluence

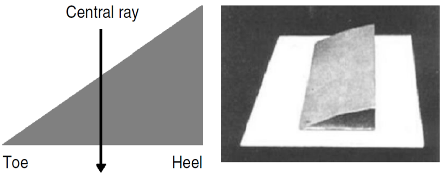
- Radiation source provides a constant radiation *flux*
    - flux: rate of particles passing through unit area
- For each aperture, we need to determine its *fluence*
    - fluence: radiation flux integrated over time
- For a fixed radiation flux, fluence $\propto$ exposure time

3D-CRT: Aperture Dose Deposition

- We determine dose deposited from an aperture in medium per unit of exposure time
  - unit of exposure time is *monitor unit* (MU)
- There are three major dose calculation methods
  - pencil beam
  - convolution-superposition
  - Monte-carlo simulation

3D-CRT: Wedges and Blocks

- *Wedges* and *blocks* can be positioned in the radiation field to create gradient in the aperture fluence

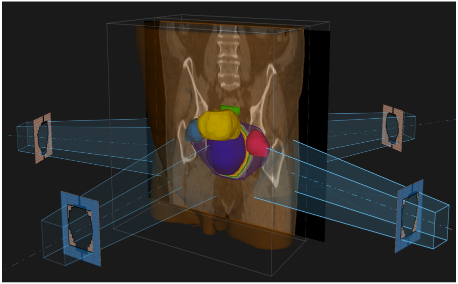


(a) A wedge filter (b) An external wedge

Figure: [Lim et al., 2007]

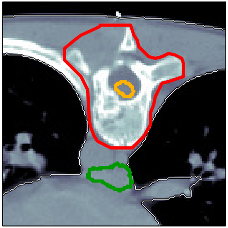
3D-CRT: Forward Planning

- *Forward Planning* involves manually determining
  - beam angles
  - wedges and blocks
  - aperture exposure time (so-called *intensity*/*weight*)



3D-CRT Example

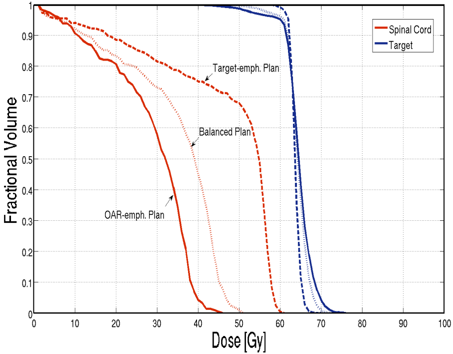
- Consider a paraspinal cancer case
  - target wraps around the spinal cord
- Prescribed and threshold doses are
  - uniform dose of 60 Gy to target
  - avoiding dose beyond 45 Gy to spinal cord
- We consider a simplified 2D voxel grid

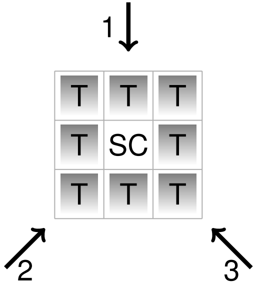


> 60	> 60	> 60
> 60	< 45	> 60
> 60	> 60	> 60

3D-CRT Example: Forward Planning

- In treatment planning system, aperture intensities are iteratively tweaked and dose distribution changes are observed until desirable intensities are achieved





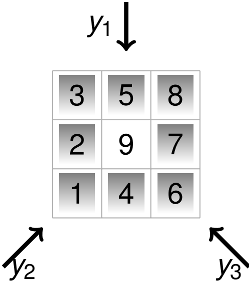
3D-CRT: Inverse Planning

- Can we avoid iterative process of aperture tweaking in forward planning?
- *Inverse planning* aims at directly determining appropriate aperture intensities using *mathematical optimization*

3D-CRT Example: Inverse Planning

- Dose distribution is calculated using

$$\mathbf{d} = \underbrace{\begin{pmatrix} D_{11} & D_{12} & \dots & D_{19} \\ D_{21} & D_{22} & \dots & D_{29} \\ D_{31} & D_{32} & \dots & D_{39} \end{pmatrix}^{\top}}_{\mathcal{D}\text{: dose deposition coefficient matrix}} \cdot \underbrace{\begin{pmatrix} y_1 \\ y_2 \\ y_3 \end{pmatrix}}_{\mathbf{y}\text{: aperture intensities}}$$

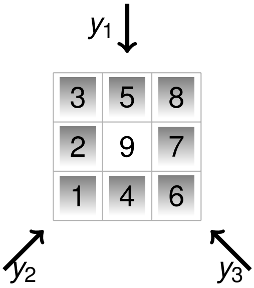


3D-CRT Example: Inverse Planning

- Given $\mathcal{D}$ and ideal dose distribution $\mathbf{d}^*$, we need to find appropriate $\mathbf{y}$ such that

$$\mathbf{d}^* = \mathcal{D}^\top \mathbf{y}$$
$$\mathbf{y} \geq \mathbf{0}$$

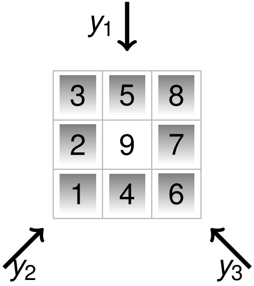
  - it is overdetermined ($\|V\| >> \|K\|$)
  - $\mathcal{D}$ is sparse
- To avoid this issue we use mathematical optimization



3D-CRT Example: Inverse Planning

- We use some dose evaluation criteria
  - e.g., piecewise quadratic voxel-based penalties

$$G(\mathbf{d}) = \underbrace{\max\{d_9 - 45, 0\}^2}_{\text{spinal cord penalty}} + \underbrace{\frac{1}{8}\sum_{v=1}^{8}(d_v - 60)^2}_{\text{target penalty}}$$



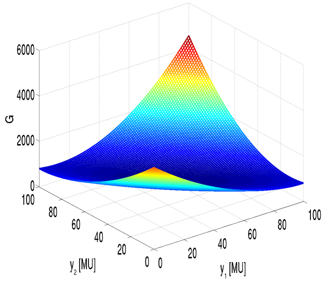
$$\mathbf{d} = \mathcal{D}\mathbf{y}$$

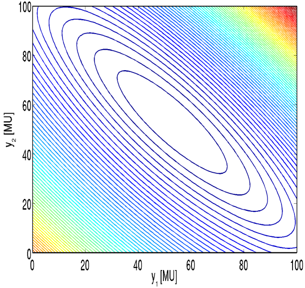
- We can also enforce constraints on dose distribution

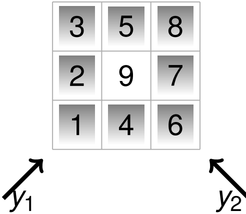
$$d_v \geq 60 \qquad v = 1, \ldots, 8$$
$$d_9 \leq 45$$

3D-CRT Example: Finding Optimal Intensities

- *G* values and contour lines as a function of aperture intensities

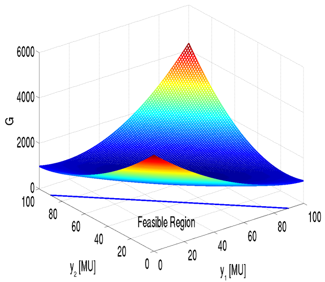


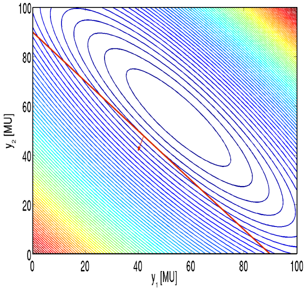


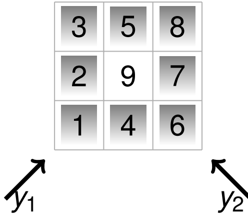


3D-CRT Example: Finding Optimal Intensities

- Optimal intensities change if constraints on dose distribution are enforced, e.g., $d_9 \leq 45$ (maximum dose in spinal cord)







3D-CRT: Mathematical Optimization

- Inverse planning uses mathematical optimization to determine aperture intensities

$$\min G(\mathbf{d})$$

subject to

$$\begin{aligned} \mathbf{d} &= \mathcal{D}^\top \mathbf{y} \\ H(\mathbf{d}) &\leq \mathbf{0} \\ \mathbf{y} &\geq \mathbf{0} \end{aligned}$$

- Notation
  - K: set of apertures
  - $\mathcal{D} = [\mathcal{D}_{kv}]$: dose deposition coefficient matrix
  - $\mathbf{d} = (d_v : v \in V)^\top$: vector of dose distribution
  - $\mathbf{y} = (y_k : k \in K)^\top$: vector of aperture intensities
  - G: dose evaluation function
  - H: dose constraints

Different Classes of Optimization Problems

- Based on properties of dose evaluation criteria and constraints problems are classified into
  - *Linear Programming* (LP)
    - e.g., piecewise linear penalties
  - *Nonlinear Programming* (NLP)
    - e.g., piecewise quadratic penalties, TCP, NTCP, EUD
  - *Integer Programming* (IP)
    - e.g., dose-volume histogram (DVH) criterion: at least 95% of target voxels receive at least 60 Gy

$$\frac{1}{\| V_T \|} \sum_{v \in V_T} z_v \leq 0.05$$

$z_v \in \{0, 1\}$indicates if $d_v \leq 60$ or not

3D-CRT Example: NLP Solution Approach

- NLP problem

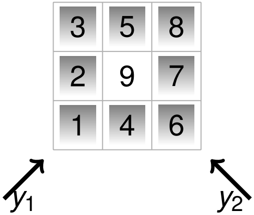
$$\min G(\mathbf{d}) = \sum_{v=1}^{8} (d_v - 60)^2$$

subject to

$$\mathbf{d} = \mathcal{D} \begin{pmatrix} y_1 \\ y_2 \end{pmatrix}$$

$$d_9 \leq 45$$

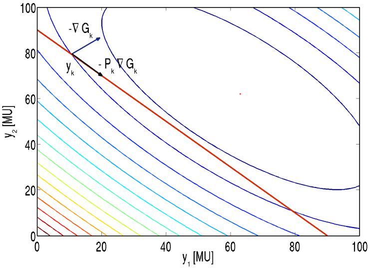
$$y_1, y_2 \geq 0$$



- Dose variables can be substituted with aperture intensities $G(\mathbf{d}) \rightarrow G\left(\mathcal{D}^\top \mathbf{y}\right)$

3D-CRT Example: Gradient Projection Method

- Gradient Projection Method (see [Rosen, 1960])
  - at iteration k, given $\mathbf{y}_k$, steepest descent is the negative gradient (i.e., $-\nabla G_k$)
  - moving along $-\nabla G_k$ may violate constraints
  - $-\nabla G_k$ is projected onto feasible region $-P_k \nabla G_k$ to obtain
    - improving and feasible direction



3D-CRT Example: Gradient Projection Method

- Steps of the algorithm at iteration k
  1. gradient: $\mathbf{y}_k = \begin{pmatrix} 10 \\ 80 \end{pmatrix}, \nabla G_k = \begin{pmatrix} -153.8 \\ -79.6 \end{pmatrix}$
  2. projection matrix: $P_k = I - A_k^\top \left(A_k A_k^\top\right)^{-1} A_k$,

     active constraints $A_k = (0.5 \;\; 0.5)$, $P_k = \begin{pmatrix} 0.5 & -0.5 \\ -0.5 & 0.5 \end{pmatrix}$
  3. projected gradient: $\mathbf{s}_k = -P_k \nabla G_k = \begin{pmatrix} 37 \\ -37 \end{pmatrix}$

3D-CRT Example: Gradient Projection Method

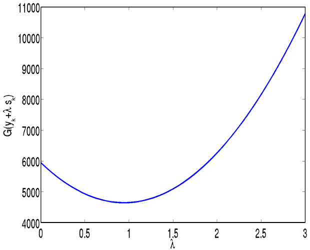
4 line search:

$$\lambda^* = \operatorname*{argmin}_{\lambda \geq 0} G(\mathbf{y}_k + \lambda \mathbf{s}_k) = 0.95$$

5 solution update:

$$\mathbf{y}_{k+1} = \mathbf{y}_k + \lambda^* \mathbf{s}_k = \begin{pmatrix} 45 \\ 45 \end{pmatrix}$$

- At iteration $k+1$
  - $\mathbf{s}_{k+1} = \begin{pmatrix} 0 \\ 0 \end{pmatrix}$ and $\mathbf{y}_{k+1}$ is the optimal solution



3D-CRT: Summary

- Radiotherapy is used to treat/control localized disease
- In 3D-CRT, aperture at each beam angle conforms to tumor shape in beam's eye-view
- In 3D-CRT, treatment planning involves determining aperture intensities
  - forward planning
    - we manually determine intensities in an iterative process
  - inverse planning
    - mathematical optimization techniques are used

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