Optimization Modelling and Computational Issues in Radiation Therapy

(lecture developed in collaboration with Peng Sun)

February 3, 2004

1 Outline

SLIDE 1

1. Radiation Therapy
2. Linear Optimization Models
3. Computation
4. Nonlinear and Mixed-Integer Models
5. Looking Ahead to the Course

2 Radiation Therapy

2.1 The Problem

2.2 Overview

SLIDE 2

- This year, 1,200,000 Americans will be diagnosed with cancer
- 600,000+ patients will receive radiation therapy
  - beam(s) of radiation delivered to the body in order to kill cancer cells
- Sadly, only 67% of "curable" patients will be cured

SLIDE 3

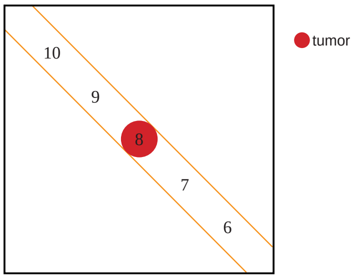
- High doses of radiation (energy/unit mass) can kill cells and/or prevent them from growing and dividing
  - true for cancer cells *and* normal cells
- Radiation is attractive because the repair mechanisms for cancer cells is less efficient than for normal cells

SLIDE 4

- Recent advances in radiation therapy now make it possible to:
  - map the cancerous region in greater detail
  - aim a larger number of different "beamlets" with greater specificity
- Spawned the new field of *tomotherapy*
- "Optimizing the Delivery of Radiation Therapy to Cancer Patients," by Shepard, Ferris, Olivera, and Mackie, *SIAM Review*, Vol. 41, pp. 721–744, 1999.

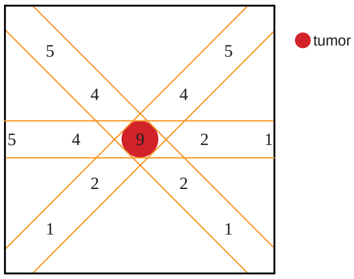
2.2.1 Conventional Radiotherapy

Slide 5



Relative Intensity of Dose Delivered

Slide 6



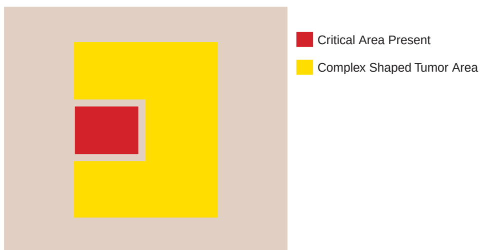
Relative Intensity of Dose Delivered

Slide 7

In conventional radiotherapy

- 3 to 7 beams of radiation
- radiation oncologist and physicist work together to
- determined by manual "trial-and-error" process

Slide 8



With only a small number of beams, it is difficult/impossible to deliver required dose to tumor without impacting the critical area.

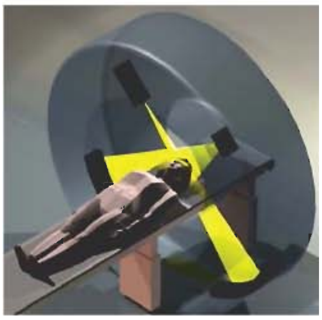
2.2.2 Recent Advances

SLIDE 9

- More accurate map of tumor area
  - CT — Computed Tomography
  - MRI — Magnetic Resonance Imaging

SLIDE 10

- More accurate delivery of radiation
  - IMRT: Intensity Modulated Radiation Therapy
  - Tomotherapy



2.2.3 Formal Problem Statement

SLIDE 11

- For a given tumor and given critical areas
- For a given set of possible beamlet origins and angles
- Determine the weight on each beamlet such that:
  - dosage over the tumor area will be at least a target level γ_L
  - dosage over the critical area will be at most a target level γ_U

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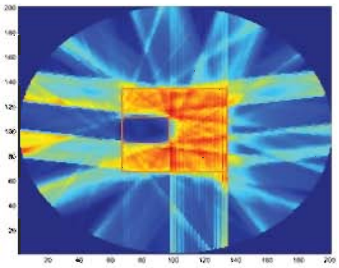

3 Linear Optimization Models

3.1 Discretize the Space

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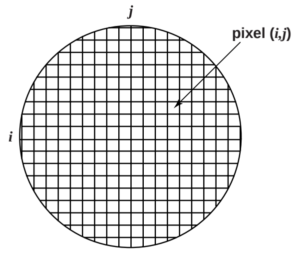
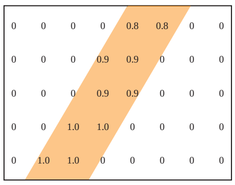
Divide up region into a 2-dimensional (or 3-dimensional) grid of pixels



3.2 Create Beamlet Data

Slide 14

Create the beamlet data for each of $p = 1, \ldots, n$ possible beamlets.
D^p is the matrix of unit doses delivered by beam p .



$D^p_{i\,j}$ = unit dose delivered to pixel (i, j) by beamlet p.

3.3 Dosage Equations

Slide 15

Decision variables $w = (w_1, \ldots, w_n)$

w_p = intensity weight assigned to beamlet p,
$p = 1, \ldots, n$.

$$D_{i\,j} := \sum_{p=1}^{n} D^p_{i\,j}\, w_p$$

(":=" denotes "by definition")

$$D := \sum_{p=1}^{n} D^p\, w_p$$

is the matrix of the integral dose (total delivered dose)

3.4 Definitions of Regions

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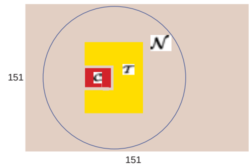

$\mathcal{T}$ is the target area
$\mathcal{C}$ is the critical area
$\mathcal{N}$ is normal tissue
$\mathcal{S} := \mathcal{T} \cup \mathcal{C} \cup \mathcal{N}$

3.5 Ideal Linear Model

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$$\begin{array}{lll} \underset{w,D}{\text{minimize}} & \sum_{(i,j)\in\mathcal{S}} D_{i\,j} & \\ \text{s.t.} & D_{i\,j} = \sum_{p=1}^{n} D_{i\,j}^{p}\, w_p & (i,j)\in\mathcal{S} \\ & w \geq 0 & \\ & D_{i\,j} \geq \gamma_L & (i,j)\in\mathcal{T} \\ & D_{i\,j} \leq \gamma_U & (i,j)\in\mathcal{C} \end{array}$$

SLIDE 18

$$\begin{array}{lll} \underset{w,D}{\text{minimize}} & \sum_{(i,j)\in\mathcal{S}} D_{i\,j} & \\ \text{s.t.} & D_{i\,j} = \sum_{p=1}^{n} D_{i\,j}^{p}\, w_p & (i,j)\in\mathcal{S} \\ & w \geq 0 & \\ & D_{i\,j} \geq \gamma_L & (i,j)\in\mathcal{T} \\ & D_{i\,j} \leq \gamma_U & (i,j)\in\mathcal{C} \end{array}$$

- Unfortunately, this model is typically infeasible.
- Cannot deliver dose to tumor without some harm to critical area(s).

3.6 Engineered Approaches

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$$\begin{array}{lll} \underset{w,D}{\text{minimize}} & \theta_{\mathcal{T}} \sum_{(i,j)\in\mathcal{T}} D_{i\,j} + \theta_{\mathcal{C}} \sum_{(i,j)\in\mathcal{C}} D_{i\,j} + \theta_{\mathcal{N}} \sum_{(i,j)\in\mathcal{N}} D_{i\,j} & \\ \text{s.t.} & D_{i\,j} = \sum_{p=1}^{n} D_{i\,j}^{p}\, w_p & (i,j)\in\mathcal{S} \\ & w \geq 0 & \\ & D_{i\,j} \;\geq\; \gamma_{i\,j}^{L} & (i,j)\in\mathcal{T} \\ & w_m \leq 0.05 \sum_{p=1}^{n} w_p & m = 1,\ldots,n \end{array}$$

SLIDE 20

Some other possible objective functions:

Let $(\text{Target})_{i\,j}$ be the target prescribed dose to be delivered to pixel (i,j)

$$\begin{array}{lll} \underset{w,D}{\text{minimize}} & \max_{(i,j)\in\mathcal{S}} |D_{i\,j} - (\text{Target})_{i\,j}| & \\ \text{s.t.} & D_{i\,j} = \sum_{p=1}^{n} D_{i\,j}^{p}\, w_p & (i,j)\in\mathcal{S} \\ & w \geq 0 & \end{array}$$

SLIDE 21

This is the same as:

$$\begin{array}{lll} \underset{w,D,\mu}{\text{minimize}} & \mu & \\ \text{s.t.} & -\mu \leq D_{i\,j} - (\text{Target})_{i\,j} \leq \mu & (i,j)\in\mathcal{S} \\ & D_{i\,j} = \sum_{p=1}^{n} D_{i\,j}^{p}\, w_p & (i,j)\in\mathcal{S} \\ & w \geq 0 & \end{array}$$

SLIDE 22

Here is another model:

$$\begin{array}{lll} \underset{w,D}{\text{minimize}} & \sum_{(i,j)\in\mathcal{S}} |D_{i\,j} - (\text{Target})_{i\,j}| & \\ \text{s.t.} & D_{i\,j} = \sum_{p=1}^{n} D_{i\,j}^{p}\, w_p & (i,j)\in\mathcal{S} \\ & w \geq 0 & \end{array}$$

SLIDE 23

This is the same as:

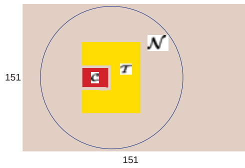
$$\begin{aligned} \underset{w,D,\Delta}{\text{minimize}} \quad & \sum_{(i,j)\in\mathcal{S}} \Delta_{i\,j} \\ \text{s.t.} \quad & D_{i\,j} = \sum_{p=1}^{n} D^{p}_{i\,j}\, w_p \qquad (i,j)\in\mathcal{S} \\ & w \geq 0 \\ & -\Delta_{i\,j} \leq D_{i\,j} - (\text{Target})_{i\,j} \leq \Delta_{i\,j} \qquad (i,j)\in\mathcal{S} \end{aligned}$$

4 Computation

4.1 Base Case Model

SLIDE 24

Consider the "base case" example problem:



$$\begin{aligned} (\text{Target})_{i\,j} &= 16, \quad (i,j)\in\mathcal{T} \\ (\text{Target})_{i\,j} &= 0, \quad (i,j)\in\mathcal{C} \\ (\text{Target})_{i\,j} &= 0, \quad (i,j)\in\mathcal{N} \end{aligned}$$

SLIDE 25

$$\begin{aligned} \underset{w,D,\Delta}{\text{minimize}} \quad & 1\cdot\sum_{(i,j)\in\mathcal{N}} \Delta_{i\,j} + 100 \sum_{(i,j)\in\mathcal{C}} \Delta_{i\,j} + 30 \sum_{(i,j)\in\mathcal{T}} \Delta_{i\,j} \\ \text{s.t.} \quad & D_{i\,j} = \sum_{p=1}^{n} D^{p}_{i\,j}\, w_p \qquad (i,j)\in\mathcal{S} \\ & w \geq 0 \\ & -\Delta_{i\,j} \leq D_{i\,j} - (\text{Target})_{i\,j} \leq \Delta_{i\,j} \qquad (i,j)\in\mathcal{S} \end{aligned}$$

4.2 Size of the Model

4.2.1 Dimensional Analysis

SLIDE 26

$$\begin{aligned} \underset{w,D,\Delta}{\text{minimize}} \quad & 1\cdot\sum_{(i,j)\in\mathcal{N}} \Delta_{i\,j} + 100 \sum_{(i,j)\in\mathcal{C}} \Delta_{i\,j} + 30 \sum_{(i,j)\in\mathcal{T}} \Delta_{i\,j} \\ \text{s.t.} \quad & D_{i\,j} = \sum_{p=1}^{n} D^{p}_{i\,j}\, w_p \qquad (i,j)\in\mathcal{S} \\ & w \geq 0 \\ & -\Delta_{i\,j} \leq D_{i\,j} - (\text{Target})_{i\,j} \leq \Delta_{i\,j} \qquad (i,j)\in\mathcal{S} \end{aligned}$$

Dimensional Analysis:

number of pixels $= 31,397 (\approx \pi * 100^2)$

number of beamlets $= 564$ $\quad (n)$

$|\mathcal{T}| = 3,859$; $\quad |\mathcal{C}| = 630$; $\quad |\mathcal{N}| = 26,908$

$|\mathcal{S}| = 31,397$

SLIDE 27

$$\begin{array}{lll} \underset{w,D,\Delta}{\text{minimize}} & 1 \cdot \sum_{(i,j)\in\mathcal{N}} \Delta_{i\,j} + 100 \sum_{(i,j)\in\mathcal{C}} \Delta_{i\,j} + 30 \sum_{(i,j)\in\mathcal{T}} \Delta_{i\,j} & \\ \text{s.t.} & D_{i\,j} = \sum_{p=1}^{n} D^{p}_{i\,j}\, w_p & (i,j)\in\mathcal{S} \\ & w \geq 0 & \\ & -\Delta_{i\,j} \leq D_{i\,j} - (\text{Target})_{i\,j} \leq \Delta_{i\,j} & (i,j)\in\mathcal{S} \end{array}$$

Decision Variables	Number
$D_{i\,j}$	31,397
w	564
$\Delta_{i\,j}$	31,397
Total	63,358

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$$\begin{array}{lll} \underset{w,D,\Delta}{\text{minimize}} & 1 \cdot \sum_{(i,j)\in\mathcal{N}} \Delta_{i\,j} + 100 \sum_{(i,j)\in\mathcal{C}} \Delta_{i\,j} + 30 \sum_{(i,j)\in\mathcal{T}} \Delta_{i\,j} & \\ \text{s.t.} & D_{i\,j} = \sum_{p=1}^{n} D^{p}_{i\,j}\, w_p & (i,j)\in\mathcal{S} \\ & w \geq 0 & \\ & -\Delta_{i\,j} \leq D_{i\,j} - (\text{Target})_{i\,j} \leq \Delta_{i\,j} & (i,j)\in\mathcal{S} \end{array}$$

4.2.2 Number of Constraints

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Simple Variable Upper/Lower Bounds	Number
$w \geq 0$	564
Total	564

Other Constraints*	Number
$D_{ij} =$	31,397
$\leq D_{ij} - (\text{Target})_{ij} \leq$	62,794
Total	94,191

*We usually exclude simple variable upper/lower bounds when counting constraints.

4.2.3 Summary

SLIDE 30

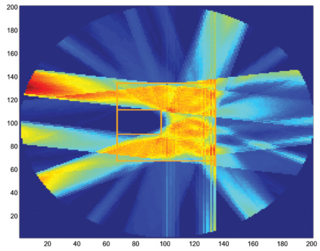
Variables	Constraints*
63,358	94,191

*Excludes variable upper/lower bounds.

4.3 Base Case Model

4.3.1 Optimal Solution

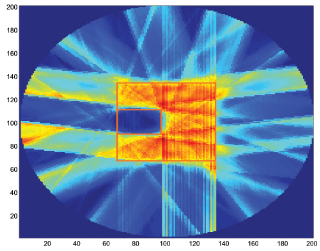
SLIDE 31



Base Case Model Solution

4.4 Another Model Solution

SLIDE 32

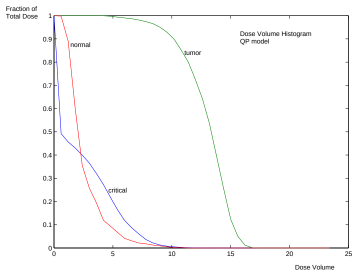


Solution of a nonlinear model.

4.5 Dose Histogram

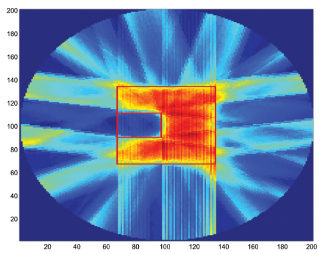
4.5.1 of Solution

SLIDE 33



4.6 Another Model Solution

SLIDE 34



Solution of a nonlinear model, where $\theta_{\mathcal{N}} = \theta_{\mathcal{C}} = \theta_{\mathcal{T}} = 1$.

5 Computation

5.1 Computational Issues

5.1.1 Software/Algorithms

SLIDE 35

- Software codes:
  - CPLEX simplex (pivoting method)
  - CPLEX barrier
  - LOQO
- Algorithms:
  - Simplex method ("pivoting" method)
  - Interior-point method (IPM) ("barrier" method)

5.1.2 Counting Iterations

SLIDE 36

- Iteration Counts:
  - Number of pivots for simplex method
  - Number of Newton steps for IPM

5.1.3 Issues in Running Times

SLIDE 37

- Running time will be affected by:
  - number of constraints
  - number of variables
  - software code
  - type of algorithm (simplex or IPM)
  - properties of linear algebra systems involved
    * density/patterns of nonzeroes of matrix systems to be solved
  - other problem characteristics specific to problem
  - idiosyncratic influences
  - pre-processing heuristics

5.2 Base Case

5.2.1 No Pre-Processing

SLIDE 38

- Base Case Model
- No Pre-Processing

Code	Algorithm	Iterations	Running Time	
			CPU (sec)	Wall (minutes)
CPLEX	Simplex	183,530	440	250
CPLEX	Barrier	49	13	37

5.3 Some Generic Rules

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1. The simplex algorithm is designed to handle variables with lower bounds and upper bounds:

$$\begin{aligned} \min_x \quad & c^T x \\ & Ax = b \\ & \ell \le x \le u \end{aligned}$$

   where $\ell_j = -\infty$ and/or $u_j = +\infty$ is allowed.

2. We say x_j has no bounds if $\ell_j = -\infty$ and $u_j = +\infty$. Otherwise x_j is a bounded variable.

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$$\begin{aligned} \min_x \quad & c^T x \\ & Ax = b \\ & \ell \le x \le u \end{aligned}$$

3. For the simplex method, the work per pivot generally depends on the number of nonzeros in A.
4. If A is very sparse (its density of nonzero elements is low), then the work per pivot will be low.
5. The number of simplex pivots in a "good" model is roughly between m and $10n$.

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$$\begin{aligned} \min_x \quad & c^T x \\ & Ax = b \\ & \ell \le x \le u \end{aligned}$$

5. The work per iteration of an interior-point method generally depends on the structure of the matrix

$$K = \begin{pmatrix} I & A^T \\ A & 0 \end{pmatrix}.$$

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$$K = \begin{pmatrix} I & A^T \\ A & 0 \end{pmatrix}.$$

6. The structure of K is often (but not always) related to the structure of the matrix AA^T because the following two matrices are "similar":

$$K = \begin{pmatrix} I & A^T \\ A & 0 \end{pmatrix} \quad P = \begin{pmatrix} I & A^T \\ 0 & -AA^T \end{pmatrix}.$$

7. The number of interior-point method iterations is typically 25–80 (*independent* of m and/or n).

5.4 Pre-Processing

5.4.1 Heuristics

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Pre-Processing Heuristics in
Commercial-Grade Software

- Designed to Eliminate Constraints and/or Variables

- Example:

$$\begin{array}{cccccc} -5x & +3y & +z & = & 17 \\ 0 \le x \le 4 & 0 \le y \le 2 & 10 \le z \le 40 \end{array}$$

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- Example:

$$\begin{array}{cccccc} -5x & +3y & +z & = & 17 \\ 0 \le x \le 4 & 0 \le y \le 2 & 10 \le z \le 40 \end{array}$$

- $z = 17 + 5x - 3y \ge 17 + 5(0) - 3(2) = 11 \ge 10$

- $z = 17 + 5x - 3y \le 17 + 5(4) - 3(0) = 37 \le 40$
- Therefore we can eliminate the bounds on z
- Therefore we can treat z as a free variable
- Therefore we can eliminate z from our model altogether.

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- Base Case Model

- With Pre-Processing

Code	Algorithm	Iterations	Running Time CPU (sec)	Running Time Wall (minutes)
CPLEX	Simplex	18,428	4.3	4
CPLEX	Barrier	16	130	133

5.5 Equivalent Formulation

5.5.1 "Small" Model

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Equivalent Formulation: (eliminate $D_{i\,j}$)
"Small" Model:

$$\begin{array}{ll} \underset{w,\Delta}{\text{minimize}} & 1 \cdot \sum_{(i,j)\in\mathcal{N}} \Delta_{i\,j} + 100 \sum_{(i,j)\in\mathcal{C}} \Delta_{i\,j} + 30 \sum_{(i,j)\in\mathcal{T}} \Delta_{i\,j} \\ \text{s.t.} & -\Delta_{i\,j} \le \sum_{p=1}^{n} D_{i\,j}^{p}\, w_p - (\text{Target})_{i\,j} \le \Delta_{i\,j} \qquad (i,j) \in \mathcal{S} \\ & w \ge 0 \end{array}$$

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	Base Case Model	Small Model
Variables	$63,358$	$31,961$
Constraints*	$94,191$	$62,794$

*always excludes simple variable upper/lower bounds

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- Small Model

Code	Algorithm	Iterations	Running Time CPU (sec)	Running Time Wall (minutes)
CPLEX	Simplex	171,656	390	216
CPLEX	Barrier	57	80	31

5.6 Comparisons

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Code	Algorithm	Model	Running Time Wall (minutes)
CPLEX	Simplex	Base Case	250
		Pre-Processed	4
		Small Model	216
CPLEX	Barrier	Base Case	37
		Pre-Processed	133
		Small Model	31

6 Nonlinear Optimization

6.1 Quadratic Model

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$$
\begin{aligned}
QP: \quad \underset{w,D}{\text{minimize}} \quad & 1 \cdot \sum_{(i,j)\in\mathcal{N}} [D_{i\,j} - \text{Target}_{i\,j}]^2 \\
& + 100 \sum_{(i,j)\in\mathcal{C}} [D_{i\,j} - \text{Target}_{i\,j}]^2 \\
& + 30 \sum_{(i,j)\in\mathcal{T}} [D_{i\,j} - \text{Target}_{i\,j}]^2 \\
\text{s.t.} \quad & D_{i\,j} = \sum_{p=1}^{n} D^p_{i\,j}\, w_p \qquad (i,j) \in \mathcal{S} \\
& w \geq 0
\end{aligned}
$$

6.1.1 Quadratic Model Output

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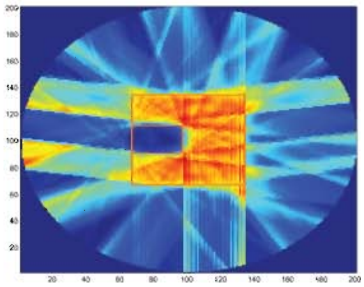

6.2 Quadratic Model

6.2.1 Computational Results

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Model	Code	Algorithm	Iterations	Running Time CPU (sec)
Base Case QP Model	LOQO	Barrier	31	82.7
Small QP Model	LOQO	Barrier	32	149.0

7 Mixed Integer Optimization

7.1 Limiting the Number of Beamlets

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$$
\begin{array}{lll}
\underset{w,D,\Delta,y}{\text{minimize}} & 1 \cdot \sum_{(i,j)\in\mathcal{N}} \Delta_{i\,j} + 100 \sum_{(i,j)\in\mathcal{C}} \Delta_{i\,j} + 30 \sum_{(i,j)\in\mathcal{T}} \Delta_{i\,j} & \\
\text{s.t.} & D_{i\,j} = \sum_{p=1}^{n} D^{p}_{i\,j}\, w_p & (i,j) \in \mathcal{S} \\
& w \geq 0 & \\
& -\Delta_{i\,j} \leq D_{i\,j} - (\text{Target})_{i\,j} \leq \Delta_{i\,j} & (i,j) \in \mathcal{S} \\
& w_p \leq 100 y_p & p = 1,\ldots,n \\
& y_p \in \{0,1\} & p = 1,\ldots,n \\
& \sum_{p=1}^{n} y_p \leq 15. &
\end{array}
$$

7.2 Computation

7.2.1 CPLEX MIP Solver

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MIP Gap (%)	Simplex Pivots	Running Time CPU (seconds)	Running Time Wall (minutes)
20	11,646	7	4
15	11,646	7	4
12	11,646	5	4
10	14,538	9	6
7	14,538	7	6
5	14,538	10	6
4	14,538	7	6
3	14,538	5	6
2	3,655,445	1,700	25.3 hours

8 Modifications of the Model

8.1 Partial Volume Constraints

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Partial Volume Constraints:

"No more than 20% of the critical region can exceed a dose of $30G_y$."

"No more than 5% of the critical region can exceed a dose of $50G_y$."

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Approach #1 (Integer Programming Model)
Let M be a very large number,

$$\begin{array}{lllll} D_{i\,j} & \leq & 30 + M \cdot y_{i\,j}, & y_{i\,j} \in \{0,1\}, & (i\,j) \in \mathcal{C} \\ D_{i\,j} & \leq & 50 + M \cdot z_{i\,j}, & z_{i\,j} \in \{0,1\}, & (i\,j) \in \mathcal{C} \end{array}$$

$$\sum_{(i\,j)\in\mathcal{C}} y_{i\,j} \leq |\mathcal{C}| \times 0.20$$

$$\sum_{(i\,j)\in\mathcal{C}} z_{i\,j} \leq |\mathcal{C}| \times 0.05$$

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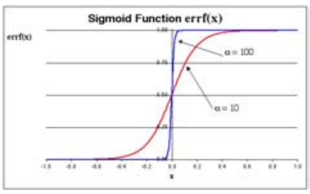
Approach #2 (Error Function Approach)
The *error function*, or *sigmoid function*, is of the form:

$$\mathrm{err}f(x) = \frac{1}{1+e^{-\alpha x}}$$



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$$\begin{array}{llll} \mathrm{err}f(x) & = & \frac{1}{2} & \text{at} \quad x = 0 \\ \mathrm{err}f(x) & \to & 1 & \text{as} \quad x \to \infty \\ \mathrm{err}f(x) & \to & 0 & \text{as} \quad x \to -\infty \end{array}$$

Instead of integer variables, we use

$$\sum_{(i\,j)\in\mathcal{C}} \mathrm{err}f(D_{i\,j} - 30) \quad \leq \quad |\mathcal{C}| \times 0.20$$

$$\sum_{(i\,j)\in\mathcal{C}} \mathrm{err}f(D_{i\,j} - 50) \quad \leq \quad |\mathcal{C}| \times 0.05$$

9 Looking Ahead

9.1 Modeling Languages

9.1.1 Used in the Course

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- Modeling languages and software used in the course
  - OPL Studio
    - linear and mixed-integer programming
    - solver is CPLEX simplex and/or CPLEX barrier
    - first half of course
  - AMPL
    - linear and nonlinear programming
    - solver is LOQO
    - second half of course

9.2 Modeling Tools

9.2.1 and Issues

SLIDE 60

- "Column Generation" (week 3)
  - generates new decision variables "on the fly"
- Exact optimization and exact feasibility
  - in models
  - in algorithms
- Computational Issues in LP (next lecture)
  - simplex method with upper/lower bounds
  - methods for updating the basis inverse