Optimization in Medicine

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The Four Questions

- WHO?
- WHAT?
- HOW?
- WHY?

Who?

Here at SIOPT:

- MS4
  - Edwin Romeijn, James Dempsey, Mustafa Sir, Marina Epelman, Karl-Heinz Küfer, Eva Lee
- PP0
  - Jorge Diaz
- CP9
  - Qing-Rong Wu, Suliman Al-Homidan, Roger Fletcher
- MS25
  - Fredrik Carlsson, Anders Forsgren, Yair Censor, Tommy Elfving, Daniel Glaser
- MS44
  - Gino Lim, Michael Ferris, Stephen Wright, Yin Zhang, Michael Merritt, Allen Holder, Vira Chankong
- MS57
  - Peter Hammer

And many many more not here!

Who (?)

Who?

Collaborators:

- NIH
  - Bradford Wood, Calvin Johnson
- Georgetown University & Medical Center
  - Brett Opell, Jianchao Zhang, Anatoly Dritschilo, Donald McCrae
- GMU
  - Masami Stahr, Fran Nelson

Contributors:

- John Bauer, John Lynch, Judd Moul, Seong Mun, Isabel Sesterhen, Xiaohu Yao, Wei Zhang,

What?

- Medical Image Reconstruction
  - Positron Emission Tomography (PET)
  - Discrete Tomography & Emission Discrete Tomography
- Diagnosis & Prognosis
  - Breast Cancer
  - Coronary Risk Prediction
  - Seizure Warning
  - Prostate Cancer

What?

Optimization of Diagnosis

What?

Treatment

- Radiation Treatment Planning
  - Conformal Radiation Therapy
  - Brachytherapy
  - Gamma Knife Radiosurgery
  - Intensity Modulated Radiation Treatment
- Thermal Therapy
  - Radiofrequency Ablation
  - Hyperthermia

How?

- LP Linear Programming
- MIP Mixed Integer Programming
- MINLP Mixed Integer NLP
- QP Quadratic Programming
- NLP Nonlinear Programming
- SP Stochastic Programmin
- GA Genetic Algorithms
- SA Simulated Anealing
- LDA Logical Data Analysis
- SVM Support Vector Machines
- MOO Multi-objective Optimization
- PDE's PDE Constrained Optimization

How?

Modeling,
Modeling,
Modeling...

The optimization is only as good as your model!

Why?

“Lets just start cutting and see what happens”

Optimization makes a difference!

Agenda

- Optimal Biopsy Protocols for Detection of Prostate Cancer
- Intensity Modulated Radiation Treatment
- Radiofrequency Ablation of Hepatic Tumors

Optimization of

Biopsy Protocols for Detection of Prostate Cancer

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Prostate Cancer & Biopsy

- Prostate cancer is the second leading cause of cancer-related death among American men.
- In 2005 in US alone
  - 230,000 new cases expected to be diagnosed
  - 30,000 men are expected to die.
- Unfortunately, imaging does not effectively differentiate cancerous tissue from normal prostate tissue
- Gold standard for prostate cancer detection: transrectal ultrasound-guided needle biopsy
- Problem: current biopsy protocols are not adequate in terms of detection rate

Systematic Prostate Biopsy

- Biopsy protocol:
  - the number of needles to be used and their location on the prostate.
- Worldwide the adopted protocol has been the “sextant” method (6 needles in mid prostate)
  - misses 20% or more of cancers
- Recently some alternative protocols shown empirically to have better detection rates
- Our goal:

Determine an optimal needle biopsy protocol

The Approach

- Use real prostate specimens obtained from prostatectomies to reconstruct 3-D prostate models (301 specimens)
- Superimpose a fine 3-D grid over each model and calculate cancer presence within the grid
- Develop a 3-D map of tumor location
- Use the map to determine the biopsy protocols that maximize the probability of detection
- Protocols should be identifiable by the physician to within the resolution of ultrasound

3-D Surface Modeling

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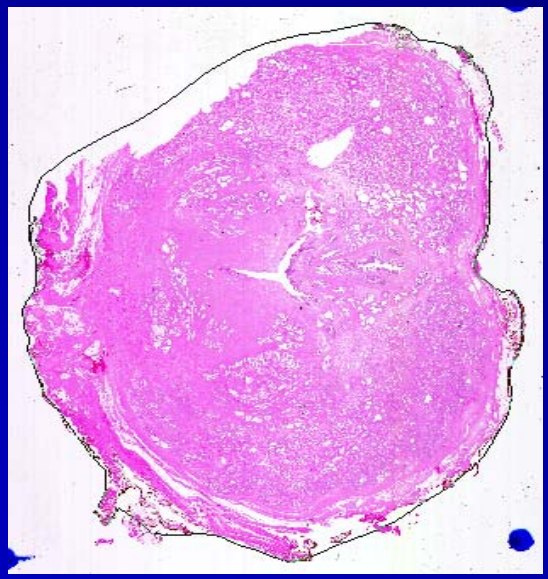

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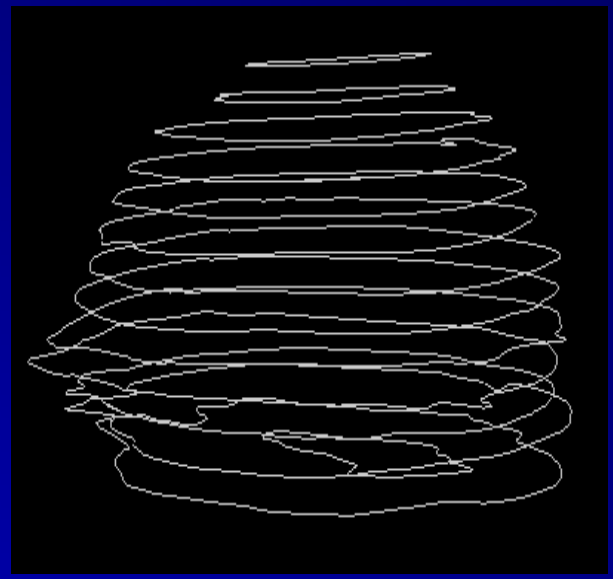

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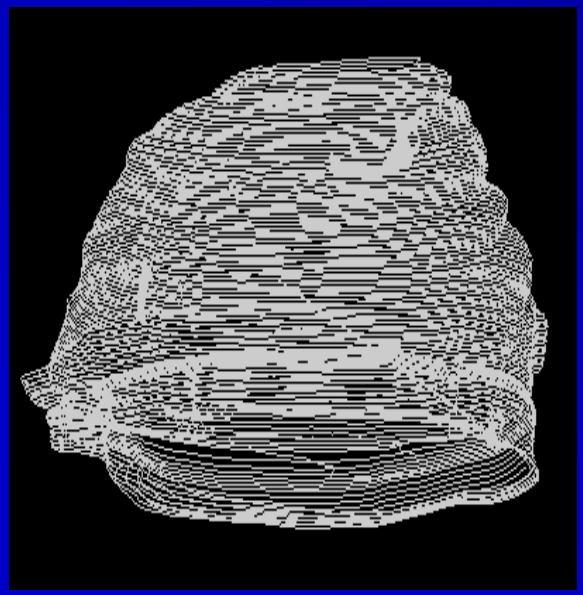

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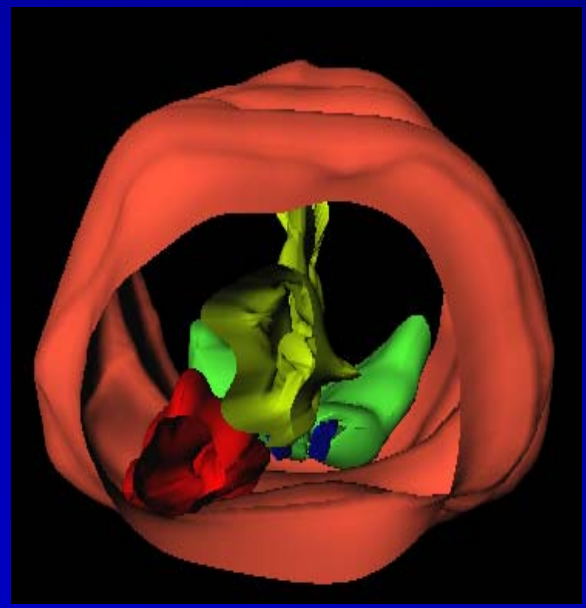
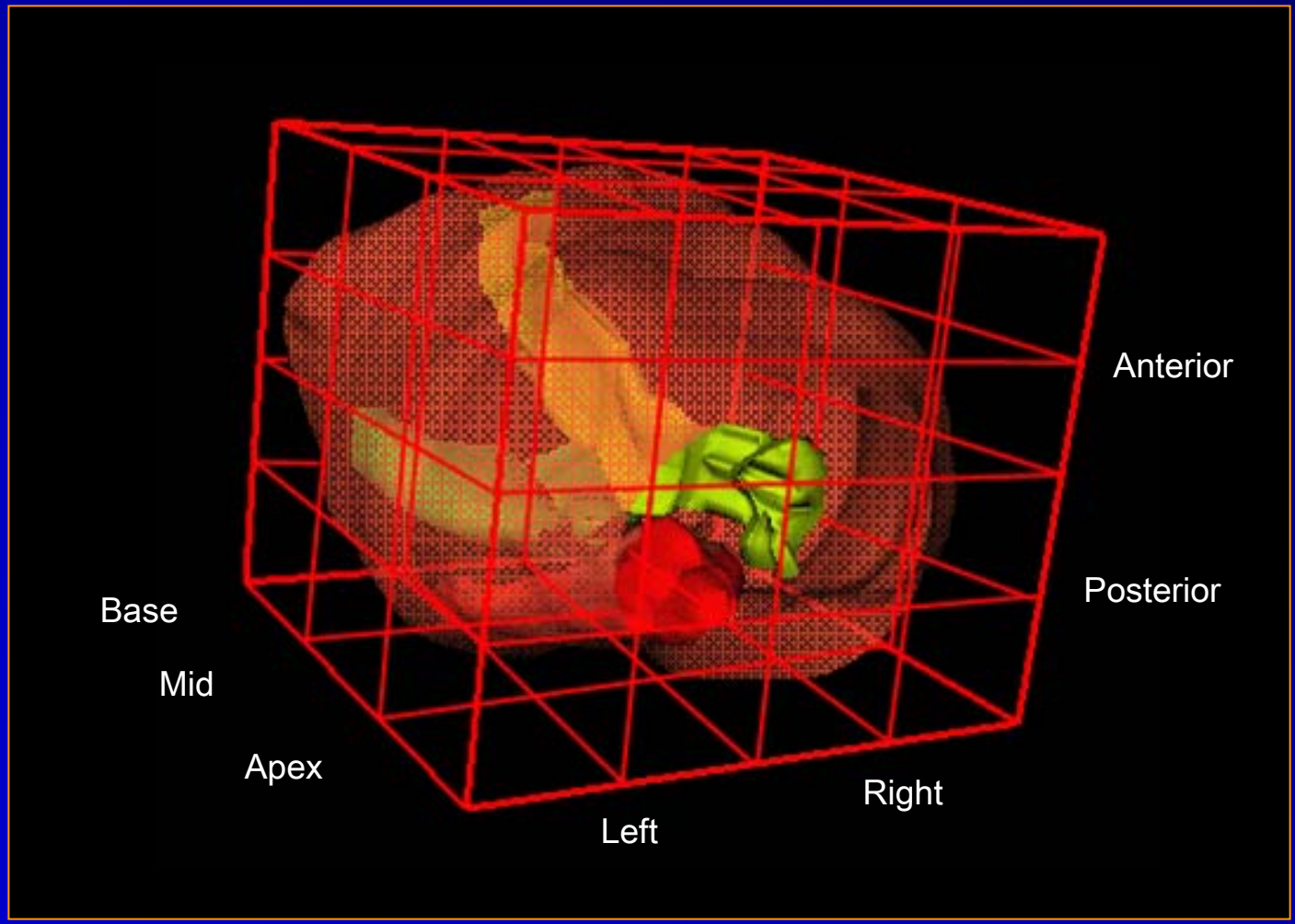


Prostate Division for Biopsy Protocols - 48 Zones



Probability of Detecting Cancer in a Zone

- Developed a fine grid cancer map for each patient
- Developed a probability model of physician's needle placement:
  - the longitudinal position of the needle insertion
  - the firing angle of the needle
  - the depth

  assumed to be independent Normal variables
- Combined the above model with
  - patient's prostate volume
  - patient's cancer map
  - needle core volume

  to estimate the probability p_{ij} that a needle probe in zone j will be positive for patient i

Optimal Protocol for a Prescribed Number of Needles

- Let

$$x_j = \begin{cases} 1 & \text{if a biopsy is taken in zone } j \\ 0 & \text{otherwise,} \end{cases}$$

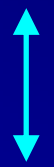
$$\begin{aligned} p_{ij} = &\ \text{probability that a needle in zone } j \\ &\ \text{detects cancer in patient } i \\ u_{ij} = &\ -\log(\max(1 - p_{ij}, \epsilon)) \end{aligned}$$

- Then the optimal biopsy protocol for *k* needles solves

$$\begin{aligned} \min \quad & \sum e^{-z_i} \\ \text{s.t.} \quad & z - Ux = 0 \\ & \sum x_j = k \\ & x \in \{0, 1\} \end{aligned}$$

Estimated Detection Rates

Number of biopsies	Estimated Detection Rate
Sextant (6)	67%
Optimized 6	79%
Optimized 8	83%
Optimized 10	85%
Optimized 12	87%



12%

Current Status

- In US physicians are moving towards a 10-12 needle biopsy
  - What are public health implications?
- Sextant still used widely in some countries
- New test of protein patterns in blood may help in diagnosis for PSA levels 4-10 ng/ml
  - Favorable results on small sample
- Ultimately only biopsy can confirm presence of cancer
- As population of biopsy patients changes, new cancer maps should be developed
- More comprehensive study for biopsy protocols by race, age, prostate size, grade of cancer & re-biopsy in progress

Optimization of

Intensity Modulated Radiation Therapy (IMRT)

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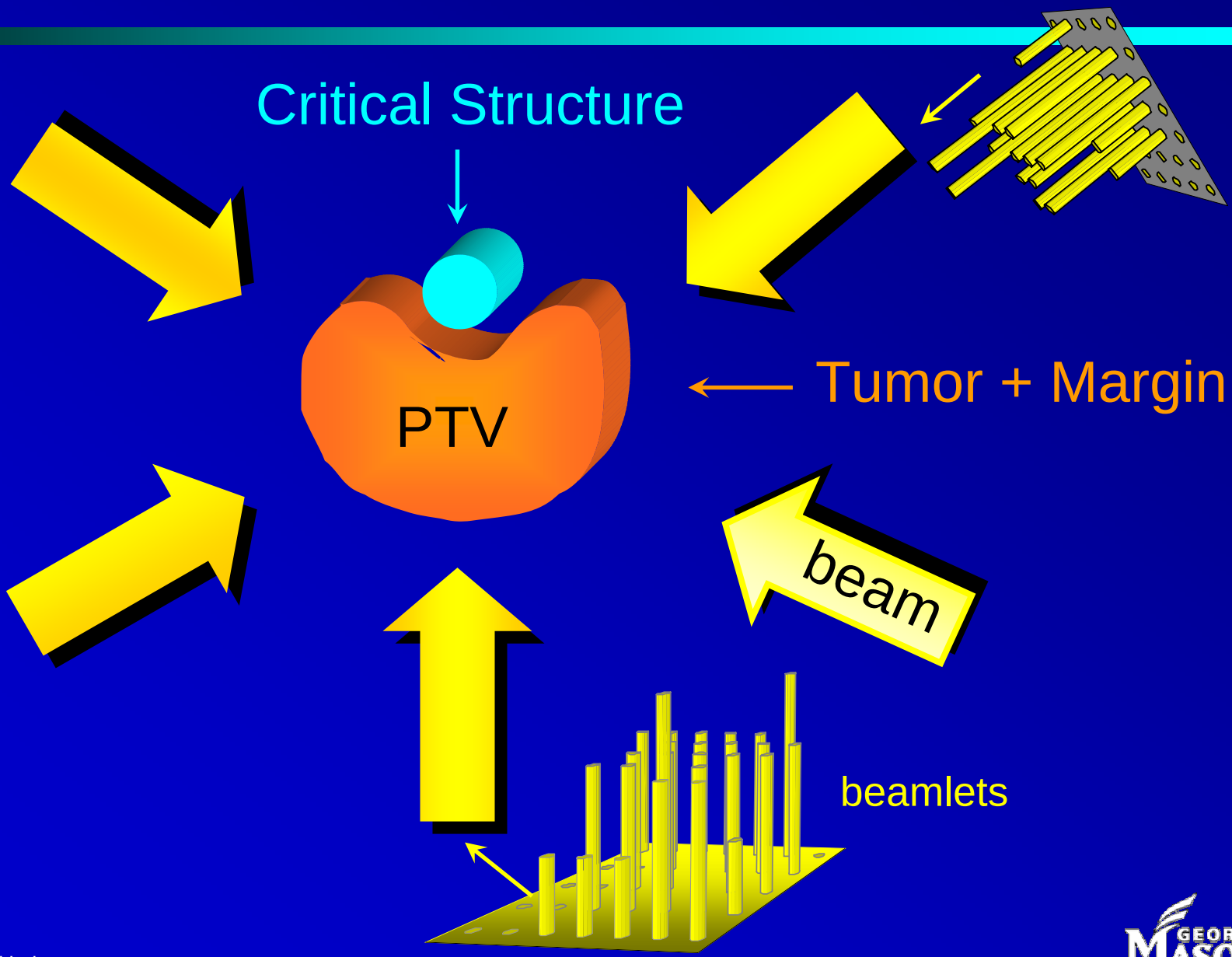
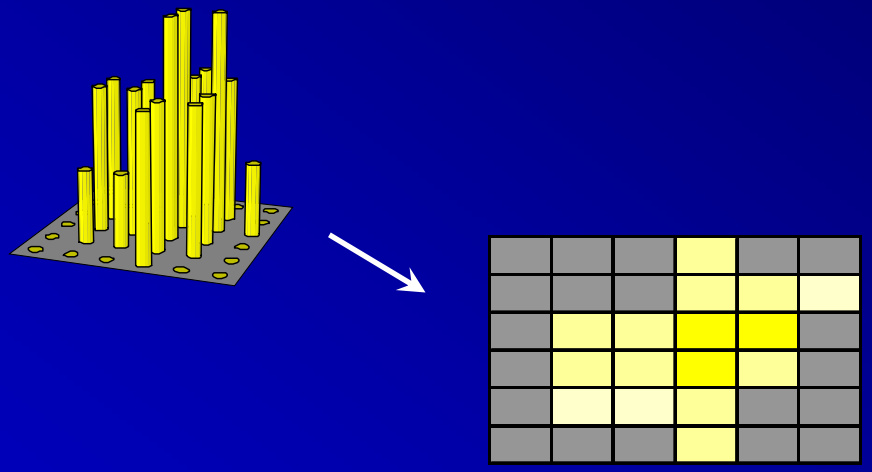
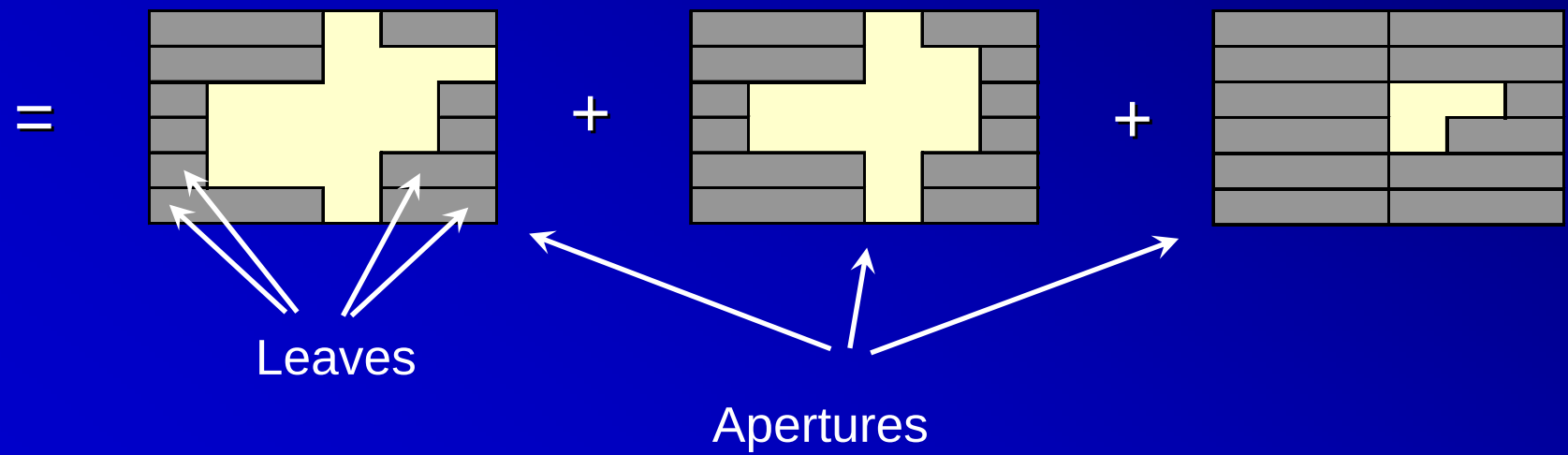
Intensity Modulated Radiation Treatment



Forming the Beam Intensity Map



Intensity map achieved via multileaf collimator whose adjustable leaves act as a filter



The Challenge

- Design a treatment plan that delivers a sufficient high radiation dose to the Planning Target Volume yet limits the radiation to the Organs at Risk

- Design the plan within a clinically reasonable time

Sample Requirements (Goals) for Dose

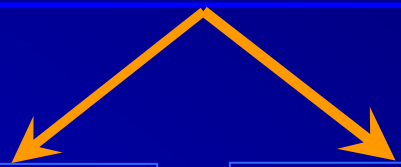
PTV excluding PTV / rectum overlap	Prescription dose Maximum dose Minimum dose 95% of volume ≥	80 Gy 82 Gy 78 Gy 79 Gy
PTV / rectum overlap	Prescription dose Minimum dose Maximum dose	76 Gy 74 Gy 77 Gy
Rectum	Maximum dose 70% of volume ≤	76 Gy 32 Gy
Bladder	Maximum dose 70% of volume ≤	78 Gy 32 Gy

Some Optimization Problems

Problem	Given	Determine
"Classical" FMO (Fluence Map Optimization)	Dose reqs., beam angles	Beam intensity maps
FMO + beam angles	Dose reqs.	# of beams, their angles & intensity maps
Leaf sequencing	Beam intensity maps	Smallest / fastest # of apertures
Aperture optimization	Dose reqs.	# of apertures & their intensities

Objectives vs. Constraints

Requirements are often conflicting.
Therefore, they are usually broken up:



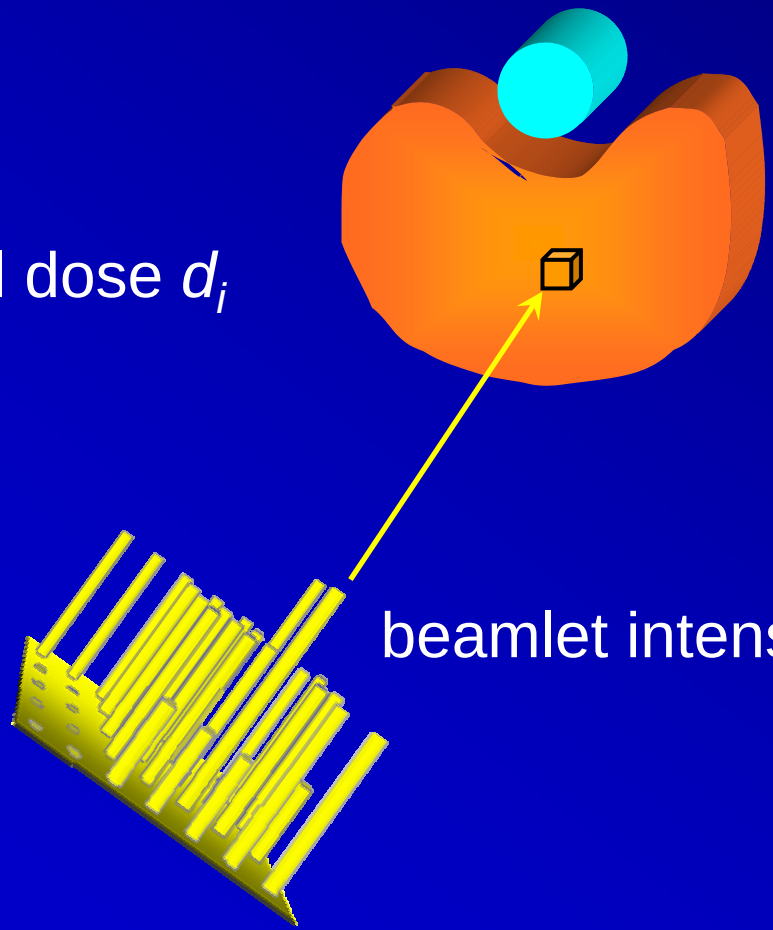
"Hard" Constraints
- Violations prohibited
- Requirements treated as explicit constraints

"Soft Constraints"
- Violation allowed
- Included in objective as weighted penalty

Plethora of different models & algorithms!

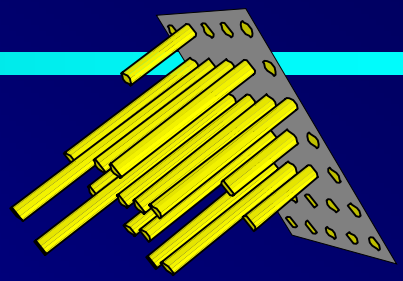
Reoptimization may be needed

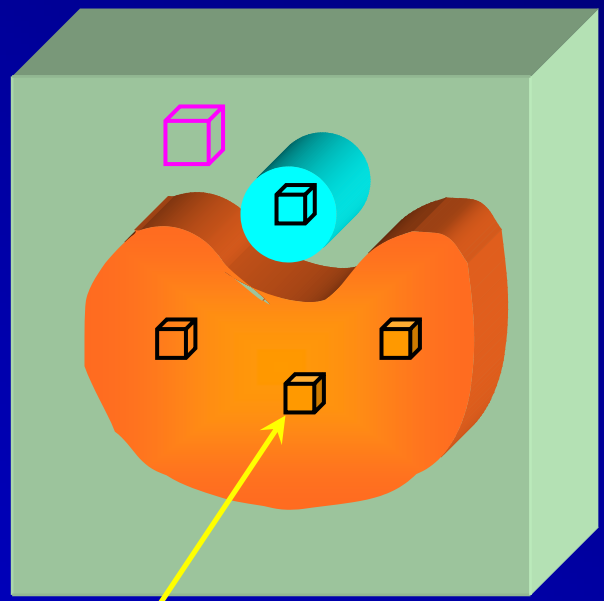
Dose Calculations



$$d = Ax$$

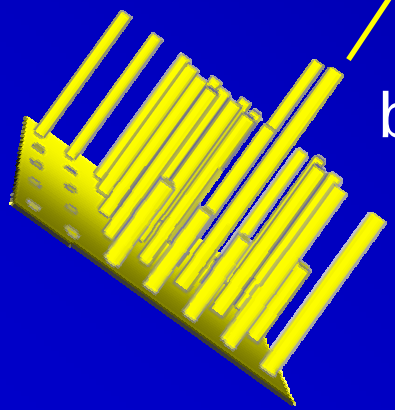
Fluence Map Optimization





voxel dose d_i

$$d = Ax$$



beamlet intensity x_j

Typically:
10^3-10^4 beamlets
10^4-10^6 voxels

Handling Bound Constraints

Explicitly:

$$l \le d_i \le u, \quad i \in S$$

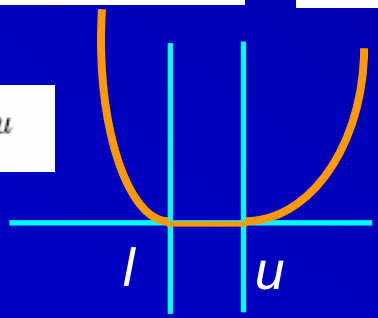
Via penalty:

$$w_l \sum_{i \in S} (\max\{0, l - d_i\})^2$$

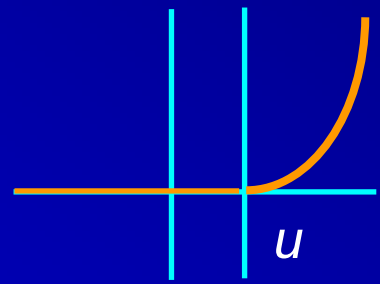
$$w_u \sum_{i \in S} (\max\{0, d_i - u\})^2$$

$$w_c \sum_{i \in S} (\max\{0, d_i - u\})^2$$

$w_l > w_u$



PTV



Critical Structure

Handling Dose Volume Constraints

"At most a fraction β of voxels in structure can exceed the dose u"

Constraint set is nonconvex.

Explicitly:

Using 0-1 variables for all voxels in structure

Via Penalty:

$$w_u \sum_{i \in S^+} (\max\{0, d_i - u\})^2$$

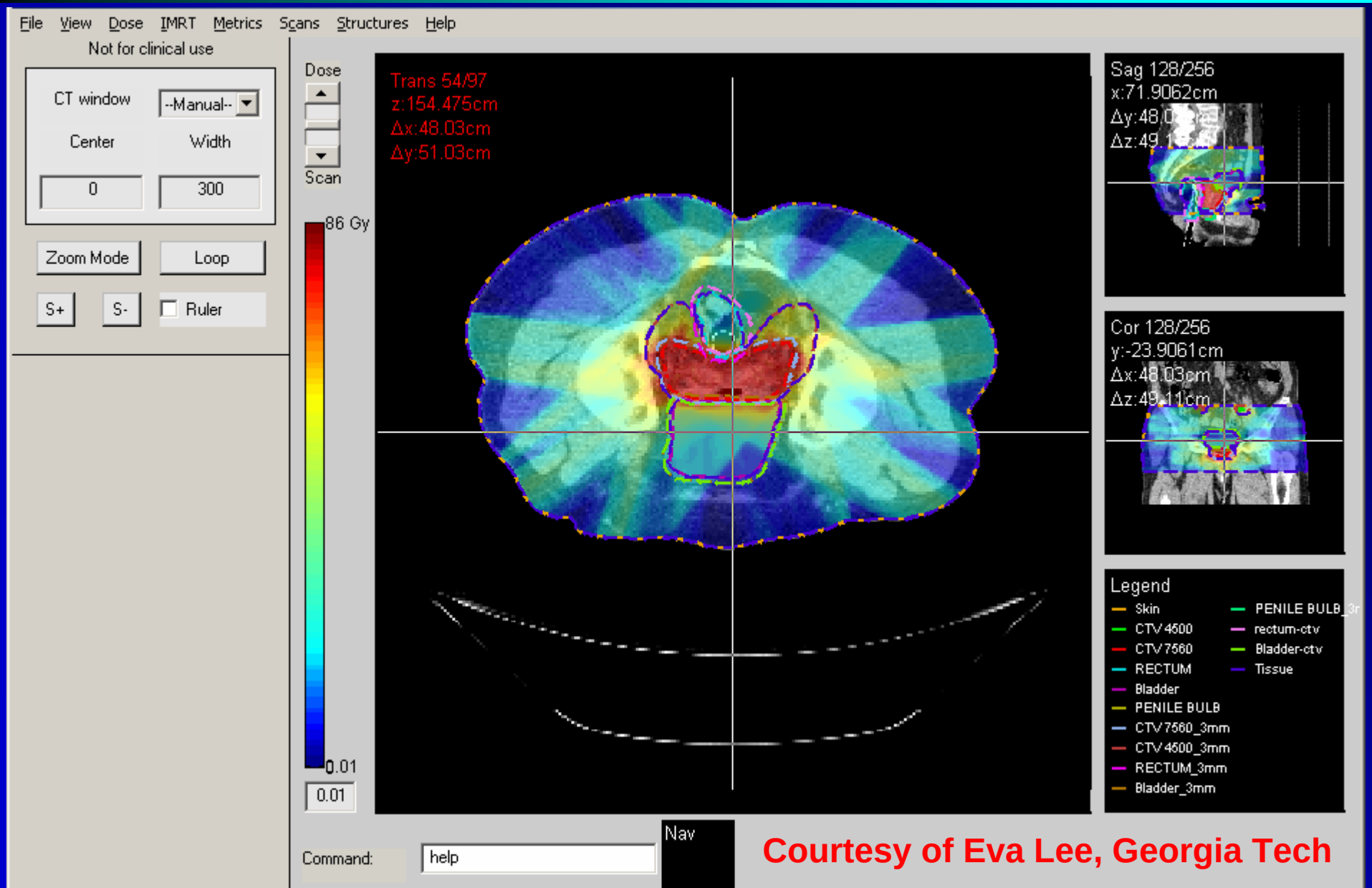
Set of smallest violators

Not guaranteed to get global solution

By estimating number of violators:

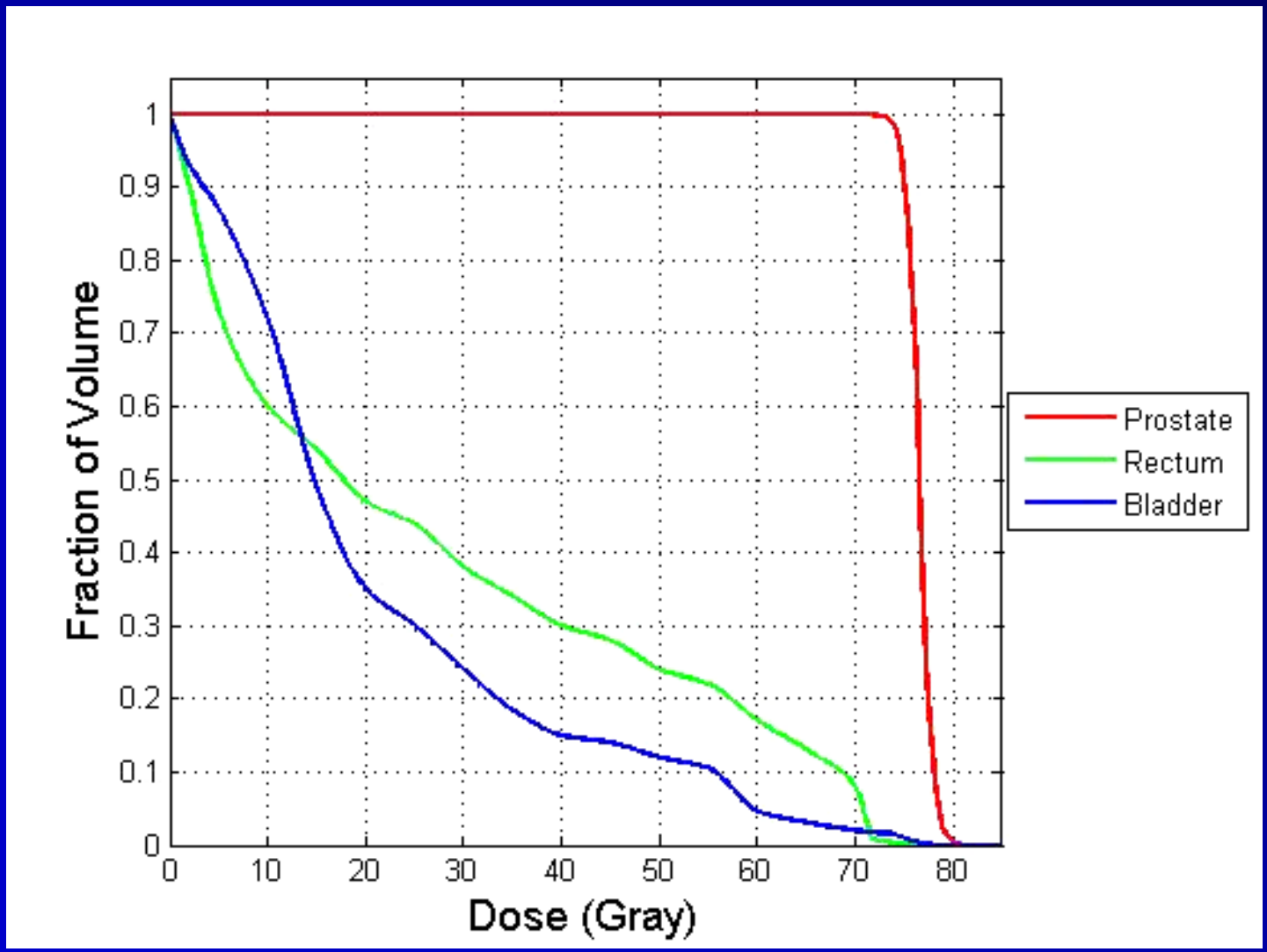
$$\sum_{i \in S} \mathrm{erf}(d_i - u)$$

Treatment Plan- Dose Distribution



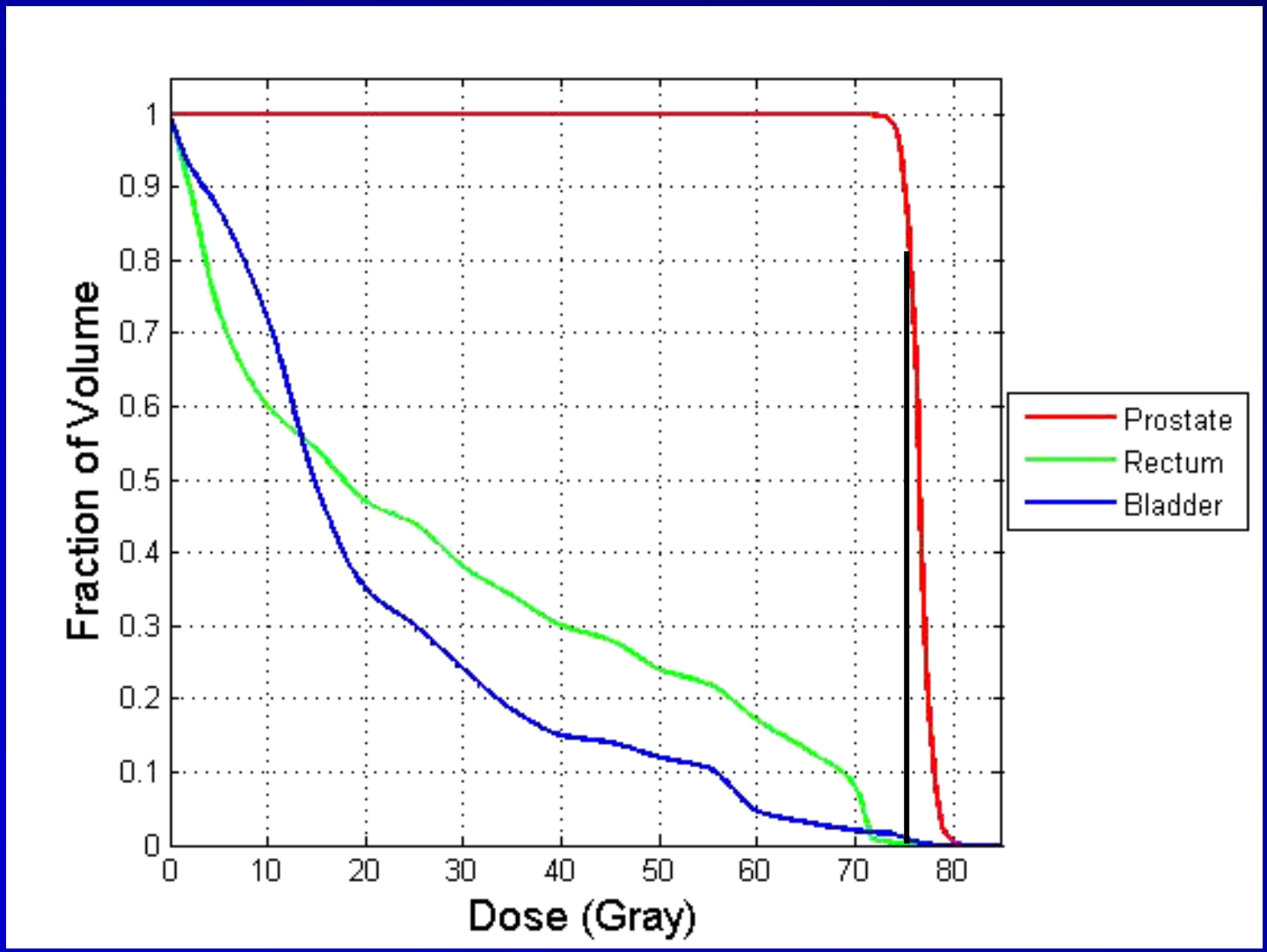
Courtesy of Eva Lee, Georgia Tech

Dose Volume Histogram*

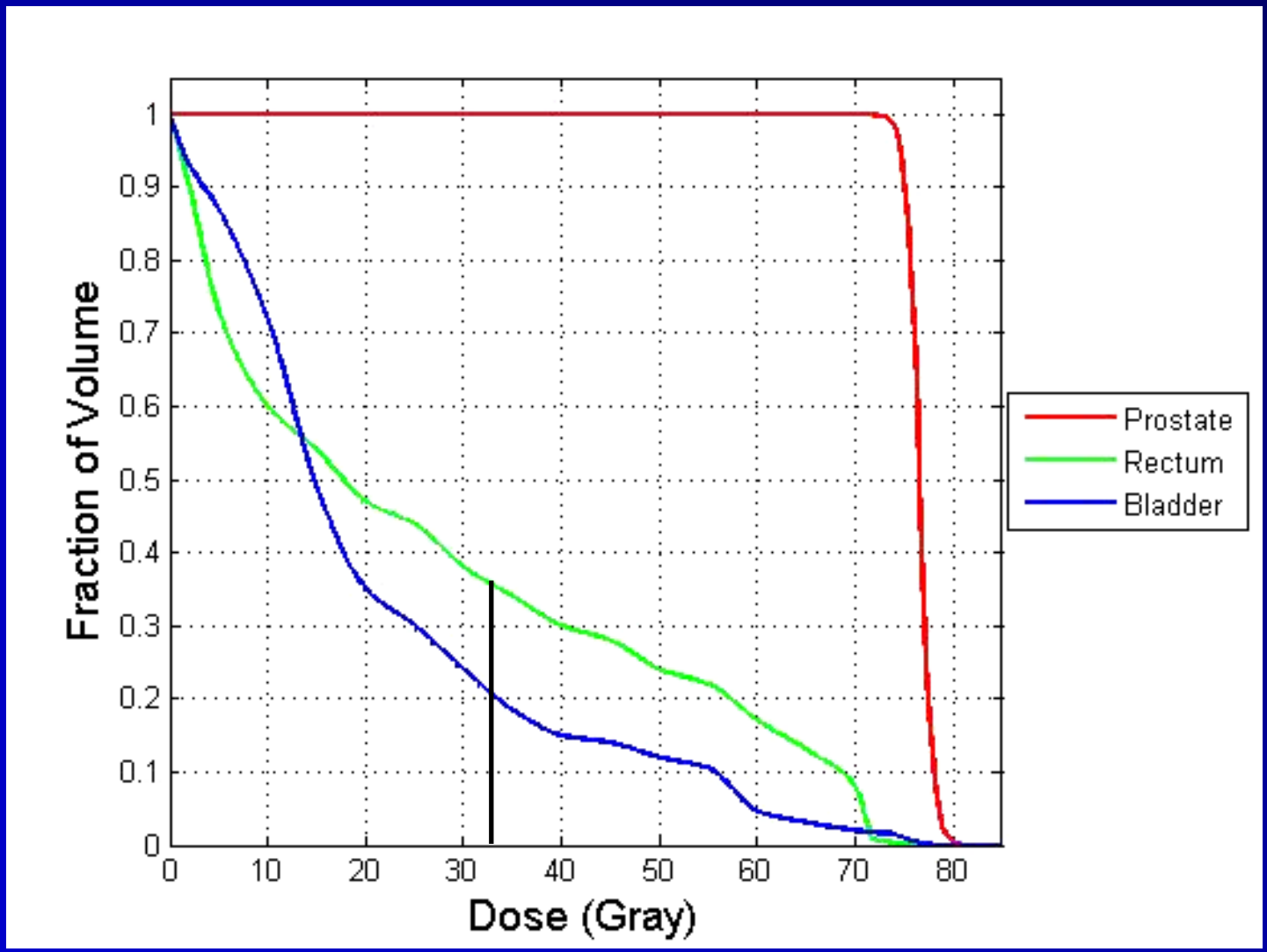


*Does not correspond to previous slide

Dose Volume Histogram



Dose Volume Histogram



Ongoing Challenges in IMRT

- Large scale optimization
  - Special-purpose techniques for IP, NLP etc
  - Sampling of voxels
- Adaptive Radiation Therapy
  - Fractionation
  - Accommodating patient motion
  - Accommodating change in organs
- Biological models
  - Tumor control probability
  - Normal tissue complication probability
- Multiobjective optimization

Optimization in

Radiofrequency Ablation of Liver Tumors

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Primary and Secondary Liver Tumors

- Primary liver cancer is among the most common cancers worldwide:
  - Over one million new cases annually
  - Death rate ~ occurrence rate
- Even higher rates for colorectal carcinoma metastases (“secondary tumors”) in the liver
- Surgical resection - the gold standard of therapy
- But most patients are poor candidates for surgery
- Radiofrequency ablation - a promising treatment option for unresectable hepatic tumors.

Radiofrequency Ablation

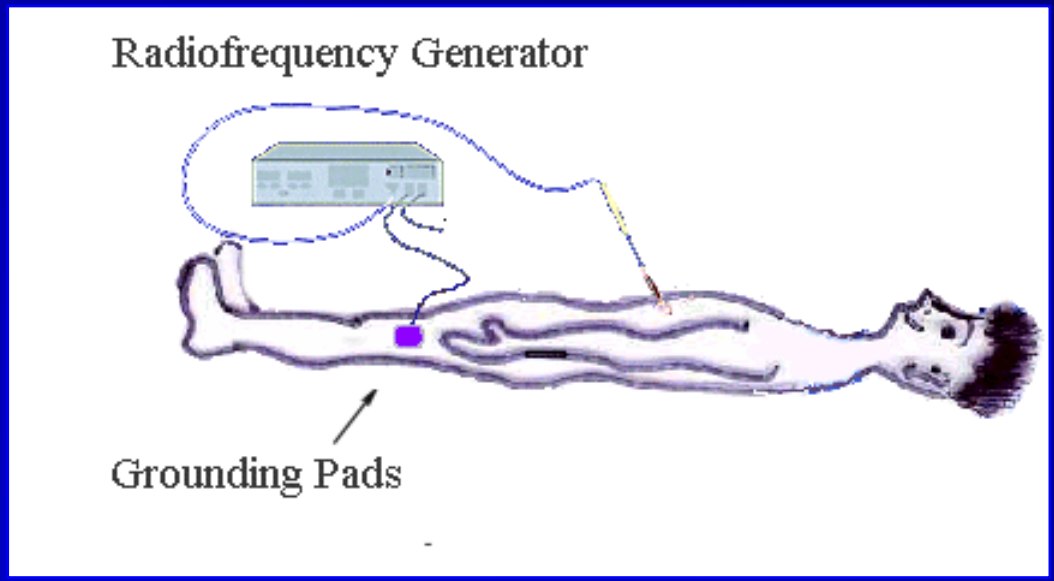
- Radiofrequency ablation is a noninvasive technique for killing tumors by heat.
- A needle electrode is placed at the tumor site and an electrical current applied. This generates frictional heat. Heat in excess of 50^{o}c will kill the tumor.

Ablation treatment planning:
Determine the number of needles, their position, size, and power applied, to guarantee that the entire tumor is killed while damage to vital healthy tissue is limited.

Features of RFA for Liver Tumors

- May be safely performed on an outpatient basis. Complex cases may require general anesthesia.
- Treatment sessions are about 10--30 minutes long.
- Can treat small and (sometimes) mid-size tumors.
- May convert inoperable patient into a surgical candidate.
- Failures of RFA often associated with under-ablation

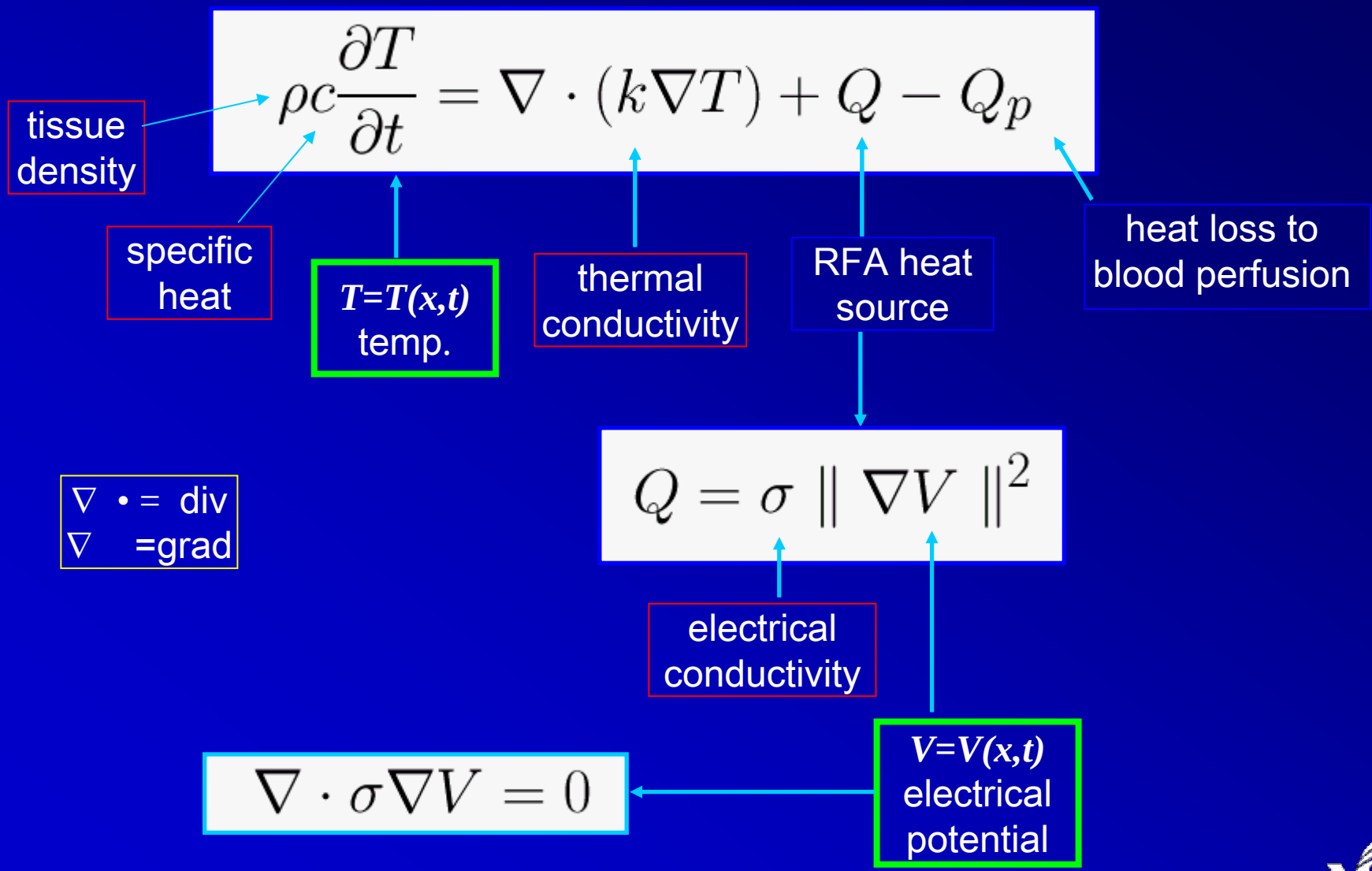
The RFA Procedure



Closed circuit made by placing grounding pads on the thighs and connecting then in series with the generator, and the needle electrode.

A variety of needles in different sizes and configurations

Temperature Distribution: the Bioheat Equation



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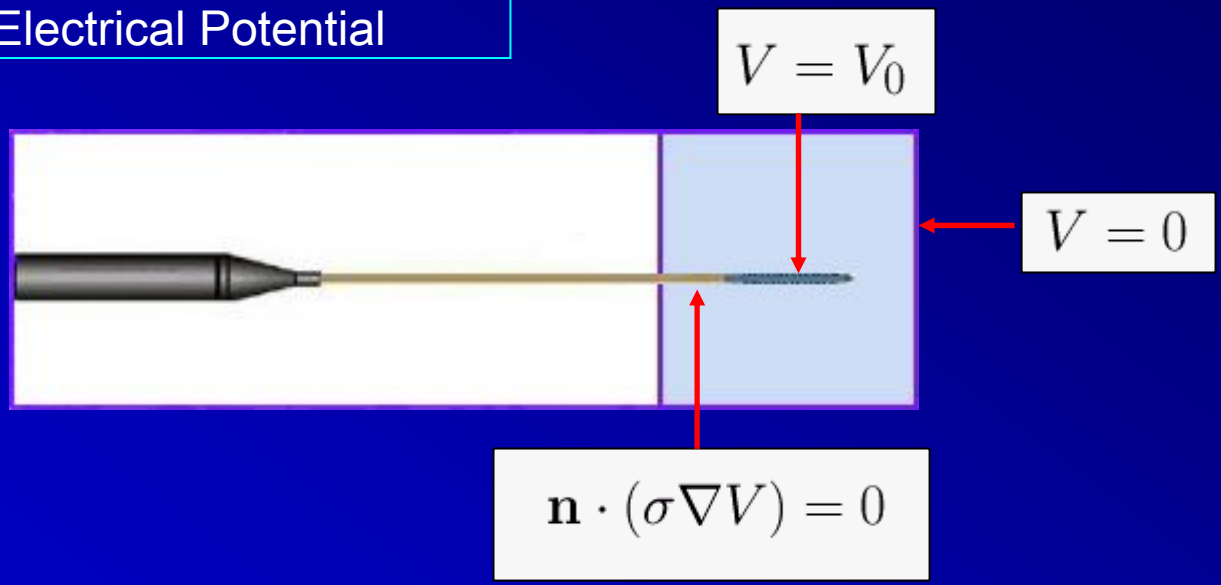
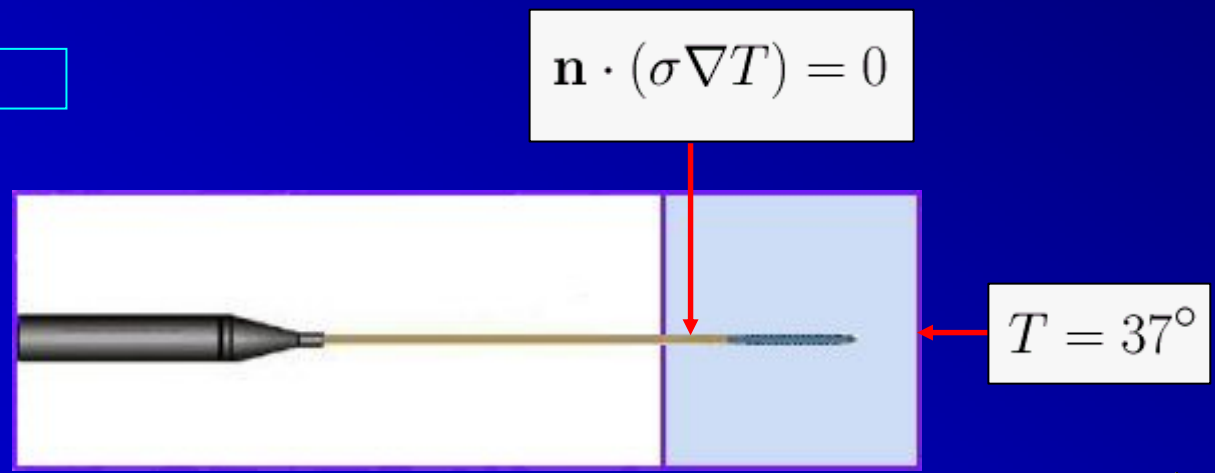
The Bioheat Equation – Boundary Conditions

Electrical Potential



Temperature



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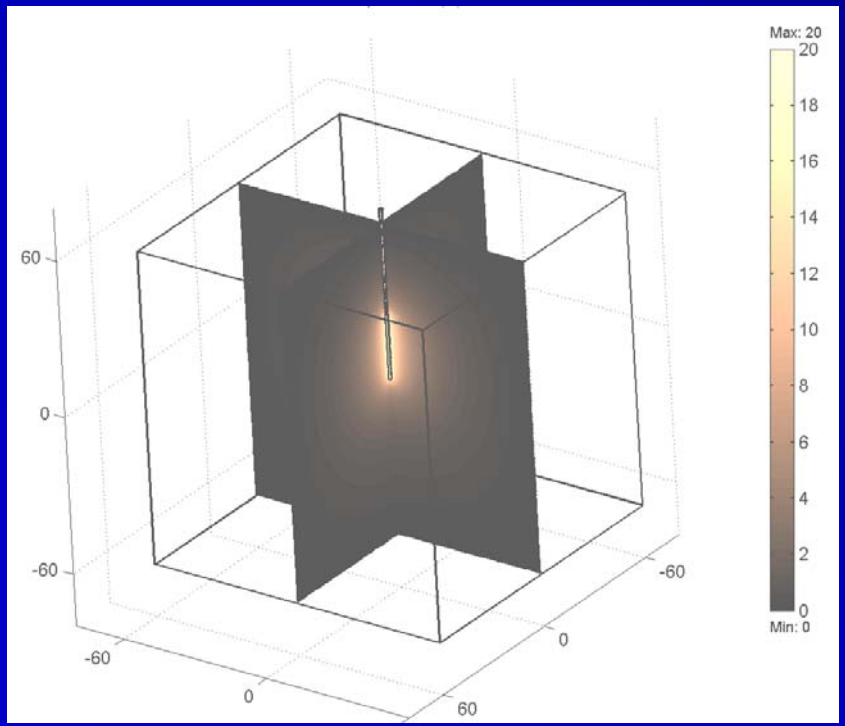
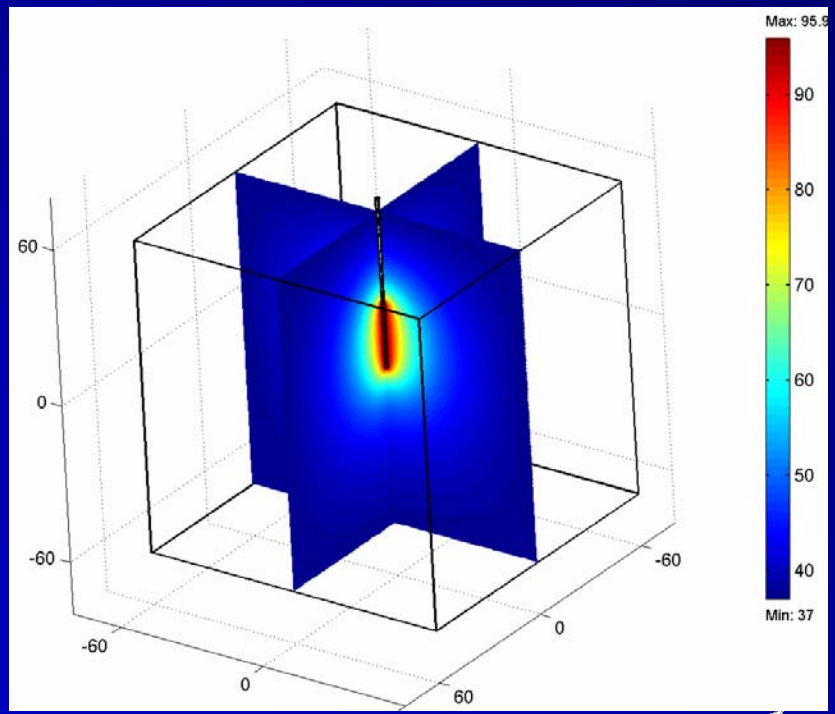
Numerical Solution of Bioheat Equation

Via the finite element method. Here: FEMLAB

Electrical Potential



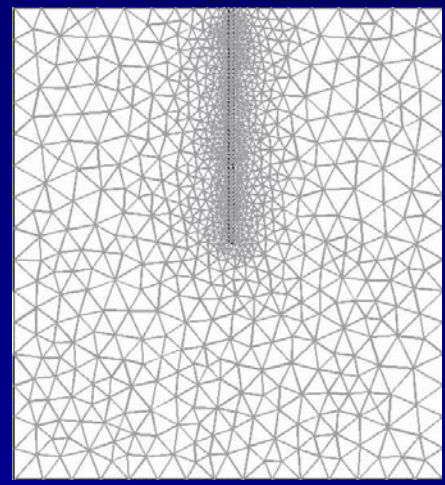
Temperature Distribution



Optimization Challenges

Difficulties:

- Each 3-D PDE solution takes many minutes
- The optimization involves repeated PDE's
- As needle position changes, the needle boundary "moves", entire mesh changes
- Additional combinatorial complexity when multiple needles are required

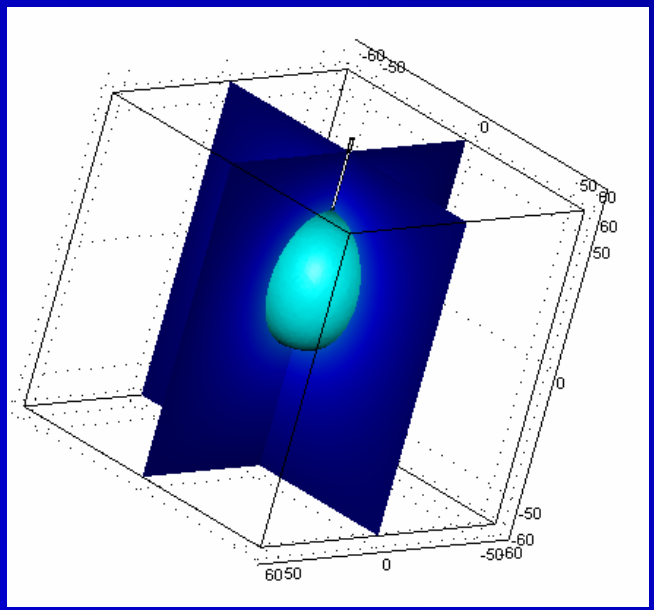


Yet:

- Treatment plans must be available within just a few hours
- Re-optimization may be required during treatment

Solution Approach

- Approximate the key iso-temperature surfaces as ellipsoids
  - The 55°C isosurface defines the burn lesion
  - The 45°C isosurface defines the “do not burn” zone

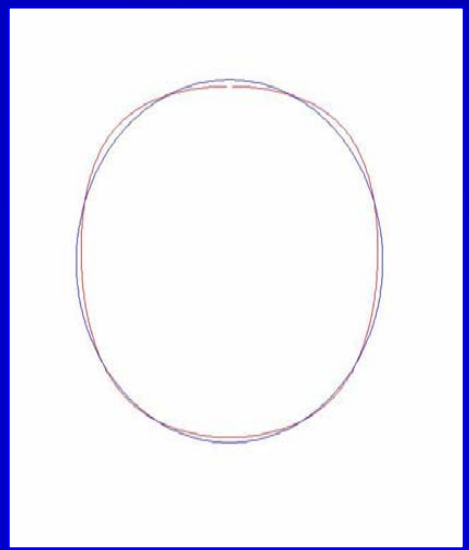


Simplifying Assumptions:

- Single-pronged needle
- Blood perfusion heat loss negligible
- c, k, ρ, σ are constant

Approximation of Temperature Surfaces

- Iso-surface modeled as ellipsoid with cylindrical symmetry
- Analysis for the 3 needle lengths in clinical use
- Maximum error in all cases less than 3^{o}C



A needle with direction *p* and "center" *c* will create a lesion of the form

$$(x-c)^T\left[\alpha I+\beta pp^T\right](x-c)\le r$$

or

$$\alpha(x-c)^T(x-c)+\beta(p^T(x-c))^2\le r$$

The Single Burn Optimization Problem

Volume of Interest:

- K = tumor +1cm margin
- C = critical structure
- N = other normal tissue

Goals

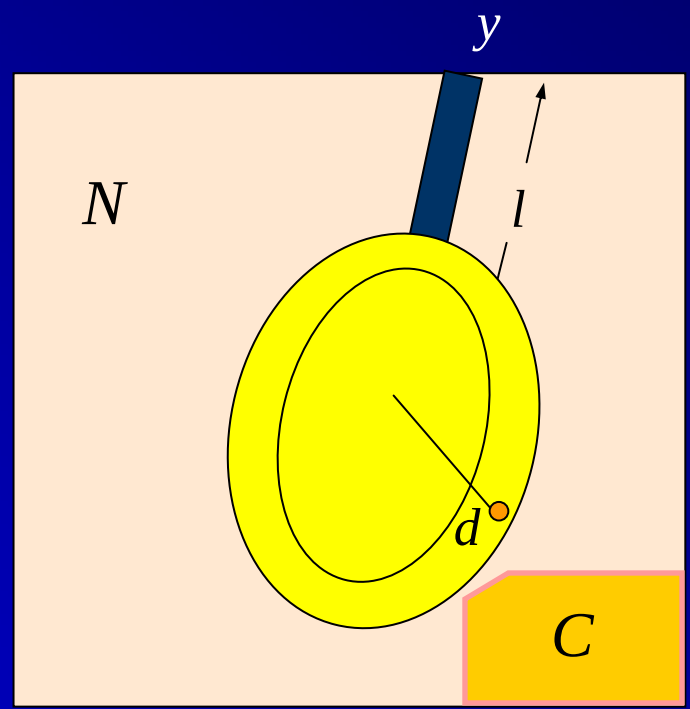
- Kill all cells in region K
- Avoid any damage in C
- Limit damage in N

Decision variables

- y = insertion point of needle (on body surface)
- p = direction of needle
- l = depth of needle

State variables

- d = elliptic ``distance" from center of burn



Problem Formulation

Minimize: damage to normal tissue N
While: prohibiting damage to critical region C
killing every cell in region K

$$\min \sum_{i \in N} damage_i$$

$$\text{s.t.} \quad d_i = e(x_i)$$

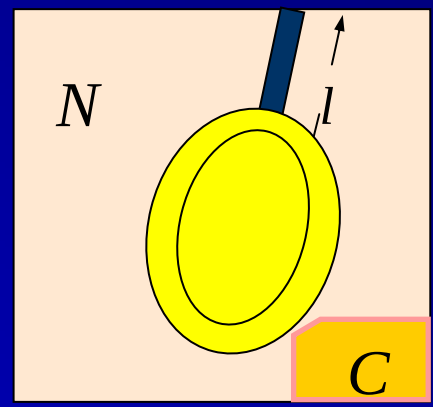
$$d_i \leq r_{kill} \quad i \in K$$

$$d_i \geq r_{damage} \quad i \in C$$

$$damage_i \geq r_{damage} - d_i \quad i \in N$$

$$damage_i \geq 0 \quad i \in N$$

Additional anatomical constraints on p,y,l.
Also $||p||=1$



$$e(x) = \alpha(x - y - lp)^T(x - y - lp) + \beta[p^T(x - y - lp)]^2$$

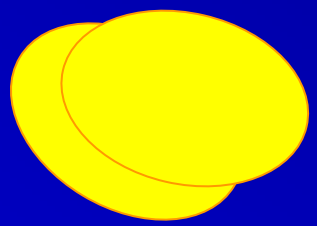
Variation: minimize weighted sum of damage to normal and critical tissue

Computational Testing for Single Burn

- 2-D test problems obtained from CT scans, and simulated data. Grid size up to 500 x 500
- 3-D testing on simulated data. Grid size up to 50 x 50 x 50
- Problems formulated in AMPL, solved using variety of nonlinear solvers.

Provided that
the initial point is sufficiently close
solution is obtained within seconds to few minutes (when solution exists).

But What If More Than One Burn Needed?

- Each tumor point must be covered by at least one needle:
- Problem is nonconvex nonlinear and either nondifferentiable or integer
- To simplify, we focus just on covering the tumor:
- 

Find centers and directions of k ellipsoids so as to cover the tumor

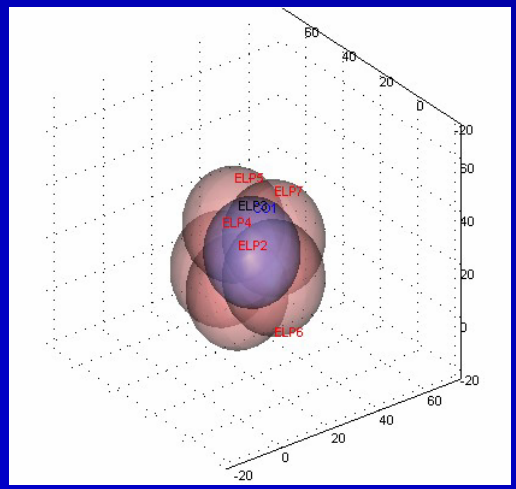
- Even the 2-D problem becomes hard
- Experience with MINLP suggests that the key difficulty is positioning the centers of the ellipses.

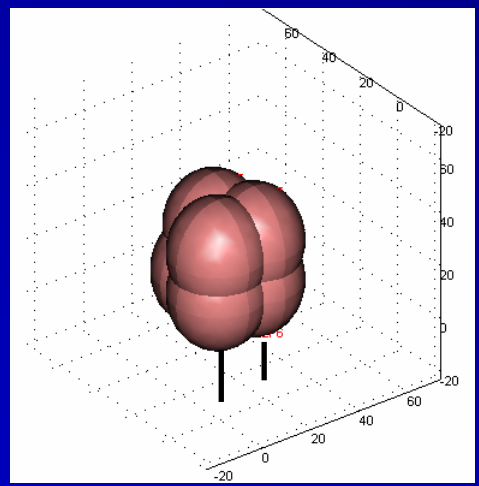
Positioning Ellipsoid Centers: Special Case

- Assume all needles have known, parallel, directions.
- Define coverage matrix:

$$a_{i,j} = \begin{cases} 1 & \text{if needle centered in pont } j \text{ covers voxel } i \\ 0 & \text{otherwise,} \end{cases}$$

- Minimizing no. of “burns” is a set covering problem
- Variation allows to get the minimum number of holes

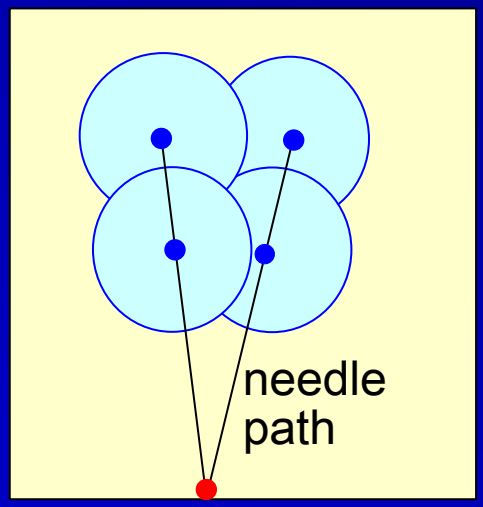




Further Detail

- Problems solved via Cplex 9.0
- Grid granularity:
  - Needle placement (vars): 5 mms
  - Tumor coverage (constraints): 2.5 mm
- Conservative assumptions in constructing *A*
  - Must account for variation in needle placement
- Handling the multiple objectives:
  - Given min no. of burns, minimize no. of holes
  - Given min. no. of burns and holes, minimize damage to normal tissue
  - May need to reiterate with relaxation on no. of burns or holes
- Can be solved in clinically feasible time

Positioning Ellipsoid Centers: The General Case



needle entry point (“hole”)

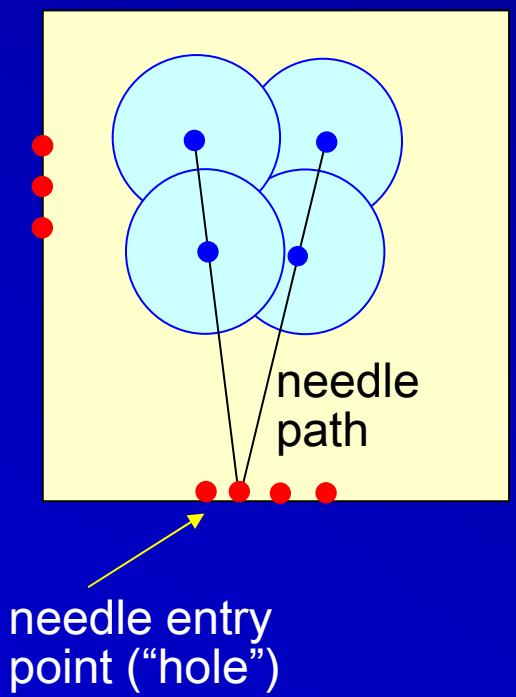
Goals:

- cover tumor
- spare critical tissue
- min needle holes at entry
- min needle paths
- min burns
- limit damage to normal tissue

But:

- many possible entry holes
- for each, many possible paths
- for each, many possible burns

Positioning Ellipsoid Centers: The General Case



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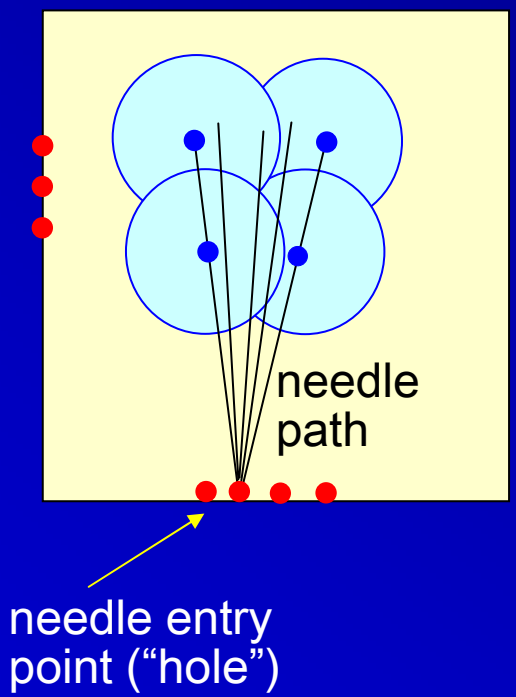

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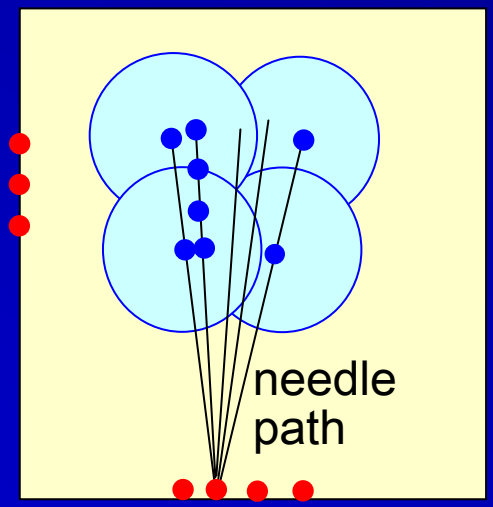

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Issues and Future Work

- A hybrid two-step ILP/MINLP multi-grid approach might offer hope
- Many other factors to consider:
  - Effect of blood flow
  - Various needle geometries
  - Varying physical parameters
  - Validation

Conclusions

Medicine is a fascinating source of challenging optimization problems

Thank You!


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"It would be a great honor for me to be counted as one of your successes."