IMRT Modeling Influence on Planning

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Conflict of Interest Statement

- James F. Dempsey owns stock in and is the C.S.O. of ViewRay Inc. and as such may benefit financially as a result of the outcomes of work or research reported in this presentation

Mathematical Disclaimer!

- While modeling is highly mathematical in nature, I have attempted to present this lecture without the use of mathematics. Unfortunately, I found it necessary to include several slides containing mathematics. In no event will the presenter or affiliates be liable for any damages or losses caused by the viewing of mathematical equations provided or not provided in this lecture. Also, the presenter accepts no responsibility for any proven or unproven side effect of viewing mathematical equations. These equations, as well as details on particular solutions to these equations, do not necessarily constitute a personal or institutional endorsement of mathematics, but are provided "as is" for your own information. As with all legal disclaimers this statement is not actually intended for reading.

Educational Objectives

- Understand the influence of the choice of physical models employed in clinical IMRT
- Understand the assumptions, merits, and limitations involved with different IMRT planning models
- Review the conditions where IMRT modeling is suspect and requires careful scrutiny in clinical implementation

Outline

- Reality, Models, Algorithms, & Your TPS
- Models in IMRT
  - Discretized Models of the Patient
    - Spatial & Temporal
  - IMRT Optimization Models
  - Dose Calculation Models
- Summary

Reality, Models, and Algorithms

What is a Model?

- By "model" we mean "mathematical model"
- A mathematical model is an abstract model that uses mathematical language to describe the behavior of a system.
- A mathematical model usually describes a system by a set of variables and a set of equations that establish relationships between the variables.
- The actual model is the set of functions that describe the relations between the different variables.

Types of Models

- Linear vs. Nonlinear
  - Dose vs. BED
- Deterministic vs. probabilistic (stochastic)
  - Convolution vs. Monte Carlo
- Static vs. dynamic
  - 3D vs. 4D
- Lumped parameters vs. distributed parameters
  - Convolution vs. Monte Carlo

These Don't Count!

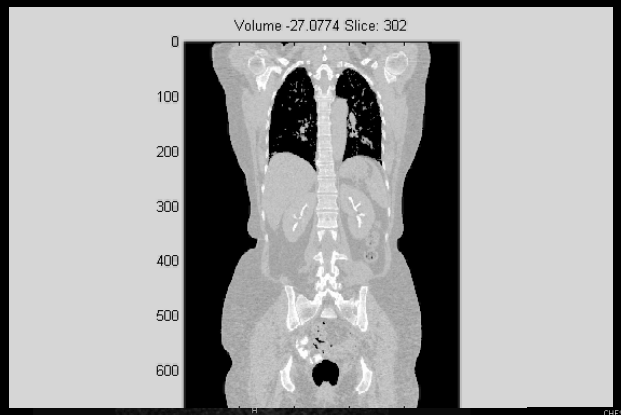
What is an Algorithm?

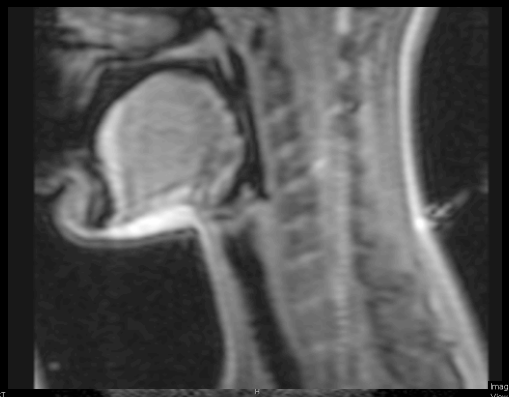
- It is a method for solving a model
- An algorithm is a procedure (a finite set of well-defined instructions) for accomplishing some task which, given an initial state, will terminate in a defined end-state
- Choice of algorithm influences computational complexity and hence efficiency of solving a given model
- We will not discuss various algorithms - just models

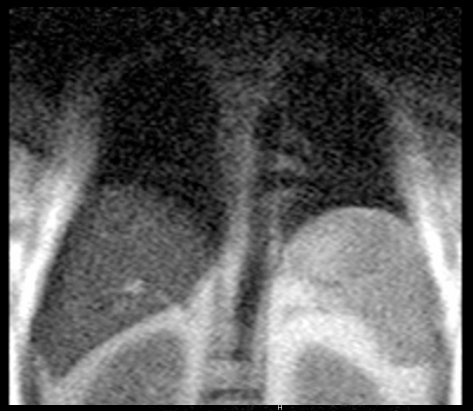
The Reality of the Delivery System

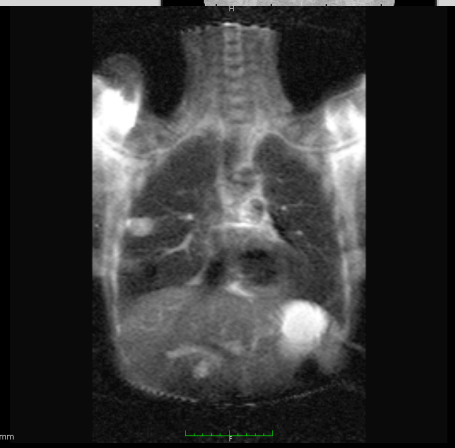
- The actual delivery system
  - spectrum
  - fluence distribution
  - collimator geometry
  - temporal and spatial output

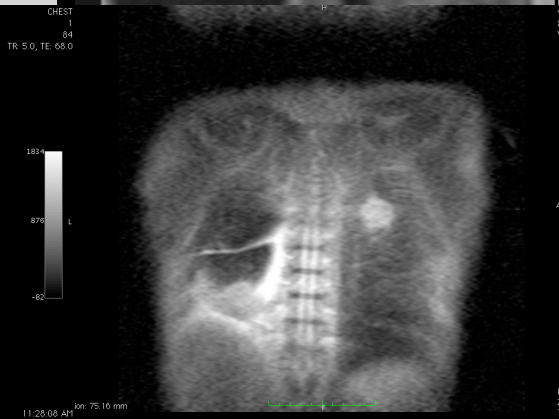
The Reality of the Patient

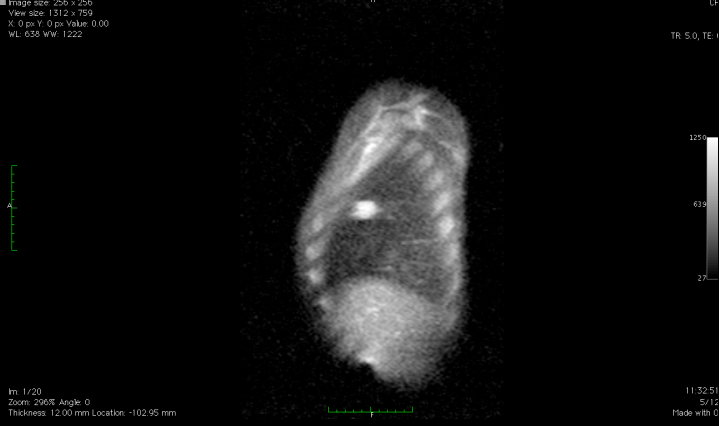












The Model of Your IMRT TPS

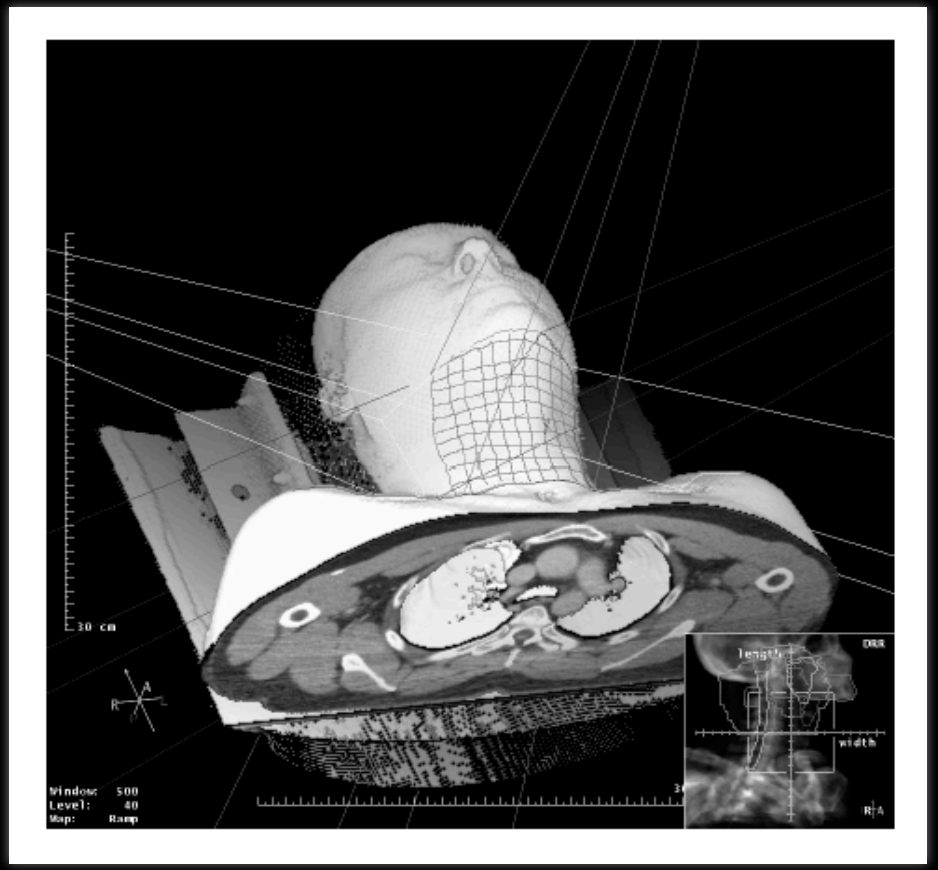
- Attempts to approximate the reality of the delivery system
  - assumptions about
    - spectrum
    - fluence distribution
    - collimator geometry
    - temporal and spatial output

- Attempts to approximate the reality of patient & modeling geometric uncertainties
- Attempts to model the trade-off between improving the treatment of the target and the sparing of the tissues

Discretization of the Patient

The Discrete Model of the Patient

- As a practical matter one "cuts" the patient into finite pieces to compute an image or calculate dose
- Imaging voxels
- Dose grids



Problem Well Studied for Conformal 3DRT

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- Smith C.W., Morrey D., and Gray K., *The influence of grid size on accuracy in radiotherapy dose plotting,* Medical Physics, 17(1) (1990) 135-136.
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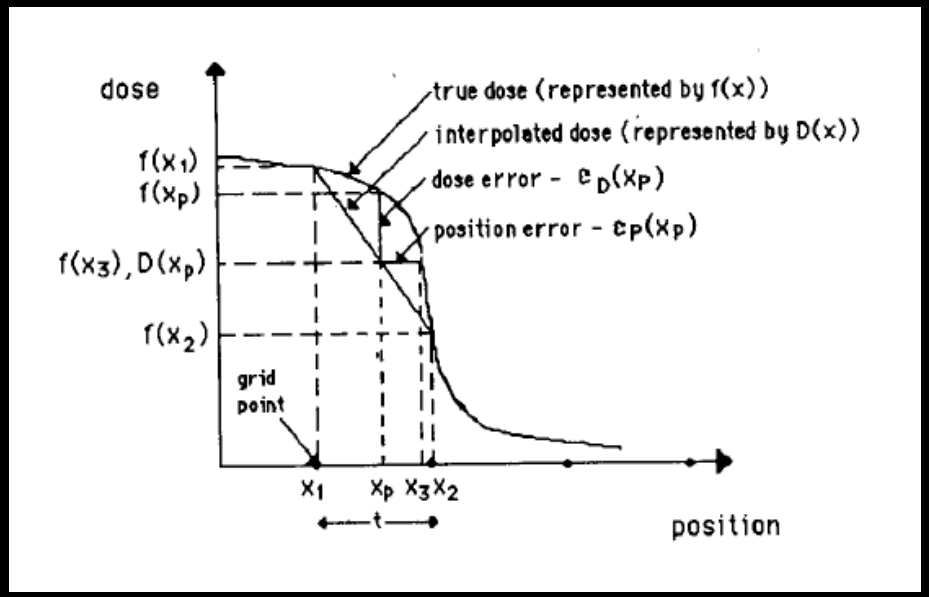
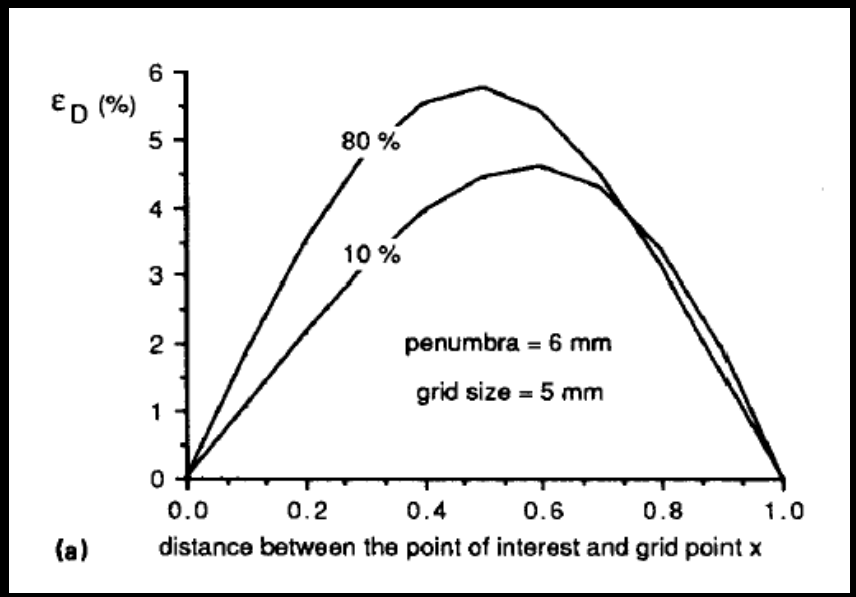
Analytical Analysis of Dose Distribution Sampling

by Niemierko and Goitein, 1988



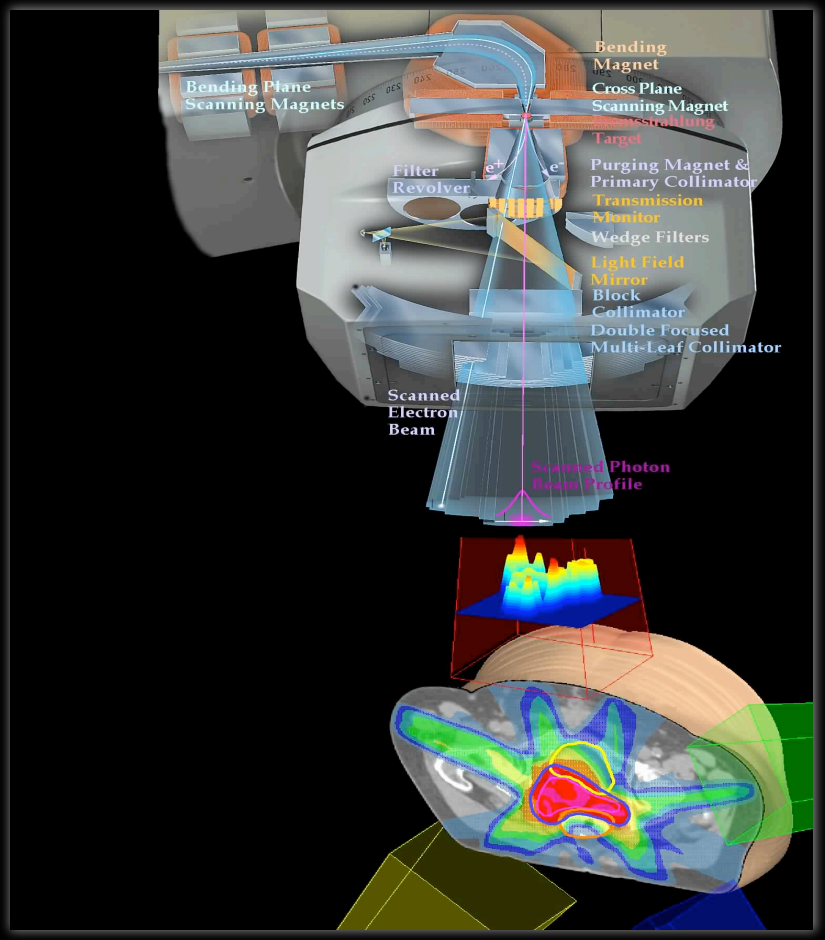


Before IMRT

- The penumbrae were not so important!
  - on the edge of the field
- Few beams added to give dose
- Analytical treatment was adequate

IMRT is More Complicated...

- Many beams are matched in complicated patterns
- Penumbrae are very important and add up to give important dose to the target
- We can not really know *a priori* where penumbrae will be or will match



Have You Ever Wondered?

- What is the relationship between dose calculation accuracy and the voxel resolution of the dose grid?
- How fast do we have to image to resolve lung tumor motion?
- Is there a theory or analysis that can answer these questions?
  - There is!

reference

- Med Phys 32(2) 380-388

A Fourier analysis of the dose grid resolution required for accurate IMRT fluence map optimization

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Jean Baptiste Joseph Fourier

- He thought about these things
- He created infinite sin and cos series to solve PDEs
- "Mathematics compares the most diverse phenomena and discovers the secret analogies that unite them."

Fourier's Idea

- Any periodic function w/ any period can be represented as the sum of periodic function, namely
- -sin and cos with different amplitudes and periods
- 1807 Fourier

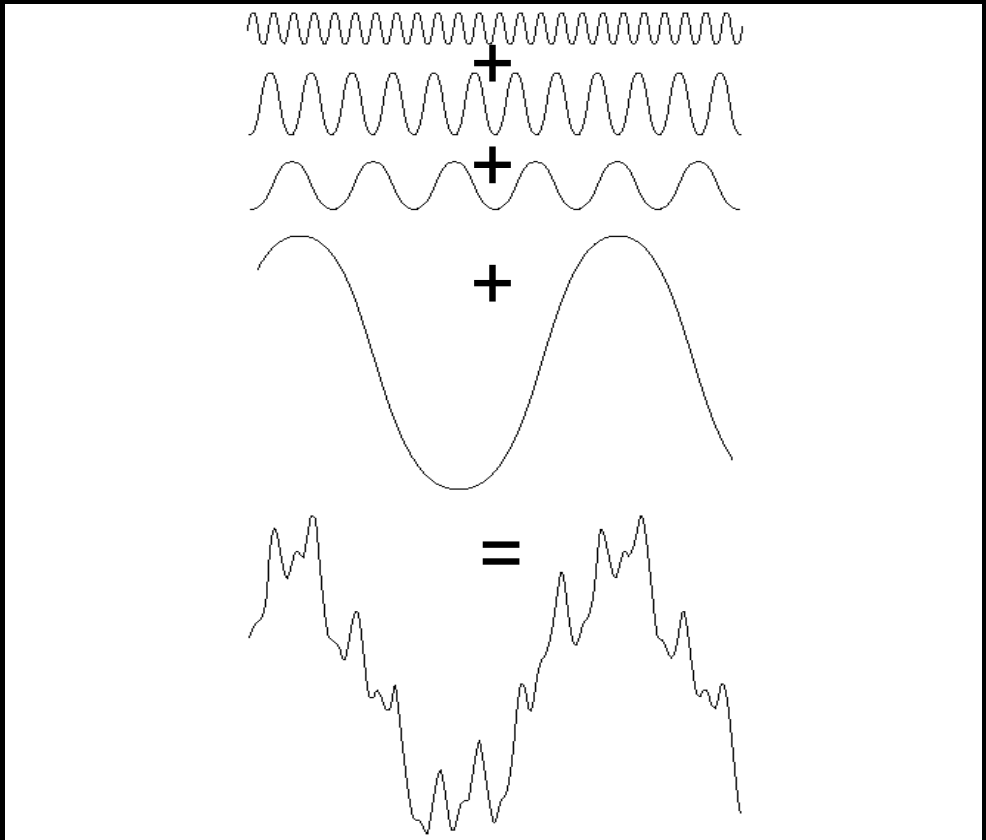
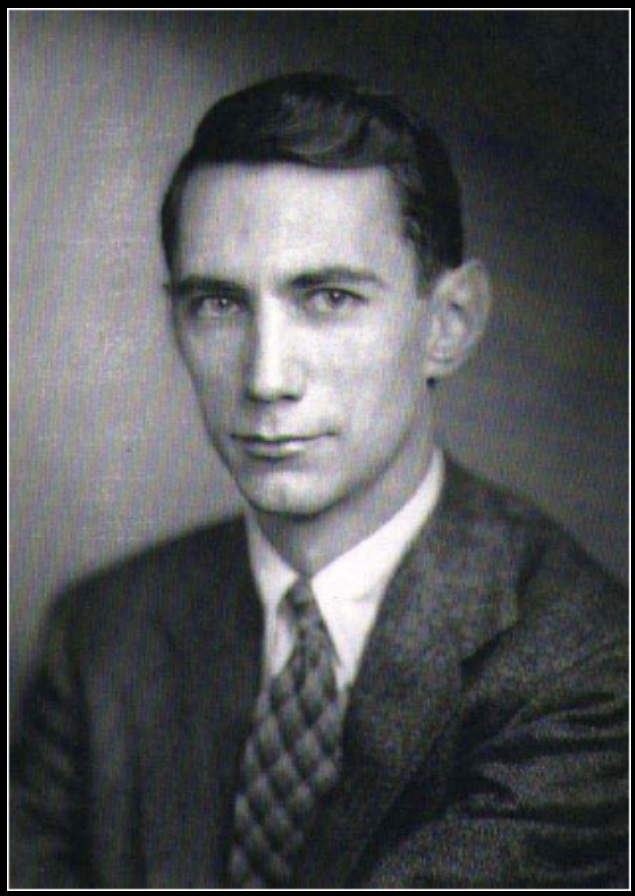


FIGURE 4.1 The function at the bottom is the sum of the four functions above it. Fourier's idea in 1807 that periodic functions could be represented as a weighted sum of sines and cosines was met with skepticism.

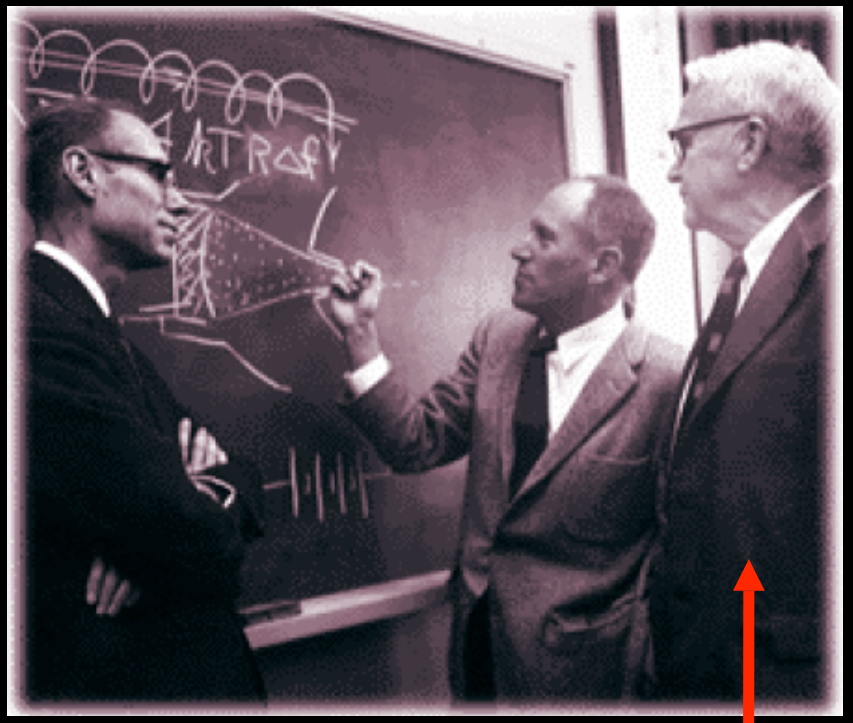
The Father of Information Theory

- The field of "Information Theory" is largely attributed to Dr. Claude Elwood Shannon (1916-2001).
- Dr. Shannon arrived at the revolutionary idea of digital representation by sampling the information source at an appropriate rate, and converting the samples to a bit stream.
- He characterized the source by the entropy to quantify the information content of the source.
- This led to the digital revolution
- Ref. :Robert Calderbank and Neil J. A. Sloane in **Nature**, Vol. 410, #6830, April 12, 2001, page 768.



The Godfather of Information Theory

It has been claimed that Dr. Harry Nyquist and Dr. Claude Shannon, are responsible for virtually all the major theoretical advances in modern telecommunication.



Harry Nyquist (1889-1976) (*right*) with John R. Pierce (*left*) and Rudolf Kompfner (*center*) – all scientists working for Bell Labs (1960).

Shannon-Nyquist Sampling Theory

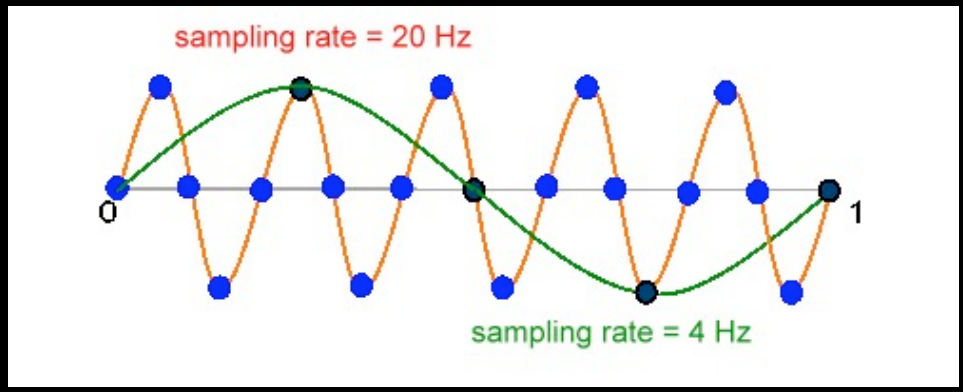
- A fundamental theorem of Information Theory is the "Shannon-Nyquist Theorem"; a.k.a. the "Nyquist Theorem" or the "Shannon Theorem".
- The sampling theorem is considered to have been articulated by Nyquist in 1928 and mathematically proven by Shannon in 1948.

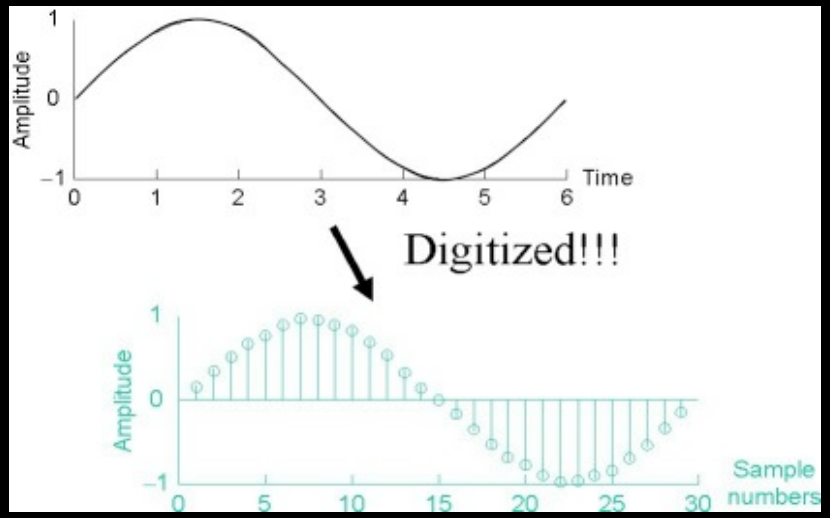
Statement of the Shannon-Nyquist Theorem

- The Shannon-Nyquist sampling theorem states that when discretizing a function the sampling rate must be at least twice the highest frequency present in the sample in order to accurately reconstruct the original signal.
- Like the Heisenberg Uncertainty Principle, it is easier to state than to understand…

Low Resolution, Aliasing, and Violating the Shannon-Nyquist Theorem

- Failure to satisfy the Shannon-Nyquist Theorem will cause the aliasing of the data and a loss of the information in the continuous function
- But How Bad Can it Be?





Reference in Medical Physics

- See Med Phys 32 (2) 2005 p 380-388
- This is essentially a homework assignment in Bracewell's Textbook on the use of the Fourier Transform

A Fourier analysis of the dose grid resolution required for accurate IMRT fluence map optimization

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We present a theoretical and empirical analysis of the errors associated with the spatial discretization of the dose grid employed in optimized intensity modulated radiation therapy (IMRT) treatment plans. An information theory based Fourier analysis of the accuracy of discrete representations of three-dimensional dose distributions is presented. When applied to beamlet-based IMRT dose distributions, the theory produces analytic integrals that can bound worst case aliasing errors that can occur regardless of the location and orientation of the dose grid. The predictions of this theory are compared to empirical results obtained by solving a linear-programming based fluence-map optimization model to global optimality. A reasonable agreement between worst case estimates and the empirical results is attributed to the fact that the optimization takes advantage of aliasing to produce an optimal plan. We predicted and empirically demonstrated that an isotropic dose grid with <2.5 mm spacing is sufficient to prevent dose errors larger than a percent. However, we noted that in practice this resolution is mostly needed in high-dose target regions. Finally, a multiresolution 2–4–6 mm spacing model was developed and empirically tested where these spacings were applied to targets, structures, and tissue, respectively. © *2005 American Association of Physicists in Medicine*. [DOI: 10.1118/1.1843354]

Key words: IMRT, treatment plan evaluation, optimization

The General Fourier Transform

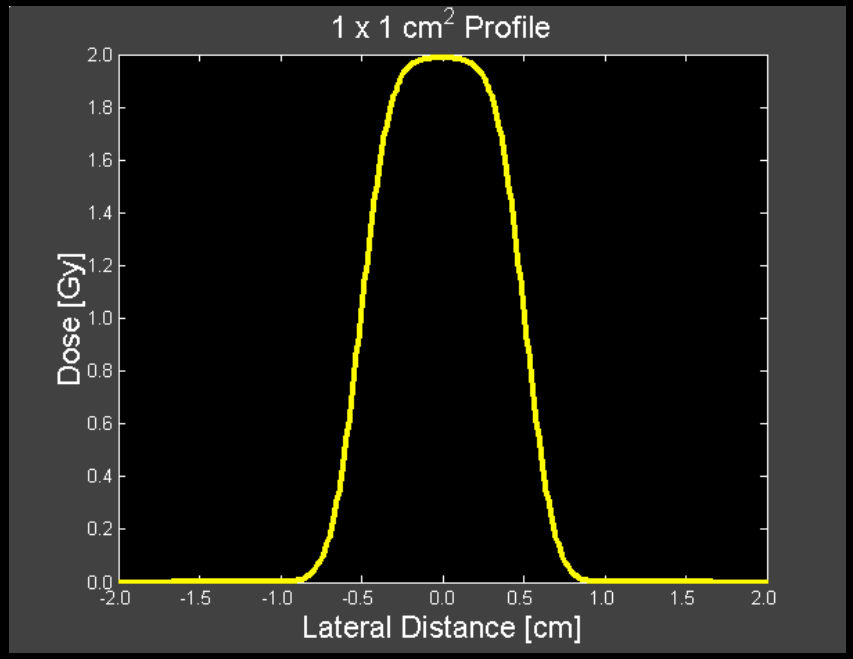
- In general a Fourier transform and inverse Fourier Transform may be defined as follows

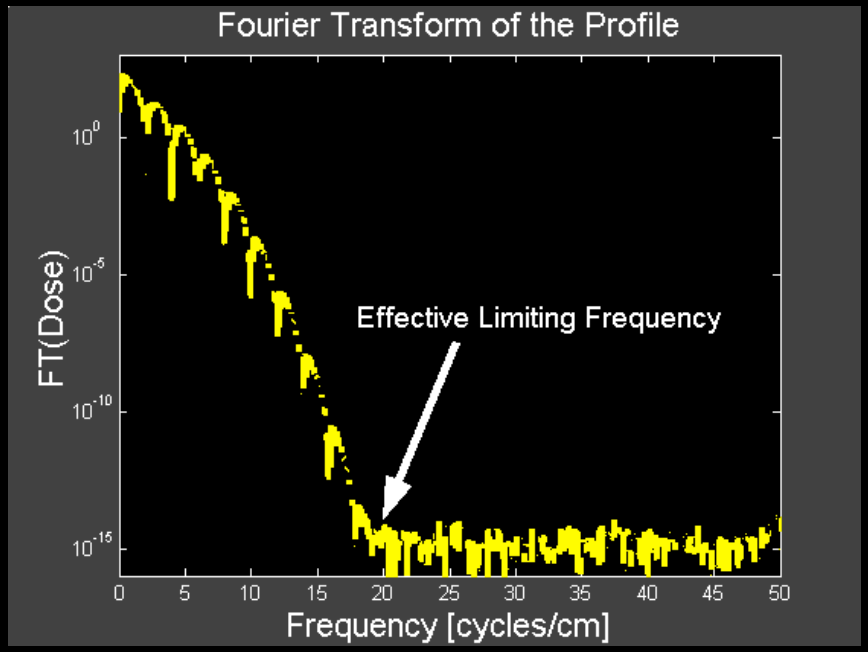
$$\tilde{f}\left(\vec{\omega}\right) = \Im\left[f\left(\vec{r}\right)\right] = A\int_{-\infty}^{+\infty} d^3\vec{r}\;\; f\left(\vec{r}\right)\times e^{Bi\vec{\omega}\cdot\vec{r}}$$

$$f\left(\vec{r}\right) = \Im^{-1}\left[\tilde{f}\left(\vec{\omega}\right)\right] = \frac{B}{2\pi A}\int_{-\infty}^{+\infty} d^3\vec{\omega}\;\; \tilde{f}\left(\vec{\omega}\right)\times e^{-Bi\vec{\omega}\cdot\vec{r}}$$

Where A and B are arbitrary constants. In our work we choose A=1 and B=2π for convenience.

Example of the Fourier Transform of Beamlet Profile

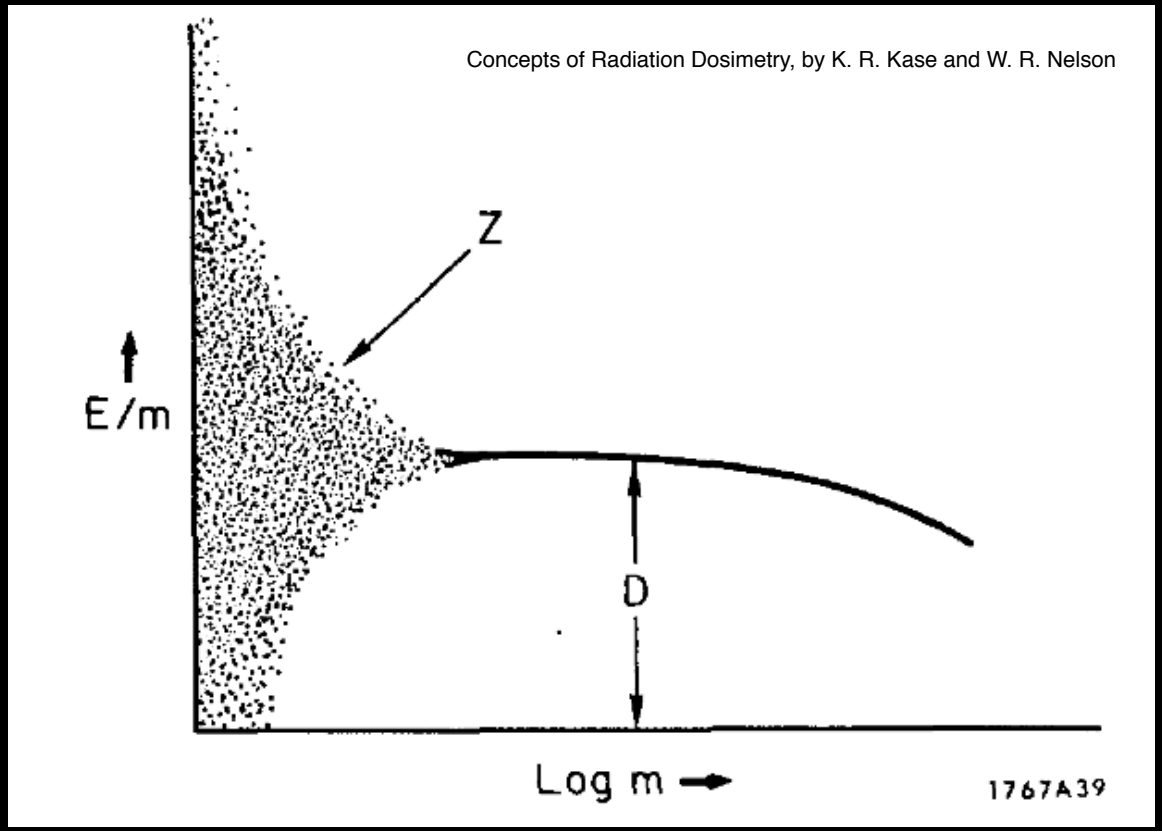




A fitted 1x1 cm^2 profile from 0.1 mm pixel RCF measurements in solid water

Is Dose a Continuous Function ?

- Dose is continuous only as a Mesoscopic Quantitiy



Note on Discretizing *d*

- It is well known that absorbed ionizing radiation dose distributions are not even theoretically continuous and well behaved functions at a microscopic scale due to discrete particle interactions giving rise to the absorbed ionizing dose. However, there should be a well behaved function of the expectation of the mean dose that is taken as a surrogate for the actual stochastic dose at some mesoscopic scale that is completely adequate for the purposes of radiation oncology. Such a coarse graining of the problem is justifiable on the order of the size of a cell as this is the intended target of radiotherapy.
- At a microscopic level dose is stochastic
- At a mesoscopic level dose is approximately continuous

Information Theory Approach

- Begin by considering the Fourier Transform & its inverse for a 3D dose distribution, d :

$$\tilde{d}(\vec{\omega}) = \Im\left[d(\vec{r})\right] = \int_{-\infty}^{+\infty}\int_{-\infty}^{+\infty}\int_{-\infty}^{+\infty} d(\vec{r})\, e^{2\pi i \vec{\omega}\cdot\vec{r}}\, d^3\vec{r}$$

$$d(\vec{r}) = \Im^{-1}\left[\tilde{d}(\vec{\omega})\right] = \int_{-\infty}^{+\infty}\int_{-\infty}^{+\infty}\int_{-\infty}^{+\infty} \tilde{d}(\vec{\omega})\, e^{-2\pi i \vec{\omega}\cdot\vec{r}}\, d^3\vec{\omega}$$

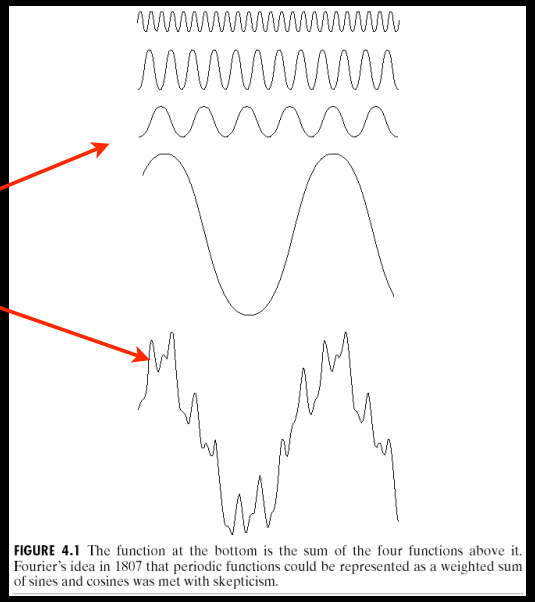


FIGURE 4.1 The function at the bottom is the sum of the four functions above it. Fourier's idea in 1807 that periodic functions could be represented as a weighted sum of sines and cosines was met with skepticism.

Similar approach to:

Bortfeld, T., Oelfke U., and Nill S. *What is the optimum leaf width of a multileafcollimator?*, Medical Physics, 27(11) (2000) , pp. 2494-2502.

Shannon-Nyquist Theorem

- According to this well known theorem, we know that if a function is band limited above some large frequency Ω, and we have

$$d(\vec{r}) = \int_{-\infty}^{+\infty}\int_{-\infty}^{+\infty}\int_{-\infty}^{+\infty} \tilde{d}(\vec{\omega}) e^{-2\pi i \vec{\omega}\cdot\vec{r}}\, d^3\vec{\omega} = \int_{-\Omega}^{+\Omega}\int_{-\Omega}^{+\Omega}\int_{-\Omega}^{+\Omega} \tilde{d}(\vec{\omega}) e^{-2\pi i \vec{\omega}\cdot\vec{r}}\, d^3\vec{\omega}$$

- Of course we cannot expect this in practical situations, i.e., finite contributions above Ω will exist… but how big are they?

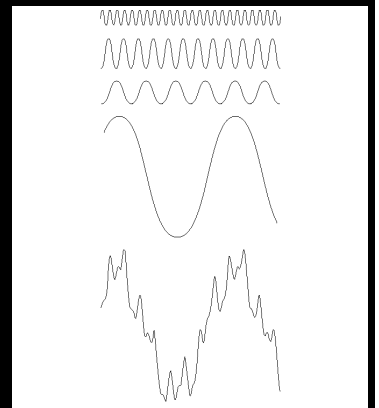
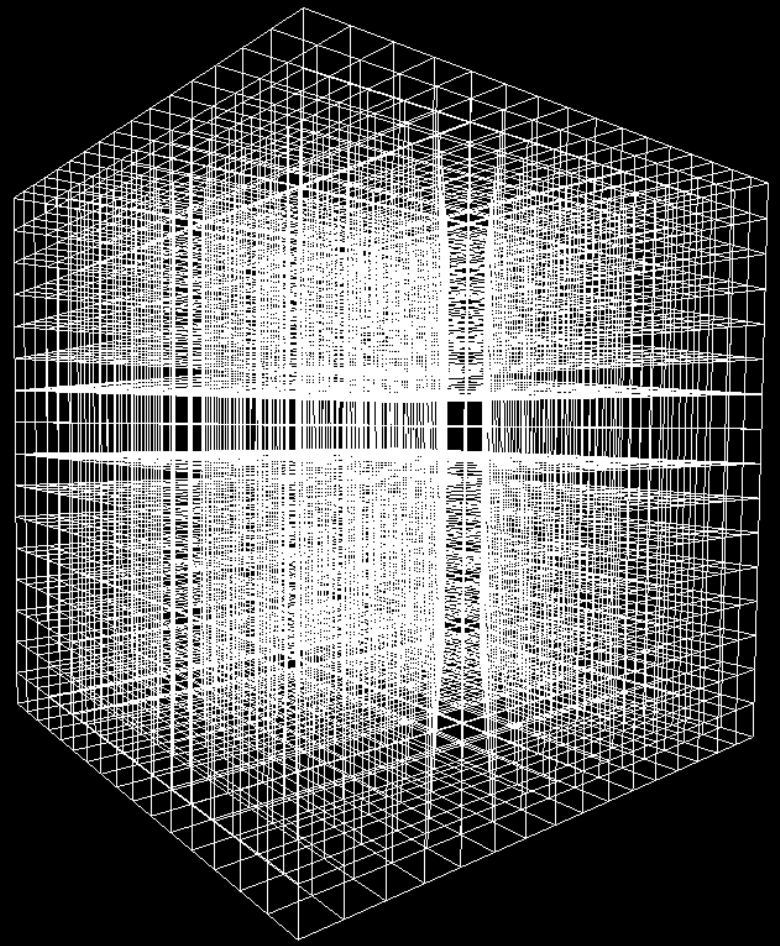


FIGURE 4.1 The function at the bottom is the sum of the four functions above it. Fourier's idea in 1807 that periodic functions could be represented as a weighted sum

Point & Voxel Sampling

- In point sampling, the dose is sampled at the center of each voxel
- In voxel sampling, the dose is averaged over each voxel
- But, how is this done mathematically

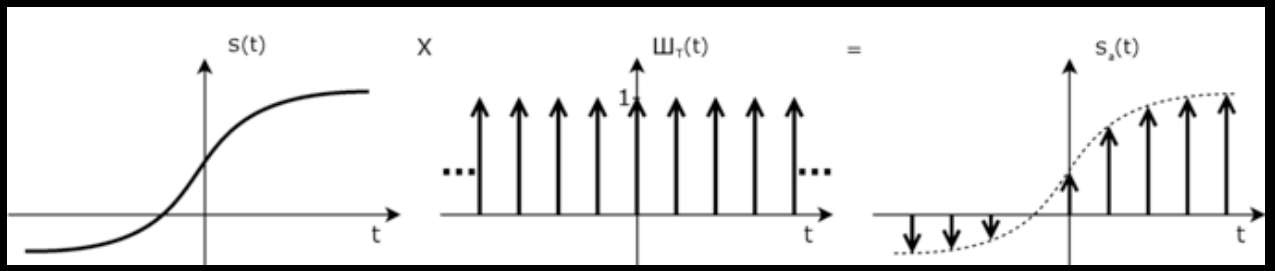


Point Sampling

- To deal with the case of discrete sampling at points we define a Cartesian 3D sampling function on a grid with isotropic spacing *h*:

$$\mathrm{III}_h\left(\vec{r}\right) = \left|h^3\right| \sum_{i=-\infty}^{\infty} \sum_{j=-\infty}^{\infty} \sum_{k=-\infty}^{\infty} \delta\left(x - hi, y - hj, z - hk\right)$$

- We now observe that the operation of discrete sampling on an isotropic grid with spacing *h* consists of taking the product $\breve{d}_h\left(\vec{r}\right) = \mathrm{III}_h\left(\vec{r}\right) \times d\left(\vec{r}\right)$



Volume Averaging

- By convolving *d* with the Cartesian 3D voxel function we obtain a volume averaged dose distribution:

$$d_h^{VA}\left(\vec{r}\right) = \int_{-\infty}^{+\infty}\int_{-\infty}^{+\infty}\int_{-\infty}^{+\infty} d\left(\vec{r}-\vec{r}'\right)\,{}^3\Pi_h\left(\vec{r}'\right)d^3\vec{r}'$$

$${}^3\Pi\left(\vec{r}\right) = \left(H\left(x+\tfrac{1}{2}\right)-H\left(x-\tfrac{1}{2}\right)\right)\left(H\left(y+\tfrac{1}{2}\right)-H\left(y-\tfrac{1}{2}\right)\right)\left(H\left(z+\tfrac{1}{2}\right)-H\left(z-\tfrac{1}{2}\right)\right)$$

- Now the operation of discrete sampling can be applied to produce a discretized approximation of the volume averaged continuous function by

$$\breve{d}_h^{VA}\left(\vec{r}\right) = \text{Ш}_h\left(\vec{r}\right)\times d_h^{VA}\left(\vec{r}\right)$$

Breaking the Inverse Transform

- We now break the inverse Fourier transform into the Shannon-Nyquist Limited/Unlimited Parts at Ω

$$d(\vec{r}) = \sum_{i=1}^{3}\sum_{j=1}^{3}\sum_{k=1}^{3}\int_{A_i}\int_{A_j}\int_{A_k}\tilde{d}(\vec{\varpi})e^{-2\pi i\vec{\varpi}\cdot\vec{r}}d^3\vec{\varpi}$$

$$d_h^{VA}(\vec{r}) = \sum_{i=1}^{3}\sum_{j=1}^{3}\sum_{k=1}^{3}\int_{A_i}\int_{A_j}\int_{A_k}\tilde{d}(\vec{\varpi})\,{}^3\tilde{\Pi}_h(\vec{\varpi})e^{-2\pi i\vec{\varpi}\cdot\vec{r}}d^3\vec{\varpi}$$

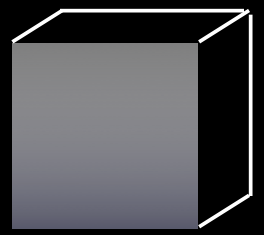
- where $A_1 = \left(-\infty, -\frac{1}{2h}\right) \quad A_2 = \left[-\frac{1}{2h}, \frac{1}{2h}\right] \quad A_3 = \left(\frac{1}{2h}, \infty\right)$
- And we note

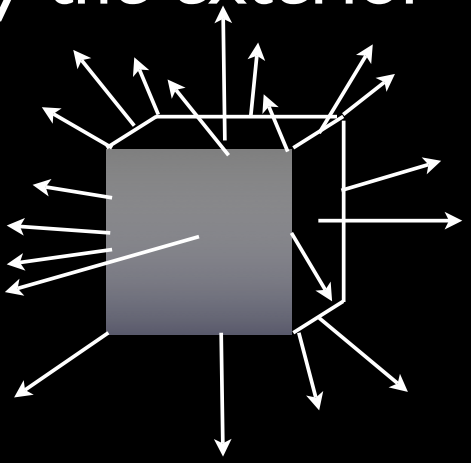
$$\breve{d}_h(\vec{r}) = \int_{A_2}\int_{A_2}\int_{A_2}\tilde{d}(\vec{\varpi})e^{-2\pi i\vec{\varpi}\cdot\vec{r}}d^3\vec{\varpi}$$

$$\breve{d}_h^{VA}(\vec{r}) = \int_{A_2}\int_{A_2}\int_{A_2}\tilde{d}(\vec{\varpi})\,{}^3\tilde{\Pi}_h(\vec{\varpi})e^{-2\pi i\vec{\varpi}\cdot\vec{r}}d^3\vec{\varpi}$$

Breaking the Inverse Transform

- The discretized function is described by the part in the central cube
- The errors are described by the exterior
- 6 faces
- 12 edges
- 8 verticies
- 26 external pieces + 1 central cube = 27

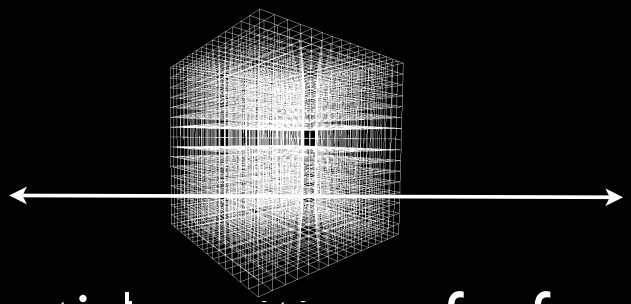




Shifting the Grid Around

- We note that the position of a discretization grid can influence the discretization error.

$$\int_{-\infty}^{+\infty} d^3\vec{r}\ \ f\left(\vec{r}-\vec{a}\right)e^{-2\pi i\vec{\varpi}\cdot\vec{r}} = \int_{-\infty}^{+\infty} d^3\left(\vec{r}-\vec{a}\right)\ \ f\left(\vec{r}-\vec{a}\right)e^{-2\pi i\vec{\varpi}\cdot\left(\vec{r}-\vec{a}\right)}e^{-2\pi i\vec{\varpi}\cdot\vec{a}} = e^{-2\pi i\vec{\varpi}\cdot\vec{a}}\,\tilde{f}\left(\vec{\varpi}\right)$$



- Therefore the spatial position of a function is accounted for by a phase shift term in frequency space which is at most a factor of 1

Worst Case Error Estimates

- We can ignore the phase terms as they always have a value of unity or less, so we make the following bound

$$\left|f\left(\vec{r}\right)\right| \leq \int_{-\infty}^{+\infty}\int_{-\infty}^{+\infty}\int_{-\infty}^{+\infty}\left|\tilde{f}\left(\vec{\varpi}\right)\right| d^3\vec{\varpi}$$

- We can also place a worst case bound on the discrepancy functions regardless of grid position!:

$$\left|\Delta_h(\vec{r})\right| \leq \left(\sum_{i=1}^{3}\sum_{j=1}^{3}\sum_{k=1}^{3}\int_{A_i}\int_{A_j}\int_{A_k}\left|\tilde{d}\left(\vec{\varpi}\right)\right| d^3\vec{\varpi}\right) - \int_{A_2}\int_{A_2}\int_{A_2}\left|\tilde{d}\left(\vec{\varpi}\right)\right| d^3\vec{\varpi}$$

$$\left|\Delta_h^{VA}(\vec{r})\right| \leq \left(\sum_{i=1}^{3}\sum_{j=1}^{3}\sum_{k=1}^{3}\int_{A_i}\int_{A_j}\int_{A_k}\left|\tilde{d}\left(\vec{\varpi}\right)^3\tilde{\Pi}_h\left(\vec{\varpi}\right)\right| d^3\vec{\varpi}\right) - \int_{A_2}\int_{A_2}\int_{A_2}\left|\tilde{d}\left(\vec{\varpi}\right)^3\tilde{\Pi}_h\left(\vec{\varpi}\right)\right| d^3\vec{\varpi}$$

A Example of Applying the Theory…

- We will now apply the theory to the case of IMRT optimization using a beamlet dose model

The beamlet has all the information!

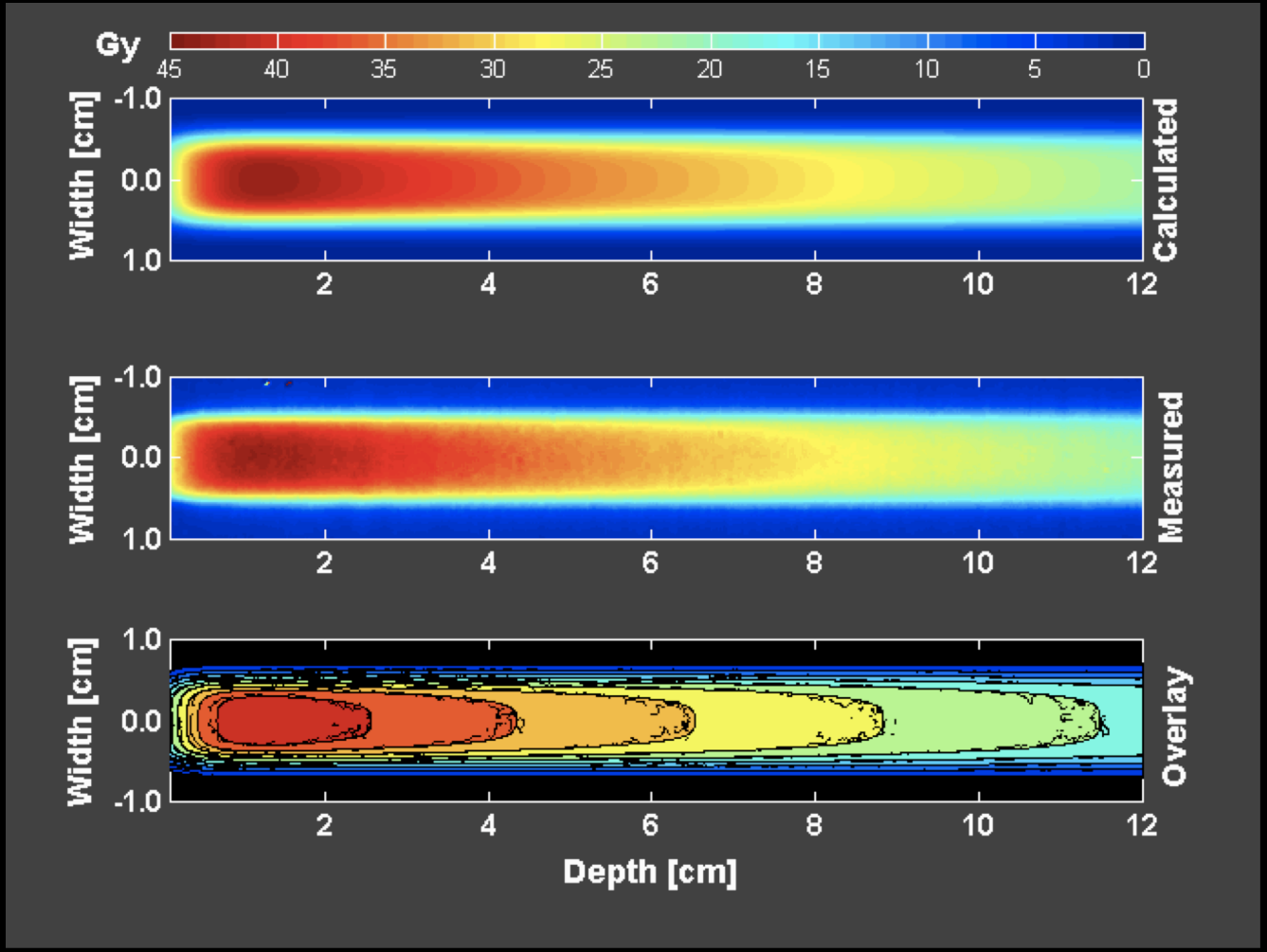
- Due to the linearity of the Fourier transform, i.e.:

$$\Im\left[af\left(\vec{x}\right)+bg\left(\vec{x}\right)\right]=a\tilde{f}\left(\vec{\omega}\right)+b\tilde{g}\left(\vec{\omega}\right)$$

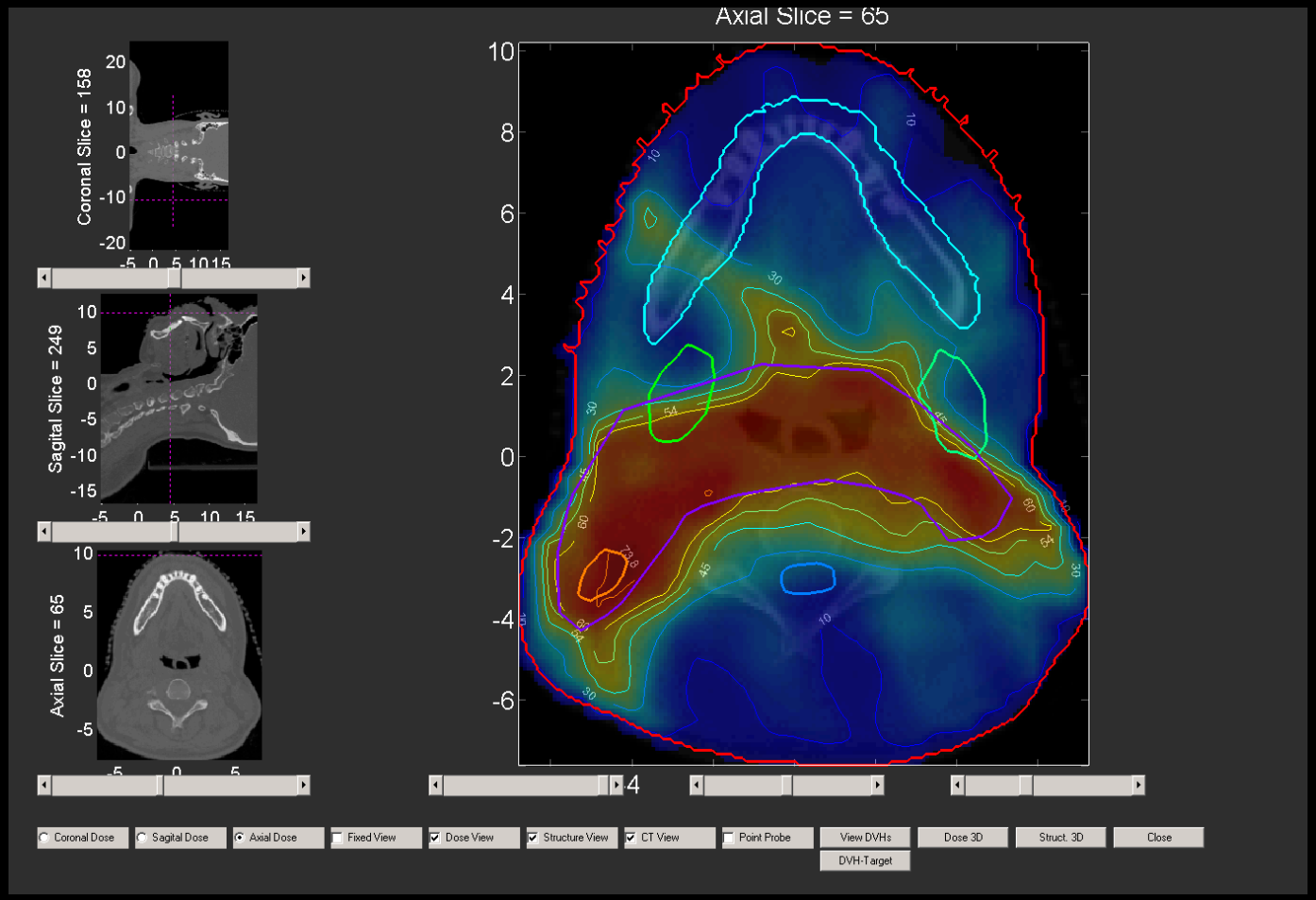
- The Fourier spectrum of D is just a weighted sum of the Fourier spectra of the d_j's where a phase factor of has been added to account for the fact that the beamlets will have different spatial locations :

$$\tilde{D}\left(\vec{\omega}\right)=\sum_{j=1}^{N_b}\mu_j\tilde{d}_j\left(\vec{\omega}\right)e^{-2\pi i\vec{\omega}\cdot\vec{a}_j}$$

An Accurate IMRT Beamlet Model in Water



Composite IMRT Treatment Plans @1,2,3,4,5,&6 mm

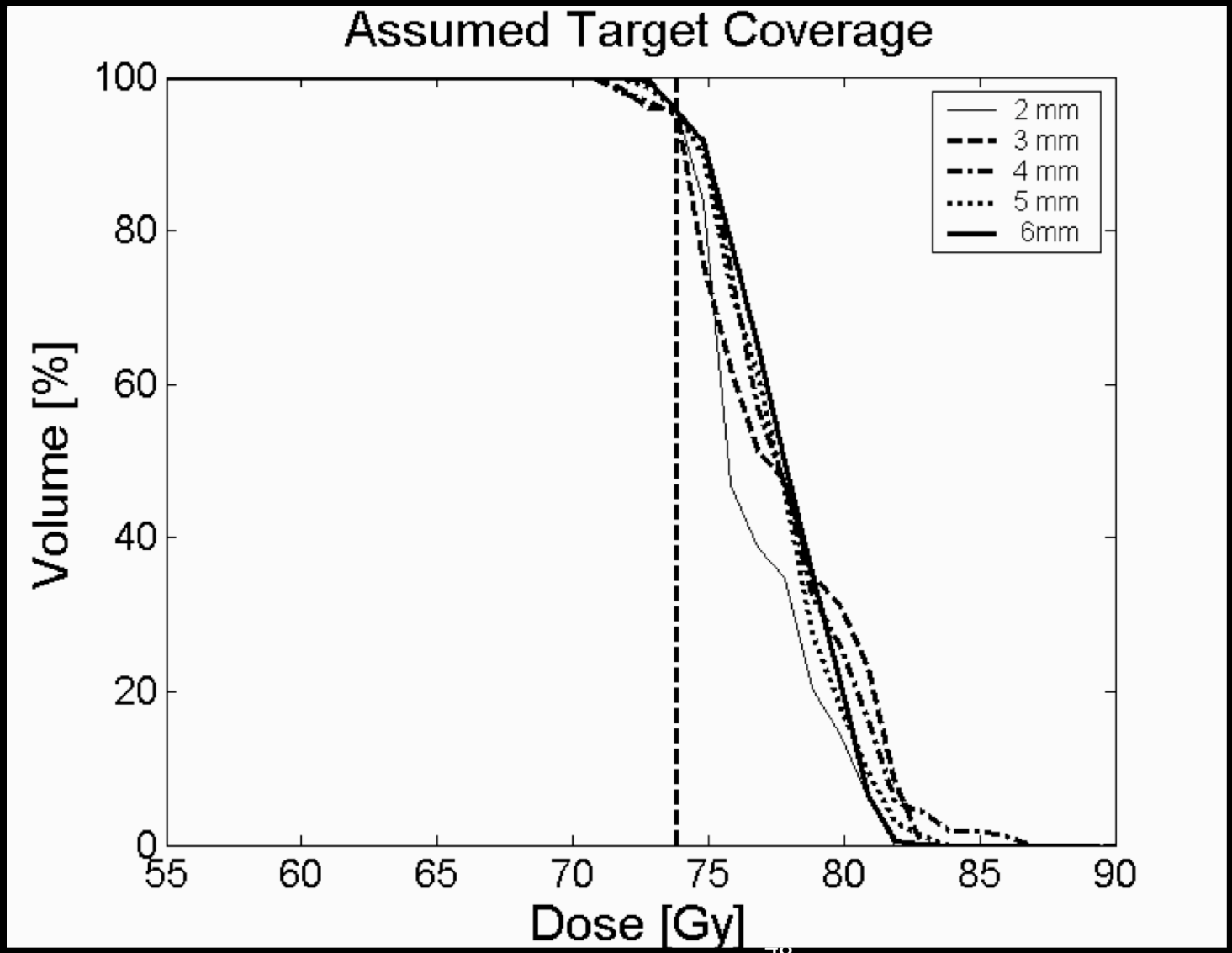


Prediction of Needed Resolution

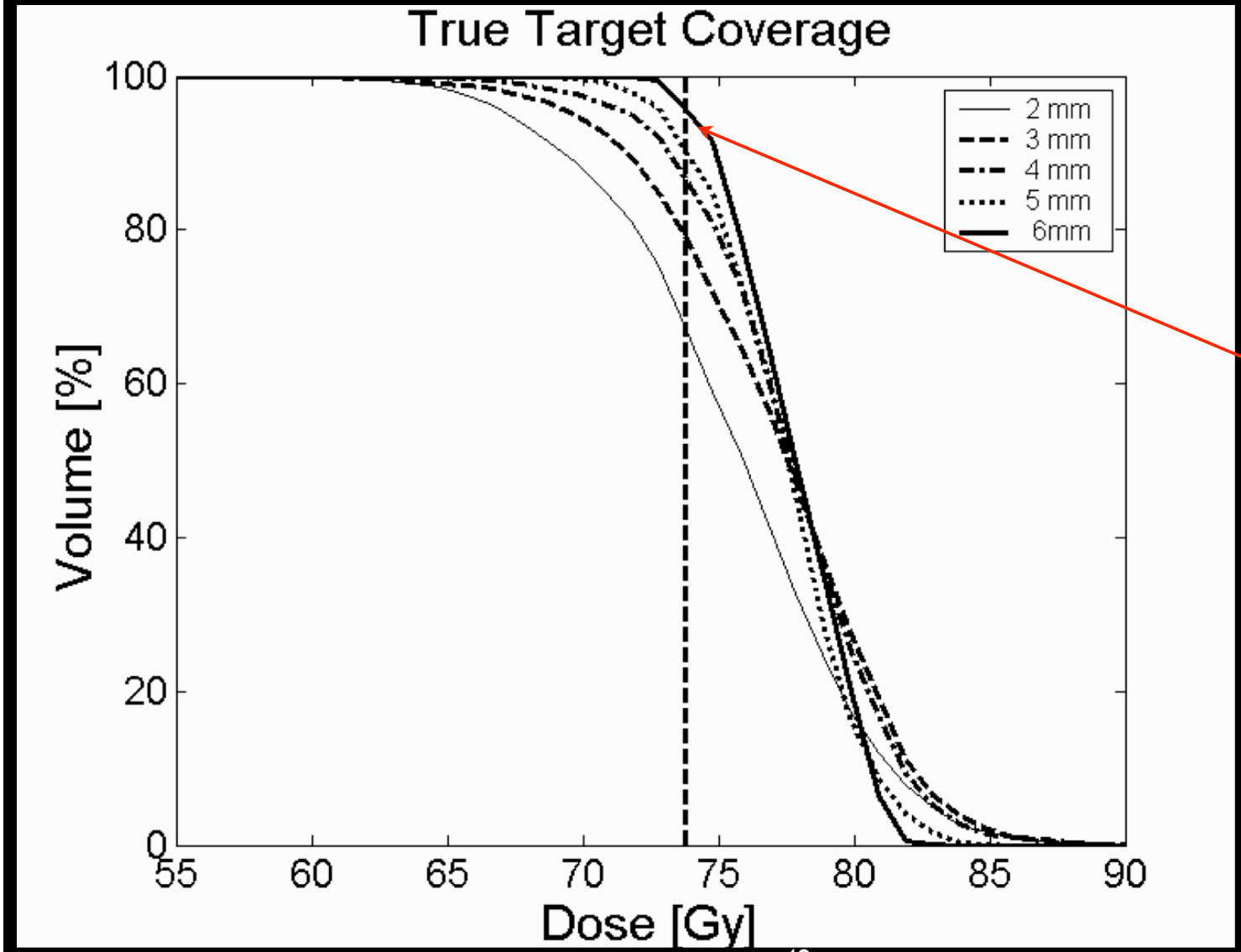
TABLE I. Discretization errors at the maximum 6 MV beamlet dose value as a function of dose grid spacing.

h (mm)	Max point sampling error at max value (%)	Max discretized volume averaging error at max value (%)
1.0	0.000 074 4	0.847
1.5	0.0616	1.93
2.0	0.575	3.59
2.5	1.66	6.04
3.0	3.30	8.46
3.5	7.01	13.2
4.0	10.6	16.1
5.0	13.6	20.9
6.0	15.8	25.4

What You Think You Get…



What You Get…



% @ D_{Rx}

95.0 -2 mm

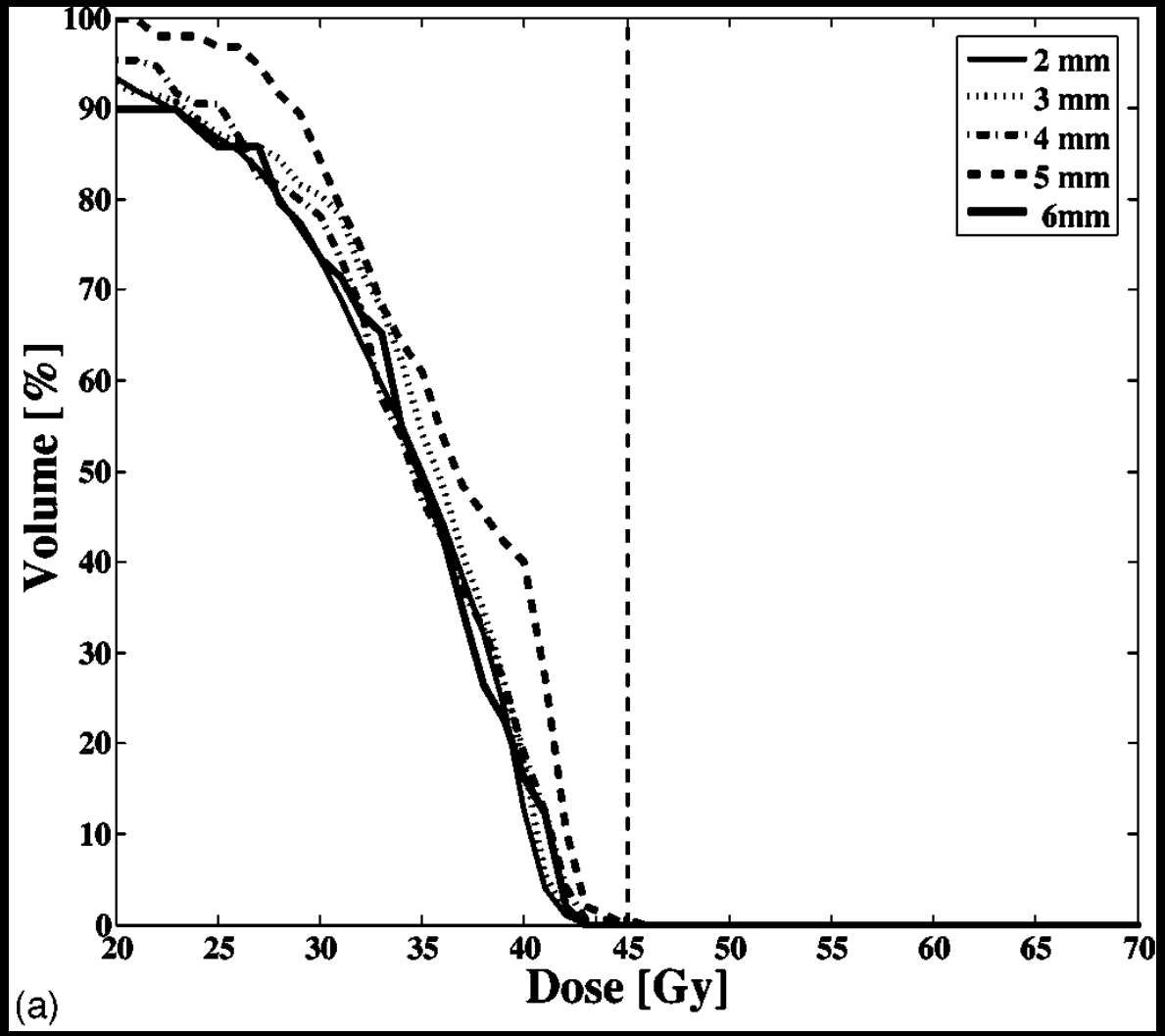
90.0 - 3 mm

86.5 - 4 mm

79.0 – 5 mm

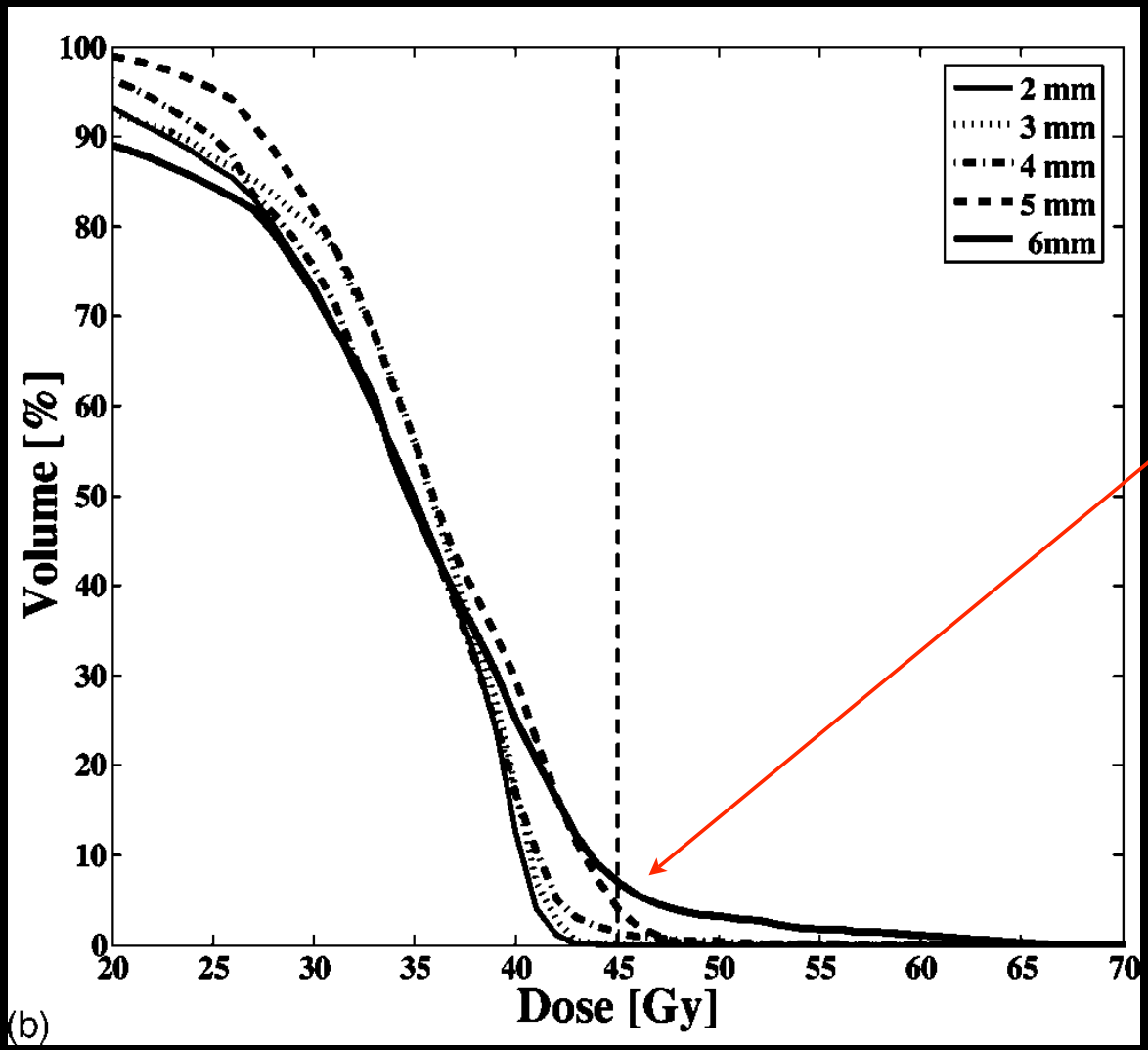
67.0 – 6 mm

What You Think You Get…



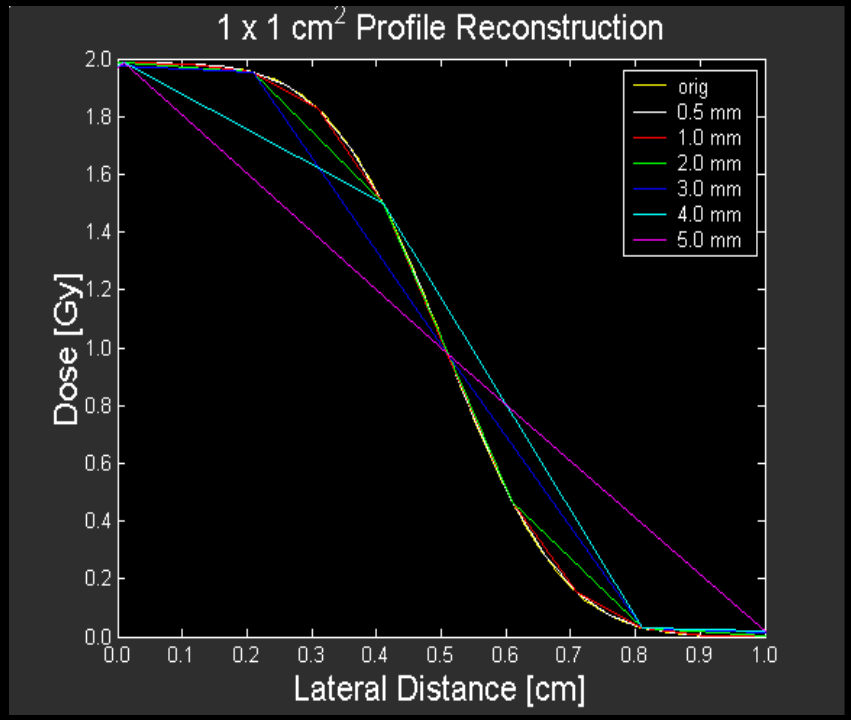
Spinal Cord Sparing

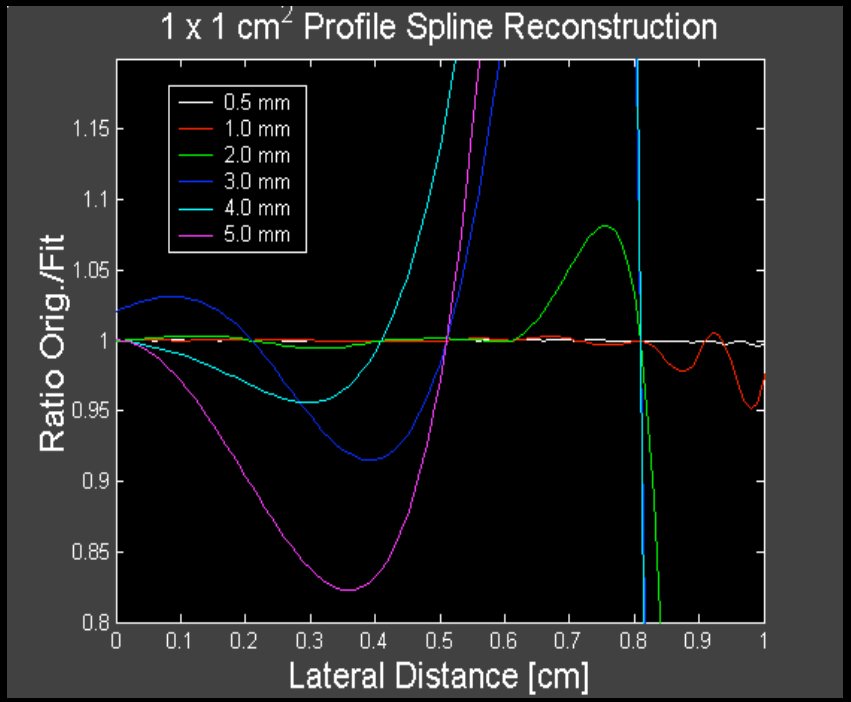
What You Get…



Spinal Cord Overdose

Optimization Takes Advantage of Aliasing of the Beamlet

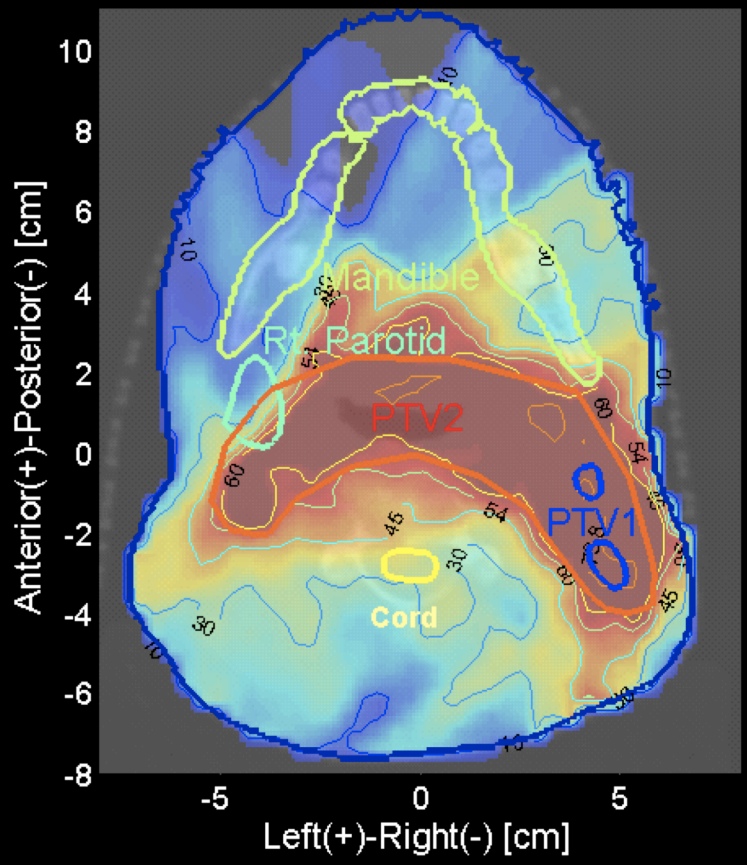




IMRT Optimization Models

IMRT Optimization: Where the Action is …

- Our ability to solve large-scale optimization problems for individual patients directly impacts:
  - Target coverage
  - Tissue sparing
  - Delivery efficiency
  - Treatment efficacy
- A powerful method, which is not completely understood



The Holistic IMRT Problem

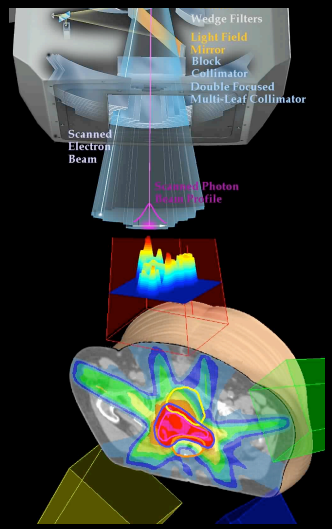
- In principle, all aspects of IMRT should be optimized!
  - What to shoot?
    - Beam Number
    - Beam Position & Orientation
    - Beam Particle & Energy
  - How Much to Shoot?
  - How to Shoot Efficiently?

ho·lis·tic (hO-'lis-tik) adj. **1:** relating to or concerned with wholes or with complete systems rather than with the analysis of, treatment of, or dissection into parts

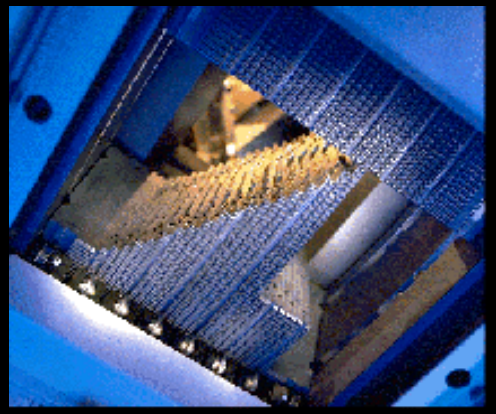
The 3 Major Subproblems we can realistically solve

Holistic IMRT

Beam Number & Orientation Optimization



Fluence Map Optimization



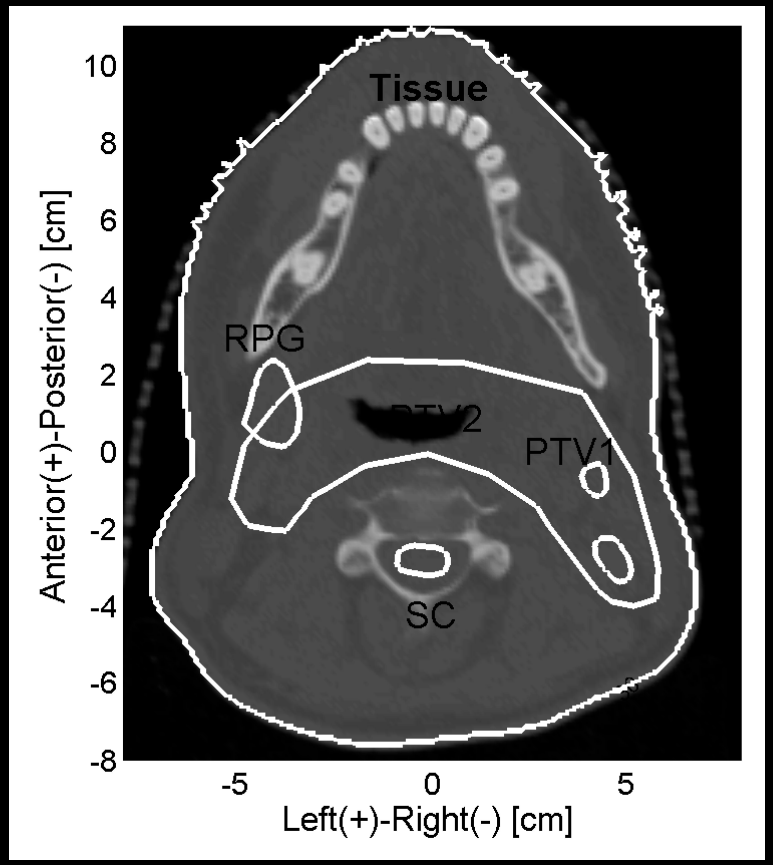
Leaf Sequencing Optimization

IMRT Models

- Modeling treatment planning problems
  - Treatment plan evaluation criteria
  - Multi-criteria optimization
  - Relationship to risk management in finance
- We will qualitatively compare different models for treatment planning
  - Equivalence (in a multi-criteria context)
  - Computational efficiency (convex vs. nonconvex)

IMRT Planning

- The goal of IMRT treatment planning is to design a treatment plan that delivers a prescribed dose to targets, while sparing, to the greatest extent possible, critical structures
- Example of a head-and-neck cancer patient
  - PTV1 and PTV2 are targets
  - Right Parotid Gland, Spinal Cord, Tissue are critical structures



reference

- PMB 49 1991-2013

A unifying framework for multi-criteria fluence map optimization models

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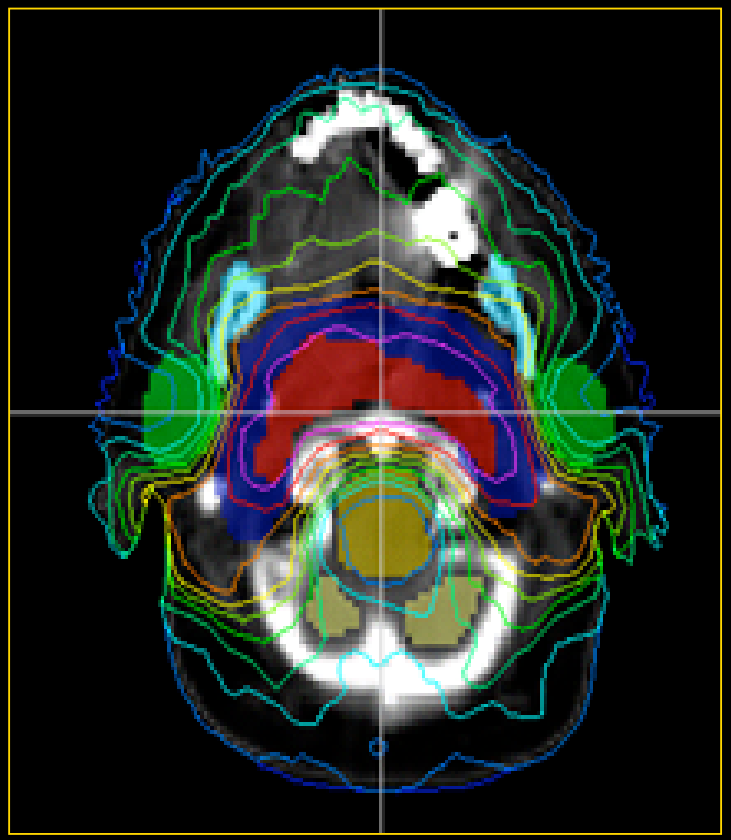
Evaluating Treatment Plans

- Treatment plans are evaluated by a physician or clinician based on the dose distribution
  - computed on a discretization of the 3-dimensional patient geometry into a regular grid of cubes (voxels)
  - overlays of CT images (3D)
- We will perform a formal comparison of existing optimization models for finding treatment plans
  - there is no fundamental way of quantifying the quality of a treatment plan



Treatment Plan Optimization

- The objective of treatment plan optimization is to control the dose distribution
  - close relationship to (financial) risk management
  - difference: there is no real randomness – the entire distribution is realized!
- The dose distribution is decomposed into individual dose distributions in the structures (targets/critical structures)
  - the objective becomes to control each of these dose distributions
  - trade-off between dose distributions in different structures
- Assumption:

spatial effects within the structure are unimportant

Summary Measures of Dose Distribution

- A common approach is to consider treatment plan evaluation criteria that summarize the dose distribution in a given structure by a single value
- For example, measures of
  - tumor control probability (TCP)
  - normal tissue complication probability (NTCP)
  - equivalent uniform dose (EUD)
- We will show that criteria of the form

$$f^{-1}\left(\frac{1}{v}\sum_{j=1}^{v} f\left(d_j\right)\right) = f^{-1}\left(E\left(f(D)\right)\right)$$

play a very important role

- the function f represents the (biological) effect of a dose distribution in a structure

Examples

- For a target
  - each tumor cell needs to be eradicated to cure the patient
  - minimum dose will be a relevant measure
- For a parallel critical structure
  - survival of part of structure can ensure full functionality
  - mean dose may be a relevant measure
- For a serial critical structure
  - survival of full structure is needed to ensure full functionality
  - maximum dose may be a relevant measure

Equivalent Uniform Dose

- Equivalent Uniform Dose (EUD) is defined as a homogeneous dose that would have the same (biological) properties as a given nonhomogeneous dose distribution
- Proposed EUD's of the form $f^{-1}(E(f(D)))$ are
  - $f(D) = D^{a}$, for $a \in [1,\infty]$ for critical structures
  - $f(D) = D^{-b}$, for $b \in [0,\infty]$ for targets, or
  - $f(D) = e^{-\alpha D}$, for $\alpha \in (0,\infty)$ for targets

Tumor Control Probability

- EUD with the latter choice of f corresponds to a measure of Tumor Control Probability (TCP)
- Based on a binomial/Poisson model that says that each cell in a voxel has a certain probability of survival based on the dose received by that voxel

$$\mathrm{TCP}\left(d;\alpha\right) = \exp\left(-N \cdot e^{-\alpha \mathrm{EUD}(d;\alpha)}\right)$$

where

- N = total number of cancer cells in the target
- α = measure of radioresistance of target cells

Other Criteria

- TCP is thus a monotone function of EUD (d;α)
- Many other criteria have been proposed that are monotone functions of EUD(d;α), EUD (d;-b), or EUD(d;a)
- For example, measures of Normal Tissue Complication Probability (NTCP)

Other Criteria

- Other criteria that have been proposed are functions of EUD, TCP, and/or NTCP
- For example
  - Homogeneity in a target
    - E.g. defined as the ratio or difference of maximum and minimum dose
  - P_+: probability of uncomplicated tumor control
    - Defined as the product of all target TCPs and critical structure (1-NTCP)'s
- Many of these criteria are nonconvex/ nonconcave
  - except EUD and some measures of homogeneity (assuming d is a convex function of the decision variables; e.g., fluence map optimization for IMRT)

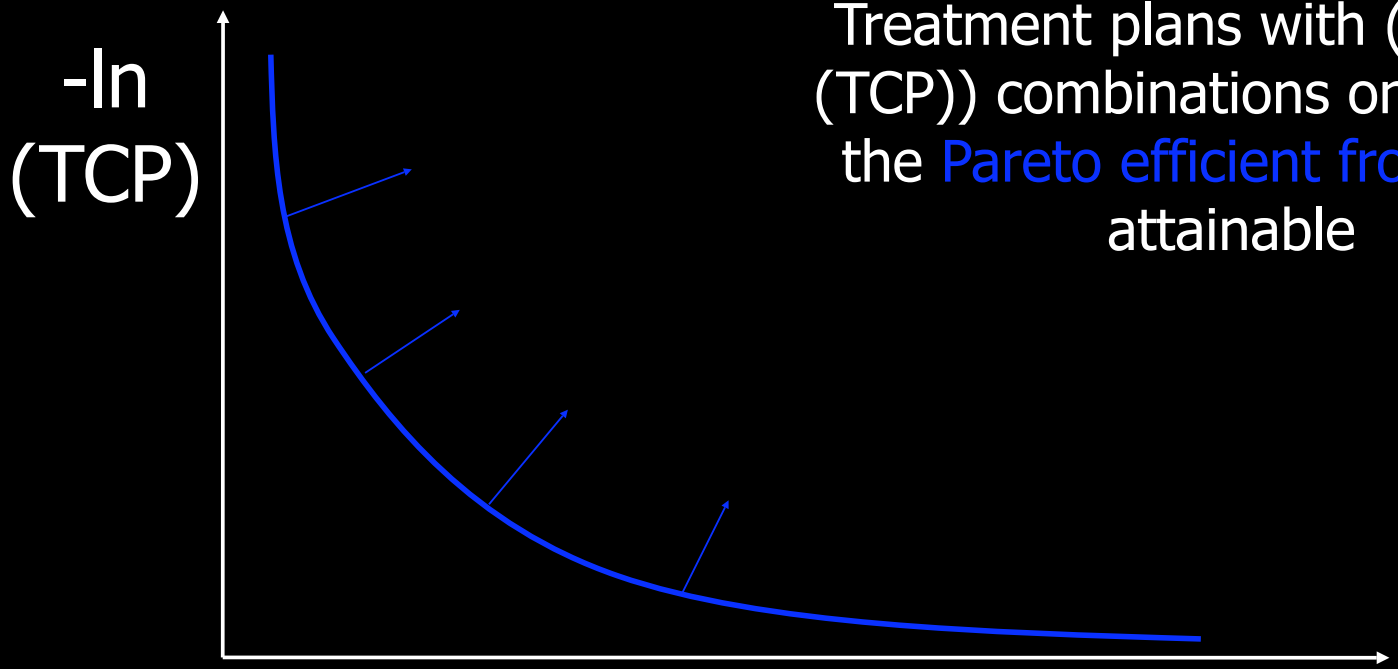
IMRT Treatment Planning

- The aim of IMRT treatment planning is to find a treatment plan that makes a trade-off between several different treatment plan evaluation criteria that measure
  - Target coverage
  - Critical structure sparing
- These criteria are clearly conflicting
- The difference between proposed models lies in the way the trade-off between the treatment plan evaluation criteria is quantified and parameterized

Multi-Criteria Optimization

- For a given set of treatment plan evaluation criteria, a multi-criteria optimization approach identifies a set of treatment plans that are Pareto efficient
  - That is, no criterion can be improved without deteriorating at least one of the other criteria
- See, e.g., Bortfeld et al. (2003), Hamacher & Kűfer (2002), Lahanas et al. (2003)

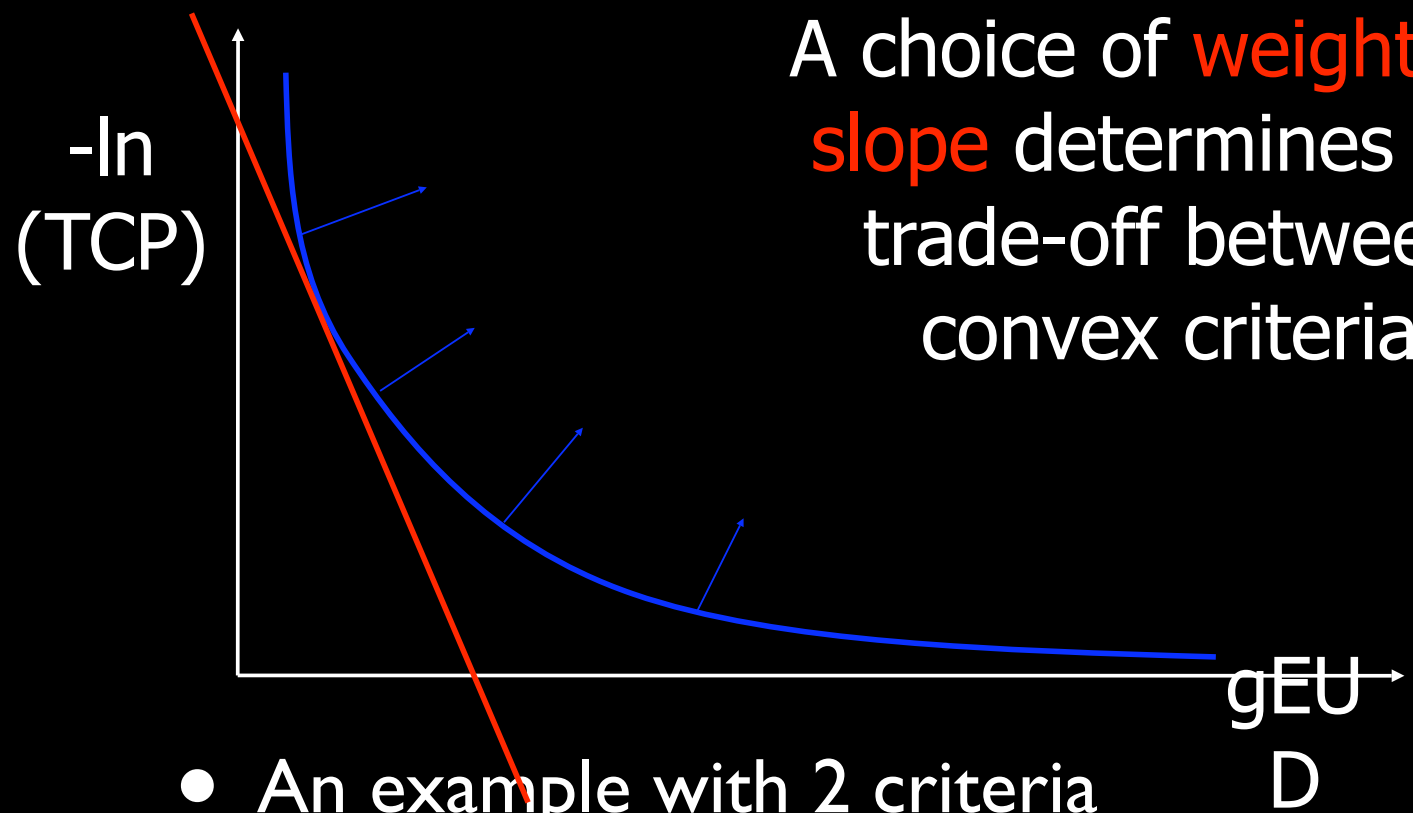
Pareto efficient treatment plans



Treatment plans with (gEUD,-ln (TCP)) combinations on or above the Pareto efficient frontier are attainable

- An example with 2 criteria

Finding Pareto efficient treatment plans



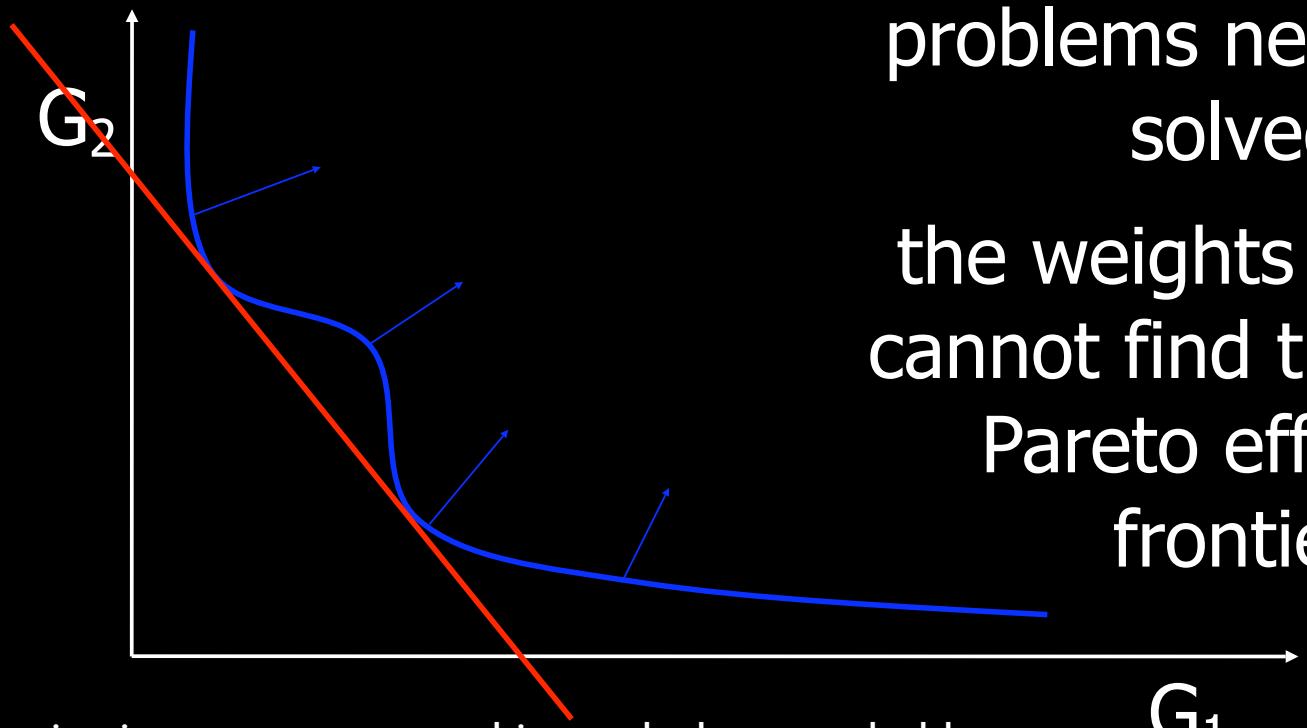
A choice of weights or slope determines the trade-off between convex criteria

- An example with 2 criteria

Finding Pareto efficient treatment plans

multimodal optimization problems need to be solved

the weights method cannot find the entire Pareto efficient frontier



When the criteria are not convex, this result does not hold anymore

Equivalence of Criteria

- Theorem:
  - Taking increasing transformations of a set of treatment plan evaluation criteria does not change the set of Pareto efficient treatment plans
- Corollary:
  - If we have nonconvex criteria, but can find increasing transformations that are convex, we can identify the Pareto efficient treatment plans by optimizing a weighted sum of these criteria
    - These are convex optimization problems

Treatment Plan Evaluation Criteria

- The nonconcave/nonconvex criteria
  - tumor control probability (TCP)
  - normal tissue complication probability (NTCP)

  are monotone functions of
  - equivalent uniform dose (EUD)
- In fact, many proposed criteria turn out to be monotone functions of (convex) criteria of the form

$$E\Big(f(D)\Big) = \frac{1}{v}\sum_{j=1}^{v} f\Big(d_j\Big)$$

Model Differences

- Many models parameterize the trade-off between criteria in such a way that
  - part of the Pareto frontier cannot be reached
  - the optimization models are unnecessarily complex (global optimization)
- A voxel-based convex objective function is able to capture all Pareto efficient solutions with respect to (almost all) other mentioned criteria

Table 1. Evaluation criteria for targets.

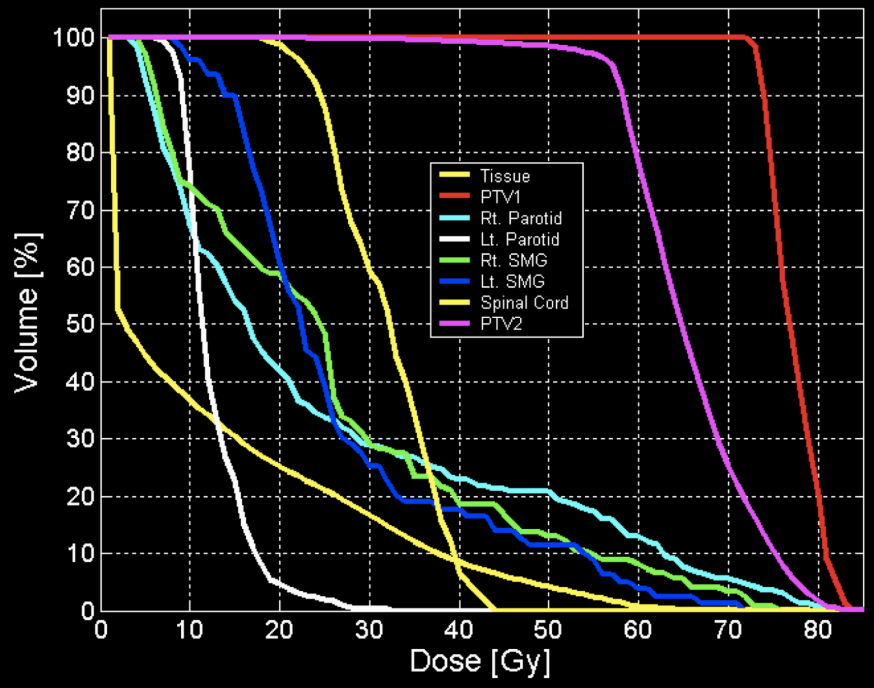
		Criterion decomposition	
Criterion	*Parameter range*	$G(\vec{d})$	$h(z)$
$\mathrm{TCP}(N, \alpha, \lambda, n, \Delta T)$	$N, \alpha > 0; n \geqslant 1; \lambda, \Delta T \geqslant 0$	$-\ln \mathrm{TCP}(\vec{d}; N, \alpha, n, \Delta T, \lambda)$	$-\mathrm{e}^{-z}$
		$-\mathrm{EUD}(\vec{d}; \alpha)$	$-\exp(-N\mathrm{e}^{\lambda(n-1)\Delta T+\alpha z})$
$\mathrm{EUD}(\alpha)$	$\alpha > 0$	$-\mathrm{EUD}(\vec{d}; \alpha)$	z
		$F(\vec{d}; \alpha)$	$\frac{1}{\alpha}\ln z$
$\mathrm{gEUD}(a)$	$-\infty \leqslant a \leqslant 0$	$-\mathrm{gEUD}(\vec{d}; a)$	z
	$-\infty < a < 0$	$F^{\mathrm{g}}(\vec{d}; a)$	$-z^{1/a}$
	$a = 0$	$F^{\mathrm{g}}(\vec{d}; 0)$	$-\mathrm{e}^{-z}$
$W(a, k, \mathrm{gEUD}^0)$	$-\infty \leqslant a \leqslant 0; k, \mathrm{gEUD}^0 > 0$	$W(\vec{d}; a, k, \mathrm{gEUD}^0)$	z
		$-\mathrm{gEUD}(\vec{d}; a)$	$\ln\left(1 + \left(-\frac{\mathrm{gEUD}^0}{z}\right)^k\right)$
$\breve{W}(a, \sigma, \mathrm{gEUD}^0)$	$-\infty \leqslant a \leqslant 0; \sigma, \mathrm{gEUD}^0 > 0$	$\breve{W}(\vec{d}; a, \sigma, \mathrm{gEUD}^0)$	z
		$-\mathrm{gEUD}(\vec{d}; a)$	$-\ln\left(1 - \Phi\left(\frac{\mathrm{gEUD}^0+z}{\sigma\cdot\mathrm{gEUD}^0}\right)\right)$
$F(\alpha)$	$\alpha > 0$	$F(\vec{d}; \alpha)$	z
	$\alpha > 0$	$-\mathrm{EUD}(\vec{d}; \alpha)$	e^z
$F^{\mathrm{g}}(a)$	$-\infty < a \leqslant 0$	$F^{\mathrm{g}}(\vec{d}; a)$	z
	$-\infty < a < 0$	$-\mathrm{gEUD}(\vec{d}; a)$	$(-z)^a$

Table 2. Evaluation criteria for critical structures.

Criterion	*Parameter range*	$G(\vec{d})$	$h(z)$
$\mathrm{gEUD}(a)$	$1 \leqslant a \leqslant \infty$	$\mathrm{gEUD}(\vec{d}; a)$	z
	$1 \leqslant a < \infty$	$F^{\mathrm{g}}(\vec{d}; a)$	$z^{1/a}$
$W(a, k, \mathrm{gEUD}^0)$	$1 \leqslant a \leqslant \infty; k, \mathrm{gEUD}^0 > 0$	$\mathrm{gEUD}(\vec{d}; a)$	$\ln\left(1 + \left(\frac{z}{\mathrm{gEUD}^0}\right)^k\right)$
$\breve{W}(a, \sigma, \mathrm{gEUD}^0)$	$1 \leqslant a \leqslant \infty; \sigma, \mathrm{gEUD}^0 > 0$	$\mathrm{gEUD}(\vec{d}; a)$	$-\ln\left(1 - \Phi\left(\frac{z-\mathrm{gEUD}^0}{\sigma\cdot\mathrm{gEUD}^0}\right)\right)$
$\mathrm{NTCP}^{\mathrm{L\&S}}(a, m, D_{50})$	$1 \leqslant a \leqslant \infty; m, D_{50} > 0$	$\mathrm{gEUD}(\vec{d}; a)$	$\Phi\left(\frac{z-D_{50}}{mD_{50}}\right)$
$\mathrm{NTCP}^{\mathrm{A\&N}}(a, \Delta)$	$1 \leqslant a < \infty, \Delta > 0$	$\mathrm{gEUD}(\vec{d}; a)$	$1 - \mathrm{e}^{-(z/\Delta)^a}$
$F^{\mathrm{g}}(a)$	$1 \leqslant a \leqslant \infty$	$F^{\mathrm{g}}(\vec{d}; a)$	z
	$1 \leqslant a < \infty$	$\mathrm{gEUD}(\vec{d}; a)$	z^a

Dose-Volume Histogram

- A tool by which the quality of a treatment plan is often evaluated is the Dose-Volume Histogram (DVH)
- There is a very close relationship between voxel-based and DVH based criteria



Criteria Based on Dose-Volume Histogram

- Traditional DVH-based criteria measure points on the DVH
- For example:
  - the proportion of a target that receives less than 70 Gy
  - the proportion of a saliva gland that receives in excess of 30 Gy
- Such criteria are inherently nonconvex

Criteria Based on Dose-Volume Histogram

- Alternative formulation:
  - the fraction of a target receiving less than 70 Gy

$$E\left(f(D)\right)$$

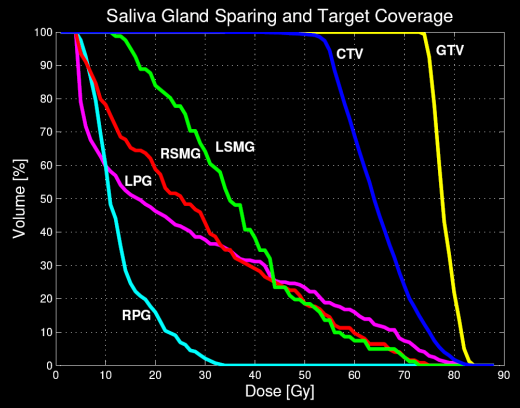
where $f(D) = I_{\{D<70\}}$

  - the fraction of a salivary gland receiving more than 30 Gy

$$E\left(f(D)\right)$$

where $f(D) = I_{\{D>30\}}$

- The functions f are nonconvex



Relation to Financial Risk Management: Stochastic Dominance

- In the (financial) risk management literature, such constraints are called stochastic dominance constraints
- In particular
  - if the DVH of a structure should be above (below) a reference DVH we say that the corresponding dose distribution should upper- (lower-) dominate the reference dose distribution to the first order

Alternative DVH Criteria

- Alternatively, we can formulate DVH criteria based on tail means of the dose distribution
- For example:
  - the average shortfall below 70 Gy of a target DVH: $E(f(D))$ where $f(D) = (70 - D)^+$
  - the average surplus above 30 Gy in a salivary gland: $E(f(D))$ where $f(D) = (D - 30)^+$
- The functions f are convex

Alternative DVH Constraints

- Formulated as constraints:
  - the average shortfall below d Gy of a target DVH should be no more than the corresponding average shortfall in a reference DVH for all d
  - The average surplus above d Gy in a saliva gland DVH should be no more than the corresponding average surplus in a reference DVH for all d
- These are called upper- and lower- dominance criteria to the second order

DVH Constraints vs. Voxel-Based Criteria

- A dose distribution D upper-dominates another distribution D′ to the first order if and only if

$$E\left(f(D)\right) \le E\left(f(D')\right)$$

for **all** nonincreasing functions f

- A dose distribution D upper-dominates another distribution D′ to the second order if and only if

$$E\left(f(D)\right) \le E\left(f(D')\right)$$

for **all** nonincreasing and convex functions f

DVH Constraints vs. Voxel-Based Criteria

- Compare this to the (voxel-based) criteria for targets that have been mentioned before:
  - A dose distribution D is preferable to another distribution D′ if and only if

$$E\left(f(D)\right) \leq E\left(f(D')\right)$$

for **a particular** nonincreasing and convex function f

DVH Constraints vs. Voxel-Based Criteria

- A dose distribution D lower-dominates another distribution D′ to the first order if and only if

$$E\left(f(D)\right) \le E\left(f(D')\right)$$

for **all** nondecreasing functions f

- A dose distribution D lower-dominates another distribution D′ to the second order if and only if

$$E\left(f(D)\right) \le E\left(f(D')\right)$$

for **all** nondecreasing and convex functions f

DVH Constraints vs. Voxel-Based Criteria

- Compare this to the (voxel-based) criteria for critical structures that have been mentioned before:
  - A dose distribution D is preferable to another distribution D′ if and only if

$$E\left(f(D)\right) \leq E\left(f(D')\right)$$

for **a particular** nondecreasing and convex function f

Dose Calculation Models

Heterogeneities & IMRT

- Reference - H A Al-Hallaq, C. Reft, and J.C. Roeske 2006 Phys. Med. Biol. 51 1145-1156
- TLD measurements in Rando phantom taken as ground truth
- Scaled density pencil beam models do very poorly near air and bone
- Convolution algorithm produced very good agreement

Pencil Beam Results

Table 1. Summary of TLD dose measurements from five separate exposures compared to doses calculated from the CORVUS treatment planning system assuming a homogeneous phantom and after heterogeneity correction.

TLD number	TLD type	Average dose (cGy)	STD (cGy)	CORVUS dose (cGy)	STD (cGy)	Per cent difference	Heterogeneity-corrected CORVUS dose (cGy)	Per cent difference
1	Bone[a]	164.5	5.1	151	0.7	8.9	154	6.8
2	Air[a]	161.9	4.4	151	1.3	7.2	154	5.1
3	Air	157.7	4.1	150	1.9	5.2	153	3.1
4	Bone[a]	157.6	3.8	149	1.5	5.8	152	3.7
5	Air[a]	81.5	3.6	74	4.5	10.2	77	5.9
6	Water/tissue[a]	159.0	1.4	156	1.5	1.9	157	1.3
7	Air	149.3	6.0	138	4.5	8.2	139	7.4
8	Water/tissue	162.0	2.9	157	0.6	3.2	158	2.5
9	Water/tissue	158.8	2.0	155	0.9	2.4	156	1.8
10	Water/tissue	159.4	3.5	156	1.1	2.2	157	1.5
11	Bone and cord	69.6	1.9	68	2.2	2.3	68	2.3
12	Water/tissue	155.1	2.4	154	2.3	0.7	155	0.1
13	Water/tissue[a]	157.7	1.9	152	1.2	3.8	154	2.4
14	Water/tissue	141.2	4.6	136	3.0	3.8	136	3.8
15	Bone and cord	78.2	4.6	70	4.3	11.7	71	10.1
16	Bone and cord	69.1	2.0	66	2.0	4.7	67	3.1
	Average	136.4	3.4	130.2	2.1	5.1	131.8	3.8

[a] Denotes TLDs in which the difference between measured and calculated dose was outside the 95% confidence interval associated with the measurement standard deviation.

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Convolution Results

Table 2. Comparison between CORVUS dose assuming a homogeneous phantom and Pinnacle[3] uncorrected and heterogeneity-corrected doses calculated for each TLD.

TLD number	TLD type	Pinnacle[3] uncorrected dose (cGy)	Pinnacle[3] heterogeneity-corrected dose (cGy)	Per cent difference of uncorrected Pinnacle[3] from CORVUS	Per cent difference of heterogeneity-corrected Pinnacle[3] from CORVUS	Geometric–effective depth difference summed over all nine beams (cm)
1	Bone	161.7	163.2	7.1	8.1	5.23
2	Air	162.4	164.5	7.6	8.9	4.78
3	Air	161.1	161.8	7.4	7.9	4.33
4	Bone	160.5	161.6	7.7	8.5	3.39
5	Air	80.7	82.4	9.0	11.4	11.93
6	Water/tissue[a]	164.0	164.4	5.1	5.4	3.45
7	Air	145.1	144.9	5.1	5.0	2.71
8	Water/tissue	164.6	163.9	4.8	4.4	1.33
9	Water/tissue	160.3	160.4	3.4	3.5	1.89
10	Water/tissue	161.4	161.4	3.5	3.5	0.41
11	Bone and Cord	68.1	67.8	0.1	−0.3	0.45
12	Water/tissue	158.2	157.3	2.7	2.1	−1.47
13	Water/tissue	155.7	155.0	2.5	2.0	0.37
14	Water/tissue	137.6	136.7	1.2	0.5	−1.24
15	Bone and Cord	71.7	73.0	2.4	4.3	4.71
16	Bone and Cord	68.2	68.9	3.3	4.3	0.93
	Average	136.3	136.7	4.6	5.0	2.7

[a] Denotes TLDs in which the difference between measured and calculated dose was outside the 95% confidence interval associated with the measurement standard deviation.

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Conclusions

- IMRT models can strongly influence the quality of IMRT
- Dose distribution must be Shannon-Nyquist resolved for accurate IMRT modeling
- Many models proposed to date are equivalent to models using (convex) voxel-based treatment plan evaluation criteria
- However, voxel-based criteria are much easier to handle than other criteria
- Dominance (DVH) criteria are much stronger than voxel-based criteria
  - they may be useful if it is not known which voxel-based function f to use for a particular structure
- Heterogeneous dose modeling is required for accurate IMRT modeling

Conclusions

- Often, criteria like EUD, TCP and NTCP have been proposed to replace traditional DVH constraints, i.e., first order dominance constraints
- However, whenever first order dominance is considered relevant, a convex voxel-based penalty criterion f will not be able to accurately capture preferences
  - a nonconvex but monotone criterion function will be required
  - probably only relevant for parallel structures such as liver, lung, and (possibly) salivary glands

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