IMRT – the inverse problem and inverse planning

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Conflicts of interest

 Court receives funding from NIH, CPIRT, Varian and Elekta

IMRT is 35 years old this year!



Brahme A, Roos JE, Lax I. Solution of an integral equation encountered in rotation therapy. Phys Med Biol1982;27:1221–9.

Introduction to IMRT and the inverse problem







Slide from Charlie Ma

Assume that intensity's add and no attenuation

					Beam 1					
		0	0	0	100	100	100	0	0	0
	0	0	0	0	100	100	100	0	0	0
	0	0	0	0	100	100	100	0	0	0
	0	0	0	0	100	100	100	0	0	0
	100	100	100	100	200	200	200	100	100	100
Beam 2	100	100	100	100	200	200	200	100	100	100
	100	100	100	100	200	200	200	100	100	100
	0	0	0	0	100	100	100	0	0	0
	0	0	0	0	100	100	100	0	0	0
	0	0	0	0	100	100	100	0	0	0

If we have a critical structure we want to avoid we can lower the intensity of one or more of the beamlets that that cross that structure

Beam 1

	0	0	0	0	100	100	100	0	0	0
_	0	0	0	0	100	100	100	0	0	0
	0	0	0	0	100	100	100	0	0	0
Beam 2	100	100	100	100	200	200	200	100	100	100
	100	100	100	100	200	200	200	100	100	100
	100	100	100	100	200	200	200	100	100	100
	0	0	0	0	100	100	100	0	0	0
	0	0	0	0	100	100	100	0	0	0
	0	0	0	0	100	100	100	0	0	0

This results in a decrease in dose to the critical structure but also to other parts of the dose distribution.



This underdose can be made up from other beamlets in other beams restoring dose to the target but resulting in dose inhomogeneity in the target, the more beam angles to more opportunity to achieve an optimal plan.



Dose calculation



Multiple fields:

$$D_i = \sum_{j=1-n} C_{ij} W_j$$

Simplified:



Desired dose:

$$\mathbf{D}_0 = \mathbf{C}\mathbf{W}_0$$

Beamlet weight:

 $\mathbf{W}_0 = \mathbf{D}_0 / \mathbf{C} = \mathbf{D}_0 \mathbf{C}^{-1}$

Can we solve this?

- No
- Huge problem
- Degenerate problem many solutions
- Ideal dose may not be achievable
- Many unknowns (>1000s beamlet weights)
- Conflicting requirements.....not all of which are clear
- Lots of structures.....
- Etc....

What is meant by optimization?

- Not necessarily looking for the true optimum plan
 - Many constraints such as deliverability, type of radiation, beam geometry, planning time....
- Many a priori choices (reduce search space) constrained optimization
 - Beam energy, gantry and collimator angles

A simple objective function:



Iteration step Partially based on slides from Charlie Ma



Figure 4. (a) The left graph shows a plot of a cost function for a problem with a well defined global minimum cost as well as several local minima. Cost is plotted on the vertical axis and position on the horizontal axis labels the particular stage of some iterative planning cycle. For example, the global minimum corresponds to having achieved the beams which deliver dose best matching the prescribed constraints. The very left hand position might represent the start of iteration when beams have not yet been properly formed. (b) The right graph conversely shows a cost function more typical of radiotherapy inverse planning problems. There is a wide plateau (basin) of beam arrangements all of which correspond to dose distributions that are much the same and best satisfy the planning constraints. There may be a small dip (global minimum) for the absolute best but continuing the iteration to find this might be futile when any position in the plateau would be acceptable.

From Webb, The British Journal of Radiology, 76 (2003), 678–689

Computer Simulated Annealing





Partially based on slides from Charlie Ma

What needs to be in the cost function?

Coverage	Good coverage of PTV			
	Look at 100% and 98% coverage			
Hot Spots	\leq 5%			
Cord	< 46 Gy			
Exp Cord	50Gy isodose line shouldn't cross			
Parotid	Mean dose ~ 26Gy			
Uninvolved	< 60 Gy			
Larynx / post cricoid	(attempt to approach 50Gy)			
Oral cavity	No hot spots outside volumes (\geq 60 Gy) and not hot spots in the mandible			

Defining the prescription

(and cost functions)

The prescription

- The prescription defines the goals of the treatment.
- Target DVH
- Sensitive structure DVH
- Set goals, priorities, penalties
- The plan quality can be scored using either physical or biological criteria.
- It is difficult to reduce all of our treatment planning goals into a set of equations or a single scoring function
- Warning: no consistency expected in terminology used by different vendors!



Based on a slide from Yakov Pipman²⁰



The Cost Function

- Cost functions are built based on objectives, there are a number of objective types possible.
 - Minimum Dose
 - Maximum Dose
 - DVH constraint no more than "x" % of the structure can exceed a dose of "y".
 - Equivalent Uniform Dose
 - ...
- Each objective can have a weighting factor
- If the weighing Factor is very high (infinite) that objective becomes a "Constraint" (in Pinnacle, at least)



		ROI	Туре	Constrain	Target cGy	% Volume	% Variation	Weight	Objective Value
	0	pPTV 🗖	Min Dose		[4600			I00	0.0806752
	0	pPTV 🗖	Uniform Dose	-	ľ 4600			Ĭ8	0.0257317
	0	Cord PRV 3mm	Max Dose	-	Į2700			ľ 1.2	0.0171266
	0	Lt Lung T50 📃	Max DVH	-	1×490	ľ 18	[Ĭ 1	0.0345553
_	\bigcirc	fsRt Lung Avoid 😐	Max DVH	-	ľ 1900	Į́70		Ĭ 1	0

Minimum/Maximum Dose

Advantages

- Constraints can be used guarantee adequate dose uniformity in the tumor.
- Useful for serial structures such as the spinal cord.

Disadvantages

- Allowing small hot and/or cold spots are often provide a significant improvement in dose conformity.
- One point can dominate the optimization.
- If target and RAR are in close proximity, these constraints often cannot be satisfied.

Mean Dose

Advantages

• Easy to formulate.

Disadvantages

- Of limited value for most sensitive structures.
- Dramatically different dose distributions can have the same mean dose.

Setting constraints

• Optimization

Structures and Constraints

Add Upper Constraint

E	7	СТУ	Volume [cc]:	142	Points:	7150	Resolution [mm]:	3.00	•
	Upper		Volume [%]:	10.0	Dose [cGy]:	5700.0	Priority:	80	
		Upper	ſ	5.0	l l	5950.0	i i	90	
		Lower	Volume [%]:	100.0	Dose [cGy]:	5400.0	Priority:	110	
Ξ	7	Cooling Ring	Volume [cc]:	657	Points:	33574	Resolution [mm]:	3.00	
-		Upper	Volume [%]:	10.0	Dose [cGy]:	2600.0	Priority:	85	
		Upper	Í	0.0	i i	3000.0	Í	95	
Ξ		Cord	Volume [cc]:	11	Points:	2876	Resolution (mm):	1.72	
		Upper	Volume [%]:	2.0	Dose [cGy]:	4200.0	Priority:	85	
Ξ	7	External	Volume [cc]:	3213	Points:	135528	Resolution (mm):	3.00	
-	7	L cochlea	Volume [cc]:	1	Points:	1314	Resolution (mm):	1.00	
-		Upper	Volume [%]:	50.0	Dose [cGy]:	2050.0	Priority:	100	
		Upper	Í	10.0	i i	4300.0	Í	75	
Ξ		L optic nerve	Volume [cc]:	1	Points:	1287	Resolution [mm]:	1.00	
		Upper	Volume [%]:	20.0	Dose [cGy]:	4000.0	Priority:	75	
Ξ	7	LT Eye	Volume [cc]:	8	Points:	2552	Resolution (mm):	1.52	
		Upper	Volume [%]:	20.0	Dose [cGy]:	1500.0	Priority:	80	
Ξ	2	PTV 3mm	Volume [cc]:	185	Points:	8965	Resolution (mm):	3.00	
		Upper	Volume [%]:	10.0	Dose [cGy]:	5950.0	Priority:	80	
		Upper	Í	5.0	l l	5950.0	Í.	90	
		Lower	Volume [%]:	95.0	Dose [cGy]:	5400.0	Priority:	100	
		Lower	Ī	98.0	Í.	5100.0	Í.	95	
E	7	R cochlea	Volume [cc]:	1	Points:	646	Resolution (mm):	1.00	
		Upper	Volume [%]:	50.0	Dose [cGy]:	2050.0	Priority:	100	
		Upper	Í	10.0	ſ	4300.0	Í.	85	
Ξ	7	R optic nerve	Volume [cc]:	1	Points:	941	Resolution [mm]:	1.00	-1-
and and a second	-	I have an	Stationa - 10/3.	20.0	Deres Local F	4000.0		77 -	•

Add Lower Constraint

<u>D</u>elete

Eclipse screen shot

Biological Objective Functions and Constraints

Biological Objectives/Constraints

- Biological objective functions and constraints are outcome related.
- Biological models are used to predict treatment outcome.
- Tumor Control Probability (TCP).
- Normal Tissue Complication Probability (NTCP).
- Uncomplicated TCP (UTCP or P+).
- Equivalent Uniform Dose (EUD).

Equivalent Uniform Dose (EUD)

- Two dose distributions are equivalent if the corresponding biological/clinical outcomes are equivalent
- Normal structures and targets.



*Niemierko A. Med Phys, 26(6), 1999.

Equivalent Uniform Dose (EUD)

Structure (Source)	End-point	a
Chordoma base of skull (MGH)	Local control	-13
Squamous cc (Brenner)	Local control	-13
Melanoma (Brenner)	Local control	-10
Breast (Brenner)	Local control	-7.2
Parotids (Eisbruch)	Salivary function (<25%)	< 0.5
Parotids (Chao)	Salivary function (<25%)	0.5
Liver (Lawrence)	Liver failure	0.6
Liver (Dawson)	Liver failure	0.9
Lung (Kwa)	Pneumonitis	1.0
Lung (Emami)	Pneumonitis	1.2
Kidney (Emami)	Nephritis	1.3
Liver (Emami)	Liver failure	2.9
Heart (Emami)	Pericarditis	3.1
Bladder (Emami)	Symptomatic contracture	3.8
Brain (Emami)	Necrosis	4.6
Colon (Emami)	Obstruction/perforation	6.3
Spinal cord (Powers)	White matter necrosis	13
Esophagus (Emami)	Perforation	18
Spinal cord (Schultheiss)	Paralysis	20

Biological Objectives/Constraints

Advantages

 Our goal is to improve patient outcome, and this is precisely what is modeled with these techniques.

Disadvantages

 Because of uncertainties in the parameters included in the models, the accuracy of the models is often called into question.

Trade Off Between Believability and Utility



Based on a slide from David Shephard

Plan Optimization Fixed Field IMRT

- Beamlet based optimization
- Direct aperture optimization

The Beamlet Model

Before an IMRT optimization, each beam is divided into a number of smaller beamlets (pencil beams), and the corresponding dose distributions are computed.



Slide from David Shephard

Beamlet-Based Inverse Planning

Beamlet weights are optimized to produce an optimized fluence map for each beam direction.





Leaf sequencing

Intensity Modulation

- Step and shoot MLC
 - The intensity pattern developed by the TPS is converted into a finite number of segments
 - For each segment the MLCs leaves are set and the beam is on for a determined amount of time
 - The summation of all the segments is equal to the planned intensity
- Pinnacle





Intensity Modulation

- Sliding Window MLC
 - MLC leaves move continuously while the treatment machine is on
 - The field is divided into a number of control points that have target positions for each leaf at each fraction amount of dose delivered
 - The linac modulates leaf speed, then dose rate to ensure the targets for each control point are within tolerance values.


How Can We Make Any Intensity Shape with an MLC?



Slide from Chen ³⁹Chui





























Done!



From Optimized Intensity Map to Treatment Leaf Sequencing

- The optimized treatment plan is not immediately ready for delivery.
- A leaf sequencing algorithm needs to be applied to translate the each optimized (theoretical) fluence map into a set of deliverable aperture shapes.
- The constraints imposed by the multileaf collimator are accounted for in the leaf sequencing step.
- Final plan dose distribution changes
- This is the approach taken by Eclipse for dynamic IMRT.
- It was the approach used by Pinnacle for step-and-shoot IMRT (older versions)

Direct aperture optimization (DAO)

Direct Aperture Optimization (DAO)

- 1. Inverse planning technique where the aperture shapes and weights are optimized simultaneously.
- 2. All of the MLC delivery constraints are included in the optimization
- 3. The number of aperture per beam angle is specified in the prescription.

Direct aperture optimization: A turnkey solution for step-and-shoot IMRT

D. M. Shepard, M. A. Earl, X. A. Li, S. Naqvi, and C. Yu University of Maryland School of Medicine, Department of Radiation Oncology, 22 South Greene St., Baltimore, Maryland 21201-1595

(Received 26 September 2001; accepted for publication 12 March 2002; published 13 May 2002)

IMRT treatment plans for step-and-shoot delivery have traditionally been produced through the optimization of intensity distributions (or maps) for each beam angle. The optimization step is followed by the application of a leaf-sequencing algorithm that translates each intensity map into a set of deliverable aperture shapes. In this article, we introduce an automated planning system in which we bypass the traditional intensity optimization, and instead directly optimize the shapes and the weights of the apertures. We call this approach "direct aperture optimization." This technique allows the user to specify the maximum number of apertures per beam direction, and hence provides significant control over the complexity of the treatment delivery. This is possible because the machine dependent delivery constraints imposed by the MLC are enforced within the aperture optimization algorithm rather than in a separate leaf-sequencing step. The leaf settings and the aperture intensities are optimized simultaneously using a simulated annealing algorithm. We have tested direct aperture optimization on a variety of patient cases using the EGS4/BEAM Monte Carlo package for our dose calculation engine. The results demonstrate that direct aperture optimization can produce highly conformal step-and-shoot treatment plans using only three to five apertures per beam direction. As compared with traditional optimization strategies, our studies demonstrate that direct aperture optimization can result in a significant reduction in both the number of beam segments and the number of monitor units. Direct aperture optimization therefore produces highly efficient treatment deliveries that maintain the full dosimetric benefits of IMRT. © 2002 American Association of Physicists in Medicine. [DOI: 10.1118/1.1477415]

Key words: IMRT, inverse treatment planning, optimization, intensity modulation

Simulated Annealing

- DAO uses simulated annealing, an optimization technique using random sampling techniques.
- The term simulated annealing derives from the roughly analogous physical process of heating and then slowly cooling a substance to obtain a strong crystalline structure.
- In each simulation, a minima of the cost function corresponds to this ground state of the substance.
- The basic principle is that by allowing occasional ascent in the search process, we might be able to escape the trap of local minima.



DAO Optimization via Simulated Annealing

- 1) Pick a parameter (leaf position, aperture weight) randomly
- 2) Change the parameter by a random amount
- 3) Calculate objective function based on the new dose distribution
- 4) Objective function lower: accept change
- 5) Objective function higher: accept change with certain probability

Prescription: 3 apertures per angle Begin with 3 identical copies



Pick an Parameter and Make a Change

Aperture 1 Leaf pair 6 Left leaf position Move leaf in 2cm



Keep or Reject the Change

Based on:

MLC constraints. Cost function & Annealing Rules.

MLC Constraints

Some sample Elekta constraints:

1) Opposed leaves cannot come closer than 1-cm from oneanother



2) Opposed-adjacent leaves cannot come closer than 1-cm from one-another



After numerous iterations...



Add them up along with their weights...

Final intensity map from DAO



Small number of apertures can produce large number of intensity levels

Example: 3 apertures/angle



Small number of apertures can produce large number of intensity levels

$$N_n = 2^n - 1$$

N = Number of intensity levels n = Number of apertures

For 3 apertures, 7 intensities For 4 apertures, 15 intensities For 5 apertures, 31 intensities For 6 apertures, 63 intensities

Volume-Modulated Arc Therapy

VMAT

Volumetric modulated arc therapy: IMRT in a single gantry arc

Karl Otto^{a)}

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(Received 25 June 2007; revised 21 September 2007; accepted for publication 5 November 2007; published 26 December 2007)

In this work a novel plan optimization platform is presented where treatment is delivered efficiently and accurately in a single dynamically modulated arc. Improvements in patient care achieved through image-guided positioning and plan adaptation have resulted in an increase in overall treatment times. Intensity-modulated radiation therapy (IMRT) has also increased treatment time by requiring a larger number of beam directions, increased monitor units (MU), and, in the case of tomotherapy, a slice-by-slice delivery. In order to maintain a similar level of patient throughput it will be necessary to increase the efficiency of treatment delivery. The solution proposed here is a novel aperture-based algorithm for treatment plan optimization where dose is delivered during a single gantry arc of up to 360 deg. The technique is similar to tomotherapy in that a full 360 deg of beam directions are available for optimization but is fundamentally different in that the entire dose volume is delivered in a single source rotation. The new technique is referred to as volumetric modulated arc therapy (VMAT). Multileaf collimator (MLC) leaf motion and number of MU per

Med. Phys. 35 (1), January 2008

Eclipse VMAT

- In Otto's paper, he used DAO to produced IMAT plans.
- Two key innovations:
 - 1. Focused on a single arc approach with more control points in the single arc. Termed "VMAT".
 - 2. Progressive sampling was used to improve the speed of the algorithm.
- This is the approach utilized in Eclipse

Dynamic Source Model

Sampling	Flexibility	Accuracy
Coarse	1	X



Courtesy of Karl Øtto

Dynamic Source Model

Sampling	Flexibility	Accuracy
Coarse	1	X
Fine	X	1



Courtesy of Karl Øtto

Progressive Sampling



Courtesy of Karl Øtto


FIG. 2. The percentage volume (target and critical structures) exceeding 10%, 5%, and 3% dose error is shown as a function of the gantry and maximum MLC leaf sample spacing.

Progressive Sampling



Courtesy of Karl Otto

Varian Eclipse



- Planning is performed using <u>Direct Aperture Optimization</u>.
- Typical plan uses 1 arc with 177 control points.
- For some cases, multiple arcs are use to improve the plan quality or provide adequate coverage of large targets.

SmartArc Optimization (Philips)

- 1. Beams are generated at the start and the stop angles and at 24° increments from the start angle.
- 2. A fluence map optimization is performed.
- 3. The fluence maps are sequenced and filtered so that there are only 2 control points per initial beam angle.
- 4. These control points are distributed to adjacent gantry angles and additional control points are added to achieve the desired final gantry spacing.
- 5. All control points are processed to comply with the motion constraints of VMAT.
- 6. The DMPO algorithm is applied with an aperture based optimization that takes into account all of the VMAT delivery constraints.
- 7. The jaws are conformed to the segments based on the characteristics of the linac.

Treatment planning is an art



Figure from Hunt et al, IJROBP 54(3), 953-962, 2002

Multi-criteria optimization (MCO)

IMRT planning process is complex

- Long planning time
- Not clear which knobs to turn
- Tradeoffs unclear
- Clinician's judgment indirect (the process does not encourage physician participation





Based on slides by Thomas Bortfeld

Pareto surface (or the Possibility Frontier)



Craft et al, IJROBP 82, e83-e90, 2012



- PC1: Liver and stomach vs. left and right kidneys
- PC2: Right kidney and stomach vs. left kidney and liver

Spalke et al, PMB 54, 3741-3754, 2009

MCO PLANNING (PARETO OPTIMIZATION) - RAYSEARCH

<u>Pareto-optimality, "efficient":</u> "You cannot make anybody better off without making someone else worse off" Vilfredo Pareto, born 1848 (Paris) – died 1923 (Geneva) Industrialist, Sociologist, Economist, Philosopher Taught in Lausanne, lived in Céligny near Geneva







2D Dose diff	Dose Statistics	Clinical Goal Definitions Clinical Goal	s		
Dose	ROI	Clinical goal	Value	Result	% out
Balance plan_1	Brachial Plexis	At most 6300 cGy dose at 1 % volume	5806 cGy		0%
Balance plan_1	Brainstem	At most 5000 cGy dose at 1 % volume	2663 cGy		0%
Balance plan_1	Lt Parotid	At most 3000 cGy dose at 50 % volume	2985 cGy		0%
Balance plan_1	Mandible	At most 7500 cGy dose at 1 % volume	7286 cGy		0%
Balance plan_1	PRV Spinal Cord	At most 5600 cGy dose at 1 % volume	4384 cGy		1%
Balance plan_1	PTV 56	At least 5208 cGy dose at 1 % volume	6636 cGy		0%
Balance plan_1	PTV 56	At least 5600 cGy dose at 95 % volume	5637 cGy		0%
Balance plan_1	PTV 56	At most 6160 cGy dose at 20 % volume	5854 cGy		0%
Balance plan_1	PTV70	At least 6510 cGy dose at 1 % volume	7323 cGy		0%
Balance plan_1	PTV70	At least 7000 cGy dose at 95 % volume	7017 cGy		0%
Balance plan_1	PTV70	At most 7700 cGy dose at 20 % volume	7177 cGy		0%
Balance plan_1	Rt Parotid	At most 3000 cGy dose at 50 % volume	2893 cGy		0%

RaySearch



MCO PLANNING (PARETO OPTIMIZATION) - RAYSEARCH

Pareto-optimality, "efficient":

"You cannot make anybody better off without making someone else worse off"



Increased physician involvement Reduced planning time

Parameter	Planner time (min)	Physician time (min)
GBM: Standard	156 ± 95.8	5.0 ± 2.5
GBM: MCO	12.4 ± 1.8	8.2 ± 2.8
LAPC: Standard	114 ± 32.9	4.5 ± 2.7
LAPC: MCO	11.6 ± 0.6	9.0 ± 2.2

GBM = glioblastoma; LAPC = locally advanced pancreatic cancer;



Technique comparison

Technique comparison: MU/cGy

Pinnacle, DAO

Eclipse

				Beam Modulation Factors [MU/Gy]								
	Confor	mal Radiot	herapy	Step-and-Shoot IMRT		Dynamic IMRT		VMAT				
Cancer Site	No.	Mean	SD	No.	Mean	SD	No.	Mean	SD	No.	Mean	SD
Breast	60	139	21				47	249	66	8	238	73
Cervical	35	114	17				69	736	292	20	262	63
Esophagus	48	113	13	18	303	94	9	707	197	7	197	41
Head and neck	32	137	55	21	392	152	147	763	277	49	230	76
Lung	55	126	35	25	336	78	79	586	188	53	267	61
Prostate	39	113	7	25	362	45	25	713	238	63	289	57
Rectum	33	142	18	26	495	135	10	883	400	4	177	38

Dynamic IMRT is less MU-efficient than step-and-shoot or VMAT ٠

McCarroll et al, Journal of Global Oncology 2017

Technique comparison: Treatment time

	Pinnacle, DAO Eclipse Average Time Required (minutes)										
	-			Conformal Radiotherapy							
	Linac VMAT	Linac Dynamic IMRT	Linac Step-and-Shoot		Cobalt-60						
Activity			IMRT	Linac	Y1 *	Y5	Y8				
Setup	3.21	3.21	3.21	3.21	3.21	3.21	3.21				
Image guidance	2.33	2.33	2.33	2.33	2.33	2.33	2.33				
Mechanical motion	0.50	1.00	2.56	1.00	1.00	1.00	1.00				
Beam-on	2.00	1.86	0.93	0.40	1.03	1.74	2.58				
Total	8.04	8.41	9.03	6.95	7.57	8.28	9.12				

NOTE. All data assume that multileaf collimators were used. Data are averaged across the top nine cancer sites for which radiotherapy is indicated in the eight African countries for which data were available.

Abbreviations: IMRT, intensity-modulated radiotherapy; Linac, linear accelerator; VMAT, volumetric-modulated arc therapy.

*Y indicates year of use of the cobalt-60 unit (ie, Y1 indicates year 1 of use).

McCarroll et al, Journal of Global Oncology 2017

End on a happy thought:

Int J Radiat Oncol Biol Phys. 2009 Jun 8. [Epub ahead of print]

Influence of Technologic Advances on Outcomes in Patients With Unresectable, Locally Advanced Non-Small-Cell Lung Cancer Receiving Concomitant Chemoradiotherapy.

Liao ZX, <u>Komaki RR</u>, Thames HD Jr, Liu HH, Tucker SL, Mohan R, Martel MK, Wei X, Yang K, Kim ES, Blumenschein G, Hong WK, Cox JD.

Department of Radiation Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, TX.



The Radiotherapy Process - IMRT



Slide from Yakov Pipman