Applied Optimization Application to Intensity-Modulated Radiation Therapy (IMRT)

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Topics

Short history of radiotherapy

Developments that has led to IMRT

The IMRT process

How to create an IMRT plan and to perform an IMRT treatment

Inverse planning for IMRT

How is the optimization problem for IMRT defined

Physical optimization criteria

Radiobiology

How does the body interact with radiation

Radiobiological modeling

Subset of models that describe radiobiological features

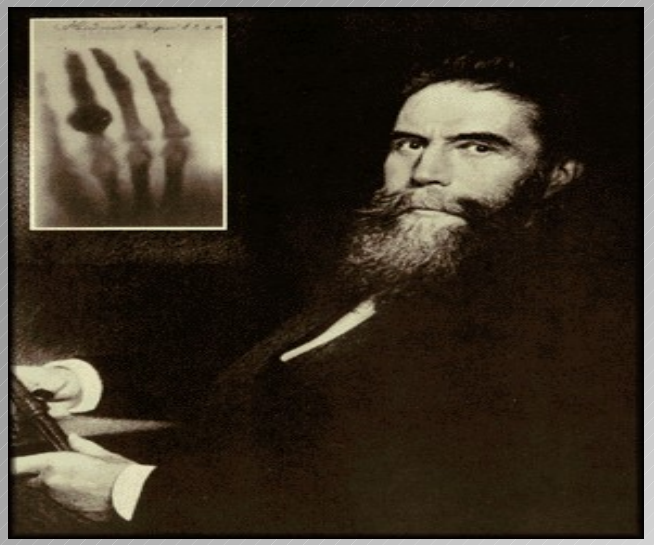
Biological optimization criteria

Optimization algorithms for IMRT

How is the optimization for IMRT solved

Short history of radiotherapy

- X-rays were discovered in 1895 by *W. C. Röntgen* (top picture); diagnostic radiology *X-rays did not penetrate bones or lead and could be captured on photographic plates*
- X-rays were noted to have a biological effect 1896 and first textbook of radiotherapy in 1903 *L. Freund* *Early treatments mainly skin (dermatological) conditions*
- Discovery of spontaneous radioactivity in 1898 *A. H. Becquerel* (bottom picture); *Marie and Pierre Curie* *γ-rays emitted by radioactive isotopes and represents the excess energy that is given off as the unstable nucleus breaks up and decays in order to reach stable form*



Short history of radiotherapy

- Radiotherapy in MeV around 1950 by the use of linear accelerators (LINAC)
- X-rays electronically produced by accelerating electrons to high energies and stopping them in a (Tungsten) target
- Some of the electrons kinetic energy is converted to X-rays through bremsstrahlung *Electromagnetic waves or streams of **photons** (packets of energy) with the ability to cause biological effects when deposited in tissue*
- Photons shaped into treatment fields by collimators situated in the head of the LINAC *Multileaf collimators (**MLC**) give flexible geometric field shaping*

Conformal radiotherapy

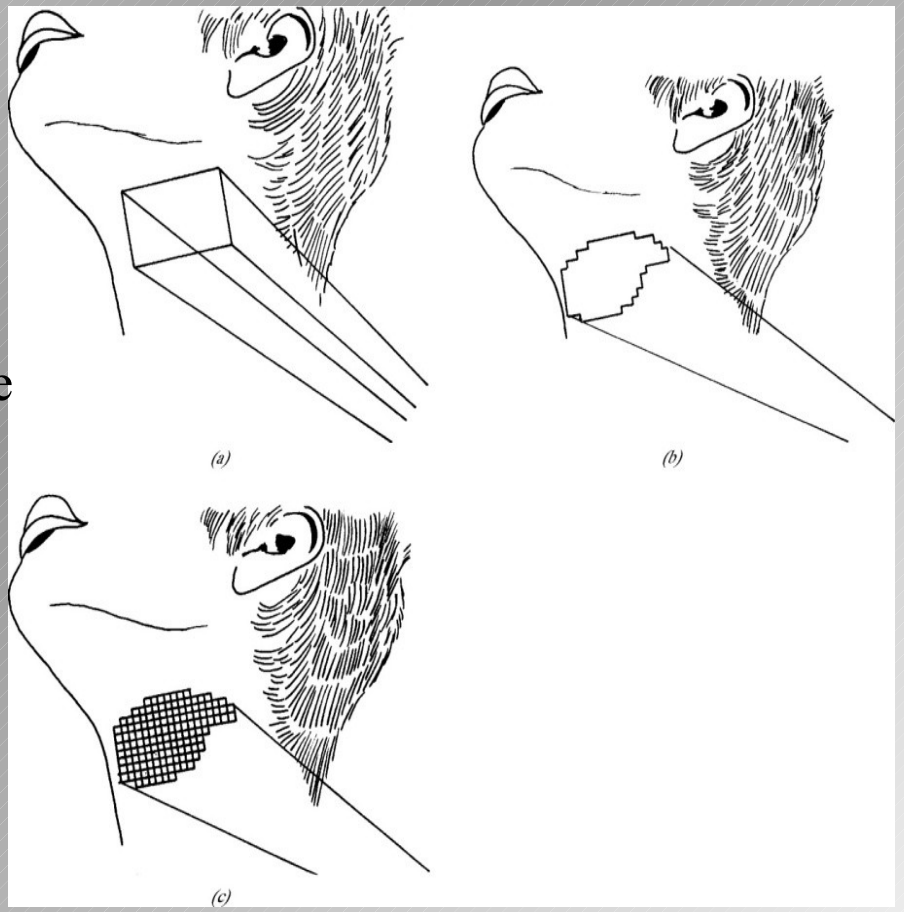
** Aim of radiotherapy is to eradicate the tumour cells while minimizing unavoidable damage to normal tissue => **maximize conformity to tumour area!***

* Beams with uniform intensities brought around the same point (isocenter) have a **convex intersection;** beams with non-uniform intensities have a **concave intersection**

(a) Early treatments (~1950s): **conventional radiotherapy** *rectangularly-shaped fields with additional blocks and wedges*

(b) Modern treatments (late 1980s): **conformal radiotherapy (CRT)** *more convenient geometric field shaping using a MLC*

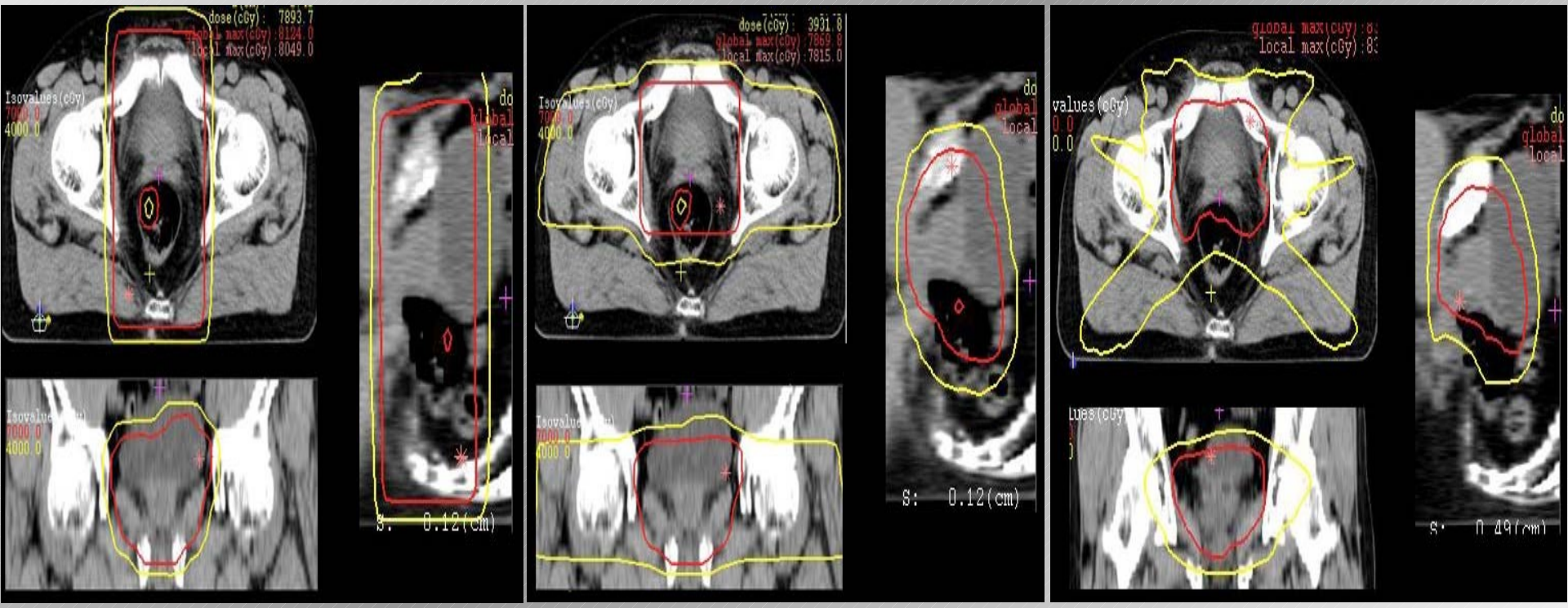
(c) CRT with non-uniform intensities or intensity modulation (mid 1990s): **IMRT** *varied intensity beamlet-by-beamlet using physical compensators or MLC*



Webb S.: *The physical basis of IMRT and inverse planning*. BJR 76, 678-689, 2003.

Different treatment techniques

Conventional	CRT uniform fluence	CRT IMRT
2 opposing beams	4 beams (AP;RL)	5 beams

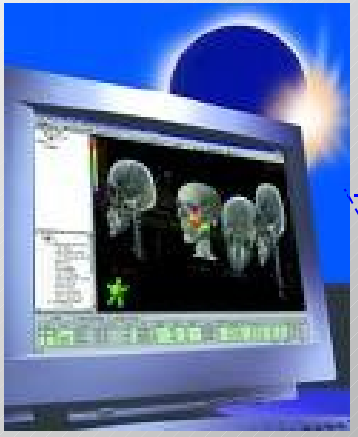


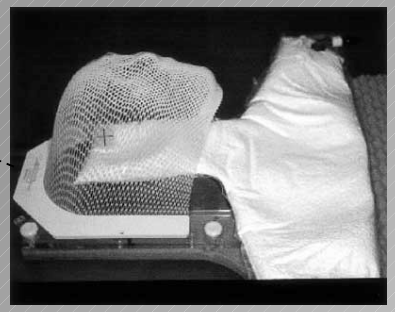
Prostate treatment AIM: Conform the high dose to the Prostate; spare Rectum as much as possible

Prostate + margin = Planning target volume (**PTV**); Rectum = Organ at risk (**OAR**)

Red isodose = 100% of prescribed dose; Yellow isodose = ~55% of prescribed dose

The IMRT process





Patient fixation

CT/imaging

Definition of target and OAR

Number of beams, entry angles, energy and optimization problem

Inverse planning and optimization

Dose calculation

Treatment plan evaluation

Intensity modulation

Redo

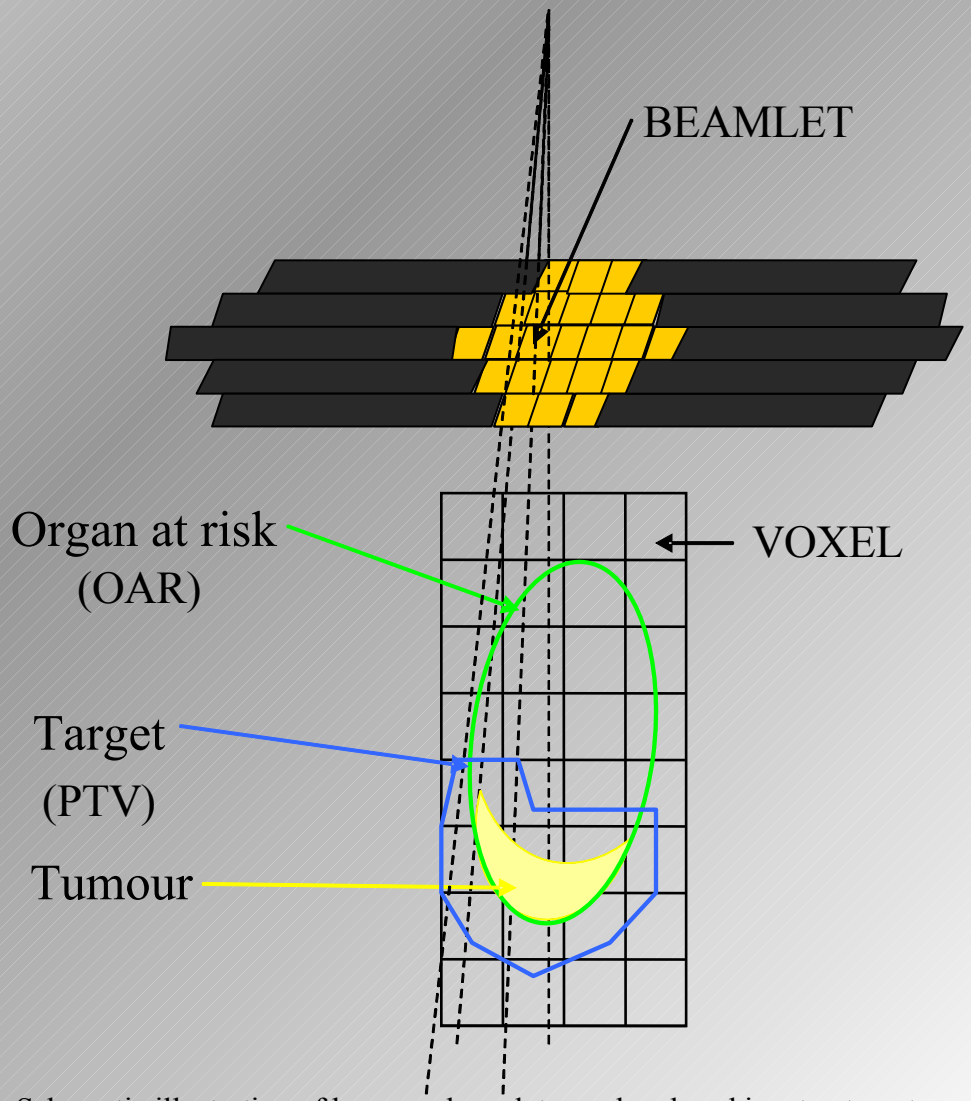
Quality assurance

Treatment

Inverse planning for IMRT

- *The process by which the intensity distribution of each beamlet in a treatment plan is determined by an optimization algorithm so that the resulting dose distribution best meets the specified criterias*

- Each beam divided into **beamlets**; ***the optimzation parameters are the beamlet intensities*** (weights)
  - >>100 beamlets / treatment field
  - beamlet size 5-10 mm^2
- Each volume (target and OAR) divided into a number of volume elements (**voxels**) organized into 3D matrices
  - >>1000 voxels / volume
  - voxel size ~5 mm^3



Schematic illustration of how one beamlet may be placed in a treatment field and its dose contribution to the voxels in the target and OAR

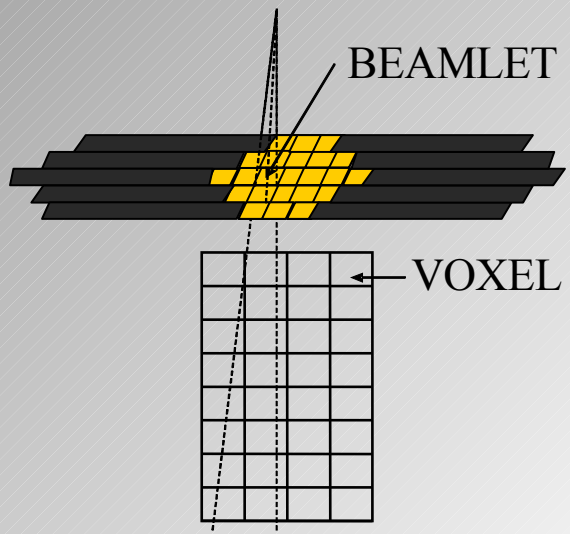
Inverse planning for IMRT

- *Dose in a voxel is the sum of dose contributions from all the beamlets taken over all the beams*
- Linear relationship between beam intensity and dose in a voxel

$$D_i = \sum_j K_{ij} w_j$$

D_i=dose in voxel i
w_j=intensity level (weight) of beamlet j
$\mathbf{K}_{ij}$=dose contribution from beamlet j to voxel i

- Elements in K depend on the physics of photon-tissue interaction *K precalculated using dose calculation algorithms that simulates the effects of radiation beam penetrating through human tissue*
- Absorbed dose measured in GRAY (**Gy**) [J/kg]



Physical optimization criteria

- Optimization criteria involves constraints to the target and OARs and are determined in terms of doses and irradiated volumes
  - Dose limits
  - Limits on volumes receiving certain specified dose
- Optimization problem formulation *Defined in terms of doses*

  (*i*) Target objective function + constraints on OARs

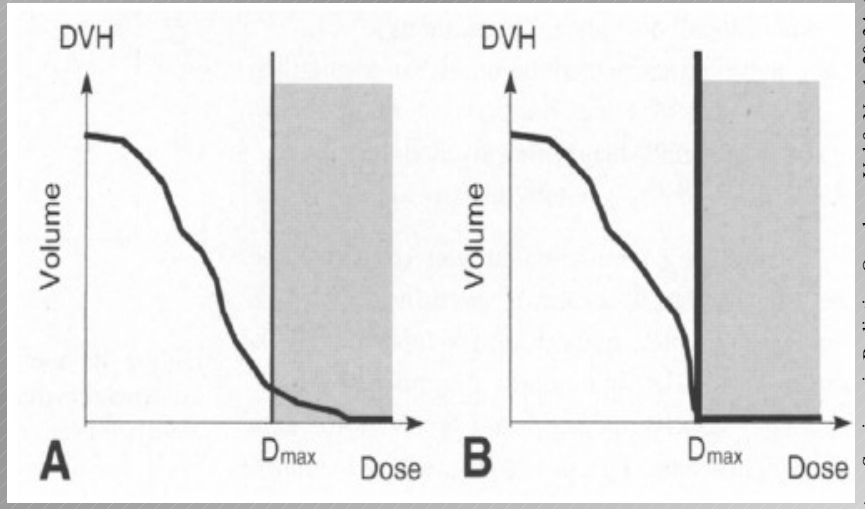
  (*ii*) OAR objective function + constraints on target

  (*iii*) Target and OAR objective function
- Penalty factors *Strict fulfillment of set limit often too restrictive; Magnitude of penalty associated with the severity of the consequence of violation*
  - Soft constraints *Mild complication*
  - Hard constraints *Severe complication*
- Relative importance factors *Bias the treatment plan towards one or more selected volumes of interest*

Physical optimization criteria
Dose limits

- Maximal dose limit
  - Limits the dose to be less than or equal to a tolerance threshold in any voxel (target and OAR)

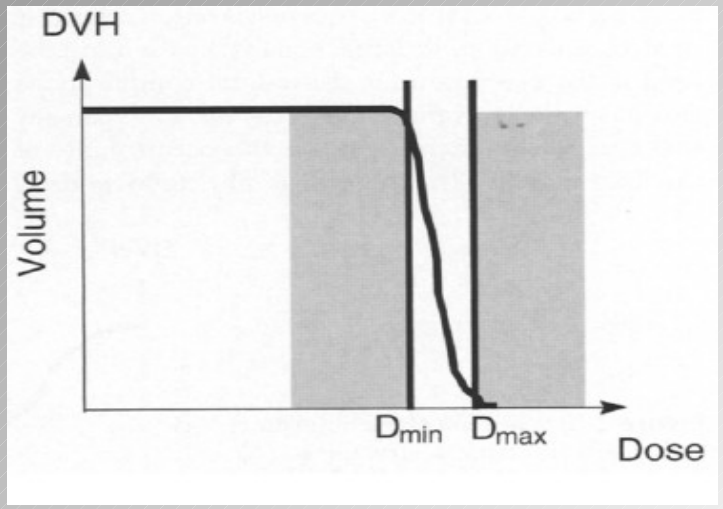
$$D_i \leq D_{max}, \forall i \in V$$



A) Effect of **soft constraint**; B) Effect of **hard constraint**

- Minimum dose limit
  - Limits the dose to be more than or equal to a tolerance threshold in any voxel (target)

$$D_i \geq D_{min}, \forall i \in V$$



Effect of **minimum and maximum constraint**

Homogeneous dose

Bortfeld T.: *Optimized planning using physical objectives and constraints.* Seminars in Radiation Oncology, Vol 9, No 1, 20-34, 1999.

Physical optimization criteria
Dose-volume limits

- Limits dose to a subvolume of a structure
  Amount of voxels fixed in number but may vary in space
- Dose-volume (DVH) limit
  - No more than V_{max} % of the volume should receive more than a dose of D_{max}

$$D_i \leq D_{max}, \ \forall i \in V_{max}$$

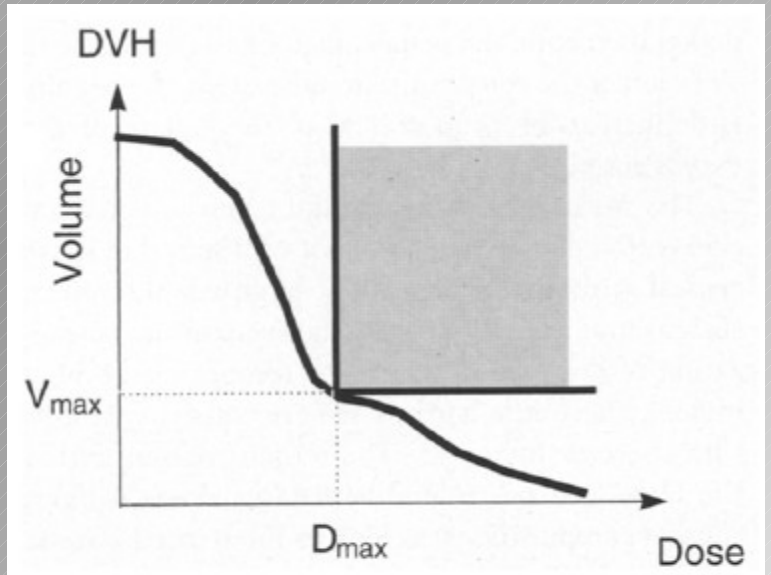


Figure 3. Structures with a large volume effect are more appropriately spared through the application of dose-volume histogram (DVH) constraints. They prevent the DVH from going above the point (D_{max}, V_{max}).

Bortfeld T.: *Optimized planning using physical objectives and constraints.*

Seminars in Radiation Oncology, Vol 9, No 1, 20-34, 1999.

Physical optimization criteria

Target and OAR objective function

F = overall objective function
w_t = relative importance of target
F_{target} = target objective function
k = number of OARs
$w_{O,k}$ = relative importance of OAR k
F_{OAR} = OAR objective function
Heaviside function
$H(D_1 - D_2) = \begin{cases} 1, D_1 > D_2 \\ 0, D_1 \le D_2 \end{cases}$

$$F = w_t F_{target} + \sum_k w_{O,k} F_{OAR}$$

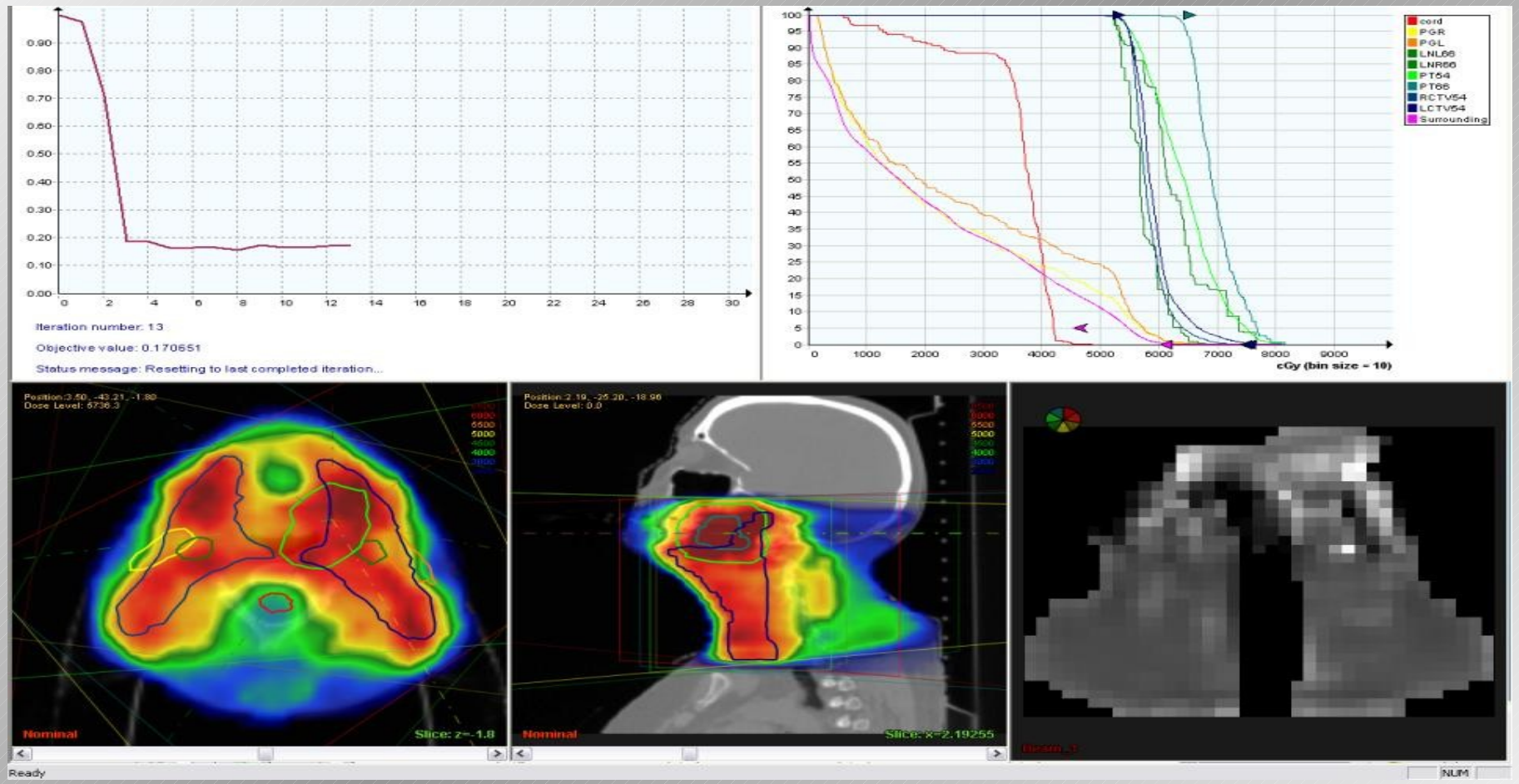
N_t = number of voxels in target
D_i = dose to voxel i
D_{presc} = prescribed dose to target
D_{min} = minimum dose to voxel i
D_{max} = maximum dose to voxel i
$c_{t,min}$ = penalty associated with underdosage
$c_{t,max}$ = penalty associated with overdosage

$$F_{target} = \frac{1}{N_t}\left(\begin{array}{l} \sum_{i=1}^{N_t} [D_i - D_{presc}]^2 \\ + c_{t,\min} \sum_{i=1}^{N_t} [D_i - D_{min}]^2 \bullet H(D_{min} - D_i) \\ + c_{t,\max} \sum_{i=1}^{N_t} [D_i - D_{max}]^2 \bullet H(D_i - D_{max}) \end{array} \right)$$

N_O = number of voxels in OAR
D_{dv} = dose-volume constraint dose
$c_{O,max}$ = relative penalty weight for overdosage
$c_{O,dv}$ = relative penalty weight for violation of dose-volume constraint
N_{dv} = number of voxels in OAR whose dose must be below the dose-volume constraint

$$F_{OAR} = \frac{1}{N_O}\left(\begin{array}{l} c_{t,max} \sum_{i=1}^{N_O} [D_i - D_{max}]^2 \bullet H(D_i - D_{max}) \\ + c_{t,dv} \sum_{i=1}^{N_{dv}} [D_i - D_{dv}]^2 \bullet H(D_i - D_{dv}) \end{array} \right)$$

IMRT treatment planning system



RaySearch Laboratories: *http://www.raysearchlabs.com*

IMRT treatment planning view – reflects dose distribution state at the 13:th iteration

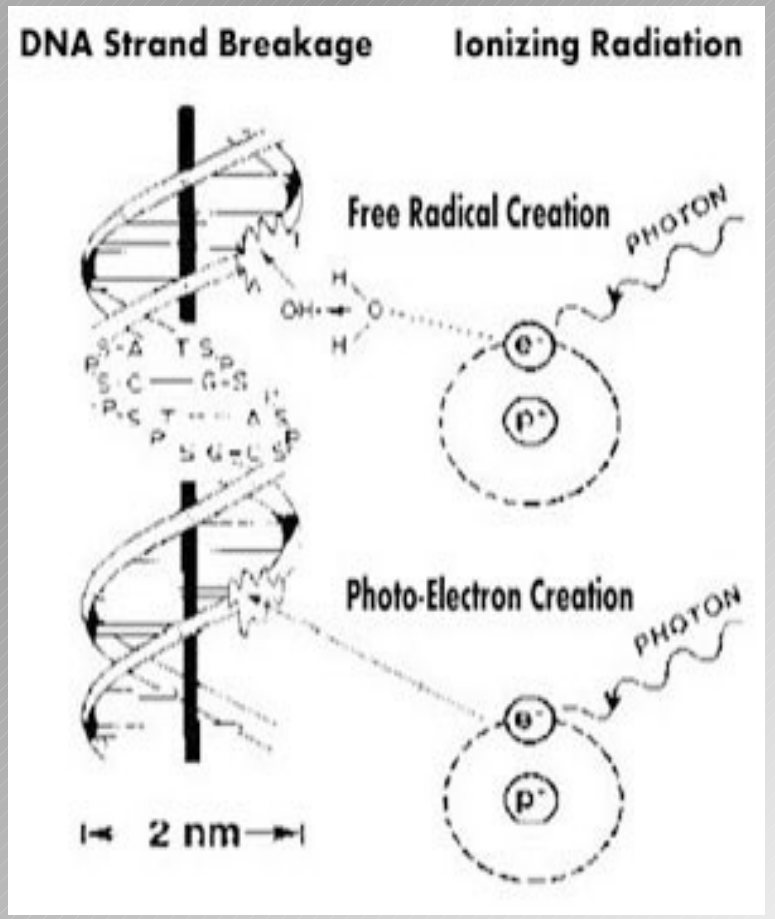
Top left: Objective function value; Top right: DVH; Bottom: Dose distribution in transversal view (left) and sagittal view (middle); Bottom right: Beamlet intensity profile in 2D for one selected treatment field

Radiobiology

What happens in the body after radiotherapy?

- The interactions when radiation is absorbed in biological material result in excitation and ionization events The photons deposit some or all of their energy to loosely bounded e^- in the tissue; e^- are raised to a higer energy level or ejected
- The electronically unstable atoms and molecules are highly chemically reactive Reacts with cellular components (mainly water) forming free radicals

  => free radicals may break chemical bonds in the cell nucleus molecules (DNA) Single strand breaks, SSB, (easy to repair) and/or double strand breaks, DSB, (hard to repair)
- The **biological effect of radiation** result principally from the unrepaired damage (DSB) to the DNA
- Tumour cells have less repair capacity than normal cells



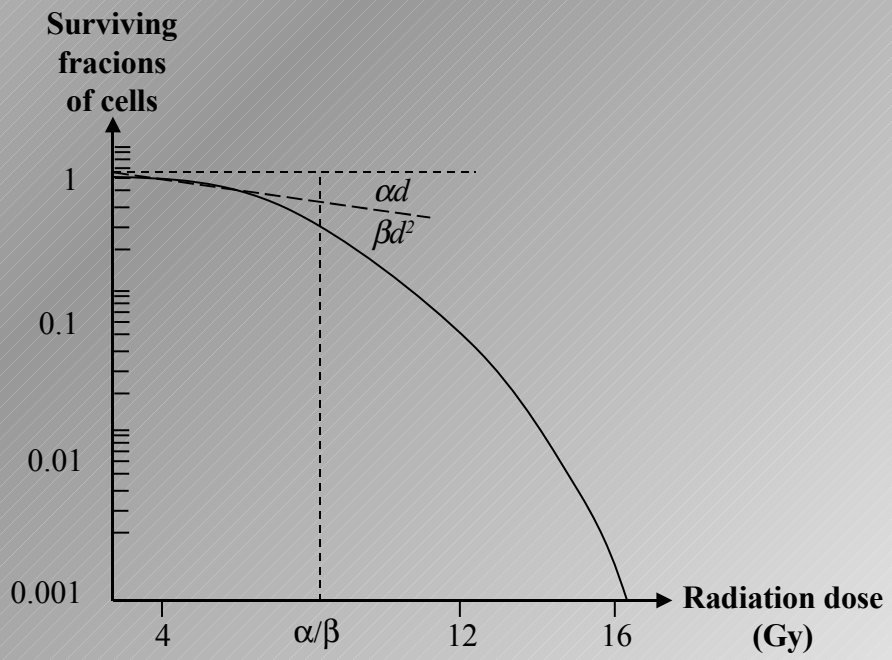
Radiobiology
Linear-quadratic (LQ) model

- The cell survival curve describes the relationship between the radiation dose and the proportion of cells that survives
- α/β term determines the bendiness of the curve and is tissue specific
- The surviving fraction of target cells *SF(d)*, after a single radiation dose *d* can be fitted to experimental data using an exponential function with the parameters α and β.

$$SF(d) = e^{-(\alpha d + \beta d^2)} \qquad (1)$$

- After a course of n fractions and total dose $D=nd$

$$(SF(d))^n = e^{-D(\alpha+\beta d)} \qquad (2)$$



- LQ model used to compare the biological effect of different treatment fractionation schedules

Corrects for the fractionation effect: higher doses of radiation gives an increased biological effect

Radiobiology
Tissue architecture

Functional sub units (FSU)

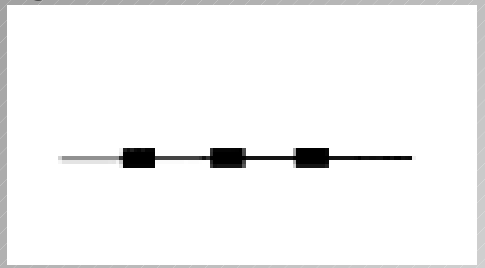
Theoretical entity

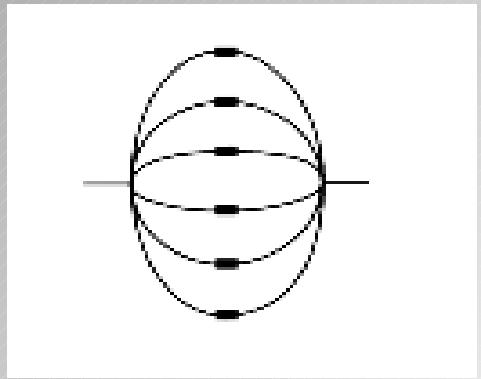
The number of critical cells/FSU

How the critical cells are organized into FSUs

The number of FSUs necessary to maintain organ function

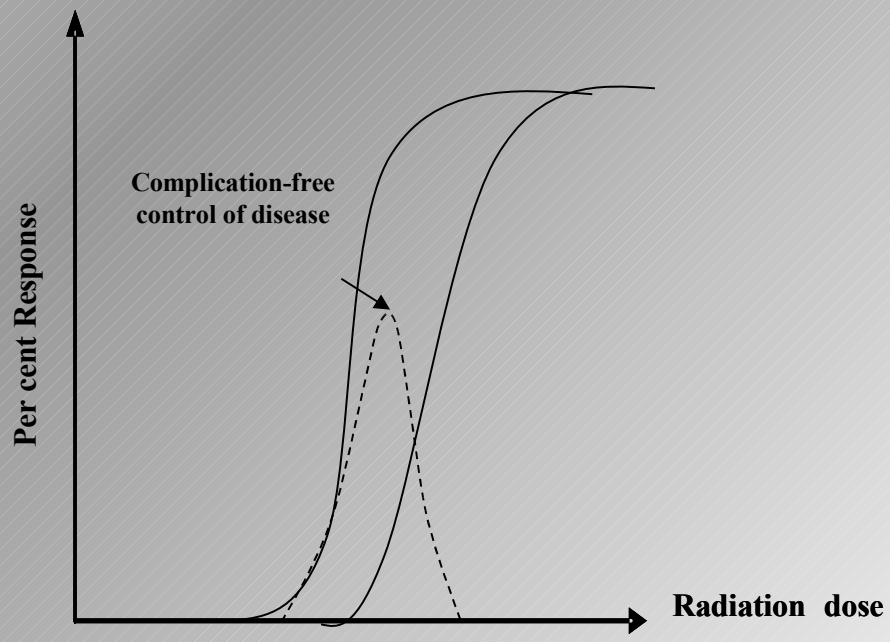
- **Serial organization** (critical element; small volume dependence)
  - Damage to any one of the FSUs will cause a complication (maximum dose important)
- **Parallel organization** (critical volume; large volume dependence)
  - Damage to a substantial fraction of the FSUs is necessary to cause a complication (mean dose important)
- The **volume effect** of an organ changes the dose tolerance threshold when an effect takes place *High dose to a small part of the organ well tolerated; same dose to whole organ not tolerated at all…*





Radiobiology
Radiobiological modeling

- *Biological models relate radiation dose plus volume of irradiated tissue to predict a biological response* *Steepness of curve gives an estimate of the change in response that will be a consequence of a change in dose*
- Basic requirements
  - Sigmoid relationship between dose and response
  - Volume and fractionation effect
  - Non-uniform dose delivery
  - Prediction of probability of tumour control (TCP) and/or normal tissue complication (NTCP)
- Mechanistic
  - Based on the hypothesis that the response of an organ is determined by the survival of the cells of that organ/tissue *Tries to model complex biological processes*
- Phenomenological
  - Derived by fitting mathematical functions to clinical data *Only valid for the situations described by original data*



TCP curve placed left of NTCP curve: normal tissue tolerates more dose than what is needed to eradicate the tumour – treatment OK

TCP curve placed right of NTCP curve: normal tissue tolerates less dose than what is needed to eradicate the tumour – treatment suitable?

Radiobiology
Mechanistic models

- Damage induction considered stochastic *Organ response assumed to depend on critical cells or FSUs; all critical cells or FSUs respond identically*
- Based on Poisson statistics (1)
  - TCP=1 when no clonogenic cells survive (n=0)
  - NTCP=1 when a critical amount of FSUs have been damaged (n=0)
  - Expected number of surviving cells/FSUs given by $N_s = N_0 S(D)$
  - Surviving fraction given by LQ-model $S(D) = e^{-\alpha D - \beta d D}$
  - Inhomogenously irradiated organ handled by taking product of subvolumes where dose can be considered homogeneous

$$P(D,n) = \frac{e^{-N_s} N_s^{\,n}}{n!} \qquad (1)$$

$$P(D,0) = e^{-N_s} \qquad (2)$$

$$= e^{-N_0 S(D)} \qquad (3)$$

$$= \mathrm{e}^{-\mathrm{N}_0 e^{-\alpha D - \beta d D}} \qquad (4)$$

P = probability of response

D = total dose

N_s = expected number of surviving cells/FSUs

N_0 = initial number of cells/FSUs

S(D) = surviving fraction of cells/FSUs

α = linear coefficient of LQ-model

β = quadratic coefficient of LQ-model

d = dose/fraction

(4) is known as the Classic TCP model (seldom used for NTCP predictions due to difficulties to practically identify FSUs)

Radiobiology
Phenomenological models

- Probit model (1)
  - Based on the cumulative normal distribution
  - Mainly used for normal tissue
- Logit model (2)
  - Based on Logistic regression
  - Used for both tumours and normal tissue
- Inhomogeneously irradiated tissue handled by using DVH reduction schemes

Reduces a non-uniform dose distribution to a uniform one; Effective volume: maximum dose to an effective volume of the organ; Effective dose: lower reference dose to whole organ

$$P(D,v) = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{x(D,v)} e^{-t^2/2}\, dt \quad (1)$$

$$P(D,v) = \frac{1}{1+e^{x(D,v)}} \quad (2)$$

$$x(D,v) = \frac{D - TD_{50}(v)}{mTD_{50}(v)} \quad (3)$$

$$TD_{50}(v) = TD_{50}(1)v^{-n} \quad (4)$$

D = total uniform dose to volume v

v = volume irradiated

TD_{50}(v) = tolerance dose giving 50% probability of effect for uniform irradiation of volume v of an organ

m = inversely proportional to the slope of the dose-response curve

n = volume dependence of organ

Radiobiology

Generalized equivalent uniform dose (gEUD)

- The gEUD is based on the concept of a generalized mean dose, and is a means to reduce a complex 3D dose distribution to a single, biologically representative dose value
- The *a* parameter is tissue specific and describes the volume effect of the tissue under consideration

$$gEUD(\mathbf{D}, a) = \left(\frac{1}{N} \sum_{i=1}^{N} D_i^{\,a} \right)^{\frac{1}{a}} \quad (1)$$

D = total dose

a = tissue specific volume parameter

N = number of voxels in tissue

D_i = dose in voxel *i*

- $a < 0$: minimum dose (tumour)
- $a \approx 1$: mean dose (parallel tissue)
- $a \rightarrow \infty$: maximum dose (serial tissue)

gEUD is not a sigmoid function and does not predict a response; it handles non-uniform dose distributions and the volume effect and is easily modified to handel fractionation effects by the use of the LQ model

gEUD values provide a biologically meaningful index to dose distributions that cause the same biological effect

Biological optimization criteria

- A biologically based objective function gives a better representation of the biological consequences of the dose distribution *It is easier for the optimization algorithm to find treatment plans that are biologically favourable*
- Same logical structure of the optimization as in the physically based, but different mathematical formulations of the optimization objectives
- Optimization problem formulation *Defined in terms of TCP and NTCP*

  (*i*) TCP objective function + NTCP constraints

  (*ii*) NTCP objective function + TCP constraints

  (*iii*) TCP and NTCP objective function
- Maximum, minimum and/or DV limits (!?) *Dose distributions suggested by the optimization algorithm based on a biologically based objective function are often different from clinical practice…*

Biological Optimization Criteria
Target and OAR objective function

F = overall objective function

F_{target} = target objective function

F_{OAR} = OAR objective function

$$F = F_{target} \prod F_{OAR}$$

$gEUD_{presc}$ = prescribed dose to target / limit to OAR

w_t = relative importance of target

w_{OAR} = relative importance of OAR

$$gEUD(\mathbf{D}) = \left(\frac{1}{N} \sum_{i=1}^{N} D_i^a \right)^{\frac{1}{a}}$$

$$F_{target} = \frac{1}{1 + \left(\frac{gEUDpresc}{gEUD(\mathbf{D})} \right)^{wt}}$$

D_i = dose to voxel i

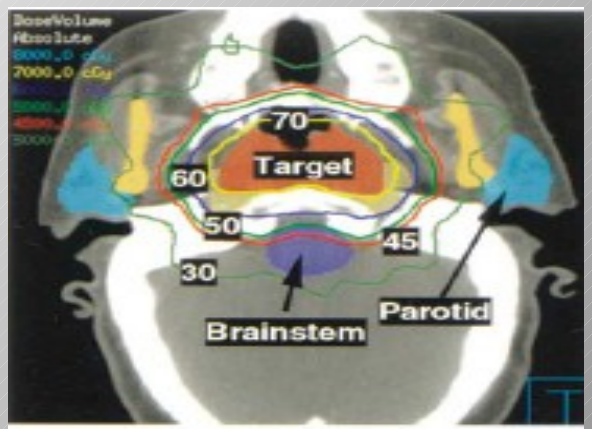
N = number of voxels in structure

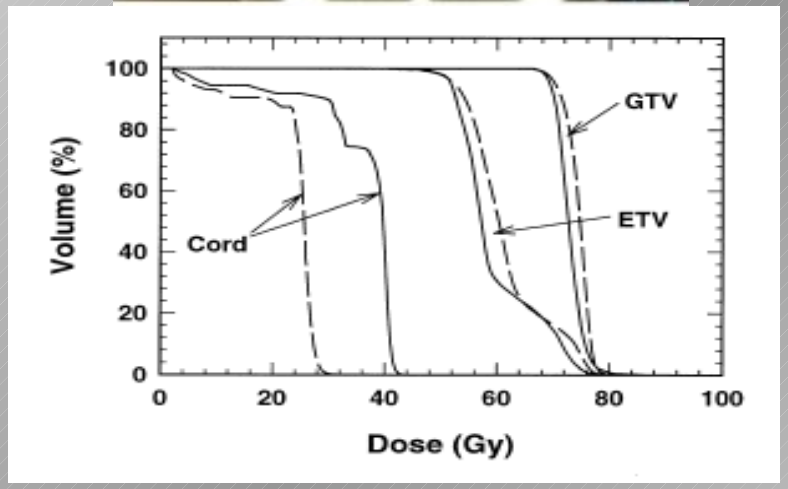
a = tissue specific volume parameter

$$F_{OAR} = \frac{1}{1 + \left(\frac{gEUD(\mathbf{D})}{gEUD_{presc}} \right)^{woar}}$$

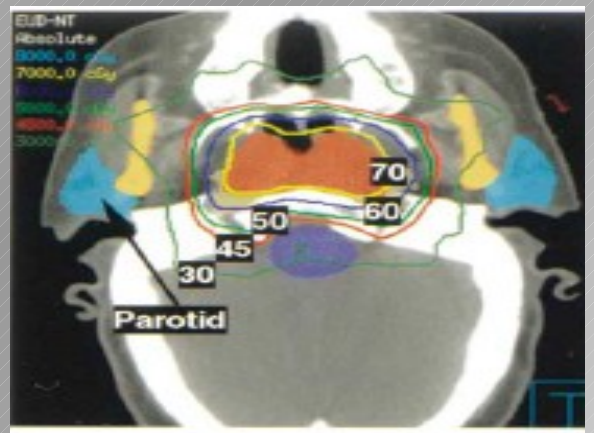
Biologically based optimization compared to physically based optimization

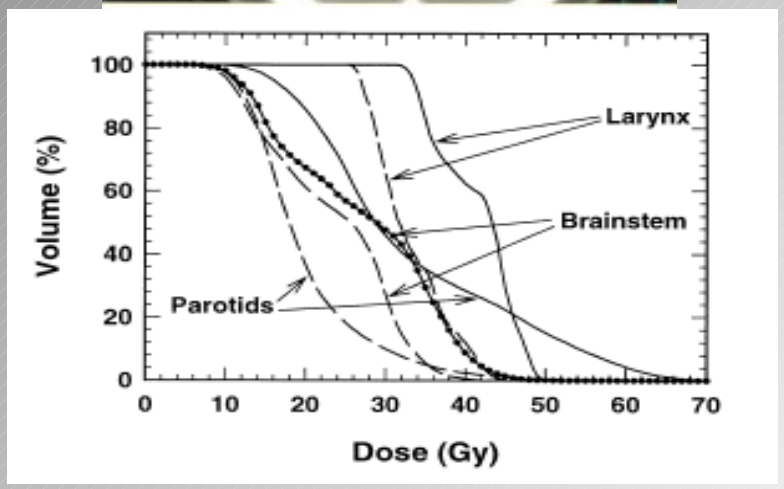
Physically based optimization





Biologically based optimization





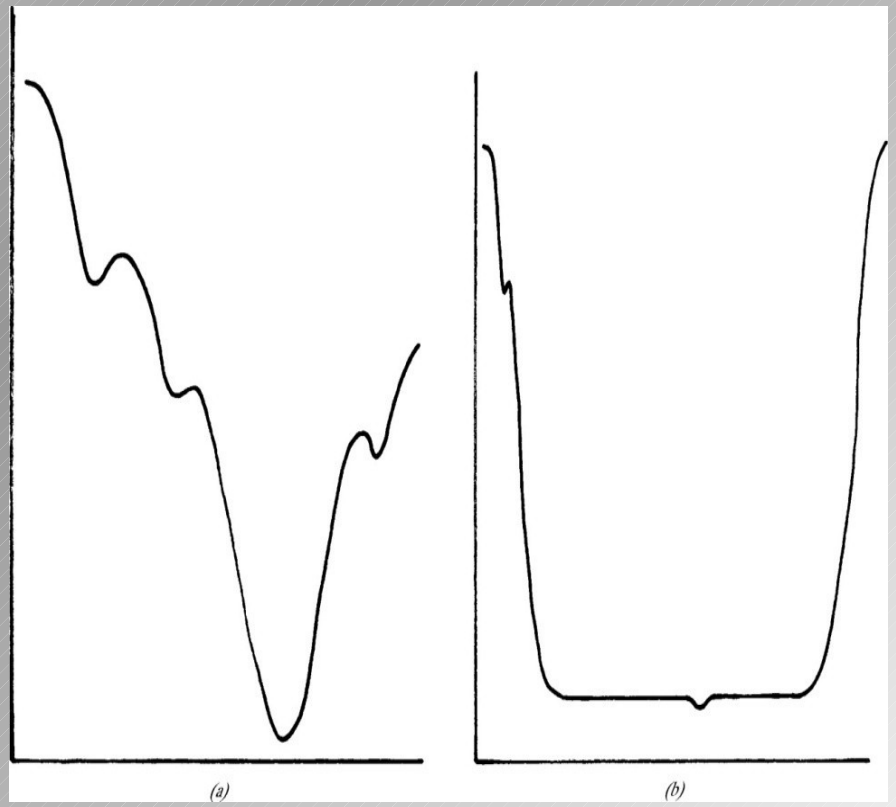
Wu *et al.*: *Optimization of intensity-modulated radiotherapy plans based on the equivalent uniform dose*. Int. J. Radiation Oncology Biol. Phys. 52(1), pp 224-235, 2002.

Aim of Head-and-neck cancer treatment: Conform the high dose to the target; spare the Brainstem and Parotid glands as much as possible

Yellow isodose = 100% of prescribed dose; Green isodose = ~40% of prescribed dose; Dotted line in DVH = BIO_OPT; Solid line= PHYS_OPT

Optimization algorithms for IMRT
Global and local extreme points

- Objective function frequently encountered in IMRT (*b*) - many beam configurations correspond to similar dose distributions
- The mathematically optimal solution may not be the clinically optimal solution
  Globally optimal dose distributions tends to be complex – harder to implement in the clinic – prone to mistakes
- Any dose distribution that meets the given requirements might be clinically acceptable

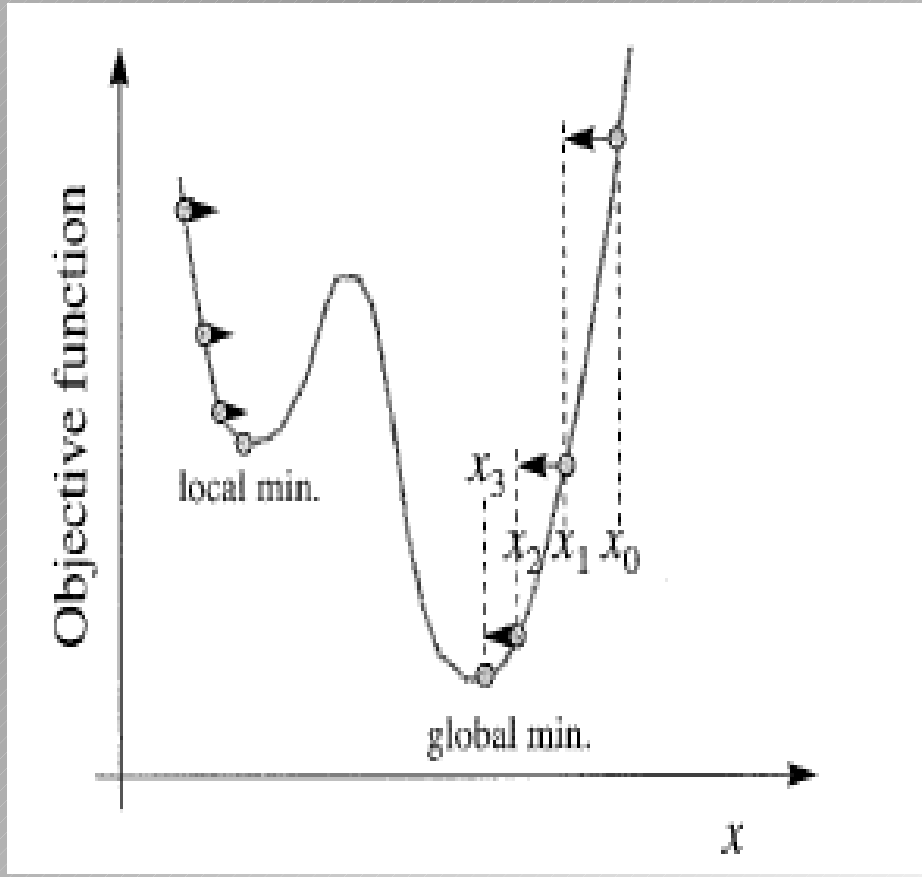


Optimization algorithms for IMRT

Deterministic methods

- Do not contain any random element
- Gradient methods *Converges to the nearest extreme point; Fast (typically less than 100 iterations)*
- Steepest descent (SD)
- Conjugate gradient (CG)
- (Quasi) Newton's method ((Q)NM)

  SD, CG, (Q)NM differs in the way they suggest the direction of minimization/maximization (first or (approximations of) second order derivatives) and how they select the step size (constant, exact line search, etc.)

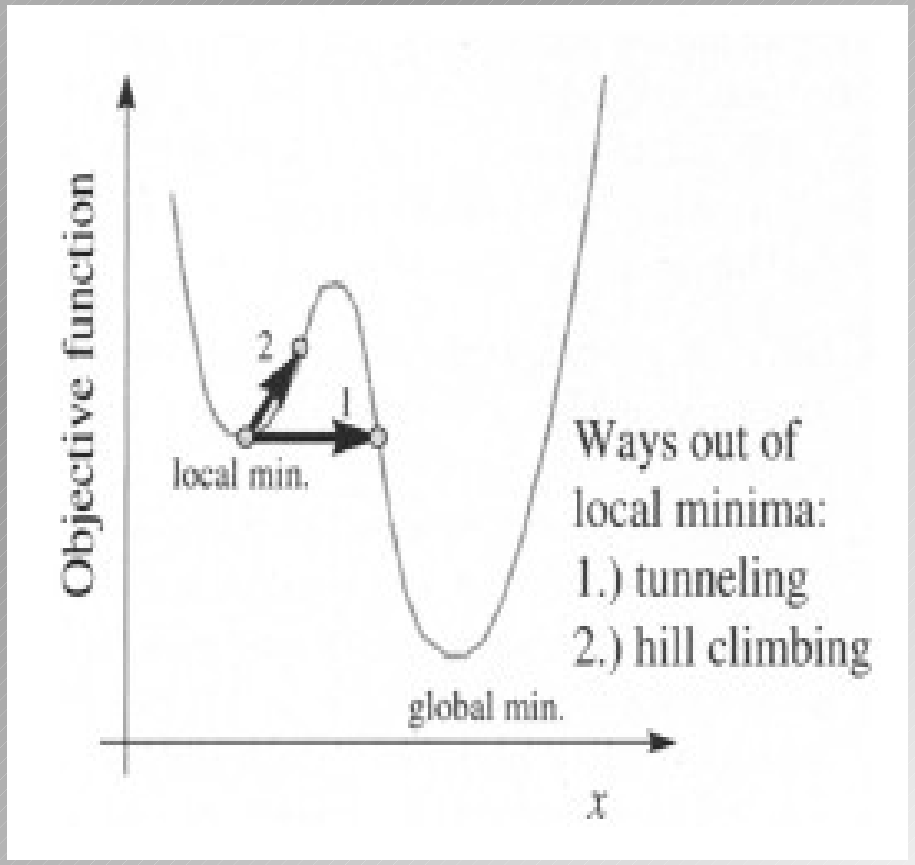


Bortfeld T. 1999: *Optimized planning using physical objectives and constraints.* Seminars in Radiation Oncology, Vol 9, No 1, 20-34.

Optimization algorithms for IMRT

Stochastic methods

- Contains a random element
- Simulated annealing *May avoid local extreme poitns; Slow (typically more than 1000 iterations)*
- *Mimics the physical process in which a material is slowly cooled down after being rapidly heated to high temperatures* *The temperature is lowered from one iteration to the next; each iteration step involves the random selection of a stepsize (from a displacement distribution of shrinking width) (**tunneling**); an improvement is always accepted, a worse value is accepted with a probability that depends on the temperature (**hill climbing**)*
- Boltzmann annealing (BA)
- Fast simulated annealing (FSA)
- *BA,FSA differs in the determination of the speed of the cooling temperature (reciprocal of the logarithm of the iteration, reciprocal of iteration) and the choice of distribution for the sampling of step sizes (Gaussian, Cauchy)*



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