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

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Topics

Short history of radiotherapy

The IMRT process

Inverse planning for IMRT

Physical optimization criteria

Radiobiology

Radiobiological modeling

Biological optimization criteria

Optimization algorithms for IMRT

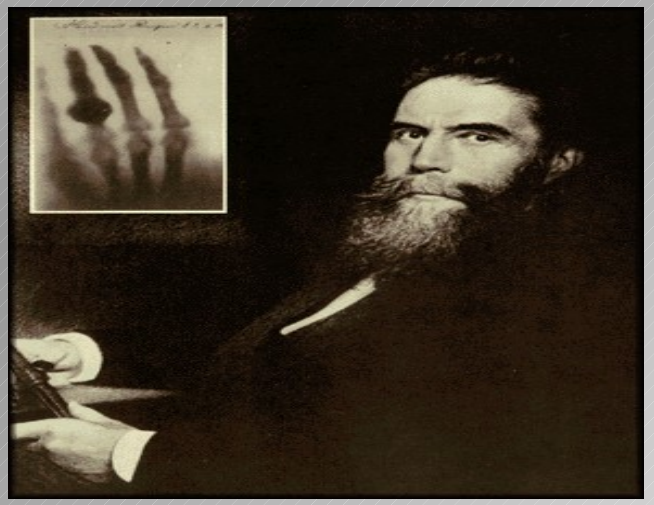
Short history of radiotherapy

- X-rays were discovered in 1895 – diagnostic radiology

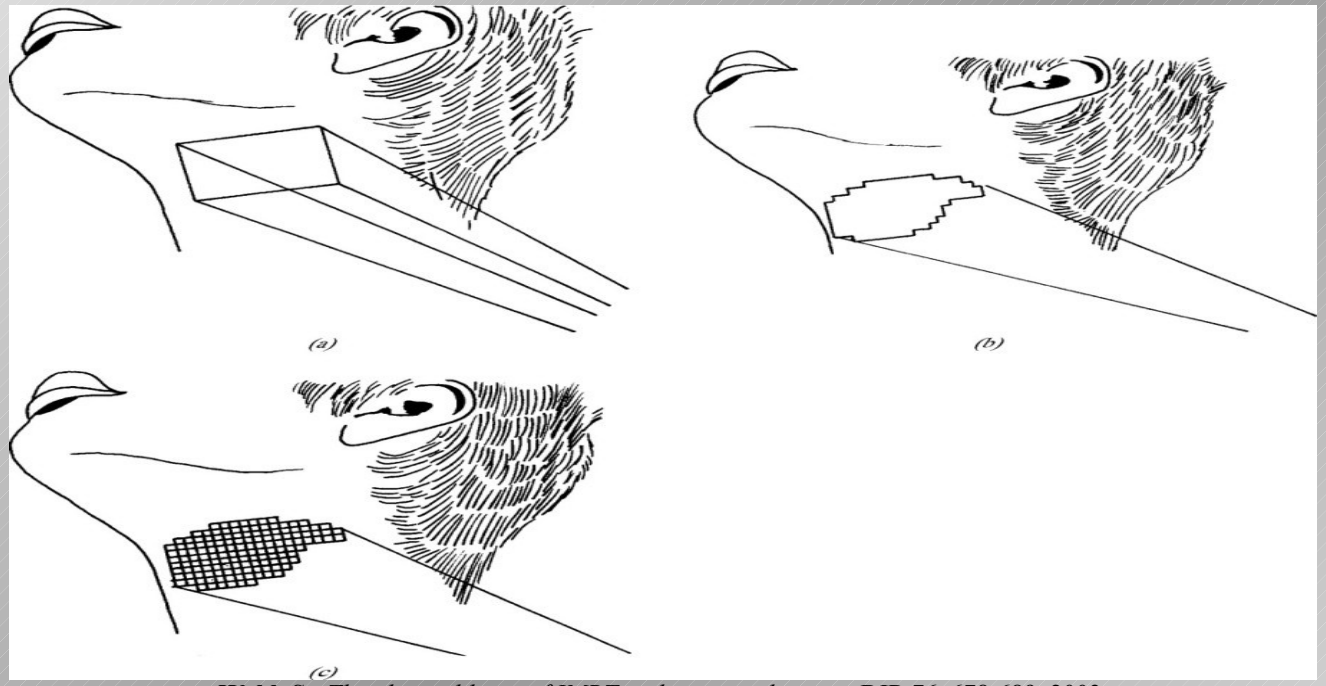
  W. C. Röntgen
- X-rays therapuetically in 1896 and first textbook of radiotherapy in 1903

  L. Freund
- Discovery of radioactivity in 1898

  A. H. Becquerel; Marie and Pierre Curie
- Radiotherapy in MeV around 1950 by the use of linear accelerators (LINAC)



Conformal radiotherapy



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

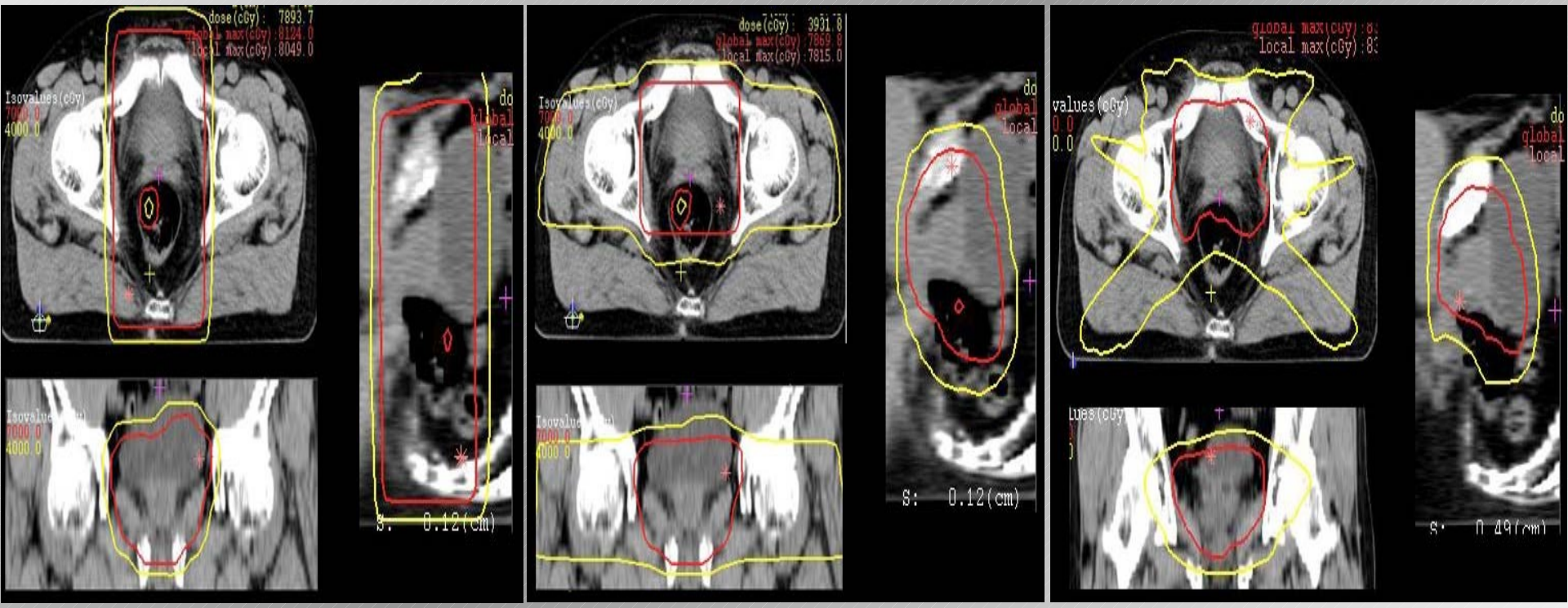
(a) conventional radiotherapy:
rectangularly-shaped fields with additional blocks and wedges

(b) conformal radiotherapy (CRT) with uniform fluence (late 1980s):
more convenient geometric field shaping using a multileaf collimator (MLC) (convex shapes)

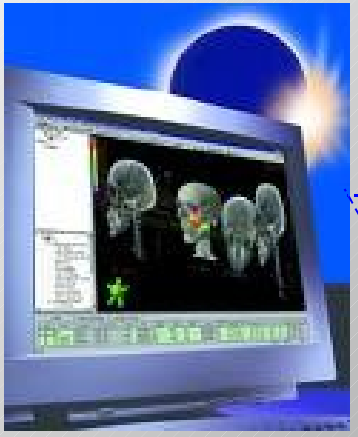
(c) CRT with non-uniform fluence or intensity modulation (IMRT) (mid 1990s):
varied intensity bixel-by-bixel within the shaped field (concave shapes)

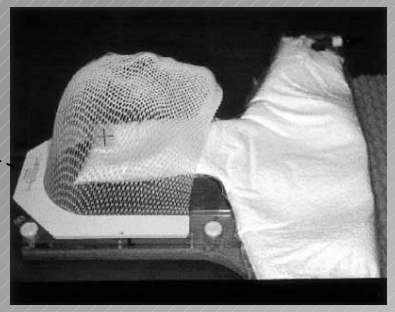
Different treatment techniques

Conventional CRT uniform fluence CRT IMRT



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

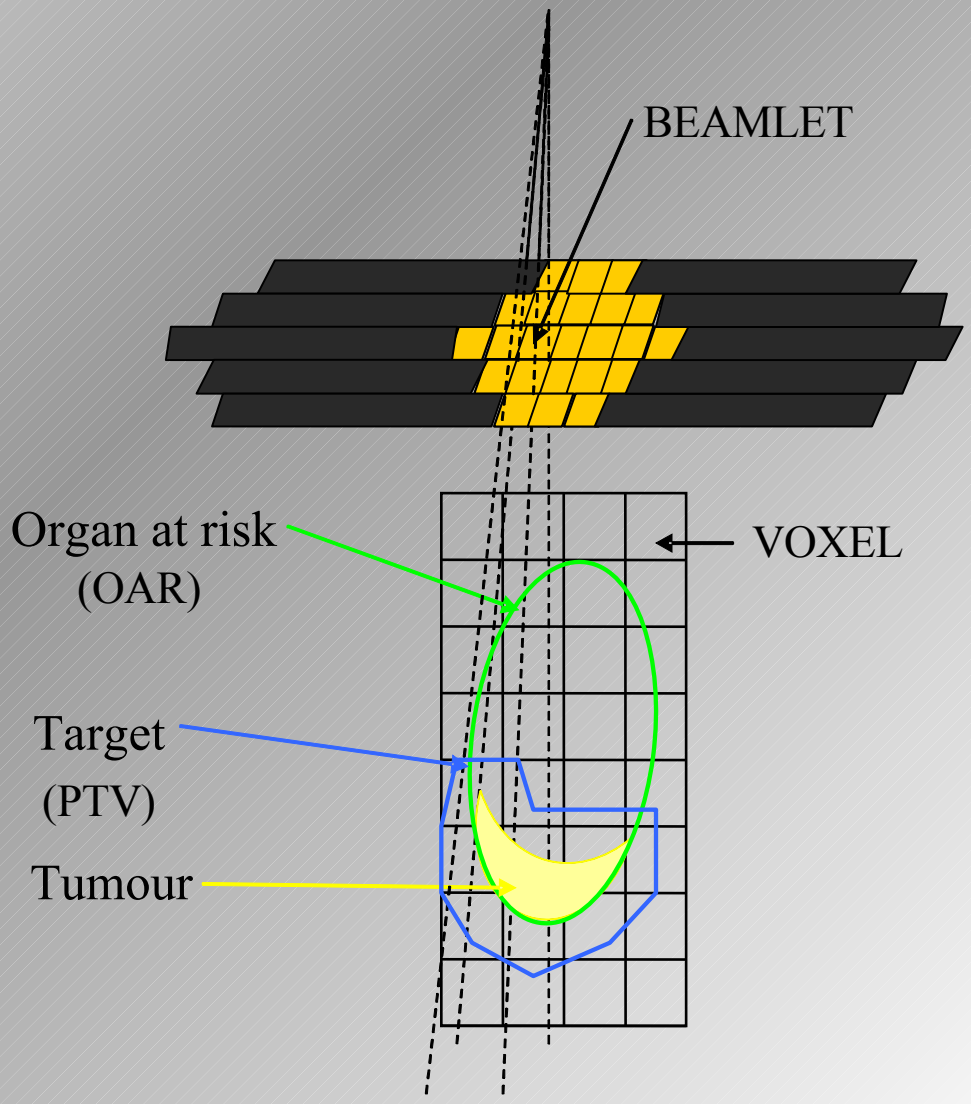
- The optimzation parameters are the beamlet intensities
  - >>100 beamlets / treatment field
  - beamlet size 5-10 mm^2)
- The anatomical volumes are represented by volume elements (voxels) organized into 3D matrices
  - >>1000 voxels / volume
  - voxel size ~5 mm^3
- Linear relationship between beam intensity and dose in a voxel

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

D_i=dose in voxel i

w_j=intensity level of beamlet j

$\mathbf{K_{ij}}$=dose contribution from beamlet j to voxel i



Physical optimization criteria

- Optimization criteria are determined in terms of doses and irradiated volumes
  - Dose limits
  - Limits on volumes receiving certain specified dose
- Optimization problem formulation

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

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

  (*iii*) Target and OAR objective function
- Penalty factors
  - Soft constraints
  - Hard constraints
- Relative importance factors

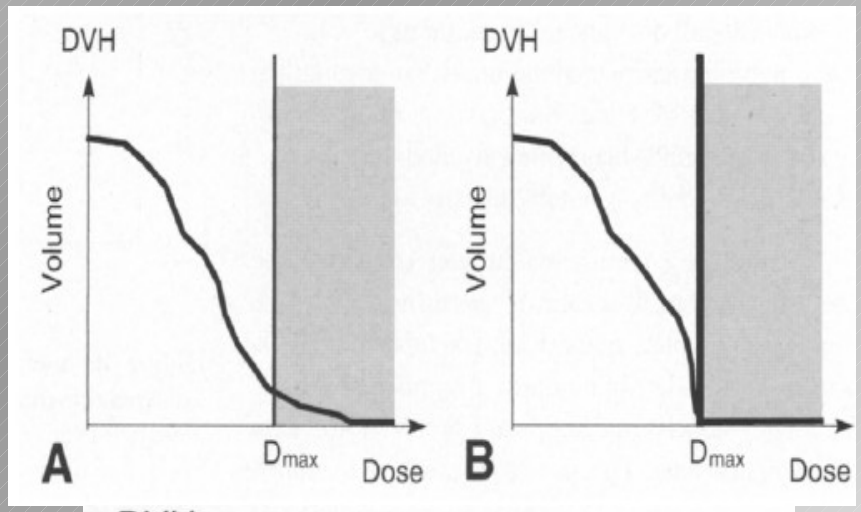
Physical optimization criteria
Dose limits

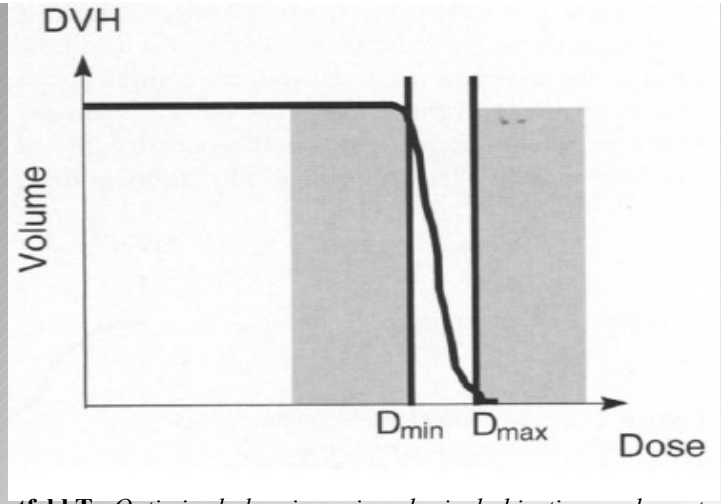
- Maximal dose limit
  - A limitation of the maximal dose to a tolerance threshold (target and OAR)

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

- Minimum dose limit
  - A limitation of the minimum dose to a tolerance threshold (target)

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





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

- Dose-volume (DVH) limit
  - No more than V_{max} % of the volume should receive more than a dose of D_{max}

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

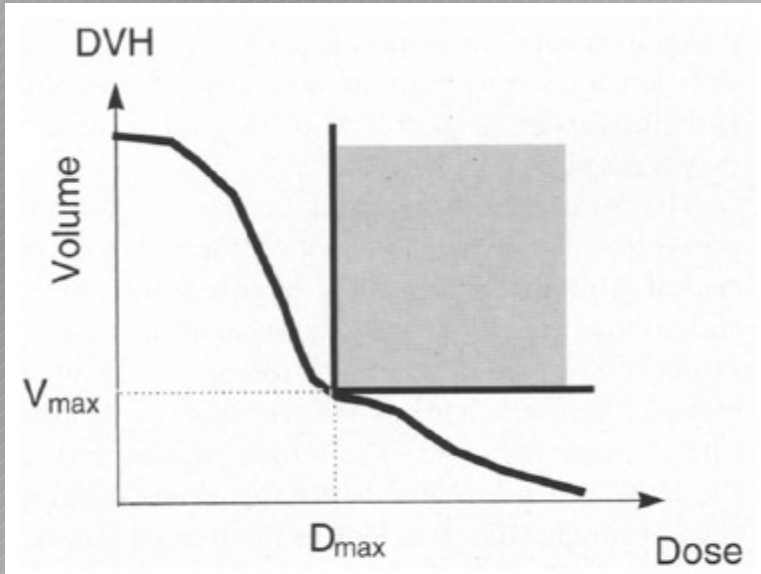


Figure 3. Structures with a large volume effect are more appropriately spared through the application of dose-volume histogram (DVH) constraints. They prevent the DVH from going above the point (D_{max}, V_{max}).

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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

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

$H(\cdot)$ = Heaviside function

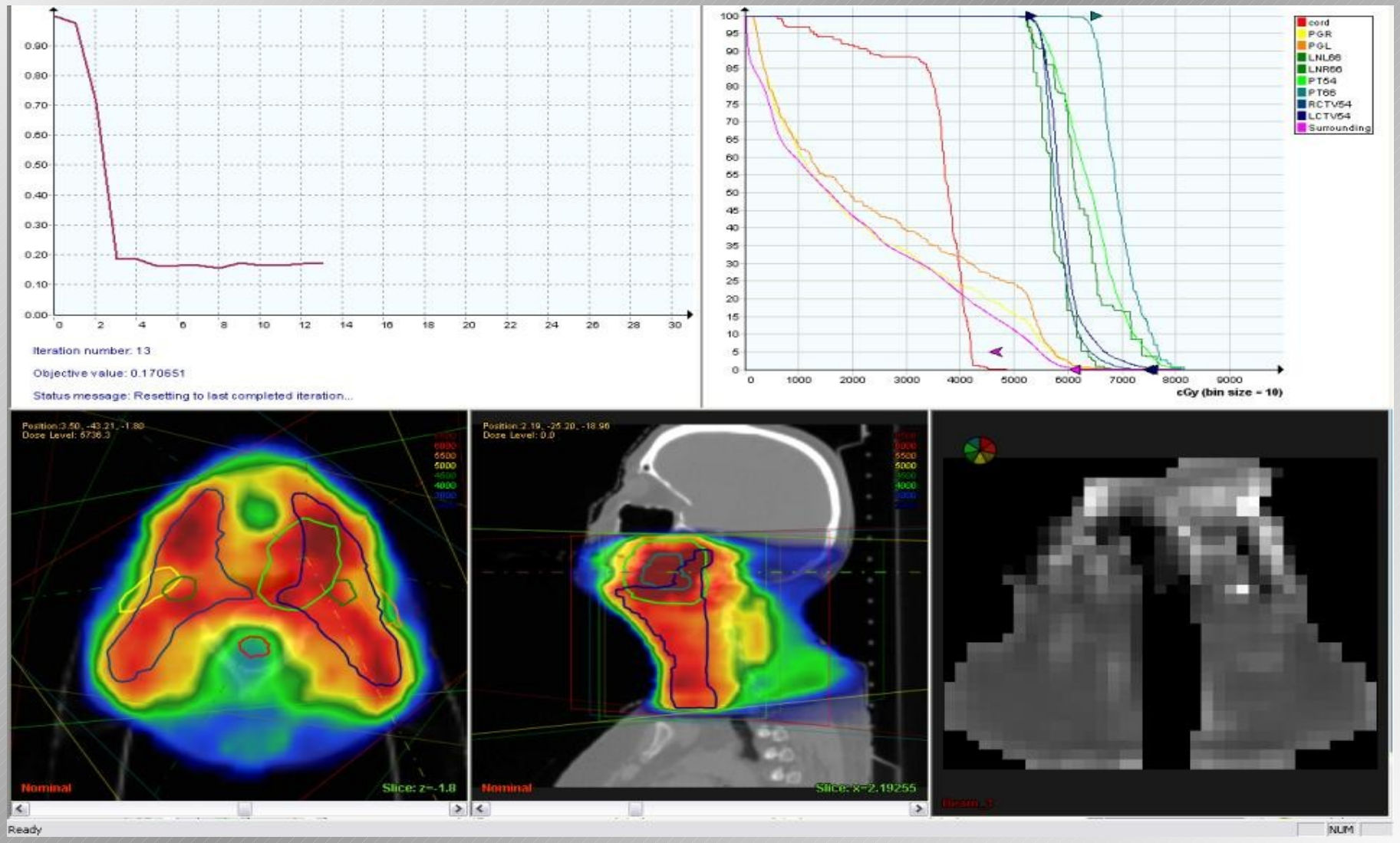
N_t = number of voxels in target
D_i = dose to voxel i
D_{presc} = prescribed dose to target
D_{min} = minimum dose to voxel i
D_{max} = maximum dose to voxel i
$c_{t,min}$ = penalty associated with underdosage
$c_{t,max}$ = penalty associated with overdosage

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

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



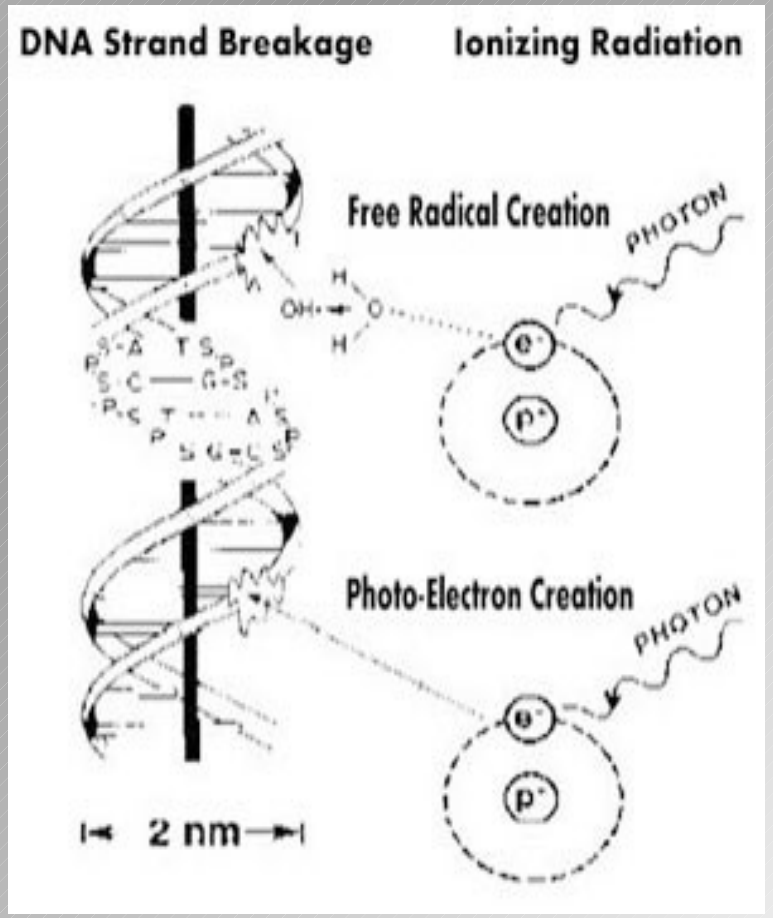
RaySearch Laboratories: *http://www.raysearchlabs.com*

Radiobiology

What happens in the body after radiotherapy?

- The interactions when radiation is absorbed in biological material result in excitation and ionization events
- The electronically unstable atoms and molecules are highly chemically reactive

  => free radicals that may break chemical bonds in cell nucleus molecules (DNA)
- In order to repair as much damage as possible, enzymatic reactions that act on the chemical damage take place
- The **biological effect of radiation** result principally from the unrepaired damage to the DNA



Radiobiology

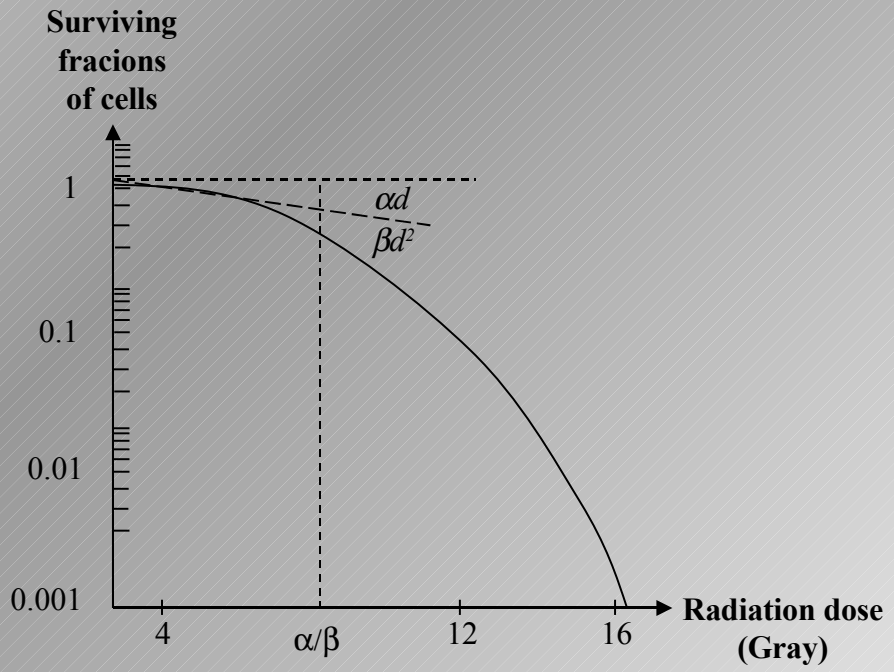
Cell survival curve after irradiation

- The cell survival curve describes the relationship between the radiation dose and the proportion of cells that survive.
- 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 parameters α and β.

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

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

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



- This model of cell kill is called the linear-quadratic model (LQ-model) and is the model of choice to describe cell survival curves at therapeutic radiation doses.

Radiobiology
Tissue architecture

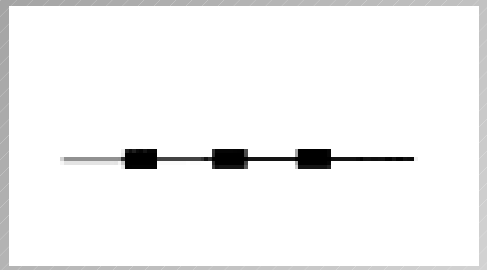
Functional sub units (FSU)

The number of critical cells/FSU

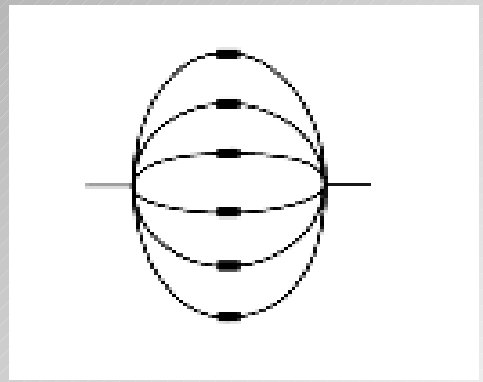
How the critical cells are organized into FSUs

The number of FSUs necessary to maintain organ function

- Serial organization (critical element)
  - Damage to any one of the FSUs will cause a complication (maximum dose important)

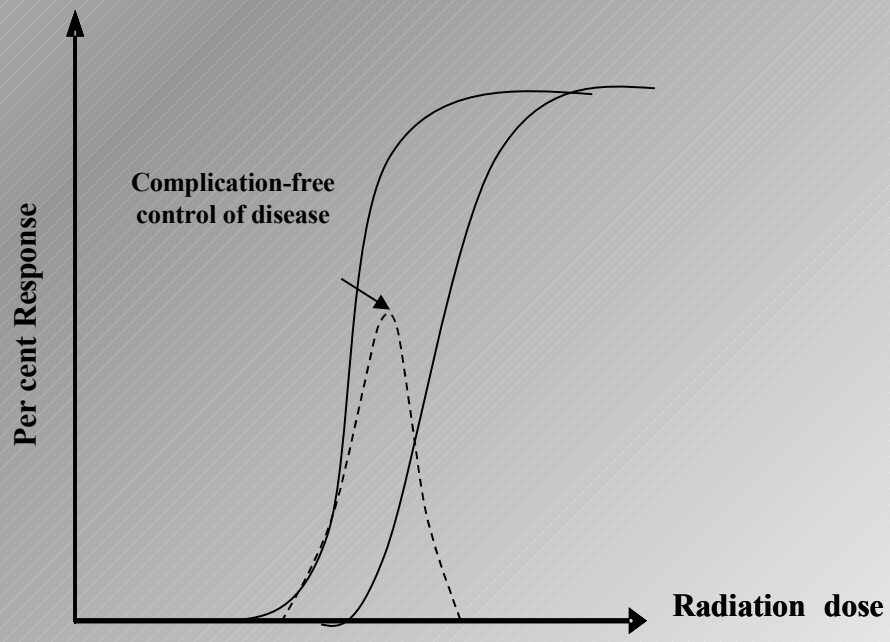


- Parallel organization (critical volume)
  - Damage to a substantial fraction of the FSUs is necessary to cause a complication (mean dose important)



Radiobiology
Radiobiological modeling

- Basic features
  - Sigmoid relationship between dose and response
  - Volume and fractionation effect
  - Non-uniform dose delivery
  - Prediction of Tumour Control Probability (TCP) and Normal Tissue Complication Probability (NTCP)
- Mechanistic
  - Based on the hypothesis that the response of an organ is determined by the survival of the cells of that organ/tissue
- Phenomenological
  - Derived by fitting mathematical models to clinical data



Radiobiology
Mechanistic models

- Based on Poisson statistics
  - Tumour is controlled when no clonogenic cells survive
  - Normal tissue complication occurs when a critical amount of FSUs have been damaged
  - Expected number of surviving cells/FSUs given by

$$N_s = N_0 S(D)$$

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

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

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

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

- Surviving fraction given by LQ-model

$$S(D) = e^{-\alpha D - \beta d D}$$

$$P(D) = e^{N_0 e^{-\alpha D - \beta d D}}$$

P = probability of response

D = total dose

N_0 = initial number of cells/FSUs

α = linear coefficient of LQ-model

β = quadratic coefficient of LQ-model

d = dose/fraction

Radiobiology
Phenomenological models

- Probit model

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

- Logit model

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

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

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

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

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
  - $a < 0$: tumour tissue
  - $a \approx 1$: parallell tissue
  - $a \rightarrow \infty$: serial tissue

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

D = total dose

a = tissue specific volume parameter

N = number of voxels in tissue

D_i = dose in voxel *i*

Biological optimization criteria

- Same logical structure of the optimization as in the physically based, but different mathematical formulations of the optimization objectives
- Optimization problem formulation

  (*i*) TCP objective function + NTCP constraints

  (*ii*) NTCP objective function + TCP constraints

  (*iii*) TCP and NTCP objective function
- Maximum, minimum and/or DV based objectives (!?)

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

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

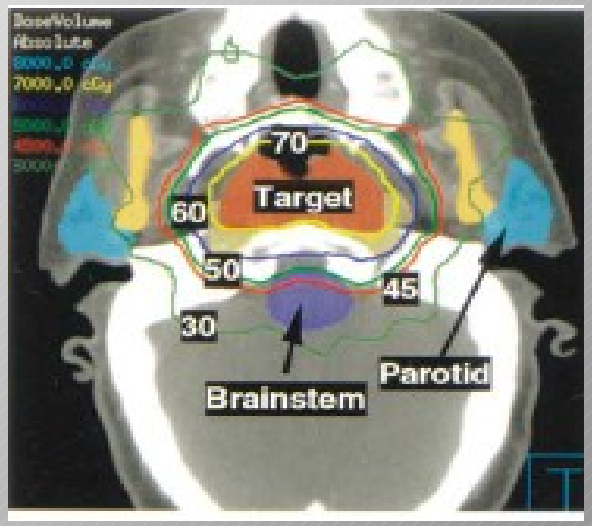
N = number of voxels in structure

a = tissue specific volume parameter

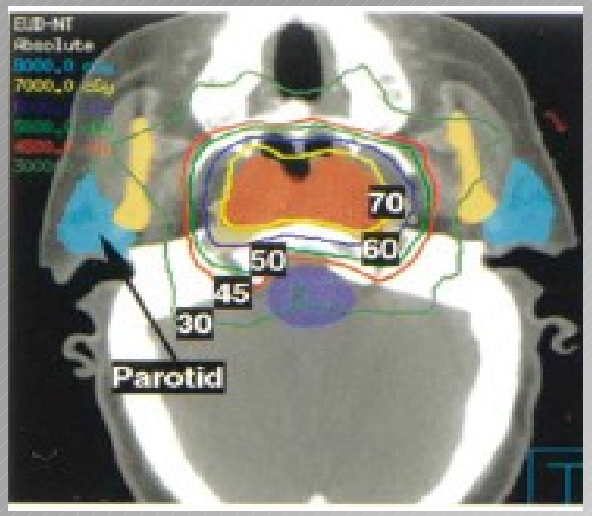
$$F_{OAR} = \frac{1}{1 + \left(\frac{gEUD(\mathbf{D})}{gEUD_{presc}} \right)^{woar}}$$

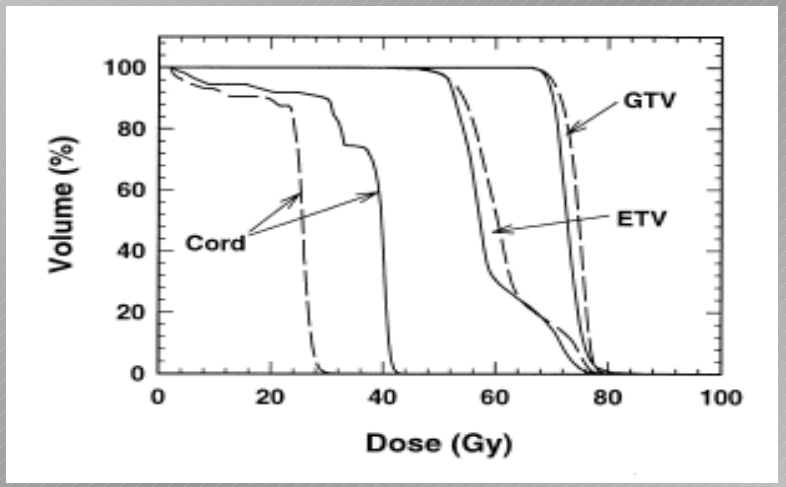
Biologically based optimization compared to physically based optimization

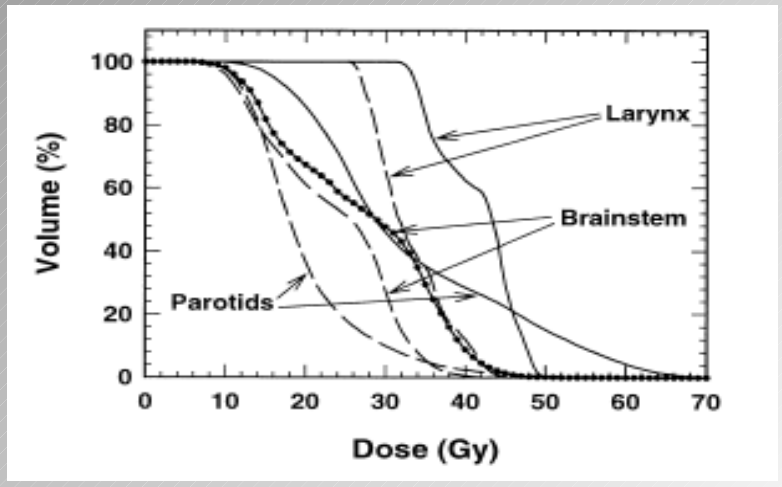
Physically based optimization



Biologically based optimization



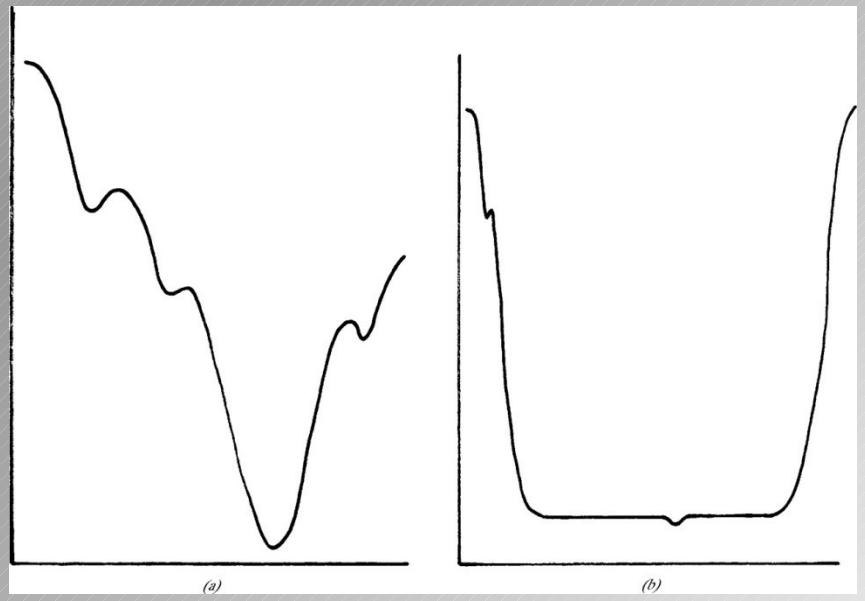




Wu *et al.*: *Optimization of intensity-modulated radiotherapy plans based on the equivalent uniform dose*. Int. J. Radiation Oncology Biol. Phys. 52(1), pp 224-235, 2002.

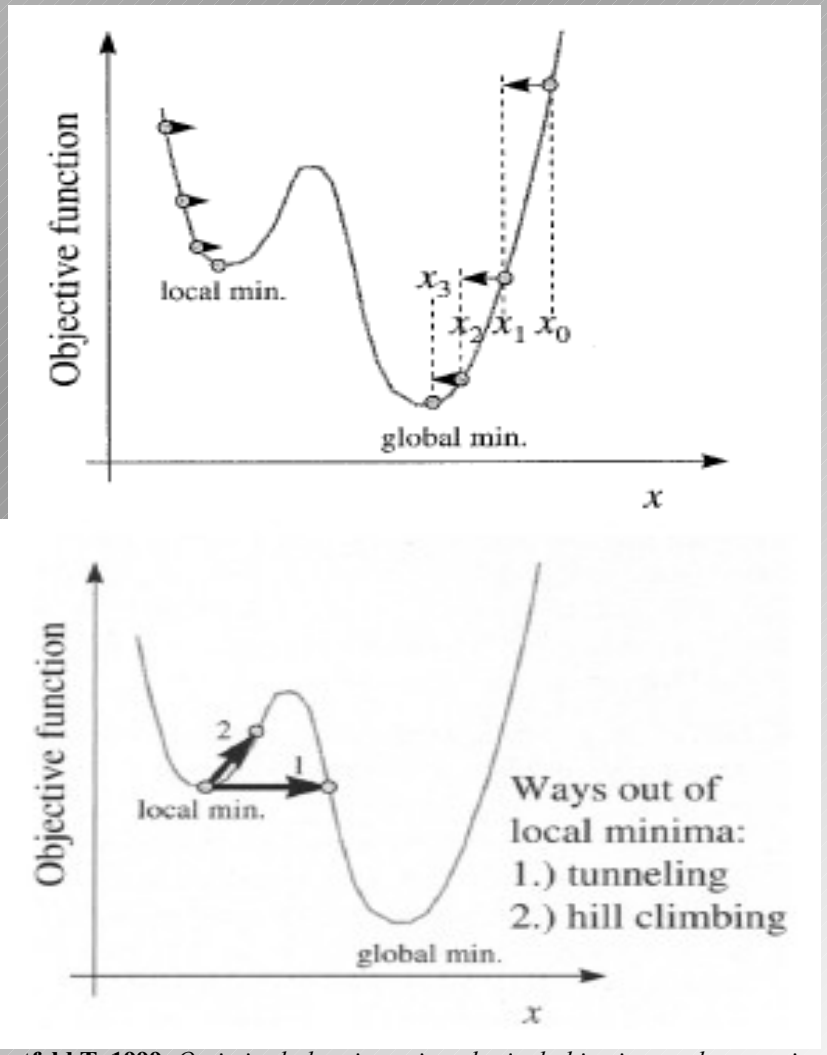
Optimization algorithms for IMRT
Global and local extreme points

- The mathematically optimal solution may not be the clinically optimal solution
- Many beam configurations correspond to similar dose distributions



Optimization algorithms for IMRT

- Deterministic methods
  - Gradient methods
    - Steepest descent
    - Conjugate gradient
    - Newton's method
- Stochastic methods
  - Simulated annealing
    - Boltzmann annealing
    - Fast simulated annealing



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