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

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Caroline Olsson, M.Sc.
caroline.olsson@vgregion.se

Topics

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

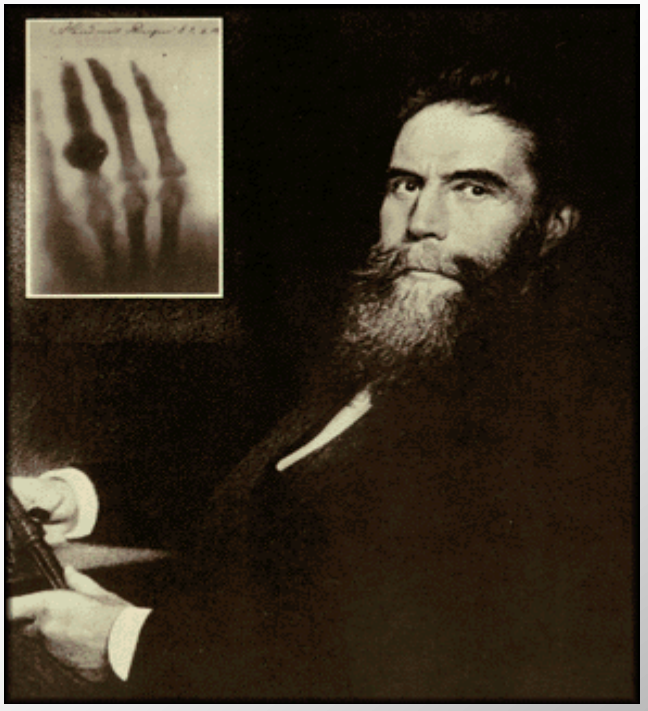
Optimization algorithms for IMRT

How is the optimization for IMRT solved

History of radiotherapy

- X-rays were accidentally discovered in 1895 by W. C. Röntgen– *first Nobel Prize in Physics*

- ”X-rays” because nature of the rays was initially unknown
  - not penetrate bones or lead
  - could be captured on photographic plates



- First used for diagnostic radiology

History of radiotherapy

- Discovery of spontaneous radioactivity in 1898 A. H. Becquerel - *Nobel Prize in Physics together with Marie and Pierre Curie who studied the "Becquerel radiation"*

- Spontaneous radioactivity (γ-rays) has similar properties as X-rays
- Emitted by radioactive isotopes and represents the excess energy given off as the unstable nucleus breaks up and decays to reach stable form

History of radiotherapy

- X-rays were noted to have the ability to cause biological effects when deposited in tissue one year after its discovery (1896)
- First textbook of radiotherapy in 1903 by L. Freund - *”Father of radiotherapy”*

- Early treatments in keV mainly skin (dermatological) conditions – deep tumors problematic

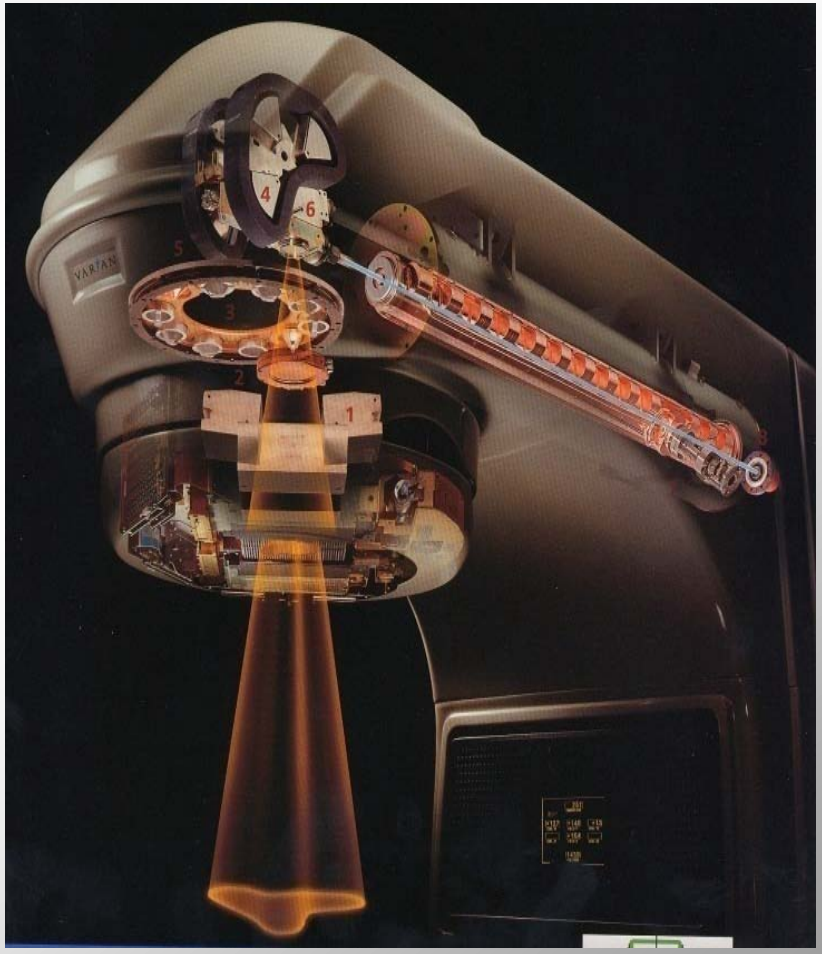
- Radiotherapy in MeV around 1950 by the use of linear accelerators (LINACs) – treatment of all tumours

  The Sahlgrenska University Hospital in Göteborg (Borås) has 8 (3) LINACs and treat approximately 4000 cancer patients yearly

History of radiotherapy

- X-rays electronically produced

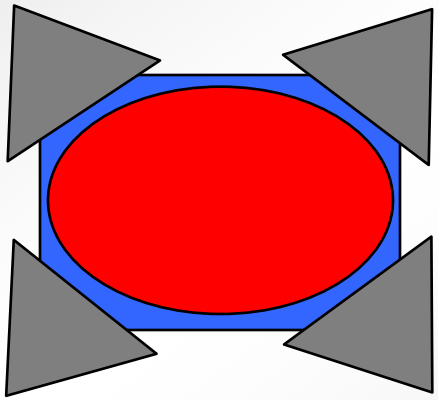
- Electrons are accelerated to high energies and stopped in a target usually made of Tungsten
- Hitting the target, some of the electrons kinetic energy is converted to X-rays (*electromagnetic waves, streams of photons=”packets of energy”*) through bremsstrahlung
- Collimators situated in head of LINAC shapes photons into beams before energy is deposited in the patient; absorbed dose measured in Gray (Gy) [J/kg]



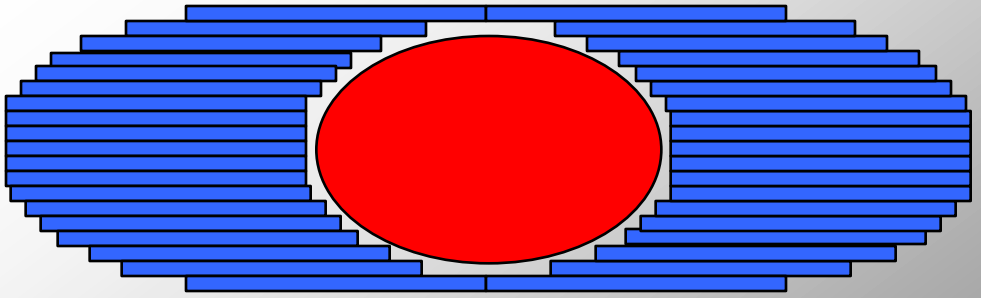
History of radiotherapy

- Photons shaped into treatment fields by collimators situated in the head of the LINAC

- *Initially only rectanglularly-shaped fields – with blocks*



- *Multileaf collimators (**MLC**) give flexible geometric field shaping*

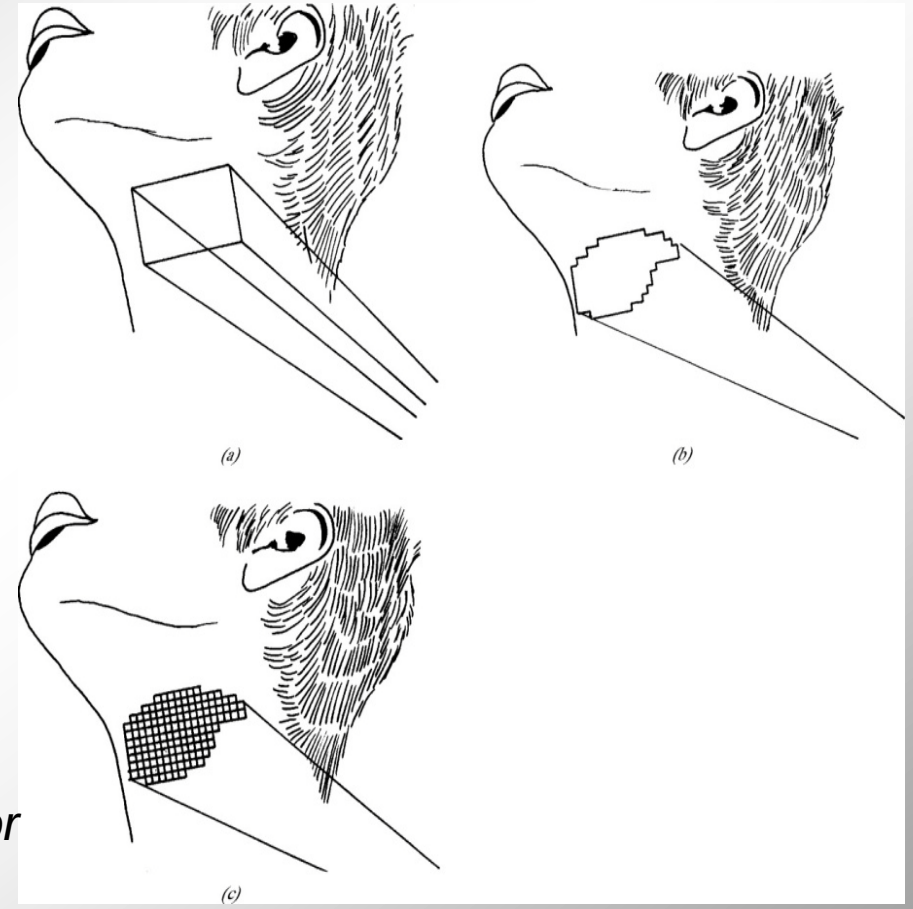


History of radiotherapy

(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 MLC*

(c) CRT with non-uniform intensities or intensity modulation (mid 1990s): **intensity modulated radiotherapy** (**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.

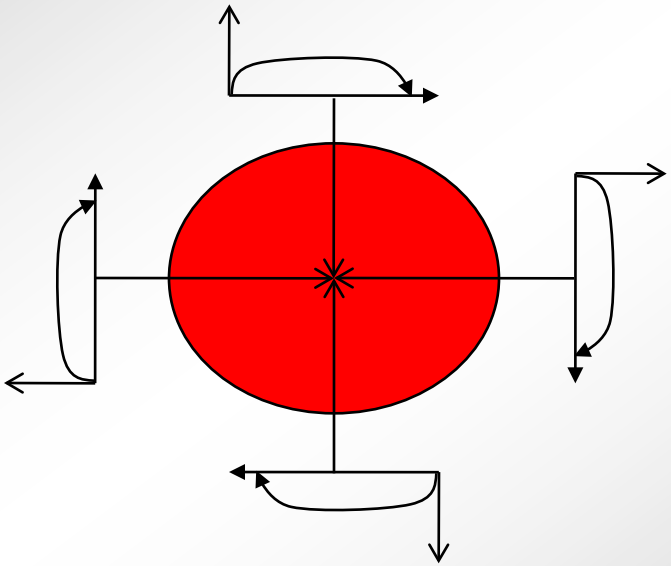
History of radiotherapy

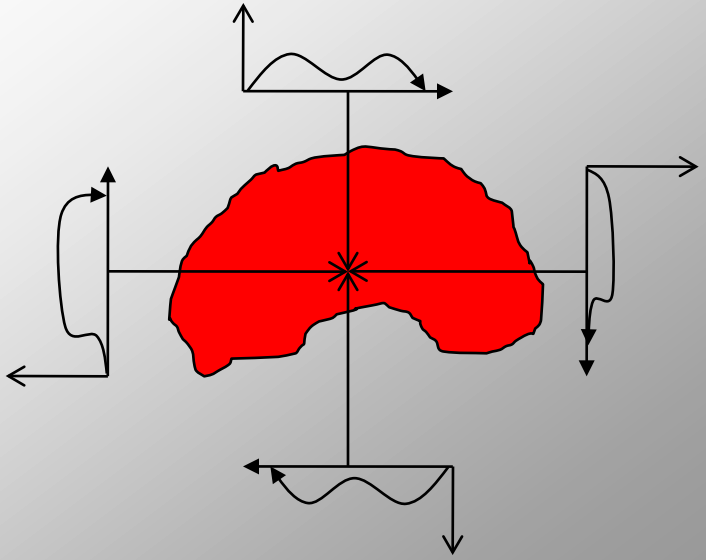
- Aim of radiotherapy is to eradicate the tumour cells while minimizing unavoidable damage to normal tissue

  => **maximize conformity to tumour volume!**

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

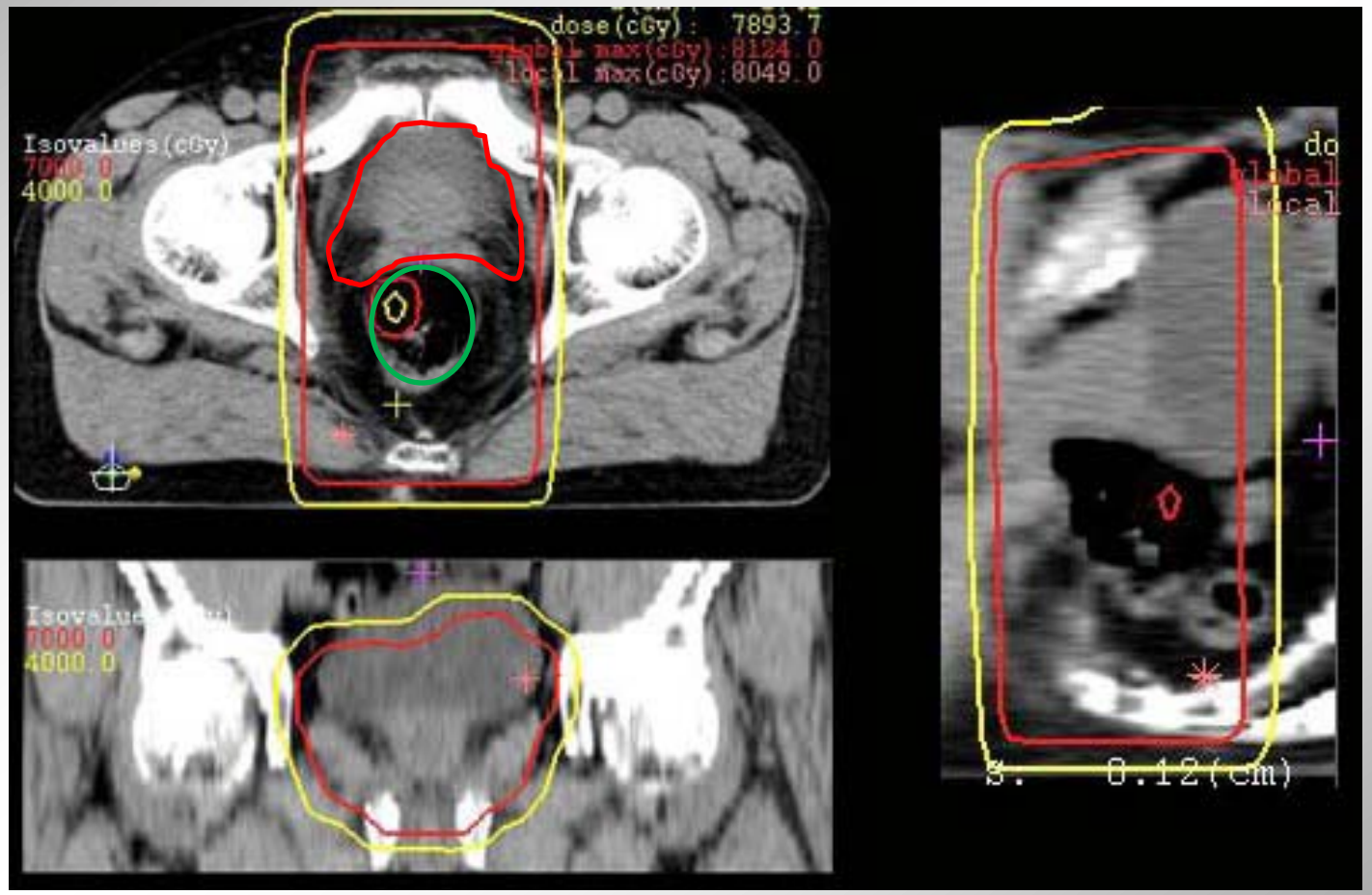
  beams with *non-uniform* intensities, a **concave intersection**





Conventional radiotherapy

Two opposing beams



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

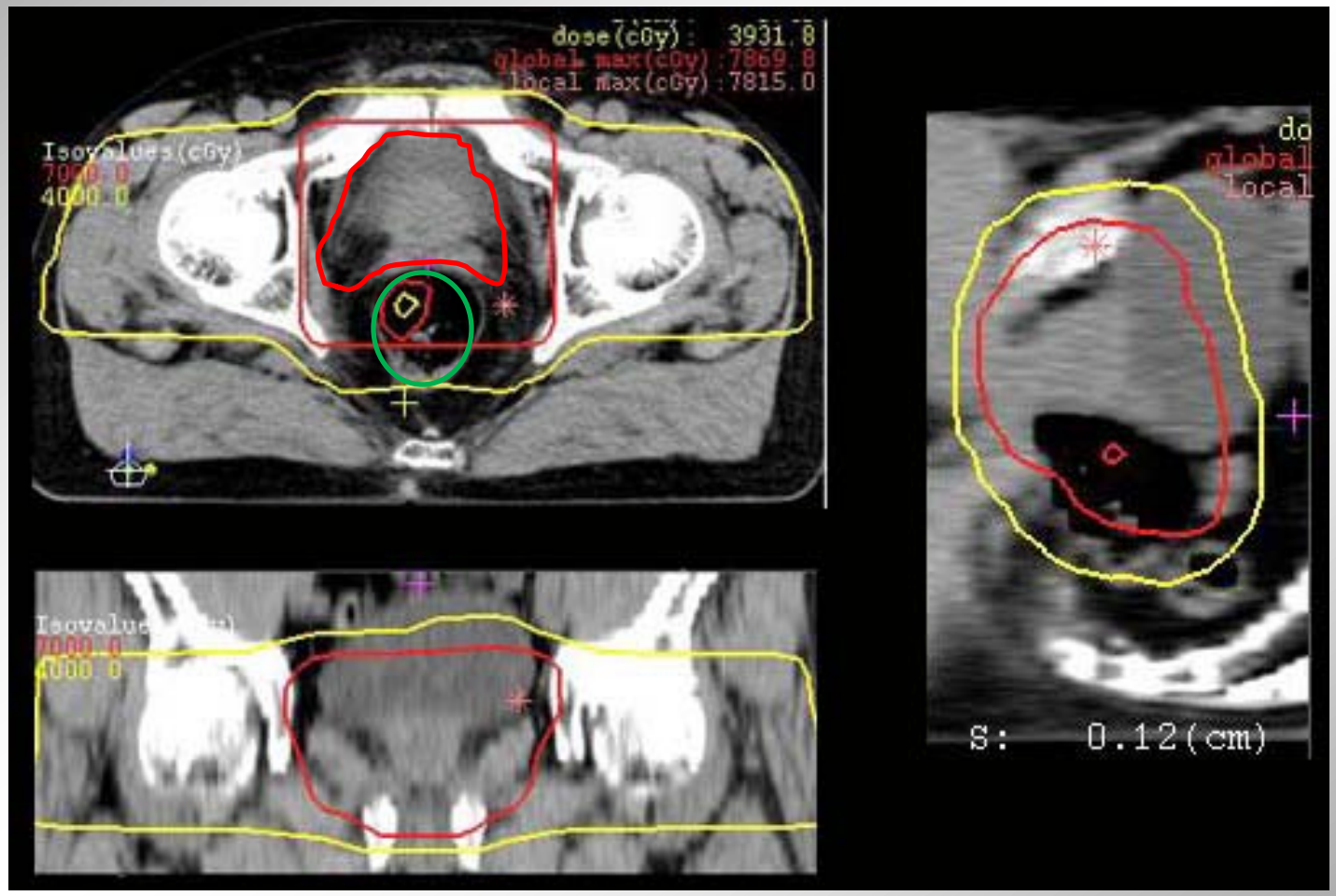
Dose to prostate limited because of rectal exposure.

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

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

CRT uniform intensity

Four beams (AP;RL)



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

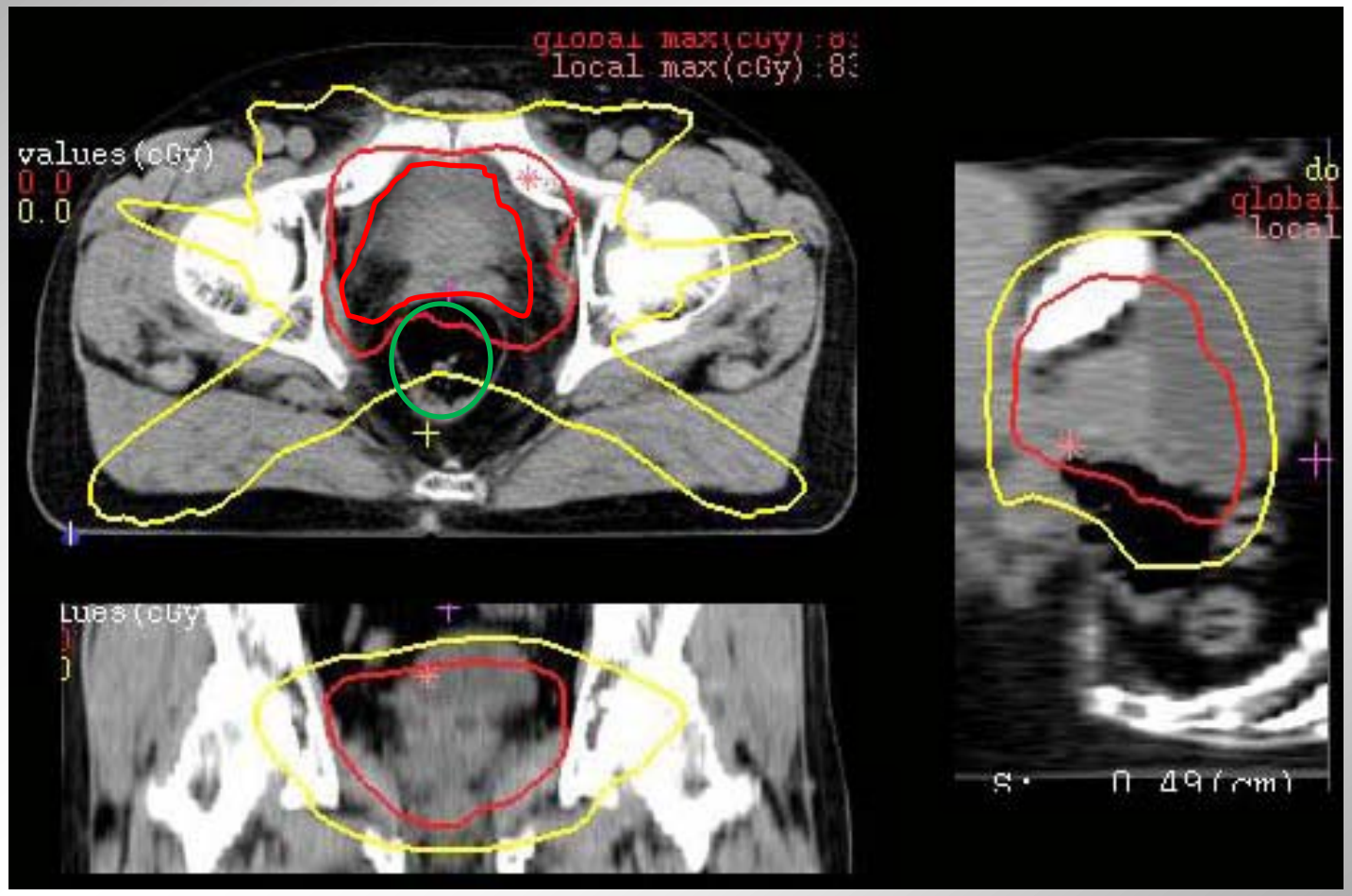
Better target conformity and sparing of rectum in some directions

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

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

CRT IMRT

Five beams



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

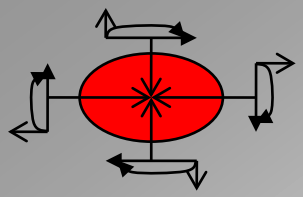
Increased target conformity and sparing of rectum in all directions

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

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

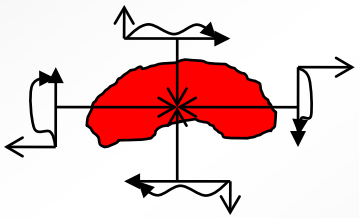
First patient treated with the IMRT-technique in Huston, Texas 1994;

first patient in Göteborg at the Sahlgrenska University Hospital 2003.



Summary #1

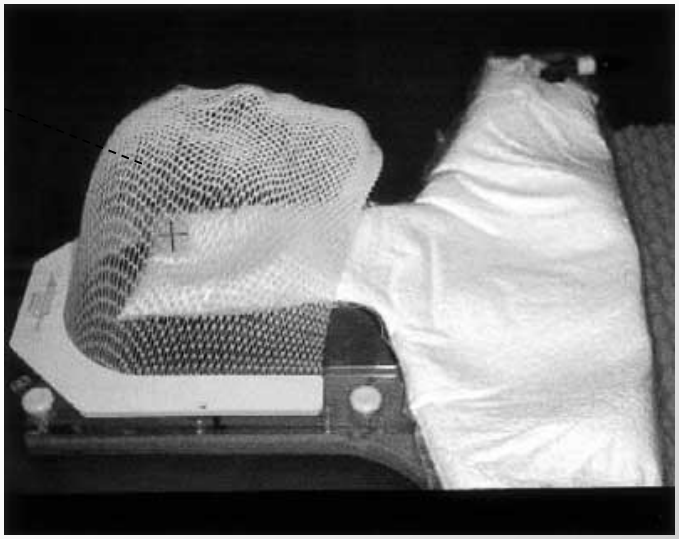
History of radiation therapy



- Ionizing radiation used to treat cancer since ~1900
- Today, X-rays are electronally produced using LINACs
- Conventional radiation therapy
  - *rectangularly-shaped fields with additional blocks and wedges*
  - dose to tumour ↓ because irradiated normal tissue ↑
- Conformal radiation therapy
  - *more convenient geometric field shaping using MLC*
  - dose to tumour ↑ because irradiated normal tissue ↓
- IMRT
  - *varied intensity beamlet-by-beamlet using physical compensators or MLC*
  - dose to tumour ↑ ↑ because irradiated normal tissue ↓ ↓

The IMRT process

Patient fixation

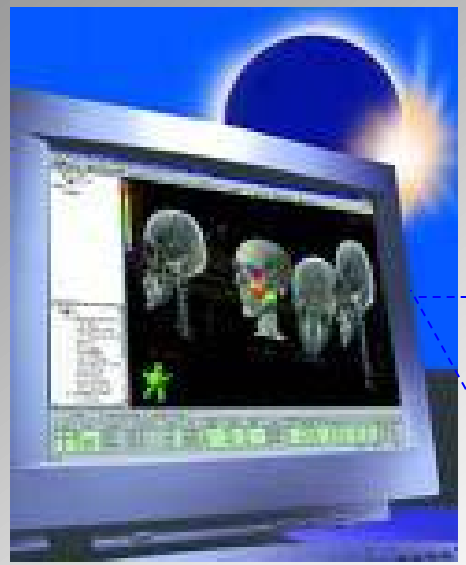


- Treatment is often delivered once or twice daily during a 3-5 week period

  => **reproduction of patient positioning cruicial**

- Aids for patient positioning by body molds such as vaacum cradels, face masks, etc.

The IMRT process



Patient fixation

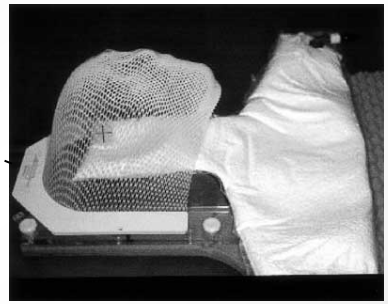
⇩

CT/imaging

⇩

Definition of target and OAR

⇩



- Three-dimensional representation of the patient

  => diagnostic CT-images transferred to the treatment planning system to create a 3D computerized electron density matrix used to calculate absorbed dose in tissue

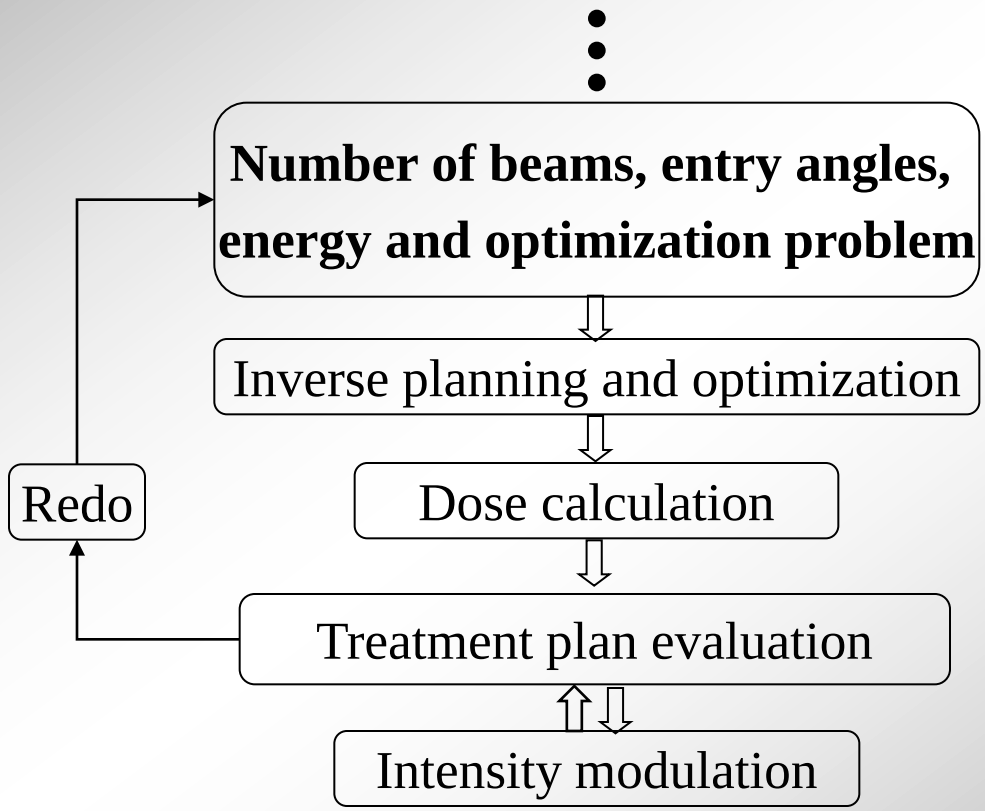
- Information about where the tumour is

  => Oncologist deliniates the tumour with surrounding margins (target) and the critical normal tissue (organs at risk, OARs)

The IMRT process

- Treatment planning for IMRT involves the definition of a given set up scenario…

=> determine # treatment fields, entry angles and energy – *fixed during optimization*



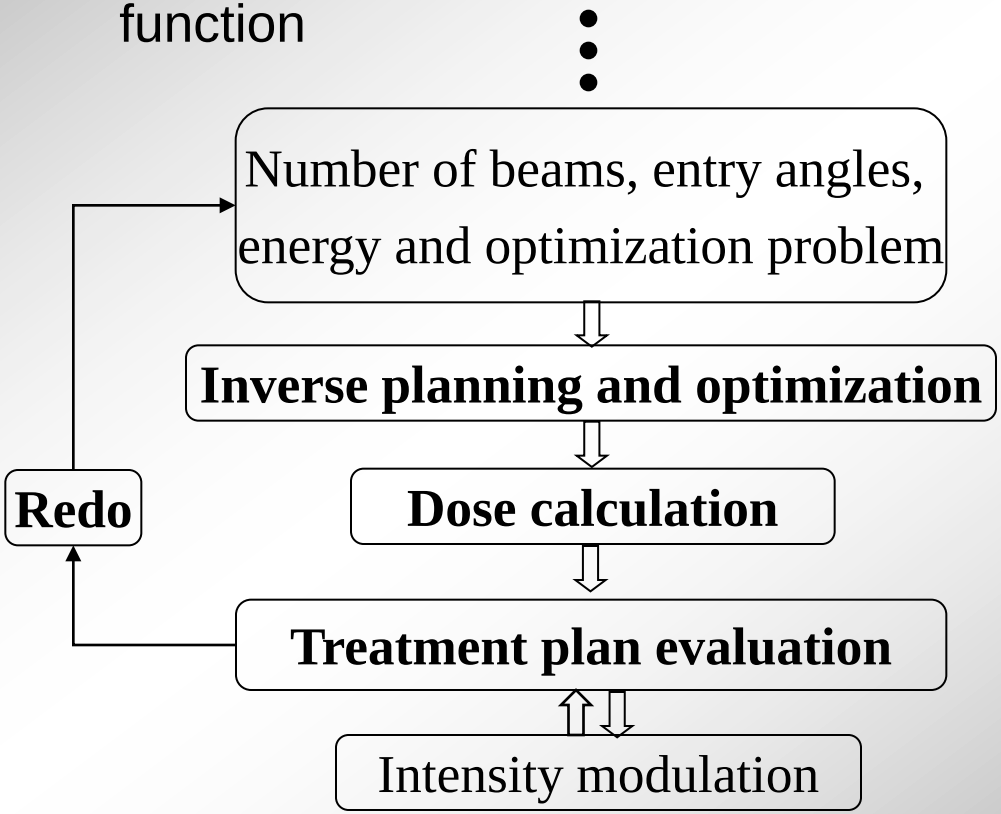
- … and an optimization problem often modeled as a constrained optimization problem
  - objective function minimized/maximized subject to certain constraints
  - physically or biologically based

The IMRT process

- Goal of optimization is to find the treatment plan that best meets the goals stated in the optimization problem

1. calculate 3D dose distribution for initial/current set of parameters (beamlet intensities)

2. reduce 3D dose distribution to a single number via the objective function



3. convergence criteria fulfilled?

a) yes => solution found or objective function value between two successive iterations ”small enough”; goto 4

b) no => suggest new beamlet intensities; goto 1

4. Satisfied with suggested dose distribution?

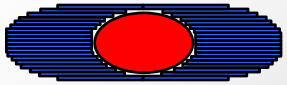
a) yes => done!

b) no => redo!

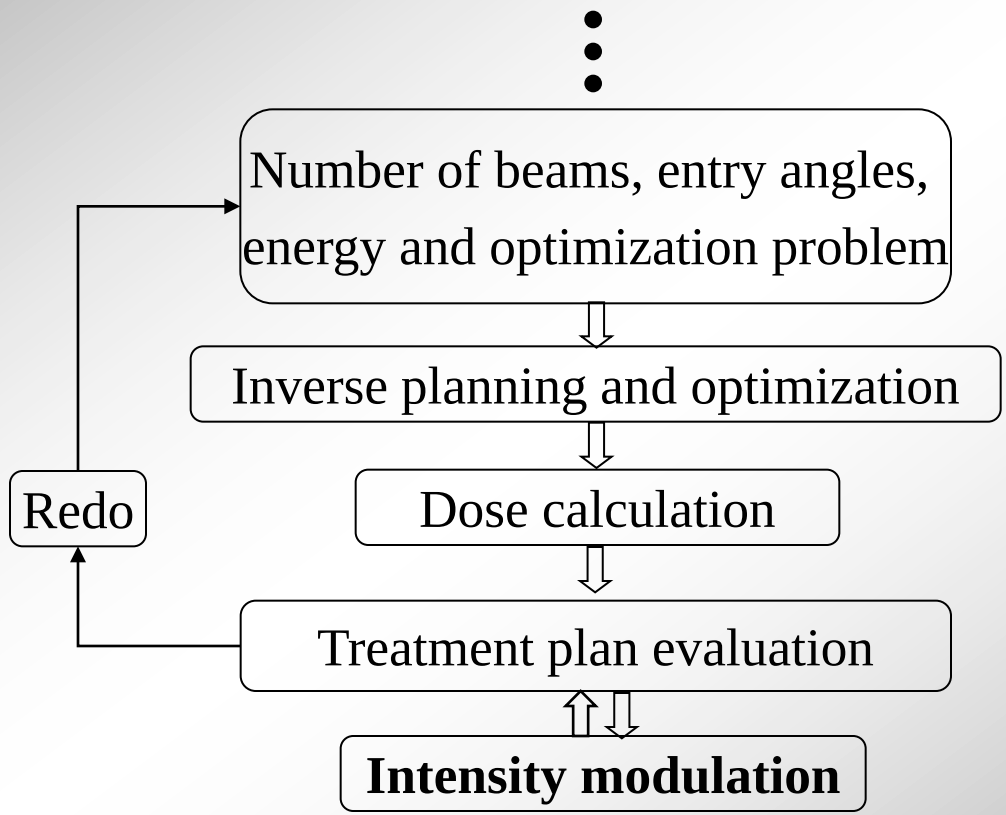
The IMRT process

- Intensity modulation is achieved by fabrication of complex physical compensators to be placed in the beam between the radiation source and the patient or..

.. by MLC



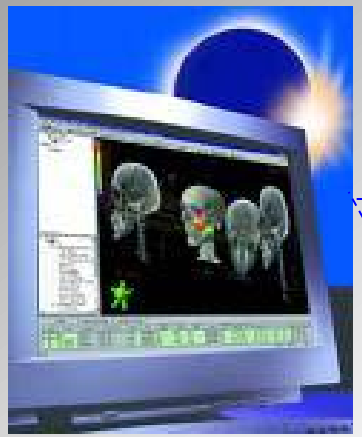
- dynamically moving during treatment
- statically altered in shape for each treatment field

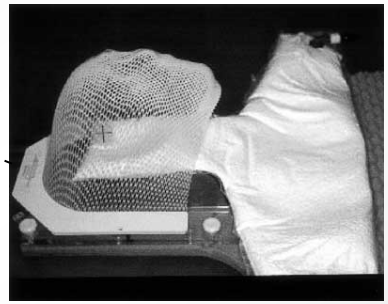


Conversion of an optimal treatment plan to a deliverable plan degrades the quality (collimator leakage, scatter and transmission) and is therefore sometimes included into the formulation of the optimization problem

Summary #2

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

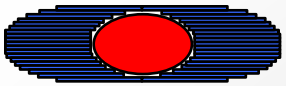
Treatment plan evaluation

Intensity modulation

Redo

Quality assurance

Treatment



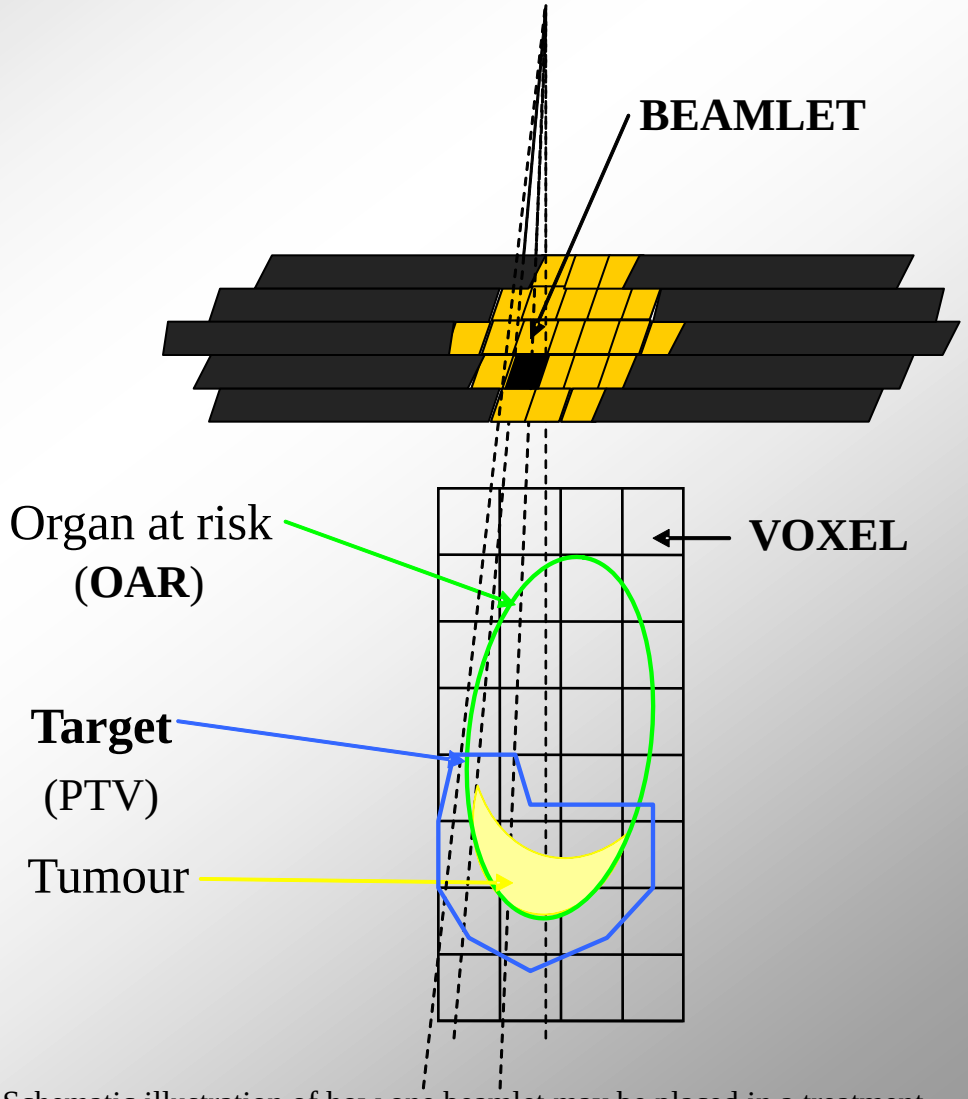
Inverse planning for IMRT

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

Methodology proposed 1988 by a Swede, Anders Brahme

Inverse planning for IMRT

- Each beam divided into **beamlets**
  - >>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 ~0.125 mm^3
- Typically, the dose contribution of one beamlet is to a small number of voxels in its neighbourhood



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

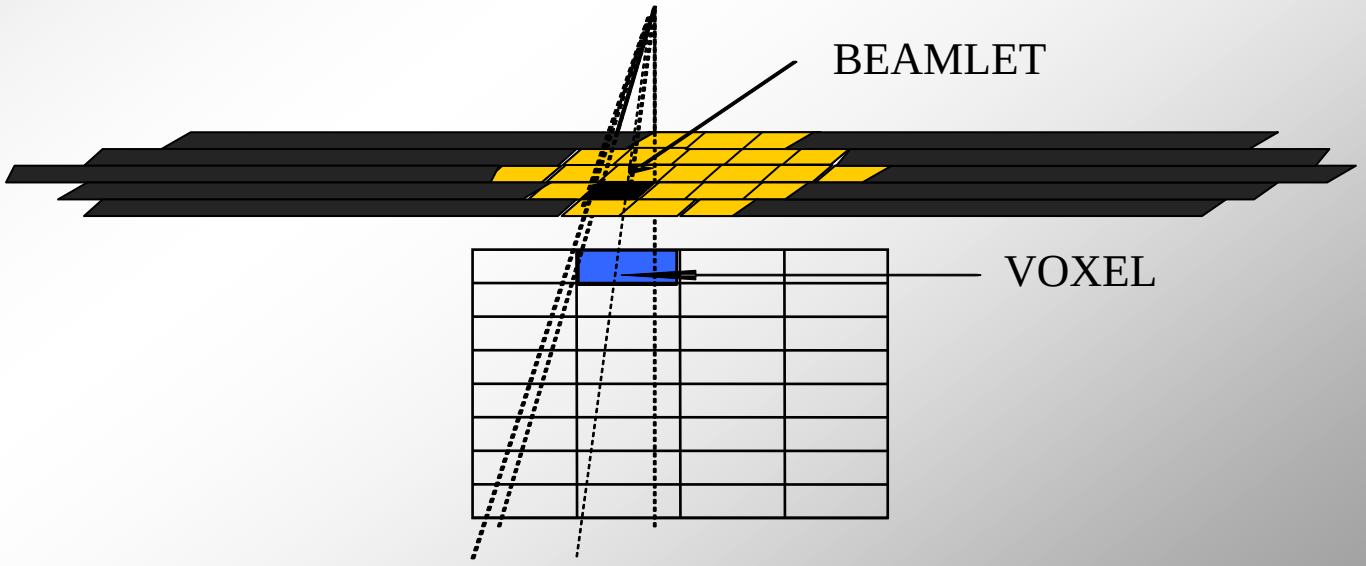
- Dose, d_i, in a voxel *i,* is the sum of dose contributions, K_{ij}, multiplied by their weights, w_j, from all the beamlets (*j*) taken over all the beams

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

d_i=dose in voxel *i*

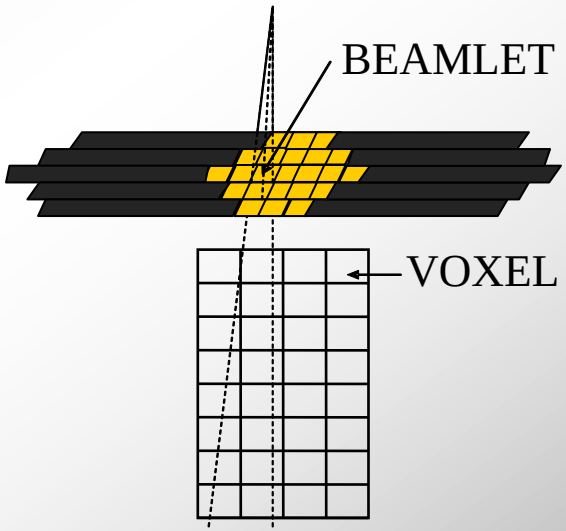
w_j=intensity level (weight) of beamlet *j*

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



Inverse planning for IMRT

- Elements in **K** (influence matrix) depend on the physics of photon-tissue interaction and are precalculated using dose calculation algorithms that simulates the effects of a beam of ionizing radiation penetrating through human tissue

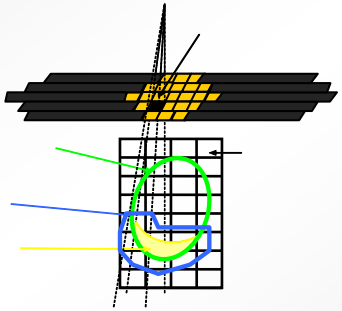


- Inversion of **K** to find beamlet weights NOT appropriate
  - negative weigths
  - **K** matrix too large
  - It takes too long…

Assumed linear relationship between beam intensity and dose in a voxel; the optimzation parameters are the beamlet intensities (weights)

Summary #3

Inverse planning for IMRT



- Finding the dose distribution best meeting the specified criterias by optimizing over the beam intensities
- A beam in divided into beamlets
- A volume is divided into voxels
- $d_i = \sum_j K_{ij} w_j$
  - The dose vector ***d*** holds the dose of each voxel
  - The influence matrix ***K*** holds the dose contribution to all voxels from all beamlets
  - The weight vector ***w*** is to be optimized

Physical optimization criteria

- Optimization problem formulation

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

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

  (*iii*) Target and OAR objective function

- Optimization criteria involves constraints to the target and OARs and are determined in terms of doses and irradiated volumes
  - Dose limits
    - Maximum dose
    - Minimum dose
  - Limits on volumes receiving certain specified dose
    - DVH

Physical optimization criteria

- A strict fulfillment of a set limit is usually too restrictive
  => **penalty factors**

- Magnitude of penalty associated with the severity of the consequence of violation
  - Mild complication - soft constraints (may be violated)
  - Severe complication - hard constraints (may NOT be violated)

Physical optimization criteria

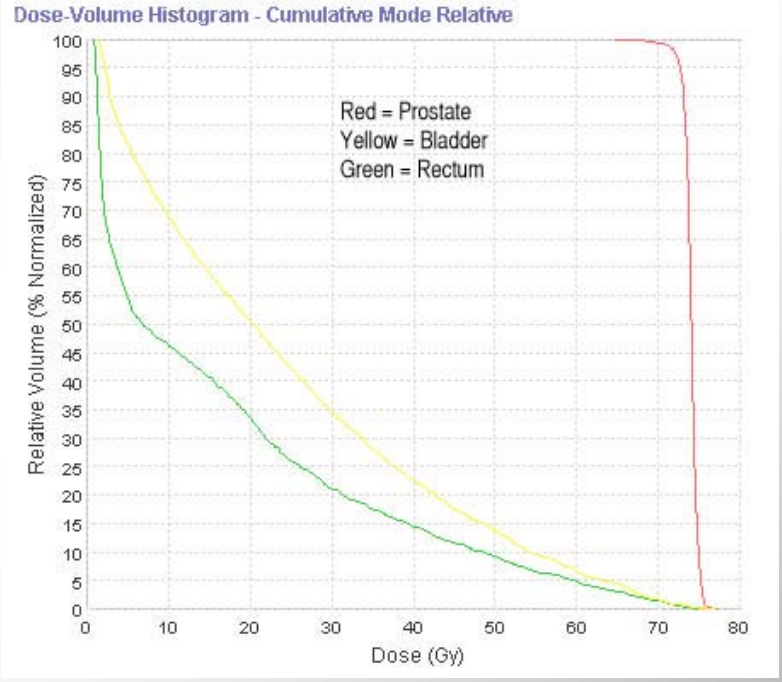
- Some volumes of interest may be of more interest

  => **relative importance factors (weights)**

- Magnitude of importance will bias the optimization algorithm to select the treatment plan that favors one or more selected volumes of interest
  - Less important – low importance factor
  - More important – high importance factor

Physical optimization criteria

- Dose limits are set by defining points on a dose-volume histogram (DVH)
- A DVH is the 2D representation of the 3D dose distribution showing the irradiated volume at each dose level



DVH over a prostate treatment

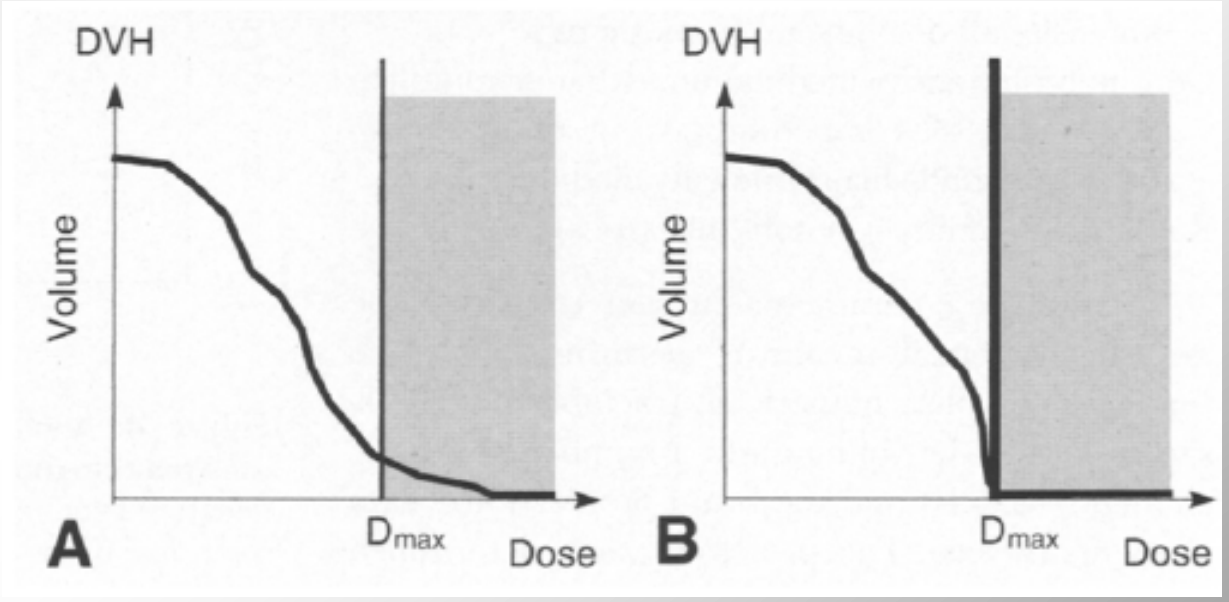
Physical optimization criteria

Maximum dose limits

- A **maximum dose limit** for the dose to be less than or equal to a tolerance threshold in any voxel of the volume (target or OAR) =>

$$d_i \leq d_{max}, \forall i \in V$$

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



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

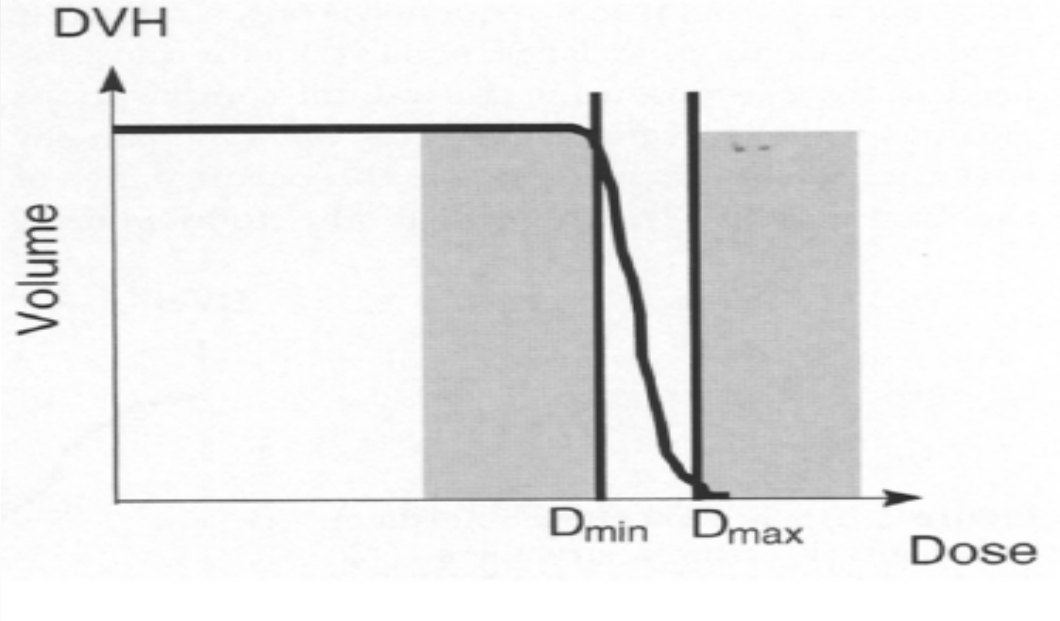
Physical optimization criteria

Minimum dose limits

- A **minimum dose limit** for the dose to be more than or equal to a tolerance threshold in any voxel of the volume (target) =>

$$d_i \geq d_{min}, \forall i \in V$$

Effect of **hard (minimum)** and **soft (maximum) constraint**



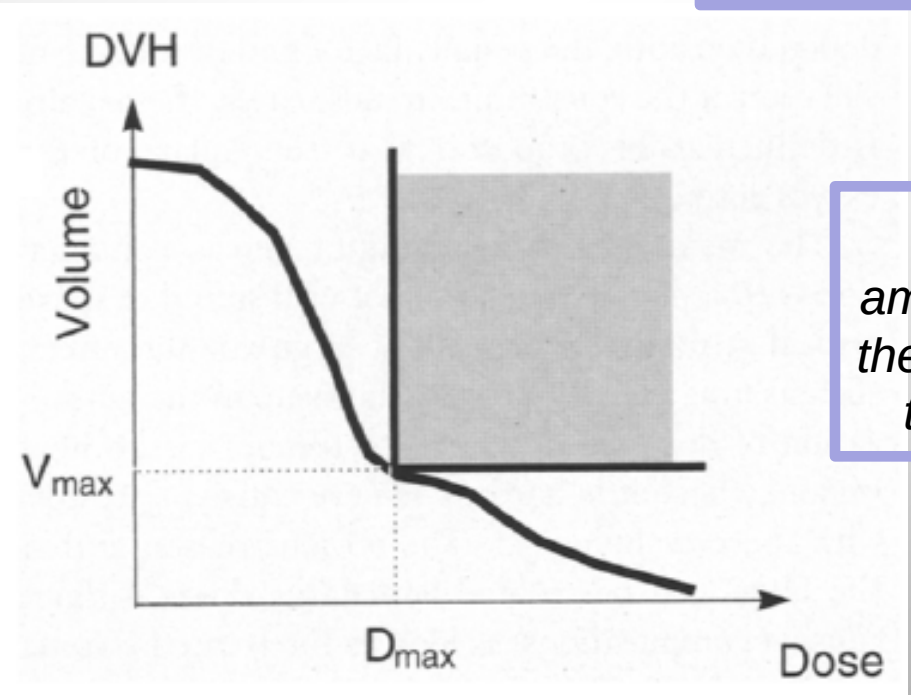
Bortfeld T.: *Optimized planning using physical objectives and constraints.* Seminars in Radiation Oncology, Vol 9, No 1, 20-34, 1999.

Physical optimization criteria

DVH limits

- A DVH limit for the dose to a subvolume of a structure to be less than a tolerance threshold
- No more than V_{max} % of the volume should receive a dose of d_{max} =>

$$d_i \leq d_{max}, \ \forall i \in V_{max}$$



V_{max} controls the amount of voxels, NOT their specific position in the 3D dose matrix

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

Physical optimization criteria

Objective function example (*iii*)

The objective function is represented by structure specific subfunctions for the target and the OARs with attached relative importance factors

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

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

$F_{\text{OAR,k}}$ = OAR objective function

Physical optimization criteria

Target objective function

The target sub-function includes the target prescription dose and dose-uniformity limits

$$F_{\text{target}} = \frac{1}{N_t}\left(\sum_{i=1}^{N_t} \left[d_i - d_{presc} \right]^2 + c_{t,\min} \sum_{i=1}^{N_t} \left[d_i - d_{min} \right]^2 \bullet H\left(d_{min} - d_i \right) + c_{t,\max} \sum_{i=1}^{N_t} \left[d_i - d_{max} \right]^2 \bullet H\left(d_i - d_{max} \right) \right)$$

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

*Heaviside function**

$$H(d_1 - d_2) = \begin{cases} 1, d_1 > d_2 \\ 0, d_1 \le d_2 \end{cases}$$

Physical optimization criteria

*Heaviside function

- Has the impact that a function only contributes to the objective function score when it is violated in the wrong direction

- For a **minimum** dose limit, Heaviside is activated when the calculated dose is **below** the given limit

- For a **maximum** dose limit, Heaviside is activated when the calculated dose is **above** the given limit

Physical optimization criteria

OAR objective function

The OAR sub-functions include maximum dose and DVH-limits

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

N_O = number of voxels in OAR

d_{max} = maximum dose to voxel i

d_{dv} = maximum dose to voxel i, $i \epsilon N_{dv}$

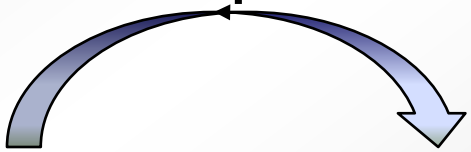
$c_{O,max}$ = penalty weight for overdosage

$c_{O,dv}$ = penalty weight for violation of dose-volume constraint

N_{dv} = number of voxels in OAR where dose must be below the DVH constraint

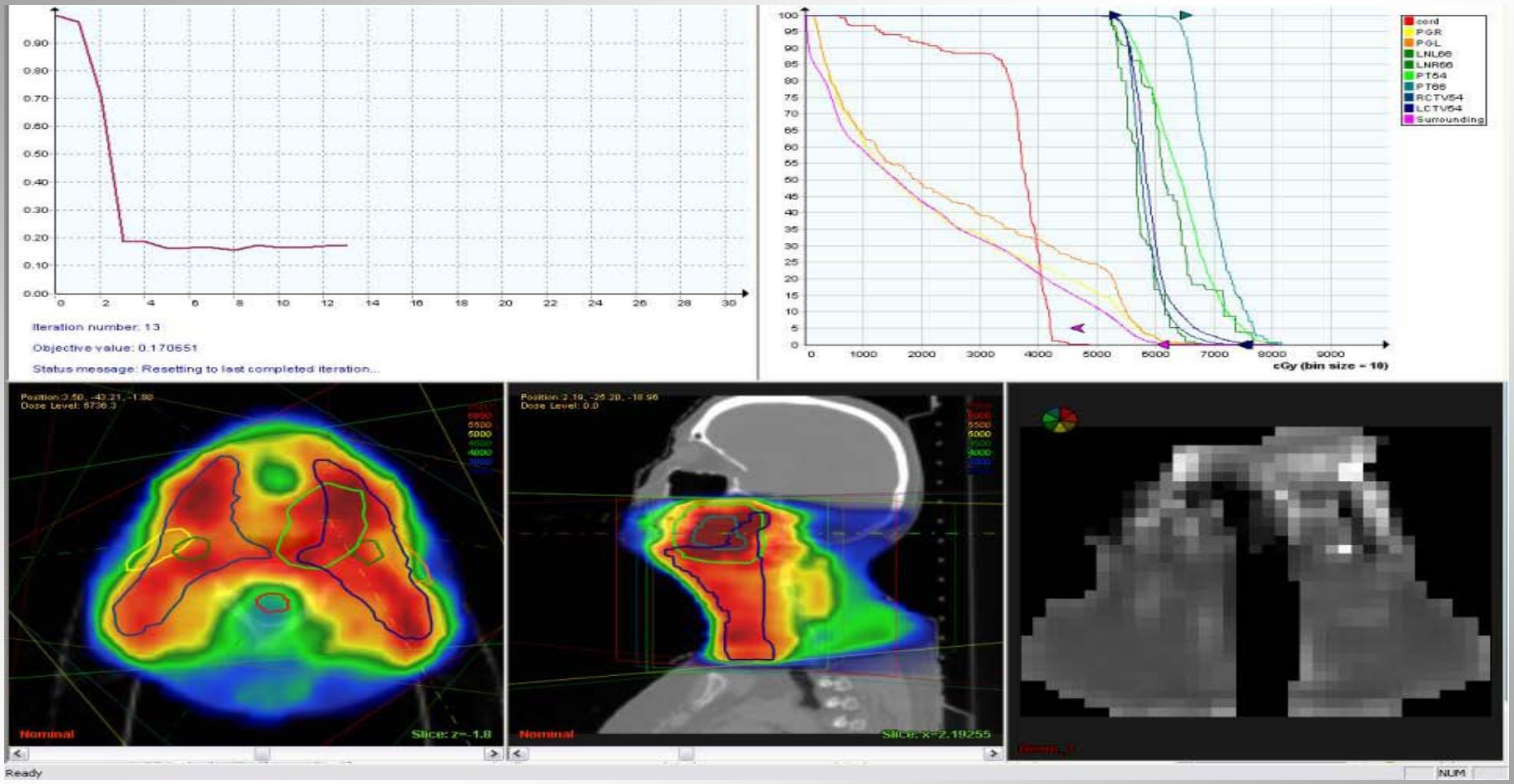
IMRT treatment planning system

- Using software for inverse planning of IMRT, each criterion that defines the patient specific optimization problem will be given as dose values or placed as points in a DVH



- The structure specific criterions will then automatically be converted to voxel-specific doses by the software

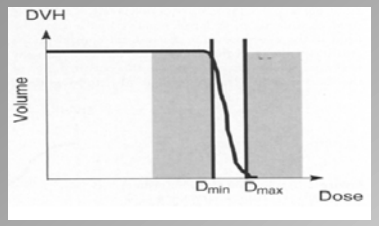
IMRT treatment planning system



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

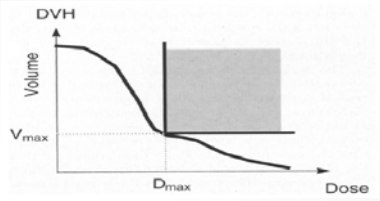
IMRT treatment planning view – reflects dose distribution state at the 13:th iteration

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



Summary #4

Physical optimization criteria



- Problem formulation
  - Target objective function + contstraints on OARs
  - OAR objective function + constraints on target
  - Target and OAR objective function
- Penalty factors associated with severity of consequence of violation
- Relative importance factors to favor selected volumes of interest
- Dose limits
  - Maximum – whole volume
  - Minimum – whole volume
  - DVH – partial volume

- Typically, quadratic dose differences and the Heaviside function are used in the problem formulation

Radiobiology

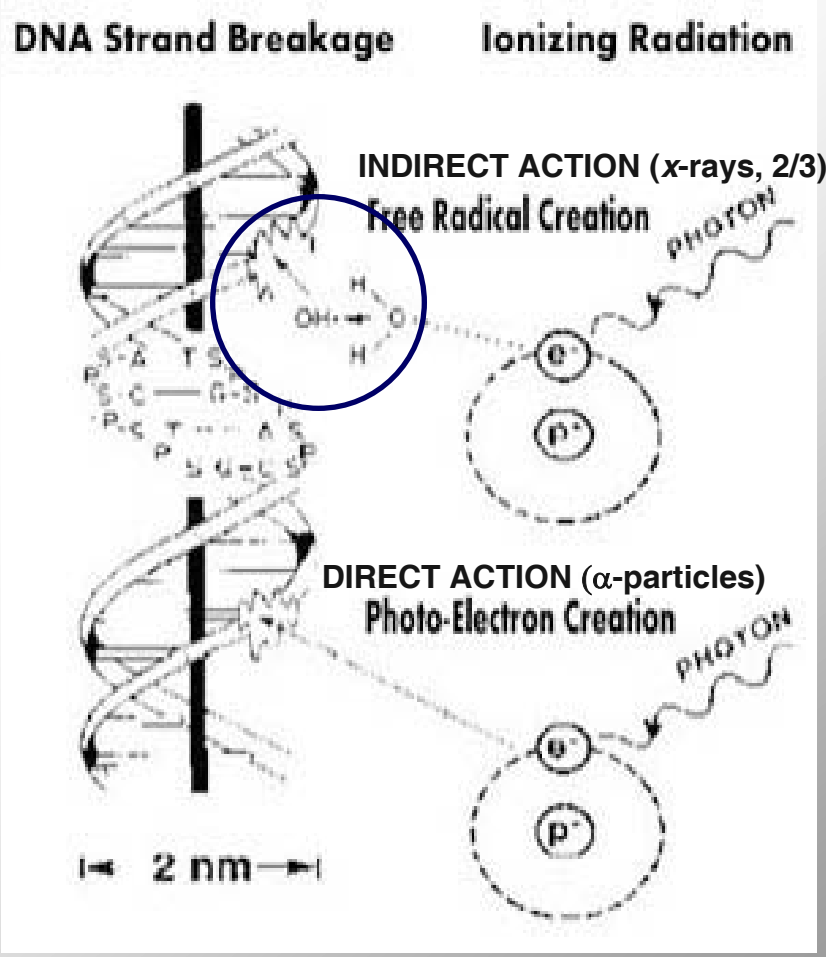
What happens in the body after radiotherapy?

- When radiation is absorbed in biological material there will be interactions with atoms and molecules in the tissue (excitations and ionisations)

- Released e^- may break chemical bonds and produce free radicals that are highly reactive

- Free radicals cause damage (double strand breaks) on the DNA in the cells which may eventually lead to cell death => biological damage

Tumour cells have less repair capacity than normal tissue



•Hall (1988): The oxygen fixation hypothesis.

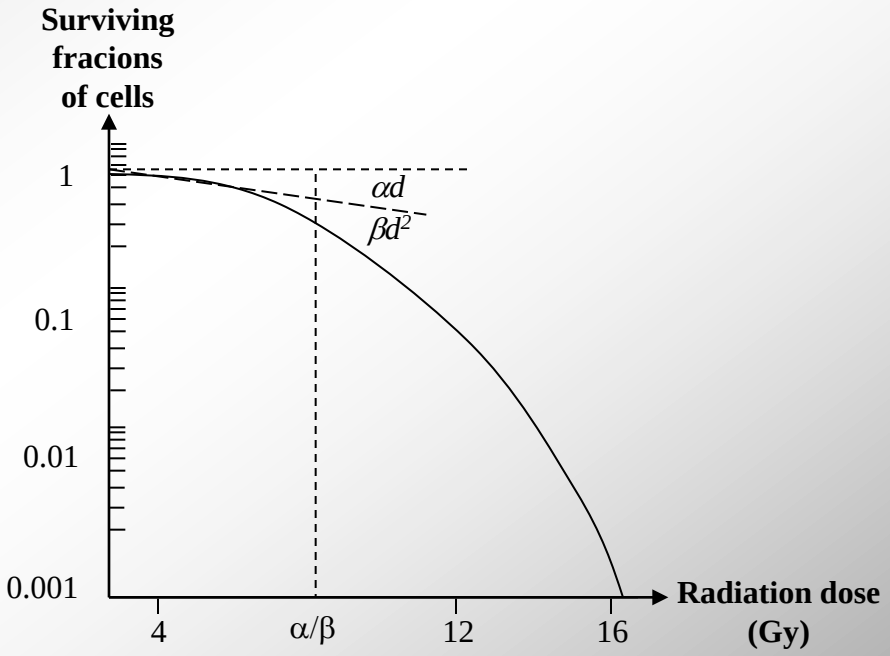
Radiobiology

Linear-quadratic (LQ) model

- The cell survival curve describes the relationship between the radiation dose and the proportion of cells that survives

- 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.

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



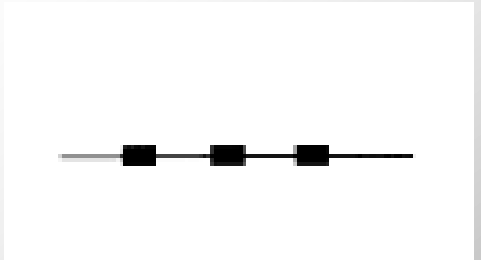
LQ model used to compare the biological effect of different treatment fractionation schedules

Radiobiology

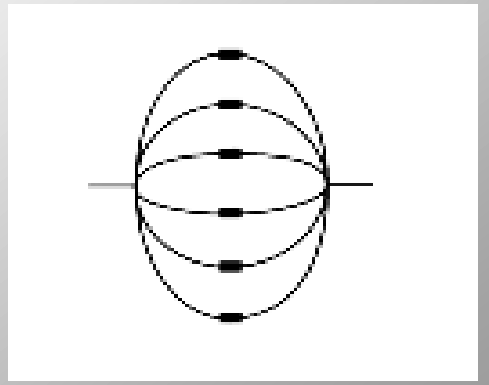
Tissue architecture

- The tolerance to irradiation in a tissue depends on
  - the radiosensitivity of the cells in the tissue
  - the **structural organisation** of the tissue/organ and its ability to maintain organ function when damage occurs

- **Serial organization**
  - damage to **any** part of the organ will cause a complication e.g. spinal cord (ryggmärg)



- **Parallel organization**
  - damage to a **substantial fraction** of the organ is necessary to cause a complication e.g. parotid gland (spottkörtel)



Radiobiology

Volume effect

- The tissue architecture of an organ is closely related to its **volume effect**

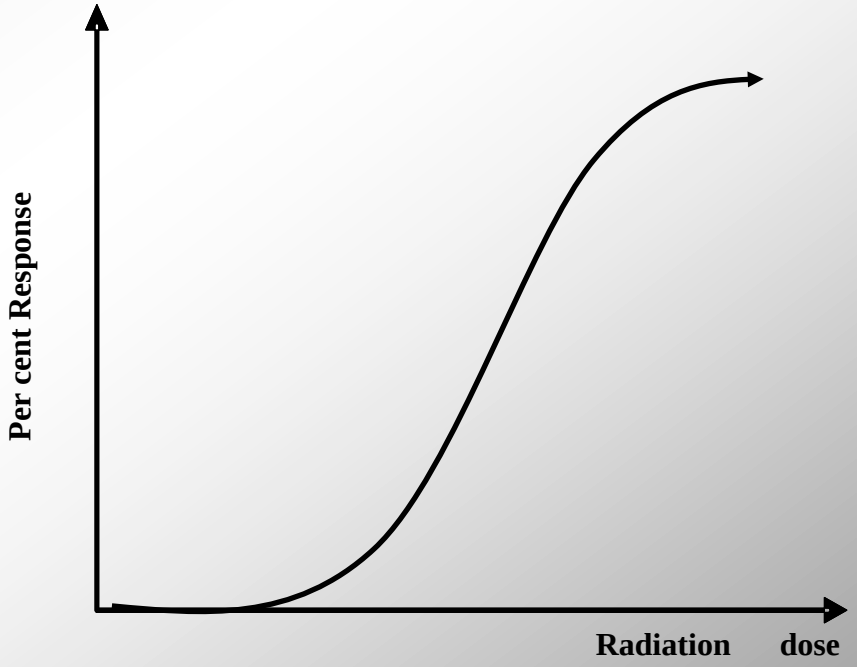
  => changes the tolerance dose of an organ

High dose to a small part of the organ may be well tolerated; same dose to whole organ not tolerated at all…

- **Serial organization**
  - small volume effect - maximum dose important
- **Parallel organization**
  - large volume effect - mean dose important

Radiobiological modeling

- Radiobiological models relate dose plus volume of irradiated tissue to predict a biological response
- Clinical and animal data show that this relation follows a sigmoid curve
  - low probability of response at low doses
  - high probability of response at high doses
- Steepness of curve gives estimate of change in response for a change of dose



Radiobiological modeling

- Basic requirements of a radiobiological model
  - the sigmoid shape,
  - volume effect
  - fractionation effect
  - non-uniform dose distributions

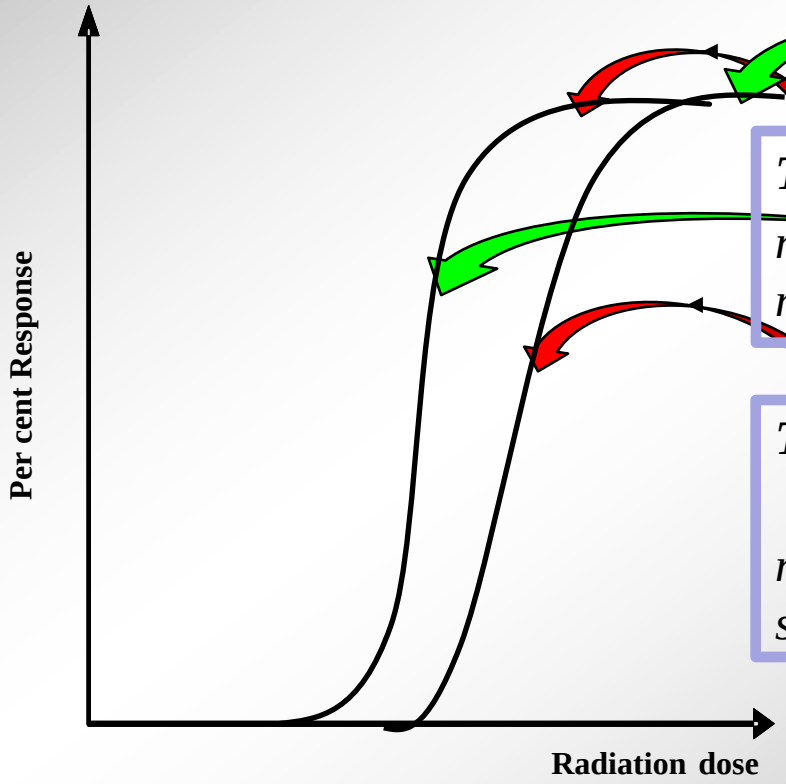
- **Mechanistic models** are developed based on our best understanding of the underlying biological process, i.e. the cell kill (LQ model) and/or other known interactions of radiation with cells and DNA

- **Phenomenological models** are based on the observed characteristics of the dose-volume-response curve , i.e. fitting functions to clinical data BUT…

  only valid for situations described by original data

Radiobiological modeling

- Different models for tumours and OARs
- Tumour probability control (TCP) models for tumurs
- Normal tissue complication (NTCP) models for OARs



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?

Radiobiological modeling

Mechanistic model

- Damage induction considered stochastic and well modeled by Poisson statistics
- All cells are assumed to respond identically
- Tumour/OAR response is assumed to depend on individual cells
  - TCP=1 when there are no clonogenic cells left in tumour
  - NTCP=1 when the critical amount of cells in OAR are lost

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

P = probability of response

D = total dose

N_0 = initial number of clonogenic or critical amount of cells

α = linear coefficient of LQ-model

β = quadratic coefficient of LQ-model

d = dose/fraction

Non-uniformly irradiated organs handled by taking product of subvolumes where dose can be considered uniform

Radiobiological modeling

Phenomenological models

- Probit model (1)
  - based on the cumulative normal distribution
  - mainly used for normal tissue

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

D = total uniform dose to volume v

v = volume irradiated

- Logit model (2)
  - based on Logistic regression
  - used for both tumours and normal tissue

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

D = total uniform dose to volume v

v = volume irradiated

- The top limit in the integral in the Probit model and the exponent in the Logit model?

Radiobiological modeling

Phenomenological models

- … are given by

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

where *m* is inversely proportional to the slope of the dose-volume-response curve;

$TD_{50}(v)$ is the tolerance dose giving a 50 % probability of effect for *uniform* irradiation of volume v assumed to be related to *uniform* whole organ irradiation by

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

and *n* is the volume effect parameter

Radiobiological modeling

Phenomenological models

- Non-uniformly irradiated tissue to uniformly irradiated tissue handled by using DVH reduction schemes

- Non-uniform dose distributions are reduced to a uniform dose distribution assumed to cause the same biological effect by
  - Effective volume – maximum dose to smaller volume of organ
  - Effective dose – reference dose to whole organ

Effective dose also known as generalized equivalent uniform dose (gEUD)

Radiobiological modeling

gEUD

- 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

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

D = total dose

a = tissue specific volume parameter

N = number of voxels in tissue

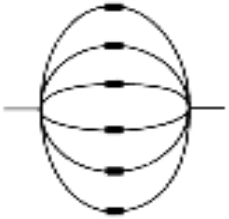
D_i = dose in voxel i

gEUD is not a sigmoid function and does not predict a response, however, it is a convex function…

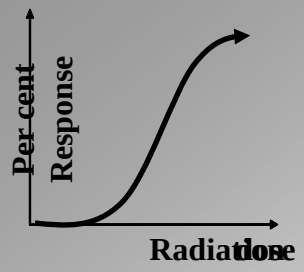
- $a < 0$: minimum dose (tumour)
- $a \approx 1$: mean dose (parallel tissue)
- $a \rightarrow \infty$: maximum dose (serial tissue)

Summary #5(1)

Radiobiology & Radiobiological modeling

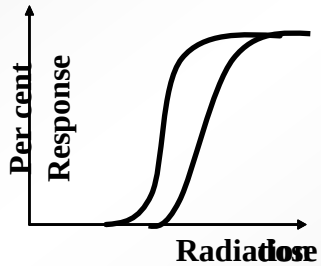


- Cells die because of damage to the DNA
  - Tumours have less repair capacity than normal tissue
- The cell survival curve after irradiation is well modeled by the LQ-model $SF(d) = e^{-(\alpha d + \beta d^2)}$
- Tolerance to irradiation for tissue depends on radiosensitivity and structural organization
  - Serial tissue – small volume effect; maximum dose important
  - Parallel tissue – large volume effect; mean dose important



Summary #5(2)

Radiobiology & Radiobiological modeling



- Radiobiological models relate dose and irradiated volume to predict a biological response
  - Sigmoid shape
  - Volume effect
  - Fractionation effect
  - Non-uniform dose distributions (DVH reduction schemes: $gEUD(\mathbf{D},a)=\left(\frac{1}{N}\sum_{i=1}^{N}D_i^{\,a}\right)^{\frac{1}{a}}$)

- Mechanistic models based on understanding of radiobiology

$$P(D)=\mathrm{e}^{-\mathrm{N}_0 e^{-\alpha D-\beta dD}}$$

- Phenomelogical modes based on fitting data to observed characteristics, e.g.

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

Biological optimization criteria

- Radiobiologically based function gives a better representation of the biological consequences of the dose distribution

- Optimization problem formulation

  (*i*) Target objective function + constraints on OARs
  (*ii*) OAR objective function + constraints on target
  (*iii*) Target and OAR objective function

- Optimization criteria involves estimated biological effects in tumours and OARs and are determined in terms of probability of an effect
  - TCP
  - NTCP

… may also include maximum, minimum and/or DV dose limits

Biological Optimization Criteria

Objective function example (*iii*)

- The objective function includes combinations of the Logistic function and the gEUD function for both target and OARs
- Target sub-function includes the gEUD prescription dose and a relative importance factor
- OAR sub-functions include the gEUD limit dose and relative importance factors

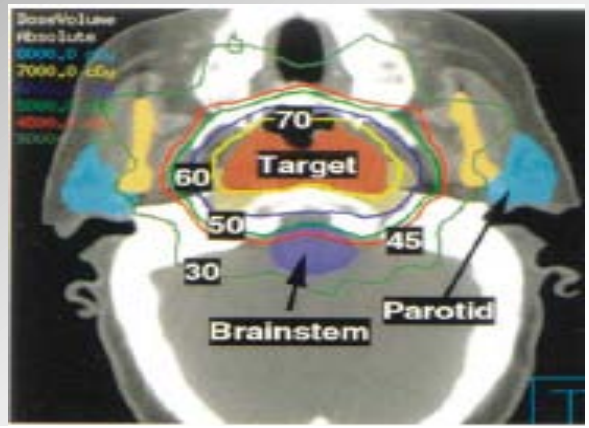
$$F = F_{\text{target}} \prod_{k} F_{\text{OAR}_k}$$

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

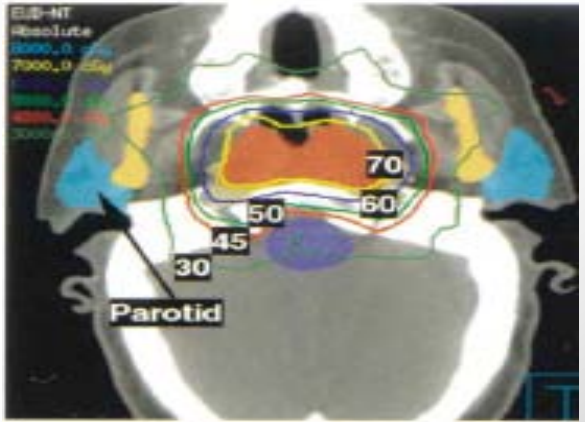
$$F_{\text{OAR}} = \frac{1}{1+\left(\frac{gEUD(\mathbf{d})}{gEUD_{presc}}\right)^{woar}}$$

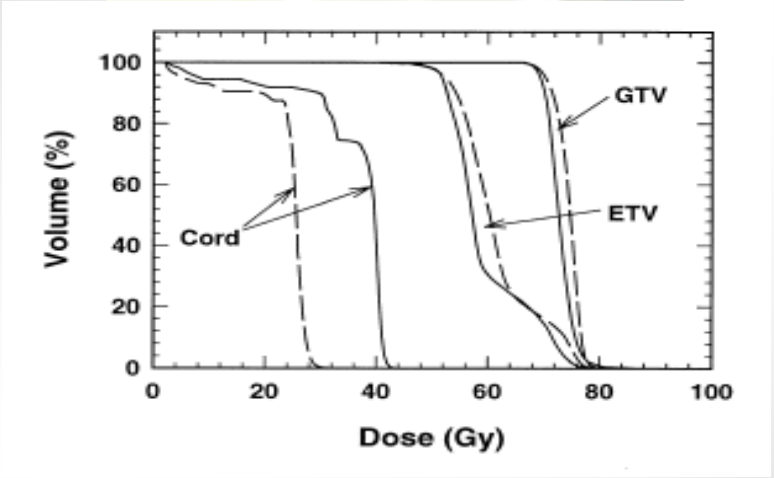
Biologically based optimization compared to physically based optimization

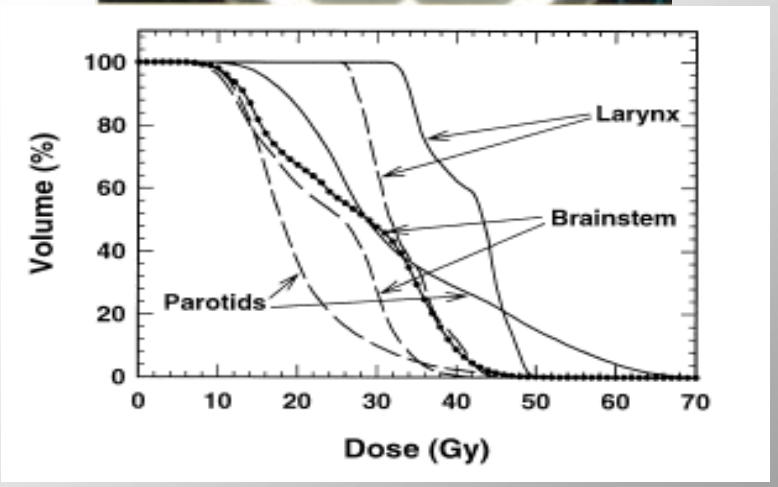
Physically based optimization



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.

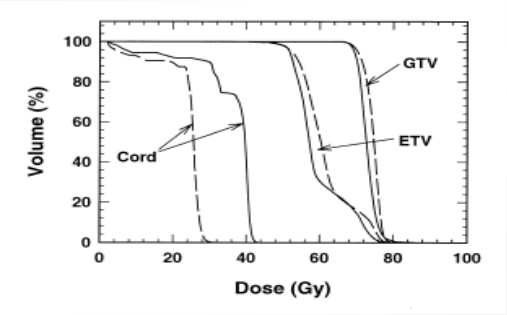
Aim of Head-and-neck cancer treatment: Conform the high dose to the target; spare the Brainstem and Parotid glands as much as possible

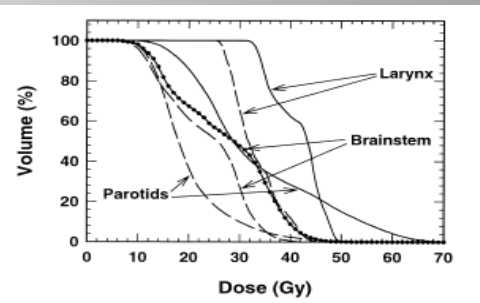
Yellow isodose = 100% of prescribed dose; Green isodose = ~40% of prescribed dose; Dotted line in DVH = BIO_OPT; Solid line= PHYS_OPT

Summary #6

Biological optimization criteria

- Problem formulation
  - Target objective function + contstraints on OARs
  - OAR objective function + constraints on target
  - Target and OAR objective function
- Physical dose limits may also be included
- Typically, TCP and NTCP models are used in the problem formulation

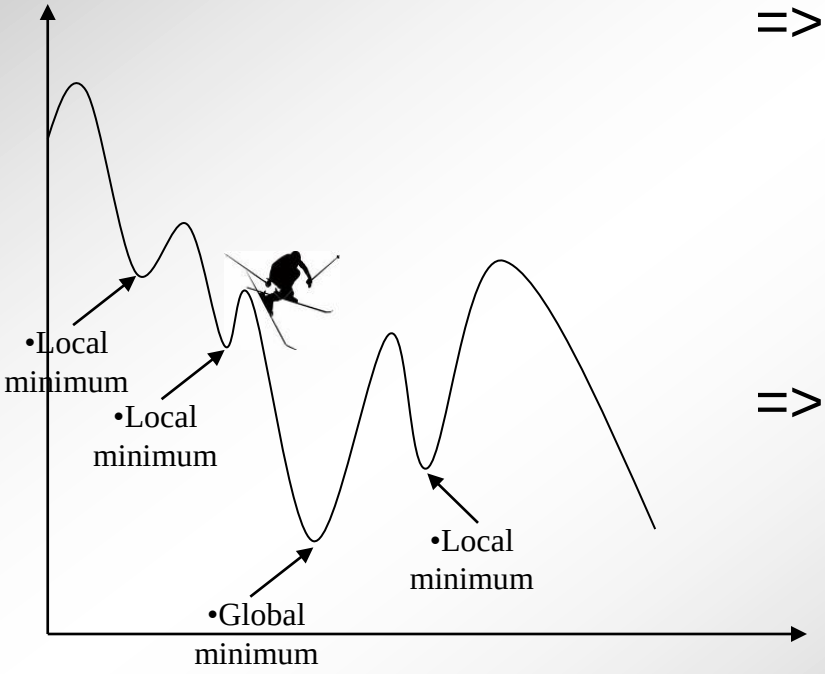




Optimization algorithms for IMRT

Global and local extreme points

- In both physically and biologically based optimization for IMRT, multiple extreme points can be present
- BUT, finding the global extreme point may not be important in a clinical application



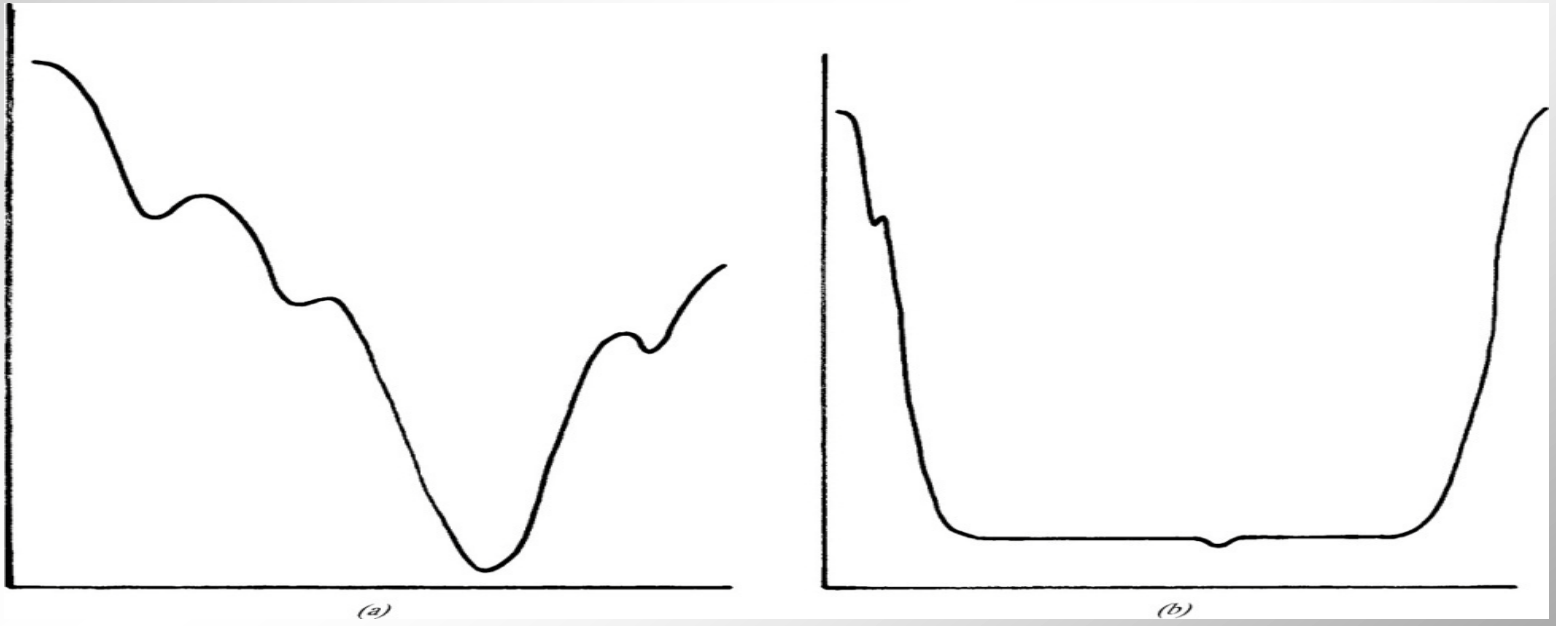
=> if a solution meets all the specified requirements, it is acceptable although it may not be the best possible solution

=> it may also be more desirable from a practical point of view – delivery of globally optimal == more complex plans may be more prone to mistakes

Optimization algorithms for IMRT

Global and local extreme points

- Objective function frequently encountered in IMRT (*b*) - many beam configurations correspond to similar dose distributions



Any *dose distribution that meets the given requirements might be clinically acceptable*

Optimization algorithms for IMRT

Deterministic methods

- The rules that determine the modifications made to the beam intensities in each iteration step does not contain any random element

- Converges to the nearest extreme point and are reasonable fast

  => typically less than 100 iterations

- Gradient optimization algorithms
  - Steepest descent
  - Conjugate gradient
  - (Quasi) Newton's method

Differs in the selection of gradient and step-size

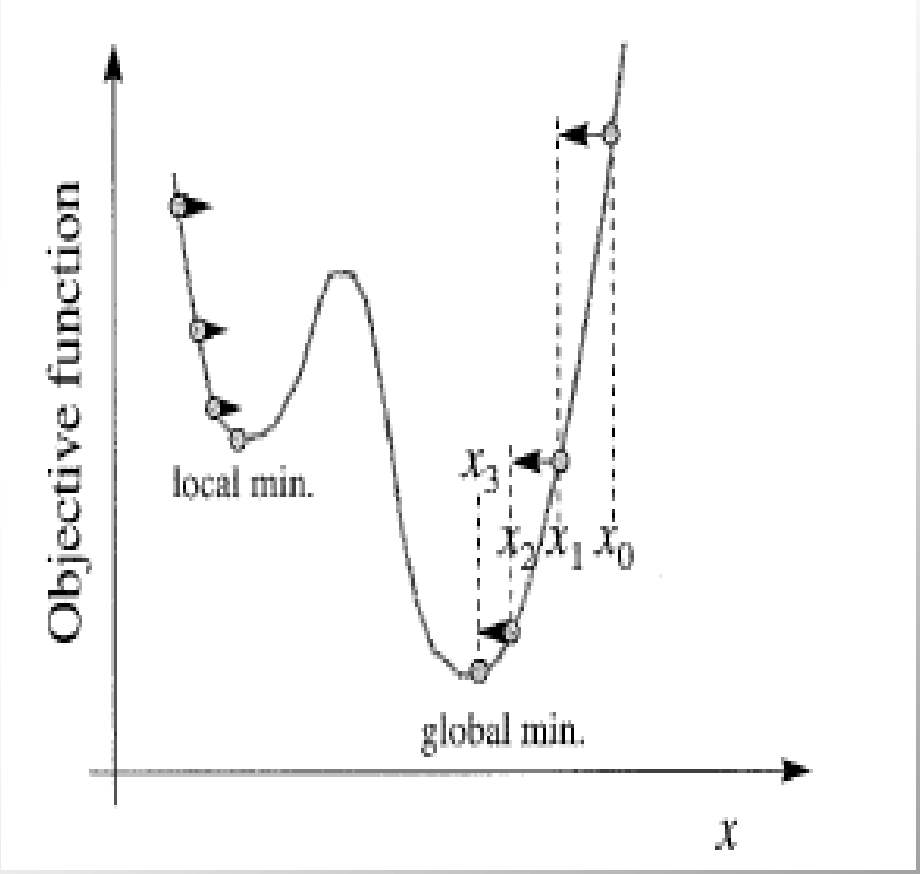
Optimization algorithms for IMRT

Gradient optimization algorithm

- **x** is the parameter to be minimized and the graph of the objective function measures the quality of the treatment plan
- Start in x_0
- At each iteration the beam intensities will be updated according to the rule

$$x_{i+1} = x_i - \alpha \nabla F(x_i)$$

- The algorithm follows the negative of the gradient of the objective function until the gradient becomes 0 at x_3



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

- The rules that determine the modifications made to the beam intensities in each iteration step involves an element of randomness - repeating the process with the same set-up and initial conditions will not necessarily yield the same result

- Element of randomness allows the escape from local extreme points but are slow

  => typically 10 000 iterations or more

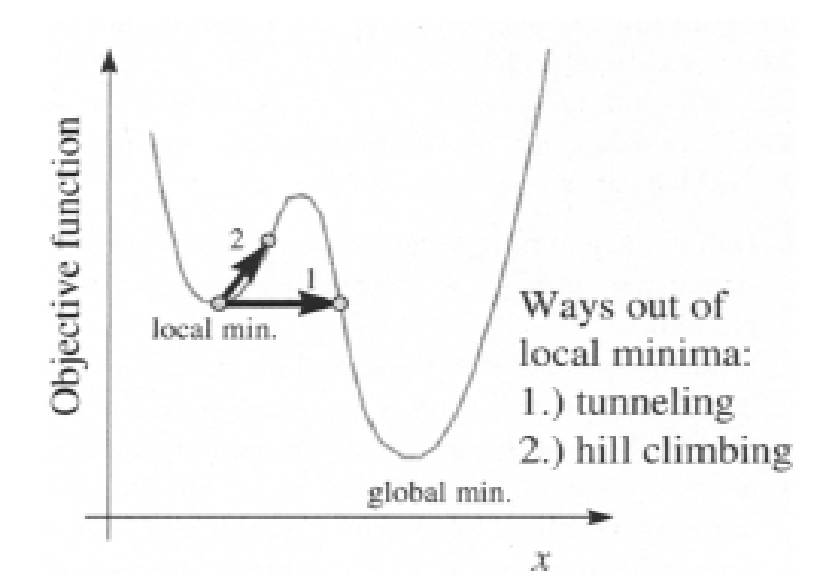
- Simulated annealing algorithm
  - Bolzmann annealing process
  - Fast simulated annealing process

Differs in the selection of cooling temperature speed and step-size

Optimization algorithms for IMRT

Simulated annealing

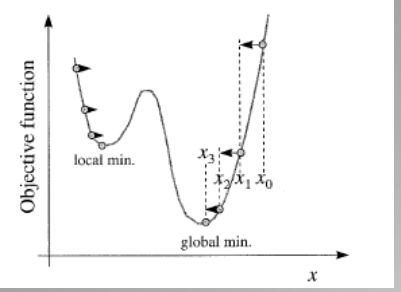
- Mimics the physical process in which a material slowly cool down after being rapidly heated to high temperatures
- The temperature is lowered from one iteration to the next and determines the average size of the amount by which the beamlet intensities are changed
- In each iteration step, a step-size is randomly selected from a displacement distribution of shrinking width (1. **tunneling**)



=> an improvement is always accepted

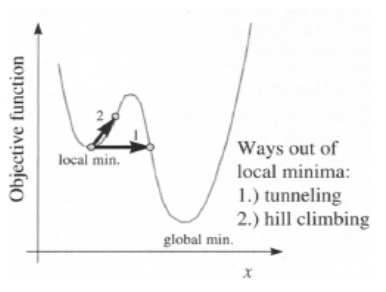
=> a worse treatment plan is accepted with a probability that depends on the temperature (2. **hill climbing**)

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



Summary #7

Optimization algorithms for IMRT



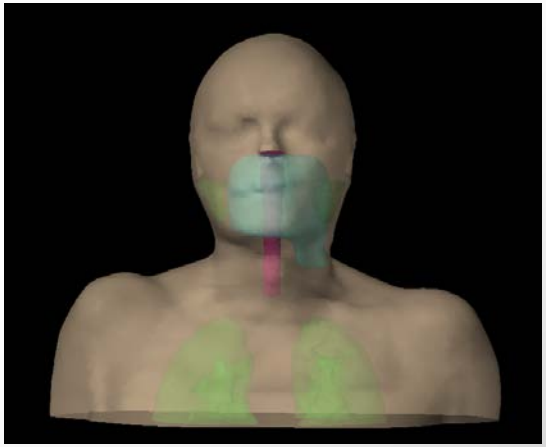
- Global solution not always necessary – satisfaction of specified requirements might be preferrable from a clinical perspective

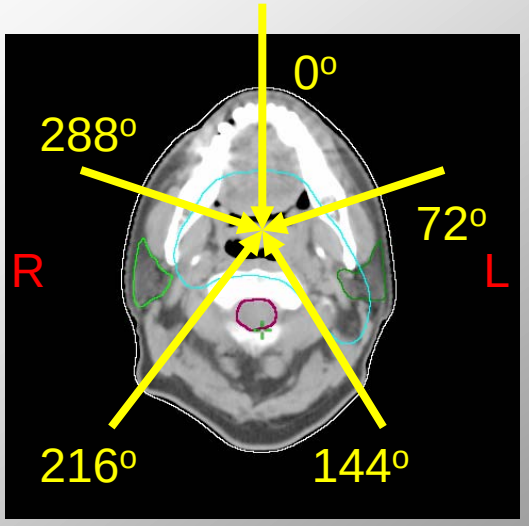
- Deterministic models do not contain any random element when modifying the beam intensities
  - Gradient methods
    - Fast
    - Gradient step size finds local solution
- Stochastic models does contain a random element when modifying the beam intensities
  - Simulated annealing
    - ”slow”
    - Random step size finds global solution

Summary #8

Assignment

- Tumour to treat placed in head and neck region (target)
- Spinal cord (ryggmärg), brain stem (hjärnstam) and parotid glands (spottkörtlar) to avoid (OARs)
- Model with physical and biological criteria
  - gEUD used with a = 1/n





Thank you!

Good luck with the assignment!