A simple example of Monte Carlo optimization in radiotherapy

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Advanced Statistics Course

A. A. 2020-21

ACTION OF X-RAYS ON MAMMALIAN CELLS*, ‡

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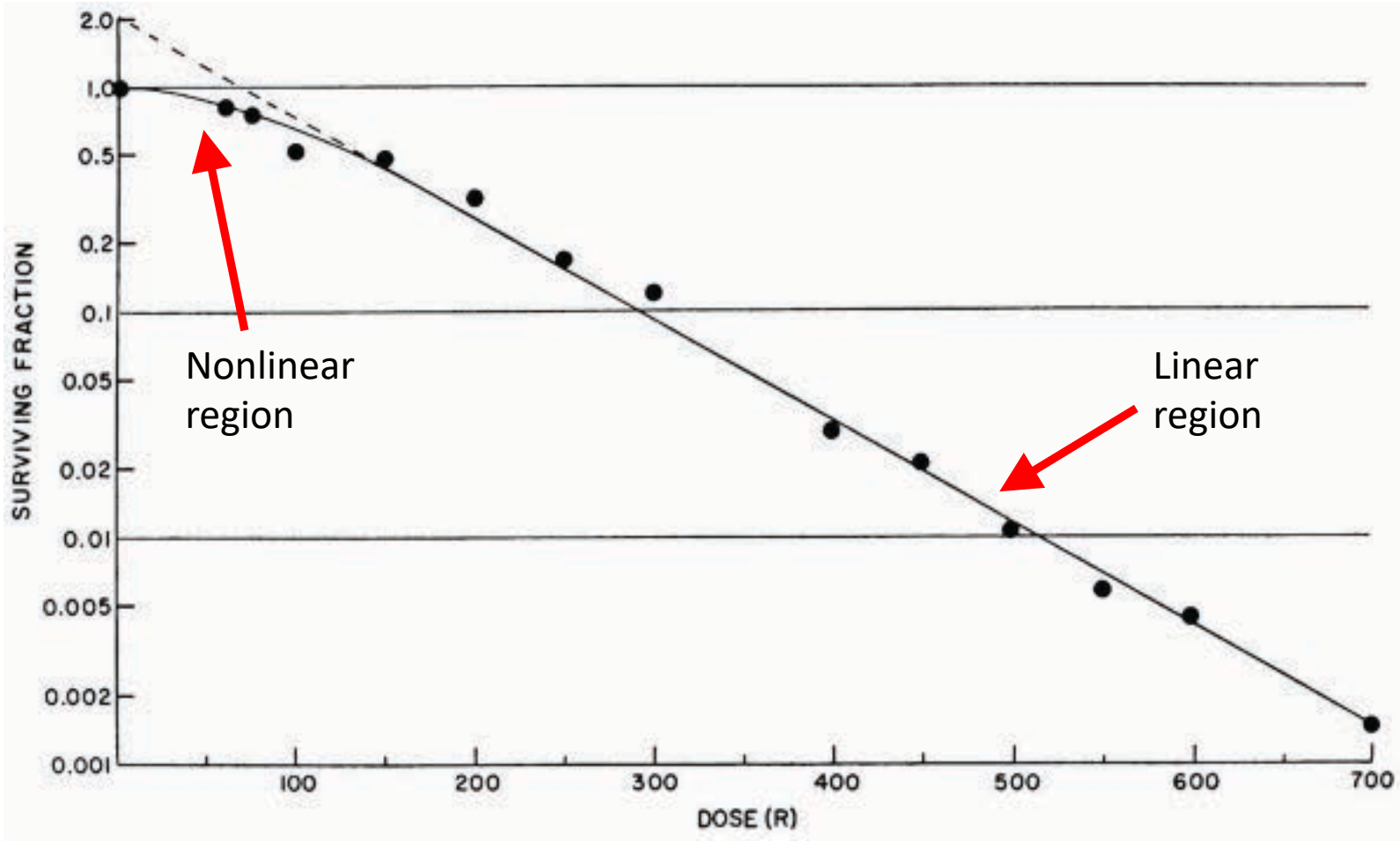
(Received for publication, February 3, 1956)

Unirradiated cells exhibit 100 per cent colony-forming efficiency under the conditions employed. Hence, it is reasonably certain that the experimental procedure subjects these cells to no major stress other than that of the irradiation. Throughout this paper the words, "survival," "viable," and "killing" are used in the sense which has become standard in microbiology; *i.e.*, referring only to the ability of the individual cell to multiply into a macroscopic colony.



Survival curve for HeLa cells in culture exposed to x-rays. Characteristically, this cell line has a small initial shoulder. (From Puck TT, Markus PI: Action of x-rays on mammalian cells. *J Exp Med* 103:653-666, 1956)

Linear-quadratic model

Actual data are fit reasonably well by the following mathematical expression for the surviving fraction

$$S(D) \approx e^{-\alpha D - \beta D^2}$$

The dose D_{eq} at which the linear and the quadratic term contribute equally is obtained from

$$\alpha D_{\mathrm{eq}} = \beta D_{\mathrm{eq}}^2$$

and therefore

$$D_{\mathrm{eq}} = \alpha / \beta$$

Target theory

Here we assume that a cell has one sensitive target, and that successive hits by ionizing particles are all statistically independent, so that we can use the Poisson statistics.

The probability of hitting *n* times a given target, when the average number of good hits is *a,* is

$$P(n) = \frac{a^n}{n!} e^{-a}$$

Then the probability missing the target is:

$$P(0) = e^{-a}$$

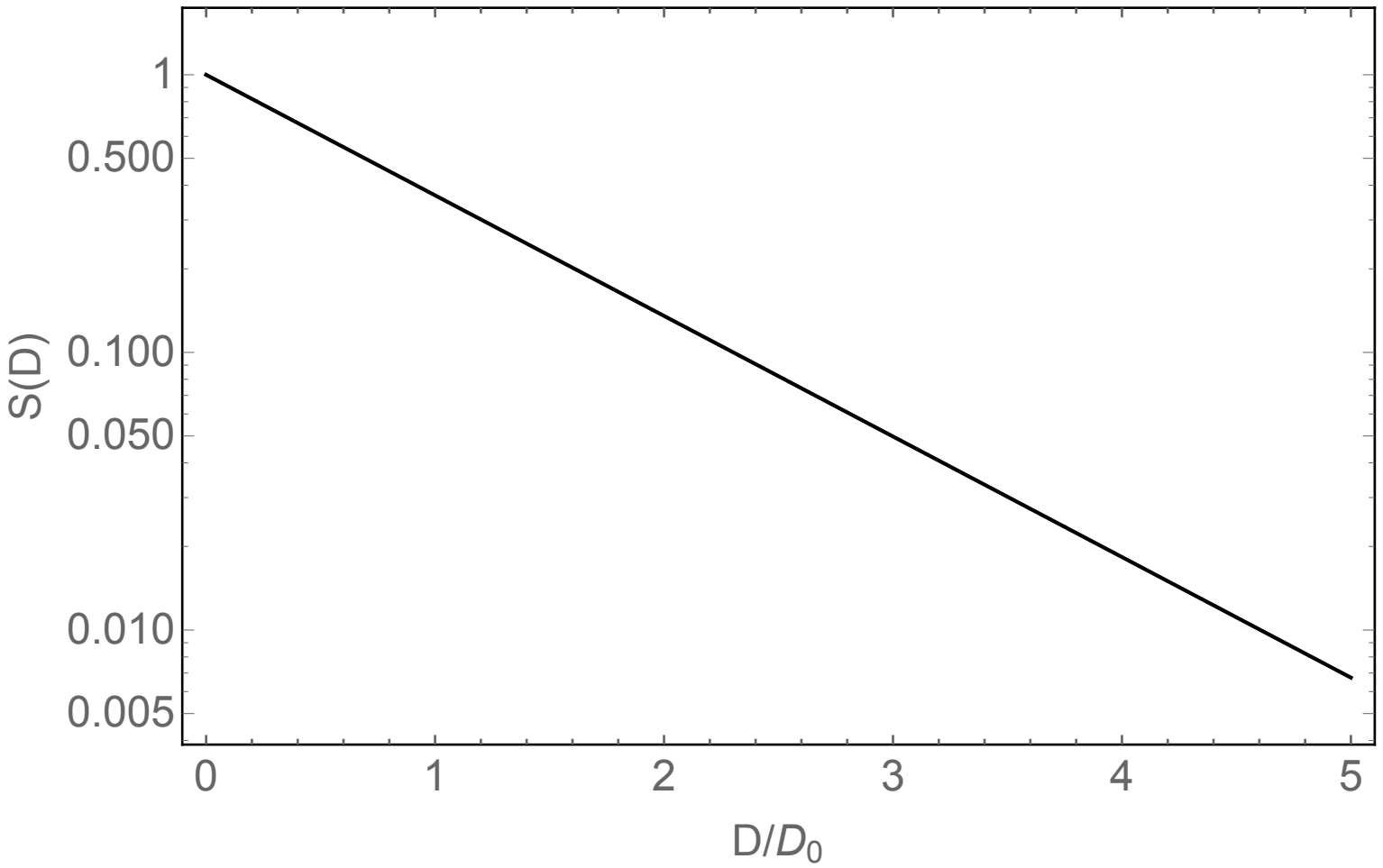
If the target is a vital function in a cell and the average number of hits depends on radiation dose *D*

$$a = D/D_0$$

then the survival probability is just the probability that the target is NEVER hit

$$S(D) = P(0, D) = e^{-D/D_0}$$

The surviving fraction in the simple Poisson approximation does not explain the LQ law



Multitarget model, asymptotic behavior and threshold effect.

If there are multiple targets, say *n* targets, all of which must be hit to kill a cell, then the probability of missing at least one of them – i.e., the survival probability – is

$$S(D) = 1 - (1 - e^{-D/D_0})^n$$

then, for large dose

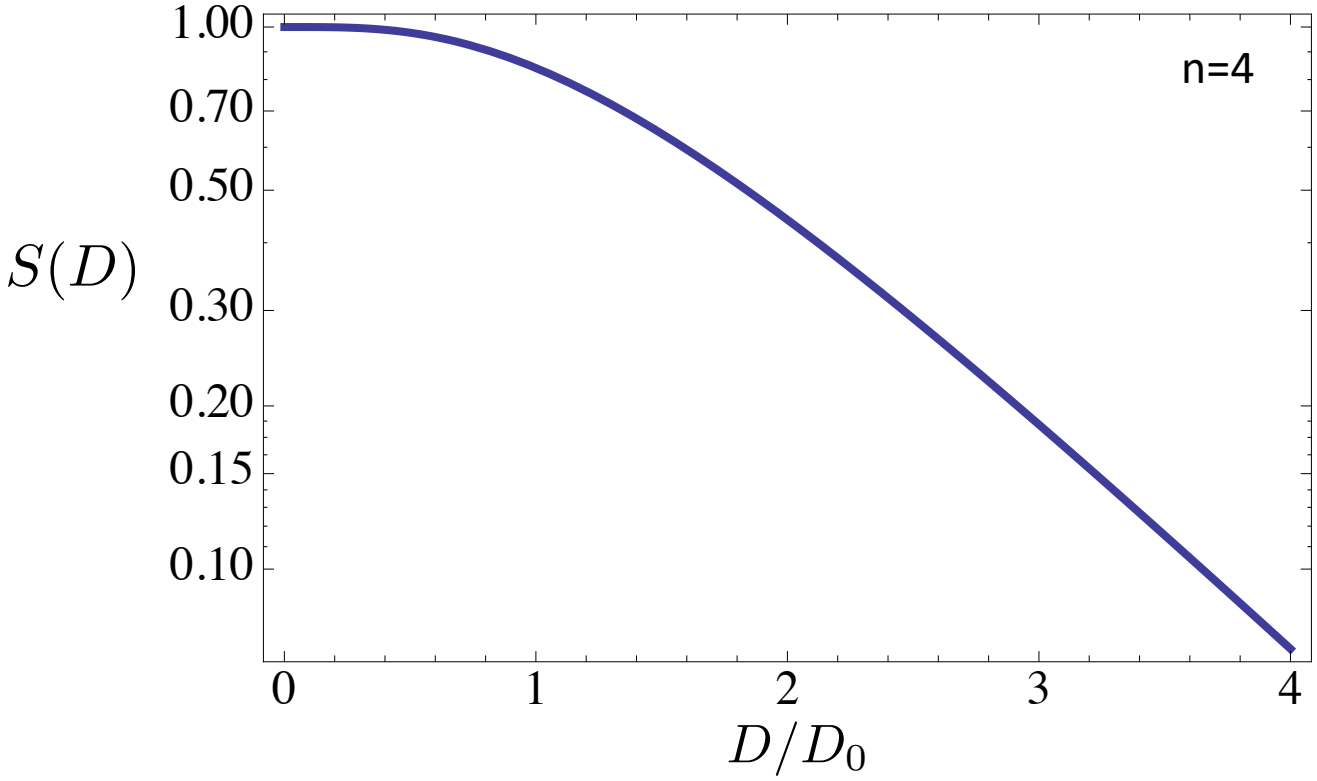
$$S(D) \approx n e^{-D/D_0}$$

i.e.,

$$\ln S(D) \approx \ln n - D/D_0$$

which is a linear relation with intercept ln *n*, and slope -1/D_0.

$$S(D) = 1 - (1 - e^{-D/D_0})^n$$



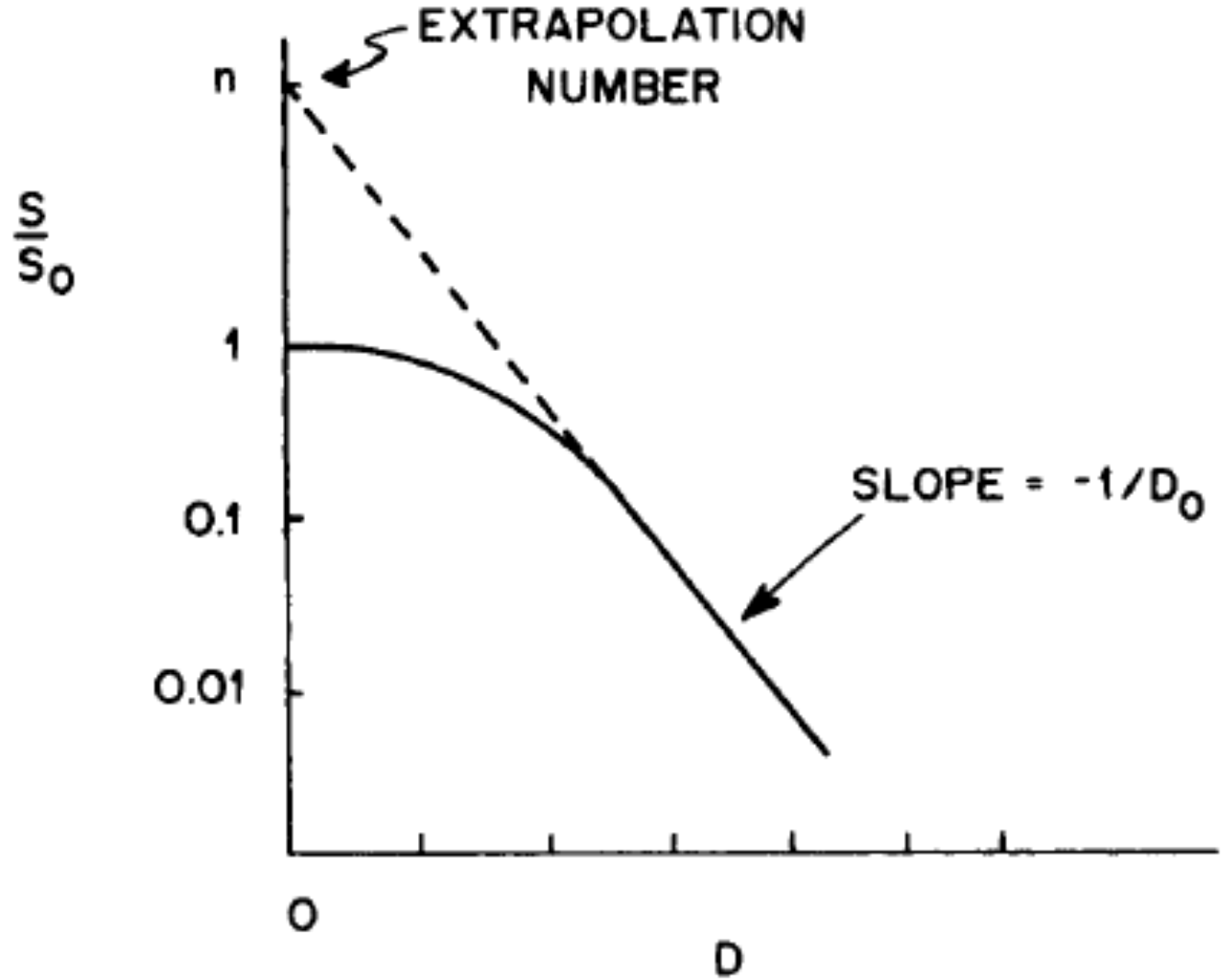


Fig. 13.14 Semilogarithmic plot of multitarget, single-hit survival.

Survival curves may deviate from the LQ model at low and high doses

- Certain cell lines and tissues, are hypersensitive at low doses of 0.05-0.2Gy.
- The survival curve plateaus over 0.05-1Gy
- Not seen for all cell lines or tissues, but has been reported in skin, kidney and lung
- At high doses, the model does not fit data well because D^2 dominates the equation

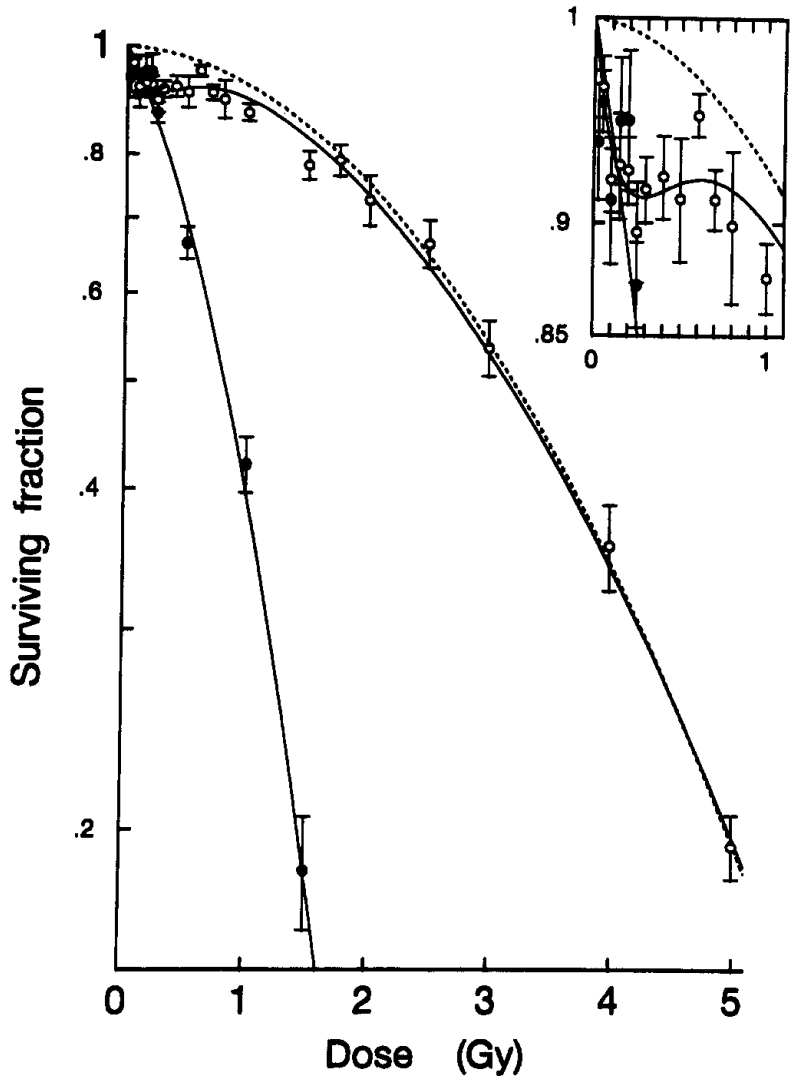


Figure 2. Survival of cells irradiated with 240 kVp X-rays (open symbols) and d(4)-Be neutrons (closed symbols). Each point shows the mean value ±SEM of the data from all five experiments. The dotted line shows the fit of the LQ model to the X-ray data ⩾2 Gy. The solid lines show the fit of the IR model to the X-ray data and the fit of the LQ model to the neutron data.

HT29 cells

(from Lambin et al., Int. J. Rad. Biol. 63 (1993) 639

Tumor Control Probability

The fraction of cells that survives a dose *D* is by definition *S(D)*, therefore when N cells are irradiated with dose *D*, on average there are *N S(D)* surviving cells.

This means that when we use a Poisson probability model, the probability of finding *n* surviving cells is

$$P(n;D) = \frac{[NS(D)]^n}{n!} e^{-[NS(D)]}$$

and the probability of finding 0 surviving cells (a total kill !) is

$$P(0;D) = e^{-[NS(D)]}$$

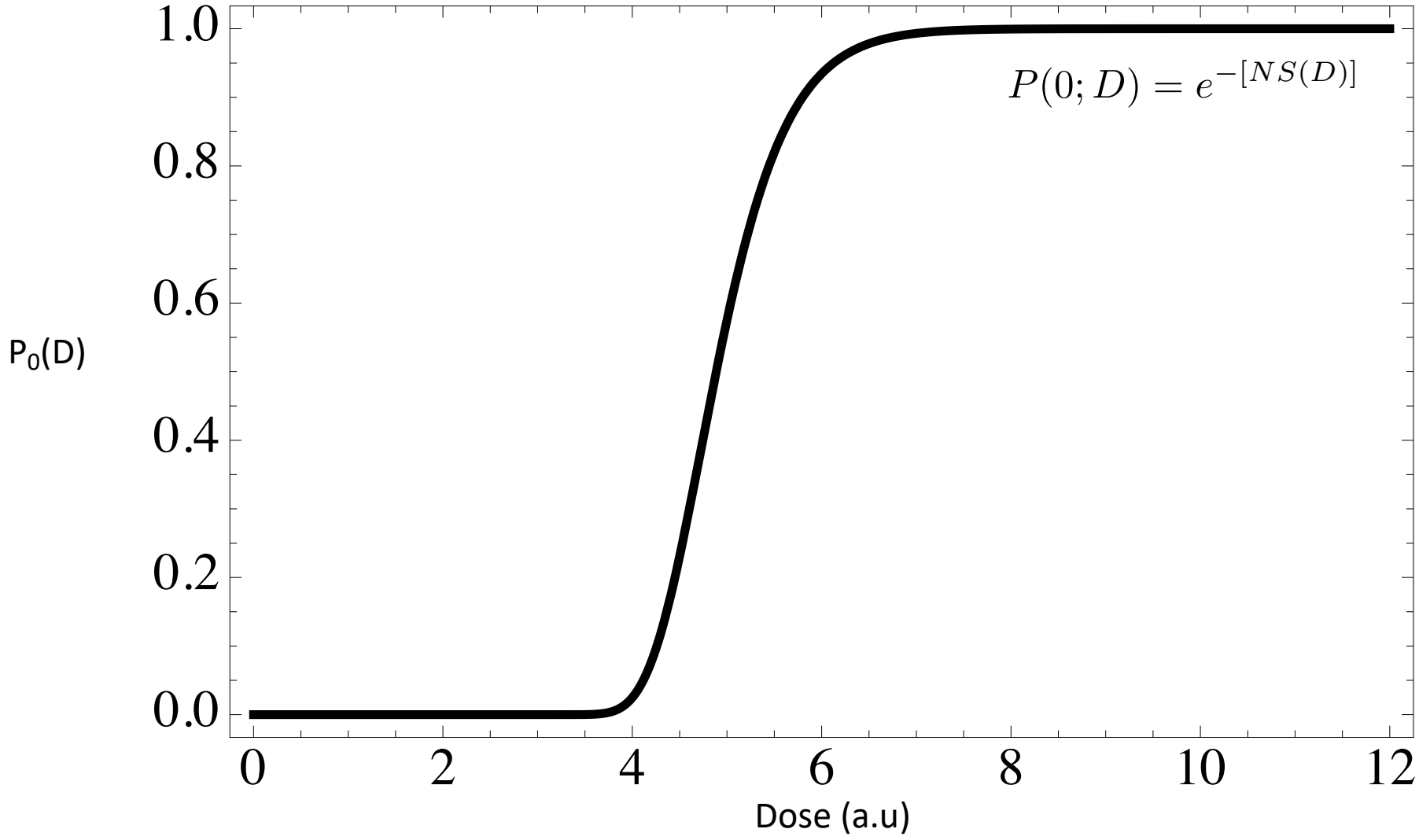
The following quantity is called Tumor Control Probability (TCP)

$$\mathrm{TCP} = P(0;D) = e^{-[NS(D)]} = e^{-\delta_C V S(D)}$$

tumor volume

density of tumor clonogens

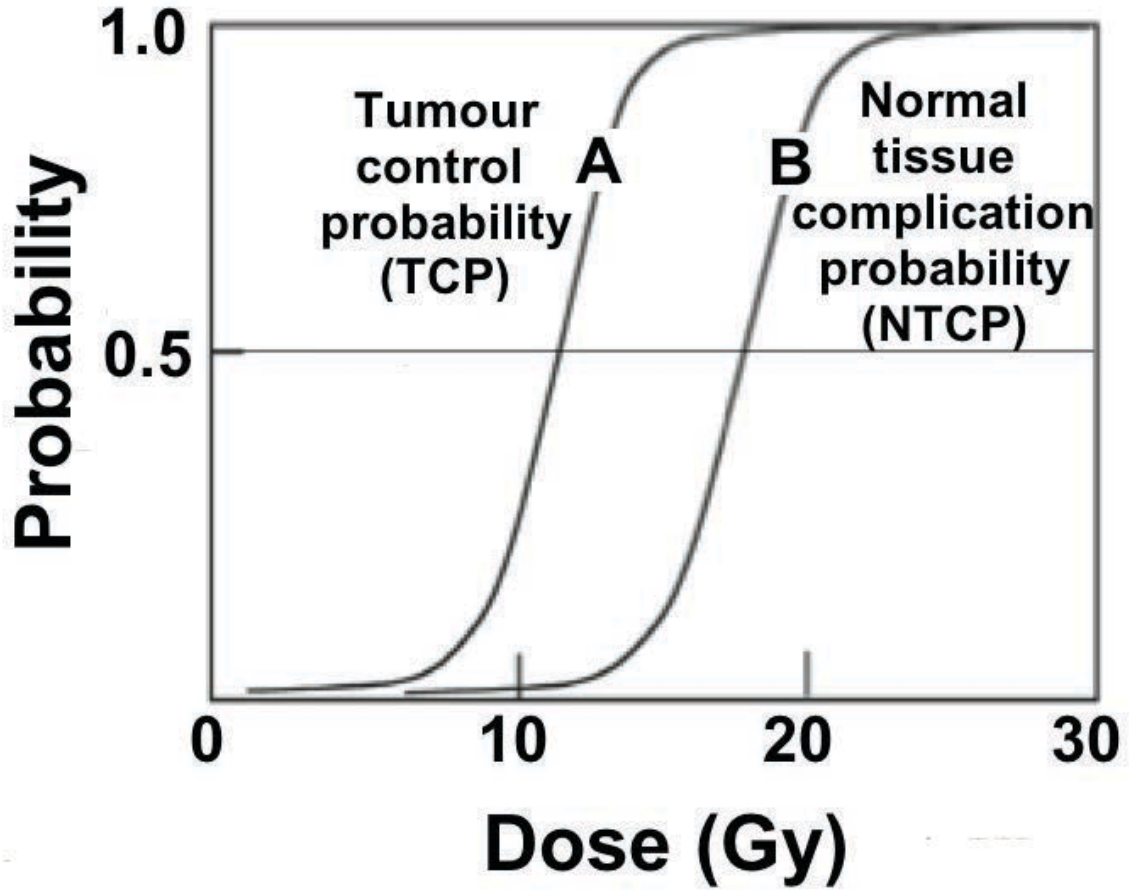
using a linear-quadratic model for S(D), one finds a sigmoid curve



Normal Tissue Complication Probability (NTCP)

Radiation is harmful for normal tissues as well as for tumors, and radiotherapy must avoid damage to normal tissues.

The NTCP reproduces phenomenologically the shape of the TCP.



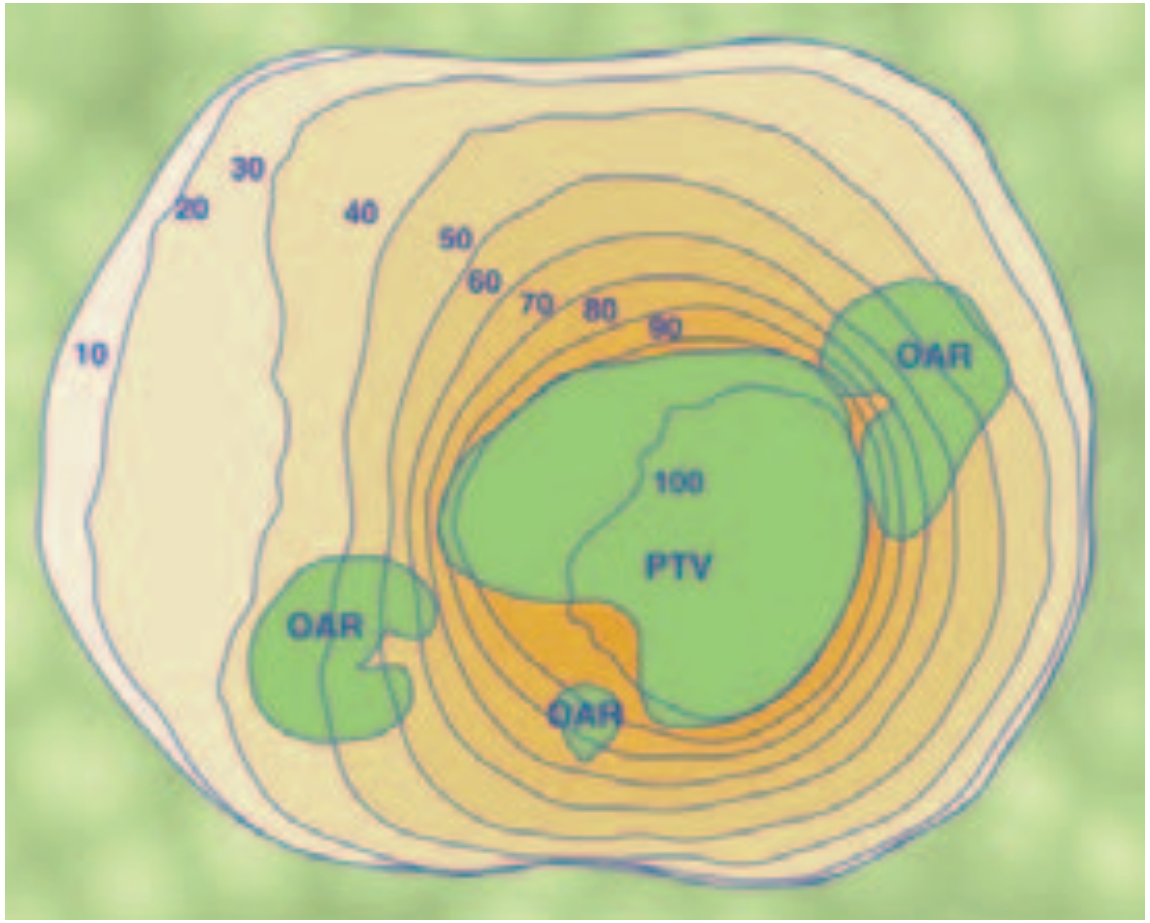
Lyman's mathematical description of the NTCP

$$\mathrm{NTCP} = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{u} e^{-t^2/2} dt$$

with

$$u = \frac{D - TD_{50}}{m \cdot TD_{50}}$$

where m is a dimensionless parameter that tunes the slope about the midpoint of the sigmoid curve, and TD_{50} is the whole-organ dose for which NTCP = 50%



Example of two-dimensional isodose curves in the treatment of retroperitoneal liposarcoma, close to critical organs – kidneys and spinal cord.

PTV = Planned Target Volume

OAR = Organ At Risk

4. Equivalent Uniform Dose (EUD)

According to Niemierko (who introduced the concept in 1997),

"For any dose distribution, the corresponding Equivalent Uniform Dose EUD is the dose in Gy, which, when distributed uniformly across the target volume, causes the survival of the same number of clonogens."

In the discussion of EUD, "it is assumed that an irradiated tumor is composed of a large number of independent clonogens, and that random killing of the clonogens is well described by Poisson statistics. The binary response – control or failure – of an irradiated tumor is assumed to be determined by the expected number of surviving clonogens. Therefore, two different target dose distributions are equivalent if the corresponding expected number of surviving clonogens are equal."

from Niemierko, Med. Phys. **24** (1997) 103

Example with a Poisson cell kill model

$$S(D) = \exp(-D/D_0)$$
$$S(D_{\mathrm{ref}}) = \exp(-D_{\mathrm{ref}}/D_0)$$

Surviving fraction for a generic dose D and for a reference dose D_{ref}

The surviving fraction can be rewritten as an explicit function of the reference dose

$$\ln S(D_{\mathrm{ref}}) = -D_{\mathrm{ref}}/D_0 \quad \rightarrow \quad D_0 = -\frac{D_{\mathrm{ref}}}{\ln S(D_{\mathrm{ref}})}$$

$$\ln S(D) = -D/D_0 = D\frac{\ln S(D_{\mathrm{ref}})}{D_{\mathrm{ref}}} \quad \rightarrow \quad S(D) = (S(D_{\mathrm{ref}}))^{D/D_{\mathrm{ref}}}$$

Now assume that there are N cells uniformly scattered in a volume V, which is subdivided in subvolumes V_i which receive each a dose D_i. Then the number of cells that survive in the whole volume is the sum of the cells that survive in subvolumes V_i

$$\sum_i n_i = \frac{N}{V} \sum_i V_i \; S(D_i) = \frac{N}{V} \sum_i V_i \; \left(S(D_{\mathrm{ref}})\right)^{D_i/D_{\mathrm{ref}}}$$

Therefore the total surviving fraction is

$$\frac{1}{N} \sum_i n_i = \sum_i \frac{V_i}{V} \; \left(S(D_{\mathrm{ref}})\right)^{D_i/D_{\mathrm{ref}}} = \sum_i v_i \; \left(S(D_{\mathrm{ref}})\right)^{D_i/D_{\mathrm{ref}}}$$

We would obtain the same surviving fraction

$$\bar{S} = \sum_i v_i \ \left(S(D_{\text{ref}})\right)^{D_i/D_{\text{ref}}}$$

with an *equivalent uniform dose* EUD such that

$$\bar{S} = \left(S(D_{\text{ref}})\right)^{\text{EUD}/D_{\text{ref}}}$$

$$\rightarrow \quad \text{EUD} = D_{\text{ref}} \frac{\ln \bar{S}}{\ln S(D_{\text{ref}})} = D_{\text{ref}} \frac{\ln \sum_i v_i \ S(D_{\text{ref}})^{D_i/D_{\text{ref}}}}{\ln S(D_{\text{ref}})}$$

This holds for the simple Poisson-model surviving fraction. More complex cases are treated in the paper by Niemierko:

- absolute volume effect
- nonuniform spatial distribution of clonogens
- dose-per-fraction effect (using the LQ model)
- proliferation effect
- inhomogenity of patient population

Optimization (basic concepts of treatment plans)

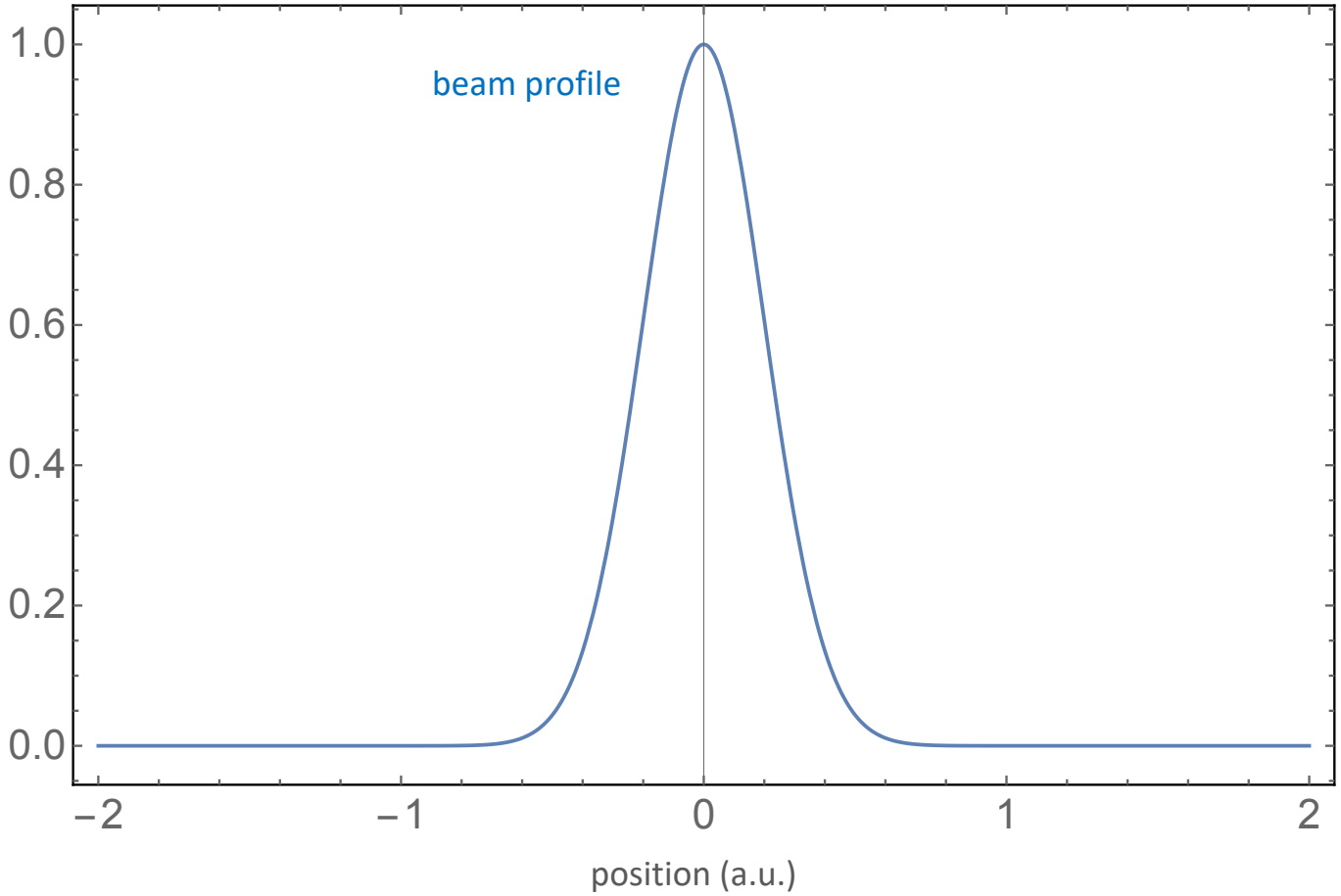
We optimize a treatment by

- maximizing damage to tumor tissue
- minimizing damage to normal tissue

This is a complex process that requires numerical solutions.

In the following slides we analyze a simple example that utilizes Monte Carlo simulation to analyze the effects of an IMRT (Intensity-Modulated Radiation Therapy) treatment (IMRT is an improved version of the 3D-treatment).

In this example the radiation is delivered by beams with the same Gaussian intensity modulation (this kind of intensity modulation is not realistic, it is just part of this specific example)

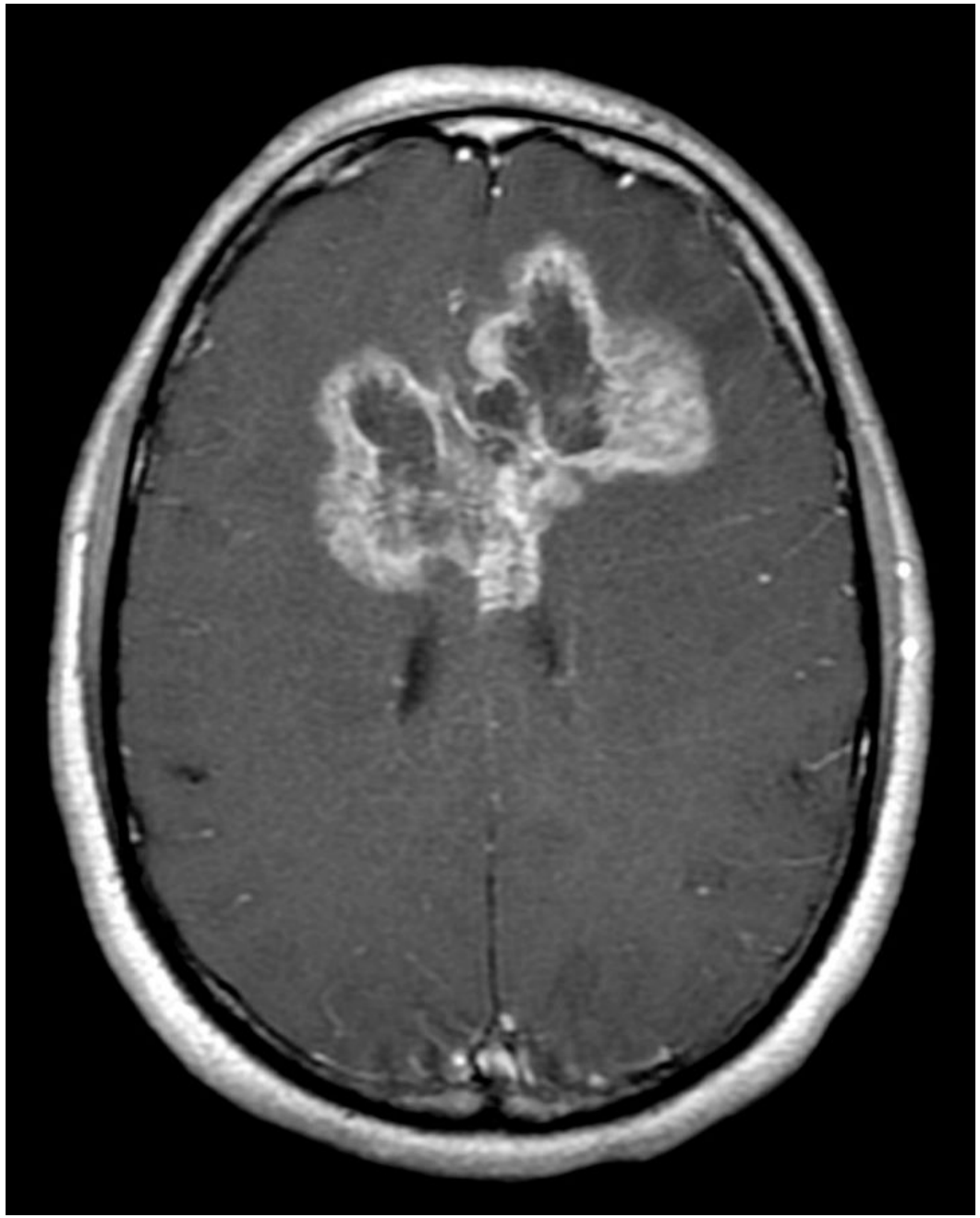


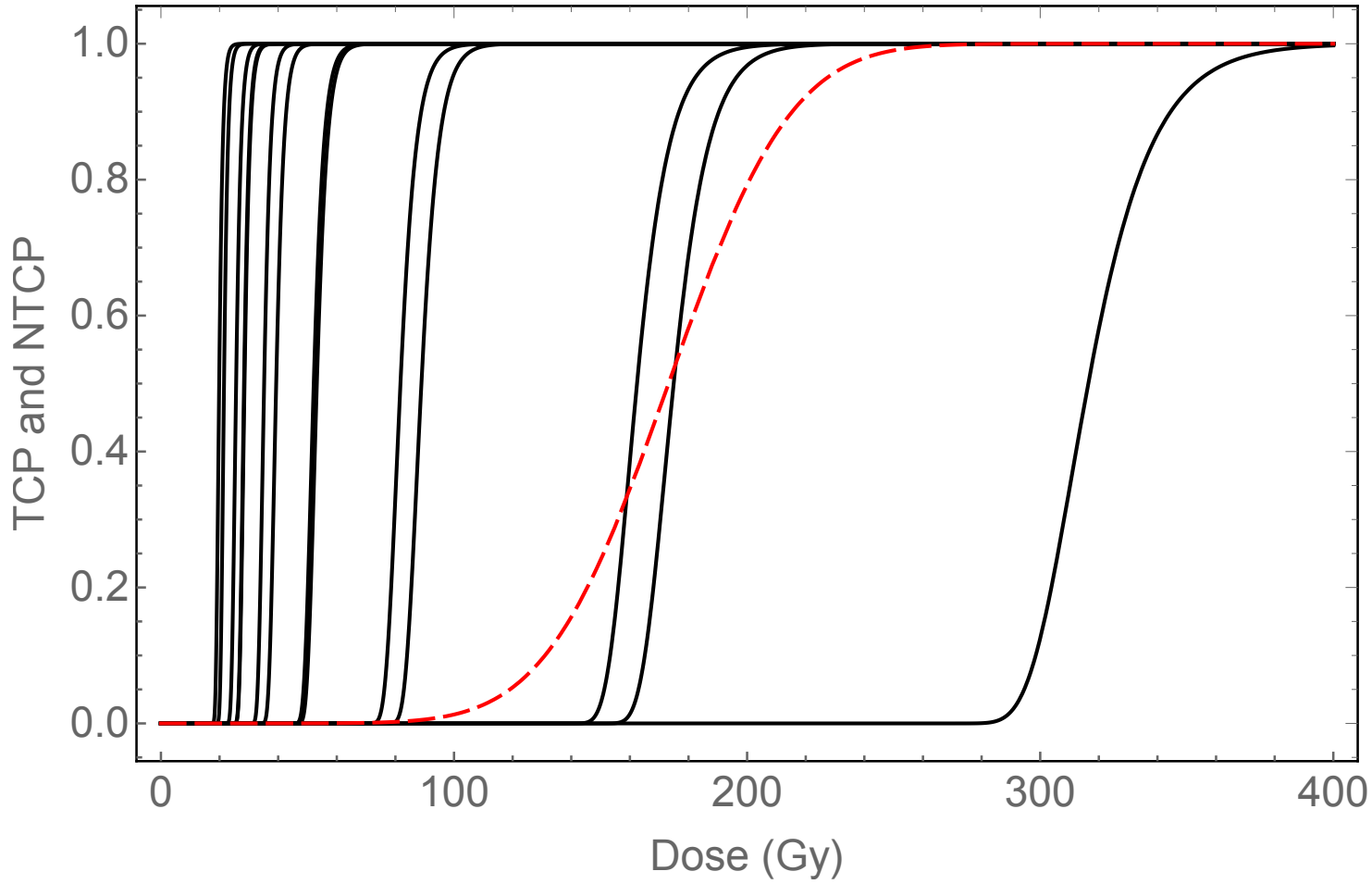
Simulation target: glioblastoma multiforme

Glioblastoma multiforme (GBM) is the most common and malignant brain tumor found in human beings, accounting for approximately 52% of all functional tissue brain tumor cases and 20% of all intracranial tumors.

GBM is comprised of heterogeneous groups of neoplasms that proliferate through various parts of the central nervous system. Although it is the most prevalent form of primary brain tumor, only 2-3 cases per 100,000 people in the Europe and North America are reported annually. However, the prognosis for patients afflicted with GBM is extremely poor, and is eventually fatal in the vast majority of cases.

(from https://sites.google.com/site/whatisglioblastomamultiforme/pathophysiology)

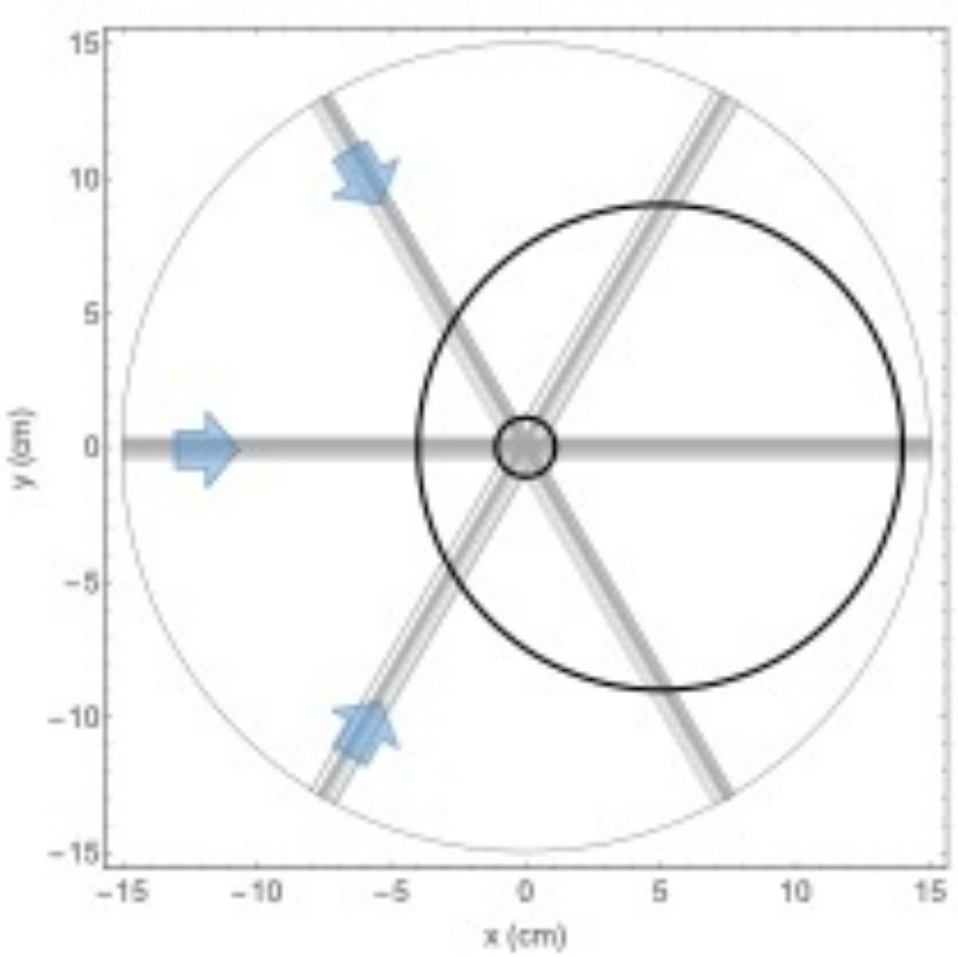


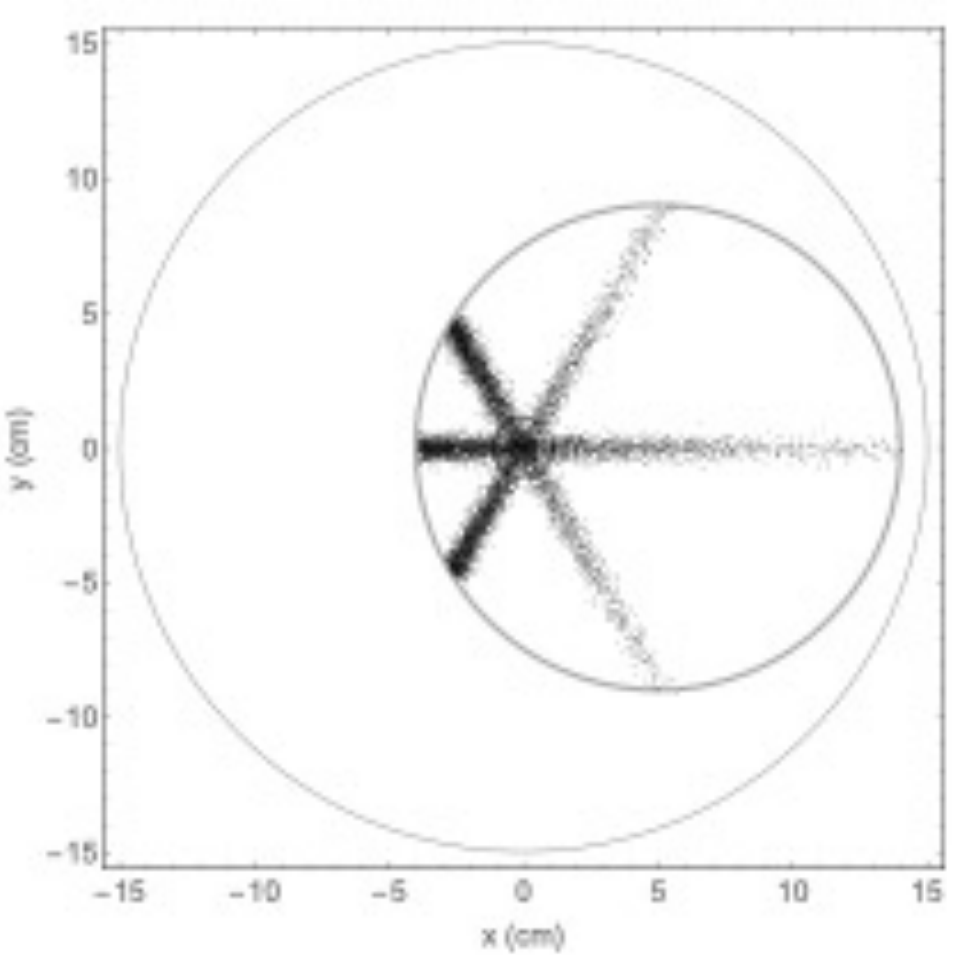


TCP curves (solid black lines) for various GBM histological types and NTCP curve (dashed red line) for brain tissue vs. dose D (Gy), for 10^9 cells (volume about 4 cm^3). The TCP curves have been drawn taking the linear extrapolation of the LQ model with the α and β parameters listed in the literature. The NTCP curve has been drawn with partial volume v = 5%.

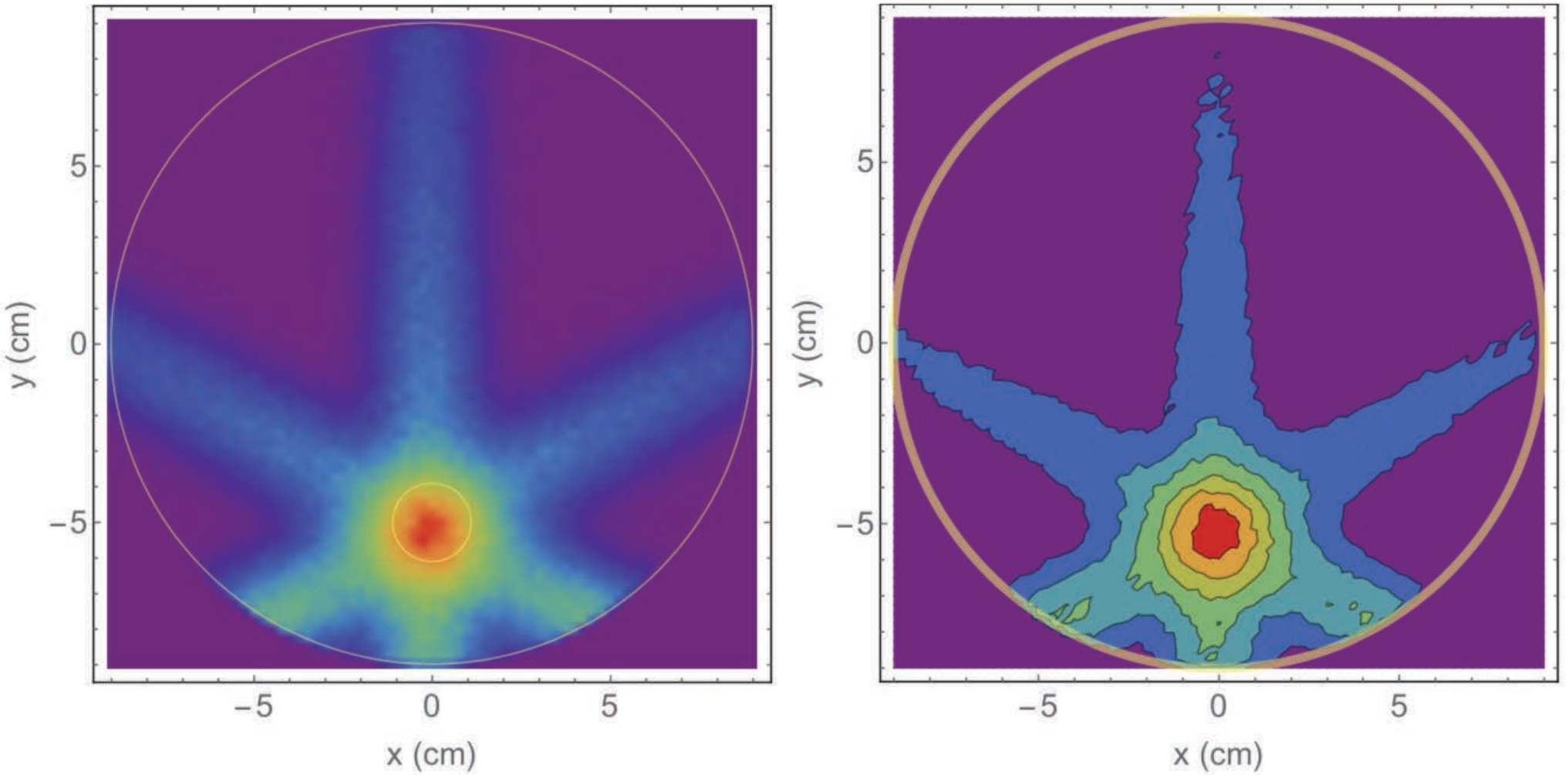
Example distribution with 3 beams

Each dot represents the position of one absorbed photon. The local dot density is proportional to the local dose. The photon beams undergo exponential attenuation, and there is a corresponding energy absorption in tissue.





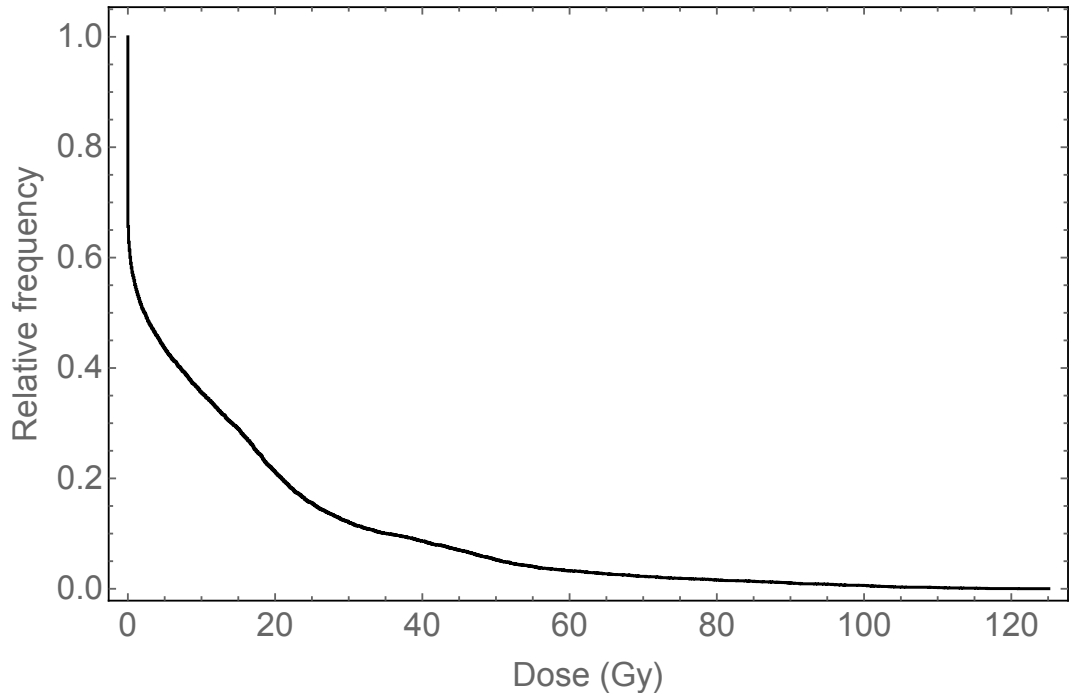
Isodose curves

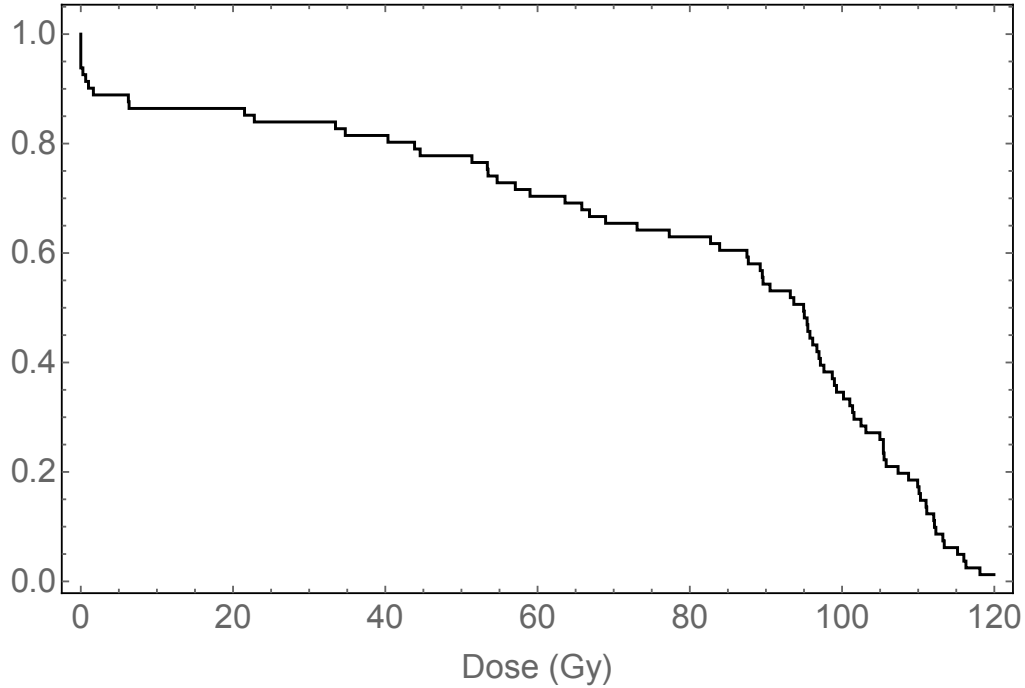


From voxels to

isodose curves

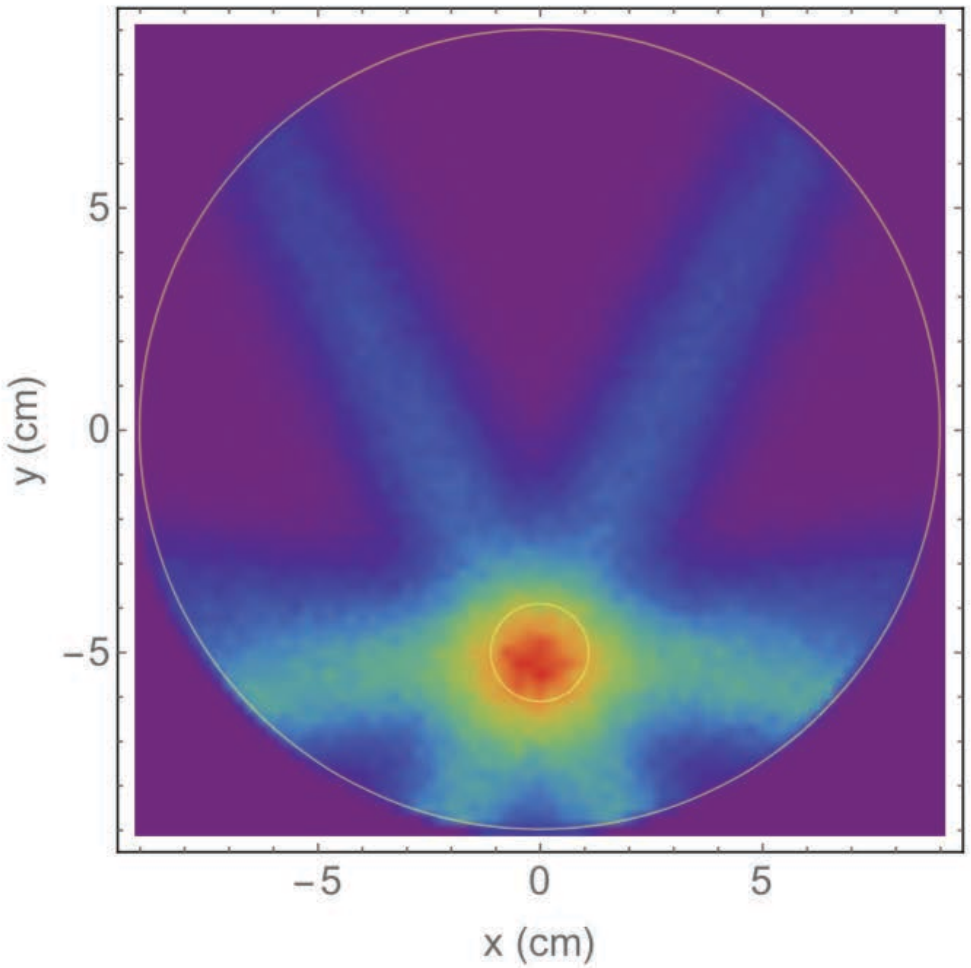
Dose-volume histograms

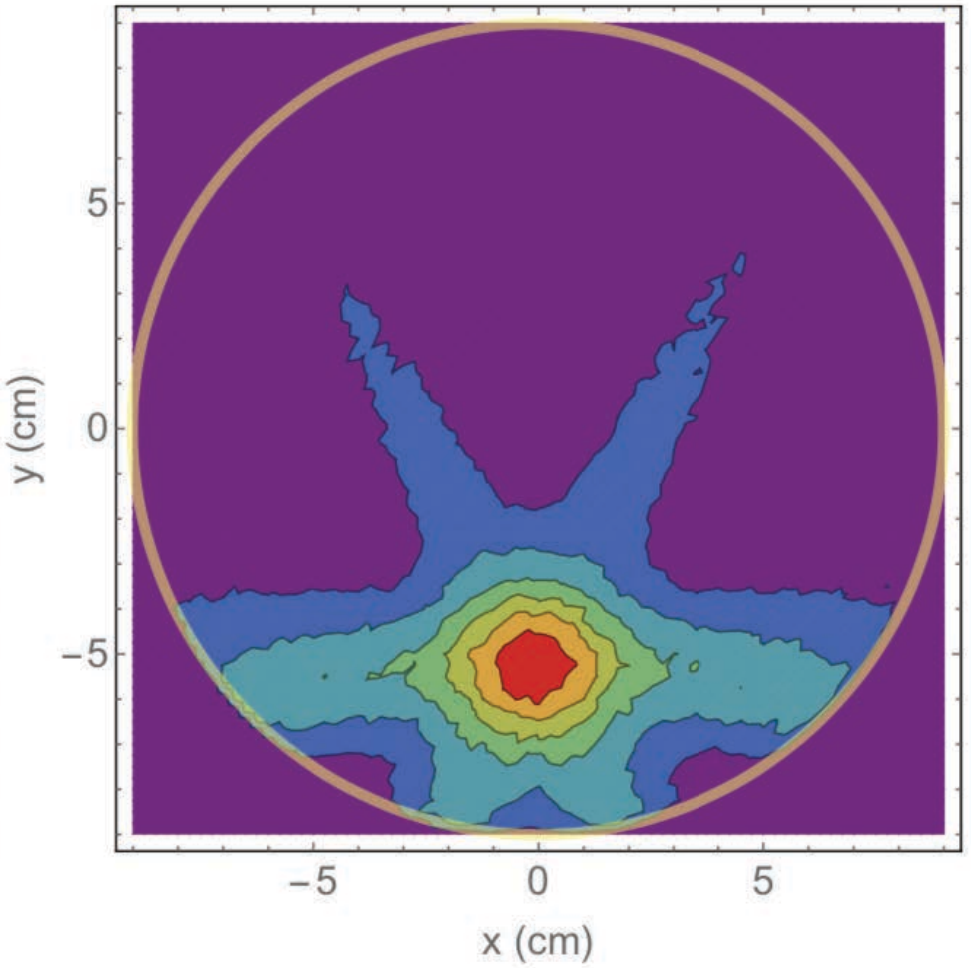




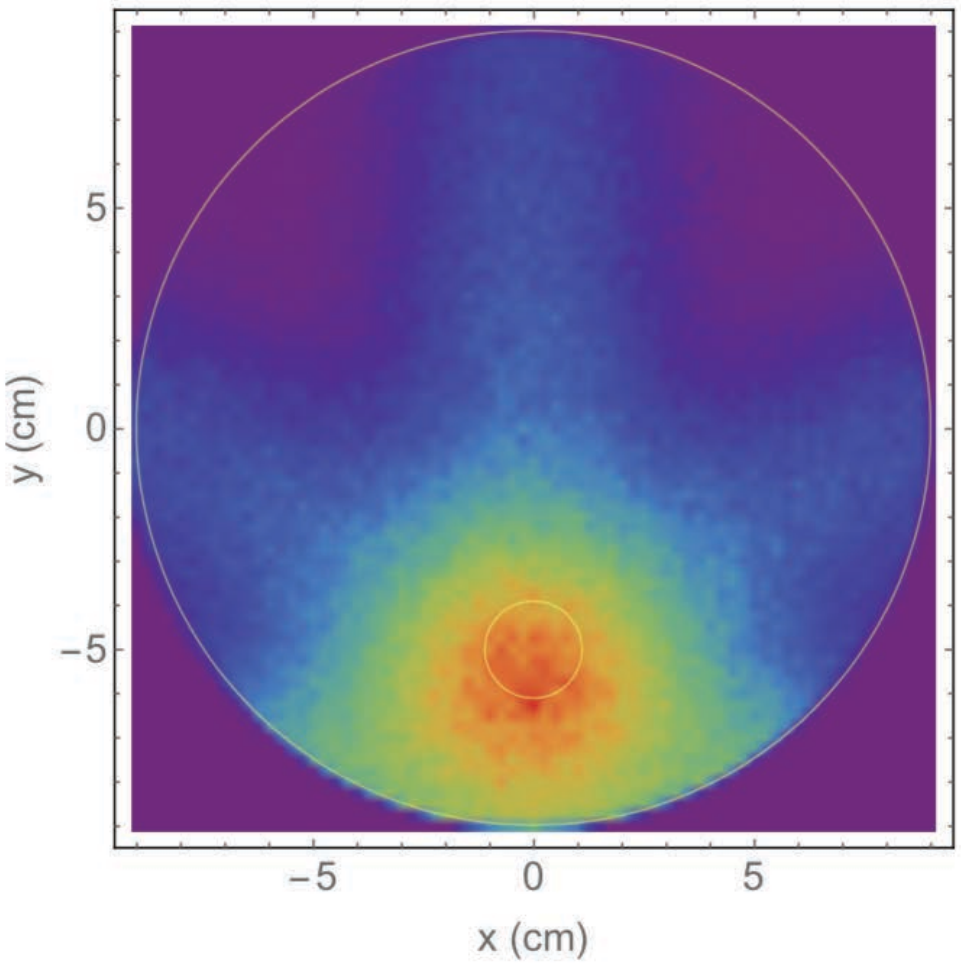
Dose-volume histograms (DVH) for the whole volume of the simulated head (left panel) and for the planning target volume (right panel). DVH's are empirical cumulative distributions of dose that are often used in radiotherapy, but they are read off differently from usual cumulative distributions. For instance, from the histogram on the right we find that about 70% of all voxels receives a dose larger than 60 Gy, and that about 30% of all voxels receives a dose larger than 100 Gy.

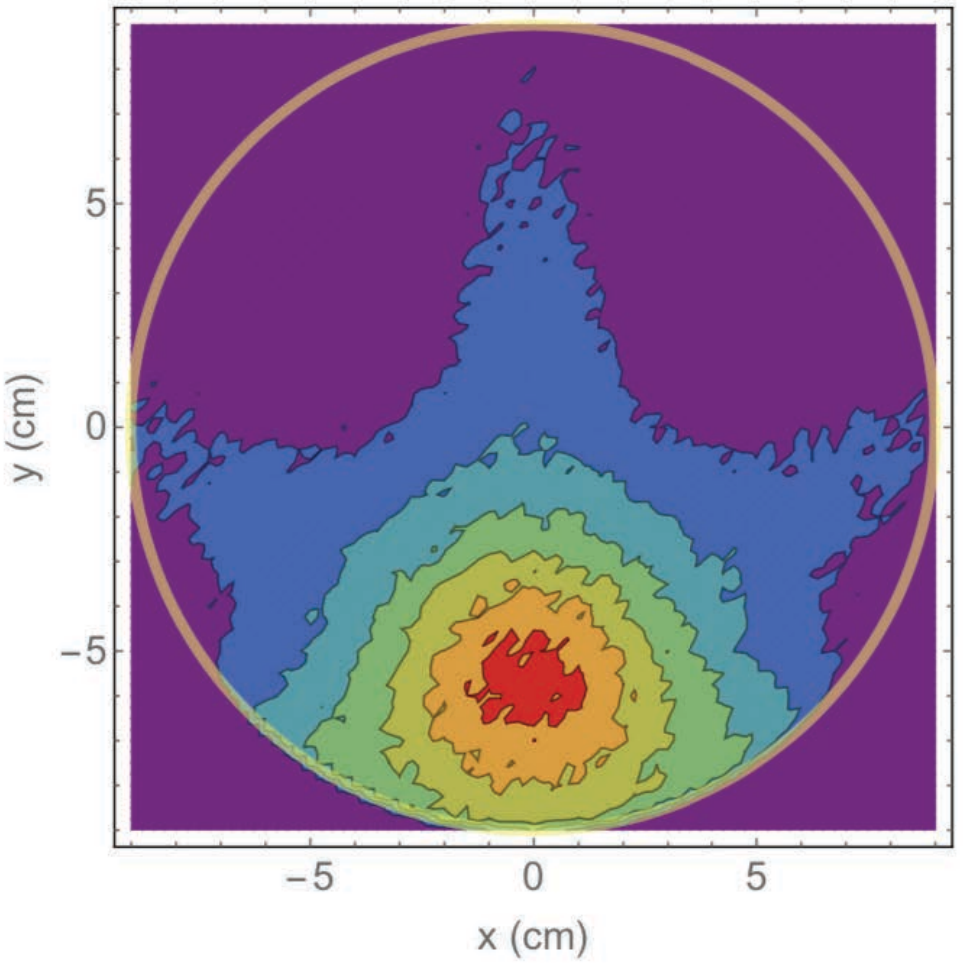
Simulation with 4 beams



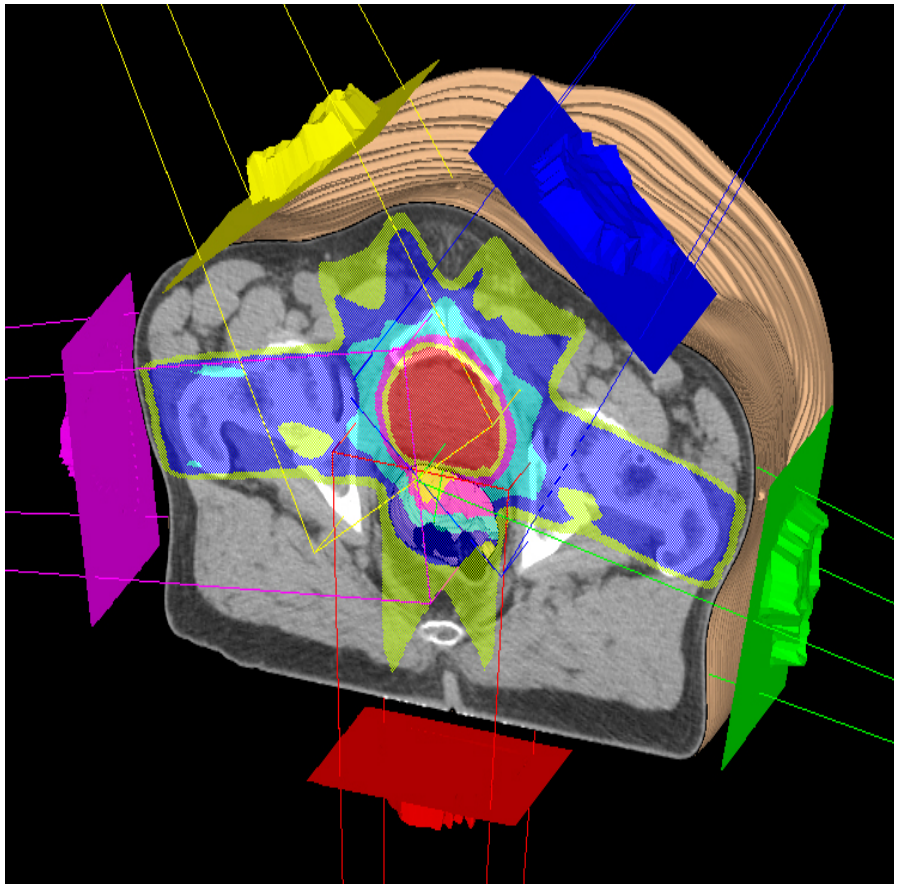


Simulation with 3 beams and doubled beam width





By carefully adjusting the beam parameters we can optimize the results of radiation therapy.



This simple example shows how to use the basic principles, however:

- example limited to 2D (real treatment plans must be 3D)
- no real physics (intensity does not change because of absorption, no Compton scattering of photons, etc.)
- quantification of damage with simplified TCP and NTCP curves
- simple structure with circular symmetry (real cases are much more complex)
- no organ-at-risk in the vicinity
- ...