Norges teknisk-naturvitenskaplige universitet

Institutt for fysikk

EKSAMENSOPPGÅVER med løysingsforslag

Examination papers with solution proposals

TFY4315

STRÅLINGSBIOFYSIKK

Biophysics of Ionizing Radiation

08.06.2012

Problem 1

a) Absorption of ionizing irradiation in biological material can be classified as either **directly** or **indirectly ionizing**.
   - Explain shortly this difference in radiation absorption.
   - What types of radiation are associated with the two forms of absorption?

   – ***Directly ionizing***
      - *Can disrupt the atomic structure of the absorber through which they pass directly and produce chemical and biological changes*
      - ***Charged particles*** *(the individual particles must have sufficient kinetic energy)*
   – ***Indirectly ionizing***
      - *Do not produce chemical and biological damage themselves, but give up their energy to produce fast moving charged particles that can produce damage (Compton process, photoelectric process)*
      - ***Electromagnetic radiation (X and γ-rays)*** *(energy high enough to initiate the processes)*

b) What is **direct and indirect action** of radiation?

   - ***Direct action****:*
      - *Radiation interact directly with the critical target*
      - *Dominant for radiation with high* ***LET (linear energy transfer)*** *(neutrons, α-particles)*
   - ***Indirect action:***
      - *Radiation interact with other atoms or molecules in the cell (particularly water) to produce* ***free radicals*** *which damage critical targets.*

c) What is a free radical and why do such particles show high degree of chemical reactivity?

   A free radical is an atom or molecule carrying an unpaired orbital electron in the outer shell.

   In atoms / molecules with
   - *(even number of electrons spins are paired → high degree of chemical stability)*
   - ***odd number of electrons one orbital electron have no other electron with opposing spin*** *→ high degree of* ***chemical reactivity***

Enumerate the main water radicals produced by radiation.

The biologically important radiolytic products ***$OH^{\cdot}$, $H^{\cdot}$ and e^{-}_{aq} are water radicals.***
(2/3 of the x-ray damage to DNA in mammalian cells is caused by the hydroxyl radical $OH^{\cdot}$)

d) The indirect action of x-rays on biological material (via radiolysis of water) can be divided into **physical, chemical and biological** stages. Which characteristic processes are connected to these stages, and in which time intervals after radiation will they appear?

Chain of events:

Time (sec)	Stage	Characteristics
$10^{-13} - 10^{-15}$	Physical	Initial ionization H_2O^{+}, e^{-}, H_2O^{*}
$10^{-9} - 10^{-10}$	Physical / Chemical	Radicals produced e^{-}_{aq}, $H^{\cdot}$, $OH^{\cdot}$
$10^{-5} - 10^{-7}$	Chemical	Reaction with biomolecules, breaking of chemical bonds
Sec – years	Biological	Effects on metabolism, gender cells , viability, genetic effects

Cell killing is expressed hours to days after radiation

Oncogenic damage may be delayed for up to 40 years

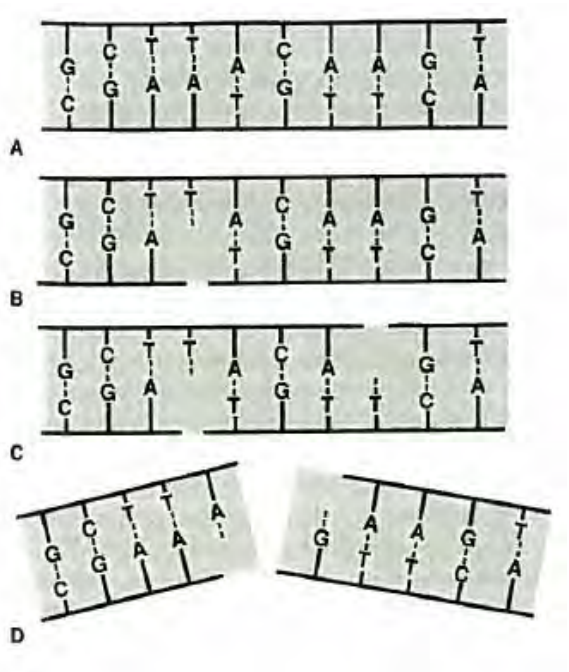
Mutation damage may not be expressed for many generations

Problem 2

a) Radiation may lead to **single strand breaks (SSB)** and **double strand breaks (DSB)** in DNA molecules. Give a <u>short</u> schematic overview of the structure of a DNA molecule and explain the differences between these two forms of DNA strand breaks and their biological consequences.

DNA double helix structure:

- **Two strands** held together by hydrogen bonds between the bases
- Attached are four bases, the sequence specify the genetic code:
- **The bases on opposite strands must be <u>complementary</u>** (fig. A)
  - Adenine (A) pairs with thymine (T)
  - Cytocine (C) pairs with guanine (G)



Radiation may break the strands on one or several places along the strands.

<u>Single strand breaks:</u>

- *break in one of the two strands in the double helix (fig. B).*
- *several well separated SSBs located in the pair of strand, (fig. C)*

can be repaired with the base on the opposite strand as template

Generally: ***No biologic consequence***

- *(An incorrect repair may result in mutation)*

Double strand breaks:

- ***brakes in two strands opposite or separated by only a few base pairs (fig. D) may lead to cleavage of the chromatin***

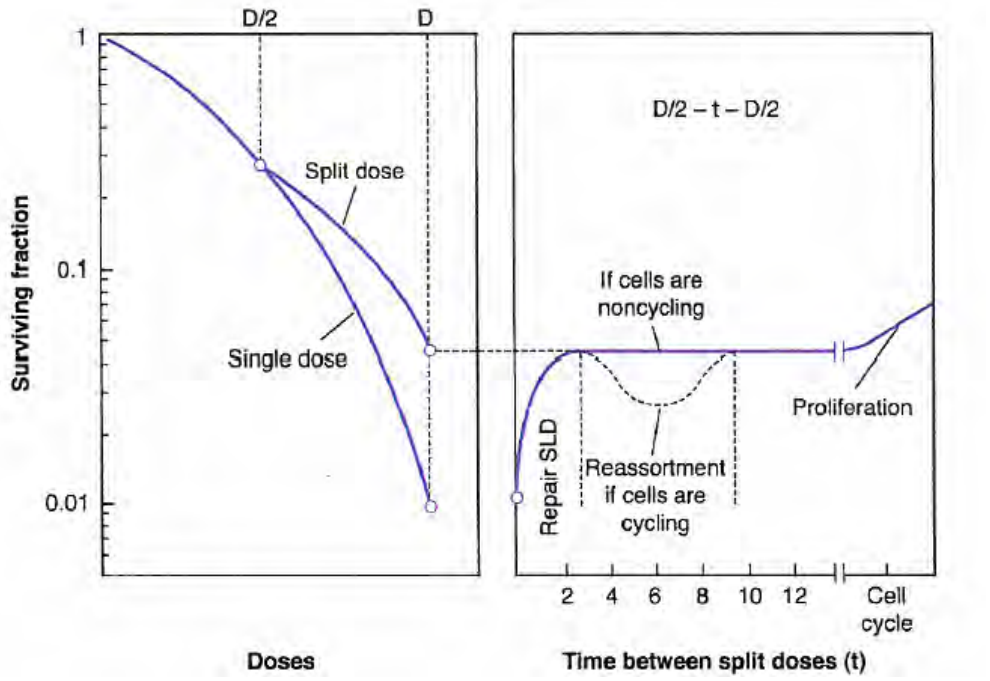
Broken ends are «sticky» can rejoin with any other broken ends:

- *The breaks may restitute (rejoin in their original configuration)*
- *The breaks may fail to rejoin – aberration (deletion at next mitosis)*
- *Broken ends may reassort and rejoin other broken ends – abnormal chromosomes*

b) Radiation damages to mammalian cells can operationally be divided into three categories; **lethal, potentially lethal, and sublethal**. What are the differences between these types of damages?

- **Lethal damages**
  - Irreversible
  - Irreparable
  - Leads irrevocably to cell death
  -
- **Potentially lethal damages (PLD)**
  - Can be modified by postirradiation environmental condition (causes cell death under normal circumstances, but if survival is increased due to manipulation of postirradiation environment, PLD can been repaired)
  -
- **Sublethal damages (SLD)**
  - Can be repaired within hours if not additional SLD is added with which it can interact to form lethal damage

c) Explain how subletal damage repair, reassortment and repopulation can be visualized in split dose experiments.



Split dose experiment: *A radiation dose to a cell population is split into two fractions with various times between the two fractions. Survival is recorded (see fig).*

<u>Sublethal damage (SLD) repair is seen as initial increase in survival</u> *if a radiation dose is split into two fractions by a time interval (the split dose survival curve increase when the split is within a few hours, before flattening)*

Reassortment *can be seen as a dip in the split dose survival curve for rapidly growing cells (when the time interval between the split doses is about 6 hours in the example shown). Explanation:*

In asynchronous populations more cells are killed in sensitive than resistant phases. The surviving population therefore tends to be synchronized.

After 1.st fraction:

- *most of the survived cells are in S-phase.*

2. fraction after 6 hours:

- *these cells are in G_2/M phases (sensitive)*

If the increase in radiosensitivity moving from late S to G_2/M exceed the repair of SLD the survival fraction falls.

Repopulation: *Increase of surviving fraction resulting from cell division (repopulation, proliferation) if the interval between the split doses is > 10 – 12 hours (exceeds the cell cycle of rapidly growing cells)*

d) A cell population is irradiated with γ-rays. Explain why the frequency of chromosomal aberrations (aberrations pr cell) can be seen as a **linear quadratic** function of the radiation dose.

*Each aberration is a consequence of the interactions of **two separate breaks** in the chromatid*

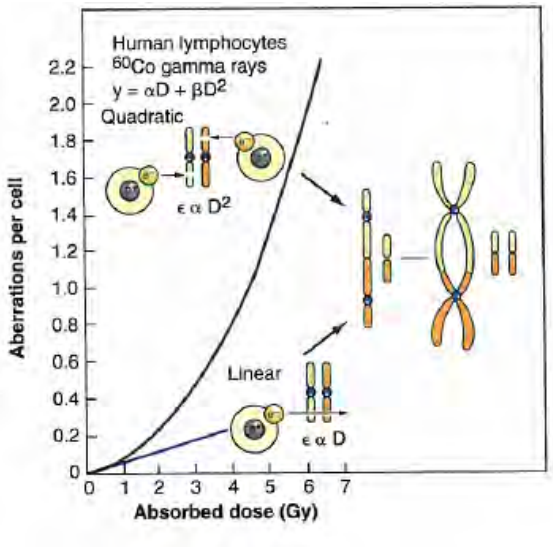
The linear component :

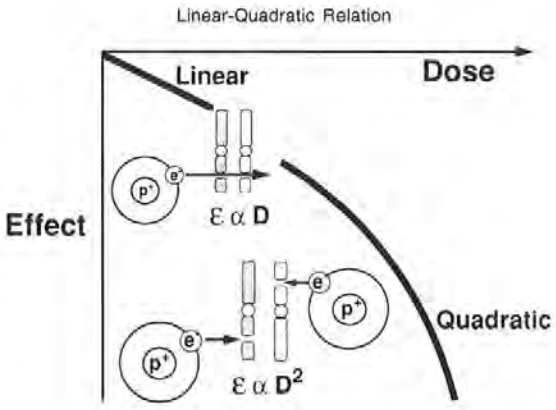
- ***Probability proportional to D***
- *The two breaks resulting from **a single charged particle***
- *Most probable at low doses*

The quadratic component:

- ***Probability proportional to D^2***
- *The two breaks resulting from **different charged particles***
- *Most probable at higher doses*

The linear quadratic relationship characteristic of the induction of chromosomal aberrations is carried over to the cell survival curve





Problem 3

a) What is ment by **hyperfractionation, accelerated treatment and hypofractionation** in radiotherapy, and what are the aims of such fractionation regimens compared to conventional fractionation?

a)

Conventional fractionation regimens are 2 Gy x 25 (- 35)

Hyperfractionation

Pure hyperfractionation:

- *Keeping the same total dose as conventional*
- *The same overall time*
- ***Twice as many fractions (Twice pr. day)***

Impure hyperfractionation:

- *Increase in the total dose*
- *(longer overall time)*
- ***More fractions delivered twice pr day***

Basic aim:

- *To further separate early and late effects*
- *Reduce late effects for the same tumor control*
- *The same (or slightly increased) early effects*

Accelerated treatment

- *The same total dose as conventional*
- *Reduce the overall treatment time*
  - *Delivered in half the overall time (pure accelerated treatment)*
- *Two or more fractions pr. day*

(Acute effects limit this treatment. Must reduce the dose slightly or interpose a rest period)

Intent: Reduce repopulation in rapidly proliferating tumors

Little or no change in the late effects because the number of fractions and the dose pr. fraction are unaltered.

Hypofractionation:

Dose fractions much larger than 2 Gy

- *Tumors with low α/β values (prostate α/β = 2 – 3) more similar to late responding normal tissue than other tumors. Remove the basic rationale for a multifraction regimen of 35 fractions or more*
- *Regimen of smaller number of larger dose fractions should result in local control without increased normal tissue damage*

b) BED (biologically effective dose) of a tumor can be calculated as:

$$BED = D\left(1+\frac{d}{\alpha/\beta}\right)$$

when a total dose D is divided in n fractions with fraction dose d , and there is suitable time for cell recovering between each fractions. Show how the linear quadratic model is used to find this equation for BED.

Linear quadratic model:

$$S = e^{-(\alpha D + \beta D2)}$$

S = surviving fraction

For a single acute dose D the biological effect (E) is given by:

$$E = \alpha D + \beta D^2$$

For n well separated fractions of dose d, the biological effect is given by:

$$E = n(\alpha d + \beta d^2)$$

Rewritten:

$$E = nd\,(\alpha + \beta d) = (\alpha)(nd)\left(1+\frac{d}{\alpha/\beta}\right)$$

$nd = D$

$$E = \alpha\, D\left(1+\frac{d}{\alpha/\beta}\right)$$

Where $(1+\frac{d}{\alpha/\beta})$ *is relative effectiveness*

$$\frac{E}{\alpha} = D\,(1+\frac{d}{\alpha/\beta}) = BED$$

BED = Biologically effective dose

c) A standard fractionation regimen for a special type of radiotherapy is 2 Gy x 30 fractions given 5 days/ week. Calculate the biological effective dose BED for early effects (α/β = 10) and late effects (α/β = 3)?

2 Gy x 30 = 60 Gy

Early effects *(α/β = 10):*

$$BED = D\,(1+\frac{d}{\alpha/\beta}) = 60\,(1+2/10) = \mathbf{72\ Gy_{10}}$$

Late effects *(α/β = 3):*

$$BED = 60\,(1+2/3) = \mathbf{100\ Gy_{3}}$$

The dose pr. fraction is reduced to 1.5 Gy. How many fractions are needed if

i) the **early** effects
ii) the **late** effects

should be equal to the standard regimens?

1.5 Gy X n

Early effects *(α/β = 10):*

$$BED = D\,(1+\frac{d}{\alpha/\beta}) = n1.5\,(1+1.5/10) = \mathbf{72\ Gy_{10}}$$

$\mathbf{n = 41.7 \approx 42}$

(total dose 63 Gy)

Late effects *(α/β = 3):*

$$BED = n1.5\,(1+1.5/3) = \mathbf{100\ Gy_{3}}$$

$\mathbf{n = 44.4 \approx 44}$

(total dose 66 Gy)

c) Assume that the rate of cellular proliferation is constant throughout the overall treatment time:

$$N = N_0 e^{\lambda t}$$

Where N = number of clonogens at time t, N_0 = initial number of clonogens and λ is a constant. How will the equation of BED be modified due to the tumor proliferation?

$$N = N_0 e^{\lambda t}$$

N = number of clonogens at time t
N_0 = initial number of clonogens

$$2N_0 = N_0 e^{\lambda T_{pot}} \rightarrow ln2 = \lambda T_{pot} \rightarrow \lambda = 0.693/ T_{pot}$$

T_{pot} = potential doubling time of the tumor

The decrease in number of clonogens because of cell killing by the fractionated regimen is balanced to some extent by cell division of the surviving clonogens. The biologic effect E becomes:

$$\boldsymbol{E = n(\alpha d + \beta d^2) - \lambda t} = n(\alpha d + \beta d^2) - 0.693\ t/T_{pot}$$

$$\boldsymbol{BED} = E/\alpha = \boldsymbol{(nd)(1+\frac{d}{\alpha/\beta})} - \boldsymbol{\frac{0.693\ t}{\alpha T pot}}$$

Problem 4

a) What **is linear energy transfer (LET)**? Why is LET an average quantity?

Linear energy transfer (LET) is the energy transferred pr. unit length of the track

*The **LET (L)** of a charged particle in medium is the quotient:*

$$\boldsymbol{L = dE/dl}$$

dE = average energy locally imparted to the medium by a charged particle of specified energy in traversing a distance of dl

Unit: eV / m

*LET is an **average** quantity because at the microscopic level the energy pr. unit length varies over a vide range. The average can be calculated in different ways:*

- ***Track average***

  Divide the track into equal lengths

  – ***Mean of energy deposed in equal lengths***

- ***Energy average***

  Divide the track into equal energy increments

  – ***Averaging the lengths of tracks with equal energy***

b) Define the concept **relative biological effectiveness (RBE)**.

*The RBE of **a test radiation** compared with a **reference radiation** is defined by:*

$$RBE = \frac{Dose\ of\ reference\ radiation}{Dose\ of\ test\ radiation} = \frac{Dref}{Dtest}$$

*Where D_{ref} and D_{test} are the doses of reference and test radiation required for **equal biological effect***

c) A typical dose survival curve (in a linear-logarithmic plot) for X-rays has a characteristic shoulder. A corresponding survival curve for neutron radiation shows no such shoulder. Using X-rays as reference radiation and neutrons as testradiation, what happens to RBE when

- Increasing the survival fraction (corresponding to lowering radiation dose)?
- Giving the X-ray and neutron radiations in several fractions separated with enough time to secure repair of sublethal damages?

Survival curves of neutrons (test) and X-rays (reference)

RBE = ratio of doses producing the same biological effect

Because the X-ray and neutron survival curve have different shapes, the resultant RBE depends on the level of biological damage (dose) chosen.

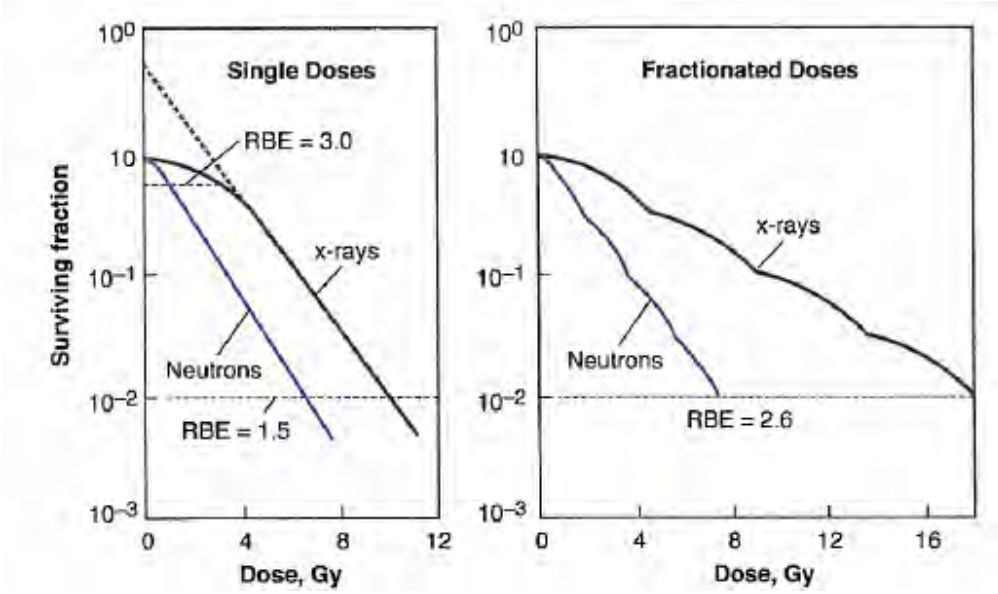
RBE generally increase as the dose is decreased, reaching a limit value that is the ratio of the initial slopes of the x-ray and neutron survival curves

Fractionation:

Neutrons become progressively more efficient than X-rays as the dose pr. fraction is reduced (the number of fractions is increased)

*→ **RBE successively increase** with increasing fractionation*

*(For **continuous low dose** irradiation (= limit of fractionation with infinitesimal doses) the shoulder will disappear and **RBE will reach a maximum value*** corresponding to the limit slope of the survival curve)

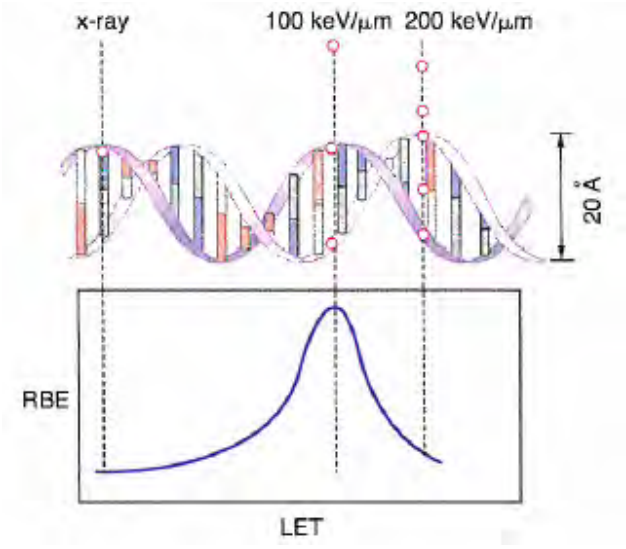


d) Why has radiation with LET of about 100 keV/μm the greatest values of RBE?

LET≈ 100 keV/μm:

*the average separation between ionizing events **coincides with the diameter of DNA double helix** (2 nm)*

*Radiation of this density has the **highest probability of causing a double strand break (DSB)** by the passage of a single charged particle*



Sparesly ionizing radiations (LET<<200 keV/μm) (X-rays):

low probability of single track causing DSB

More than one track required

Low relative biological effectiveness RBE

Densely ionizing radiations (LET>200 keV/μm)

Readily produce DSB

Energy «wasted» because the events are too close together

Have lower RBE than optimal LET

Is just as effective per track but less effective pr unit dose

d) Sketch out a typically depth dose curve for proton radiation. Why is use of protons a very good alternative to photons in radiation therapy?

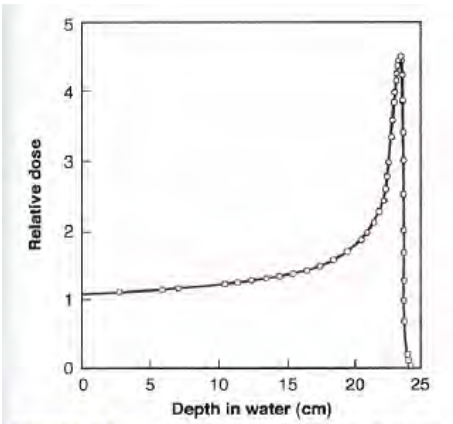


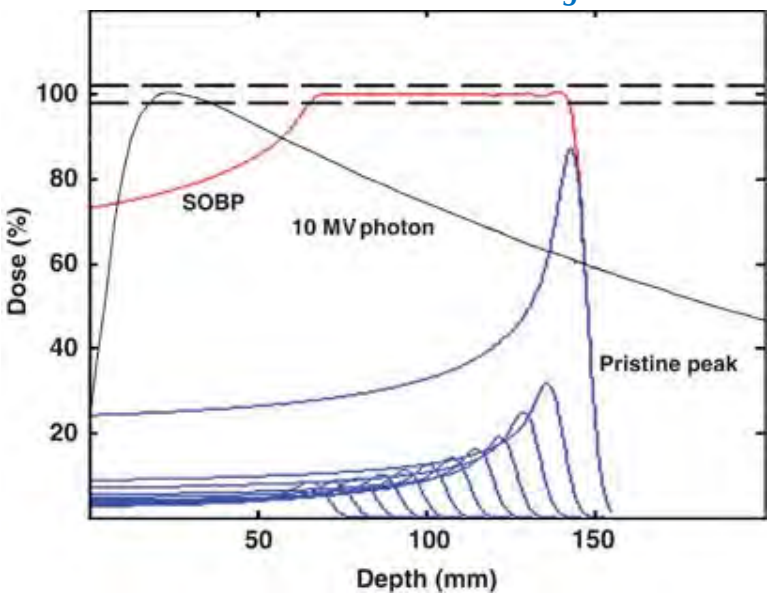
FIGURE 25.2 Depth-dose curve for 187-MeV protons from the Uppsala synchrocyclotron. The dose reaches a sharp peak at a depth of about 23 cm.(Adapted

The dose deposited by beam of monoenergetic protons:

- *increase slowly with depth*
- *reach a sharp maximum near the end of the particles' range* ***(Bragg peak)***
- *falls to zero after the Bragg peak, at the end of the particles' range*
- *The Bragg peak occurs at a depth in tissue depending on the initial energy of the protons*
- *The beam has sharp edges with little side scatter*

Good possibilities to:

- ***precisely confine the high dose region to the tumor volume***
- ***minimize the dose to surrounding normal tissue***



Red line: Spread out Bragg peak in a typically therapeutic radiation distribution.
The depth dose plot of a 10 MV photon beam is provided for comparison

Proton therapy delivers a lower absorbed dose to normal tissues than high energy X-rays for the same dose to target volume

- ***Little differences in the radiobiological properties of protons used for therapy and high energy X-rays concerning***
  - ***repair,***
  - ***OER,***
  - ***response through cell cycle***

The only relevant difference therefore is the dose distribution

- ***Marked advantage…***
  - *Clinical results lean in that direction*