Radiobiology: A Briefing for the Brachytherapist

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Plan of Presentation:

- *Who needs radiobiology*?
- *The nuts and bolts* (kinds of effects, dose-response curves, hits, temporal aspects, RBE and OER, cellular proliferation)
- *Mechanisms of radiation action* (rudiments of microdosimetry, LQ model, temporal aspects redivivus)
- *Applications* (equivalent treatments, radiation quality)

The role of radiobiology in treatment planning is threefold:

- To provide information on biologically-equivalent temporal patterns of dose delivery
- To quantify the effect of radiation quality (relevant to low-energy brachytherapy)
- To guide biologically-based optimization algorithms

Kinds of Effects:

- ***Stochastic*** (all or none): where radiation has no effect on the nature of the observed outcome; instead, it may change the *probability* of causing the effect.

- ***Deterministic***: where the severity of the effect may change as a function of dosage.

Exercise: classify the following as stochastic or deterministic

- Effect of radiation on normal tissues
- Normal tissue complication probability (NTCP)
- Tumor control probability (TCP)
- Answering correctly these questions (including this one…)

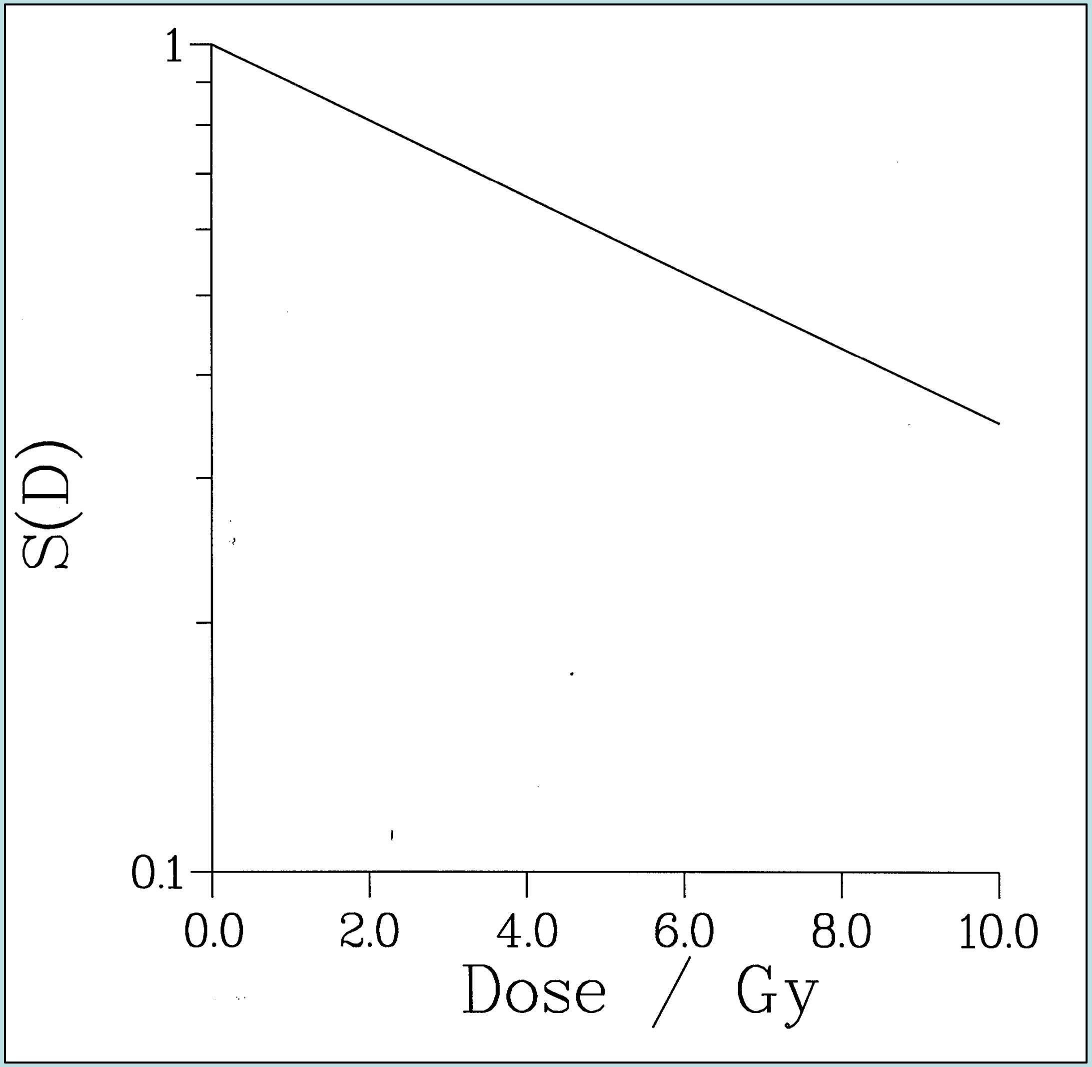
Notation and conventions:

- E(D): probability of effect (any effect!)
- S(D)=1-E(D): probability of the ***absence*** of effect (aka *survival probability*, although nothing needs to actually survive…)

Dose response curves are important because they help us understand, for instance, whether:

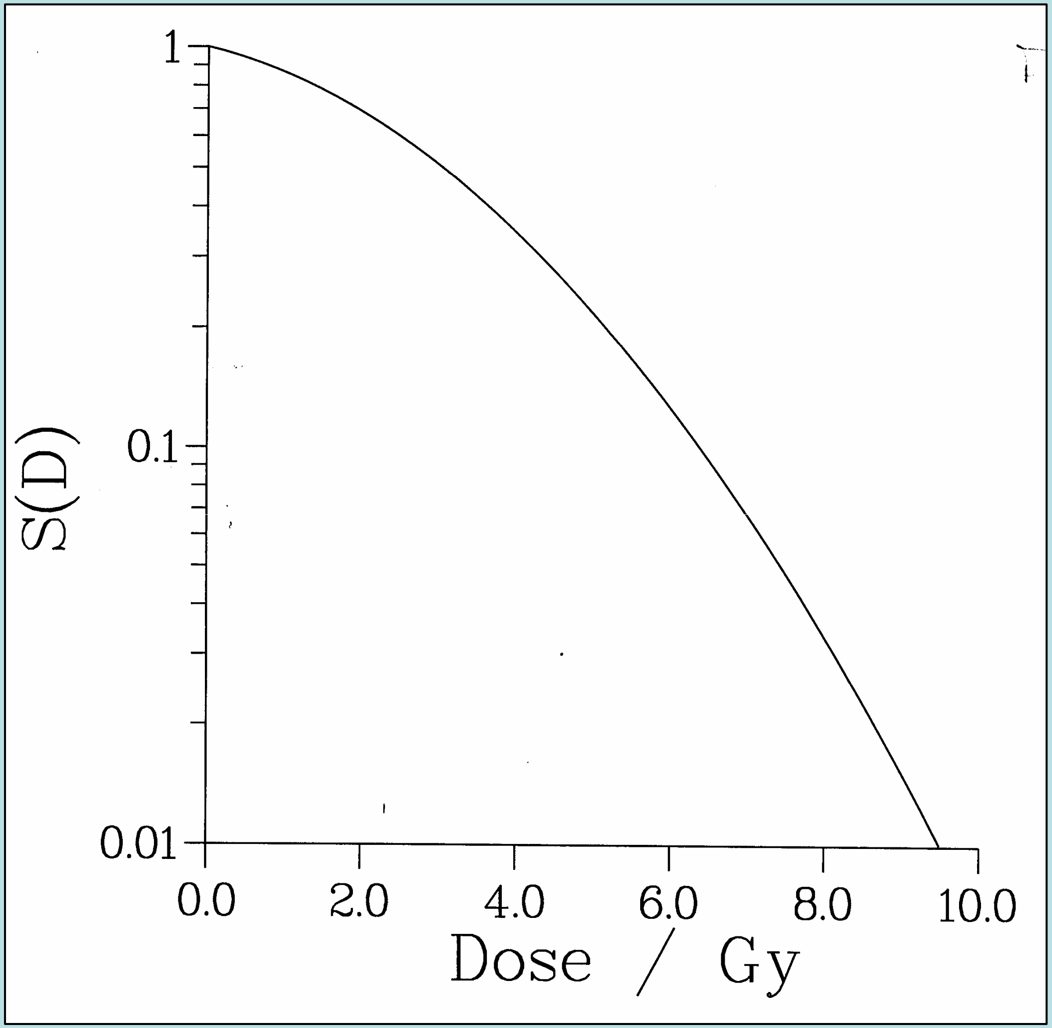
- the effect is a result of single or multiple radiation-induced lesions
- the temporal pattern of dose delivery matters
- the outcome depends of the position of the cell in the cell cycle
- the radiation-induced damage is repairable

$$S(D) = e^{-\alpha D}, \quad \alpha > 0$$



An ***exponential*** dose response curve indicates a ***single-hit*** mechanism of radiation action

$$S(D) = e^{-\alpha D - \beta D^2},$$
$$\alpha, \beta > 0$$

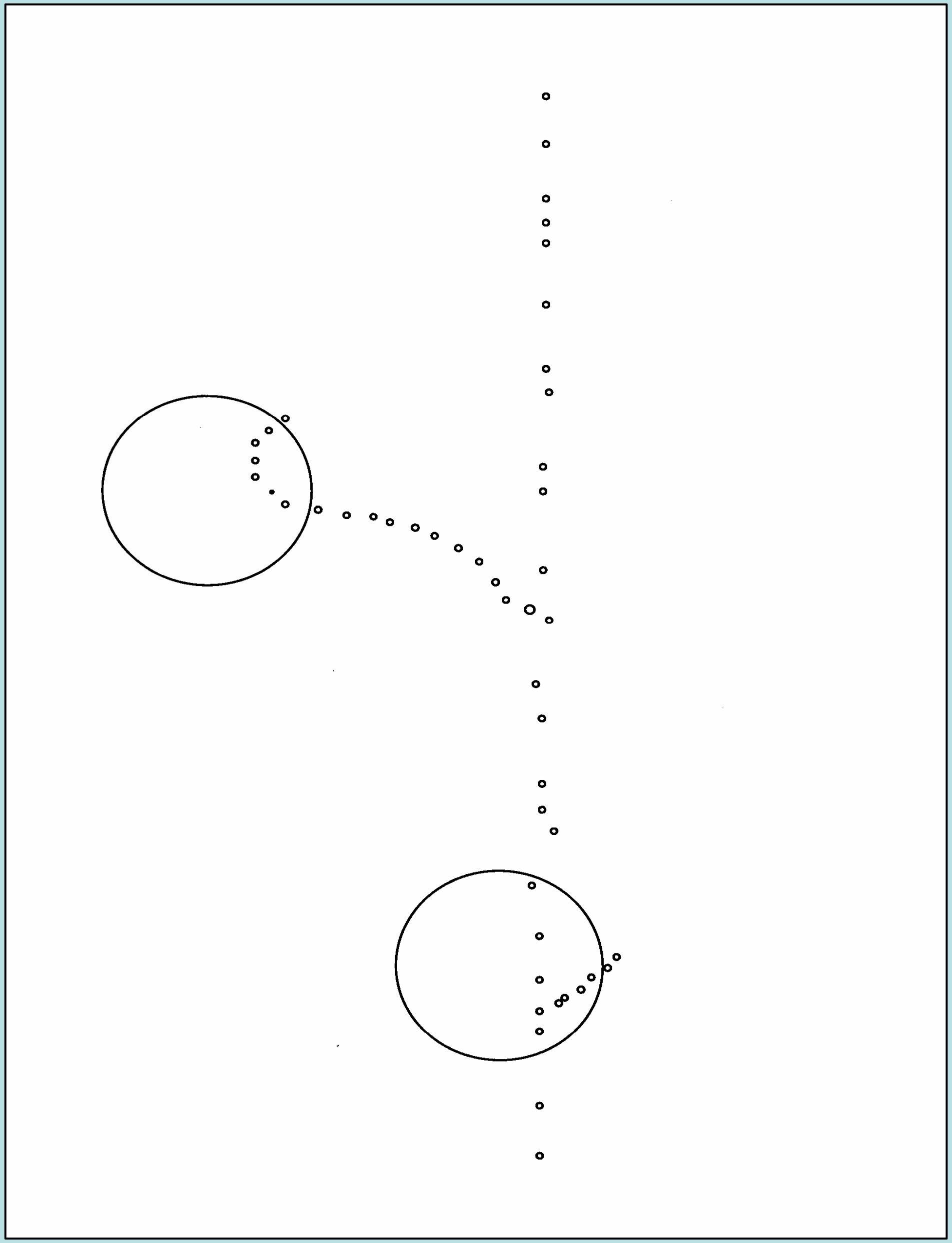


A concave downward dose effect curve shows an accumulation of sublesions and represents a ***multi-hit*** mode of radiation action.

Interpretation:

- *Exponential* response: Surviving cells have no memory of previous exposure to radiation (single-hit effect)

- *Concave* response: cells carry residual damage (*sublesions*), several of which produce *lesions* (multi-hit effect)

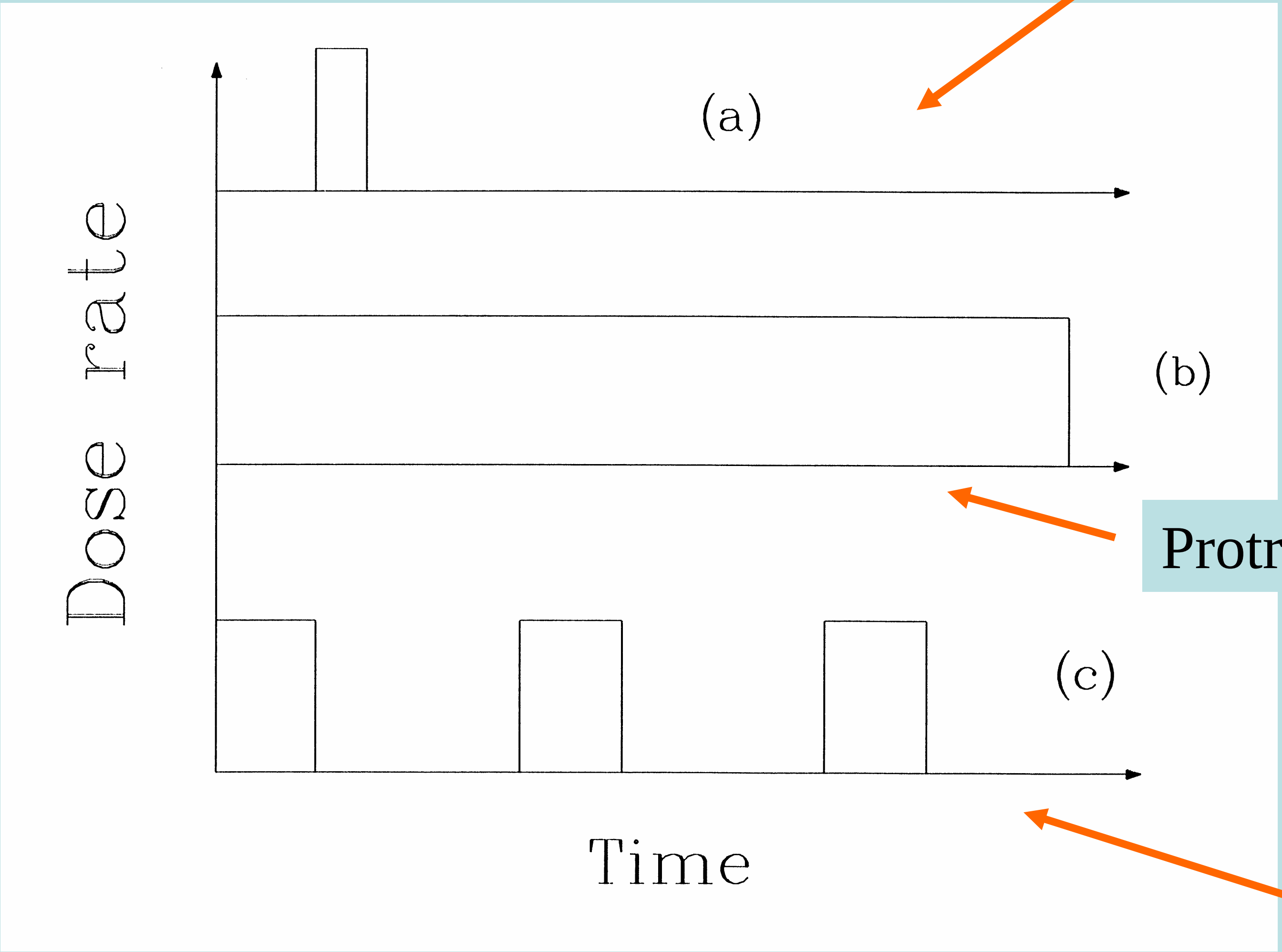


Hits: what are they?

The dots indicate the locations of energy deposition (ionizations or excitations) by a hypothetical charged-particle track in tissue. Also shown are two cells – one traversed by the main track and the other by a secondary electron (delta ray). The ensemble of energy deposition sites within the radiosensitive volume which are associated with one track defines a (microdosimetric) ***event***.

Different patterns of dose delivery:

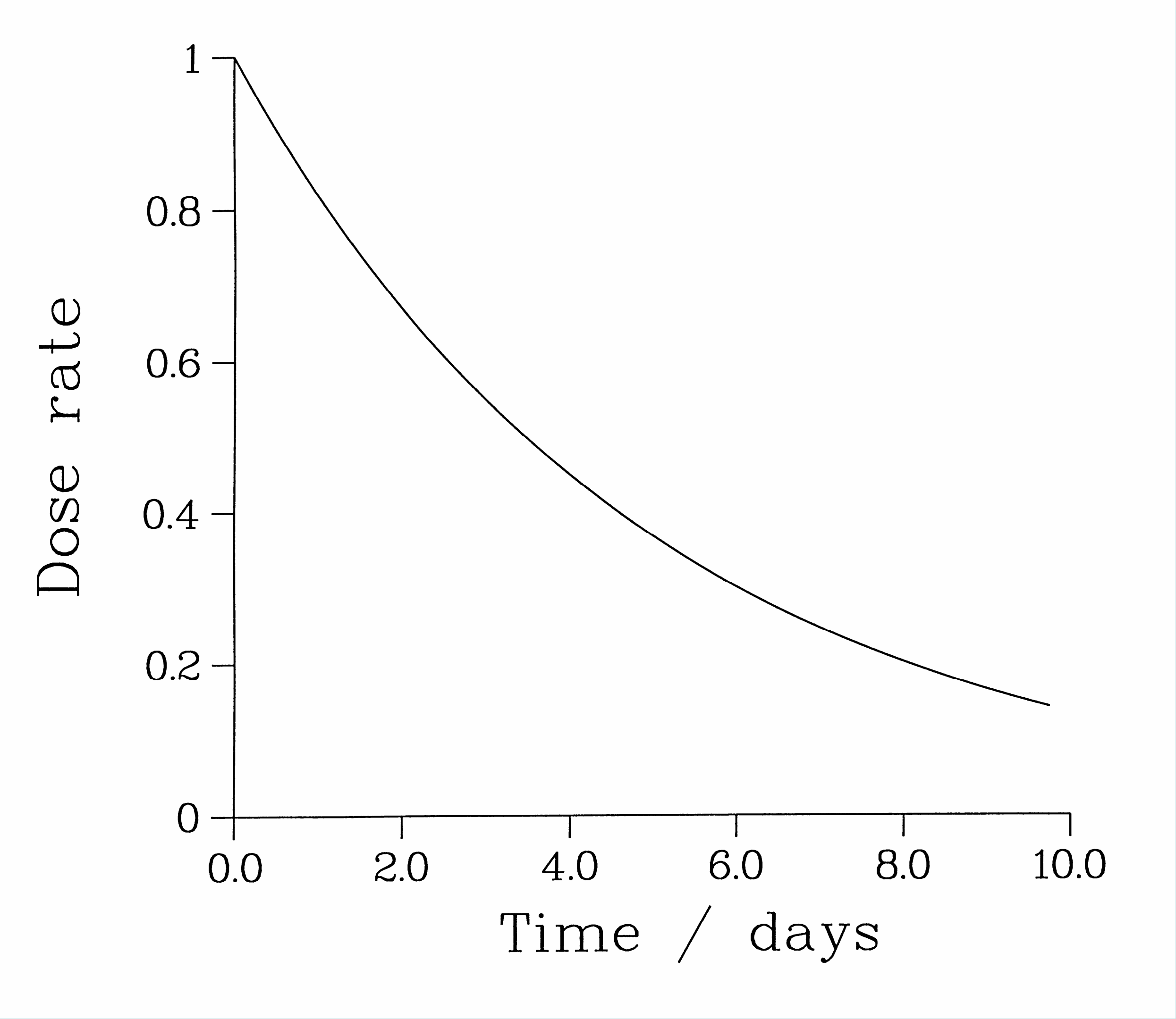
Single (acute) exposure



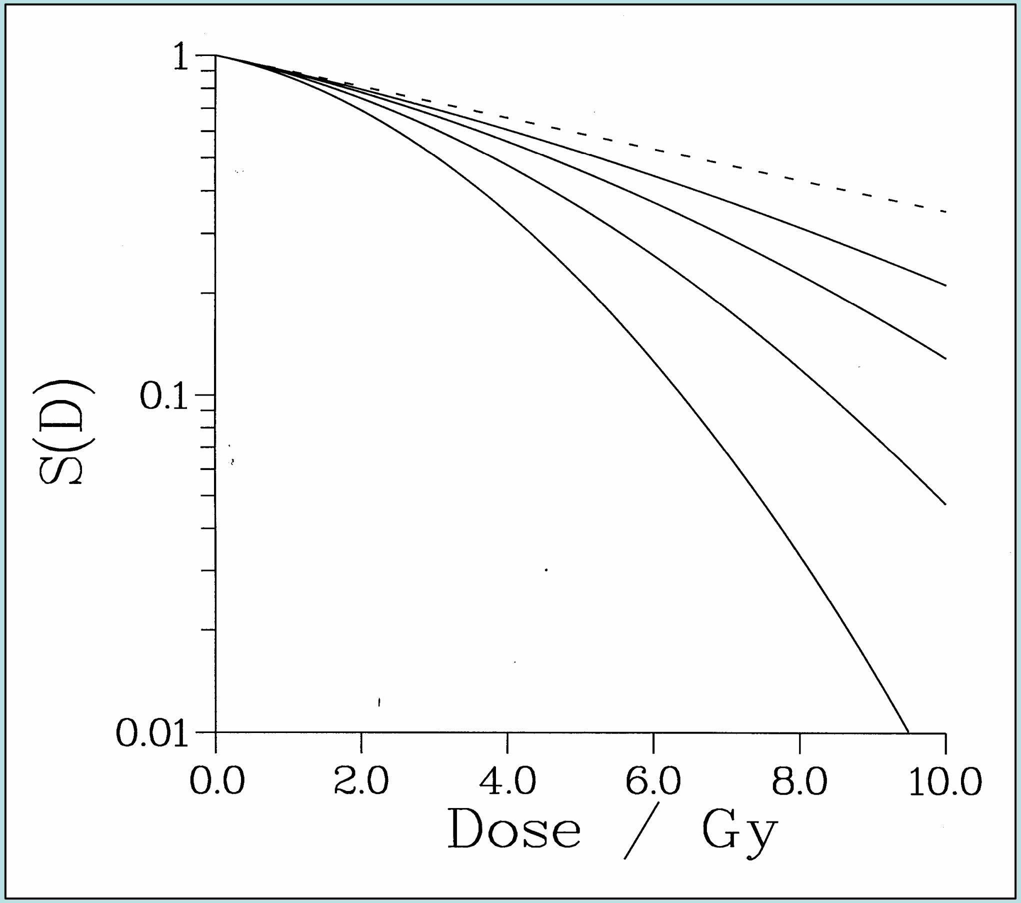
Protracted irradiation

Fractionation

Treatment with an exponentially-decaying dose rate (this is typical of brachytherapy):



Temporal aspects:



As the dose rate decreases the quadratic term (βD^2) becomes increasingly smaller. At very low dose rates only the linear term, αD, remains (dashed curve). Lower solid curve: acute exposure; upper dashed curve: protracted exposure.

Terminology:

- ***Event*** (physical hit): the traversal of a cell by an ionizing particle. Events are instantaneous, and occur randomly in space and in time.
- ***Lesion*** (biological hit): cellular damage that results in the observed effect
- ***Sublesion***: damage not sufficient to produce the effect but enough to enhance its induction probability at subsequent exposures.
- ***Low dose***: dose where the effect is proportional to dose and independent of dose rate

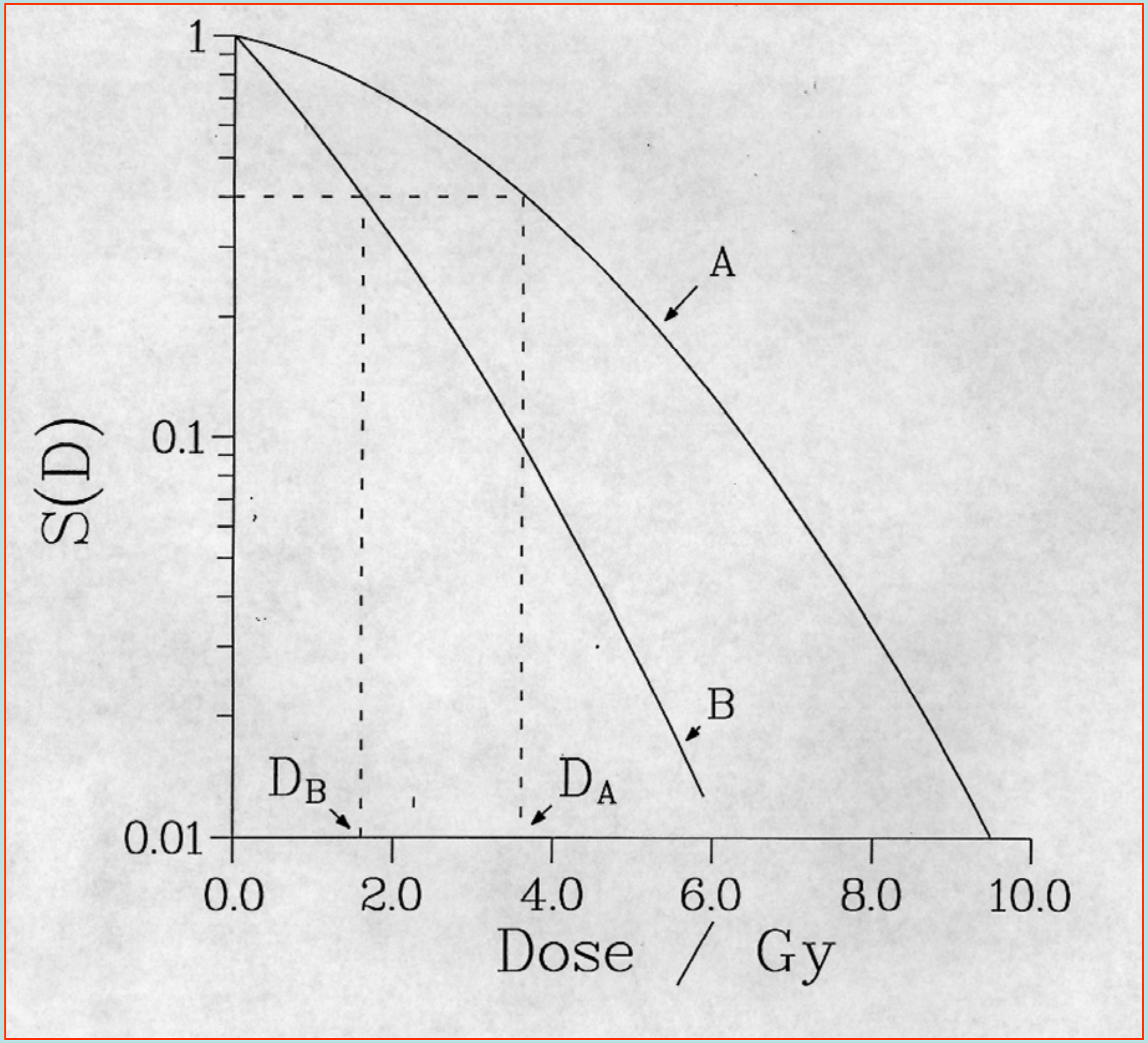
Definition of *Relative Biological Effectiveness* (RBE)

A comparison of two ionizing radiations for producing the same biological effect.

$$RBE = \frac{\text{Dose of } \textit{reference} \text{ radiation to give some biological effect}}{\text{Dose of } \textit{test} \text{ radiation to give the } \textit{same} \text{ effect}}$$

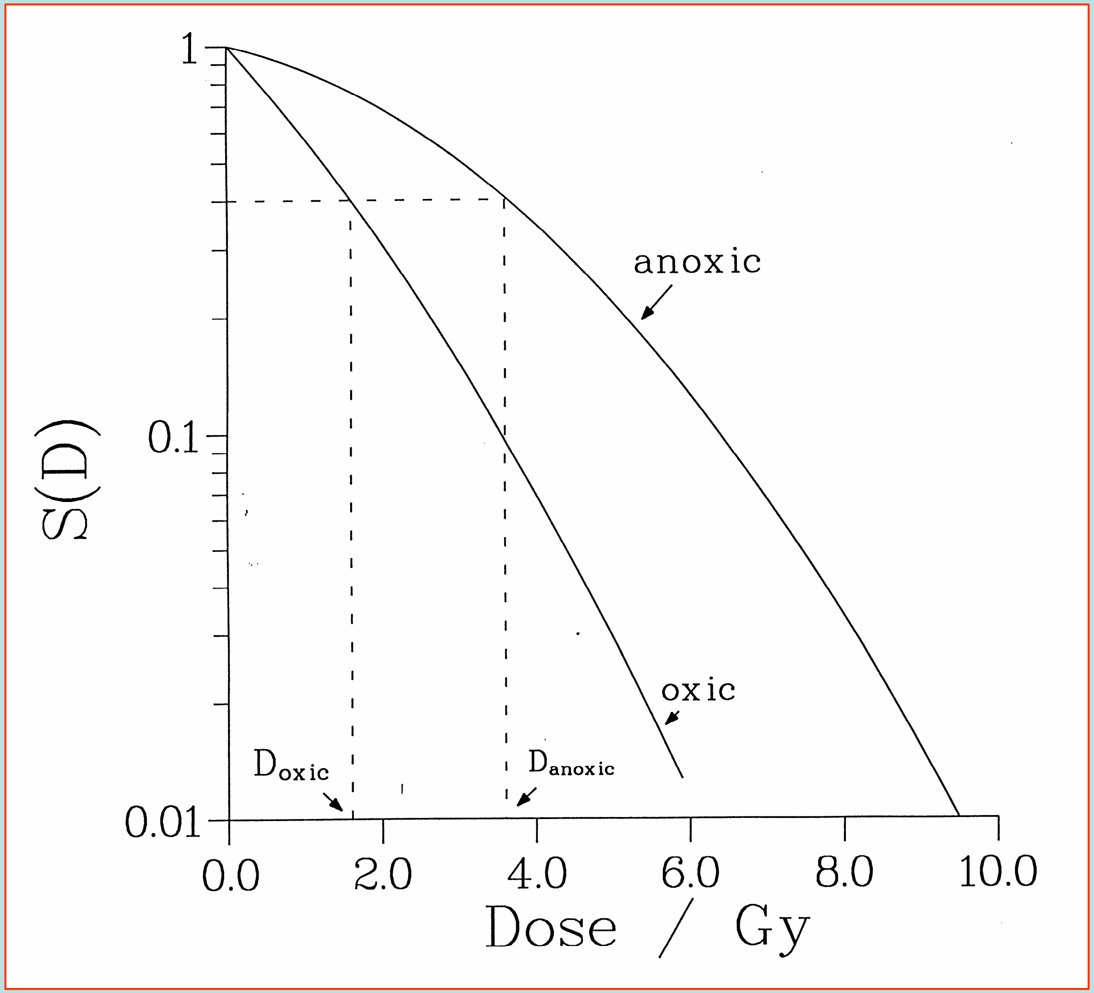
(all other experimental condition being equal)

Relative Biological Effectiveness (RBE)



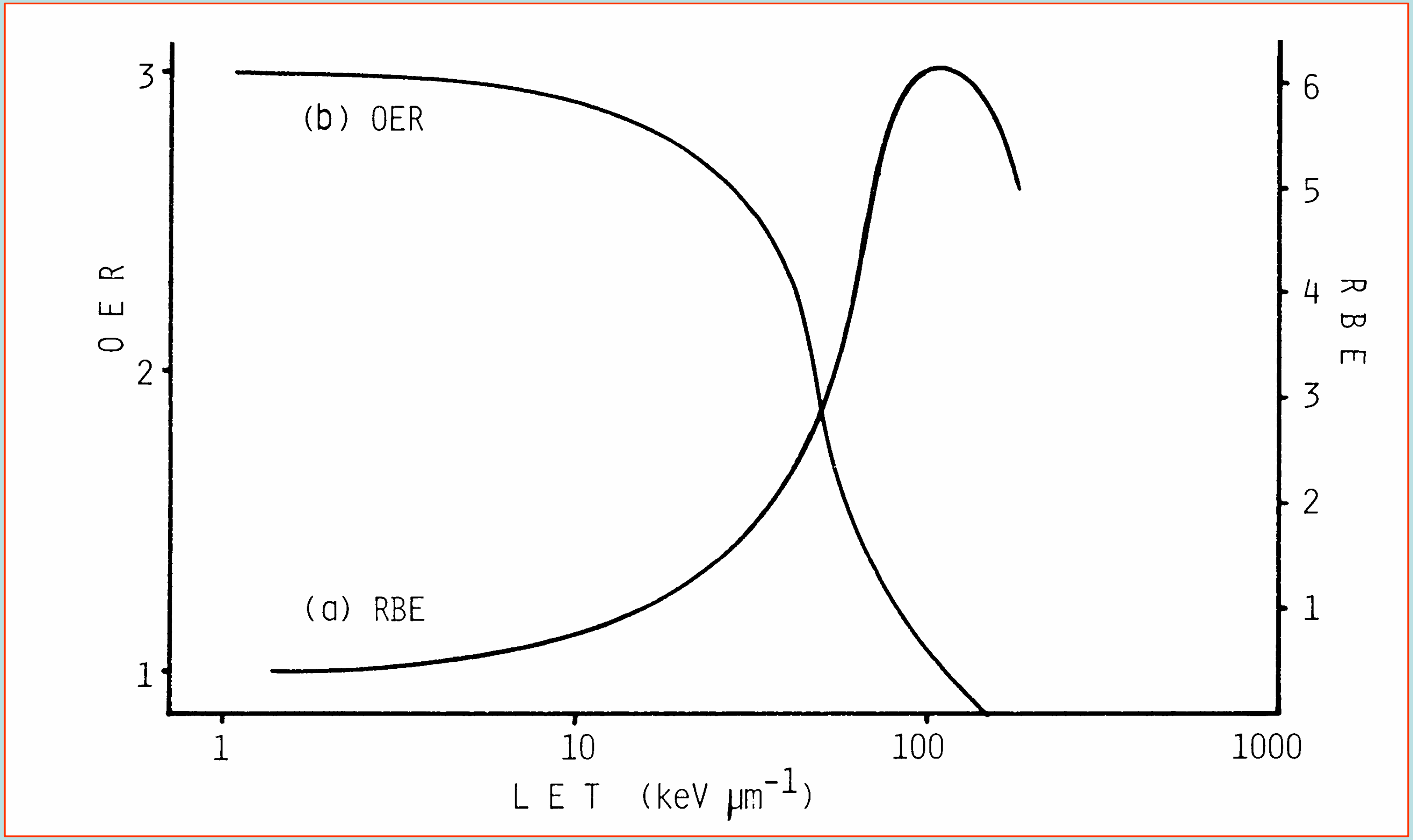
$$RBE = \frac{D_A}{D_B}$$

Oxygen enhancement ratio (OER)



$$OER = \frac{D_{anoxic}}{D_{oxic}}$$

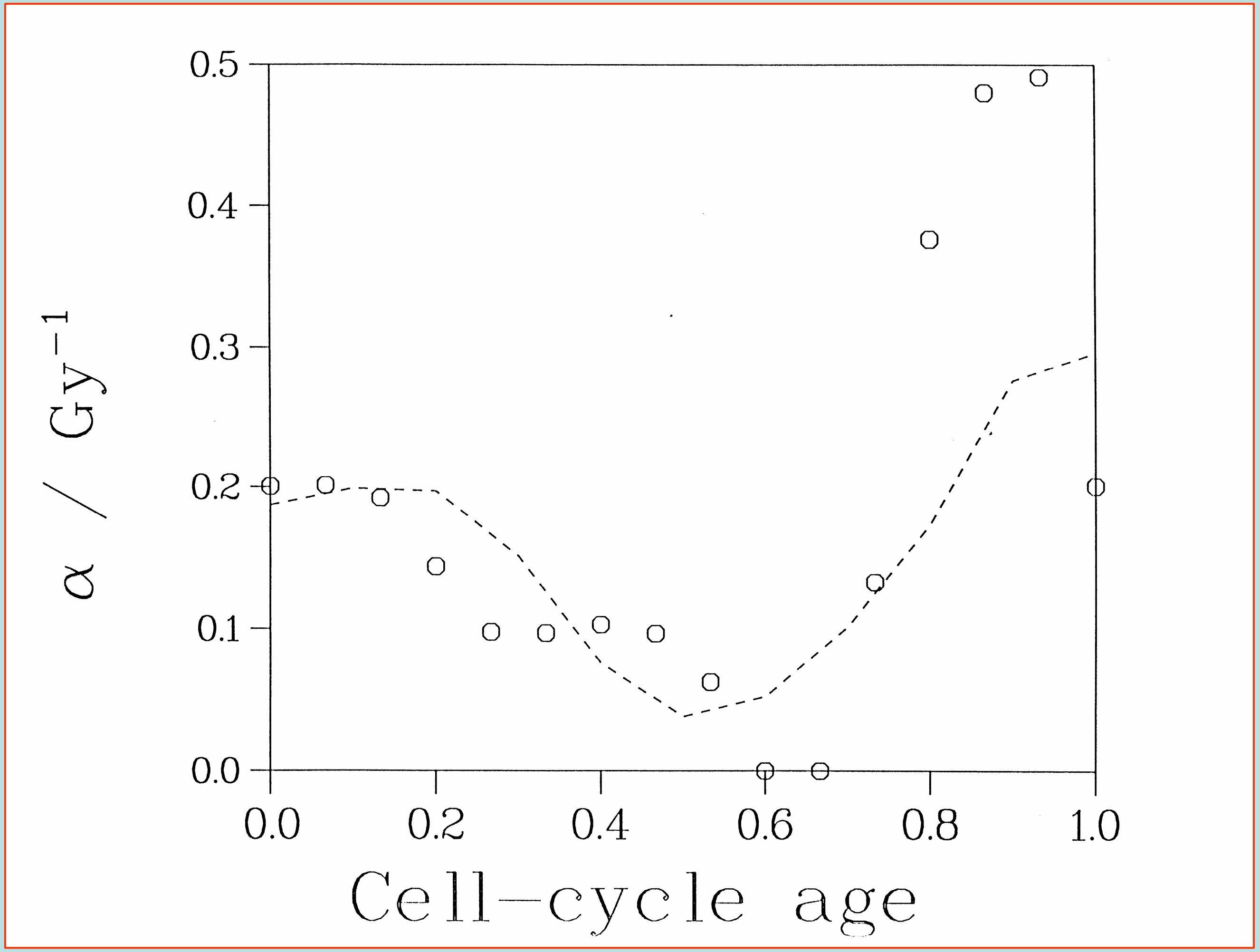
RBE and OER as a function of LET



Cellular proliferation

- The cell cycle of actively dividing cells is conventionally divided in four stages: G1, S, G2 and M.
- Cells are most radiosensitive in M phase and most radioresistant in the latter part of S
- Exposure to radiation results in a lengthening of the G2 phase (this is known as the *G2 block*)
- Exposure to radiation decreases the division probability

α and β (and thus RBE) depend on cell-cycle age



Cell proliferation in tumors

- Proliferating cells (P)
- Quiescent cells (Q) in G_0
- Differentiated cells (sterile)
- Necrotic cells

Transfer of cells between compartments

- Q to P (recruitment)
- P to Q
- *Cell loss*: failure to divide, differentiation, leaving the tumor volume (metastasis), death

Tumor growth rate

- $\mathbf{T_d}$ = tumor volume doubling time
- $\mathbf{T_c}$ = cell cycle time (clonogen doubling time)
- $\mathbf{T_{pot}}$ = potential doubling time (no cell loss)
- Cell loss factor: $\varphi = 1-T_{pot}/T_d$
- **GF**=growth factor (fraction of cells actively proliferating)

Kinetic parameters of a typical human tumor

- Cell cycle time (T_c): ~ 2 days
- Growth fraction: ~ 40%
- Potential doubling time (T_{pot}): ~ 5 days
- Cell loss: ~ 90%
- Volume doubling time (T_d): ~ 60 days

The kinetics of cell growth:

$$T_d = T_c \frac{1}{1-\varphi} \frac{\ln 2}{\ln(1+GF)}$$

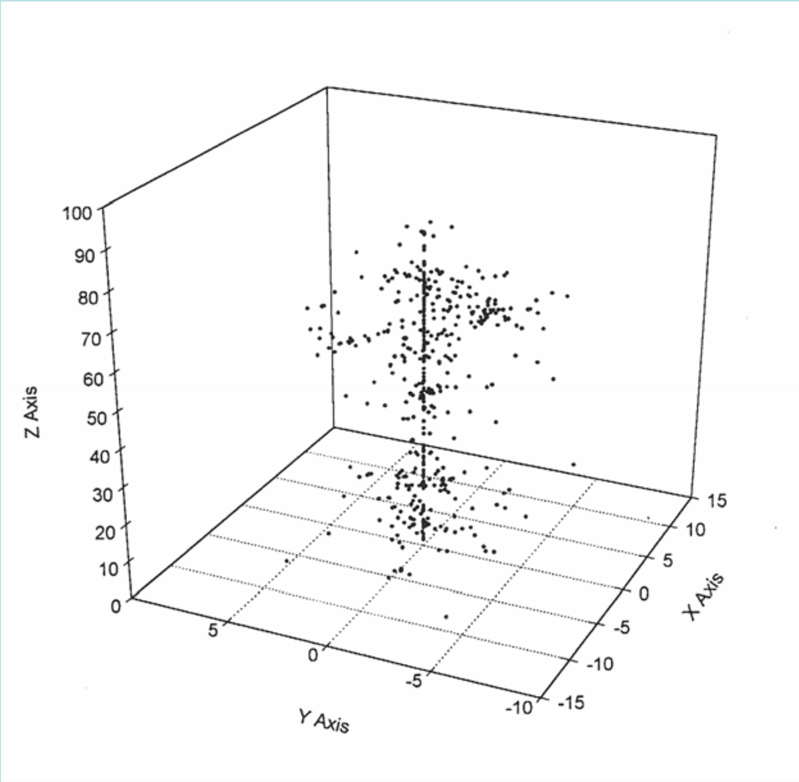
$$T_{pot} = T_c \frac{\ln 2}{\ln(1+GF)}$$

$$\varphi = 1 - \frac{T_{pot}}{T_d}$$

Microdosimetry is the systematic study and quantification of the *spatial* and *temporal* distribution of absorbed energy in irradiated matter. It deals with the *stochastics* of energy deposition.

Ionizing radiation is uniquely efficient in its action on matter (including living matter) because:

- it transfers energy in a highly concentrated form,
- ionizations are produced in spatially correlated patterns in the tracks of charged particles.



Definitions (I):

- Ionizing particles: charged or uncharged particles capable of ionization in primary or secondary interactions.
- Energy deposit: $\varepsilon_i = T_{in} - T_{out} + Q$
- Transfer point: the point of interaction
- Energy imparted in a volume (site): $\varepsilon = \sum_i \varepsilon_i$
- Specific energy:

$$z = \frac{e}{m}$$

Definitions (II):

- Absorbed dose: $$D = \lim_{V \to 0} \bar{z}$$

- Frequency distributions: $f(z)$, $f_1(z)$, $f(y)$
- Dose distributions:

$$d(z) = \frac{z f(z)}{D}$$

Definitions (III):

- Frequency averages:

$$z_F = \int_0^\infty z\, f_1(z)dz$$

- Dose averages:

$$z_D = \frac{1}{z_F}\int_0^\infty z^2\, f_1(z)dz$$

- Event frequency: $n = \frac{D}{z_F}$

A microdosimetric account of the LQ formalism

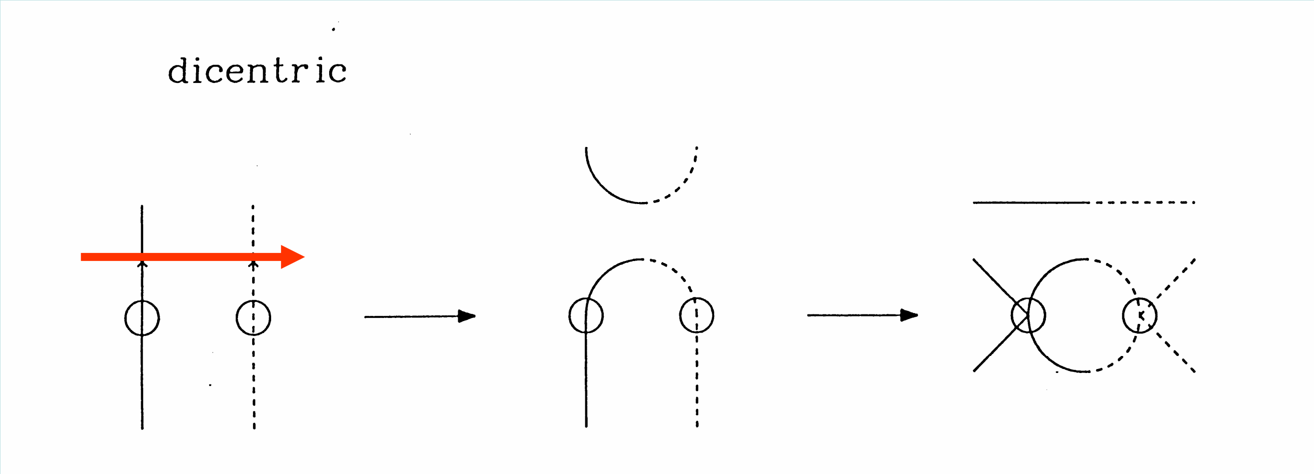
$$E(z) = \beta\, z^2$$

$$\overline{E(D)} = \beta\ \overline{z^2} = \beta\,(z_D D + D^2)$$

$$z_D = \frac{\alpha}{\beta}$$

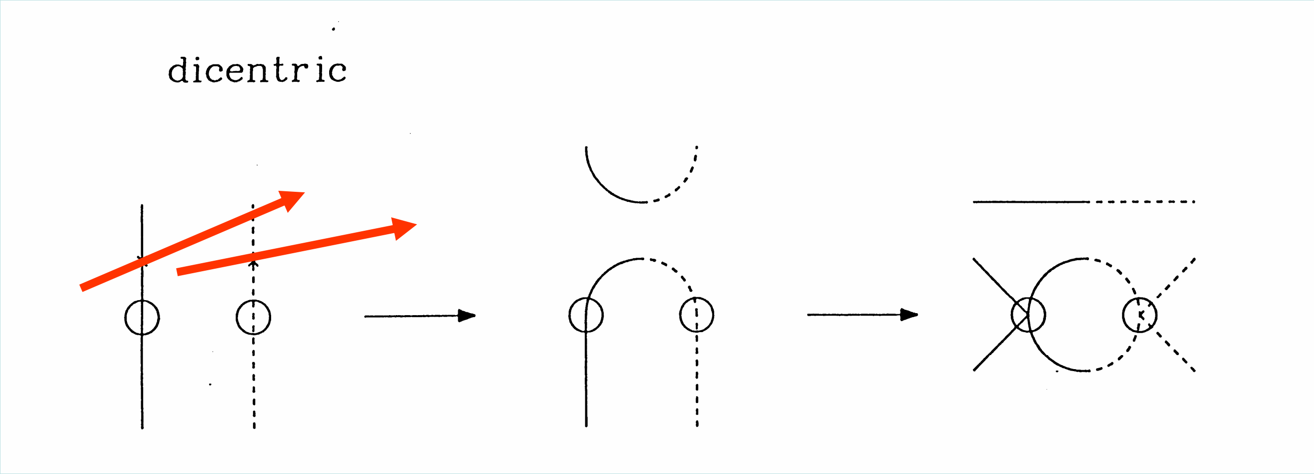
$$\overline{\varepsilon(D)} = \alpha D + \beta D^2$$

Intra-track event (single track)



$\Rightarrow \alpha D$

Inter-track event (two tracks)



$\Rightarrow \beta D^2$

Temporal aspects (II):

$$\overline{\varepsilon(D)} = \alpha D + q(t)\beta D^2$$

$$q = \int_0^\infty \tau(t)h(t)dt$$

q(t/τ)

For irradiation at a constant dose rate (t=irradiation time, τ= mean repair time)

$$r = \frac{t}{\tau}$$

$$q(r) = \frac{2}{r} - \left(\frac{2}{r^2}\right)\left(1 - e^{-r}\right)$$

To find equivalent treatments use:

$$\alpha D + \beta q D^2 - \frac{t}{T_{pot}} = \alpha_1 D_1 + \beta_1 q_1 D_1^2 - \frac{t_1}{T_{pot,1}}$$

t= total treatment time

T_{pot}= mean potential doubling time

τ= mean repair time of sublesions

For f fractions: **q=1/f**

For t >> τ : **q=2τ/t** (τ~1 hour)

Other relations: t=D/R (R=dose rate)

Some typical numerical values

$$\tau = 0.5 \;\; h \quad (repair \;\; time)$$

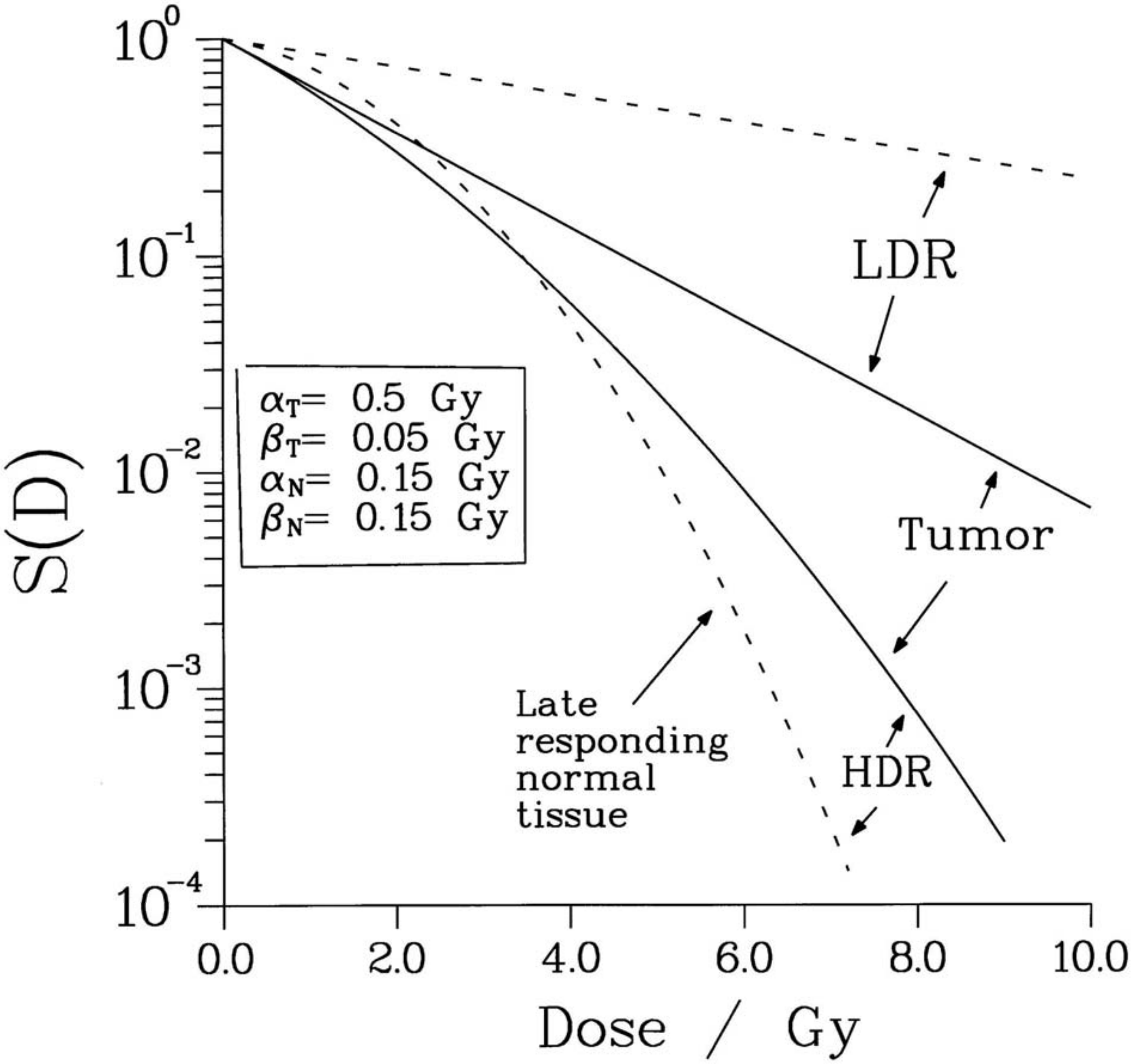
$$(\alpha / \beta)_{early-responding} = 10 \;\; Gy$$

$$(\alpha / \beta)_{late-responding} = 3 \;\; Gy$$

$$({}^{125}I) \; \dot{D}_{LDR} = 0.07 \;\; Gy / h$$

$$({}^{103}Pd) \; \dot{D}_{LDR} = 0.20 \;\; Gy / h$$

$$\dot{D}_{HDR} = 90 \;\; Gy / h$$



S(D)
10^0
10^{-1}
10^{-2}
10^{-3}
10^{-4}
0.0
2.0
4.0
6.0
8.0
10.0
Dose / Gy
α_T= 0.5 Gy
β_T= 0.05 Gy
α_N= 0.15 Gy
β_N= 0.15 Gy
LDR
Tumor
HDR
Late responding normal tissue

Radiation quality

Radionuclide	$z_D/z_D(Co)$
Pd-103	2.3
I-125	2.1
Am-241	2.1
Ir-192	1.3
Co-60	1.0