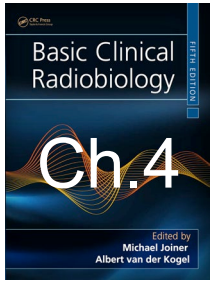
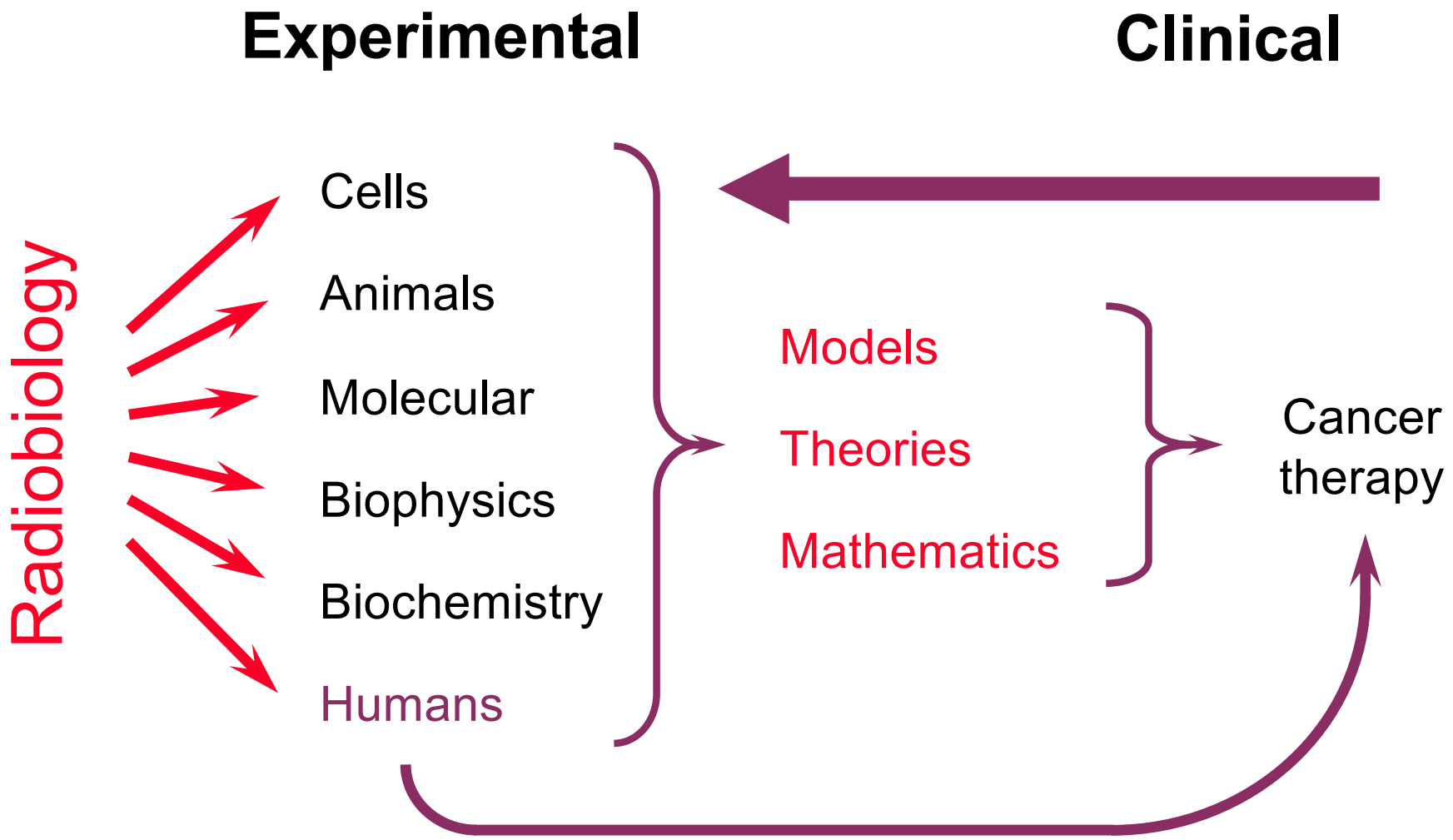
Basic Clinical Radiobiology

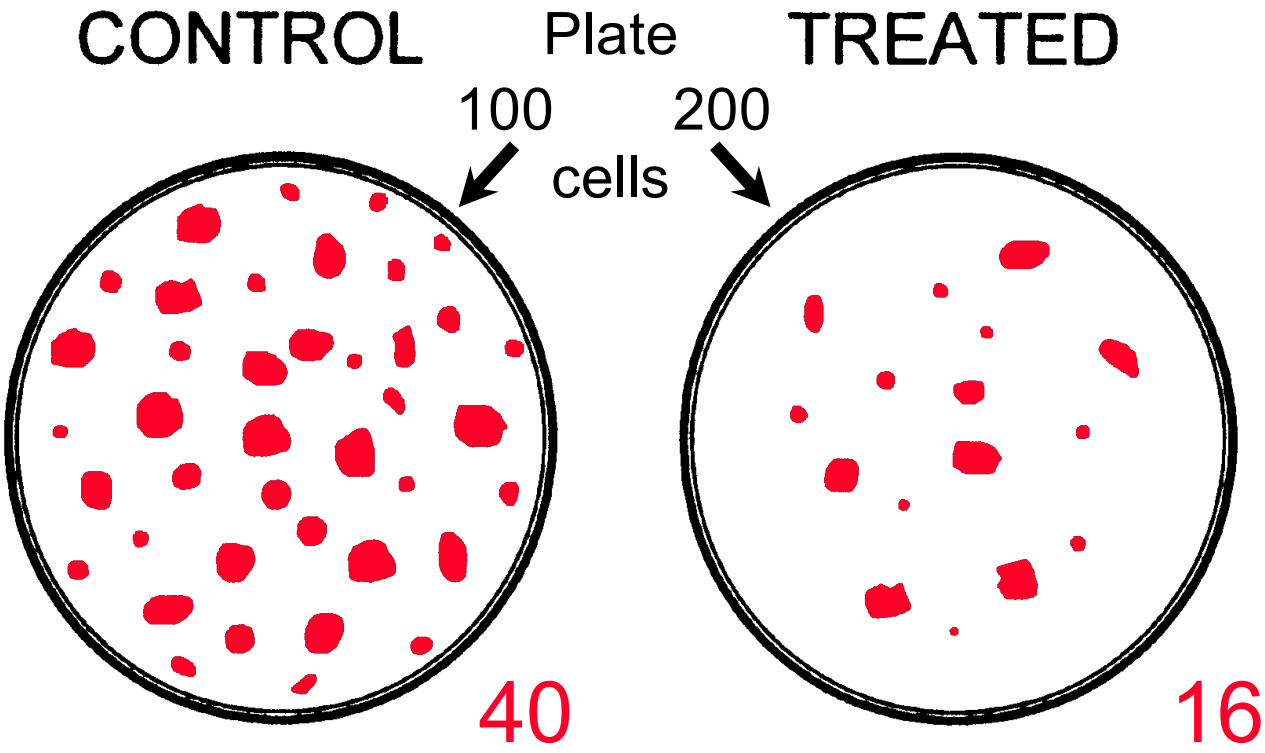
Quantifying cell kill and cell survival

Michael Joiner



Toronto 2022


Experimental
Clinical
Radiobiology
Cells
Animals
Molecular
Biophysics
Biochemistry
Humans
Models
Theories
Mathematics
Cancer therapy

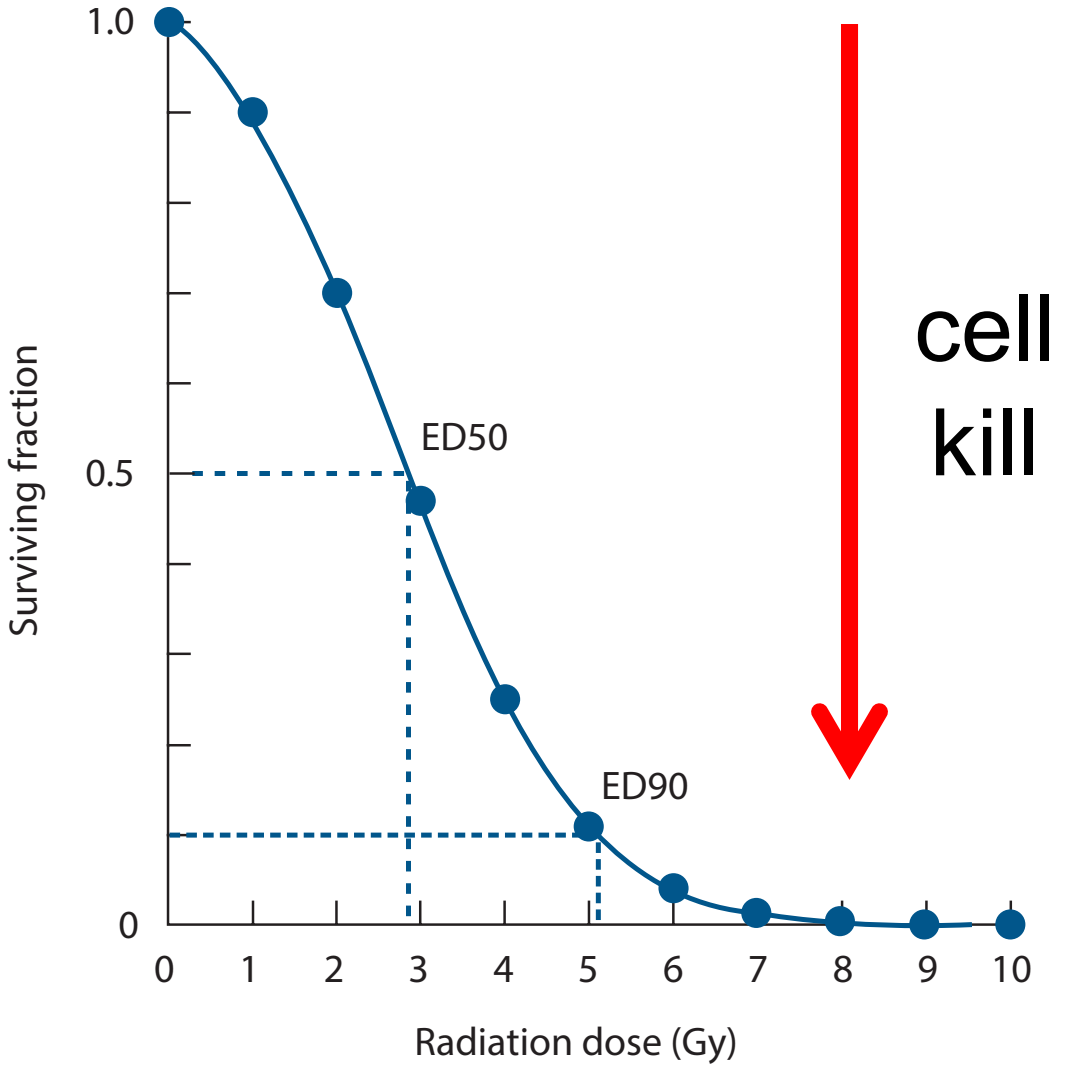


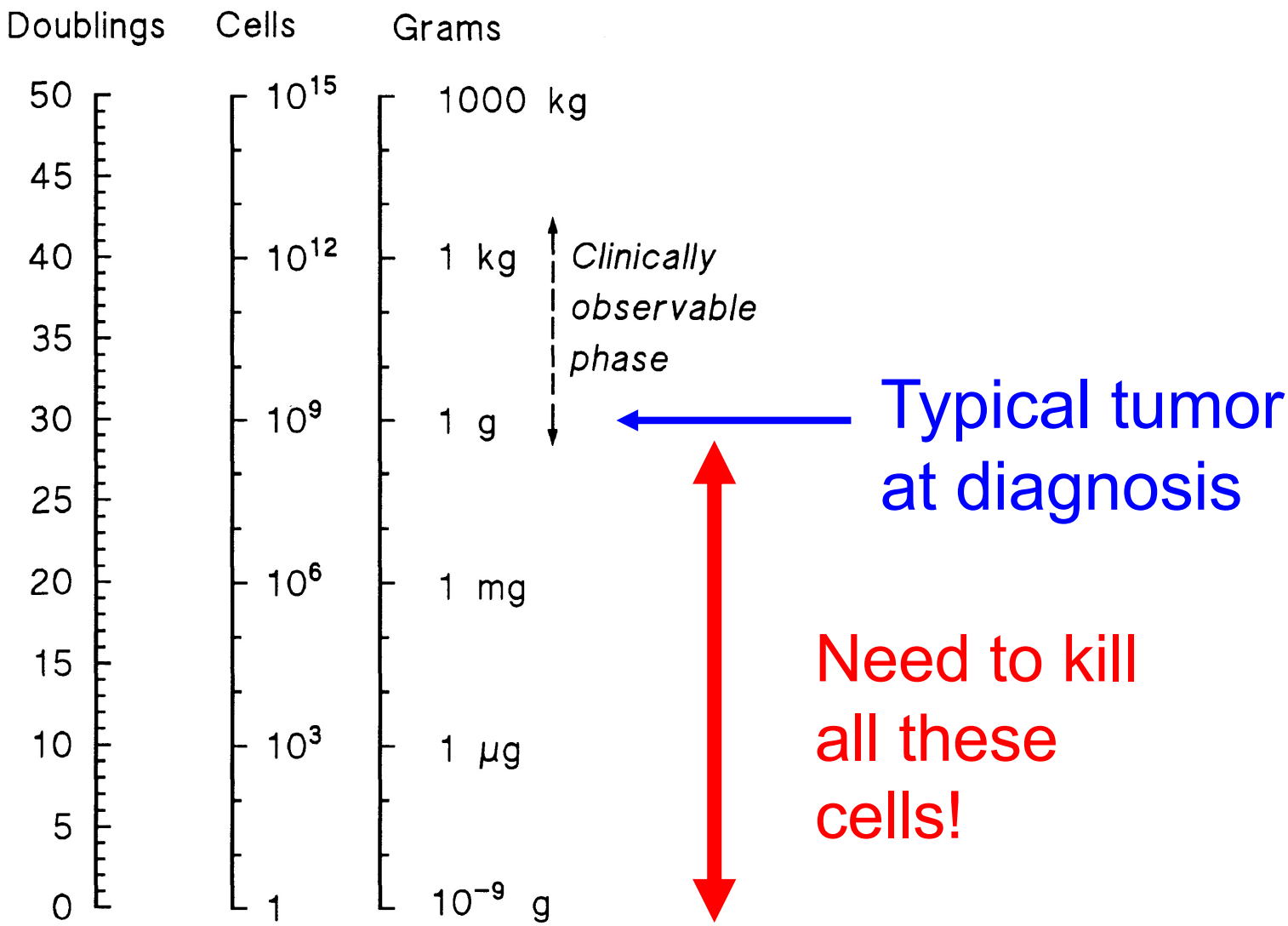
Plating efficiency (PE)

40/100 = 0.4 16/200 = 0.08

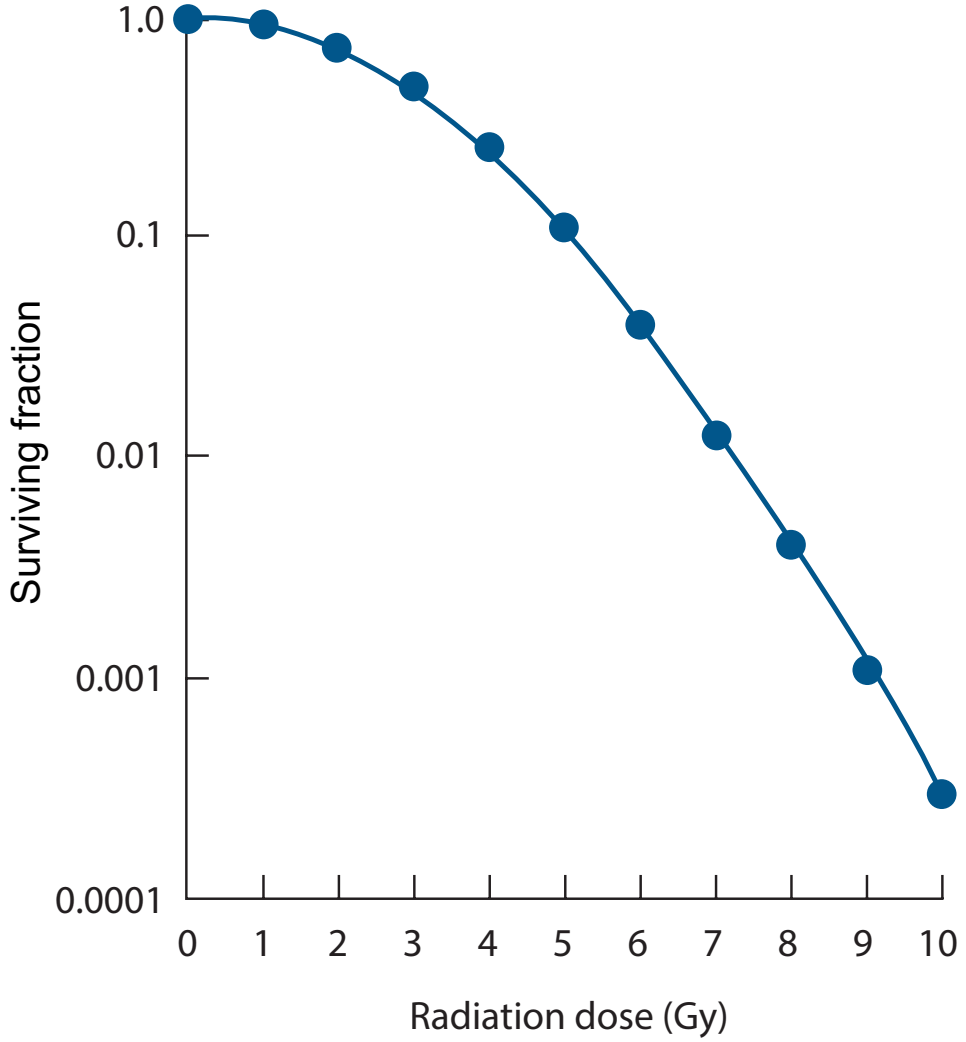
Surviving fraction (SF) = 0.08/0.4 = 0.2

Linear scale of
Surviving fraction




Doublings
Cells
Grams
50
45
40
35
30
25
20
15
10
5
0
10^{15}
10^{12}
10^{9}
10^{6}
10^{3}
1
1000 kg
1 kg
1 g
1 mg
1 μg
10^{-9} g
Clinically observable phase
Typical tumor at diagnosis
Need to kill all these cells!

Plot
Surviving Fraction
on a
Log scale



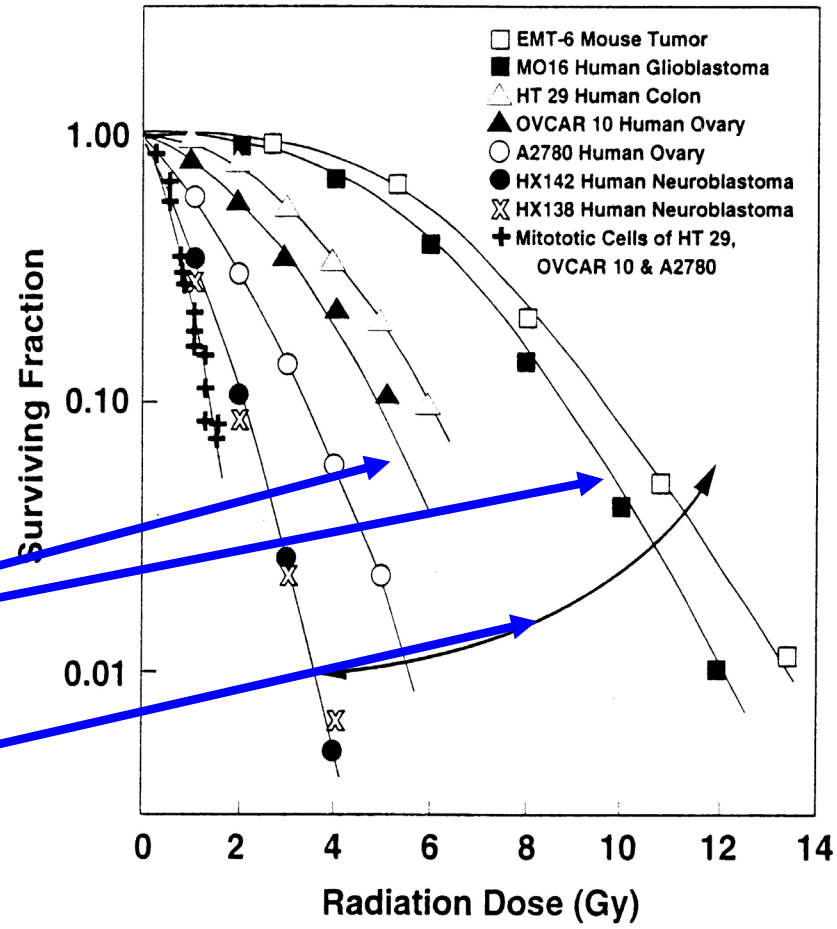
Cell sensitivity to radiation

Cells show a wide range of sensitivity

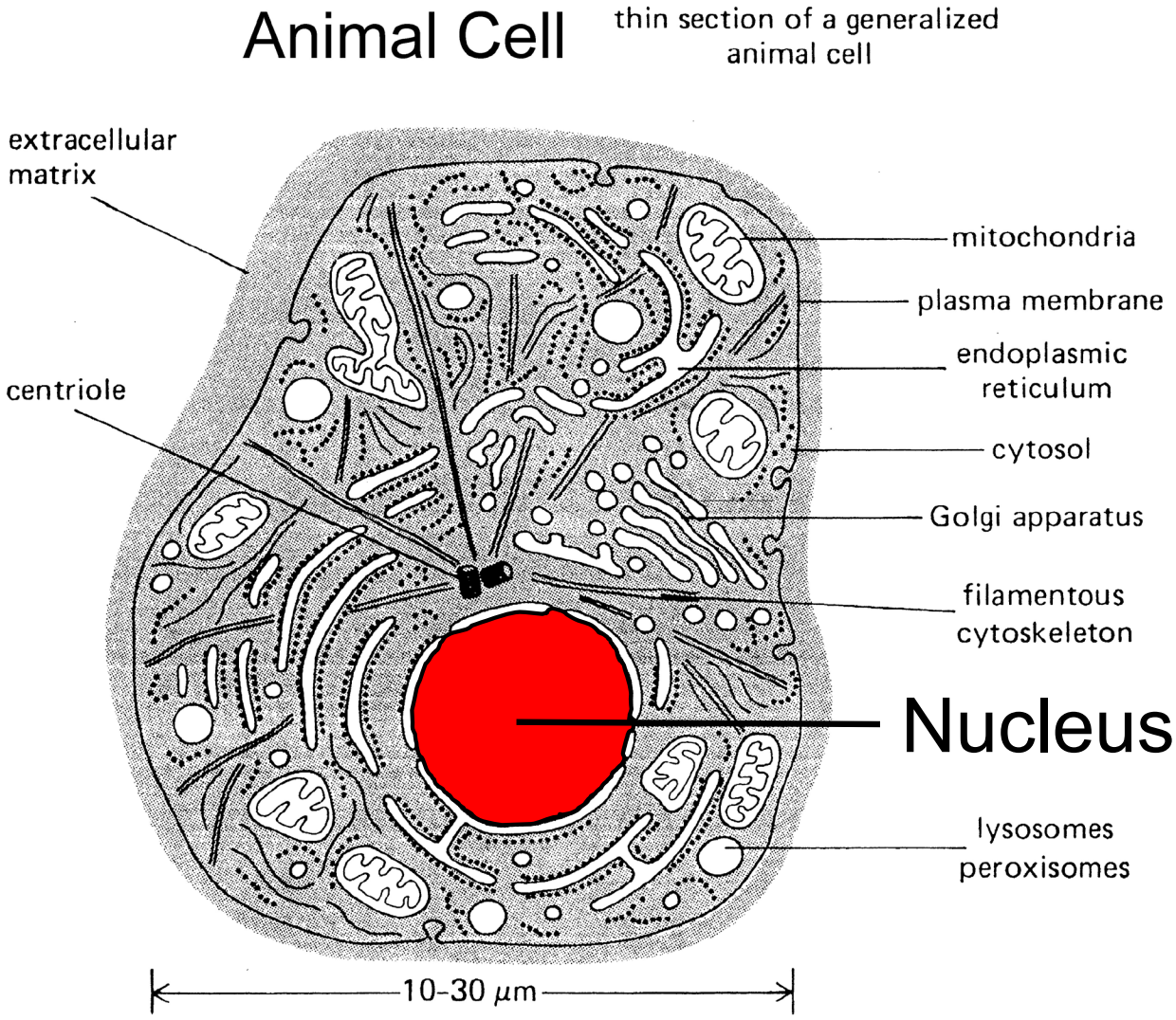
After exposure to radiation, tumor cells die through mitotic catastrophe

How to draw these lines?

How to describe different sensitivity?



Cell survival:
lesion production
versus
lesion repair



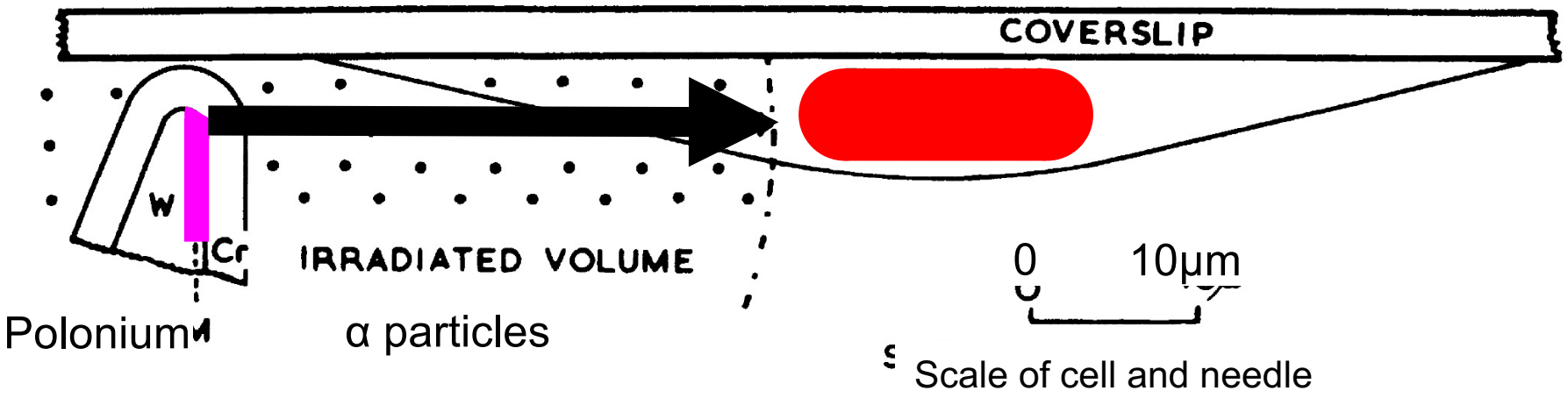
DNA is the principal target

Radiation Source	*Subcellular dose (Gy)*		
	Nucleus	*Cytoplasm*	*Membrane*
X-ray	3.3	3.3	3.3
^{3}H-Tdr	3.8	0.27	0.01
^{125}I-concanavalin	4.1	24.7	516.7

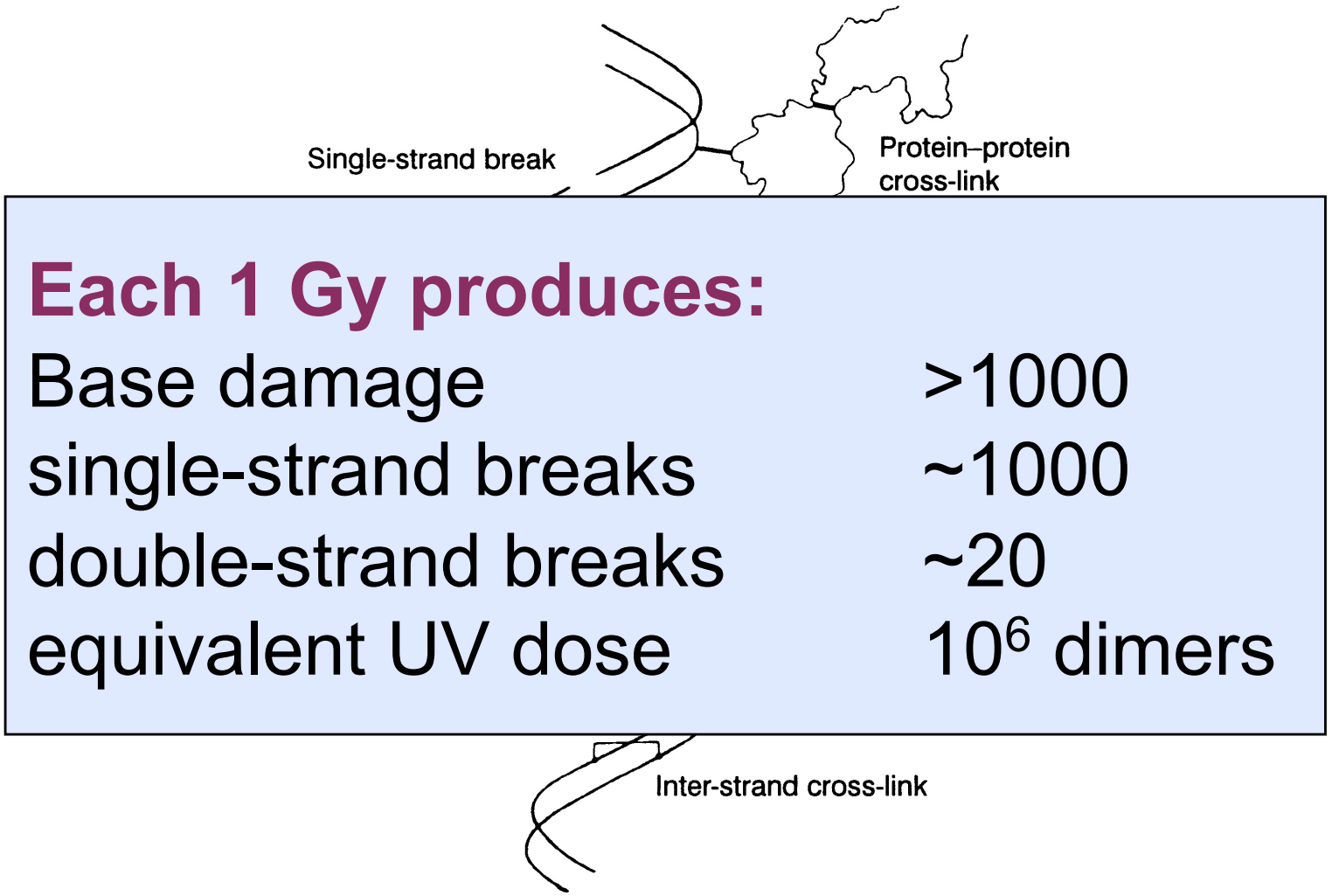
Warters et al. *Curr Top Radiat Res Q* 1977;12:389

DNA is the principal target

Microbeam experiments with α particles from polonium show that the cell nucleus is the sensitive site



Munro TR. *Radiat Res* 1970;42:451

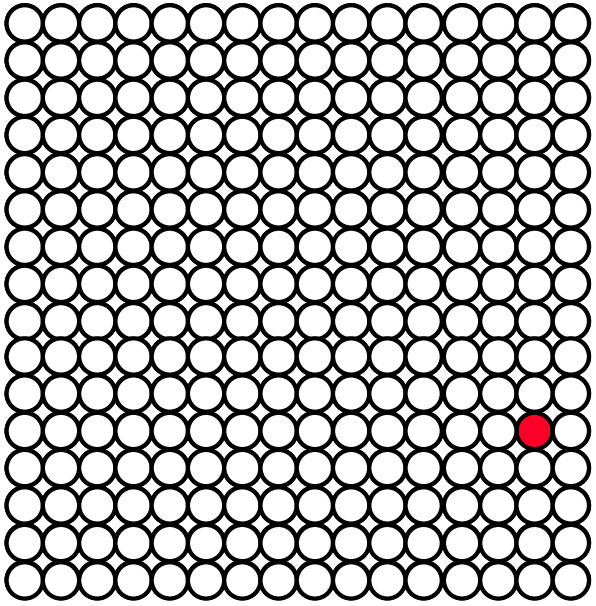


Each 1 Gy produces:

Base damage	>1000
single-strand breaks	~1000
double-strand breaks	~20
equivalent UV dose	10^6 dimers

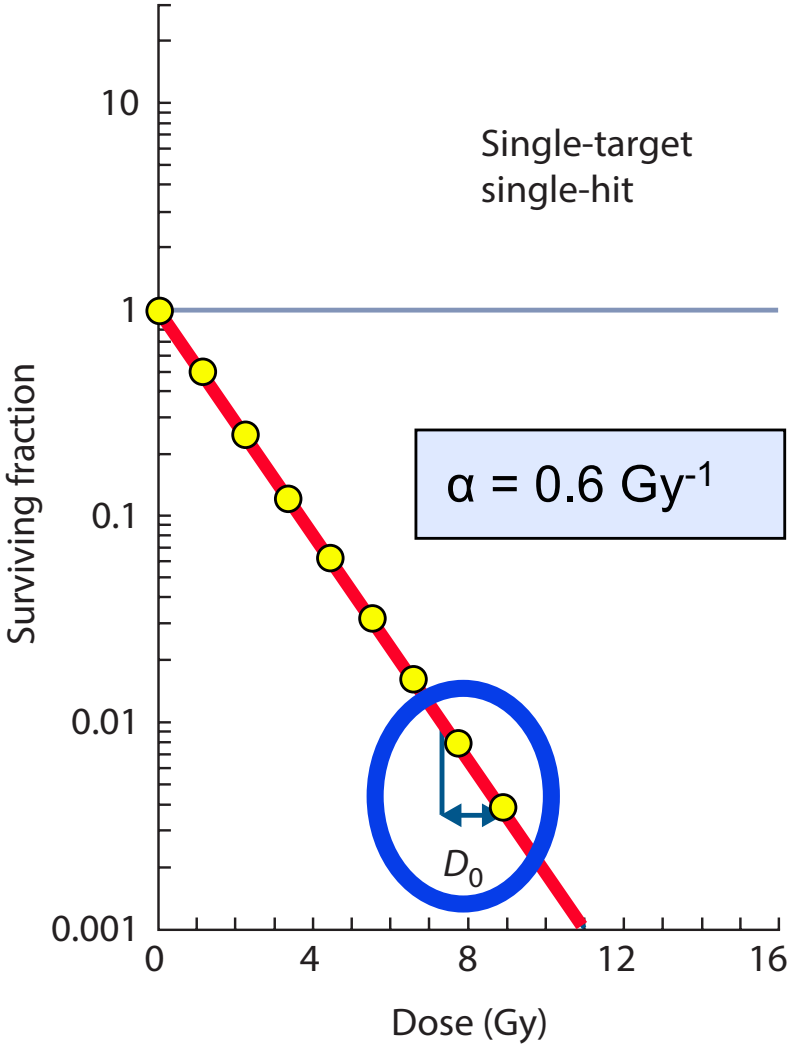
Modifier	Cell kill	**DSB**	SSB	Base damage	DPC
↑ LET	↑	↑	↓	↓	–
↑ hypoxia	↓	↓	↓	0	↑
↑ thiols	↓	↓	↓	0	↓
↑ heat	↑	↑	0	0	0

From Frankenberg-Schwager (1989)



$$\frac{N}{N_0} = S = e^{-\alpha D}$$

$$D_0 = 1/\alpha$$



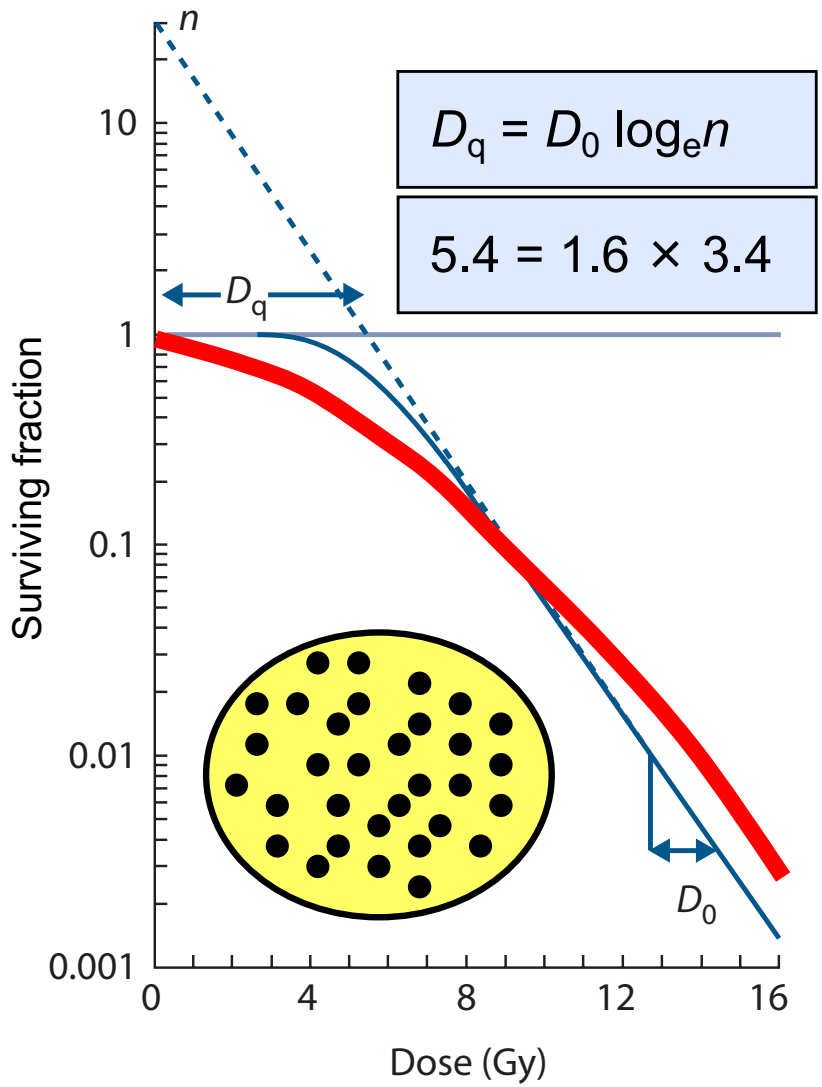
P(0 hits on a target) $= e^{-D/D0}$

P(≥1 hit on a target) $= 1 - e^{-D/D0}$

P(≥1 hit on n targets) $= (1 - e^{-D/D0})^n$

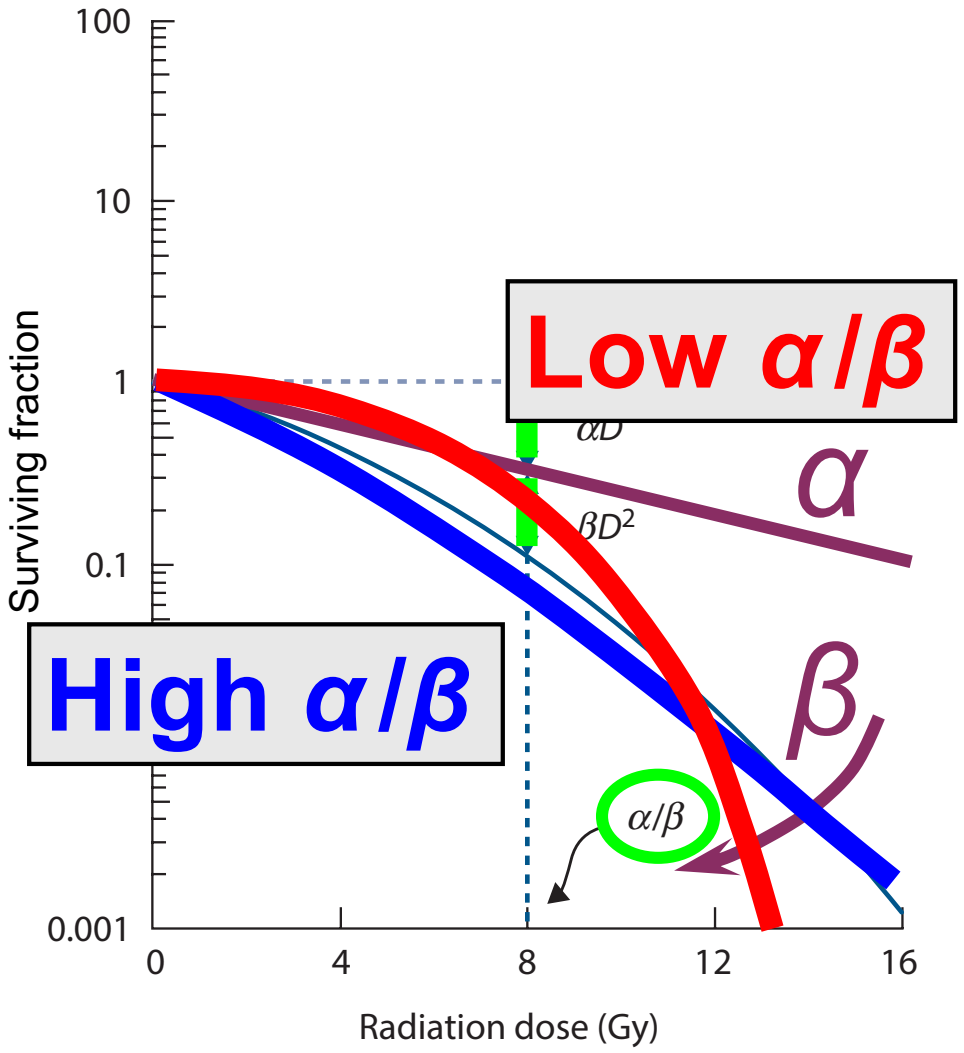
P(not **all** targets hit) $= 1 - (1 - e^{-D/D0})^n$

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

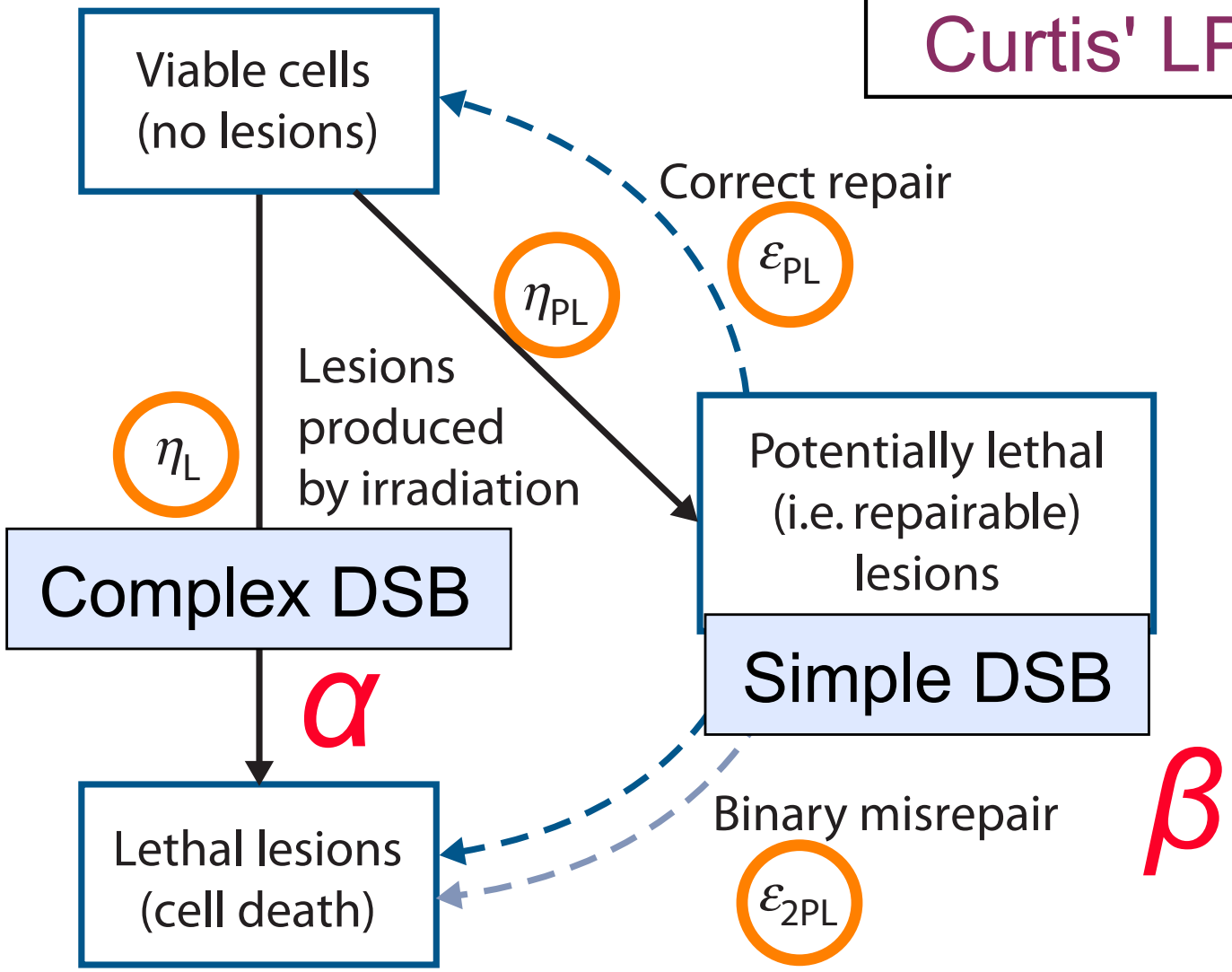


$$S = e^{-\alpha D - \beta D^2}$$

$$-\log_e S = \alpha D + \beta D^2$$

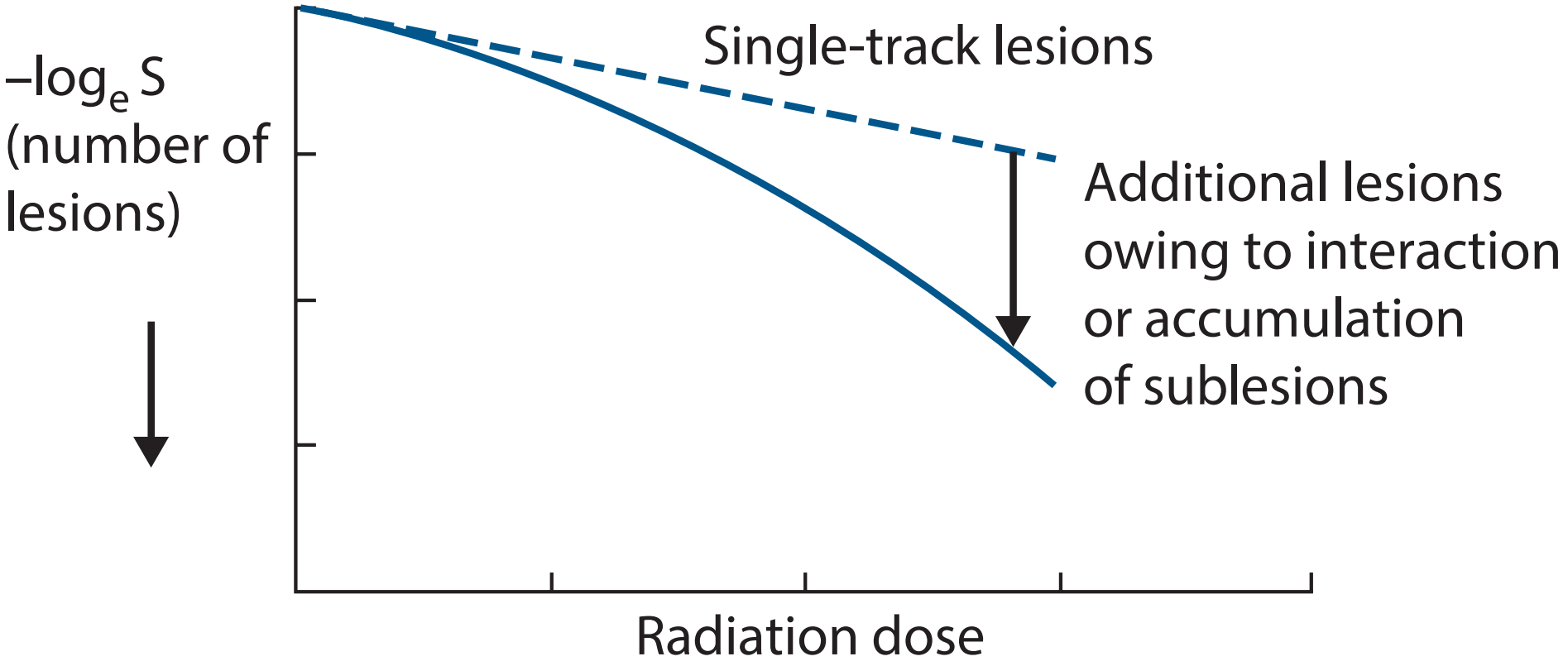


Curtis' LPL model

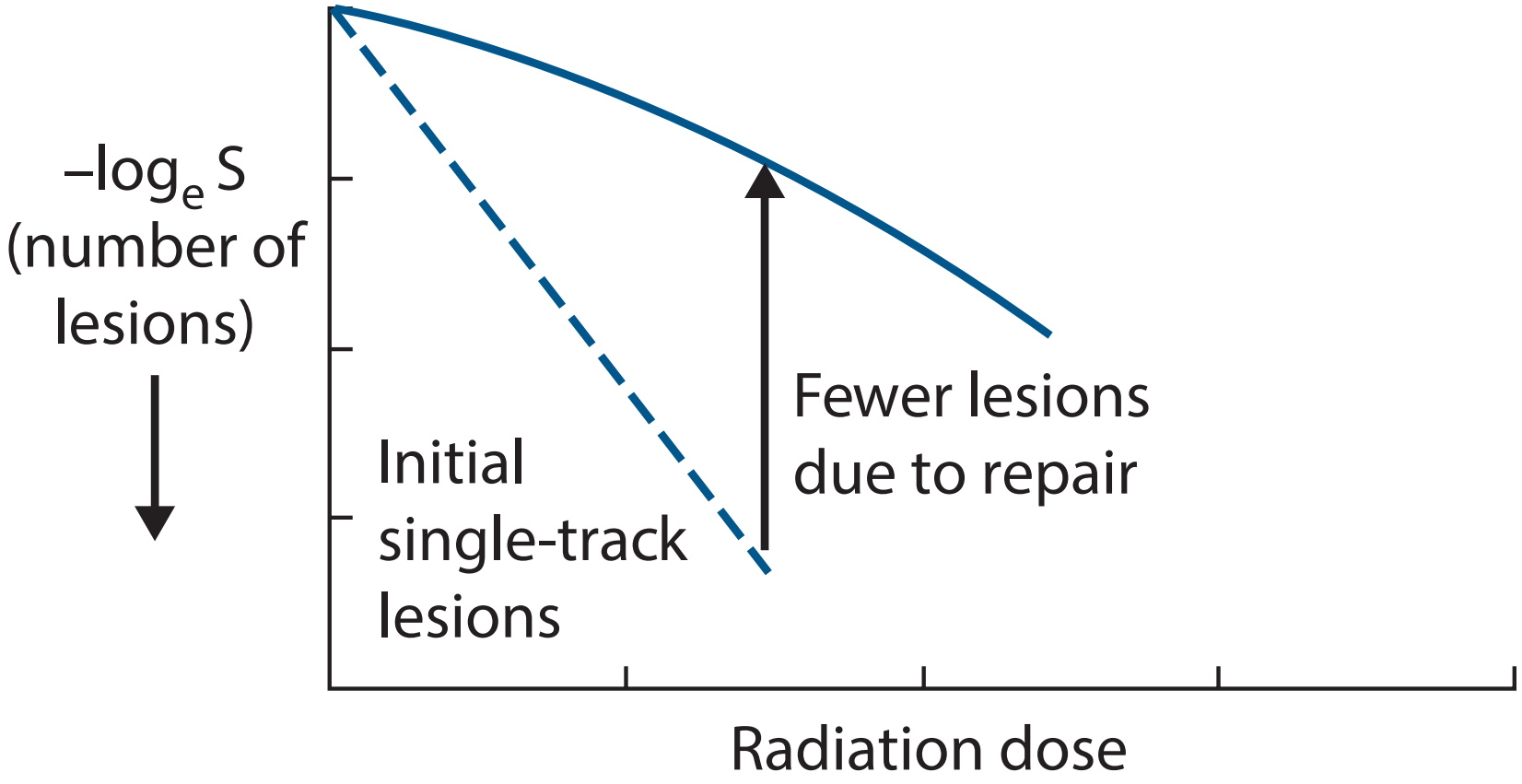


Curtis SB.
Radiat Res
1986;106:252

Curtis' LPL model

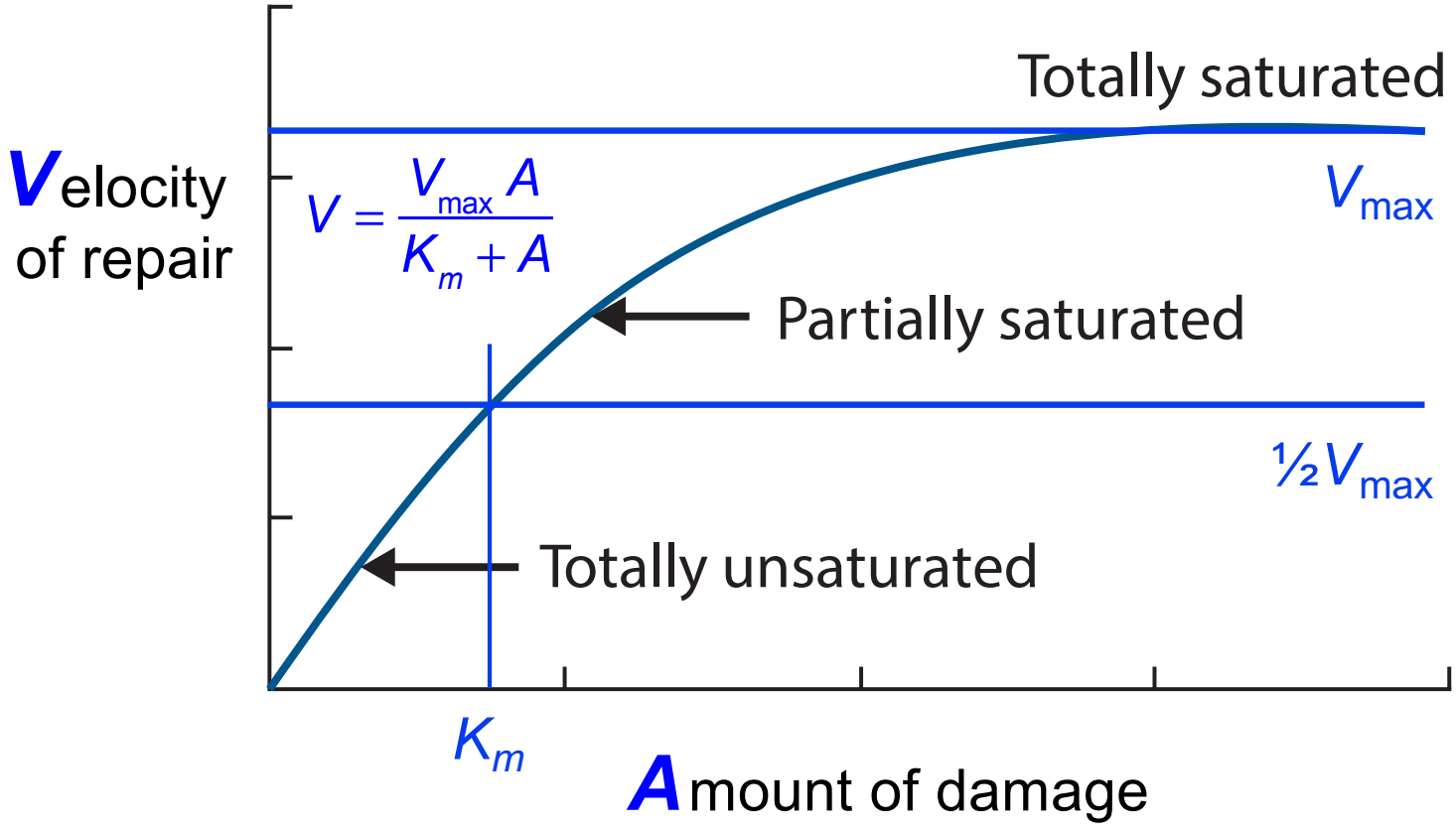


The concept of repair saturation



The concept of repair saturation

Michaelis-Menten kinetics



Lesion interaction vs repair saturation

Table 4.1 Different interpretations of radiobiological phenomena by lesion-interaction and saturable-repair models

Observation	Explanation Lesion interaction	Repair saturation
Curved dose–effect relationship	Interaction of sublesions	Saturation of capacity to repair sublesions
Split-dose recovery	Repair of sublesions (sublethal damage repair)	Recovery of capacity to repair sublesions
RBE increase with LET	More non-repairable lesions at high LET	High-LET lesions are less repairable
Low dose rate is less effective	Repair of sublesions during irradiation	Repair system not saturating

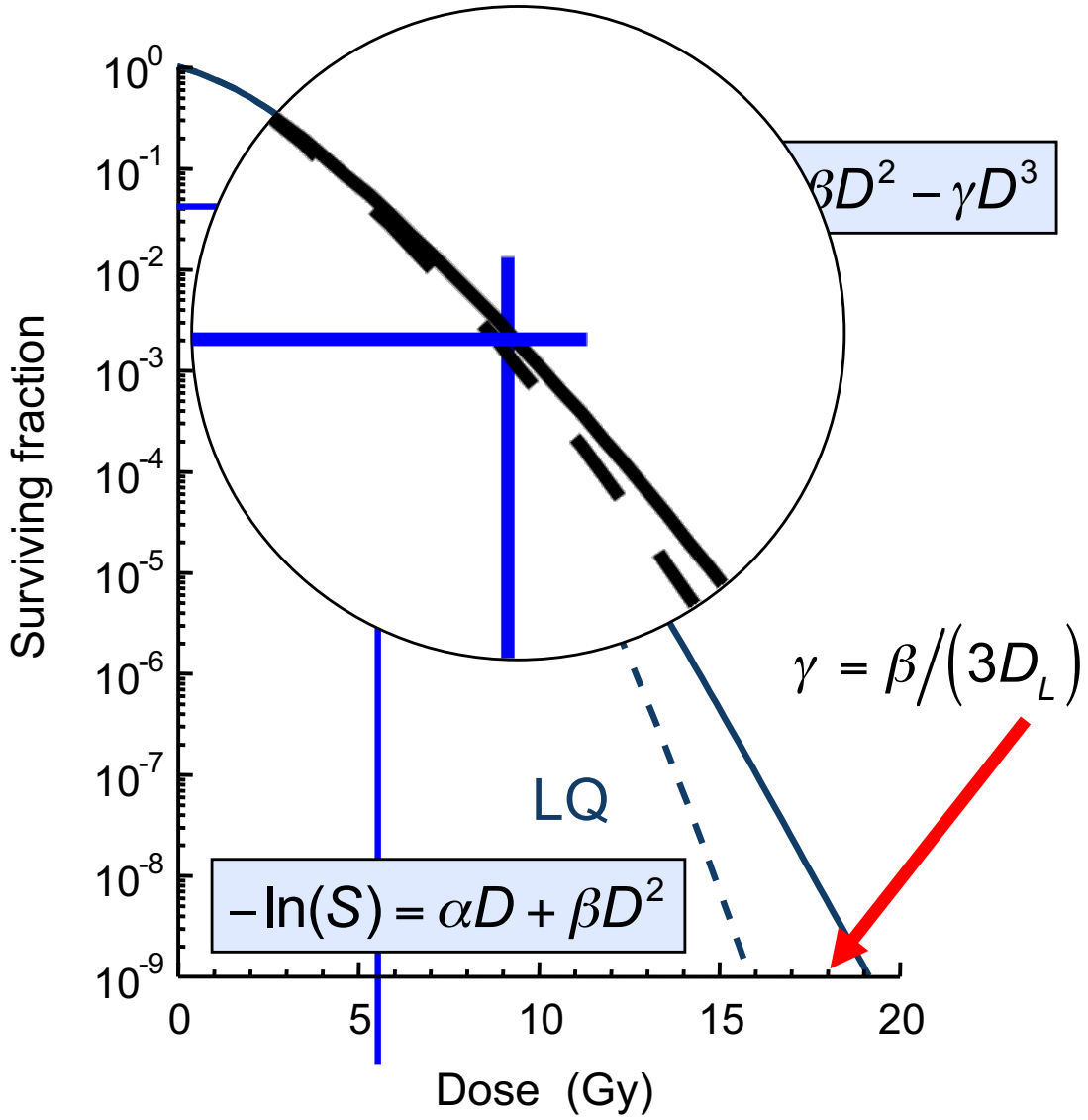
LET, linear energy transfer; RBE, relative biological effectiveneness.

Adapted from Goodhead (1985).

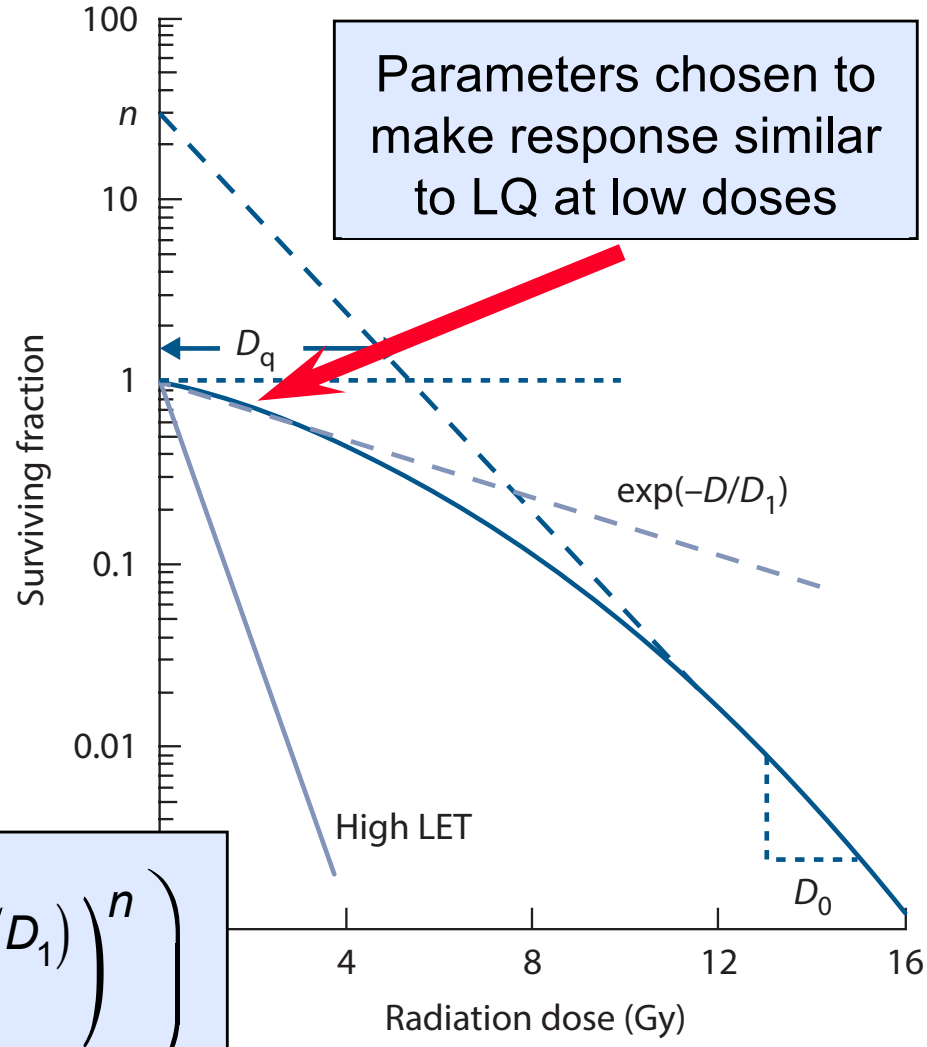
The **L**inear **Q**uadratic **C**ubic model

α/β = 3 Gy

SF2 = 0.5



Two-component model may also better describe response to **high-dose** fractions



$$S = e^{-D/D_1}\left(1-\left(1-e^{-D\left(1/D_0-1/D_1\right)}\right)^n\right)$$

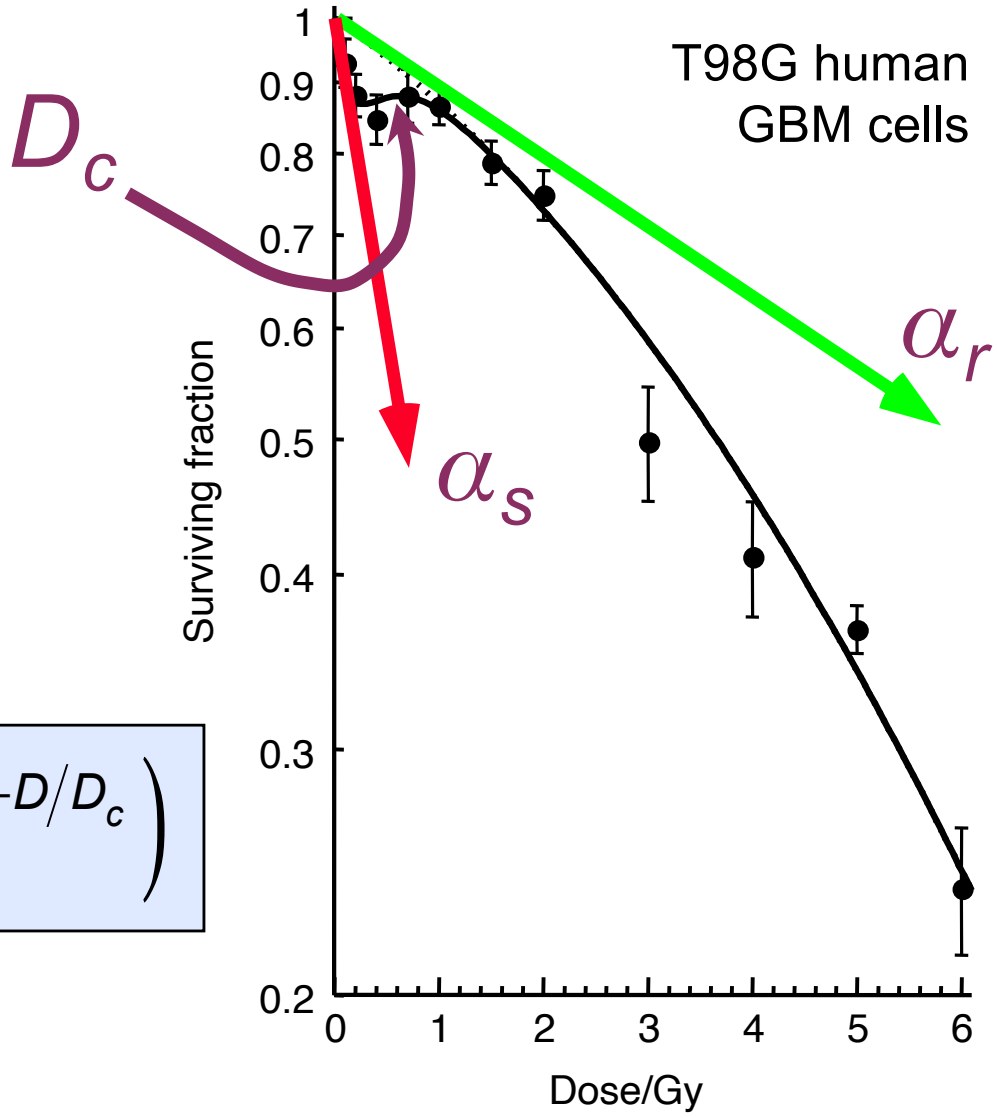
Low-dose hyper-radiosensitivity

Short S, Mayes C, Woodcock M, Johns H, Joiner MC.
Int J Radiat Biol 1999;75:847–55.

$$S = e^{-\alpha D - \beta D^2}$$

$$\alpha = \alpha_r \left(1 + \left(\alpha_s / \alpha_r - 1\right) e^{-D/D_c}\right)$$

First reported in 1986 in mouse epidermis and kidney



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Biology Contribution

Cytogenetic Low-Dose Hyperradiosensitivity Is Observed in Human Peripheral Blood Lymphocytes

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…Here we provide the first cytogenetic evidence of low-dose hyperradiosensitivity in human cells subjected to γ radiation in the G2 phase of the cell cycle…

- We use models to:
  - help make clinical predictions from experimental data
  - predict the change in outcome when we alter treatment
- This is possible because radiation biology is a quantitative discipline