Illinois Institute of Technology

PHYSICS 561
Radiation Biophysics

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Lecture 5:
Survival Models
and Curves
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Survival Models II

We'll present some cell-survival models that are more sophisticated than the single-hit and MTSH models; and we'll look at some results.

Overview

- Linear-Quadratic Model
- Repair-Misrepair Model
- Lethal Potentially-lethal model
- Survival Curves
- Elkind-Sutton Experiment
- Repair
- Cell cycles

Deficiencies in MTSH Model

- MTSH model has two problems—one at low dose and one at high:
- Doesn't predict nonzero slope near D = 0
- Doesn't predict nonuniform slope at high D
- Tweak for first problem:
  $S=\exp(-q_1 D)[1 - (1-\exp(q_1 D))^n]$
- No tweak for second problem:
  need a different model

Poisson survival

- Alpen's comment:
  A cell can be killed only once, and further action on the remaining cells is constrained to that smaller number of cells
- This is equivalent to saying
  $dN= N * d(f(D))$, i.e. $dN/N = d(f(D))$, or
  $\ln N = f(D)\ln N_0$, or $\ln(N/N_0) = f(D)$
- but $S = N/N_0$, so we have a basic formalism
  $\ln S = f(D)$, where $f(D)$ is a function of dose

Linear-Quadratic Model: generalized form

- Back away from mechanistic approaches and say that given Poisson statistics for lethality $\ln S = f(D)$, where f is some function
- Taylor-expand in D
  $\ln S = a_0 + a_1 D + a_2 D^2 + \ldots a_n D^n + \ldots$
- We take $a_0 = 0$ because at $D = 0$ the survival fraction is 1, I.e. $\ln S = 0$.
- Thus the second-order expansion is
  $\ln S = a_1 D + a_2 D^2$

Molecular Model

- Emphasizes double-stranded breaks in DNA as the source of lasting damage
- Distinguishes between single hits causing DSBs and pairs of hits causing DSBs; ultimately the pairs of hits give rise to the quadratic dependency on D in the formulas
- Derivation in Alpen is okay, but we end up with a lot of constants that aren't independently determinable

Dual Radiation-Action Formulation

- Emphasizes that a single interaction between a high-LET radiationevent and a cell produces a DSB, whereas low-LET radiation requires pairs of events.

- Gives rise to a linear-quadratic model, where the one-event DSB (linear) coefficient predominates for high-LET radiation and the two-event (quadratic) cofficient predominates for low-LET radiation

Tobias's Repair-Misrepair Model

- Posits linear and quadratic mechanisms up front for repair, with explicit time-dependence
- Time-independent formulas arise at times that are long compared with cell-cycle times
- In those cases
  $S = \exp(-\alpha D)(1 + \alpha D/\epsilon)^{\epsilon}$
  where $\epsilon = \lambda/k$ is the ratio of the repair rates for linear damage to quadratic damage.
  This gives roughly quadratic behavior for ln$S$.

Lethal—Potentially Lethal Model

- Sets up three-state system: Undamaged (A), potentially-lethally-damaged (B), and lethally damaged (C) cells
- Eurepair returns state B to state A
- B automatically becomes C at long times
- Gives rise to explicit quadratic formulation $\ln S = \alpha D + \beta D^2$ with α and β having explicit time-dependence
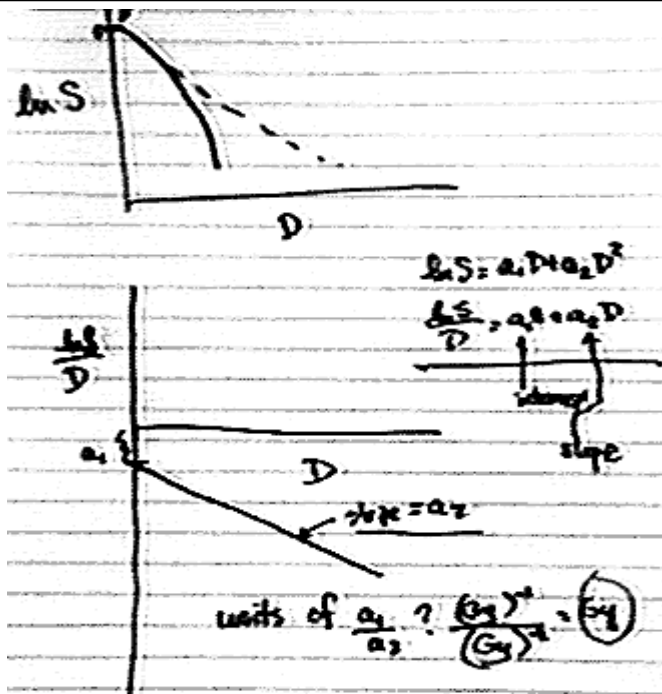
what happens if

$$D = \frac{a_1}{a_2}?$$

$$\ln S = a_1 D + a_2 D^2$$

$$= a_1 \cdot \frac{a_1}{a_2} + a_2 \left(\frac{a_1}{a_2}\right)^2$$

$$\ln S = \frac{a_1^2}{a_2} + \frac{a_1^2}{a_2} = \frac{2a_1^2}{a_2}.$$

so the quadratic and linear contributions to $\ln S$ are equal.

if $D < \frac{a_1}{a_2}$, linear mechanisms predominate

but if $D > \frac{a_1}{a_2}$ quadratic mechanisms predominate

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Clonogenic survivability

- Even the unirradiated cells don't provide 100% survival;
- The survival for the irradiated cells has to be normalized against what's happening to the controls
- That sets an upper limit on the accuracy of the determinations
- You also need to set up a lot of plates! (Possion statistics)

Feeder cells

- Irradiate some cells enough that they can't divide but they can metabolize
- Plate out your cells you're going to study on top of those
- This gives you a layer to feed the cells under study
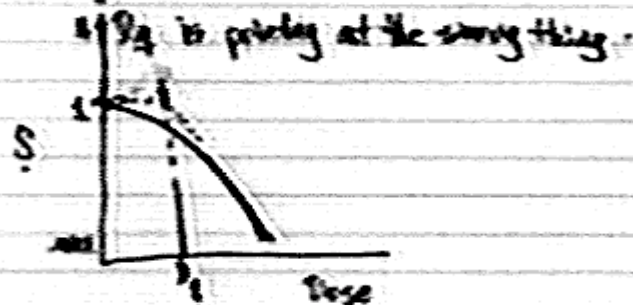- Recently, other methods have been developed

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1. Errata in ch. 8:

    p.169, ¶2, 6th sentence

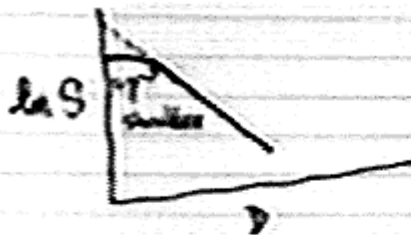   "Until the later 1950's it was not possible to use ..."

2. Fig 8.1, p173:

    ¶¶¶ is pointing at the wrong thing.

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Shoulder of the
survival curve

$\ln S$

T shoulder

D

$\ln S$

T shoulder

D
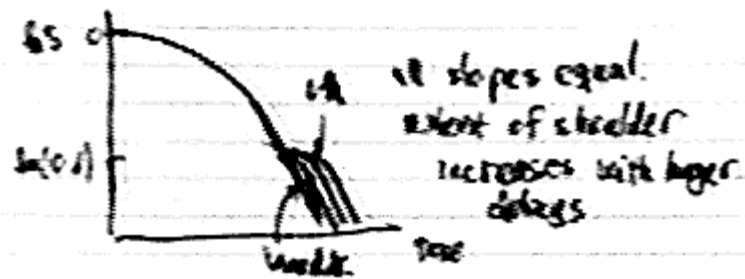
Elkind-Sutton experiment:

1. Irradiate & establish survival curve.

2. Take cells remaining at $S \sim 0.1$ and subject them to further radiation at varying time intervals after reaching $S = 0.1$

Results of an Elkind-Sutton experiment (fig. 8.3, p 176)

ln S
ln(S/S₀)

all slopes equal
extent of shoulder
increases with longer
delays

width   Dose

at both results of the same trial

at both results of the same trial

combine low-LET & high-LET radiation?
(fig 8.5, p 178)
1. high first

ln S   Dose

2. low first (fig. 9.4, p 180)

independent of
dose rate
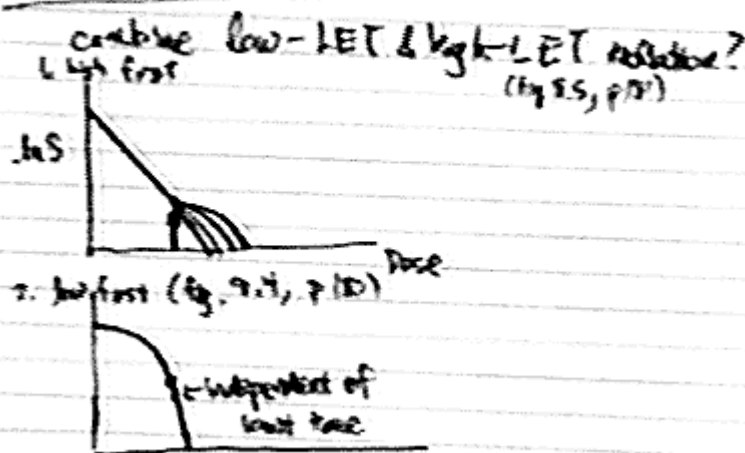
the Cell Cycle

Cells have a definable cycle over which specific activities occur. Particular activities are limited to specific parts of the cycle.

Mitosis → Growth

M
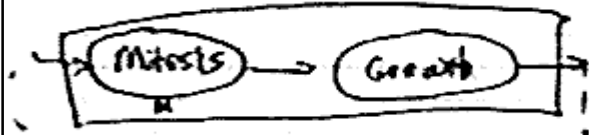
Howard & Pelc (1953): characterized by four (five) specific phases:

M   mitosis
S   synthesis (DNA & being synthesized) (replicated)
G   before S, after M

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how long? (hrs)

	CHO	HeLa
M	1	1
G1	1	11
S	6	8
G2	3	4
total		24

11

It turns out that many cells are
much more sensitive to radiation
in some parts of the cell cycle
than they are in others.

⟨Why⟩ ⟶ (1) repair is more vigorous
              in some stages

        ⟶ (2) unrepaired damage has not
               of a chance to progress on

CHO cells (p.137 X fig 4.8)