Illinois Institute of Technology

Physics 561
Radiation Biophysics

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Radiation Biophysics
Lecture 12: Genetics
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Class Overview

- ◆ Exam postmortem
- ◆ Cancer
    - Animal studies & human populations
    - Human populations
    - Dose-response relationships
    - Latency
    - Absolute and relative risk
    - Where tumors happen
    - ED01 study - quantitative carcinogenesis
- ◆ Stochastic Genetic Effects
    - Structural changes in chromosomes
    - DNA-level effects
    - . . . More next week

Exam Postmortem: Problem 1

Write down the analytical forms of the MTSH model for cell survival and the LQ model. What are the advantages that either of these models holds relative to the simple exponential model? What is the property of the low-dose portion of the survival curve that makes the LQ model more appropriate for many experiments in that dose range?

The cell-survival formula associated with the MTSH model is $S = 1 - (1 - \exp(-qD))^n$ or
$S = 1 - (1 - \exp(-D/D_0))^n$
where S = survival fraction, D = dose,
and $q = 1 / D_0$ and n are parameters.

Problem 1, continued

◆ The cell-survival formula associated with the linear-quadratic or molecular model is

◆ $\ln S = -p(\alpha D + \beta D^2)$, where p, α, and β are parameters. This can also be written

◆ $(\ln S)/D = -p(\alpha + \beta D)$
In the case of fractionated doses we combine p into α and β and define the formula in terms of the dose per fraction, Δ, and the number of doses, n, as
$$\ln S = -n(\alpha\Delta + \beta\Delta^2)$$

Exam problem 1, concluded

◆ The advantage of either model over a simple exponential is that each accounts for at least some of the nonlinearities in the $\ln S$ vs. D curve.

◆ The LQ model is more appropriate for many experiments in the low-dose range because it does not display a flat (zero-slope, or zero-derivative) behavior over that range. To the degree that we believe that $dS/dD < 0$ even at very low dose, LQ fits that better, since with LQ, $dS/dD = -p\alpha$ at $D = 0$, whereas with MTSH, $dS/dD = 0$ at $D=0$.

correct $\dfrac{dS}{dD} = -p\alpha$

at low dose

Exam Problem 2

◆ *Summarize the relationship between radiosensitivity and cell cycle. Would you expect cells in the G0 phase to be radiosensitive? Why or why not?*

◆ Cells that are most radiosensitive are those in mitosis at the time of radiation and those that are in the G2 (post-replicational) stage. Cells in G1 are less sensitive; those in early S, less still; and those in late S, even less sensitive.
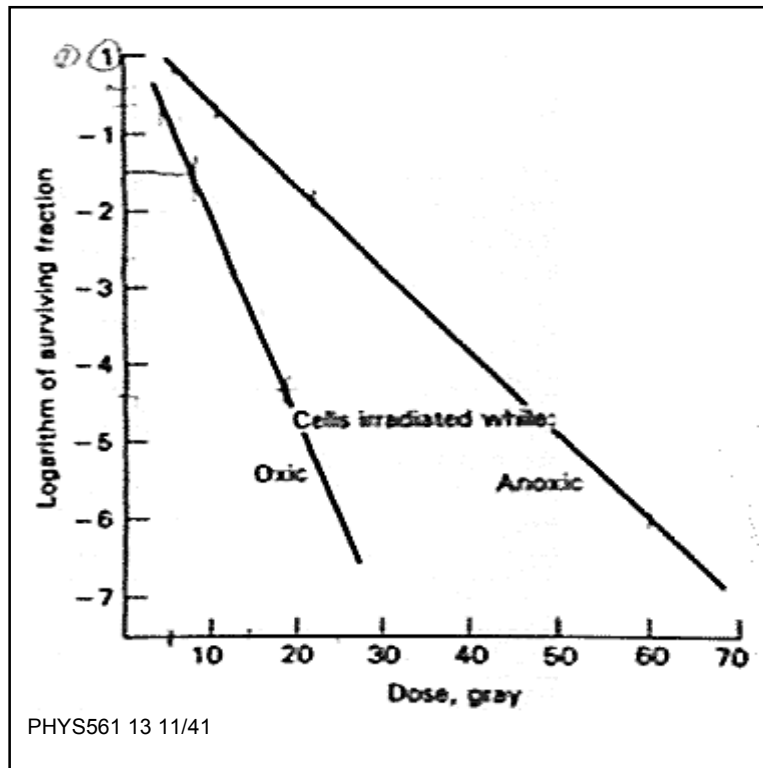
Exam problem 2, concluded

◆ One would expect cells in G0 to be radiation-insensitive since they are not involved in DNA replication or cell division. Thus any DNA damage that occurs will be either clonally irrelevant (if the cell stays in G0) or else the cell will have a long time to repair the damage (if it eventually re-enters the cell cycle).

Exam Problem 3

◆ *Examine fig. 10.3, noting that there is a misprint at the top of the page (the 1 should be a zero). Estimate the oxygen enhancement ratio in the systems shown. Does this OER depend on whether we take S/S0 at 1 percent survival or 0.1 percent survival? Why or why not?*

◆ OER = (dose required for given effect under anoxic conditions)/(dose required for same effect under oxic conditions)

◆ So if the relevant endpoint is 1% survival, i.e. log$S$ = -2, then

$$\text{OER} = (23 \text{ Gy}) / (11 \text{ Gy}) = 2.09.$$

Problem 3, concluded

- If, instead, we take the endpoint to be 0.01% survival, i.e. $\log S = -4$, then OER = 43 Gy / 18 Gy = 2.39.

  OER depends slightly on whether we look at 1% or (for example) 0.01% survival as the endpoint measured in the definitional ratio because the two survival curves are not actually lines with intercept at S=1.

Exam Problem 4

◆ *The effect of dose fractionation is examined in a system and it is found that $\alpha = 0.3$ Gy^{-1} and is found that $= 0.06$ Gy^{-2}. If we deliver one dose of 2 Gy to the system, what will the surviving fraction be? If we fractionate the same total dose into ten equal parts, what will the surviving fraction be?*

◆ Use equation 11.9:
$\ln S = -n(\alpha\varDelta + \beta\varDelta^2)$, $\alpha = 0.3$Gy^{-1}, $\beta = 0.06$ Gy^{-2}.
For $\varDelta = 2$ Gy, $n = 1$, $\ln S = -1(0.3 * 2 + 0.06 * 4)$
$\quad \ln S= -(0.6 + 0.24) = -0.84$.
Thus $S = \exp(-0.84) = 0.432$.

Problem 4, concluded

◆ For the fractionated version,
Δ = 0.2 Gy, n = 10,
ln S = -10 * (0.3 * 0.2 + 0.06 * 0.04)
   = -10*(0.06 + 0.0024) =   -10*(0.0624)
ln S = -0.624
S = exp(-0.624) = 0.536.
So more cells survive in the fractionated instance.

Problems 5, 6

◆ 5. Define *potentially lethal damage.*
◆ Potentially lethal damage is damage to cells which, if left unrepaired, will result in [clonogenic] death; or, to put it another way, it is injury that will kill the cell unless intervention occurs to change the outcome.
◆ 6. Define *radiation-induced cell progression delay.*
◆ Radiation-induced cell progression delay is the phenomenon wherein the progression of a cell through its maturation cycle is interrupted or slowed by exposure to radiation.

Problems 7, 8

◆ 7. Define a *stem cell population.*
◆ A stem cell population is a group of relatively undifferentiated cells that are capable of division and maturation into a functional group of cells.
◆ 8. Define a *functional subunit* and give two examples.
◆ A functional subunit of an organ is a volume of tissue that can be regenerated from a single   surviving cell without loss of functional integrity. The nephron is the FSU of the filtration system of the kidney; the alveolus is the FSU of the lung.

Problem 9 (extra credit)

◆ *Examine problem 2 in chapter 11 of Alpen, but don't actually do the problem. Instead, Compute α/β for the mouse-foot system. This value lies substantially outside the range of 1.5 - 30 that is given on p. 303. Why?*
◆ Since $\alpha/E = 1.32 * 10^{-4}$
and $\beta/E = 1.27*10^{-7}$,
◆ $\alpha/\beta = (1.32/1.27) * 10^3$
$= 1.04*10^3 = 1040$.
This is outside the range quoted in Alpen because the doses are given in rads, not Gy.

PROBLEMS

1. One of the most widely used treatment schedules for radiotherapy is the administration of daily fractions on weekdays (Monday through Friday) for four consecutive weeks. The most widely used dose per fraction is 2 Gy. Assuming that NSD is 17 and that the exponents given in the text for the Strandqvist and Ellis NSD equations are appropriate, what change in the daily dose per fraction would be required if the total dose in the standard four week schedule is 60 Gy and this dose must be given in three weeks instead of four weeks.

2. For skin reactions in the mouse foot Douglas and Fowler found that the values of α/E and β/E are, respectively, 1.32×10^{-4} and 1.27×10^{-7} when the doses were expressed in rad. Using the equations in the text and, as desired, referring to the original reference, deduce the survival curve for the clonogenic cells responsible for maintaining the integrity of the skin of the foot of the mouse.

Problem 9, concluded

◆ E iself is unitless,
so α/E must be in units of rad^{-1}
and β/E must be in units of rad^{-2}.

◆ Thus the units on the just-completed calculation of α/β is rad, not Gy.
1 Gy = 10^2 rad, so
α/β = 1040 rad = 10.40 Gy.
This is a very typical biological value.

◆ Note: if $\Delta = \alpha/\beta$, then the contributions from linear and quadratic terms are equal:
$\alpha\Delta=\alpha^2/\beta, \beta\Delta^2 = \beta\alpha^2/\beta^2 = \alpha^2/\beta$

Animal Cell-line Cancer Studies

◆ How similar are rodent cells to human cells?
Human cells are:
- – More resistant to spontaneous immortalization
- – Less repair-capable (more linear responses)
- – Radical scavengers and cold help less:
That suggests direct mechanisms in humans,
water-mediated effects in rodent cells

◆ High-LET studies: repair is less effective

◆ Promotion can be studied in animals, along with
initiation

Radiation Carcinogenesis in Human populations

◆ Occupational: radiologists, miners, dial painters

◆ Medical
- – Ankylosing spondylitis
- – Nonmalignant disease in pelvis and breast
- – Multiple fluoroscopies to chest (TB patients)
- – Infants & children with enlarged thymus and
ringworm
- – Children exposed *in utero*--diagnostic Xrays

◆ Nuclear accidents and weapon detonations

◆ Environmental (see final chapter)

Dose-Response in Cancer Studies

- We want the relation between cancer incidence I_D as a function of dose D & normal incidence I_n
- Linear: $I_D = I_n + \alpha_1 D$
- Quadratic: $I_D = I_n + \alpha_2 D^2$
- Linear-Quadratic: $I_D = I_n + \alpha_1 D + \alpha_2 D^2$
- Correct for loss of clonogenic potential:
  $I_D = I_n + (\alpha_1 D + \alpha_2 D^2)exp\text{-}(\beta_1 D + \beta_2 D^2)$

PHYS561 13 23/41

Linear, LQ, Quadratic models

- We try to devise low-dose models based on high-dose data, where the three models are close together. It's often difficult:
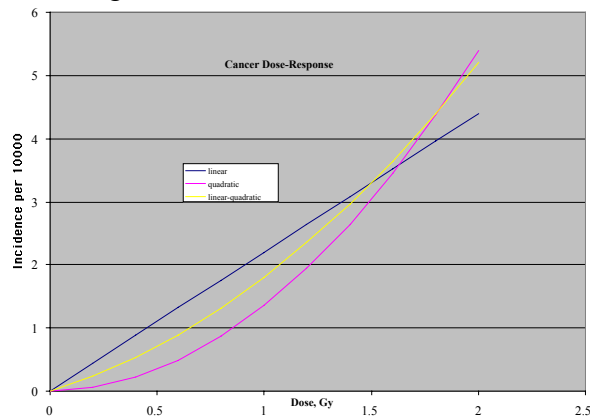
PHYS561 13 24/41

Latent Period

- Cancer takes a long time to arise
- Causes:
  - Often we need several mutations to arise
  - Promotion often involves gradual exposure
  - Cell turnover can be slow (weeks to years)
- Confusing:
- Why are there still excess leukemia cases in Hiroshima even though the latency is short?
- Requires careful correction for other forms of mortality to get meaningful data (e.g. smoking)

Absolute and Relative Risk

- Does a change in background incidence influence the dose-dependent incidence?
- Absolute risk:
  - Dose-dependent risk is independent of spontaneous (non-dose-dependent) risk
  - $I_D = I_n + f(D)$ such that $f(0) = 0$
- Relative risk:
  - Likelihood of radiogenic cancer is related to natural incidence
  - Risk is multiplicative of spontaneous risk
  - $I_D = I_n * g(D)$ such that $g(0) = 1$

So which one is right?

- ◆ Very difficult to sort out
  - – Data are shaky
  - – Need to find ways to change background
- ◆ Animal studies:
  most data favor relative-risk model
- ◆ Human studies: most people accept relative-risk model

Where in the body do radiogenic cancers appear?

- ◆ Tricky to study because of latency.
- ◆ Bomb results for acute exposure > 1Gy:

	Deaths/10^5	
	Multiplicative model	Additive model
Leukemia	97	93
Bladder	39	23
Breast	60	43
Colon	79	29
Lung	151	59
Multiple Myeloma	22	9
Ovary	31	26
Esophagus	34	16
Stomach	126	86
Remainder	114	103
Total	*707*	*453*

ED01 Study, Revisited

- Headed by scientists @ NIEHS (RTP, NC)
- 2-acetylaminofluorene
- Known rodent carcinogen
- 24000 mice - dose-dependence studied
- Elements of study:
    - Time to tumor
    - Fractionation (?)
- Sophisticated statistical analyses
- Reinterpreted it later
- Compared various dose-response models

ED01 quantitation

- Analyze tumor incidence according to
  $P(t,d) = 1 - \exp(-F(t,d))$
- t = time
- d = dose
- P is like 1 - S

Stochastic Genetic Effects

Mechanisms of damage to genetic materials
- ◆ Chromosome damage
    - – Very common
    - – Numerous response mechanisms
- ◆ DNA-level damage
    - – Missing bases
    - – Added bases
    - – Local dislocations in sequence
    - – Mispairing

Chromosome Breakage

- ◆ Quite common result of radiation exposure
- ◆ Can happen before replication:
  then the structural defect will be replicated (if the cell survives)
- ◆ Can happen afterward:
  then one of the two chromatids will differ from the other one.
- ◆ Types of damage:
  Subchromatid, Chromatid, Chromosome
- ◆ Repair tends to be rapid

Single-Hit Breaks

- ◆ Cartoons show * as centromere and ^ as break
- ◆ Single-Hit:
  A B C * D E F^G H I ->
  A B C * D E F   +   *G H I*
- ◆ This can recombine in a number of ways:
  A B C * D E F *I H G*
  I H G A B C * D E F
  G H I A B C * D E F
- ◆ … or a circle plus a fragment without a centromere, which won't be able to use the spindle machinery to get sorted.

PHYS561 13 33/41

Double Hits

- ◆ A B C * D^E F^G H I ->
  A B C * D   +   *E F*   +   *G H I*
- ◆ Numerous ugly combinations can arise, e.g.
 *E F* A B C * D *I H G*
- ◆ Acentrics can readily arise

PHYS561 13 34/41

Multiple Hits in Replicated Chromosomes

- ◆ See figs. 13.2 and 13.2
- ◆ Major losses of genetic information possible
- ◆ Balanced Translocations: no harm done!
- ◆ Dicentrics--two centromeres in one pair of chromosomes.
- ◆ Sister chromatid exchange: exchange of DNA fragments from one chromatid to another between the two chromatids of a single chromosome
    - – Important for chemical mutagens
   - – Not common with radiation
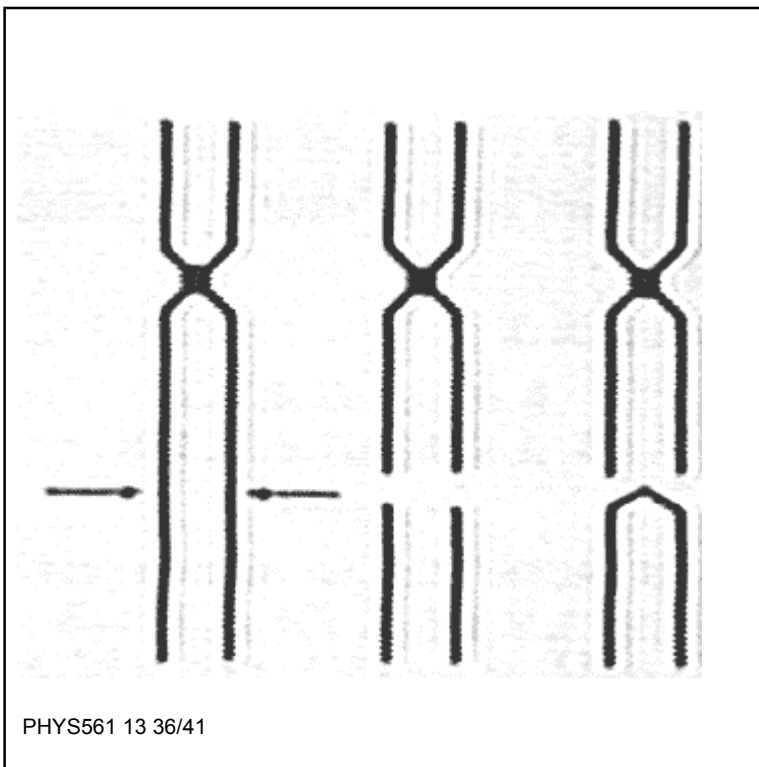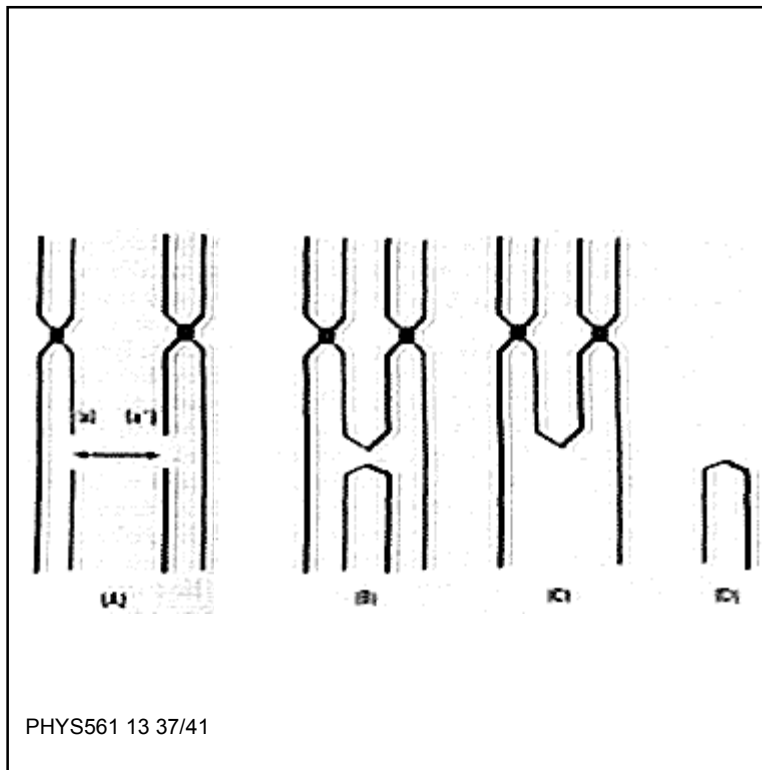
Breakage and Exchange Hypotheses

◆ Breakage hypothesis:
Types of aberrations that require one break follow linear dose-response; those requiring two or three follow quadratic or cubic dose-response.

◆ Exchange hypothesis:
emphasizes reciprocal exchanges among chromosomal materials
Data don't support this one much.

Gene Mutations

◆ We've discussed these in detail previously
◆ Types:
  – Deletions (frameshift)
  – Additions (slightly less likely) (frameshift)
  – Substitutions (e.g. C for T; no frameshift)
◆ Remember that three bases code for an amino acid!
◆ If we skip a single base, we can throw off every single amino acid that is coded for downstream of the error.
◆ Mutation frequencies are often linear with dose
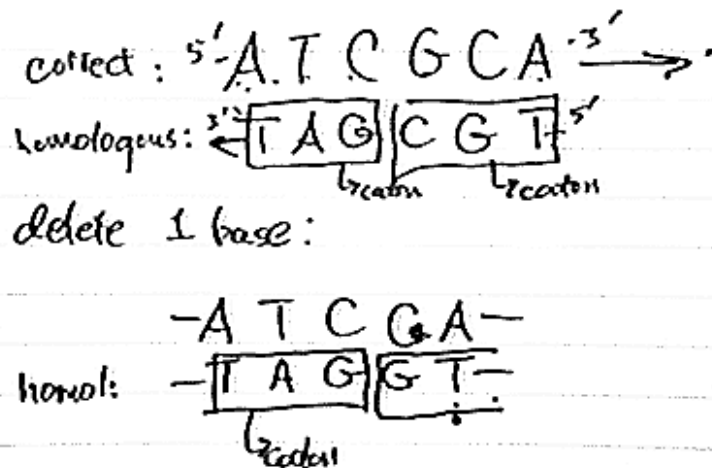
Assignment for Friday 20 April

◆ Explain why a frameshift of 3 bases is less likely to be fatal than a frameshift of 1 or 2 bases.

PHYS561 13 41/41