Illinois Institute of Technology

Physics 561
Radiation Biophysics

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Class Overview

- Genetics II
  - Review of definitions
  - Frameshifts and substitutions
  - Relative sensitivities of cell types
  - Organismal differences
- High-LET Radiation
  - Review of definitions
  - Physics of energy deposition
  - Impact on DNA
  - Resistance to repair

Frameshifts

- Most common form of DNA damage
- Chemistry
    - Deletion of bases
    - Fragmentation of sugar-phosphate backbone
    - Distortion of base-base hydrogen bonds and other 3-D elements
- Results in complete misreading of remainder of message

Genes

- Unit of DNA that codes for a specific function
- Contain exons and introns
- Genes and the Processes for which DNA is Responsible

Structural elements

- Bases
  - Adenine
  - Cytosine
  - Guanine
  - Thymine
- Phosphate-deoxyribose backbone

Special Features

- Code is redundant
- $4^3 = 64$ codons
- 20 amino acids + 1 or 2 control codes;
  so most amino acids have more than one codon associated with them.
- Middle base is conserved, i.e. all the codons for a given amino acid have the same middle base.
- First RNA base can be sloppy

Errors in Fidelity and Their Consequences

- How do Chemicals & Radiation Affect Fidelity (rate of mutation)?
- Increase likelihood of replication error
- Radiation: bond disruption in bases (or sugars)
  - Direct
  - Indirect

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Repair

- Cell has mechanisms to recognize & replace faulty bases before they have a chance to be replicated
- Some injury may disrupt a large enough segment of DNA that repair either fails or is error-prone

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High LET Radiation

- Review definition of LET:
  Rate of change of energy with distance along a track
- Caveat I: Local Deposition
- Caveat II: LET only assoc. with charged particles

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LET Equation: Bethe-Block Formulation

- If we let:
  - z^* = Effective charge of projectile particle
  - Z = Atomic number of atoms in medium
  - A = Atomic weight of atoms in medium
  - C = sum of electron shell corrections
  - $\delta/2$ = condensed medium correction
  - β = v/c for particle
- $-dE/dx = (0.307z^{*2}Z/A\beta^2)\bullet$
  $(\ln(2m0c^2\beta^2)/(1-\beta^2)I - \beta^2 - C/Z - \delta/2)$

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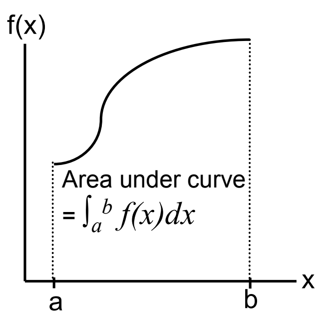
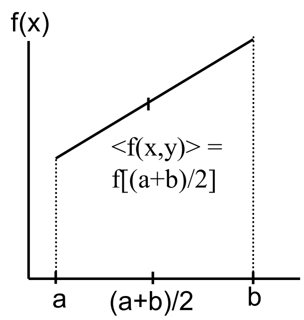
Where is Energy Deposited?

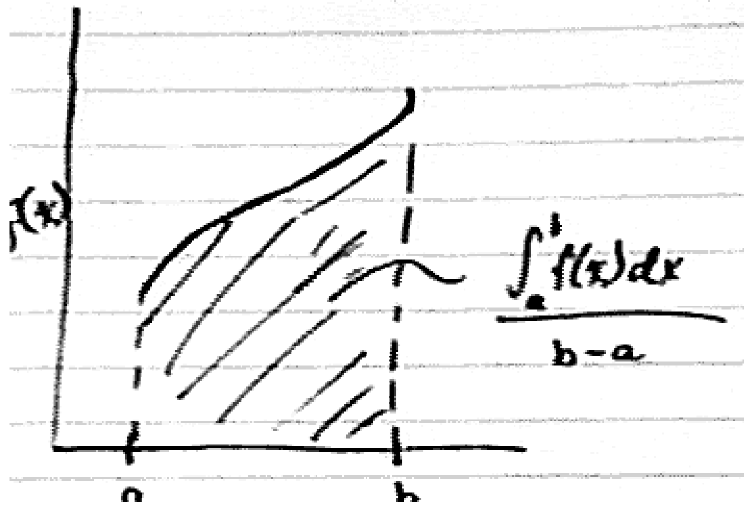
- Most of the energy is deposited just before the particle stops moving
- We're interested in *average* LET over a region or track

Calculating Averages of Continuous Variables

We wish to calculate the mean of a continuous function $f(x)$ over a range of x from a to b,
Then $<f(x)>_{a,b} = [\int_a^b f(x)dx\ ] / (b-a)$







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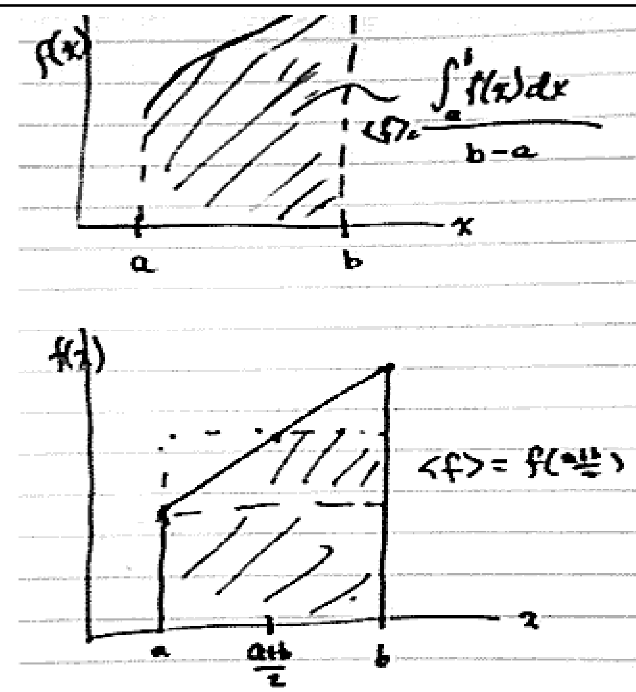

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Average LET, keVμm^{-1}

Table 14.1:

Radiation type	*$(LETav)_T$*	*$(LETav)_E$*
^{60}Co γ-rays	0.27	19.6
250 kVp x-rays	2.6	25.8
3 MeV neutrons	31	44
Radon α rays	118	83
14 MeV neutrons	11.8	125
Recoil protons	8.5	25
Heavy recoils	142	362

Direct & Indirect Effects

- High LET means that many ionizations occur in a small neighborhood

	LET Kev/μm	Spur energy eV	Events/μm	Spacing nm
60Co γ	0.25	60	4	250
Radon α	118	60	2000	0.5

- This fact by itself accounts for much of the difference in biological consequence of high LET radiation

Biological Effects of High-LET Radiation

- RBE = relative biological effectiveness
- analogous to OER in its definitional form:
  RBE = (dose for given end point for reference radiation) / (dose for given end point for test radiation)
- Problem with this formulation:
  - assumes that dose-response curves are described by identical functions, i.e.
  - RBE is independent of the response level at which it is estimated. Often not true!

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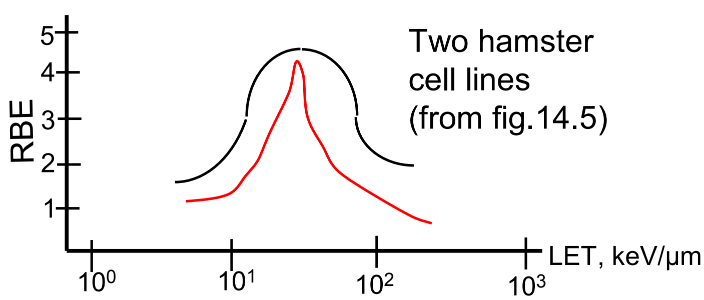
Relationship between RBE and LET

- RBE vs LET:
- Generally higher LET radiations have higher RBE, up to a certain point.
- With some systems the curve turns over.



Two hamster cell lines (from fig.14.5)

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Cell-Cycle Dependence for RBE

- Low LET radiations exert much more effect in late G2 & M than elsewhere
- High LET radiation exerts approximately equal effects throughout the cell cycle
- Reason: irreparable damage early in the cycle will persist through mitosis, so it's just as bad!

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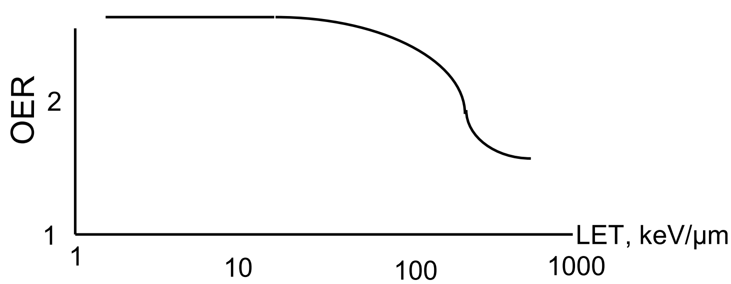
OER vs LET

- OER for High-LET Radiation is generally smaller than for low-LET radiation because the damage is less dependent on oxygen fixation of radical species.
- This plot shows OER going not to 1 but to ~1.5--because water-derived radicals are still produced at high LET; cf. Fig. 14.6.



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LET vs Fractionation

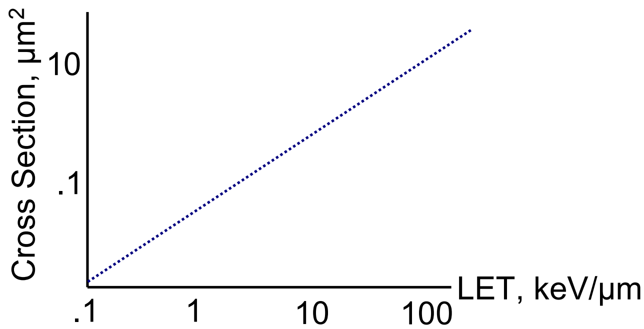
- Recall that repair-competent systems respond less to fractionated doses than to single doses whereas repair-deficient systems are fractionation-independent
- For high-LET radiation fractionation does not decrease biological effects
- Sometimes in tumors fractionation increases biological effect!
  - Why? - no explanation in Alpen
  - 2-stage model for cancer: (Ullrich)
  - Also: high dose rate is more likely to simply kill the cell rather than producing clonogenically competent but mutated cells

Late Effects of High LET Radiation

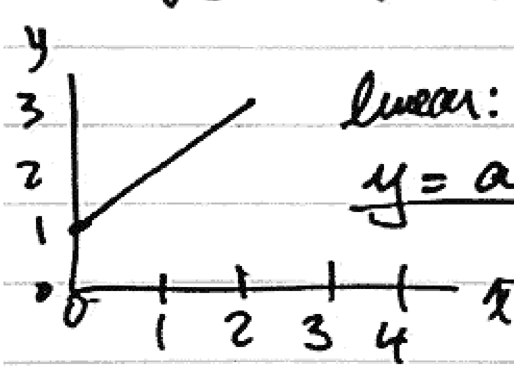
- You can induce cancer with neutrons
- Ignores fractionation or (!) is more likely with fractionation
- Tumors also arise from heavy-ion irradiation

LET vs. Cross Section

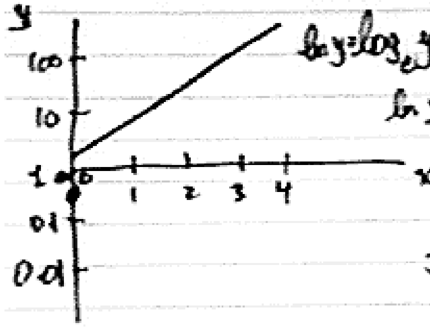
- Alpen looked at particle fluence as a dose parameter--requires constant LET over volume
- Result: power-law relationship between cross section for tumor induction and LET (fig.14.7)



General Note
re linearity



linear:
$y = ax + b$

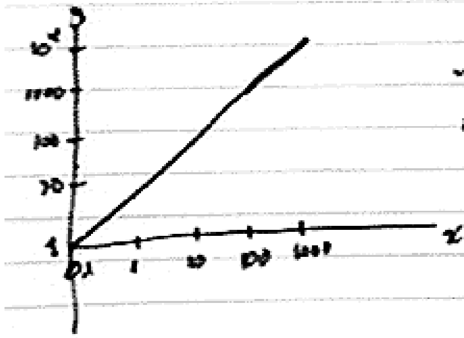


$\ln y = \log_e y = \underline{ax + b}$

$\ln y = ax + b$

$y = e^{ax+b}$

$\underline{\underline{y = \underbrace{e^{b}}_{k} e^{ax} = ke^{ax}}}$



$\ln y = a\ln x + b$

$e^{\ln y} = e^{a\ln x + b}$

$y = e^{a\ln x} \cdot \underbrace{e^{b}}_{k}$

$y = ke^{a\ln x}$

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$y = ke^{a\ln x}$

but $a\ln x = \underline{\underline{\ln x^{a}}}$

$y = ke^{\ln x^{a}} = kx^{a}$

$\underline{\underline{y = kx^{a}}}$ power law

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Probability of Traversals

- Table 14.2 shows that multiple traversals of the nucleus are very rare even at high doses
- It also shows a close correspondence between cross section for tumor production and cross-section for traversal

Dose, Gy	<fluence/ cell>	Probability of traversals 0	1	2	>= 1
0.01	0.006	0.993	0.006	2.1×10^{-5}	0.006
0.02	0.013	0.987	0.013	6.8×10^{-5}	0.013
0.05	0.032	0.968	0.031	5.0×10^{-4}	0.032
0.15	0.097	0.907	0.088	4.0×10^{-3}	0.092
0.20	0.129	0.878	0.114	7.0×10^{-3}	0.121
0.30	0.193	0.823	0.159	1.5×10^{-2}	0.176
0.40	0.258	0.772	0.199	2.5×10^{-2}	0.227

Cell Transformation in High-LET Irradiation

- Assertion: non local effects on DNA predominate over point mutation events
- Certain assay systems suggest this assertion:
- Kronenberg et al, human TK6 lymphoblasts--entire *hprt* gene is missing after irradiation
- "If large genomic changes are brought about by heavy ion radiation, then a multistep process may be short circuited to a single event."