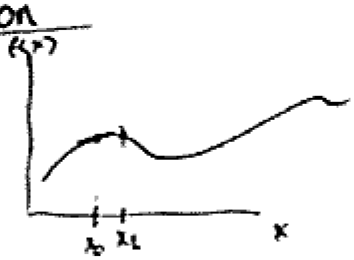
Illinois Institute of Technology

PHYSICS 561
Radiation Biophysics

Andrew Howard

Taylor Expansion

continuous function $f(x)$



if we know $f(x_0)$
can we approximate $f(x_1)$
if $x_0 \approx x_1$?

Yes, if we also know $f'(x_0) \equiv \left.\frac{df}{dx}\right|_{x_0}$

$$f(x_1) \approx f(x_0) + \left.\frac{df}{dx}\right|_{x_0} \cdot (x_1 - x_0)$$

$$f(x_1) \approx f(x_0) + \left.\frac{df}{dx}\right|_{x_0} \cdot (x_1 - x_0)$$

if f is a line then this is exact.

in a wide general case:

$$f(x) = \sum_{k=0}^{\infty} \frac{f^{(k)}(x_0)(x-x_0)^k}{k!}$$

where $f^{(0)}(x_0) \equiv f(x_0)$, $f^{(2)}(x_0) = \left.\frac{d^2f}{dx^2}\right|_{x_0}$

$f^{(1)}(x_0) = \left.\frac{df}{dx}\right|_{x_0}$ and so on.

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$$f(x) = \sum_{k=0}^{\infty} \frac{f^{(k)}(x_0)(x-x_0)^k}{k!}$$

remember $0! = 1$ $\quad 3! = 6$

$1! = 1$

$2! = 2$

$$f(x) = f(x_0) + \left.\frac{df}{dx}\right|_{x_0} \cdot (x-x_0) + \frac{1}{2}\left.\frac{d^2f}{dx^2}\right|_{x_0} (x-x_0)^2$$

$+$ h.o.t.

(higher order terms)

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$+$ h.o.t.
(higher order terms)

this formula only works if $f^{(n)}$ exists at x_0.
this is not an approximation; it's exact.
even if $(x-x_0)$ large.

Example: $f(x) = (1-x^2)^{-1/2}$ for $x \approx 1$
we could do this one ...
Instead do $f(x) = (1-x^2)^{1/2}$ for $x \approx 1$

$x_0 = 1$. $f(x_0) = 0$. $\frac{df}{dx} = +\frac{1}{2}(1-x^2)^{-1/2}$

but the derivative goes to ∞ at $x = 1$

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instead, try $f(x) = (1-x^2)^{1/2}$ near $x = 0$.

$f(x_0) = 1$. $\frac{df}{dx} = \frac{1}{2}(1-x^2)^{-1/2}$, $\left.\frac{df}{dx}\right|_0 = \frac{1}{2}(1)^{-1/2} = \frac{1}{2}$

$\frac{d^2f}{dx^2} = -\frac{1}{4}(1-x^2)^{-3/2}$, $\left.\frac{d^2f}{dx^2}\right|_{x=0} = -\frac{1}{4}$.

so the first three terms in Taylor expansion of $f(x)$ are:

$f(x) = 1 + \frac{1}{2}x - \frac{1}{4 \cdot 2}x^2 = 1 + \frac{x}{2} - \frac{1}{8}x^2$.

subsequent terms are small for small x.

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APS Electron:

$$E = 7\,\mathrm{GeV} = 7\cdot 10^9\ \mathrm{eV}$$

$$E = \frac{m_0 c^2}{\sqrt{1 - v^2/c^2}}$$: calculate c-v.

then $$E^2 = \frac{m_0^2 c^4}{1 - v^2/c^2}$$

$$1 - \frac{v^2}{c^2} = \frac{m_0^2 c^4}{E^2}$$

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$$1 - \frac{v^2}{c^2} = \frac{m_0^2 c^4}{E^2}$$

$$1 - \frac{m_0^2 c^4}{E^2} = \frac{v^2}{c^2}$$

$$c^2\left(1 - \frac{m_0^2 c^4}{E^2}\right) = v^2$$

$$c\sqrt{1 - \frac{m_0^2 c^4}{E^2}} = v$$

$$c\sqrt{1 - \left(\frac{m_0 c^2}{E}\right)^2} = v$$

we want $c - v = c\left(1 - \sqrt{1 - \left(\frac{m_0 c^2}{E}\right)^2}\right)$

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$m_0c^2 = 0.511$ MeV

$E = 7$ GeV

therefore $\frac{m_0c^2}{E}$ is small.

so we apply our formula:

$f(x) = 1 + \frac{1}{2}x - \frac{1}{8}x^2 + \text{h.o.t.}$

for $f(x) = (1-x^2)^{1/2}$ near $x = 0$.

$\frac{m_0c^2}{E} = x$ is small so this formula is reasonable to use.

$c - v = c\left(1 - \sqrt{1 - \left(\frac{m_0c^2}{E}\right)^2}\right)$. for $x = \frac{m_0c^2}{E}$

$c - v = c\left(1 - \sqrt{1 - x^2}\right)$

instead, try $f(x) = (1-x^2)^{1/2}$ near $x = 0$.

$f(x_0) = 1$. $\frac{df}{dx} = \frac{1}{2}(1-x^2)^{-1/2}(2x)$

$\frac{df}{dx} = -(1-x^2)^{-1/2}x$ $\frac{d^2f}{dx^2} = -\frac{1}{2}(1-x^2)^{-3/2} + \frac{1}{2}(1-x^2)^{-1/2}$ $\frac{d^2f}{dx^2}\Big|_{x=0} = -\frac{1}{4}$.

so the first three terms in Taylor expansion of $f(x)$ are:

$f(x) = 1 + x - \frac{1}{4!}x^2 = 1 + \frac{x}{2} - \frac{1}{8}x^2$

subsequent terms are small for small x.

Instead, try $f(x) = (1-x^2)^{1/2}$ near $x=0$

$$\frac{df}{dx} = \frac{1}{2}(1-x^2)^{-1/2}(-2x) = \underline{-x(1-x^2)^{-1/2}}$$

$$\frac{d^2f}{dx^2} = -(1-x^2)^{-1/2} - x(-\tfrac{1}{2})(-2x)(1-x^2)^{-3/2}$$

$$= -(1-x^2)^{-1/2} + \tfrac{1}{2}x(1-x^2)^{-3/2}$$

so near $x=0$

$$f(x) = f(x_0) + \frac{df}{dx}\Big|_{x_0}(x-x_0) + \frac{1}{2}\frac{d^2f}{dx^2}\Big|_{x_0}(x-x_0)^2$$

but $x_0=0$ so

$$f(x) = f(0) + \frac{df}{dx}\Big|_0 x + \frac{1}{2}\frac{d^2f}{dx^2}\Big|_0 x^2$$

$$f(0) = 1.\quad \frac{df}{dx}\Big|_{x=0} = 0,\quad \frac{d^2f}{dx^2}\Big|_{x=0} = -1.$$

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$$\frac{df}{dx} = \frac{1}{2}(1-x^2)^{-1/2}(-2x) = \underline{-x(1-x^2)^{-1/2}}$$

$$\frac{d^2f}{dx^2} = -(1-x^2)^{-1/2} - x(-\tfrac{1}{2})(-2x)(1-x^2)^{-3/2}$$

$$= -(1-x^2)^{-1/2} + \tfrac{1}{2}x(1-x^2)^{-3/2}$$

so near $x=0$

$$f(x) = f(x_0) + \frac{df}{dx}\Big|_{x_0}(x-x_0) + \frac{1}{2}\frac{d^2f}{dx^2}\Big|_{x_0}(x-x_0)^2$$

but $x_0=0$ so

$$f(x) = f(0) + \frac{df}{dx}\Big|_0 x + \frac{1}{2}\frac{d^2f}{dx^2}\Big|_0 x^2$$

$$f(0) = 1.\quad \frac{df}{dx}\Big|_{x=0} = 0,\quad \underline{\frac{d^2f}{dx^2}\Big|_{x=0} = -1.}$$

$$\text{so } f(x) = 1 + 0x + \tfrac{1}{2}\cdot(-1)x^2 = \underline{1 - \tfrac{1}{2}x^2}$$

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$\frac{m_\nu c^2}{E} = x$ is small so this formula

is reasonable to use.

$$c-v = c\left(1-\sqrt{1-\left(\frac{m_\nu c^2}{E}\right)^2}\right) \quad \text{for } x = \frac{m_\nu c^2}{E}$$

$$c-v = c\left(1-\sqrt{1-x^2}\right)$$

$$\approx c\left(1 - \underbrace{\left(1-\tfrac{1}{2}x^2\right)}_{1}\right) = c\left(0+\tfrac{1}{2}x^2\right)$$

$$c-v = c\cdot\frac{x^2}{2} \quad \text{now } x = \frac{m_\nu c^2}{E} = \frac{.50\cdot 10^6\,eV}{7\cdot 10^9\,eV}$$

$$= .072\cdot 10^{-3}$$

$$x = 7.2\cdot 10^{-5}$$

so

$$c-v = c\left(0+\tfrac{1}{2}\left(72\cdot 10^{-9}\right)\right) = \frac{c}{2}\left(53\cdot 10^{-10}\right)$$

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so near $x=0$

$$f(x) = f(x_0) + \left.\frac{df}{dx}\right|_{x_0}(x-x_0) + \frac{1}{2}\left.\frac{d^2f}{dx^2}\right|_{x_0}(x-x_0)^2$$

but $x_0=0$ so

$$f(x) = f(0) + \left.\frac{df}{dx}\right|_0 x + \frac{1}{2}\left.\frac{d^2f}{dx^2}\right|_0 x^2$$

$$f(0) = 1. \quad \left.\frac{df}{dx}\right|_{x=0} = 0, \quad \left.\frac{d^2f}{dx^2}\right|_{x=0} = -1.$$

$$\text{so } f(x) = 1 + 0x + \tfrac{1}{2}\cdot(-1)x^2 = \underline{1-\tfrac{1}{2}x^2}$$

comes from 2!

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$$c-v = c\left(1-\sqrt{1-\left(\frac{m_\nu c^2}{E}\right)^2}\right). \text{ for } x = \frac{m_\nu c^2}{E}$$

$$c-v = c\left(1-\sqrt{1-x^2}\right)$$

$$\approx c\left(1-\underbrace{\left(1-\tfrac{1}{2}x^2\right)}\right) = c\left(0+\tfrac{1}{2}x^2\right)$$

$$c-v = c\cdot\frac{x^2}{2} \quad \text{now } x = \frac{m_\nu c^2}{E} = \frac{.50\cdot10^6 eV}{7\cdot10^9 eV}$$

$$= .072\cdot10^{-3}$$

$$x = 7.2\cdot10^{-5}$$

so

$$c-v = c\left(0+\tfrac{1}{2}\left(7.2\cdot10^{-5}\right)^2\right) = \frac{c}{2}\left(53\cdot10^{-10}\right)$$

$$c-v = 26\cdot10^{-10}c = \underline{2.6\cdot10^{-9}c}$$

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$c = 3\cdot10^8$ m/sec so $c-v = 2.6\cdot10^{-9}\cdot3\cdot10^8$ m/sec

$\underline{c-v = 0.8 \text{ m/sec}}$

This does not require a high-precision calculator

If we were to do an exact calculation we would get the same answer to within $\underline{\sim10^{-3}}$

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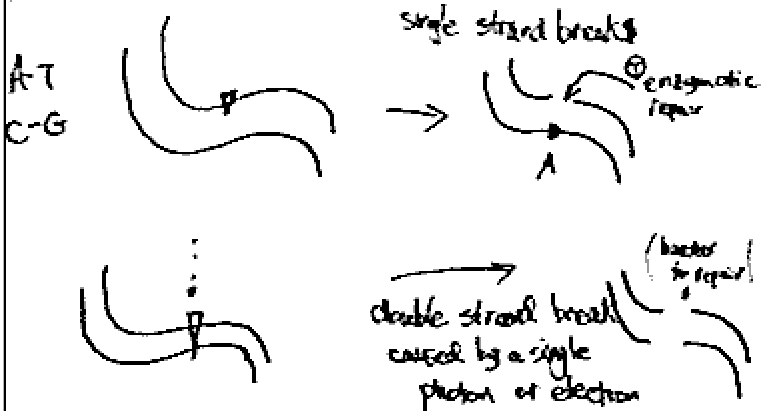
Reactions of radiation with DNA



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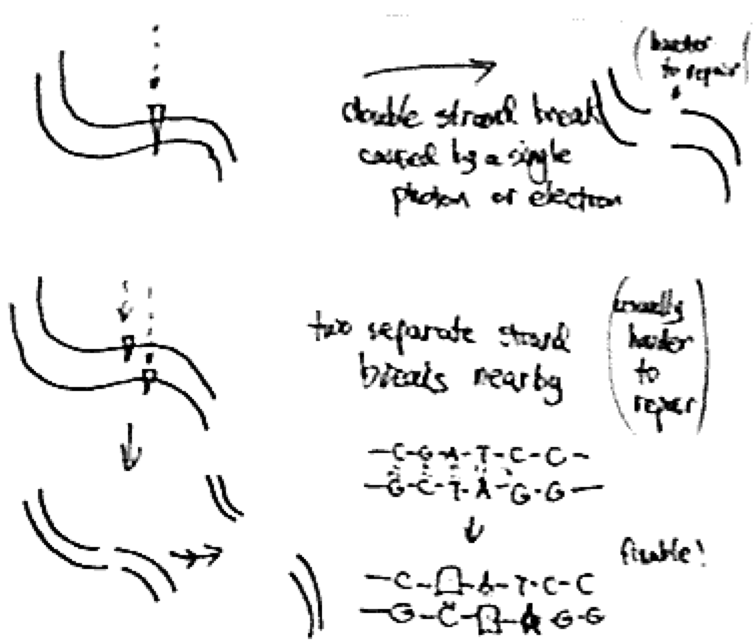

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Chemistry of Damage:

1) damage to sugars and bases (not removed but damaged)
2) loss of base
3) strand scission due to radical chemistry on a base
4) SSBs (backbone)
5) DSBs (backbone)
   ↳ two kinds - see previous of

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Chromatin:

DNA in a cell.

In between cell divisions DNA is spread out in the cell.

At a particular stage of the cell cycle, DNA becomes highly coiled & organized

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DNA in a cell.

In between cell divisions
DNA is spread out in the cell.
At a particular stage of the
cell cycle, DNA becomes highly
coiled & organized

DNA wraps itself around ~~these~~ a set of protein
molecules — histones

DNA has many phosphate groups - carrying negative charge
histones are (+) charged.

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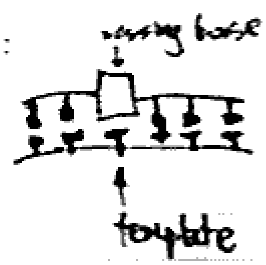
DNA Repair:

it can ~~fix~~ repair (in principle)
- SSB, DSB
- chemically altered bases
- chemically altered sugars
- damage to DNA-related proteins

1. Excision repair:

generally accurate



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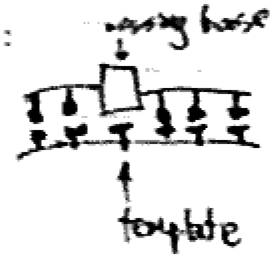
1. Excision repair:

generally accurate



2. Error-prone repair the RecA and similar proteins

3. Recombination repair – fig. 6.5

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Fricke dosimetry

mostly bookkeeping

results on p. 112 for ^{60}Co rays:

$G(H) = 3.65$

$G(H_2O_2) = 0.75$

$G(OH) = 3.15$

then directly formula 6.9 to get $G(Fe^{3+})$ from those numbers

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$G(H) = 3.65$
$G(H_2O_2) = 0.75$
$G(OH) = 3.15$

then directly formula 6.9 to get $G(Fe^{3+})$ from these numbers

Recall under high- conditions

$$G(Fe^{3+}) = 3\,G(H) + 2\,G(H_2O_2) + G(OH)$$
$$= 3 \cdot 3.65 + 2(0.75) + 3.15$$
$$= 15.6$$

under anaerobic conditions: 6.9 applies

$$G(Fe^{3+}) = G(H) + G(OH) + 2G(H_2O_2) = 8.3.$$

Physics 561, Lecture 5

Theories and Models for Cell Survival

Clonogenic Survival.

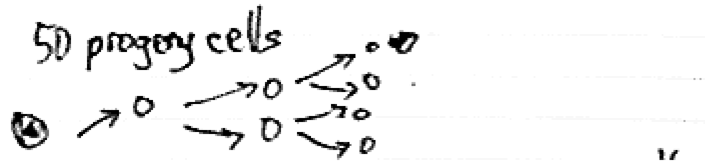
It is difficult to use radiation to make a cell stop metabolizing. The amount of radiation necessary to actually disrupt [illegible] processes (glycolysis, electron transport, ion mobility, etc.) is two or more orders of magnitude higher than the amou[illegible] cell from producing viable daughter cells. Therefore the most commonly measured endpoint for quantitating the effect[illegible] clonogenic or reproductive death, i.e. the inability of the cell to reproduce itself with fidelity.

To characterize a cell as capable of reproduction with fidelity we require that it be capable of producing viable offspri[illegible] generations. The practical definition given by Alper is that cell must be able to produce 50 offspring; this correspon[illegible] divisions, since $2^6 = 64$, fairly close to 50.

Why is reproductive death so significant? Certainly we have some interest in an organism's ability to reproduce itsel[illegible] production of viable offspring are important in that regard. But even within the lifespan of a single individual orga[illegible] divide correctly is significant. Many cells in an organism turn over, i.e. are replaced by newly-matured cells, a few [illegible] mature, so the inability to replace those cells when the time comes will have a direct effect on the health of the indiv[illegible] are concerned with the transmission of correct genetic information, not just any genetic information. Thus if a cell [illegible] its phenotype has been altered due to mutations in its genes, then the cell will not perform its assigned role. Cancer [illegible]

(Clonogenic or Reproductive Death) at cellular level : damage that prevents production of viable offspring for several generations

50 progeny cells



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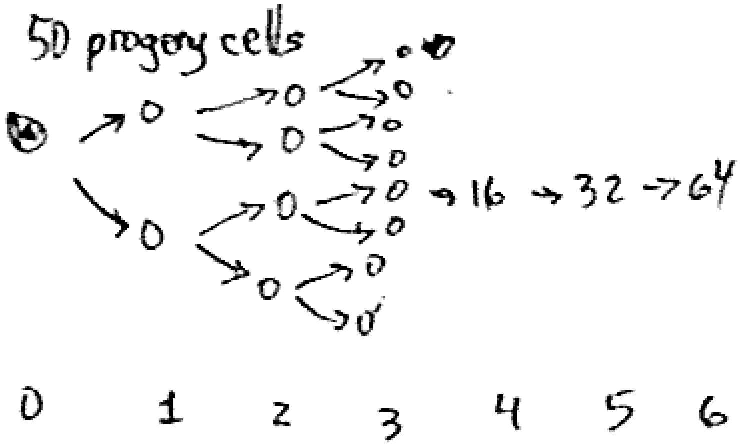
50 progeny cells



6 cell divisions corresponds to ~50 offspring in the generation

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Mechanisms of ~~Cell~~ Reproductive Cell Survival/Death

History: up to ~ 1970

Modelers
↓
mathematical studies of dose-response

biologists: mechanisms
- enzymatic
- biochemical
- molecular biological

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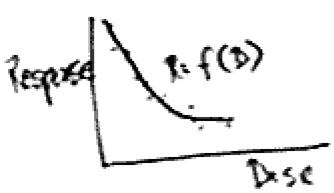
mathematical studies of dose-response

- enzymatic
- biochemical
- molecular biological

Since 1970: more communication!



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How do we study
reproductive death

→ (1) human studies ? no (except for some epidemiological data)
⇓
(2) animal studies
(too slow)
(expensive)
(ethically declines)
⇓
(IRB)

(3) bacterial studies
model is poor

Uranium miners who smoke D	Uranium miners who don't smoke C
non-miners who smoke	non-miners who don't smoke

lung cancer (A) & lung

Uranium miners who smoke D	Uranium miners who don't smoke C
non-miners who smoke B	non-miners who don't smoke A

lung cancer (A) & lung cancer (B)

lung cancer (B) >> lung cancer (A)

lung cancer (D) > lung cancer (B)

→ (1) human studies ? no (except for some epidemiological data)

(2) animal studies
(too slow)
(expensive)
(ethically delims)
(IRB)

(3) bacterial studies
model is poor

(4) cultured mammalian cells

	Uranium miners who smoke D	Uranium miners who don't smoke C
lung cancer (A) & lung cancer (B)	non-miners who smoke B	non-miners who don't smoke A

lung cancer (B) >> lung cancer (A)

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1. Clonogenic killing is a multi-step process.
2. Absorption of energy in some critical volume is the first step.
3. Deposition of energy as ionization or excitation in the critical volume will lea
4. This molecular damage will prevent normal DNA replication and cell division.

This theory, as advanced by Lee in 1955, did not specifically name DNA as the target t have come as a surprise even to mid-50's biophysicists: 1955 is, after all, two years al structure of DNA and the relationship between its structure and its capacity to carry ge "A Structure for Deoxyribose Nucleic Acid" *Nature* 171: 737-738).
Lee did make a set of assumptions that we will employ:

1. There exists a specific target for the action of radiation.
2. There may be more than one target in the cell, and the inactivation of *n* of tho
3. Deposition of energy is discrete and random in time and space.
4. Inactivation of multiple targets does not involve any conditional probabilitie second.

Using these assumptions we can derive a variety of models for radiation's effects on detail, and in class we will discuss his derivations. There are several errors in his deri

The next level of sophistication beyond models of the kind that are based on Lee's a role of double-strand breaks (DSB's) in the target molecule, DNA. DSB's can be prod ... covalent bonds in both DNA strands at the same time;

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Single-hit model

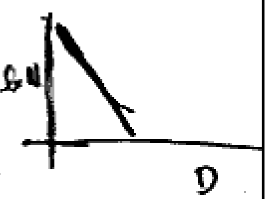
single event is sufficient to inactivate the cell

$\Rightarrow$ Exponential survival

$$\frac{dN}{N} \propto dD \Rightarrow N = N_0 e^{-D/D_0}$$

N_0 = cells present before irradiation.

$$\ln \frac{N}{N_0} = -D/D_0$$



very typical of bacterial cells.

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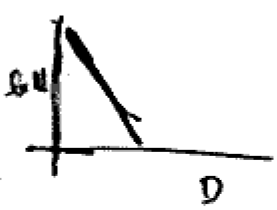
N_0 = cells present before irradiation.

$$\ln \frac{N}{N_0} = -D/D_0$$



very typical of bacterial cells.

pp 136 - 137: fig. 7.1(b)
7.2(b)

the lowest # on y axis should be 0.01, not 0.001

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Another error:

Eqn. (7.3):

$$P(p,h,D) = ({}_{D}C_{h})\, p^{h} (1-p)^{D-h}\, H(h)$$

7.4:

$$S(p,D) = \sum_{h=0}^{D} P(p,h,D)$$

Cells ~~[illegible]~~ with volume V

- target volume v.

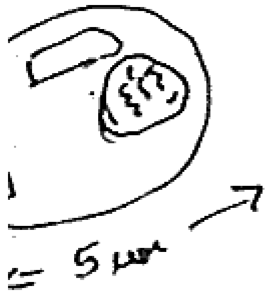
5 μm

Volume of cell V

volume of targets: v

volume that is close enough to DNA that absorption of energy will result in DNA damage s ~~the~~ with volume V

target volume v.



Volume of cell V

volume of targets: v

volume that is close enough to DNA that absorption of energy will result in DNA damage

model with n≥1 resulting in fatality gives $S = e^{-vD}$ (7.7) $\Rightarrow S = e^{-D/D_0}$

Multi-target - Single hit model

$$S = 1 - (1 - e^{-qD})^n$$

D = dose

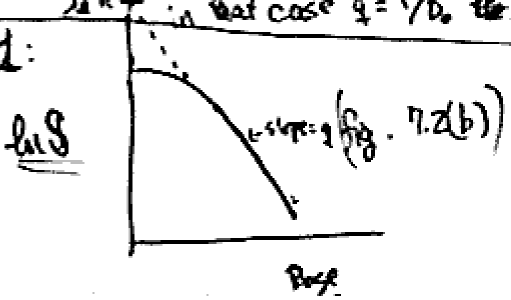
q = constant

n = # target that have to be hit.

if $n = 1$: $S = 1-(1-e^{-qD})^1 = e^{-qD}$

ln n ... in that case $q = 1/D_0$ the log-linear

$n \neq 1$:



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p 143:

- explains q
- explains n = extrapolation of linear portion
- if $n > 1$ then curve has zero slope @ zero dose

wrong

$$\frac{d(\ln S)}{dD} = 0 \text{ at } D = 0$$

- define $D_0 = 1/q$

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

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· define $D_0 = 1/q$

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

in that case we also define $D_q = D_0 \ln n$

then D_q = dose for which the linear portion extrapolated back reaches $S = 1$