

Illinois Institute of Technology

RADIATION BIOPHYSICS Fifth Lecture: Chemistry and Biology of Radiation ANDREW HOWARD

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Relevant references

- ◆ Some significant references on photoelectric effect and the interactions of photons with biological tissue:
- ◆ 1. J.H. Hubbell (1977) *Radiation Research* **70**: 58–81.
- ◆ 2. J.H. Scofield (1973) Theoretical Photoionization Cross Sections from 1 to 1500 keV, Report UCRL-51326, University of California Lawrence Livermore National Laboratory, National Technical Information Center, Springfield, VA
- ◆ 3. A.M. Kellerer and H.H. Rossi (1971) *Radiation Research* **47**: 15–34
- ◆ 4. H.H. Rossi (1959) *Radiation Research* **10**: 522–531

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Some thought problems

1. Alpen, Ch. 6, #3
2. Why is cancer more likely to occur in individuals deficient in DNA repair enzymes?
(2 - 3 paragraphs)
3. Would you expect that the rate of restitution of an altered molecule to be temperature-dependent? Why?

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Typos of the Day

- ◆ Page 79, first paragraph under “IMPORTANCE OF THE COMPTON PROCESS”, 4th line:
“with attention the the”
“with attention to the”
- ◆ Page 87, 2nd paragraph, 1st line:
“The four principle” -> “The four principal”

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Outline of Session

- ◆ Left over from chapter 5:
 - Interaction of photons with matter
 - . Contributions of Compton, other processes
 - . Attenuation coefficients: molecules + mixtures
 - Interaction of charged particles with matter
 - Size scales and biological cells
- ◆ Chapter 6:
 - Energy Deposition at different physical scales (ch.5)
 - Types of energy transfer from electrons (ch.6)
 - Free Radicals
 - Radiation Chemistry of water
 - Recombination, Restitution, Repair
 - Molecular Biology 101

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Photons interacting with matter

The interaction of a high-energy photon with a chunk of matter involves

- Photoelectric effect
- Coherent scatter
- Compton scatter
- Pair production

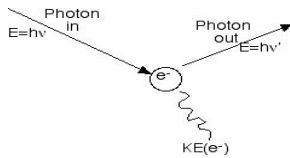
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Compton Scattering

- ◆ The most important of these processes for $h\nu > 100$ KeV is Compton scatter, especially if the matter is water or tissue
- ◆ See fig. 5.2(B) in the text to see why: μ_{ab}/ρ (Compton) predominates above 100KeV



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Attenuation Coefficients for Molecules (and mixtures)

- ◆ Calculate mole fraction f_{mi} for each atom type i in a molecule or mixture, subject to $\sum_i f_{mi} = 1$
- ◆ Recognize that, in a molecule, f_{mi} is proportional to the product of the number of atoms of that type in the molecule, n_i , and to the atomic weight of that atom, m_i : $f_{mi} = Qn_i m_i$ (Q a constant to be determined)
- ◆ Thus $\sum_i f_{mi} = \sum_i Qn_i m_i = 1$ so $Q = (\sum_i n_i m_i)^{-1}$
- ◆ Then (σ/ρ) for the compound will be $(\sigma/\rho)_{Tot} = \sum_i f_{mi}(\sigma/\rho)_i$

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Calculating Mole Fractions and Attenuation Coefficients

- ◆ Example 1: Water (in book):
 - H_2 : $n_H = 2$, $m_H = 1$; O : $n_O = 1$, $m_O = 16$
 - $Q = (\sum_i n_i m_i)^{-1} = (2 \cdot 1 + 1 \cdot 16)^{-1} = 1/18$
 - Thus $f_{H_2} = 2/18$, $f_O = 16/18$,
 - $(\sigma/\rho)_{Tot} = \sum_i f_{mi}(\sigma/\rho)_i = (2/18) \cdot (0.1129 \text{ cm}^2 \text{ g}^{-1}) + (16/18) \cdot (0.0570 \text{ cm}^2 \text{ g}^{-1}) = 0.0632$
- ◆ Benzene (C_6H_6):
 - C_6 : $n_C = 6$, $m_C = 12$; H_6 : $n_H = 6$, $m_H = 1$
 - $Q = (6 \cdot 12 + 6 \cdot 1)^{-1} = 1/78$, $f_{C_6} = 72/78$, $f_{H_6} = 6/78$

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Interaction of Charged Particles with Matter

- ◆ Recall diagram 5.3, p.84.
- ◆ The crucial equation is for $\Delta E(b)$, the energy imparted to the light particle:

$$\Delta E(b) = z^2 r_0^2 m_0 c^4 M / (b^2 E)$$
 where E is the kinetic energy of the moving particle = $(1/2)Mv^2$.
- ◆ Thus it increases with decreasing impact parameter b
- ◆ Energy imparted is inversely proportional to the kinetic energy E of the incoming heavy particle!

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Dose

- Dose is defined as: energy deposited per unit mass
- i.e. dE_{dep}/dm
- size scales $\sim 1 \mu\text{m}$
- $\rho \sim 1 \text{ g/cm}^3$ for water or soft tissue
- mass of $(1 \mu\text{m})^3 \cdot \rho = (10^{-4} \text{ cm})^3 \cdot \rho$
- $= 10^{-12} \text{ cm}^3 \cdot 1 \text{ g/cm}^3$
- $= 10^{-12} \text{ g} = 10^{-15} \text{ kg}$

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Energy Absorbed in a Cell

- ◆ Suppose N Joules of energy are deposited in a 70 kg human. Nominally the dose is $N/70$ Gy.
- ◆ How much energy is deposited in a single $(1 \mu\text{m})^3$ cell? $(N/70) \text{ Gy} \cdot 10^{-15} \text{ kg}$

$$= (N/70) \cdot 10^{-15} \text{ J} = (1.3 \cdot 10^{-17}) \cdot N \text{ J}$$

$$= [(1.3 \cdot 10^{-17}) \cdot N] / 1.609 \cdot 10^{-19} \text{ J}$$

$$= 85 \cdot N \text{ eV. So it's a lot of energy!}$$
- ◆ Is the Bethe-Blocke continuous slowing-down approximation applicable here? No! Too much energy is being stopped per cell for it to be applicable. But we try to use it anyway.

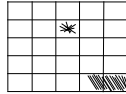
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Mozumder & Magee

| | [1 MeV "typical" electron] | Portion of energy deposited |
|----------|----------------------------|-----------------------------|
| ◆ Spurs | 6 - 100 eV | 65% |
| ◆ Blobs | 100 - 500 eV | 15% |
| ◆ Tracks | 500 - 5000 eV | 20% |



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Demonstration That Events Don't Interact Much

Spurs are 400 nm apart

1 nm = 10^{-9} m

400 nm = 0.4 μ m

Hydrogen radical diffusion

$8 \times 10^{-5} \text{cm}^2 \text{s}^{-1}$ diffusion constant for H•

Typical lifetime $\sim 10^{-6}$ s

Typical diffusion distance = 180 nm

This is smaller than the distance between spurs!

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Free Radicals - Definitions and Illustrations

A free radical is defined as molecular species containing an unpaired electron. It may be charged or uncharged.

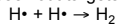
Most biological free radicals are uncharged

Exception: superoxide ($\text{O}_2^{\bullet -}$)

OH $^-$ Hydroxide ion -9 protons, 10 electrons

OH $^{\bullet}$ Hydroxyl Radical -9 protons, 9 electrons

Free radicals are reactive because the unpaired electrons tend to seek out targets, either other unpaired electrons:



... Or other acceptors of the unpaired electron

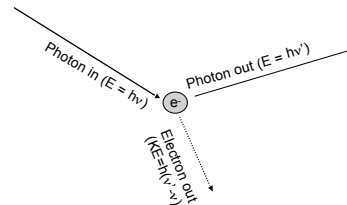
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Compton processes in tissue (review)

- ◆ For water: fig. 5.2(b) in the text shows that Compton scattering (μ_{ab}/ρ) predominates above 100keV.



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Dose

Remember Dose = energy deposited per unit mass.

What is the meaningful size scale for a mammalian cell?

We'll need to know this to estimate dose on a cell.

size scales $\sim 5 \mu\text{m}$

$\rho \sim 1 \text{g/cm}^3$ for water or soft tissue

mass of $(5 \mu\text{m})^3 \cdot \rho = (5 \times 10^{-4} \text{cm})^3 \cdot \rho$

$= 125 \times 10^{-12} \text{cm}^3 \cdot 1 \text{g/cm}^3$

$= 125 \times 10^{-12} \text{g} = 1.25 \times 10^{-13} \text{kg}$

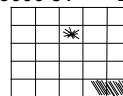
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Mozumder & Magee

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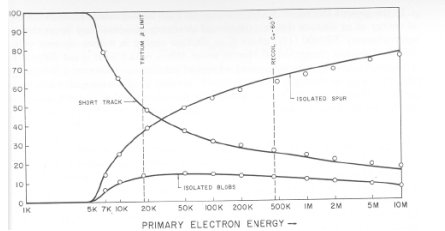
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Blobs, Spurs, and Tracks: Distribution is Energy-Dependent

- ◆ Mozumder & Magee: short tracks dominate at low primary electron energy; spurs more important at high energy



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Free Radicals: Definitions and Illustrations

- ◆ A free radical is defined as a molecular species containing an unpaired electron. It may be charged or uncharged.
- ◆ Most biological free radicals, with the significant exception of superoxide ($O_2^{\cdot -}$), are uncharged.
 - OH^- Hydroxide ion (9 protons, 10 electrons)
 - OH^\cdot Hydroxyl radical (9 protons, 9 electrons)
- ◆ Free radicals are reactive because the unpaired electrons tend to seek out targets, either other unpaired electrons: $H^\cdot + \cdot H \rightarrow H_2$... or other acceptors of unpaired electrons.

Moses Gomberg:
Characterized the
triphenylmethyl
radical in 1900



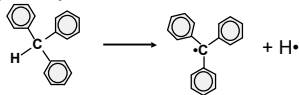
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Radical Stability

- ◆ This has nothing to do with political psychology :-)
- ◆ Highly unstable free radicals tend not to stay around long enough for ordinary spectroscopic methods to detect.
- ◆ Radicals where the unpaired electron can be highly *delocalized* last long enough to detect.
- ◆ Triphenylmethyl radical:



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Cartoons of Electron Distributions in ions, molecules, and radicals

- ◆ Hydroxyl radical
 $\cdot OH$ (8 paired e⁻, 1 unpaired e⁻, 9 p⁺)
- ◆ Hydroxide ion
 OH^- (10 paired e⁻, 9 p⁺)
- ◆ Molecular oxygen
 O_2 (16 paired e⁻, 16 p⁺)
- ◆ Superoxide ionic radical
 $O_2^{\cdot -}$ (16 paired e⁻, 1 unpaired e⁻, 16 p⁺)

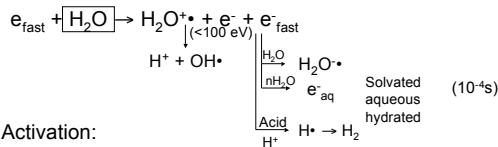
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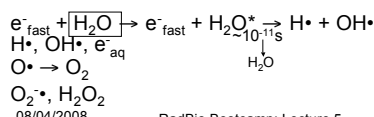
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10^{-16} - 10^{-12} s Scale Events and After

Ionization:



Activation:



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Radiation Chemistry of Water

- ◆ Since biological tissue is mostly water, we're very interested in the products produced when water absorbs ionizing radiation
- ◆ The reactive species formed out of water are responsible for a large fraction of the biological activities of radiation
- ◆ Ordinary ions (H^+ , OH^- , H_3O^+) are among these species, as is hydrogen peroxide (H_2O_2);
- ◆ So are free radicals: H^\cdot , OH^\cdot , O_2^\cdot , HO_2^\cdot
- ◆ We often discuss the "solvated electron", e_{aq}^- .

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Fricke Dosimeter

- ◆ Bookkeeping tool for aqueous radical chemistry, based on $\text{Fe}^{2+} \rightarrow \text{Fe}^{3+} + e^-$
ferrous ferric
- ◆ Sequence of reactions:
 $\text{H}\cdot + \text{O}_2 \rightarrow \text{HO}_2\cdot$ (i.e. $\text{H-O=O}\cdot$)
 $\text{HO}_2\cdot + \text{Fe}^{2+} \rightarrow \text{HO}_2^- + \text{Fe}^{3+}$
 $\text{HO}_2^- + \text{H}^+ \rightarrow \text{H}_2\text{O}_2$
 $\text{OH}\cdot + \text{Fe}^{2+} \rightarrow \text{Fe}^{3+} + \text{OH}^-$
 $\text{H}_2\text{O}_2 + \text{Fe}^{2+} \rightarrow \text{Fe}^{3+} + \text{OH}^- + \text{OH}\cdot$
- ◆ In absence of O_2 : $\text{H}\cdot + \text{H}_2\text{O} \rightarrow \text{OH}\cdot + \text{H}_2$

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Fricke Dosimeter: bookkeeping

- ◆ Each hydrogen radical $\text{H}\cdot$ causes the oxidation of three molecules of ferrous ion
- ◆ H_2O_2 produced by radiolysis will oxidize two ferrous ions: one directly, one indirectly.
- ◆ A radiolytically-produced $\text{OH}\cdot$ radical gives rise to one more oxidation
- ◆ Therefore at acidic pH in the presence of oxygen,
 $G(\text{Fe}^{3+}) = 2G(\text{H}_2\text{O}_2) + 3G(\text{H}\cdot) + G(\text{OH}\cdot)$

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Definition of Yield

$G = \text{Yield} = \text{Number of events produced per } 100 \text{ eV energy deposition}$

We're often interested in $dG(E)/dE$

Yield is either unitless or has units of $(\text{energy})^{-1}$ depending on your perspective

Fricke dosimeter provides a way of measuring yield

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Fricke bookkeeping

- ◆ Results on p. 112 for ^{60}Co photons:
 $G(\text{H}\cdot) = 3.65$
 $G(\text{H}_2\text{O}_2) = 0.75$
 $G(\text{OH}\cdot) = 3.15$
- ◆ We then apply formula 6.8 to determine $G(\text{Fe}^{3+})$
- ◆ Recall that under appropriate conditions
 $G(\text{Fe}^{3+}) = 3 * G(\text{H}\cdot) + 2 * G(\text{H}_2\text{O}_2) + G(\text{OH}\cdot)$
 $= 3 * 3.65 + 2 * 0.75 + 3.15 = 15.6$
- ◆ Under anaerobic conditions: eqn. 6.9 applies:
 $G(\text{Fe}^{3+}) = G(\text{H}\cdot) + G(\text{OH}\cdot) + 2G(\text{H}_2\text{O}_2) = 8.3$

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Interactions of Energetic Electrons With Biological Tissue

- ◆ Direct
 - $e^-_{\text{fast}} + \text{DNA} \rightarrow \text{DNA}_{\text{broken}} + e^-_{\text{fast}}$ (log-linear)
 - $e^-_{\text{fast}} + \text{Protein} \rightarrow \text{Protein}_{\text{broken}} + e^-_{\text{fast}}$ (dose-response)
- ◆ Indirect Action
 - $e^-_{\text{fast}} + \text{H}_2\text{O} \rightarrow \text{H}_2\text{O}^+ + e^-_{\text{fast}}$
 - $e^-_{\text{fast}} + \text{H}_2\text{O} \rightarrow \text{H}_2\text{O}^{\cdot+} + e^-_{\text{fast}}$
 - further radical chemistry

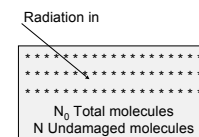
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Direct Action: the model

- ◆ Direct action of radiation on a species says that a single hit of radiation onto a molecule damages it. Then if N is the number of undamaged molecules after irradiation with dose D , we expect the change in N , ΔN , with a small increase ΔD in dose is proportional to N and to ΔD .



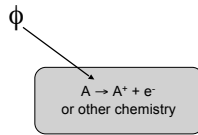
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Physical model and mathematics

- ◆ Let N = number of undamaged molecules after irradiation with dose D . Then $dN \propto N dD$.
- ◆ More radiation dose implies more response
- ◆ More undamaged molecules implies more damage.



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Why should the damage be log-linear?

- ◆ The relationship $dN \propto N dD$ can be rewritten $dN = -kN dD$, where k = inactivation constant.
- ◆ Then $dN / N = -k dD$. Integrating both sides,
- ◆ $\ln N = -kD + C$. Raising e to a power on both sides,
- ◆ $e^{\ln N} = e^{(-kD + C)} = e^{-kD} * e^C$. Defining $e^C = N_0$,
- ◆ $N = N_0 e^{-kD}$
- ◆ Thus the physical meaning (boundary condition) of N_0 is that it is the number of entities present at dose $D=0$.

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Significance of the inactivation constant

- ◆ Inactivation constant, k , is in units of inverse dose (e.g. Gy^{-1}) and is the reciprocal of the dose required to reduce the number of undamaged molecules by $1/e$.
- ◆ $N = N_0 e^{-kD}$; if $D_1 = 1/k$, then
- ◆ $N(D_1) = N_0 e^{-kD_1} = N_0 e^{-k/k} = N_0 e^{-1} = N_0/e$
- ◆ We could define a half-inactivation dose $D_{1/2}$, analogous to the half-life of an emitter:
- ◆ For $D = D_{1/2}$, $N = N_0/2 = N_0 e^{-kD_{1/2}}$, $\ln 1/2 = -kD_{1/2}$
- ◆ Thus $-\ln 2 = -kD_{1/2}$, so $D_{1/2} = \ln 2 / k = 0.693 / k$

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Indirect action of radiation

- ◆ Initial absorption of radiative energy gives rise to secondary chemical events
- ◆ Specifically, in biological tissue
- ◆ $R + H_2O \rightarrow H_2O^*$ (R = radiation)
- ◆ $H_2O^* + \text{biological macromolecules} \rightarrow \text{damaged biological macromolecules}$
- ◆ The species " H_2O^* " may be a free radical or an ion, but it's certainly an activated species derived from water.
- ◆ Effects are usually temperature-dependent, because they depend on diffusion of the reactive species to the biological macromolecule.

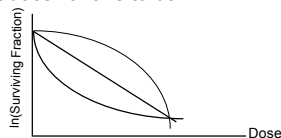
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Dose-response for indirect action

- ◆ Unlike the direct-action case, we can't write down a simple mathematical model for what's going to happen. The dose-response curve may be log-linear, but it doesn't have to be:



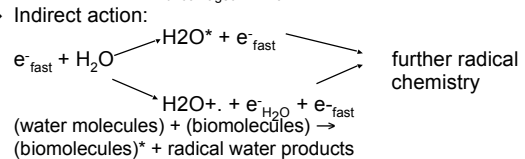
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Interaction of energetic electrons with biological tissue

- ◆ Direct action:
 - $e^-_{\text{fast}} + \text{DNA} \rightarrow \text{DNA}_{\text{broken}} + e^-_{\text{fast}}$ (log-linear)
 - $e^-_{\text{fast}} + \text{protein} \rightarrow \text{protein}_{\text{broken}} + e^-_{\text{fast}}$ (log-linear)
- ◆ Indirect action:



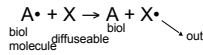
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Radical Fates/ Damaged Biomolecule Fates

- ◆ Recombination $A\cdot + B\cdot \rightarrow A - B$ (timescale 10^{-11} s)
Generally $A = B$ i.e. $A\cdot + \cdot A \rightarrow A - A$
- ◆ Restitution: Non catalyzed regeneration of non-radical species (microsecond timescale)



- ◆ Repair: Catalyzed regeneration of undamaged species
 $A\cdot + E + R \rightarrow A^{\text{mod}} + E + R\cdot$ where E is enzyme (ms-sec)

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Some definitions from biochemistry

- ◆ A *catalyst* is a species that increases the rate of a reaction without ultimately being changed in the net reaction
- ◆ An *enzyme* is a biological macromolecule capable of catalysis
- ◆ Most enzymes are proteins
- ◆ In the last two decades we have begun to study RNA molecules that function as enzymes (may do damage surveillance in RNA?)

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Catalytic vs. noncatalytic mechanisms

- ◆ Uncatalyzed reaction: $A \rightarrow B$ (slow)
- ◆ Catalyzed reaction, with E as the catalyst:
 $A + E \rightarrow A-E \rightarrow B-E \rightarrow B + E$
All three of these reactions are likely to be much faster than the uncatalyzed reaction ($\sim 10^7$ times faster)



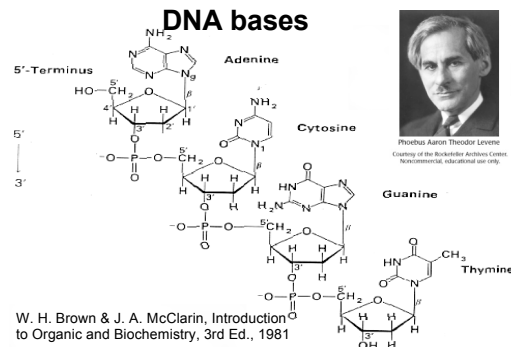
Hermann Emil Fischer

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DNA bases

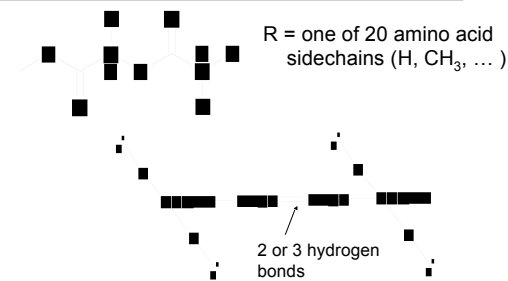


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Protein Backbones and Nucleic Acid Backbones



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Realities of DNA damage

- ◆ Covalent damage to one strand doesn't always result in failure to replicate correctly
- ◆ ... but it increases the rate of copying errors
- ◆ Base-pairing can be destroyed by covalent damage
- ◆ A-T pairs (2 hydrogen bonds per base pair) are more fragile than C-G pairs (3 H-bonds / pair)

H.J. Muller:
characterized
DNA damage
from X-radiation



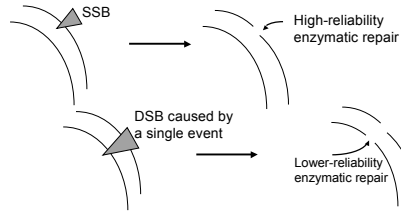
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Reactions of Radiation with DNA

- ◆ Single-strand breaks and double-strand breaks

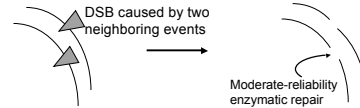


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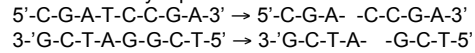
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DSBs from two events



- ◆ If the breaks are not at the same position, they can be more readily repaired:



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Chemistry of DNA damage

- ◆ Damage to sugars and bases (not removed but covalently damaged)
- ◆ Loss of base (apurinization or apyrimidization)
- ◆ Strand scission due to radical chemistry on a base
- ◆ Single-strand breaks on the backbone
- ◆ Double-strand breaks (see above) on the backbone

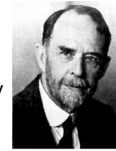
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Chromatin

- ◆ This refers to DNA in a cell.
- ◆ In between cell divisions, DNA is spread out in the cell.
- ◆ At a particular stage in the cell cycle, the DNA becomes highly coiled and organized in preparation for replication.



Thomas Hunt Morgan, pioneer in the understanding of the role of chromosomes in heredity

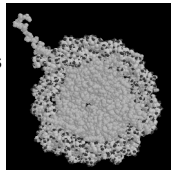
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How does chromatin become organized?

- ◆ At the lowest level of organization, ~200 base-pairs of DNA wrap themselves around a group of nitrogen-rich proteins called histones which have been organized into the nucleosome core particle
- ◆ That interaction is stabilized by charge-charge interactions between the negatively-charged phosphate groups in the DNA and positively charged amino acids in the histone



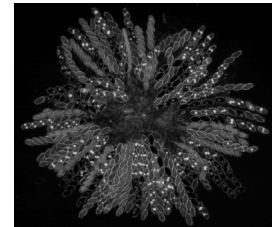
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Higher levels of organization

- ◆ Neighboring nucleosomes group together to form even higher levels of coiling through an interaction with another histone, H₁. This forms a solenoid-like structure.



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Why does this matter?

- ◆ DNA tends to be more radiation-sensitive when it is more organized
 - More tightly packed—harder for the repair enzymes to get access to the lesions
 - Closer to the time of replication
- ◆ So we need to be conscious of these levels of organization

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DNA repair

- ◆ All organisms have some DNA repair mechanisms.
- ◆ DNA repair enzymes can recognize and repair
 - SSBs
 - DSBs
 - Chemically altered bases
 - Chemically altered sugaars
 - Damage to DNA-related proteins (e.g. histones)
- ◆ Some mechanisms are more error-prone than others
- ◆ Certain kinds of damage are effectively irreparable
- ◆ Repair in eukaryotes is much more effective than in prokaryotes

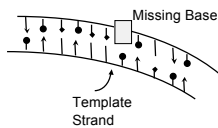
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Excision repair

- ◆ The least error-prone type of repair



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Other forms of repair

- ◆ "Error-prone repair": recA and similar mechanisms
- ◆ Recombination repair: see figure 6.5.

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