Radiation Chemistry

Ionizing radiation produces abundant **secondary electrons** that rapidly slow down (thermalize) to energies below 7.4 eV, the threshold to produce electronic transitions in liquid water.

For both the primary charged particle and the secondary electrons, this slowing down process is accomplished by transfer of energy to the medium in a sequence of **discrete events**.

Stopping power (-dE/dx) treats the slowing down process as a continuous function, sometimes referred to as the *continuous slowing down approximation.*

Depending on the amount of energy transferred to the electron, the molecule can undergo:
- Ionization (threshold in water ~ 13 eV)
- excitation   (threshold in water ~ 7.4 eV)
- thermal transfer

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The example shown is for 20 keV electrons.
[Thermal transfers (vibration, rotation, translation) are largely inconsequential. A dose of 10^4 Gy would be necessary before the thermal effects (a few degrees centigrade) became large enough to affect cellular biochemistry.]

Initial Physical Events

The **initial event** is the transfer of ~ 7 - 100 eV, an amount of energy sufficient to cause (multiple) ionizations or excitations in water molecules.
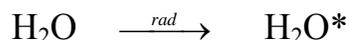
Transfer of energy to the medium in **biological systems** usually involves ionization of a **water** molecule, but can also involve the cellular macromolecules (e.g., DNA) directly.

Through ionizations and excitations the passage of a charged particle through biological medium creates **three** species in the *local vicinity of the particle track*:

Direct ionization of water produces a **radical ion** and a free **subexcitation electron** (E < 7.4 eV).

$$H_2O \xrightarrow{rad} H_2O^{\cdot +} + e^-$$

Energy transfer can produce a water molecule in an **excited state.**

$$H_2O \xrightarrow{rad} H_2O^*$$

The time scale for the creation of these species is on the order of **10^{-16} seconds**.

Prechemical Reactions

The **three initial species** begin to diffuse and react with each other or other molecules in the medium.

Some of these reactions produce **radicals.**
  ➢ Radical refers to an atom or molecule that contains an unpaired electron.
  ➢ Radicals are highly reactive.
  ➢ Radicals can be neutral or charged.

The electron is captured by water through dipolar interactions, becoming solvated, and referred to as an **aqueous electron** or a **solvated electron:**

$$e^- + H_2O \rightarrow e^-_{aq} \text{ surrounded by a "cage" of water;}$$

$$e^- + H^+ \rightarrow H\cdot \qquad \text{or it can react with } H^+ \text{ to form a radical.}$$

• The radical ion of water can dissociate to produce a hydroxyl radical and a hydrogen ion.

$$H_2O\cdot^+ \rightarrow H^+ + HO\cdot$$

• The excited water molecule can dissipate excess energy by *bond breakage* to produce hydroxyl and hydrogen radicals.

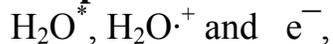$$H_2O^* \rightarrow HO\cdot + H\cdot$$

It takes ~ 5 eV to break the O-H bond.

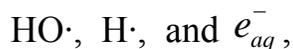Example of the dissociation of excited water to form hydroxyl and hydrogen radicals (from Tubiana, 1990).

[Image removed due to copyright concerns]

The actual concentrations of the radicals are very small, especially when compared to the concentrations of ions present from the dissociation of water.

Thus, the **three initial species**:
$$H_2O^*, H_2O\cdot^+ \text{ and } e^-,$$

react further to produce **chemically reactive species**:
$$HO\cdot, \; H\cdot, \; \text{and } e^-_{aq},$$

Water radiolysis produces highly reactive HO· and H· radicals.

These radicals are much more reactive than HO^- or H^+ from ionic dissociation.

$HO\cdot$ is a powerful oxidizing agent, very reactive chemically.

> **Oxidation:** the loss of electrons. The electrons are transferred to the oxidizing agent, which becomes reduced.

> **Reduction:** the addition of electrons. May involve the addition of electron only, or the addition of hydrogen together with an electron.

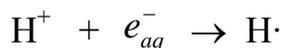[Image removed due to copyright concerns]

Chemical Stage

After $\sim 10^{-12}$ sec, the chemically reactive species are still located in the vicinity of the original H_2O^*, $H_2O\cdot^+$ and e^- species that caused their creation.

Three of the new species created are radicals: $HO\cdot$, $H\cdot$, e^-_{aq}.

These species now begin to **migrate randomly** about their initial positions. As this diffusion proceeds, individual pairs may come close enough together to *react with each other.*

A variety of reactions are possible in the track of the charged particle.

$$HO\cdot \; + \; HO\cdot \; \rightarrow \; H_2O_2$$
$$HO\cdot \; + \; e^-_{aq} \; \rightarrow \; OH^-$$
$$HO\cdot \; + \; H\cdot \; \rightarrow \; H_2O$$
$$H^+ \; + \; e^-_{aq} \; \rightarrow \; H\cdot$$
$$e^-_{aq} \; + \; e^-_{aq} \; + 2\,H_2O \; \rightarrow \; H_2 + 2\,OH^-$$
$$e^-_{aq} \; + \; H\cdot \; + \; H_2O \; \rightarrow \; H_2 + \; OH^-$$
$$H\cdot \; + \; H\cdot \; \rightarrow \; H_2$$

Most of these reactions **remove** chemically reactive species from the system.

With time (by $\sim 10^{-6}$ sec) all of the reactive species have diffused sufficiently far that further reactions are unlikely.

The **chemical development** of the track is over by 10^{-6} sec.

Radical Diffusion

TABLE 13.2. Diffusion Constants D and Reaction Radii R for Reactive Species

Species	D $(10^{-5}$ cm^2 s$^{-1})$	R (Å)
OH	2	2.4
e_{aq}^-	5	2.1
H_3O^+	8	0.30
H	8	0.42

If the measured diffusion constant for a given species is D, then, on average, it will move a small distance, λ, in a time, τ, such that

$$\frac{\lambda^2}{6\tau} = D$$

The reaction radius, R, is a measure of the reactivity of the individual species. If a reactive species diffuses closer to a "target" than the reactive radius. It will react.

Simulations of Charged-Particle Tracks

The diffusion formula and the recombination reactions described above allow Monte Carlo simulation of the charged-particle tracks.

Monte Carlo codes are used to model:
- passage of the charged particle,
- generation of secondary electrons,
- generation of chemically reactive species,
- diffusion of the reactive species through a series of "random walk" jumps,
- recombination events in any pairs that come closer than the reactive radius.

Examples of Track Simulations

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When the electron stops, in the upper left region of the figure, the track density is higher.

This illustrates the high-LET nature of the electron track end.

Examples of track simulations

High-LET particle (proton) produces a **straight track,** in contrast to the torturous tracks of electrons**.**

High LET particles have a dense formation of reactants along the particle track.

[Image removed due to copyright concerns]

In the simulation, clusters and spurs are also generated along the track.

Examples of Simulated Particle Tracks

Expanded view of
the high-LET proton
track.

Expanded scales
show a close-up view
of track development
as a function of time.

[Image removed due to copyright concerns]

Radiochemical Yield: G values

In simulations, the numbers of the various chemical species can be tabulated as a function of time.

G value: the number of a particular species produced **per 100 ev** of energy loss by the charged particle and its secondaries when it stops in water.

- Some species will decrease with time, others will increase with time.

- By about 10^{-6} sec, all chemical development of the track is over. G values will not change much after that.

TABLE 13.4. *G* Values (Number per 100 eV) for Various Species at 10^{-7} s for Protons of Several Energies and for Alpha Particles of the Same Velocities

Species Type	Protons (MeV)				Alpha Particles (MeV)			
	1	2	5	10	4	8	20	40
OH	1.05	1.44	2.00	2.49	0.35	0.66	1.15	1.54
H_3O^+	3.53	3.70	3.90	4.11	3.29	3.41	3.55	3.70
e_{aq}^-	0.19	0.40	0.83	1.19	0.02	0.08	0.25	0.46
H	1.37	1.53	1.66	1.81	0.79	1.03	1.33	1.57
H_2	1.22	1.13	1.02	0.93	1.41	1.32	1.19	1.10
H_2O_2	1.48	1.37	1.27	1.18	1.64	1.54	1.41	1.33
Fe^{3+}	8.69	9.97	12.01	13.86	6.07	7.06	8.72	10.31

- The alpha particle has 4 times higher LET.

- LET decreases at higher energies, the initial density of reactants is lower, more survive without recombining (lines 1-4), less produced (lines 4+5).

- The alpha track is denser, the G values are lower, because more recombine.

❖ Electrons, protons and alpha particles **all produce the same species** in track regions (at 10^{-15} sec), H_2O^*, $H_2O\cdot^+$ and e^-.

❖ The chemical (and biological) differences later are due to the **different spatial patterns** of energy deposition along the track, ie., track density.

Effect of LET on G values

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The Fricke Dosimeter

Originally developed as a dose-measuring device. Strong LET dependence limits this application.

Most useful as a method to directly measure the numbers of reactive species in solution.
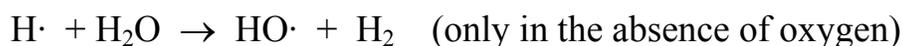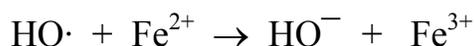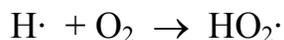
- The standard solution: 1 mM $FeSO_4$ in 0.8 N H_2SO_4

- When irradiated, the Fe^{2+} is **oxidized** to Fe^{3+}.

- Fe^{3+} generates a blue color that can be quantified with a spectrophotometer.

- The colorimetric dose response is linear up to 400 Gy.

- The oxidation is complete at ~ 700 Gy.

[Image removed due to copyright concerns]

[Tubiana, 1990]

Fricke Dosimeters

The chemical reactions involved in Fricke dosimetry are:

$$H\cdot \ + O_2 \ \rightarrow \ HO_2\cdot$$

$$HO_2\cdot \ + \ Fe^{2+} \ \rightarrow \ HO_2^{-} \ + \ Fe^{3+}$$

$$HO_2^{-} \ + \ H^{+} \ \rightarrow \ H_2O_2$$

$$HO\cdot \ + \ Fe^{2+} \ \rightarrow \ HO^{-} \ + \ Fe^{3+}$$

$$H_2O_2 \ + \ Fe^{2+} \ \rightarrow \ HO^{-} \ + \ Fe^{3+} \ + \ HO\cdot$$

$$H\cdot \ + H_2O \ \rightarrow \ HO\cdot \ + \ H_2 \quad \text{(only in the absence of oxygen)}$$

- Each $H\cdot$ will produce $3 \ Fe^{3+}$

- Each H_2O_2 (radiolytic) will produce $2 \ Fe^{3+}$

- Each $HO\cdot$ (radiolytic) will produce $1 \ Fe^{3+}$

Overall, when O_2 is present,

$$G(Fe^{3+}) = 2 \ G(H_2O_2) + 3 \ G(H\cdot) + G(HO\cdot)$$

What is the use of a Fricke Dosimeter?

- Demonstrates that scavenger molecules will react, cell components should react similarly.

- Can be used to test other competing scavengers.

- Demonstrates that not all energy deposition translates into scavengable species, i.e., at high LET there is considerable intratrack recombination.

Direct Action, Indirect Action and the Oxygen Effect

- So far, the radiation chemistry of water has been considered.

- It is possible that energy can be deposited directly in the biological molecule of interest (e.g., DNA).

- The result would still be ionization and/or excitation leading to radical formation in the biological molecule.

- Biological radicals can undergo reactions similar to those described for water.

[Image removed due to copyright concerns]

Direct action: energy deposition directly in the biological molecule (e.g., the DNA as shown here). The dose response relationship should be linear.

Indirect action: Relies on the ionization of the solvent molecules as intermediaries. Indirect action is diffusion limited, the dose response relationship can be complex.

Water radiolysis produces many reactive species.

Experiments with scavengers specific for individual reactive species have shown that it is primarily the **hydroxyl radical (HO·)** that is responsible for radiation damage to DNA.
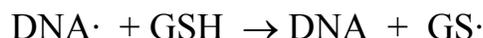
[Hall,2000]

For high-LET radiation, direct action is the predominant mechanism of DNA damage.

[Image removed due to copyright concerns]

Radiation damage in DNA can be repaired by several processes.

- **Recombination:** reaction of nearby radical with the DNA radical to regenerate the original DNA. Timescale is $< 10^{-11}$ sec.

- **Restitution:** chemical restoration of the DNA; no enzyme involved. There are a number of intracellular reducing agents that can react with radicals, the most important of which is glutathione (GSH). The sulfhydryl group on GSH can donate H· to the DNA, producing the restored DNA and a more stable (and less reactive) sulfur radical. The time scale is $< \sim 10^{-3}$ sec.

$$DNA· + GSH \rightarrow DNA + GS·$$

- **Repair:** there are many cellular enzymes that recognize and repair DNA damage. Time scale is minutes to hours.

"Fixation" of damage by oxygen

- O_2 is a powerful oxidizing agent. O_2 has two unpaired electrons: a stable biradical.

- O_2 reacts readily with organic radicals:

$$DNA\cdot + O_2 \rightarrow DNA\text{-}O\text{-}O\cdot \quad (DNA\ hydroperoxy\ radical)$$

$$DNA\text{-}O\text{-}O\cdot\ \ H\cdot\ \rightarrow\ DNA\text{-}O\text{-}OH \quad (DNA\ hydroperoxide)$$

- If oxygen reacts with the DNA radical before it is repaired, the damage becomes harder, if not impossible, to repair. Cannot be repaired by chemical restitution.

[Image removed due to copyright concerns]

[Hall, 2000]

Scavengers

Chemicals that can react with reactive species, like HO·, can block the ***indirect*** effects of radiation.

- Scavengers provide a way to estimate relative contributions of direct and indirect effects.

- Scavengers for specific reactive species can help define the radiation chemistry.

- Scavenger experiments suggest that 60 - 70% of the damage in cells exposed to low-LET radiation is caused by **HO·** radicals.

Radical Scavenging

In order to simplify complex chemistry in solutions or cells, scavengers can be added to selectively react with one or more types of radicals.

Additive	Reaction	Active Species Remaining
N_2O	$N_2O + e^-_{aq} + H_2O \rightarrow {}^\bullet OH + OH^- + N_2$	${}^\bullet OH$ ($H^\bullet$)
${}^\bullet OH$ scavengers	$RH + {}^\bullet OH \rightarrow R^\bullet + H_2O$	e^-_{aq} ($H^\bullet$)
oxygen	$O_2 + e^-_{aq} \rightarrow O_2^{-\bullet}$ $O_2 + {}^\bullet H \rightarrow HO_2^\bullet$	${}^\bullet OH, O_2^\bullet{}^-, HO_2^\bullet$
acid	$e^-_{aq} + H^+ \rightarrow H^\bullet$	$H^\bullet, {}^\bullet OH$