Radiation chemistry and oxidative stress

1. Introduction

Water is a major constituent of all living matter, representing 70-85% of the weight of cells. For this reason, water plays a major role in radiobiology, because its radiolysis produces reactive species which are responsible for indirect and/or quasi-direct effects. Its absorption properties being very similar to those of the human body, water is also widely used for clinical dosimetry. For these reasons, radiolysis of water and aqueous solutions has been extensively studied for more than a century. In fact, very shortly after the discovery of X rays by Wilhelm Conrad Roentgen in 1895, the natural radioactivity of uranium compounds by Henri Becquerel in 1896, and the radioactive element radium by Pierre Curie, Marie Curie and Gustave Bémont in 1898, dissolved radium salt has been shown to decompose aqueous solutions by liberating hydrogen gas continuously, due principally to the release of α-particles from the decomposition of radium[1]. H_2O_2 was also found in the irradiated solution[2]. Excellent texts on the history of radiation chemistry can be found in references[3,4,5].

2. Energy deposition and radiation track structure

There are several types of ionizing radiations, such as _electrons_, _photons_ (including X-rays and γ-rays), _heavy ions_ and _neutrons_. The energy deposition is highly dependent on the type and energy of radiation. The final common point of the energy deposition by all ionizing radiation is excitation and ionization of water molecules with production of electrons in the irradiated medium, the great majority with low energy[6].

2.1 Linear Energy Transfer (LET)

Linear Energy Transfer (LET) is commonly used to characterize ionizing radiation. It is defined as the energy deposition per unit length:

$$LET = -\frac{dE}{dx}$$

(1)

where dE is the energy deposited in the distance dx. The units of the LET are usually given in keV/μm. In SI units, 1 keV/μm $\approx 1.602 \times 10^{-19}$ J/nm.

In most cases, the LET is equal to the « stopping power ». The _Bethe theory of stopping power_ describes the mean energy loss by a charged particle due to the electrostatic interactions between the particle and the electrons of atoms in the medium[7]. For non-relativistic ions, the Bethe formula can be written as:

$$ -\frac{dE}{dx} = \left(\frac{1}{4\pi\varepsilon_0}\right)^2 \frac{4\pi Z^2 e^4}{m_0 V^2} N \ln\left(\frac{2m_0 V^2}{I}\right) \tag{2} $$

In this equation, Ze and V are the charge and velocity of the incident ion, m_0 is electron mass, N is target electron density and I is the mean of ionization potentials. Several important aspects are illustrated in this formula. Since dE/dx α Z^2/V^2, the LET of two ions of the same charge is higher for the ion with the lowest energy. This can be understood by noting that a slower ion has more time to interact with electrons of the medium than a faster ion; thus, the LET of the ion with the lowest energy is higher.

LET values for radiations. Values from ref. [8]

Radiation	LET (keV/μm)	Radiation	LET (keV/μm)
1 MeV electrons	0.3	$^1H^+$ 300 MeV/amu	0.3
^{60}Co γ-rays	0.3	$^4He^{2+}$ 6 MeV/amu	26
^{137}Cs γ-rays	0.9	$^{56}Fe^{26+}$ 1 GeV/amu	150
200 kV X-rays	1.7		

2.1.1 Low-LET radiation

The average LET of a 1 MeV electron or a ^{60}Co γ-ray is ~0.3 keV/μm. The average energy loss of a fast electron at each interaction is ~57 eV[9]. Thus, on average, energy deposition events are separated by ~200 nm. Ionized electrons become thermalized ~8-12 nm from their original molecule[10]. This thermalization distance defines a more or less spherical region called spur. Because the radius of spurs is much smaller than their average separation distance, the spurs generated by low-LET radiation do not overlap when they are created. This is the basis for the theory of spurs, introduced in the 1950's[11].

2.1.2 High-LET radiation

The LET of heavy ions is highly dependent on their energy. At low energy, the LET may increase to very high values. For LET higher than 10-20 keV/μm, the distance between spurs is less than ~6-8 nm, which corresponds to their size. Thus, spurs will overlap and create a dense cylindrical region of spurs called _core_ surrounded by a concentric cylindrical region called _penumbra_. Computed tracks of $^4He^{2+}$ (0.45 MeV/amu), $^{12}C^{6+}$ (10 MeV/amu), $^{28}Si^{14+}$ (90 MeV/amu) and $^{56}Fe^{26+}$ (1 GeV/amu), of LET ~150 keV/μm are shown in ref.[12].

3. Mechanisms of water radiolysis

The radiolysis of water is usually divided in three more or less overlapping stages: physical ($<10^{-15}$ s), physico-chemical stage ($\sim10^{-15}$-10^{-12} s) and non-homogeneous chemical stage ($\sim10^{-12}$-10^{-6} s). Although this time division is controversial, it gives a convenient way to describe the mechanisms involved in water radiolysis.

3.1 Physical stage ($<10^{-15}$ s)

The physical stage is the absorption of ionizing radiation by matter. The main consequences are the _ionization_ and _excitation_ of water molecules. An ionization event is the removal of an electron from the water molecule:

$$H_2O \rightsquigarrow H_2O^{\cdot +} + e^-$$ (3)

Similarly, an excitation is the transfer of an electron from a fundamental state to an excited state:

$$H_2O \rightsquigarrow H_2O^*$$ (4)
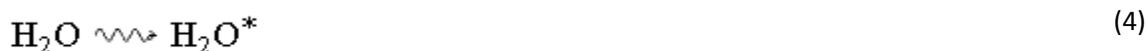
There are several molecular orbitals and excitation levels in the water molecule. The description of these states is beyond the scope of this text and is not necessary for the discussion that follows.

3.2 Physico-chemical stage ($\sim10^{-15}$-10^{-12} s)

The ionized and excited molecules created during the physical stage are highly unstable. During this stage, lasting $\sim10^{-12}$ s, the ionized and excited water molecules dissipate their energy by energy transfer to neighboring molecules and bond rupture. The sequence of events of the physico-chemical stage is, in fact, not well characterized experimentally. However, some important physico-chemical stage events worth mentioning: proton transfer to a neighboring molecule, dissociation of excited water molecule and electron thermalization and solvatation.

The proton transfer to a neighboring water molecule is very important, because it leads to the production of an $^{\cdot}$OH radical[*]:

$$H_2O^{\cdot +} + H_2O \rightarrow {}^{\cdot}OH + H_3O^+$$ (5)

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[*]In chemistry, a _radical_ (also referred to as _free radical_) is an atom, molecule or ion with at least one unpaired electron. The unpaired electron usually cause them to be highly chemically reactive. The radical site is usually noted by putting a dot on the atom (ex.: $^{\cdot}$OH)

They are several channels for the dissociation of an excited water molecule:

$$H_2O^* \rightarrow H^\bullet + {}^\bullet OH \tag{6a}$$

$$H_2O^* \rightarrow H_2 + O(^1D) \tag{6b}$$

$$H_2O^* \rightarrow 2H^\bullet + O(^3P) \tag{6c}$$

Where $O(^1D)$ and $O(^3P)$ are the singlet and triplet state of the atomic oxygen, respectively[(Link to other text)].
The excited water molecule can also return to its fundamental state without dissociation (by heat loss):

$$H_2O^* \rightarrow H_2O \tag{7}$$

Most secondary electrons have low energy[6], but some of them may have energy in the keV or even in the MeV range. These electrons lose their energy into medium by doing further ionization, excitations until they eventually reach thermal equilibrium with the liquid. The electron, which is negatively charged, interacts with the dipoles of the surrounding water molecules and becomes trapped in a state called « trapped electron ». Finally, this electron becomes a « _hydrated electron_ », which behaves like chemical specie. This rapid sequence of events can be written as follows:

$$e^- \rightarrow e^-_{th} \rightarrow e^-_{tr} \rightarrow e^-_{aq} \tag{8}$$

The hydrated (or solvated) electron is of great importance in water radiolysis. However, its existence has been proposed only in the 1950's and it was observed experimentally in the 1960's.

### 3.3 Non-homogeneous chemical stage ($\sim 10^{-12}$-10^{-6} s)

At the end of the physico-chemical stage, the species $H^\bullet$, $^\bullet OH$, H_2, H_2O_2 are created in very high concentration in the spurs. Other species such as $O(^3P)$ may also be present, in small quantity. They diffuse in the medium and eventually encounter chemical species created in other spurs, which gives them the opportunity to react. In general, the radical species (such as $H^\bullet$, $^\bullet OH$ and e^-_{aq}) react in ~ 1 μs to form the molecular species H_2 and H_2O_2. For example, H_2O_2 is formed by the reaction $^\bullet OH + ^\bullet OH \rightarrow H_2O_2$. Another important reaction is $H^\bullet + ^\bullet OH \rightarrow H_2O$, which forms back water.

Many reactions are known to occur in pure, irradiated liquid water; the most important are given in the following table.

Chemical reactions table

Reactions			
$H^{\cdot}+H^{\cdot}\rightarrow H_2$	$^{\cdot}OH+^{\cdot}OH\rightarrow H_2O_2$	$H_2O_2+e^{-}_{aq}\rightarrow OH^{-}+^{\cdot}OH$	$H^{+}+O_2^{\cdot-}\rightarrow HO_2^{\cdot}$
$H^{\cdot}+^{\cdot}OH\rightarrow H_2O$	$^{\cdot}OH+H_2O_2\rightarrow HO_2^{\cdot}+H_2O$	$H_2O_2+OH^{-}\rightarrow HO_2^{-}+H_2O$	$H^{+}+HO_2^{-}\rightarrow H_2O_2$
$H^{\cdot}+H_2O_2\rightarrow H_2O+^{\cdot}OH$	$^{\cdot}OH+H_2\rightarrow H^{\cdot}+H_2O$	$H_2O_2+O(^3P)\rightarrow HO_2^{\cdot}+^{\cdot}OH$	$H^{+}+O^{\cdot-}\rightarrow^{\cdot}OH$
$H^{\cdot}+e^{-}_{aq}\rightarrow H_2+OH^{-}$	$^{\cdot}OH+e^{-}_{aq}\rightarrow OH^{-}$	$H_2O_2+O^{\cdot-}\rightarrow HO_2^{-}+OH^{-}$	$OH^{-}+HO_2^{\cdot}\rightarrow O_2^{\cdot-}+H_2O$
$H^{\cdot}+OH^{-}\rightarrow H_2O+e^{-}_{aq}$	$^{\cdot}OH+OH^{-}\rightarrow O^{\cdot-}+H_2O$	$H_2+O(^3P)\rightarrow H^{\cdot}+^{\cdot}OH$	$OH^{-}+O(^3P)\rightarrow HO_2^{-}$
$H^{\cdot}+O_2\rightarrow HO_2^{\cdot}$	$^{\cdot}OH+HO_2^{-}\rightarrow O_2+H_2O$	$H_2+O^{\cdot-}\rightarrow H^{\cdot}+OH^{-}$	$HO_2^{-}+O(^3P)\rightarrow O_2+^{\cdot}OH$
$H^{\cdot}+HO_2^{\cdot}\rightarrow H_2O_2$	$^{\cdot}OH+O_2^{\cdot-}\rightarrow O_2+OH^{-}$	$e^{-}_{aq}+e^{-}_{aq}\rightarrow H_2+2OH^{-}.$	$HO_2^{\cdot}+HO_2^{\cdot}\rightarrow H_2O_2+O_2$
$H^{\cdot}+O_2^{\cdot-}\rightarrow HO_2^{-}$	$^{\cdot}OH+HO_2^{\cdot}\rightarrow HO_2^{-}+OH^{\cdot}$	$e^{-}_{aq}+H^{+}\rightarrow H^{\cdot}$	$HO_2^{\cdot}+O_2^{\cdot-}\rightarrow HO_2^{-}+O_2$
$H^{\cdot}+O(^3P)\rightarrow^{\cdot}OH$	$^{\cdot}OH+O(^3P)\rightarrow HO_2^{\cdot}$	$e^{-}_{aq}+O_2\rightarrow O_2^{\cdot-}$	$HO_2^{-}+O(^3P)\rightarrow O_2^{\cdot-}+^{\cdot}OH$
$H^{\cdot}+O^{\cdot-}\rightarrow OH^{-}$	$^{\cdot}OH+O^{\cdot-}\rightarrow HO_2^{-}$	$e^{-}_{aq}+HO_2^{\cdot}\rightarrow HO_2^{-}$	$O(^3P)+O(^3P)\rightarrow O_2$

At the end of the non-homogeneous chemical stage, the following equation for the radiolysis of water can be written:

$$H_2O \rightsquigarrow e^{-}_{aq}, H^{\cdot}, {}^{\cdot}OH, H_2, H_2O_2, H^{+}, OH^{-} \tag{9}$$
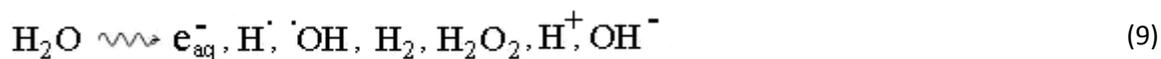
3.3.1 Yields of radiolytic species

The *radiolytic yield* of the species X, noted G(X), is defined as:

$$G(X) = \frac{\text{Number of species created (or destroyed)}}{100\,\text{eV deposited energy}} \tag{10}$$

The units of the radiolytic yields are molec./100 eV. In SI units, 1 molec./100 eV $\approx$ 0.10364 µmol/J. An equivalent definition of G(X) is G(X)=(1/ρ)(d[X]/dD), where ρ is the density of the irradiated medium, [X] is the concentration of X and D is the dose. It is usually obtained by using the slope of the graph [X] vs D at origin. If D=It, where I is the dose-rate and t is the time, we can write G(X)=(1/ρI)(d[X]/dt).

The yield of the radiolytic species at the end of spur expansion, at ~10^{-6} s, is called *primary yield* and is noted G_X. In pure liquid water, the primary yields of the principal radiolytic species are (in molec./100 eV)[13]:

$$G_{e^{-}_{aq}} = 2.50;\ G_{H^{\bullet}} = 0.56;\ G_{H_2O_2} = 0.7;\ G_{H_2} = 0.45;\ G_{{}^{\bullet}OH} = 2.50 \tag{11}$$

Experimentally, the yield values can be obtained by pulsed-radiolysis.

3.3.2 Radiation track structure

The radiolytic species created by the incident radiation are spatially deposited in a non-homogeneous manner, the _radiation track structure_. The radiation track structure is highly dependent on the type and energy of the incident radiation.

The first 3D simulations of the time evolution of an electron track during the non-homogeneous chemical stage were published in the 1980's[14,15]. These simulations were difficult to perform at that time because computer power was insufficient. There is now a renewed interest for time evolution of 3D tracks, because these 3D images of radiation tracks are able to provide insight on spurs chemistry by direct visualization of chemical reactions[16,17,18].

Radiation track video
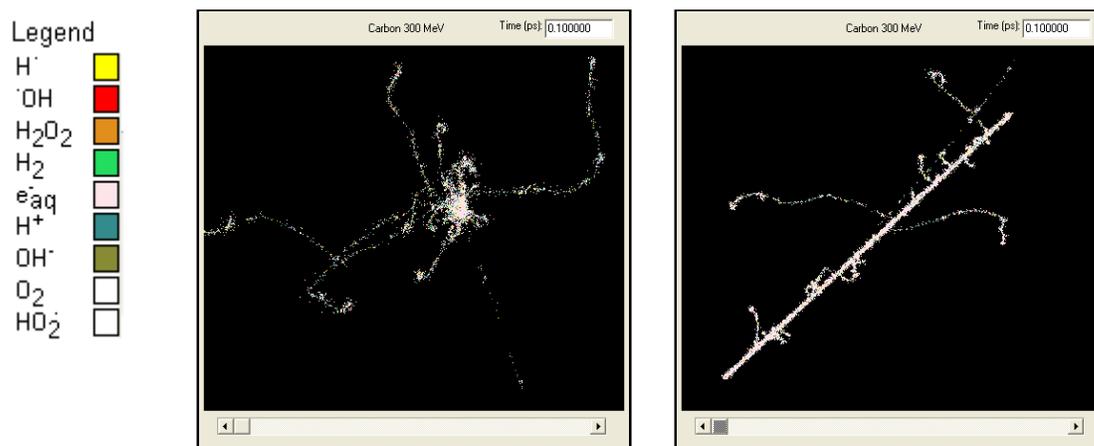
This is the radiation track video of a 300 MeV $^{12}C^{6+}$ ion (LET ~ keV/μm), from ~10^{-12} to ~10^{-6} s. The left picture is the 3D track; the right picture is the XZ projection of the same track. Each dot represents radiolytic specie. The changes in color indicate chemical reactions.

These simulations are now much more accessible thanks to the phenomenal increase in computer power. These simulations will allow a better comprehension of the biological effects of radiation by linking the radiation track structure with biomolecular damage[17,19]. This is of great interest for the growing field of heavy ion therapy in medicine[20] and for space radiation protection[21].

4. Reactive oxygen species and oxidative stress

Radiation action on water produces excited oxygen species, the reactive oxygen species (ROS). Examples of ROS are the hydroxyl radical ($^{\bullet}OH$), hydrogen peroxide (H_2O_2), superoxide anion (O_2^-), hydroperoxyl radical ($HO_2^{\bullet}$) and singlet oxygen ($^1O_2$). In cells, normal biochemical and physiological processes such as the β-oxidation of fatty acids in the peroxisomes, the electron transport chain in the

mitochondria and ATP production by cells are endogenous source of ROS[22]. Being able to produce ROS, ionizing radiation is an exogenous source of ROS.

ROS are involved in the oxidative stress of cells. Very reactive species such as the $^{\bullet}$OH radicals react in a restricted radius from their site of creation with neighboring molecules such as proteins, lipids and nucleic acid by chemical modification. Other radiolytic species like H_2O_2 are much less reactive. However, in the presence of transition metals such as iron or copper, H_2O_2 can generate an $^{\bullet}$OH radical by the Fenton reaction:

$$H_2O_2 + Fe^{2+} \rightarrow {}^{\bullet}OH + OH^- + Fe^{3+} \tag{12a}$$
$$H_2O_2 + Cu^+ \rightarrow {}^{\bullet}OH + OH^- + Cu^{2+} \tag{12b}$$
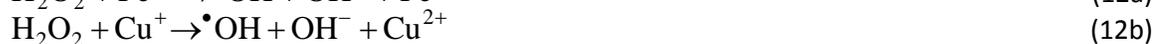
Cells are continuously exposed to ROS from endogenous and exogenous sources. Several systems exists to protect the cell from unwanted ROS: enzymatic system (ex.: Superoxide Dismutase (SOD)), antioxidant molecules (ex.: vitamin C, glutathione) and metal sequestration (ex.: ferritin) to prevent Fenton reactions. ROS are known to play an important role in several diseases, since disequilibrium between ROS production and ROS destruction may lead to carcinogenesis, cell senescence, cell death or apoptosis[23].

Selective irradiation of cell organelles by focused micro beams of α-particles have shown that the nucleus is the most sensitive part of cells to irradiation[24]. These studies suggest that DNA is the most sensitive target of ionizing radiation. For this reason, a great number of studies in radiobiology have focused on DNA. However, several experiments have shown that cells do not need to be exposed directly to ionizing radiation to be affected. This is called the _bystander effect_[25], which has been observed in many cells types for different endpoints such as increase in mutation frequency and apoptosis in non-irradiated cells. Similarly, a group of cells and their environment have been shown to react collectively rather than individually when they are irradiated[26]. These data suggest that cell response is also a very important factor in the irradiated tissues and that several molecular mechanisms implicating ROS are involved. The mechanisms and consequences of the bystander effect on the radiation risk are poorly understood.

5. Direct and indirect effects of radiation

Several biological effects of radiation results from DNA damage; DNA is still considered the most critical target molecule within a cell. The _direct effect_ is the interaction of radiation with DNA, which ionizes DNA, leaving a DNA radical cation ($DNA^{+\bullet}$) and an electron. Excited DNA (noted DNA^*) may also be formed, indirectly or by recombination of the electron with its parent cation. The _indirect effect_ is the interaction between the DNA and chemical species generated during water radiolysis, the most important being the $^{\bullet}$OH radical. The proportion of DNA damage resulting from the indirect effect of radiation is estimated to be ~2/3 of the total radiation damage, but this proportion depends on radiation type and energy.

The most frequent types of radiation-induced DNA damage are base and sugar modification, single strand breaks (SSB), double strand breaks (DBS), DNA-DNA and DNA-proteins crosslinks, base loss and tandem lesions[27]. DSB are likely caused by multiple DNA lesions in close proximity (~10-20 base pairs); they are considered the most important for the acute and long-term effects of radiation[28]. These

clustered types of lesions results from the spatial heterogeneity of the energy deposition events that follow the passage of radiation through matter.

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