



HAL
open science

Monte Carlo simulations of microdosimetry and radiolytic species production at long time post proton irradiation using GATE and Geant4-DNA

Giovanna Rosa Fois, Hoang Ngoc Tran, Vincent Fiegel, Guillaume Blain, Sophie Chiavassa, Emeline Craff, Grégory Delpon, Manon Evin, Ferid Haddad, Sébastien Incerti, et al.

► To cite this version:

Giovanna Rosa Fois, Hoang Ngoc Tran, Vincent Fiegel, Guillaume Blain, Sophie Chiavassa, et al.. Monte Carlo simulations of microdosimetry and radiolytic species production at long time post proton irradiation using GATE and Geant4-DNA. *Medical Physics*, 2024, 51 (10), pp.7500-7510. 10.1002/mp.17281 . hal-04645973

HAL Id: hal-04645973

<https://hal.science/hal-04645973v1>

Submitted on 6 Nov 2024

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

1 **Monte Carlo simulations of microdosimetry and radiolytic species production at long time**
2 **post proton irradiation using GATE and Geant4-DNA.**

3

4 Giovanna Rosa Fois¹, Hoang Ngoc Tran², Vincent Fiegel³, Guillaume Blain⁴, Sophie
5 Chiavassa⁵, Emeline Craff³, Grégory Delpon⁵, Manon Evin⁴, Ferid Haddad^{3,4}, Sébastien
6 Incerti², Charbel Koumeir³, Vincent Métivier⁴, Quentin Mouchard⁴, Freddy Poirier³, Vincent
7 Potiron^{5,6}, Noël Servagent⁴, Johan Vandendorre⁴ and Lydia Maigne^{1*}

8

9 ¹ Université Clermont Auvergne, CNRS, LPCA, 63000 Clermont-Ferrand, France

10 ² Univ. Bordeaux, CNRS, LP2I, UMR 5797, F-33170 Gradignan, France

11 ³ GIP ARRONAX, Saint-Herblain, France

12 ⁴ Laboratoire SUBATECH, UMR 6457, CNRS/IN2P3, IMT Atlantique, Université de Nantes,
13 France

14 ⁵ Institut de Cancérologie de l'Ouest, Saint-Herblain, France

15 ⁶ US2B, Nantes Université, CNRS, UMR 6286, France

16

17

18 *Corresponding author: lydia.maigne@clermont.in2p3.fr

19

20

21

22

23

24

25

26

1 ABSTRACT

2 **Purpose:** The radiobiological effectiveness of radiation in cancer treatment can be studied at
3 different scales (molecular to organ scale) and at different times post-irradiation. The
4 production of free radicals and reactive oxygen species during water radiolysis is particularly
5 relevant to understanding the fundamental mechanisms playing a role in observed biological
6 outcomes. The development of Monte Carlo tools integrating the simulation of physical,
7 physico-chemical, and chemical stages after radiation should be validated with experimental
8 data. Therefore, in this study, we propose to validate Geant4-DNA chemistry through the
9 simulation of water radiolysis and Fricke dosimetry experiments on a proton preclinical beam
10 line.

11 **Material and methods:** In this study, we used the GATE Monte Carlo simulation platform
12 (version 9.3) to simulate a 67.5 MeV proton beam produced with the ARRONAX isochronous
13 cyclotron (IBA Cyclone 70XP) at conventional dose rate (0.2 Gy/s) to simulate the irradiation
14 of ultra-pure liquid water samples and Fricke dosimeter. We compared the depth dose profile
15 with measurements performed with a plane parallel Advanced PTW 34045 Markus ionization
16 chamber. Then, a new Geant4-DNA chemistry application proposed from Geant4 version 11.2
17 has been used to assess the evolution of HO^\bullet , e_{aq}^- , H_3O^+ , H_2O_2 , H_2 , HO_2^\bullet , HO_2^- , $\text{O}_2^{\bullet-}$ and HO^-
18 reactive species along time until one-hour post-irradiation. In particular, the effect of oxygen
19 and pH has been investigated through comparisons with experimental measurements of
20 radiolytic yields for H_2O_2 and Fe^{3+} .

21 **Results:** GATE simulations reproduced, within 4%, the depth dose profile in liquid water. With
22 Geant4-DNA, we were able to reproduce experimental H_2O_2 radiolytic yields one-hour post-
23 irradiation in aerated and deaerated conditions, showing the impact of small changes in oxygen
24 concentrations on species evolution along time. For the Fricke dosimeter, simulated $G(\text{Fe}^{3+})$ is
25 15.97 ± 0.02 molecules/100 eV which is 11% higher than the measured value (14.4
26 ± 0.4 molecules/100 eV).

27 **Conclusions:** These results aim to be consolidated by new comparisons involving other
28 radiolytic species, such as e_{aq}^- or $\text{O}_2^{\bullet-}$ to further study the mechanisms underlying the FLASH
29 effect observed at ultra-high dose rates (UHDR).

30 **Keywords:** Monte Carlo, GATE, Geant4-DNA, microdosimetry, water radiolysis

31

1. INTRODUCTION

In recent years, many preclinical beams have been set up to study the radiobiological effect of radiation at different scales, from cells to small animals. The radiobiological effectiveness depends on various parameters: the radiation quality of the beam, the dose, the dose rate, and the fractionation used. It has been shown that changes in cell sensitivity, cell repair capacities, repopulation, oxygenation, and modifications to the cell microenvironment can play a significant role^{1,2}. The production of free radicals through water radiolysis represents a major part of radiation effect on biological matter³. Comprehension of radiolysis mechanisms along irradiation would definitively help understand biological outcomes observed.

Monte Carlo Track Structure codes have an important role to play in predicting direct and indirect effects of radiation at molecular scale. To that purpose, the open source and open access Geant4-DNA code⁴⁻⁸ has been extensively developed and validated to model physical (10^{-15} s), physico-chemical (10^{-15} to 10^{-12} s) and chemical stages (10^{-12} to 10^{-6} s) following irradiation⁹⁻¹². With the Geant4-DNA chemistry module, reactions and diffusion of molecules during water radiolysis can be simulated using two methods: the step-by-step (SBS)¹⁰ and the independent reaction time (IRT)^{13,14}. Recently, the code has been developed to be able to follow the diffusion and chemical interactions of radiolytic species until minutes post-irradiation¹⁵. In the new version of the code, a compartment-based model is developed to simulate the distribution of species along time, from heterogeneous distribution (a few ns after irradiation) to homogeneous distribution (minutes after irradiation). By using the reaction-diffusion master equation (RDME), this mesoscopic model divides the simulation volume into sufficiently small sub-volumes (so-called voxels) where species are assumed homogeneously mixed and can react between each other. Reactions between molecules take place within the voxels, while species can move from one voxel to an adjacent one by diffusion. The resolution of the system can change along time with voxels increasing in size. However, at the beginning of water radiolysis (from a few ps to ns), since the spatial distribution of the chemical species is concentrated in very small volumes mimicking radiation-induced spurs along the track, the evolution of the chemical species is described by using the step-by-step (SBS) Brownian dynamics model. The SBS is used to simulate the detailed trajectories of the individual species until 5 ns post-irradiation, and then the RDME method is applied. The combination between SBS and RDME methods is called SBS-RDME model. Further, a scavenger model has been implemented in the SBS method of Geant4-DNA to be able to simulate the presence of scavengers in water radiolysis experiments¹⁶.

1 In this study, we used the Geant4-DNA Monte Carlo Track structure code (MCTS) available
2 in version 11.2 of Geant4 with the SBS-RDME method proposed by Tran et al.¹⁵ and Chappuis
3 et al.¹⁶ to simulate water radiolysis experiments for 67.5 MeV protons produced with the
4 ARRONAX isochronous cyclotron (IBA Cyclone 70XP) at conventional dose rate (0.2 Gy/s).
5 We first describe the beamline setup that has been simulated with the GATE platform¹⁷⁻²⁰ to
6 irradiate a volume of 1.4 mL of pure water to reproduce the exact experimental conditions of
7 Blain et al.²¹. Then, we provide a method to assess information about physics processes
8 occurring in a cubic micrometric target localized at the center of the irradiated volume, and
9 about HO[•], e_{aq}⁻, H₃O⁺, H₂O₂, H₂, HO₂[•], HO₂⁻, O₂^{•-} and HO⁻ species evolution along time (from
10 10⁻¹² s to 1 hour) in aerated and deaerated conditions. We also conducted experiments and
11 simulations using a Fricke dosimeter.

12 2. MATERIAL AND METHODS

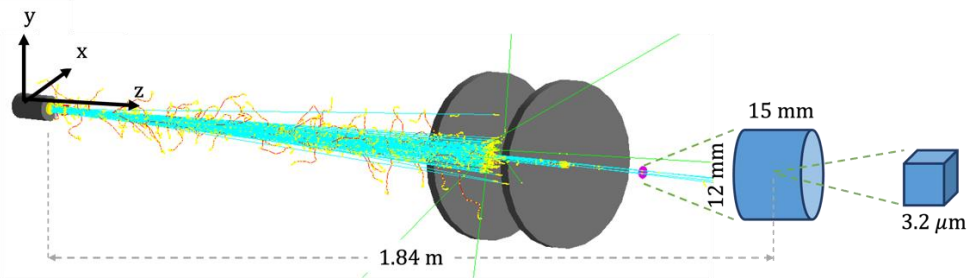
13 2.A. Description of the ARRONAX cyclotron dose delivery

14 ARRONAX is an isochronous cyclotron (IBA Cyclone 70XP) producing protons (30
15 MeV to 70 MeV), deuterons (15 MeV to 35 MeV), and alpha particles (67.5 MeV). Using a
16 dedicated pulsing device²² at various beam intensities (from 1 pA to 20 μA), the cyclotron can
17 provide proton beams with a range of dose rates varying from 0.2 Gy/s (conventional dose rate)
18 to 60 kGy/s (Very-High Dose Rate). The beam intensity was monitored in line by using an
19 ionization chamber, which was calibrated to the signal of a Faraday cup at the sample position.
20 All experiments were performed with a beam intensity of 40 pA at a dose-rate of 0.2 Gy/s.

21 2.B. Calculation of dose profiles

22 67.5 MeV proton beam line available at the ARRONAX isochronous cyclotron (IBA
23 Cyclone 70XP) has been simulated using the GATE platform (version 9.3)¹⁷⁻²⁰ based on
24 Geant4²³ version 11.2. The proton source, placed in a vacuum environment, had a Gaussian
25 energy distribution of 67.5 MeV with 0.35 MeV FWHM. At the first collimator, it was elliptical
26 with a FWHM of 2 and 3 mm in X and Y directions, respectively. The monodirectional beam
27 was then obtained getting through a 50 μm thick Kapton exit window positioned at 0.01 mm
28 from the source, a 51.7 μm tungsten foil diffuser at 50.06 mm from the source, and two
29 aluminum collimators of 15 mm internal diameter positioned at 1.5 m and 1.7 m respectively
30 from the source to spread and homogenize the beam before interacting with a water volume
31 (1.4 mL filled with the G4_WATER material) at 1.84 m from the source (Figure 1). The range
32 thresholds (cuts) for secondary particles have been fixed to 10 mm in all geometries and 0.1

1 μm in the water target volume. The QGSP_BIC_EMZ physics list has been selected with a
2 limitation on the step size to 1 mm in all geometries and 100 μm in the target volume. The
3 number of simulated protons was fixed to 10^7 to keep a statistical uncertainty below 2%. The
4 simulated depth dose profile was then calculated using a DoseActor (GATE tool allowing the
5 recording of energy deposited in a voxel volume) attached to the target volume with a $5 \times 5 \times 0.1$
6 mm resolution respectively in X, Y, and Z directions to integrate the dose in the XY plane. The
7 Pristine Bragg Peak was also measured in a $15 \times 10 \times 40 \text{ cm}^3$ water phantom using a **parallel plane**
8 Advanced PTW 34045 Markus ionization chamber according to the International Atomic
9 Energy Agency Technical Report Series (IAEA TRS) 398 Code of Practice²⁴. Measurements
10 were performed every millimeter until 30 mm depth and every 0.5 mm after. The measured
11 dose fluctuations were estimated within 1%. Range estimations were conventionally calculated
12 as the position of the 80% level of the distal fall-off.



13
14 Figure 1 - GATE simulation of the beamline setup.

15 2.C. Calculation of microdosimetry spectra

16 To reproduce the irradiation conditions encountered during water radiolysis
17 experiments, we used the beam described in section 2.A. using 1.64×10^{10} primary protons. **The**
18 **target volume was a** cylindrical water phantom (diameter: 12 mm, height: 15 mm), **irradiated**
19 **from the bottom surface and** centered at 1.84 m from the source in the plateau region ensuring
20 a mean linear energy transfer (LET) of $1.20 \text{ keV} \cdot \mu\text{m}^{-1}$ and LET variations below 5% along
21 particle tracks. A phase space (PhSp) file collecting information about 166 particles (146
22 protons and 21 **delta-rays produced outside the volume**) entering a $3.2 \mu\text{m}$ side cubic volume
23 placed at the center of the cylindrical volume was collected. Phase space analysis for protons
24 shows a Gaussian energy distribution with a mean value of 59.41 MeV and a full width at half
25 maximum (FWHM) of 0.95 MeV, such protons were then considered as source particles for
26 microdosimetry study. Using GATE with the Geant4-DNA (Geant4 version 11.2) physics lists
27 options 2, 4, and 6, we first evaluated the percentage contribution of every physical process for
28 every Geant4-DNA option. While option 2 is an accelerated version of the default Geant4-DNA

1 physics list, simulating electron interactions up to 1 MeV; in option 4, alternative models²⁵⁻²⁷
2 for electron elastic scattering, ionization and excitation are included at low energy (10 eV –
3 10 keV) but vibration and attachment processes are not considered. In option 6, the
4 implementation of the interaction cross sections of the CPA100 track structure code²⁸ is
5 available for electrons (applicable between 11 eV and 255 keV).

6 Using protons with 59.41 MeV energy, we evaluated the total energy spectrum using the
7 Geant4-DNA physics list option 2. The electrons leaving the 3.2 μm side target volume were
8 ignored. We highlighted the contribution of dominant processes for protons and electrons to the
9 total energy spectrum.

10 **2.D. Calculation of radiolytic species production**

11 Time-dependent radiolytic G values are calculated from 10^{-12} s until one hour after irradiation
12 for the HO^\bullet , e_{aq}^- , H_3O^+ , H_2O_2 , H_2 , HO_2^\bullet , HO_2^- , $\text{O}_2^{\bullet-}$ and HO^- radiolytic species in the 3.2 μm
13 side liquid water box using **Geant4-DNA** physics list option 2. We used a new Geant4-DNA
14 example, named UHDR (examples/extended/medical/dna/UHDR), available **from Geant4.11.2**
15 **version** to activate the SBS-RDME model, as described in Tran et al.¹⁵. In this model, the
16 chemical stage is simulated through three sub-stages: the microscopic stage where the SBS
17 method is used to follow the exact position of species produced in discrete time steps, then, at
18 time $t_1 = 5$ ns starts the mesoscopic stage where a uniform 3D Cartesian mesh of 512^3 voxels
19 (corresponding to an initial voxel size of 6.25 nm) is created for the compartment-based model,
20 to evolve to a single voxel when the homogeneous sub-stage starts describing the time-
21 evolution probability of the chemical species until the end of the simulation.

22 The Geant4-DNA SBS model uses by default an approach called “dynamic time step”¹⁰.

23 **In this approach, time steps are chosen as a function of the distance between reactants.**
24 **Depending on this distance, a probability of diffusion without any reactions is converted into a**
25 **diffusion time where species is considered free to diffuse. However, the dynamic time step**
26 **approach may lead to numerous small-time steps. To avoid this scenario, the Minimum Time**
27 **Step technique and the Brownian Bridge technique have been added to limit the number of time**
28 **steps. While Minimum Time Step limits the minimum time step allowed for each pair of**
29 **reactants, the Brownian Bridge technique computes the probability of encounter during**
30 **their Minimum Time Step and compensates for “missed” reactions. The Minimum Time Step**
31 **is set to 1 ps in this work. During mesoscopic stage, the hRDME²⁹ approach is used to adapt**
32 **the size of the voxels from the mesh of 512^3 voxels until there is only one voxel covering the**

1 whole simulation volume. Note that in these simulations, molecules diffuse and react in the
2 bounded volume (that is, limited by geometrical boundaries). These conditions enabled to
3 confine the chemical molecules in the considered volume by bouncing them off the walls of the
4 volume.

5 A parameter named “cutoff dose” allows to set the number of particles reaching the target
6 volume at the same time. In this study, we considered a low cutoff value of 0.01 Gy. Primary
7 protons (part of a run) are generated until the total energy deposited in the volume results in a
8 dose of at least 0.01 Gy (corresponding to the cutoff value). For this low cutoff value, one or
9 two protons are enough to reach this dose threshold. Protons in the same run are not
10 independent, they come at the same time and, once the energy deposition ends, the chemistry
11 is activated for all incident protons. Note that the secondary electrons leaving the 3.2 μm side
12 target volume will be ignored.

13 Since the homogeneous stage can extend the simulation to a long-time post proton irradiation
14 (a few minutes), the presence of oxygen and pH acid-base equilibrium in the medium is crucial
15 to chemical species evolution. Geant4-DNA simulates the presence of oxygen and pH acid-
16 base equilibrium in scavenger models for both SBS and IRT models. In these models,
17 scavengers are treated as a continuum that is homogeneously distributed in water. In this work,
18 this effect is incorporated during the chemical stage by specifying scavenger chemical reactions
19 and scavenger concentrations¹⁶. The pH is determined by the concentrations of acids and bases
20 (scavengers) in the solution. The direct interaction between radiation and scavenger, which
21 would normally occur in the physical stage of the Geant4-DNA simulation, is not considered.
22 All equations corresponding to the simulated water radiolysis reactions are listed in the
23 Appendix. The computation time, for less than 1% uncertainty, was about 10 hours on 100
24 CPUs (3.4 GHz, AMD EPYC 7542).

25 2.D.1. Aerated conditions

26 We compared simulated H_2O_2 G values obtained 1-hour post-irradiation with experimental
27 measurements from Blain et al.²¹ who measured track segment $G_{\text{TS}}(\text{H}_2\text{O}_2)$ radiolytic creation
28 yields in the plateau region using the well-known Ghormley’s tri-iodide protocol³⁰; $[\text{H}_2\text{O}_2]$ was
29 determined under 19% of oxygen for 5 doses from 20 to 80 Gy, and each dataset was replicated
30 2 or 3 times, as described in previous work²¹. Further, the simulated pH was fixed to 5.5
31 according to the ultra-pure water pH measured; this value is due to the CO_2 absorption in water
32 during the purification process. Because all other ions have been removed, the ultra-pure water

1 pH becomes driven by the chemistry of the couple $\text{CO}_2/\text{HCO}_3^-$ causing the pH level to drop to
 2 a value of 5.5. CO_2 concentration was $1.4 \cdot 10^{-5} \text{ mol.L}^{-1}$. In simulation we neglected the reactions
 3 between the radiolytic species and $\text{CO}_2/\text{HCO}_3^-$. For pH 5.5, the concentration of HO^- and H_3O^+
 4 were fixed to $3.16 \cdot 10^{-9}$ and $3.16 \cdot 10^{-6} \text{ mol.L}^{-1}$ respectively. Further, we considered only oxygen,
 5 neglecting the effect of nitrogen and other compounds.

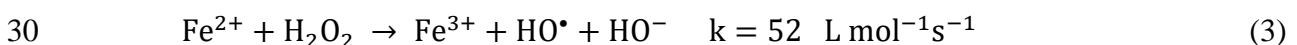
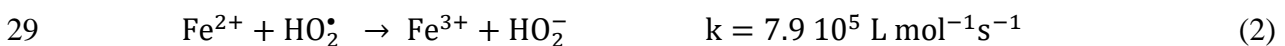
6 2.D.2. Deaerated conditions

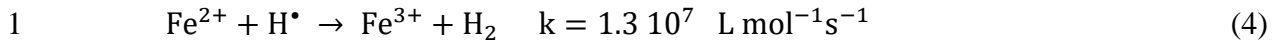
7 The simulated G values for H_2O_2 , one hour post-irradiation, obtained for different levels of
 8 O_2 (from a fully deoxygenated condition hypothesis equivalent to a 0% O_2 atmosphere to 3
 9 %), were compared to experimental measurements from co-authors²¹. pH was fixed to 5.5 to
 10 reproduce the ultra-pure water used in experiments. Experimental deaerated conditions were
 11 obtained by degassing the water in a Duran flask for one hour, reaching 0.3% in O_2 . Water was
 12 then transferred to the radiolysis cell achieving an O_2 concentration between 2 and 3%.

13 2.E. Fricke dosimeter

14 We simulated the evolution of ferric ion (Fe^{3+}) G value (molecule/100 eV) as a function of
 15 time and compared with experimental data performed with a Fricke dosimeter on the
 16 ARRONAX beam line. The super Fricke version of this chemical dosimeter was used, allowing
 17 increased dose rates studies. This dosimeter was prepared with $0.4 \text{ mol.L}^{-1} \text{ H}_2\text{SO}_4$, $10^{-3} \text{ mol.L}^{-1}$
 18 NaCl and $10^{-2} \text{ mol.L}^{-1}$ of Mohr salt (ammonium ferrous sulfate hexahydrate) as initial Fe^{2+}
 19 source. The concentrations of Fe^{3+} ions created from water radiolysis species were measured
 20 (with at least 3 replicates) by their absorbance at 304 nm one hour after proton irradiation for
 21 32.9, 43.9, 55.1, 66.0, 77.4 and 88.6 Gy. The pH was measured using a pH-meter (PHM220
 22 model, Radiometer SAS, Copenhagen, Denmark) and a pH probe (Crison InstrumentsTM,
 23 Barcelona, Spain). The measured pH was 0.4 ± 0.1 . For pH 0.4, the concentrations of HO^- and
 24 H_3O^+ were $2.51 \cdot 10^{-14}$ and 0.398 mol.L^{-1} respectively.

25 For simulations, the concentration of ferrous ions (Fe^{2+}) was set to 10 mM, pH was
 26 fixed to 0.4 and oxygen concentration was 19 %. We complemented the code with the following
 27 specific reactions (equations 1, 2, 3, and 4)³¹ and associated rate constants:





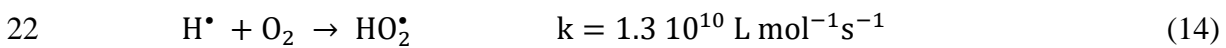
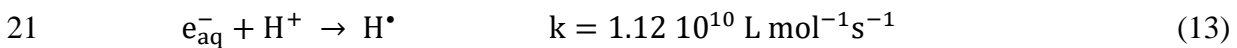
2 Further, we tested the effect of the solution acidity on ionic strength modification. For
 3 that purpose, we performed simulations using corrected reaction rate constants (see Appendix),
 4 as proposed by Ramos-Méndez et al.³².

5 Finally, to take into account the presence of H₂SO₄ we added 0.4 mol.L⁻¹ of HSO₄⁻ in
 6 our simulation (concentration of SO₄²⁻ was 1.4 · 10⁻² mol.L⁻¹) implementing the following
 7 reactions³³ (from 5 to 12) with their reaction rate constants corrected for ionic strength:



16 *Corrected reaction rate constant for ionic strength

17 We also studied the influence of small pH variation (from 0.3 to 1) on the G(Fe³⁺) yield
 18 1 hour post-irradiation. Further, to consolidate the consistent functioning of the code, we
 19 followed e_{aq}⁻ and H[•] species along time responsible for HO₂[•] species production (see equations
 20 13 and 14) at early time post-irradiation.

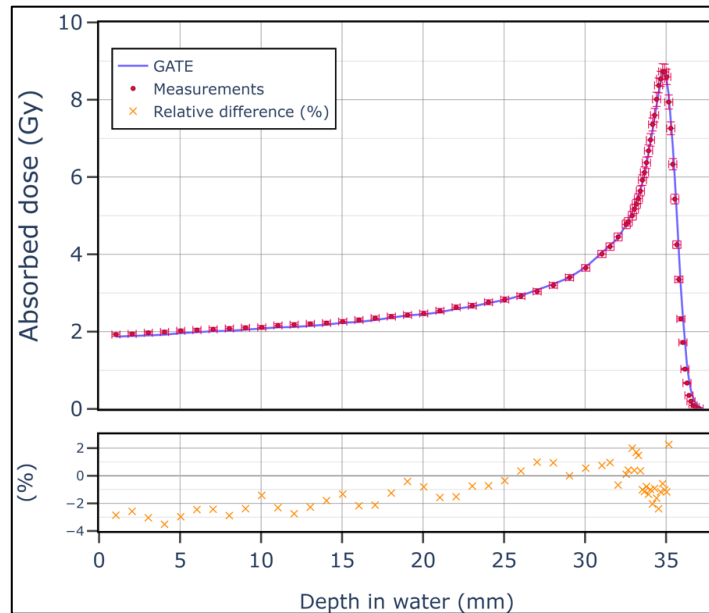


23 3. RESULTS

24 3.A. Depth-dose profile

25 Figure 2 shows the depth dose curve in G4_WATER (I=78 eV) obtained with GATE
 26 and measurements for the 67.5 MeV proton beam considering the same number of initial
 27 protons (experimentally measured using a Faraday cup). Statistical errors were too small to be

1 plotted in the figure. The point-to-point relative differences between the simulation and
2 measurements were superimposed. Relative differences remain below 4% until 15 mm and 2%
3 after this depth value. A range value of 34.79 mm was obtained for GATE and measurements.



4

5 Figure 2 - Depth dose curves in water ($I = 78$ eV) obtained using GATE (blue curve) and measurements (red dots)
6 for the ARRONAX 67.5 MeV proton beam line considering the same number of initial protons. Point-to-point
7 relative dose differences (%) between measurements and simulations are plotted at the bottom.

8

9 3.B. Physical processes at the microscale

10 Figure 3 presents the percentage contribution of every physical process for Geant4-DNA
11 options 2, 4, and 6, calculated in the $3.2 \mu\text{m}$ side cubic liquid water target with GATE using a
12 59.41 MeV ($\text{LET}=1.20 \text{ keV}\cdot\mu\text{m}^{-1}$) monoenergetic proton beam. Processes involved are
13 ionization, excitation for both protons and electrons and vibration, solvation, and elastic
14 scattering for secondary electron processes. The two dominant processes are electron and
15 proton ionizations.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24

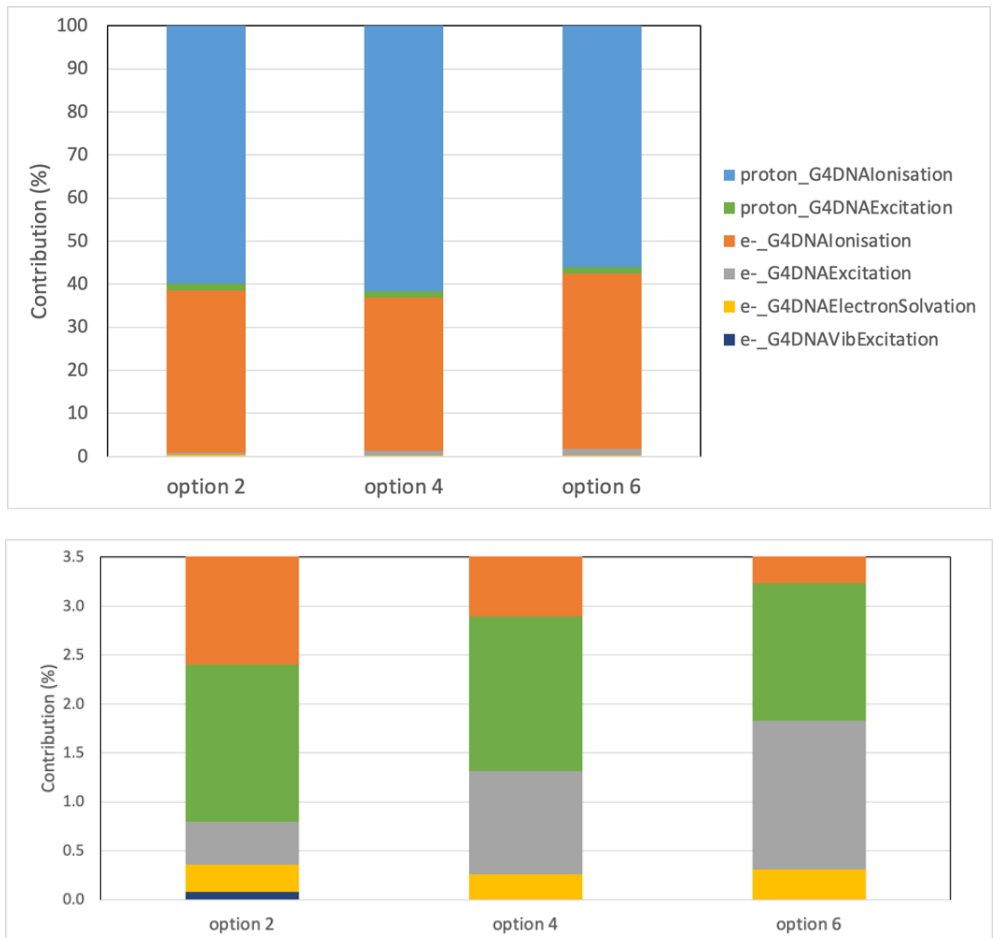
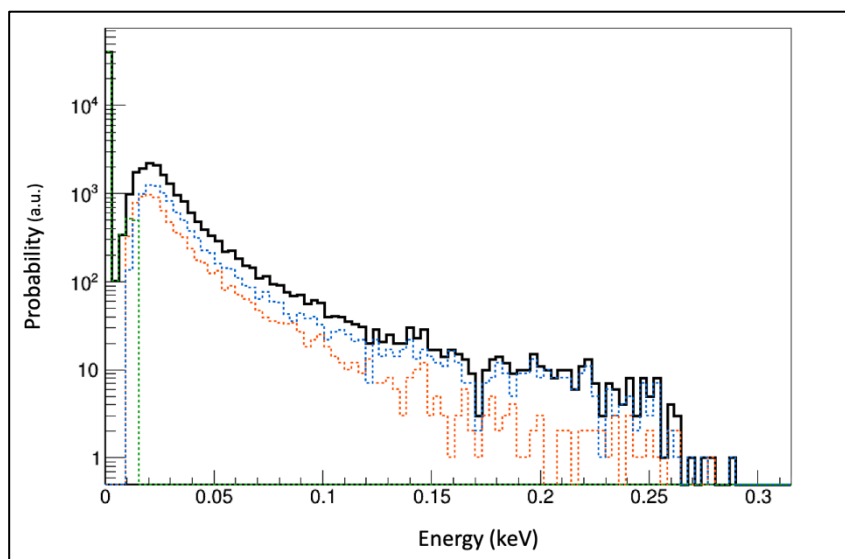


Figure 3 - Percentage contribution of every physical process to the energy deposition: proton ionization in blue, proton excitation in green, electron ionization in orange, electron excitation in grey, electron solvation in yellow, and electron vibration in dark blue. At the bottom, Contributions between 0 and 3.5% are highlighted.

In addition, in Figure 4, we present the energy spectrum obtained with Geant4-DNA option 2 and we emphasized the contributions of proton and electron ionization to the total energy spectrum. Other processes (electron and proton excitations as well as electron solvation) are contributing to energy depositions at very low energies (below 15 eV).

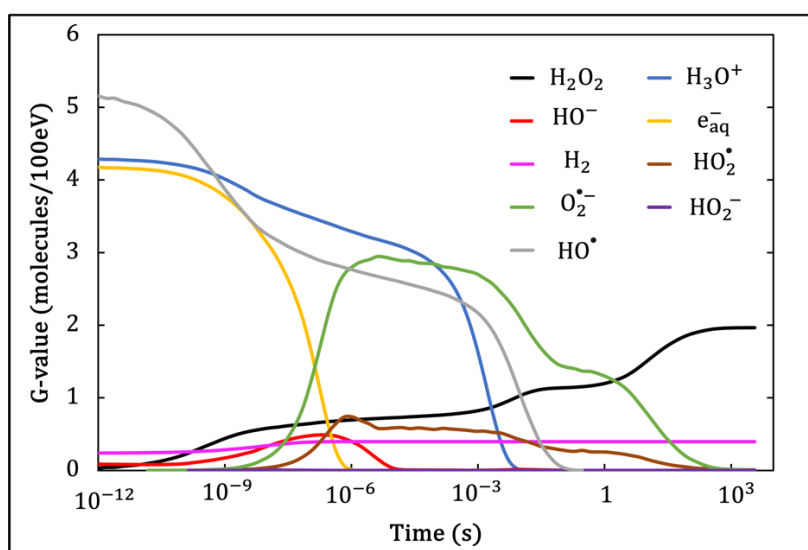


1
 2 Figure 4 - Energy spectrum (black line) obtained with Geant4-DNA option 2. Contributions from proton (blue)
 3 and electron (red) ionization are shown. Contributions from all the other processes are responsible for the very low
 4 energy part of the plot (green).

5 3.C. Radiolytic species yields under conventional radiation

6 3.C.1 Aerated conditions

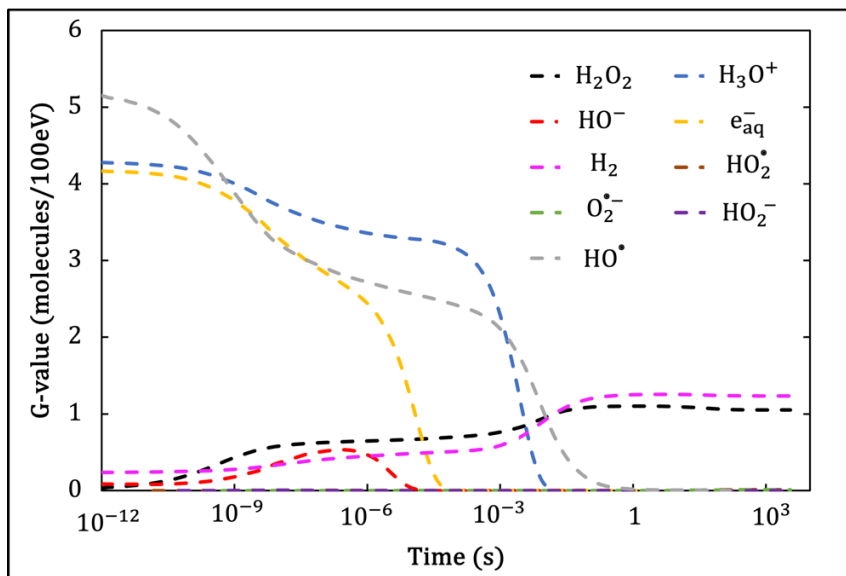
7 Figure 5 presents the simulated time-dependent yields (from 10^{-12} s to 1 hour) of
 8 different chemical species (HO^\bullet , e_{aq}^- , H_3O^+ , H_2O_2 , H_2 , HO_2^\bullet , HO_2^- , $\text{O}_2^{\bullet-}$ and HO^-) obtained in a
 9 $3.2 \mu\text{m}$ side cubic liquid water volume (19% of oxygen) irradiated with a monoenergetic 59.41
 10 MeV proton beam ($\text{LET}=1.20 \text{ keV}\cdot\mu\text{m}^{-1}$). The yield uncertainty values remain under 5%. At 60
 11 min, G values for H_2O_2 and H_2 species are respectively 1.96 and 0.39 molecules/100 eV.



12
 13 Figure 5 – Simulated time-dependent radical yields (G values) for water irradiations with 59.41 MeV proton beam
 14 in aerated conditions (19% of oxygen). HO^\bullet (grey), e_{aq}^- (yellow), H_3O^+ (dark blue), H_2O_2 (black), H_2 (magenta),
 15 HO^- (red), HO_2^- (purple), HO_2^\bullet (brown), $\text{O}_2^{\bullet-}$ (green).

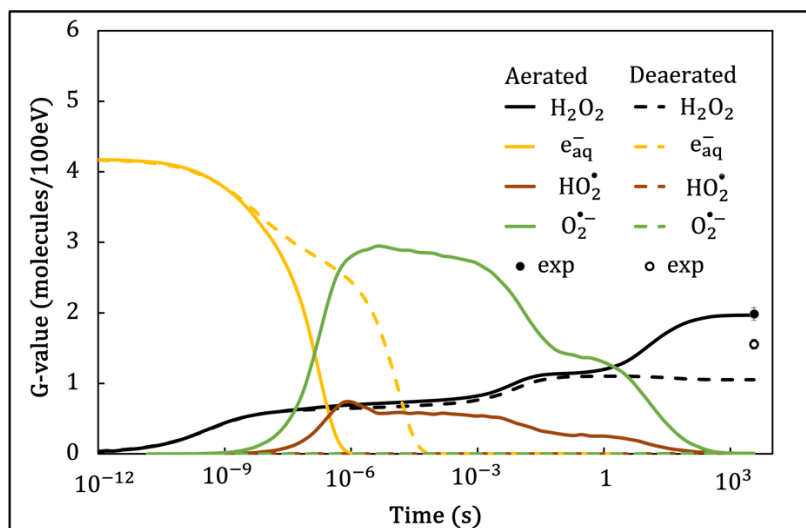
1 3.C.2 Deaerated conditions

2 In Figure 6 we present the simulated time-dependent yields (from 10^{-12} s to 60 min) for
 3 different chemical species (HO^\bullet , e_{aq}^- , H_3O^+ , H_2O_2 , H_2 , HO_2^\bullet , HO_2^- , $\text{O}_2^{\bullet-}$ and HO^-) obtained in a
 4 $3.2 \mu\text{m}$ cubic liquid water irradiated with a monoenergetic 59.41 MeV proton beam ($\text{LET}=1.20$
 5 $\text{keV}\cdot\mu\text{m}^{-1}$). At 1 hour, G values for H_2O_2 and H_2 species are respectively 1.05 and 1.24
 6 molecules/100 eV.



8 Figure 6 – Simulated time-dependent radical yields (G values) for water irradiations with 59.41 MeV proton beam
 9 in deaerated conditions (0% oxygen). HO^\bullet (grey), e_{aq}^- (yellow), H_3O^+ (dark blue), H_2O_2 (black), H_2 (magenta),
 10 HO^- (red), HO_2^- (purple), HO_2^\bullet (brown), $\text{O}_2^{\bullet-}$ (green).

11 In Figure 7 we summarize the evolution of H_2O_2 , HO_2^\bullet , $\text{O}_2^{\bullet-}$, and e_{aq}^- species along time
 12 in aerated and deaerated conditions. After continually increasing along time, G value of H_2O_2
 13 remains almost constant (1.05 ± 0.01 molecules/100 eV) from 50 ms until 1 hour in deaerated
 14 conditions. In aerated conditions (19% of oxygen), we can observe a final increase from 2 s to
 15 reach 1.96 ± 0.02 molecules/100 eV at 1 hour representing 46 % difference at this time.
 16 $G(\text{H}_2\text{O}_2)$ values measured 1 hour post-irradiation are 1.98 ± 0.19 molecules/100 eV and $1.55 \pm$
 17 0.20 molecules/100 eV for aerated and deaerated conditions respectively.



1
 2 Figure 7 – Simulated time-dependent radical yields (G values) for water irradiations with 59.41 MeV proton beam
 3 in aerated (19% Oxygen - filled circles) and deaerated (0% Oxygen - open circles) conditions. H_2O_2 (black), e_{aq}^-
 4 (yellow), HO_2^\bullet (brown), $\text{O}_2^{\bullet-}$ (green). G values for H_2O_2 are compared to experimental values (exp) measured 1-
 5 hour post-irradiation.

6
 7 In Table 1 are summarized the simulated $G(\text{H}_2\text{O}_2)$ values obtained 1 hour post-
 8 irradiation, while in Figure 8 we show the evolution of $G(\text{H}_2\text{O}_2)$ along time for $3 \cdot 10^{-4} \%$ and 19
 9 % of O_2 . We understand that a minimal change in the oxygen level leads to important
 10 differences in $G(\text{H}_2\text{O}_2)$ 1 hour post-irradiation. In Figure 8, we show that we can reproduce the
 11 experimental value of $G(\text{H}_2\text{O}_2)$ obtained in deaerated conditions with an oxygen concentration
 12 of $3 \cdot 10^{-4} \%$.

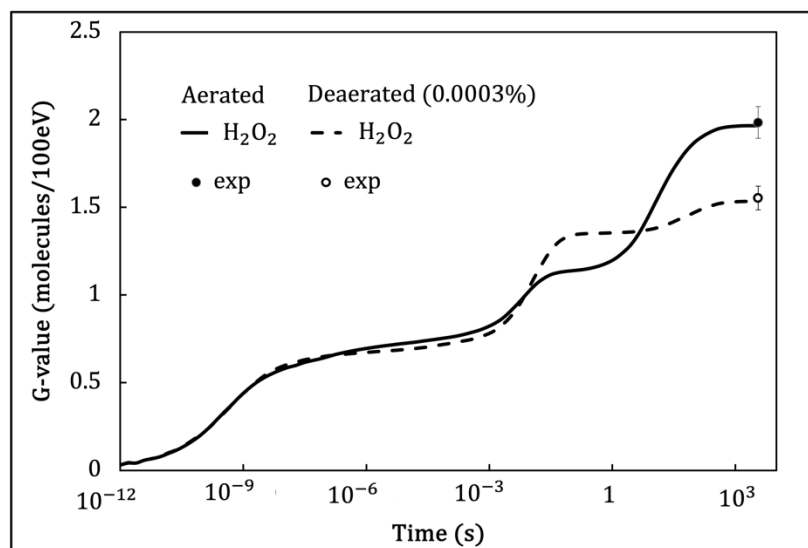
13
 14

O_2 concentration (%)	0	$3.0 \cdot 10^{-4}$	2	3	19
O_2 concentration (mol.L^{-1})	0	$3.9 \cdot 10^{-9}$	$2.6 \cdot 10^{-5}$	$3.9 \cdot 10^{-5}$	$2.5 \cdot 10^{-4}$
$G(\text{H}_2\text{O}_2)$ at 1 hour post-irradiation (molecules/100 eV)	1.05	1.53	1.89	1.92	1.96

15
 16
 17

18 Table 1 – Simulated $G(\text{H}_2\text{O}_2)$ (molecules/100 eV) at 1 hour post-irradiation for different oxygen concentrations
 19 (% and mol.L^{-1}).

20

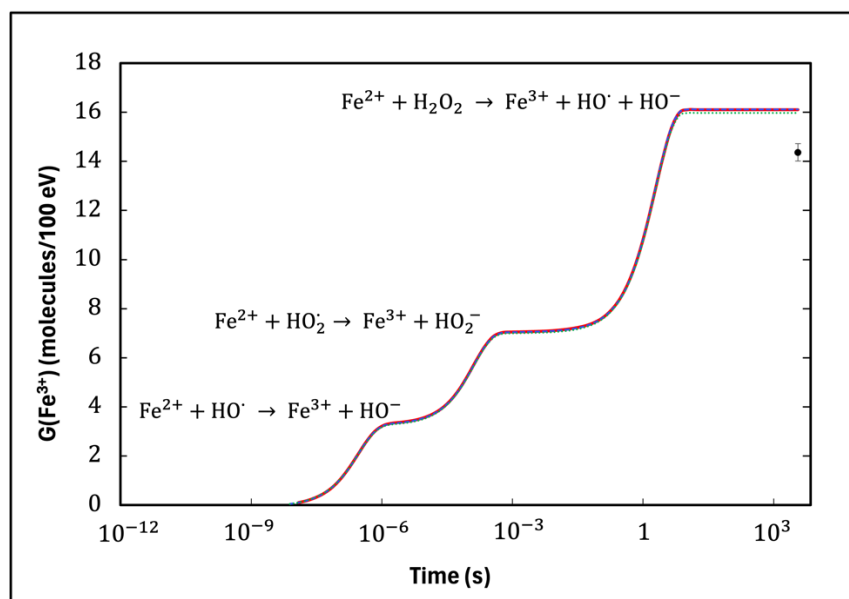


1
 2 Figure 8 – Evolution of simulated time-dependent radical yields (G values) of H₂O₂ species along time for water
 3 irradiations with 59.41 MeV proton beam for 19 % and 3.10⁻⁴ % of O₂. Measured values obtained 1-hour post-
 4 irradiations in aerated and deaerated conditions are also presented.

5

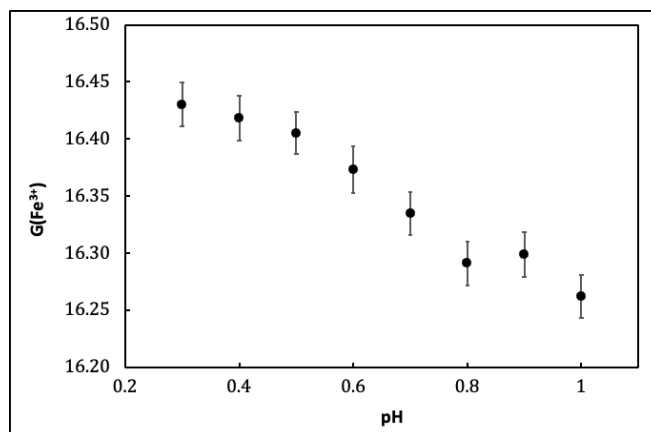
6 3.D Fricke dosimeter

7 In Figure 9 we present the time evolution of G value of Fe³⁺ for 3 different simulation
 8 setups. First, we only considered the reactions for Fe²⁺ (equations 1 to 4). Second, we used
 9 corrected reaction rate constants for ionic strength (see Appendix). Third, we added reactions
 10 due to the presence of H₂SO₄ (equations 5 to 12). At one-hour post-irradiation, simulated
 11 G(Fe³⁺) are 16.09 ± 0.03 molecules/100 eV (when only Fe²⁺ reactions are considered); 16.14
 12 ± 0.03 molecules/100 eV (when correcting reaction rate constants for ionic strength); 15.97
 13 ± 0.02 molecules/100 eV (when adding reaction involving HSO₄⁻); while the measured yield is
 14 14.4 ± 0.4 molecules/100 eV.



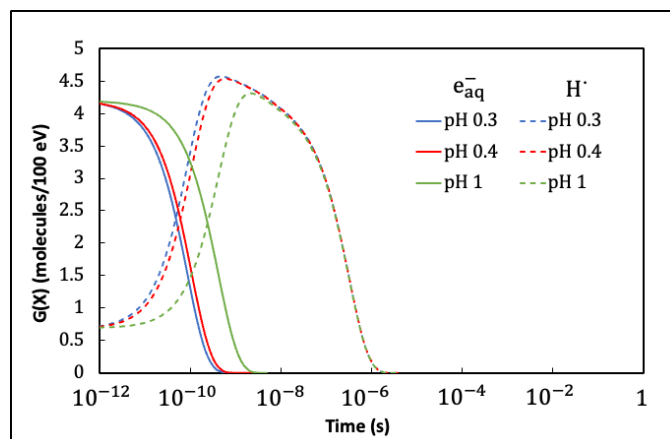
1
 2 Figure 9 – Simulated time-dependent radical yields (G values) of Fe^{3+} from a 59.41 MeV proton beam irradiation
 3 of a Fricke solution for pH 0.4. The red curve is obtained with only Fe^{2+} reactions with HO^\bullet , HO_2^\bullet , H_2O_2 and H^\bullet .
 4 A blue dashed curve is obtained by modifying the reaction rate constants for ionic strength as proposed by Ramos-
 5 Mendez et al.³². A dashed green curve is obtained by adding H_2SO_4 scavenging reactions. Measurement is shown
 6 with a black dot (uncertainty 2.5%). The reactions between Fe^{2+} and HO^\bullet , HO_2^\bullet and H_2O_2 are presented in the plot
 7 near the step when they contribute to the G value.

8
 9 In Figure 10, we show the evolution of $G(\text{Fe}^{3+})$ as a function of pH. $G(\text{Fe}^{3+})$ yields decrease by
 10 1.02 % between pH 0.3 and 1.



11
 12 Figure 10 – Simulated time dependent radical yields (G values) of Fe^{3+} from a 59.41 MeV proton beam irradiation
 13 of a Fricke solution for pH values between 0.3 and 1 at one-hour post-irradiation.

14 In Figure 11, the evolution of $G(\text{e}_{\text{aq}}^-)$ and $G(\text{H}^\bullet)$ values is plotted along time as a function of
 15 pH. The more pH is acid, the more e_{aq}^- species react faster with H^+ and the more HO_2^\bullet species
 16 are produced to then foster the oxidation of Fe^{2+} .



1
2 Figure 11 – Simulated time dependent radical yields (G values) of H^\bullet and e_{aq}^- from a 59.41 MeV proton beam
3 irradiation of a Fricke solution for pH 0.3 and pH 1 in aerated conditions.

4

5 4. DISCUSSION

6 4.1 Physical processes at the microscale

7 The contributions of physical processes obtained with the different Geant4-DNA
8 physics lists are very comparable. As expected, proton and electron ionization processes are
9 predominant with an energy contribution larger than 90 %. We can notice that the contribution
10 of electron ionizations and excitations in Geant4-DNA option 6 are about 6% and 1% larger
11 than in options 2 and 4. Option 2 is the only option simulating attachment and vibration
12 processes while solvation, to reproduce the thermalization of electrons, is contributing equally
13 whatever the option. From Figure 4, we notice that the maximum energy deposited in the 3.2
14 μm water cube is 300 eV with a maximum probability at 20 eV. Below 15 eV, electron and
15 proton excitations as well as electron solvation are involved.

16 4.2 Radiolytic yields

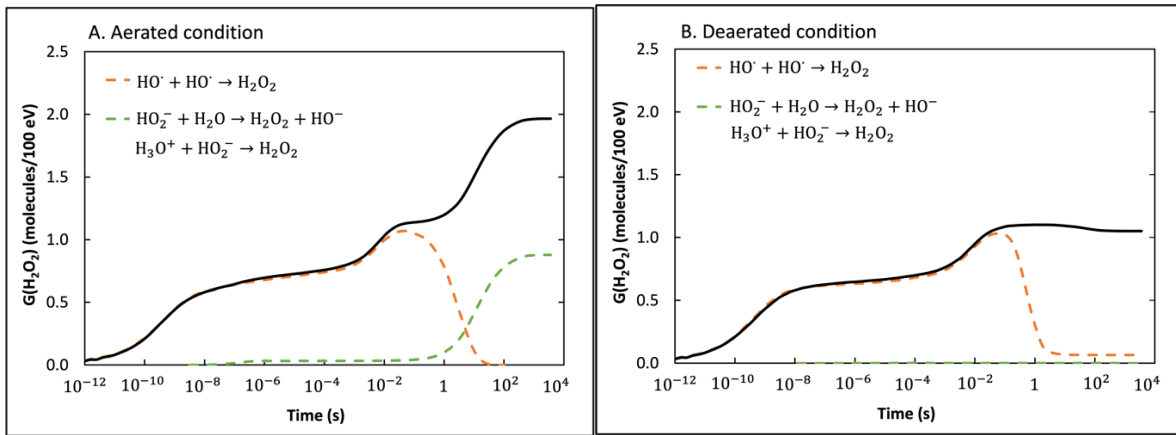
17 The H_2O_2 production results from the competition of chemical reactions forming
18 (equations 15 to 22 in Table 2) and consuming (equations 23 to 26 in Table 2) this species.
19 While H_2O_2 is mainly formed by the recombination of hydroxyl radicals (equation 15), it can
20 also be produced by chemical reactions involving dissolved oxygen (equations 16 to 19 in Table
21 2), especially in aerated conditions. To understand if the dissolved oxygen is impacting
22 $G(H_2O_2)$ values at 1-hour post-irradiation, we plotted in the same figure (see Figure 7), H_2O_2 ,
23 HO_2^\bullet , $O_2^{\bullet-}$ G values along time. We can notice that, in aerated conditions, while $G(HO^\bullet)$ is not
24 significantly impacted by the level of dissolved oxygen in solution (see Figure 5 and Figure 6),

1 e_{aq}^- species are depleted within 1 μ s under oxygenated conditions, while they persist until 1 ms
2 when the conditions are deaerated. Among the three main reactions involving hydrated
3 electrons, equation 16 is not simulated in deaerated conditions explaining their slow
4 consumption compared to aerated conditions. To emphasize the reactions involved in the
5 production of H_2O_2 as a function of time (in aerated and deaerated conditions), we highlighted
6 in Figure 12 the main reactions involved: from 1 ps to 7 s the main reaction is the recombination
7 of hydroxyl radicals while after, the main reactions are involving HO_2^- species. In deaerated
8 conditions, only reaction $HO^\bullet + HO^\bullet \rightarrow H_2O_2$ is involved in H_2O_2 production, we observe that
9 $G(H_2O_2)$ at 1-hour post-irradiation is increasing to 1.05 molecules/100 eV (46.6% decrease
10 compared to the value in aerated conditions) explaining the ability for Geant4-DNA simulations
11 to faithfully reproduce oxygen depletion by the pathway of ROS ($HO_2^-/O_2^{\bullet-}$) recombination
12 through reactions (19-20).

13 Table 2 – Water radiolysis equations involving the formation and consumption of H_2O_2 .

H_2O_2 formation reactions	H_2O_2 consumption reactions
$HO^\bullet + HO^\bullet \rightarrow H_2O_2$ (15)	$H_2O_2 + e_{aq}^- \rightarrow HO^\bullet$ (23)
$e_{aq}^- + O_2 \rightarrow O_2^{\bullet-}$ (16)	$H_2O_2 + H^\bullet \rightarrow HO^\bullet + H_2O$ (24)
$H^\bullet + O_2 \rightarrow HO_2^\bullet$ (17)	$H_2O_2 + HO^\bullet \rightarrow HO_2^\bullet + H_2O$ (25)
$O_2^{\bullet-} + H^+ \rightleftharpoons HO_2^\bullet$ (18)	$H_2O_2 + HO^- \rightarrow HO_2^-$ (26)
$HO_2^\bullet + O_2^{\bullet-} \rightarrow HO_2^- + O_2$ (19)	
$HO_2^- + H_2O \rightarrow H_2O_2 + HO^-$ (20)	
$H_3O^+ + HO_2^- \rightarrow H_2O_2$ (21)	
$HO_2^\bullet + HO_2^\bullet \rightarrow H_2O_2 + O_2$ (22)	

14



1
2 Figure 12 - Simulated $G(\text{H}_2\text{O}_2)$ values for water irradiations with 59.41 MeV proton beam are shown with black
3 bold lines in aerated conditions (A) and deaerated conditions (B). Dashed curves are obtained only considering the
4 production of H_2O_2 molecules through $\text{HO}^\bullet + \text{HO}^\bullet \rightarrow \text{H}_2\text{O}_2$ reaction (in orange) and only considering the production of
5 H_2O_2 molecules through $\text{HO}_2^\bullet + \text{H}_2\text{O} \rightarrow \text{H}_2\text{O}_2 + \text{HO}^-$ and $\text{H}_3\text{O}^+ + \text{HO}_2^\bullet \rightarrow \text{H}_2\text{O}_2$ reactions (in green). In aerated conditions, the first part
6 of the curve, from 0 to 7 s, involves a dominant chemical reaction: $\text{HO}^\bullet + \text{HO}^\bullet \rightarrow \text{H}_2\text{O}_2$, the second part from 7 s to 1 hour involves two dominant reactions:
7 $\text{HO}_2^\bullet + \text{H}_2\text{O} \rightarrow \text{H}_2\text{O}_2 + \text{OH}^-$ and $\text{H}_3\text{O}^+ + \text{HO}_2^\bullet \rightarrow \text{H}_2\text{O}_2$. In
8 deaerated conditions, $G(\text{H}_2\text{O}_2)$ is dominated by the reaction $\text{HO}^\bullet + \text{HO}^\bullet \rightarrow \text{H}_2\text{O}_2$.

9 4.3 Fricke dosimeter

10 In this study, we reproduced Fricke dosimetry by implementing chemical reactions
11 involving the oxidation of ferrous ions (Fe^{2+}), corrected reaction rate constants for ionic
12 strength, and reactions associated with the presence of sulfuric acid. Simulated $G(\text{Fe}^{3+})$ obtained
13 1-hour post-irradiation (15.97 ± 0.02 molecules/100 eV) is 11% higher than the experimental
14 value (14.4 ± 0.4 molecules/100 eV). As shown in Figure 9, neither the consideration of ionic
15 strength nor the implementation of reactions involving H_2SO_4 play a major role in the
16 calculation of $G(\text{Fe}^{3+})$.

17 We tested the consistency of the code concerning the variation of pH following e_{aq}^- and
18 H^\bullet . The code reproduces well the decrease of $G(\text{Fe}^{3+})$ as the pH increases.

19 When comparing to the literature, Pimblott and Laverne³⁴ show the effect of particle energy
20 on $G(\text{Fe}^{3+})$ yield in IRT simulation for protons until one-second post-irradiation. For the same
21 proton energy as used in this study, they obtain a $G(\text{Fe}^{3+})$ value of 14.45 molecules/100 eV.
22 This value is 21.8% higher than our value (11.3 molecules/100 eV) obtained after one second,
23 while our simulation shows an increase of $G(\text{Fe}^{3+})$ after one second and until one-minute post-
24 irradiation to finally remains constant until one hour. However, the Pimblott and Laverne³⁴
25 $G(\text{Fe}^{3+})$ value remains very comparable with measurements.

26 Further, Audouin et al.³⁵ studied the chemistry of super-Fricke solutions along the Bragg
27 peak curve for different 62 MeV proton beam intensities. In the low LET region, they obtained

1 an average $G(\text{Fe}^{3+})$ value of 14.9 ± 1.2 molecules/100 eV associated with an intensity range of
2 0.25 nA corresponding to a beam dose rate of 35 Gy/s. This value is 10 % lower than our
3 simulated value but is very close to the measured value (3.3 % difference).

5 5. CONCLUSION

6 The reactive oxygen species (ROS) play a major role in the biological evolution of a cell
7 system under irradiation (cell survival, cell death, cell signaling and inflammation-related
8 factors). To compare the production of radiolytic species over a long-time post-irradiation,
9 simulation tools must provide mechanisms for the diffusion of these species under the same
10 conditions. In this paper, using Geant4-DNA version 11.2 implementing, in the UHDR
11 example, a hybrid SBS method to follow diffusion and reactions of species until long-time post-
12 irradiation, we reproduced water radiolysis experiments for different oxygen concentrations for
13 a preclinical proton beam at conventional dose rates (0.2 Gy/s). At 1 hour post-irradiation,
14 simulated $G(\text{H}_2\text{O}_2)$ agrees within 2% with measured values. We also explored the ability of the
15 Geant4-DNA toolkit to simulate Fricke dosimetry experiments. Simulated $G(\text{Fe}^{3+})$ differs by
16 11% from measurement. The simulations developed in this study will be provided to the user
17 community through two new Geant4-DNA examples. This study aims to be complemented, in
18 the near future, to understand the mechanisms underlying the FLASH effect occurring at ultra-
19 high dose rates (UHDR), where higher concentration of radiolytic species within a short time
20 interval may modify the chemical pathways. In particular, simulations of H_2O_2 yields will be
21 compared with measurements proposed by Blain et al.²¹ until 60 kGy/s.

22 6. ACKNOWLEDGEMENTS

23 This work was funded by Inserm Cancer PCSI “FLASHMOD” program and in part has
24 been supported by grants from the French National Agency for Research “France 2030
25 investment plan” and ISITE NExT “Transformed” (ANR-16-IDEX-0007). We thank also the
26 Geant4-DNA collaboration for their valuable support.

7. REFERENCES

1. Nickoloff JA, Taylor L, Sharma N, Kato TA. Exploiting DNA repair pathways for tumor sensitization, mitigation of resistance, and normal tissue protection in radiotherapy. *Cancer Drug Resist.* 2021;4(2):244. doi:10.20517/CDR.2020.89
2. Busato F, Khouzai B El, Mognato M. Biological Mechanisms to Reduce Radioresistance and Increase the Efficacy of Radiotherapy: State of the Art. *Int J Mol Sci.* 2022;23(18). doi:10.3390/IJMS231810211
3. Riley PA. Free Radicals in Biology: Oxidative Stress and the Effects of Ionizing Radiation. <https://doi.org/10.1080/09553009414550041>. 2009;65(1):27-33. doi:10.1080/09553009414550041
4. Tran HN, Chappuis F, Incerti S, Bochud F, Desorgher L. Geant4-DNA modeling of water radiolysis beyond the microsecond: an on-lattice stochastic approach. *Int J Mol Sci.* 2021;22:6023. doi:10.3390/ijms22116023
5. Bernal MA, Bordage MC, Brown JMC, et al. Track structure modeling in liquid water: A review of the Geant4-DNA very low energy extension of the Geant4 Monte Carlo simulation toolkit. *Phys Medica.* 2015;31(8):861-874. doi:10.1016/J.EJMP.2015.10.087
6. Incerti S, Ivanchenko A, Karamitros M, et al. Comparison of GEANT4 very low energy cross section models with experimental data in water. *Med Phys.* 2010;37(9):4692-4708. <http://link.aip.org/link/MPHYA6/v37/i9/p4692/s1&Agg=doi>
7. Incerti S, Baldacchino G, Bernal M, et al. The Geant4-DNA project. *Physics (College Park Md).* 2009;01(02):1-27. <http://arxiv.org/abs/0910.5684>
8. Incerti S, Kyriakou I, Bernal MA, et al. Geant4-DNA example applications for track structure simulations in liquid water: A report from the Geant4-DNA Project. *Med Phys.* 2018;45(8):e722-e739. doi:10.1002/MP.13048
9. Karamitros M, MANTERO A, INCERTI S, et al. Modeling Radiation Chemistry in the Geant4 Toolkit. *Prog Nucl Sci Technol.* 2011;2(0). doi:10.15669/pnst.2.503
10. Karamitros M, Luan S, Bernal MA, et al. Diffusion-controlled reactions modeling in Geant4-DNA. *J Comput Phys.* 2014;274:841-882. doi:10.1016/J.JCP.2014.06.011
11. Baldacchino G, Bouffard S, Balanzat E, et al. Direct time-resolved measurement of

- 1 radical species formed in water by heavy ions irradiation. *Nucl Instruments Methods*
2 *Phys Res Sect B Beam Interact with Mater Atoms*. 1998;146(1-4):528-532.
3 doi:10.1016/S0168-583X(98)00463-7
- 4 12. Ramos-Méndez J, Shin WG, Karamitros M, et al. Independent reaction times method in
5 Geant4-DNA: Implementation and performance. *Med Phys*. Published online 2020.
6 doi:10.1002/mp.14490
- 7 13. Clifford P, Green NJB, Oldfield MJ, Pilling MJ, Pimblott SM. Stochastic models of
8 multi-species kinetics in radiation-induced spurs. *J Chem Soc Faraday Trans 1 Phys*
9 *Chem Condens Phases*. 1986;82(9):2673-2689. doi:10.1039/F19868202673
- 10 14. Plante I, Devroye L. Considerations for the independent reaction times and step-by-step
11 methods for radiation chemistry simulations. *Radiat Phys Chem*. 2017;139:157-172.
12 doi:10.1016/j.radphyschem.2017.03.021
- 13 15. Tran HN, Chappuis F, Incerti S, Bochud F, Desorgher L. Geant4-DNA Modeling of
14 Water Radiolysis beyond the Microsecond: An On-Lattice Stochastic Approach. *Int J*
15 *Mol Sci*. 2021;22(11). doi:10.3390/IJMS22116023
- 16 16. Chappuis F, Grilj V, Tran HN, et al. Modeling of scavenging systems in water radiolysis
17 with Geant4-DNA. *Phys Med*. 2023;108:102549. doi:10.1016/j.ejmp.2023.102549
- 18 17. Jan S, Santin G, Strul D, et al. GATE: A simulation toolkit for PET and SPECT. *Phys*
19 *Med Biol*. 2004;49(19):4543-4561. doi:10.1088/0031-9155/49/19/007
- 20 18. Sarrut D, Bardiès M, Bousson N, et al. A review of the use and potential of the GATE
21 Monte Carlo simulation code for radiation therapy and dosimetry applications. *Med*
22 *Phys*. 2014;41(6):064301. doi:10.1118/1.4871617
- 23 19. Jan S, Benoit D, Becheva E, et al. GATE V6: a major enhancement of the GATE
24 simulation platform enabling modelling of CT and radiotherapy. *Phys Med Biol*.
25 2011;56(4):881-901.
- 26 20. Sarrut D, Arbor N, Baudier T, et al. The OpenGATE ecosystem for Monte Carlo
27 simulation in medical physics. *Phys Med Biol*. 2022;67(18). doi:10.1088/1361-
28 6560/ac8c83
- 29 21. Blain G, Vandenborre J, Villoing D, et al. Proton Irradiations at Ultra-High Dose Rate
30 vs. Conventional Dose Rate: Strong Impact on Hydrogen Peroxide Yield.

- 1 <https://doi.org/10.1667/RADE-22-000211>. 2022;198(3):318-324. doi:10.1667/RADE-
2 22-00021.1
- 3 22. Poirier F, Dr C, Goiziou X, et al. The pulsing chopper-based system of the ARRONAX
4 C70XP cyclotron. In: *IPAC 2019 - 10th International Particle Accelerator Conference*.
5 ; 2019:1948-1950. doi:10.18429/JACoW-IPAC2019-TUPTS008
- 6 23. Agostinelli S, Allison J, Amako K, et al. Geant4—a simulation toolkit. *Nucl Instrum*
7 *Methods Phys Res A*. 2003;506(3):250-303. doi:10.1016/s0168-9002(03)01368-8
- 8 24. IAEA TRS 398. Absorbed Dose Determination in External Beam Radiotherapy. *At*
9 *Energy*. Published online 2000:1-229. Accessed July 18, 2023.
10 [https://www.iaea.org/publications/5954/absorbed-dose-determination-in-external-](https://www.iaea.org/publications/5954/absorbed-dose-determination-in-external-beam-radiotherapy)
11 [beam-radiotherapy](https://www.iaea.org/publications/5954/absorbed-dose-determination-in-external-beam-radiotherapy)
- 12 25. Kyriakou I, Incerti S, Francis Z. Technical Note: Improvements in geant4 energy-loss
13 model and the effect on low-energy electron transport in liquid water. *Med Phys*.
14 2015;42(7):3870-3876. doi:10.1118/1.4921613
- 15 26. I. Kyriakou, M. Sefl, V. Nourry SI. The impact of new Geant4-DNA cross section
16 models on electron track structure simulations in liquid water. *J Appl Phys*.
17 2016;119(19). doi:10.1063/1.4950808
- 18 27. Kyriakou I, Emfietzoglou D, Ivanchenko V, et al. Microdosimetry of electrons in liquid
19 water using the low-energy models of Geant4. *J Appl Phys*. 2017;122(2):024303.
20 doi:10.1063/1.4992076
- 21 28. MC B, J B, S E, et al. Implementation of new physics models for low energy electrons
22 in liquid water in Geant4-DNA. *Phys Med*. 2016;32(12):1833-1840.
23 doi:10.1016/J.EJMP.2016.10.006
- 24 29. Hellander S, Hellander A. Hierarchical algorithm for the reaction-diffusion master
25 equation. *J Chem Phys*. 2020;152(3):34104. doi:10.1063/1.5095075
- 26 30. Schwert GW, Neurath H, Kaufman S, et al. The yields of hydrogen and hydrogen'
27 peroxide in the irradiation of oxygen saturated water with cobalt gamma-rays. *J Am*
28 *Chem Soc*. 1954;76(12):3351-3352. doi:10.1021/JA01641A085
- 29 31. Plante I. Développement de codes de simulation Monte-Carlo de la radiolyse de l'eau
30 par des électrons, ions lourds, photons et neutrons. Applications à divers sujets d'intérêt

- 1 expérimental. 2008;(2008).
2 [https://savoirs.usherbrooke.ca/bitstream/handle/11143/4292/Plante_Ianik_PhD_2008.p](https://savoirs.usherbrooke.ca/bitstream/handle/11143/4292/Plante_Ianik_PhD_2008.pdf?sequence=3&isAllowed=y)
3 [df?sequence=3&isAllowed=y](https://savoirs.usherbrooke.ca/bitstream/handle/11143/4292/Plante_Ianik_PhD_2008.pdf?sequence=3&isAllowed=y)
- 4 32. Ramos-Méndez J, Domínguez-Kondo N, Schuemann J, McNamara A, Moreno-Barbosa
5 E, Faddegon B. LET-dependent intertrack yields in proton irradiation at ultra-high dose
6 rates relevant for FLASH therapy. *Radiat Res.* 2020;194(4):351-362. doi:10.1667/rade-
7 20-00084.1
- 8 33. Autsavapromporn N, Meesungnoen J, Plante I, Jay-Gerin JP. Monte Carlo simulation
9 study of the effects of acidity and LET on the primary free-radical and molecular yields
10 of water radiolysis - Application to the Fricke dosimeter. *Can J Chem.* 2007;85(3):214-
11 229. doi:10.1139/V07-021/ASSET/IMAGES/V07-021D.GIF
- 12 34. Pimblott SM, LaVerne JA. Effects of Track Structure on the Ion Radiolysis of the Fricke
13 Dosimeter. *J Phys Chem A.* 2002;106(41):9420-9427. doi:10.1021/JP020830U
- 14 35. Audouin J, Paris C, Petter S, et al. Post-Bragg Peak keV-Secondary Electron Radiolysis
15 Revealed by Track-Ends Imaging of High-Energy Protons. Published online 2023.
16 doi:10.21203/rs.3.rs-2752706/v1
- 17

Water radiolysis reactions		
Chemical reactions	Reaction rates ($\text{L. mol}^{-1} \cdot \text{s}^{-1}$)	Corrected reaction rates ($\text{L. mol}^{-1} \cdot \text{s}^{-1}$)
$\text{H}^\bullet + \text{H}^\bullet \rightarrow \text{H}_2$	$0.5 \cdot 10^{10}$	
$\text{e}_{\text{aq}}^- + \text{H}^\bullet + \text{H}_2\text{O} \rightarrow \text{H}_2 + \text{HO}^-$	$2.5 \cdot 10^{10}$	
$\text{e}_{\text{aq}}^- + \text{e}_{\text{aq}}^- + 2\text{H}_2\text{O} \rightarrow \text{H}_2 + 2\text{HO}^-$	$0.636 \cdot 10^{10}$	
$\text{H}_3\text{O}^+ + \text{HO}^- \rightarrow 2\text{H}_2\text{O}$	$1.13 \cdot 10^{11}$	
$\text{HO}^\bullet + \text{H}^\bullet \rightarrow \text{H}_2\text{O}$	$1.55 \cdot 10^{10}$	
$\text{HO}^\bullet + \text{HO}^\bullet \rightarrow \text{H}_2\text{O}_2$	$0.55 \cdot 10^{10}$	
$\text{e}_{\text{aq}}^- + \text{HO}^\bullet \rightarrow \text{HO}^-$	$2.95 \cdot 10^{10}$	
$\text{e}_{\text{aq}}^- + \text{H}_2\text{O}_2 \rightarrow \text{HO}^- + \text{HO}^\bullet$	$1.10 \cdot 10^{10}$	
$\text{e}_{\text{aq}}^- + \text{H}_3\text{O}^+ \rightarrow \text{H}^\bullet + \text{H}_2\text{O}$	$2.11 \cdot 10^{10}$	$1.12 \cdot 10^{10}$
$\text{H}^\bullet + \text{O}^- \rightarrow \text{HO}^-$	$2.00 \cdot 10^{10}$	
$\text{H}_3\text{O}^+ + \text{O}_3^- \rightarrow \text{OH} + \text{O}_2$	$9.00 \cdot 10^{10}$	$4.77 \cdot 10^{10}$
$\text{H}^\bullet + \text{HO}_2^\bullet \rightarrow \text{H}_2\text{O}_2$	$1.00 \cdot 10^{10}$	
$\text{H}^\bullet + \text{O}_2^- \rightarrow \text{HO}_2^-$	$1.00 \cdot 10^{10}$	
$\text{HO}^\bullet + \text{O}_2^- \rightarrow \text{O}_2 + \text{HO}^-$	$1.07 \cdot 10^{10}$	
$\text{e}_{\text{aq}}^- + \text{O}_2^- \rightarrow \text{H}_2\text{O}_2 + \text{HO}^- + \text{HO}^-$	$1.3 \cdot 10^{10}$	$2.43 \cdot 10^{10}$
$\text{e}_{\text{aq}}^- + \text{HO}_2^- \rightarrow \text{O}^- + \text{HO}^-$	$3.51 \cdot 10^9$	$6.61 \cdot 10^9$
$\text{e}_{\text{aq}}^- + \text{O}^- \rightarrow \text{HO}^- + \text{HO}^-$	$2.31 \cdot 10^{10}$	$4.35 \cdot 10^{10}$
$\text{H}_3\text{O}^+ + \text{O}_2^- \rightarrow \text{HO}_2^\bullet$	$4.78 \cdot 10^{10}$	$2.53 \cdot 10^{10}$
$\text{H}_3\text{O}^+ + \text{HO}_2^- \rightarrow \text{H}_2\text{O}_2$	$4.78 \cdot 10^{10}$	$2.65 \cdot 10^{10}$
$\text{H}_3\text{O}^+ + \text{O}^- \rightarrow \text{HO}^\bullet$	$4.78 \cdot 10^{10}$	$2.53 \cdot 10^{10}$
$\text{e}_{\text{aq}}^- + \text{HO}_2^\bullet \rightarrow \text{HO}_2^-$	$1.29 \cdot 10^{10}$	
$\text{HO}^\bullet + \text{HO}^- \rightarrow \text{O}^-$	$1.27 \cdot 10^{10}$	
$\text{HO}^\bullet + \text{HO}_2^\bullet \rightarrow \text{O}_2$	$7.90 \cdot 10^9$	
$\text{HO}^\bullet + \text{HO}_2^- \rightarrow \text{HO}_2^\bullet + \text{HO}^-$	$8.32 \cdot 10^9$	
$\text{HO}^\bullet + \text{O}^- \rightarrow \text{HO}_2^-$	$1.00 \cdot 10^9$	
$\text{HO}^\bullet + \text{O}_3^- \rightarrow \text{O}_2^- + \text{HO}_2^\bullet$	$8.50 \cdot 10^9$	
$\text{HO}^- + \text{HO}_2^\bullet \rightarrow \text{O}_2^-$	$1.27 \cdot 10^{10}$	
$\text{H}_2\text{O}_2 + \text{HO}^- \rightarrow \text{HO}_2^-$	$1.3 \cdot 10^{10}$	
$\text{H}_2\text{O}_2 + \text{O}^- \rightarrow \text{HO}_2^\bullet + \text{HO}^-$	$5.55 \cdot 10^8$	
$\text{H}_2 + \text{O}^- \rightarrow \text{H}^\bullet + \text{HO}^-$	$1.21 \cdot 10^8$	
$\text{O}_2^- + \text{O}^- \rightarrow \text{O}_2 + \text{HO}^- + \text{HO}^-$	$6.0 \cdot 10^8$	$1.13 \cdot 10^9$
$\text{HO}_2^- + \text{O}^- \rightarrow \text{O}_2^- + \text{HO}^-$	$3.5 \cdot 10^8$	$6.59 \cdot 10^8$
$\text{O}^- + \text{O}^- \rightarrow \text{H}_2\text{O}_2 + \text{HO}^- + \text{HO}^-$	$1.0 \cdot 10^8$	
$\text{O}^- + \text{O}_3^- \rightarrow \text{O}_2^- + \text{O}_2^-$	$7.0 \cdot 10^8$	
$\text{H}^\bullet + \text{HO}^- \rightarrow \text{e}_{\text{aq}}^-$	$2.51 \cdot 10^7$	
$\text{H}^\bullet + \text{H}_2\text{O}_2 \rightarrow \text{HO}^\bullet$	$3.50 \cdot 10^7$	
$\text{HO}^\bullet + \text{H}_2\text{O}_2 \rightarrow \text{HO}_2^\bullet$	$2.88 \cdot 10^7$	
$\text{HO}^\bullet + \text{H}_2 \rightarrow \text{H}^\bullet$	$3.28 \cdot 10^7$	
$\text{HO}_2^\bullet + \text{HO}_2^\bullet \rightarrow \text{H}_2\text{O}_2 + \text{O}_2$	$9.80 \cdot 10^5$	
$\text{HO}_2^\bullet + \text{O}_2^- \rightarrow \text{HO}_2^- + \text{O}_2^\dagger$	$9.70 \cdot 10^7$	
$\text{O}_2^- + \text{O}_2^- \rightarrow \text{H}_2\text{O}_2 + \text{O}_2 + 2\text{HO}^-$	$1.00 \cdot 10^2$	
Oxygen scavenging reactions		
$\text{e}_{\text{aq}}^- + \text{O}_2 \rightarrow \text{O}_2^-$	$2.3 \cdot 10^{10}$	
$\text{H}^\bullet + \text{O}_2 \rightarrow \text{HO}_2^\bullet$	$1.3 \cdot 10^{10}$	

$\text{O}^- + \text{O}_2 \rightarrow \text{O}_3^-$	$3.7 \cdot 10^9$	
Water scavenging reactions		
$\text{O}_3^- + \text{H}_2\text{O} \rightarrow \text{O}^- + \text{O}_2$	$2.66 \cdot 10^3$	
$\text{HO}_2^- + \text{H}_2\text{O} \rightarrow \text{H}_3\text{O} + \text{O}_2^-$	$7.58 \cdot 10^5$	
$\text{H}^\bullet + \text{H}_2\text{O} \rightarrow \text{e}_{\text{aq}}^- + \text{H}_3\text{O}$	6.32	
$\text{e}_{\text{aq}}^- + \text{H}_2\text{O} \rightarrow \text{H}^\bullet + \text{HO}^\bullet$	$1.58 \cdot 10^{11}$	
$\text{O}_2^- + \text{H}_2\text{O} \rightarrow \text{HO}_2^\bullet + \text{HO}^-$	0.15	
$\text{HO}_2^- + \text{H}_2\text{O} \rightarrow \text{H}_2\text{O}_2 + \text{HO}^-$	$1.36 \cdot 10^6$	
$\text{O}^- + \text{H}_2\text{O} \rightarrow \text{HO}^\bullet + \text{HO}^-$	$1.8 \cdot 10^6$	
$\text{e}_{\text{aq}}^- + \text{H}_3\text{O}^+ \rightarrow \text{H}^\bullet + \text{H}_2\text{O}$	$2.09 \cdot 10^3$	
$\text{O}_2^- + \text{H}_3\text{O}^+ \rightarrow \text{HO}_2^\bullet + \text{H}_2\text{O}$	$4.78 \cdot 10^{10}$	$2.53 \cdot 10^{10}$
$\text{HO}^- + \text{H}_3\text{O}^+ \rightarrow 2\text{H}_2\text{O}$	$1.13 \cdot 10^{11}$	
$\text{HO}_2^- + \text{H}_3\text{O}^+ \rightarrow \text{H}_2\text{O}_2 + \text{H}_2\text{O}$	$4.78 \cdot 10^{10}$	
$\text{O}^- + \text{H}_3\text{O}^+ \rightarrow \text{HO}^\bullet + \text{H}_2\text{O}$	$9.56 \cdot 10^{10}$	$2.53 \cdot 10^{10}$
$\text{O}_3^- + \text{H}_3\text{O}^+ \rightarrow \text{HO}^\bullet + \text{O}_2 + \text{H}_2\text{O}$	$9.0 \cdot 10^{10}$	$4.77 \cdot 10^{10}$
$\text{H}_3\text{O}^+ + \text{HO}^- \rightarrow 2\text{H}_2\text{O}$	$1.13 \cdot 10^{11}$	$6.26 \cdot 10^{10}$
$\text{H}^\bullet + \text{HO}^- \rightarrow \text{H}_2\text{O} + \text{e}_{\text{aq}}^-$	$2.49 \cdot 10^7$	
$\text{HO}^\bullet + \text{HO}^- \rightarrow \text{O}^- + \text{H}_2\text{O}$	$1.27 \cdot 10^{10}$	
$\text{H}_2\text{O}_2 + \text{HO}^- \rightarrow \text{HO}_2^\bullet + \text{H}_2\text{O}$	$1.27 \cdot 10^{10}$	
$\text{HO}_2^\bullet + \text{HO}^- \rightarrow \text{O}_2^- + \text{H}_2\text{O}$	$1.27 \cdot 10^{10}$	

1