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Generation of ultrafast, transient, highly acidic pH spikes in the radiolysis of water at very high dose rates. Relevance for FLASH radiotherapy

by

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Abstract

Monte Carlo multi-track chemistry simulations were carried out to study the effects of high dose rates on the transient yields of hydronium ions (H_3O^+) formed during low linear energy transfer (LET) radiolysis of both pure, deaerated and aerated liquid water at 25 °C, in the interval ~ 1 ps–10 μs . Our simulation model consisted of randomly irradiating water with N interactive tracks of 300-MeV incident protons (LET ~ 0.3 keV/ μm), which simultaneously impact perpendicularly on the water within a circular surface. The effect of the dose rate was studied by varying N . Our calculations showed that the radiolytic formation of H_3O^+ causes the entire irradiated volume to temporarily become very acidic. The magnitude and duration of this abrupt “acid-spike” response depend on the value of N . It is most intense at times less than ~ 10 –100 ns, equal to ~ 3.4 and 2.8 for $N = 500$ and 2000 (*i.e.*, for dose rates of $\sim 1.9 \times 10^9$ and 8.7×10^9 Gy/s, respectively). At longer times, the pH gradually increases for all N values and eventually returns to the neutral value of seven, which corresponds to the non-radiolytic, pre-irradiation concentration of H_3O^+ . It is worth noting that these early acidic pH responses are very little dependent on the presence or absence of oxygen. Finally, given the importance of pH for many cellular functions, this study suggests that these acidic pH spikes may contribute to the normal tissue-sparing effect of FLASH radiotherapy.

Keywords: Liquid water, radiolysis, absorbed dose rate, yields (G -values), multiple track model, Monte Carlo multi-track chemistry simulations, hydronium and hydroxide ions, pH, acid spike, FLASH effect.

1. Introduction

Understanding the radiation-induced physicochemical processes in aqueous systems is critical for many areas of basic and applied chemistry, biology, medicine, space radiobiology, *etc.*, as well as a variety of technological and industrial applications, including nuclear reactors, hydrogen production, and storage of nuclear waste. While in many cases a general understanding of the phenomena underlying the radiation chemistry of water and dilute aqueous solutions has been gained,¹⁻⁶ certain quantitative aspects of this radiolysis remain unresolved. This is especially true for ultrafast processes that link physics and chemistry following the initial energy deposition. According to Platzman's classification,⁷⁻⁹ this time frame essentially corresponds to the so-called physical, physicochemical and chemical stages of the radiolysis process, which can be assumed to occur sequentially and more or less separately.

1.1. *The radiolysis of water*

In short, the initial or physical stage consists in the transfer of energy from the ionizing radiation to the water ($\sim 1\text{--}100$ attoseconds), resulting in a large number of ionizations (H_2O^{++}) and excitations (H_2O^*) along and around the path of radiation, which are spatially distributed in a specific, highly non-homogeneous track structure that strongly depends on the type and energy of the radiation. During the ionization events, considerable numbers ($\sim 10^4$ electrons per MeV of deposited energy) of secondary electrons¹⁰⁻¹² with mean kinetic energies below ~ 100 eV are produced.

In a condensed phase such as liquid water, the various initial radiolysis products are very unstable and undergo fast reactions and reorganization in the second or physicochemical stage,¹³⁻¹⁶ which lead to the establishment of thermal equilibrium in the bulk medium with the formation of new chemical species such as stable molecules and water free radicals. During this stage (~ 1 ps), secondary electrons slow down to

subexcitation (below ~ 7.3 eV) and then thermal energies, and, following thermalization, they become trapped and finally hydrated (e^-_{aq}). Low-energy electrons of less than 20 eV can undergo resonant “dissociative electron attachment” (DEA) resulting in an anion (mainly H^-) in addition to an $\cdot OH$ radical.¹⁷ Upon being ionized into H_2O^{+} , water molecules dissociate rapidly (in times as short as 46 ± 10 fs)¹⁸ to produce hydroxyl radicals $\cdot OH$ and hydronium ions H_3O^+ :

In addition, secondary electrons that are formed in the vicinity of their parent ions can be recaptured by them due to their Coulomb attraction, forming excited water molecules, which in turn can dissociate into $H\cdot$ and $\cdot OH$ radicals, H_2 and $O(^1D)$, or yet $2H\cdot$ and $\cdot O(^3P)$. If $\cdot O(^3P)$, the oxygen atom in its triplet 3P ground state, is rather inert towards water, its singlet 1D first excited state reacts quickly with it to form H_2O_2 (or possibly also $2\cdot OH$). At the end of the physicochemical stage, radiolytic products formed in pure, deaerated liquid water, exposed to either low- or high-linear energy transfer (LET) radiation, include^{15,16} e^-_{aq} , $H\cdot$, H_2 , $\cdot OH$, H_2O_2 , H_3O^+ , OH^- , $O_2^{\cdot-}$, $\cdot O(^3P)$, *etc.* Of these, H_3O^+ , $\cdot OH$, and e^-_{aq} are produced in the highest concentrations,¹⁶ and $\cdot OH$ is considered the most harmful from a radiobiological point of view.⁴ The third or chemical stage^{1-3,15,19} consists of diffusion (according to macroscopic diffusion laws) and chemical reactions of the various radiolytic species present at the end of the physicochemical stage, which lead to the restoration of chemical equilibrium. During this stage, a fraction of these species within the tracks will react together as they develop in time, while the rest will escape into the bulk solution. At 25 °C and under the conditions of lack of dose-rate effects, the track expansion is essentially complete by $\sim 0.1\text{--}1$ μs .¹⁻³ At this point in time, the species that have escaped from the track

reactions are homogeneously distributed throughout the bulk solution and the radiation track structure no longer exists.^{20,21}

1.2. *The early, transitory acidic pH response*

As previously mentioned,²²⁻²⁵ an important question is how the reactive “primary” species H_3O^+ , $\cdot\text{OH}$ and e^-_{aq} are distributed at the beginning of the chemical stage. On the one hand, the H_3O^+ and $\cdot\text{OH}$ produced in reaction (1) are very close to the position where the ionization event occurred. On the other hand, the secondary electron, which is ejected with an energy of a few tens of electron-volts, travels an average distance on the order of 10 nm²⁶ from the initial ionization site to its final position after hydration. Since the e^-_{aq} is formed quite far away from H_3O^+ and the $\cdot\text{OH}$ radical, no immediate recombination between them through the following reactions:

can occur (note here that k_2 and k_3 are the rate constants for the two individual reactions¹⁹). In other words, this initial charge separation between the more concentrated positive-ion core (mainly H_3O^+ and $\cdot\text{OH}$) of the track and the negative ions (mainly hydrated electrons, OH^- , and H^+) in the surrounding medium creates an early and transient acidic pH response along and around the track of the radiation (which we termed an “acid spike”^{16,27}). As a function of time, it is easy to see that this charge separation and the associated local acidity will continue until the diffusion of the slowly moving H_3O^+ and $\cdot\text{OH}$ has brought these species to the distant positions occupied by the e^-_{aq} , eventually forming H^+ and the hydroxide ion OH^- through reactions (2) and (3). Although several authors^{2,28-31} have reported experimental evidence indicating early intra-track acidity, these acid-spike effects have largely gone unnoticed in water or in living cells exposed to ionizing radiation.³² From a chemical and radiobiological point of

view, this is rather surprising considering that many cellular processes and properties can potentially be affected by changes in pH.^{16,32-34}

In recent work, we carried out several calculations combining Monte Carlo track chemistry simulations of the radiolysis of pure, deaerated water with simple, LET-dependent, space-time radiation track models to determine the extent and duration of these early, intra-track acidic pH spikes. It was assumed that the dose rates were sufficiently low that there was no overlap between tracks.³⁵ We calculated the yields (or G-values)³⁶ and the concentrations of radiolytically formed H_3O^+ and the corresponding pH values that prevailed in these track regions immediately after irradiation as a function of time for both low and high LET,^{16,25} at ambient and elevated temperatures,³⁷ even under supercritical conditions.^{38,39} In all cases studied, an abrupt, transient acid-spike response was observed around the “native” radiation tracks. This response is a very sensitive function of radiation quality (LET) and temperature. At 25 °C, for example, the effect was greatest for times shorter than ~1 ns in a “spur” (or “cluster” – in the nomenclature of refs. 40 and 41 – of reactive species), “spherical” in shape, and characteristic of low-LET radiation, such as ~1 MeV Compton electrons produced by ^{60}Co γ -rays, fast electrons, or 300-MeV protons; ~0.3 keV/ μm). In this time range the pH remained nearly constant, equal to ~3.3. At longer times, the pH gradually increased, ultimately reaching a value of seven (pH of the solution at 25 °C) at ~1 μs . As can be seen, this highly acidic environment generated *in situ* in spurs/tracks persists for periods of more than six orders of magnitude during the track stage of radiolysis.

While the acidic pH spikes described above implies low dose rates, *i.e.*, only individual, non-overlapping radiation tracks,³⁵ the question now arises as to whether these spikes of acidity persist even under high dose-rate irradiation conditions in which track overlap is assumed to be completed at an early point in time. If so, it would indicate the early generation of a transient acid response over the entire irradiated

volume.³³ This study aims precisely to explore this question in greater depth. For this, we extended our previous calculations^{42,43} to study the influence of high dose rates on the transient yields and concentrations of hydronium ions, that are formed early during radiolysis of water by 300-MeV incident protons, which mimic the low LET of ^{60}Co γ rays or fast electrons. Our objective here is to determine the corresponding pH values that prevail in the irradiated solution over time.

1.3. *The FLASH effect*

In this study, we focus on the fundamental physicochemical bases of the radiolysis of water under conditions of high dose rates. This is of general interest as it may also improve the overall understanding of “FLASH radiotherapy” (FLASH-RT),⁴⁴ a new method of irradiation in radiotherapy in which large single doses of radiation are delivered to tumors almost instantly (in milliseconds). Strikingly, FLASH irradiation (intra-pulse dose rates of $\sim 10^6$ – 10^7 Gy/s with mean values in excess of 40–100 Gy/s) spares the surrounding healthy tissue while maintaining the same anti-tumor activity compared to conventional-dose-rate radiotherapy (~ 0.03 Gy/s) as shown in several animal model and pre-clinical studies (for reviews, see refs. 45–49). Moreover, a recent first human patient treatment with FLASH-RT⁵⁰ has demonstrated that this technique may be transferable to the clinic. To date, however, the underlying molecular mechanisms of FLASH-RT are largely unknown. Since living cells and tissues consist mainly of water and pH can affect many cellular functions, we previously suggested³³ that the early, transitory, strongly acidic pH spikes mentioned above (and further investigated here) may play a role in the observed FLASH effect. The present study can thus be seen as a continuation of this previous work.

2. Multi-track model for high-dose-rate effects in water radiolysis

2.1. *Modeling the effect of dose rates*

We recently developed an irradiation model to study the effects of high dose rates on the radiolysis of water by incident protons^{42,43} at ambient and elevated temperatures. In short, the simulation model consists of the random irradiation of water with single and instantaneous pulses of N incident 300-MeV protons ($\text{LET} \sim 0.3 \text{ keV}/\mu\text{m}$), which simultaneously impact perpendicularly with the water surface within a circle of radius R_0 (see Fig. 1 of ref. 42). This is the so-called “model of the instantaneous pulse”,⁵¹ in which the pulse duration is assumed to be zero. An advantage of using energetic protons is that their trajectories are essentially rectilinear,²⁰ which makes it possible to define a cylindrical geometry of the beam at the time of entry. With this geometry, all proton tracks run parallel to the cylinder axis over the entire track length chosen for the calculations. Since this irradiated cylinder is embedded in non-irradiated bulk water, the various radiolytic species initially formed in it are obviously not restricted to this volume, but rather diffuse as a function of time through the entire bulk water (infinite in fact). This situation is very similar to the one we have been dealing with for many years in Monte Carlo simulations of the radiolysis of water in the limit of low dose rate,^{15,52} only that instead of simulating a single-proton track, we simulate N interactive tracks at the same time. Under these conditions, the effect of the dose rate is studied by simply varying N .

2.2. Modeling the multi-track chemistry: Monte Carlo simulations

We used a modified version of our Monte Carlo track-chemistry computer code IONLYS-IRT¹⁵ to simulate the radiolysis of deaerated or aerated water at ambient temperature by 300-MeV irradiating protons under conditions of high dose rates. This code has been described in detail elsewhere,^{42,43,53} and only its most essential features are given below.

Our “IONLYS” program⁵⁴ first models the early physical and physicochemical stages of the radiation action up to ~ 1 ps in track development in a 3D geometric environment. Since this program can only simulate the spatio-temporal history of one single-proton track at a time (low dose rate limit), we have modified it⁴² so that simultaneously incident tracks in close spatial proximity can be calculated. In this study, the number of impacting protons per pulse was chosen to vary from $N = 1$ to 2100 (the maximum achievable value given our computing capacity). These N protons reach the front of the cylinder at the same time, which was chosen as time zero.

The complex spatial distribution of the reactants of the considered track system at the end of the physicochemical stage is provided as an output of the IONLYS program. It then serves directly as the starting point for the subsequent chemical stage (>1 ps). Here, the various radiolytic species diffuse randomly at rates determined by their diffusion coefficients and react with each other or in competition (scavenging reaction) with dissolved, uniformly distributed solutes (in the case studied here, O_2) that are present in the solution at the time of irradiation. This third stage is covered by our “IRT” program,⁵⁵ which uses the “independent reaction time” (IRT) method (or the independent pairs approximation),⁵⁶⁻⁶⁰ a computationally efficient stochastic simulation technique that generates reaction times without having to monitor the trajectories of the diffusing species. Its implementation has been described elsewhere.^{42,55} The ability of this method to provide reliable time-dependent chemical yields has been well validated under a variety of different irradiation conditions by comparison to full Monte Carlo random flight simulations^{61,62} that follow the reactant trajectories in detail. Obviously, taking a large number of proton tracks into account for the implementation of our IRT program at high dose rates led to much longer computation times than for the simulation of single tracks.

The reaction scheme and rate constants, as well as the diffusion coefficients of the reactive species used in our IRT program for aerated or deaerated water at 25 °C, are the same as those used previously.^{19,55,63,64} For aerated water, the concentration of dissolved oxygen is taken to be 0.25 mM.

All calculations were carried out by simulating short (typically 1–50 μm , depending on N) segments of 300-MeV irradiating proton tracks. The energy and the LET of the protons are well defined over these simulated track segments and remain nearly constant. For a given value of N , the number of simulation “histories” (usually ~2–50) was chosen to ensure only minor statistical fluctuations (less than a few percent) in the calculated average chemical yields while maintaining acceptable computer time limits.

3. Results and discussion

3.1. Time profiles of the yields of H_3O^+ and OH^-

Figures 1A–1B show the time evolution of $G(\text{H}_3\text{O}^+)$ as obtained from our Monte Carlo simulations of the radiolysis of pure deaerated water and aerated water, respectively, by 300 MeV protons at 25 °C, in the interval ~1 ps–10 μs , for different values of N between 1 and 2100. Data for $N = 1$ correspond to the radiolysis of water with ^{60}Co γ rays or fast electrons in the limit of low dose rates (*i.e.*, without interaction between the different incident tracks);⁵² as previously shown,^{16,27} these data agree very well with measured H_3O^+ yields at ambient temperature and are used here as a reference. Using our previous calibration⁴² of N in terms of dose rate,⁶⁵ the range of N values chosen in Figs. 1A–1B to illustrate dose-rate effects corresponds to dose rates (expressed in Gy/s) that vary between $\sim 1.5 \times 10^9$ ($N = 400$) and 9×10^9 ($N = 2100$) under our irradiation conditions.

Our simulated time-dependent yields of OH^- are also included in Figs. 1A–1B. While the radiolytic formation of H_3O^+ causes the irradiated volume to become

temporarily acidic (see *infra*), hydroxide ions, which are mainly formed by reaction (3) during the expansion of the tracks, contribute to the generation of an early, transient alkaline response, which may therefore counteract this acidity spike. However, as can be seen in the figures, $G(\text{OH}^-)$ remains much lower than $G(\text{H}_3\text{O}^+)$ over the time range of interest, regardless of the value of N considered (*i.e.*, of dose rate). As a result, it affects the quantitative features of the pH only slightly and can be neglected to a reasonably good approximation. Unfortunately, to the best of our knowledge, there are no experimental data in the literature on the radiolysis of water under conditions of high dose rates with which to compare our results on the time dependences of $G(\text{H}_3\text{O}^+)$ or $G(\text{OH}^-)$ shown in Figs. 1A–1B.

As shown in Figs. 1A–1B, the yields of hydronium and hydroxide ions generated by radiolysis at ~ 1 ps under both deaerated and aerated irradiation conditions are essentially the same (namely, ~ 4.5 and 0.15 molecules/100 eV, respectively) regardless of the value of N . Such a result is obviously to be expected, since in an irradiated aerated solution, the influence of oxygen (which acts as a very efficient scavenger of e^-_{aq} and $\text{H}^\bullet$ atoms) only occurs at $\sim 0.1\text{--}1$ μs (see *infra*). With increasing time, $G(\text{H}_3\text{O}^+)$ and $G(\text{OH}^-)$ initially remain unchanged, regardless of N , until a critical time is reached, after which the various yield curves begin to deviate from their respective one-single proton irradiation ($N = 1$) reference curves. With increasing N , these deviations occur at ever-shorter times and with greater amplitude. As discussed previously in detail,^{24,42,43} this critical time (τ_c), which clearly depends on N , can be viewed as a signature of the “onset” of dose-rate effects in the solution. It corresponds to the time at which the average distance between tracks becomes sufficiently small that interaction between adjacent tracks starts to occur.²⁴ Under these conditions, the increase in the density of primary events favors the occurrence of inter-track radical-radical

combination/recombination reactions in the solution, thus leading to lower radical and higher molecular yields.^{24,42,43,53}

As noted above, the influence of dissolved molecular oxygen on the time profiles of $G(\text{H}_3\text{O}^+)$ and $G(\text{OH}^-)$ begins to set in at $\sim 0.1\text{--}1\ \mu\text{s}$ regardless of N . This is easily explained, because in the radiolysis of aerated water, O_2 scavenges the primary radicals e^-_{aq} and $\text{H}^\bullet$ atoms on the microsecond time scale,⁶⁶ and converts them to superoxide anion ($\text{O}_2^{\bullet-}$) and hydroperoxyl ($\text{HO}_2^\bullet$) radicals, according to^{2,3,19}

where $\text{O}_2^{\bullet-}$ is always in a pH-dependent equilibrium with its conjugate acid, the hydroperoxyl radical $\text{HO}_2^\bullet$ [$\text{p}K_{\text{a}}(\text{HO}_2^\bullet/\text{O}_2^{\bullet-}) \approx 4.8$ in water at $25\ ^\circ\text{C}$].⁶⁷

As for the hydronium ions, the decrease in $G(\text{H}_3\text{O}^+)$ observed in Figs. 1A–1B is predominantly due to H_3O^+ reacting with OH^- , which is formed by reaction (3), via reaction (6):

and, but to a lesser extent, with e^-_{aq} via reaction (2) and, in the radiolysis of aerated water at times longer than $\sim 0.1\text{--}1\ \mu\text{s}$, with $\text{O}_2^{\bullet-}$ via reaction (7)

Other reactions such as $\text{H}_3\text{O}^+ + \text{O}^- \rightarrow \bullet\text{OH} + \text{H}_2\text{O}$ and $\text{H}_3\text{O}^+ + \text{HO}_2^- \rightarrow \text{H}_2\text{O}_2 + \text{H}_2\text{O}$ also contribute to the decay of $G(\text{H}_3\text{O}^+)$ but only very weakly. This is clearly seen in Figs. 2 and 3, where we compare the time profiles of the extents $\Delta G(\text{H}_3\text{O}^+)$ of the various components of $G(\text{H}_3\text{O}^+)$ calculated from our Monte Carlo simulations of radiolysis of deaerated and aerated water for $N = 1$ (Figs. 2A–2B) and 2100 or 2000 (Figs. 3A–3B). Compared to the results obtained for $N = 1$ (limit of low dose rates), Figs. 3A–3B show

that the contribution of the H_3O^+ reaction with OH^- increases strongly with increasing dose rate and becomes largely predominant in the decay of $G(\text{H}_3\text{O}^+)$ on the timescale considered in this work. This reflects the increasing intervention of inter-track radical-radical reactions (in the present case e^-_{aq} and $\cdot\text{OH}$) in the bulk of the solution, which in turn allows for the formation of more and more OH^- in the nonhomogeneous stage of the radiolysis and thus has a greater chance to react with H_3O^+ . This readily explains the faster decay kinetics of $G(\text{H}_3\text{O}^+)$ which are observed with increasing dose rates (see Figs. 1A–1B).

3.2. The ultrafast, transient, highly acidic pH response

Using our previously developed cylindrical, multi-track irradiation model (see Sect. 2.1)^{42,43} and our calculated $G(\text{H}_3\text{O}^+)$ values reported above (Figs. 1A–1B), the concentrations of the radiolytically generated hydronium ions, $[\text{H}_3\text{O}^+]_{\text{radiolytic}}$, can simply be derived from the relationship:⁶⁸

$$(8) \quad C = \rho \mathcal{D} G,$$

where C is the concentration, ρ is the density of the solution, $\mathcal{D}$ is the radiation dose and G is the chemical yield. Assuming that for N incident protons the hydronium ions are evenly distributed in the considered circular cylinder with a length of 1 μm and an initial radius $R_0 = 0.1 \mu\text{m}$ (at ~ 1 ps; see Fig. 1 of ref. 42), $[\text{H}_3\text{O}^+]_{\text{radiolytic}}$ (expressed in mM) can then be written^{42,43}

$$(9) \quad [\text{H}_3\text{O}^+]_{\text{radiolytic}}(t) \approx 5.3 \times 10^{-6} \times \left(\frac{N \times \text{LET}}{R(t)^2} \right) \times G(\text{H}_3\text{O}^+)(t),$$

where $\text{LET} \sim 0.3 \text{ keV}/\mu\text{m}$ for 300-MeV irradiating protons, $G(\text{H}_3\text{O}^+)$ is in molecules per 100 eV, and

$$(10) \quad R(t)^2 \approx R_0^2 + 4Dt$$

represents the change in R_0 (in μm) over time due to the two-dimensional diffusive expansion of the tracks. Here, t is the time and D is the diffusion coefficient of the various track species involved in our IRT simulations.⁶⁹

Finally, the total concentration of H_3O^+ is the sum of $[\text{H}_3\text{O}^+]_{\text{radiolytic}}$ given by eqs. (9) and (10) and of the non-radiolytic, pre-irradiation concentration $[\text{H}_3\text{O}^+]_{\text{autoprotolysis}}$ (10^{-7} M in the present study) that results from the autoprotolysis of water:

$$(11) \quad [\text{H}_3\text{O}^+]_{\text{total}}(t) = [\text{H}_3\text{O}^+]_{\text{radiolytic}}(t) + [\text{H}_3\text{O}^+]_{\text{autoprotolysis}}.$$

The pH in the irradiated solution is then simply given by the negative logarithm (to the base 10) of $[\text{H}_3\text{O}^+]_{\text{total}}$:

$$(12) \quad \text{pH}(t) = -\log \{[\text{H}_3\text{O}^+]_{\text{total}}(t)\}.$$

Figures 4A–4B show the evolution of the pH values over time which can be estimated directly from eqs. (9)–(12) for N 300 MeV irradiating protons in both deaerated and aerated liquid water at 25 °C for a few values of N chosen as examples between 1 and 2100, using the $G(\text{H}_3\text{O}^+)$ values given in Figs. 1A–1B. As can be seen, an abrupt transient acid pH effect occurs immediately after the initial energy deposition. Its magnitude and duration depend on the value of N (*i.e.*, the dose rate). This observed “acid-spike” effect is most intense at times less than ~10–100 ns. In this time range the pH remains nearly constant, equal to ~3.4, 3.1, and 2.8 under aerated irradiation conditions for $N = 500$, 1000, and 2000 (*i.e.*, for dose rates of $\sim 1.9 \times 10^9$, 4.2×10^9 , and 8.7×10^9 Gy/s, respectively^{42,65}). Beyond ~10–100 ns, the pH gradually increases over time in all cases and eventually reaches a constant value of seven, when the pH value of the body of the solution at room temperature equals $-\log ([\text{H}_3\text{O}^+]_{\text{autoprotolysis}})$ according to eqs. (11) and (12). Finally, examination of Figs. 4A–4B confirms, as expected, that these early acidic pH responses depend only very little on the presence or absence of oxygen.

3.3. The acid-spike effect: A potential role in FLASH-RT?

Remarkably, Figs. 4A–4B show that the timescale of transient acidic conditions generated at high dose rates over the entire irradiated volume exceeds five or six orders of magnitude. In view of the importance of the pH value for many cellular functions (e.g., see ref. 34) this finding raises the question of a possible role for these acid spikes in connection with the current radiobiological puzzle that seeks to explain the counter-intuitive, normal tissue-sparing effect of FLASH-RT.^{33,70} As noted previously,²⁵ this question becomes even more relevant when one considers that the diffusion of H_3O^+ in intracellular water is 100–1000 times less than in free water. In this case, the reduced H_3O^+ mobility in the cell water should indeed lead to a marked increase in the period in which the strong acidic pH is observed,²⁵ which further underscores the potential role of pH in the FLASH effect.

In any case, although it is currently unclear, on a purely radiation chemistry basis, whether these high-dose-rate radiation-induced acid spikes contribute to the healthy tissue-sparing effect of FLASH-RT (compared to tumors), they certainly remain a worthwhile research avenue to be explored further.³³

4. Conclusion

Monte Carlo multi-track chemistry simulations of the radiolysis of both pure, deaerated and aerated water at 25 °C were used in combination with a cylindrical, “instantaneous pulse” irradiation model in an attempt to assess the effects of high dose rates on the radiolytic formation of hydronium ions and the corresponding pH values observed across the irradiated volume. In the current work, we simulated the irradiation of water by N interactive tracks of 300-MeV incident protons, which mimic the low-LET limit of ^{60}Co γ rays or a beam of fast (e.g., MeV) electrons. The effect of dose rate was studied by varying N , the “number of irradiating protons per pulse”.

An abrupt, transient, highly acidic pH response was observed at early times, confirming our previous work.³³ The results showed that this “acid-spike” effect was most intense at less than 10–100 ns, with its magnitude and duration depending on the value of N (*i.e.*, the dose rate). In this time range, the pH remained nearly constant; for example, pH ~ 2.8 under aerated irradiation conditions for $N = 2000$ ($\sim 8.7 \times 10^9$ Gy/s) proton tracks per pulse. At longer times, the pH gradually increased for all N values, ultimately reaching a constant value (7), which corresponds to the non-radiolytic, pre-irradiation concentration of H_3O^+ , due to the autoprotolysis of water. It is noteworthy that these early acidic pH responses were found to depend very little on the presence or absence of oxygen.

Interestingly, these acidic pH conditions persist regardless of N for periods of more than five or six orders of magnitude across the entire irradiated volume. To the best of our knowledge, the potential implications of such a transient acid pH effect have never been studied in water or in a cellular environment. Given the importance of the pH value for many cellular functions, the question arises whether the generation of such spikes of acidity in cell water under high-dose-rate ionizing radiation plays a role in the mechanisms underlying the FLASH effect. For example, it is currently unclear whether these acidic pH spikes can induce biological advantages in normal tissue while maintaining targeted treatment of the tumor. Addressing this is critical as it may provide important clues for better understanding the mechanistic basis of the FLASH effect.

Conflict of interest statement

The authors have no conflict of interest to declare.

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- (35) Under these conditions, the chemical effect of the irradiation can simply be pictured as the sum of the separate effects of individual tracks. In other words, the history of only one single track needs to be considered. This is in contrast to high dose-rate conditions where neighboring tracks begin to overlap (*i.e.*, inter-track interactions occur) even before the intra-track reactions are complete ([ref. 24](#)).
- (36) Recall that radiation-chemical yields are traditionally described in terms of *G* values, where *G*(*X*) is the number of molecules of product *X* that are formed or consumed per 100 eV of absorbed energy. In this paper, *G*-values are given in units of “molecules per 100 eV”. For conversion into SI units (mol J⁻¹), 1 molecule per 100 eV $\approx 0.10364 \mu\text{mol J}^{-1}$ ([refs. 2 and 3](#)).
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- (65) In [ref. 42](#), we used experimental data of the yield $G(\text{Fe}^{3+})$ of the “super-Fricke” dosimeter (oxygen-saturated solution of 10 mM FeSO_4 in aqueous 0.4 M H_2SO_4) as a function of dose rate up to $\sim 10^{10}$ Gy/s to *calibrate* N in terms of “dose rate” (in Gy/s) at 25 °C. The resulting calibration curve was well described by a straight line (see Fig. 3B of [ref. 42](#)) over most of the range of values of N considered here.
- (66) The lifetime of reactions of hydrated electrons and $\text{H}^\bullet$ atoms with oxygen can be estimated from the reciprocal of the “scavenging power”, which is defined by the product $k[\text{O}_2]$ (in units of s^{-1}) of the oxygen concentration $[\text{O}_2]$ and its rate constant k for the reaction with e^-_{aq} and $\text{H}^\bullet$. For 0.25 mM oxygen, reactions (4) and (5) occur at 0.17 and 0.31 μs , respectively.

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- (69) At room temperature, the diffusion coefficients used in our simulations are $D = 9.46 \times 10^{-9} \text{ m}^2 \text{ s}^{-1}$ for H_3O^+ , $5.3 \times 10^{-9} \text{ m}^2 \text{ s}^{-1}$ for OH^- , $2.2 \times 10^{-9} \text{ m}^2 \text{ s}^{-1}$ for $\bullet\text{OH}$, $2.3 \times 10^{-9} \text{ m}^2 \text{ s}^{-1}$ for H_2O_2 , $4.9 \times 10^{-9} \text{ m}^2 \text{ s}^{-1}$ for e_{aq}^- , and $7 \times 10^{-9} \text{ m}^2 \text{ s}^{-1}$ for $\text{H}^\bullet$ (see [ref. 63](#)).
- (70) FLASH-RT has become a hot topic in radiotherapy. The field has grown very quickly and several promising explanations of FLASH have been proposed (for a recent review, see, for example, [ref. 49](#)). However, there is a lively debate today about the various hypotheses proposed as the available data are not robust enough to validate one hypothesis against another.

Figure captions

Figure 1:

Temporal evolution of the yields (in molecule per 100 eV) of radiolytically produced H_3O^+ (solid lines) and OH^- (dashed lines) ions, obtained from our Monte Carlo multi-track chemistry simulations of the radiolysis of pure, deaerated water (panel A) and aerated water (panel B) by 300-MeV irradiating protons ($\text{LET} \sim 0.3 \text{ keV}/\mu\text{m}$) at 25°C , over the interval of $\sim 1 \text{ ps}$ to $10 \mu\text{s}$. The values of N (number of irradiating protons per pulse) chosen to illustrate the dose-rate effects vary from 1 to 2100. Data for $N = 500$, 1000, and 2000 correspond to dose rates of $\sim 1.9 \times 10^9$, 4.2×10^9 , and $8.7 \times 10^9 \text{ Gy/s}$, respectively (refs. 42 and 65). Data for $N = 1$ correspond to the absence of dose-rate effects and are used here as a reference. In panel B, the dissolved oxygen concentration used in the calculations is 0.25 mM.

Figure 2:

Time dependence of the extents $\Delta G(\text{H}_3\text{O}^+)$ (in molecule per 100 eV) of the various reactions that are involved in the decay of H_3O^+ , obtained from our Monte Carlo simulations of the radiolysis of pure, deaerated water (panel A) and aerated water (panel B) by 300-MeV irradiating protons ($\text{LET} \sim 0.3 \text{ keV}/\mu\text{m}$) in the interval of $\sim 1 \text{ ps}$ to $10 \mu\text{s}$, in the absence of dose-rate effects ($N = 1$) at 25°C . In panel B, the concentration of dissolved oxygen used in the calculations is 0.25 mM.

Figure 3:

Time dependence of the extents $\Delta G(\text{H}_3\text{O}^+)$ (in molecule per 100 eV) of the various reactions involved in the decay of H_3O^+ , obtained from our Monte Carlo multi-track chemistry simulations of the radiolysis of pure, deaerated water (panel A) and aerated

water (panel B) by 300-MeV irradiating protons ($\text{LET} \sim 0.3 \text{ keV}/\mu\text{m}$) in the interval of ~ 1 ps to $10 \mu\text{s}$, under conditions of high dose rates at 25°C . In panel B, the concentration of dissolved oxygen used in the calculations is 0.25 mM .

Figure 4:

Temporal evolution of the pH calculated from eqs. (9)–(12) for 300-MeV irradiating protons ($\text{LET} \sim 0.3 \text{ keV}/\mu\text{m}$) in pure, deaerated water (panel A) and aerated water (panel B) at 25°C in the interval of ~ 1 ps to $10 \mu\text{s}$. The values of N (the number of irradiating protons per pulse) chosen to illustrate the dose-rate effects vary from 1 to 2100. In our model system, data for $N = 500$, 1000, and 2000 correspond to dose rates of $\sim 1.9 \times 10^9$, 4.2×10^9 , and $8.7 \times 10^9 \text{ Gy/s}$, respectively (refs. 42 and 65). In panel B, the concentration of dissolved oxygen used in the simulations is 0.25 mM .

FIGURE 1

FIGURE 2

FIGURE 3

FIGURE 4