

Conjecture of classical e-h liquid for understanding the FLASH modality of radiation cancer treatment

Diana Shvydka^{1,*}, Victor Karpov^{2,†} and Nilendu Gupta^{1,‡}

¹*Department of Radiation Oncology, [The Ohio State University Wexner Medical Center](#), Columbus, Ohio 43221, USA*

²*Department of Physics and Astronomy, [University of Toledo](#), Toledo, Ohio 43606, USA*



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We consider physics behind the FLASH modality of cancer radiation treatment, where extremely short treatment times are achieved with ultrahigh dose rates maintaining the conventional antitumor effectiveness and yet substantially reducing damage to normal tissues (sparing effect). The difference in responses between normal and tumor tissues is attributed here to the structure transformation rates related to their morphologies: ordered in the normal tissues versus disordered in tumor tissues. Correspondingly different are nonequilibrium charge densities accumulated in the two phases under ionizing radiation. In normal tissues, it is high enough to form a classical electron-hole liquid (EHL). The low EHL diffusivities slow down the generation of biologically active free radicals, hence sparing effect. To the contrary, a disordered tumor tissue renders efficient energy relaxation channels forming free radicals. We describe the FLASH thresholds for doses and dose rates.

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I. INTRODUCTION

While radiation therapy (RT) is a powerful method for treating cancers, its potential to damage healthy tissues often limits the prescribed dose. The past decades of technological advances were focused on the equipment and treatment approaches, providing high radiation beam conformity to the tumor target and real-time imaging. This conventional radiotherapy (CONV-RT) typically requires multiple sessions, often spanning weeks, and relies on the classical radiobiology principles. Recently, the focus has shifted to a dose rate modulation, unexpectedly providing a drastic increase in the therapeutic index with FLASH radiotherapy (FLASH-RT), leveraging ultra high dose rates (UHDRs; orders of magnitude higher than those of CONV-RT). A unique characteristic of FLASH-RT is that its significantly reduced damage to healthy tissues does not compromise the antitumor effectiveness of the treatment. The physics and biology underlying that striking effect remain to be understood yet, in spite of more than 60 years since the concept of FLASH-RT was introduced [1].

*Contact author: diana.shvydka@osumc.edu

†Contact author: victor.karpov@utoledo.edu

‡Contact author: Nilendu.Gupta@osumc.edu

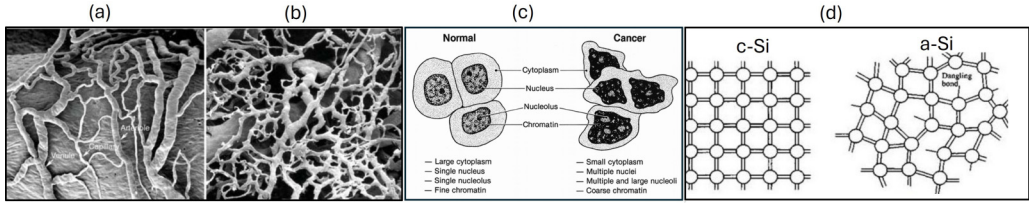


FIG. 1. Schematics of ordered vs disordered counterpart structures. (a) Scanning electron microscopy image of polymer cast of normal microvasculature; (b) same for tumor microvasculature showing disorganization and lack of conventional hierarchy of blood vessels [12]. (c) Cell structure in healthy tissue vs that of cancer tissue [13]. (d) Crystalline (c-Si) vs amorphous (a-Si) silicon structure. Note the dangling bonds that can play the role of recombination centers [14].

Recent reviews describe FLASH-RT techniques, implementations, results, and hypothetical mechanisms [2–8]. The FLASH effect (normal tissue sparing and local tumor control) has been demonstrated with high-energy electron, proton, and x-ray radiation sources for various subjects, from multiple animal models to limited human treatments. Despite many positive findings, a few studies reported the absence of FLASH effect [6]. Anecdotal communications point at cases where, once successful, the FLASH effect was not observed in the follow-up nominally identical experiments, thus calling upon further work to make the modality reliable enough for clinical implementations. From our point of view, the latter outlined observations of (1) the FLASH effect itself and (2) the degree of its elusiveness introduce the essence of FLASH enigma, solving which is necessary to clear a way to further progress. At this time, we are not aware of sufficient answers to the FLASH enigma, although many attempts have been made. Here, we limit ourselves to citing the summary part of a very recent review devoted to the proposed FLASH mechanisms: “...oxygen depletion, radical recombination, mitochondrial preservation, DNA repair and immune response modulation, have all been proposed as contributing factors, but no single mechanism fully explains the FLASH effect” [7].

A more recent review [9] exhibits a trend toward mechanistic explanations of FLASH-RT. Its underlying novel hypothesis is that FLASH distinguishes healthy tissues from tumors based on subtle functional and structural biological differences, such as a specific class of proteins (termed long-lived proteins, LLPs), which are present in nearly every healthy tissue that is FLASH radiotherapy resistant yet are absent in tumors. It is tacitly implied there that LLPs are resistant to FLASH, but not so much to conventional treatments. The authors extend this structural hypothesis further by suggesting that tumor and extracellular matrix rigidity affects sensitivity to changes in radiotherapy dose rate, where more rigid and dense desmoplastic tumors are more sensitive to FLASH radiotherapy than those possessing more elasticity. That novel FLASH mechanism remains to be validated experimentally and theoretically.

Our earlier [10,11] mechanistic approach here takes the FLASH problem down to basic physics.

(1) The FLASH process originates in a two-phase system formed by the material of tumor embedded in a material of healthy tissues.

(2) Upon energy relaxation, the radiation-generated charge carriers (electrons and holes) can participate in processes creating reactive secondary species (RSS), such as free radicals, essential for destroying cancer cells or healthy cells.

(3) The tumor phase exhibits strong structural disorder illustrated in Fig. 1.

(4) Due to random structural “defects” (vacancies, dangling bonds, impurities, etc.; illustrated in Fig. 1), the disorder renders efficient energy relaxation (also known as recombination) pathways consuming all supplied electrons and holes without jamming to produce RSS [15]. The ansatz of recombination in disordered systems is outlined in the Supplemental Material [16]. See the Supplemental Material [16] for the characteristic details of energy spectra and electronic transitions in disordered systems (see also Refs. [17–21] therein).

(5) A much less disordered healthy tissue does not render efficient enough energy relaxation pathways. Hence, charge carriers accumulate there forming classical electron-hole liquid (EHL) as described in Sec. III. The relevance of that description is due to very strong interaction of electrons and holes with surrounding material making them “hydrated” with effective masses on the order of atomic masses.

(6) Our classical EHL behaves similar to most of the classical molecular liquids with diffusivities much lower than those in their corresponding gas phases. The arrested diffusivity suppresses reactions between electrons and holes, thus substantially slowing down RSS generation rates, hence sparing effect.

II. FLASH ENIGMA

We recall that hydroxyl radical ($\bullet\text{OH}$) is a commonly recognized RSS important with RT applications. It can be generated in a variety of ways [6,22,23] under all types of ionizing radiations.

The radiation-generated electrons and holes are initially distributed nonuniformly in random regions (spurs). Those nonuniformly distributed charge carriers diffuse and take part in chemical reactions forming RSS such as $\bullet\text{OH}$. The role of diffusion is central here: Should the charge carriers be immobile, they would undergo nonradiative recombination, returning the system back to its original radical-free state. In what follows, we show how the diffusion of charged species becomes arrested when their concentration grows above a certain value; i.e., a dense conglomerate of charged particles behaves as an electron-hole liquid instead of the conventional low-concentration electron-hole gas (plasma). The latter understanding is consistent with a general observation that diffusivity drops by 4–6 orders of magnitude in the course of phase transformations from gas to liquid.

The radiation-ionized electrons decrease their energy by exciting multiple atomic vibrations and/or generating secondary ionization events. As a result, they reach the lowest unfilled molecular orbital separated by a significant energy gap G from a positive hole in the highest occupied molecular orbital. That gap is significant and the probability of overcoming it is extremely low as explained in the Supplemental Material [16]. In the meantime, that energy relaxation is necessary to create RSS because the energy levels of participating electron and hole must be close to allow a chemical reaction. As argued in the Supplemental Material [16], such energy closeness is facilitated by a disordered tumor morphology but not in normal tissues under UHDRs. Our approach to FLASH enigma is sketched as a process flow in Fig. 2 (cf. Fig. 1 in Ref. [5]). The top row elements are common between CONV-RT and FLASH-RT. They include ionization and excitation with electrons (e) and holes (h) capable of diffusing and forming RSS. Interaction with radiation is practically the same for malignant and normal tissues and so are concentrations of initially generated charge carriers. The subsequent processes of molecular dissociation are almost the same as well because the microscopic molecular structures of those phases are similar.

The rightmost upper box is where the difference between tumor and normal tissues originates. The CONV-RT regime (left bottom sub-box) presenting here the tumor phase takes place when the charge carrier concentrations are not very high and their created stand-alone RSS give rise to DNA transformations. The assumed RSS concentration remains limited even for high dose rates as controlled by strong energy relaxation/recombination channels provided by the high defect concentration characteristic of disordered materials. The right bottom sub-box presents the healthy tissue phase, where the defect concentration is relatively low and so are the energy relaxation/recombination rates. Given the high dose rate, the slow recombination makes the e-h concentration high enough to result in strong Coulomb coupling with energy gain similar to that between the anions and cations in ionic systems, where each charge is bound to the multitude of other charges and cannot be moved. In such a system, there are practically no stand-alone charge carriers and corresponding structural transformations are suppressed, hence spared healthy tissues. The above described scenario is illustrated in Fig. 2.

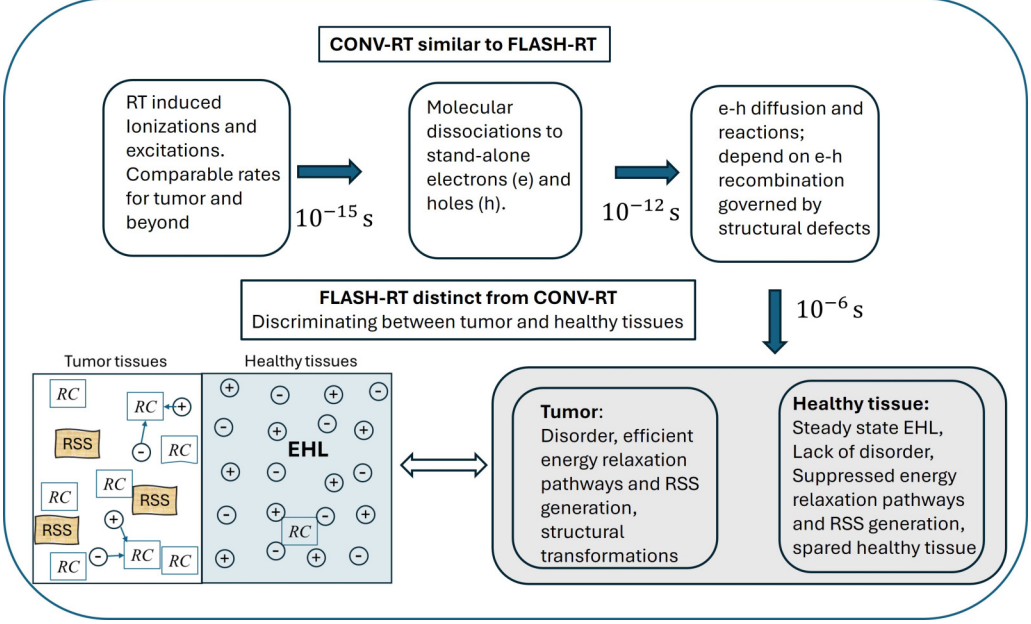


FIG. 2. Flow chart aimed at answering the FLASH enigma. The top row boxes (following Fig. 1 of the earlier published review [5]) present the general physicochemical processes found with both CONV-RT and FLASH-RT modalities. The bottom row discriminates between CONV-RT (left) and FLASH-RT (right), as explained in the text. The insert figure in the left bottom corner presents a graphical illustration of the electronic processes under irradiation in the tumor (left) and healthy tissue (right) regions. Thin arrows show the e-h recombination processes, and RC stand for recombination centers (defects). + and - denote holes and electrons, respectively.

III. ELECTRON-HOLE LIQUID

Increase in dose rates leads to qualitative changes in the ionized radiation products toward denser e-h conglomerates, through excitons, and then biexcitons, toward the EHL. The *quantum* EHL [24–33] remained the only type of EHL known so far. It was developed for perfect crystalline semiconductors, which are irrelevant here. The quantum EHL implies a perfect crystalline material where electrons and holes have “normal” effective masses m on the order of bare electron mass and kinetic energies on the order of their corresponding bandwidths, on a scale of electron volts. To form a bound EHL conglomerate, that huge kinetic energy must be counterbalanced by strong Coulomb interactions between electrons and holes, which makes the problem highly nontrivial. For such a quantum EHL, the theoretically and experimentally based consensus [24–33] is that there exists the critical temperature T_c , below which EHL remains stable; with a few exceptions, $T_c \sim 100$ K. Quantum EHL reveals itself in the observed optical spectra, magnetism, and electrical conduction. For example, it was demonstrated [30] that EHL photoluminescence emerges hundreds of picosecond later than the stand-alone charge carrier excitations, which reflects the kinetics of EHL condensation from e-h plasma to droplets.

Unlike the quantum EHL, here introduced *classical* EHL pertains to charge carriers with extremely heavy effective masses on the order of atomic masses, expected in biological systems where the charge carriers strongly interact with soft atomic subsystem creating local atomic rearrangements (polarons, solvated electrons, etc.) in a matter of picoseconds [34–37]. Because they carry clouds of atomic deformations, the diffusivities of such charge carriers are extremely low, qualitatively similar to ionic melts. Their kinetic energies are low as well, on the order of $k_B T$,

where k_B is the Boltzmann's constant and T is the absolute temperature; $k_B T \approx 0.026$ eV for room temperature $T = 300$ K.

Following the standard description of ionic systems, the binding energy in such EHL is given by

$$U = \frac{\mathfrak{M}e^2}{\kappa r}. \quad (1)$$

Here, e is the electron charge, κ is the dielectric permittivity, r is the nearest-neighbor charge distance, and $\mathfrak{M}$ is the Madelung constant [38–40] accounting for interactions with charges beyond the nearest neighbors. Typically, $\mathfrak{M} \sim 2$ varying between different structures. However, it was argued that much higher values $\mathfrak{M} \gtrsim 10$ are possible in liquid systems. For definiteness, we will assume $\mathfrak{M} = 2$ in our numerical estimates below. Because of the much lower kinetic energy, the interaction of Eq. (1) prevails, and the criterion of *classical* EHL turns out to be much softer than the above *quantum* limitations.

A. Ultimate dose criterion for EHL

To establish the EHL criterion, it is natural to introduce a dimensionless parameter,

$$L = \frac{U}{k_B T} = \frac{\mathfrak{M}e^2}{\kappa r k_B T}. \quad (2)$$

Depending on its value, an e-h system can behave as a low-concentration plasma ($L \ll 1$), EHL ($L \gtrsim 1$), or ionic crystal ($L \gg 1$). We will see next that $L \gtrsim 1$ for realistic FLASH-RT parameters; i.e., the concept of EHL applies. The latter EHL concept is qualitatively consistent with the observation of bound pairs between solvated electrons and hydronium cations [41].

The binding energy U acts as a diffusion barrier. The probability to overcome it is described by the Boltzmann's exponent,

$$p = \exp(-U/k_B T) = \exp(-L), \quad (3)$$

predicting the FLASH disappearance with temperature.

To estimate L , we start with the integral radiation dose D . Assuming that ionized charge carriers do not recombine yields their ultimate concentration,

$$n = 2D\rho/I, \quad (4)$$

in units of $1/\text{cm}^3$, where $\rho \approx 1 \text{ g/cm}^3$ is density of water as the main component, I is the energy of e-h pair creation, and the coefficient 2 accounts for two charge carriers per pair. (Effects of recombination are described next.) The particle concentration and the average distance r between them are related through the standard approximation,

$$n(4\pi r^3/3) = 1. \quad (5)$$

Substituting here the above n yields

$$r = \left(\frac{3I}{8\pi D\rho} \right)^{1/3} \quad \text{with} \quad D(t) = \int_0^t \dot{D}(t) dt, \quad (6)$$

where the dose rate $\dot{D}(t)$ can be time dependent. As a numerical example, the average nearest-neighbor distance in EHL is estimated as 7 nm assuming the dose $D = 30$ Gy (escalated under the FLASH regime compared to the standard therapeutic values).

Using the latter r in Eq. (1) and setting $L > 1$ defines a condition on integral dose under which EHL can form,

$$D > D_{\min} = \left(\frac{\kappa k_B T}{\mathfrak{M}e^2} \right)^3 \frac{3I}{8\pi\rho}. \quad (7)$$

For numerical estimates, we assume $I \sim 10$ eV and $\kappa \approx 5$ based on the published data for fat in human tissues [42], and in bacterial cell [43], and in the high-frequency general water response corresponding to short-time pulses used with FLASH-RT as discussed below. This yields $D_{\min} \sim 10$ Gy, consistent with the data [2–8].

B. Recombination and screening effects

While the criterion of Eq. (7) is given in terms of dose, it is a general perception that the FLASH modality is defined by the dose rate $\dot{D}$. Our resolution here is that the dose of Eq. (7) was derived assuming zero recombination. In reality, a degree of recombination does take place even in healthy phase, imposing additional restrictions on the FLASH criterion as explained next.

Assuming zero recombination in Eq. (7) implies that, in the very beginning of radiation exposure, the initial recombination time $\tau(t=0) \equiv \tau_0$ is long enough to allow charge accumulation under charge generation rate g related to the dose rate as

$$g = \frac{2\rho\dot{D}}{I}. \quad (8)$$

The standard recombination-driven decrease in carrier concentration as $n = n_0 \exp(-t/\tau_0)$ [44], corresponds to the recombination rate $(\partial n/\partial t)_{\text{recomb}} = -n/\tau_0$. Adding here the generation yields $dn/dt = g - n/\tau_0$. We thus require $dn/dt > 0$, i.e., $g > n/\tau_0$. Using the above expression for g and $n = 2\rho D/I$, the latter inequality yields

$$\frac{\dot{D}}{D} > \frac{1}{\tau_0}, \quad (9)$$

which should be applied along with the previously derived criterion $D > D_{\min}$ of Eq. (7). Identifying $\dot{D}/D$ with a reciprocal of the time of dose application, the latter criterion states that the entire dose $D > D_{\min}$ must be delivered during a short time not exceeding the initial recombination time in healthy tissues.

For numerical estimate, we assume $\tau_0 \sim 0.01$ – 1 s from independent study of water electrolysis [45]. Using again $I = 10$ eV and $\kappa \approx 5$ yields the following criterion for FLASH modality:

$$\dot{D} > \dot{D}_{\min} = \frac{D_{\min}}{\tau_0} \sim 10$$
– 10^3 Gy/s. (10)

τ_0 can be sensitive to a particular water composition. (With regard to our numerical estimates, we note that starting from Eq. (1) and on we used the Gaussian system expressing D in unit erg/g = 10^{-4} Gy.)

Yet another constraint defining the minimum dose rate is related to the time (frequency) dispersion of dielectric permittivity, which, in the low-frequency region, is known as α dispersion [46]. It originates from the relatively slow processes of molecular movements, protein reorientations, etc. determining the low-frequency dielectric permittivity of water and related substances. These slow processes make low-frequency dielectric permittivity very high, $\kappa \approx 80$ for water. With such dielectric constants, our parameter L in Eq. (2) decreases by more than order of magnitude, which would eliminate the EHL concept.

However, the slow atomic processes start showing up only at times exceeding 1–10 ms [46]. At shorter time intervals (or frequencies above kilohertz), they do not contribute, and dielectric permittivity must be mostly of electronic nature, thus about the same as in the above-mentioned fat tissues (we note parenthetically that the dielectric permittivity of ice is close to 3.17 [47]). Coincidentally, the molecular movement constraint time turns out to be of almost the same order of magnitude as our first culprit of recombination, i.e., ~ 1 – 10 ms. Therefore, our estimate in Eq. (10) remains qualitatively the same [11].

IV. KINETIC FEATURES AND SPARING

The above kinetic equation ignores the diffusion suppression caused by EHL. Taking the latter into account dictates renormalization $\tau_0 \rightarrow p\tau_0$, with p from Eq. (3) and r expressed through n according to Eq. (5). As a result, our kinetic equation takes the form

$$\frac{dn}{dt} = -\frac{n}{\tau_0} \exp \left[-\frac{\mathfrak{M}e^2}{\kappa k_B T} \left(\frac{4\pi n}{3} \right)^{1/3} \right] + g, \quad (11)$$

where we have added as well the EHL generation rate g . RSS concentration rate dR/dt reaches its maximum and then decreases as the EHL binding becomes strong enough. Upon turning the radiation off ($g = 0$), the EHL binding persists during the time interval of several τ_0 . The initial stage of temporal decay reveals time dependence close to logarithmic. It accelerates toward exponential when EHL concentration decreases enough to weaken the binding, making it possible for electrons and holes to diffuse and engage into chemical reactions creating RSS. Therefore, RSS concentration increases. Overall, our modeled “kinetic” is rather sensitive to the parameters’ choice, making our results here merely illustrative; more comprehensive modeling will become possible when the system parameters are better defined.

RSS concentration $R(t)$ generated by charge carriers overcoming the EHL binding is given by

$$R(t) = \int_0^t \frac{n}{\tau_0} \exp \left[-\frac{\mathfrak{M}e^2}{\kappa k_B T} \left(\frac{4\pi n}{3} \right)^{1/3} \right] dt, \quad (12)$$

which enables one to explore the concept of sparing (inflicted damage decreasing with dose rate).

Following the typical experimental setup [2–8], we consider short pulses during which the carrier concentration remains unsaturated. Using $n = gt$ and introducing a new variable,

$$t = \theta x^3 \quad \text{with} \quad \theta = \frac{3}{4\pi g} \left(\frac{\kappa k_B T}{\mathfrak{M}e^2} \right)^3, \quad (13)$$

one gets

$$R = \frac{3g\theta^2}{\tau_0} \int_0^{(t/\theta)^{1/3}} x^5 \exp(-x) dx. \quad (14)$$

The integrand is a sharp maximum at $x = 5$. Therefore, if the upper limit $(t/\theta)^{1/3} \gg 5$, the integral is approximately equals to $\Gamma(6) = 120$, yielding the saturated RSS *decreasing* indeed with dose rate $\dot{D}$:

$$R_{\text{saturated}} = \frac{360g\theta^2}{\tau_0} = 360 \left(\frac{D_{\min}\rho}{I} \right) \left(\frac{\dot{D}_{\min}}{\dot{D}} \right). \quad (15)$$

Here, the final expression was written with Eqs. (7), (8), and (10) taken into account.

In the opposite limiting case $(t/\theta)^{1/3} \ll 5$, the integral is estimated as $(1/6)(t/\theta)^2$ yielding the time-dependent RSS concentration,

$$R(t) = \frac{\rho \dot{D} t^2}{3\tau_0 I}, \quad (16)$$

where we again used Eqs. (7) and (8). The results of Eqs. (15) and (16) can be traced in the three-dimensional (3D) plot of Fig. 3 presenting $R(t)$ from Eq. (12). The sparing effect is predicted by our theory.

EHL is not expected to exist in the cancer phase, where the intrinsic disorder suppresses characteristic recombination times down to $\sim 0.1\text{--}1\ \mu\text{s}$ [48], i.e., several orders of magnitude shorter than the above used $\tau_0 \sim 0.01\text{--}1\ \text{s}$. Correspondingly, creating the tissue sparing EHL in cancer phase would require extremely high dose rates $\dot{D} = D_{\min}/\tau_0 \sim 10^6\text{--}10^9\ \text{Gy/s}$, below which the cancer killing effect prevails.

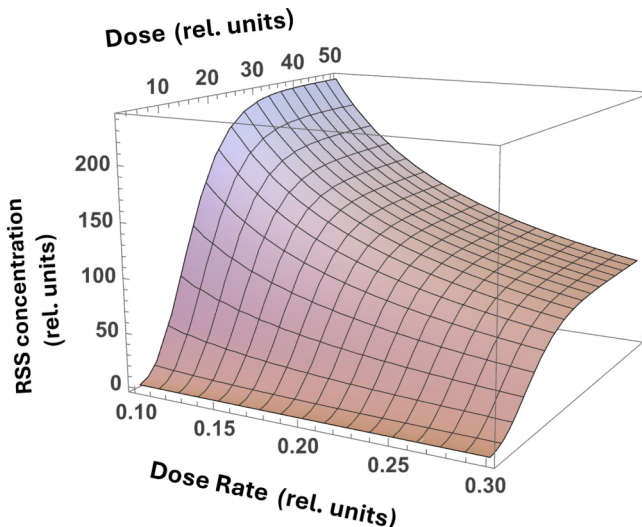


FIG. 3. A calculated sketch of sparing effect showing how RT-created modifications *decrease* with the dose rate for fixed recombination parameters representing normal tissue.

V. OBSERVATIONS CONSISTENT WITH EHL

A recent publication [49] experimentally evaluated dose rate effects on oxidative damage to peptides, as a simplified model for the FLASH underlying mechanisms. Utilizing high-energy x-ray and electron sources, the peptides were oxidatively modified depending on dose rate and oxygen availability. It was found that the higher dose rates resulted in less damage. Similarly, a recent publication [50] explored the molecular basis of FLASH effect in healthy human bronchial epithelial cells with the conclusion that FLASH administration resulted in lower RSS production. We hope that our EHL paradigm can be relevant here, explaining how the recombination time $\tau = \tau_0 \exp(L)$ increases slowing down the radical supply rate n/τ . Neither our model nor the experiment [49,50] invokes a broad spectrum of biological features often considered for FLASH interpretation.

Because the concept of EHL in biological systems is new, no attempts to experimentally observe that state of matter have been performed. However, a substantial effort was made to experimentally observe hydrated electrons under high dose rate radiation in water and aqueous solutions starting from pivotal work several decades ago [51–54] and continuing to this day [55–57]. While the FLASH-RT concept had not yet been conceived then, the founding work [51–54] coincidentally used the dose rates in the contemporary FLASH domain. That coincidence opens a venue to reattributing some of the existing hydrated electron data [51–55,57] to EHL. Indeed, a strong observation underlying the hydrated electron interpretation was that the spectral features observed in optical absorption in the irradiated water and aqueous solutions turned out to be independent of specific chemical compositions of a wide range of alkaline substances, thus pointing at the intrinsic nature of the observed spectra, reducible to solely water components, hence the hydrated electron. However, EHL appears to be as intrinsic to water as the hydrated electrons, thus rendering an equally satisfying hypothesis. Furthermore, the irradiation-induced light absorption did not appear with weakly alkaline or acidic solutions. Therefore, while intrinsic with alkaline substances, the species responsible for the radiation-induced additional light absorption disappear when the hydrogen concentration is suppressed. Overall, we note that due to the general requirement of electric neutrality under irradiation, every hydrated electron must have its positively charged counterpart particle. Regardless of its chemical nature of the latter, they, together with hydrated electrons, can form EHL.

From a broader perspective, our EHL conjecture introduces a concept of Coulomb correlations applicable to various concentrated electrolytes. The related observations can be revisited in a quest for such correlations. As our example, we point at the observed change of trend where electrostatic screening length increases with electrolyte concentration above a certain value n_c [58]. That trend correlates with our EHL effects where the charge carriers lose the ability to screen upon forming strongly correlated conglomerate. As a quick observation, using the concentration of mobile charges from Eqs. (11) and (12),

$$n_{\text{mob}} = n \exp \left[-\frac{\mathfrak{M}e^2}{\kappa k_B T} \left(\frac{4\pi n}{3} \right)^{1/3} \right], \quad (17)$$

one can estimate the characteristic concentration n_c via $dn_{\text{mob}}/dn = 0$, where n is the total concentration of electrolyte charges, which yields

$$n_c = \frac{3}{4\pi} \left(\frac{3\kappa k_B T}{\mathfrak{M}e^2} \right)^3, \quad (18)$$

consistent with the data [58] at least semiquantitatively [59].

We shall finish this section with a brief overview of more recent (5-year interval) FLASH-related publications [9,60–68], some of which may contain observations consistent with the EHL concept, while others remain inconclusive (although they were not aimed at EHL verifications). Simultaneously, this overview will emanate flavor of the ongoing FLASH research.

A 2021 Monte Carlo modeling [60] of 300 MeV proton irradiation created various species versus radiation dose rate and linear energy transfer (LET). For each of the species, the yields remain nearly the same irrespective of the dose rate. With increasing time, these yields remained unchanged, up to a certain critical time τ_c , after which the yield curves deviate from their one-proton reference shapes. τ_c , which depends on the number of irradiated protons, can be viewed as a signature for the “onset” of dose-rate effects. With increasing dose rate, these deviations occur at shorter times and with greater magnitudes. For the geometry chosen, τ_c was found to decrease with the number of protons involved and with the radiation dose rate. Furthermore, it was observed that τ_c marks the process of individual tracks’ overlap pointing at the increase in the density of primary events, which (1) can favor the occurrence of radical-radical recombination and/or (2) suppresses the rate of radical generation (due to EHL arrested mobility of electrons and holes), leading to fewer radicals, the sparing effect. Here, we have added the possibility (2) trying to connect the modeling [60] with EHL mechanism. Note that the track overlap phenomenon is physically different from our EHL mechanism. The former assumes interparticle interactions due to their overcrowdedness in the track overlap regions, unlike EHL that assumes purely Coulomb forces responsible for such interactions. As a result, the FLASH threshold predictions can be different for those two mechanisms.

In a subsequent 2025 publication [68], the authors implemented a similar Monte Carlo simulation with much more in detailed chemical analysis of concomitant radiation-induced processes. They confirmed the relevance of individual tracks’ overlap as a necessary *but not sufficient* FLASH condition and concluded that given their modeling design the widely accepted radiochemical oxygen depletion hypothesis does not suffice to explain FLASH and some other mechanisms may be necessary, such as the EHL conjecture, to be defined.

By 2022, the clinical implications of this new area of research were proven highly significant, rendering the potential to enhance the therapeutic index and opening new possibilities for eradicating radioresistant tumors without toxicity. A multidisciplinary research team focused on investigating the mechanisms and clinical translation of the FLASH effect. They presented a review in the field of UHDR, discussing the physicochemical and biological mechanisms [61]. Also, in 2022, a two-step FLASH-RT mechanism was proposed [62]; an early step at the microsecond scale mainly controlled by heterogeneous radiolysis corresponding to the well-known spur theory in radiation chemistry, and a second, slower, dominated by depletion and biochemical processes. Here, we do not see any potential for EHL concept.

In 2023, two mutually nonexclusive hypothesis have been proposed that could explain the sparing effect: (1) a reduction in radical diffusion due to a higher recombination rate of primary radicals and (2) a reduction in tissue oxygenation levels able to alter downstream responses to FLASH-RT. In this respect, lipid peroxidation is a chemical reaction consuming oxygen, which might be involved in the FLASH effect. A chemistry-based research [63] was the first to identify the lack of lipid peroxidation after FLASH-RT and point to lipids as potentially critical target in rationalizing possible mechanisms underlying the FLASH effect across multiple normal tissue sites.

As another year 2023 example [64], we mention a simplistic system, consisting of pBR322 plasmid DNA in $1 \times$ Tris-EDTA buffer, employed for proton beam exposure with the goal to quantify DNA single-strand breaks (SSBs) and double-strand breaks (DSBs) by agarose gel electrophoresis. It was found that the SSB induction rate (SSB per plasmid DNA/Gy) at UHDR and the induction of Fpg enzyme-sensitive sites were significantly reduced in UHDR compared to conventional dose rate. However, there was no significant difference in DSB induction and non-DSB cluster damages. A critical analysis of chemical aspects potentially involved with FLASH-RT was accomplished by Wardman [65].

A 2025 publication [66] explored a wide range of energies and intensities for various radiation types. It provided the first evidence that live organisms are sensitive to variations of electron beam *intensity* (which characterizes the impeding rather than absorbed radiation), where the momentum flux of beam can impact biological response. The shortest timescale of ~ 1 ps presenting such unexpected response can be related to the reciprocal of characteristic atomic frequencies in media, hinting that best results can be obtained when the charged components remain “frozen”, consistent with the EHL physics.

In 2025, proton FLASH radiation on plasmid DNA was investigated [67], conclusively demonstrating that plasmid DNA strand breakage is dose rate independent at doses below 10 Gy and does not constitute a high-throughput assay end point predictive of the biological effect of FLASH.

VI. DISCUSSION AND CONCLUSIONS

Overall, our work introduces the concept of EHL attributing sparing of healthy tissues to suppressed chemical reactivity of charge carriers due to EHL binding. Phenomenologically, our mechanism of sparing correlates with the “free radical hypothesis” [8] and hypothetical scavenger effects [69], according to which some undefined processes diminish the concentration of free radicals. Our paper attributes such processes to the EHL binding under UHDR radiation. The successes, the remaining questions, and possible experimental verifications of our theory are briefly summarized next.

(1) *What is understood.* Why FLASH exists. Why FLASH has low value thresholds for both the doses and dose rates. A degree of irreproducibility can be explained by ill-controlled impurities, imperfections affecting EHL conditions.

(2) *What is not understood.* The quantitative temporal kinetic of tumor evolution under FLASH-RT. Thermal, electromagnetic, and optical responses of EHL as means for experimental verifications. Possible relations between our theory and biological descriptions.

(3) *Possible experimental verifications.* Electric conduction and optical properties under UHDR. Verification of criteria in Eqs. (7) and (10) for FLASH effect. Doping effects on EHL, which would destroy or enhance the FLASH effect. Temperature dependence of the FLASH effect. Calorimetric verification of EHL formation.

From the practical standpoint, our model validates the principal possibility of testing the FLASH-RT parameters at the cellular or subcellular level (cell cultures or proteins as opposed to typically stated organismal level) that significantly simplifies RT planning and verification [49,70,71]. In the meantime, there are certain aspects of FLASH that can only be investigated in the context of the organism-level response, such as the blood volume irradiated fraction, inflammatory or immune modulation, etc. Our theoretical framework for the FLASH effect involves microenvironmental properties only through physical/chemical parameters of the medium, assumed water-based, and

therefore similar for cellular, subcellular, or organismal level. We predict that for nominally identical subjects their irradiation to the same dose with conventional versus UHDR radiation sources can result in a protective effect for the latter source, once the EHL is formed. Hence, our proposal for suborganismal experiments as the main focus of preclinical FLASH studies. These experiments have been successfully conducted for multiple sources and suborganismal systems, as reviewed in Refs. [49,50,70,71].

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DATA AVAILABILITY

There are no publicly available research data or software supporting this manuscript. Requests for further information or data should be sent to the authors.

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