

# Chapter 2

## Laser-Plasma Accelerators Based Ultrafast Radiation Biophysics

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**Abstract** The innovating advent of TeraWatt lasers able to drive laser-plasma accelerators and produce ultra-short relativistic electron beams in the MeV range, combined with ultrafast spectroscopy methods, opens exciting opportunities for the emerging domain of high energy radiation femtochemistry (HERF). In synergy with low energy radiation femtochemistry (LERF), HERF favours the development of new conceptual approaches for pulsed radiation biology and medicine. The unprecedented high dose rate delivered by ultrashort relativistic electron beams ( $10^{12}$ – $10^{13}$  Gy s<sup>-1</sup>) with laser techniques can be used to investigate the spatio-temporal approach of early radiation processes. The chapter focuses on early physico-chemical phenomena which occur in the prethermal regime of secondary electrons, considering the sub-structures of tracks and very short-lived quantum probes. This interdisciplinary breakthrough would provide guidance for the real-time nanodosimetry of molecular targets in integrated biologically relevant environments and would open new perspectives for the conceptualisation of time-dependent molecular RBE (Relative Biological Effectiveness), in synergy with particle based anticancer radiotherapies.

### 2.1 General Introduction

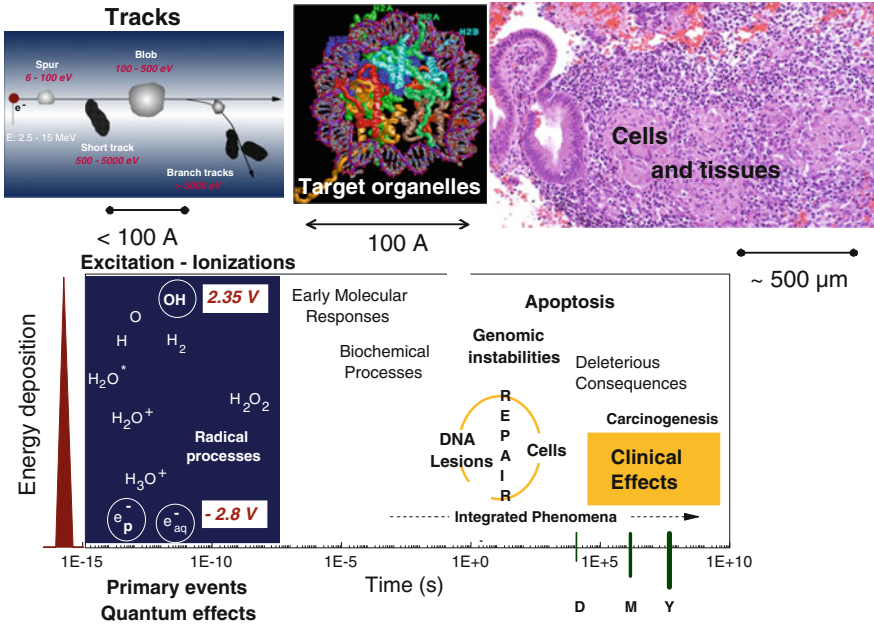
The innovating advent of powerful TW laser sources ( $\sim 10^{19}$  W cm<sup>-2</sup> on target) and laser-plasma interactions provide ultra-short relativistic particle beams (electron, proton) in the MeV domain [1–5]. These advances open exciting opportunities for the simultaneous development of high energy radiation femtochemistry (HERF) and ultrafast radiation biology [6–10]. The complex links that exist between the physical aspects of early radiation events and the delayed evolution of biological endpoints, carcinogenesis or cell survivals need the development of an advanced

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**Fig. 2.1** Synthetic representation of spatio-temporal radiation effects that take place over several orders of magnitude, from an initial energy deposition in molecular targets (quantum events) to more delayed consequences at the biological and clinical levels (*D* Day, *M* Month, *Y* Year)

*spatio-temporal radiation biomedicine* [11]. A very important challenge of this emerging domain concerns the thorough understanding of multiple events that are triggered by an initial energy deposition inside confined clusters of ionization. These multiple electronic and molecular events evolve over several orders of magnitude, typically from femtosecond and sub-micrometric scales (Fig. 2.1).

Nanoscale insight into early physico-chemical processes and native ionisation tracks represents a prerequisite for the complete knowledge of radiation-induced bio-effects in the confined environments of integrated biomolecular targets. Some innovative aspects of spatio-temporal radiation biomedicine are growing rapidly as a result of advanced technical solutions enabling improved pulsed radiation sources and selective protocols for anticancer radiotherapies.

## 2.2 Ultrafast Laser Science and Real-Time Radiation Processes: the Synergy Between LERF and HERF Domains

The real-time investigation of elementary physico-chemical processes in condensed phase of biological interest can be carried out in synergy with the most recent developments of ultra-short laser sources, combining the complementary concepts

of low and high energy radiation femtochemistry (LERF and HERF respectively) [6–8, 10, 12–15]. The course of ultrafast elementary events occurring in nascent ionization tracks (see Fig. 2.1) are largely unknown because up to now the pulse widths of contemporary radiations sources like LINAC accelerators are technically limited to several picoseconds. The magnitude of these primary radiation events remains uncertain, depending on indirect approaches such as stochastic modeling of non-homogeneous processes with different simulations: Monte Carlo calculations of particle pathway during the energy scattering, semi-quantum simulations of ultrafast electronic trajectories taking into account the local structure of reactive environment [15–21].

With the intensive development of ultra-short laser technologies leading to the generation of ultrafast photon or particles sources and advanced high-time resolved spectroscopic methods, the courses of short lived non-equilibrium trajectories are more and more observable on the molecular motion scale [12–15]. The most fundamental aspects of radiation damage in condensed molecular environments concerns the dissociative electron attachment processes that take place in confined ionization spaces. Such processes involve a hierarchy of electronic states of delocalized electrons whose energy varies from the thermal value ( $kT \sim 0.025$  eV) to the sub-excitation and relativistic levels i.e. a few eV and MeV respectively. These primary phenomena are crucial for the solvent of life, i.e. water molecules. The microscopic understanding of primary physico-chemical processes triggered by ionizing radiation requires the real-time probing of multiple non-equilibrium states whose the lifetimes are mostly in the sub-picosecond regime.

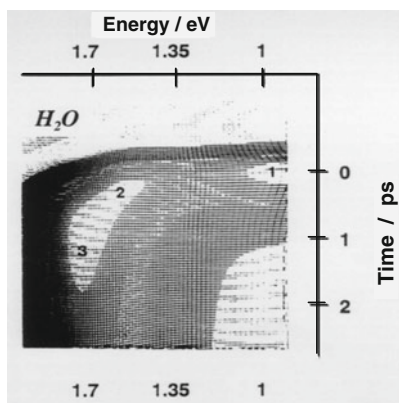
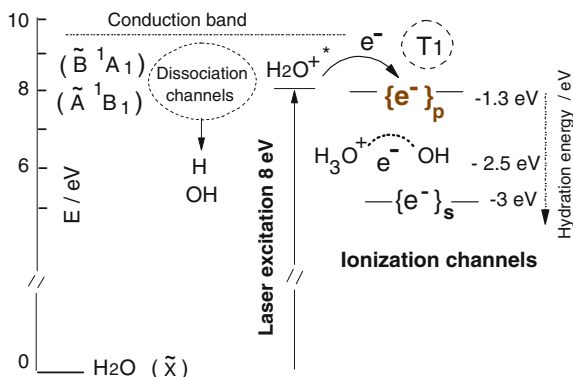
### 2.2.1 Low Energy Radiation Femtochemistry of the Life Solvent

In the framework of non-linear interactions of neat water molecules in liquid phase with femtosecond UV laser pulses whose peak power density is around  $10^{10}$  W cm<sup>-2</sup>, a direct excitation can be triggered by a two-photon process [15, 22]. For a wave plane propagation through an aqueous sample, this phenomenon is expressed by the (2.1), for which  $I$  represents the radiation intensity,  $B$  the two photon absorption coefficient and  $v$  the light velocity in the medium.

$$\partial I / \partial x + \left( \frac{1}{v} \right) \partial I / \partial t = -BI^2 \quad (2.1)$$

Considering an excited  $A^{\sim}$  state of water molecules ( $1b1 \rightarrow 3a1$  for instance), a nonlinear two-photon UV excitation process ( $E_{\text{Excit}} = 2 \times 4$  eV) can be considered to investigate the LERF signals dynamics of early water molecules radical processes. Femtosecond UV-IR absorption spectroscopic investigations in the energy range 3–1 eV allow to discriminate the sequential events of ionization channels (Fig. 2.2). The non-linear two-photon energy deposition of 8 eV in a water bulk

**Fig. 2.2** LERF of neat liquid water at 294 K. *Upper part:* Energy diagram levels of transient electronic configurations induced by two-photon excitation with of femtosecond UV pulses ( $2 \times 4$  eV). *Lower part:* 2D spectral signatures of transient electronic states due to ionization channels. 1: p state of excited electron, 2: electron radical pairs, 3: s-state of fully relaxed electron. Adapted from Gauduel et al. [23–27]



triggers early water defects including the hydronium ion ( $\text{H}_3\text{O}^+$ ) and hydroxyl radical ( $\text{OH}$ ) via an ultrafast positive hole  $\text{H}_2\text{O}^{*+}-\text{H}_2\text{O}$  reaction in less than 100 fs, the generation of multiple non-equilibrium delocalized electron configurations such as quasi-free delocalized electron  $\{\text{e}_{\text{qr}}^-\}$ , p-like excited prehydrated electrons  $\{\text{e}_{\text{p}}^-\}$ , electron-radical pairs and hydrated electron ground state  $\{\text{e}_{\text{s}}^-\}$ . All these ultrafast physico-chemical channels mostly occur in less than  $5 \times 10^{-13}$  s [23–27].

During the last two decades, LERF researches have permitted to clearly establish that a nonlinear femtosecond excitation of neat liquid water leads to an electron hydration process via a nonadiabatic relaxation of an infrared 2p-like excited prehydrated electron; this  $2\text{p}(\text{e}_{\text{prehyd}}^-) \rightarrow 1\text{s}(\text{e}_{\text{hyd}}^-)$  transition occurs in the range 250–500 fs at 294 K [24, 27–29]. Additional ultrafast pathway contributes to the formation of transient solvent bridged three-bodies complex  $[\text{OH}^* \dots \text{e}^- \dots \text{H}_3\text{O}^+]_{\text{nH}_2\text{O}}$  in less than 500 fs. The deactivation frequency of these transient solvent bridged pairs ( $0.29 \times 10^{13} \text{ s}^{-1}$ ) remains comparable to the estimate of a vibrationally excited water molecules relaxation frequency ( $\nu_{\text{H}_2\text{O}}^* \sim 0.33 \times 10^{13} \text{ s}^{-1}$ ) [26]. Indeed, LERF of neat

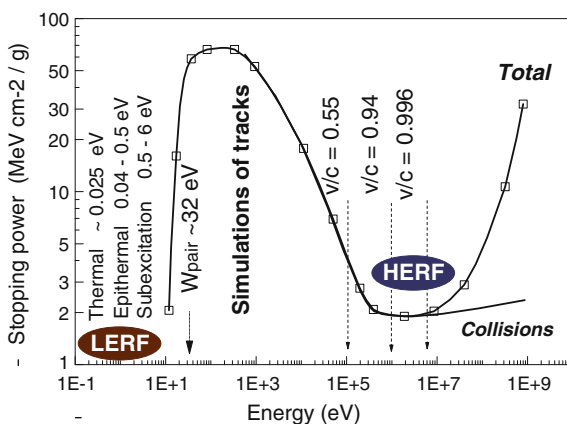
liquid water contributes to deeply understand (i) the nature of complex branching between ultrafast radical pathways, (ii) the contribution of ultrashort-lived solvent configurations within multiple potential energy surface crossing zones.

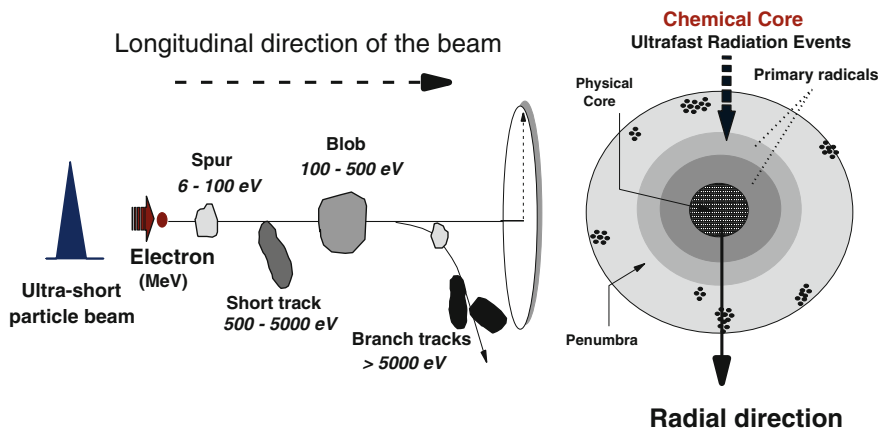
## 2.2.2 Multiparametric Approach of High Energy Radiation Femtochemistry

The advanced TW laser plasma accelerators delivering ultrashort high energy electron bunches [1–5, 30–37] foreshadow the development of innovative researches in the field of radiation physical-chemistry, on the time scale of molecular motions, i.e. angstrom or sub-angstrom displacements [6, 38–42]. Laser-plasma accelerators based High Energy Radiation Femtochemistry (HERF) represents a newly emerging interdisciplinary field which can be driven in strong synergy with the generation of ultrashort particle beams in the MeV energy domain. In the framework of multiparametric approaches that include energy, time and space, innovating developments of HERF would favour, in synergy with LERF data, the investigation of prethermal radiation processes in aqueous and biochemically relevant environments [43].

Considering the energy dependence of the electron stopping power in liquid water for instance (Fig. 2.3) and [44], the real-time investigation of early radiation events in native tracks becomes accessible. This approach requires also the contribution of LERF which is generally devoted to the ultrafast spectroscopy of low energy radiation processes, typically for  $E < 6$  eV. The interactions of relativistic MeV electrons with water molecules induce ultrafast energy scattering processes and the formation of fractionated ionization clusters (Fig. 2.4). These ionization processes involve a hierarchy of electron populations for which the energy varies from relativistic levels to the thermal value kT.

**Fig. 2.3** Energy dependence of the electron stopping power in liquid water. The specific domains of energy covered by low and high energy radiation femtochemistry (LERF and HERF respectively) are indicated on the figure





**Fig. 2.4** Simplified representation of a spatial distribution of inhomogeneous ionisation tracks following the interaction of relativistic MeV particles with an aqueous environment. In the radial direction of the radiation beam, early radiation events take place within the chemical core i.e. at the interface of the physical core and penumbra zone. Adapted from Gauduel and Malka [76]

Typically, in less than  $10^{-16}$  s, different energy quanta of 20–200 eV are delivered in nanometric tracks and spurs [17, 45]. Due to the uncertainty relation for time and energy, the fastest ionising events occurring in confined clusters take place in less than  $0.33 \times 10^{-16}$  s (2.2).

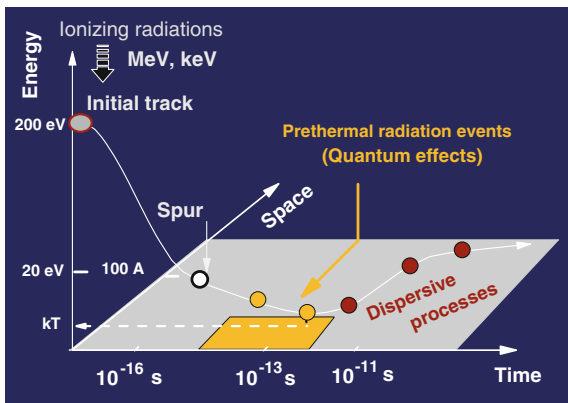
$$\Delta t \cdot \Delta E = \hbar = 6.6 \times 10^{-16} \text{ eV s} \quad (2.2)$$

A second uncertainty principle for the position and momentum of relativistic particle must also be considered:  $\Delta p \cdot \Delta x = \hbar$  with  $p$  the momentum of the particle and  $\Delta p = \Delta E/u$  if  $u$  represents the particle velocity ( $\sim 3 \times 10^{10}$  cm s $^{-1}$ ). From these two incertitude principles, an expression of  $\Delta x$  can be extracted (2.3).

$$\Delta x = \hbar \cdot u / \Delta E \quad (2.3)$$

In this condition, an energy of 20 eV deposited by relativistic particles would occur on  $10^{-6}$  cm ( $\sim 100$  Å) and involve a nanometric distribution of ionization clusters (Fig. 2.5). As early radiation damages can be highly dependent on the survival probability of low-energy secondary electrons and of the spatial distribution of primary radicals produced from water molecules, a thorough knowledge of native tracks requires the real-time probing of radiation events in the  $10^{-15}$ – $10^{-11}$  s range. For aqueous environment, this temporal domain concerns mainly prethermal events for which quantum states of very low excited electrons involve ultrafast nonadiabatic transitions. These ultrafast events lead to the sub-picosecond localization of secondary electrons in water bath. Beyond  $10^{-11}$  s, fully relaxed electrons contribute to sub-micrometric dispersive diffusion processes which can be carefully described by more classical approaches such as the master diffusion equation [16, 45–49].

**Fig. 2.5** Synthetic representation of a time-space-energy relationship for primary events triggered by the MeV-keV ionising radiation of a water environment. In nanometric ionisation tracks, the prethermal regime of very low energy secondary electrons corresponds to the specific temporal window  $10^{-14}$ – $10^{-12}$  s for which quantum effects predominate



The ionisation densities being a major factor of biological radiation efficiencies, the spatio-temporal radiation physico-chemistry and biomedicine beneficiate of recent advances of ultrashort particle bunches delivered by TW laser-plasma accelerators. In the MeV domain, the most promising aspects concern the real-time investigation of early radical events in the radial direction of a particle beam, using molecular sensors at the interface of a physical core and a penumbra zone (Fig. 2.4).

## 2.3 High Energy Electron Bunches and Ultrafast Radiation Chemistry

### 2.3.1 Laser-Accelerated High Energy Electron Beams

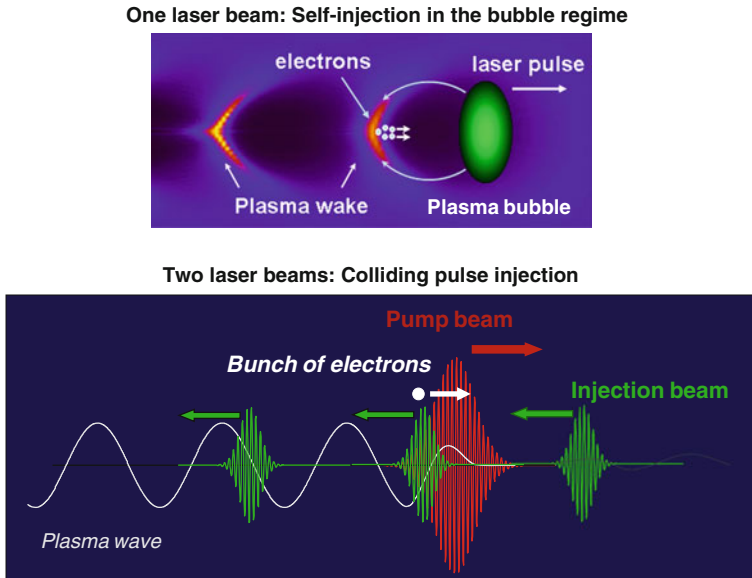
The injection of femtosecond electron bunches into plasma wakefields has been one of the greatest experimental challenge in the field of laser plasma accelerators. Inspired by the pioneering work of Tajima and Dawson [1], the development of laser-plasma accelerators began in the early 1980s. Plasma can support immense electric fields of 100 GV/m and greater [2]. This value is 3–4 orders of magnitude higher than the 10–100 MV/m achieved in radiofrequency cavities of conventional accelerators. Such large electric fields generation can be achieved by focusing an ultra-short and powerful TW laser onto the edge of a supersonic helium gas jet. Rapidly ionized by the intense laser pulse, the helium gas provides a plasma medium in which the laser is then able to generate the wakefield. Large electric field is obtained by separating ions from electrons. This charge separation can be achieved using a high-intensity and ultra-short laser: the ponderomotive force, a force related to the laser intensity gradient, is able to push electrons away from regions of high laser intensity, while the ions stay immobile because of their higher mass. The passage of an intense laser pulse into a underdense plasma generates an electron density perturbation in the wake of the laser pulse. This travelling density

perturbation is referred to as an electron plasma wave and is the source of an accelerating longitudinal electric field, the wakefield. In low density underdense plasma, the laser propagates at a velocity close to  $c$  the velocity of light in vacuum, so that the phase velocity of the wakefield is also close to the light velocity. By surfing on this travelling wave, the electrons are boosted to high energies, typically 100 MeV, over a millimetric distance. For getting an efficient excitation, the laser pulse has to be “resonant” with the plasma wave, which occurs when the laser pulse duration is on the order of half the plasma period:  $\tau_{\text{laser}} \approx \lambda_p/(2c)$ . Consequently, the pulse duration needs to be ultra-short, typically around 30 fs. Two injection techniques have recently lead to the generation of ultrashort electron bunches, with high quality parameters for experimental and medical applications [36].

Previously, a first injection procedure has favored the successful generation of quasi-monoenergetic electrons beams and is wave breaking (Fig. 2.6, upper part). In this regime, a very intense TW-laser focused pulse is used to drive a nonlinear wakefield: plasma bubbles filled with ions and surrounded by a wall of electrons. Electrons are expelled by the laser and circulate around this plasma bubble. At the back of the plasma bubble, electrons accumulate and form an electron density spike. Above a certain threshold value, this density spike collapses by injecting some of its electrons into the plasma bubble, where they are subsequently accelerated. This bubble regime had been initially predicted by Pukhov and Meyer-ter-Vehn [31] which showed that the injection is sufficiently local and short to produce high quality mono-energetic electron beams. The breakthrough experiments, performed in 2004 by different groups from Imperial College, Lawrence Berkeley National Laboratory (USA) and Laboratoire d’Optique Appliquée (France), were the first demonstration of such regime [32, 33, 50]. The electron energy distribution is “quasi-monoenergetic” and generally consists of a single narrow spike which could have a small energy bandwidth of about few percents. The electron beams are extremely collimated, the full width half maximum (FWHM) divergence is smaller than 10 milliradians.

A second configuration provides enhanced control over the injection of electrons and requires two counterpropagating femtosecond laser pulses at the same wavelength (Fig. 2.6, lower part). A first laser beam called “pump” creates a strong wakefield which can be nonlinear but does not lead to wave breaking as in the previous case. In consequence, no electron beam is produced when using this laser pulse alone. A second laser pulse called “the injection pulse” counter propagates to the first laser and injects electrons. When the two pulses collide, the laser beams interfere and generate an electromagnetic beatwave pattern. In this beatwave, the plasma electrons are heated and can gain sufficient kinetic energy to be injected in the wakefield. Electron injection occurs during the laser pulse collision which only lasts about 30 fs, so that the injected electron bunch is ultrashort. Once injected, electrons are accelerated in the wakefield to relativistic energies. The first laser-plasma accelerator using injection by colliding pulse was demonstrated by Faure et al. [34]. Experimental developments emphasize that the electron beams showed enhanced stability when compared to the previous self-injection regime. Although, the stability is not perfect, the peak energy only varies by about 5 %.





**Fig. 2.6** Principles of two laser-plasma accelerator configurations used for HERF experiments and spatio-temporal radiation biology in the MeV energy domain. *Upper part:* self-injection in the plasma bubble regime. The electronic density configuration is greatly non-linear. The with arrows show the electron motions in the reference frame of the pulsed laser. *Lower part:* configuration of colliding pulse injection. The laser pump propagates from the left to right and the injection pulse propagates in the opposite direction. During the collision, the laser pulses interfere and induce a beat pattern. The electrons are injected by the second laser pulse and then accelerated by the wakefield of the pump beam [5, 7, 34]. Adapted from [10]

Energy spreads of a few percent have already been observed [35]. With this colliding pulse configuration, the beam parameters can be adjusted: (i) the beam energy can be tuned by choosing the location of the collision in the plasma, (ii) the beam charge and energy spread can be tuned by changing the parameters of the electron beam. Indeed, femtosecond electron bunch energy can be continuously tuned from 10 to 250 MeV by adjusting the position of the collision in the supersonic gas jet. This is realized by changing the injection distance  $Z_{inj}$  via the delay between the two counter propagating laser pulses [35]. The charge can be adjusted in the 0–100 pC range, with a relative energy spread in the 1–20 % range. Experimental developments demonstrate that relativistic electron bunches have a duration shorter than 100 fs.

### 2.3.2 High Energy Radiation Femtochemistry

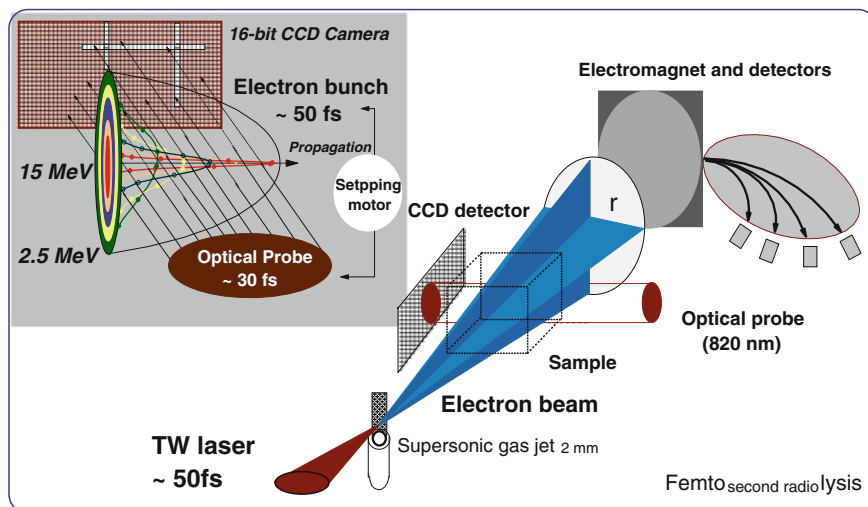
In the framework of innovative developments of pulsed radiation sources such as LINACs, synchrotrons, table-top laser system, proton and ion accelerators, it appears that new physical concepts on radiation-matter interactions would include

time-dependent energetic fluence profile, peak dose delivery energy radial distribution functions and spatio-temporal dose rate profiles. Recently, TW laser plasma accelerators that provide ultrashort high and very high energy electron bunches (HEE: 50 MeV, VHEE: 150–200 MeV respectively) open several exciting opportunities for a careful investigation of ultrafast radiation events in native ionization tracks. The specific qualities and properties of these ultrashort relativistic particle bunches foreshadow the development of advanced researches to deepen the understanding of primary molecular damage triggered by physical radiation processes. In this way, the powerful laser techniques (table-top terawatt Ti:Sa laser oscillators followed by amplifier systems) combined to laser plasma interactions provide femtosecond high-energy electrons beams in the MeV energy domain. These new accelerators foreshadow the development of innovative researches in the field of high energy radiation physical-chemistry [6, 39, 41] and might conjecture the direct observation of primary radiation events in heterogeneous spur and track distributions (Fig. 2.4).

Regarding the temporal range  $10^{-15}$ – $10^{-10}$  s, an emerging research field concerns the High-Energy Radiation Femtochemistry (HERF) of prethermal radiation events (Fig. 2.5). One major challenge concerns the real-time investigation of radiation processes triggered by an initial energy deposition in confined ionization tracks, using the high potentialities of femtosecond laser-plasma accelerators in the MeV domain [3, 4, 51]. Based on advanced TW laser accelerator previously developed by Malka et al. [7], recent investigations concern the implementation of a pump-probe configuration mixing: (i) the generation of laser-plasma accelerator that delivers femtosecond electron bunches in the MeV energy domain, with an initial duration of the order of 50–100 fs, a total charge of the collimated electron beam around 150 pC and characterized by a very high dose rate of  $10^{13}$  Gys<sup>-1</sup> per pulse; (ii) a femtosecond optical beam operating in the visible or near-infrared spectral range for real-time probing of early radiation processes.

During the last decade, pioneered femtolysis experiments (Femto<sub>second</sub> radio<sub>lysis</sub>) of aqueous targets performed with femtosecond electron bunches in the energy domain 2.5–15 MeV have provided new insights onto the early behaviour of secondary electrons in native ionisation clusters.

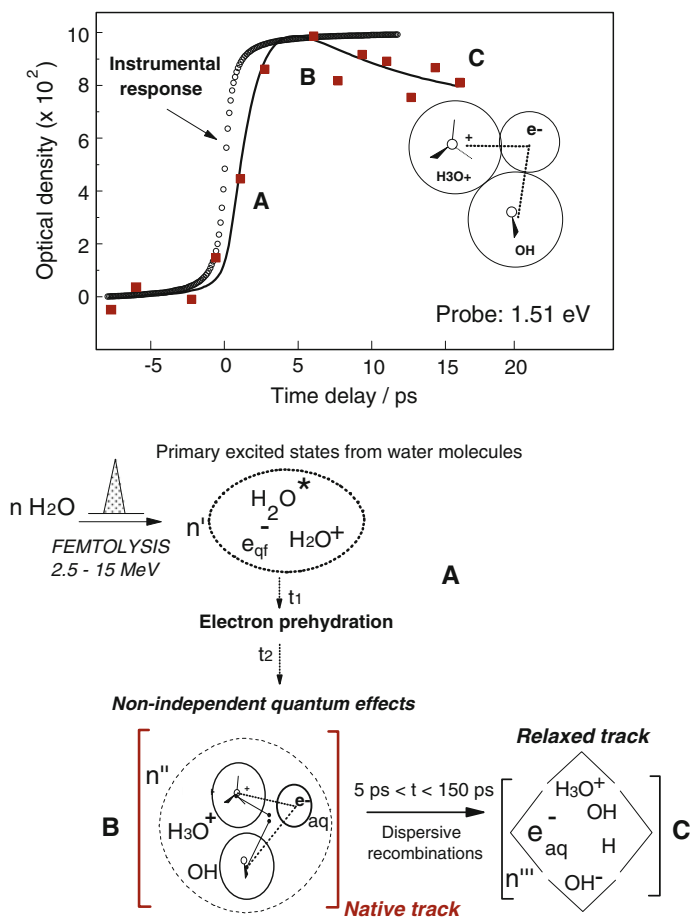
These researches have emphasized the pre-eminent role of non-independent radiations events during ultrafast electronic relaxation processes [41]. For instance, a 820 nm TW titanium-doped sapphire laser beam with an on-target energy of 960 mJ in 30 fs FWHM pulses can be focused onto the sharp edge of a 2 mm diameter supersonic helium gas jet. With intensities on the order of  $2.7 \times 10^{19}$  W/cm<sup>2</sup> in vacuum, the femtosecond laser pulse ionises the gas and excites relativistic plasma waves within the underdense plasma. A total charge of the electron beam determined by an integrating current transformer equals  $2.5 \pm 0.2$  nC and corresponds to a mean number of  $(1.55 \pm 0.15) \times 10^{10}$  electrons. For an effective temperature of the femtosecond electron beam of about 4.5 MeV, the integrated energy flux in aqueous samples equals  $5.8 \times 10^{10}$  MeV cm<sup>-2</sup>. The specific qualities and properties of ultra-short relativistic particle bunches foreshadow the development of high energy radiation femtochemistry. Using a



**Fig. 2.7** Experimental set-up used for the development of HERF in aqueous liquid phase [9, 55]. The energy of the femtosecond relativistic electron bunches is in the range 2.5–15 MeV. The electron beam radius is “ $r$ ”. The typical Femtolysis set-up is defined with a perpendicular pump (electron bunch)—probe (optical pulse) configuration

highly-time-resolved pump (femtosecond electron bunch)—optical probe (femtosecond photon pulse) orthogonal configuration (Fig. 2.7) and a detection system based on cooled 16-bit CCD camera (Andor Technology), the real-time investigation of primary radiation processes is performed in the radial direction of femtosecond electron bunches (Fig. 2.4). Concerning recent water femtolysis studies, laser-plasma accelerator based high energy radiation femtochemistry gives new insights into the time dependence of early events occurring in native ionisation clusters (Fig. 2.8).

Different transient HERF absorption signals can be analysed in the framework of non-homogeneous ionising events that lead to the formation of fully hydrated electrons (steps A and B in Fig. 2.8): a first dynamics ( $t_1$ ) characterizes the trapping process of secondary electrons in water bath (prehydration of delocalised electrons) and the second one ( $t_2$ ) corresponds to a nonradiative relaxation of trapped electron (p-like state of prehydrated electron) towards a 1s-like electron ground state (complete hydration process). A prehydration time  $t_1$  of  $150 \pm 30$  fs has been determined from computed analysis. The best fit of the overall near-infrared HERF signal risetime is obtained with a  $t_2$  value of  $850 \pm 50$  fs. Femtolysis experiments emphasize the electron hydration process within nascent tracks is slightly slower than low-energy electron localization dynamics in water bath [24, 25, 27]. Femtolysis studies suggest also that local anisotropic configurations due to electric field effects of charged prototropic entities slacken the relaxation dynamics of infrared p-like excited electron towards a 1s-like ground state ( $e_{aq}^-$ ).



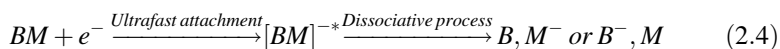
**Fig. 2.8** Femtolytic ionization tracks in neat liquid water at 294 K. *Upper part*: the steps A, B, C of a time-resolved absorption curve correspond respectively to an electron ejection from water molecule, a sub-picosecond electron relaxation (prehydration) in the vicinity of water radicals and an early recombination processes leading to fully relaxed radicals having. A typical instrumental response obtained with orthogonal pump-probe configurations is also reported. *Lower part*: synthetic representation of main events occurring in native ionization tracks following the interaction of ultra-short relativistic electron bunches (2.5–15 MeV) with water molecules. Adapted from Gauduel et al. [41]

Femtolytic ionization tracks in neat water has also revealed that in native ionisation tracks, the short-time behavior of the ubiquitous  $e_{aq}^-$  radical (1s ground state) is mainly governed by ultrafast geminate recombination processes (steps B and C in Fig. 2.8). These phenomena are highly dependent on the transient distribution of electron-hole pairs and the short-time spatial configurations of electron-prototropic entities (hydronium ion  $H_3O^+$  and radical hydroxyl OH). Indeed, when an electron ejected from a water molecule is directly trapped by the structured hydration shell

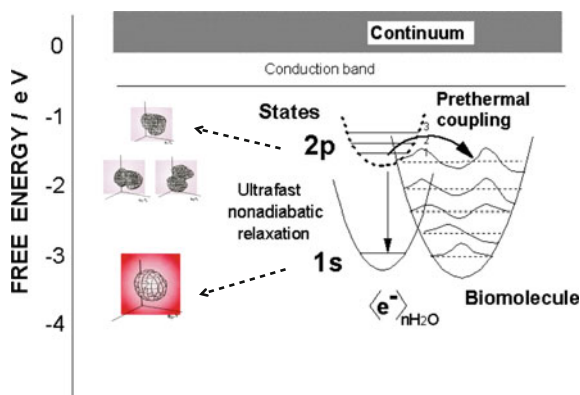
of hydronium ion ( $\text{H}_3\text{O}^+$ ) or hydroxyl radical ( $\text{OH}^\bullet$ ), the initial separation distances are shorter than the Onsager radius ( $R_c \sim 7 \text{ \AA}$  in water) [52]. A limit case corresponds to very short-range electron-proton couplings for which hydronium ion ( $\text{H}_3\text{O}^+$ ) undergoes one jump (1D motion by a finite process). Considering a diffusion coefficient of  $\text{H}_3\text{O}^+$  expressed as  $D \sim \lambda d^2/6$  [17, 53] and an experimental jump frequency  $\lambda = 1/T_j = 0.5 \times 10^{12} \text{ s}^{-1}$ , the initial proton jump distance would be around  $2.8 \text{ \AA}$ . The favorable configurations of three-bodies radical complexes [ $\text{OH}^\bullet \dots e^- \dots \text{H}_3\text{O}^+$ ], also named non-independent radical pairs, recombine fastly or execute a 1D random walk within a fluctuating hydrogen bonds network. The early quantum yield of hydrated electron measured at  $t \sim 5 \text{ ps}$  is higher than the predictions of classical stochastic modeling of irradiated water [46, 47, 54–58]. This important result of high energy radical femtochemistry of water molecules strongly argues for the pre-eminence of a quantum character of ultrafast water radiation damage in native tracks. Laser-plasma accelerators based HERF may contribute to a better knowledge of tracks sub-structure and allow the direct observation of primary radiation events in function of local environments induced by the presence of short-lived prototropic entities.

### 2.3.3 *Towards a Real-Time Probing of Prethermal Events in the Ionization Tracks*

The advent of powerful laser techniques (table-top terawatt Ti:Sa laser amplified systems) and laser-plasma interactions providing bright and ultra-short high-energy particle sources of several MeV, typically in the 5–250 MeV range, open also promising opportunities for the real time investigation of high energy radiation effects in the prethermal regime of secondary electrons. In this regime, the energy of partially localized electrons is higher than the thermal energy kT ( $\sim 0.025 \text{ eV}$ ) [45]. Ultrafast radiation events occurring in less than  $1 \text{ ps}$  ( $10^{-12} \text{ s}$ ) after an energy deposition induced by a ionizing radiation represent a specific domain for which the quantum character of short-lived events becomes preminent. This is particularly important when biomolecular damages take place during the prethermal regime of secondary electrons (Fig. 2.5). One of the most fundamental aspects of a biomolecule (BM) damage induced by ionising radiations concerns the dissociative electron attachment processes occurring in confined ionization spaces (2.4). An important challenge concerns the spatio-temporal understanding of events induced by the initial energy deposition of an electromagnetic ray or energetic particle in the medium and their subsequent effects on solvated biomolecules (Fig. 2.9).



These molecular damages involve generally a hierarchy of secondary electron populations for which the energy varies from the thermal value ( $\sim 0.025 \text{ eV}$ ) to the



**Fig. 2.9** Energy diagram of an ultrafast coupling between the quantum state of a localized electron (p-state of an excited electron) and a disulfide biomolecule. In aqueous environment, this coupling competes with an ultrafast nonadiabatic p-s transition that leads to the formation of a fully relaxed electron (1s-state hydrated electron) [24]. The representations of 2p and 1s state wave-functions calculated by semi-quantum molecular dynamic simulations [70] are reported on the left part of the figure

sub-excitation and relativistic levels i.e. few eV and MeV respectively. The prethermal processes and early spatial distributions of transient couplings between secondary low energy electron and biomolecules may play an important role during the early steps of radiation damage [59–62]. Previous Gauduel's researches devoted to low and high energy radiation effects on water molecules have suggested the crucial role of ultra-fast quantum effects for which short-lived configuration of very low energy quasi-delocalized secondary electrons would be involved [63–65]. For instance, in the framework of a nonlinear two-photon excitation process of water molecules by femtosecond UV pulses, multiple non-equilibrium configurations of delocalized electron are generated in less than  $5 \times 10^{-13}$  s at 294 K. One of these short-lived configurations (p like state excited electron) has been analyzed in term of quantum eigenstates [66–70]. In a water environment, these transient delocalized electron configurations can be considered as specific probes for investigating ultrafast prethermal reactions linked to biomolecular damage induced by the interaction of ionizing radiations (photons or accelerated particles) [6, 61, 64, 71–75].

The spatio-temporal coherences which are required to get an efficient coupling between a very short-lived quantum probe (p-state electron) and a biomolecule need additional investigations of ultrafast phenomena by infrared spectroscopy techniques. Indeed, the nano-scale insight of primary radical processes triggered by ionizing radiation requires the real-time probing of non-equilibrium states for which the lifetimes are typically in the sub-picosecond regime. Advanced laser-plasma accelerator based femtolysis experiments permit to extend our understanding of

very short-time radical events in the prethermal regime of nascent ionization tracks, typically in the  $10^{-14}$ – $10^{-12}$  s window. Following a dose delivery of 15 Gy in less than 500 fs, it has been shown that an ultrafast collapse takes place between a low energy electron (precursor of fully hydrated electrons) and biomolecules localized in the chemical core of the tracks i.e. at the interface between the physical core and penumbra zone. In presence of biomolecules, a decrease of the early signal amplitude assigned to the hydrated electron population in native ionization tracks has been observed [38, 42, 43]. This early effect argues for a prethermal attachment of a p-state excited electron on biomolecules in less than  $0.85 \times 10^{-12}$  s. Consequently, in sub-nanometric ionization tracks, a biomolecular radical formation ( $\text{BM}^-_{\text{aq}}$ ) would occur faster than the nonadiabatic radiationless relaxation of excited prehydrated electrons ( $p \rightarrow s$  transition). A major stride of a short-range biomolecular alteration triggered by an ultrafast electron attachment in the prethermal regime of ionization clusters will be the quantitative characterization of two parameters at very short time ( $t \ll 1$  ps): the effective reaction radius and interaction cross section of the fleeting quantum probe (2p state electron) with a biomolecule. Real-time infrared spectroscopic measurements in the spectral range 1.1–1.6  $\mu\text{m}$ , based on laser-plasma accelerator technologies and HERF considerations, are still in progress.

In the framework of an energy/time/space approach of the prethermal regime of very low energy secondary electron ( $E \ll 1$  eV), sub-picosecond IR spectroscopy of short-lived eigenstates of p-like excited prehydrated electron in the radial directions of ultrashort electron bunches would be used as quantum probe for the sub-nanometric investigation of radiation-induced biomolecular damage at early time. The ubiquitous character of this short-lived electronic probe will be essential to (i) explore the dynamics of prethermal radical processes and the early sub-structure of ionization tracks, (ii) define short-time interaction cross section and characterize pertinent bio-effect parameters in function of a pulsed radiation quality. In a near future, new physical concepts on biodosimetry at nanometer scale would provide guidance to estimate radiation-induced molecular alterations in environments of biological interest [76].

## 2.4 Spatio-Temporal Radiation Biomedicine

The innovative aspects of radiation therapy in cancer domain are growing rapidly as a result of new technical solutions enabling improved radiation sources, diagnostics and precision treatments [8, 10, 77–84]. The exposure of living systems to different types of ionizing radiations (X- and  $\gamma$ -rays, electrons, protons or ions) induces a broad range of complex physical responses and signalling processes that cells and tissues integrate or remove to maintain their functional integrity and prevent tumor formation [85–90]. It is commonly admitted that the early spatial distribution of energy deposition events triggered by ionizing radiation interacting with simple or complex biomolecular architectures is decisive for the control of damages at

cellular or tissue levels and for the prediction of delayed responses in radiation medicine and cancer therapy [86, 91–93]. Cancer radiotherapy based on X-ray photons and high energy electron, proton or ions represents about 45 % of curative and palliative treatments. Clinical accelerators currently delivering electron beams of 5–50 MeV are used for conventional surface therapy of shallow tumors but the innovative developments of radiation sources (LINACs, synchrotrons, ultrashort table-top laser systems, proton and ion accelerators) with specific dose distribution profiles make them suitable for treating deep tumors.

The potential interest of ultra-short particle bunches for clinical applications such as protontherapy is totally dependent on the development of compact laser-plasma accelerator providing quasi monoenergetic particle with an energy spread of 10 % and having lower cost investment than conventional radiotherapy machines [83, 93]. However, compared to classical dose rate used in conventional radiotherapy ( $\sim 1 \text{ Gy min}^{-1}$  or 2 Gy per session, with a total integrated dose delivery of  $\sim 60 \text{ Gy}$  for 6 treatment weeks), the very high dose rate delivered by laser plasma accelerators  $\sim 10^{13} \text{ Gy s}^{-1}$  may challenge new concepts for interactive radiotherapy planning, taking into account multicriteria optimization of fractionated doses and personalized clinical treatments.

Deeply understanding the multi-scale mechanism of radiation damage in living matter, starting from the early radical and molecular processes to mutagenic DNA lesions, cell signalling, genomic instability, apoptosis, microenvironment and bystander effects, would have many practical consequences like the customization of more predictive and selective radiotherapy protocols. The complex links that exist between the physical aspects of early radiation events and the delayed evolution of biological endpoints such as those involved in double strand break (DSB) repair pathways of DNA (pH2AX, pATM, MRE11...), during carcinogenesis or cell survivals need the development of advanced spatio-temporal radiation biomedicine [92, 95]. For this transdisciplinary and interfacial domain, new physical concepts on radiation-matter interactions are more and more considered, taking into account several important parameters of pulsed radiation sources such as the time-dependent energetic fluence profile, peak dose delivery, energy radial distribution functions or spatial dose rate [7–10, 82, 92–99].

Reducing the dose deposition before the tumor would limit some deleterious radiation effects on health tissue while the presence of a significant dose deposition after tens of centimeters could be beneficial to cure deep cancer tumors of obese patients. Some undeniable prerequisites such as a well-defined dosimetric characterization have to be realized in tissue-like medium. From the theoretical point of view, the isodose distributions of very high-energy electron and accelerated proton or ion beams are generally investigated with semi-classical Monte Carlo methods performed with the code GEANT 4 [8, 82, 100, 101]. These approaches take into account various parameters of the electron beam such as the fact that electrons are accelerated in a very limited region of a few microns, the divergence, energy spectrum of relativistic electrons and particle cross section at the phantom entrance (aqueous-like phantom). Indeed, a detailed investigation of the dosimetric properties of very high monoenergetic electrons beams (VHEE) in the range of



150–250 MeV have demonstrated that for parallel and opposed beams, the sharpness of the lateral penumbra is of comparable quality to characteristic values of clinical photon beams.

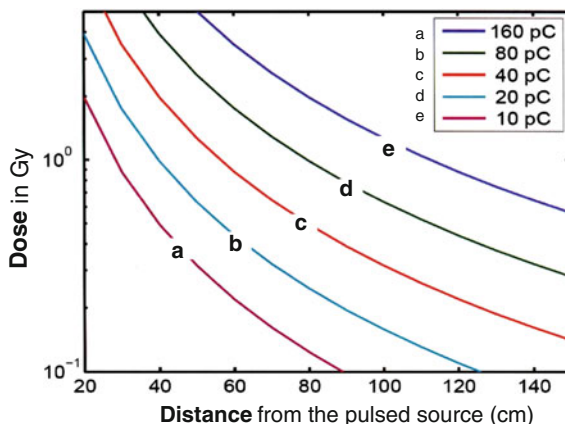
Regarding the physical aspects of particle-target interactions, Monte Carlo simulations include electromagnetic, electron and photonuclear processes. Most of these semi-classical simulations address the fundamental question of dose deposition at macro or microscopic levels [20, 88]. These approaches, whose TRAX simulation code, are quite suitable to define the physical dose delivered in living cells and tissues during cancer radiotherapy planning [86, 102] but do permit to estimate the biological dose profile at the local order i.e. at the scale of biomolecular architectures. This fundamental point seems also particularly important for radiotherapy protocols with targeted radiosensitizers such as nanoparticles [103–107]. An accurate description of the initial processes at extremely short space (nanometer scale) and time scale (sub-picosecond level) is mandatory.

Spatio-temporal radiation biomedicine is expected to provide new insights into yet unknown domains such as cell and tissue responses to pulsed high dose rate or determine the fate of confined cluster of ionization in the nanometric environment of biological target [92, 108–110]. Whatever the ionizing radiation is (electromagnetic radiation, accelerated particles or ions), the deposition of energy takes place in confined ionization spaces (tracks) for which the nanoscopic dimensions correspond to those of biomolecular entities in living matter (DNA and nucleosomes, proteins pockets, enzymatic machinery). Despite a considerable body of knowledge on nucleic lesions formation and repair, identification of protein damage and signalling pathways in normal and cancer cells [89, 92, 111], little is known on biological alterations in native tracks. Indeed, correlations between early radiation effects and cell surviving fraction cannot be defined from a macroscopic dose profile and require the innovating concept of radiation biomedicine at the nanometer scale. This newly emerging interdisciplinary field can be driven in strong synergy with the development of innovating ultrashort radiation sources and the most recent progresses of semi-quantum simulations, optical methods for sub-cellular imaging, molecular biology, genomics and proteomics, biomarkers detection, vectorized nanoparticles and radionuclides.

#### ***2.4.1 Ultrashort Pulsed Irradiation Effects at Sub-cellular Level***

During the last decade several attempts were focused on nanosecond or picosecond irradiations of living cells [112–115] and the deleterious consequence of pulsed radiations on cell populations were analyzed in the framework of classical dose-survival curves and 2D imaging of foci [82, 97, 116]. When multi-shot irradiations of several Grays are performed, the integrated irradiation time greatly interferes with the multi-scale dynamics of biomolecular damage-repair sequences

**Fig. 2.10** Calculated influence of the irradiation distance from the laser-plasma source on the dose delivered by monochromatic electron bunches (150 MeV) in a biological sample (water phantom). A typical divergence is 5 mrad FWHM and dispersive effects can be investigated for different charges of the high-energy electron beam

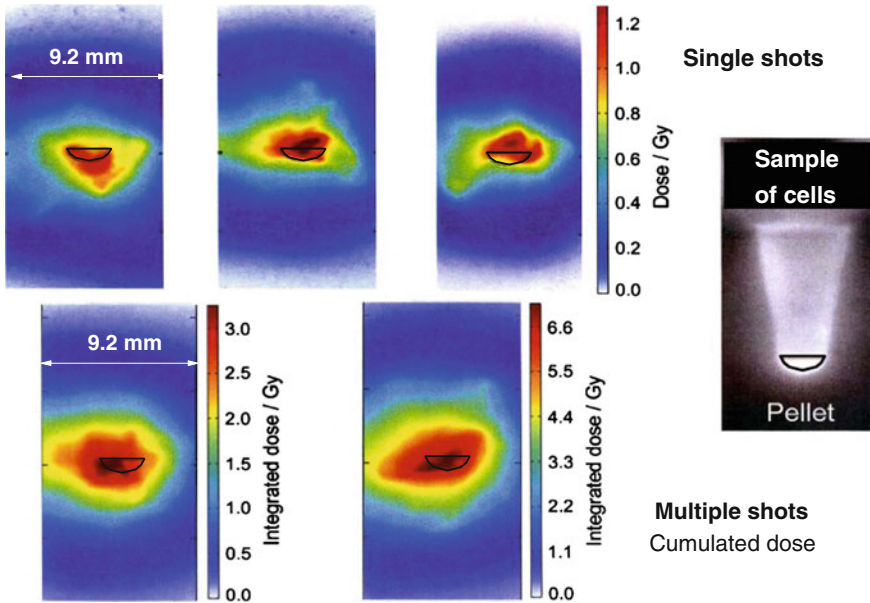


and cell signalling steps. Ultra-short radiation accelerators offer interesting perspectives for exploring the complex biological effects of single shot irradiation, considering that the irradiation time ( $\sim 100$  fs) is the same order of magnitude that early molecular damage such as bond breaking [117]. The energy and charge of ultrashort electron beam can be modulated, considering colliding beam geometry of laser-plasma source. In the energy range 90–200 MeV, as the electron beam area varies with the distance between the accelerator source and the sample, the dose delivered in living matter can be properly adjusted (Fig. 2.10). For that, the physical dose delivered in a cell pellet is determined from Monte Carlo calculations, taking into account the exact number of electrons determined from scintillator measurements. Mylar window of 300  $\mu\text{m}$  can be used to extract the electron beam from the vacuum and different mini-tubes containing the biological sample are positioned in air.

Experimental conditions with an electron beam diameter of 9.2 mm permit an optimized overlap between a 2D dose deposited by a femtosecond quasi-monoenergetic electron bunch at a mean energy of 95 MeV (Fig. 2.11) and a semi-ellipse pellet profile of 1.5–2 mm containing about  $5 \times 10^5$  human skin carcinoma cells (A431 carcinoma cell line).

Two different approaches can be considered: either an *ultrafast single irradiation shot* for which the dose delivered in the tumor cell pellet is  $1.02 \pm 0.13$  Gy and the dose rate  $10^{13}$  Gy  $\text{s}^{-1}$  or *multiple high dose rate irradiation shots* permitting higher dose deposited in the biological sample (Figs. 2.11 and 2.12). In this later case, the integrated irradiation time remains long compared to the 100 fs pulse duration of a quasi-monoenergetic electron bunch [117].

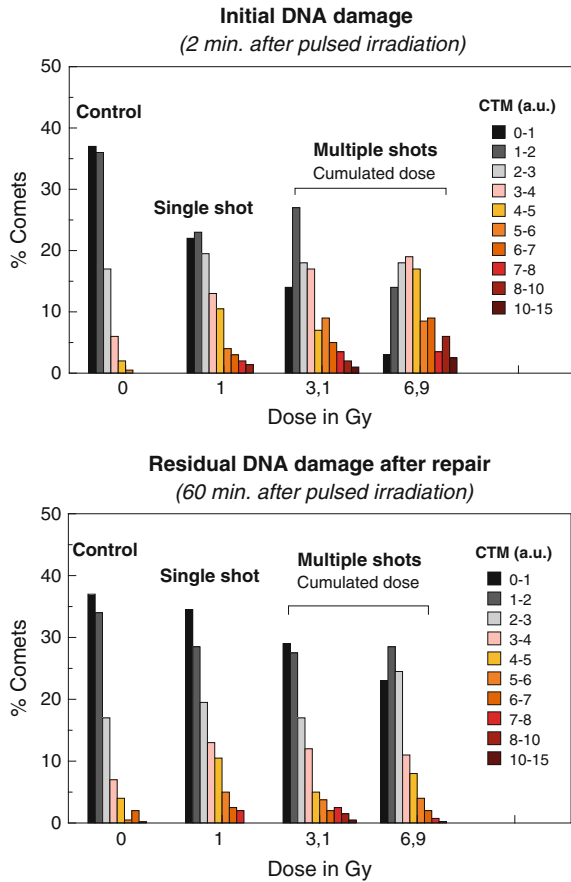
One of the most promising aspect of a single shot irradiation of living mater damage within a very short temporal window would be the real-time investigation of early high dose rate radiation-induced molecular damage in the confined spaces of cell compartments (nucleus, cytoplasm of membranes for instance). Considering that DNA represents an important molecular target for radiation biology, a first decisive step has been obtained by the investigation of the impact of a 100 fs single



**Fig. 2.11** Ultrashort irradiation of skin carcinoma cells (A431 carcinoma cell line) with femtosecond high energy electron bunches (95 MeV). *Upper part*: set of images showing the overlap between the pellet containing human skin carcinoma cells and the 2D single shot dose profile. The dose ( $\sim 1$  Gy) delivered in the semi-ellipse of the cell pellet by ultrafast single shot is determined by Monte Carlo calculations. *Lower part*: cumulated 2D dose profile showing multiple shots irradiation: 5 shots (*left*) and 10 shots (*right*) respectively. Adapted from [10]

shot with 1 Gy exposure on the level of DNA damage, using a well-established alkaline comet assay [116]. This procedure quantifies global radiation DNA damage (single and/or double-strand breaks) in individual cells. From a statistical distribution of comet tail moment with a 300 cells population, an initial distribution of single shot irradiated cells exhibits a shift towards a population of more damaged cells as compared to non-irradiated cells (Fig. 2.12). The fraction of cells with damage above a control tail moment value of 4 exhibited an 8-fold increase over that of the control cells. The recovery of a near homogeneous distribution of low comet tail moments, one hour after the ultrafast irradiation, argues for an efficient repair of the global DNA lesions. The complete reparability of DNA damage triggered by a single femtosecond irradiation shot at 1 Gy is not entirely observed when the same comet assays are performed on carcinoma cell populations submitted to multiple shots irradiations (Fig. 2.12). The initial nuclear DNA damages can be amplified by increasing the dose level delivered by femtosecond electron bunches. Two minutes after a multiple shot irradiation, a significant shift towards high comet tail moments can be progressively observed with the dose level. Compared to control sample (0 Gy) and single shot data at 1 Gy, the distribution of low comet tail moments is not entirely recovered, one hour after the end of multiple

**Fig. 2.12** Distribution of DNA damage induced by an Irradiation of human carcinoma cells (A431 carcinoma cell line) with ultrashort electron bunches (95 MeV). For single or multiple shots configurations, the statistical distribution of DNA damage in function of time delay after an irradiation (2 or 60 min) is expressed from the determination of comet tail moments [116, 117]. Adapted from [10]



shot irradiations at 3.1 and 6.9 Gy for instance. These single and multiple shots studies suggest that repair process of DNA damage in tumor cells are dose dependent and become less efficient when multiple irradiation exposures are performed with ultrafast electron bunches.

In the framework of innovative applications of pulsed radiation sources for medical physics and cancer radiotherapy, ultrafast *in vivo* irradiation in the MeV domain can be achieved by single and multiple shot strategies. Recent investigations performed by different research groups are mainly focalised on integrated cellular responses, using cumulative effects of multiple radiation shots. In this approach, the integrated irradiation time (few minutes) remains very long compare to ultrafast molecular responses such as DNA single-double strand breaks (SSB and DSB respectively) or more generally molecular bond breakings (few hundred femtoseconds) [113–115]. The spatio-temporal radiation processes must be underpinned by advanced biophysical concepts on the impact of native tracks in biologically relevant environments. Some fundamental aspects of spatio-temporal

radiation biomedicine concern the adaptative responses of cells and tissues to clustered DNA damage-repair processes that may take place on the time scale of molecular motion.

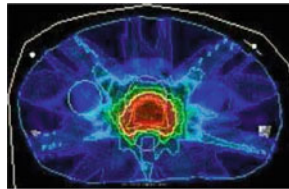
### ***2.4.2 Potential Applications for Pulsed Cancer Therapies***

From a strict biomedical point of view, the progresses of conventional and conformational radiotherapies are highly dependent on innovative developments of radiation source quality. Up to now, X rays and accelerated electron beams in the energy range of 4–25 MeV represent the essential of ionizing radiations currently used for cancer radiotherapy of several millions of patients all over the world. Proton and hadron therapies are still at their emerging stage but they represent very promising methods for the specific treatment of deep tumors and radio-resistant solid cancers [118, 119]. Concerning relativistic particle accelerated by laser-plasma interaction, very high energy electron (VHEE) in the range 150–250 MeV correspond to very penetrating radiation. They would be of interest for new radio-therapeutic approaches, considering the dose deposition profiles and high dose rate delivery. Compared to low energy electron curves ( $E < 20$  MeV) currently used in classical therapy protocols whose penetration depth is below 5 cm, the deposited dose profile of 170 MeV electron is very broad with a maximum around 20 cm of depth path. The potential interest of VHEE for clinical applications is totally dependent on the development of compact laser-plasma accelerators which provide quasi-monoenergetic electron spectrums with high quality and stability of particle beams [120] and an energy spread of 10 % [50, 101]. However, compared to classical dose rate delivery in conventional radiotherapy i.e. 1 Gy/min, 2 Gy per session, the very high dose rate delivered with laser plasma accelerators  $\sim 10^{13}$  Gy  $s^{-1}$  may challenge new concepts for interactive radiotherapy planning, in the framework of multicriteria optimization of fractioned doses and personalized clinical treatments. Up to now, the isodose distributions of very high energy electron beams are investigated, from the spatial point of view, with Monte Carlo calculations (GEANT 4), including electromagnetic, electron and photonuclear processes but also specific parameters of the electron beam: electron beam divergence, energy spectrum of relativistic electrons, cross section of the particle beam at the phantom entrance (aqueous like phantom). The shape of isodose curves is strongly dependent on the initial distribution of electron and multiple scattering collisions in depth. For medical application of pulsed electron bunches in cancer therapy, the control of the integrated dose curve with the depth of the tumor remains essential. The difference between VHEE beams and X-rays or low energy electrons of a few MeV indicates that the dose deposited by VHEE in the tissue depth is higher and remains still efficient after a few tens of centimeters. Reducing the dose deposition before the tumor environment would limit some deleterious radiation effects on health tissue while the presence of a significant dose deposition after tens of centimeters could be beneficial to cure deep cancer tumors of obese patients. Some undeniable

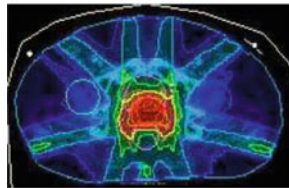
prerequisites such as a well-defined dosimetric characterization have to be realized in tissue-like medium. For instance, some detailed investigation of the macro-dosimetric properties (physical dose) of very high monoenergetic electrons beams (VHEE) in the range of 150–250 MeV have predicted that for parallel and opposed beams, the sharpness of the lateral penumbra is of comparable quality to characteristic values of clinical photon beams [80]. Radially, the dose deposition profile is narrow and longitudinally, the penetration distance of these energetic electrons is higher than for 20 MeV conventional accelerators. The high laser energy conversion into accelerated electrons (10 %) and the control of the interaction parameters may allow, in the future, the optimisation of a tunable electron source adapted for new developments in pulsed radiotherapy, considering specific aspects such as a high dose rate delivery or a short-time control of fractionating protocol. Some predictive comparisons between classical radiation sources and new laser-driven particle accelerators based protocols would be of significant interest before developing preclinical trials. Indeed, in the framework of an approved treatment planning of prostate cancer in with 6 MV photons, detailed comparisons between classical X ray source and 250 MeV electron beam have been performed [121]. Compared to classical irradiation with X-ray photons, the target coverage is the same or even slightly better for VHEE sources (Fig. 2.13). Except for an over-irradiation of the femora, the dose sparing of sensitive structures and organs at risk is improved (up to 19 %) with high energy electron beams. A difference of the two dose distributions shows this more clearly on the lower part of the figure.

Predictive dose simulations permit reasonably to emphasize that electron beams produced with laser plasma accelerators would be well suited for delivering a high dose peaked on the propagation axis, a sharp and narrow transverse penumbra,

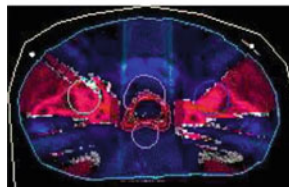
**Fig. 2.13** *Upper part:* calculated transversal dose distributions in human pelvis for laser-accelerated VHEE of 250 MeV, in the framework of a treatment planning. The physical dose distribution shows the same target coverage as 6 MV photons (*middle part*). But the dose sparing of sensitive structures (except for the femurs) is improved with VHEE of 250 MeV, as shown in the difference of the two dose distributions (*lower part*). Adapted from Fuchs et al. [121]



**Dose distribution with VHEE of 250 MeV**



**Dose distribution with Photons of 6 MV**



**Difference between the two dose distributions**

combined with a deep penetration in the human body. However, VHEE produce energetic bremsstrahlung photons around 50 MeV which can, in return, activate the medium. In particular, photons of a few tens of MeV can induce efficiently photo-nuclear reactions, with neutron generation, via Giant Dipole Resonance of nuclei [120]. Additional effects inherent to VHEE, such as neutron contamination, would be also investigated in order to clarify the exact conditions for using ultra-short particle beams during anticancer pulsed radiotherapy protocols.

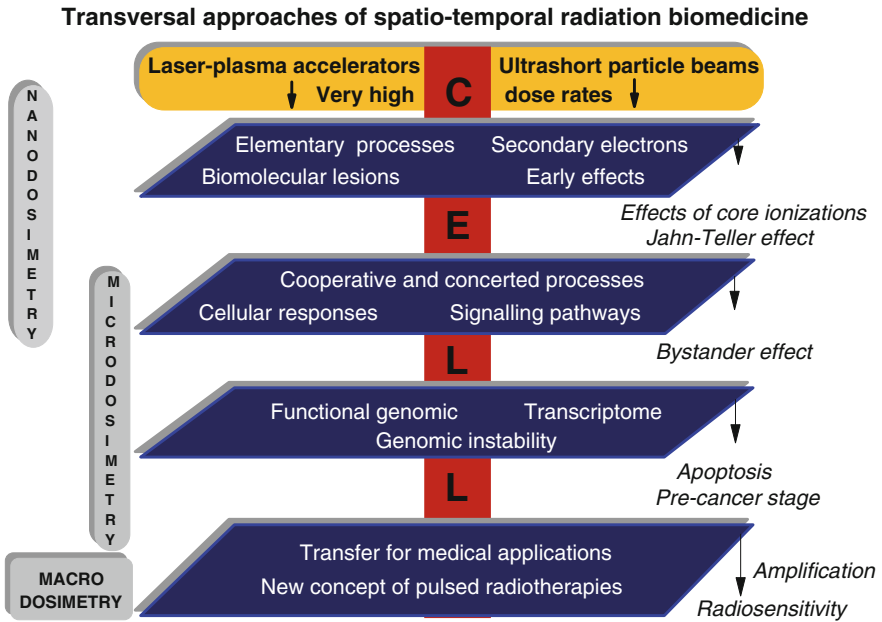
The Gaussian shape of the radial dose profile being dependent on Coulomb scattering effects, the importance of penumbra width during a single shot dose delivery seems crucial to establish a link between the concept of very high dose rate delivery in the range  $10^{12}$ – $10^{13}$  Gy s<sup>-1</sup> and the biomolecular consequence of a local dose fractioning at very short time. They concerns the adaptative responses of cells and tissues to clustered DNA damages-repairs processes, following ultrafast radiation perturbations triggered on the time scale of molecular motion. For a relativistic particle beam, the spatial distribution of primary radical events being dependant on the sub-structure of ionization tracks at the physical core-penumbra interface (Fig. 2.4), well collimated femtosecond electron beams should be useful for the development of spatio-temporal radiation biology and medicine. Significant advances would concern the quantification of an effective biological dose in the prethermal regime of secondary electrons. An extension of these innovating concepts to other pulsed sources such as pulsed X ray and relativistic particles beams (proton and heavy ions for instance) would be of a significant interest for conceiving selective medical treatment plannings [9, 77, 81–83, 93, 102, 122].

## 2.5 Concluding Remarks on Future Challenges

The physics of advanced TW laser plasma accelerators delivering ultrashort high and very high energy electron bunches (50 and 150–200 MeV respectively) open promising perspectives for ultrafast radiation physico-chemistry and biomedicine [9, 19, 38, 41–43, 81, 83, 92, 123, 124]. The specific qualities and properties of short relativistic particle bunches foreshadow the development of advanced researches to deepen our biophysical understanding of early radiation events in native ionization tracks close to complex biomolecular architectures (membranes, nuclear and cytoplasmic environments, intercellular junctions).

Deeply understand the multi-scale mechanism of radiation damage in living matter, starting from the early radical and molecular processes to mutagenic DNA and protein lesions, cell signalling, genomic instability, apoptosis, and microenvironment effects [59, 60, 85, 87, 92, 95, 125, 126], would have, in a near future, many practical consequences like the customization of more predictive and selective radiotherapy protocols. The complex links that exist between the physical aspects of early radiation events and the delayed evolution of biological endpoints,





**Fig. 2.14** Importance of laser-plasma accelerators and ultrashort particle beams for getting significant advances in transversal approaches of spatio-temporal radiation biomedicine. One of the main domains concerns the emerging concept of real-time nanodosimetry. (The Jahn-Teller effect corresponds to a geometrical distortion of non-linear molecules in specific conditions, including vibronic interactions [127]; in a cell, the transcriptome represents the set of different RNA molecules [128])

carcinogenesis or cell survivals need the reinforcement of interdisciplinary researches of advanced spatio-temporal radiation biomedicine (Fig. 2.14).

This interdisciplinary domain would provide guidance for the future development of physical and theoretical researches devoted to nanobiosimetry for radiation cancer therapy and concerns main topics such as: the spatio-temporal description of processes cascade leading to cell DNA damage response (foci formation) and multiple gene amplification following an initial and local energy deposition by radiation; 3D identification of specific biomolecular markers of DNA damages and cell signalling in function of radiation quality (electromagnetic, particle or ion beams, energy and temporal characteristics); biophysical effects of secondary low-energy electrons in the prethermal regime of radiation interactions with living matter; semi-quantum simulations of biomolecular clustered damages in native ionization tracks, taking into account the time-dependent track sub-structure, within the temporal window  $10^{-14}$ – $10^{-11}$  s; the conceptualisation of time-dependent molecular RBE (Relative Biological Effectiveness) for normal and cancerous tissues [86]. These major issues are ubiquitous and concern the different types of radiation characterized either by low (X and  $\gamma$  rays, electron, proton) or high density of ionisation (ions). All the innovating aspects of protontherapy and



hadrontherapy require also a strong synergy between experimental developments performed with ultrashort particle beams and advanced numerical quantum simulations of ultrafast radiation phenomena [72, 129, 130].

One of the most promising developments of future laser-accelerator based HERF researches will concern the real-time investigation of ultrafast nanometric and sub-nanometric biomolecular damages in the prethermal regime of native ionization tracks, considering the presence of short-lived low energy secondary electrons at the frontier of physical core and penumbra zone. The quantum character of very-short lived p-like configuration of excited electron provides a sub-nanometric probe to explore their short-time interactions with bio-molecules and offers the opportunity to characterize the pertinent bio-effect parameters in native ionization tracks. This approach opens the new concept of real-time nanobiodosimetry as a function of the pulsed radiation quality factors [9, 81–84, 91, 100, 102, 130–132], considering the transient sub-structures of ionization tracks. For biomolecular targets whose the size is less than 20 Å at a density of  $1.0 \text{ g cm}^{-3}$ , the corresponding target areal mass will be less than  $1 \times 10^{-6} \text{ g cm}^{-2}$  [133, 134]. The femtosecond electron bunches are more adapted than picosecond proton beams for this new challenge, owing to the fact that these primary bio-effects take place mainly in less than  $10^{-12} \text{ s}$ . Establishing an innovating approach of nanobiodosimetry on the temporal and spatial scales of biomolecular architectures, the laser-plasma accelerators based spatio-temporal radiation biomedicine represents a prerequisite for the control of pulsed radiotherapy of cancerous cells and tissues at very high dose rates.

The modulated response of non-irradiated cell localized in the vicinity of irradiated cells (Bystander effect [126]) represents also a real challenge (see Fig. 2.14) for getting (i) the predictive molecular response to dose delivery profile (biological dose) in normal tissue/cancerous tumor, (ii) the optimized control of ultra-high dose-rate effects in order to reduce the deleterious complications of radiation cancer therapy. The high laser energy conversion into accelerated electrons and the control of the interaction parameters may allow the optimization of a tunable electron source adapted for new developments of pulsed radio-chemotherapy of cancers, considering the specific aspects of a high dose rate delivery, the advanced prodrug and radiosensitizer strategies [106, 107, 134–138] and the complex control of short-time fractionating treatments. These future developments are crucial to fully understand the early biomolecular consequences of ultra-short pulsed radiations performed with laser-driven particle sources and to predict and estimate, at cell and tissue levels, the time-dependence of radiation risks linked to pulsed radiotherapy protocols.

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