Optical control of DNA-base radio-sensitivity

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Purpose: Manipulation of the radio-sensitivity of the nucleotide-base driven by the spin blockade mechanism of diffusive free radicals against ionizing radiation.

Materials and methods: We theoretically propose a mechanism which uses the simultaneous application of circularly polarized light and an external magnetic field to control the polarization of the free radicals and create $S=1$ electron-hole spin excitations (excitons) on nucleotide-base. We deploy an ab-initio molecular dynamics model to calculate the characteristic parameters of the light needed for optical transitions.

Results: As a specific example, we present the numerical results calculated for a Guanine, in the presence of an OH free radical. To increase the radio-resistivity of this system, a blue light source for the optical pumping and induction of excitons on guanine can be used.

Conclusions: The effect of spin-injection on the formation of a free energy barrier in diffusion controlled chemical reaction pathways leads to the control of radiation-induced base damage. The proposed method allows us to manipulate and partially suppress the damage induced by ionizing radiation.

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INTRODUCTION

Ionizing radiation is both hazardous and beneficial to living organisms, and is extensively used for cancer treatment in radiation therapy [1]. A major problem in the application of ionizing radiation to cancer treatment is the protection of normal cells and tissues against unavoidable exposure to radiation during radiation treatment. It is now well understood that the ionization or excitation of the DNA molecules, either directly or indirectly, can lead to DNA single or double strand breaks. As a result, misrepaired DNA molecules can lead to specific genetic aberrations and/or mutations which could cause carcinogenesis in normal cells or lead to fatal damage in normal or cancer cells [2, 3]. It has been shown that low linear-energy-transfer (LET) ionizing radiation creates approximately 1,000 single strand breaks (SSBs) and 40 double strand breaks (DSBs) per gray (1Gy=1J/Kg) in typical mammalian cells [4, 5, 6, 7]. The level of DNA molecular base damage is around 2,500 to 25,000 per Gy in a cell, which is about 2.5 to 25 times the yield of sugar-phosphate induced damage in the DNA backbone [4, 7]. In indirect mechanisms, the water molecules surrounding the DNA molecule which compose 80% of a cell, may be excited by ionizing radiation in form of free radicals, e.g., a charged neutral hydroxyl (OH). The motion of OH-radicals which are randomly produced throughout the cell is governed by diffusion processes. Massive DNA damage can result from a large number of DNA dehydrogenations caused by free radicals. For example, a free radical can diffuse to reach a DNA molecule and remove a hydrogen ion from it to form a water molecule. Detailed studies at the molecular level is necessary to bring the radiation-induced DNA damage under control.

METHOD

In this work, we apply a quantum physical description of molecular interactions to propose a mechanism that could allow the manipulation of DNA radio-sensitivity. In particular the Pauli exclusion principle [8] which prevents two electrons with parallel spin form occupying a single spatial orbital, plays a major role and is used to magnetically manipulate the diffusion of hydroxyl radicals and the OH-DNA relative motion. It has been shown in studies in semiconductor physics and quantum optics that the Pauli exclusion principle can be used to rectify electrical currents passing through weakly coupled quantum dots [11] and to induce ferromagnetic ordering by photo-generated carriers in magnetic semiconductor hetero-structures [12].

A free radical carries an odd number of electrons with an unpaired spin in the outermost open shell. Due to the reduction of the exchange interaction, the pairing of opposite spin electrons in the open shell of the free radical with an electron in a DNA molecule makes free radicals highly reactive. In the process of dehydrogenation of a DNA molecule by free radicals an unpaired hole (a half-empty orbital) is transferred to the DNA. In the absence of spin-orbit coupling and hyperfine interaction the spin of transferred electron is conserved. The electronic ground state of DNA molecule is $S = 0$ spin-singlet (in the absence of an external magnetic field). The OH-radical which contains nine electrons is a doubly degenerate ground state with $S_z = \pm 1/2$, where we have conveniently taken the quantization axis along the $z$-axis. The degeneracy of the ground state can be lifted by applying a weak magnetic field which couples to the electron spin through the Zeeman interaction [5], $E_Z = g\mu_B\vec{S} \cdot \vec{B}$. 

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Here $E_Z$ is the Zeeman energy, $g$ is the electron $g$-factor ($g \approx 2$), $\mu_B$ is the Bohr magneton ($\mu_B \approx 5.8 \times 10^{-5}$ eV/Tesla), and $B$ is the strength of external magnetic field.

In a random interaction of radiation with a biological system the initial direction of OH-radical magnetic moment immediately after its generation is also random. However, by applying a weak external magnetic field ($B_{\text{ext}}$) (which defines the quantization axis) and using a circularly polarized light field parallel to the direction of the light propagation, as shown in Fig. 1a, a molecular transition corresponding to $\Delta J = \pm 1$ can be induced by means of optical pumping [13] of the OH-radicals [14]. Here $J$ denotes the total angular momentum of diatomic OH-radical [15]. Alternatively, techniques such as electron spin resonance (ESR) can be used to achieve strong polarization of free radicals, as recent advances in ESR have demonstrated the capability of detecting the transfer of electron spin polarization between radicals [9][10]. In this case microwaves can be used for the optical transitions. In a similar fashion, by applying a second circularly polarized light field one may excite an electron-hole pair (exciton) in the DNA molecule. Because the circularly polarized light carries angular momentum $\pm 1$, the exciton has a particular spin polarization. Here the spin of exciton is $S = 1$ with polarization along the light propagation direction (because of angular momentum selection rules). Fig. 1 schematically shows the generation of the optically pumped exciton by circularly polarized light. The injection of photo-electrons with the spin out of equilibrium may lead to a dramatic effect in the collective dynamical behavior of DNA-molecules and the interaction with OH-radicals. For example the OH-DNA repulsive magnetic force provides a potential barrier which blocks the diffusion pathway (see Fig. 1b) of OH-radicals toward the DNA-molecules. This is expected to hinder the DNA dehydrogenation and consequently increase the cell radio-resistivity. To verify this hypothesis, an $ab$-initio molecular dynamical model, which is the mathematical formulation that governs the appropriate dynamics of the molecular system [16] is deployed. We have used the Car-Parrinello molecular dynamics (CPMD) [18][19] model, in which the potential energy of the system can be calculated on-the-fly, as needed for the conformations of the dynamical trajectory to simulate the chemical reaction pathways. Because the absorption of a circularly polarized photon alters the local electronic state of a DNA-molecule, we confine our simulation to a particular segment, e.g., only a part of the DNA where the injected exciton is localized and the optical transition takes place. To illustrate this, let us consider a system of interest consisting of a DNA nucleotide base, (e.g., guanine) in the presence of the OH-radical. We assume that a photon with circular polarization interacting with guanine can induce an optical transition in the form of an $S = 1$ exciton. Here we investigate the effect of an exciton produced in this way on the guanine-dehydrogenation pathway, assuming that another photon generated through interactions with ionizing radiation (such as radiotherapy x-rays or cosmic rays) creates a free radical in the vicinity of guanine. Because the local density of free radicals and excitons are large and are comparable, the events described in our calculation can be observed with reasonable probability. We adopt computational parameters and variables needed for the CPMD calculation of the dynamical trajectory of the gas phase nucleotide bases in the presence of OH-radicals following Refs. [17], where the consistency of CPMD results for guanine with other quantum chemistry approaches has been investigated.

RESULTS

We identify the dehydrogenation of the nucleotide bases as a function of their spin multiplicity. The ground and excited states of the nucleotide correspond to spin singlet ($S = 0$), and spin triplet ($S = 1$) states. The latter can be realized through the application of circularly polarized light as discussed above (see Fig. 1). Our CPMD is implemented in a plane-wave basis within local spin density approximation (LSDA) with an energy cutoff of 70 Rydberg (Ry), and with Becke 20 exchange and Lee-Yang-Parr (BLYP) gradient-corrected functional [21]. Norm conserving ultrasoft Vanderbilt pseudo-potentials were used for oxygen, hydrogen, nitrogen and carbon. The CPMD micro-canonical dynamics (constant energy ensemble) were performed after wavefunction optimization following dynamical equilibration at $T=300K$ and re-quenching of the wave-function. An isolated cubic cell of length 13.229 $\AA$ with Poisson solver of Martyna and Tuckerman [22] was used. Our CPMD studies consist of two classes of spin-restricted calculations, as the total spin along the quantum axis is subjected to the constraints $S_z = 1/2$, and $3/2$, corresponding to doublet and quartet spin configurations. In both calculations the initial distance between OH-radical and nucleotide is considered to be about 1.5 $\AA$. We selectively choose an initial coordinate for OH-radical in the neighborhood of the nucleotide where the Hydrogen transfer shows a reactive path in normal state of DNA (the doublet spin configuration in the absence of circularly polarized light and magnetic field).

The initial and final states of the molecules are shown in Figs. 2-4. The final configurations of the molecules have been obtained after 0.6 ps where the rearrangement of the atomic coordinates have been deduced from a dynamical trajectory calculated by CPMD. According to our results, a rapid dehydrogenation of the nucleotides takes place for a system with $S_z = 1/2$ (total spin-doublet) as shown in Fig. 3. This process leads to the formation of a water molecule. In contrast, as shown in Fig. 4 in the quartet spin configuration the repul-
FIG. 1: Schematically shown in (a) the injection of photo-generated electrons in DNA-nucleotides with spin polarization (shown by arrows) along the direction of circularly polarized light and external magnetic field. The net magnetic force between two parallel magnetic moments localized in OH and DNA-nucleotide is repulsive. This is similar to two separated magnetic moments which interact like Heisenberg antiferromagnetic exchange coupling (b).

FIG. 2: Initial state of Guanine molecule in the presence of irradiated induced OH free radical.

FIG. 3: The state of de-hydrogenated Guanine by OH free radical at $t = 0.6$ ps. The polarization state of the system is spin doublet ($S = 1/2$).

(sive exchange interaction, analogous to Heisenberg antiferromagnetic coupling which originates from the Pauli exclusion principle, blocks the exchange of hydrogen and hence the chemical reaction. In Fig. 5 the evolution of the $N_1$ Hydrogen in the guanine and free radical oxygen distance is shown. As it is seen the abstraction of Hydrogen occurs around $t \approx 50$fs in the spin singlet state of guanine, and the injection of $S = 1$ exciton in guanine blocks the hydrogen abstraction. Fig. 6 shows the Kohn-Sham energies (equivalent to potential energy in classical molecular dynamics) of the spin singlet and spin triplet of the Guanine in the presence of the OH free radical as a function of time, calculated by the CPMD at $T=300K$ corresponding to a canonical dynamics (constant temperature ensemble). A drop in Kohn-Sham energy in spin singlet multiplicity is indication of dehydrogenation of $H_{N1}$ in the guanine by OH free radical. To systematically check the convergence of the results, we increased the size of the molecule by adding sugar-phosphate rings to guanine and found that this has no influence on the spin-blocking effect. To estimate the energy needed for the polarization of the nucleotide in the absence of OH-radicals, we calculated the energy of the ground and excited states of the gas-phase nucleotide in spin singlet and triplet multiplicities. For guanine we calculated the spin singlet-spin triplet energy gap $\Delta_0 \equiv E_{\text{triplet}} - E_{\text{singlet}} \approx 2.68$ eV. This
FIG. 4: The state of radio-resistive Guanine at $t = 0.6$ ps. The polarization state of the system is spin quartet ($S = 3/2$) induced by circularly polarized light in the presence of weak magnetic field. Due to injected polarized photo-electrons localized in Guanine, the dehydrogenated Guanine does not form.

provides an estimate for the frequency of the circularly polarized light, which is within the range of the visible spectrum of the electromagnetic waves, $\lambda = 463$ nm (light blue). To calculate the stored magnetic energy due to the optical injection of spin, we calculated the energy of the gas-phase nucleotide in the presence of one OH-free radical with spin doublet and quartet multiplicities. For the molecules shown in Fig. 2, we find the energy gap $\Delta_1 \equiv E_{\text{quartet}} - E_{\text{doublet}} \approx 3.54$ eV. Here the excessive magnetic energy which originated from spin-spin repulsive interactions (which resemble the anti-ferromagnetic exchange interaction in the Heisenberg model) can be deduced to be $\Delta_1 - \Delta_0 \approx 0.86$ eV. This energy can be interpreted as the excessive energy barrier due to the alignment of the spins in the DNA molecule and OH, and is the source of the magnetic repulsive force which makes the diffusion of OH toward DNA-molecules less likely. This is in agreement with the results obtained from CPMD, shown in Figs. 2-4 In addition, by switching the polarization of one of the light sources to the opposite direction, the relative direction of the DNA-OH polarization switches to antiparallel, and hence the magnetic repulsive force changes to an attractive force that lowers the OH diffusion barrier and decreases the radio-sensitivity of the DNA-molecule.

FIG. 5: The evolution of the distances in Angstrom from oxygen atom in the OH radical to the H$_{N1}$ in the guanine as a function of guanine spin multiplicity. The hydrogen abstraction occurs around $t \approx 50$fs in spin singlet state of guanine. The injection of $S = 1$ exciton in guanine blocks the hydrogen abstraction.

FIG. 6: The Kohn-Sham energy as a function of time and spin multiplicity of Guanine, spin triplet (top) and spin singlet (bottom). A drop in Kohn-Sham energy in spin singlet multiplicity is indication of dehydrogenation of H$_{N1}$ in the guanine by OH free radical.

After photon absorption, the nucleotide is spin polarized along the direction determined by the polarization state and the propagation direction of the circularly polarized light. The polarized state of the nucleotide then decays quantum mechanically to its unpolarized ground state either by spontaneous photon emission (electron-hole recombination) or through photon-electron spin decoherence. There are radiative and non-radiative channels that contribute to this process. Since spin-orbit coupling governs one of the decay mechanisms in non-
radiative channel, we use Fermi’s golden rule to estimate the
life-time of the triplet state. It then follows that
\[ \Gamma_{T \rightarrow S} = \frac{(2\pi/\hbar^2)\Omega}{\int k^3/(2\pi)^3 |T[H_{SO}]S|^2 \delta(\omega_0 - \omega)} \]
Here, \( \Gamma_{T \rightarrow S} \) is the transition rate from the spin-
triplet \( T \) to the spin-singlet \( S \) state, \( \Omega \) is the
volume, \( k = 2\pi/\lambda \) is the emitted photon wave-number,
\( H_{SO} = -e/2m^2 c^2 \sum_{i=1}^{\infty} \mathbf{s}_i \cdot (\mathbf{p}_i \times \nabla \Phi_{KS}(\mathbf{r}_i)) \) is the
spin-orbit Hamiltonian, \( m \) is the electron mass, \( c \) is the
speed of light, \( s_i, p_i \) are the spin and momentum of the
ith electron, \( \Phi_{KS} \) is the Kohn-Sham effective
potential, and \( \omega_0 = \Delta_0 / \hbar \). This calculation shows that
\( \tau = \Gamma_{T \rightarrow S}^{-1} \approx 100 \text{ ps} \). However, the electronic relaxed
excitonic states with empirical lifetime of several 100 ps
has been reported recently [23]. The spin-triplet life-
time of nucleotide \( \tau \) turns out to be significantly larger than
the dehydrogenation time scale. It is therefore possible to
increase the radio-resistivity of the DNA molecule within
this time scale through optically pumped spin polarization.
It is important to compare \( \tau \) with other time-scales
in the process. The initial ionization takes place in about
1 fs \((10^{-15} \text{ second})\). The primary free radicals produced
by ejection of electrons have a life time of nearly 100 ps,
and the reported OH radical life-time is about \( 1 \text{ ns} \) \((10^{-9}
\text{ second})\). The electron spin-lattice relaxation time of
the OH radical has been estimated to be approximately
between 0.1 and 0.5 ns in water at room temperature [10].
In order to estimate the technical requirements for the
above described approach one could assume that an aque-
ous solution of DNA will be irradiated with a dose of 1Gy
\((1 \text{ J/Kg})\). It is known [24] that 100eV of absorbed pho-
ton/electron energy produce about 6 OH radicals. There-
fore 1Gy of radiation produce about \( 4 \times 10^{13} \) OH radicals
in 0.1 cm\(^3\) of water. If the number of injected excitons can
be exceeded up to at least ten times, by applying a laser
pump with moderate intensity it is possible to increase
significantly the resistance of DNA-molecules against ir-
radiation. For example at a dose rate of 1.4 Gy/min a
laser pump power of \( P = 10 N_{OH} \hbar \omega_0 / \tau_{tr} \approx 12 \times 10^{-6}
\) watt would be required, which is well within the tech-
nically achievable limits.

CONCLUSION

In conclusion, we have theoretically explored a mecha-
nism which involves the injection of spin polarized ex-
citons in DNA molecules to control and manipulate the
radio-sensitivity of cells by using a circularly polarized
light field and external magnetic field. The mechanism
proposed here is based on the selection rules applica-
tible to optical transitions between energy levels of the
DNA-molecules and optical pumping of the OH-radicals,
and we have employed a microscopic ab-initio molecular
dynamics model to computationally study the dehydro-
genation mechanism at the molecular level. The results
of this study may be used as a guideline to develop new
techniques for radiation therapy and radiation protection
purposes.

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