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Understanding radiation damage on sub-cellular scale using RADAMOL simulation tool

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HIGHLIGHTS

- Review of RADAMOL simulation tool for ionizing radiation action on biomolecules.
- Analysis of DNA radiation damage by electrons, protons and alpha particles.
- Effect of charge migration and scavenger concentration on DNA damage quality.
- Protective effect of DNA binding protein in lac repressor – lac operator complex.

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ABSTRACT

We present an overview of the biophysical model RADAMOL developed as a Monte Carlo simulation tool for physical, physico-chemical and chemical stages of ionizing radiation action. Direct and indirect radiation damage by 10 keV electrons, and protons and alpha particles with energies from 1 MeV up to 30 MeV to a free DNA oligomer or DNA in the complex with lac repressor protein is analyzed. The role of radiation type and energy, oxygen concentration and DNA interaction with proteins on yields and distributions of primary biomolecular damage is demonstrated and discussed.

1. Introduction

Numerous theoretical models and corresponding computer codes have been developed to describe the radiation action on DNA, cells and tissue. To note few of them, the PARTRAC (Friedland et al., 2011; Friedland and Kundrát, 2013; Friedland and Kundrát, 2015) and KURBUC teams (Taleei and Nikjoo, 2013a, 2013b, 2013c) are progressing towards systems biology and DNA damage repair modeling, new studies are available on multiple ionizations and their effect on the chemical stage (Meesungnoen and Jay-Gerin, 2005; Gervais et al., 2006), track characteristics from detailed track structure codes are utilized in radiation therapy planning (Sato et al., 2009, Krämer and Durante, 2010). New models of radiation-induced cell death linked to chromosome aberrations are available, namely the BIANCA model (Ballarini et al., 2014).

Thanks to open source projects such as the Geant4 (Agostinelli et al., 2003) toolkit and its Geant4-DNA part (Incerti et al., 2014; Bernal et al., 2015), tools for modeling of radiation action are now available and accessible for the scientific community to build on. The Geant4 capabilities cover the physical stage as well as the consequent water radiolysis (Karamitros et al., 2014), and there are several publicly available geometrical models of biological target structure that enable scoring of direct DNA damage – from the PDB atomic level description (Delage et al., 2015) to the nucleus level (Dos Santos et al., 2014). The DnaFabric tool provides a visual way to aid in building atomic-level DNA descriptions (Meylan et al., 2016).

The choice of models and algorithms in the mentioned codes reflects the targeted domain of application. The physical stage of radiation action is commonly described using a condensed history approach when the goal is the evaluation of macroscopic observables or using event-by-event track structure codes when the detailed structure of the track has to be taken into account (Nikjoo et al., 2006). Two most common approaches for modeling of the chemical stage are the independent reaction times method (Green et al., 1990; Bluett and Green, 2006) and the random flight method

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(Plante, 2011a, 2011b; Karamitros et al., 2014, Bigildeev and Michalik, 1996).

In this paper, we review the biophysical model RADAMOL developed as a Monte Carlo simulation tool for early stages of radiation action. A human cell is a complex system, with mechanisms still hard to fully encompass in the computer models. The RADAMOL tool targets a simple, better reproducible biological model systems used in studies of initial DNA damage induction by ionizing radiation, such as DNA double helix oligomers and DNA plasmid loops. Radiation damage by 10 keV electrons, and protons and alpha particles with energies up to 30 MeV to a free DNA oligomer or DNA in the complex with lac repressor protein simulated using RADAMOL is presented and the role of radiation type and energy, charge migration, oxygen concentration and DNA interaction with proteins on yields and distributions of primary DNA damage is demonstrated.

2. RADAMOL simulation tool

The RADAMOL (RAdiation DAmage to bioMOLecules) simulation tool developed as a modular code written in ANSI C (Štěpán 2012) is aimed at a detailed description of the biological effects of ionizing radiation on the DNA macromolecule and DNA-protein complexes. RADAMOL has been built up as an extension of the RADACK model of radical attack to biomolecules (Běgusová et al., 2001a, Davídková and Spotheim-Maurizot, 2008). In RADAMOL, the radiation track structure is taken into account, and both the direct and indirect effects of radiation damage are simulated.

The input track structures of ionizing particles in liquid water are obtained by the Monte Carlo code TRIOL (Bigildeev and Michalik, 1996), but can be generated using Geant4 (Incerti et al., 2014) or other code providing event by event simulation of radiation transport. The processes of water radiolysis are described by the STOCHECO code (Michalik et al., 1998). The DIRADACK and RADACK (Běgusová et al., 2003) codes are used for modeling of the unscavengeable and scavengeable DNA damage respectively.

RADAMOL uses a static, atomic-level description of the target molecules. The position and element type for every atom in the target structure is read from a PDB format data file. The water molecules and ions surrounding the target are not explicitly taken into account. Conformations of DNA oligomers, proteins, and DNA-protein complexes are obtained using molecular dynamics computations or from crystallography and nuclear magnetic resonance experiments. Molecular conformations for many structures are available from the RCSB Protein Data Bank (http://www.pdb.org).

In the prechemical stage, the energy deposition events in bulk water are converted to the corresponding chemical products. Each ionization event is replaced by H_2O^+ cation. Electrons with sub-excitation energy are recorded as localized. Two pathways are taken into account for excitations. In the case of A^1B_1 excitations, 50% lead to the OH• + H• dissociation. The B^1A_1 excitation leads a to OH• + H• or to H_2 + O• dissociation with the probabilities of 37% and 25%, respectively. The Rydberg states Ry(A+B) and Ry(C+D) and diffusion band superexcitations lead to autoionizations. The electron thermalization, geminate recombination of e^- with geminate water molecule H_2O^+ and fast ion-molecular reaction $H_2O^+ + H_2O \rightarrow H_3O^+ + OH•$ are modeled at the end of the prechemical stage (Michalik et al., 1998).

The chemical stage simulation starts from the initial spatial distribution of species produced during the prechemical stage. The diffusion motion, chemical reactions between explicitly followed species, reactions of chemical species with oxygen and scavengers and reactions of chemical species with the molecular target are modeled. The stochastic code STOCHECO (Michalik et al., 1998) describes the time-space evolution of charged particle tracks from 10^{-12} up to a defined end time, usually 10^{-6} s.

Fig. 1 illustrates the time-space evolution of 2 MeV alpha particle track and the production of primary radiation damage in free DNA and in the complex with lac repressor protein simulated by RADAMOL. At 1 ps, water cations and free radicals are formed within the particle track. Solvated electrons are formed by the polarization of several water molecules around the previously thermalized secondary electrons and are therefore located further from the track core due to the mean thermalization distance of 24.5 nm (Michalik et al., 1998).

The radiolytic species produced by the ionizations and dissociation of excited water molecules diffuse and undergo mutual chemical reactions. The random flight method is applied to simulate the chemical reactions and diffusion motion of all radiolytic species e_{aq}^-, OH•, H•, O^-, H_2, H_3O^+, H_2O_2, OH^-, O^-, O_2^-, HO_2•, and HO_2^-. The STOCHECO module of the RADAMOL code explicitly models 21 chemical reactions between radiolytic species and molecular products. The three most important reactions with dissolved oxygen $e_{aq}^- + O_2 \rightarrow O_2^-$•, H• + $O_2 \rightarrow HO_2$• and $O^- + O_2 \rightarrow O_3^-$ and the reactions with radical scavengers are also included in the list of possible chemical reactions. The radiation chemical yields of radical species and molecular products are followed as a function of time (see Fig. 2).

A chemical reaction takes place whenever two chemical species approach within corresponding reaction distance, and reactants are replaced by the products of the reaction. The reaction distance for species A and B is calculated as $r_{A,B}=k/[4N_A(D_A + D_B)]$, where k is the rate constant of the reaction, N_A is the Avogadro number; D_A and D_B are diffusion constants of the participating species. Chemical reactions of free radicals with the DNA or proteins are evaluated in a similar way. The OH•, e_{aq}^- or H• can react with an atom accessible from the solvent if there exists a corresponding reaction pathway, like the H atom abstraction or addition to π bonds of heterocycles by OH• radicals, or the e_{aq}^- and H• addition to aromatic cycles of bases and amino acids, and if the radical approaches closer than the sum of Van der Waals radii of both reactants and the reaction distance (Běgusová et al., 2003).

For scoring of the DNA damage, we consider that a radical attack to deoxyribose moieties leads to a strand break, single (SSB) or double strand break (DSB). All reactions with the bases are assumed to produce modified bases (MB). If several damages are formed within a 10 base pair distance, they are classified as complex damage involving DSB (CDSB) or other complex damage (OCD). In the case of proteins, radical attacks to individual amino acids are scored.

3. Applications of the RADAMOL code

The observable cellular response to a radiation exposure is a consequence of the primary damage of cell components, namely the chromosomal DNA. The main goal of biophysical modeling is to provide information about yields and complexity of DNA damage. Up to now, the RADAMOL code has been applied to a 100 base pair DNA oligomer. The yields of simple and complex DNA damages predicted for protons and alpha particles are presented in Fig. 3. The particle tracks were obtained using the TRIOL and Geant4 codes. The calculated primary yields of DNA damages are consistent for both simulations tools, which confirm the usability of the RADAMOL code with different simulation tool of radiation transport. The following text is divided into several sections related to different applications of the RADAMOL code.

3.1. Indirect effect of ionizing radiation

The biological efficiency of ionizing radiation is governed by the

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