Journal of Computational Physics 274 (2014) 841–882

Contents lists available at ScienceDirect

Journal of Computational Physics

www.elsevier.com/locate/jcp

Diffusion-controlled reactions modeling in Geant4-DNA ☆

M. Karamitros [a,b,*], S. Luan [c], M.A. Bernal [d], J. Allison [e], G. Baldacchino [f,g], M. Davidkova [h], Z. Francis [i], W. Friedland [j], V. Ivantchenko [k,e], A. Ivantchenko [e], A. Mantero [l], P. Nieminem [m], G. Santin [m], H.N. Tran [n], V. Stepan [a,h], S. Incerti [a,1]

[a] CNRS, IN2P3, CENBG, UMR 5797, F-33170 Gradignan, France
[b] CNRS, INCIA, UMR 5287, F-33400 Talence, France
[c] University of New Mexico, Department of Computer Science, Albuquerque, NM, USA
[d] Instituto de Física Gleb Wataghin, Universidade Estadual de Campinas, SP, Brazil
[e] Geant4 Associates International Ltd, United Kingdom
[f] CEA Saclay, IRAMIS, LIDYL, Radiation Physical Chemistry Group, F-91191 Gif sur Yvette Cedex, France
[g] CNRS, UMR3299, SIS2M, F-91191 Gif sur Yvette Cedex, France
[h] Nuclear Physics Institute of the ASCR, Prague, Czech Republic
[i] Saint Joseph University, Faculty of Sciences, Department of Physics, Mkalles, Beirut, Lebanon
[j] Helmholtz Zentrum München, German Research Center for Environmental Health, Institute of Radiation Protection, Ingolstädter Landstr. 1, 85764 Neuherberg, Germany
[k] Ecoanalytica, 119899 Moscow, Russia
[l] SwHaRD s.r.l., via Buccari 9, 16153 Genova, Italy
[m] ESA-ESTEC, 2200 AG Noordwijk, The Netherlands
[n] Division of Nuclear Physics & Faculty of Applied Sciences, Ton Duc Thang University, Tan Phong Ward, District 7, Ho Chi Minh City, Vietnam

ARTICLE INFO

Article history:
Received 26 July 2013
Received in revised form 3 June 2014
Accepted 9 June 2014
Available online 17 June 2014

Keywords:
Chemical kinetics simulation
Radiation chemistry
Fokker–Planck equation
Smoluchowski diffusion equation
Brownian bridge
Dynamical time steps
k–d tree
Radiolysis
Radiobiology
Geant4-DNA
Brownian dynamics

ABSTRACT

Context Under irradiation, a biological system undergoes a cascade of chemical reactions that can lead to an alteration of its normal operation. There are different types of radiation and many competing reactions. As a result the kinetics of chemical species is extremely complex. The simulation becomes then a powerful tool which, by describing the basic principles of chemical reactions, can reveal the dynamics of the macroscopic system.
To understand the dynamics of biological systems under radiation, since the 80s there have been on-going efforts carried out by several research groups to establish a mechanistic model that consists in describing all the physical, chemical and biological phenomena following the irradiation of single cells. This approach is generally divided into a succession of stages that follow each other in time: (1) the physical stage, where the ionizing particles interact directly with the biological material; (2) the physico-chemical stage, where the targeted molecules release their energy by dissociating, creating new chemical species; (3) the chemical stage, where the new chemical species interact with each other or with the biomolecules; (4) the biological stage, where the repairing mechanisms of the cell come into play. This article focuses on the modeling of the chemical stage.
Method This article presents a general method of speeding-up chemical reaction simulations in fluids based on the Smoluchowski equation and Monte-Carlo methods, where all molecules are explicitly simulated and the solvent is treated as a continuum. The model describes diffusion-controlled reactions. This method has been implemented in Geant4-DNA. The keys to the new algorithm include: (1) the combination of a method to compute time steps dynamically with a Brownian bridge process to account for chemical

☆ On the behalf of the Geant4-DNA collaboration.

* Corresponding author at: CNRS, IN2P3, CENBG, UMR 5797, F-33170 Gradignan, France.
E-mail addresses: matkara@gmail.com (M. Karamitros), incerti@cenbg.in2p3.fr (S. Incerti).

[1] Project coordinator.

http://dx.doi.org/10.1016/j.jcp.2014.06.011

reactions, which avoids costly fixed time step simulations; (2) a k–d tree data structure for quickly locating, for a given molecule, its closest reactants. The performance advantage is presented in terms of complexity, and the accuracy of the new algorithm is demonstrated by simulating radiation chemistry in the context of the Geant4-DNA project.

Application The time-dependent radiolytic yields of the main chemical species formed after irradiation are computed for incident protons at different energies (from 50 MeV to 500 keV). Both the time-evolution and energy dependency of the yields are discussed. The evolution, at one microsecond, of the yields of hydroxyls and solvated electrons with respect to the linear energy transfer is compared to theoretical and experimental data. According to our results, at high linear energy transfer, modeling radiation chemistry in the trading compartment representation might be adopted.

1. Introduction

1.1. Context

A major challenge in radiobiology is the understanding and prediction of the consequences of interactions between ionizing particles and biomolecules. When penetrating into biological materials, ionizing radiation changes the electronic properties of the targeted biomolecules and initiates a cascade of chemical reactions, which are known to contribute significantly to cell death [1], genetic mutations and carcinogenesis. The quantitative understanding of the relation between these microscopic interactions and the macroscopic observables will have a major impact on biology and health science. However, the kinetics of these chemical reactions can become extremely complex. Indeed, not only are simultaneous and competitive reactions possible, but also the initial concentrations of chemical species strongly depend on the quality and type of the incident radiation.

Even in recent and well designed radiation chemistry experiments dedicated to the study of the kinetics of elementary chemical reactions, it can be difficult to measure the impact of simultaneous side reactions on the observables [2]. In this context, the use of a simulation toolkit, by diving into the heart of both the elementary physical interactions of radiation with biological materials and the elementary mechanisms of chemical reactions, can reveal complex dynamics of macroscopic observables such as time-dependent local concentrations of the different chemical species, or changes inflicted on DNA molecules.

Recent efforts [3–5] try to reproduce such dynamics using numerical techniques. These simulations are sliced into different stages that follow each other in time. They start with the fastest events where the ionizing particles, by interacting with biological materials, such as DNA, yield to the initial and direct modifications of the material. This first stage is called the “physical” stage. Second, the targeted molecules release their energy by dissociating, creating new chemical species; this is the so-called “physico-chemical” stage. This stage lasts up to approximately 1 picosecond. Third, from 1 picosecond to 1 microsecond, in the “chemical stage”, the new chemical species interact with each other, or with the biomolecules already in the cell, leading to indirect alterations of the cellular material. Finally, the cellular repair mechanisms start fixing the biological damage. This paper describes contributions to the chemical stage of simulation.

1.2. Towards the modeling of biology and radiobiology at the cellular level

1.2.1. Databases and models

Since the late 20th century, much effort has been made to model the behavior of biological systems. Pioneering studies combining experimental data with quantitative modeling have emerged to help understanding both the chemical networks of single cells and the chemical and mechanical interactions of cellular networks [6–9]. However, whole-cell simulation is still a challenge for computational biology in the 21st century [10]. The use, by emerging software, of standard format(s) describing biological processes is the key to interchanging data, software coherence, compatibility and development. In this context, standardized models and databases are being discussed and built.

A database for biological models, called BioModels, is already available. This database handles standard formats for representing chemical reactions and models (Systems Biology Markup Language[2] and Cell Markup Language[3]) and biological pathways (BioPAX[4]). Among them, the Systems Biology Markup Language (SBML) is a standard format based on XML whose goal is to describe computational models for biological processes. It was also recently extended to describe geometries.

[2] http://sbml.org.
[3] http://www.cellml.org.
[4] http://www.biopax.org.