Computer Physics Communications 185 (2014) 697–707

Contents lists available at ScienceDirect

Computer Physics Communications

journal homepage: www.elsevier.com/locate/cpc

Calculations of distance distributions and probabilities of binding by ligands between parallel plane membranes comprising receptors

Ianik Plante [a,*], Luc Devroye [b], Francis A. Cucinotta [c]

[a] Division of Space Life Sciences, Universities Space Research Association, 3600 Bay Area Boulevard, Houston, TX 77058, USA
[b] School of Computer Science, McGill University, 3480 University Street, Montreal H3A 0E9, Canada
[c] Department of Health Physics and Medical Diagnostics, University of Nevada Las Vegas, Las Vegas, NV 89154, USA

ARTICLE INFO

Article history:
Received 6 December 2012
Received in revised form
6 September 2013
Accepted 17 September 2013
Available online 26 September 2013

Keywords:
Green's functions
Diffusion equation
Brownian dynamics algorithm
Monte Carlo simulations
Cell signaling
Non-targeted effects of radiation

ABSTRACT

Cell communication through biochemical signaling pathways is a key determinant of tissue responses to radiation. Several molecules, such as the transforming growth factor β (TGFβ), are implicated in radiation-induced signaling between cells. Brownian Dynamics (BD) algorithms have recently been used to simulate the interaction of ligands with receptors and to elucidate signal transduction and autocrine loops in ligand–receptors systems. In this paper, we discuss the simulation of particle diffusion and binding kinetics in a space bounded by two parallel plane membranes, using an exact algorithm to sample the propagator (Green's function) of a particle located between 2 membranes. We also show that the simulation results are independent of the number of time steps used, in accordance with time discretization equations. These simulations could be used to simulate the motion and binding of ligand molecules in a cell culture, and possibly in neuronal synapses.

1. Introduction

Many experiments have shown that cells may respond both collectively and individually to radiation [1,2] and that non-irradiated cells may be affected through signaling by those directly damaged by radiation [3]. Regarding this, non-targeted effects (NTE) refer to effects observed in cells not traversed by radiation, including in the progeny of cells many generations after exposure. A great number of NTEs have been observed, such as micronuclei formation, mutations, reduction in clonogenic survival, and apoptosis (reviewed in [4]). The mechanisms of NTE are poorly understood but several molecules such as the transforming growth factor (TGF-β) [5], reactive oxygen species (ROS) [6], NO$^{\cdot}$ radical [7], and membrane-bound NADPH oxidases [8] have been shown to be implicated in radiation-induced cell signaling. In particular, TGF-β is of great interest in radiobiology. This molecule is secreted by cells in an inactive or latent form, denoted as LTGF-β [9]. Latent TGF-β can be activated by many factors, notably by the $^{\cdot}$OH radicals produced by ionizing radiation [10]. After activation, TGF-β binds to membrane receptors and initiates a cascade of signaling events mediated by the Smad proteins [11]. Activated TGF-β has several effects on cells and is known to mediate cellular response to DNA damage [12] and to suppress apoptosis in irradiated cell cultures [5].

To investigate the mechanisms of cell signaling, computational models have been developed and applied to simulate the interaction between the epidermal growth factor (EGF) and its receptor (EFGR) in cell cultures [13–16]. These simulations use stochastic Brownian Dynamics (BD) algorithms to characterize the spatial range of secreted ligands and to discriminate the roles of autocrine and paracrine actions of ligands in cell culture. In a recent paper [17], we have developed exact BD algorithms based on analytical Green's functions of the diffusion equation (DE) to simulate the Brownian motion of a particle near a plane membrane with bound receptors and initiation of signal transduction by the ligand–receptor complex. In this paper, we present algorithms to sample the Green's functions of the DE of the Brownian motion of a molecule located between two parallel planes with receptors, which may be representative of cell cultures and possibly neuronal synapses. The algorithms have several advantages over those used in similar calculations [13], they are: (1) able to reproduce the exact distribution of particles predicted by the Green's functions for this problem; (2) efficient regarding computational speed and cost, and (3) can be used for any value of time step or position of a particle. Importantly, the time step does not need to be smaller when the particle is near the absorbing membrane. As in our previous paper [17], the Green's functions are presented first. Then,

* Correspondence to: NASA Johnson Space Center, 2101 NASA Parkway, Mail Code SK, Houston TX 77058, USA. Tel.: +1 281 244 6426; fax: +1 281 483 3058.
E-mail addresses: ianik.plante-1@nasa.gov (I. Plante), lucdevroye@gmail.com (L. Devroye), Francis.Cucinotta@unlv.edu (F.A. Cucinotta).

0010-4655/$ – see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.cpc.2013.09.011

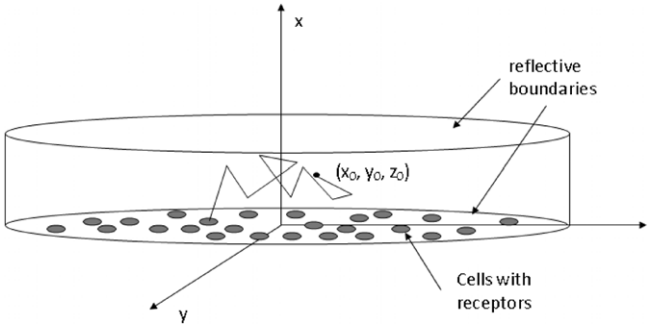

Fig. 1. 3D representation of ligand molecules in a cell culture. The cells are located at the bottom of the dish. A ligand initially at position (x_0, y_0, z_0) diffuses until it binds to a cell receptor.

we provide the time discretization equations and the sampling algorithms of the Green's functions. Finally, we present the results from our simulations and discuss how these simulations could be used to link radiation track structure models with existing DNA repair models to improve our understanding of the radiation risks.

2. Mathematical description

2.1. Description of the system

A ligand molecule is considered to be a particle located between two parallel membranes, that are described by the equations $x = 0$ and $x = L$ in Cartesian coordinates. The particle may diffuse freely in the directions Y and Z (i.e. no boundaries). This is illustrated in Fig. 1.

The trajectories of particles are obtained by randomly sampling the Green's function [18] of the diffusion equation (DE) in 3D:

$$\frac{\partial p(x, y, z, t \mid x_0, y_0, z_0)}{\partial t} = D\nabla^2 p(x, y, z, t \mid x_0, y_0, z_0), \tag{1}$$

where D is the diffusion coefficient, (x_0, y_0, z_0) is the initial position of the particle, (x, y, z) is a position in space, $p(x, y, z, t \mid x_0, y_0, z_0)$ is the Green's function of the DE (also called the *Brownian propagator*), t is the time and ∇^2 is the Laplacian. The initial condition is $p(x, y, z, t = 0 \mid x_0, y_0, z_0) = \delta(x - x_0)\delta(y - y_0)\delta(z - z_0)$, where $\delta(x)$ is the Dirac's delta function. In our system, $p(x, y, z, t \mid x_0, y_0, z_0)$ can be written as [19]:

$$p(x, y, z, t \mid x_0, y_0, z_0) = p_x(x, t \mid x_0)p_y(y, t \mid y_0)p_z(z, t \mid z_0), \tag{2}$$

where $p_x(x, t \mid x_0)$, $p_y(y, t \mid y_0)$ and $p_z(z, t \mid z_0)$ are solutions of their respective 1D diffusion equations:

$$\frac{\partial p_x(x, t \mid x_0)}{\partial t} = D\frac{\partial^2}{\partial x^2}p_x(x, t \mid x_0), \tag{3a}$$

$$\frac{\partial p_y(y, t \mid y_0)}{\partial t} = D\frac{\partial^2}{\partial y^2}p_y(y, t \mid y_0), \tag{3b}$$

$$\frac{\partial p_z(z, t \mid z_0)}{\partial t} = D\frac{\partial^2}{\partial z^2}p_z(z, t \mid z_0). \tag{3c}$$

Since the boundary conditions in the direction Y are $p_y(y \to \infty, t \mid y_0) \to 0$ and $p_y(y \to -\infty, t \mid y_0) \to 0$, and similar boundary conditions apply in the direction Z, $p_y(y, t \mid y_0)$ and $p_z(z, t \mid z_0)$ are Gaussian functions with variance $\sigma^2 = 2Dt$ and mean $\mu = y_0$ and $\mu = z_0$:

$$p_y(y, t \mid y_0) = \frac{1}{\sqrt{4\pi Dt}} \exp\left[-(y - y_0)^2/4Dt\right], \tag{4a}$$

$$p_z(z, t \mid z_0) = \frac{1}{\sqrt{4\pi Dt}} \exp\left[-(z - z_0)^2/4Dt\right]. \tag{4b}$$

As the diffusion in the directions Y and Z is independent from the diffusion in the direction X, only $p_x(x, t \mid x_0)$ is considered in the following discussion. In this paper, we considered two cases: (1) two reflecting membranes (at $x = 0$ and $x = L$) and (2) partially absorbing membrane at $x = 0$ and reflecting membrane at $x = L$.

2.2. Two reflecting plane membranes

The boundary conditions for a particle located between reflective membranes at $x = 0$ and $x = L$ are written as:

$$D\left.\frac{\partial p_x(x, t \mid x_0)}{\partial x}\right|_{x=0} = 0, \tag{5a}$$

$$D\left.\frac{\partial p_x(x, t \mid x_0)}{\partial x}\right|_{x=L} = 0. \tag{5b}$$

2.2.1. Green's function

The Green's function of the DE for the system with the boundary conditions given by Eq. (5) is [18,19]:

$$\begin{aligned} p_x(x, t \mid x_0) &= \frac{1}{L}\left(1 + 2\sum_{n=1}^{\infty} e^{-\pi^2 n^2 Dt/L^2} \cos\frac{n\pi x}{L}\cos\frac{n\pi x_0}{L}\right) \\ &\equiv \frac{1}{L}\sum_{n=-\infty}^{\infty} e^{-\pi^2 n^2 Dt/L^2} \cos\frac{n\pi x}{L}\cos\frac{n\pi x_0}{L}. \end{aligned} \tag{6}$$

This function is complicated by the presence of an infinite sum and may converge slowly for small values of t. It can be written in an equivalent form by using the Jacobi theta function

$$\theta(x) = \sum_{n=-\infty}^{\infty} \exp(-n^2\pi x), \quad x > 0. \tag{7}$$

This function has the remarkable property that $\sqrt{x}\theta(x) = \theta(1/x)$, which follows from the Poisson summation formula. In particular, Jacobi's theta function identity can be written:

$$\begin{aligned} &\frac{1}{\sqrt{\pi x}}\sum_{n=-\infty}^{\infty} \exp\left[-\frac{(n + y)^2}{x}\right] \\ &= \sum_{n=-\infty}^{\infty} \cos(2\pi ny)\exp(-n^2\pi x), \quad y \in \Re,\ x > 0. \end{aligned} \tag{8}$$

Using trigonometric identities, Eq. (6) can be written as:

$$\begin{aligned} p_x(x, t \mid x_0) = \frac{1}{L}\sum_{n=-\infty}^{\infty} &e^{-\pi^2 n^2 Dt/L^2} \\ &\times \left[\cos\frac{2\pi n(x + x_0)}{2L} + \cos\frac{2\pi n(x - x_0)}{2L}\right]. \end{aligned} \tag{9}$$

The application of Jacobi's theta function identity on Eq. (9) yields:

$$\begin{aligned} &p_x(x, t \mid x_0) \\ &= \frac{1}{\sqrt{4\pi Dt}}\sum_{n=-\infty}^{\infty}\left[e^{-(x-x_0-2nL)^2/4Dt} + e^{-(x+x_0-2nL)^2/4Dt}\right]. \end{aligned} \tag{10}$$

Therefore, $p_x(x, t \mid x_0)$ can also be expressed as an infinite sum of Gaussian functions.