Journal of Computational Physics 340 (2017) 617–638

Contents lists available at ScienceDirect

Journal of Computational Physics

www.elsevier.com/locate/jcp

Multiscale models and stochastic simulation methods for computing rare but key binding events in cell biology ☆

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ARTICLE INFO

Article history:
Received 8 January 2017
Accepted 27 March 2017
Available online 7 April 2017

Keywords:
Multiscale modeling
Reaction–diffusion PDEs
Stochastic simulations
Mass-action laws
Markov chain
Computational neurobiology

ABSTRACT

The main difficulty in simulating diffusion processes at a molecular level in cell microdomains is due to the multiple scales involving nano- to micrometers. Few to many particles have to be simulated and simultaneously tracked while there are exploring a large portion of the space for binding small targets, such as buffers or active sites. Bridging the small and large spatial scales is achieved by rare events representing Brownian particles finding small targets and characterized by long-time distribution. These rare events are the bottleneck of numerical simulations. A naive stochastic simulation requires running many Brownian particles together, which is computationally greedy and inefficient. Solving the associated partial differential equations is also difficult due to the time dependent boundary conditions, narrow passages and mixed boundary conditions at small windows. We present here two reduced modeling approaches for a fast computation of diffusing fluxes in microdomains. The first approach is based on a Markov mass-action law equations coupled to a Markov chain. The second is a Gillespie's method based on the narrow escape theory for coarse-graining the geometry of the domain into Poissonian rates. The main application concerns diffusion in cellular biology, where we compute as an example the distribution of arrival times of calcium ions to small hidden targets to trigger vesicular release.

1. Introduction

Stochastic simulations of many Brownian particles are routinely used to predict how cellular responses are triggered from molecular events. Computing statistics of chemical reactions provide usually a complementary and fundamental insights into cellular processes, that cannot be necessarily resolved by live cell microscopy imaging, especially at the nanometer resolution. Running a simulation is however limited by small binding targets in an often sparse geometry containing a large bulk, narrow passages and hidden targets [1]. In that context long time simulations are expected, but they are necessary to compute any statistical quantities of interest. Naive simulations consist in following all Brownian particles [2], but this approach is in general inefficient and leads to heavy computational time. Several efforts were developed for simulating chemical reactions based on sampling discrete events from continuous ensemble in simplified geometries [3–6]. These approaches avoid simulating large number of particles in an infinite space and are based on numerical conservation laws for the appearance

☆ This research was supported by a Marie Curie Award.
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http://dx.doi.org/10.1016/j.jcp.2017.03.058
0021-9991/

and disappearance of particles computing at each time step. A key ingredient in these models is the probability density function of stochastic particles at an artificial boundary separating the continuum and the discrete description.

We present here two methods to study stochastic chemical reactions that involve small and large numbers of molecules. In the first approach, we shall replace the Fokker–Planck system of partial differential equations for the joint probability of the location and the chemical state distribution by a Markov chain that represents the coarse-grained mass-action law. This approach simplifies the model of molecular binding [7], which cannot be resolved analytically. This system consists in coupled diffusion–reaction equations with small targets and time dependent boundary conditions. We shall replace this system by mass-action law equations coupled to a Markov chain as described above. This new simplified model accounts for the transition from the continuous to the discrete level, where a finite number of particles activate an ensemble of small targets to trigger a cellular event. We also discuss a second method which consists in coarse-graining a particle stochastic simulations by a Poissonian rate model, using the narrow escape theory [8–11]. To coarse-grain Brownian trajectories into Gillespie's simulations, we will define and compute rates from the narrow escape theory (NET) [11,12], where the arrival rate of a Brownian particle to a small target is well approximated by a Poissonian distribution.

We apply these two approaches to compute efficiently the distribution of the release times of a vesicle in the pre-synaptic terminal of a neuronal cell. This process called vesicular release, involves tracking ions until they bind to targets positioned underneath balls located on the surface membrane. We recall the physiological context: following the propagation of an action potential [13], hundreds of ions enter the synaptic domain of a neuronal cell. For the past 20 years, a large modeling effort to understand vesicular release led to Monte Carlo algorithms [14–17] that follow individual particles. Other simulations use reaction–diffusion of discrete molecules in complex spatial environments [18]. The stochastic opening kinetics of the Voltage-Gated-Calcium-Channel (VGCCs) are the main contributor to the variability observed in the release probability [18]. An other mathematical modeling study [19] predicted that a certain type of calcium channel (CaV2.2) can create calcium nanodomains, that can activate a calcium-fusion sensor located on the proximal face of synaptic vesicles.

The biological consequences of the present results were announced in a recent brief communication [20] and we provide here the mathematical details and modeling approach. The paper is organized as follows: first, we present the continuum model based on reaction–diffusion equations for the dynamic of particles. We describe the model and its limitations that prevented us to use it. In the next sections, we develop two reduced models. The first one is a Markov model coupled to a system of mass-action law equations, and the second is the Gillespie approach, where we derived the on-rates from the biophysical modeling of calcium dynamics in neuronal cells. Finally, we compare the numerical results given by the two models that are in good agreement for the problem of vesicular release. The present approach is generic and can be applied to extract statistics of stochastic bindings in a confined domain that contains both large and small scales.

2. Multi-scale model of diffusing ions in cellular microdomains

Although multi-scale modeling of diffusing particles is generic in cell biology, we shall focus here on a specific example to build coarse-grained models. This example concerns the dynamic of calcium ions in the pre-synaptic terminal of neuronal cells that we will describe now.

2.1. Modeling calcium ion dynamic in the pre-synaptic terminal of a neuronal cell

The pre-synaptic terminal of a neuron contains vesicles that are released following an action potential, but the exact pathway and underlying molecular mechanisms are still under investigation. The molecular processes involved in vesicular release start after an action potential has triggered the opening of voltage-gated calcium channels (VGCCs), followed by calcium influx into the pre-synaptic domain. When several diffusing ions have succeeded to find small molecular targets, such as synaptotagmin located underneath a vesicle, a complex molecular machinery is activated leading to vesicular fusion with the cell membrane and neurotransmitters release [21]. Calcium ions can also bind and unbind to buffer molecules located in the bulk of the pre-synaptic terminal. Finally, they can be extruded through small pumps located on the surface of the domain or can exit at the end of the terminal, although this process is not completely documented. The success of the process where calcium ions find the target molecules by diffusion, depends also on the relative position between vesicles and calcium channels and on their organization on the surface [22–24]. We model the pre-synaptic terminal geometry as a sphere (head) smoothly connected to a short cylinder (neck) (Fig. 1A). Vesicles are located in a region called the Active Zone (AZ), a small surface of the domain boundary that contains VGCCs, that can be distributed uniformly or form clusters. Calcium ions entering through VGCCs are modeled as Brownian particles. The terminal also contains calcium buffer molecules and pumps, modeled as spherical binding sites located respectively inside the head and at the boundary.

All ions, called here particles, exit the domain when they are extruded through pumps or when they reach the end of the neck. Upon hitting a pump, a particle is absorbed during an extrusion time τ_{pump}, during which the pump is deactivated [2]. To trigger vesicular fusion, we assume that four to six calcium ions need to find the small target located at the junction between the vesicle, modeled as a sphere, and the surface membrane. This molecular target is represented by a small ribbon of height ε, located underneath the vesicle, which defines a geometrical cusp (Fig. 1B). After vesicular fusion, calcium ions previously bound to the target are released into the bulk.

The central question that motivates this analysis and stochastic simulations is the following: how to compute the release probability of a vesicle and the distribution of release events following an AP? And how does this process depend on key