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Spatial modeling of dimerization reaction dynamics in the plasma membrane: Monte Carlo vs. continuum differential equations

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Abstract

Bimolecular reactions in the plasma membrane, such as receptor dimerization, are a key signaling step for many signaling systems. For receptors to dimerize, they must first diffuse until a collision happens, upon which a dimerization reaction may occur. Therefore, study of the dynamics of cell signaling on the membrane may require the use of a spatial modeling framework. Despite the availability of spatial simulation methods, e.g., stochastic spatial Monte Carlo (MC) simulation and partial differential equation (PDE) based approaches, many biological models invoke well-mixed assumptions without completely evaluating the importance of spatial organization. Whether one is to utilize a spatial or non-spatial simulation framework is therefore an important decision. In order to evaluate the importance of spatial effects a priori, i.e., without performing simulations, we have assessed the applicability of a dimensionless number, known as second Damköhler number (*Da*), defined here as the ratio of time scales of collision and reaction, for 2-dimensional bimolecular reactions. Our study shows that dimerization reactions in the plasma membrane with $Da \sim > 0.1$ (tested in the receptor density range of 10^2–$10^5/\mu m^2$) require spatial modeling. We also evaluated the effective reaction rate constants of MC and simple deterministic PDEs. Our simulations show that the effective reaction rate constant decreases with time due to time dependent changes in the spatial distribution of receptors. As a result, the effective reaction rate constant of simple PDEs can differ from that of MC by up to two orders of magnitude. Furthermore, we show that the fluctuations in the number of copies of signaling proteins (noise) may also depend on the diffusion properties of the system. Finally, we used the spatial MC model to explore the effect of plasma membrane heterogeneities, such as receptor localization and reduced diffusivity, on the dimerization rate. Interestingly, our simulations show that localization of epidermal growth factor receptor (EGFR) can cause the diffusion limited dimerization rate to be up to two orders of magnitude higher at higher average receptor densities reported for cancer cells, as compared to a normal cell.

Keywords: Receptor dimerization; Monte Carlo; Spatiotemporal modeling; Plasma membrane; Damköhler number; Reaction–diffusion systems; Systems biology; EGFR

1. Introduction

Extracellular signaling molecules, or ligands, bind to receptors that are either on the cell surface or within the cell. When the ligand binds a plasma membrane receptor, a signaling network is activated that relays the signal from the extracellular environment to the nucleus where the cell typically responds by a change in transcription rates. In order to tranduce the signal, the ligand bound receptors interact with a number of other proteins and lipids. For example, activation of the ErbB signaling networks leads to receptor hetero- and homodimerization and clustering; and the subsequent recruitment of other proteins, i.e., Shc, Grb2, Sos, Ras. Therefore, understanding dynamics of protein–protein interaction reactions, or bimolecular reactions, of the plasma membrane receptors along with its implications on signaling are of great importance for a wide variety of signaling pathways.

There has been a significant interest in developing predictive models to understand protein–protein interactions of signaling networks; see reviews [1–9], and most of the previous models

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are ordinary differential equation (ODE) models. ODE models rely on two key assumptions: (1) the system is well-mixed (spatially homogeneous, a situation also termed as global mean-field in statistical mechanics) and (2) the system is deterministic, i.e., given an initial condition, the transient evolution of the system is precisely determined [10]. For some biological processes, in particular signaling pathways, where there is a large degree of spatial organization, these assumptions may break down because every bimolecular process requires diffusion of two molecules whose collision, if successful, leads to signal propagation. Therefore, the transients of a bimolecular signaling process depend generally on the kinetic as well as the diffusive properties of the reacting proteins [2,11–13].

Partial differential equations (PDEs) are a conventional tool for incorporating the effect of diffusion in reacting systems. PDEs have been used to represent receptor–ligand dynamics [14,15] and some intracellular signaling processes [16–18]. Furthermore, the diffusion and Smoluchowski equations have been used to study diffusion-aspects of synaptic transmission [19–24]. PDEs have also been used to represent signaling processes in the plasma membrane [25–27]. Extensive research efforts have utilized PDE models for analyzing ligand–receptor interactions; see [14,15,28–41] and references therein. Similar treatments are more difficult for capturing transient receptor–receptor interactions, e.g., the bimolecular reaction between A and B can lead to different behaviors depending on the diffusivity of the higher density reactant [42]. This is because tracking the transient evolution of bimolecular reactions with reactants is, in general, a many-body problem [43]. There is a lot of research in this area; see references in [44–46]. Most of these efforts are based on the Smoluchowski [47,48] and Collins–Kimball [49] approaches. Our intent here is not to review these efforts; however, we want to point out that an exact relation between the effective reaction rate constant and diffusivity is difficult to obtain for a general two-dimensional bimolecular reaction, especially if one is interested in the transient behavior of the system. In passing, we should remark that Cahn–Hilliard and Allen–Cahn PDE formalisms, based on a free energy factional, are often used to study phase separation [50]. Finally, stochastic PDEs, such as the Langevin equation, are also used to capture the effect of noise in spatiotemporal dynamics. However, these may run in difficulties when the number of copies of proteins is small. In addition, analytical, simple solutions that could be easily used to compare to experimental data do not usually exist. A brief overview of continuum equations can be found in [51]. In this paper, we use the simplest, analytical results for the effective reaction rate constant from the standard diffusion equation (second Fick's law) [14,52] with reaction between proteins as a boundary condition (see Methods below).

Kinetic or dynamic Monte Carlo (MC) based spatial modeling is an attractive choice for modeling cell surface receptor dynamics because its computational implementation can explicitly consider (1) the creation of a spatially non-random distribution of proteins due to bimolecular reactions, (2) the spatial heterogeneity in the plasma membrane due to microdomains, and (3) the noise and the correlations resulting from a small number of copies of activated receptors. These factors are explained in detail in the next section. Another stochastic approach is based on Brownian motion (off lattice dynamics) followed by reactions [53–64]. Such studies have recently been used for bimolecular processes in the plasma membrane [65]. However, in this work we will consider only a spatial (lattice) kinetic MC model.

The importance of spatial MC modeling has recently been emphasized in several reviews [13,66,67]. Despite the existence of several spatial MC algorithms [66,68–74], the majority of MC studies have been carried out under well-mixed conditions [1,75–79]. The assumption of well-mixed condition may be justified in some biological systems, whereas for others, spatial modeling may be necessary. Currently, there is lack of a criterion which can be used to assess the need for spatial modeling for a biological system of interest, specifically bimolecular processes in the plasma membrane. Furthermore, only a few studies have emphasized the necessity of stochastic spatial modeling over deterministic spatial modeling for biological systems [66,67,69].

Herein, we assess the validity of a dimensionless number, known as the Damköhler number (Da), as a criterion to determine the importance of spatial effects of the membrane proteins on cellular signaling pathways. Furthermore, we show that the effective reaction rate changes with time due to the changes in the spatial organization of receptors. As a result, we demonstrate that the transient effective reaction rate constant of a bimolecular activation cannot be accurately captured by simple PDEs, resulting in more than one order of magnitude difference from that of MC. In biological networks, stochasticity (or noise) adds another dimension to complexity [80,81]. In the final part of this work, the effect of diffusion on noise is explored using a simple reaction network.

2. Features motivating the use of spatial MC methods

2.1. Reaction-induced spatial non-random distribution in receptor density

An initial random distribution of receptors can change into a non-random distribution due to receptor dimerization. The creation of depletion zones at steady state in receptor–receptor reactions has been discussed nicely in the past [69]. These authors showed that at steady state the effective kinetic rate constants of a PDE and a spatial MC model can differ by a factor of ~1–4. However, their study did not consider the transient variations in the distribution of receptors. Changes in distribution require a better understanding and characterization to capture the signaling receptor dynamics as well as in extracting information from experimental data.

2.2. Microenvironment heterogeneities

Recent experimental studies [82–85] suggest that understanding the dynamics and regulation of signaling pathways requires an analysis of the spatial features of the plasma membrane. Considering the advances in our knowledge about various spatial features of the plasma membrane [85–88], the