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Approaches and tools for modeling signaling pathways and calcium dynamics in neurons

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ABSTRACT

Signaling pathways are cascades of intracellular biochemical reactions that are activated by transmembrane receptors, and ultimately lead to transcription in the nucleus. In neurons, both calcium permeable synaptic and ionic channels as well as G protein coupled receptors initiate activation of signaling pathway molecules that interact with electrical activity at multiple spatial and time scales. At small temporal and spatial scales, calcium modifies the properties of ionic channels, whereas at larger temporal and spatial scales, various kinases and phosphatases modify the properties of ionic channels, producing phenomena such as synaptic plasticity and homeostatic plasticity. The elongated structure of neuronal dendrites and the organization of multi-protein complexes by anchoring proteins imply that the spatial dimension must be explicit. Therefore, modeling signaling pathways in neurons utilizes algorithms for both diffusion and reactions. The small size of spines coupled with small concentrations of some molecules implies that some reactions occur stochastically. The need for stochastic simulation of many reaction and diffusion events coupled with the multiple temporal and spatial scales makes modeling of signaling pathways a difficult problem. Several different software programs have achieved different aspects of these capabilities. This review explains some of the mathematical formulas used for modeling reactions and diffusion. In addition, it briefly presents the simulators used for modeling reaction–diffusion systems in neurons, together with scientific problems addressed.

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1. Introduction

Signaling pathways are cascades of intracellular biochemical reactions and diffusion. They are typically activated by transmembrane receptors, and ultimately produce signaling to the nucleus, i.e., gene transcription. Many of these transmembrane receptors are G protein coupled receptors, where the bound receptor acts as an enzyme to catalyze the exchange of GDP for GTP, followed by dissociation of the Gα subunit from the Gβγ dimer (Premont and Gainetdinov, 2007). Both parts of the G protein can have downstream targets, either directly binding to and modifying activity of ion channels, or binding to enzymes such as

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adenylyl cyclase or phospholipase C to produce diffusible second messengers (Pierce et al., 2002). These pathways ultimately lead to phosphorylation or dephosphorylation events which change the state of key transmembrane receptors and ion channels, and also induce transcription and translation of new proteins (Hawk and Abel, 2011; Tanaka, 2001).

Calcium is a part of these signaling pathways in its role as a multi-functional, diffusible second messenger (Greer and Greenberg, 2008). Calcium can directly bind to and modulate ion channel activity; it can modulate the activity of G protein activated enzymes such as adenylyl cyclase and phospholipase C; through its binding to calmodulin, calcium can directly activate calcium calmodulin dependent protein kinase II (CaMKII) and protein phosphatase type 2B (calcineurin). What makes calcium unique from other second messengers is that it derives from influx through voltage dependent or synaptic ion channels. In addition, under some circumstances a major source of calcium is release from the smooth endoplasmic reticulum through calcium sensitive, calcium permeable channels (Hartmann and Konnerth, 2005).

Intense interest in the function of signaling pathways is due to their implication in disease. More than 50% of pharmaceuticals target G protein coupled receptors or downstream effectors (Howard et al., 2001). Signaling pathways are critically important for all cell types, from bacteria to mammalian systems. Modeling of signaling pathways has contributed to discovery in many areas of systems biology such as development (von Kriegsheim et al., 2009), cell cycle (Novak et al., 2007), cardiology (Jafri, 2012), immunology (Fallahi-Sichani et al., 2011), and cancer biology (Aksamitiene et al., 2011; Fey et al., 2012).

Although most research in computational neuroscience involves modeling or analysis of action potentials, understanding the signaling pathways underlying plasticity of intrinsic excitability or plasticity of synaptic responses is crucial for understanding learning and information storage. Signaling pathways interact with electrical activity at multiple spatial and time scales (Fig. 1), and the complexity of feedback loops and other pathway structures precludes a deep understanding of information processing without dynamical modeling. At the smallest time scales, calcium activates calcium dependent potassium channels (Berkefeld et al., 2006; Hirschberg et al., 1999) and inactivates voltage dependent calcium channels (Rankovic et al., 2011). The spatial scale for this temporal interaction tends to be small because tight regulation of calcium limits spread of the signal. At longer time scales, the phosphorylation or dephosphorylation of ionic and synaptic channels modulates neuron excitability (Daoudal and Debanne, 2003) and shapes synaptic integration (Lisman et al., 2002). The spatial scales for these longer time scales depend on whether the second messengers, kinases and phosphatases are highly diffusible, or are spatially confined by anchoring (Hulme et al., 2003) or rapid degradation (Tostevin et al., 2007). At the longest time scales, signaling pathways that lead to gene transcription and protein translation can produce changes that last the lifetime of the organism (Costa-Mattioli et al., 2009). Behavioral experiments have demonstrated the importance of various kinases and protein synthesis for long term memory (Abel et al., 1997; Shalin et al., 2006), but the interaction among all of these spatial and temporal scales implies that all of them are involved in learning, memory and information processing.

In summary, a complete understanding of neuronal function requires integration of electrical models of neurons with signaling pathway models of neurons. Both the spatial gradients produced by the elongated structure of neuronal dendrites and the organization of multi-protein complexes by anchoring proteins implies that the spatial structure must be explicit. Therefore, to model and simulate second messenger pathways in neurons requires algorithms for both diffusion and reactions, both deterministic and stochastic. This paper describes the various biochemical processes involved in signaling pathways, and also the modeling tools used to investigate signaling pathways. The first part of this review presents the biochemical reactions and mathematical equations used to describe and model signaling pathways. The second part of the review provides a brief description of several useful modeling tools and the models implemented using those tools.

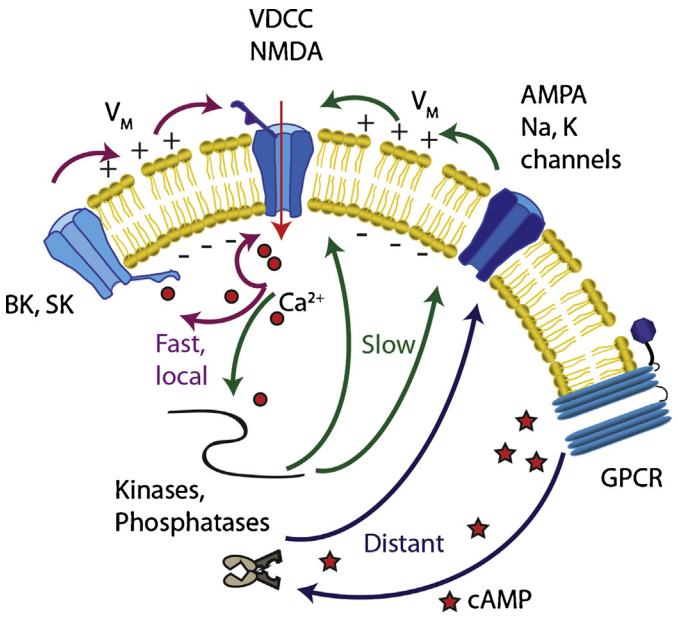

Fig. 1. Signaling pathways interact with electrical activity at multiple spatial and time scales. At the smallest spatial and temporal scales, calcium directly binds to and modulates ionic and synaptic channels. At longer time scales, calcium and second messengers produced by G protein coupled receptors (GPCR) lead to the phosphorylation or dephosphorylation of ionic channels and synaptic channels. The spatial scales for these longer time scales vary depending on the balance between diffusion and inactivation mechanisms. Feedback loops can be negative, as when phosphorylation enhances an outward current, or positive, as when phosphorylation enhances an inward current.

2. Biochemical reactions and diffusion

Both signaling pathways and mechanisms controlling calcium concentration are modeled as systems of uni- and bi-molecular reactions and diffusion. The rate at which reactions occur depends on factors such as frequency of collision between reacting molecules, energy of such collisions, and conformation of the collision (Stenesh, 1993). In order to simulate large systems of signaling pathways, various approximations are made in describing rates of reactions. Typically, the frequency of collision is captured by the concentration or density of reacting molecules, and the other factors governing the rate of reaction are captured in a single rate constant parameter. If the number of molecules is sufficiently large (e.g. in the cell body), the rate of change in molecule quantities can be described deterministically, whereas with small numbers of molecules (e.g. in spines) the reactions are more accurately simulated stochastically (Liu et al., 2012).

2.1. Uni- and bi-molecular reactions

Uni-molecular reactions are transformations of a molecule from one form to another. For example, a single sodium channel gate can transform from the closed state (m_c) to the open state (m_o) with forward rate k_f and backward rate k_b.

$$m_c \underset{k_b}{\overset{k_f}{\rightleftharpoons}} m_o \tag{1}$$