EONS an Online Synaptic Modeling Platform

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INTRODUCTION

The nervous system is composed of billions of interconnected neurons. These neurons communicate with each other primarily through fast chemical synapses. Such category of synaptic transmission involves (i) the conversion from electrical to chemical signal at the presynaptic membrane; (ii) the chemical transmission (diffusion of neurotransmitter) across the synaptic cleft; and (iii) the conversion from chemical to electrical signal at the postsynaptic membrane. Chemical synapses, although representing the smallest unit of communication between two neurons in the nervous system, comprise a complex ensemble of mechanisms. Understanding these mechanisms and the way synaptic transmission occurs and is regulated by activity is critical for our comprehension of central nervous system (CNS) functions in general and learning and memory in particular.

The objective of the work presented here is to develop a computational tool designed specifically for the study of the complex mechanisms that occur at chemical synapses. This tool should enable students and researchers (biologists with very little training in computational biology, as well as experienced modelers) worldwide to study the roles of diverse parameters that impact synaptic transmission from presynaptic to postsynaptic depolarization in an integrated modeling platform, using an easy, user-friendly and modular graphical interface.

BACKGROUND

Computational neuroscience has since its inception been mainly focusing on capturing the essential features of biological systems at multiple spatiotemporal scales, from membrane currents, protein and chemical coupling to network oscillations and learning and memory. These computational models are used to test hypotheses that can be directly verified by current or future biological experiments.

Recent technological advances have provided a better understanding of the mechanisms involved in synaptic transmission and integration; in particular, calcium imaging (Oertner, Sabatine, Nimchinsky, & Svoboda, 2002) and more accurate electrophysiological measurements have provided precise information on calcium concentration and dynamics (Oakley, Schwindt, & Crill, 2001), density, and types of channels and receptors, as well as different molecular pathways.

Likewise, the collection of tools available for computational approaches in biology has also grown significantly in recent years. This collection contains (as a nonexhaustive list): Neuron, ECELL, BioSpice, MCell, Genesis, and Virtual Cell (more information is available on their respective Web sites). Among those tools, modeling platforms have been developed to study complex cellular mechanisms. Some approaches focus on studying very specific mechanisms in simple geometries (Bennett, Farnell, & Gibson, 2000; Matveev, Zucker, & Sherman, 2004), while others study cellular mechanisms in complex and up to three-dimensional geometry (MCell) and offer a much more general framework (virtual cell).

Chemical synapses have been the subject of extensive research very early in the history of neuroscience (Rall, 1974). They have been shown to play a significant role in learning and memory; thus, synaptic structure is a critical determinant of synaptic properties, while temporal changes in postsynaptic calcium concentration and CaMKII or phosphatase activation generated by various stimulation conditions are believed to be good predictors for the induction of Long Term Potentiation

(LTP) or Long-Term Depression (LTD). Furthermore, chemical synapses also constitute a primary target for a multitude of drugs used in pathologies affecting the central nervous system (such as AMPAkines or NMDA receptor antagonist in the case of Alzheimer's disease).

The parameters that affect the efficacy of chemical synapses are numerous. A nonexhaustive list would include presynaptic mechanisms (calcium channels kinetics and distribution, presynaptic calcium binding and buffering mechanisms, kinetics of vesicle cycling, calcium extrusion from the terminal, and so forth), synaptic mechanisms (diffusion of neurotransmitters in the synaptic cleft, reuptake mechanisms, width of the cleft, relative position of the release site with respect to the receptors, and so forth), and postsynaptic mechanisms (receptor affinity and distribution, channel-gated kinetics, second-messenger pathways, postsynaptic spine geometry, and so forth).

Given the complexity of the mechanisms involved and the importance of chemical synaptic transmission in the central nervous system, we believe it is of paramount importance to develop a computational platform to specifically study the contribution of different parameters to synaptic transmission and regulation.

MAIN FOCUS OF THE ARTICLE

Requirements, Architecture of EONS

The EONS synaptic modeling platform is an integrated modeling framework that allows the user to specify in a structured environment using a graphical user interface the characteristics of the synaptic elements one wants to study. From a computational standpoint, EONS consists of a Java WebStart application that can be downloaded from the World Wide Web (http://eons. no-ip.info). The application communicates with a central database in which various models and elements are stored. Hence, users can save and retrieve models and/or parts of these models.

The platform contains models, structures, elements, reactions, and simulations. Models are entities in which all simulated components are defined. They represent the whole system one is interested in. This system can be an entire synapse, or simply a calcium channel. Structures are containers for modeling elements. A container can

be conceptual (one can think of it as a dimensionless toolbox in which several elements can be grouped) or can become a physical container when associated to a specific geometry. It then adopts the dimensions of the two-dimensional mesh with which it is associated. A model can contain several structures (e.g., presynaptic, cleft, postsynaptic, and so forth). Elements are unitary entities that can be added or removed from the rest of the model. An element contains parameters which can be constant or variable. As an example, an element can be a calcium channel, a calcium pump, or a postsynaptic receptor. Elements interact with their environment. These interactions are described as Reactions in EONS. Reactions represent a set of mathematical expressions that describe the events or interactions occurring in the system. Simulations represent the actual in-silico experiment. A simulation can solely be run on an entire model. Results of a given simulation are observed in the form of graphs and an array of values for every time step of the simulation.

Mathematics

The description of biological models and their subsequent computation often requires mathematical tools. EONS uses the linear algebra module available in jScience (Dautelle, 2006) to generate matrices and calculate the values of its coefficients. This is used in particular for the diffusion process using Finite Element Method (FEM). In the same way, modeling requires the users to define the behavior of the elements they intend on modeling. To do so, EONS allow users to enter their own sets of mathematical expressions and parses these expressions using a mathematical expression parser called Java Math Expression Parser (JEP) (Funk & Morris, 2006). JEP is a Java package for parsing and evaluating mathematical expressions. It supports user-defined variables, constants, and functions. A number of common mathematical functions and constants are included (see reference Web site). To complement the functions available in JEP, a set of mathematical methods has also been implemented to serve the specific needs of physiological and cellular modeling which require the use of different solving methods for ordinary differential equations. Hence, numerical methods such as forward Euler, backward Euler, and Runge-Kutta 2nd and 4th order have also been implemented.

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