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EONS: An Online Synaptic Modeling Platform

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***Abstract*— Chemical synapses, although representing the smallest unit of communication between two neurons in the nervous system constitute a complex ensemble of mechanisms. Understanding these mechanisms and the way synaptic transmission occurs is critical for our comprehension of CNS functions in general and learning and memory in particular. Here we describe a modeling platform called EONS (Elementary Object of Neural System) accessible online, which allows neuroscientists throughout the world to study qualitatively, but also quantitatively the relative contributions of diverse mechanisms underlying synaptic efficacy: the relevance of each and every elements that comprise a synapse, the interactions between these components and their subcellular distribution, as well as the influence of synaptic geometry (presynaptic terminal, cleft and postsynaptic density).**

I. Introduction

The nervous system is composed of billions of interconnected neurons. These neurons communicate with each other primarily through fast chemical synapses. Such chemical synaptic transmission involves (i) the conversion from electrical to chemical signal at the presynaptic membrane; (ii) the chemical transmission (diffusion of neurotransmitter) across the synapse and (iii) the conversion from chemical to electrical transmission at the post-synaptic membrane. Recent technological advances have provided a better understanding of the mechanisms that comprise this complex machinery (calcium imaging, information on density and types of channels and receptors, etc…).

The collection of tools available for computational approaches in biology has also grown significantly in recent years. This collection contains (as a non-exhaustive list): Neuron, ECELL, BioSpice, MCell, Genesis and Virtual Cell (more information is available on their respective websites). Among those tools, modeling platforms have been developed to study complex cellular mechanisms. Some approaches focus on studying very specific mechanisms in simple geometries [1], [2], while others study cellular mechanisms in complex and up to three-dimensional geometry (MCell) and offer a much more general framework (Virtual Cell).

The parameters that affect the efficiency of chemical synapses are numerous and include presynaptic mechanisms (calcium channels kinetics and distribution, presynaptic calcium binding and buffering mechanisms, vesicular kinetics and recovery, calcium extrusion from the terminal, etc…), synaptic mechanisms (diffusion of neurotransmitters in the cleft, reuptake mechanisms, width of the cleft, relative position of the release site with respect to the receptors, etc…) and postsynaptic mechanisms (receptor affinity and distribution, channel-gated kinetics, etc…).

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

II. METHODS

A. Requirements, architecture of EONS

The EONS simulation platform contains a graphical interface that allows the user to specify in a structured environment the characteristics of the synaptic elements he/she wants to study. From a computational standpoint, EONS consists of a Java WebStart application (http://eons.no-ip.info) that communicates with a central database in which the 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

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conceptual (one can think of it as a dimensionless toolbox) 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, etc…). *Elements* are unitary entities that can be added or removed from the rest of the model. An element contains parameters which can be constants or variables. 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 *Reaction*s 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.

B. Mathematics

EONS uses the linear algebra module available in jScience [3] to generate matrices and calculate the values of its coefficients. This is used in particular for the diffusion process using Finite Element Method (FEM).

To allow users to enter their own sets of mathematical expressions and hence provide them with the ability to define their own models, EONS uses a mathematical expression parser called JEP (Java Math Expression Parser) [4]. 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 website).

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.

C. Diffusion: From image to mesh

In most current approaches to modeling relevant to our problem, the regions of interest are often simplified into basic geometrical shapes [5]. Hence, information that depends on the spatial organization of molecules and cellular organelles cannot be accommodated.

In EONS, we propose to retain this critical information and to model diffusion in realistic complex geometry using *finite element method*. The first step in this process consists in tracing the contours of the structure of interest using real geometrical information (i.e., electro microscopy picture) and scaling them to the original size (generally in nanometers). Then, we use an external C program [6] to generate the mesh which will be uploaded into EONS. These steps are illustrated using a perforated presynaptic terminal [7] in figure 1.

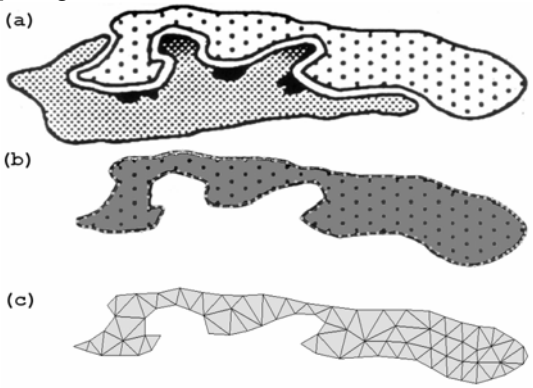

Fig.1: Creation of the 2D mesh. (a) Initial raster contour drawn from the EM picture. (b) Creation of the to-scale contours (white dots around the presynaptic terminal. (c) Output of *mesh2D* mesh generation program that is used as an input to EONS. The triangles form a mesh through out the geometry, where each vertex in called a node.

D. Diffusion: finite element method

Finite element method allows us to discretize the computational domain by approximating the continuum problems [8]. The diffusion equation in the continuum structure is:

$$\frac{\partial c(x,y,t)}{\partial t} = D_c.\{\frac{\partial^2 c(x,y,t)}{\partial x^2} + \frac{\partial^2 c(x,y,t)}{\partial y^2}\} - B(t),$$

where c(x,y,t) represent the concentration functions, D_c is the diffusion coefficient (for free calcium ions, its value is 2.2 . 10^{-6} cm2/sec in the cytoplasm [9]). *B(t)* is the buffering process when it is assumed to be immobile and uniformly distributed.

In the presynaptic terminal, the process of calcium binding to buffers occurs in a much faster time scale than diffusion and local equilibrium is rapidly reached between free and bound calcium ions [10]. Therefore, the above equation can be approximated by

$$\frac{\partial c(x,y,t)}{\partial t} = \frac{D_c}{1+\beta}.\{\frac{\partial^2 c(x,y,t)}{\partial x^2} + \frac{\partial^2 c(x,y,t)}{\partial y^2}\},$$

where β is the ratio of bound to free calcium in the cytoplasm.

To discretize the computational domain, we define the shape function N such that the value of the concentration is equal to the discrete values of [c] on the points of the mesh, which in the case of one triangle yields:

$$c = \sum_{i=1} C_i.N_i(x,y) = [C_1 \quad C_2 \quad C_3][N_1 \quad N_2 \quad N_3]^T = C.N^T$$

The utilization of Galerkin principle applied to the diffusion equation yields:

$$Dc.\int_S \nabla c.N.n.dS - D_c.[c]\int_V (\frac{\partial N}{\partial x}^T \frac{\partial N}{\partial x} + \frac{\partial N}{\partial y}^T \frac{\partial N}{\partial y})dx.dy - [\dot{c}].\int_V N^T.N.dx.dy = 0$$

Solving this system gives us the values of $[\dot{c}]$, values of the gradient of concentration in the mesh and hence the values of the concentration at every node at the next iteration.

III. RESULTS

A. Modeling synaptic elements

EONS already contains a library of synaptic models. As of the redaction of this manuscript, those elements include calcium channels (L, N and T type channels) as well as postsynaptic elements such as AMPA and NMDA receptor channels. This library can easily be expanded to contain other elements such as calcium pumps, deterministic vesicular release, exchange and reuptake mechanisms, etc…). The AMPA receptor channels modeled are the 5-states receptor introduced in [11] and the 7-states described in [12]. The NMDA receptor channel modeled is the 11 states model presented in [13].

As an example, figure 2 illustrates the results obtained during the simulation of the 5-states AMPA receptor channel. The input to the model is a pulse of glutamate. In this case, no diffusion is applied to the model (results of the diffusion process will be explained in details in the next section). The model is stated as a set of 5 ordinary differential equations, each represented in EONS using the syntax presented in figure 2(b).

B. Modeling diffusion

Simulating diffusion in complex arbitrary geometrical shapes can easily be done in EONS. Accessing the diffusion method is done using the following statement:

var*iable* = *FEM* ("*mesh _ name*",
initial concentration,
diffusion coefficient)

The effect of this mathematical expression is twofold: (i) it initializes a matrix (named 'Variable') according to the specified mesh in which every cell contains the value of the initial concentration provided as second parameter. (ii) It calculates the diffusion throughout the simulation of a molecule for which the diffusion coefficient in the medium is given as third parameter.

In order for a specific element to have an effect on the concentration at a specific location, one must apply the function:

inject(*mesh _ matrix*,
position in the mesh,
var*iable to be added*)

For a calcium channel for example, the increase in concentration observed when the channel is in open state is added to the mesh matrix at the position where the channel is located.

To determine the effect of geometry on synaptic function, it is important to have access to the value of the concentration of a molecule at every position throughout the mesh. To do so, it is possible to simulate a recording electrode at any position on the mesh using the function:

record(*mesh _ matrix*,
position in the mesh)

Initial results show that the non-optimized computation time needed to calculate the diffusion in a presynaptic terminal such as the one presented in figure 3 is equal to 10 minutes for a 12 ms. simulation on a 3.2 GHz Pentium workstation (with a time step equal to 0.1 μs.).

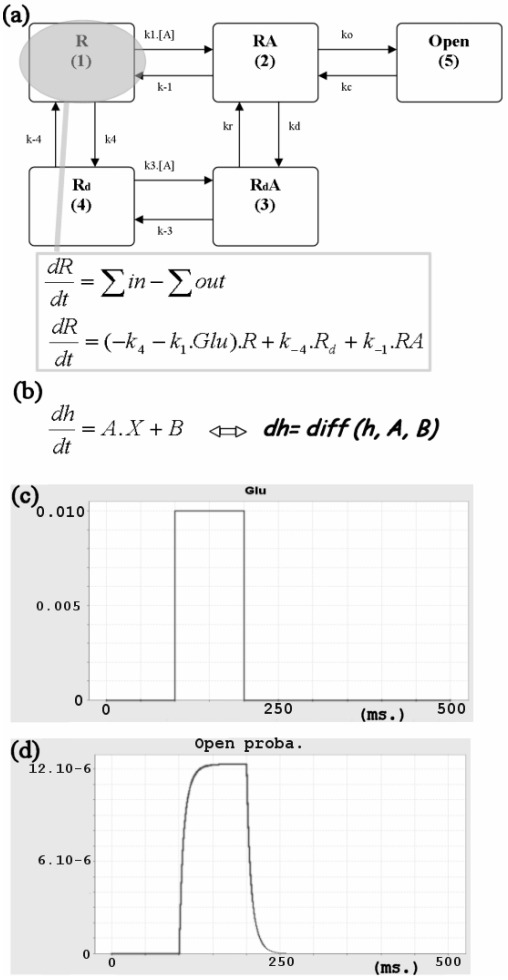

Fig.2: 5-states AMPA receptor channel modeling in EONS. (a) Kinetic schema of the receptor. The ordinary differential equation generated for state R is represented. (b) Ordinary differential equation and its corresponding syntax in EONS. (c) Input of the model: Pulse of glutamate (10 microM. for a duration of 100 ms. during a 500 ms. simulation with a 0.01 ms. time step). (d) Output of the model: opening probability of the associated channel.

IV. DISCUSSION

The current version of EONS can handle a large number of models as well as reaction-diffusion processes. However, many further enhancements are planned. There is currently no way to specify a non-uniform population of molecules in a physical space (such as calcium-binding molecules in the presynaptic terminal [1]). The current library of models will be extended, and we hope to incorporate more efficient solvers. In the same way, work will be done with respect to

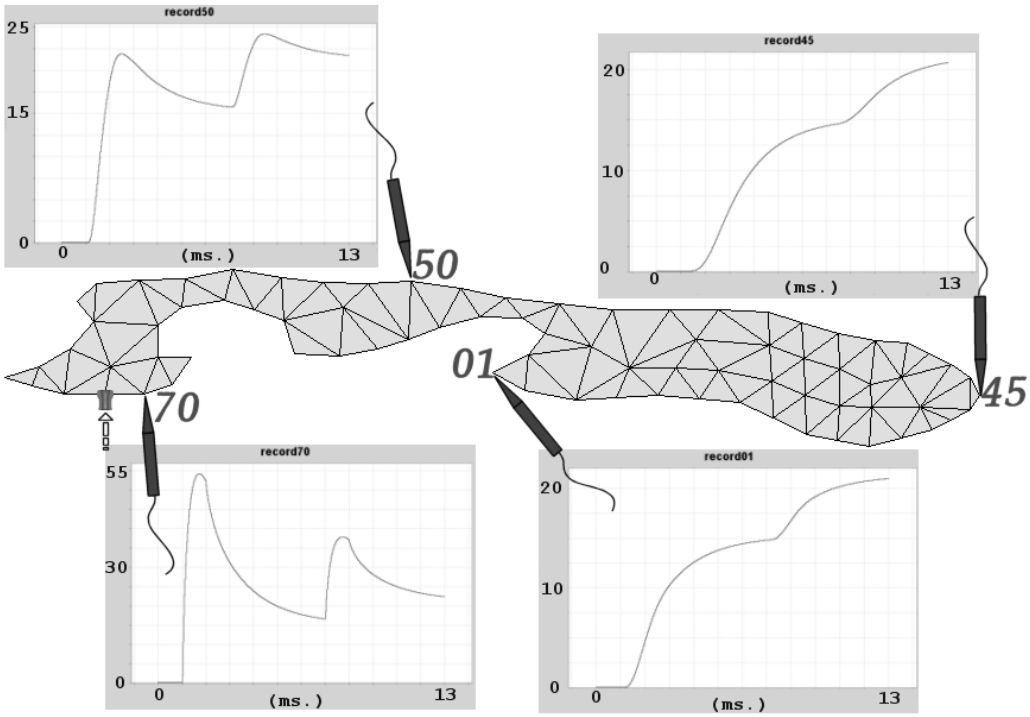

Fig.3: Virtual simulated electrodes and their corresponding plots. These 'electrodes' record the concentration of calcium at different locations throughout the presynaptic terminal (mesh containing 86 triangles) following a paired-pulse depolarization (0mV and 1 milliseconds long with a 6 milliseconds interval) with calcium entering the terminal through one N-type calcium channel with no buffering mechanisms.

compatibility between EONS and other modeling platforms. This will enable the interchange of models between modeling tools. Such modularity between computational tools bodes well for the future of the field of computational biology.

In its current state, EONS provides both researchers and students with a well-defined environment for testing specific hypotheses about the dynamics of multiple presynaptic mechanisms, such as the type of Ca^{2+} channels, buffering mechanisms, Ca^{2+} pumps, diffusion coefficients, binding proteins, etc., as well as several key postsynaptic mechanisms, such as the kinetics of AMPA and NMDA receptor-channel subtypes. In addition, one of the unique features of EONS with respect to other neural modeling tools is its ability to preserve the effect of synaptic geometry, e.g., the relative locations of presynaptic Ca^{2+} channels and neurotransmitter release sites, the relative locations of presynaptic release sites and postsynaptic receptor-channels, and the relative numbers and locations of postsynaptic receptor-channels, while integrating mechanisms that are both pre- and postsynaptic.

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