SIM-CE: An Advanced Simulation Platform for Studying the brain of Caenorhabditis elegans

Ramin M. Hasani[1*], **Victoria Beneder**[2], **Magdalena Fuchs**[1], **David Lung**[1],**Radu Grosu**[1]
[1]Institute of Computer Engineering, Vienna University of Technology, Austria
[2]University of Natural Resources and Life Sciences, Vienna, Austria
*ramin.hasani@tuwien.ac.at

Abstract

We introduce SIM-CE, an advanced, user-friendly modeling and simulation environment in Simulink for performing multi-scale behavioral analysis of the nervous system of *Caenorhabditis elegans* (*C. elegans*). SIM-CE contains an implementation of the mathematical models of *C. elegans*'s neurons and synapses, in Simulink, which can be easily extended and particularized by the user. The Simulink model is able to capture both complex dynamics of ion channels and additional biophysical detail such as intracellular calcium concentration. We demonstrate the performance of SIM-CE by carrying out neuronal, synaptic and neural-circuit-level behavioral simulations. We show that Such environment enables the user to capture unknown properties of the neural circuits, test hypotheses and determine the origin of many behavioral plasticities exhibited by the worm such as neuronal habituation, a simple non-associative learning mechanism.

1 Introduction

C. elegans is most likely the world's best-understood animal [1]. However, the fundamental principles underlying its behavior are yet to be understood. Its relatively simple nervous system is constructed from 302 neurons, hardwired by means of about 8000 chemical and electrical synapses [2]. Despite its simplicity, it has shown remarkable complex behavioral features which make it an attractive model system. Multi-scale behavioral analyses have been conducted on the worms nervous system [3, 4], and global attempts on modeling its emergent behavior have been commenced [5]. In this regard, there is a high demand for a comprehensive neuron-by-neuron model platform which incorporates many electrophysiological properties of neurons while being able to handle a large parameter space [4, 6].

In the present study, we construct a modular simulation platform, SIM-CE, for investigating fundamental principles underlying physiological processes within the neural circuits of the brain of *C. elegans*, in Simulink. We show that SIM-CE can capture behavioral features of the neural circuits in multi-scale details including biophysics of neurons and synapses. We can determine weights and polarities synapses in the wiring diagram, reveal unknown properties of neural circuits and find the origin of neuronal non-associative learning mechanisms [7].

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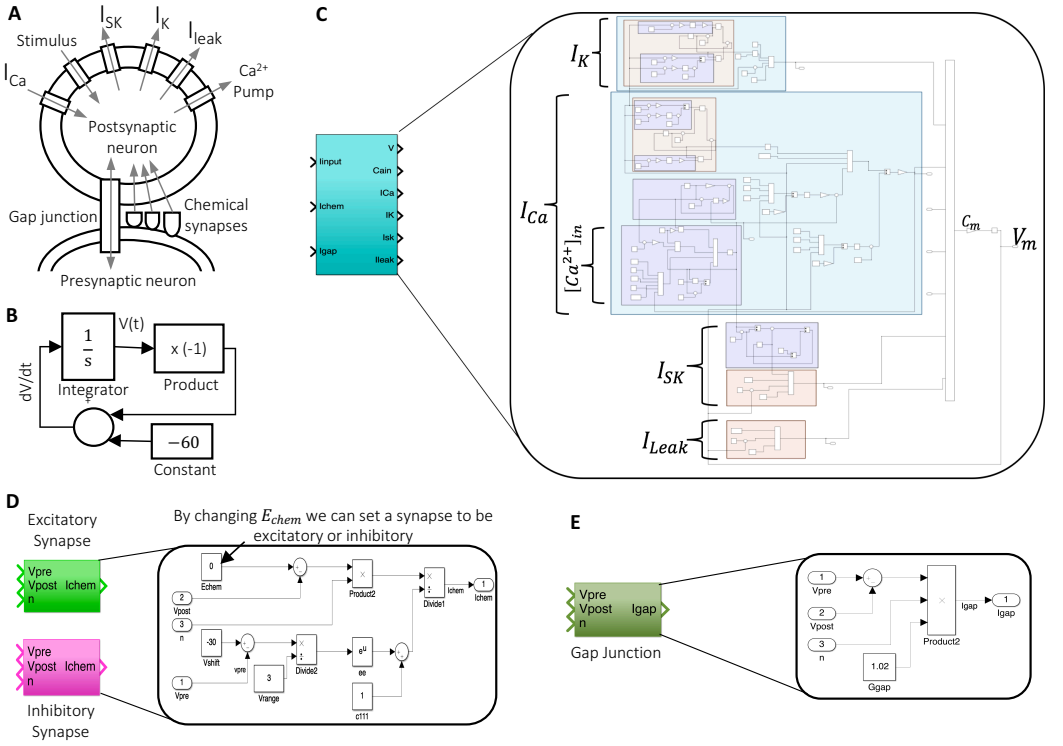

Figure 1: SIM-CE implementation of neurons and synapses. A) Representation of a single neuron of *C. elegans* reproduced from [8]. B) ODE implementation in Simulink. C) Simulink model of a single *C. elegans* neuron D) Chemical excitatory and inhibitory synapse models E) Model of a gap junction.

2 SIM-CE Simulation Platform Implementation

Structure of a single-compartmental neuron model inspired by Hodgkin and Huxley neuron model in [9] and [8], is represented in Figure 1A. It comprises several ordinary differential equations (ODE) describing dynamics of the cell. Such ODEs are implemented by using the integrator block in Simulink. For instance, the equation $\frac{dV}{dt} = -60 - V$, is constructed as shown in Figure 1B. The input to the integrator block is the derivative term dv/dt. The output is $V(t)$, which is multiplied by -1, summed up with the constant and is fed back to the integrator's input. The initial condition of the variable V is defined inside the integrator block. The equation is then solved by using the ode45 solver of MATLAB which realizes the Dolman-Prince [10], a numerical method for solving ODEs. Figure 1C shows the architecture of a single neuron designed in Simulink. The model includes voltage-gated potassium channel, a calcium-gated potassium channel, voltage-gated calcium channel, potassium leakage channel and dynamics of the intracellular calcium concentration. Parameters of the model are conveniently adjustable. The model enables the user to input external stimuli, from the environment or from a presynaptic synapse in real time, while monitoring the physiological behavior of the membrane potential, intracellular calcium concentration and the ion channel currents. Note that there are several types of ion channels determined in the neurons of *C. elegans* [11]. One can easily implement models of any arbitrarily chosen ion channel and include it in the neuron dynamics. Comprehensive details of the design, can be found in [12]. Similarly, Chemical and electrical synapses are also realized as building blocks of neural circuits and shown in Figure 1D and 1E, respectively.

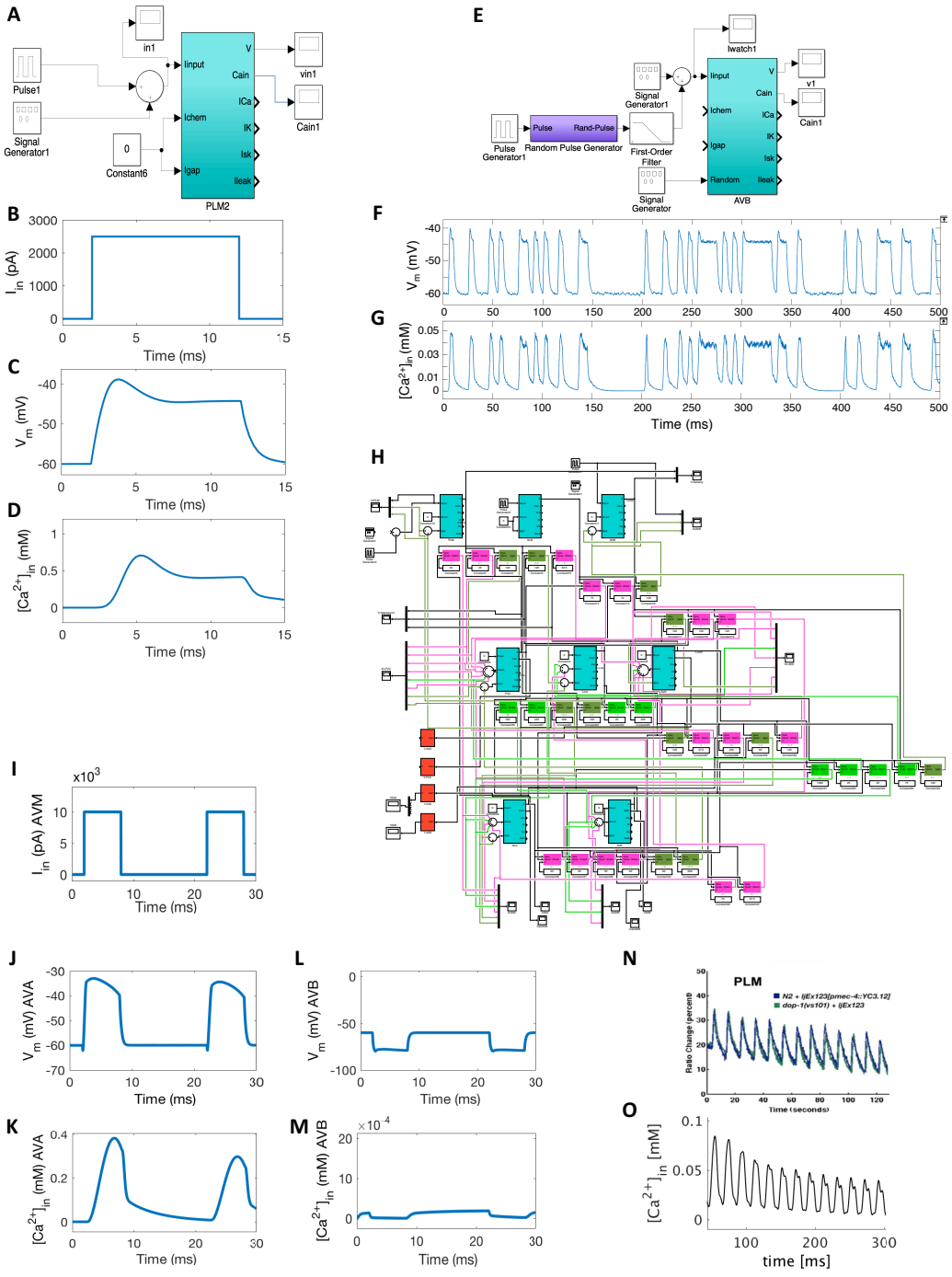

Figure 2: SIM-CE Performance. A to D) Simulation of the deterministic response of a neuron to an input current stimulus. E to G) Simulation of the stochastic response of the neuron to an intrinsic random current-pulse generator. E) The simulation setup. F) Membrane potential response G) Calcium concentration response. H)Tap-withdrawal neural circuit implemented in SIM-CE platform. I to M) Responses of the tap-withdrawal neural circuit I) Inputs to the sensory neurons J) Output of the AVA command neuron K) Intracellular calcium concentration of the AVA neuron L) Output of the AVB command neuron M) Intracellular calcium concentration of the AVB neuron. N) Habituation of a real sensory neuron (reprinted with permission from [13] O) Model of a neuronal habitation in SIM-CE.

3 SIM-CE Performance

We now show how SIM-CE can be beneficial in various scenarios. We first simulate the response of a single neuron to an external current stimulus. Figure 2A to 2D illustrates the simulation setup together with responses of the neuron which is quite similar to the response of a real sensory neuron in *C. elegans* [14].

Intrinsic random activity of neurons observed in *C. elegans* [3], is captured by including noise on the ion channel and pumps' conductances together with an internal random pulse generator. Figure 2A to 2D depict such simulation. The calcium dynamics of such neuron behaves similar to the interneuron, AVA, recorded in calcium imaging experiments, with a reasonable degree of accuracy [3]. In this way, the model additionally allows the user to study the intrinsic stochastic behavior of cells and neural circuits [4].

In additions, one can construct neural circuits in SIM-CE. An example of a well-understood neural circuit within the nervous system of *C. elegans*, is the tap-withdrawal (TW) circuit which is modeled and shown in Figure 2H. The circuit modulates a reflexive response to a mechanical stimulus subjecting the petri dish in which the worm crawls. TW circuit comprises 8 neurons optimally hardwired through almost 360 synapses. A mechanical stimulus excites specific sensory neurons (PLM, AVM or ALM) and results in the activation of the corresponding command neurons (AVA or AVB) through a group of interneurons (PVC, LUA, AVD). AVA activates the motor neurons responsible for reversal movement while AVB command neuron initiates forward locomotion. Depending on the strength of the stimulation on the sensory neurons, AVA or AVB gets activated and results in a reflexive motion [15]. We take the wiring diagram of the circuit from the initial *C. elegans* connectome data [16]. Previously, polarity of the synaptic connections are predicted experimentally and computationally [15]. What has not yet cleared is the weights of the synaptic connections for generation of the correct behavior. Here, we heuristically determine the weights of the synapses and generate the correct behavior by stimulating the anterior touch-neuron, AVM, and observing a reflexive behavior on the backward command neuron AVA (See Figure 2I to 2M).

Figure 2N shows the calcium response of a touch-neuron exposed to a periodic stimulus [13]. Gradual reduction in the concentration of the intracellular Ca^{2+} indicates neuronal habituation, a simple form of non-associative learning in the brain of the worm [13, 17, 1]. Habituation is determined as a reduction in the sensitivity of reflexive behavior of an organism subjected to repetitive stimulations. Within SIM-CE, electrophysiological parameters inducing habituation are indicated at the sensory neuron level. Cai et al [17] showed that auto-phosphorylation of subunits of a K^+ channel, causes sensory habituation. We captured such behavior by inducing dynamic electrophysiological variables in the model of a neuron (See Figure 2O). We hypothesize that the main mechanisms involved in such short-term memory behavior are the dynamic reduction of the K^+ channel conductivity, existence of a Ca^{2+} channel with an inactivation gating mechanism, and dynamic increase in the conductivity level of a Ca^{2+} pump.

4 Future work

We aim to explore the dynamics of more neural circuits in multi-scale physiological conditions, provide valuable predictions about the unknown properties of such circuits and ultimately include the dynamics of the entire nervous system of the worm. We will also integrate an efficient parameter optimization method based on evolution strategies, in SIM-CE platform.

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