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Modeling of the Nervous System: From Molecular Dynamics and Synaptic Modulation to Neuron Spiking Activity

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Abstract— **The brain is a perfect example of an integrated multi-scale system, as the complex interactions taking place at the molecular level regulate neuronal activity that further modifies the function of millions of neurons connected by trillions of synapses, ultimately giving rise to complex function and behavior at the system level. Likewise, the spatial complexity is accompanied by a complex temporal integration of events taking place at the microsecond scale leading to slower changes occurring at the second, minute and hour scales. In the present study we illustrate our approach to model and simulate the spatio-temporal complexity of the nervous system by developing a multi-scale model integrating synaptic models into the neuronal and ultimately network levels. We apply this approach to a concrete example and demonstrate how changes at the level of kinetic parameters of a receptor model are translated into significant changes in the firing of a pyramidal neuron. These results illustrate the abilities of our modeling approach and support its direct application to the evaluation of the effects of drugs, from functional target to integrated system.**

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I. Introduction

One of the fundamental characteristics of the brain lies in its high level of hierarchical organization. Indeed, complex molecular interactions at the level of receptors and channels regulate activity at the level of neurons and interactions between multiple populations of neurons ultimately give rise to complex neural system function and behavior. This spatial complexity takes place in the context of a composite temporal integration of multiple scales, ranging from microseconds, to hours or even longer. This organization, spanning many spatial and temporal dimensions, makes the task of modeling the central nervous system extremely complex.

Most attempts at neuronal multi-scale simulation start at a relatively high level of modeling, spanning mostly from cellular to systems levels. Simulators that allow multi-scale modeling of neural function include NEURON [1], GENESIS [2], NEST and CSIM [3]. While the majority of those efforts start at a relatively high level of modeling (cellular level), we propose to focus our attention starting at the molecular level and evolve towards the cellular and network scales to better understand how events occurring at the molecular level affect neuronal and network activities. To do so, we have developed the EONS (Elementary Objects of the Nervous System) / RHENOMS (RHENOVIA Modeling and Simulation) modeling platforms.

In the present study, we illustrate the utilization of these platforms to generate perturbations at the molecular level, more specifically on the kinetics of the AMPA receptor model, and observe their effect on the postsynaptic dendritic signal integration and neuronal spiking. Our results indicate that small modifications of critical parameters at the molecular subsynaptic level may have a significant impact at the dendritic and neuronal levels. In parallel, these results illustrate the abilities of our modeling platform to successfully capture the events and observables at different scales, and predict neuronal firing based on perturbations at the molecular level.

II. METHODS

In our quest towards a better understanding of the mechanisms underlying nervous system function, the spatio-temporal hierarchical complexity can be subdivided as described in Fig. 1. The 'lower' level of this system is the molecular level. This is the level where biochemical reactions, ion exchanges and diffusion, and protein/protein

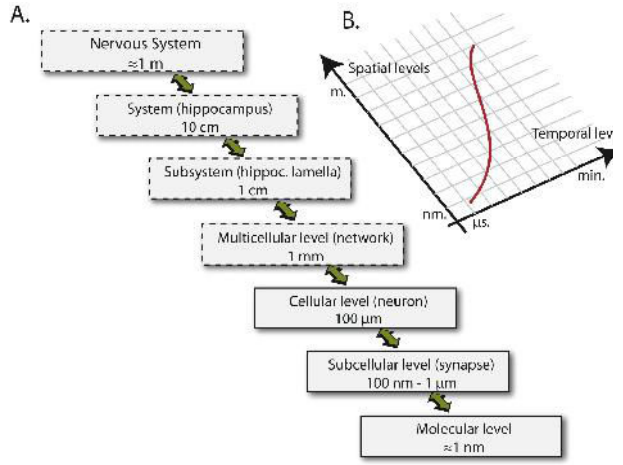

Fig. 1. Schematic representation of the spatial and temporal integrations taking place in the nervous system. A. Adapted from [4]: spatial scales necessary for multi-scale modeling ranging from molecular (nanometer scale) to nervous system. B. In parallel to spatial complexity, temporal complexity must be taken into account, as events take place from the microsecond range to the minute and hour range. Determining the appropriate level of detail (red line) both in terms of spatial and temporal accuracy allows for reasonable approximation, while covering a wide range of spatio-temporal scales.

interactions occur. Above this, the second level consists in the spatial clustering of some of these molecular events, e.g. at a presynaptic terminal, which incorporates all the events taking place in this spatially defined compartment. The third level consists in the integration of all the subcellular compartments into a cell. The fourth level is the structured organization of cells into cellular networks. Right above this, those networks are organized into subsystems (i.e. hippocampal subfields or cortical columns), which are then compounded into anatomical structures of systems (i.e. hippocampus, prefrontal cortex); ultimately, the structured organization of these systems composes the nervous system.

A. Molecular level

At the biomolecular level (also referred to as the level of elementary models), the first challenge consists in channeling the computational power where and when it is needed most; to reach this goal, we calculate the dynamic evolution of elementary models using variable-step numerical methods. Since the models are highly dynamic, they exhibit periods of intense activity (in the tens of microsecond range), yet may remain silent for long periods of time. Using a solver with variable-step numerical methods decreases the computational demand at times when it is not needed while maintaining a high level of accuracy at all times.

B. From molecular to synaptic level: the EONS/RHENOMS platforms

As higher spatial levels are taken into account, elementary models become highly interconnected, i.e., they depend on each other to determine their temporal evolution. To take into account this high level of inter-connectivity and inter-dependence, events are generated to trigger recalculation of models if significant changes occur in the values of that model's input variables. Similarly, if a model requires an input value at a specific time point, but this value does not exist (as the model that generates this value was not updated due to the utilization of variable-step algorithm), the input value is then interpolated based on the previous outputs of the input model. This asynchronous event-constrained communication protocol between elementary models is the second concept put to work in our framework. Its utilization ensures that, at any moment of the simulation, only results of models that are essential at that particular moment are calculated.

The EONS/RHENOMS modeling platforms we have developed contain a very large number of complex and highly interconnected models (represented by thousands of differential equations). These models simulate synaptic function in the presynaptic terminal, in the synaptic cleft (incorporating diffusion processes [5], uptake and astrocytic modulation) and in the postsynaptic spine (for more details on the elements contained in the platform, read [6], [7]). All elementary models are written in the Systems Biology Markup Language (SBML) standard [8]. The simulation engine in the synaptic platform is based on the event-constrained asynchronous principle described above, allowing us to reach reasonable computation speeds while maintaining acceptable accuracy.

C. From synaptic to neuron and extension to the network level

To allow for efficient integration of these levels, we elected to combine well-established modeling tools – each in its area of proficiency (level), and to define a bidirectional communication protocol in such a way that they can perform their calculations in parallel and communicate with each other as the simulation evolves. At the molecular and synaptic levels, we use the EONS integrated synaptic modeling platform that we developed; for the rest of the neuron, we are using the NEURON simulator; communications between EONS and NEURON are handled using a protocol that we developed based on MPJ express [7] on the Java side, and Python for NEURON. The frequency at which NEURON and EONS communicate (1 kHz) is much lower than the temporal sampling frequency used at the subcellular level (> 1 MHz), as dynamics of synaptic currents and potentials have lower time constants and therefore slower variations than intrasynaptic mechanisms.

The framework presented is implemented on our high performance cluster and can be directly extended to network level simulations (Fig. 2). Indeed, synapses (connection points between neurons) can be configured as either an entry point in which input signals can be entered in the system, or exit points, allowing an action potential generated by a neuron to be sent to another layer of neurons. This structure allows complete flexibility in terms of network connectivity (in parallel or series) with minimal overhead.

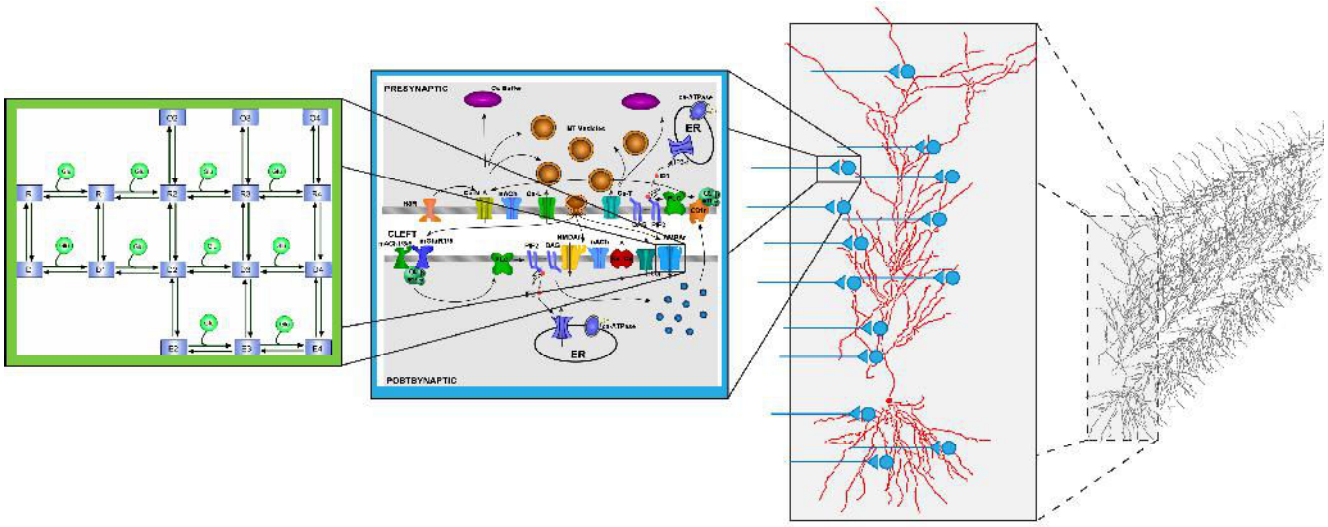

Fig. 2. Schematic representation of the different levels of complexity addressed in the current multi-scale modeling platform. Molecular mechanisms, such as the AMPA receptors, are represented by a 16-state kinetic model [9]. At the subcellular level, these mechanisms are geometrically coupled based on their location in the cell (presynaptic, extracellular, postsynaptic, or along the dendritic tree); the resulting changes in postsynaptic currents are then injected in a CA1 pyramidal cell neuron [11], which can be studied in isolation, or within a network. The results presented here are up to the neuron level.

III. RESULTS

To illustrate the utilization of our modeling framework, we investigated how perturbations at the molecular level impact observables at higher levels. As a concrete example, we modified kinetic parameters of the AMPA receptor model to simulate application of a positive AMPA receptor modulator (CX614). The stimulation protocol consisted in presenting a train of action potentials with random inter-pulse intervals at a mean frequency of 4 Hz as presynaptic input; our observable readouts were molecular, synaptic (excitatory postsynaptic current and voltage), dendritic and neuronal (somatic potential and firing pattern). The kinetic model of the AMPA receptor we used is the one proposed by [9]; it was adapted to fit the results presented in [10] in the presence of 5 and 10 µM of a positive AMPA receptor modulator, CX614. The NEURON model used in our simulations was a CA1 pyramidal cell, as described in [11].

Fig. 3 displays the effects of CX614 on AMPA receptor currents profiles as a function of time observed at the receptor level (voltage clamp conditions). As the synaptic currents are integrated along dendritic branches (60 synapses in the stratum radiatum area, all receiving the same presynaptic input), we then recorded dendritic potentials at

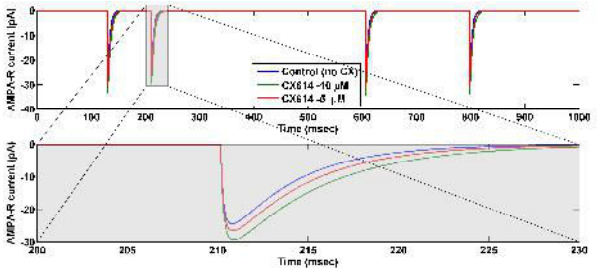

Fig. 3. Molecular level. Observable: AMPA receptor current. Effect of different concentrations of CX614 on the AMPA receptor profile as a function of time.

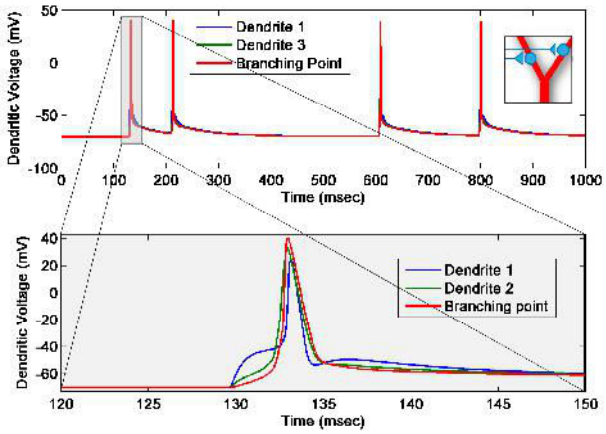

Fig. 4. Dendritic level. Observable: dendritic depolarization. Simulations are performed without CX614. We record the potentials on dendrites containing one synapse each, and at their branching point.

three different locations: on two dendrites each containing one synapse, and at a branching point (Fig. 4). Note that these results are presented in the control case only (no CX614) for clarity reasons. Finally the resulting somatic voltage was computed with 0, 5 and 10 µM CX614 (Fig. 5).

Interestingly, results at distinct levels, independently and combined, underscore the high levels of non-linearities that arise when modeling various aspects of neuronal integration. In this particular case, increases in AMPA receptor conductance at the molecular level, once combined with other ionotropic receptors currents and integrated along the dendritic tree and the soma induce a radical increase in neuronal excitability (Fig. 5). In particular, as the concentration of modulator increases, two phenomena can be observed: (i) neuronal spike timing is shifted, as spikes occur earlier than in control conditions, and (ii) additional spikes appear for the same stimulation protocol. Additional simulations (results not presented here) in which even higher

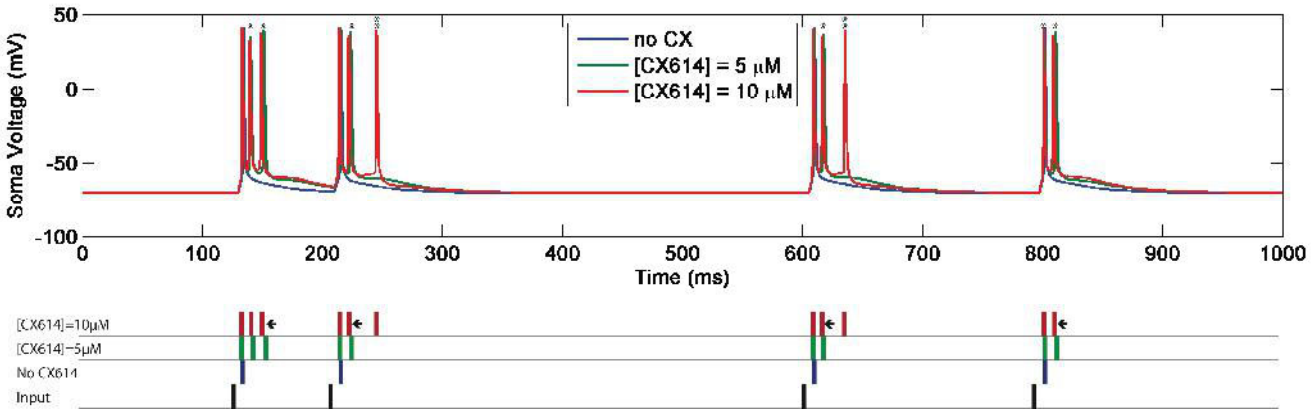

Fig. 5. Top: Effects of different concentrations of the positive AMPA receptor modulator, CX614, on postsynaptic somatic potential of a CA1 hippocampal neuron in response to a random inter-pulse interval stimulation at a mean frequency of 4 Hz. Responses are shown for a 1000 millisecond window. In the presence of CX614, note the increase in frequency of action potentials: in some cases, one additional spike (*) and other cases two additional spikes (**) for the same presynaptic single action potential. Bottom: Timing of the postsynaptic spikes at various concentrations of CX614; presynaptic action potential (input) is compared to the timing of the postsynaptic spikes. Note that spikes occur earlier with increasing CX614 concentration.

concentrations of modulator were applied generated a much stronger excitability, suggesting the potential rise of epileptiform activity.

IV. CONCLUSION

We herein highlighted the main principles of our modeling approach that incorporates complex non-linear dynamics ranging from subsynaptic biomolecular level up to the neuron level. Our modeling approach uses adaptive levels of detail concepts emphasizing (i) variable step numerical method, (ii) event-constrained asynchrony and (iii) temporal relaxation. Utilization of these methods allowed us to successfully incorporate highly detailed molecular mechanisms and model up to the neuron level; the structure of the framework should provide sufficient flexibility for a straightforward extension towards network level.

We provided an example of utilization of our approach in the determination of the effects of perturbations of parameters at the molecular level on the functional properties observed at the dendritic and neuronal levels. One useful direct application of our approach is the study of the effect of drugs (or combinations thereof) on the nervous system, as it provides for the integration of the effects at the molecular level into a multi-scale pathophysiological modeling framework. In the example presented above, our results show how a glutamatergic receptor modulator could produce a beneficial effect at low concentrations (increased synaptic responses) but also potentially harmful effects at higher concentrations.

Future perspectives of this work consist in (i) testing the modeling framework in a network simulation to verify our ability to investigate network-levels changes and (ii) further increasing the temporal range to include slower mechanisms (i.e. signal transduction). In parallel, as the levels of spatial and temporal complexity increase, it will become crucial to develop a multi-scale, multi-objective optimization framework to facilitate calibration of all models and parameters.

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