34th Annual International Conference of the IEEE EMBS
San Diego, California USA, 28 August - 1 September, 2012

# Modeling of the Nervous System: From Modulation of Glutamatergic and Gabaergic Molecular Dynamics to Neuron Spiking Activity

Jean-Marie C. Bouteiller*, *Member, IEEE*, Arnaud Legendre, Sushmita L. Allam, Nicolas Ambert, Eric Y. Hu, Renaud Greget, Anne F. Keller, Fabien Pernot, Serge Bischoff, Michel Baudry, Theodore W. Berger, *Fellow, IEEE*

*Abstract*— **One of the fundamental characteristics of the brain is its hierarchical and temporal organization: scales in both space and time must be considered to fully grasp the system's underlying mechanisms and their impact on brain function. 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. These integrations across hierarchies of the nervous system are sufficiently complex to have impeded the development of routine multi-level modeling methodologies. The present study describes an example of our multiscale efforts to rise from the biomolecular level to the neuron level. We more specifically describe how we integrate biomolecular mechanisms taking place at glutamatergic and gabaergic synapses and integrate them to study the impact of these modifications on spiking activity of a CA1 pyramidal cell in the hippocampus.**

Manuscript received March 29th, 2012. This work was supported in part by National Institute of Biomedical Imaging and BioEngineering (NIBIB, grant number 5 P41 EB001978-25) and ONR (N00014-10-1-0685) for Theodore W. Berger, by NINDS (1R01N057128-01A2) for Michel Baudry and Theodore W. Berger, and by the French Agency of Innovation (OSEO), the French 'Fonds Unique Interministériel', the Region Alsace, Mulhouse Alsace Agglomeration and the French Association against Myopathies for Rhenovia Pharma.

J-M. C. Bouteiller is with the Department of Biomedical Engineering, University of Southern California, 1042 Downey Way, DRB Building, Los Angeles, CA 90089-1111 USA (phone: 213-740-8062; fax: 213-740-5687; e-mail: jbouteil@usc.edu).

S. L. Allam is with the Department of Biomedical Engineering, University of Southern California, Los Angeles, USA (e-mail: allam@usc.edu).

E. Y. Hu is with the Department of Biomedical Engineering, University of Southern California, Los Angeles, USA (e-mail: ehu@usc.edu).

S. Bischoff is with Rhenovia Pharma, Mulhouse, FRANCE (e-mail: serge.bischoff@ rhenovia.com).

R. Greget is with Rhenovia Pharma, 20c, rue de Chemnitz, 68100 Mulhouse, FRANCE (phone: +33 3 89 32 11 80; fax: +33 3 89 55 51 45; e-mail: renaud.greget@rhenovia.com).

N. Ambert is with Rhenovia Pharma, Mulhouse, FRANCE (e-mail: nicolas.ambert@ rhenovia.com).

A. F. Keller is with Rhenovia Pharma, Mulhouse, FRANCE (e-mail: florence.keller@ rhenovia.com).

F. Pernot is with Rhenovia Pharma, Mulhouse, FRANCE (e-mail: fabien.pernot@ rhenovia.com).

M. Baudry is with the Department of Biological Sciences and Biomedical Engineering, University of Southern California, Hedco Neuroscience Building, Los Angeles, CA 90089-2520 USA (e-mail: baudry@usc.edu).

T. W. Berger is the David Packard Professor of Engineering with the Department of Biomedical Engineering, University of Southern California, Los Angeles, CA 90089-1111 USA (e-mail: berger@bmsr.usc.edu).

## 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 on the kinetics of the NMDA receptor model and the GABA A receptor model, and observe their effect on neuronal spiking. Our results indicate that 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

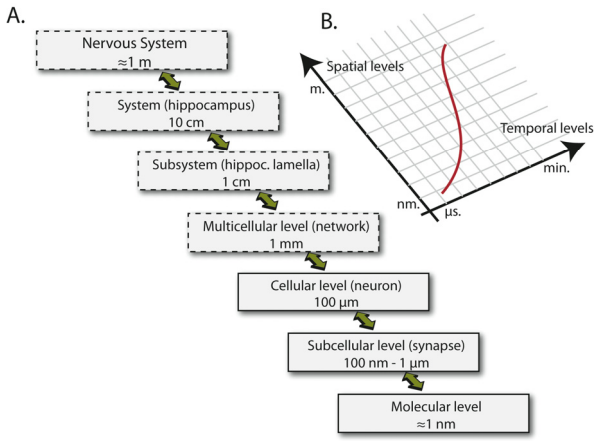


**Fig. 1.** Schematic representation of the spatial and temporal integrations taking place in the nervous system. A. Adapted from [4]: spatial scales necessary for multi-scale modeling ranging from molecular (nanometer scale) to nervous system. B. In parallel to spatial complexity, temporal complexity 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.

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 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, we use the asynchronous event-constrained communication protocol described in detail in [5] and integrate both excitatory and inhibitory synaptic inputs.

The EONS/RHENOMS modeling platforms we have developed contain a very large number of complex and highly interconnected models, represented by hundreds to thousands of differential equations. These models simulate synaptic function in the presynaptic terminal, in the synaptic cleft (incorporating diffusion processes [6], uptake and astrocytic modulation) and in the postsynaptic spine for both glutamatergic and gabaergic synapses (for more details on the elements contained in the platform, read [7], [8]). All elementary models are written in the Systems Biology Markup Language (SBML) standard. 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 use the NEURON simulator; communications between EONS and NEURON are handled using a protocol that we developed based on MPJ express [9] on the Java side, and Python for NEURON.

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.

## 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 NMDA receptor model to simulate application of the NMDA receptor antagonist AP5 [10] and the application of a GABA A receptor antagonist. Both compounds are considered at IC50 concentrations (concentrations at which the amplitude signal reaches 50% of its maximum value). The stimulation protocol consisted in presenting a train of action potentials with random inter-pulse intervals at a mean frequency of 10 Hz as presynaptic input on both glutamatergic and GABAergic synapses; our observable readouts were molecular, synaptic (excitatory postsynaptic current and voltage), and neuronal (somatic potential and firing pattern). The kinetic model of the NMDA receptor we used is a modified version of the model

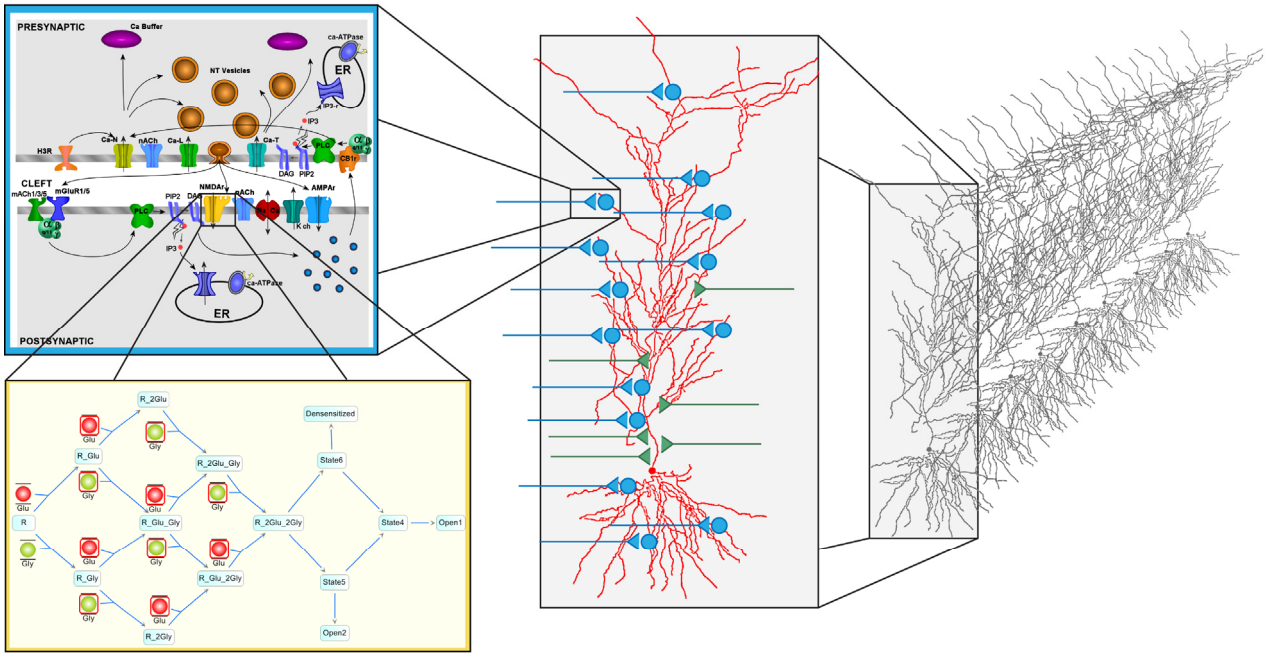


**Fig. 2.** Schematic representation of the different levels of complexity addressed in the current multi-scale modeling platform. Molecular mechanisms, such as the NMDA receptors, are represented by a 15-state kinetic model [11]. At the subcellular level, these mechanisms are geometrically coupled based on their location on the cell membrane (presynaptic, extracellular, postsynaptic, or along the dendritic tree); the resulting changes in postsynaptic currents (both excitatory illustrated in blue, and inhibitory in green) are then injected in a CA1 pyramidal cell neuron [12], which can be studied in isolation, or within a network. The results presented here are up to the neuron level.

presented in [11]. The kinetic model for the GABA A receptor is the one presented in [13]. The NEURON model used in our simulations is a CA1 pyramidal cell described in [12], in which the synaptic currents are integrated along dendritic branches (112 glutamatergic synapses in the stratum radiatum area, all receiving the same presynaptic input, and 14 GABAergic synapses located close to the soma). The resulting somatic voltage was computed in four conditions: the control (no modulator), with IC50 concentration of the NMDA receptor antagonist AP5, with a similar 50% decrease in GABA A receptor current amplitude and both modulators combined. Fig. 3 displays the percentage of inhibition of the NMDA-R in response to applications of different concentrations of AP5. The concentration of AP5 we apply for the results presented here is 100 microM.

Results obtained at the soma of the postsynaptic neuron underscore the high levels of non-linearities that arise when

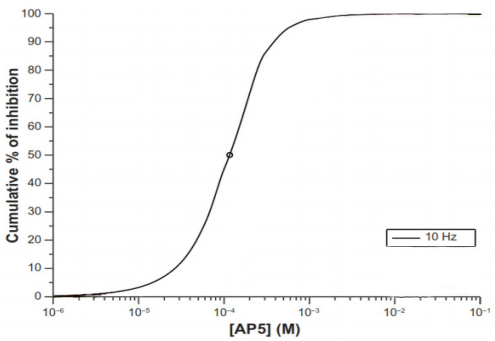


**Fig. 3**. Response at the level of the NMDA receptor elementary model: receptor channel current inhibition as a function of concentration of AP5 applied.

modeling various aspects of neuronal integration. Decreases in NMDA receptor conductance at the molecular level, once combined with other ionotropic receptor currents and integrated along the dendritic tree and the soma induce a radical decrease in neuronal excitability (Fig. 5C with 2 spikes versus Fig. 5B with 9 spikes for the control condition). Adversely, when the GABA A receptor is antagonized at IC50 concentration of antagonist (without modulation on the glutamatergic synapse), the postsynaptic spiking activity increases (Fig. 5D with 14 spikes). When both modulators are applied, the number of spikes returns to a value close to the control condition (8 spikes, Fig. 5E), but with a very different, more regular, spiking pattern.

## IV. CONCLUSION

We herein outlined 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 in excitatory (glutamatergic) and inhibitory (gabaergic) synapses on the

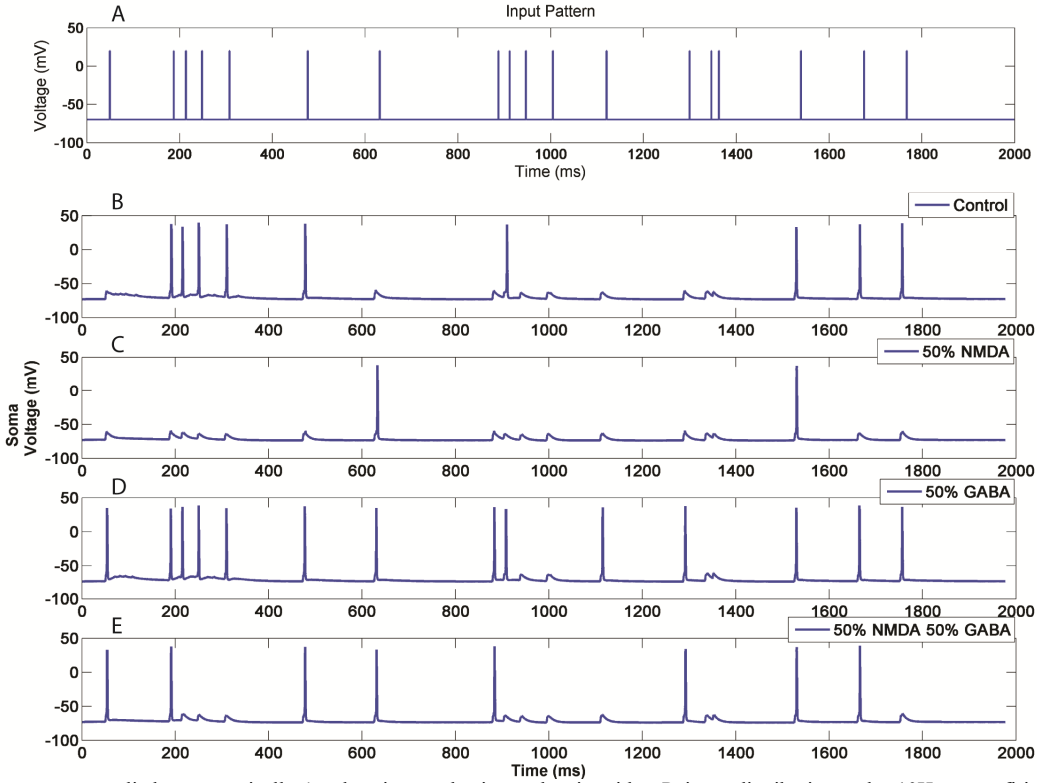


**Fig. 5.** (A) Input pattern applied presynaptically (random inter-pulse interval train with a Poisson distribution and a 10Hz mean firing frequency). (B) CA1 neuron output spiking pattern with no modulation. (C) Response with 100 microM. AP5. (D) Response with a 50% decrease in GABA A current. (E) Response with both glutamatergic and gabaergic modulations combined.

functional properties observed at the neuronal level. 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 NMDA receptor antagonist could decrease spiking activity. This is reversed using a GABA A receptor antagonist, but results in a completely different spiking pattern.

Future perspectives of this work consist in (i) testing the modeling framework in a network simulation to verify our ability to investigate network-level changes and (ii) further increasing the temporal range to include slower mechanisms (i.e. long term potentiation and 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.

## REFERENCES


[1] N.T. Carnevale, and M. L. Hines, *The NEURON Book*. Cambridge, UK: Cambridge University Press, 2006.

[2] J. M. Bower and D. Beeman, *The Book of GENESIS: Exploring Realistic Neural Models with the GEneral NEural SImulation System*, Springer, 1998.

[3] R. Brette, M. Rudolph, T. Carnevale, M. Hines, D. Beeman, J. M. Bower, et al., "Simulation of networks of spiking neurons: A review of tools and strategies," Journal of Computational Neuroscience, vol. 23, no. 3, pp. 349-98, 2007.

[4] P. Churchland and T. Sejnowski, *The Computational Brain*, MIT Press, Cambridge, 1992.

[5] J-M. C. Bouteiller, S. L. Allam, E. Y. Hu, R. Greget, N. Ambert, A. F. Keller, S. Bischoff, M. Baudry, T. W. Berger, "Integrated multiscale modeling of the nervous system: predicting changes in hippocampal network activity by a positive AMPA receptor modulator," IEEE Trans Biomed Eng., vol. 58(10), pp. 3008-3011, 2011.

[6] L. P. Savtchenko and D. A. Rusakov, "The Optimal Height of the Synaptic Cleft," *PNAS*, vol.104, no.6, pp 1823-1828, February 6, 2007.

[7] J.-M. C. Bouteiller, M. Baudry, S. L. Allam, R. J. Greget, S. Bischoff and T. W. Berger, "Modeling Glutamatergic Synapses: Insights into Mechanisms Regulating Synaptic Efficacy," Journal of Integrative Neuroscience, vol. 7(2), pp.185-97, 2008.

[8] N. Ambert, R. Greget, O. Haeberlé, S. Bischoff, T. W. Berger, J-M. C. Bouteiller, M. Baudry, "Computational studies of NMDA receptors: differential effects of neuronal activity on efficacy of competitive and noncompetitive antagonists," Open Access Bioinformatics, vol. 2010, no.2, pp. 113 – 125, 2010.

[9] M. Baker, B. Carpenter, A. Shafi, "MPJ Express: Towards Thread Safe Java HPC," 2006 IEEE International Conference on Cluster Computing, pp.1-10, 25-28 Sept. 2006.

[10] RG. Morris, "Synaptic plasticity and learning: selective impairment of learning rats and blockade of long-term potentiation in vivo by the N-methyl-D-aspartate receptor antagonist AP5," J Neurosci. vol. 9 pp. 3040–3057, 1989.

[11] S. Schorge, S. Elenes and D. Colquhoun, "Maximum likelihood fitting of single channel NMDA activity with a mechanism composed of independent dimers of subunits," J Physiol vol. 569 no.2 pp. 395-418, 2005.

[12] M. Ferrante, K. T. Blackwell, M. Migliore, G. A. Ascoli, "Computational models of neuronal biophysics and the characterization of potential neuropharmacological targets," Curr. Med. Chem., vol.15, pp. 2456-71, 2008.

[13] J. R. Pugh and I. M. Raman, "GABA Receptor Kinetics in the Cerebellar Nuclei: Evidence for Detection of Transmitter from Distant Release Sites," Biophys J., vol. 88(3), pp. 1740–1754, 2005.