33rd Annual International Conference of the IEEE EMBS
Boston, Massachusetts USA, August 30 - September 3, 2011

Modeling Neuron-Glia Interactions: From Parametric Model to Neuromorphic Hardware

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Abstract—Recent experimental evidence suggests that glial cells are more than just supporting cells to neurons – they play an active role in signal transmission in the brain. We herein propose to investigate the importance of these mechanisms and model neuron-glia interactions at synapses using three approaches: A parametric model that takes into account the underlying mechanisms of the physiological system, a non-parametric model that extracts its input-output properties, and an ultra-low power, fast processing, neuromorphic hardware model.

We use the EONS (Elementary Objects of the Nervous System) platform, a highly elaborate synaptic modeling platform to investigate the influence of astrocytic glutamate transporters on postsynaptic responses in the detailed micro-environment of a tri-partite synapse. The simulation results obtained using EONS are then used to build a non-parametric model that captures the essential features of glutamate dynamics. The structure of the non-parametric model we use is specifically designed for efficient hardware implementation using ultra-low power subthreshold CMOS building blocks. The utilization of the approach described allows us to build large-scale models of neuron/glial interaction and consequently provide useful insights on glial modulation during normal and pathological neural function.

I. INTRODUCTION

OVER the past few decades neuroscientists have found that glial cells, the most abundant type of cell in the mammalian brain, play a more significant role than just providing nutritional and structural support to their neuronal counter parts. A specific type of glial cells, astrocytes, have been found to be positioned very close to neurons and often ensheath synapses to form the so-called tripartite synapses, the sites of tri-fold structural and functional interaction between the pre- and postsynaptic terminal and the fine astrocytic processes. Astrocytes are large cells and contact hundreds of neuronal processes and tens of thousands of synapses. Limitations in imaging and experimental techniques to investigate chemical signal transmission of astrocytes have resulted in decades of neuro-centric explanations of signal transmission inside the brain [1].

Today, it is known that in the hippocampus, (where information is transformed from short-term to long-term memory) more than 50% of excitatory synapses form tripartite synapses. Furthermore, astrocytes are now known to have many of the same mechanisms as neurons, such as secondary messenger processes and receptors that bind to glutamate and other neurotransmitters [2]. These characteristics strongly suggest that astrocytes play an active role in signal transmission. Due to limitations of experimental techniques, the extent of this role has recently become a topic of debate and is still to be determined in the years to come [3]. Since research in the field of astrocytic modulation is relatively new and rapidly evolving, both software and hardware modeling tools can provide very useful insights into the role of glial cells.

One astrocytic role that has been clearly identified in tri-partite synapses is glutamate uptake. Glial uptake of glutamate from the extracellular space of neighboring synapses via excitatory amino acid transporters is required for the survival and normal operation of neurons as it regulates the activity of glutamatergic synapses [2]. In the following sections, we propose a multi-modal approach (Fig.1) and illustrate it with the results we obtained at each implementation step.

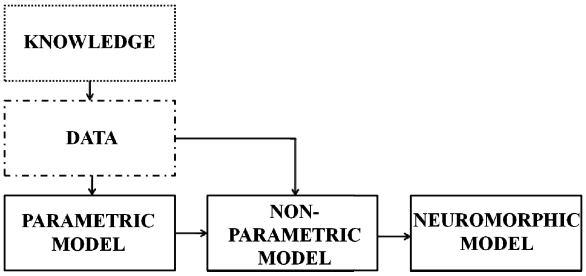

Fig. 1. The multi-modal approach of parametric, non-parametric and neuromorphic modeling methodologies for a system that investigates neuron-glia interactions. The data driven non-parametric model is obtained from direct experimental evidence or from the understanding of a complete set of parameters provided by the parametric model.

II. METHODS

Our multi-modal approach leverages the advantages of parametric and non-parametric modeling as well as neuromorphic systems to optimally model glial-neuronal interaction (Fig. 1). We first developed a kinetic schema for the glutamate transporter and incorporated it into the EONS synaptic modeling platform to explore its effects on synaptic transmission. We then implemented a non-parametric system using the Laguerre polynomial expansion method to approximate input-output characteristics of the above

Manuscript received April 14th, 2011.
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mentioned parametric model. Finally, this model was implemented in hardware for ultra-low power fast computation using subthreshold CMOS Laguerre polynomial building blocks that serve as a foundation for future large scale neuron/glia systems.

As mentioned above, our multi-modal approach consists of three steps: parametric modeling, non-parametric modeling and hardware implementation. We provide the details on each approach and their implementation below.

A. Parametric Computational Model

Parametric models inherently take into account knowledge from literature and experimental data [4]. Using these data, a kinetic model of the astrocytic glutamate transporter was added to the EONS synaptic modeling platform to explore how glutamate concentration is modulated in a tripartite synapse comprised of presynaptic, post-synaptic and astrocytic components. The EONS synaptic modeling platform allows a detailed parametric exploration of glutamate dynamics at a single synapse as it contains a large number of kinetic models of receptors, ion channels and second-messenger pathways (both pre- and postsynaptically) while taking into account diffusion processes and elements localization [5].

Glutamate is the principal excitatory neurotransmitter in the central nervous system. It plays a functional role in all learning and memory mechanisms by binding to the postsynaptic ionotropic and metabotropic receptors thereby chemically transferring information from one neuron to another neuron. Using our modeling framework, an in-depth understanding of the specific impact of each parameter in the model can be accomplished. The EONS platform was herein enhanced with the addition of a glial/astrocytic component, which contains glutamate transporters and a metabotropic glutamate receptor mechanism coupled to calcium release from ER astrocytes [6].

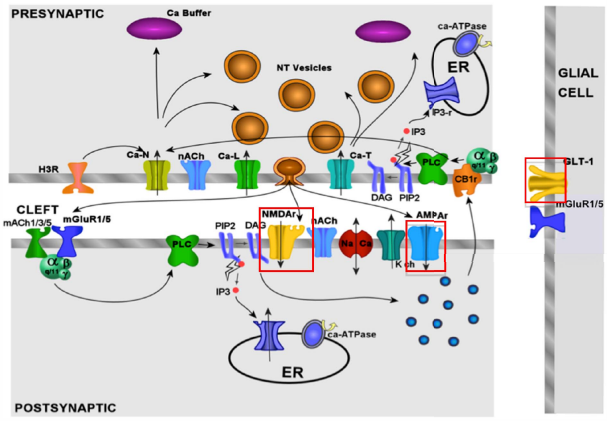

Fig. 2. An overview of some of the mechanisms modeled inside the EONS synaptic modeling platform. In this work, we study the influence of glial glutamate transporters (GLT-1) on the EPSC mediated by AMPA and NMDA receptors (highlighted in red boxes).

We have developed a glial glutamate transporter model, a mathematical representation of the several kinetic states the transporter undergoes from glutamate binding in resting state to the state of inward flow of anionic currents. Glutamate transporters uptake glutamate from the vicinity of synapses by transporting 3 Na+ ions, H+ and Glu and counter-transporting K+ and uncoupled Cl- ions [7]. The amount of glutamate taken up by the transporters is subtracted from the glutamate available to the postsynaptic receptors AMPA and NMDA. This amount depends on the position of glutamate transporters and their density around the synapse. Experimental evidence indicates a density of 2,500 to 10,000 transporters per μm^2 [8]. Assuming a cylindrical ensheathment around the synapse with a cleft height of 20nm and a 200nm diameter postsynaptic disk, we have estimated a minimum of 30 to a maximum of 120 transporters surrounding a single synapse. Calibration of our parametric model was performed using experimental evidence of glutamate transporter effect on AMPA and NMDA currents. Using this methodology an accurate model of glutamate uptake was implemented. We will discuss our findings in the following results section.

B. Non-parametric Computational Model

To build a foundation for a neuromorphic signal processing system Laguerre basis functions are implemented as the initial building blocks. Laguerre polynomial expansion provides a powerful modeling tool that allows close approximation of most signals encountered in physiology and biology. The Laguerre polynomials defined as

$$L_n(x) = \frac{e^x}{n!}\frac{d^n}{dx^n}(e^{-x}x^n) \tag{1}$$

are orthogonal functions in the interval from 0 to infinity with weight function e^{-x}:

$$\int_0^\infty e^{-x} L_n(x) L_m(x) dx = \begin{cases} 1 \text{ for } m = n \\ 0 \text{ for } m \neq n \end{cases} \tag{2}$$

This implies that the set of functions $l_n(x) = e^{-x/2}L_n(x)$ form an orthonormal basis. For time domain neuromorphic signals, $x/2$ is replaced with $p * t$ (p acting as a time scaling factor) and proper normalization factor is applied to yield the following orthonormal basis, which we will hereafter refer to as Laguerre Functions (LF):

$$\begin{cases} l_0(t) = \sqrt{2p}e^{-pt} \\ l_1(t) = \sqrt{2p}(2pt-1)e^{-pt} \\ l_2(t) = \sqrt{2p}(2p^2t^2 - 4pt + 1)e^{-pt} \\ \dots \end{cases} \tag{3}$$

A linear combination of these functions can be used to approximate causal signals that asymptotically decay in an exponential manner for large t, such as typical EPSC waveforms generated by a single action potential excitation. The coefficients c_k for this linear combination depend on the number of glutamate transporters. The Moore-Penrose Pseudoinverse provides a least squares solution for c_k:

$$LC = D, \tag{4}$$

where L is a matrix of the LF samples, D is a vector of the EPSC samples and C is the vector containing the expansion coefficients c_k. Using least square error estimation provides increased estimation accuracy in the presence of noise and reduces the requirements in terms of length of experimental data-records [9]. Additionally, the parameter p is used to adjust the decay rate of the LF. Therefore, if the number of glutamate transporter in the tripartite synapse is to be modified, the expansion coefficients and p change in order to account for this modification.

C. Neuromorphic Hardware Model

A neuromorphic hardware implementation can be used to build novel processing systems that mimic the brain signal processing methodology in its compactness, robustness, and, most importantly, power-efficiency. It can also be employed to implement multiple-input-multiple-output (MIMO) implantable brain-on-chip systems [10] that can perform on-chip spike processing.

Subthreshold CMOS analog circuit design is a natural candidate for bioelectronics because of its low power consumption as well as the inherent exponential current-voltage relation of a transistor in subthreshold that resembles biological signals and can emulate biomedical signal processing. Peripheral digital circuitry can be added to allow for more flexibility and programmability.

A CMOS analog multiplier operating in subthreshold region, as shown in Fig. 3 can simultaneously perform the generation of multiplication and exponential functions.

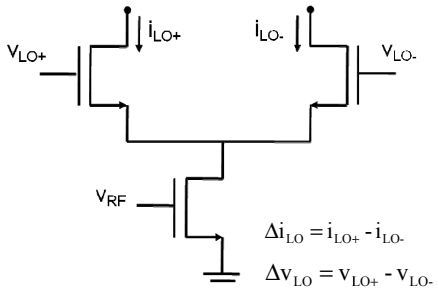

Fig. 3. Circuit Diagram of the CMOS subthreshold analog multiplier and exponential block.

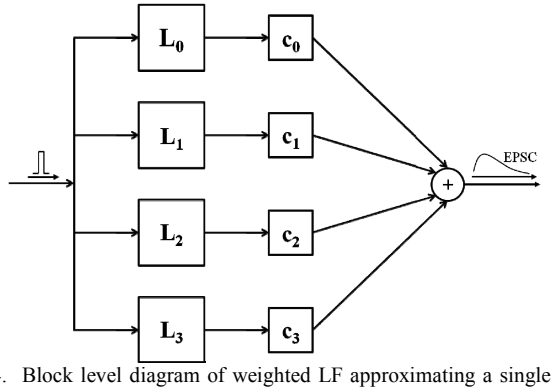

Fig. 4. Block level diagram of weighted LF approximating a single pulse EPSC.

It can be shown that for small Δv_{LO}:

$$\Delta i_{LO} = I_0 \frac{\kappa}{2u_T} \exp\left(\frac{\kappa v_{RF}}{u_T}\right) \Delta v_{LO} \quad (5)$$

where κ is the inverse of the subthreshold slope factor (typically around 0.6) and u_T is the thermal voltage (26mV at room temperature). To implement the zero order LF, $l_0(t)$, a voltage ramp is applied to v_{RF} while Δv_{LO} is a constant voltage to adjust the gain. Higher order functions are implemented in a similar fashion. Finally, linearly combining the outputs of these building blocks, EPSC signals can be generated (Fig. 4).

III. RESULTS

The data presented consists of the results obtained at different steps as our implementation shifted from parametric to non-parametric model toward hardware implementation. The post-synaptic responses in Fig. 5 were elicited by a single pulse, in principle equivalent to an action potential, which then triggers one release event responsible for glutamate diffusion which in turn activates post-synaptic receptors such as AMPA and NMDA. In the presence of glutamate transporters, our results indicate a 10% decrease in the total current and half-width measured (as also demonstrated by experimental procedures [9]. Observations from the parametric model suggest that a significant decrease in the EPSC response mediated by NMDA and AMPA receptors in the presence of glutamate. This illustrates the underlining role of astrocyte glutamate transporters in regulating glutamate receptors activation from opposing synapses. This change at the synaptic scale will become more pronounced at the neuronal level and can influence the spike timing dynamics [11].

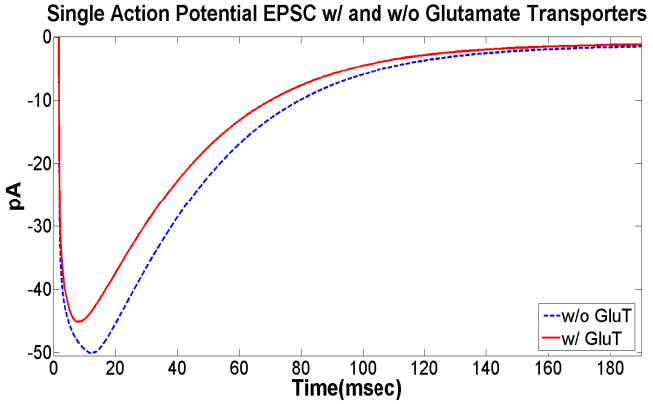

Fig. 5. Effect of glutamate transporters on the excitatory postsynaptic current as a function of time following a single release of neurotransmitter. Glutamate receptors inside the synaptic cleft receive less glutamate due to the uptake mechanism of the transporters in the vicinity of the synapse.

The following results focus on the non-parametric model and its hardware implementation. Fig. 6 shows the normalized rms error for the Laguerre approximation of a single action potential EPSC, as shown in Fig. 5, with (red) and without (blue) glutamate transporters vs. the number of LFs used. It can be seen that reasonably small error (< 3.5%) can be achieved if only 4 LF (n=0–3) are employed. This error falls within the range of acceptable experimental measurement error. If more precision is required higher order LF can be added.

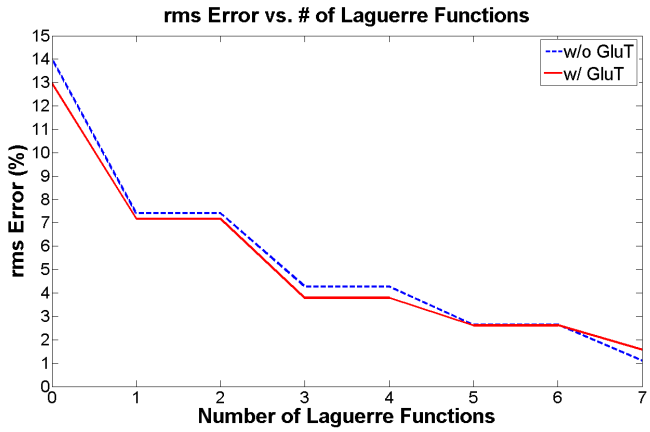

Fig. 6. Normalized rms error in percent vs. the number of Laguerre Functions used to approximate the EPSC due to a single action potential without transporters.

Finally, the Laguerre hardware model was designed and simulated in subthreshold 0.18 µm TSMC CMOS technology. The simulation result for typical corner of the 2nd order LF (n=1) circuit (blue) as compared to the ideal LF (red) can be seen in Fig. 7. The normalized rms error between the ideal curve and the circuit implementation result is 3.25%. The power consumption of each LF building block from n=0-3 is less than 15nW. Each block consumes power only if there is an action potential input and during the time the output is computed. An implementation with the first four LFs has around ten of these blocks and a large scale replication of these blocks linearly increase the area and power consumption, depending on the desired scale. Problems of variations and mismatches are alleviated by applying proper calibration schemes [12].

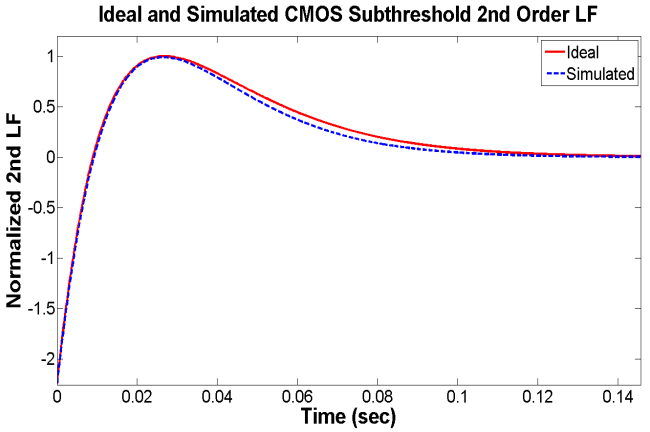

Fig. 7. Ideal 2nd Order Laguerre Function compared to the simulated CMOS subthreshold implementation.

IV. CONCLUSION

In our multi-modal approach, we leveraged the advantages of parametric and non-parametric modeling as well as neuromorphic hardware to efficiently model glial-neuronal interaction. We developed a kinetic schema for the glutamate transporter and incorporated it into the EONS synaptic modeling platform to explore its effects on synaptic transmission. We then implemented a non-parametric system using the Laguerre polynomial expansion method to replicate input-output characteristics of the parametric model. Finally, this model was implemented in CMOS for ultra-low power fast computation using subthreshold ultra-low power building blocks that serve as a foundation for future large scale neuron-glia systems.

In our future work we will extend the non-parametric model to capture multiple input pulse non-linear addition and build a compact low power hardware model that will allow us to test several stimulation paradigms. We herein focused our attention on the effect of astrocytic glutamate transporters; we plan on broadening our research to incorporate more glial mechanisms to make this system more accurate to provide insights on glial modulation during normal and pathological neural function.

ACKNOWLEDGEMENT

We would like to thank Qualcomm for support through the Qualcomm Innovation Fellowship 2010 and Rhenovia Pharma. The EONS project is funded by NIBIB and NIMH.

REFERENCES

[1] M.M. Halassa and P.G. Haydon "Integrated Brain Circuits: Astrocytic Networks Modulate Neuronal Activity and Behavior," *Annu. Rev. Physiol*. Vol. 72, Feb. 2010, p. 335-355.

[2] E.A. Newman "New Roles for Astrocytes: Regulation of Synaptic Transmission," *Trends in Neuroscience*, Vol 26, 2003, p. 536-542.

[3] K. Smith "Settling the Great Glial Debate," *Nature*, Vol. 468, November 2006, p. 160-162.

[4] D. Song, et al "A Modeling Paradigm Incorporation Parametric and Non-parametric Methods," *Conf Proc. IEEE EMBS*, 2004, p. 647-650.

[5] J-M. C. Bouteiller et al "Modeling Glutamatergic Synapses: Insights into Mechanisms Regulating Synaptic Plasticity," *Journal of Integrative Neuroscience*, Vol. 7. No.2, June 2008, p. 185-197.

[6] V.S. Ghaderi et al "Extension of EONS/Rhenoms Biosimulation Platform to a Tri-partite Synapse," Society for Neuroscience, November 2010.

[7] T.S. Otis et al "Anion Currents and Predicted Glutamate Flux through a Neuronal Glutamate Transporter," *Journal of Neuroscience*, Vol 18, No. 18, September 1998, p. 7009-110

[8] A.V. Tzingounis et al "Glutamate Transporters: Confining Runaway Excitation by Shaping Synaptic Transmission," *Nature Review Neuroscience*, Vol. 8, No.12, December 2007, p. 935-947.

[9] V.Z. Marmarelis "Identification of nonlinear biological systems using Laguerre expansions of kernels" *Annals of Biomedical Engineering,* Vol. 21, 1993, p.573-589.

[10] T.W. Berger, et al "The Neurobiological Basis of Cognition" *Proceedings of the IEEE*, Vol. 88, No. 3, 2010, p. 356-374.

[11] J.S. Diamond "A Broad View of Glutamate Spillover. *Nature Neuroscience,* Vol 5, 2002, p. 291-292.

[12] R. Serrano-Gotarredona, et al "The Stochastic I-Pot: A Circuit Block for Programming Bias Currents" *IEEE Transactions on Circuits and Systems – II: Express Briefs*, Vol. 54, No.9, 2007, p. 760-764.