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Development of a Detailed Model of Calcium Dynamics at the Postsynaptic Spine of an Excitatory Synapse

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Abstract

Postsynaptic calcium dynamics play a critical role in synaptic plasticity, but are often difficult to measure in experimental protocols due to their relatively fast rise and decay times, and the small spine dimensions. To circumvent these limitations, we propose to develop a computational model of calcium dynamics in the postsynaptic spine. This model integrates the main elements that participate in calcium concentration influx, efflux, diffusion and buffering. These consist of (i) spine geometry; (ii) calcium influx through NMDA receptors and voltage-dependent calcium channels (VDCC); (iii) calcium efflux with plasma membrane calcium pumps (PMCA) and sodium-calcium exchangers (NCX); (iv) intracellular calcium stores; and (v) calcium buffers. We herein present computational results we obtained and compare them with experimentally measured data, thereby validating the proposed model. Overall the development of such postsynaptic calcium model may help us better understand the intricacies of interplay between the different elements that shape calcium dynamics and impact synaptic plasticity in normal functions and pathologies. This model also constitutes a first step in the development of a nonlinear input-output calcium dynamics model for multi-scale, large scale neuronal simulations.

I. Introduction

Calcium has been shown to play a major role in synaptic plasticity, which involves the strengthening and weakening of the interactions between neurons and leads to long lasting changes in the signaling dynamics. The induction of this long term plasticity has been shown to involve the complex signaling of calcium in the postsynaptic spine[1]. Experimental studies undertaken to better understand calcium signaling and long term plasticity, however, are often difficult due to the physical dimensions of the synapse, as the synapse is extremely small in size, as well as the required use of fluorescence buffers which intrinsically alter the overall concentration of calcium in the spine. As such, providing a simulation platform for calcium can help supplement the current findings and may provide alternative measures for investigating these important calcium dynamics.

Here we propose to develop a mechanistic model that accounts for the major factors contributing to calcium concentration in the spine. The components of the model are based off experimental studies and findings detailing the channels, pathways and receptors which

affect calcium concentration at the spine. In the following we describe the properties accounted for in the postsynaptic calcium model, which consists of: (i) the physical properties of the synapse; (ii) channels and receptors that contribute to calcium influx into the spine; (iii) pumps and exchangers which contribute to calcium efflux; (iv) intracellular calcium stores; and (v) calcium buffering properties (Figure 1).

II. Methods

A. CURRENT IMPLEMENTATION

Spine Volume and Diffusion—The shape of the spine heavily influences the dynamics of postsynaptic calcium. Spines come in a variety of shapes and sizes, and may be categorized as thin spines, stubby spines, and mushroom spines [2]. In a traditional mushroom spine, the spine is separated by a neck and while calcium can diffuse through the neck, the diffusion is restrained by the width of the neck. As such, the spine can be considered as an isolated compartment from the dendrite [3]. In the postsynaptic calcium model, the spine volume was set to be 0.04 um^3 , the size of an average synapse, with a surface area of 0.671 um^2 and a radius of 0.267 um [2]. The diffusion rate of calcium from the spine into the dendrite was approximated to decay with a time constant of about 300 msec, in accordance with results found in [3].

Aside from diffusion from the spine to the dendrite, diffusion within the spine was also approximated using the spine diffusion model from [4]. Here, we designated a postsynaptic density area (PSD) (volume of 0.0032 um^3) for calcium influx through the NMDA receptor channels, then had the calcium diffuse into the rest of the spine volume. The diffusion rate is modeled as:

$$\left(\frac{d[X]_{spine}}{dt} \right)_{diffusion} = D \frac{A}{dist * V_{spine}} ([X]_{PSD} - [X]_{spine})$$

where A is the surface area between the PSD and the rest of the spine volume, dist is the distance between the midpoints of the PSD and the spine, V_{spine} is the total volume of the spine, and $[X]_{PSD}$ and $[X]_{spine}$ is the calcium concentration at the postsynaptic density and the spine, respectively.

Calcium Influx—The spine has two major sources of calcium influx - through NMDA receptor channels, and through voltage dependent calcium channels (VDCC).

The NMDA receptor channel is represented as a kinetic states model as described in [5]. The model consists of 8 states that represent the resting, activation, opening, and desensitization states of the NMDA receptor and its associated channel. Additionally, the magnesium ion blockade of the NMDAr channel must be considered and as such, the following equations describe the magnesium ion binding properties in the channel pore:

$$g_0 = g_1 + \frac{g_2 - g_1}{1 + e^{\alpha \psi m}}$$

$$g_{max} = \frac{g_0}{1 + \left(\frac{Mg_0^{2+}}{K_0} \right) e^{-\delta z F \psi_m / RT}}$$

$$g_{NMDA} = g_{max} \times O(t)$$

where g_0 represents the total conductance in the absence of any magnesium, g_1 , g_2 represent the open state conductances with one glutamate bound and 2 glutamate molecules bound, respectively. g_1 is set at 40 pS while g_2 is set at 247 pS. The value $\alpha=0.01$ represents the steepness of the transition between g_1 and g_2 . Mg_0^{2+} represents the external magnesium concentration and is set at 1 mM. K_0 is the equilibrium constant for magnesium set at 3.57, F is Faraday's Constant (9.64867.104 C mol⁻¹), R is the molecular gas constant (8.31434 J mol⁻¹ K⁻¹), and T is the temperature at 299.5 K. The variable ψ_m represents the holding membrane potential. δ is the affinity between NMDAr and magnesium, which is dependent on the postsynaptic potential of the synapse; the value is set to 0.8.

The calcium permeability of the NMDA channel is about 11% of the ions that flow through the channel [6]. The number of NMDA receptors is proportional to the surface area of the PSD, and approximates to about 15 [7]. Under these conditions, calcium influx upon NMDA activation reaches approximately 1.2 uM, which closely approximates the 1 uM change due to synaptically activated calcium transients described by [8].

Voltage dependent calcium channels (VDCCs) introduce calcium into the spine during backpropagation [8]. There are many different variations of VDCCs that have different channel properties and mechanics, have different functions and are found on different types of cells [9]. For dendritic spines, it was found that T-type VDCCs contribute the most to overall calcium concentration [10]. L type and R type VDCCs also appear to be activated, however calcium influx through these channels are localized into microdomains and activate secondary messenger pathways rather than contribute to overall calcium concentration [8]. Thus in this model the VDCC influx is represented through T-type channels, while it is proposed in the future that R type and L type can possibly play a role in secondary messenger modulation of calcium dynamics.

In the postsynaptic spine model, the T-type VDCCs are modelled as Hodgkin-Huxley equations using parameters defined in [11]. Additionally, the driving force attributed to the calcium gradient is considered with modifications to the Hodgkin Huxley equation shown in [12]. The single channel conductance for VDCC was set to be 7.5 pS [13] and the average number of VDCCs opened for each AP-evoked transient is approximately 5 [14]. In order to simulate AP-evoked transients in our model, we stimulate a number of synapses on the neuron model to invoke an action potential. Calcium concentration is then measured on a non-stimulated synapse, where the back-propagating action potential opens VDCCs and prompts calcium entry into the spine. Results of our simulation yield a peak amplitude of

calcium concentration that reaches about 600 nM and decays back to baseline after about 30 milliseconds - in line with results found by [15].

Calcium Efflux—Calcium is removed from the intracellular space through pumps and exchangers. In particular, Plasma Membrane Calcium Pumps (PMCA) and Sodium-Calcium Exchangers (NCX) are the major Ca^{2+} extrusion pathways in the spines and small dendrites of CA1 pyramidal cell neurons [16]. The plasma membrane calcium pump is an ATP activated pump that actively removes calcium to keep calcium at basal levels. PMCA binds to calcium with high affinity to ensure calcium is extruded, although the rate of removal is considerably slow [17]. Sodium-calcium exchangers (NCX) rely on the sodium ion gradient to pass calcium through the channels. The binding affinity of calcium to these exchangers is low, however, the exchanger transports calcium ions rapidly and is useful for quickly reducing large concentrations of calcium (i.e. after an action potential) in a short amount of time [18].

The calcium efflux channels in our platform are represented by the Hill equation, which is often used to describe binding properties of a ligand to the receptor:

$$I = I_{MAX} \frac{[Ca^{2+}]^{hc}}{K^{hc} + [Ca^{2+}]^{hc}}$$

Here, I_{MAX} is the maximum calcium current extruded from the model, K is the equilibrium constant and hc is the hill coefficient. The PMCA model has a hill coefficient of 2 and a maximum calcium extrusion current of about 0.0001 pA[19]. The NCX model has a hill coefficient of 5 with a conductance of 0.0117 pS[20]; maximal current is calculated from the sodium/calcium gradient and the given conductance. The higher hill coefficient represented in the NCX model indicates a higher affinity for calcium ions when more calcium is bound. Furthermore, the NCX model accounts for the sodium/calcium gradient in which threesodium ions are exchanged for one calcium ion [19]. In the current model, intracellular and extracellular sodium is considered constant at 10 mM and 140 mM respectively; however, in the future a dynamic model of sodium concentration may be considered for a better representation of the NCX model.

B. FUTURE WORK

Intracellular Calcium Stores—Intracellular calcium stores, such as the endoplasmic reticulum and the mitochondria, play a vital role in maintaining calcium homeostasis. The endoplasmic reticulum (ER) influences intracellular calcium concentration through SERCA pumps, which removes calcium from the intracellular space into the ER, and the IP3 and Ryanodine receptor gated channels, which release calcium from the stores. Our platform currently is in process of calibrating the model previously developed by [21], where mGluR triggers calcium release in ER stores. The mitochondria, in addition to storing calcium, plays a role in ATP energy production and cell death. Mitochondria have sodium-calcium exchangers and uniporters to maintain calcium homeostasis. Implementation of a mitochondria model is currently in the works.

Calcium Buffering—Because of calcium buffering, the actual concentration of free calcium within the spine and dendrite is relatively low compared to the total calcium present. Much of the buffers that are within the dendritic spine are ubiquitous and can be found in many different types of cells. Our postsynaptic calcium model accounts for two types of buffers, calmodulin and calcineurin, that are represented as kinetic states models, as was implemented in [21]. Calmodulin is a ubiquitous molecule involved in many cell signaling pathways and can alter properties of receptors and channels such as PMCA [17], [22]. Calcineurin is a phosphatase activated by calcium and is also involved in many physiological and development pathways [22]. The buffers in the model currently account only for the calcium buffering properties of these molecules - other downstream activities may be considered at a later time.

III. ResultS

Here, two protocols were simulated: (i) synaptically activated transients, where presynaptic neurotransmitters are released, diffuse, and bind to postsynaptic receptors AMPAr and NMDAr and leads to their channel pore opening. NMDAr being permeable to calcium generates a calcium influx in the PSD which diffuses into the spine; and (ii) AP-evoked calcium transients, where the action potential of the postsynaptic cell induces calcium influx via voltage dependent calcium channels. Results generated with the model are shown in Figure 2, and appear to be consistent with experimental results found in the literature [8], [15], thereby validating the simulated model.

IV. Conclusion

Here we created a mechanistic model of intracellular postsynaptic calcium concentration integrating the knowledge of the various channels and pumps that influence its dynamics. This work is still in progress, and aims to yield an in-silico platform for studying postsynaptic calcium dynamics and homeostasis.

Following the development of the calcium model, our research will adapt the postsynaptic calcium model to multi-scale simulations, integrating previous work involving Volterra representation of nonlinear dynamics [23] with the mechanistic calcium model presented here. The development of this input-output relationship based model of postsynaptic calcium will mitigate the computational cost otherwise needed to simulate all channels, receptors, and pathways which contribute to calcium concentration. As a result, incorporation of realistic nonlinear calcium dynamics in large scale network models would thus become feasible. Integrating the calcium dynamics can, in turn, vary the synaptic strengths and provide a better understanding of synaptic plasticity in simulated neuron network models. Additionally, pathological cases and effects of therapeutics on calcium dynamics would become observable in both the micro-scale (biomolecular) and macro-scale (network), potentially shedding light on the interplay between the various mechanisms behind debilitating diseases such as Alzheimer's disease.

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V. References

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Figure 1. Overview Diagram of the Postsynaptic Calcium Model and its Components.

The components of the model are separated into five categories: (i) Spine Properties, which account for calcium dynamics due to the physical features of the synapse; (ii) Calcium influx, concerning channels and receptors which allow calcium to flow in from the extracellular space; (iii) Calcium Efflux, includes pumps and exchangers responsible for extruding calcium from the intracellular space; (iv) Intracellular calcium stores, where calcium is stored and released internally from the cell; and (v) Diffuse calcium Buffers, which control the amount of free calcium present in the spine.

Figure 2. Preliminary Results from the postsynaptic calcium model.

Calcium can flow into the spine either through NMDA receptor channels or through voltage dependent calcium channels. A.) The synaptically activated calcium influx in response to a ten 5 Hz fixed interval pulses. For synaptically activated transients, NMDA receptor channels are the major source of calcium. Levels reach up to 1.2 uM, which is within the ~1 uM range as reported by [8]. B.) Action potential-evoked calcium transients induce calcium influx into the cell during backpropagation via T-type voltage dependent calcium channels. Simulated calcium levels reach about 700 nM (blue), which is very similar to the fluorescence results seen in [15] (red).