**Toward Accurate Modeling of Calcium Transients in Astrocytes**

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* **Introduction**

Neurodegenerative diseases such as Alzheimer’s and Huntington’s diseases as well as other neurological disorders such as epilepsy occur as a result of remodeling or loss of homeostatic functions of the central nervous system (CNS) [1, 2]. A major modulator of these functions are astrocytes, star-shaped cells that reside among neurons and blood vessels [3]. Although not excitable, astrocytes generate intracellular calcium transients that regulate their activities, including a) the release of neuroactive compounds such as D-serine and adenosine 5-triphosphate (ATP) [4, 5]; b) regulation of blood flow in several brain regions such as the formation the blood-brain barrier (BBB) [2]; and c) uptake of neurotransmitters such as glutamate and GABA [6]. The mechanisms of these calcium transients are not fully characterized. This is due to the intricate interplay among a multitude of neurotransmitters, channels, pumps, receptors, and internal organelles in an astrocyte [7]. An example of such a mechanism is the calcium release from the endoplasmic reticulum (ER) initiated by glutamate, an excitatory neurotransmitter synthesized in presynaptic neurons during synaptic transmission [4]. Moreover, the strong emphasis on calcium as a basis to study the CNS is due to the well-established knowledge of its role as a second messenger in many cellular processes [7].

Astrocytes interact with the surrounding extracellular space primarily via a variety of surface receptors such as Metabotropic G-protein-coupled receptor (GPCR). This receptor enables essential communication pathways between astrocytes and neurons [4, 8]. The binding of glutamate molecules released from synaptic clef activates GPCRs (see figure 1). Once activated, GPCRs cause the elevation of intracellular calcium concentration via the release of inositol (1,4,5)-trisphosphate (IP3) into the cytosol [4, 7]. IP3, a second messenger molecule, binds to the IP3 receptor (IP3R) on the membrane of the ER. This binding induces the release of calcium into the cytosol of an astrocyte [7].

GPCRs exhibit dynamical processes that modulate the intracellular calcium release in astrocytes. At the presence of a high concentration of glutamate, the responsiveness of GPCRs decreases, and so does the production of IP3 [8, 9]. This biochemistry-based phenomenon, which is known as desensitization, occurs when a GPCR undergoes phosphorylation by a family of kinases called the G protein-coupled receptor kinases (GRKs) [9]. When phosphorylated, the receptor is uncoupled from the G-protein with the aid of β-Arrestins, a regulating protein [8]. The GPCR-Arrestin complex is then removed from the signaling cascade and internalized in the endosome [9].

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**Figure 1: A simplified schematic showing an astrocyte, calcium transient generation process, and dynamics of GPCRs.** On the left side, glutamate molecules released from the synaptic clef bind to GPCRs releasing IP3 into the cytosol. IP3 molecules then bind to the IP3 receptors on the surface of the endoplasmic reticulum leading to the release of calcium into the cytosol and occasioning the calcium transient. On the right side, above a certain threshold, glutamate binding to a GPCR causes desensitization and removal of the GPCR from the surface. The GPCR subsequently is either degraded or restored back to the surface via resensitization.

Depending on the affected GPCR subtypes, desensitization is classified into two types: a) homologous desensitization where agonist-bound GPCRs are solely phosphorylated; and b) heterologous desensitization where, in addition to agonist-bound GPCRs, other GPCRs subtypes are phosphorylated. The termination process of a desensitized GPCR occurs via degradation in the lysosome [9]. Alternatively, it is recycled to the plasma membrane to be reused in a process known as resensitization [9].

In recent years, several computational and quantitative methods have been employed to strictly study IP3-induced calcium release in astrocytes. For example, several models analyzed information encoding modes in astrocytes [10, 11], the role of astrocytes in neuronal networks in the brain [12, 13], and factors leading to the experimentally observed variation in calcium transients [14]. However, many of these models were not specific for astrocytes. In addition, experimental recordings of calcium transients in astrocytes exhibits sharp decrease although glutamate stimuli are still applied [14]. It is hypothesized that this decrease is due to the contribution of GPCR dynamics, that is the cycle of activation, inactivation, desensitization and desensitization (see figure 1). Moreover, the effect of realistic glutamate time courses on the IP3 production and degradation processes are thought to contribute to such a decline.

Our aim is to quantify the influential factors that lead to the calcium transients in astrocytes. For this purpose, we formulate a model that describes the dynamics of GPCRs upon glutamate binding. Then, we examine the plausibility of incorporating such a model with well-established IP3 production and degradation models. This will constituent a well-understood framework that could be incorporated into larger models of calcium transients. This approach will provide more insightful results about calcium transients in astrocytes, and hence probing their influence on the functions of the CNS.

* **Methods**

To extend the current models of calcium transients in astrocytes, we began by formulating a model that describes the process of desensitization and resensitization which resulted in four-variable system of differential equations. Then, a previously proposed model for IP3 dynamics [10], denoted by was modified to account for the GPCRs contribution. This resulted in a single differential equation for IP3 dynamics. We then solved the model numerically with a verity of glutamate inputs, mimicking experimental setups and biological time course. Table 1 in the appendix presents the used symbols and parameters of the model and their significances.

**GPCR dynamics**

We modeled the dynamics of GPCRs by considering their three possible states and the fact that their total number is conserved. Figure 2 shows the transition among these states and the associated rate constants. The activated GPCRs is denoted by and is expressed as:

Where γ is the extracellular glutamate concentration, is the activation rate from the original state to the activated state , is the deactivation rate from the activated state to the original state, and is the desensitization rate from the activated state to the homologous desensitization state The GPCRs that undergo homologous desensitization and heterologous desensitization are expressed by the following equations:

Where is the recovery rate from the homologous desensitization state to the original state , is the desensitization rate from the activated state to the heterologous desensitization state , and is the recovery rate from the heterologous desensitization state to the original state . By conservation, the total number of GPCRs is accounted for by the following equation:

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**Figure 2: A diagram of the biochemical processes and the associated rate constants involved in the calcium transients in astrocytes.** The upper left portion represents the dynamics of GPCR where G is the total number of GPCRs, Gd1 is the fraction of desensitized GPCRs via homologous desensitization, Gd2 is the fraction of desensitized GPCRs via heterologous desensitization, and G\* is the fraction of activated GPCRs which is influenced by the amount of glutamate (γ) present.The process of IP3 production and degradation leading to intracellular calcium transients are presented from PLCβ and onward.

**IP3 dynamics**

To model the production and degradation of IP3 in astrocytes, we modified the formulation proposed by De Pittà et al. [10] to account for the dynamics of GPCRs. For the production, we considered the two phosphoinositide-specific phospholipase C (PLC) pathways of the hydrolysis of phosphatidylinositol 4,5-bisphosphate (PIP2), these are PLCβ and PLCδ [16, 17]. The modified IP3 production through the PLCβ pathway, denoted by , is expressed by the following equation:

where is the maximum IP3 production via PLCβ pathway. The IP3 production through the PLCδ pathway, denoted by , remained as proposed by De Pittà et al. [10]:

where is the maximal rate of IP3 production via PLCδ, is the inhibition constant of PLCδ activity, is the calcium affinity of PLCδ, is the IP3 concentration, and is the intracellular calcium concentration.

As to the IP3 degradation, we follow the linear approximations proposed by De Pittà et al. [10]. The IP3 degradation through the dephosphorylation by inositol polyphosphate 5-phosphatase (IP-5P), denoted by , is expressed as:

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Where is the maximal rate of degradation of IP3 via IP-5P. The IP3 degradation through the phosphorylation by the IP3 3-kinase (IP3-3K), denoted by , is expressed as:

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Where is the maximal rate of degradation of IP3 by IP3-3K, is the maximal rate of degradation of IP3 via IP3-3K and is the calcium affinity of IP3-3K. The complete IP3 dynamics is thus expressed as:

**Simulation and Data Analysis**

The system was solved numerically using MATLAB ode15s solver. The initial conditions of the system were set to be the steady-state values of each variable (see table 1 in the appendix). The bifurcation analysis in Handy et al. [20] was referred to validate the model. The extracellular glutamate concentration was set as a varied input to the system. The calcium responses were obtained with square pulse mimicking bath application of glutamate, as well as brief spikes of glutamate which resembles biological glutamate pulses. The strength, duration, and intermediate time among pulses and spikes were varied. The maximum values of each variables were detected. Further, the total amount of receptors was calculated as the area under curve.

* **Results**

In order to characterize the GPCR model, several glutamate inputs with varied durations, frequencies, and shapes were applied. First, long bath applications of glutamate with duration of 600 seconds and varied strengths were applied to the system, and the numerical results of the model are presented in Figure 5. Clearly, as the strength of glutamate increases, the fractions of GPCRs in each state stabilize at certain values. Yet, at low levels of glutamate, say less than 50 GPCRs transition among states. It is worth noting that the sum of the different states at each level of glutamate sum to unity.

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**Figure 9: The behavior of GPCRs with long bath applications of glutamate.** The glutamate baths were applied for 600 second and their strengths were varied from 1 to 100 Each variable approaches its steady state

Additionally, as shown in figure 6, two consecutive short-bath glutamate square pulses with duration of 150 seconds were applied at different frequency regimes. The red curves correspond to high frequency of applied glutamate pulses while the blue curves correspond to low frequency of applied glutamate pulses. Once glutamate is applied, the fraction of activated GPCRs (G\*) increases sharply and then declines. Concurrent with this decline, the fractions of desensitized GPCRs, both homologues (Gd1) and heterologous (Gd2), start to increase, yet at different rates. When the glutamate bath is turned off, the fraction of GPCRs in the original state (G) increases. In addition, the behavior of each of the GPCR states differ under each of the two regimes. The second blue glutamate square pulse results in a higher amplitude of G\* relative to preceding one, whereas the second red glutamate square pulse results in a lower amplitude of G\*. Further, the increase in the homologous desensitization (Gd1) induced by the glutamate input is sharper than the increase in the heterologous desensitization (Gd2).

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**Figure 6: The results of GPCR model dynamics. Left Panel:** GPCR dynamics evoked by two consecutive 150 s square glutamate pulse. **Right Panel:** GPCR dynamics evoked by several 60 ms glutamate spikes.Starting from the top, glutamate inputs induce the transition from the original state (G) to the activated state (G\*), and subsequently to the desensitized state which includes homologous Gd1 and heterologous Gd2 desensitization.

To put the factors that contribute to GPCR activation and desensitization into perspective, the effect of varying the intermediate time between glutamate stimuli was examined. Figure 7 shows the effect of varying the intermediate time between two consecutive short-bath glutamate square pulses with duration of 150 seconds. As the intermediate time between the glutamate stimuli increases, the fraction of the GPCRs at the original state (G) increases, and so does the fraction of activated GPCRs (G\*). Simultaneously, the fraction of desensitized GPCRs, Gd1 and Gd2, decrease.

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**Figure 7: The effect of varying the intermediate time between glutamate pulses on the GPCRs states.** As the intermediate time increases, the GPCRs transition from the desensitized state to the original and activated state.

The recovery percentage of GPCRs was determined by comparing the total amount of activated GPCRs evoked by the second glutamate pulse to the initial amount of activated GPCRs evoked by the first glutamate pulse. Figure 8 shows the result of applying two bath applications of glutamate and varied strengths, duration and frequencies. While increasing the intermediate time between glutamate pulses is correlated with an increase in the recovery rate of GPCRs, varying the strength and duration of the glutamate bath do not change the recovery rate drastically. In addition, around 95% of the desensitized GPCRs recover to the original state if the intermediate time pulses is around 500 seconds, and 100% recovery occurs at an intermediate time of 2000 seconds. Moreover, in the regime where the duration of the glutamate bath is 50 seconds and unlike the 150 seconds duration regime, the recovery rate exhibits a notable decrease at small values intermediate time, as apparent by the trough at 10-100 seconds.

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**Figure 8: The effect of varying strength, duration and intermediate time on the recovery of GPCRs.** Increasing the intermediate time between glutamate pulses increases the recovery rate. Varying the strength and duration of glutamate bath does not affect the recovery rate.

A biologically realistic train of glutamate spikes with a strength of 500 was applied to the model. Figure 9 shows the fraction of activated of GPCRs evoked by a train of glutamate spikes with varied intermediate time among spikes. Comparing the different regimes, as the intermediate time among spikes increases, the fraction of activated GPCRs increases as noted by the different lines. At the regime where the intermediate time is 1000 seconds, the fraction of activated GPCRs is relatively constant at all spikes. Further, within each regime, as the number of spikes increases, the fraction of activated GPCRs decreases. In addition, as shown in figure 10, the fraction of desensitized GPCRs changes as a function of the intermediate time among the spikes. The maximum rate of homologous and heterologous desensitization occurs at a specific range of intermediate time, that is less than 100 seconds. The rate continues decreasing as the intermediate time increases.

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**Figure 9: The effect of varying the intermediate time in a train of glutamate spikes.** The fraction of activated GPCRs increases as the intermediate time among pulses increases. The fraction of activated GPCRs decreases as the number of spikes increases.

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**Figure 10: The effect of varying the intermediate time in a train of glutamate spikes on the desensitization rate.** The maximum rate of desensitization occurs at a specific range of intermediate time.

* **Discussion**

In order to model the sharp decrease observed in experimental recordings of calcium transients in astrocytes, we developed a model of the GPCR dynamics upon glutamate binding, and modified the model proposed by De Pittà et al. [10] for IP3 production and degradation accordingly. We performed several numerical simulations with a variety of glutamate time courses to characterize the factors that control the dynamics of GPCRs. It was found the frequency and number rather than the strength and duration of glutamate stimuli play a critical role in the activation, inactivation, desensitization, and resensitization of GPCRs.

GPCR dynamics are controlled by the presence of extracellular glutamate. As figure 9 showed, the increase in the concentration of glutamate is associated with an increase in the transition of GPCRs from the original state (G) to the activated state (G\*). Concurrent with that, the GPCRs start to be desensitized mainly through the homologous desensitization (Gd1) and less through the heterologous desensitization. The reason why the latter decreases as the glutamate concentration increases is that most of the GPCRs are being desensitized directly through the homologous desensitization at a high rate; hence there is not enough time for GPCRs to desensitize adjacent GPCRs. Moreover, the rate of resensitization- the transition from Gd1 and Gd2, to G- decreases as the strength of glutamate increases. As the concentration of glutamate increases, less activated GPCRs are inactivated, contributing to the decrease in G.

The length of the intermediate time among pulses or spikes of glutamate was shown to be the most crucial in determining the rate of activation of GPCRs. As in figure 7, increasing the intermediate time among glutamate stimuli allows for higher level resensitization (i.e. higher level of transition to G state). Thus, more GPCRs are available in the original state to be activated which is manifested by the increase in G\*. While the rate of desensitization, both Gd1 and Gd2, decreases as the intermediate time increases, heterologous desensitization exhibits a peak at small values of the intermediate time. This increase is due to the mechanism of the heterologous desensitization, which occurs when homologously desensitized GPCRs lead adjacent GPCRs to desensitize. In other words, more frequent glutamate stimuli limit the desensitization of GPCRs to the homologous pathway. Moreover, a further increase in the intermediate time allows for GPCRs recovery to original state and hence the rate of desensitization will decrease.

The recovery rate of GPCRs was shown to be dependent solely on the length of the intermediate time among glutamate stimuli. As shown in figure 8, varying the strength and duration of glutamate pulses does not affect number of recovered GPCRs. Furthermore, it was shown that total recovery of desensitized GPCRs takes around 2000 seconds. In addition, the number of sequential glutamate stimuli affect the rate of activation of GPCRs. Figure 9 showed that as the number of glutamate spikes increases, the activation of GPCRs decreases at each spike. This is due to the fact that desensitization of GPCRs increases as the number of glutamate stimuli increases (see figure 6, left panel) and GPCRs at the original state G are depleted. Hence, no GPCRs are available to be activated.

Several previous works on calcium transients in astrocytes did not take into account effect of GPCR dynamics. The work by Taheri et al [14] and Handy et al [20] modeled the calcium transients in astrocytes without considering the effect of GPCRs on the IP3 production and degradation. In addition, the work by De Pittà et al. [10] developed an IP3-induced calcium dynamics without considering the effect of GPCRs and other essential players in astrocytes. We think that GPCRs (re)desensitization processes are essential players in the calcium signaling in astrocytes as they a) control the activation of GPCRs and hence the production of IP3, and b) cannot be approximated by simple constant parameters as evident by their complicated cyclicity and dependency on the glutamate parameters. Building upon these works by incorporating the GPCRs dynamics as well as biologically realistic glutamate time courses will result in a more accurate simulation and understanding of calcium dynamics in astrocytes.

While our model obeys the well-established biological description of the activity of GPCRs [8-9], there are several assumptions that underlie it. First, the distinction between the homologous and heterologous desensitization and the mechanism of each are still not well understood [9]. Second, due to the lack of experimental recordings of glutamate and the induced IP3, it is not possible to test the GPCRs model alone. Most of the related works report ultimate calcium transient recordings. Therefore, to verify our model, the formulation of GPCRs and IP3 dynamics have to be incorporated into the full model of calcium transients and compared to such experimental data.

As we developed a well characterized and understood computational model for GPCR dynamics and modified the IP3 production and degradation accordingly, the next step is to integrate them into previously established models of calcium dynamics in astrocytes, specifically the work of Handy et al [20]. Such integration will result in a comprehensive model of calcium transients that can be tested against experimental recordings of calcium. Our model is falsifiable, that is, if it turns out when integrated that it does not reproduce the observed decrease in the experimental data, it can be modified or discarded if necessary. If, on the other hand, it turns out that it reproduces such an observation, it will constitute a useful diagnostic tool to simulate biophysical mechanisms or predict alterations during disease states in the CNS such as epilepsy or astrogliosis [2].

* **Appendix**

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| --- | --- | --- | --- |
| **Symbol** | **Description** | **Value** | **Units** |
| **State variables** | | | |
| *c* | Intracellular calcium concentration. | 0.165 | μM |
| *p* | Intracellular IP3 concentration. | 0.147 | μM |
| *G* | Total number of GCPRs | 1 | μM |
| *G\** | Fraction of activated GPCRs | 0 | μM |
| *Gd1* | Desensitized GPCRs (homologous desensitization) | 0 | μM |
| *Gd2* | Desensitized GPCRs (heterologous desensitization) | 0 | μM |
| **Parameters** | | | |
| γ | Extracellular glutamate concentration |  | μM |
|  | Calcium concentration in the ER |  | μM |
|  | Time constant of IP3 receptors inactivation |  | s-1 |
| q | Ratio between cytosol volume and ER volume  Maximum calcium flux through IP3R  The maximum leak from cytosol to ER | 5.4054  0.222  0.002 | ----  s-1  s-1 |
| a2 | Calcium inhiation constant | 0.2 | s-1 |
|  | Maximal rate of IP3 production by PLCδ | 0.01 | μM s-1 |
|  | Inhibition constant of PLCδ activity | 1.5 | μM |
|  | Calcium affinity of PLCδ | 0.1 | μM |
|  | Maximal rate of IP3 production by PLCβ | 0.2 | μM s-1 |
|  | Glutamate affinity of the receptor | 1.3 | μM |
|  | Calcium/PKC-dependent inhibition factor | 10 | μM |
|  | Ratio of membrane transport to ER transport | 0.2 | ------ |
|  | Calcium affinity of PKC | 0.6 | μM |
|  | Maximal rate of degradation of IP3 by IP3-5P | 0.08 | s-1 |
|  | Maximal rate of degradation of IP3 by IP3-3K | 2 | μM s-1 |
|  | Calcium affinity of IP3-3K | 0.7 | μM |
|  | Rate of leak into cytosol from plasma membrane | 0.05 | μM s-1 |
|  | Rate of leak out of cytosol from plasma membrane  half-saturation level of SERCA  the maximum calcium flux through SERCA | 1.2  0.1  0.9 | μM  μM  μM s-1 |
|  | Maximal calcium flux through plasma membrane ATPase pumps | 10 | μM s-1 |
|  | Half saturation of plasma membrane ATPase pumps | 2.5 | μM |
|  | Maximum calcium flux through store-operated channels | 1.57 | μM s-1 |
|  | Half saturation of store-operated channels | 90 | μM |
|  | Homologous desensitization rate from G\* to Gd1 | 0.01 | s-1 |
|  | Heterologous desensitization rate from G to Gd2 | 0.003 | s-1 |
|  | Recovery rate from Gd1 to G | 0.005 | s-1 |
|  | Recovery rate from Gd2 to G | 0.0007 | s-1 |
|  | Activation rate from G to G\* | 0.03 | s-1 |
|  | Deactivation rate from G\* to G | 0.04 | s-1 |

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