UBC ISCI 422 "Models in Science"

Project 3: Model Construction – Report

Relating Calcium Influx Induced Dendritic Expansion to the Increased Conductance in Long-Term Potentiation Maintenance

by

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Abstract

Long-term potentiation has been implicated in memory formation and learning in the hippocampus. While the presynaptic terminal is associated with the induction of LTP, the postsynaptic terminal is associated with the maintenance of it. This paper examines the possible role of calcium-induced postsynaptic restructuring in LTP by constructing a numerical model based on the characterized kinetic properties of the individual components. The model simulates the proposed pathway from calcium influx to AMPA receptor insertion and the subsequent increase in membrane conductance. As predicted by the hypothesis, the magnitude of conductance increase was found to be dependent on the peak calcium concentration. However, because the increases were only minimal, it was

proposed other postsynaptic mechanisms also contribute to the increased conductance in addition to AMPA insertion.

1 Introduction

Hippocampus, located in both temporal lobes, has been implicated in learning and memory formation (Bliss & Lomo, 1973). The hippocampal neurons are known to exhibit experience-dependent changes in morphology and electrophysiology: the postsynaptic dendritic heads enlarges and responds to stimuli differently (Fukazawa et al., 2003; Matsuzaki et al., 2004). These changes have predicted learning performances in animals and have been attributed to memory formation. Hippocampal neurons signaling utilize glutamate, an excitatory neurotransmitter. Presynaptically secreted glutamate molecules induce excitatory postsynaptic potentials (EPSP) in the postsynaptic neuron. The membrane potential increases as spatial and temporal summation of EPSPs occurs. When the membrane potential reaches a critical threshold, the neuron fires an action potential, which propagates along the neuron to the next synapse. Long-term potentiation (LTP) refers to the relative permanent increase in the amplitude of the individual EPSPs elicited in response to stimuli. In other words, the neurons become more sensitive to voltage differences across the membrane, since the threshold has been lowered.

LTP is currently the most accepted molecular model of learning. Upon exposure to new stimuli or environment, the neurons are primed or become more susceptible, for LTP induction. Subsequent exposure to further stimulations would induce LTP. And it is the maintenance of this potentiation that has been implicated as the underlying mechanism of memory formation. LTP has two phases: early vs. late (Mockett, 2002). Each phase

involves different cellular mechanisms and contributes to different aspects of learning performance. In general, early LTP (E-LTP) induces short-term memory formation and is dependent on presynaptic activities such as increased neurotransmitter secretions (Lundh, 1998). On the other hand, late LTP (L-LTP) occurs postsynaptically to amplify and maintain the potentiation induced in the early phase. L-LTP also requires protein synthesis and receptor insertions and modifications. This paper focuses on L-LTP, which is involved in the maintenance of this potentiation.

Calcium plays an important role in neural transduction. Not only does it induce neurotransmitter release in the presynaptic axon, calcium influx in the postsynaptic dendrite is also necessary for the initiation of L-LTP. The sources of calcium influx include extracellular matrix and intracellular stores and the rate of influx is dependent on the intensity of the presynaptic stimulus (Connor et al., 1999). The hippocampus neurons express glutamate-gated calcium channels: NMDA receptors and AMPA receptors. Over-expression of either channel has been shown to increase calcium influx and enhance LTP in the postsynaptic neuron. While NMDA receptors are constantly present on the cell membrane, most AMPA receptors are inserted during L-LTP stage (Lu, 2001). AMPA receptors have lower activation energy thereby lowering the threshold for action potential (Matus et al, 2000). Other calcium channels include voltage-gated calcium channels (VGCC or VOCC), IP3 receptors and store-operated-calcium channels (SOCC). These channels are activated later in L-LTP and they also contribute to calcium influx that is necessary for LTP maintenance. This paper focuses on AMPA receptors and attributes the lowered threshold to the increased sensitivity of postsynaptic neurons.

Accumulation of the regulator protein calcium/calmodulin-dependent kinase II (CaMKII) in the postsynaptic neuron, on the other hand, has also been positively correlated to learning and memory formation. CaMKII has diverse functions in synaptic transmission, ranging from cytoskeleton rearrangement to induction of signaling pathways (Matus, 2000). In addition, direct binding of CaMKII to actin filament has been associated with stabilized cytoskeleton and reduced synaptic plasticity (Otmakhor et al., 2004). CaMKII is activated by calmodulin, which is activated by calcium (Vetter, 2003). Despite the diverse characterized roles of CaMKII defined in synaptic plasticity, the exact mechanism underlying CaMKII-dependent cellular activities are not known.

This paper utilizes the established correlations and kinetic equations of the elements to propose a mechanism underlying the LTP-dependent shift in threshold. Based on the current knowledge on the impact of LTP on the individual components mentioned, I hypothesized glutamate induced calcium influx promote cytoskeleton rearrangement and elongation of filaments which leads to enlargement of the dendritic head. Assuming that the density of AMPA receptor is constant, this increase in surface area would also increase the number of AMPA receptor inserted, thereby increasing the overall conductance of the postsynaptic neuron. It is noteworthy that pathways initiating protein synthesis are also activated upon calcium influx and is necessary for supplying the extra demand of AMPA receptors.

2 Methods

Despite the current knowledge on the different elements underlying LTP, the possible interactions between the individual elements have not been closely examined. This paper

thus proposed a model addressing the interrelationships between the elements. Based on the current established relationship and kinetics properties of individual components involved in synaptic plasticity, the proposed relationship was modeled numerically using Netlogo. Numerical modeling allows quantification of LTP induced phenomenon that cannot be accomplished by physical constructs. Furthermore, since individual proteins and endogenous molecules within a subclass are identical, analytical modeling was used instead of agent-based modeling to avoid complexity.

2.1 Model Description

The different effects of LTP on synaptic activities range from transient to permanent, including calcium influx, lowered critical activation threshold, CaMKII accumulation, and enlarged dendritic head. Calcium influx mediates multiple reactions such as protein synthesis, neurotransmitter secretion, and cytoskeleton rearrangement in both presynaptic and postsynaptic neurons. In particular, calcium activates of CaMKII, a protein which has been implicated in conversion of transient electric signal to permanently enhanced synaptic transmission. CaMKII has been associated with activity and number of AMPA receptor on the neuronal surface (Benke et al., 1998; Hayashi et al., 2000; Lisman et al., 2001; Poncer et al., 2002). The increased insertion of AMPA receptors and enhanced activity of these receptors via phosphorylation have been attributed to the shifted threshold, as they have lower activation energy than that of other glutamate receptors and are thus more sensitive to voltage differences.

In general, the rate law was used to approximate the rate of substrate consumption or product formation. However, because the order of the reactions can only be determined empirically, most reactions were assumed to be pseudo-first order reaction. In other

words, it was assumed either the rate of substrate consumption or product formation is dependent on one reactant. The rate constants and initial concentrations are given in Table 1.

Calcium influx and Calmodulin Activation. As aforementioned, calcium can enter via multiple channels. However, the activation of the various channels is time dependent and asynchronous. Upon presynaptic glutamate release, the ligand-gated calcium channels are activated first, inducing the initial calcium influx. This calcium influx in turn activates calcium release from the intracellular stores. Together, this creates a voltage difference sufficient to activate the voltage-gated calcium channel. Despite the different stages in calcium influx during LTP induction, peak calcium concentration is reached within one second after glutamate binding. Therefore, the process of calcium influx itself was not examined and the initial calcium level was assumed to have reached the maximal value.

Since the intracellular level of calmodulin is much higher than that of the peak calcium level measured, the activation of CaM by calcium was assumed to be first order. According to the rate law, the rate of production formation in a first order reaction is:

$$4\ Ca^{2+} + CaM \rightarrow Ca_4.CaM$$

$$\text{Rate of formation} = k \times [Ca^{2+}] \qquad \text{Eq 1}$$

, where k is the rate constant for calcium binding.

Ca/CaM complex and CaMKII. Although CaMKII expression and activity have been associated with LTP induction and maintenance, the exact role and target substrates of CaMKII remains unknown. Assuming each filament binds to one CaMKII, the concentration of CaMKII can be deduced from the concentration of filament. Calcium was assumed to be consumed at the rate of Ca/CaM complex formation as though

calcium chelators absent in the solution. In addition, it was further assumed that the calcium stock was not replenished and intracellular calcium store was depleted upon presynaptic stimulation. This allows us to maximize Ca/CaM formation and amplify the impact of calcium influx on dendritic restructuring.

Filament Uncapping. Although various studies have shown CaMKII stabilizes and binds directly to F-actin, kinetic properties relating the two have not been characterized (Shen et al., 1998). CaMKII-filament dissociation was assumed to occur at the rate of Ca/CaM-CaMKII association in the model. In other words, the concentration of uncapped filaments was assumed to be increasing at the rate of Ca/CaM-CaMKII association. To establish a stable cytoskeleton, actin filaments are stabilized by capping proteins, which are added to the polymerization sites on the filaments. Since the underlying mechanism of CaMKII mediated stabilization of cytoskeleton is unknown, it was assumed CaMKII either functions as capping proteins or is tightly associated with the proteins. Therefore as CaMKII are phosphorylated by Ca/CaM complex and falls off from the filaments, the filaments are now able to polymerize and elongate. The rate of filament uncapping was thus assumed to be proportional to the rate of Ca/CaM binding to CaMKII. Conversely, the uncapped filaments are depleted as they become capped again.

Enlongation & Surface Area.. G-actins, or granular actins, are actin monomers which polymerize to form filaments, also known as F-actin. Since one mole of G-actin would have the length by $l = 1.32 \times 10^{18}$ nm, the mole of G-actin transformed was multiplied by l to calculate the increase in length in general. This increase was divided by the concentration of filament to approximate the increase in the individual filament, which in turn determines the increase in the length of the major axis. Assuming the rate of

polymerization equals to the rate of G-actin transformation to F-actin state and the rate of F-actin dissociation was considered irrelevant, the filaments are elongating at the rate of:

h = [F-actin] x l / [filament] Eq. 2

Consider the spine head as a cylinder (Figure 1), LTP induces an increase in the surface area of the head at synapses. In other words, actin elongation increases the major axis of the dendritic head. The concentration of filament at the onset up of calcium influx was estimated based on the initial F-actin concentration. In addition, the concentration of filament was assumed to be constant as actin monomers polymerize, thereby attributing all the G-actin transformed to cytoskeletal elongation. surface area is dependent on the length of the cylinder.

Surface area = $2\pi r^2 + 2\pi r\, h$ Eq. 3

Therefore, the surface area changes in accordance with h.

Conductance (g). Conductance is the reciprocal of resistance and is equal to the ratio of current influx to potential differences between extracellular and intracellular environment. Current influx is mediated by channels on the plasma membrane surface; however, the channels are usually inactive in the absence of presynaptic stimulation. As aforementioned, AMDA receptors are inserted in L-LTP stage. Assuming the density of channels is consistent on the plasma membrane, an increase in surface area would also increase receptors proportionally, thereby increasing the conductance of the postsynaptic dendrite.

g = G x surface area Eq. 4

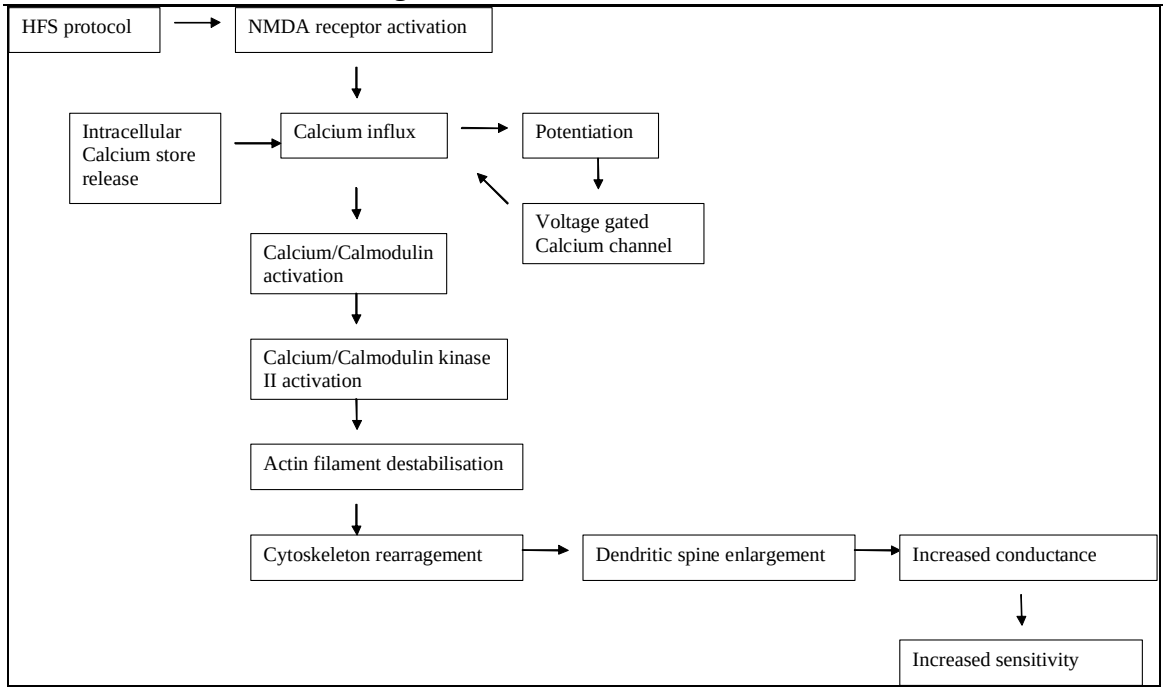

Figure 1. A schematic diagram illustration the proposed mechanism of LTP maintenance. Upon stimulation by high-frequency electric impulses, NMDA receptors are activated, causing a calcium influx from the extracellular matrix, and an initial depolarization as the neurons become more positive. This calcium influx triggers the release of intracellular stores of calcium, further increasing the cytoplasmic calcium level and depolarizing the membrane potential. Lastly, this depolarization activates the voltage-gated-calcium-channel on the plasma membrane, letting in more calcium ions. This high concentration of calcium ions activates calcium/calmodulin kinase II (CaMKII) via calcium/calmodulin (CaM). An increased level of CaMKII increases dendritic spine size and increase ion flow between neurons, innervating the target neurons with a larger current. This increase in current would result in the maintenance of LTP.

2.2 Model Verification

This paper models a pathway which relates calcium influx to dendritic head enlargement. The kinetic properties of the individual elements were incorporated to simulate one of

various phenomena underlying LTP. A trial run using the literature values was conducted to test the validity of the model. The values for the various constants are listed in table 1. The general trends produced were analyzed: an increase in intracellular calcium concentration resulted in an increase in surface area and conductance

However, this model only focuses on one of the many calcium dependent pathways upon synaptic stimulation and has a limited scope. The surface area and conductance may increase in a different magnitude when other LTP-induced changes were incorporated. For example, not only are more AMDA receptors inserted, the activation energy of the initial AMDA receptors are also lowered as they become phosphorylated. This would also contribute to the lowered action potential threshold.

In addition, EPSP of individual neuron can only be potentiated once, unless the memory is lost and EPSP has returned to baseline level. Other factors contributing to this limitation were not incorporated; thus upon arrival of another wave of calcium influx, the conductance would increase again. Therefore, this model can only be applied to the initial calcium influx which initiates the potentiation of neuron.

2.3 Experiment Description

Based on the proposed mechanism, the characteristic constants of each element were incorporated into the model. The model was hypothesized to yield an increase in conductance upon calcium influx. Following the initial increase, the conductance would reach a new steady state, allowing a permanent increase in the excitability of the neurons.

To examine the dependence of the magnitude and the rate of conductance increase on calcium concentration, a slider function was incorporated. Although the value of peak calcium level reported differs with literatures, the value lies within the range of 10~ 30

uM. In addition, as excitatory and depressive signals are known to initiate different levels of calcium influx, this would allow us to monitor the impact of the different types of stimuli on conductance.

Sliders were also incorporated for the various rate constants. The rate constants used were reported by in vitro studies, under room temperature and in artificial solvents. As the rate constants are temperature dependent, the results simulated may not be an accurate depiction of the phenomena. The slider function permits flexibility in the value of rate constants and allows us to monitor the effects of temperature might have on the magnitude of conductance increase.

3 Results

Calcium influx to LTP maintenance. Upon presynaptic stimulation, there is a 100-fold increase in intracellular calcium concentration. Figure 2 graphs the subsequent changes induced by the calcium influx. In general, there is an increase in Ca/CaM activity, actin elongation, and conductance.

After the onset of calcium influx, accumulation of active Ca/CaM complex is followed by a gradual depletion of the complexes as they bind to CaMKII. The concentration of G-actin also increases accordingly as the filaments are uncapped and become free to elongate. The physical restructuring of the cytoskeleton is eventually translated into a permanent increase in EPSP as the conductance of the postsynaptic membranes increases. Despite the rapid onset of dendritic enlargement, the rates of interactions among the individual components eventually reached plateau, though at different time point (Figure 2).

Rate constant and LTP maintenance. As rate constants are temperature-dependent properties and most of the literature values were obtained in vitro at room temperature, the validity and accuracy of the rate constants were evaluated. In the trial run, in which the literature values were used as a control, the peak conductance was 1.89000000141174 x 10^{-07} mS. The amplitude of conductance increase varied as I changed the rate constants. The experimental results were expressed as percent control value (Figure 3a). In general, increasing the Ca/CaM binding rate to CaMKII by 50% did not affect the results as much as increasing either the capping rate constants or polymerization rate constants by 50%. However, when all the rate constants were increased by 50%, the overall conductance was still increased. In addition, a similar magnitude of increase was observed when the peak calcium level was raised to 30 uM and the rate constants by 50%.

Conversely, a 50% increase in any of the rate constants reduced the magnitude of increase in surface area (Figure 3b). The change in rate constant of capping had the most impact on surface area relative to the control while simultaneous increase of the rate constants had the least impact. Similarly, a three-fold increase in calcium level yielded similar results.

Calcium and conductance. At 10uM calcium solution, the conductance was 1.89 x 10^{-07} mS. The differences in conductance measured at various calcium levels were reported as percent control conductance value. Figure 4a demonstrates a proportional increase in conductance as the initial calcium level increases. Similar patterns and slope can be observed in Figure 4b in which relative increase in surface area was examined. In addition, at lower calcium concentration, it took longer for the system to reach an equilibrium or steady state (data not shown). Ca/CaM complexes were activated at

smaller amplitude and the rate of conductance increase was also slower than of the control.

4 Discussion

Synaptic plasticity is the activity dependent modification of the sensitivity of neurons and has been implicated in learning and memory formation. On the other hand, hippocampi are believed to encode the different aspects of spatial memory via long-term potentiation and depression of EPSP. Upon exposure to stimuli, the presynaptic neurons release glutamate to activate the postsynaptic neuron. Depending on the amplitude of stimuli, the glutamate molecules are released at different rates and concentrations. These differences are amplified by postsynaptic neurons. Prolonged exposure to low glutamate concentration would result in depressed EPSP and consequently, a higher action potential threshold. Conversely, excitatory signals are translated into acute high level of glutamate levels and a lowered threshold.

Although there is an overall increase in conductance, the magnitude was not significant relative to the increase recorded empirically (~120%). This indicates the involvement of other parameters. In other words, the results implied an increase in surface area alone cannot be attributed to the increased excitability of postsynaptic neuron. Either the density of AMPA receptor or the individual conductance of the receptors is different from the initial condition. This is possible because as many studies have demonstrated activity-dependent phosphorylation of AMPA receptors in addition to their insertion. It was not incorporated in the model because the phosphorylation of AMPA receptors is not directly mediate by calcium influx. Furthermore, since LTP also induces the insertion of

NMDA receptors in addition to that of AMPA receptors, LTP may also enhance calcium influx via other mechanisms upon stimulations, such as increased rate of intracellular store release or increased affinity of CaM for calcium. However, since rate constants and reaction orders can only be experimentally determined, the modifications were not incorporated. The magnitude of calcium influx is nevertheless positively correlated to the surface area of the dendritic head. This is possible because the concentration of calmodulin is relatively large compared to that of calcium, allowing increased formation of Ca/CaM complexes, which in turn promote filament proliferation.

Because the synaptic machineries were designed to work optimally at body temperature, the reactions should be faster in vivo than in vitro. This justification was demonstrated via modification of the rate constants. Assuming these synaptic machineries work optimally in vivo, the rate constants should be larger in vivo. Thus increasing the rate constants would allow us to have a more accurate approximation of the phenomenon. As expected, when the rate constants were increased by 50%, the conductance and surface area also increased accordingly. Therefore, this synaptic phenomenon may occur at a faster rate than in vitro to trigger the onset of memory formation.

Lastly, the time dependent effect of calcium concentration provides insights into the different mechanism underlying LTD and LTP. Both LTD and LTP requires NMDA-mediated calcium influx (Ismailov et al., 2004). Different NMDA receptors have different kinetic properties, which determine their sensitivity to synaptic stimulations. NR1/NR2A respond to strong stimuli, and has higher open probability and lower activation energy yet shorter opening time, allowing rapid onset of calcium influx for a brief period of time (Erreger et al., 2005). Thus NR1/NR2A receptors have been

implicated in initiating LTP at the postynaptic terminal (Erreger et al., 2005). NR1/NR2B, on the other hand, can be activated in the presence of low glutamate concentration. They are inactivated at a slower rate than NR1/NR2A, allowing more calcium influx over time (Erreger et al., 2005). However, because NR1/NR2B receptors are also activated slower, there is a delay in calcium influx relative to NR1/NR2A mediated response. The prolonged activation and gradual calcium influx have been associated with the induction of long-term depression. This coincides with the simulated results. At high calcium concentration, not only did the system reach equilibrium sooner relative to the control, there was also a larger increase in conductance and surface area. On the other hand, it took longer for the system to reach steady state at lower calcium concentration as observed in LTD induction in vitro. However, because they are mediated by different intracellular mechanism, the proposed pathway and model do not accurately predict the subsequent change in conductance.

4.1 Summary

Upon calcium influx to the postsynaptic terminal initiated by presynaptic stimulation, a series of calcium dependent pathway is also activated, leading to spine restructuring and expansion. As the surface area of the dendritic head increases, so did the conductance. However, the simulated results indicated a minimal increase in conductance. This implies other mechanisms are also activated simultaneous at the onset of calcium influx to mediate the maintenance of LTP in vivo. The values rate constants were manipulated to justify for higher body temperature in vivo. This resulted in an increase in both the magnitude of conductance and the rate of reactions.

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Figures & Tables

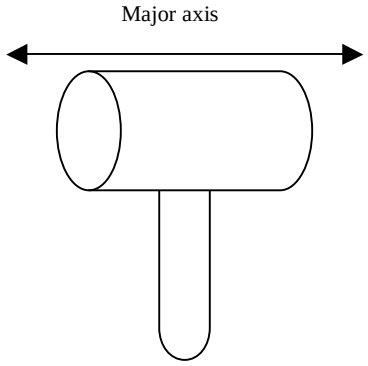

Figure 1. A schematic representation of a dendritic head.

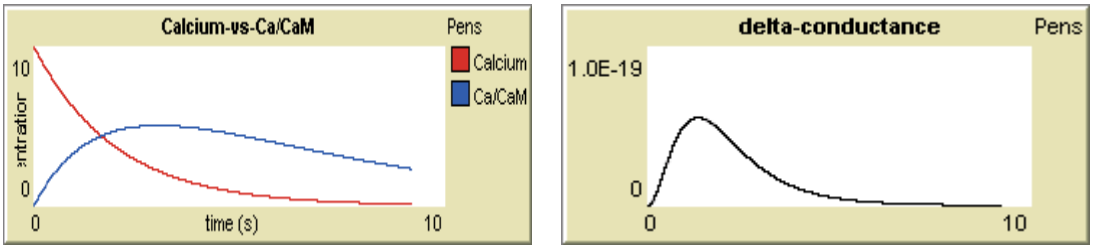

Figure 2. Following initial onset of Ca/CaM activity and rapid increase in conductance, the rate of reactions decreases and the system gradually reached a steady state.

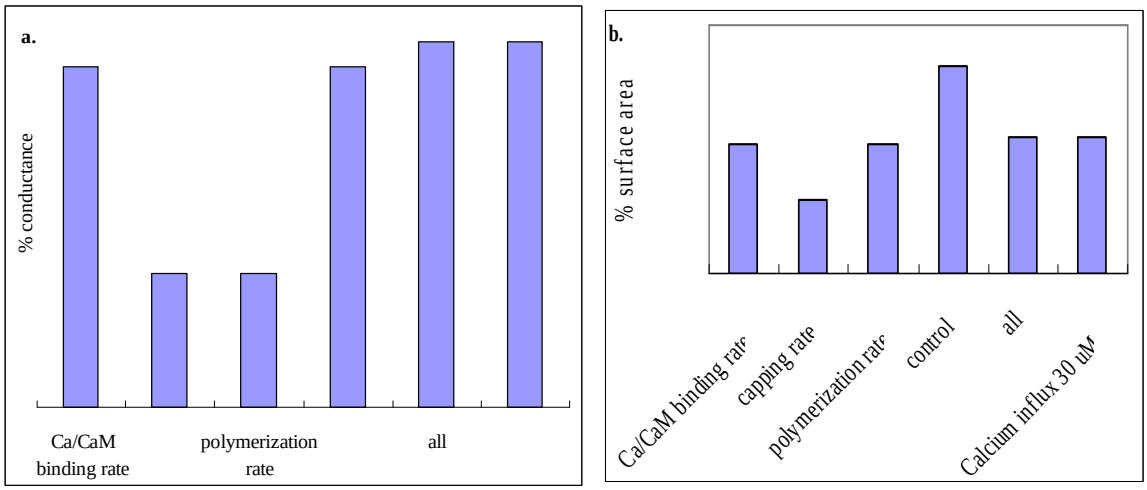

Figure 3. The magnitude of increase in conductance and surface at different values of rate constants were usedl. a. 50% increase in rate constants vs. % conductance. From left to right: Ca/CaM binding rate, capping rate, polymerization rate, control, all of the three at 10uM calcium level, and all of the three at 30uM calcium level. b.50% increase in rate constant vs. subsequent changes in surface area. Order the same as figure 3a.

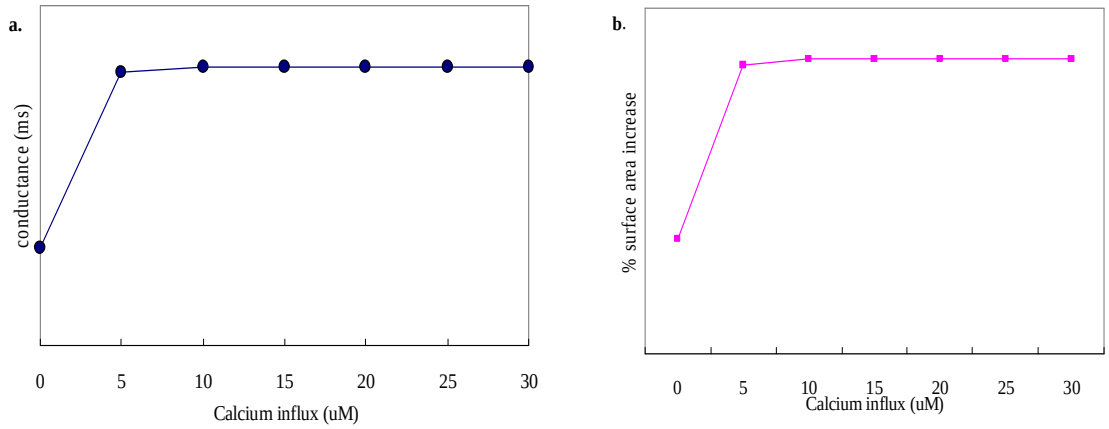

Figure 4. The magnitude of increase in conductance and surface at different calcium concentration relative to the control. a. calcium influx vs. % conductance. b. calcium influx vs. % surface area.

Table 1. Base Parameter Values

	Base value	Reference
Rate constants		
Calcium binding rate	2.0	Baylet et al., 1984
Calcium dissociation rate	0.2	Vetter et al., 2003
Ca/CaM binding rate	0.15	Lundh, D., 1998
Capping rate	3.5	Moginer & Edelstein-Keshet, 2004
Polymerization rate	2.2	Moginer & Edelstein-Keshet, 2004
Spine morphology		
Major-axis	1.23 um	Benavides-piccione et al., 2002

Minor-axis	0.53 um	Benavides-piccione et al., 2002
Conductance, G	5 x 10-8 mS	Rubin et al., 2005
Intracellular species		
Calcium	10uM	Moginer & Edelstein-Keshet, 2004
G-actin	40uM	Moginer & Edelstein-Keshet, 2004
F-actin	210uM	Moginer & Edelstein-Keshet, 2004
Others		
Actin monomer length	2.2nm	Moginer & Edelstein-Keshet, 2004

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	Raw Score		
Criterion	Instructor:	Instructor:	**Comments**
Student worked independently without requiring too much instructor assistance.			
Motivation and research question clear and interesting from a scientific perspective.			
Model clearly explained.			
Model original and ambitious.			
Assumptions are thoroughly considered and well justified.			
Experiments are appropriate to answer research question.			
Experimental results clearly explained.			
Thoroughly explores implications of results and insights gained in regard to research question.			
The page limits were satisfied.			
Total =			Final Grade: