

A Compartmental Model for Activity-Dependent Dendritic Spine Branching

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Running Head: Dendritic Spine Branching

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1 Abstract

Dendritic spines are small, mushroom-like protrusions from the arbor of a neuron in the central nervous system. Interdependent changes in the morphology, biochemistry, and activity of spines have been associated with learning and memory. Moreover, post-mortem cortices from patients with Alzheimer's or Parkinson's disease exhibit biochemical and physical alterations within their dendritic arbors and a reduction in the number of dendritic spines. For over a decade, experimentalists have observed perforations in postsynaptic densities on dendritic spines after induction of long-term potentiation, a sustained enhancement of response to a brief electrical or chemical stimulus, associated with learning and memory. In more recent work, various experimentalists suggest that activity-dependent intraspine calcium may regulate the surface area of the spine head, and reorganization of postsynaptic densities on the surface.

In this paper, we develop a model of a dendritic spine with the ability to split its transmission and receptor zones, as well as the entire spine head. Simulations are initially performed with fixed parameters for morphology to study the electrical properties of these configurations and identify parameters that increase efficacy of the synaptic connection. Equations are then introduced to incorporate calcium as a second messenger in regulating morphology. Activity affects compartmental calcium, which regulates spine head morphology. Conversely, spine head morphology affects the level of local activity, whether the spines are modeled with passive membrane properties, or excitable membrane using Hodgkin-Huxley kinetics. Results indicate that merely splitting the postsynaptic receptors on the surface of the spine may add to the diversity of circuitry, but does not change the efficacy of the synapse. However, when the surface area of the spine is a dynamic variable, efficacy of the synapse can change continuously over time.

Key Words: synapse restructuring, intraspine calcium, dendritic spine branching

2 Introduction

A spine is a mushroom-like protrusion from the surface of a dendrite in the central nervous system (CNS), with stem length of order $1.0\mu\text{m}$, stem diameter of order $0.1\mu\text{m}$, and head surface area of order $1.0\mu\text{m}^2$. A dendritic tree may be populated with hundreds to thousands of spines of different sizes, shapes and configurations. (reviewed in Segev and Rall, 1998, Segev and London, 2000, Sorra et al., 1999). Unlike electrical current in a transmission line, the CNS makes use of structural change in response to ionic potential, rather than magnetic properties, to propagate waves of communication between neurons (Johnston and Miao-Sin Wu, 1995). For many years, it was thought that axons were responsible for transmission of all information, while the dendritic arbors were merely receivers, passing the information along to the soma by integrating impulse frequencies and/or magnitudes. However, recent advances in measuring electrical potential and enhanced electron and confocal microscopy indicate that communication between axon and dendrite is a two-way street. Variations in the morphology of protrusions from the dendrite modulate transmitted or received signals, and there are active channels present in dendritic spines (Segev and Rall, 1998, Barinaga, 2000, Hausser et al., 2000, Araya et al., 2007).

Dendritic spines are abundant in brain regions involved with learning and memory. Their structure has been linked to cellular mechanisms that mediate the induction, associativity, specificity and endurance of long term potentiation (LTP). A basic assumption in electrophysiology is that memories are stored as changes in the strength of synaptic connections, and changes in the structure of dendritic spines is intrinsically linked to changes in synaptic activity (Geinisman et al., 1993, Edwards, 1995). Conversely, cortices from patients with Alzheimer’s or Parkinson’s disease exhibit biochemical and physical alterations within their dendritic arbors. Post-mortem cortices from Alzheimer’s patients exhibit reduced levels of drebin, an F-actin binding protein of dendritic spines and shafts, and may reflect an alteration in the transfer of synaptic molecules within the spines, and contribute to the decline of synaptic function and plasticity. (Mahadomrongkul et. a., 2005). The density of dendritic spines has been found to be reduced by 27% on spiny neurons in basal ganglia regions for Parkinson’s patients, along with a reduction in their dendritic arbors in the cuadate nucleus. (Stephens et al., 2005). An enhanced understanding of the interdependence of activity, biochemistry and morphology of dendritic spines will increase our knowledge of these complex and devastating diseases.

Postsynaptic densities (PSDs) are electron-dense regions on the surface of a dendrite or spine, made up of proteins, such as glutamate receptors. Luscher et al. (2000) confirm an association between LTP and an increase in the number of spines with discontinuous (perforated) and larger PSD surface areas. They report that perforated (bifurcated) synapses express more AMPA (amino-3-hydroxy-5-methylisoxazole-4-propionic acid) receptors, and a higher proportion of smooth endoplasmic reticulum and spine apparatus, thought to be involved in membrane synthesis and calcium storage. They conjecture an increase in the number of AMPA receptors may initiate growth, discontinuity, and eventual splitting of PSDs. Release of calcium may be required for AMPA receptor transport to the surface of the spine, and insertion of these receptors into the PSD may increase PSD size and efficacy of the circuit, and eventually lead to spine branching.

Neuhoff et al. (1999) endorse the notion that perforated synapses are an early morphological consequence of synaptic activation, closely associated with LTP, and correlated to enhanced synaptic efficacy. They report that perforated synapses have discontinuous PSDs which are larger, suggesting that perforations could function to increase perimeter length of receptor areas and total surface area on the spine for the location of active channels. They also conjecture that perforated synapses may be more efficient, or more specialized if released transmitters act exclusively on a given segment of the PSD, and note that a perforated postsynaptic band is correlated with a perforated presynaptic grid, which must also be involved with changes in synaptic strength. Even a short-term increase in synaptic activity connected to NMDA (N-methyl-D-aspartic acid) receptors induces an increase in perforated synaptic structures. Their results point to activity-dependent Ca^{2+} from intracellular stores as a second messenger for delivering the variety of spine head shapes and connections observed in recent experiments (Neuhoff et al., 1999). Perforated synapses, perforated PSDs, and spine branching are hot topics in the literature, and conjectures about how these morphological adaptations affect efficacy and diversity of circuitry invites theoretical modeling.

The purpose of this paper is to introduce a limited, but tractable model for a spine that can incorporate these effects, and to study various physical configurations in simulation. In Methods, the three-compartment spine head is first developed with fixed morphology. Dynamic equations are then introduced to incorporate

calcium as a second messenger in regulating continuous morphological adaptation. Activity affects compartmental calcium, which regulates spine head morphology. Conversely, spine head morphology affects the level of local activity, whether the spines are modeled with passive membrane properties, or excitable membrane using Hodgkin-Huxley (HH) kinetics. In Results, simulations for single-cycle activations identify morphologies that increase efficacy of the synapse, and those that do not, for active spines. Then a simulation over many cycles of activation with dynamic morphology leads to a periodic orbit for interdependent calcium and spine branching in passive spines. The last section is Discussion. Tables of parameters and variables, as well as a summary of equations and stability analysis are presented in the Appendix.

3 Methods

In 1988, Segev and Rall formulated a model for a single spine attached to a dendrite, using HH kinetics to generate excitable membrane properties in the spine head. Contemporary models continue to utilize HH, or more tractable versions for their kinetics, validating their output by comparison to the HH model (Gurkiewics and Korngree, 2007, Schmid and Hanggi, 2006). Moreover, recent experimental results indicate spines exhibit back-propagating *a.p.*, driven by sodium channel currents, the predominant spiking mechanism in HH (Araya et al., 2007, Rose and Konnerth, 2001, Rose et al., 1999). We are predominantly interested in the interdependence of morphology and activity, mediated locally by calcium released from internal stores. Therefore, we do not concern ourselves here with recent models for slow and fast calcium currents. Rather, we build on the work of Segev and Rall (1988) to construct a single spine attached to a dendrite, with the capability of splitting its transmission and receptor zones, as well as the entire spine head, resulting in two distinct (branched) spine heads that are attached to the dendrite through a common compartment and a single spine stem. Our goal is to study the electrical properties of these morphologies, and conversely to consider how local activity may influence the development of observed configurations.

Consider an active spine with two PSD compartments (Comp. 1 and Comp. 2) available for synaptic reception and electrically/chemically connected to each other by a resistor. These regions are also individually connected to a common, active region of the spine head (Comp. 3) that, likewise, connects to the dendrite through the spine stem (See spine schematic in Fig. 1). Each comp. of the spine is assumed to be isopotential, and we utilize HH kinetics to simulate excitable membrane properties. The spine stem is modeled as a lumped ohmic resistor (R_{ss}) in the same manner as Segev and Rall (1988), as are the resistors between spine head comps. (r_{12}, r_{13}, r_{23}). The dendrite is modeled as a cable with passive membrane properties, using a compartmental version of the cable equation (Baer and Rinzel, 1991).

3.1 Dynamic Activity

We model the spine head as three isopotential cylinders with surface area A_i (μm^2) and specific membrane capacitance C_m ($\mu\text{F}/\text{cm}^2$). Each compartment has a capacitance of $C_i = A_i C_m$ (μF). An equation for the membrane potential in the PSD comps. is obtained from a current balance relation for the capacitive, ionic,

inter-compartment, and synaptic currents, given by

$$C_1 \frac{dV_1}{dt} = -A_1 I_{ion-1} - K I_{syn} - \frac{(V_1 - V_2)}{r_{12}} - \frac{(V_1 - V_3)}{r_{13}} \quad (1)$$

$$C_2 \frac{dV_2}{dt} = -A_2 I_{ion-2} - (1 - K) I_{syn-2} + \frac{(V_1 - V_2)}{r_{12}} - \frac{(V_2 - V_3)}{r_{23}} \quad (2)$$

Current flowing between two compartments is computed as an Ohm's law voltage drop over the resistor between them (r_{ij}). Resistors between comps. are set to resting values as the average resistance of the comps. they connect ($r_{ij} = (r_i + r_j)/2$, where r_i represents internal resistance for Comp. i). These values (r_{ij} may be increased from rest to simulate varying degrees of comp. isolation. The terms I_{syn-i} represent synaptic current, and the terms I_{ion-i} represent ionic currents passing through the head membrane. We simulate synaptic activation of the spine by applying to Comps. 1-2

$$I_{syn-i} = g_p \frac{t}{t_p} e^{(1-\frac{t}{t_p})} (V_i - V_{syn}), \quad i = 1, 2 \quad (3)$$

where V_{syn} is the synaptic reversal potential, and g_p is the maximum applied conductance, occurring at time t_p . Equation (3) models a chemical synapse and is similar to applied current used in other models (Baer and Rinzel, 1991, Segev and Rall, 1988). The parameter K in Eqs. (1)-(2) may be varied to change the amount of current received in each receptor comp., where K is a number between 0 and 1. In simulations over long periods of time, Eq. (3) is repeated every 10ms, allowing the system to come to full rest between activations.

The remaining area of the spine (Comp. 3) is also modeled as a cylinder. Comp. 3 integrates the signal from the PSD comps., and is connected to the dendrite through the spine stem. An equation for the membrane potential in this comp. is obtained from a current balance relation for the capacitive, ionic, inter-compartment, and spine stem currents, given by

$$C_3 \frac{dV_3}{dt} = -A_3 I_{ion-3} + \frac{(V_1 - V_3)}{r_{13}} + \frac{(V_2 - V_3)}{r_{23}} - I_{ss}. \quad (4)$$

Terms containing the resistor r_{12} in Eq. (1-2) is a source for Comp. 1 and a leak for Comp. 2 if $V_1 > V_2$. The opposite situation occurs if $V_2 > V_1$. If $V_2 = V_1$, there is no flux through the resistor. Likewise, Comp. 3 receives current from Comps. 1 and 2 and leaks current to the dendrite when current is flowing from spine head to base (see spine schematic in Fig. 1).

In simulations where the spine membrane is assumed passive,

$$I_{ion-i} = \frac{V_i}{r_i}, \quad i = 1 - 3, \quad (5)$$

but for simulations where the membrane is assumed excitable, we use HH for voltage-dependent ionic channel currents:

$$I_{ion-i} = \gamma A_i \left((V_i - V_{Na}) \bar{g}_{Na} m^3 h + (V_i - V_K) \bar{g}_K n^4 + (V_i - V_L) g_L \right), \quad i = 1 - 3. \quad (6)$$

The activation/inactivation variables m , n and h in Eq. (6) satisfy first-order rate equations with V_i -dependent time constants and steady-state functions, set to a temperature of $22^\circ C$ (Hodgkin and Huxley, 1952). The parameters V_{Na} , V_K and V_L are synaptic reversal potentials for sodium, potassium and leakage currents with maximal conductances \bar{g}_{Na} , \bar{g}_K and g_L , respectively. The parameter γ sets channel density (see Appendix for HH details). Spine heads with excitable membrane properties can boost the signal with an action potential (*a.p.*) should voltage reach threshold for HH kinetics in any of Comps. 1, 2 or 3, and this *a.p.* may propagate to adjacent comps. and increase current delivered to the dendrite. The last term in Eq. (4) represents the spine stem current, once again as an Ohm's law voltage drop across the resistor:

$$I_{ss} = \frac{(V_3 - V_4)}{R_{ss}}. \quad (7)$$

The dendrite, here, is considered a distal branch. Potential is modeled with a compartmentalization of the cable equation (Baer and Rinzel, 1991). It is a passive cylinder of diameter d (μm) and unit electrotonic length ($\lambda = 180\mu\text{m}$ physical length). The cable is composed of ten comps. connected by resistors, each representing the average internal resistance of connecting comps. The spine stem is connected to one end of the dendrite (V_4) and the distal end (V_{13}) is sealed. This is computationally equivalent to a spine attached to the midpoint of a dendrite of the same diameter with dimensionless length 2 (Segev and Rall, 1988).

$$\tau_m \frac{dV_4}{dt} = \frac{-2(V_4 - V_5)}{(dx)^2} - V_4 + \frac{2R_\infty}{dx} I_{ss} \quad (8)$$

$$\tau_m \frac{dV_i}{dt} = \frac{(V_{i+1} - 2V_i + V_{i-1}))}{(dx)^2} - V_i, \quad i = 5 - 12 \quad (9)$$

$$\tau_m \frac{dV_{13}}{dt} = \frac{-2(V_{13} - V_{12})}{(dx)^2} - V_{13}. \quad (10)$$

Here, $\tau_m = R_m C_m$ represents the membrane time constant, where R_m is the resistance across a unit area of passive membrane ($\Omega \cdot \text{cm}$), and C_m is the specific membrane capacitance ($\mu\text{F}/\text{cm}^2$). The parameter $R_\infty = R_m/\pi\lambda d$ represents the cable's input resistance. For a detailed derivation of the cable equation, see Baer and Rinzel (1991). Parameter values for dynamic activity are identified in the Appendix.

3.2 Dynamic Spine Branching

Recent experiments implicate intraspine calcium as a mediator for changes in dendritic spine structure. In one experiment, release of calcium from internal stores, in response to pulse applications of caffeine, induced a small transient rise in C_a^{2+} (200 – 400nM), and an increase in the length of spine stems (Korkotian and Segal, 1999). Conversely, a second experiment (Halpain et al., 1998) induced a rapid collapse of dendritic spine stems by stimulating cultured neurons with glutamate. This caused maximal calcium influx, raising intraspine calcium to much high levels. Harris conjectured (1999a) that a small amount of electrical/chemical activity may increase a spine's level of free calcium within the cytosol, initiating synapse restructuring

through actin polymerization. However, a higher level of activity may cause calcium influx and induce a breakdown in circuitry, perhaps due to actin depolymerization.

An earlier paper (Verzi and Baer, 2004) theoretically explored the hypothesis that activity-dependent free intraspine calcium levels regulate spine/dendrite connectivity, utilizing dynamic stem resistance as a measure for spine stem geometry. Since the surface area of the spine head affects its capacitance, as well as the amount of available receptor channels, it is of interest to explore how free intraspine calcium levels may regulate spine head branching, and ultimately the signal delivered to the dendrite, utilizing dynamic total spine head surface area as a measure. While the internal cross-sectional area of spine compartments or the spine stem is inversely proportional to the unit's conductance, that spine surface area is considered proportional to the surface area covered by PSDs, and therefore directly proportional to the number of channels available for ionic transfer (see Fig. 2).

Suppose the exposed surface area of the spine head is not fixed, but instead a dynamic variable ($A_{sh} = A_1 + A_2 + A_3$), changing in response to the amount of free calcium within the cytosol of the spine. The work by Luscher et al. (2000) indicates that morphological remodeling of the postsynaptic membrane and functional changes in synaptic strength are related: That induction of LTP through a rise in postsynaptic calcium concentration and activation of signaling cascades enhances actin-dependent dynamics and promotes endo/exocytotic mechanisms in receptor channels. We propose a phenomenological model, wherein activity-dependent total intraspine calcium (C_a) serves as a second messenger for the surface area of the spine head: A moderate level of local activity, over time, increases intraspine free calcium and induces spine branching, but very large and sustained levels of local activity may ramp-up calcium to a critical level (C_{crit}), inducing the branches to coalesce, decreasing the available surface area and ionic transfer through channels. With a reduction in exposed channels, synaptic potential is reduced for passive spines, and the probability for *a.p.*-generation (bursting) decreases for active spines, thereby decreasing the amount of current delivered to the dendrite. These assumptions are similar to those proposed in Verzi and Baer (2004) for calcium mediated spine stem restructuring. However, the Verzi-Baer model (2004) suggested that spines may retract into the dendrite to re-emerge to create two new synapses, while the model for spine branching presented here merely suggests structural change within a single spine to modulate signal transduction.

We view the spine stem current given in Eq. (7) as an important measure, over time (minutes to hours), of local electrical/chemical activity, regardless of whether the current is flowing from dendrite to spine head, or spine head to dendrite. The following subsystem, appended to the model for dynamic activity explores the possibility that this interaction controls slow, local changes in free intraspine calcium, that regulates spine branching:

$$\frac{dC_a}{dt} = \epsilon_0(\eta|I_{ss}| - \rho)(C_a - C_{min}) \quad (11)$$

$$\frac{dA_{sh}}{dt} = -\epsilon_1(C_a - C_{crit})(A_{max} - A_{sh})(A_{sh} - A_{min}), \quad (12)$$

$$(13)$$

where A_{sh} represents the dynamic sum of surface areas for Comps. 1-3 above.

Free intraspine calcium (nM) changes proportional to activity (regardless of direction), relative to a minimal level (ρ), increasing when $|I_{ss}| > \rho/\eta$ and leaking away slowly when $|I_{ss}| < \rho/\eta$. The magnitude of $|I_{ss}|$ is related to the total spine head area ($A_{sh}(t)$), imposing a kinetic upper bound for calcium when the sum crosses a threshold that changes the sign of $\eta|I_{ss}| - \rho$. The lower bound for calcium assures a minimal calcium level required to maintain the spine (Luscher et al., 2000). Equations (12)-(12) model slow, bounded changes in spine head structure as measured by compartmental surface area. Activity-dependent calcium regulates a change in surface area, and a critical intraspine calcium level (C_{crit}) controls the direction of change, decreasing for $C_a > C_{crit}$, simulating branch reabsorption, and increasing for $C_a < C_{crit}$, simulating spine branching. The lower bound (A_{min}) assures a minimal spine with total surface area $> 1.0\mu\text{m}^2$, and the upper bound (A_{max}) assures a total surface area $<$ an average spine head that has been split down the middle (see Fig. 2). Initial conditions and parameter values for dynamic spine branching may be found in the Appendix.

The parameters $\epsilon_i \ll 1$ for $i = 0-1$ deliver slow, biochemically-mediated changes in spine head morphology (minutes to hours), relative to the rapid changes in dynamic activity (ms). Therefore, stimulation with I_{syn} is repeated every 10ms, allowing the system to come to rest between activations. Since spine branching has been observed over minutes to hours, and ions flow on a time scale of milliseconds (ms), the computation time for a single simulation could be on the order of hours. For simulations involving dynamic morphology, synaptic input is repeated every 10ms, long enough to allow potentials in the head and dendrite to return to resting values. We seek values for ϵ_i , $i = 0-1$, that reduces computation time, but preserves the basic dynamics of the system as $\epsilon_i \rightarrow 0$. Using a computer animation program, we choose an initial values for ϵ_i and animate the time course over 60 cycles of synaptic activation. Next, we halve ϵ_i , compute results over 120 cycles, and superimpose the animation of every-other cycle over the 60-cycle run. As we successively halve ϵ_i , the animations converge. We repeat this process for $i = 0-1$, and choose $\epsilon_i = \epsilon_i^*$, sufficiently small and computationally efficient, without compromising the integrity of the dynamics for $\epsilon_i < \epsilon_i^*$, $i = 0-1$.

4 Results

Equations for dynamic activity were resolved using a FORTRAN program with a GEAR solver on a Sun V880, running Solaris 9. To validate the model, we initially ran two simulations for a spine with excitable membrane properties, one with $R_{ss} = 780\text{M}\Omega$ (below threshold for *a.p.*) and the other with $R_{ss} = 830\text{M}\Omega$ (above threshold for *a.p.*), with all other resistances set to resting values. This simulates a single spine head receiving transmission from a single presynaptic grid. Results were similar to those shown in Segev and Rall (1988).

Segev and Rall identified spine stem resistance as an important parameter in attaining threshold for *a.p.* generation in the spine head (Segev and Rall, 1988). In the simulations that follow, we model varying connections between the spine and the dendrite, as well as between distinct comps. within the spine. Lower values of resistance model well-connected comps., where connecting stems are assumed to be shorter and broader (or non-existent). Long and thin stems, or an occusion such as a spine apparatus, may significantly

increase resistance to current flow (Harris, 1999b, Miller et al., 1985). Luscher et al. (2000) report that perforated synapses express a higher proportion of spine apparatus, and experiments preferentially locate synaptopodin in hippocampal spine necks, closely associated with the spine apparatus. Synaptopodin may be involved in actin filament bundling for spine motility, or linked to intracellular calcium stores (Deller et al., 2000).

We report on simulations for dynamic activity in the three-comp. spine, varying stem resistance, resistance between comps., the portion of synaptic input received by PSD comps., and finally the surface areas of Comps. 1 and 2. The same spine membrane exhibits no variation in electrical properties for some geometric configurations, while others alter the efficacy of the synapse. After comparing results for dynamic activity with two different values for PSD surface areas, when spines are modeled with excitable membrane properties, we run a long simulation with dynamic activity and dynamic morphology, this time modeling the spines with passive membrane properties.

4.1 Dynamic activity with fixed morphology for active spines

In this section, we simulate activity for the observations made by Geinisman et al. (1993, 1996) of a single spine head with perforated PSDs and a spine with two heads, both apposing a multiple transmission zone, utilizing equations developed in the Dynamic Activity section. The three-comp. spine is modeled for different activation, geometry and resistance parameters, with excitable membrane properties using Eq. (6).

In Fig. 3a, we compare potential in a single spine head, observing results for connected and perforated PSDs. Comps. 1 and 2 are activated symmetrically, with $K = 0.5$ in Eq. (3), and results are graphed for potential in Comp. 1. There are four simulations shown here, with two pairs of superimposed results. For the upper/lower graphs, R_{ss} was set above/below threshold for *a.p.* generation. In each of the superimposed results, one simulation set all internal resistors to rest, modeling a single spine apposing a single transmission zone. For the other simulation in each pair of superimposed results, r_{12} is increased to eliminate direct flow between Comps. 1-2 (with other internal resistors at rest), to model splitting the PSDs and transmission zone, without splitting the spine head, since there is no change in the surface area of the spine. Results are identical for these configurations whether the spine responds with or without an *a.p.*

In Fig. 3b, two sets of 350 activations are applied as in Fig. 3a, varying only R_{ss} within the sets, and graphing maximum potential in an activation cycle for each value of spine stem resistance. In one set, all resistors are fixed at rest, while for the second set, r_{12} is, again, set to eliminate a direct connection between Comps. 1-2, with the other internal resistors set to rest. The two sets of results are, again, superimposed, so the same value for R_{ss} is identified as the bifurcation point for *a.p.* generation, regardless of whether the PSDs are connected or perforated. Likewise, the maximum potential reached during a single activation cycle was not affected by splitting the PSDs on the surface of the spine head, since the graphs are superimposed.

In Fig. 3c, we consider potential in a spine with two transmission and receptor zones, comparing results for a symmetric versus an asymmetric synapse. In this simulation, R_{ss} is above threshold, and r_{12} blocks direct current between Comps. 1-2, with remaining resistors at rest, to model PSDs perforated on the surface

of the spine. Results shown here are for two different simulations. In one simulation, Comp. 1 receives all of the synaptic input, ($K = 1.0$), while the second simulation models symmetric activation ($K = 0.5$). The upper curve graphs potential over time in Comp. 1 for both simulations, while the lower curve shows potential in the dendrite at the base of the spine (Comp. 4) for both simulations. The two sets of results are superimposed, so that there is no difference here in the spine head’s response, nor in the amount of current delivered to the dendrite, for symmetric or asymmetric input when the PSDs are separated on the surface of a single spine head. We repeated this simulation for other values of K (not shown here), also with no difference in postsynaptic response.

We next consider the three-comp. spine for electrical isolation of one part of the spine in Figs. 4a-b, and changes in spine surface area in Figs. 4c-d, to observe how these geometric configurations alter excitable membrane response to symmetric activation ($K = 0.5$ in Eq. (3)). In Fig. 4a, we activate the three-comp. spine symmetrically as in Fig. 3. The spine stem resistance is set above threshold to generate and *a.p.*, and the resistor between Comps. 1-2 is set to prevent direct current flow. This time, however, the resistor between Comps. 1-3 is increased to $1100\text{M}\Omega$ so that Comp. 1 is somewhat isolated from the remainder of the spine, effectively, creating a spine atop a spine. Comps. 2 and 3 remain well-connected. Results graph potential in all comps. of the spine head, as well as in the dendrite at the base of the spine stem. Observe that an *a.p.* is initiated in Comp. 1 that elevates potential (with a slight time-delay) in Comps. 2 and 3 above threshold to initiate an *a.p.* in those comps. as well. Since Comps. 1 and 2 are electrically isolated, the propagated wave travels from Comp. 1 to Comp. 3, and then into Comp. 2, but there is no time-delay or decrease in magnitude between Comps. 2 and 3. Note the minor attenuation in response time and magnitude between Comp. 1 and Comps. 2-3, but the major attenuation between the spine and the dendrite. Comparing response here to Fig. 3, there is a slight elevation in Comp. 1 response and also in the amount of current reaching the dendrite for this configuration when compared to the simulation in Fig. 2c which did not increase r_{13} , but rather set R_{ss} higher.

Figure 4b graphs peak potentials achieved in Comp. 1 when we repeat the simulation in Fig. 4a for two sets of 350 activations each, varying R_{ss} , with Comps. 1-2 prevented from direct current flow, and the remaining spine resistors set to rest for all activations on the lower curve. However, current flow between Comps. 1-3 is gradually reduced as r_{13} increases with R_{ss} for all activations on the upper curve. The two curves are superimposed until the bifurcation occurs slightly sooner for higher values of r_{13} . Continued isolation of Comp. 1 raises the magnitude of the spine’s response, and may increase the amount of current delivered to the dendrite, if it is not attenuated by increased stem resistance (R_{ss}).

In Fig. 4c, we compare results for two different surface areas in Comps. 1-2, keeping the surface area for Comp. 3 fixed. Comps. 1-2 are symmetrically activated, and stem resistance is fixed for both simulations. The resistor between Comps. 1-2 prevents direct current flow, with the remaining intraspine resistors set to rest. This configuration is below threshold for reduced surface areas in Comps. 1-2. However, an *a.p.* is generated for the simulation when the surface area in the PSD comps. are increased. This enhanced response occurs because the larger surface area reveals more channels for ion transfer. Increasing only the resistor value r_{12} models perforated PSDs, as in Fig. 3a-b, but increasing both the surface areas for Comp.

1-2 and the resistor between them models splitting the spine head (branching).

In Fig. 4d, peak potentials achieved in Comp. 1 are graphed when we repeat the geometric configurations in Fig. 4c for two sets of 350 activations each, varying R_{ss} . For both sets of activations, the resistor between Comps. 1-2 prevents direct current flow, while remaining intraspine resistors are set to rest. Threshold for stem resistance to generate an *a.p.* occurs significantly sooner for the set of simulations with the larger surface area for PSD comps. Notice, however, that maximum potential is lower for the increased surface area simulations below threshold. Peak potentials at the right side of the graphs is comparable in Fig. 4d and Fig. 4b, but these peaks rise more quickly over R_{ss} after threshold for simulations with increased surface area (Fig. 4d) than for simulations with increased isolation for one part of the spine (Fig. 4b).

4.2 Interdependent activity and spine branching

Simulations in Fig. 4c-d with fixed morphology (above) indicate that increasing spine surface area while separating the PSDs on the surface of the spine enhances postsynaptic response to input for spines with excitable membrane properties. Likewise, simulations in Fig. 3a-b indicate that increasing one internal resistor while the others remain at rest does not impede current flow, and therefore does not affect efficacy. We now seek to demonstrate a continuous change in surface area exposed to the synaptic cleft for a spine with passive membrane properties. In this section, we utilize equations developed in both *Dynamic Activity* and *Dynamic Spine Branching* sections. Since the spines are considered to have passive membrane properties, ionic current is modeled by Eq. (5), and synaptic parameters are reset in Eq. (3) (see fig. legend). The system is numerically integrated over 500 cycles of symmetric activation, repeating the stimulus every 10ms, allowing activity to come to full rest between activations. The surface area of the spine $A_{sh}(t)$ is now a dynamic variable, and we assume that increases in this surface area correspond to an increase in PSDs on the surface of the spine (see Fig. 2), so that A_3 is fixed, and $A_{sh}(t) = A_1(t) + A_2(t) + A_3$. Figures 5a-b graph voltage in the integrator compartment of the spine head (Comp. 3) and in the dendrite at the base of the spine (Comp. 4), respectively. Figure 5c is a state portrait for the slow variables calcium C_a and total spine surface area ($A_{sh}(t)$) over the same 500 cycles of activation. In this interdependent system, calcium is mediated by activity, as measured by the spine stem current, and mediates spine surface area, which in turn affect the level of activity. There is a subtle difference in the magnitude of $|V_3 - V_4|$, when the larger spine surface area causes an increase in stem current, but it is sufficient to change the sign of our measure for activity, relative to a minimal amount ($\eta|I_{ss}| - \rho$.) This may be observed by comparing differences in the height of potential in the spine head (Fig. 5a) to the stem base comp. (Fig. 5b) during periods of high and low voltage.

The reader may divide the results in Fig. 5c into four quadrants, separated vertically by $C_{crit} = 600nM$ in Eq. (12), and horizontally by the total surface area that produces $\eta|I_{ss}| = \rho$ in Eq. (11). The cycle begins just above the left end turning point in the orbit, and proceeds clockwise. With $C_a < C_{crit}$ and $\eta|I_{ss}| > \rho$, surface area and calcium both increase until $C_a = C_{crit}$, then the spine comps. begin to coalesce, driving down the level of activity, as calcium continues to increase to the right end of the orbit, where

$\eta|I_{ss}| = \rho$. The lower half of the orbit proceeds with a reduced level of activity that decreases calcium as surface area continues to decrease, until calcium falls below critical concentration, and the spine begins to split again, which increases the level of activity. In this way, we model a continuous, biochemically-mediated, interdependence between activity and morphology.

The parameters η was selected here so that $\eta|I_{ss}| - \rho$ was negative for passive spines with smaller surface area, and positive for passive spines with larger exposed membrane. By changing these parameters, one could similarly define a periodic orbit for active spine branching, to cover a wide range of dendritic activity. Rusakov et. al (1996) suggests that spine branching may serve as a mechanism for controlling synaptic efficacy in active dendritic spines. A similar cycle for calcium mediated spine stem restructuring was demonstrated in Verzi and Baer (2004), modeling spines with excitable membrane properties. Analysis of the slow subsystem for calcium-mediated spine branching indicates that the cycle in Fig. 5c is stable for spines under synaptic activation, regardless of membrane properties, so that robustness of results should not be affected by low levels of noise in the slow subsystem.

5 Discussion

In this paper, we simulate dynamic activity in a spine head composed of three separate comps., testing several geometric configurations to identify parameters that enhance the postsynaptic response to synaptic input. When the PSD was perforated on the surface of the spine, it did not change efficacy of the circuit. This is similar to Rall's (1953) theoretical result for spherical soma, where he showed that synaptic potentials sum independent of where they are located on the surface of the soma. However, separating the PSDs may add to diversity of the circuitry, permitting multiple neuron communication at a single synapse. Injecting varying percentages of total input into each part of a perforated PSD also did not affect the postsynaptic membrane potential, an indication of conservation of channels for an asymmetric synapse. However, asymmetric input into a spine with two electrically isolated heads may alter the postsynaptic response if one of the heads is more isolated from the integrator comp.

Isolating one part of the spine by increasing resistors between comps. effectively creates a new spine stem, or a spine atop a spine, adding diversity of circuitry. We found that isolating one comp. from the remainder of the spine enhanced efficacy by decreasing threshold stem resistance to initiate an *a.p.*, and increased the level of potential within the spine head, much like water in a garden hose that has an obstruction. However, this heightened potential may not be delivered to the dendrite due to resistor attenuation, particularly if a resistor between receptor and integrator comps. is so high that it precludes *a.p.* propagation. On the other hand, increasing the postsynaptic response by increasing spine surface area may induce LTP in excitable spines, since this change increases head potential and also decreases resistance threshold to generate an *a.p.*, thereby promoting wave propagation, and raising dendritic potential.

The interdependent system of activity and spine branching qualitatively captures observed phenomena for spine splitting (Geinisman et al., 1993, Luscher et al., 2000, Neuhoff et al., 1999), and presents an initial hypothesis by which calcium may continually mediate spine head restructuring to regulate activity. We do

not imply here that calcium and surface area cycle on a time-dependent basis, but rather to demonstrate that the continuum of postsynaptic responses observed in Fig. 4c-d may be mediated by calcium-induced changes in spine surface area. Calcium oscillations within each cycle of activation are more pronounced, for this model, when $C_a > C_{crit}$. These oscillations would be reduced for smaller values of ϵ_i for $i = 0 - 1$, but this would increase computation time. Since morphology is relatively stable for each activation cycle, one could also model the slower subsystem on a different time scale, changing only once in each cycle of activation (suggested in analysis of the cycle for spine branching in the Appendix). Simulations within this paper demonstrate the range of results that may be captured with the model, consistent with experimental observations (Harris 1999a, Segev and Rall, 1998). The range for calcium concentration recovered in Fig. 5 (400nM) is consistent with observed experimental results for calcium released from internal stores (Korkotian and Segal, 1999). Since spine surface area is dynamic only for comps. containing PSDs, an increase in surface area in the model is consistent with observed increases in PSD diameter (Luscher et al., 2000). The length of time for structural transition in the model depends on the magnitudes of ϵ_i , $i = 0 - 1$, selected here for computational efficiency and convergence of results as we decrease the rate of structural change. To achieve the structural changes shown in this paper over 13 days, as observed by Geinisman et al. (1996), one would need to set the rate of change in spine structure on the order of $\epsilon_i = 10^{-12}$ for $i = 0 - 1$.

The phenomenological model presented here kinetically limits the time period for sustained higher levels of activity, particularly for bursting in spines with excitable membrane, and prevents calcium from reaching a toxic level for compact areas of the neuron. Decreasing surface area causes comps. in the spine to become more electrically connected, since resistance is proportional to surface area, thereby reducing activity and calcium levels in an isolated part of the cell. The simple relationship between calcium and activity, presented here as a first step in the modeling process, cannot capture all of the dynamic processes involved in a system with activity-dependent morphology. We expect this model to evolve, over time, with communication between theoretical and experimental biologists. Nevertheless, the strength of this model is that, like experimental studies, it helps to dissect complex phenomena. The model looks at restructuring the geometry of spine heads (branching), rather than the creation of an entirely new spine (splitting) with its own connection to the dendrite, resulting from spine splitting. Neuroscientists (Fiala et al., 2002) have recently observed mature axons between same dendrite multiple synaptic boutons (sdMSBs) and conclude that spines do not split during Hippocampal LTP, but rather that sdMSBs may, in fact, be more closely associated with spine density, rather than strengthening an existing synaptic contact.

The spatial distribution of channels in the CNS are believed to contribute to temporal filtering for information processing. Timofeeva et al. (2000) has examined the role of spines in spatio-temporal filtering using the spike-diffuse-spike model. It would be interesting to extend their work to consider the role of sdMSBs contacting more than one axon (Fiala et al., 2000). Alternatively, one could use a continuum model (Baer and Rinzel, 1991) to look at how spine branching may affect a population of spines along the dendrite. The equation for ionic current (Eq. (6)) could include voltage-dependent calcium currents, and calcium-dependent potassium currents (Aradi and Holmes, 1999), and the formulation could include a spatio-temporal profile for Ca^{2+} in the spines and the dendritic shaft, addressing calcium diffusion and

the influx of calcium through spine stems. This work could then be combined with our previous modeling for calcium-mediated spine stem restructuring (Verzi and Baer, 2005) for a more complete look at calcium regulated dendritic morphology.

A second line of theoretical work could consider a calcium-dependent, dynamic peak synaptic conductance (g_p in Eq. (3)), modeling AMPA receptor activation for low levels of presynaptic input, and NMDA receptor activation for higher levels, since entry of Ca^{2+} through activated NMDA receptor channels is required to depolymerize postsynaptic actin, a basic building block for the spine (Luscher et al., 2000, Neuhoff et al., 1999). Recent work connects NMDA receptor dependent LTP and LTD (long-term depression) with the redistribution of AMPA receptors into and out of the postsynaptic plasma membrane. Luscher et al. (2000) conjecture a mobile pool of AMPA receptors that cycle between cytoplasm and surface membrane comps. of the spine on a scale of tens of minutes, via exo- and endocytotic pathways. They suggest a model for sequentially occurring expression mechanisms. One might also include inhibitory currents since depolarization is required to release NMDA channels from Mg^{++} block and allow them to respond to synaptic input from their innervating axons (Holmes and Levy, 1997). In a similar manner, synaptic dysfunction from beta-amyloid channel blockade is viewed as an early manifestation of Alzheimer's disease, but the cellular mechanisms remain unclear. A reduction in PSD-95, a protein involved in recruiting and anchoring glutamate receptor subunits to the PSD, along with an early reduction in surface expression of glutamate receptor subunits GluR1 in APP mutant transgenic mice implicate these changes in biochemistry to reduced levels of synaptic activity (Almeida et al., 2005).

And finally, one might consider actin-dependent structural modifications for spine shape to accommodate AMPA insertion. Electron microscopy suggests a relationship between changes in spine shape and the redistribution of AMPA receptors, and adhesion molecules have been found in PSDs (Neuhoff et al., 1999, Matus, 2000). We have previously worked on mechanical models for cell extension, adhesion and contraction to effect morphology and motility, based on the reconfiguration of proteins, to build or break down a cytoskeleton in response to cues from the extracellular environment (Mogilner and Verzi, 2003). Growth of the leading edge of these cells depends on polymerization of proteins to extend filopodia, and adhesion to regulate direction. One may similarly consider the extension of dendritic spines from networked actin as the leading edge of the neuron cell, extending, contracting and morphing in response to changes in the synaptic cleft environment.

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6 References

1. C. G. Almeida, D. Tampellini, R. H. Takahashi, P. Greengard, M. T. Lin, E. M. Snyder and G. K. Gouras, (2005), Beta-amyloid accumulation in APP mutant neurons reduces PSD-95 and GluR1 in synapses. *Neurobiology of Disease*. 20(2), 187-198.
2. I. Aradi and W. R. Holmes, (1999), Role of multiple calcium and calcium-dependent conductances in regulation of hippocampal dentate granule cell excitability. *J. Comp. Neur.* 6, 215-235.
3. R. Araya, V. Nikolenko, K. B. Eisenthal, and R. Yuste, (2007), Sodium channels amplify spine potentials. *Proc. Natl. Acad. Sci. USA*. 104(30), 12347-52.
4. S. M. Baer and J. Rinzel, (1991), Propagation of dendritic spikes mediated by excitable spines: a continuum theory. *J. Neurophysiol.* 65, 874-890.
5. M. Barinaga, (2000), Synapses call the shots (review article). *Science*. 290, 736-738.
6. F. Brauer and J. A. Nohel (1969) *Qualitative Theory of Ordinary Differential Equation*. New York: W. A. Bejamin, Inc.
7. F. A. Edwards, (1995), LTP—a structural model to explain the inconsistencies. *Trends Neurosci.* 18(6), 250-255.
8. J. C. Fiala, B. Allwardt and K. M. Harris, (2002), Dendritic spines do not split during hippocampal LTP or maturation. *Nat. Neur.* 5(4), 297-298.
9. Y. Geinisman, L. deToledo-Morrell, F. Morrell, R. E. Heller, M. Rossi and R. F. Parshall, (1993), Structural synaptic correlate of long-term potentiation: Formation of axospinous synapses with multiple, completely partitioned transmission zones. *Hippocampus*. 3(4), 435-446.
10. Y. Geinisman, L. deToledo-Morrell, F. Morrell, I. S. Persina and M. A. Beatty, (1996), Synapse restructuring associated with the maintenance phase of hippocampal long-term potentiation. *J. Comp. Neurol.* 368(6), 413-423.
11. M. Gurkiewicz, and A. Korngreen, (2007), A numerical approach to ion channel modelling using whole-cell voltage-clamp recordings and a genetic algorithm. *Plos Comp. Biol.* 3(8), 169.
12. K. M. Harris, (1999a), Calcium from internal stores modifies dendritic spine shape. *Proc. Natl. Acad. Sci.* 96, 12213-12215.
13. K. M. Harris, (1999b), Structure, development, and plasticity of dendritic spines. *Curr. Opin. Neurobiol.* 9, 343-348.
14. M. Hausser, N. Spruston and G. L. Stuart, (2000), Diversity and dynamics of dendritic signaling. *Neuron*. 290, 739-744.
15. A. Hodgkin, and A. Huxley, (1952), A quantitative description of membrane current and its application to conduction and excitation in nerve. *J. Physiol. (Lond.)* 117, 500-544.
16. D. Johnston and S. Miao-Sin Wu (1995) *Foundations of Cellular Neurophysiology*, MIT Press, Cambridge, MA.
17. W. R. Holmes and W. B. Levy, (1997), Quantifying the role of inhibition in associative long-term potentiation in dentate granule cells with computational models. *J. Neurophysiol.* 78, 103-116.

18. C. Luscher, R. A. Nicoll, R. C. Malenka and D. Muller, (2000), Synaptic plasticity and dynamic modulation of the postsynaptic membrane (review article). *Nat. Neur.* 3(6), 545-550.
19. V. Mahadomrongkul, P. T. Huerta, T. Shirao and C. Aoki (2005) Stability of the distribution of spines containing drebrin A in the sensory cortex lay I of mice expressing mutated APP and PS1 genes. *Br. Res.* 164(1-2), 66-74.
20. A. Matus, (2000), Actin based plasticity in dendritic spines. *Science.* 290, 754-758.
21. J. P. Miller, W. Rall, J. Rinzel, (1985), Synaptic amplification by active membrane in dendritic spines. *Brain Res.* 325, 325-330.
22. A. Mogilner and D. W. Verzi, (2003), A simple 1-D physical model for the crawling nematode sperm cell. *J. Stat. Phys.* 110, 1169-1189.
23. H. Neuhoff, J. Roeper and M. Schweizer, (1999), Activity-dependent formation of perforated synapses in cultured hippocampal neurons. *Eur. J. of Neur.* 11, 4241-4250.
24. W. Rall, (1953), Electrotonic theory for spherical neurone. *Proc. Univ. Otago Med. School.* 31, 14-15.
25. C. R. Rose, Y. Kovalchuk, J. Eilers, and A. Konnerth, (1999), Two-photon Na⁺ imaging in spines and fine dendrites of central neurons. *Eur. J. of Physiol.* 439(1-2), 201-7.
26. C. R. Rose and A. Konnerth, (2001), NMDA receptor-mediated Na⁺ signals in spines and dendrites. *J. Neurosci.* 21(12), 4207-14.
27. D. A. Rusakov, M. G. Stewart, and S. M. Korogod (1996) Branching of active dendritic spines as a mechanism for controlling synaptic efficacy. *Neurosci.* 75-1, 315-323.
28. G. Schmid, and P. Hanggi (2007) Intrinsic coherence resonance in excitable membrane patches. *Math. Biosci.* 207(2), 235-45.
29. I. Segev and W. Rall, (1988), Computational study of an excitable dendritic spine. *J. Neurophysiol.* 60, 499-523.
30. I. Segev and W. Rall, (1998), Excitable dendrites and spines: Earlier theoretical insights elucidate recent direct observations. *Trends Neurosci.* 21, 453-460.
31. I. Segev and M. London, (2000), Untangling Dendrites with Quantitative Models. *Science.* 290, 744-749.
32. K. E. Sorra, J. C. Fiala, K. M. Harris, (1999), Critical assessment of the involvement of perforations, spinules, and spine branching in hippocampal synapse formation. *J. Comp. Neur.* 398, 225-240.
33. B. Stephens, A. J. Mueller, A. F. Shering, S. H. Hood, P. Taggart, G. W. Arbuthnott, J. E. Bell, L. Kilford, A. E. Kingsbury, S. E. Daniel and C. A. Ingham, (2005), Evidence of a breakdown of corticostriatal connections in Parkinson's disease. *Neurosci.* 132(3), 741-754.
34. Y. Timofeeva, G. J. Lord, and S. Coombes, (2006), Spatio-temporal filtering properties of a dendritic cable with active spines: A modeling study in the spike-diffuse-spike framework. *J. Comput. Neurosci.* 21, 293-306.
35. D. W. Verzi, (2004), Modeling activity-dependent synapse restructuring. *B. Math. Biol.* 66, 745-762.

36. D. W. Verzi and S. M. Baer, (2005), Calcium-mediated spine stem restructuring. *J. Math. and Comp. Modeling.* 42, 151-165.
37. P. Waltman (1986) *A Second Course in Elementary Differential Equations*, Academic Press, Inc. Orlando.

7 Appendix

7.1 Table of Model Parameters

A_1, A_2	surface area Comps. 1-2	(see fig. legends)
A_3	surface area Comp. 3	$0.5 \mu\text{m}^2$
A_{max}	PSD-comp. surface upper bound	$0.73 \mu\text{m}^2$
A_{min}	PSD-comp. surface lower bound	$0.25 \mu\text{m}^2$
C_m	specific membrane capacitance	$1 \mu\text{F}/\text{cm}^2$
C_i	$i = 1 - 3$, spine comp. capacitance	$C_m A_i$
C_{crit}	critical intraspine calcium level	600nM
C_m	specific membrane capacitance	$1 \mu\text{F}/\text{cm}^2$
C_{min}	critical intraspine calcium level	100nM
d	diameter of the dendrite	$0.63 \mu\text{m}$
ϵ_0	rate of change in calcium	10^{-4}
ϵ_1, ϵ_2	rate of change in surface area Comp. 1	0.1
η	scaling parameter for stem current	10^9
\bar{g}_{Na}	maximal sodium conductance	$120 \text{mS}/\text{cm}^2$
\bar{g}_K	maximal potassium conductance	$36 \text{mS}/\text{cm}^2$
g_L	maximal leakage conductance	$0.3 \text{mS}/\text{cm}^2$
γ	channel density	2.5
Γ	parameter to shift $r_{12}(t)$	3.54
g_p	peak synaptic conductance	(see fig. legends)
λ	dendrite length constant	$R_m d / 4R_i$
M	scaling parameter for $r_{12}(t)$	10^9
ϕ	HH kinetic temperature control	$5.6115(C)$
Φ	rate of change for $r_{12}(t)$	5.612
ρ	measure of minimal local activity	1.0
r_i	internal resistance for Comp. i	(varies by geometry)
r_{12}	resistance between Comps. 1-2	resting value $42.03 \text{M}\Omega$
r_{13}	resistance between Comps. 1-3	resting value $23.64 \text{M}\Omega$
r_{23}	resistance between Comps. 2-3	resting value $23.64 \text{M}\Omega$
R_i	dendrite specific cytoplasmic resistivity	$70 \Omega \cdot \text{cm}$
R_m	dendrite passive membrane resistance	$1400 \Omega \cdot \text{cm}^2$
R_{ss}	spine stem resistance	(see fig. legends)
t_p	time to peak in each activation cycle	(see fig. legends)
V_{Na}	sodium reversal potential	115mV
V_K	potassium reversal potential	-12mV
V_L	leakage reversal potential	10.56mV
V_{syn}	synaptic reversal potential	100mV

7.2 Table of Model Variables

$A_{sh}(t)$	dynamic total spine surface area
$I_{ss}(t)$	spine stem current
$I_{syn-i}(t), i = 1 - 2$	synaptically applied currents
$I_{ion-i}(t), i = 1 - 3$	spine membrane ionic currents
$m_i(t), i = 1 - 3$	rate for opening sodium channels
$h_i(t), i = 1 - 3$	rate for closing sodium channels
$n_i(t), i = 1 - 3$	rate for opening potassium channels
$r_{12}(t)$	resistor between Comps. 1 and 2
$V_i(t), i = 1 - 3$	potential in comps. of the spine
$V_i(t), i = 4 - 13$	potential in comps. of the dendrite
$V_{sh}(t)$	potential in spine head for continuum model
$V_d(t)$	potential in dendrite for continuum model

7.3 Summary of Equations

Dynamic Activity

The spine head is modeled with two PSD comps. receiving input from the axon, and one integrator comp.:

$$C_1 \frac{dV_1}{dt} = -A_1 I_{ion-1} - K I_{syn-1} - \frac{(V_1 - V_2)}{r_{12}} - \frac{(V_1 - V_3)}{r_{13}} \quad (14)$$

$$C_2 \frac{dV_2}{dt} = -A_2 I_{ion-2} - (1 - K) I_{syn-2} + \frac{(V_1 - V_2)}{r_{12}} - \frac{(V_2 - V_3)}{r_{23}} \quad (15)$$

$$C_3 \frac{dV_3}{dt} = -A_3 I_{ion-3} + \frac{(V_1 - V_3)}{r_{13}} + \frac{(V_2 - V_3)}{r_{23}} - I_{ss} \quad (16)$$

where

$$I_{ss} = \frac{(V_3 - V_4)}{R_{ss}} \quad (17)$$

$$I_{syn-i}(V_i, t) = \left(g_p \frac{t}{t_p} e^{(1-\frac{t}{t_p})} \right) (V_i - V_{syn}), \quad i = 1, 2, \quad t > 0. \quad (18)$$

For spines with passive membrane, ionic currents in the spine head are modeled using

$$I_{ion-i}(V_i, t) = \frac{V_i}{r_i}, \quad i = 1 - 3, \quad (19)$$

and with HH kinetics for spines with excitable membrane properties:

$$I_{ion-i}(V_i, t) = \gamma A_i ((V_i - V_{Na}) \bar{g}_{Na} (m(V_i, t))^3 h(V_i, t) + (V_i - V_K) \bar{g}_K (n(V_i, t))^4 + (V_i - V_L) g_L), \quad i = 1 - 3. \quad (20)$$

We follow Baer and Rinzel (1991) and set $\gamma = 2.5$ for increased channel densities. The functions m, n, h

consider voltage and time dependent probability that sodium and potassium channels are open with

$$\frac{dm_i}{dt} = \alpha_{m_i}(1 - m_i) - \beta_{m_i}m_i \quad (21)$$

$$\frac{dh_i}{dt} = \alpha_{h_i}(1 - h_i) - \beta_{h_i}h_i \quad (22)$$

$$\frac{dn_i}{dt} = \alpha_{n_i}(1 - n_i) - \beta_{n_i}n_i, \quad i = 1 - 3. \quad (23)$$

where α_{j_i} , and β_{j_i} incorporate variable conductances for $j = m, n, h$:

$$\alpha_{m_i} = \frac{0.1\phi(25 - V_i)}{\exp 0.1(25 - V_i) - 1} \quad (24)$$

$$\beta_{m_i} = 4\phi \exp \frac{-V_i}{18} \quad (25)$$

$$\alpha_{h_i} = 0.7\phi \exp \frac{-V_i}{20} \quad (26)$$

$$\beta_{h_i} = \frac{\phi}{\exp 0.1(30 - V_i) + 1} \quad (27)$$

$$\alpha_{n_i} = \frac{0.1\phi(10 - V_i)}{\exp 0.1(10 - V_i) - 1} \quad (28)$$

$$\beta_{n_i} = 0.125\phi \exp \frac{-V_i}{80}, \quad i = 1 - 3. \quad (29)$$

Here ϕ adjusts the kinetics for membrane temperature at 22^o C (Hodgkin and Huxley, 1952).

The dendrite is modeled as a distal branch of the neuron, of unit dimensionless length, with both ends sealed (no flux). A compartmentalization of the cable equation (Baer and Rinzel, 1991) yields:

$$\tau_m \frac{dV_4}{dt} = \frac{-2(V_4 - V_5)}{(dx)^2} - V_4 + \frac{2R_\infty}{dx} I_{ss} \quad (30)$$

$$\tau_m \frac{dV_i}{dt} = \frac{(V_{i+1} - 2V_i + V_{i-1}))}{(dx)^2} - V_i, \quad i = 5 - 12 \quad (31)$$

$$\tau_m \frac{dV_{13}}{dt} = \frac{-2(V_{13} - V_{12})}{(dx)^2} - V_{13}. \quad (32)$$

The parameters τ_m and R_∞ represent the dendrite's membrane time constant and input resistance, respectively. The cable models a distal dendritic branch, sealed at both ends (no flux), with an initial and uniform resting potential of zero in all comps. of the cable and the spine head ($V_i(X, 0) = 0.0, i = 1 - 13$).

Dynamic Spine Branching

For the interdependent system of dynamic activity and calcium-mediated dynamic morphology, append to the above:

$$\frac{dC_a}{dt} = \epsilon_0(\eta|I_{ss}| - \rho)(C_a - C_{min}) \quad (33)$$

$$\frac{dA_{sh}}{dt} = -\epsilon_1(C_a - C_{crit})(A_{max} - A_{sh})(A_{sh} - A_{min}), \quad (34)$$

$$(35)$$

with initial conditions $C_a(0) = 350nM$, and $A_{sh}(0) = 1.31\mu m^2$.

7.4 Analysis of the cycle for dynamic spine branching

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The equations for changes in calcium and spine surface area (Eq. (11)-(12)) constitute a slow subsystem to the model for activity-dependent spine branching. Insight may be obtained into the stability of stationary points in this system for the spine under periodic synaptic activation by considering the average contribution of the fast (activity) variables to the measure for change in the slow system (I_{ss} in Eq. (7) over each activation cycle of length T . Let

$$|I_{ss}|^{avg} = \frac{1}{T} \int_{T_{i-1}}^{T_i} |I_{ss}| dt. \quad (36)$$

Numerical simulations indicate that $|I_{ss}|^{avg}$ is approximately piecewise constant. We may, therefore, average over the fast variables since the slow variables are relatively constant within activation cycles. Insights into the dynamics of the slow system may be obtained by averaging over the fast system to obtain the following system of ordinary differential equations for dynamic spine branching:

$$\frac{dC_a}{dT} = \epsilon_c \left(\eta \frac{|V_{sh} - V_d|^{avg}}{R_{ss}} - \rho \right) (C_a - C_{min}) \quad (37)$$

$$\frac{dA_{sh}}{dT} = -\epsilon_a (C_a - C_{crit}) (A_{sh} - A_{min}) (A_{max} - A_{sh}). \quad (38)$$

This system has three viable critical points at $(C_a^*, A_{sh}^*) = (C_{min}, A_{max})$, (C_{min}, A_{min}) and $(C_{crit}, A_{sh}^* \rightarrow \eta|I_{ss}| = \rho)$. To first order, the stability of these points in the non-linear system is related to the eigenvalues of the operator matrix (Jacobian) for the corresponding linearized system, evaluated at the fixed points (Waltman, 1986). The generalized Jacobian for the above system is

$$\begin{bmatrix} \epsilon_c (\eta |I_{ss}|^{avg} - \rho) & 0 \\ -2\epsilon_a (A_{sh}^* - A_{min}) (A_{max} - A_{sh}^*) & 2\epsilon_a (C_{crit} - C_a^*) (2A_{sh}^* - A_{min} - A_{max}) \end{bmatrix}. \quad (39)$$

Evaluating the Jacobian at the point (C_{min}, A_{max}) , yields

$$\begin{bmatrix} \epsilon_c (\eta |I_{ss}|^{avg} - \rho) & 0 \\ 0 & 2\epsilon_a (C_{min} - C_{crit}) (A_{max} - A_{min}) \end{bmatrix}, \quad (40)$$

with eigenvalues along the diagonal. The sign of (a_{11}) is positive since $\eta|I_{ss}|^{avg} > \rho$ under synaptic activation when $A_{sh} = A_{max}$, and the sign of (a_{22}) is negative since $C_{crit} > C_{min}$ and $A_{max} > A_{min}$. Therefore, the matrix has one positive and one negative eigenvalue, and the fixed point is unstable in both the linearized and the nonlinear systems. A similar analysis for the critical point (C_{min}, A_{min}) indicates that $(a_{11}) < 0$ and $(a_{22}) > 0$ so that the matrix again has real eigenvalues with opposite signs, and the fixed point is unstable in both the linearized and the nonlinear system (Waltman, 1986).

For the fixed point $C^* = C_{crit}$ and A_{sh}^* that delivers $|I_{ss} = \rho/\eta$, the Jacobian equals

$$\begin{bmatrix} 0 & 0 \\ -2\epsilon_a(A_{sh}^* - A_{min})(A_{max} - A_{sh}^*) & 0 \end{bmatrix}. \quad (41)$$

The trace and determinants of this matrix are both zero, so that the eigenvalues are both zero. Regretably this indeterminate form yields little information about the stability of the critical point for the nonlinear system (Waltman, 1986). However, the state variables in the slow subsystem are bounded since $A_{min} < A_{sh} < A_{max}$, $C_{min} < C_a$, and calcium is kinetically bounded above for our periodically activated synapse. In a neighborhood of the central critical, all eigenvalues are non-positive, so that every solution that starts nearby will stay nearby (Brauer and Nohel, 1969). If we remove the last critical point from the plane, the Poincare-Bendixson theorem (Waltman, 1986) allows us to conclude that trajectories in this region would be either periodic, or have an omega limit set that is periodic. This suggests that the periodic orbit observed in Fig. 5c is stable for spines under synaptic activation, for properly selected parameters η and ρ , whether ionic current models excitable or passive membrane, so that small amounts of noise within the system should not affect the robustness of results.

Fig. 1. Schematic of a synapse with the ability to split its transmission and receptor zones, as well as the entire spine head. The spine head consists of three comps., with Comps. 1 and 2 receiving input from the presynaptic bouton, and Comp. 3 connecting to the dendrite. The axon delivers varying levels of input to the spine through I_{syn-1} and I_{syn-2} , modeled as time-dependent α -functions. The receptor areas containing PSDs (Comps. 1 and 2) are modeled by two cylinders. Their surface areas (A_i , $i = 1 - 2$) equal $0.5\mu\text{m}^2$ and diameters equal $0.15\mu\text{m}$, with cylinder-lengths of $1.06 \times 10^{-4}\text{cm}$ and an internal resistance of $r_i = 42.03\text{M}\Omega$, for $i = 1 - 2$. Comp. 3 is also modeled as a cylinder, with surface area (A_3) $0.5\mu\text{m}^2$, but with diameter $0.3\mu\text{m}$, for a cylinder-length $0.53 \times 10^{-4}\text{cm}$, and an internal resistance $r_3 = 5.25\text{M}\Omega$. Resistors between comps. are set to resting values as the average resistance of connecting comps. (Appendix). Comp. 3 is connected to the dendrite by the spine stem, modeled here as a lumped ohmic resistor (R_{ss}). The dendrite is modeled as a passive cylinder of diameter $0.63\mu\text{m}$, with membrane resistance $R_m = 1400\Omega \cdot \text{cm}^2$ and cytoplasmic resistance $R_i = 70\Omega \cdot \text{cm}$. The cylinder is of unit electrotonic length, composed of ten comps. connected by resistors set as the average of resistance in the comps. they connect. The spine stem is connected to one end of the dendrite and the distal end is sealed, equivalent to a spine in the center of a cable with electrotonic length 2. Voltage in each comp. of the model is assumed isopotential (V_i for $i = 1 - 13$.)

Fig. 2. Drawing of a branching spine head. The spine head is now considered as one unit with total surface area exposed to the synaptic cleft $A_{sh} = A_1 + A_2 + A_3$, when all internal resistors are at rest. The spine receives input from the presynaptic bouton $I_{syn} = I_{syn-1} + I_{syn-2}$. **(a)** The spine has not branched, so that total surface area is minimal with respect to the fixed volume of the spine head. **(b)** As the spine head branches, the total surface area exposed to ionic transfer is increased. If the number of PSDs is proportional to this surface area, then the number of channels available for ionic transfer has also increased, while maintaining a fixed volume for this new geometry of the spine head.

Fig. 3. Parameters that do not affect synaptic efficacy for the three-comp. spine with excitable membrane properties. The three-comp. spine is modeled with excitable membrane properties (I_{ion} as in Eq. (6)) for different activation and resistance parameters. Comps. 1 and 2 are activated with Eq. (3), with $g_p = 0.074\text{nS}$ and $t_p = 0.035\text{ms}$. **(a)** Potential in Comp. 1 is shown here for four different simulations, with Comps. 1 and 2 receiving equal amounts of synaptic input. In two simulations (superimposed lower curve), $R_{ss} = 1000\text{M}\Omega$ is below threshold to generate an *a.p.* One of these lower curves shows results when all internal spine head resistors are at rest (r_{12}, r_{13}, r_{23} - Appendix). The other lower curve shows results when $r_{12} = 3000\text{M}\Omega$, splitting the PSDs on the surface of the spine, leaving r_{13} and r_{23} at rest. In the remaining two simulations, (superimposed upper curve), $R_{ss} = 1100\text{M}\Omega$ is above threshold to generate an *a.p.* Once again, there are two (superimposed) simulations on the upper curve, showing results for one when all internal spine head resistors are at rest, and for the other when $r_{12} = 3000\text{M}\Omega$ and r_{13}, r_{23} are set to rest. **(b)** Peak potential achieved in Comp. 1 is shown here when we repeat the simulation in Fig. 2a (above) for two sets of 350 activations each, with R_{ss} ranging from $1\text{M}\Omega$ to $1600\text{M}\Omega$. The graphs are (again) superimposed. In one of the curves, all spine head resistors (r_{12}, r_{13}, r_{23}) are set to rest, and in the other curve, $r_{12} = 3000\text{M}\Omega$, while r_{13}, r_{23} are set at rest. **(c)** Results are shown here for two different simulations when $R_{ss} = 1200\text{M}\Omega$, $r_{12} = 3000\text{M}\Omega$, and r_{13}, r_{23} are set at rest. In one simulation, Comp. 1 receives all of the synaptic input ($K = 1.0$ in Eq. (3)), and in the other simulation Comps. 1 and 2 each receive half of the synaptic input ($K = 0.5$). The upper curve graphs potential over time in Comp. 1 for both simulations, while the lower curve shows potential in the dendrite at the base of the spine for both simulations.

Fig. 4. Parameters that affect synaptic efficacy for the three-comp. spine with excitable membrane properties. The three-comp. spine is modeled with excitable membrane properties (I_{ion} as in Eq. (6)). Comps. 1 and 2 are activated with Eq. (3), with $g_p = 0.074\text{nS}$ and $t_p = 0.035\text{ms}$. Resistance and geometric parameters are varied to study electrical isolation for one part of the spine in 3a-b, and increasing spine surface area through branching in 3c-d. **(a)** Potentials are shown here for a single activation, with potentials in all three comps. of the spine, and in the dendrite at the base of the spine. Comps. 1 and 2 are stimulated symmetrically ($K = 0.5$ in Eq. (3)). Resistors are set to $r_{13} = R_{ss} = 1100\text{M}\Omega$, $r_{12} = 3000\text{M}\Omega$, and r_{23} at rest (Appendix), partially isolating Comp. 1 from the remainder of the spine. An *a.p.* is initiated in Comp. 1 that travels to Comps. 2 and 3, but the magnitude of response is greater than in the previous slide (c.p. Fig. 2(a)). **(b)** Peak potentials achieved in Comp. 1 during each cycle are shown here when we repeat the simulation in Fig. 3a (left) for two sets of 350 activations each, with R_{ss} ranging from $1\text{M}\Omega$ to $1600\text{M}\Omega$. The resistor $r_{12} = 3000\text{M}\Omega$, and r_{23} is at rest for both sets of activations. The resistor r_{13} is set to rest for all activations on the lower curve, but $r_{13} = R_{ss}$ for all activations on the upper curve. **(c)** The results from two simulations are shown here for variations in PSD surface area (Comp. 1-2), graphing potential in Comp. 1. Stem resistance $R_{ss} = 1000\text{M}\Omega$, and $r_{12} = 3000\text{M}\Omega$, with remaining internal resistors at rest. For the lower curve, $A_1 = A_2 = 0.405\mu\text{m}^2$ and $A_3 = 0.5\mu\text{m}^2$. For the upper curve, $A_1 = A_2 = 0.73\mu\text{m}^2$ and $A_3 = 0.5\mu\text{m}^2$. **(d)** Peak potential achieved in Comp. 1 during each cycle is shown here when we repeat the simulation in Fig. 3c (left) for two sets of 350 activations each, with R_{ss} ranging from $1\text{M}\Omega$ to $1600\text{M}\Omega$. For both sets of activations, $r_{12} = 3000\text{M}\Omega$, with remaining internal resistors at rest (Appendix) in both graphs. Total spine surface area is fixed at $1.31\mu\text{m}^2$ for all activations on the lower curve, and $1.96\mu\text{m}^2$ for all activations on the upper curve.

Fig. 5. A cycle of calcium-mediated spine branching with passive membrane properties. The interdependent systems of dynamic morphology and activity are stimulated symmetrically for 500 cycles of activation, occurring every 10ms, so that the system comes to full rest between applications. In this simulation, the spines are modeled with passive membrane properties so that ionic current is modeled by Eq. (5), and synaptic parameters are reset to $g_p = 0.37nS$, $t_p = 0.2ms$, and $K = 0.5$ in Eq. (3). Resistors are set at $R_{ss} = 950M\Omega$, with r_{13} and r_{23} at rest. The resistor $r_{12}(t)$ is now computed algebraically from the average of the dynamic variables $A_1(t)$ and $A_2(t)$, but the parameter A_3 remains fixed at $0.5\mu m^2$. **(a)** Voltage in Comp. 3, the integrator comp. for the spine, is graphed over 500 synaptic activation cycles of length 10ms. Higher/lower levels of potential occur during periods of elevated/reduced total surface area, resulting from dynamic PSD comp. surface areas. **(b)** Voltage in Comp. 4, in the dendrite at the base of the spine, is graphed for the same 500 synaptic activation cycles. The dendrite receives an elevated/reduced signal from the spine when total surface area is increased/decreased. **(c)** A state portrait is shown here for the slow variables calcium and total spine head surface area ($A_1(t) + A_2(t) + A_3$) over the same 500 cycles of activation. Initial conditions for this simulation set $C_a(0) = 350nM$, and $A_1(0) = A_2(0) = 0.4\mu m^2$, so that the cycle begins just above the left-end point on the graph.