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► **To cite this version:**

Nathan Skene, Slawomir Nasuto. Methods for comparing and constraining models of dendritic spines. Deuxième conférence française de Neurosciences Computationnelles, "Neurocomp08", Oct 2008, Marseille, France. hal-00331611

**HAL Id: hal-00331611**

**<https://hal.science/hal-00331611>**

Submitted on 17 Oct 2008

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# METHODS FOR COMPARING AND CONSTRAINING MODELS OF DENDRITIC SPINES

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## ABSTRACT

Physiological evidence using Infrared Video Microscopy during the uncaging of glutamate has proven the existence of excitable calcium ion channels in spine heads, highlighting the need for reliable models of spines. In this study we compare the three main methods of simulating excitable spines: Baer & Rinzel's Continuum (B&R) model, Coombes' Spike-Diffuse-Spike (SDS) model and paired cable and ion channel equations (Cable model). Tests are done to determine how well the models approximate each other in terms of speed and heights of travelling waves. Significant quantitative differences are found between the models: travelling waves in the SDS model in particular are found to travel at much lower speeds and sometimes much higher voltages than in the Cable or B&R models. Meanwhile qualitative differences are found between the B&R and SDS model over realistic parameter ranges. The cause of these differences is investigated and potential solutions proposed.

## KEY WORDS

Spike-Diffuse-Spike; Excitable Dendritic Spine

## 1 Introduction

Dendritic Spines are small protrusions that branch off neuronal dendrite. They come in a diverse range of shapes and sizes which are known to quickly change with synaptic input [1]. Spines receive most of the excitatory synaptic inputs in the human forebrain and occur in huge numbers on the majority of neurons. They consist of a very thin neck approximately 0.15 microns wide and 0.5 microns long with a bulbous head on the distal end [2]. Recent advances in imaging techniques along with increased use of two-photon glutamate uncaging have lead to a wealth of new discoveries; we now know that there are voltage-dependant sodium [3], potassium [4] and calcium [5] channels in the spine heads.

The discovery of calcium channels in spine heads lead to the theory that spines can detect the temporal coincidence of pre- and post-synaptic activity. This is due to the significant delay between back propagating action potentials invading the spine head and the diffusion of the calcium generated by them; the process termed calcium

compartmentalization. This hypothesis was furthered when Holthoff discovered that spines can use different methods to diffuse calcium [6].

Another theory proposed for spine function is that they allow neurons to adaptively regulate their synaptic input by up- or down-regulating spine density and morphology; this follows from the observation that spine density increases after pharmacological blockades of particular post-synaptic receptors [7]. Various attempts have been made to use computational experiments to test these ideas. Notably in [8] a modified B&R model of excitable spines is used to explore the outputs of dendritic branches with the ability to change spine density and neck length. Given recent work on calcium signalling and proteomic models of synapses it is likely that there will soon be an increased demand for accurate and reliable spine models.

In most models of spines excitable properties are overlooked and compartments passive properties are simply adjusted to account for the additional volume. However, various works such as [9] have suggested this is not appropriate when there are known to be excitable ion channels in the spine head. There are numerous methods that have been used for modelling spines. Some approaches model each spine as additional two compartments: one for the spine neck, the other for the head. The later compartment may have been endowed with voltage gated ion channels, which adds to the heavy computational burden of this method.

The Baer & Rinzel continuum model was introduced to resolve this problem, the central idea was that as spines attached to each compartment would all receive the same input voltage, there is no necessity to model each one as the value can be computed for an individual spine and multiplied by a spine density coefficient,  $\bar{n}$  [10]. A further simplification is made by reducing the spine neck to a lumped ohmic resistance  $R_{ss}$  defined by the equation

$$R_{ss} = (4R_i l_{ss}) / (\pi d_{ss}) \quad (1)$$

where  $R_i$  is specific cytoplasmic resistivity and  $l_{ss}$  and  $d_{ss}$  are neck length and diameter respectively. The voltage in the spine heads in the model is given by

$$C_{sh} \frac{\delta V_{sh}}{\delta t} = -I_{ion} - I_{ss} - I_{syn}(X, t) \quad (2)$$

where  $C_{sh}$  is the spine head capacitance,  $I_{ion}$  represents the voltage-dependent ionic channel currents, often modeled as the HH equations,  $I_{syn}$  represents the synaptic input function (treated throughout as an alpha synapse with  $g_{max} = 0.037$ ) and  $I_{ss}$  is the current between the dendrite and spines according to

$$I_{SS} = -\frac{(V_{sh} - V_d)}{R_{SS}} \quad (3)$$

The actual voltage in the dendrite is given by a modified cable equation

$$\tau \frac{\delta V_d}{\delta t} = \frac{\delta^2 V_d}{\delta X^2} - V_d + \bar{n}(X) R_\infty I_{ss} \quad (4)$$

where  $X$  is the electrotonic distance  $x/\lambda$  (where  $\lambda$  is the length constant  $(R_m d/4R_i)^{1/2}$ ),  $\tau$  is the membrane time constant and  $R_\infty$  is the input resistance of the semi-infinite branch  $(R_m/\pi\lambda d)$  and  $\bar{n}(X)$  gives the spine density at  $X$ .

While the B&R model captures spine dynamics in a continuum model it still is not analytically tractable; the Spike-Diffuse-Spike model was created to address this. Instead of using the continuum approximation the model consists of a passive dendrite coupled to excitable spines at discrete points. Membrane dynamics in the spines are modelled using integrate and fire processes. The spike events are modelled in a discrete fashion with the wave form conventionally represented as a rectangular function. The voltage in the dendrite is given by

$$\frac{\delta V_d}{\delta t} = D \frac{\delta^2 V_d}{\delta X^2} - \frac{V_d}{\tau} + D R_i p(X) I_{ss} \quad (5)$$

where  $D$  denotes the diffusion coefficient of the cable  $(\lambda/\tau)$  and  $p(X)$  is a discrete set containing the locations of the spines. Spine head voltage is not given explicitly in the same way as in the B&R model, there is instead a spike generator equation which resets itself after crossing a parametric threshold. This is given as

$$C_{sh} \frac{\delta U_n}{\delta t} = -\frac{U_n}{R_{sh}} + I_{ss} - C_{sh} h \sum_m \delta(t - T_n^m) \quad (6)$$

where  $n$  is the index of current spine,  $R_{sh}$  is the spine head resistance ( $T\Omega$ ),  $h$  is the firing threshold (mV). The  $\delta(t)$  represents the delta function and the term in which it is included is used to reset the spike generator after a spike event occurs. A spike is generated when  $U_n$  reaches  $h$  and the spike time is added to the  $m^{th}$  position of  $T_n^m$ , a discrete set of spike times

$$T_n^m = \text{inf}\{t | U_n(t) \geq h, t > T_n^{m-1} + \tau_R\} \quad (7)$$

where  $\tau_R$  is an absolute refractory time period.

A pseudo spine head voltage is obtained by converting the spiking events into a voltage that can be passed to the dendrite. We obtain as

$$V_{sh}(X_n, t) = \sum_m \eta(t - T_n^m) \quad (8)$$

where  $m$  is an iterator over the spikes which have occurred. It should be clear that if no spikes have occurred then the spine head can be considered to be at resting potential. In all the published work done using the SDS model the shape of an action potential has been given as a rectangular pulse  $\eta(t) = n_0 H(t) H(\tau_s - t)$ , where  $\eta_0$  and  $\tau_s$  are its strength and duration and  $H(t)$  is the Heaviside step function.

In [11] an attempt is made to validate the SDS model against the B&R model. A method for comparison was established which has also been used in this paper. The method investigates how a common characteristics measured in simulation of both models changes as a function of spine density. Part of the current work involves extending this approach to a range of other characteristics leading to a comparison of the B&R model to a compartmental spine model which is treated as a control. Automated search of model parameters allows us to characterize systematically the differences in their behaviour and analyse the relationship between the parameter ranges.

## 2 Method

The original Baer & Rinzel model predicted that local excitatory synaptic input into spine heads could cause a chain reaction of spine firings along a branch, known as a travelling wave. Its physiological basis is the opening of voltage gated ion channels in one spine leading to increase of the voltage at the neighbouring spine to such a level that it too can spike thereby initiating a chain reaction. This sustained wavelike response is possible for a certain range of realistic spine densities and electrical parameters. On a uniform cable with constant parameters the travelling waves can be said to have a specific speed and voltage; these are the values compared most frequently throughout this study.

An effect of the simplifications made in the SDS model is that most of the parameter space also leads to periodic travelling waves. These occur when the residual voltage from the last wave is sufficient to trigger the generation of a second wave. Without external input this will continue for infinity with measurable periodicity. The occurrence of periodic travelling waves has never been observed in the B&R or Cable models. We seek to confirm that these models do not produce such periodic waves under realistic parameter ranges. A set of parameters for the SDS model which exclusively produce non-periodic travelling waves across a realistic parameter set is also sought using first trial-and-error then a multiple objective optimization. A sub-model termed F-SDS is created which treats two of the free variables as dependant on spine density, this allows it to only generate non-periodic travelling waves.

To run the simulations, the SDS and B&R model have been written as mod files for the NEURON simulation package [12]. The B&R model is setup as a distributed

mechanism and inserted into cables, typically with a number of compartments comparable to the number of spines that would be on the cable for the given density. The SDS model is setup as a point-process and spines are inserted individually to specific compartments within the cable. The cable model, which takes each spine to be two compartments, generates the required number of spines and connects the neck compartment to the desired locations on the dendrite.

All the simulations involve an unbranched dendritic segment where stimulations are initialised with a single EPSP from an AlphaSynapse with  $g_{max} = 0.037nS$  located at the beginning of the dendrite (dend(0) - dendrite locations in NEURON are indexed by the cable name—here dend—and the distance along is an argument between 0 and 1). The cable parameters are kept constant throughout all the simulations so their effects on the model do not interfere. The values for the cable are: Length =  $360\mu m$ , diam =  $0.36\mu m$ , Ra =  $70\Omega cm$ ,  $C_m = 1\mu F/cm^2$ ,  $R_m = 0.0004\Omega cm^2$  and the temperature = 22 degrees celsius; this gives an electrotonic length of two. Though better estimates for the kinetics and densities of ion channels extant within the dendrites have now been published, for these experiments only the standard Hodgkin-Huxley ion channels are used, with the base densities of  $\bar{g}_{na} = 120$ ,  $\bar{g}_k = 30$  and  $g_l = 0.3$ , as this allows for better validation against existing results in the literature.

The decisions about spine parameters were based on two main studies. The first of these analysed spines from a region of the basal dendrites from layer III cells from the Temporal and Occipital cortex of mice and men [2]. In the second study [13], the distribution of spine densities across single cells was explored in neurons from layers 2/3 and 5 of the rat cortex. The studies noted a lack of correlation between a majority of spine structural parameters. No explicit attempt has been made to account for stubby spines in selecting the parameter ranges, however it may be assumed that investigating lower spine densities than those used would account for this.

One key experimental setup formed the basis of the majority of simulations in this study. All the spine parameters bar one, as well as the dendrite parameters are fixed, the independent parameter is then varied over a range and the number of resultant waves and their speed and voltage is recorded. For parameter sweeps this is of course done across multiple parameters at a time. A further element of the study involved the use of automatic parameter estimation techniques, as discussed in [14] and [15] to further compare the models. Here, initial attempts are made to get SDS on an unbranched cable to constrain its free parameters based on simulations of B&R and Cable models.

### 3 Results

The first step was to confirm that only SDS produces periodic travelling waves under realistic parameter ranges. A parameter search confirmed that this was indeed the case as

they occurred in the B&R model under an extreme and unrealistic low density of the potassium channel. Therefore, subsequently we sought the free parameters for the SDS model which would exclusively produce non-periodic travelling waves for any physiologically-based spine parameters.

The regions of the parameter space of the SDS model resulting in non-periodic travelling waves were identified. By constructing functions linking the spike shape function parameters to spine density at the parameter space points where the travelling waves occurred, a form of SDS, referred to as F-SDS, was created with some of the free variables removed. In this sub-model the height of the spike function and the length of the refractory period are treated as dependant on the values of the stimulus length and spine density. As a result, non-periodic travelling waves were generated in F-SDS model throughout a range of spine densities from 0–500 spines per electrotonic length. However, the effect of such spine density variation upon wave speed and voltage, exhibited by all the other models, is greatly diminished. This formed the basis for further investigation of the parameter space aimed to find parameter values for SDS which could match B&R’s wave speed and voltage at various values of spine density.

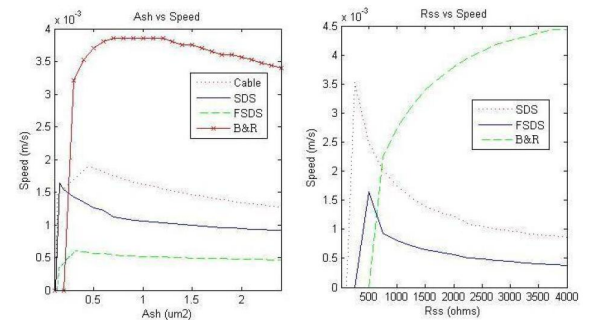


Figure 1. Wave speed in a uniform cable as a function of spine head area (left) and spine neck resistance (right). In both we see B&R operates at significantly higher speeds than SDS and that variation in F-SDS is dampened. Dependence of the speed on the spine neck resistance in B&R is qualitatively different than in the other two models.(right)

Subsequently, the difference in wave speed and voltage between models was examined for variation in single variables. Several sets of values were chosen as representative of the realistic parameter ranges, and where applicable the values were set to be the same for all three models. The most important results are depicted in Figure 1. The B&R model always resulted in much higher speeds than the other models, while SDS always seems to be slower than the cable model. In terms of voltage, over much of its parameter space the SDS model is prone to excessive excitation and rapidly reaches unrealistically high voltage values.

Interestingly, while many of the qualitative characteristics of the models were the same, variation in spine neck resistance causes the speed of waves in the B&R model to increase, in contrast to all the other models. By running the

same simulations for variation in  $R_{ss}$  over a greater—and hence unrealistic—range of values it is revealed that the appropriate qualitative behaviour is recovered. This suggests that rather than an outright flaw in the model its response to change in neck resistance is reduced which allows greater insight to the problems cause. Further simulations involving comparison with the cable model and informed by the above results were aimed at validating the assumption behind the B&R and SDS approach to model spine neck. This was performed by treating neck length and diameter as variables dependent on  $R_{ss}$  and recording resultant speeds. The results suggested that the lumped ohmic resistance in its given form was an inappropriate way to represent the spine neck.

## 4 Conclusion

These results have confirmed the need for further investigation into reliable spine models. Neither the SDS nor B&R model form a close approximation to the cable model, which seems to be the closest match to biophysics. Both the simplified models produce significant quantitative differences and also exhibit peculiar qualitative phenomena not shared by other models. Further simulations will be carried out in order to investigate whether more complex models of spine neck can better account for the biologically behaviour of a model of dendrites with active spines, while still easing computational complexity.

The discrepancies found between these models are all the more important when one considers why someone would be likely to perform a study including excitable spines. The most likely reason for this would be to examine the effects of calcium transients on synaptic potentiation. For this the arrival time and voltage of back propagating waves would be of exceptional importance, especially so if an attempt was to be made to infer parameters from this model. Furthermore, numerous studies have looked at how dynamic variation in spine shape affects calcium processing; if free variables need tweaking for even minor perturbations of shape parameters then almost any result desired could be obtained from this kind of modelling.

## References

- [1] Anna Dunaevsky, Richard Blazeski, Rafael Yuste, and Carol Mason. Spine motility with synaptic contact. *Nat Neurosci*, 4(7):685–686, 2001.
- [2] Ruth Benavides-Piccione, Inmaculada Ballesteros-Yáñez, Javier DeFelipe, and Rafael Yuste. Cortical area and species differences in dendritic spine morphology. *Journal of Neurocytology*, 31(3):337–346, 2002.
- [3] Roberto Araya, Volodymyr Nikolenko, Kenneth B. Eisenthal, and Rafael Yuste. Sodium channels amplify spine potentials. *Proceedings of the National Academy of Sciences of the United States of America*, 104(30):12347–12352, July 24, 2007.
- [4] Jennifer Ngo-Anh, Brenda L. Bloodgood, Michael Lin, Bernardo L. Sabatini, James Maylie, and John P. Adelman. Sk channels and nmda receptors form a ca2+-mediated feedback loop in dendritic spines. *Nat Neurosci*, 8(5):642–649, 2005.
- [5] Rafael Yuste and Winfried Denk. Dendritic spines as basic functional units of neuronal integration. *Nature*, 375(6533):682–684, 1995.
- [6] Knut Holthoff, David Tsay, and Rafael Yuste. Calcium dynamics of spines depend on their dendritic location. *Neuron*, 33(3):425–437, 2002.
- [7] M. Segal M. Papa. Morphological plasticity in dendritic spines of cultured hippocampal neurons. *Neuroscience*, 71:1005–1011, 1996.
- [8] D. W. Verzi, M. B. Rheuben, and S. M. Baer. Impact of time-dependent changes in spine density and spine shape on the input-output properties of a dendritic branch: A computational study. *Journal of Neurophysiology*, 93(4):2073–2089, April 1, 2005.
- [9] David Tsay and Rafael Yuste. Role of dendritic spines in action potential backpropagation: A numerical simulation study. *Journal of Neurophysiology*, 88(5):2834–2845, November 1, 2002.
- [10] S. M. Baer and J. Rinzel. Propagation of dendritic spikes mediated by excitable spines: a continuum theory. *Journal of Neurophysiology*, 65(4):874–890, April 1, 1991.
- [11] Yulia Timofeeva, Gabriel Lord, and Stephen Coombes. Spatio-temporal filtering properties of a dendritic cable with active spines: A modeling study in the spike-diffuse-spike framework. *Journal of Computational Neuroscience*, 21(3):293–306, 2006.
- [12] Nicholas Carnevale and Micheal Hines. *The NEURON Book*. Cambridge University Press, 2006.
- [13] U. Larkman. Dendritic morphology of pyramidal neurones of the visual cortex of the rat: Iii. spine distributions. *The Journal of Comparative Neurology*, 306(2):332–343, 1991.
- [14] A. Gidon F. Schurmann S. Druckmann, Y. Banitt. A novel multiple objective optimization framework for constraining conductance-based neuron models by experimental data. *Frontiers in Neuroscience*, 1(1):7–18, 2007.
- [15] L. Paninski Q.J. Huys, M.B. Ahrens. Efficient estimation of detailed single-neuron models. *Journal of Neurophysiology*, 96:872–890, 2006.