Chapter 7
Discussion

7.1 Theories of spine function

The function of dendritic spines is a mystery that has long plagued neuroscientists. Many different theories have been put forth on their functions, but until recently, they have largely been untestable due to lack of appropriate experimental techniques. With the advent of devices such as fluorescence microscopy and other advances in laboratory equipment, some direct observation of spine function has been possible in recent years. This has intensified the interest in the field amongst experimentalists and theoreticians alike. The main goal of this thesis was to review some of the major theories and study mathematical models put forth on spine function.

In order to understand spine function, one has to understand that spines are the main site of reception of excitatory synaptic transmission. The exact reason for why this is the case has been debated for many years. There are two predominant theories within the field of research. One theory holds that the primary reason is to allow for spatially localized regions in which biochemical reactions mediating changes in synaptic efficacy can be sequestered. This was the primary focus of Chapter 2. The other major theory suggests that spines may have special electrical properties that allow them to modify the size of the EPSP at the axon hillock compared to a neuron without spines. This is the focus of much of Chapter 3. We subsequently explored in greater detail one particular
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continuum model of excitable spine heads and proceeded to derive an analogue model based on the Fitzhugh–Nagumo equations. The mathematical analysis of three different models was the focus of Chapters 4, 5, and 6. The main purpose behind these analogue models was that the forms of their equations allow for analytical results which cannot be attained by numerical simulation and may give a deeper understanding of the underlying phenomena.

7.2 Discussion of spines and LTP

7.2.1 Spines and LTP

In Chapter 2, we focused primarily on evidence suggesting a role for spines in mediating a localized memory phenomena known as long-term potentiation (LTP). We introduced some of the important features of LTP such as cooperativity, associativity and input-specificity. We explored three initial models suggesting how spines can play an important role in LTP by allowing high localized concentrations of \([\text{Ca}^{2+}]_i\) to develop within the spine head in response to high frequency stimulation. This high level of intracellular calcium then could activate a number of calcium-dependent enzymes and unleash a biochemical cascade which eventually culminates in an increased postsynaptic response when that synapse is subsequently activated. These theories focused primarily on the contributory roles of spine morphology, the presence of a specialized postsynaptic receptor known as a NMDAR which has a high calcium conductance and is largely inactive during low frequency activation but highly active during high frequency stimulation, and the presence of calcium buffers and pumps. These models went a long way in demonstrating that the special features of a spine, its shape and size, may be critical in creating a biochemical compartment specific to a particular synapse.

We then proceeded to explore some ideas concerning calcium dynamics within spines. The work of Woolf and Greer [118] showed that spines could develop localized calcium
transients if they had long spine necks, high amounts of buffers, and the absence of calcium–induced calcium release mechanisms in the spine neck. The unfortunate aspect of the above numerical result was that it failed to give one a true qualitative feeling about how all the different factors interplay to produce localized calcium transients in the spine heads. Zador and Koch managed to shed a great deal of light on the subject through a linearization of calcium dynamics through the use of asymptotics [121]. They showed that under certain conditions, the nonlinear calcium dynamics reduce to the cable equation and were able to identify analogues to the concepts of input resistance, time constant and space constant. They showed that the chemical input resistance of the spine head was much larger than the parent dendrite, which allows for much higher increases in $[\text{Ca}^{2+}]_i$ in the spine head than the same input would cause on the parent dendrite. Furthermore, the chemical space constant of the spine was also much smaller than the parent dendrite. This means that much higher levels of $[\text{Ca}^{2+}]_i$ will be seen in the spine head than at the base of the spine head, which allows for spatial localization of calcium transients. Finally, they showed that the chemical time constant of the spine head was much smaller than the parent dendrite. This only further amplifies the difference in $[\text{Ca}^{2+}]_i$ between the spine head and parent dendrite during calcium transients.

We proceeded to explore the temporal nature of calcium transients required in LTP. It was shown that there may be an important role for calcium–induced calcium release processes to keep the level of $[\text{Ca}^{2+}]_i$ in the spine head elevated for long enough to allow for the biochemical cascade controlling LTP induction to become sufficiently activated. Finally, we looked at the presumed final common pathway involved in LTP induction, the activation of protein kinases. We focused on how CaMKII’s peculiar autophosphorylation capacity may be critical in the induction of LTP, and briefly reviewed the results from a finite Markov chain model of CaMKII function.

We felt it was important to give the reader an understanding of LTP and its relationship
to spine function as this is one of the major fields of interest in neuroscience today.

7.2.2 The electrical properties of spines

In Chapter 3, we explored a number of theories proposed for the unique electrical properties that the presence of spines may confer to neurons. Some of the more prominent ideas put forth in the past include:

- Spines mediate synaptic potential attenuation such that there is a large voltage gradient between the spine head and parent dendrite upon synaptic excitation.

- Spines may allow for linear summation of EPSPs by decreasing nonlinear interactions with neighboring spines.

- The spine neck resistance may be a controller of synaptic weight.

- Spines increase the low–pass filtering capacity of neurons simply by increasing the surface area of dendrites.

- Spines effectively decrease the space constant and input resistance of dendrites while having little effect on the time constant.

- Spines with active channels are computationally richer than passive spines and may allow for a form of pseudosaltatory conduction in dendrites.

We finished the chapter by exploring a continuum model of active dendritic spines. The goal of this model was to simplify the problem of modeling spines by averaging them over the dendrite as a continuous density and thus significantly simplify the problem. Active continuous channels based on the Hodgkin–Huxley equations were placed in the spine head, and a thorough numerical investigation of changing various parameters such as spine neck resistance was made. This model went a long way in allowing more detailed analysis of the possible role of active spine dynamics on dendritic action potentials.
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However, the model is still far too complicated to allow for the derivation of any significant numerical results. Instead, it must rely upon brute force numerics to simulate a solution for each individual parameter set.

In order to obtain a better qualitative feeling for the nature of the various parameters in dendritic action potentials, we decided to employ the simpler Fitzhugh–Nagumo dynamics for the Hodgkin–Huxley dynamics. This approach has proven to be very successful in allowing insights to be made into action potential generation in axons by maintaining the basic flavor of the equations, while drastically simplifying the functional form of the PDEs involved. Thus, we derived a continuum model based on active spines with Fitzhugh–Nagumo–type dynamics. We decided to simplify the model in the manner of Bell and Cosner [8] by removing the recovery variable as justified by asymptotics. This reduced the problem to a third-order problem which is analogous to a Fitzhugh–Nagumo system with bistable steady states, which was studied previously by Rinzel and Keller [92].

We now compare and contrast the results from our analogue models.

7.3 Results for the 3 analogue models

7.3.1 The piecewise linear discontinuous model

In Chapter 4, we used the piecewise linear term $-v + H(v - a)$ where $H$ is a Heaviside function instead of the cubic which classically is used in the Fitzhugh–Nagumo equations. We used this equation as it is the simplest one that retains the salient features of a cubic and allows for an initial exploration of the behaviour of the system of PDEs. We started by deriving the conditions under which a bistable steady state exists,

$$\frac{\gamma}{1 + \kappa} < \frac{1 - a}{a}. \quad (7.1)$$

We further demonstrated that both steady states are stable.
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We then began to search for constant speed traveling front solutions that travel with constant speed which go from one steady state to the other. We then proceeded to change the variables into the moving wave frame which allowed us to reduce the problem to a third-order system of ODEs with boundary conditions at \( z = \pm \infty \). Since the problem was translation invariant, and we knew that there was some value of \( z \), say \( z_0 \), for which \( v(z_0) = a \), we arbitrarily imposed the condition that \( z_0 = 0 \).

Since we were primarily interested in determining the parameter range which corresponded to positive speed traveling front solutions, we can simplify the problem by mapping out the boundary of this region. That is, we can attempt to study the region in parameter space corresponding to zero-speed solutions. This has the effect of reducing the problem to a simple second-order ODE which can be solved explicitly. Moreover, we find that zero-speed waves correspond to

\[
\frac{\gamma \kappa}{(1 + \gamma)(1 + \gamma + \kappa)} = 2a, \tag{7.2}
\]

and positive speed solutions occur for the inequality

\[
\frac{\gamma \kappa}{(1 + \gamma)(1 + \gamma + \kappa)} > 2a. \tag{7.3}
\]

Interestingly, it can be shown that there are no positive speed solutions for \( a > \frac{1}{2} \).

We then proceeded to examine positive speed traveling front solutions in the appropriate parameter range. Our technique was to try and solve the set of nonlinear equations by a Newton's method, but we needed a reasonable approximate solution initially for a given parameter set. An initial guess for a solution corresponding to a slow moving wave was made by perturbation techniques. Having accomplished this, we then could explore the dependence of the shape and speed of the wave in terms of the parameter set by holding three of the parameters fixed and altering the fourth using the method of continuation. Since we were mainly interested in the speed of the wave, we will not comment any further on the shape of the wave.
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We were most interested in the effects of the parameters on the speed of the wave. We found that the speed is a monotonic decreasing function of $a$. This is intuitively obvious since low values of $a$ correspond to more highly excitable systems which should have faster propagating solutions. The speed of the wave has a skewed hump solution for $\kappa$ with a lower value which corresponds to a zero-speed solution. This is due to the fact that $\kappa$ is a measurement of the extent to which spines can depolarize the dendritic shaft. However, there is a value of $\kappa$ corresponding to a maximum speed because increasing spine density beyond a certain limit creates a very large conductance load on the dendritic shaft which must be overcome to bring spines that are on the leading edge of the wave up to threshold. The graph of the speed of the wave against $\gamma$ also had a skewed hump appearance, but there were two values of $\gamma$ which corresponded to zero-speed solutions. If $\gamma$ was too small, the spine would achieve voltage saturation too quickly and not enough current would be delivered to the parent dendrite to bring the set of spines ahead of the front to threshold. Conversely, if $\gamma$ was too large, too much current would be lost to the parent dendrite, and the spine would be unable to reach voltage threshold. The graph of the speed of the wave against $\tau$ was monotonic increasing. This is not surprising since it is intuitively obvious that speeding up the dynamics of the nonlinearities within the spine head should speed up the wave as well. This is seen, and there appears to be a definite maximum speed of the wave.

Our technique of simplifying the original set of equations and parameters to more manageable sets allowed us to do some analytical work suggesting the appropriate balances in parameters to achieve propagating solutions. This gives one a better qualitative feel for the features of dendrites and spines required to allow for dendritic action potentials. This is much more intuitive than studying each of the numerous parameters of the individual model with time-consuming and computationally expensive nonlinear PDEs.
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7.3.2 The piecewise linear continuous model

In Chapter 5, we used a piecewise linear continuous (PWLC) approximation of the FitzHugh–Nagumo cubic. This approximation, \( \hat{f} \), satisfied \( \hat{f}(0) = 0 = \hat{f}(1) \), and \( \hat{f} \) achieved the same maximum and minimum as the FitzHugh–Nagumo cubic at the same points. The general aim in using this approximation was to attempt to reflect more accurately the true shape of the FHN cubic while still retaining the feature that the problem could be reduced down to solving a set of nonlinear algebraic equations.

Most of the salient features of piecewise linear discontinuous (PWLD) model were retained in the piecewise linear continuous model. There were again two stable steady states in the traveling front frame so long as the inequality

\[
\frac{\gamma}{1 + \kappa} < \frac{f_{\text{max}}}{v_{\text{max}}}
\]

is satisfied. This is clearly analogous to the result in the piecewise linear discontinuous model. However, in the PWLC model, there was a third steady state which is a saddle point. Thus, as in the PWLD model, we looked for traveling front solutions going from one stable steady state to the other.

As in the PWLD model, we showed there were no traveling wave solutions for \( a > \frac{1}{2} \), and that for a parameter set with \( a < \frac{1}{2} \), there are two values of \( \gamma \) which correspond to zero-speed traveling fronts for fixed \( \gamma \) and \( \kappa \), but only one value for \( a \) and \( \kappa \) when the other two parameters are set. Finally, the dependence of the speed of the wave on the different parameters was generally the same in the two models.

One of the major differences between the two models is that the piecewise linear continuous model has an “inner matching region” that the PWLD model lacks, and this generates a new set of eigenvalues. This creates a difference in how the smaller value of \( \gamma \) which corresponds to zero-speed waves, can be calculated. In the PWLC model, this cannot be accomplished directly as in the PWLD model, because the solution is
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degenerate. That is, as $\gamma$ decreases towards its critical value, $c \to 0$ and $z_1 \to 0$. In this case, we can circumvent this problem and discover the lower value of $\gamma$ by recognizing the disappearance of the "internal matching layer" and the problem becomes similar to the PWLD model in that there is a jump discontinuity in $v$.

Another dimension that has to be accounted for in the PWLC model is the parametric dependence of $z_1$ on $a$, $\gamma$, $\kappa$ and $\tau$. $z_1$ is a monotonic decreasing function of $a$, meaning that as $a$ decreases, the distance required for $v$ to reach $v_{\text{max}}$ increases. This is to a certain extent counterintuitive. However, it should be noted that $z_1$ is the distance required for the value of $v$ to go from $v_{\text{min}}$ to $v_{\text{max}}$ and

$$v_{\text{max}} - v_{\text{min}} = \frac{2\sqrt{a^2 - a + 1}}{3}, \quad (7.5)$$

so the difference between $v_{\text{max}}$ and $v_{\text{min}}$ is a decreasing function of $a$ for $a < \frac{1}{2}$. In terms of the relationship between $z_1$ and $\kappa$, we note that $z_1$ becomes large as $\kappa$ goes its critical value which corresponds to zero-speed waves, develops a local minimum at roughly the same value of $\kappa$ for which the maximum speed is obtained, and then begins to increase thereafter as the speed begins to fall. It can easily be reasoned that the same line of reasoning which explained the relationship of speed to $\kappa$ in terms of the excitability of the system applies to $z_1$ in terms of the steepness of the solution. The relationship between $z_1$ and $\gamma$ is a bit more interesting. For large values of $\gamma$, we see that the value of $z_1$ decreases, which corresponds to the decreased excitability of the system due to excess current loss to the dendrite. However, we also noticed that the value of $z_1$ went to 0 as $\gamma$ approached its smaller critical value which corresponds to zero-speed waves. This can be seen to be due to the overexcitability of the spines due to the fact that little current is lost to the dendrite. This results in the rapid firing of spines which is reflected in the small absolute value of $z_1$, and the small value of $c$ due to the voltage saturation of the spine choking off current transfer to the dendrite. In terms of $\tau$, we get the expected result that $z_1$ is an increasing function of $\tau$ which plateaus at some level. The reasoning
here is related to an increased level of excitability as \( r \) increases which steepens the wave profile.

### 7.3.3 The cubic model

The cubic model presents unique challenges that are lacking in the PWLC and PWLD models. The foremost problem is the presence of a cubic nonlinearity. In the other models, we knew the general form of the solution would be a linear combination of exponentials in different regions of space. This allowed us to reduce the problem from solving a series of ODEs to solving a system of nonlinear algebraic equations, for which a certain amount of analysis was possible.

Our first step was to analyze the problem in phase space. As in the PWLC model, there are three steady states when

\[
\frac{4\gamma}{1 + \kappa} < (1 - a)^2
\]  

(7.6)

is satisfied. Furthermore, the first and third roots again can be shown to be stable, while the middle root corresponds to a saddle point. Thus, we again looked for solutions going from one stable steady state to another.

We proceeded to look for zero-speed traveling wave solutions. By using integration techniques, we demonstrated that zero-speed solutions exist when

\[
\frac{\gamma}{1 + \kappa} = \frac{2}{9} (a - \frac{1}{2})(a - 2)
\]  

(7.7)

is satisfied. This result is analogous to the upper limit value of \( \gamma \) corresponding to zero-speed solutions in the PWLC and PWLD models as positive speed solutions exist when

\[
\frac{\gamma}{1 + \kappa} < \frac{2}{9} (a - \frac{1}{2})(a - 2).
\]  

(7.8)
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It also shows the same relationship in \( \kappa \) and \( a \) in that there is some lower value of \( \kappa \) and upper value of \( a \) which correspond to zero-speed waves. However, an important difference was that it was not immediately obvious whether there was a lower value of \( \gamma \) which corresponded to zero-speed solutions. We were able to show in a more general manner later that there were zero-speed solutions, but they were degenerate and occurred in the limit as \( \gamma \to 0 \). The fact that the PWLC and PWLD models had zero-speed solutions for positive values of \( \gamma \) is a consequence of the lack of sufficient continuity in the equations.

Finally, we calculated the profile of the zero-speed solutions by integrating in phase space and demonstrated that this technique was applicable to all similar degenerate reaction-diffusion systems. The ability to calculate this profile gives us a technique to perturb off this solution using asymptotics to determine an approximate profile of a slow moving wave.

7.4 Future areas of investigation

We reviewed the field of research of mathematical models of LTP induction, and clearly much remains to be done. The biggest challenge that remains to be worked out here are the exact mechanisms of regulation of a huge biochemical cascade of calcium-dependent protein kinases and phosphatases. An interesting project here would be to look into viable forms of regulation that could explain the spatiotemporal requirements of calcium transients required to induce LTP.

There is also much work that can be done in following up theories of the electrical functions of dendritic spines. The two problems that could immediately be taken up are the utilization of asymptotic techniques to perturb off of the zero-speed wave profile that we have calculated to generate approximations of the profile of slow moving waves. Additionally, reaction-diffusion systems with one small diffusion coefficient and a functional form similar to our set of equations also could be handled using asymptotics to perturb
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off the degenerate solution profile that we have calculated. Lastly, an interesting problem to pursue would be to try to determine traveling pulse solutions by not excluding the recovery variable that we have dropped. This problem is much more difficult as it greatly increases the dimension of the parameter space and increases the order of the system of ODEs involved from three to four.

7.5 Conclusion

The field of mathematical neurobiology is developing rapidly and many new interesting problems surface every day. It offers an excellent opportunity for theoreticians and experimentalists to work together in gaining a better understanding of the functioning of the central nervous system. Dendritic spines present a unique challenge to theoreticians due to the sparsity of experimental data and the compelling belief that they must be there for some reason. The challenge as always is to determine what they are doing, and how they accomplish it.
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