

Research Statement

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Mathematics has played an increasingly useful role in gaining insight into biological systems across a wide range of areas. Used alongside traditional experimental techniques, mathematical models can elucidate the structure and mechanisms of biological systems and sometimes are able to make predictions that are experimentally testable. Working closely with mathematicians and experimentalists, I develop and apply mathematical models to gain insight into the function of neurons and networks of neurons. These models range in scope from detailed, realistic representations of individual cells to models of entire brain regions.

Numerical Methods for Neuroscience

Background

While in graduate school I worked with an applied mathematician (David Chopp) and an experimental neurophysiologist (Nelson Spruston) to carry out research in computational neuroscience. My research focused on developing spatially adaptive numerical methods for simulating electrical activity in neurons. Many neurons have a tree-like shape, with several slender branches extending out from a cell body. The governing set of equations for this system consists of a reaction-diffusion equation for the voltage across the cell membrane plus kinetics equations for the motion of ions through membrane channels. The most common numerical methods that have been developed to solve this system on branched structures are implicit methods. These methods are desirable for their numerical stability properties and robustness. However, a trade-off of this approach is the fact that the voltage update for the entire cell is coupled, meaning that every location in the cell is updated at each time step regardless of the amount of local activity. This is a significant issue particularly in neural simulations because electrical activity in neurons is often very localized in space, meaning that much efficiency can be gained if computations are focused only on those parts of the cell that are active. The numerical algorithm I developed allows for de-coupling the computation on distinct regimes of the cell structure by splitting apart the branches using a predictor-corrector scheme (Rempe & Chopp, 2006).

Once the computation is reduced to the level of branches instead of cells, spatial adaptivity is straightforward: the active regions of the cell are detected and computational effort is focused there, while effort is saved in other regions of the cell that are at or near rest. I applied this novel numerical

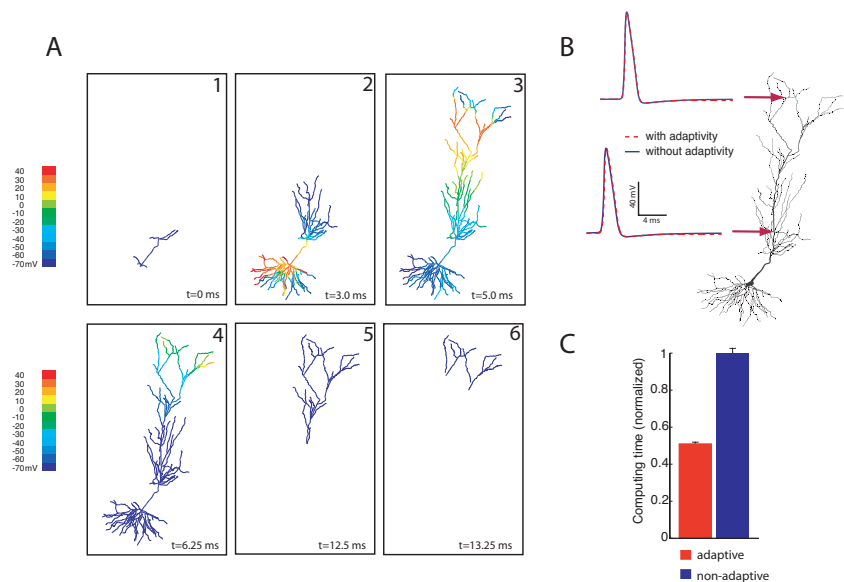


Figure 1: *Spatial adaptivity in a simulation of a CA1 pyramidal cell. See Rempe et al., 2008 for details.*

method to reproduce several computational studies of hippocampal pyramidal cells originally performed in the Spruston lab. In each case the simulations performed with adaptivity were more efficient than the original simulations. Additionally, I used the algorithm to perform some novel simulations that would be difficult or impossible with previous numerical methods. Overall, I found that when using the adaptive algorithm the computational cost of a simulation scales with the amount of activity present, rather than the physical size of the system being simulated. For certain problems spatial adaptivity reduces the computation time by up to 80%.

Future Research

I am still active in further development of these computational tools. With my former advisor and a new graduate student we will extend the numerical method to make it parallelizable. The algorithm itself has split apart the computations into many small calculations that can be performed essentially independently of one another, so making it fully parallel is a natural extension. Ultimately this algorithm will benefit the neuroscience community the most if it can be incorporated into a neural simulator that already enjoys widespread use. Therefore I have been in communication with some neuron simulator developers about incorporating my adaptive algorithm into future versions of these tools.

Directionally-selective neurons in the retina

Background

One of the main ways that I'm applying my dissertation research now is in the study of starburst amacrine cells in the retina. These cells respond to a bar of light moving in only one direction (for instance, right-to-left, but not left-to-right) even though the cells themselves are spatially symmetric. Called directionally-selective cells, their mechanism for responding to light motion in only one direction is still not fully understood even though much experimental work has been done in this area (Demb, 2007). Experimentalists in the neuroscience department of Ohio State University have determined several key factors in this phenomena (Gavrikov et al., 2003, 2006), but they recognize that a model could be very useful in elucidating some of the mechanisms. Previously, only a relatively simple model of the cells has been used to investigate the hypotheses of the experimentalists (Enciso et al., submitted). Using the algorithm I developed during my graduate training, I am constructing a detailed, morphologically-accurate model of a network of these cells to investigate the mechanism of the directional response. In this case the shape of the cells is important since each cell receives input from the light signal everywhere on each of its branches, but only produces output from the tips. Therefore, single compartment models are not appropriate for these cells as a model must include the cell's detailed morphology to account for the phenomena of interest.

Future directions

This modeling will give us insight into the mechanism of directional selectivity and will help us determine which parameters are most important. Also, we can investigate the robustness of the phenomena by varying several parameters in the simulation and studying the resulting outcomes. My experimental collaborators are investigating different light stimuli apart from moving bars including annuli and circles. Once the basic mechanism is understood using moving light bars I will scale up the mathematical model to simulate these other stimuli in order to understand how they give rise to directional selectivity.

Temperature-sensitive neurons in the hypothalamus

Background

A second interdisciplinary neuroscience project I have been involved with during my postdoctoral fellowship is a collaboration with Jack Boulant in the physiology department of Ohio State. The Boulant lab studies temperature-sensitive neurons in the rat hypothalamus. The portion of the hypothalamus that they study is the region of the brain that monitors the organism's body temperature and controls it by causing responses like shivering or panting. These neurons themselves are sensitive to the local temperature of the brain tissue around them. While the vast majority of neurons in the brain become more active as the local temperature increases, in the hypothalamus there are three different kinds of cells: those cells that become more active with higher temperature, cells that don't respond at all to temperature changes, and those that fire less with higher temperature. Working with a former post-doc, Martin Wechselberger, and building on his previous work (Wechselberger et al., 2006), I have been developing simple models of these cells to understand why some of them are warm-sensitive and some are temperature-insensitive. For this project we represent the cell as a single compartment whose voltage is governed by Hodgkin-Huxley style ion channels. Taking this approach allows us to investigate the distinct contributions of a handful of different currents known to be present in these cells. With this model we can make predictions about what is different between the temperature-sensitive cells and those that are insensitive to temperature. These predictions have led to new experiments and eventually will help elucidate the mechanisms of temperature-sensitivity in these cells.

Future directions

Taking this approach, I have identified an ion channel that may be important for determining whether or not a cell is warm-sensitive or not. In the simulations, the cells that have high levels of this channel are temperature-sensitive while those without it are relatively insensitive to temperature. The hypothesis that this channel is important for temperature-sensitivity of these cells remains to be tested experimentally.

Mathematical modeling of human sleep

Background

The main project that I am working on as a postdoc in the Mathematical Biosciences Institute is a study of sleep in the human brain. This is a collaboration with David Terman and Janet Best, both of the mathematics department at OSU. While sleep is a daily process for most of us, compared to other physiologic processes, it is relatively poorly understood. Through both animal and human studies, several of the brain regions that are important for sleep have been identified, but it is still not entirely clear how they interact to bring about the separate stages of sleep and wakefulness. An important conceptual model for understanding the sleep/wake cycle is called the "flip-flop" model (Saper et al., 2001). In this model the regions of the brain that cause wakefulness oppose those that cause sleepiness so the system is stable in either state, but does not spend much time in-between sleep and wakefulness. This is called a flip-flop because the system quickly "flips" from one state into another, instead of gradually changing from one to the other. The same researchers also proposed a second flip-flop switch for REM sleep (Lu et al., 2006). This model is helpful conceptually, but it does not have a mathematical foundation. In an effort to better understand sleep dynamics, and the "flip-flop" model, we use reduced Hodgkin-Huxley style oscillators to model the activity of four brain regions: one that is active during sleep, one that is active during wakefulness, one that is active during REM sleep, and one that is active during non-REM sleep. Taking this approach, we analyze the dynamics of the system using phase plane analysis. This helps us to understand the possible underlying mechanisms for the sleep-wake system, including the sleep disorder narcolepsy.

Our model does a good job of matching many of the important features of the human sleep-

wake cycle including the timing of normal sleep, the main features of the sleep disorder narcolepsy, and the dynamics of REM sleep (Rempe et al., submitted). To see the correct behavior out of the model, we needed to make an additional assumption about the connections present between cell groups. This serves as a hypothesis that can be investigated by experimentalists. The construction of the model was not simply done to reproduce the features of the sleep cycle, but to help us gain insight and make predictions about how features of the sleep cycle arise from the interaction of a few relatively simple oscillators.

Future Research

We are currently investigating how the model behavior depends on parameters to give variations in sleep behavior between individuals. Human sleep data typically shows a lot of variation, both between individuals and between trials of one individual. We have received human sleep data from a sleep lab and we are currently working on techniques to incorporate inter-individual and inter-trial differences into the model. Investigating which parameters give rise to individual sleep patterns in the model will give us insight into how these differences arise biologically. Also, now that we have a working mathematical model of human sleep, I will apply it to the study of stress-induced insomnia. Stress during the day has been shown to have strong impact on sleep the following night and I would like to understand how this works from a neuroscience perspective.

A key component in successful mathematical biology research is a healthy connection between mathematicians and experimental biologists. I have experience establishing and maintaining connections with experimentalists. As a graduate student my co-advisor was an electrophysiologist and I regularly attended weekly lab meetings and neurophysiology journal clubs. In addition I spent a quarter in the laboratory to learn how to perform the experiments that I was simulating with my numerical method. As a post-doc I regularly visit my experimental collaborators and observe experiments. I have learned how to communicate across disciplines with experimentalists and mathematicians. As a faculty member I would like to draw from this cross-disciplinary experience to develop new courses in mathematical biology and develop or contribute to interdisciplinary programs between mathematics and life sciences departments. Having developed a strong foundation for cross-disciplinary research in computational neuroscience, I hope to build on this foundation in the next step of my career as I explore new questions, not only in neuroscience, but in other areas of mathematical biology as well.

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