NEURAL CONTROL AND ADAPTATION IN BLOOD PRESSURE CONTROL

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Abstract
The baroreceptor reflex and the neurons which produce it are modeled in order to better understand the neuronal computations involved in blood pressure control. The baroreceptor reflex is an interesting example of a biological control system: sensors measuring blood pressure send signals through a network of neurons which calculate a control signal which is sent to the heart to determine heart beat frequency. This is a feedback control system, but it is nontrivial in that it requires combining the results from the thousands of sensors controlling a system, blood pressure, that varies with each beat as well as having slower secular changes. The baroreceptor reflex is remarkably robust to the destruction of neurons and it shows both short and long term adaptation to neuron destruction and to changes in the "plant" (the heart and body). To better understand the computations performed in this system we are constructing detailed neural models and comparing their predictions to experimental observations. This paper gives an overview of our modeling efforts and discusses the form and significance of adaptation in the baroreceptor reflex.

INTRODUCTION

The blood pressure control system is in many ways an ideal system to study. It is MIMO, has what appears to be both feedforward and feedback, and involves the control of multiple interconnected "devices" (the organs). The solution which has evolved is, compared to the current state-of-the-art in engineering, remarkably robust with respect to disturbances and sensor or neuron failures, and adapts well as the plant (the body) changes. Unlike many of the neural systems studied, such as vision, the inputs and outputs of the baroreflex are well characterized, and the number of neurons is small enough to run system simulations that incorporate neuronal dynamics. Thus this circuit can be restricted enough that there is actually hope of truly understanding the complete system.

The heart of our research effort is in developing accurate models of the different kinds of neurons which participate in the baroreceptor reflex. Neural models are built by combining experimental descriptions of ionic channels taken from the biological literature. These descriptions form the basis of a kinetics library which can be called upon to reproduce a large variety of experimentally observed neural behaviors. Adjusting the parameters in these library components to reproduce observations is difficult because the neural models are highly nonlinear and contain many parameters. We use a random search technique to adjust these parameters so that the spike trains predicted by the neuron models fit closely to those observed experimentally from in vivo and in vitro studies. The resulting fits are improved by including biophysically accurate information as well as by fitting over a wide range of stimuli. Neural models for several different types of neurons in the NTS, a region of the brain which controls blood pressure, were constructed using these methods. These neural models help explain the representation of information and the computations performed in the NTS to combine sensor data and control blood pressure. They also provide a starting point for studying adaptation.

Learning (or adaptation) occurs in this system on several time scales. The "sensors" (baroreceptors) measuring pressure adapt on a scale of seconds to minutes, the central system (the NTS) adapts on a scale of minutes to hours, and classical conditioning of the heart rate can last on a scale of years. We focus on adaptation on the shorter time scales, which can occur in many forms: on the time scale of seconds, build-up or depletion of ions and neurotransmitters lead neurons to give very different responses to the same input signal depending on their recent input history. On slightly longer time scales, it is believed that modulators can greatly change the dynamics of the channels. Compared to the artificial neurons often used by engineers, the neuron models we study here have a much more complex set of behaviors, including state-dependent behaviors such as habituation (reduced response to repeated stimuli) and potentiation (increased response to repeated stimuli), and strong sensitivity of neuron behavior to changes in the dynamics of components.

This paper starts with a short introduction to the baroreceptor reflex and the neuron models we use to model it. After describing these neuron models, and what simulations reveal about the computations that they perform, we conclude with a more speculative description of the form and role of adaptation in blood pressure control.

THE BARORECEPTOR REFLEX

The baroreceptor vagal reflex, or baroreflex, is a multiple-input, multiple-output (MIMO), multi-level, nonlinear, adaptive controller. Blood pressure, heart rate and blood gasses are regulated on a heartbeat-to-heartbeat time scale by circuitry localized within the lower brainstem (reviewed in Spyer, 1990; see Figure 1 and legend for circuit summary). Various pressure-sensing inputs (primarily the baroreceptors) project onto sec-
ond order neurons in the nucleus tractus solitarii (NTS), where they are integrated with signals from other parts of the brain reflecting various demands on the cardio-respiratory performance. Output control signals are sent to the heart to regulate its rate, rhythm and force of contraction, to the individual vascular beds to determine flow and resistance, and to multiple endocrine systems. This system is open loop stable when the sensory inputs to the brain are cut, as the brain continues to produce stable output control signals. But the cardio-respiratory performance (the “plant”) is unstable if the control system is extensively damaged and produces poorly regulated output control signals.

In order to analyze the mechanisms by which these functions are achieved, we are “reverse engineering” the biological system by modeling its neural network and the functions of its neurons.

In the analysis of this control system it appears that, in addition to the role of the neural network, the computational role of single neuron dynamics are also important. For example, at the first synapse in the baroreflex second order neurons receive a strong excitatory drive from the primary afferents, but their activity does not represent the input spike pattern in any obvious manner. Specifically, second-order neurons recorded in vivo show strong excitatory responses to shock of the afferent nerves or to activation of the pressure transducers by stretch, but they very rarely demonstrate the bursting pattern or the pulse-synchronous activity of their sensory inputs (see Spyer, 1990 for review). These neurons show time and voltage-dependent responses to inputs, and these dynamics may largely account for the observed nonlinearities in second order neuron responses to primary afferent drive. Capturing these dynamics in neuron models allows analysis of the mechanisms of the signal processing and control functions of second order cells, for example in representing sensory space, adapting to disturbances of inputs and fusing or integrating multiple inputs.

### SPECIFICS OF NEURON SIMULATIONS

To better understand the details of the baroreceptor reflex, we are modeling the neurons of which it is composed using single compartment neural models based on the formalism and techniques of Hodgkin and Huxley (1952). This formalism treats a neuron as a capacitive membrane with voltage, concentration

![Experiment Simulation](image)

**Figure 2:** Comparison of experimentally measured outputs with model predictions.

and time dependent selective permeabilities to ionic species. The selective permeabilities arise from ionic channels. Many researchers have used this approach to produce descriptions of ionic channel kinetics in various neuron types in various species. In spite of considerable experimental work, however, detailed kinetic data are rarely available for any particular neural class of interest. Thus in modeling a neuron, either a full experimental program requiring significant effort must be undertaken, or methods must be developed to approximate the kinetics.

We have developed a methodology to do this. Our approach is to take kinetic descriptions of ion channels from the biological literature and adjust them to fit experimental observations. Figure 2 shows examples of experimentally observed neural behavior and corresponding fits. The fits were obtained by manually adjusting the number and the kinetics of ionic channels present in the neuron.

Though neurons created from a kinetics library are capable of fitting a wide range of experimental behaviors, manual tuning of parameters is time consuming, and the resulting fits are only qualitative. We have automated the fitting procedure to address these shortcomings. Parameters are adjusted based on an objective function which emphasizes the features of the data which
addressed by improving the physiological accuracy of the models, restricting models to physiological input ranges, and by using a wide range of input signals in the model identification process.

We are interested in using neural models to explore the contribution of neural dynamics to blood pressure regulation in the baroreceptor vagal reflex. Stretch sensitive receptors, or “first order neurons” in various locations in the body transduce pressure driven strain into a series of action potentials which feed into a set of “second order neurons” in a well defined area of the brain (the NTS). Each neuron has a large number of dendrites which take in the signals which other neurons have produced and sent out their axons. The gap between axons and dendrites are synapses and, as discussed below, play important roles in adaptation. The outputs from the brain are the action potentials of vagal motor neurons which contribute to the control of heart rate. The inputs and outputs of the control system are rhythmical while the activity of central neurons is non-rhythmical and a non-linear function of the inputs. This non-linear integration of inputs by central neurons is captured by our model neurons even though the relevant input regime was not specifically fit.

COMPUTATIONS PERFORMED BY NETWORKS OF NEURONS
The first order sensory neurons (A-fiber neurons) are highly sensitive, rapidly adapting neurons that transduce and encode each blood pressure pulse with a train of spikes on the rising phase of pressure, in which the amount of activity is sensitive to the rate of change in the pressure, dP/dt, (Abboud & Chapleau, 1988; Seagard et al., 1990). To capture this function our first order neuron model has two terms for the transducer current, one proportional to P(t) and the other to dP/dt, and encodes the transducer current into spike trains by an active membrane with gNa(fast), gK(DR) and gK(A) ionic currents. There are approximately 100 baroreceptor afferent fibers per nerve. In creating a quantitative model we became aware that variations in the pressure thresholds of these fibers are considerably more than a scattering around mean pressure, but rather cover a range from well below (approx. 35 mm/Hg) to well above (170 mm/Hg) the range of pressure at rest. We analyzed raw data from several researchers to determine the distribution of pressure thresholds and matched this distribution in an array of model first order neurons by varying the transducer current.

Given the pressure threshold distribution, we hypothesized that this might be maintained as a spatial topographical ('barotopic') mapping of inputs by pressure onto the second order neurons in the NTS. This suggests that individual baroreceptor afferents have restricted, distinct terminal fields within the extent of the NTS. Evidence from cholera toxin-horseradish peroxidase conjugate (ct-HRP) connection tracing experiments from the baroreceptor afferent nerves suggests that this is the case, showing baroreceptor afferents with parallel areas of local, restricted branching.

It is not clear why such an array of pressure thresholds should exist, nor is it clear how the resulting activity pattern seen in the afferent array is represented in the second-order population. In preliminary work to address this question, one of the second order neuron models was driven synaptically by first order neurons from Figure 3. Synapses were modeled as ligand-gated (ort-\textsuperscript{I}N) conductances, with reversal potentials and time constants matched to in vitro measured epsp’s. The model second order neuron response in Figure 4, Panel C is not linearly related to pressure or afferent input. Its response never reflects the bursting pattern of the inputs, shows nonlinear responses to increases in the input, and paradoxically actually decreases activity with increases in afferent input. This unexpected result.

A arterial pressure recorded from a cat
B raster plot of 100 simulated baroreceptors

Figure 3: Output of 100 baro-aferents to pressure stimul.
is the product of the intrinsic membrane dependent dynamics of the model neuron. Note that the cardiac period is clearly represented in the population response in Figure 4, Panel D, but not by all cells. Many cells have bursts of action potentials during the change in pressure. This suggests that this second order neuron model can detect and respond to pressure transients.

ADAPTATION AND HABITUATION

A great many neurons exhibit some form of plasticity: responses that change with time or treatment. Of these responses, the most prevalent is accommodation, in which a decrease in response is observed when a response is repeated. Figure 5 shows a version of this effect in which the same model neuron gives very different results to the same stimulus depending on whether there was no prior disturbance, a positive prior input to the cell, or a negative (hyperpolarizing) input. In the above example, a positive stimulus decreased the strength of the response; it can equally increase the response, or “sensitize” the neuron.

Figure 5: Effect of prior stimuli on cellular response.

The short term changes in neural response typically arise due to the depletion of the transmitters in the synapses. These transmitters are used up when the cell is stimulated, and then gradually restored, returning the cell to its former activity level. It is, however, quite possible to have adaptive behavior governed not only by the channel dynamics in the cellular membrane, as was shown in Figure 5. There is a great deal of speculation about changes on the intermediate time scale. There are a numbers of “modulators” such as the catecholamines (e.g. dopamine, epinephrine, and norepinephrine) and neuropeptides which effect both the magnitude and the direction of the effect of classical transmitters (such as amino acids). The mechanisms for long term learning are not known, but probably also result from changes in synaptic strength.

HABITUATION AND PROCESS CONTROL

As would be expected, adaptation performs important roles in securing the efficient control of blood pressure. As a concrete example, consider the function of habituation.

Standard controllers attempt to drive an output to its setpoint. In the event of a sustained step-like disturbance this may require continuing control action. Since control actions can be expensive and since the setpoint may be arbitrary (perhaps because other controllers affect the same output), it can be desirable to have the controller adjust its setpoint to reduce control action. Baroreceptors and many other neurons effectively do this when they habituate. For example, a step change in the pressure causes a flurry of output from the baroreceptors which soon ceases. A second change will again cause the neurons to fire. Habituation is important to physiological systems such as blood pressure regulation because the cost of the control response may, over the long run, be greater than the cost of the original deviation. The blood pressure regulation system applies a series of different regulatory mechanisms at relatively short time-scales,
each habituating, but keeping blood pressure sufficiently regulated until the slower, fluid system (a second controller) can solve the problem completely. This same approach can also be useful in process control. When there is a faster, more expensive (e.g. in terms of energy use) and a slower, less expensive response which can reject the same disturbance, the rapid controller can be used to reject the disturbance. It can then slowly habituate, reducing its control action as the slower controller takes over the task of rejecting the disturbance.

CONCLUSIONS

The baroreceptor reflex provides a useful useful context in which to study the neurological basis of biological sensor fusion and control. Fundamental to the “design philosophy” of biological controllers is the use of large numbers of relatively crude sensors, whose outputs are then combined to give a highly precise controller. Since these sensors die and the plant changes, it is critical that they be able to adapt. We are only starting to understand some of the many mechanisms by which this adaptation occurs.

Bibliography

