

COMPUTATIONAL MODELING OF SENSORY CIRCUITRY
IN THE NUCLEUS TRACTUS SOLITARIII FROM ARTERIAL
BARORECEPTOR AND SOMATOSENSORY INPUTS

A Thesis presented to
The Faculty of the Graduate School
University of Missouri – Columbia

In Partial Fulfillment
of the Requirement for the Degree
Master of Science

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DECEMBER 2007

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**COMPUTATIONAL MODELING OF SENSORY CIRCUITRY IN THE NUCLEUS TRACTUS
SOLITARIUS FROM ARTERIAL BARORECEPTOR AND SOMATOSENSORY INPUTS**

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**To my family
for their love, support and encouragement.**

ACKNOWLEDGEMENTS

I would like to express my deepest appreciation to my thesis advisor Dr. Satish Nair whose guidance and persistent help has made this thesis a success.

I would also like to thank and acknowledge the efforts and contributions of my co advisor Dr. Jeffrey Potts whose guidance in understanding the subject and encouragement helped in the outcome of this thesis.

Additional gratitude is extended to my third committee member Dr. Chun Lin.

I would also like to thank all my friends who have been a constant source of encouragement to me in all aspects.

I also want to thank all the people I worked with in the lab. Working with them was great and I wish success for them in all their future endeavors.

Last but not the least I would like to thank my family who has been a constant source of encouragement and support.

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ABSTRACT

Baroreflex function regulates the arterial blood pressure in our body. The baroreflex is considered to be an integrated negative feedback system. NTS (Nucleus tractus solitarius) is one of key subsystems in this baroreflex loop. In the past, NTS has been considered primarily as a relay cell but later it was determined that it plays a major role in the baroreflex function. It has been found that the NTS is a site for the integration of sensory information from different variables in the body. This lead to further studies on the properties of the NTS neurons and how it affects the baroreflex function.

The present study is an effort to characterize the NTS at both the single cell and network levels using computational models which are subsequently used to investigate hypotheses regarding NTS functions. With known biological data about NTS cells, the models are used to investigate properties such as pulse synchronicity at intermediate stages in the NTS. The input-output relationship at the first synapse of the NTS is studied first using a single cell network and a transfer function model. The underlying causes for a lack of pulse synchronicity at the second order NTS neuron is then investigated using a population level network model. Finally, a somatic afferent is added to the population model through another GABA population to study the possible effect of exercise on this baroreflex function.

CHAPTER 1: INTRODUCTION AND OBJECTIVES

1.1 INTRODUCTION

Cardiovascular system plays an essential role in maintaining the constancy (homeostasis) of the pressure and flow in the vasculature. Regulation of the system involves reflex negative feedback loops. One of the reflex loops of interest in this research is the carotid sinus baroreflex. Baroreflex is one of the body's homeostatic mechanisms which maintain blood pressure in the body. When arterial blood pressure is elevated this negative feedback loop reflexively causes a decrease in sympathetic nerve activity and an increase in parasympathetic nerve activity, and similarly increases sympathetic nerve activity and decreases parasympathetic nerve activity when blood pressure is reduced. The arterial baroreflex monitors the blood pressure of the body and relays this information to the brain stem through mechanosensitive receptors located on the bifurcation of the carotid arteries and the aortic arch, and is carried by the glossopharyngeal and vagal afferents, respectively. These receptors transmit the information about the ongoing levels of the blood pressure to the central nervous system (CNS) and based on the information received, it sends a signal back to regulate arterial blood pressure.

Arterial Baroreceptors

Arterial baroreceptors are mechanoreceptors that respond to mechanical deformation produced by changes in arterial pressure. We are interested in the baroreceptors in the carotid sinuses which are called the carotid sinus baroreceptors. The carotid sinus baroreceptors are innervated by the Hering nerve, which is a branch of the glossopharyngeal nerve while the aortic arch baroreceptors are innervated by the aortic depressor nerve. The baroreceptors are of two

types, the A-type baroreceptors with low pressure threshold and higher sensitivity to pressure, and the other C-type Baroreceptors with high pressure threshold and comparatively lower sensitivity to pressure. The A type baroreceptors are lightly myelinated and the C type baroreceptors are unmyelinated. The presence of myelin causes an increase in the speed of the impulse transmission. Therefore the A-type baroreceptors fire more compared to the C-type baroreceptors. Information from the arterial baroreceptors travels through these nerves and synapse in the nucleus tractus solitarii (NTS).

The basic negative feedback loop is shown in Figure 1 in the rest position, and is described next in more detail.

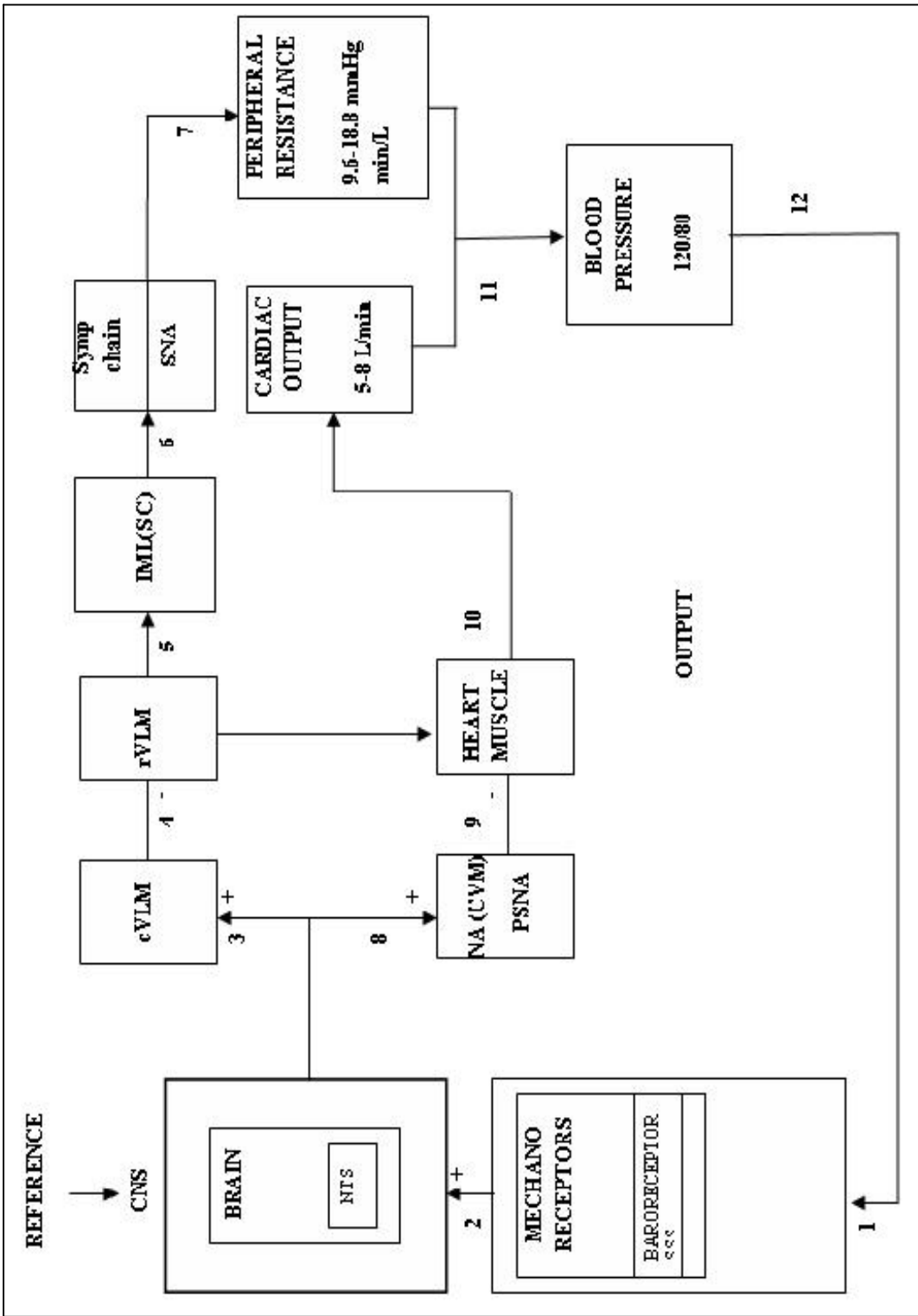


Figure 1: Baroreceptor Reflex

Block diagram components:

cVLM stands for caudal ventro lateral medulla which contains inhibitory GABA neurons.

The input to the cVLM is the excitatory output from the NTS.

NA (Nucleus ambiguus) which contains the **CVM** which is the cardiac vagal motoneurons which project to the heart.

The output of the cVLM goes to the **rVLM** which is the rostral ventro lateral medulla whose output goes to the sympathetic nervous system.

SNA stands for the sympathetic nerve activity. **PSNA** stands for the parasympathetic activity. The **cardiac output** is given as the product of the heart rate and the stroke volume.

$$\text{Cardiac Output (CO)} = \text{Heart Rate (HR)} * \text{Stroke Volume (SR)}$$

The **Heart rate** changes according to the age but the resting heart rate of range 50-100 beats per minute for resting heart rate has been established as normal heart rate.

The **stroke volume** ranges from 60-130 ml.

The range of the **cardiac output** is 5-8 liters per minute.

The **blood pressure** is the product of the cardiac output and the total peripheral resistance.

$$\text{Arterial Blood pressure (ABP)} = \text{CO} * \text{Total Peripheral Resistance (TPR)}$$

Peripheral resistance is the resistance due to the arterioles and the capillaries to the flow of blood. The range of the **TPR** is 9.6-18.8 mmHg min/L.

The range of the **Heart rate** is 120/80 mmHg which is 120 mmHg systolic and 80 mmHg diastolic.

The baroreceptors are more sensitive to pulsatile pressure than constant pressure. The blood pressure change will change the frequency of the baroreceptor output.

The reference input is the blood pressure. Considering special cases like exercise and hypertension this reference point rises.

The output of the baroreceptor is connected to the **NTS** in the brain. The output from the brain is phasic to a phasic input but the individual NTS response lacks the phasic nature which

shows that the NTS is not only one which can just transmit information. This may be a place where the sensory information from different afferents gets integrated but this is poorly understood presently. The output of the NTS determines the compensation required. Based on the output the sympathetic nervous system and the parasympathetic nervous system react to affect the blood pressure, thus forming the feedback loop. The numbers 1 to 12 in the figure represent the synapses in the system.

Functionality

An increase in the blood pressure activates arterial baroreceptors, i.e., increases their firing rates. This may, for instance, be due to exercise or hypertension. The baroreceptors are activated if the mean arterial pressure is above the threshold which is usually in the range of 70-90mm Hg. The baroreceptors are also sensitive to the rate of pressure change. At a given mean arterial pressure, decreasing the pulse pressure, which is the difference between the systolic pressure and the diastolic pressure, decreases the baroreceptor firing rate. An increase in the blood pressure means an increase in the excitatory drive to the NTS. The input to the NTS from the carotid sinus and aortic baroreceptors respond rapidly to beat to beat changes in the arterial pressure. Output neurons of the NTS project to the nucleus ambiguus (NA) which is the location of cardiac vagal motoneurons (CVM) that controls heart rate. NTS output neurons also project to a region of the caudal ventrolateral medulla (cVLM) which contains GABA neurons which provide a degree of inhibition to sympathetic premotor neurons of the rostral ventrolateral medulla (rVLM). The heart rate (HR) and sympathetic nerve activity (SNA) are under tonic control by the arterial baroreflex. An increase in blood pressure activates the baroreceptors which in turn activates the NTS. The NTS in turn activates the GABA neurons in the cVLM which inhibits the sympathetic premotor neurons, which in turn reduces SNA. This results in a decrease in cardiac contractility and decreased peripheral vascular resistance. Now blood pressure falls since both cardiac output and vascular resistance have decreased. Conversely, a decrease in the blood pressure will produce increases in cardiac output and peripheral vascular resistance which increases blood pressure.

1.2 OBJECTIVES

The overall objective of this project is to get a better idea of the interactions of the blood pressure regulatory circuit with the NTS of the brain. These regulatory mechanisms are very important in maintaining or controlling the blood pressure and other variables. Towards the end a biophysical model of parts of this system are developed to provide ideas of how pieces of this function might be implemented. A computational model also serves to study several 'if then' scenarios, after validation using experimental data.

The specific objectives of the research are listed below under individual chapters. Following an introductory chapter (chapter 1), each of the chapters 2 to 4 is written in the form of stand-alone journal papers, with chapter 5 summarizing the thesis and listing future research.

- 1) A dynamic analysis of the first synapse on the NTS is performed using a computational model, to determine its transfer function. This is done using a computational model that includes two types of baroreceptors A and C type connected to an NTS neuron. The gain, phase and the coherence are determined to identify the transfer characteristics (Chapter 2).
- 2) There is phasic activity at the output of the brain given that there is no phasic activity observed experimentally at the output of the NTS. A network model is developed to determine the reason for the loss in the phasic activity in second order neurons and the changes that can be made in order to achieve the pulse synchronous activity in the output neurons (Chapter 3).
- 3) Sensory feedback from the somatic afferents inhibits the barosensitive NTS neurons and changes the baroreflex function whose function is restored as soon as the stimulation of the somatic afferents is terminated. A network model is developed to explain this phenomenon. A second GABA population activated by somatic afferents is added to the model in 2) above (Chapter 4).

CHAPTER 2: TRANSFER FUNCTION ANALYSIS AT THE FIRST SYNAPSE OF THE NUCLEUS TRACTUS SOLITARII (NTS) TRANSMITTING ARTERIAL BARORECEPTOR SIGNALS- A COMPUTATIONAL ANALYSIS

2.1 ABSTRACT

One of the major negative feedback systems providing short-term control of arterial blood pressure is the carotid sinus baroreflex. This plays a major role in the regulation of arterial blood pressure, heart rate and sympathetic nerve activity. Many studies have been done describing the transfer function between carotid sinus pressure and baroreflex control of sympathetic nerve activity. However, these studies did not quantify the transfer function between baroreceptor input and output from the nucleus tractus solitarii, the site for synapse of primary baroreceptor afferents. The NTS has been shown to be the site for integration of sensory information rather than just being a relay center which affects the output of the baroreflex. There is virtually no data describing the transfer function at this first synapse in the NTS. In this study, we developed a simple computational model that includes primary baroreceptor afferents and barosensitive NTS neurons and estimated the open-loop transfer function between baroreceptor input and NTS output.

2.2 INTRODUCTION

The baroreflex system is a negative feedback control system that regulates the arterial blood pressure (Spyer 1990). Several researchers have attempted to determine the input-output relationships of the arterial baroreflex arc using a transfer function analysis (Kawada et al 2005, Ikeda et al 1996, Julien et al 2003, Kawada et al 2003). The transfer function analysis uses input

and output data to characterize the system using gain and phase information. The transfer function analysis is known presently only for certain blocks. One of them is between carotid sinus pressure (blood pressure) and the baroreceptor whose transfer function gain characteristics were similar to a first order high pass (Kawada et al 2005⁸). Another one is from the baroreceptors to the heart rate whose transfer function gain is first order low pass. Similarly, studies have been performed for the input-output relationships between baroreceptors and the sympathetic nerve activity. This transfer function was found to be similar to a first order high pass filter (Kawada et al 2005, Kawada et al 2003, Ikeda et al 1996). All the above transfer function analysis studies have been performed using a white noise technique in anesthetized animals, a technique that is used for analyzing dynamic characteristics (Ikeda et al 1996). The high pass characteristics found in vivo between the baroreceptors to SNA does not specify the intermediate variable at which these characteristics are implemented in reality. So one could hypothesize the possibility of high pass characteristics at the first synapse of the NTS.

The findings from in vitro studies contradict some of these results from in vivo studies. In vitro studies use longitudinal slices of the brain stem and examine the properties of the synaptic transmission at these sites. The solitary tract, which carries sensory axons of the glossopharyngeal and vagus nerves, is stimulated electrically and the post-synaptic potentials are measured using standard electrophysiological techniques. The post-synaptic responses to solitary tract stimulation are depressed with an increase in stimulation frequency, which indicates characteristics of a low pass filter. This response pattern of the first barosensitive synapse in the NTS is referred to as frequency dependent depression (Miles et al 1986, Liu et al 2000, Fan et al 1996). This difference in the dynamic characteristics between in vivo and in vitro studies may be due to the method used to characterize the system. Electrical stimulation of the solitary tract may not be a physiologically relevant stimulus. This may be due to the fact that there will be random perturbations in the blood pressure which are transmitted to afferent fibers and the increase in frequency of the stimulus to the solitary tract over time may not give a good approximation of the dynamic behavior involved in the system, whereas the white noise technique comes closer to this approximation of dynamic behavior. Also, no studies have obtained the transfer function at the

first synapse of the NTS from the arterial baroreceptor to 2nd order NTS neurons. Therefore, the purpose of the present study is to determine the transfer function characteristics at the first synapse for arterial baroreceptor signaling in the NTS using the white noise technique and a computational model of NTS circuitry.

A computational model is developed to investigate the transfer function from the primary arterial baroreceptor afferent neurons to the 2nd order NTS neurons. An explanation for how arterial baroreflex control of sympathetic nerve activity has high pass filter characteristics and the region in the brain where this information is transferred and amplified is not yet known. We hypothesize that it might be at the NTS since recent studies have shown that the NTS functions not only as a relay but it is a place where all the information from other sources gets integrated (Paton et al 2001, Potts et al 2001, Seagard et al 2001). We also studied the effect on the transfer function with the change in the calcium concentration decay time constant of NTS. This decay time constant of the calcium controls the Ca^{+2} level in the cell which in turn controls the activation of the calcium dependent potassium current. Here we do the transfer function analysis for different calcium decay time constant values.

2.3 METHODS

The computational model consists of a primary baroreceptor neuron connected a 2nd order glutamatergic NTS cell via a glutamatergic AMPA synapse. AMPA is α -amino-3-hydroxy-5methylisoxazole-4-propionic acid receptor which is an ionotropic receptor for glutamate. Glutamate helps in the fast transmission of impulses through the synapse. The model is generated in software called GENESIS (ver 2.3).

A single cell of the baroreceptor is modeled with the following channels: voltage-dependent sodium (I_{Na}), persistent sodium (I_{NaP}), delayed rectifier potassium (I_{DR}), C-type potassium current (I_C), calcium current (I_{HVA}), cationic current (I_{CAT}), calcium dependent potassium from (I_{AHP}) and a leak current (I_L). The leakage current (I_L), a fast, spike-generating Na^+ current (I_{Na}), the delayed rectifier potassium current (I_{DR}), and persistent current (I_{NaP})

are taken from Durstewitz et al. (2000), the high-voltage activated Ca^{2+} current (I_{HVA}) from Brown et al. (1993), the voltage-dependent C-type K current (I_C) were from Wang et al (1993), the calcium dependent potassium (I_{AHP}) from Warman et al. (1994), and the Ca^{2+} dependent cationic current (I_{CAT}) from Kang et al (1998). Here we use a single compartment model that only represents the soma.

Sodium channel is a voltage-gated channel which has activation and inactivation constants and the conductance equation governing this is given by $g_{Na} = g_{Na\max}m^3h$ (where $g_{Na\max} = 0.118 \text{ S/cm}^2$). Similarly the persistent sodium also has activation and inactivation constants and is governed by the conductance equation $g_{Nap} = g_{Nap\max}mh$ (where $g_{Nap\max} = 0.022 \text{ S/cm}^2$). The delayed rectifier has a single inactivation constant and the equation governing them is the $g_{DR} = g_{DR\max}n^4$ (where $g_{DR\max} = 0.033 \text{ S/cm}^2$). The high-voltage activated calcium current has an activation and an inactivation constant with the conductance equation to be $g_{HVA} = g_{HVA\max}u^2v$ (where $g_{HVA\max} = 0.00323$). Similarly, the C type potassium current, calcium dependent potassium and the calcium dependent cationic current have the conductance equations of $g_C = g_{C\max}c^2$, $g_{AHP} = g_{AHP}q$ and $g_{cat} = g_{cat\max}m_{cat}$ (where $g_{C\max} = 0.0022 \text{ S/cm}^2$, $g_{AHP\max} = 0.00002 \text{ S/cm}^2$, $g_{cat\max} = 0.005$) respectively. The reversal potentials of the sodium and potassium are taken to be $E_{Na} = 55 \text{ mV}$ and $E_K = -94 \text{ mV}$. The reversal potential of the cationic current is taken as $E_{cat} = -42 \text{ mV}$. There are two types of baroreceptors: thinly myelinated and unmyelinated. The thinly myelinated A- type baroreceptors have faster conduction velocity compared to the unmyelinated C-type baroreceptor. To vary the firing profiles of the A and C type baroreceptor to that shown in Schild et al (1994), the membrane capacitance is changed with the rest of the channels remaining the same. The equations for these currents can be summarized as shown below and the rate equations are shown in the Table 1 below.

$$I_L = g_L(V - E_L) \quad (2-1)$$

$$I_{Na} = g_{Na}m^3h(V - E_{Na}) \quad (2-2)$$

$$I_{NaP} = g_{NaP} m h (V - E_{Na}) \quad (2-3)$$

$$I_{DR} = g_{DR} n^4 (V - E_K) \quad (2-4)$$

$$I_{HVA} = g_{HVA} u^2 v (V - E_{Ca}) \quad (2-5)$$

$$I_C = g_C c^2 (V - E_K) \quad (2-6)$$

$$I_{AHP} = g_{AHP} q (V - E_K) \quad (2-7)$$

$$I_{cat} = g_{cat} m_{cat} (V - E_{cat}) \quad (2-8)$$

A single cell model of a barosensitive NTS neuron is generated based on the channels from Rogers et al (2000). The channels involved in this NTS model are the voltage-gated fast sodium (I_{Na}), delayed rectifier potassium channel (I_{DR}), leak channel (I_L), transient potassium channel (I_A), high threshold calcium (I_{CaI}) and calcium dependent potassium (I_{Cak}) channel after hyper polarization. Here we are only considering the cell body. The reversal potential for sodium was set to $E_{Na} = 55$ mV and that of the potassium to a value of $E_K = -94$ mV. In order to have a change in the amount of calcium concentrations, we modeled a calcium pool where there is a change in the internal calcium concentration due to the calcium current. The channels used can be described as follows:

- 1) Voltage-gated fast sodium channel is a Hodgkin-Huxley (HH) type channel. The conductance equation governing this channel is: $g_{Na} = g_{Na_{max}} m_{Na}^3 h_{Na}$ (where $E_{Na} = 55$ mV $g_{Na_{max}} = 0.12$ S/cm²) where m and h represent the activation and inactivation of the channel. In general, the rate constants depend on the membrane voltage.
- 2) Delayed rectifier potassium channel is also a HH type channel. There is only an activation constant without an inactivation constant. The conductance equation governing this channel is: $g_{DR} = g_{DR_{max}} m_{DR}^4$ (where $E_K = -94$ mV $g_{DR_{max}} = 0.036$ S/cm²). This is also a voltage gated type channel where the rate constants depend on the voltage of the membrane. Transient potassium channel is a voltage gated HH type channel which

contains two activation constants and two inactivation constants which are governed by the conductance equation as follows: $g_A = g_{Amax}(0.6m_{A1}^4h_{A1}+0.4m_{A2}^4h_{A2})$. (Where $g_{Amax} = 0.006 \text{ S/cm}^2$).

- 3) High threshold calcium channel a HH type channel where the activation constants depend on the voltage with no inactivation which is governed by the conductance equation $g_{Cal} = g_{Calmax}m_{Cal}^3$ (where $g_{Calmax} = 0.00006 \text{ S/cm}^2$). The reversal potential depends on the intracellular concentration taking the extra cellular calcium to be constant.
- 4) Calcium dependent potassium channel is governed by the conductance equation $g_{cak} = g_{cakmax}m_{cak}^2$ (where $g_{cakmax} = 0.006 \text{ S/cm}^2$) and the rate constants purely depend on the internal calcium concentration. In order to have a calcium concentration, we introduce a pool of calcium where the internal calcium concentration changes based on the calcium current. Concentration of the calcium pool inside the cell, $[Ca_i^{2+}]$, is modeled using a first order equation, assuming the external concentration to be constant. The amount of the calcium entry depends on the calcium current. The current equations of the above described channels are similar to $I = g(V - E)$ where g is the conductance which depends on the rate equations which are shown in the Table 2 below. I represent current and V represents membrane voltage and E represents the equilibrium potential.

The single cell baroreceptor neuron and the NTS neuron are connected through an ionotropic AMPA receptor expressed post-synaptically on the NTS neuron. The AMPA receptor is modeled is a dual exponential function with two different time constants: one for the rise time and the other for the decay. The conductance equation is given as:

$G_K = (g_{AMPAMAX} / (\tau_{rise} - \tau_{decay})) \{ \exp(-t / \tau_{decay}) - \exp(-t / \tau_{rise}) \}$. The current equation for the AMPA follows $I_{AMPA} = G_K (V - E_{AMPA})$. The values for the rise and fall time constant, maximum ion conductance and the reversal potential for the AMPA receptor is taken from the Durstewitz et al.(2000). The values used for the AMPA receptor are shown in the Table 3 below.

Model Inputs

To determine the transfer function, a random binary input is applied. The random binary input is generated in MatLab (7.0) and incorporated into the GENESIS (ver 2.3) model as an injection into the primary baroreceptor neuron. The random binary input is generated by taking a 100 Hz sampled Gaussian white noise which is then passed through a Butterworth filter whose corner frequency is 2Hz. The resultant signal is compared with a reference level which is taken as zero and the resultant random binary signal is based on the comparison with the reference signal.

The baroreceptor output which is the input to the NTS neuron and the output of the NTS neuron are used to compute the transfer function using Matlab (7.0). The data are stored at a sampling rate of 10 KHz and read into Matlab. The spike outputs of the baroreceptor and the NTS are compared to a threshold value and converted into short pulses of 1ms duration. These pulse outputs of the baroreceptor and NTS are later down-sampled by a factor of 4. Now the transfer function analysis is done with the baroreceptor pulses as input and the NTS pulses as the output. The auto and cross power spectral density of the input and output are calculated. The power spectral densities are calculated using Welch's averaged, modified periodogram method. The data set of input and the output are divided into 8 segments with 50% overlap. A Hamming window is then applied to each section and eight modified periodograms are found out and averaged. Periodogram is a spectral density estimate of a signal. Transfer function gain and the phase are obtained from the quotient of the cross power spectral density of the input, output, and the auto power spectral density of the input. If x is the input and y is output then the transfer function can be represented as follows:

$$Tf = \frac{S_{xy}}{S_{xx}} \quad (2-9)$$

where S_{xy} is the cross power spectral density of x, y and S_{xx} is the auto power spectral density of x. Coherence is obtained from the quotient of the magnitude squared cross power spectral density of the input, output and the product of the auto power spectral densities of the input and output, and can be calculated mathematically as shown in Eqn. (2-10)

$$Coh = \frac{|S_{xy}|^2}{S_{xx}S_{yy}} \quad (2-10)$$

where S_{xy} is the cross power spectral density of x, y and S_{xx} , S_{yy} are the auto power spectral densities of x, y.

Gain, phase and coherence plots were calculated over the frequency range of 0.01 – 1 Hz. A quadratic fit of span 20% is performed on the transfer function and coherence plots, where span is the number of the data points used in order to calculate each element of the resultant, to remove the distortions in the plot. To check for the effect on the transfer function by changing the calcium concentration decay time constant, the different values we use are 25ms, 50ms, 75ms, 150ms, 500ms and 2000ms.

2.4 RESULTS

The output of primary A and C type baroreceptors for a constant current injection of 50 pA is shown in Figure 1. The A type baroreceptors fired at a higher frequency when compared to the C-type. The single cell model for the baroreceptor showed repetitive firing which is the characteristic observed in a baroreceptor cell experimentally.

The firing profiles of individual NTS neuron in Figures 2, 3 and 4 show their basic intrinsic properties such as spike frequency adaptation (SFA) and the delayed excitation (DE). A depolarized current of 100 pA was injected into the NTS neuron which demonstrated a reduction in firing frequency over time which is consistent with spike frequency adaptation (Figure 2). In order to observe DE two different current injection experiments were performed. First, a constant current of 100 pA was injected for 500 ms (Figure 3). Next, an initial hyperpolarizing current of -200 pA for 1000ms is used, followed immediately by a positive current injection of 100 pA for 500 ms (Figure 4). In the experiment where the cell is preconditioned by the hyperpolarized current, the time taken for the cell to fire is more compared to the case where there is no hyperpolarized current to the cell.

After validating the individual baroreceptor and NTS neuron models as described above, these cells are connected to each other via an AMPA synapse mediated by glutamate (Figure 5). To determine the transfer function, a random binary input is applied with a flat auto power spectrum that rolls off at 1Hz as shown in Figure 6. A transfer function analysis is performed using the input and output data to derive the gain, phase and the coherence responses which are shown in Figures 7 and 8. For the network model with the A-type baroreceptor, the gain plot showed an initial decrease below 0.1 Hz but later on it started to increase with increasing input frequency. For the C-type baroreceptor, the gain curve was almost flat up to 0.1 Hz and then increased with increasing input frequency.

After observing these input-output characteristics the effect of the change in the decay time constant of the calcium concentration in the NTS neuron was studied. The output of the NTS neuron with calcium concentration decay time constant of 25 ms and 150 ms to synaptic input from a A-type baroreceptor is shown in the Figures 10 and 11, respectively. The response of the A-type baroreceptor is shown in Figure 9. For the calculation of the transfer function the output spike data was converted into TTL pulses of width 1ms, which are also shown in the figures 9, 10, and 11 of baroreceptor and the NTS. Based on the input and the output data the transfer function analysis was calculated. Similarly, the transfer function analysis was also calculated using other decay time constants of 50 ms, 75 ms, 500 ms and 2000 ms. Plots of the gain, phase and the coherence for different decay time constants are shown in the Figure 12. This experiment was also repeated using a C-type baroreceptor and the respective gain, phase and the coherence plots for each decay time constants of the calcium are shown in the Figure 16. You can see that for an increasing order of cytosolic calcium concentration decay time constant in the NTS neuron the gain curve showed a progressive reduction in the gain with increasing frequency. Also there was a reduction in the coherence as the decay time constant was reduced too with an increase in the decay time constant.

2.5 DISCUSSION AND CONCLUSION

A transfer function analysis of the first baroreceptor synapse in the NTS is reported. The spike profiles for the A-type and C-type baroreceptor showed that the A-type baroreceptor has faster conduction velocity, a lower pressure threshold and higher sensitivity compared to the C-type baroreceptor. The transfer function gain calculated using a A-type baroreceptor starts at -2.387 dB for 0.01 Hz and decreases to a level of -4.4dB at 0.1 Hz. From this point the gain increases to a level of -2.6 dB at 0.5 Hz and increases later to -2.16 for 0.8 Hz. The transfer function gain using a C-type baroreceptor started at -3.392 dB at 0.01 Hz and increased to a level of -2.171 dB at 0.1 Hz. The coherence of both the responses was greater than 0.5 for the majority of the frequency range. All of these calculations were done using a cytosolic calcium concentration decay constant of 25 ms. Now, when we the decay time constant of the calcium concentration in the NTS neuron was increased the Ca^{+2} levels remained elevated which, in turn, activated the calcium dependent potassium currents to limit neuronal excitability. This resulted in failures of spiking and we expect that this contributed to the marked reduction in the magnitude of the transfer function gain at higher calcium decay time constants. In other words, if the baroreceptor input to the NTS was at higher frequencies there would be insufficient time for the cytosolic Ca^{+2} levels to return to normal levels which would result in a loss of spiking. This is effectively what is shown in Figures 12 and 16 when an increase in the calcium decay time constant demonstrates that gain decreases for higher frequencies. When considering Figure 12 a gain plot for a time constant of 150ms at which we can see some failures in the spiking of the NTS, the gain reduces from a starting value of -5.103 dB at 0.01 Hz to a value of -6 dB at 0.5 Hz. If we increase the decay time constant to 500 ms the gain reduces from -5.878 dB at 0.01 Hz to a value of -7.68 at 0.5 Hz and at 2000 ms it decreases from -9.496 dB at 0.01 Hz to -15.57 dB at 0.5 Hz. The coherence level also decreases with an increase in the decay time constant.

2.6 REFERENCES

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2.7 TABLES AND FIGURES

Channel	Conductance, g	Parameters
Fast sodium, I_{Na}	$g_{Na} = g_{Na_{max}} m^3 h$	$\alpha_m = \frac{-0.2816(V + 28)}{\exp(-(V + 28)/9.3) - 1} \quad \beta_m = \frac{0.2464(V + 1)}{\exp((V + 1)/6) - 1}$ $\alpha_h = 0.098 \times \exp(-(V + 43.1)/20) \quad \beta_h = \frac{1.4}{\exp(-(V + 13.1)/10) + 1}$
Potassium delayed rectifier, I_{DR}	$g_{DR} = g_{DR_{max}} n^4$	$\alpha_n = \frac{-0.018(V - 13)}{\exp(-(V - 13)/25) - 1} \quad \beta_n = \frac{0.0054(V - 23)}{\exp((V - 23)/12) - 1}$
C-type potassium current I_C	$g_C = g_{C_{max}} c^2$	$\alpha_c = \frac{-0.00642V_s - 0.1152}{\exp(-(V_s + 18)/12) - 1} \quad \beta_c = 1.7 \times \exp(-(V_s + 152)/30)$ $V_s = V_m + 40 \log_{10}([Ca_i])$
Calcium-dependent potassium, I_{AHP}	$g_{AHP} = g_{AHP_{max}} q_{AHP}$	$\alpha_q = \frac{0.0048}{\exp(-(10 \log[Ca^{2+}]_{i2} - 35)/2)} \quad \beta_q = \frac{0.012}{\exp((10 \log[Ca^{2+}]_{i2} + 100)/5)}$ $\tau_q = 48 \text{ ms}$

High voltage activated calcium current I_{HVA}	$g_{HVA} = g_{HVAm_{\max}}$ $u^3 v$	$u_{\infty} = \frac{1}{\exp(-(V + 24.6)/11.3) + 1}$ $\tau_u = 1.25 \times \text{sec } h(-0.031(V + 37.1))$ $v_{\infty} = \frac{1}{\exp((V + 12.6)/18.9) + 1}$ $\tau_v = 420.0 \text{ ms}$
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Table 1: Rate equations of the Baroreceptor cell

Channel	Conductance, g	Parameters
Fast sodium, I_{Na}	$g_{Na} = g_{Na\max} m^3_{Na} h$	$m_{\infty Na} = \frac{0.091(V+38)}{\exp(-(V+38)/5)}$ $\tau_{mNa} = \frac{0.091(V+38)}{(V+38)/5 + 0.062(V+38)/(\exp((V+38)/5) - 1)}$ $h_{\infty Na} = \frac{0.016 \exp(-(V+55)/15)}{(V+55)/15 + 2.07/(1 + \exp(-(V-17)/21))}$ $\tau_{hNa} = \frac{1}{(0.016 \exp(-(V+55)/15) + 2.07/(1 + \exp(-(V-17)/21)))}$
Potassium delayed rectifier, I_{DR}	$g_{DR} = g_{DR\max} m^4_{DR}$	$m_{\infty DR} = \frac{0.01(V+45)}{\exp(-(V+45)/5)}$ $\tau_{mDR} = \frac{0.01(V+45)}{(V+45)/5 + 0.17 \exp(-(V+50)/40)}$
Transient potassium-A, I_A	$g_A = g_{A\max} (0.6 m^4_{A1} h_{A1} + 0.4 m^4_{A2} h_{A2})$	$m_{\infty A1} = 1/(1 + \exp(-(V+60)/8.5))$ $\tau_{mA1} = 1/((\exp(V+35.82)/19.69) + \exp(-(V+79.69)/12.7) + 0.37)$ $h_{\infty A1} = 1/(1 + \exp(-(V+78)/6))$ $\tau_{hA1} = \begin{cases} 63, & \text{if } V < - \\ 19.0, & \text{else} \end{cases} \frac{1}{(1 + \exp((V+46.05)/5) + \exp(-(V+238.4)/37.45))}$ $m_{\infty A2} = 1/(1 + \exp(-(V+36)/20))$ $\tau_{mA2} = 1/((\exp(V+35.82)/19.69) + \exp(-(V+79.69)/12.7) + 0.37)$ $h_{\infty A2} = 1/(1 + \exp(-(V+78)/6))$ $\tau_{hA2} = \begin{cases} 73, & \text{if } V < - \\ 60.0, & \text{else} \end{cases} \frac{1}{(1 + \exp((V+46.05)/5) + \exp(-(V+238.4)/37.45))}$
Calcium-dependent potassium, I_{Cak}	$g_{Cak} = g_{Cak\max} m^2_{Cak}$	$m_{\infty AHP} = \frac{1.25 \times 10^8 [\text{cai}]^2}{(1.25 \times 10^8 [\text{cai}]^2 + 2.5)}$ $\tau_{mAHP} = \frac{1000}{(1.25 \times 10^8 [\text{cai}]^2 + 2.5)}$

High-threshold calcium, I_{Cal}	$g_{\text{Cal}} = g_{\text{Calmax}} m_{\text{Cal}}^3$	$m_{\infty\text{cal}} = \frac{1.6}{1 + \exp(-0.072 * (V - 5))} / \left(\frac{1.6}{1 + \exp(-0.072 * (V - 5))} + \frac{0.02 * (V - 1.31)}{\exp((V - 1.31)/5.36) - 1} \right)$ $\tau_{\text{mcal}} = \frac{1.0}{\left(\frac{1.6}{1 + \exp(-0.072 * (V - 5))} + \frac{0.02 * (V - 1.31)}{\exp((V - 1.31)/5.36) - 1} \right)}$
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Table 2: Rate equations of the NTS cell

Parameter	Range of Values (citation)	Model Value
AMPA activation time constant (ms)	0.4– 0.8 (Koch et al,1998)	0.5
AMPA deactivation time constant (ms)	2-8 (Koch et al,1998, Spruston et al,1995a)	3
Maximal AMPA conductance(nS)		15.1392

Table 3: Ranges of synaptic parameters

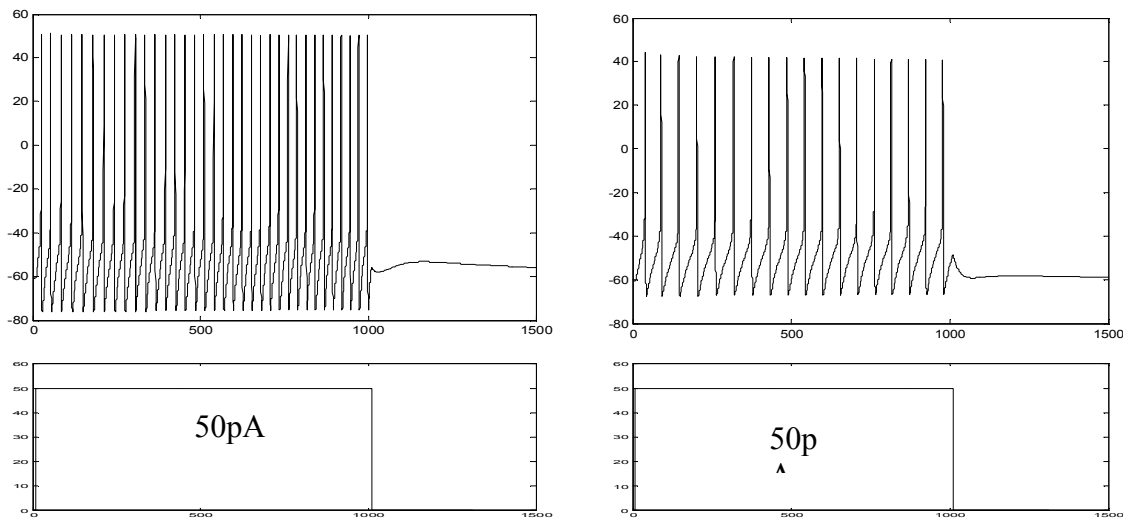


Figure 1: Bottom figures show current injection of 50pA. The top left figure shows the output of the A-type baroreceptor and the top right figure shows the output of C-type baroreceptor

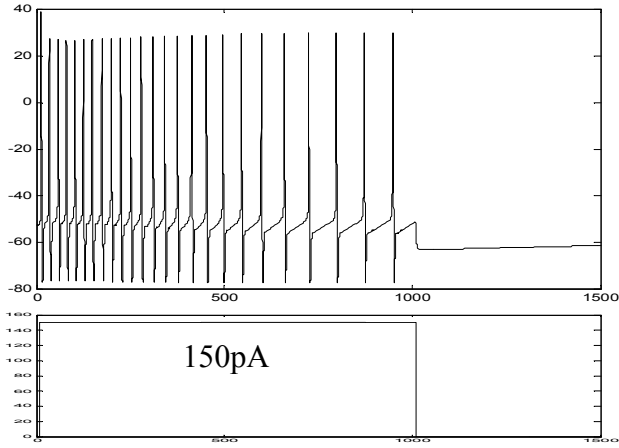


Figure 2: Bottom figure shows a current injection of 150pA into the NTS cell and the top figure shows the output of the NTS which exhibits the spike frequency adaptation.

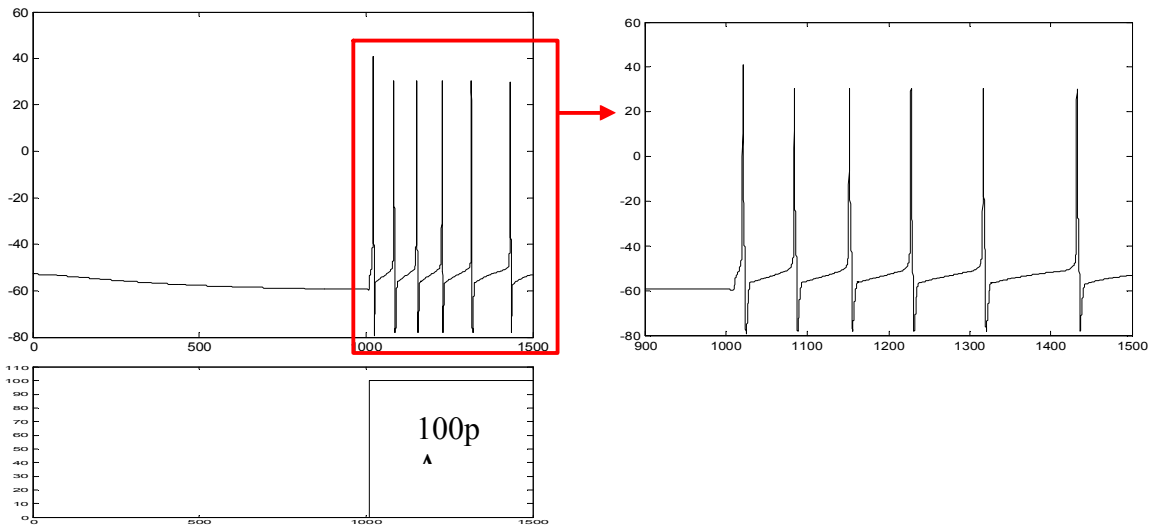


Figure 3: Bottom figure shows current injection of 0pA for 1000ms and 100pA later on. The top figure shows the output of the NTS and the time taken for the first spike.

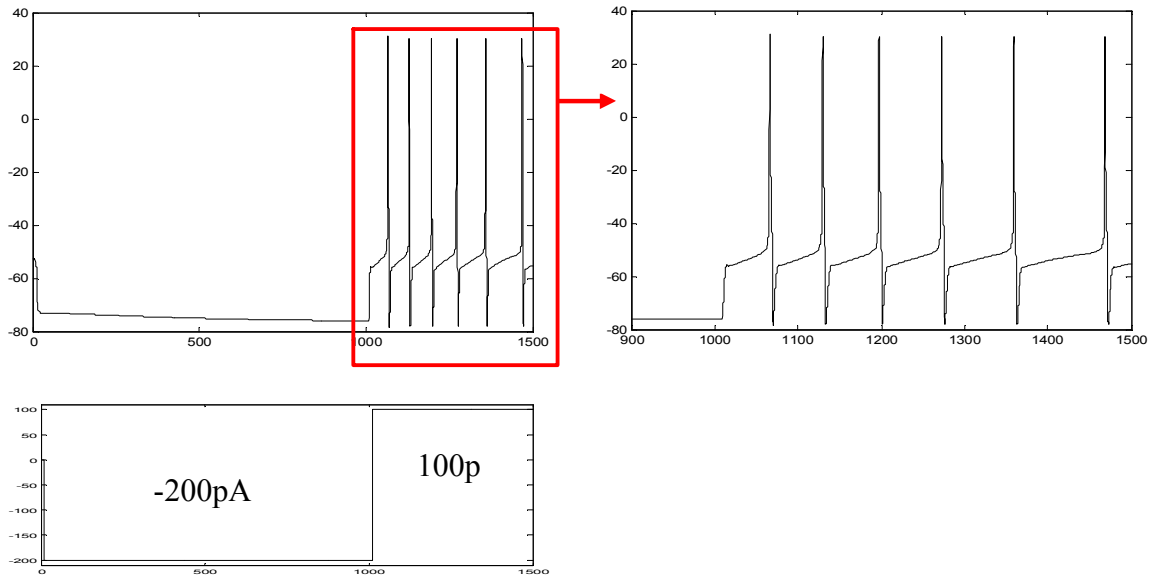


Figure 4: Bottom figure shows current injection of -200pA for 1000ms and 100pA later on. The top figure shows the output of the NTS and the time taken for the first spike. This exhibits a delayed excitation compared to figure 3

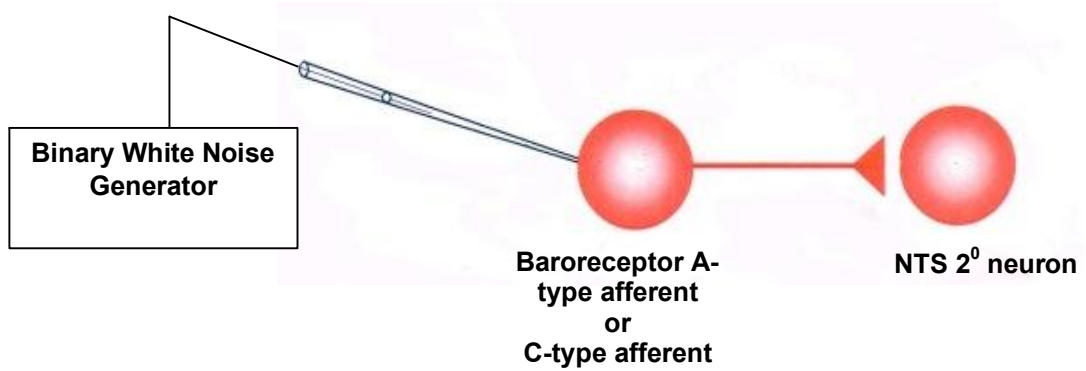


Figure 5: Two cell network with a random binary input injected into the baroreceptor which in turn is connected to the NTS through an AMPA synapse.

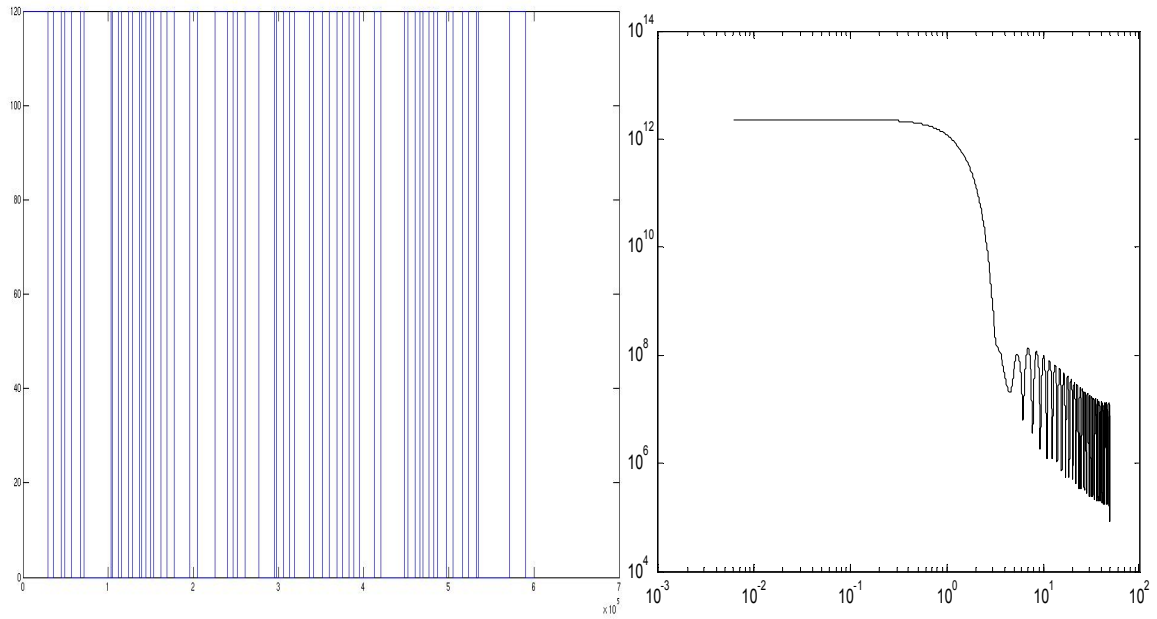


Figure 6: Random Binary Input and Auto Power Spectral density

CASE 1:

A-type baroreceptor connected to the NTS through AMPA synapse

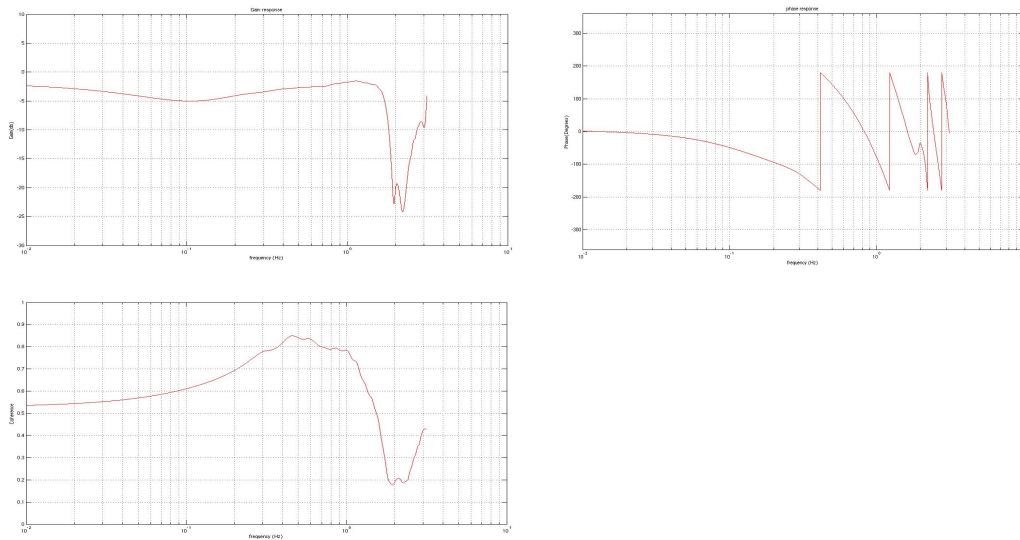


Figure 7: Top 2 figures show the gain and the phase responses and the bottom figure shows the coherence

CASE 2:

C-type baroreceptor connected to the NTS through AMPA synapse

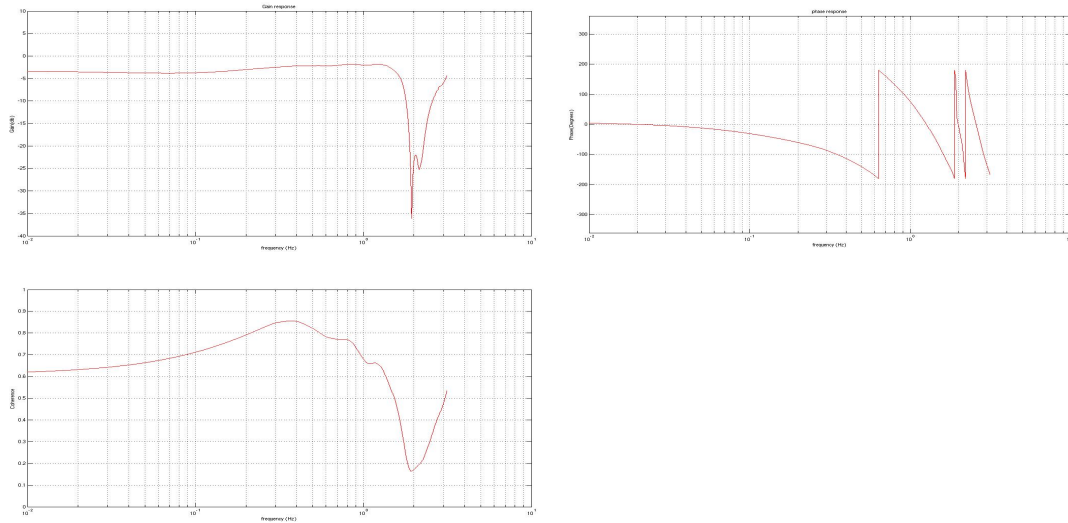


Figure 8: Top 2 figures show the gain and the phase responses and the bottom figure shows the coherence

CASE 3:

A-type baroreceptor connected to NTS with changes in calcium concentration decay time constant in the NTS neuron

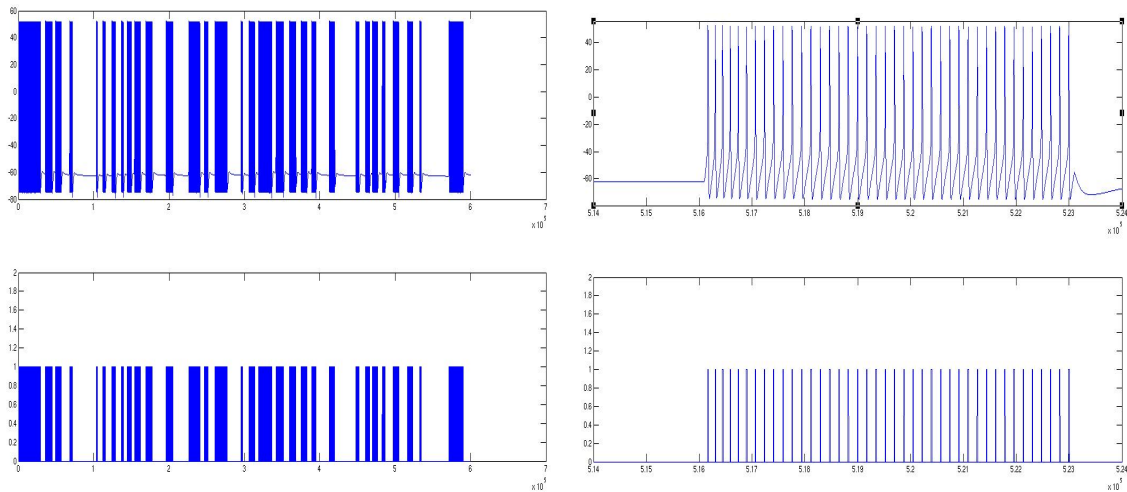


Figure 9: The figure on the left top shows the common A type baroreceptor output independent of the change in the calcium decay time constant in NTS. The equivalent TTL pulses for the spikes are shown in the left bottom figure. The figures on the right top and the bottom are the expanded views of a section from the figures on the left.

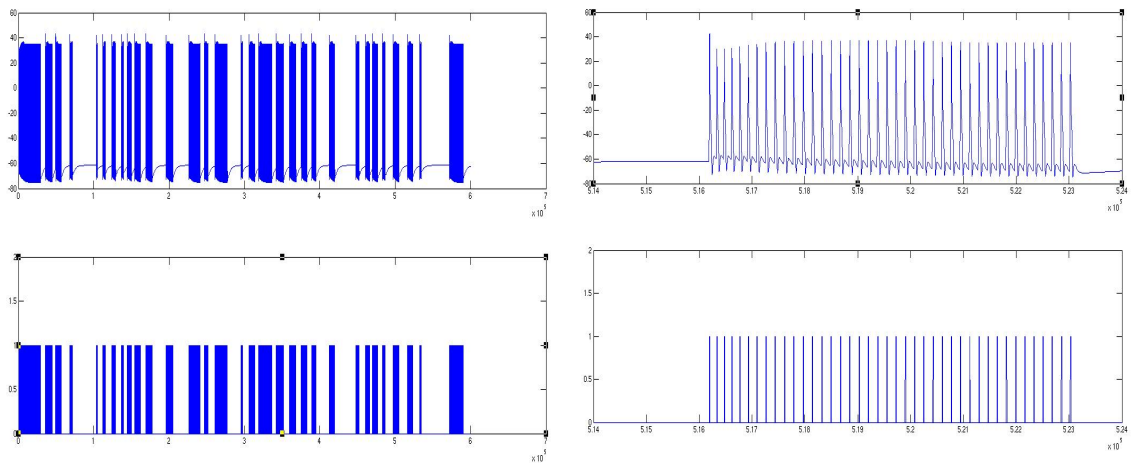


Figure 10: The figure on the left top shows the NTS output for a calcium decay time constant of 25 ms. The equivalent TTL pulses for the spikes are shown in the left bottom figure. The figures on the right top and the bottom are the expanded views of a section from the figures on the left.

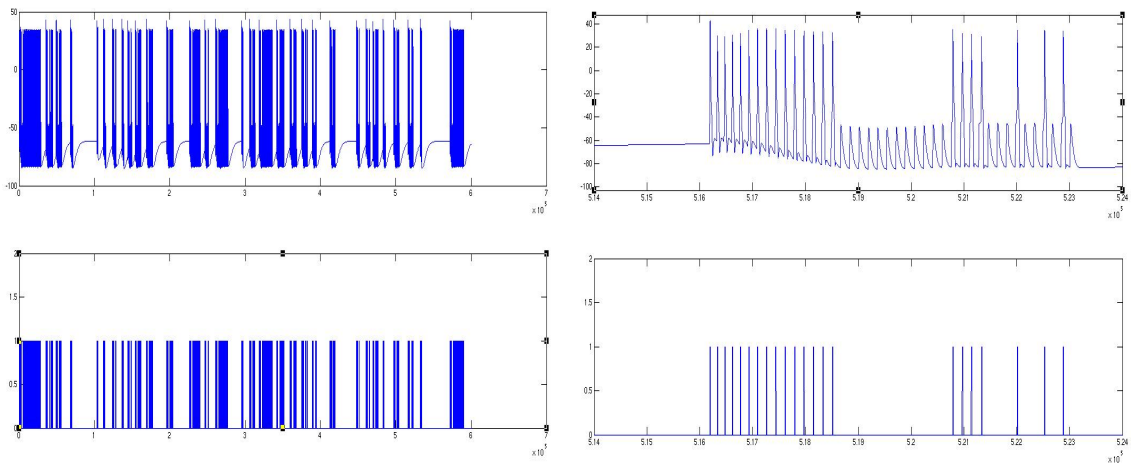


Figure 11: The figure on the left top shows the NTS output for a calcium decay time constant of 150 ms. The equivalent TTL pulses for the spikes are shown in the left bottom figure. The figures on the right top and the bottom are the expanded views of a section from the figures on the left.

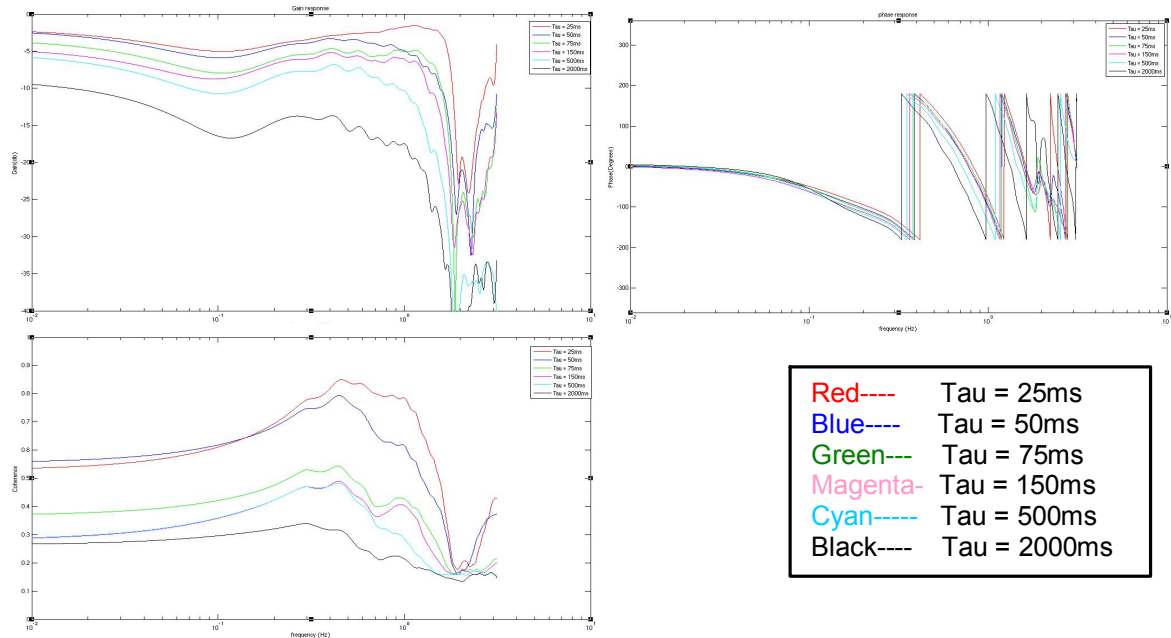


Figure 12: This figure shows the Gain, Phase and the coherence plots with the change in the calcium concentration decay time constant values in NTS with A type baroreceptor type taken into consideration.

CASE 4:

C-type baroreceptor connected to NTS neuron with changes in the calcium concentration decay time constant in the NTS neuron

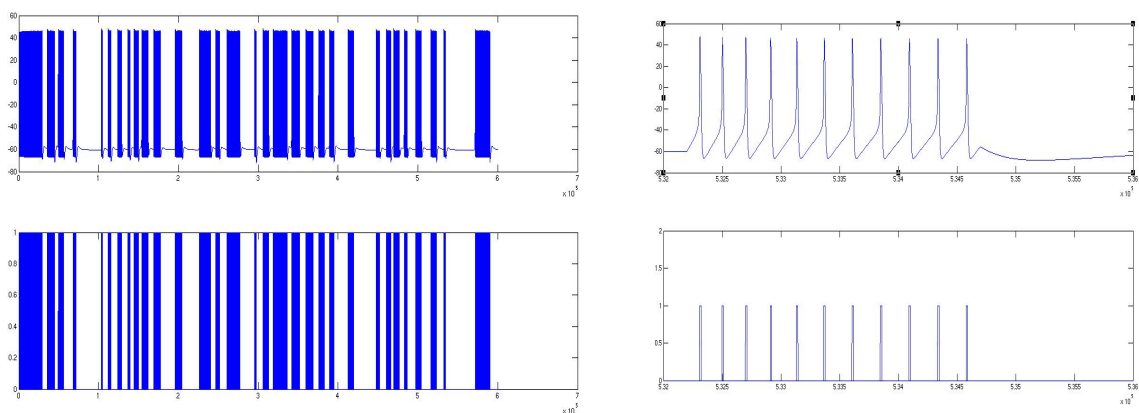


Figure 13: The figure on the left top shows the common C-type baroreceptor output independent of the change in the calcium decay time constant in NTS. The equivalent TTL pulses for the spikes are shown in the left bottom figure. The figures on the right top and the bottom are the expanded views of a section from the figures on the left.

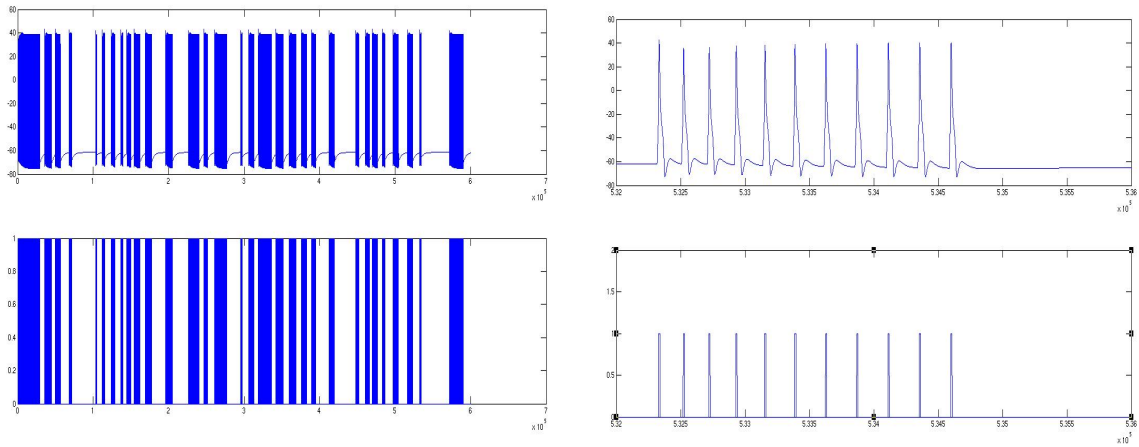


Figure 14: The figure on the left top shows the NTS output for a calcium decay time constant of 25 ms. The equivalent TTL pulses for the spikes are shown in the left bottom figure. The figures on the right top and the bottom are the expanded views of a section from the figures on the left.

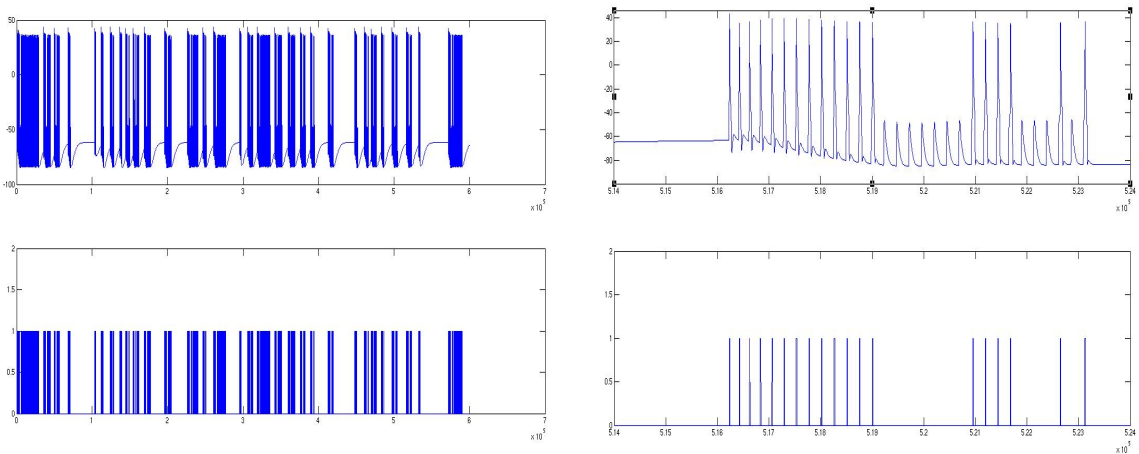


Figure 15: The figure on the left top shows the NTS output for a calcium decay time constant of 150 ms. The equivalent TTL pulses for the spikes are shown in the left bottom figure. The figures on the right top and the bottom are the expanded views of a section from the figures on the left.

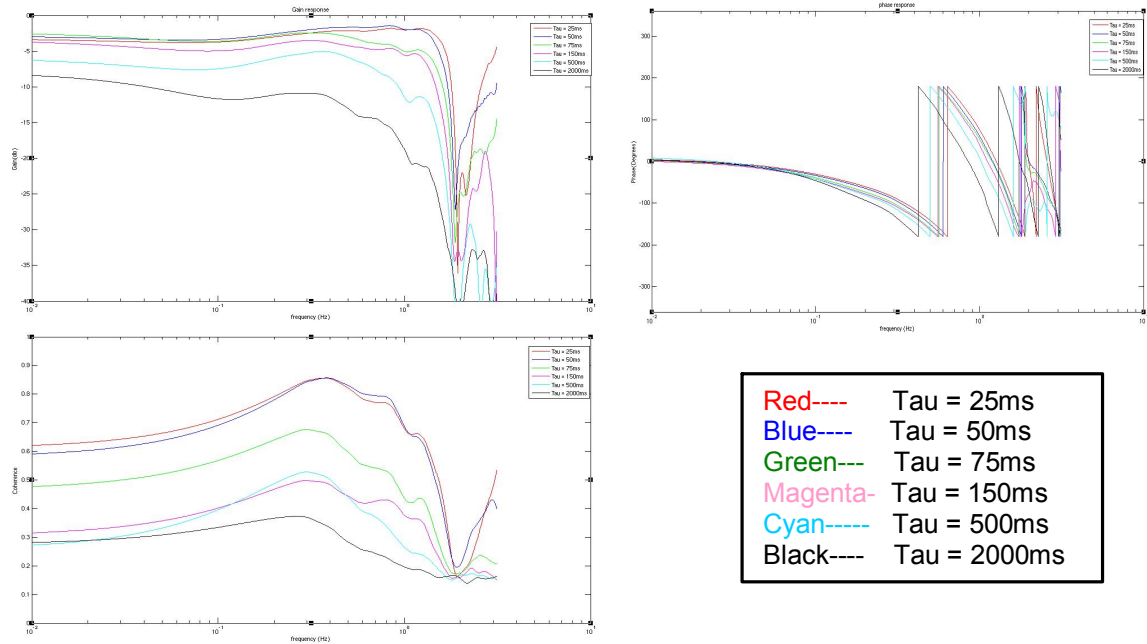


Figure 16: This figure shows the Gain, Phase and the coherence plots with the change in the calcium concentration decay time constant values in NTS with C-type baroreceptor type taken into consideration.

CHAPTER 3: NETWORK MODEL OF BARORECEPTOR-NTS PATHWAY

3.1 ABSTRACT

The output from the arterial baroreceptors is pulse synchronous with respect to the arterial blood pressure waveform. The brainstem neurons which receive output from the NTS also show this pulse synchronicity. However, barosensitive NTS neurons typically exhibit low pulse synchronous discharge. In the present study, we developed a computational network model which shows less pulse synchronicity in the second order barosensitive NTS neurons and the expected pulse synchronicity in NTS output neurons by varying the level of GABA inhibition on second order barosensitive NTS neurons. This model demonstrates the role of GABAergic inhibition in the NTS on the transmission of primary baroreceptor input.

3.2 INTRODUCTION

Arterial baroreceptors are the sensory neurons which provide the compensation to regulate the vascular system. These baroreceptors respond to changes in carotid sinus pressure (CSP) caused by constriction or the expansion of the vessels. Sensory information from these baroreceptors is processed in the brain and the resultant compensatory signals are sent back to different organs in the body such as the vagal and sympathetic outflow to the heart and peripheral vasculature (Spyer 1990).

The baroreceptors discharge phasically in response to the phasic pattern of blood pressure oscillations developed by the heart. Two types of baroreceptors respond to a change in the blood pressure: the myelinated A-type and unmyelinated C-type baroreceptors. The output of these baroreceptors connects to neurons in the nucleus tractus solitarii (NTS) in the brain. It is

not known if the outputs from these baroreceptors converge entirely onto the same second order NTS population. The firing patterns in the NTS depend upon the amount of input received from different baroreceptors (Rogers et al 2000, Seagard et al 2001). The output from the NTS is expected to be pulse synchronous given the pulse synchronous discharge of the baroreceptors themselves (Schreihofer et al, 2003). Previous studies have shown that despite the phasic nature of the output from the baroreceptors, only a limited number of the NTS neurons show the pulse synchronicity while the majority fail to show any pulse synchronicity (Seagard et al 2001, Rogers et al 1993, Mifflin et al 1988). The loss of pulse synchronicity can be attributed to factors such as the convergence of inputs from different baroreceptors and/or the type of neurotransmitter receptors present in the neuron. This is the instance where it shows that the NTS is not only a relay center for sensory input but these barosensitive neurons act together to alter sensory neurotransmission (Seagard et al 2001). Lack of pulse synchronicity at the second order NTS neuron led us to investigate the intrinsic properties of NTS neurons and the organization of these neurons in the NTS network. Such a study is necessary to have a better understanding of why there is limited phasic activity in second order NTS neurons.

In order to have a better idea of the possible reasons for the lack of this pulse synchronicity, a comprehensive network model is developed. Information about the synaptic connections within the NTS is limited but it is known that the connection between the primary baroreceptors and the second order NTS neurons is via a non-NMDA (N-methyl d-aspartic acid) synapse which is an α -amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA synapse) mediated by glutamate, since most studies report that glutamate is the primary neurotransmitter in the NTS (Seagard et al 2001, Andresen et al 2001). Blocking of AMPA receptors at the second order NTS neurons resulted in the reduction of neuronal activity which shows that AMPA receptors are involved. Studies have revealed that NTS have densely populated GABA neurons which are activated by the depolarization of NTS cells. This activation will affect sensory neurotransmission in the NTS (Chan et al 1998; Paton et al 2001). Also, it has been shown that the number of the GABA neurons in the NTS is approximately 25 percent of the total NTS neurons (Chan et al 1998, Weston et al 2003). The output of the NTS is governed by the network

connectivity via glutamatergic and GABAergic transmission in the NTS. The loss of pulse synchronicity can be attributed to this connectivity and/or the influence of synaptic inhibition.

So far there have been few studies done on the organization and the behavior of the network model in the NTS which governs the baroreflex function (Kawai et al 1996, Paton et al. 2001, Andresen et al 2001) but not many studies using a computational model (Schildt et al, 1993, 1994; Rogers et al 2000). The present study is an effort to explain sensory transmission of primary baroreceptor afferent input across the NTS with the help of a computational model.

3.3 METHODS

A computational model is developed consisting of a primary baroreceptor neuron and a 2nd order glutamatergic NTS cell. The baroreceptor is connected to the NTS neuron via a glutamatergic AMPA synapse. AMPA is an ionotropic receptor for glutamate. The second order NTS neurons connect to GABA cells which in turn inhibit the NTS cells. GABA is also an ionotropic receptor. The computational model was generated using GENESIS (ver 2.3) software.

A single baroreceptor neuron was modeled with the following channels: voltage-dependent sodium (I_{Na}), persistent sodium (I_{NaP}), delayed rectifier potassium (I_{DR}), C-type potassium current (I_C), calcium current (I_{HVA}), cationic current (I_{CAT}), calcium dependent potassium from (I_{AHP}) and a leak current (I_L). The I_L , I_{Na} , I_{DR} and I_{NaP} were taken from Durstewitz et al. (2000), while I_{HVA} was taken from Brown et al. (1993), I_C from Wang et al (1993), I_{AHP} from Warman et al. (1994) and I_{CAT} from Kang et al (1998). Here, we use a single compartment model that represents the soma.

I_{Na} is a voltage-gated channel which has activation and inactivation constants and the conductance equation governing this is given by $g_{Na} = g_{Na_{max}}m^3h$ (where $g_{Na_{max}} = 0.118 \text{ S/cm}^2$). Similarly, the I_{NaP} has activation and inactivation constants and is governed by the conductance equation $g_{NaP} = g_{NaP_{max}}mh$ (where $g_{NaP_{max}} = 0.022 \text{ S/cm}^2$). The I_{DR} has a single inactivation constant and the equation governing them is the $g_{DR} = g_{DR_{max}}n^4$ (where $g_{DR_{max}} = 0.033 \text{ S/cm}^2$).

The I_{HVA} has an activation and an inactivation constant with the conductance equation to be $g_{HVA} = g_{HVAmax}u^2v$ (where $g_{HVAmax} = 0.00323$). Similarly, the I_C , I_{AHP} and I_{CAT} have the conductance equations of $g_C = g_{Cmax}c^2$, $g_{AHP} = g_{AHP}q$ and $g_{cat} = g_{catmax}m_{cat}$ (where $g_{Cmax} = 0.0022$ S/cm², $g_{AHPmax} = 0.00002$ S/cm², $g_{catmax} = 0.005$), respectively. The reversal potentials of the Na⁺ and K⁺ are taken to be $E_{Na} = 55$ mV and $E_K = -94$ mV. The reversal potential of the cationic current is taken as $E_{cat} = -42$ mV. There are 2 types of baroreceptors: thinly myelinated and unmyelinated. The thinly myelinated A- type baroreceptors have faster conduction velocity compared to the unmyelinated C-type baroreceptor (Schildes et al 1994). To vary the firing profiles of the A and C type baroreceptor to that shown in Schildes et al (1994), the membrane capacitance is changed with the rest of the channels remaining the same. The equations for these currents can be summarized as shown below and the rate equations are shown in the Table 1 below.

$$I_L = g_L(V - E_L) \quad (3-1)$$

$$I_{Na} = g_{Na}m^3h(V - E_{Na}) \quad (3-2)$$

$$I_{Nap} = g_{Nap}mh(V - E_{Na}) \quad (3-3)$$

$$I_{DR} = g_{DR}n^4(V - E_K) \quad (3-4)$$

$$I_{HVA} = g_{HVA}u^2v(V - E_{Ca}) \quad (3-5)$$

$$I_C = g_Cc^2(V - E_K) \quad (3-6)$$

$$I_{AHP} = g_{AHP}q(V - E_K) \quad (3-7)$$

$$I_{cat} = g_{cat}m_{cat}(V - E_{cat}) \quad (3-8)$$

A single cell model of a barosensitive NTS neuron is generated based on the channels from Rogers et al (2000). The channels involved in this NTS model are the I_{Na} , I_{DR} , I_L , transient potassium channel (I_A), high threshold calcium (I_{Ca}) and calcium dependent potassium (I_{AHP}) channel after hyper polarization. Here we are only considering the cell body. The reversal

potential for Na⁺ was set to $E_{Na} = 55$ mV and that of the K⁺ to a value of $E_K = -94$ mV. In order to have a change in the amount of Ca⁺² concentrations, we modeled a calcium pool where there is a change in the internal Ca⁺² concentration due to the I_{Cal} . The channels used can be described as follows:

- 1) Voltage-gated fast sodium channel is a Hodgkin-Huxley (HH) type channel. The conductance equation governing this channel is: $g_{Na} = g_{Na_{max}} m_{Na}^3 h_{Na}$ (where $E_{Na} = 55$ mV $g_{Na_{max}} = 0.12$ S/cm²) where m and h represent the activation and inactivation of the channel. In general, the rate constants depend on the membrane voltage.
- 2) Delayed rectifier potassium channel is also a HH type channel. There is only activation constant without an inactivation constant. The conductance equation governing this channel is: $g_{DR} = g_{DR_{max}} m_{DR}^4$ (where $E_K = -94$ mV $g_{DR_{max}} = 0.036$ S/cm²). This is also a voltage gated type channel where the rate constants depend on the voltage of the membrane.
- 3) Transient potassium channel is a voltage gated HH type channel which contains two activation constants and two inactivation constants which are governed by the conductance equation as follows: $g_A = g_{A_{max}} (0.6 m_{A1}^4 h_{A1} + 0.4 m_{A2}^4 h_{A2})$. (Where $g_{A_{max}} = 0.006$ S/cm²).
- 4) High threshold calcium channel a HH type channel where the activation constants depend on the voltage with no inactivation which is governed by the conductance equation $g_{Cal} = g_{Cal_{max}} m_{Cal}^3$ (where $g_{Cal_{max}} = 0.00006$ S/cm²). The reversal potential depends on the intracellular concentration taking the extra cellular calcium to be constant.
- 5) Calcium dependent potassium channel is governed by the conductance equation $g_{AHP} = g_{AHP_{max}} m_{cak}^2$ (where $g_{AHP_{max}} = 0.006$ S/cm²) and the rate constants purely depend on the internal calcium concentration. In order to have a calcium concentration, we introduce a pool of calcium where the internal calcium concentration changes based on the calcium current. Concentration of the calcium pool inside the cell, $[Ca_i^{2+}]$, is modeled using a first

order equation, assuming the external concentration to be constant. The amount of the calcium entry depends on the calcium current. The current equations of the above described channels are similar to $I = g(V - E)$ where g is the conductance which depends on the rate equations which are shown in the Table 2 below. I represent current and V represents membrane voltage and E represents the equilibrium potential.

In the network modeled here the connections include the connections through an ionotropic AMPA and GABA receptors expressed post-synaptically on the NTS neuron. The AMPA receptor is modeled is a dual exponential function with two different time constants: one for the rise time and the other for the decay. The conductance equation is given as: $G_K = (g_{AMPAMAX} / (\tau_{rise} - \tau_{decay})) \{ \exp(-t / \tau_{decay}) - \exp(-t / \tau_{rise}) \}$. The current equation for the AMPA follows: $I_{AMPA} = G_K (V - E_{AMPA})$. The values for the rise and fall time constant, maximum ion conductance and the reversal potential for the AMPA receptor is taken from the Durstewitz et al.(2000). The GABA receptor is modeled as an alpha function. When the time constant for the raise and fall is the same, the conductance equation shown below reaches the maximum value of $g_{GABAMax}$ after a particular time constant τ_{GABA} . The rise of the conductance is linear and the decay is exponential at a time constant of τ_{GABA} . The conductance equation is given as follows: $G_K = g_{GABAMAX} (t / \tau_{GABA}) (\exp(1 - t / \tau_{GABA}))$. This is the alpha function. The current equation for the GABA is as follows: $I_{GABA} = G_K (V - E_{GABA})$. The value of the decay time constant is taken from the Durstewitz et al. (2000). The values used for the AMPA and the GABA receptors are shown in the Table 3 below. Information regarding the GABA interneuron is limited. Therefore, we took the interneuron to have all the channels as the normal NTS neurons which acts to inhibit the NTS neurons through a GABA synapse.

Single cell models are developed based on the above channels and the equations. These single cell models are validated by checking for their intrinsic properties. For instance, the baroreceptors repetitively generate action potentials to a depolarizing current injection with A-type baro firing at higher frequency than the C-type baro which is shown in the Figure 1. Furthermore,

NTS neurons have the properties of spike frequency adaptation (SFA) and delayed excitation (DE) which are shown in the Figure 2, Figure 3 and Figure 4 respectively.

After validating the single cells they are implemented in the network population model. This network model is as shown in Figure 5. In this network, we have a population of 30 baroreceptor neurons of both A and C type connected to a population of 25 NTS neurons which in turn is connected a population of 25 GABAergic neurons. These GABAergic neurons are in turn connected back to the NTS population. The A and C type baroreceptors are also connected to a second NTS population of 25 neurons which are again connected to the same population of GABAergic neurons which in turn are connected back to the second NTS population. Now the outputs of the first NTS population and the second NTS population are together connected to a population of 25 NTS output neurons. The number of the NTS cells and the GABAergic cells are determined based on recent studies which have shown that the GABAergic population represents roughly 25% of the total NTS neurons (Chan et al 1998, Weston et al 2003). The connectivity between the baroreceptor afferent populations and the NTS neuron has a probability of 25 percent. Probability of connection means total number of baroreceptor inputs coming to an individual NTS neuron. Here, 25% of the A-type baroreceptor neurons and 25% of the C- type baroreceptor neurons are connected to an individual neuron in both of the second order NTS populations. Similarly, the probability of connection from the first NTS population onto the GABA neurons is 25% and the probability of the GABA population connectivity onto the first NTS population is 20 percent. The probability of the connection from the second NTS population to the GABA neurons is 25% and the probability of the connection from the GABA to the second NTS population is 5 percent. So far there is no evidence about the connectivity of different populations in the baroreceptors to the NTS and the intrinsic connection between the NTS and the GABA neurons. So we cannot say for sure that all the connections are done at the same probability. In order to show the effect of the GABA inhibition strength on the second order NTS neuron population and the output NTS neurons we have introduced randomness in the strength of the connectivity's from the GABA population to the second order NTS neurons. Finally, the probability of the connection from the first and the second NTS population onto the output NTS neurons is

100 percent. The baroreceptors are given a sinusoidal current injection of frequency 5 Hz. The initial amplitude of the current injection is 15 pA which increases as a ramp over time to show the effects of the increase in blood pressure. This change in the current level is analogous to the increase in the blood pressure from 100 mm Hg to a maximum of 200 mm Hg. The results are quantified using 500 ms bins over the entire time to get plots of the baroreceptor activity and the NTS output activity over time, as well as the plot for baroreceptor activity vs. NTS output activity.

3.4 RESULTS

The output profiles for single cell A and C type baroreceptors are shown in Figure 1. Also the characteristics of the single NTS neuron, including SFA and DE, are shown in the Figures 2, 3 and 4, respectively. The network model proposed is shown in Figure 5. The input current injected into the baroreceptors is shown in the Figure 6. The current injection starts with an amplitude of 15 pA and ramps up to a maximum of 125 pA. The response for the A and C type baroreceptor population to this input is shown in the Figure 7. The A-type baroreceptors fire more action potentials compared to the C-type, while the C-type baroreceptors started firing when the input given to it was increased after a time of 2000 ms and later on it continued firing with an increase in the input. With the same probability of connections, the firing profiles of the NTS1 and NTS2 are shown in the Figure 8. The probability of the connections from the NTS1 and NTS 2 to the GABA neurons was also the same but the connectivity from the GABA to the NTS1 and NTS 2 was different which affects the output of the NTS1 and NTS2 populations. If there is very high inhibition on both of the NTS neurons there will be very less firing in them which results in less firing of the output even though the input from the baroreceptors increases over time. We expect that the output NTS neurons fire more when there is an increase in the input which will not be the case if both of the NTS populations receive high inhibition. So in order to preserve the baroreflex function there should be less inhibition from the GABA neurons on one NTS population compared to the other. The inhibition onto the NTS1 is high when compared to the inhibition on the NTS2. This is the reason why neurons in the NTS1 population have less activity compared to those in

NTS2 population. The NTS1 and NTS2 have full connectivity to the output NTS neurons. The activity of the NTS output neurons is shown in the Figure 9.

3.5 DISCUSSION AND CONCLUSION

The present study is an effort to develop a network model which can replicate certain NTS characteristics observed with an increase in the arterial blood pressure, such as a lack of pulse synchronicity in the second order NTS neurons. The computational model showed that this lack of pulse synchronicity could be due to inhibition provided by the GABA neurons. The lower level of pulse synchronous activity in the NTS1 population with a higher inhibition and comparatively higher pulse synchronous activity in the NTS2 population with lesser inhibition demonstrates that GABA inhibition plays a major role in reducing the level of pulse synchronicity in second order barosensitive NTS neurons. The NTS output neurons are pulse synchronous with the input and the amount of the output increases with the amount of input which is what we expect to see at the output NTS neurons. The major reason that the output NTS neurons show this pulse synchronicity is due to the randomness in the connections from the GABA to NTS1 and NTS2 populations, and a full connectivity from the NTS1 and NTS2 populations to the output NTS population. The current injected into the baroreceptors from a range of 15 pA to 125 pA is analogous to the range of blood pressure from 100 mm Hg to 200 mm Hg. In this range of pressure, the baroreceptors output should increase with pressure and saturate. We expect the output from the NTS neurons to follow a similar profile with an increase in the blood pressure. The model predictions also show this characteristic.

3.6 REFERENCES

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3.7 TABLES AND FIGURES

Channel	Conductance, g	Parameters
Fast sodium, I_{Na}	$g_{Na} = g_{Na_{max}} m^3 h$	$\alpha_m = \frac{-0.2816(V + 28)}{\exp(-(V + 28)/9.3) - 1} \quad \beta_m = \frac{0.2464(V + 1)}{\exp((V + 1)/6) - 1}$ $\alpha_h = 0.098 \times \exp(-(V + 43.1) / 20) \quad \beta_h = \frac{1.4}{\exp(-(V + 13.1)/10) + 1}$
Potassium delayed rectifier, I_{DR}	$g_{DR} = g_{DR_{max}} n^4$	$\alpha_n = \frac{-0.018(V - 13)}{\exp(-(V - 13)/25) - 1} \quad \beta_n = \frac{0.0054(V - 23)}{\exp((V - 23)/12) - 1}$
C-type potassium current I_C	$g_C = g_{C_{max}} c^2$	$\alpha_c = \frac{-0.00642V_s - 0.1152}{\exp(-(V_s + 18)/12) - 1} \quad \beta_c = 1.7 \times \exp(-(V_s + 152) / 30)$ $V_s = V_m + 40 \log_{10}([Ca_i])$
Calcium-dependent potassium, I_{AHP}	$g_{AHP} = g_{AHP_{max}} q_{AHP}$	$\alpha_q = \frac{0.0048}{\exp(-(10 \log[Ca^{2+}]_{i2} - 35)/2)} \quad \beta_q = \frac{0.012}{\exp((10 \log[Ca^{2+}]_{i2} + 100)/5)}$ $\tau_q = 48 \text{ ms}$

High voltage activated calcium current I_{HVA}	$g_{u^3 v}^{HVA} = g_{HVAmax}$	$u_{\infty} = \frac{1}{\exp(-(V + 24.6)/11.3) + 1} \quad \tau_u = 1.25 \times \sec h(-0.031(V + 37.1))$ $v_{\infty} = \frac{1}{\exp((V + 12.6)/18.9) + 1} \quad \tau_v = 420.0 \text{ ms}$
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Table 1: Rate equations of baroreceptor cell

Channel	Conductance, g	Parameters
Fast sodium, I_{Na}	$g_{Na} = g_{Na_{max}} m_{Na}^3 h$	$m_{\infty Na} = \frac{0.091(V+38)/(1-\exp(-(V+38)/5))}{0.091(V+38)/(1-\exp(-(V+38)/5)+0.062(V+38)/(\exp((V+38)/5)-1)}$ $\tau_{mNa} = \frac{1}{0.91 \times (V+38)/(1-\exp(-(V+38)/5)+0.062(V+38)/(\exp((V+38)/5)-1)}$ $h_{\infty Na} = \frac{0.016 \exp(-(V+55)/15)}{0.016 \exp(-(V+55)/15)+2.07/(1+\exp(-(V-17)/21))}$ $\tau_{hNa} = \frac{1}{0.016 \exp(-(V+55)/15)+2.07/(1+\exp(-(V-17)/21))}$
Potassium delayed rectifier, I_{DR}	$g_{DR} = g_{DR_{max}} m_{DR}^4$	$m_{\infty DR} = \frac{0.01(V+45)/(1-\exp(-(V+45)/5))}{0.01(V+45)/(1-\exp(-(V+45)/5)+0.17 \exp(-(V+50)/40)}$ $\tau_{mDR} = \frac{1}{0.01(V+45)/(1-\exp(-(V+45)/5)+0.17 \exp(-(V+50)/40)}$
Transient potassium-A, I_A	$g_A = g_{A_{max}} (0.6 m_{A1}^4 h_{A1} + 0.4 m_{A2}^4 h_{A2})$	$m_{\infty A1} = 1/(1+\exp(-(V+60)/8.5))$ $\tau_{mA1} = 1/((\exp(V+35.82)/19.69)+\exp(-(V+79.69)/12.7)+0.37)$ $h_{\infty A1} = 1/(1+\exp(-(V+78)/6))$ $\tau_{hA1} = \begin{cases} \text{if } V < -63, 1/(1+\exp((V+46.05)/5)+\exp(-(V+238.4)/37.45)) \\ \text{else } 19.0 \end{cases}$ $m_{\infty A2} = 1/(1+\exp(-(V+36)/20))$ $\tau_{mA2} = 1/((\exp(V+35.82)/19.69)+\exp(-(V+79.69)/12.7)+0.37)$ $h_{\infty A2} = 1/(1+\exp(-(V+78)/6))$ $\tau_{hA2} = \begin{cases} \text{if } V < -73, 1/(1+\exp((V+46.05)/5)+\exp(-(V+238.4)/37.45)) \\ \text{else } 60.0 \end{cases}$
Calcium-dependent potassium, I_{AHP}	$G_{AHP} = g_{AHP_{max}} m_{Cak}^2$	$m_{\infty AHP} = \frac{1.25 \times 10^8 [cai]^2}{(1.25 \times 10^8 [cai]^2 + 2.5)}$ $\tau_{mAHP} = 1000 / (1.25 \times 10^8 [cai]^2 + 2.5)$

High-threshold calcium, I_{Cal}	$g_{Cal} = g_{Calmax} m_{Cal}^3$	$m_{\infty Cal} = \frac{1.6}{1 + \exp(-0.072 * (V - 5))} / \left(\frac{1.6}{1 + \exp(-0.072 * (V - 5))} + \frac{0.02 * (V - 1.31)}{\exp((V - 1.31)/5.36) - 1} \right)$ $\tau_{mcal} = \frac{1.0}{\left(\frac{1.6}{1 + \exp(-0.072 * (V - 5))} + \frac{0.02 * (V - 1.31)}{\exp((V - 1.31)/5.36) - 1} \right)}$
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Table 2: Rate equations for NTS cell

Parameter	Range of Values (citation)	Model Value
AMPA activation time constant (ms)	0.4– 0.8 (Koch et al,1998)	0.5
AMPA deactivation time constant (ms)	2-8 (Koch et al,1998, Spruston et al,1995a)	3
Maximal AMPA conductance(nS)		15.1392
GABA synaptic time constant (ms)	1.5 (Durstewitz et al, 2000)	1.5
Maximal GABA conductance(nS)		8.4

Table 3: Ranges of synaptic parameters

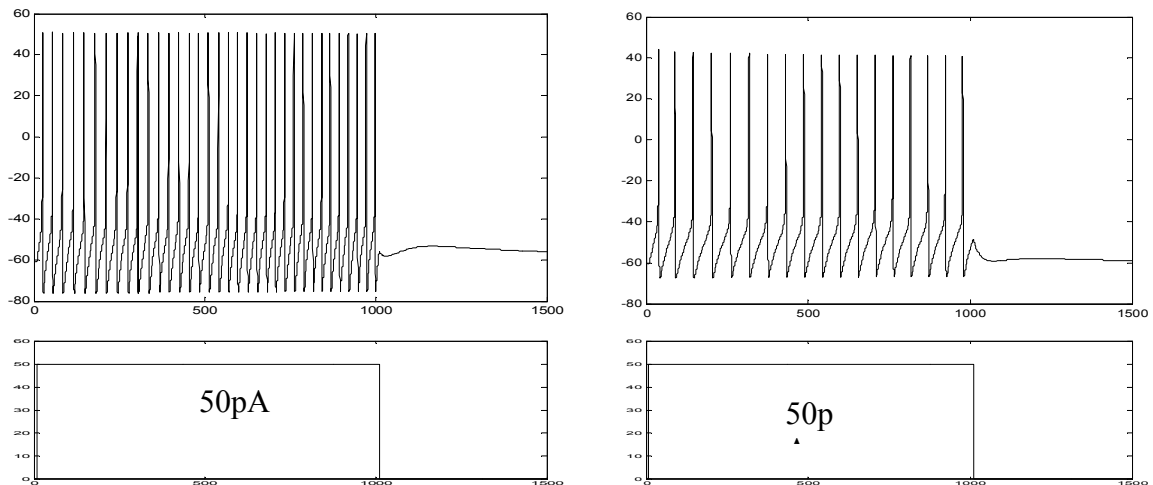


Figure 1: Bottom figures show current injection of 50 pA. The top left figure shows the output of the baroreceptor A and the top right figure shows the output of baroreceptor C

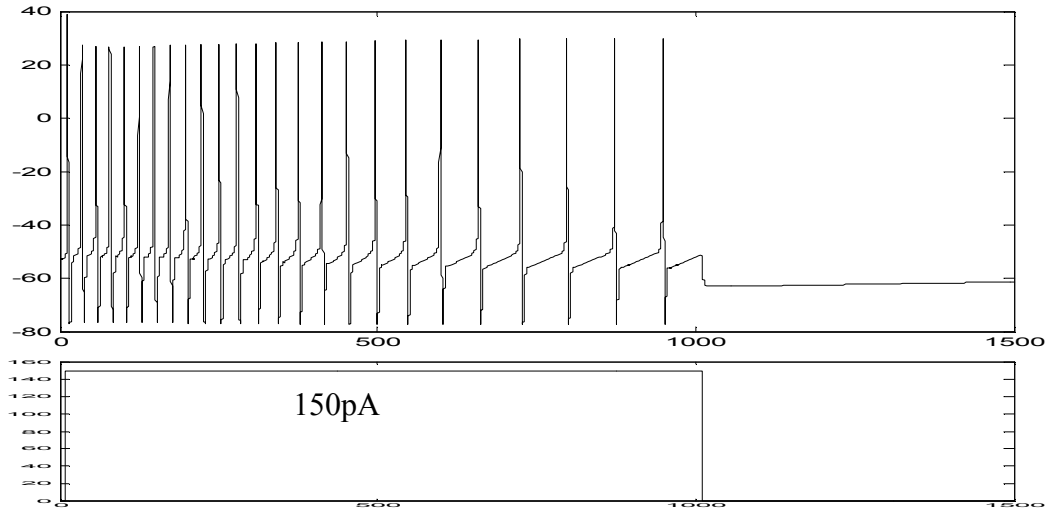


Figure 2: Bottom figure shows a current injection of 150 pA into the NTS cell and the top figure shows the output of the NTS which exhibits the spike frequency adaptation.

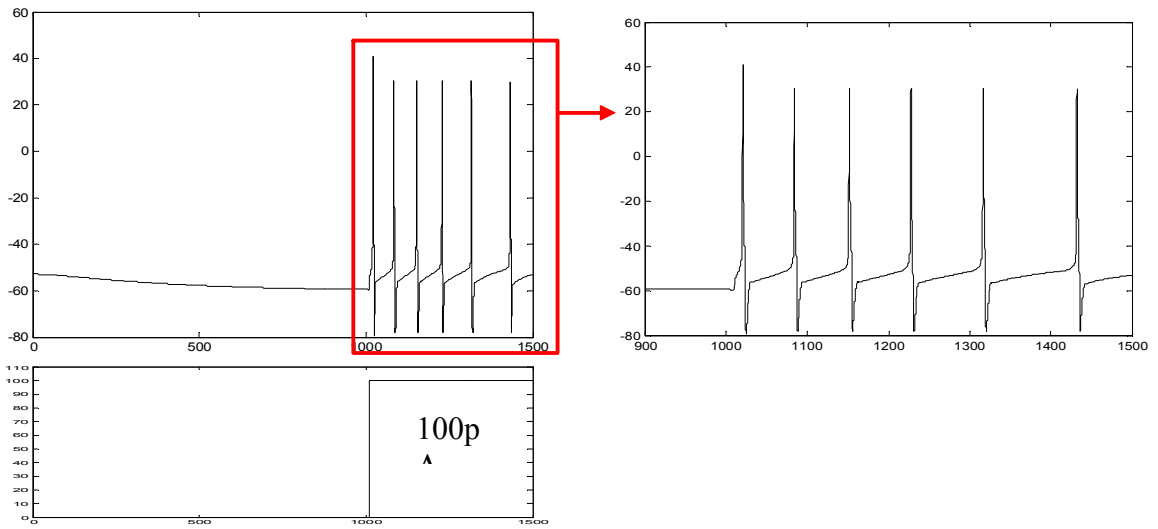


Figure 3: Bottom figure shows current injection of 0 pA for 1000 ms and 100 pA later on. The top figure shows the output of the NTS and the time taken for the first spike.

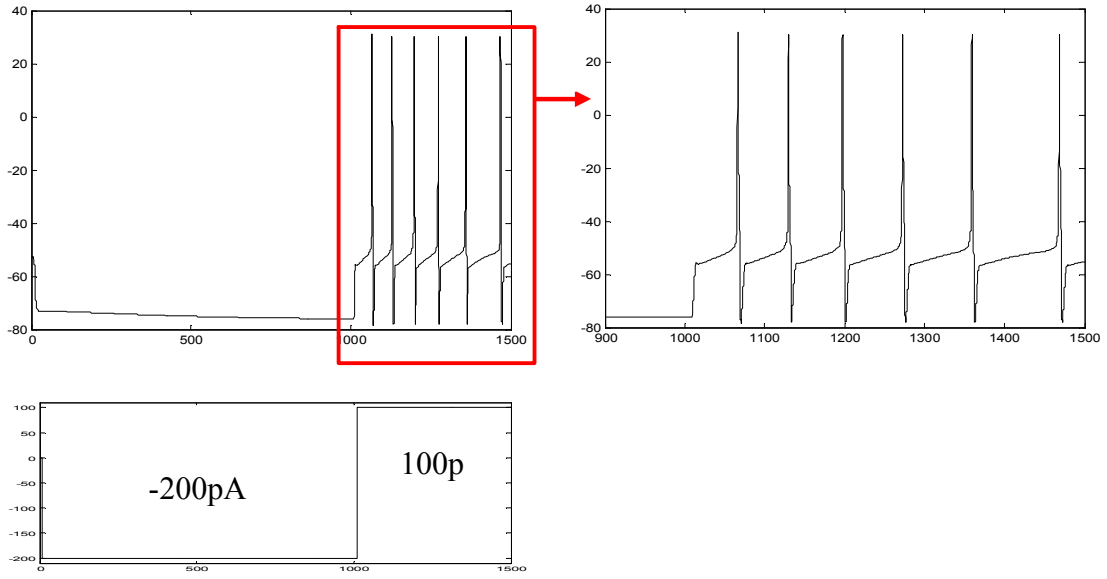


Figure 4: Bottom figure shows current injection of -200 pA for 1000 ms and 100 pA later on. The top figure shows the output of the NTS and the time taken for the first spike. This exhibits a delayed excitation compared to Figure 3

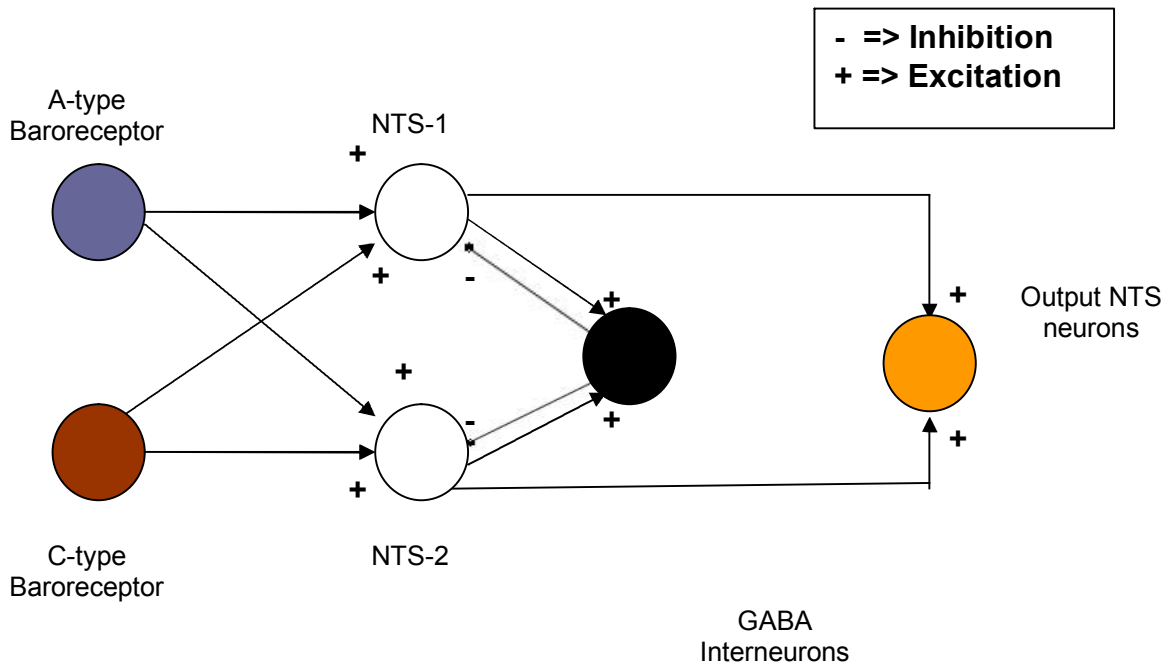


Figure 5: Network Model

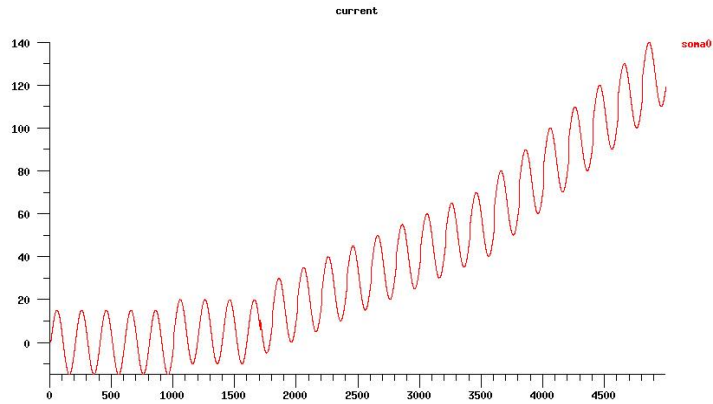


Figure 6: Input to the baroreceptor A and C-type populations

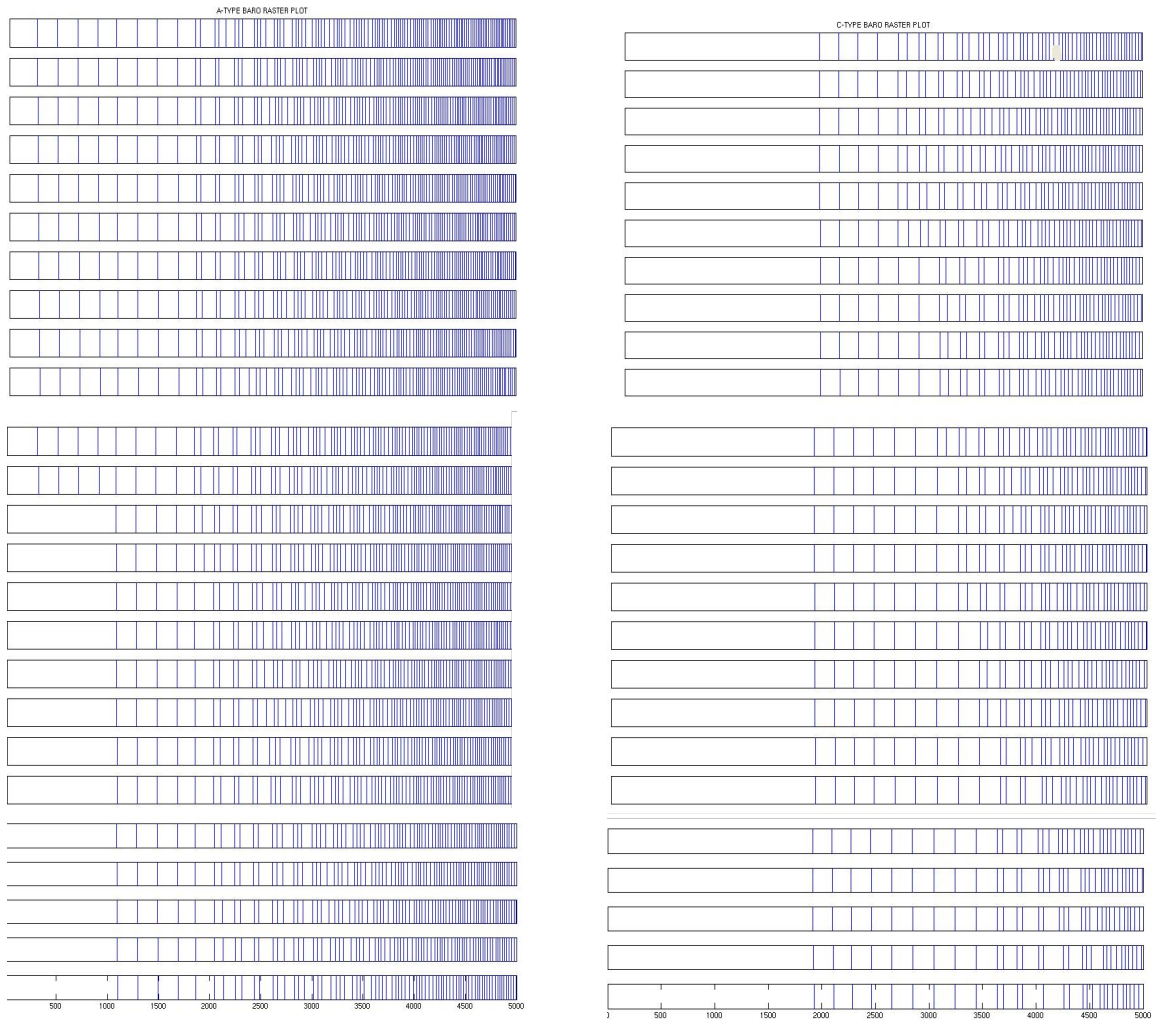


Figure 7: A-type baroreceptor output on the left and C-type baroreceptor output on the right

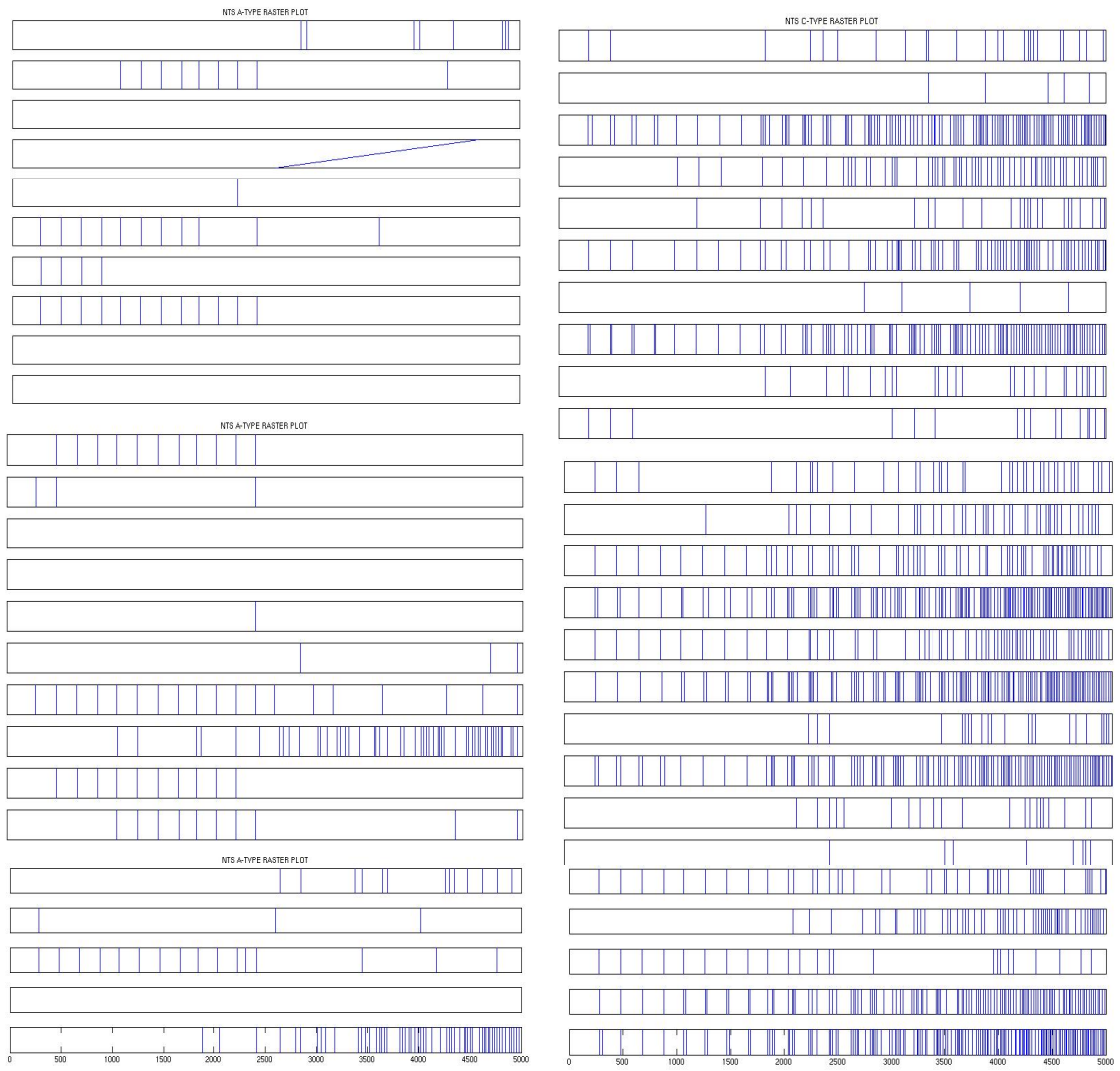


Figure 8: NTS 1 population output on the left and NTS 2 population output on the right

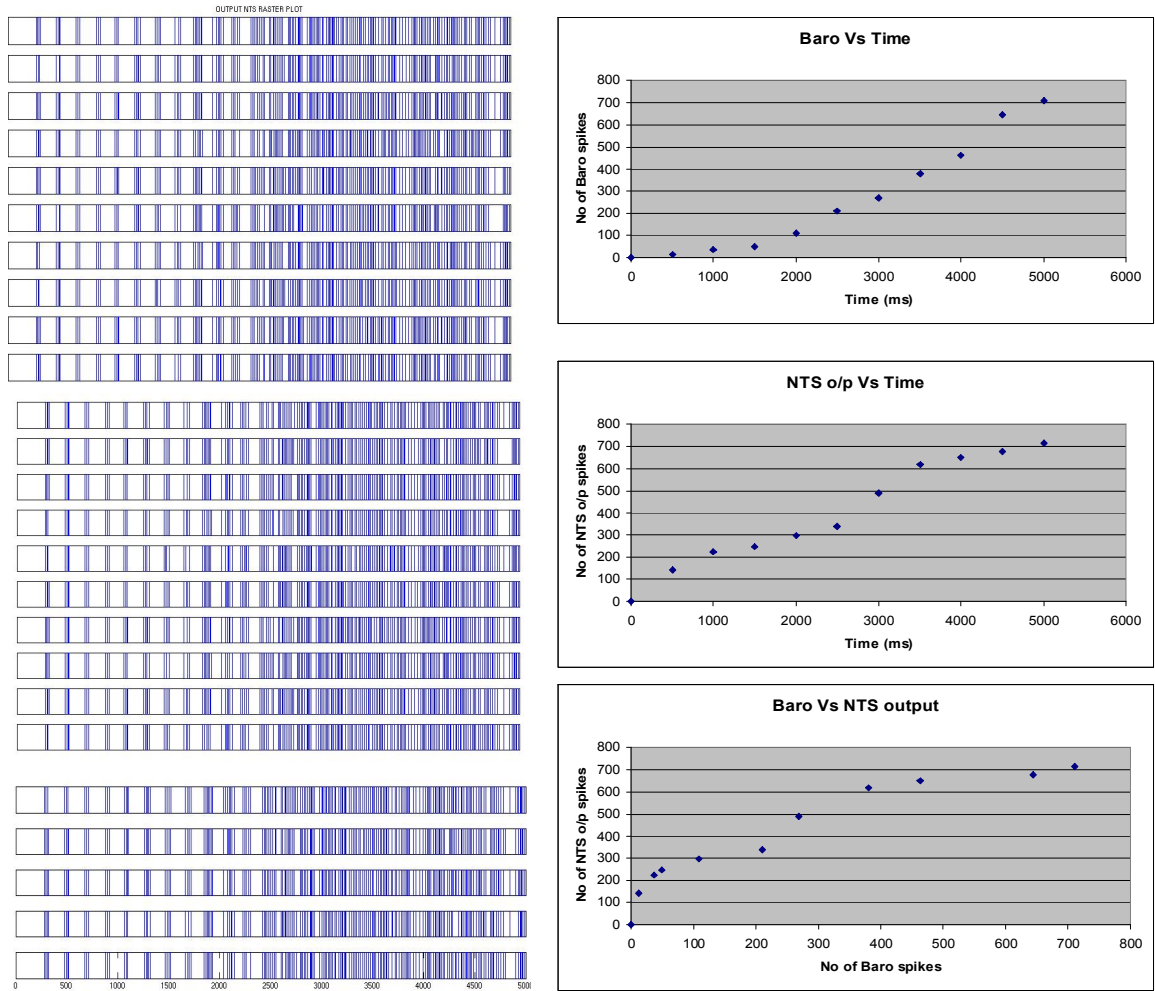


Figure 9: NTS output population on the left. Baro output Vs time on the right top. NTS output Vs Time on the right middle. Baro output Vs NTS output response on the right bottom

CHAPTER 4: NEURAL NETWORK MODEL

4.1 ABSTRACT

Sensory information transmitted from the NTS plays a major role in resetting of the baroreflex control of heart rate and blood pressure while preserving the baroreflex function during exercise. Previous studies have reported that the sensory information is processed by the intrinsic GABA neurons within the NTS in order to limit the excitation of the barosensitive NTS neurons which resets the baroreflex function. It has also been shown that the activation of the inhibitory neurons is due skeletal muscle inputs. In this study a computational network model is developed to investigate the effect of the skeletal muscle inputs on the output of the NTS.

4.2 INTRODUCTION

Several studies have investigated the role of baroreflex mechanism in regulating the level of the arterial blood pressure during physical activity or exercise, with somewhat different findings. Some studies showed that the reflex changes in the heart beat, in response to the arterial blood pressure, was reduced during exercise suggesting that the arterial baroreflex does not play a major role in the regulation of blood pressure (Pickering et al 1972). The conflicting argument was that the baroreflex function was preserved by the resetting of the arterial baroreceptor reflex, specifically, the carotid sinus baroreflex control of heart rate and blood pressure with the onset of exercise (DiCarlo and Bishop 1992). Later it was successfully proven that the arterial baroreceptor reflex was reset during sustained changes in the blood pressure (Potts et al 1993). This shows that the function of the arterial baroreflex was preserved by the baroreflex resetting which means that the baroreflex is able to maintain the continuous regulation

of the arterial blood pressure. The next step would be to determine the neural mechanisms involved in the baroreflex resetting. In this process it was found that inputs from either the central command, i.e., inputs from the locomotor centers, or neural feedback from the skeletal muscle receptors, is capable of modulating the baroreflex function during exercise (Potts and Mitchell 1998, Potts and Li 1998, Potts et al 2006, Fadel et al 2001, Gallagher et al 2001). It has been shown that the skeletal muscle afferents project onto the NTS but the somatic afferent population responsible for the baroreflex resetting is not yet identified (Potts et al 2006). The neural inputs from the skeletal muscle afferents inhibit the baroreflex function which is done by the involvement of the intrinsic GABA interneurons in processing of the sensory signals before they are transmitted to the other regions in the brain (Boscan et al. 2002, Potts et al 2003).

During exercise there is an increase in the heart rate (tachycardia) and the blood pressure (pressor response). There is an increase in the amount of the baroreceptor input to the NTS neurons due to the increase in the input to the baroreceptors. The increase in the baroreceptor activity occurs independent of baroreflex resetting. An increase in the baroreceptor activity means more excitatory drive to NTS neurons whose output projects to inhibitory neurons in the caudal ventrolateral medulla (cVLM) which, in turn, inhibits sympathetic pre-motor neurons in the rostral VLM. The output of the NTS also strongly excites the cardiac vagal motoneurons (CVM) which reduces heart rate. Therefore, in the absence of baroreflex resetting during the exercise, heart rate would decrease (bradycardia) along with inhibition of sympathetic nerve activity (SNA) which is contradictory to expectation. We get the expected results of the baroreflex during exercise along with maintaining the baroreflex function by baroreflex resetting (Potts et al 2006, Potts and Mitchell 1998, Potts and Li 1998). This can be achieved by controlling the amount of the excitation of the barosensitive NTS neurons which in turn reduces the amount of inhibition of CVM and SNA. The excitation of the barosensitive NTS neurons can be controlled by the activation of GABA neurons present in the NTS. It has been reported that GABA neurons in the NTS are activated by the skeletal muscle afferents (Potts et al 2003). Controlling the output of the NTS results in a lateral resetting which does not account for the increase in heart rate and

sympathetic nerve activity. Therefore, it is proposed that the skeletal muscle afferents also directly excite sympathetic premotor neurons in the rostral VLM (Potts et al 2006).

In the present study, a hypothesized computational model is developed that includes the somatosensory input from the skeletal muscle receptors. It is proposed that this somatic input to the NTS activates a population of inhibitory GABA neurons which regulates the degree of the excitation of the barosensitive NTS neurons. This will result in a greater degree of baroreceptor input that is required to evoke a baroreflex response. Excitation of this population of GABA neurons in the NTS resets the baroreflex which normalizes the level of NTS activity to aid in preserving baroreflex function during exercise. To evaluate this, a population-based network model between primary baroreceptor afferents and the NTS is developed. To this NTS network a somatosensory input from the skeletal muscles has been applied through GABAergic interneurons. Then the responses of the output from the network, in the presence and absence of skeletal muscle input, was compared to highlight the effect of the skeletal muscle input on the output of the network model.

4.3 METHODS

The basic population network data is initially based from the paper Rogers et al (2000). The population model is a simplified model with each cell having a single compartment which is the soma. The single cells we consider here are the baroreceptors and the NTS cells.

A single baroreceptor neuron was modeled with the following channels: voltage-dependent sodium (I_{Na}), persistent sodium (I_{NaP}), delayed rectifier potassium (I_{DR}), C-type potassium current (I_C), calcium current (I_{HVA}), cationic current (I_{CAT}), calcium dependent potassium from (I_{AHP}) and a leak current (I_L). The I_L , I_{Na} , I_{DR} and I_{NaP} were taken from Durstewitz et al. (2000), while I_{HVA} was taken from Brown et al. (1993), I_C from Wang et al (1993), I_{AHP} from Warman et al. (1994) and I_{CAT} from Kang et al (1998). Here, we use a single compartment model that represents the soma.

The reversal potentials of the sodium and potassium are taken to be $E_{Na} = 55$ mV and $E_K = -94$ mV. The reversal potential of the cationic current is taken as $E_{cat} = -42$ mV. There are two types of baroreceptors: thinly myelinated and unmyelinated. The thinly myelinated A type baroreceptors have faster conduction velocity compared to the unmyelinated C-type baroreceptor (Schilders et al. 1994). To vary the firing profiles of the A and C type baroreceptor to that shown in (Schilders et al. 1994), the membrane capacitance is changed with the rest of the channels remaining the same. The equations for the above currents can be summarized as shown below and the rate equations for the conductances and the maximum conductances are shown in the Table 1 below.

$$I_L = g_L(V - E_L) \quad (4-1)$$

$$I_{Na} = g_{Na} m^3 h (V - E_{Na}) \quad (4-2)$$

$$I_{Nap} = g_{Nap} m h (V - E_{Na}) \quad (4-3)$$

$$I_{DR} = g_{DR} n^4 (V - E_K) \quad (4-4)$$

$$I_{HVA} = g_{HVA} u^2 v (V - E_{Ca}) \quad (4-5)$$

$$I_C = g_C c^2 (V - E_K) \quad (4-6)$$

$$I_{AHP} = g_{AHP} q (V - E_K) \quad (4-7)$$

$$I_{cat} = g_{cat} m_{cat} (V - E_{cat}) \quad (4-8)$$

A single cell model of a barosensitive NTS neuron is generated based on the channels from Rogers et al (2000). The channels involved in this NTS model are the I_{Na} , I_{DR} , I_L , transient potassium channel (I_A), high threshold calcium (I_{Cat}) and calcium dependent potassium (I_{AHP}) channel after hyper polarization. Here we are only considering the cell body. The reversal potential for Na⁺ was set to $E_{Na} = 55$ mV and that of the K⁺ to a value of $E_K = -94$ mV. In order to have a change in the amount of Ca²⁺ concentrations, we modeled a calcium pool where

there is a change in the internal Ca²⁺ concentration due to the I_{CaL} . The current equations of the above described channels are similar to $I = g(V - E)$ where g is the conductance which depends on the rate equations which are shown in the Table 2 below. I represent current and V represents membrane voltage and E represents the equilibrium potential. The maximum conductance values for the channels are also shown in the Table 2.

In the network modeled here the connections include the connections through an ionotropic AMPA and GABA receptors expressed post-synaptically on the NTS neuron. The AMPA receptor is modeled is a dual exponential function with two different time constants: one for the rise time and the other for the decay. The conductance equation is given as: $G_K = (g_{AMPAMAX} / (\tau_{rise} - \tau_{decay})) \{ \exp(-t / \tau_{decay}) - \exp(-t / \tau_{rise}) \}$. The current equation for the AMPA follows: $I_{AMPA} = G_K (V - E_{AMPA})$. The values for the rise and fall time constant, maximum ion conductance and the reversal potential for the AMPA receptor is taken from the Durstewitz et al.(2000). The GABA receptor is modeled as an alpha function. When the time constant for the raise and fall is the same, the conductance equation shown below reaches the maximum value of $g_{GABAMax}$ after a particular time constant τ_{GABA} . The rise of the conductance is linear and the decay is exponential at a time constant of τ_{GABA} . The conductance equation is given as follows: $G_K = g_{GABAMAX} (t / \tau_{GABA}) (\exp(1 - t / \tau_{GABA}))$. This is the alpha function. The current equation for the GABA is as follows: $I_{GABA} = G_K (V - E_{GABA})$. The value of the decay time constant is taken from the Durstewitz et al. (2000). The values used for the AMPA and the GABA receptors are shown in the Table 3 below. Information regarding the GABA interneuron is limited. Therefore, we took the interneuron to have all the channels as the normal NTS neurons which acts to inhibit the NTS neurons through a GABA synapse.

Single cell models are developed based on the above channels and the equations. These single cell models are validated by checking for their intrinsic properties. For instance, the baroreceptors repetitively generate action potentials to a depolarizing current injection with A-type baro firing at higher frequency than the C-type baro which is shown in the Figure 1. Furthermore,

NTS neurons have the properties of spike frequency adaptation (SFA) and delayed excitation (DE) which are shown in the Figure 2, Figure 3 and Figure 4 respectively.

After validating the single cells they are implemented in the network population model. This network model is as shown in Figure 5. In this network, we have a population of 30 baroreceptor neurons of both A and C type connected to a population of 25 NTS neurons which in turn is connected a population of 25 GABAergic neurons. These GABAergic neurons are in turn connected back to the NTS population. The A and C type baroreceptors are also connected to a second NTS population of 25 neurons which are again connected to the same population of GABAergic neurons which in turn are connected back to the second NTS population. Now the outputs of the first NTS population and the second NTS population are together connected to a population of 25 NTS output neurons. The number of the NTS cells and the GABAergic cells are determined based on recent studies which have shown that the GABAergic population represents roughly 25% of the total NTS neurons (Chan et al 1998, Weston et al 2003). The connectivity between the baroreceptor afferent populations and the NTS neuron has a probability of 25 percent. Probability of connection means total number of baroreceptor inputs coming to an individual NTS neuron. Here, 25% of the A-type baroreceptor neurons and 25% of the C- type baroreceptor neurons are connected to an individual neuron in both of the second order NTS populations. Similarly, the probability of connection from the first NTS population onto the GABA neurons is 25% and the probability of the GABA population connectivity onto the first NTS population is 20 percent. The probability of the connection from the second NTS population to the GABA neurons is 25% and the probability of the connection from the GABA to the second NTS population is 5 percent. So far there is no evidence about the connectivity of different populations in the baroreceptors to the NTS and the intrinsic connection between the NTS and the GABA neurons. So we cannot say for sure that all the connections are done at the same probability. In order to show the effect of the GABA inhibition strength on the second order NTS neuron population and the output NTS neurons we have introduced randomness in the strength of the connectivity's from the GABA population to the second order NTS neurons. Finally, the probability of the connection from the first and the second NTS population onto the output NTS neurons is

100 percent. The output from the NTS output neurons is observed here. The results from this network model are quantified initially.

Now we add a somatic C fiber population of 30 neurons to the above network model. The somatic C fiber cell has the same composition as of the baroreceptor C-type cell. This somatic cell is connected to a second GABA neuron population of 25. The probability of connection from the somatic cell to the GABA is 25 percent. This GABA population is connected to the two second order neuron populations NTS 1 and NTS 2 at a probability of 25 percent connectivity. The results from this network model are compared with the results from the previous model.

The input to the baroreceptors is a sinusoidal current of frequency 5 Hz with initial amplitude of 15 pA which ramps up over time to show the effect based on the increase in the blood pressure. The results from the network model with and without the somatic input are quantified using a 500 ms bin over the entire time to get the plots of the baroreceptor activity and the NTS output activity over time and also the plot for baroreceptor activity Vs NTS output activity.

4.4 RESULTS

The output profiles for single cell A and C type baroreceptors are shown in Figure 1. Also the characteristics of the single NTS neuron, including SFA and DE, are shown in the Figures 2, 3 and 4, respectively. The network model proposed is shown in Figure 5. The inputs given to the baroreceptors and the somatic C fiber are shown in the Figure 6. The current injection starts with an amplitude of 15 pA and ramps up to a maximum of 125 pA which we can say is the maximum current the cell can take before it dies. The current given to the somatic C fiber is a constant sinusoidal current of frequency 1 Hz and constant amplitude of 50 pA. The response for the somatic C fiber and the A and C type baroreceptor population is shown in the Figure 7 and Figure 8 respectively. The somatic C fiber fires synchronously to the input given. The firing profiles for the NTS 1 and NTS 2 are shown in the Figure 9. The response of the GABA 1 population is shown in the Figure 10. The GABA 1 has higher inhibition onto the NTS 1 and lower inhibition on the NTS 2. With the connection of the GABA 2 population onto both the NTS 1 and the NTS 2 the

strength of the inhibition increases on both of the second order NTS population. The response of the GABA 2 population is shown in the Figure 10. This effects the output population of the NTS. The output population responses are shown in the Figure 11. The quantified results for the second order NTS populations and the output NTS population with and without the somatic inputs are shown in the Figure 12.

4.5 DISCUSSION AND CONCLUSION

Somatic afferent input onto the NTS plays a major role in the baroreflex function. The proposed computational model predicts that the NTS output activity is reduced in the presence of the somatic afferents, when compared to the output activity without somatic afferents. The output activity in the presence of the somatic afferents still increase with an increase in the input but the activity is lower. This shows that the baroreflex function is preserved. The activation of the GABA neurons in the NTS by the somatic input increases the inhibition on the second order NTS populations. This increase in the inhibition causes a greater loss of phasic activity in the second order NTS population which reduces the activity in the output population of the NTS. These results suggest that the somatic inputs from the skeletal muscle afferents have an inhibitory effect on the sensory information from the NTS.

4.6 REFERENCES

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4.7 TABLES AND FIGURES

Channel	Conductance, g	Maximum conductance (S/cm ²)	Parameters
Fast sodium, I _{Na}	$\frac{g_{Na}}{g_{Na_{max}} h} = m^3$	0.118	$\alpha_m = \frac{-0.2816(V+28)}{\exp(-(V+28)/9.3) - 1} \quad \beta_m = \frac{0.2464(V+1)}{\exp((V+1)/6) - 1}$ $\alpha_h = 0.098 \times \exp(-(V+43.1)/20) \quad \beta_h = \frac{1.4}{\exp(-(V+13.1)/10) + 1}$
Potassium delayed rectifier, I _{DR}	$\frac{g_{DR}}{g_{DR_{max}} n^4} =$	0.033	$\alpha_n = \frac{-0.018(V-13)}{\exp(-(V-13)/25) - 1} \quad \beta_n = \frac{0.0054(V-23)}{\exp((V-23)/12) - 1}$
C-type potassium current I _C	$\frac{g_C}{g_{C_{max}} C^2} =$	0.0022	$\alpha_C = \frac{-0.00642V_s - 0.1152}{\exp(-(V_s+18)/12) - 1} \quad \beta_C = 1.7 \times \exp(-(V_s+152)/30)$ $V_s = V_m + 40 \log_{10}([Ca_i])$
Calcium-dependent potassium, I _{AHP}	$\frac{g_{AHP}}{g_{AHP_{max}} Q_{AHP}} =$	0.00002	$\alpha_q = \frac{0.0048}{\exp(-(10 \log[Ca^{2+}]_{i2} - 35)/2)}$ $\beta_q = \frac{0.012}{\exp((10 \log[Ca^{2+}]_{i2} + 100)/5)}$ $\tau_q = 48 \text{ ms}$
High voltage activated calcium current I _{HVA}	$\frac{g_{HVA}}{g_{HVA_{max}} u^3 v} =$	0.00323	$u_\infty = \frac{1}{\exp(-(V+24.6)/11.3) + 1} \quad \tau_u = 1.25 \times \sec h(-0.031(V+37.1))$ $v_\infty = \frac{1}{\exp((V+12.6)/18.9) + 1} \quad \tau_v = 420.0 \text{ ms}$

Table 1: Rate equations and maximum conductances of the baroreceptor

Channel	Conductance, g	Maximum conductance (S/cm ²)	Parameters
Fast sodium, I _{Na}	$g_{Na} = g_{Na_{max}} m^3_{Na} h$	0.12	$m_{\infty Na} = \frac{0.091(V+38)/(1-\exp(-(V+38)/5))}{0.091(V+38)/(1-\exp(-(V+38)/5))+0.062(V+38)/(\exp((V+38)/5)-1)}$ $\tau_{mNa} = 1/(0.91 \times (V+38)/(1-\exp(-(V+38)/5))+0.062(V+38)/(\exp((V+38)/5)-1))$ $h_{\infty Na} = \frac{0.016 \exp(-(V+55)/15)}{0.016 \exp(-(V+55)/15)+2.07/(1+\exp(-(V-17)/21))}$ $\tau_{hNa} = \frac{1}{(0.016 \exp(-(V+55)/15)+2.07/(1+\exp(-(V-17)/21)))}$
Potassium delayed rectifier, I _{DR}	$g_{DR} = g_{DR_{max}} m^4_{DR}$	0.036	$m_{\infty DR} = \frac{0.01(V+45)/(1-\exp(-(V+45)/5))}{0.01(V+45)/(1-\exp(-(V+45)/5))+0.17 \exp(-(V+50)/40)}$ $\tau_{mDR} = \frac{1}{(0.01(V+45)/(1-\exp(-(V+45)/5))+0.17 \exp(-(V+50)/40))}$
Transient potassium m-A, I _A	$g_A = g_{A_{max}}(0.6m^4_{A1}h_{A1}+0.4m^4_{A2}h_{A2})$	0.006	$m_{\infty A1} = 1/(1+\exp(-(V+60)/8.5))$ $\tau_{mA1} = \frac{1}{((\exp(V+35.82)/19.69)+\exp(-(V+79.69)/12.7)+0.37)}$ $h_{\infty A1} = \frac{1}{(1+\exp(-(V+78)/6))}$ $\tau_{hA1} = \begin{cases} \text{if } V < -63, 1/(1+\exp((V+46.05)/5))+\exp(-(V+238.4)/37.45) \\ \text{else } 19.0 \end{cases}$ $m_{\infty A2} = 1/(1+\exp(-(V+36)/20))$ $\tau_{mA2} = \frac{1}{((\exp(V+35.82)/19.69)+\exp(-(V+79.69)/12.7)+0.37)}$ $h_{\infty A2} = \frac{1}{(1+\exp(-(V+78)/6))}$ $\tau_{hA2} = \begin{cases} \text{if } V < -73, 1/(1+\exp((V+46.05)/5))+\exp(-(V+238.4)/37.45) \\ \text{else } 60.0 \end{cases}$
Calcium-dependent potassium, I _{AHP}	$g_{AHP} = g_{AHP_{max}} m^2_{CaK}$	0.006	$m_{\infty AHP} = \frac{1.25 \times 10^8 [\text{cai}]^2}{(1.25 \times 10^8 [\text{cai}]^2 + 2.5)}$ $\tau_{mAHP} = \frac{1000}{(1.25 \times 10^8 [\text{cai}]^2 + 2.5)}$

High-threshold calcium, I_{Cal}	$g_{Cal} = g_{Calmax} m^3_{Cal}$	0.00006	$m_{\infty cal} = 1.6 / (1 + \exp(-0.072 * (V - 5))) / ((1.6 / (1 + \exp(-0.072 * (V - 5))) + (0.02 * (V - 1.31) / (\exp((V - 1.31) / 5.36) - 1))))$ $\tau_{mcal} = 1.0 / ((1.6 / (1 + \exp(-0.072 * (V - 5))) + (0.02 * (V - 1.31) / (\exp((V - 1.31) / 5.36) - 1))))$
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Table 2: Rate equations and maximum conductances of the NTS cell

Parameter	Range of Values (citation)	Model Value
AMPA activation time constant (ms)	0.4– 0.8 (Koch et al,1998)	0.5
AMPA deactivation time constant (ms)	2-8 (Koch et al,1998, Spruston et al,1995a)	3
Maximal AMPA conductance(nS)		15.1392
GABA synaptic time constant (ms)	1.5 (Durstewitz et al, 2000)	1.5
Maximal GABA conductance(nS)		8.4

Table 3: Ranges of synaptic parameters

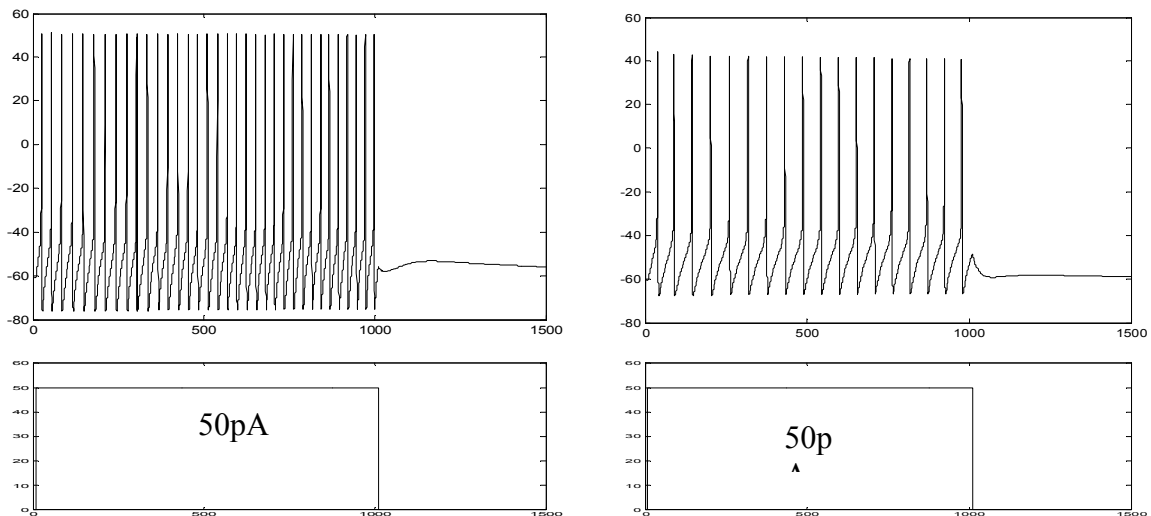


Figure 1: Bottom figures show current injection of 50pA. The top left figure shows the output of the baroreceptor A and the top right figure shows the output of baroreceptor C

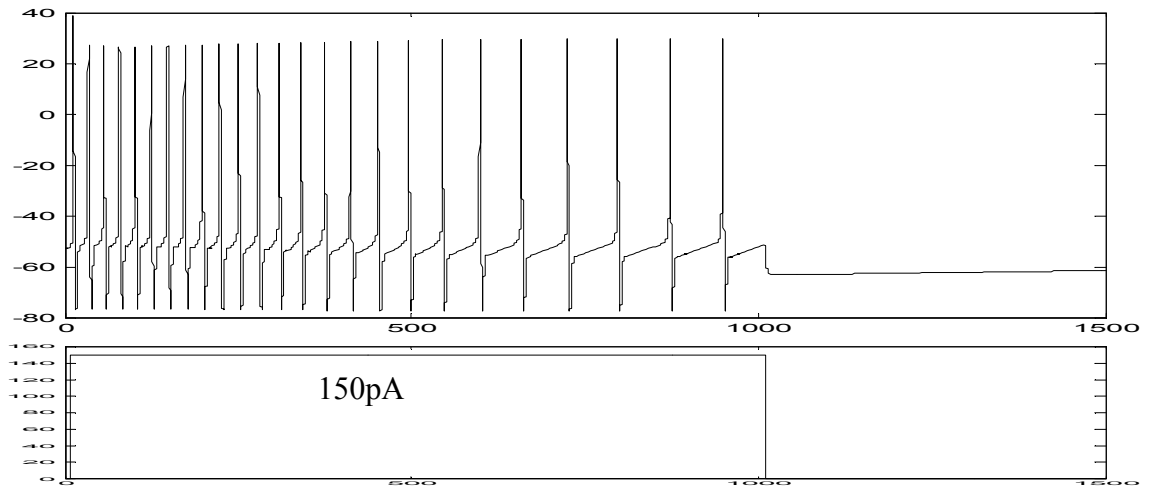


Figure 2: Bottom figure shows a current injection of 150 pA into the NTS cell and the top figure shows the output of the NTS which exhibits the spike frequency adaptation(SFA).

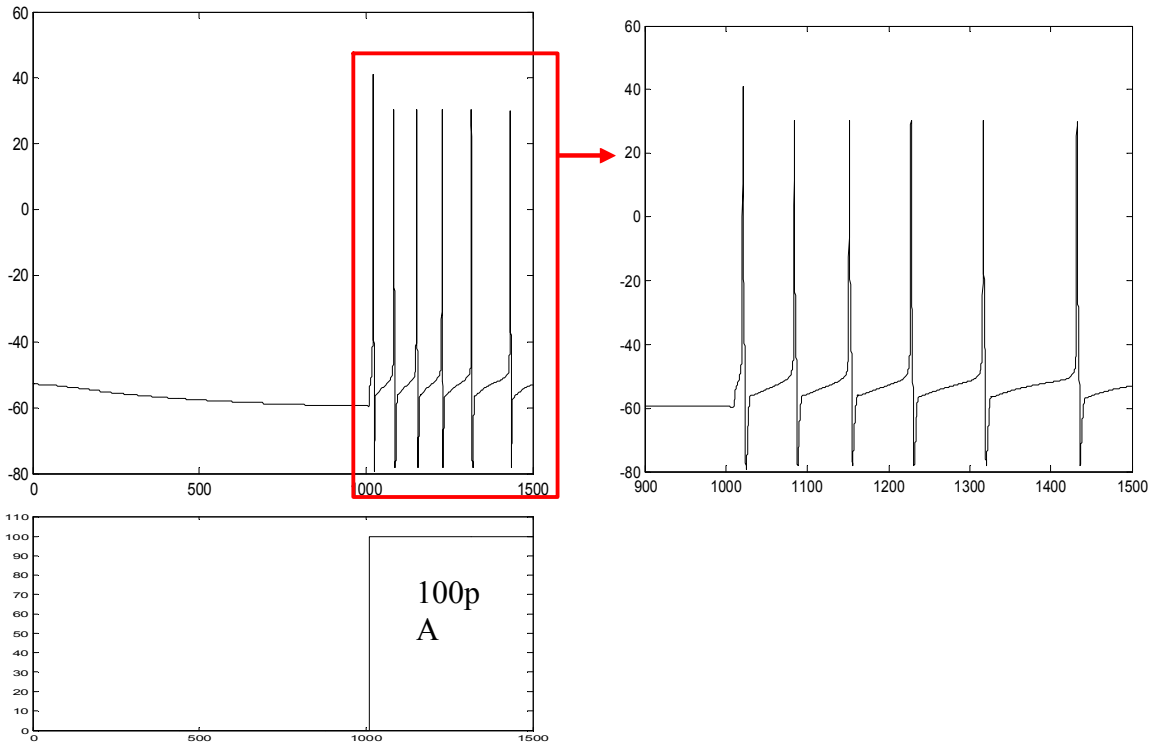


Figure 3: Bottom figure shows current injection of 0 pA for 1000 ms and 100 pA later on. The top figure shows the output of the NTS and the time taken for the first spike.

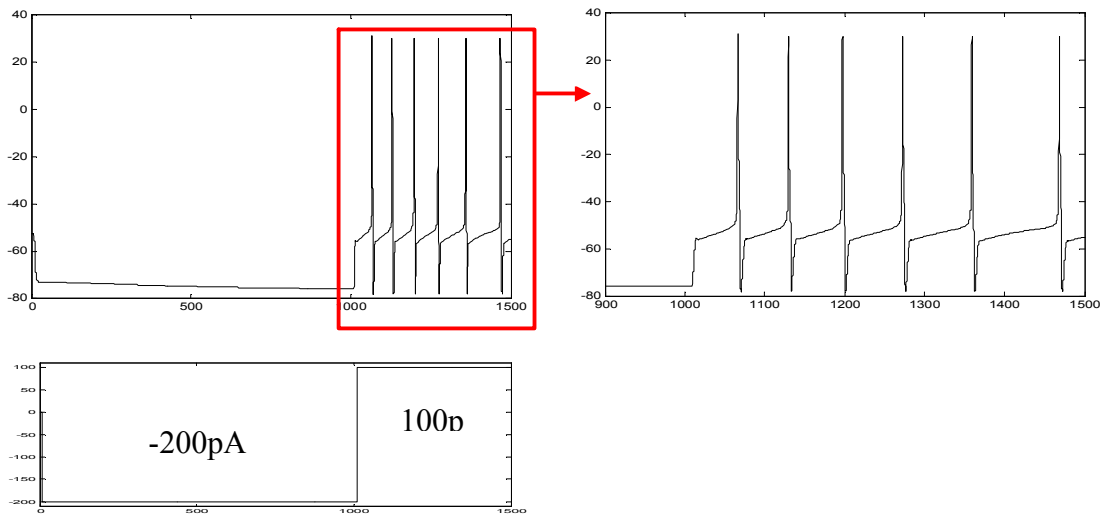


Figure 4: Bottom figure shows current injection of -200 pA for 1000 ms and 100 pA later on. The top figure shows the output of the NTS and the time taken for the first spike. This exhibits a delayed excitation (DE) compared to Figure 3.

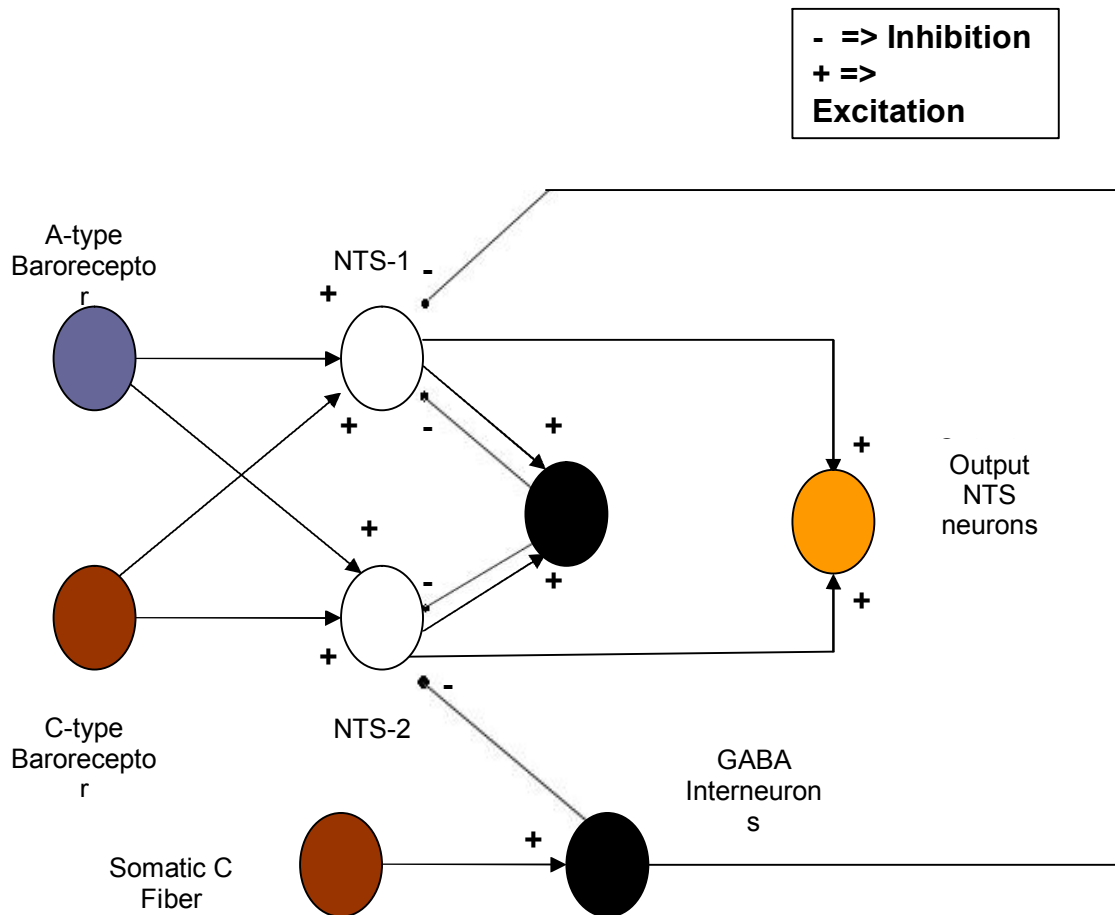


Figure 5: Network model with the somatic fiber input

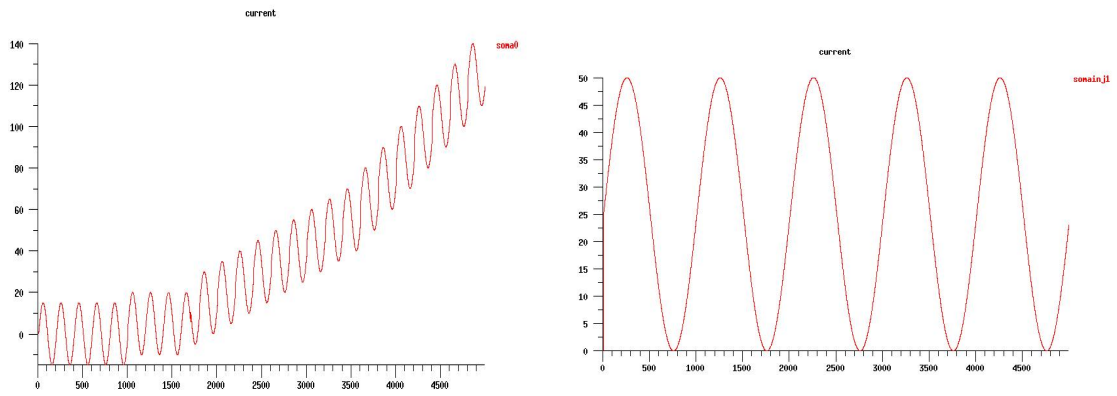


Figure 6: The left figure shows the inputs to baroreceptor A and C type populations and the right figure shows the input to the somatic C cell

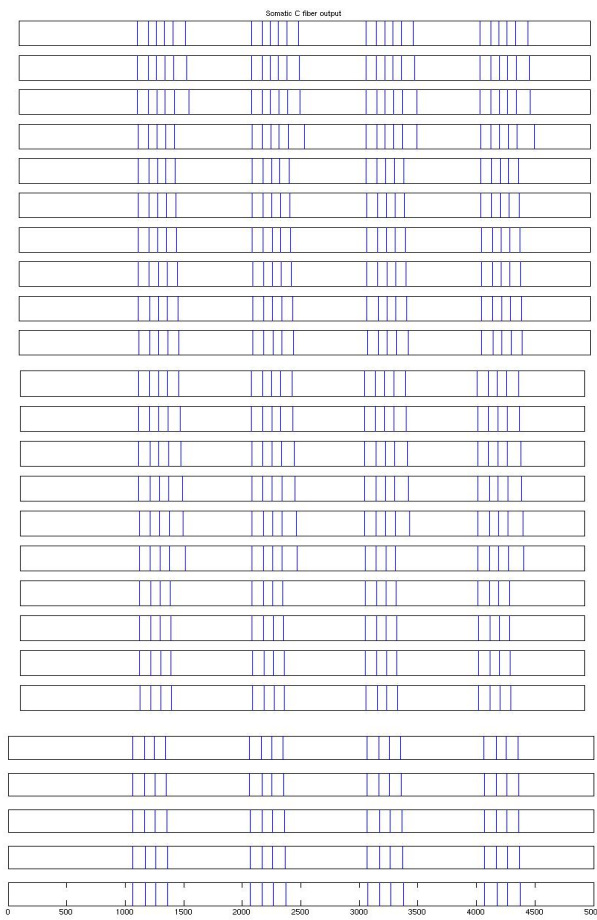


Figure 7: Somatic C fiber response

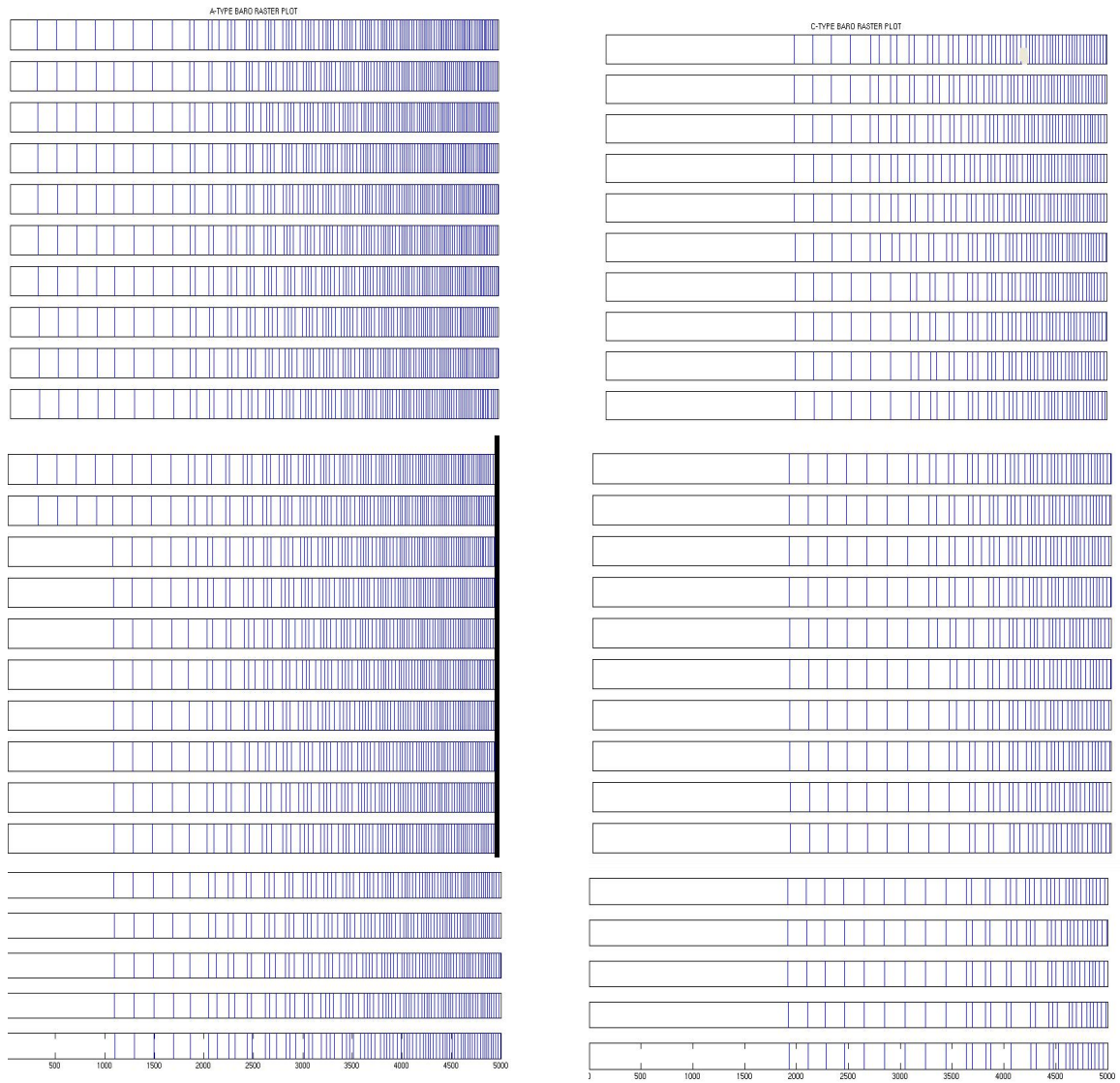


Figure 8: A type baroreceptor output on the left and C type baroreceptor output on the right

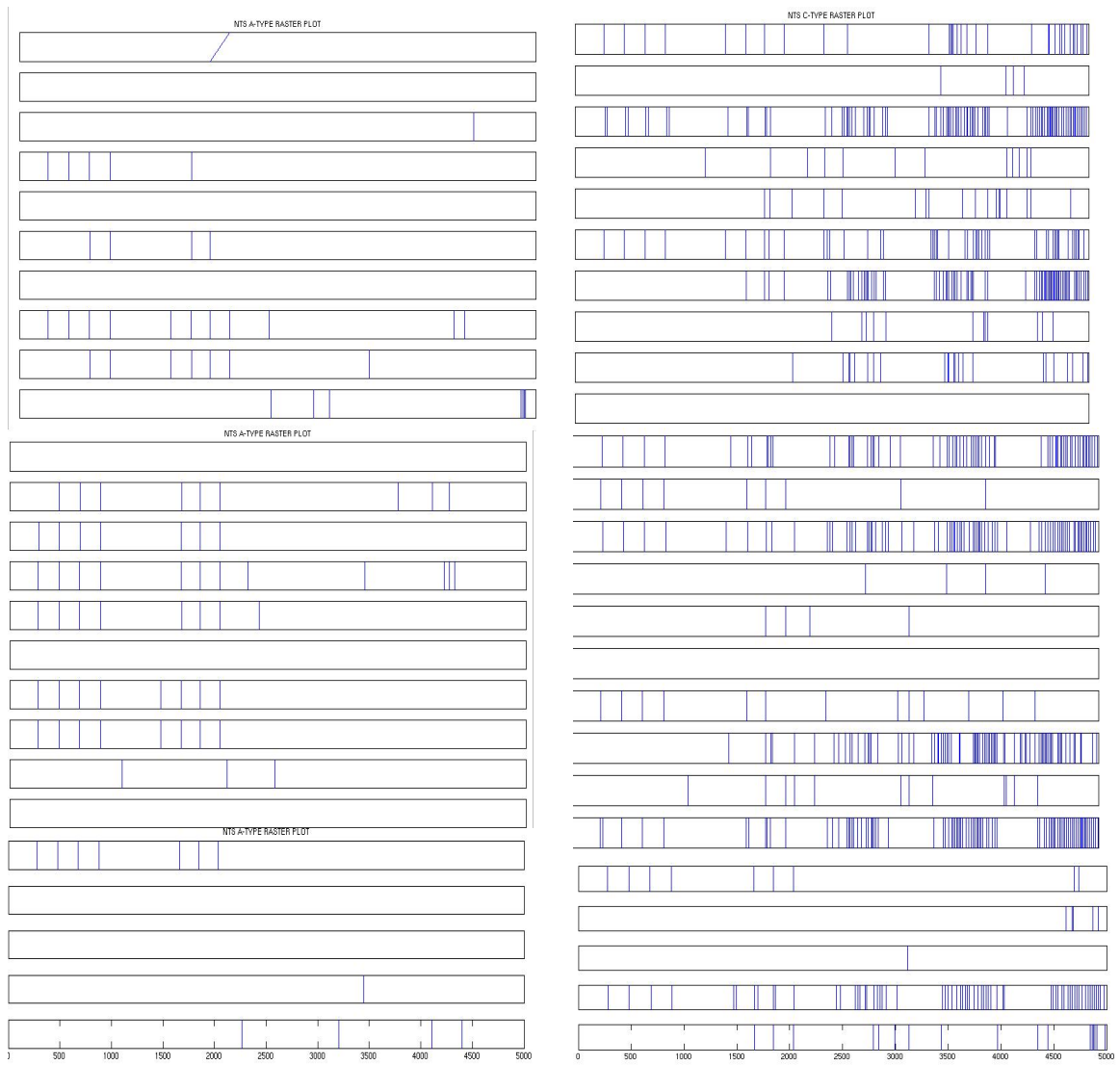


Figure 9: NTS 1 population response on the left and NTS 2 population on the right

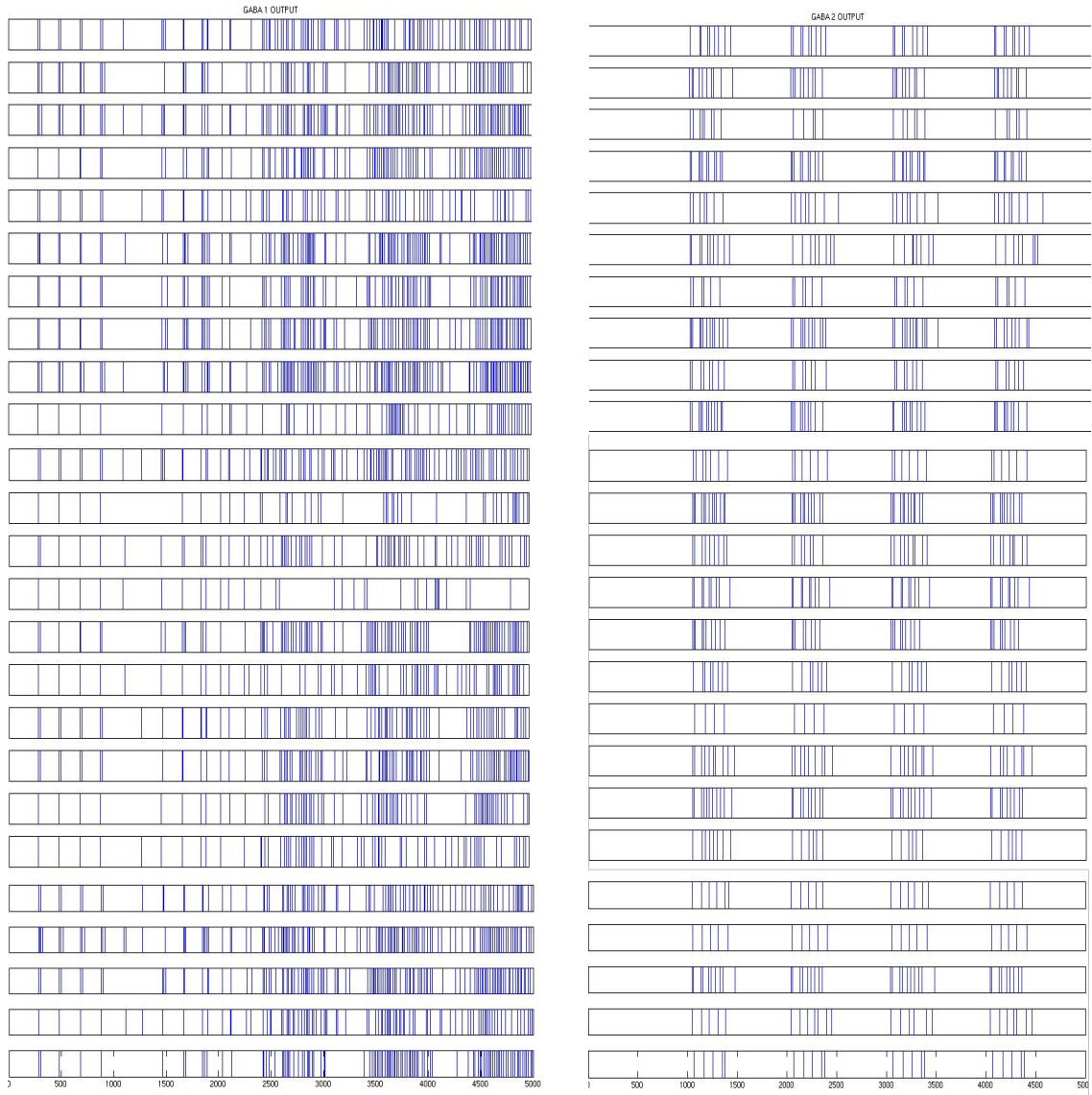


Figure 10: GABA 1 population response on the left and GABA 2 population response on the right

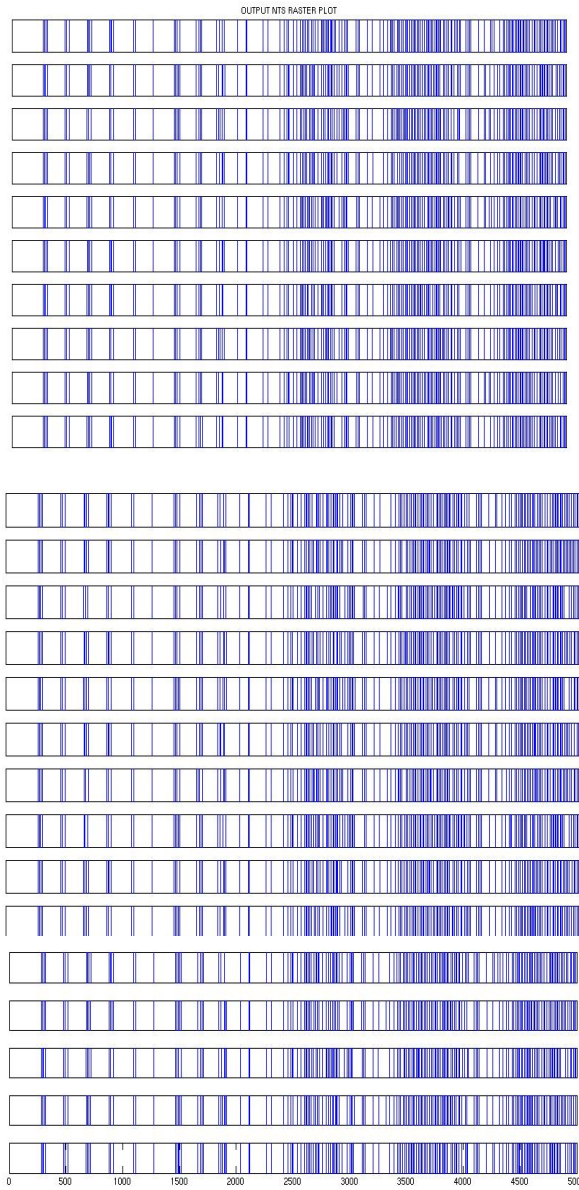


Figure 11: NTS output response

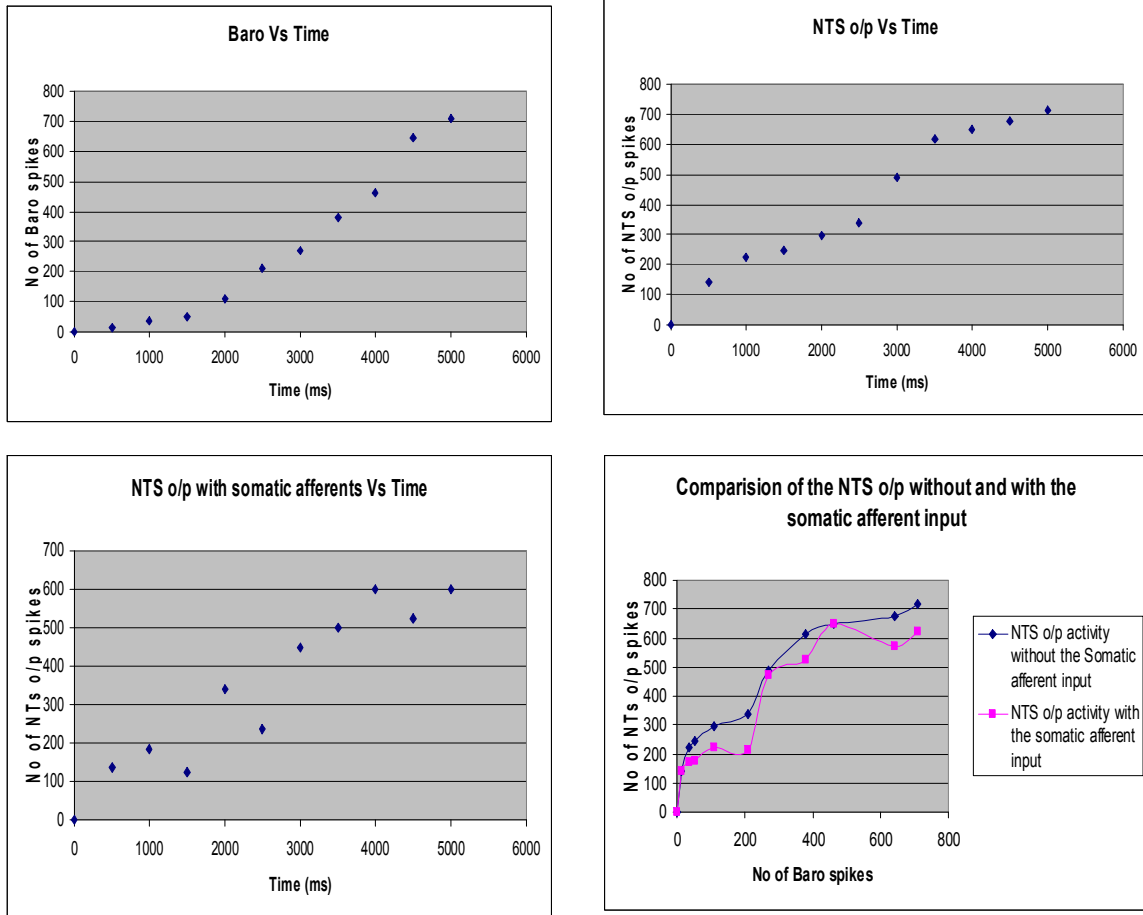


Figure 12: The first figure in the first row shows the baroreceptor activity Vs time. The second figure in the top row shows the NTS o/p activity Vs time without the somatic input. The first figure in the second row shows the NTS o/p activity Vs time with the somatic input. The second figure in the second row shows the comparison of the NTS o/p activity with the baroreceptor activity with and without the somatic input

CHAPTER 5: SUMMARY AND FUTURE WORK

5.1 SUMMARY

Computational models for the baroreceptors and NTS neurons are developed at single cell, network, and population levels to study the role of NTS in the baroreflex circuitry. Each chapter was written in the form of stand-alone journal papers, and the key points in each are listed below.

Chapter 2

- A biologically relevant model for the baroreceptor to the NTS neuron is developed in order to find the input-output relation at the first synapse of the NTS.
- This relation is found out by using the transfer function analysis where we find the gain, phase and the coherence using a white noise input to the baroreceptors and the output from the NTS. The random binary input has an auto power spectrum that rolls off at 1Hz.
- The gain plot of the transfer function shows high pass characteristics for the stimulation of both A and C type baroreceptors with only a difference in the slope.

Chapter 3

- A network model at population level is developed to investigate the lack of pulse synchronicity in second order barosensitive NTS neurons to investigate the possible role of GABA inhibition in the process.
- The network model has populations of baroreceptors, NTS and GABA neurons. The probabilities of connectivity from the GABA to the second order NTS neurons are randomized. The output from the second order NTS population shows very weak pulse synchronicity and the output NTS neurons show strong pulse synchronicity.

- The baroreceptor output increase with an increase in input magnitude. The output NTS neuron responses increase with an increase in the input to the baroreceptors, analogous to the change in the arterial blood pressure which is the basic baroreflex function. The response of the output NTS neurons also increases with an increase in the baroreceptor activity.

Chapter 4

- Skeletal muscle inputs are included through a second population of GABA neurons to the model of the previous chapter. This second population of GABA inhibits the second order barosensitive NTS neurons.
- The response of the output NTS neurons is compared with the response of the output NTS neurons without the skeletal muscle input. It is shown that the response is decreased when compared to the response where we do not apply the skeletal muscle inputs. An increase in the input still shows an increase in the response of the output NTS which indicates that the baroreflex function is preserved even after the application of the skeletal muscle inputs.

5.2 FUTURE WORK

- The transfer function analysis performed computationally needs to be verified in the laboratory.
- Similar to the transfer function analysis done at the first synapse of the NTS models can be developed to determine transfer functions at other synapses of figure 1 of chapter 1.
- The pulse synchronicity shown in the network model due to the GABA inhibition can be investigated in experiments by blocking GABA near second order NTS neurons.
- A model including the signalling pathway of the glutamate spill over onto the presynaptic mGluRs (metabotropic glutamate receptors) on the GABA terminal of a second order NTS neurons, can possibly be used to show pulse synchronicity of the output.

APPENDIX A.1: MODELING OF SIMPLE NETWORK MODEL WITH TWO CELLS USING PGENESIS

INSTRUCTIONS

PGENESIS is a parallel form of genesis which is used to increase the speed of the simulation for simple and larger models. We consider a single cell baroreceptor connected to an NTS neuron through an AMPA synapse. Initially this model is entirely modeled in serial genesis as it is recommended to do in order to debug the errors and see that the model is working right functionally and also to compare these results to the results from the pgenesis. The following files are the main files for the serial genesis code 'barnts.g', 'barntsnet.g', 'constbaro.g', 'protobarnts3.g'. The output of the NTS and the baroreceptor are stored in the text files named 'barout1.txt' and 'ntsynout.txt' which can be used in matlab to get the output in the required format. Now this serial genesis code does not have any major errors in the modeling of the cells and its channels. If we encounter any errors while implementing them in the pgenesis then it should be mostly due to the programming errors. The basic files for the implementation of the serial code in pgenesis are 'bntsc', 'pbnts.g', 'mainbnts.g', 'bnts.g', 'protobarnts3.g', 'constbaro.g'. The time of run for both the serial and pgenesis programs is 500 ms. To run the pgenesis program the main file is the 'bntsc' file. This file has no extension. In the terminal first you should navigate to the directory where all the files of pgenesis program exist. Then submit the job using the command `bsub <bntsc`. This starts the run for the pgenesis program. Here we use 2 different nodes, one for the baroreceptor cell and the other for the NTS cell. In the pgenesis we use, there is no XODUS which is a graphical interface. So we will not be able to see the graphs during the simulation. Therefore the outputs from the baroreceptors and the NTS are stored in the text files named 'newbar.txt' and 'newnts.txt'. To check the status of the job you submitted use the command `bjobs -a`. In any case if you want to

terminate the job in the middle then the command `kill jobid` is used where the *jobid* is the job number given by the program. The output text files are then compared with the serial code outputs with the help of matlab. The serial and the parallel genesis codes used are given below:

Serial Genesis Code

barnts.g

```
// genesis
create neutral /cell_nts

////////////////////////////////////
//
//      CREATING NTS
//
////////////////////////////////////
copy /library/compartment
    /cell_nts/soma
setfield /cell_nts/soma \
    Rm {0.1} \
    Cm {25} \
    Em {-53} \
    dia {30}

// Creating the modules

copy /library/HH_Na_current_nts
    /cell_nts/soma/HH_Na_current_nts
setfield /cell_nts/soma/HH_Na_current_nts
Gbar {3*1000}

copy /library/K_current_nts
    /cell_nts/soma/K_current_nts
setfield /cell_nts/soma/K_current_nts Gbar
{0.9*1000}

copy /library/A1_current_nts
/cell_nts/soma/A1_current_nts
setfield /cell_nts/soma/A1_current_nts Gbar
{0.15*0.6*1000}

copy /library/A2_current_nts
/cell_nts/soma/A2_current_nts
setfield /cell_nts/soma/A2_current_nts Gbar
{0.15*0.4*1000}

copy /library/AHP_current_nts
/cell_nts/soma/AHP_current_nts
setfield /cell_nts/soma/AHP_current_nts
Gbar {0.15*1000}
```

```
copy /library/cal_nts
    /cell_nts/soma/cal_nts
setfield /cell_nts/soma/cal_nts Gbar
{.0015*1000}

copy /library/Nernst_nts
    /cell_nts/soma/CaNernst_nts
setfield /cell_nts/soma/CaNernst_nts \
    T {21} \
    Cout {4}

copy /library/pool
    /cell_nts/soma/Capool_nts
setfield /cell_nts/soma/Capool_nts \
    tau {50} \

    Ca_base {0.05} \
    B {1*0.006/(2*96489*0.00025)}

copy /library/pool
    /cell_nts/soma/Capool2_nts
setfield /cell_nts/soma/Capool2_nts \
    tau {500} \
    Ca_base {0.05} \
    B {-1.0/(2*96489*0.00025*18)}

copy /library/AMPA_channel_nts
/cell_nts/soma/AMPA_channel_nts
copy /library/NMDA_channel_nts
/cell_nts/soma/NMDA_channel_nts
copy /library/Mgblock_nts
/cell_nts/soma/NMDA_channel_nts/Mgblock
_nts

copy /library/spike_nts
/cell_nts/soma/spike_nts
copy /library/spike_nts2
    /cell_nts/soma/spike_nts2

ce /cell_nts/soma
// LINKING THE MODULES TOGETHER.
// link in HH Na current

addmsg HH_Na_current_nts . CHANNEL
Gk Ek
addmsg . HH_Na_current_nts VOLTAGE
Vm
```

```

// link in K current
addmsg K_current_nts . CHANNEL Gk Ek
addmsg . K_current_nts VOLTAGE Vm

//Link in A current
addmsg A1_current_nts . CHANNEL Gk Ek
addmsg . A1_current_nts VOLTAGE Vm

addmsg A2_current_nts . CHANNEL Gk Ek
addmsg . A2_current_nts VOLTAGE Vm
// link in AHP current

//Link in AHP current

addmsg AHP_current_nts . CHANNEL Gk
Ek
addmsg . AHP_current_nts VOLTAGE Vm

addmsg Capool_nts AHP_current_nts
CONCEN Ca

// link in High Threshold Ca current
addmsg cal_nts . CHANNEL Gk Ek
addmsg . cal_nts VOLTAGE Vm
addmsg cal_nts Capool_nts I_Ca Ik

//link in AMPA synaptic channel to nts
addmsg AMPA_channel_nts . CHANNEL
Gk Ek
addmsg . AMPA_channel_nts VOLTAGE
Vm //link in NMDA synaptic channel
with Mg block to nts
addmsg NMDA_channel_nts
NMDA_channel_nts/Mgblock_nts
CHANNEL Gk Ek
addmsg NMDA_channel_nts/Mgblock_nts .
CHANNEL Gk Ek
addmsg . NMDA_channel_nts/Mgblock_nts
VOLTAGE Vm
addmsg . NMDA_channel_nts VOLTAGE
Vm

//link in spikegen to soma
addmsg . spike_nts INPUT Vm

//=====
// CREATING BARO
//=====

create neutral /acell

copy /library/compartment /acell/soma

setfield /acell/soma \
Rm {0.55} \
Cm {33} \
Em {-55} \
dia {d_soma} \
Ra {Ra_s}

copy /library/HH_Na_current
/acell/soma/HH_Na_current
setfield /acell/soma/HH_Na_current Gbar
{GNa_soma}

copy /library/HH_NaP_current
/acell/soma/HH_NaP_current
setfield /acell/soma/HH_NaP_current Gbar
{GNaP_soma}

copy /library/HVA_current
/acell/soma/HVA_current
setfield /acell/soma/HVA_current Gbar
{GHVA_soma}

copy /library/K_current
/acell/soma/K_current
setfield /acell/soma/K_current Gbar
{GDR_soma}

copy /library/C_current
/acell/soma/C_current
setfield /acell/soma/C_current Gbar
{GC_soma}

copy /library/cat_current
/acell/soma/cat_current
setfield /acell/soma/cat_current Gbar
{Gcat_soma}

copy /library/AHP_current
/acell/soma/AHP_current
setfield /acell/soma/AHP_current Gbar
{GAHP_soma}

copy /library/H_current
/acell/soma/H_current
setfield /acell/soma/H_current Gbar
{GH_soma}

copy /library/pool
/acell/soma/Capool
setfield /acell/soma/Capool \
tau {50} \
Ca_base {0.05} \
B {B_soma_shelli}

```

```

copy /library/Capool2_pump
/acell/soma/Capool2_pump

copy /library/pool
  /acell/soma/Capool3
setfield /acell/soma/Capool3 \
  tau {tau2} \
  Ca_base {Ca_rest} \
  B {B_soma_shell3i}

copy /library/pool
  /acell/soma/Kpool
setfield /acell/soma/Kpool \
  tau {tau2} \
  Ca_base {K_rest} \
  B {B_soma_shello}

copy /library/spike /acell/soma/spike
copy /library/spike2 /acell/soma/spike2

ce /acell/soma
// LINKING THE MODULES TOGETHER.
// link in cat current

addmsg cat_current . CHANNEL Gk Ek
addmsg . cat_current VOLTAGEVm

addmsg Capool cat_current CONCEN C

// link in HH Na current
addmsg HH_Na_current . CHANNEL Gk Ek
addmsg . HH_Na_current VOLTAGE Vm

// link in HH persistent Na current
addmsg HH_NaP_current . CHANNEL Gk Ek
addmsg . HH_NaP_current VOLTAGE Vm

// link in High Voltage Activated Ca current
addmsg HVA_current . CHANNEL Gk Ek
addmsg . HVA_current VOLTAGE Vm

// link in K current
addmsg K_current . CHANNEL Gk Ek
addmsg . K_current VOLTAGE Vm

// link in C current
addmsg C_current . CHANNEL Gk Ek
addmsg . C_current VOLTAGE Vm
addmsg Capool C_current CONCEN1 Ca

// link in inward-going Cation Current I_H
addmsg H_current . CHANNEL Gk Ek
addmsg . H_current VOLTAGE Vm

// link in AHP current
addmsg AHP_current . CHANNEL Gk Ek
addmsg Capool AHP_current CONCEN Ca

//link in Ca current to Ca pool within soma
addmsg HVA_current Capool I_Ca Ik

//link in spikegen to soma
addmsg . spike INPUT Vm

float A_zap = 300 //25.0 // [pA]

float t=0
create script_out /transient
setfield /transient command "time"
function time

t = t + {getclock 0}
if (t >= {transient + 0.02} && t <= {transient
+100000+.02} )
    setfield /acell/soma inject 300

end

end

//=====
addmsg /acell/soma/spike
/cell_nts/soma/AMPA_channel_nts SPIKE

setfield /cell_nts/soma/AMPA_channel_nts
synapse[0].weight 3 synapse[0].delay 3

barntsnet.g

//genesis
deleteall -force

include constbaro.g
include protobarnts3.g
include barnts.g

create xform /barout
xshow /barout
create xgraph /barout/voltage
addmsg /acell/soma /barout/voltage PLOT
Vm *barout *red

create xform /HVA
xshow /HVA
create xgraph /HVA/current

```

```

addmsg /acell/soma/HVA_current
/HVA/current PLOT Ik *HVA *black

create xform /cat
xshow /cat
create xgraph /cat/current
addmsg /acell/soma/cat_current /cat/current
PLOT Ik *cat *black

create xform /AHP
xshow /AHP
create xgraph /AHP/current
addmsg /acell/soma/AHP_current
/AHP/current PLOT Ik *AHP *black

create xform /AHP_m
xshow /AHP_m
create xgraph /AHP_m/Z
addmsg /acell/soma/AHP_current /AHP_m/Z
PLOT Z *Z *black

create xform /conc
xshow /conc
create xgraph /conc/concen
addmsg /acell/soma/Capool /conc/concen
PLOT Ca *conc *black

create xform /kdr
xshow /kdr
create xgraph /kdr/current
addmsg /acell/soma/K_current /kdr/current
PLOT Ik *kdr *black

create xform /c
xshow /c
create xgraph /c/current
addmsg /acell/soma/C_current /c/current
PLOT Ik *c *black

create xform /Na
xshow /Na
create xgraph /Na/current
addmsg /acell/soma/HH_Na_current
/Na/current PLOT Ik *Na *black

create xform /Nap
xshow /Nap
create xgraph /Nap/current
addmsg /acell/soma/HH_NaP_current
/Nap/current PLOT Ik *Nap *black

create xform /Injection
xshow /Injection
create xgraph /Injection/current
addmsg /acell/soma /Injection/current PLOT
inject *soma0 *red

```

```

//=====
//                               NTS graphs
//=====
create xform /ntsout
xshow /ntsout
create xgraph /ntsout/voltage
addmsg /cell_nts/soma /ntsout/voltage
PLOT Vm *ntout *red

create xform /cal
xshow /cal
create xgraph /cal/current
addmsg /cell_nts/soma/cal_nts /cal/current
PLOT Ik *cal *black

create xform /AHP_m_nts
xshow /AHP_m_nts
create xgraph /AHP_m_nts/Z
addmsg /cell_nts/soma/AHP_current_nts
/AHP_m_nts/Z PLOT Z *Z_nts *black

create xform /AHP_nts
xshow /AHP_nts
create xgraph /AHP_nts/current
addmsg /cell_nts/soma/AHP_current_nts
/AHP_nts/current PLOT Ik *AHP_nts *black
create xform /conc_nts
xshow /conc_nts
create xgraph /conc_nts/concen
addmsg /cell_nts/soma/Capool_nts
/conc_nts/concen PLOT Ca *conc_nts
*black

create xform /kdr_nts
xshow /kdr_nts
create xgraph /kdr_nts/current
addmsg /cell_nts/soma/K_current_nts
/kdr_nts/current PLOT Ik *kdr_nts *black

create xform /k1
xshow /k1
create xgraph /k1/current
addmsg /cell_nts/soma/A1_current_nts
/k1/current PLOT Ik *A1 *black

create xform /k2
xshow /k2
create xgraph /k2/current
addmsg /cell_nts/soma/A2_current_nts
/k2/current PLOT Ik *A2 *black

create xform /Na_nts
xshow /Na_nts

```

```

create xgraph /Na_nts/current
addmsg /cell_nts/soma/HH_Na_current_nts
/Na_nts/current PLOT lk *Na_nts *black

```

```

create xform /AMPA
xshow /AMPA
create xgraph /AMPA/current
addmsg /cell_nts/soma/AMPA_channel_nts
/AMPA/current PLOT lk *AMPA *black

```

```
// setting the simulation clocks
```

```

setclock      0 {0.01} // msec
randseed 34521

```

```
create asc_file /ntsynout
```

```

setfield /ntsynout \
  filename ntsynout.txt \
  leave_open 1 \
  flush 1 \
  append 0 \
  notime 0
addmsg /cell_nts/soma /ntsynout SAVE Vm

```

```
create asc_file /barout1
```

```

setfield /barout1 \
  filename barout1.txt \
  leave_open 1 \
  flush 1 \
  append 0 \
  notime 0
addmsg /acell/soma /barout1 SAVE Vm

```

```

reset // This initialises and gets
everything ready to go.

```

Parallel genesis code

bntsc

```

#BSUB -J pbntsjob
#BSUB -oo pbntsjob.o%J
#BSUB -eo pbntsjob.e%J
#BSUB -n 2
#BSUB -a mvapich
/share/apps/bin/pggenesis -nox -nodes 2
pbnts.g

```

pbnts.g

```

//genesis

mainbnts.g

echo Genesis started at {getdate}

int am_bar, am_nts

paron -parallel -silent 0 -nodes 2 -output
o.out \
  -executable pgenesis
setfield /post msg_hang_time 100000 //
set a very long timeout in case //

we need to do debugging
am_bar = {mynode} == 0
am_nts = {mynode} == 1

echo I am node {mynode}
echo Completed startup at {getdate}

// CREATE ELEMENTS ON EACH NODE
if (am_bar)
  create_baro

elif (am_nts)
  create_nts

end
echo Completed element creation at
{getdate}

// CONNECT UP ELEMENTS
barrier // wait for all elements to be
created // on every node before
trying to // connect them up

if (am_bar)
  connect

end
echo Completed connections at {getdate}

barrierall

if (am_bar)
  output_baro

```

```

elif (am_nts)

    output_nts
end

echo Completed sending data at {getdate}

// START SIMULATION
reset
if (am_bar)

    set_bar
    set_input
    echo Simulation started at {getdate}
elif (am_nts)

    set_nts
    echo Completed setup at {getdate}

end

paroff
quit

```

mainbnts.g

```

//genesis
//mainnts.g
deleteall -force
include constbaro.g
include protobarnts3.g
include bnts.g

// setting the simulation clocks

setclock      0 {0.01}      //
msec
randseed 34521

```

bnts.g

```

// genesis

function create_nts end
function create_baro end
function connect end
function output_nts end
function output_baro end
function set_input end
function set_bar end
function set_nts end
function create_nts

```

```

create neutral /cell_nts

////////////////////////////////////
//
//          CREATING NTS
//
////////////////////////////////////

copy /library/compartment
    /cell_nts/soma
    setfield /cell_nts/soma \
        Rm {0.1} \
        Cm {25} \
        Em {-53} \
        dia {30}

// Creating the modules
copy /library/HH_Na_current_nts
    /cell_nts/soma/HH_Na_current_nts
setfield /cell_nts/soma/HH_Na_current_nts
    Gbar {3*1000}

copy /library/HH_Na_current_nts1
    /cell_nts/soma/HH_Na_current_nts1
setfield /cell_nts/soma/HH_Na_current_nts1
    Gbar {3*1000}

copy /library/K_current_nts
    /cell_nts/soma/K_current_nts
setfield /cell_nts/soma/K_current_nts Gbar
{0.9*1000}

copy /library/A1_current_nts
    /cell_nts/soma/A1_current_nts
setfield /cell_nts/soma/A1_current_nts Gbar
{0.15*0.6*1000}

copy /library/A2_current_nts
    /cell_nts/soma/A2_current_nts
setfield /cell_nts/soma/A2_current_nts Gbar
{0.15*0.4*1000}

copy /library/AHP_current_nts
    /cell_nts/soma/AHP_current_nts
setfield /cell_nts/soma/AHP_current_nts
    Gbar {0.15*1000}

copy /library/AHP_current_nts1
    /cell_nts/soma/AHP_current_nts1
setfield /cell_nts/soma/AHP_current_nts1
    Gbar {0.15*1000}

copy /library/AHP_current_nts2
    /cell_nts/soma/AHP_current_nts2

```

```

setfield /cell_nts/soma/AHP_current_nts2
Gbar {0.15*1000}

copy /library/AHP_current_nts3
/cell_nts/soma/AHP_current_nts3
setfield /cell_nts/soma/AHP_current_nts3
Gbar {0.15*1000} //{0.15}

copy /library/cal_nts
/cell_nts/soma/cal_nts
setfield /cell_nts/soma/cal_nts Gbar
{.0015*1000}

copy /library/Nernst_nts
/cell_nts/soma/CaNernst_nts
setfield /cell_nts/soma/CaNernst_nts \
T {21} \
Cout {4}

copy /library/pool
/cell_nts/soma/Capool_nts
setfield /cell_nts/soma/Capool_nts \
tau {50} \

Ca_base {0.05} \
B {1*0.006/(2*96489*0.00025)}

copy /library/pool
/cell_nts/soma/Capool2_nts
setfield /cell_nts/soma/Capool2_nts \
tau {500} \
Ca_base {0.05} \
B {-1.0/(2*96489*0.00025*18)}

copy /library/AMPA_channel_nts
/cell_nts/soma/AMPA_channel_nts
copy /library/NMDA_channel_nts
/cell_nts/soma/NMDA_channel_nts
copy /library/Mgblock_nts
/cell_nts/soma/NMDA_channel_nts/Mgblock_nts

copy /library/spike_nts
/cell_nts/soma/spike_nts
copy /library/spike_nts2
/cell_nts/soma/spike_nts2

copy /library/spike
/cell_nts/soma/spike
copy /library/spike2
/cell_nts/soma/spike2

ce /cell_nts/soma

```

```

// LINKING THE MODULES TOGETHER.

// link in HH Na current
addmsg HH_Na_current_nts . CHANNEL
Gk Ek
addmsg . HH_Na_current_nts VOLTAGE
Vm

// link in K current
addmsg K_current_nts . CHANNEL Gk Ek
addmsg . K_current_nts VOLTAGE Vm

//Link in A current
addmsg A1_current_nts . CHANNEL Gk Ek
addmsg . A1_current_nts VOLTAGE Vm

addmsg A2_current_nts . CHANNEL Gk Ek
addmsg . A2_current_nts VOLTAGE Vm

// link in AHP current
addmsg AHP_current_nts . CHANNEL Gk
Ek
addmsg . AHP_current_nts VOLTAGE Vm

addmsg Capool_nts AHP_current_nts
CONCEN Ca

// link in High Threshold Ca current
addmsg cal_nts . CHANNEL Gk Ek
addmsg . cal_nts VOLTAGE Vm
addmsg cal_nts Capool_nts I_Ca Ik

//link in AMPA synaptic channel to nts
addmsg AMPA_channel_nts . CHANNEL
Gk Ek
addmsg . AMPA_channel_nts VOLTAGE
Vm

//link in NMDA synaptic channel with Mg
block to nts
addmsg NMDA_channel_nts
NMDA_channel_nts/Mgblock_nts
CHANNEL Gk Ek
addmsg NMDA_channel_nts/Mgblock_nts .
CHANNEL Gk Ek
addmsg . NMDA_channel_nts/Mgblock_nts
VOLTAGE Vm
addmsg . NMDA_channel_nts VOLTAGE
Vm

//link in spikegen to soma
addmsg . spike_nts INPUT Vm

```

```

//link in spikegen to soma
addmsg . spike INPUT Vm

end

//*****
function create_baro

create neutral /bar

////////////////////////////////////
//
//      CREATING BARO
//
////////////////////////////////////

// Creating the modules

copy /library/compartment      /bar/soma

        setfield /bar/soma \
        Rm {0.55} \ //{{1/Gleak_soma} \
        Cm {33} \ //{{Cm_soma} \
        Em {-55} \ //{{ELeak} \
        dia {d_soma} \
        Ra {Ra_s}

copy /library/HH_Na_current
        /bar/soma/HH_Na_current
setfield /bar/soma/HH_Na_current Gbar
{GNa_soma}

copy /library/HH_NaP_current
        /bar/soma/HH_NaP_current
setfield /bar/soma/HH_NaP_current Gbar
{GNaP_soma}

copy /library/HVA_current
        /bar/soma/HVA_current
setfield /bar/soma/HVA_current Gbar
{GHVA_soma}

copy /library/K_current
        /bar/soma/K_current
setfield /bar/soma/K_current Gbar
{GDR_soma}

copy /library/C_current
/bar/soma/C_current
setfield /bar/soma/C_current Gbar
{GC_soma}

copy /library/cat_current
/bar/soma/cat_current
setfield /bar/soma/cat_current Gbar
{Gcat_soma}

copy /library/AHP_current
/bar/soma/AHP_current
setfield /bar/soma/AHP_current Gbar
{GAHP_soma}

copy /library/H_current
/bar/soma/H_current
setfield /bar/soma/H_current Gbar
{GH_soma}

copy /library/pool
        /bar/soma/Capool
setfield /bar/soma/Capool \
        tau {50} \
        Ca_base {0.05} \
        B      {B_soma_shelli}

copy /library/pool
        /bar/soma/Capool3
setfield /bar/soma/Capool3 \
        tau {tau2} \
        Ca_base {Ca_rest} \
        B      {B_soma_shell3i}

copy /library/pool
        /bar/soma/Kpool
setfield /bar/soma/Kpool \
        tau {tauK} \
        Ca_base {K_rest} \
        B      {B_soma_shello}

copy /library/spike      /bar/soma/spike
copy /library/spike2    /bar/soma/spike2

        ce /bar/soma
// LINKING THE MODULES TOGETHER.
// link in cat current

addmsg cat_current . CHANNEL Gk Ek
addmsg . cat_current VOLTAGEVm

addmsg Capool cat_current CONCEN C

// link in HH Na current
addmsg HH_Na_current . CHANNEL Gk Ek
addmsg . HH_Na_current VOLTAGE Vm

// link in HH persistent Na current

```



```

addmsg HH_NaP_current . CHANNEL Gk
Ek
addmsg . HH_NaP_current VOLTAGE Vm

// link in High Voltage Activated Ca current
addmsg HVA_current . CHANNEL Gk Ek
addmsg . HVA_current VOLTAGE Vm

// link in K current
addmsg K_current . CHANNEL Gk Ek
addmsg . K_current VOLTAGE Vm

// link in C current
addmsg C_current . CHANNEL Gk Ek
addmsg . C_current VOLTAGE Vm
addmsg Capool C_current CONCEN1 Ca

// link in inward-going Cation Current I_H
addmsg H_current . CHANNEL Gk Ek
addmsg . H_current VOLTAGE Vm

// link in AHP current
addmsg AHP_current . CHANNEL Gk Ek
addmsg Capool AHP_current CONCEN Ca

//link in Ca current to Ca pool within soma
addmsg HVA_current Capool I_Ca Ik

//link in spikegen to soma
addmsg . spike INPUT Vm

end

function connect

raddmsg /bar/soma/spike
/cell_nts/soma/AMPA_channel_nts@1
SPIKE
setfield@1
/cell_nts/soma/AMPA_channel_nts
synapse[0].weight 3 synapse[0].delay 0.003
end

function output_nts

create asc_file /out1
setfield /out1 filename newnts.txt
leave_open 1 flush 1
addmsg /cell_nts/soma /out1 SAVE
Vm

end

function output_baro

create asc_file /out2
setfield /out2 filename newbar.txt
leave_open 1 flush 1
addmsg /bar/soma /out2 SAVE Vm

end

function set_bar

ce /
create hsolve /bar/solve1
setfield /bar/solve1 path
"/bar/###[TYPE=compartment]"
setfield /bar/solve1 chanmode 1
call /bar/solve1 SETUP
setmethod 11
reset

end

function set_input

int nsteps = 50000

if (nsteps>{0} && nsteps<{300000})

setfield /bar/soma inject 300

end

step@all {nsteps}
echo finished {nsteps} steps

end

function set_nts

ce /

create hsolve /cell_nts/solve1
setfield /cell_nts/solve1 path
"/cell_nts/###[TYPE=compartment]"
setfield /cell_nts/solve1 chanmode 1
call /cell_nts/solve1 SETUP
setmethod 11
reset

end

Common files

```

Protobarnts3.g

```
// genesis
// prototypes.g

create neutral /library
// We don't want the library to try to calculate
// anything,
// so we disable it.
disable /library

//-----
//                               NTS channels
//-----

// NOTE: Input and synaptic channels at end
// of this file.

//=====
//                               COMPARTMENT
//=====

create compartment /library/compartment

//=====
//                               LEAKAGE
//=====

create leakage /library/leak

float xmin = -100
float xmax = 60
int xdivs = 65

int i
float x,dx,y1,y2
float tao,ss,taod,ssd,tao2,ss2
float alpha, beta

dx=(xmax-xmin)/xdivs

////////////////////////////////////
//                               CAN BE USED FOR THE
//                               INTERNEURON
////////////////////////////////////

//*****
//                               SODIUM
//*****

create tabchannel /library/HH_Na_current1
```

```
setfield /library/HH_Na_current1 Ek {55}
Xpower 3 Ypower 1 Zpower 0

call /library/HH_Na_current1 TABCREATE X
{xdivs} {xmin} {xmax}

    x=xmin

    for(i=0;i<={xdivs}; i=i+1)

        alpha = 4.2*{exp {(x+34.5)/11.57}}
        beta = 4.2*{exp {-(x+34.5)/27}}

        setfield /library/HH_Na_current1 X_A-
>table[{i}] {alpha}
        setfield /library/HH_Na_current1 X_B-
>table[{i}] {alpha+beta}

        x=x+dx

    end

    setfield /library/HH_Na_current1 X_A-
>calc_mode 0 X_B->calc_mode 0
    call /library/HH_Na_current1 TABFILL X
3000 0

    call /library/HH_Na_current1
TABCREATE Y {xdivs} {xmin} {xmax}

    x=xmin

    for(i=0;i<={xdivs}; i=i+1)

        alpha = 0.09*{exp {-(x+45)/33}}
        beta = 0.09*{exp {(x+45)/12.2}}

        setfield /library/HH_Na_current1 Y_A-
>table[{i}] {alpha}
        setfield /library/HH_Na_current1 Y_B-
>table[{i}] {alpha+beta}

        x=x+dx

    end

    setfield /library/HH_Na_current1 Y_A-
>calc_mode 0 Y_B->calc_mode 0
    call /library/HH_Na_current1 TABFILL Y
3000 0

//*****
//                               POTASSIUM
//*****

create tabchannel /library/K_current1
```

```

setfield /library/K_current1 Ek {-94} Xpower
4 Ypower 0 Zpower 0

call /library/K_current1 TABCREATE X
{xdivs} {xmin} {xmax}

    x=xmin

    for(i=0;i<={xdivs}; i=i+1)

        alpha = 0.3*{exp {(x+35)/10.67}}
        beta = 0.3*{exp {-(x+35)/42.68}}

        setfield /library/K_current1 X_A-
>table[{i}] {alpha}
        setfield /library/K_current1 X_B-
>table[{i}] {alpha+beta}

        x=x+dx

    end

    setfield /library/K_current1 X_A-
>calc_mode 0 X_B->calc_mode 0
    call /library/K_current1 TABFILL X 3000
0

//=====
//          FAST, SPIKE-GENERATING
NA CURRENT1 (I_Na)
//=====

create tabchannel
/library/HH_Na_current_nts1
    setfield /library/HH_Na_current_nts1
\
    Ek {55} \ // mV
    Xpower 3 \
    Ypower 1 \
    Zpower 0

    call /library/HH_Na_current_nts1
TABCREATE X 28571 -100.0 100.0
    file2tab tables/alphanNa.txt
/library/HH_Na_current_nts1 X_A -xy 28572
    file2tab tables/betamNa.txt
/library/HH_Na_current_nts1 X_B -xy 28572
    tweakalpha /library/HH_Na_current_nts1
X
    setfield /library/HH_Na_current_nts1 X_A-
>calc_mode 0 X_B->calc_mode 0

    call /library/HH_Na_current_nts1
TABCREATE Y 22222 -100.0 100.0

```

```

file2tab tables/alphanNa.txt
/library/HH_Na_current_nts1 Y_A -xy 22223
file2tab tables/betahNa.txt
/library/HH_Na_current_nts1 Y_B -xy 22223
    tweakalpha /library/HH_Na_current_nts1
Y
    setfield /library/HH_Na_current_nts1 Y_A-
>calc_mode 0 Y_B->calc_mode 0

//=====
// NTS- Na CURRENT - I_Na - Rogers 2000
//=====

create tabchannel
/library/HH_Na_current_nts
setfield /library/HH_Na_current_nts Ek {55}
Xpower 3 Ypower 1 Zpower 0

call /library/HH_Na_current_nts
TABCREATE X {xdivs} {xmin} {xmax}

    x=xmin

    for(i=0;i<={xdivs}; i=i+1)

        alpha = 0.091*(x+38)/(1-{exp {-
(x+38)/5}})
        beta = -0.062*(x+38)/(1-{exp
{(x+38)/5}})

        setfield /library/HH_Na_current_nts
X_A->table[{i}] {alpha}
        setfield /library/HH_Na_current_nts
X_B->table[{i}] {alpha+beta}

        x=x+dx

    end

    setfield /library/HH_Na_current_nts X_A-
>calc_mode 0 X_B->calc_mode 0
    call /library/HH_Na_current_nts TABFILL
X 3000 0

    call /library/HH_Na_current_nts
TABCREATE Y {xdivs} {xmin} {xmax}

    x=xmin

    for(i=0;i<={xdivs}; i=i+1)

        alpha = 0.016*{exp {-(x + 55)/15}}
        beta = 2.07/(1 +{exp {-(x-17)/21}})

```

```

    setfield /library/HH_Na_current_nts
Y_A->table[{i}] {alpha}
    setfield /library/HH_Na_current_nts
Y_B->table[{i}] {alpha+beta}

    x=x+dx

end

    setfield /library/HH_Na_current_nts Y_A-
>calc_mode 0 Y_B->calc_mode 0
    call /library/HH_Na_current_nts TABFILL
Y 3000 0

//=====
//      NTS- DELAYED RECTIFYING
POTASSIUM CURRENT (I_DR)- Rogers
//=====

create tabchannel /library/K_current_nts
setfield /library/K_current_nts Ek {-94}
Xpower 4 Ypower 0 Zpower 0

call /library/K_current_nts TABCREATE X
{xdivs} {xmin} {xmax}

    x=xmin

    for(i=0;i<={xdivs}; i=i+1)

        alpha = 0.01*(x + 45)/( 1-{exp {-(x +
45)/5}})
        beta = 0.17*({exp {-(x + 50)/40}})

        setfield /library/K_current_nts X_A-
>table[{i}] {alpha}
        setfield /library/K_current_nts X_B-
>table[{i}] {alpha+beta}

        x=x+dx

    end

    setfield /library/K_current_nts X_A-
>calc_mode 0 X_B->calc_mode 0
    call /library/K_current_nts TABFILL X
3000 0
//=====
//      NTS- A1 POTASSIUM CURRENT
(A1)- Rogers
//=====

```

```

create tabchannel /library/A1_current_nts
setfield /library/A1_current_nts Ek {-94}
Xpower 4 Ypower 1 Zpower 0

call /library/A1_current_nts TABCREATE X
{xdivs} {xmin} {xmax}

    x=xmin

    call /library/A1_current_nts TABCREATE
X 22222 -100.0 100.0
    file2tab tables/tau_nm.txt
/library/A1_current_nts X_A -xy 22223
    file2tab tables/nminf.txt
/library/A1_current_nts X_B -xy 22223
    tweaktau /library/A1_current_nts X
    setfield /library/A1_current_nts X_A-
>calc_mode 0 X_B->calc_mode 0

call /library/A1_current_nts TABCREATE Y
{xdivs} {xmin} {xmax}

    x=xmin

    call /library/A1_current_nts TABCREATE
Y 22222 -100.0 100.0
    file2tab tables/tau_nm2.txt
/library/A1_current_nts Y_A -xy 22223
    file2tab tables/nminf2.txt
/library/A1_current_nts Y_B -xy 22223
    tweaktau /library/A1_current_nts Y
    setfield /library/A1_current_nts Y_A-
>calc_mode 0 Y_B->calc_mode 0

//=====
//      NTS- A1 POTASSIUM CURRENT
(A2)- Rogers
//=====

create tabchannel /library/A2_current_nts
setfield /library/A2_current_nts Ek {-94}
Xpower 4 Ypower 1 Zpower 0

call /library/A2_current_nts TABCREATE X
{xdivs} {xmin} {xmax}

    x=xmin

    call /library/A2_current_nts TABCREATE
X 22222 -100.0 100.0
    file2tab tables/tau_am.txt
/library/A2_current_nts X_A -xy 22223

```

```

file2tab tables/aminf.txt
/library/A2_current_nts X_B -xy 22223
tweaktau /library/A2_current_nts X
setfield /library/A2_current_nts X_A-
>calc_mode 0 X_B->calc_mode 0

call /library/A2_current_nts TABCREATE Y
{xdivs} {xmin} {xmax}

x=xmin

call /library/A2_current_nts TABCREATE
Y 22222 -100.0 100.0
file2tab tables/tau_am2.txt
/library/A2_current_nts Y_A -xy 22223
file2tab tables/aminf2.txt
/library/A2_current_nts Y_B -xy 22223
tweaktau /library/A2_current_nts Y
setfield /library/A2_current_nts Y_A-
>calc_mode 0 Y_B->calc_mode 0
//=====================================================
//          SLOW afterhyperpolaring
POTASSIUM CURRENT (I_AHP) - Rogers
//=====================================================

float v1
float vin

float minC=0.01
float maxC= 5
float dc
int divsC=100
dc=(maxC-minC)/divsC
float x1

create tabchannel /library/AHP_current_nts
setfield /library/AHP_current_nts \
Ek {-94} \
Xpower 0 \
Ypower 0 \
Zpower 2

call /library/AHP_current_nts TABCREATE
Z {divsC} {minC} {maxC}

x1 = minC

for(i=0;i<={divsC}; i=i+1)

vin = x1*x1

tao=1000/(1.25*100*vin+2.5)

```

```

ss=(1.25*100*vin)/(1.25*100*vin+2.5)

setfield /library/AHP_current_nts Z_A-
>table[{i}] {ss/tao}
setfield /library/AHP_current_nts Z_B-
>table[{i}] {1/tao}

x1=x1+dc

end

//tweaktau library/AHP_current_nts Z
setfield /library/AHP_current_nts Z_A-
>calc_mode 0 Z_B->calc_mode 0
call /library/AHP_current_nts TABFILL Z
3000 0

//=====================================================
//          High threshold calcium (cal)
(From rogers)
//=====================================================

create tabchannel /library/cal_nts
setfield /library/cal_nts Ek {150} Xpower 3
Ypower 0 Zpower 0

call /library/cal_nts TABCREATE X {xdivs}
{xmin} {xmax}

x=xmin

for(i=0;i<={xdivs}; i=i+1)

alpha = 1.6/( 1+{exp {-0.072*(x - 5)}})
beta = 0.02*(x-1.31)/({exp {(x -
1.31)/5.36}}-1)

setfield /library/cal_nts X_A->table[{i}]
{alpha}
setfield /library/cal_nts X_B->table[{i}]
{alpha+beta}

x=x+dx

end

setfield /library/cal_nts X_A->calc_mode
0 X_B->calc_mode 0
call /library/cal_nts TABFILL X 3000 0

//=====================================================
//create Ca_concen /library/pool
//=====================================================
//          2nd Ca(2+) Pools

```

```

=====
create difshell /library/Capool2_nts
  setfield /library/Capool2_nts \
    C {Ca_rest} \
    Ceq {Ca_rest} \
    D 0.0 \
    val 2.0 \
    leak 0.0 \
    shape_mode 3 \
    vol 1.0 \
    surf_up 1.0 \
    surf_down 1.0

create fixbuffer /library/Capool2_buffer_nts
  setfield /library/Capool2_buffer_nts \
    Btot {Bconc} \
    kBf {kplus} \
    kBb {kminus}

create mmpump /library/Capool2_pump_nts
  setfield /library/Capool2_pump_nts \
    vmax {gpump} \
    val 0.0 \
    Kd {Kmpump}

=====
//                               Ion Nernst Potential
=====
create nernst /library/Nernst_nts
  setfield /library/Nernst_nts \
    valency 2.0 \
    scale 1.0

=====
//                               AMPA synaptic CHANNEL
=====
create synchan
/library/AMPA_channel_nts
  setfield /library/AMPA_channel_nts
  \
    Ek {EAMPA} \
    gmax {GAMPA} \
    tau1 {tau1_AMPA} \
    tau2 {tau2_AMPA}

// gmax {GAMPA*tau1_AMPA*tau2_AMPA}
\
=====
//                               NMDA synaptic CHANNEL
=====

create synchan
/library/NMDA_channel_nts
  setfield /library/NMDA_channel_nts
  \
    Ek {ENMDA} \
    gmax {GNMDA} \
    /*tau1_NMDA*tau2_NMDA*1.50265} \
    tau1 {tau1_NMDA} \
    tau2 {tau2_NMDA}

create Mg_block /library/Mgblock_nts
  setfield /library/Mgblock_nts \
    KMg_A {1/0.33} \
    KMg_B {1/0.06} \
    CMg {1}

=====
// CASE 2      GABAA synaptic
CHANNEL : case 2 PC to IN
=====

create synchan
/library/GABAA_channel_nts
  setfield
/library/GABAA_channel_nts \
    Ek {-75} \
    gmax {GGABA} \
    tau1 {2.5} \
    tau2 {15.5}

=====
// CASE 2      GABAA synaptic
CHANNEL : case 2 PC to IN
=====

create synchan
/library/GABAA_channel_nts1
  setfield
/library/GABAA_channel_nts1 \
    Ek {-75} \
    gmax {GGABA} \
    tau1 {2.5} \
    tau2 {15.5}

=====
//                               Spikegen
=====

create spikegen /library/spike_nts
  setfield /library/spike_nts \
    thresh 0 \
    abs_refract 1 \
    output_amp 1

=====

```

```

//          Spikegen2
//=====

create spikegen /library/spike_nts2
  setfield /library/spike_nts2 \
  thresh -40 \
  abs_refract 1 \
  output_amp 1

//=====
//          Randomspike
//=====

create randomspike /library/RandSpike_nts
  setfield /library/RandSpike_nts \
  min_amp 0.0 \
  max_amp 1.0 \
  abs_refract 0.001 \
  reset 1 \
  reset_value 0

//-----
//          BaroReceptor
Channels
//-----

//=====
//          SLOW afterhyperpolarizing
POTASSIUM CURRENT (I_AHP)
//=====

create tabchannel /library/AHP_current
  setfield /library/AHP_current \
  Ek {-94} \
  Xpower 0 \
  Ypower 0 \
  Zpower 1

  call /library/AHP_current TABCREATE Z
25001 0.0 5.0
  //call /library/AHP_current TABCREATE Z
101 0.000001 0.001
  file2tab tables/Aq.txt /library/AHP_current
Z_A -xy 25001
  file2tab tables/Bq.txt /library/AHP_current
Z_B -xy 25001
  setfield /library/AHP_current Z_A-
>calc_mode 0 Z_B->calc_mode 0

//=====
//          FAST, SPIKE-GENERATING
NA CURRENT (I_Na)

```

```

//=====

create tabchannel /library/HH_Na_current
  setfield /library/HH_Na_current \
  Ek {ENa} \ // mV
  Xpower 3 \
  Ypower 1 \
  Zpower 0

  call /library/HH_Na_current TABCREATE
X 28571 -100.0 100.0
  file2tab tables/alphanNa.txt
/library/HH_Na_current X_A -xy 28572
  file2tab tables/betamNa.txt
/library/HH_Na_current X_B -xy 28572
  tweakalpha /library/HH_Na_current X
setfield /library/HH_Na_current X_A-
>calc_mode 0 X_B->calc_mode 0

  call /library/HH_Na_current TABCREATE
Y 22222 -100.0 100.0
  file2tab tables/alphahNa.txt
/library/HH_Na_current Y_A -xy 22223
  file2tab tables/betahNa.txt
/library/HH_Na_current Y_B -xy 22223
  tweakalpha /library/HH_Na_current Y
setfield /library/HH_Na_current Y_A-
>calc_mode 0 Y_B->calc_mode 0

//=====
//          PERSISTENT NA CURRENT
(I_NaP) -- 0 % DA
//=====

create hh_channel /library/HH_NaP_current
  setfield /library/HH_NaP_current \
  Ek {ENa} \
  Xpower 1 \
  Ypower 1 \
  X_alpha_FORM 3 \
  X_alpha_A -0.2816 \
  X_alpha_B -9.3 \
  X_alpha_V0 {NaPmalphavo} \
  X_beta_FORM 3 \
  X_beta_A 0.2464 \
  X_beta_B 6.0 \
  X_beta_V0 {NaPmbetavo} \
  Y_alpha_FORM 1 \
  Y_alpha_A {NaPhalphaA} \
  Y_alpha_B -4.0248 \
  Y_alpha_V0 -42.8477 \
  Y_beta_FORM 2 \
  Y_beta_A {NaPhbetaA} \
  Y_beta_B -148.2589 \
  Y_beta_V0 413.9284

```

```

//=====
//      HIGH VOLTAGE ACTIVATED
//      CALCIUM CURRENT (I_HVA)
//=====

create tabchannel /library/HVA_current
  setfield /library/HVA_current \
    Ek {150} \
    Xpower 2 \
    Ypower 1 \
    Zpower 0

  call /library/HVA_current TABCREATE X
  22222 -100.0 100.0
  file2tab tables/tau_u.txt
  /library/HVA_current X_A -xy 22223
  file2tab tables/uinf.txt /library/HVA_current
  X_B -xy 22223
  tweaktau /library/HVA_current X
  setfield /library/HVA_current X_A-
  >calc_mode 0 X_B->calc_mode 0

  call /library/HVA_current TABCREATE Y
  22222 -100.0 100.0
  file2tab tables/tau_v.txt
  /library/HVA_current Y_A -xy 22223
  file2tab tables/vinf.txt /library/HVA_current
  Y_B -xy 22223
  tweaktau /library/HVA_current Y
  setfield /library/HVA_current Y_A-
  >calc_mode 0 Y_B->calc_mode 0

//=====
//      DELAYED RECTIFYING
//      POTASSIUM CURRENT (I_DR)
//=====

create tabchannel /library/K_current
  setfield /library/K_current \
    Ek {-94} \
    Xpower 4 \
    Ypower 0 \
    Zpower 0

  call /library/K_current TABCREATE X
  22222 -100 100
  file2tab tables/alphanDR.txt
  /library/K_current X_A -xy 22223
  file2tab tables/betanDR.txt
  /library/K_current X_B -xy 22223
  tweakalpha /library/K_current X
  setfield /library/K_current X_A-
  >calc_mode 0 X_B->calc_mode 0

//=====

```

```

//      SLOWLY INACTIVATING
//      POTASSIUM CURRENT (I_KS)
//=====

create tabchannel /library/KS_current
  setfield /library/KS_current \
    Ek {-94} \
    Xpower 1 \
    Ypower 1 \
    Zpower 0

  call /library/KS_current TABCREATE X
  22222 -100.0 100.0
  file2tab tables/tau_a.txt
  /library/KS_current X_A -xy 22223
  file2tab tables/ainf.txt /library/KS_current
  X_B -xy 22223
  tweaktau /library/KS_current X
  setfield /library/KS_current X_A-
  >calc_mode 0 X_B->calc_mode 0

  call /library/KS_current TABCREATE Y
  22222 -100.0 100.0
  file2tab tables/tau_b.txt
  /library/KS_current Y_A -xy 22223
  file2tab tables/binf.txt /library/KS_current
  Y_B -xy 22223
  tweaktau /library/KS_current Y
  setfield /library/KS_current Y_A-
  >calc_mode 0 Y_B->calc_mode 0

//=====
//      FAST, BK CALCIUM AND VOLTAGE-
//      GATED 'C-TYPE' POTASSIUM CURRENT
//      (I_C)
//=====

create tab2Dchannel /library/C_current
  setfield /library/C_current \
    Ek {-94} \
    Xpower 2 \
    Ypower 0 \
    Zpower 0 \
    Xindex {VOLT_C1_INDEX}

float tabxstep = 0.09 //1 //0.009
float xmin = -75.0
float xmax = 50.0
float xdivs = ({xmax} - {xmin})/{tabxstep}
float tabystep = 0.01 //0.001
float Ca_i_min = 0.05
float Ca_i_max = 0.4
float Ca_i_divs = ({Ca_i_max} -
{Ca_i_min})/{tabystep}

```



```

call /library/C_current TABCREATE X
{xdivs} {xmin} {xmax} \
{Ca_i_divs} {Ca_i_min} {Ca_i_max}

int j, i
float x, dx, Ca_i, dCa_i, alphac, betac, cinf,
tauca, tauc, Avalue, Bvalue

Ca_i = Ca_i_min
for (j=0 ; j<={Ca_i_divs} ; j=j+1)
    float A_alpha = -0.2568 * {log
{Ca_i}}/{log 10.0} - 0.1152
    float B_alpha = -0.00642
    float C_alpha = -1.0
    float D_alpha = 40.0 * {log
{Ca_i}}/{log 10.0} + 18.0
    float F_alpha = -12.0

    float A_beta = 1.7
    float B_beta = 0.0
    float C_beta = 0.0
    float D_beta = 40.0 * {log
{Ca_i}}/{log 10.0} + 152.0
    float F_beta = 30.0

    x = xmin
    for (i=0 ; i<={xdivs} ; i=i+1)

        alphac =
({A_alpha}+{B_alpha}*{x})/({C_alpha}+{exp
{({x}+{D_alpha})/{F_alpha}}})
        betac =
({A_beta}+{B_beta}*{x})/({C_beta}+{exp
{({x}+{D_beta})/{F_beta}}})
        cinf =
{alphac}/({alphac}+{betac})
        tauca =
1.0/({alphac}+{betac})
        tauc = {max {tauca} 1.1}
        Avalue = {cinf}/{tauc}
        Bvalue = 1.0/{tauc}
        setfield /library/C_current
X_A->table[{i}][{}] {Avalue}
        setfield /library/C_current
X_B->table[{i}][{}] {Bvalue}

        x = x + tabxstep
    end
    Ca_i = Ca_i + tabystep
end

//setfield /library/C_current X_A->calc_mode
{NO_INTERP}
//setfield /library/C_current X_B->calc_mode
{NO_INTERP}

=====
//
//          AMPA synaptic CHANNEL
=====

create synchan /library/AMPA_channel
setfield /library/AMPA_channel \
Ek {EAMPA} \
gmax {GAMPA} \
tau1 {tau1_AMPA} \
tau2 {tau2_AMPA}

// gmax {GAMPA*tau1_AMPA*tau2_AMPA}
\

=====
//
//          NMDA synaptic CHANNEL
=====

create synchan /library/NMDA_channel
setfield /library/NMDA_channel \
Ek {ENMDA} \
gmax
{GNMDA*tau1_NMDA*tau2_NMDA*1.50265
} \
tau1 {tau1_NMDA} \
tau2 {tau2_NMDA}

create Mg_block /library/Mgblock
setfield /library/Mgblock \
KMg_A 1.0 \
KMg_B 0.33 \
CMg {1.0/0.06}

=====
//
//          Ca(2+)-Dependent cationic
CURRENT (I_cat)
=====

create tabchannel /library/cat_current
setfield /library/cat_current \
Ek {Ecat} \ // mV
Xpower 0 \
Ypower 0 \
Zpower 1

call /library/cat_current TABCREATE Z
26667 0.0 40.0
file2tab tables/taumcat.txt
/library/cat_current Z_A -xy 26667
file2tab tables/mcatinf.txt
/library/cat_current Z_B -xy 26667
tweaktau /library/cat_current Z

```

```

setfield /library/cat_current Z_A-
>calc_mode 0 Z_B->calc_mode 0

//=====================================================
//      LA- Hyperpolarization-activated
inward-going Cation Current I_H(I_Q)
//=====================================================
create tabchannel /library/H_current
  setfield /library/H_current \
    Ek {EH} \ // mV
    Xpower 1 \
    Ypower 0 \
    Zpower 0 \
    instant {INSTANTX}

float xminh = -100
float xmaxh = 60
int xdivsh = 65
float tao,ss

call /library/H_current TABCREATE X
{xdivsh} {xminh} {xmaxh}

x=xmin

for(i=0;i<={xdivsh}; i=i+1)

  //ss=1.0/(1.0+{exp {(x+89.2)/9.5}})

  ss=1.0/(1.0+{exp {(x+75.2)/5.5}})

  setfield /library/H_current X_A->table[{i}]
  {ss/1000}
  setfield /library/H_current X_B->table[{i}]
  {1.0/1000}

  x=x+dx

end

setfield /library/H_current X_A-
>calc_mode 0 X_B->calc_mode 0
call /library/H_current TABFILL X 3000 0

//=====================================================
//      2nd Ca(2+) Pools
//=====================================================

create difshell /library/Capool2
  setfield /library/Capool2 \
    C {Ca_rest} \
    Ceq {Ca_rest} \
    D 0.0 \
    val 2.0 \
    leak 0.0 \
    shape_mode 3 \
    vol 1.0 \
    surf_up 1.0 \
    surf_down 1.0

create fixbuffer /library/Capool2_buffer
  setfield /library/Capool2_buffer \
    Btot {Bconc} \
    kBf {kplus} \
    kBb {kminus}

create mmpump /library/Capool2_pump
  setfield /library/Capool2_pump \
    vmax {gpump} \
    val 0.0 \
    Kd {Kmpump}

//=====================================================
//      Ion Nernst Potential
//=====================================================

create nernst /library/Nernst
  setfield /library/Nernst \
    valency 1.0 \
    scale 1.0

//=====================================================
//      Spikegen
//=====================================================

create spikegen /library/spike
  setfield /library/spike \
    thresh -40 \
    abs_refract 10 \
    output_amp 1

//=====================================================
//      Spikegen2
//=====================================================

create spikegen /library/spike2
  setfield /library/spike2 \
    thresh -40 \
    abs_refract 1 \
    output_amp 1

//=====================================================
//      Spikegen4
//=====================================================

```

```

create spikegen /library/spike4
    setfield /library/spike4 \
    thresh -40 \
    abs_refract 1 \
    output_amp 1

//=====
//          Spikegen6
//=====

create spikegen /library/spike6
    setfield /library/spike6 \
    thresh -40 \
    abs_refract 1 \
    output_amp 1

//=====
//          Randomspike
//=====

create randomspike /library/RandSpike
    setfield /library/RandSpike \
    min_amp 0.0 \
    max_amp 1.0 \
    abs_refract 0.001 \
    reset 1 \
    reset_value 0

constbaro.g

//genesis
//constants.g

float PI=3.141592

float delta=0.01 //msec
float transient=0 // 10.0//msec

// COMPARTMENTAL DIAMETERS
float d_soma=23.0 // mu m

// COMPARTMENTAL AREAS
// Surf Area of sphere = 4*PI*r^2
// Surf Area of cylinder = PI*diameter*length
float A_soma=PI*d_soma*d_soma
// (mu m)^2

// COMPARTMENTAL MEMBRANE
CAPACITANCE
float c_soma=1.2 // mu F/cm^2
float Cm_soma=36 //c_soma*A_soma*0.01
// pF

// COMPARTMENTAL MEMBRANE
RESISTANCE
float Rm=20000
float Gleak_soma =
((1.0/(Rm*1e8))*(A_soma))*1e9 //
nS

// COMPARTMENTAL AXIAL RESISTANCE
float Ra =15
float Ra_b =
((Ra*10000.0*4.0*I_bdend)/(PI*d_bdend**2)
)*1e-9 // 1/nS
float Ra_s =
((Ra*10000.0*8.0)/(PI*d_soma))*1e-9 //
1/nS
float Ra_p =
((Ra*10000.0*4.0*I_pdend)/(PI*d_pdend**2)
)*1e-9 // 1/nS
float Ra_d =
((Ra*10000.0*4.0*I_ddend)/(PI*d_ddend**2)
)*1e-9 // 1/nS

// COMPARTMENTAL CHANNEL
CONDUCTANCE
////////////////////////////////////
// For I_Na:
float gNa_soma=86.0//86.0 control//1.5
// mS/cm^2
float GNa_soma=gNa_soma*A_soma*0.01
// nS

////////////////////////////////////
// For I_NaP:
float gNaP_soma=2.2
// mS/cm^2

float
GNaP_soma=gNaP_soma*A_soma*0.01
// nS

// For I_DR:
float gDR_soma= 33.8 //28 //33.8
// mS/cm^2
float GDR_soma=gDR_soma*A_soma*0.01
// nS

// For I_KS:
// 0% DA:
float gKS0_soma=0 //0.14
// mS/cm^2

// 100% DA:
float gKS100_soma=0.07
// mS/cm^2

float GKS_soma=gKS0_soma*A_soma*0.01
// nS

```

```

////////////////////////////////////
// For I_C:
float gC_soma=2.2 //3 //2.2
// mS/cm^2
float GC_soma=gC_soma*A_soma*0.01
// nS
////////////////////////////////////

////////////////////////////////////
// For I_H, the larger the Gh, the more
spikes produces!
float EH = -80

float gH_soma = 2 // 0= 8spikes 2=7spikes
3.6=5 spikes 5 =3spikes ONLY SOMA//
mS/cm^2
float GH_soma = gH_soma*A_soma*0.01
// nS

// CONSTANTS FOR CA_CONCEN
OBJECT --> used for changing Ca2+ & K+
concen.

// For both Ca2+ and K+:
float F=23061.0 // cal/volt-
mol
float F2=96485 // C/mol
float R=1.9872 // cal/mol-
deg

// For Ca2+:
float tauc_bdend=120.0 // ms
float tauc_soma=500 //250.0 //
ms
float tauc_pdend=120.0 // ms
float tauc_ddend=80.0 // ms

float Ca_rest=0.00005
float Ca_out=2000.0

float phiCa_soma=386.0e-9
float phiCa_dend=965.0e-9

float thick_shelli=2.0e-4 // mu m
float d_soma_shelli = d_soma -
2.0*thick_shelli //mu m
float V_soma_shelli =
(PI*d_soma*d_soma*d_soma)/6.0 -\
(PI*d_soma_shelli*d_soma_shelli*d_soma_
shelli)/6.0 // (mu m)^3

// B = -(phi/(F*Vshell))

float B_soma_shelli =
(phiCa_soma/(F2*V_soma_shelli))*1000000
.0 //no -ve due to GENESIS convention
//0.00025

// For K+:
float tauk=7.0 // ms
// tauk_soma = tauk_dends
float K_rest=3.82 * 1000 // micromol/l
float K_in=140.0 * 1000 //
micromol/l

float phiK=2.0
float thick_shello=70.0e-3 //
mu m

float d_soma_shello = d_soma +
2*thick_shello //mu m

float V_soma_shello =
(PI*d_soma_shello*d_soma_shello*d_soma
_shello)/6.0 \
-(PI*d_soma*d_soma*d_soma)/6.0 //-
PI/4*70.0e-3*(2.6**2 + 16.0**2) // (mu m)^3

// B = -(phi/(F*Vshell))
float B_soma_shello = -
(phiK/(F2*V_soma_shello))*1000000.0

// CONSTANTS FOR SYNAPTIC
CHANNELS

// Synaptic conductances:
float GAMPA=15.1392
// nS
float GNMDA=0.0912
// nS
float GGABA= 8.4
float GAMPA_back=5.312
// nS
float GNMDA_back=0.032
// nS
float GGABA_back=2.6796
// nS

// Synaptic time constants:
float tau1_AMPA=0.55 // ms
float tau2_AMPA=3 // ms
float tau1_NMDA=10.6 // ms
float tau2_NMDA=285.0 // ms
float tau_GABA= 1.5 // ms

// Synaptic reversal potentials

```

```

float EAMPA=-10.0          //          float z = 2
mV                          float f2 = 0.009
float ENMDA=0.0           //          float tau2 = 500 //1050
mV                          //ms

float EGABA= -65          // mV
////////////////////////////////////
// IONIC CHANNEL REVERSAL
POTENTIALS
float Eleak = -72.0       // mV
float ENa = 55 // mV

////////////////////////////////////

// For I_HVA:
// 0% NE:
float gHVA0_soma=0.34
// mS/cm^2

// 100% NE: Hyperpolarizes the pyramidal
cell ?????????
float gHVA100_soma=0 //0.34-0.34*0.05
//0.272 // mS/cm^2

float
GHVA_soma=gHVA0_soma*A_soma*0.01
// nS

// For I_AHP:
float gAHP_soma=20.002
// mS/cm^2

float
GAHP_soma=gAHP_soma*A_soma*0.01
// nS

float w = 1
//microm

float z = 2
float f2 = 0.009
float tau2 = 500 //1050
//ms

// B = f2/(w*z*F2*A_i) for the 3rd Ca(2+) pool
used for the AHP current
float B_soma_shell3i =
(f2/(w*z*F2*A_soma))*1000000.0 //no -ve
due to GENESIS convention

// For I_cat:
float gcat_soma=5.0 //
mS/cm^2
float Gcat_soma=gcat_soma*A_soma*0.01
// nS

float Ecat = -42.0 //mV
float Kdcat = 15
//microM
float psicat = 2.8
//microM-ms
float Bconc = 30
//microM
float kminus = 0.3 //ms^-1
1
float kplus = 0.1
//((ms*microM)^-1
float Kmpump = 0.75
//microM
float gpump = 3.6
//microM/ms
float eta = 0.027
float shift_taumcat = 2000
float fraction = eta*9.6487e4*2

```

APPENDIX A.2

Appendix A.2 provides simulation results validating the single cell models for the baroreceptors and the NTS cells in the chapters 2, 3 and 4. The baroreceptor cells A and C have been validated based on their repetitive firing properties and the difference in the firing frequencies by comparing with data in the literature (Schildts et al 1994 page 2348). The NTS cells have been validated by showing the intrinsic properties of the NTS cell such as spike frequency adaptation and the Delayed Excitation, again by comparing with data in the literature (Schildts et al 1993 page 357, Schildts et al 1993 page 358). In this appendix we show some more data on the validation of the A and C type baroreceptor cells by using different stimulus inputs like a constant current injection, an impulse input and a sinusoidal input.

C-type baroreceptor cells exhibit a characteristic 'hump' during the recovery phase for a constant current injection which is shown in Fig A1 where a constant current injection of 25pA is injected into the C-type baroreceptor cell. We can see the hump characteristics from the Fig A1 during the recovery. These characteristics match the characteristics shown in Fig 6B of Schildts et al 1994. Similarly a constant current injection of 40pA is given to the A type baroreceptor as shown in Fig A1 whose response is similar to what we see in the Fig 5B of Schildts et al 1994. The responses of the A and C type baroreceptors to 2ms impulse current injections of 300pA and 500pA in Fig A2 showed similarity to the responses in Fig 5A and Fig 6A of Schildts et al 1994 respectively. The modeling of the baroreceptor A and C type cells have been differed by the change in the membrane capacitance of the cell which changes the firing rate. Application of a sinusoidal input to the baroreceptor cells with different membrane capacitances for the cell is shown in Fig A3.

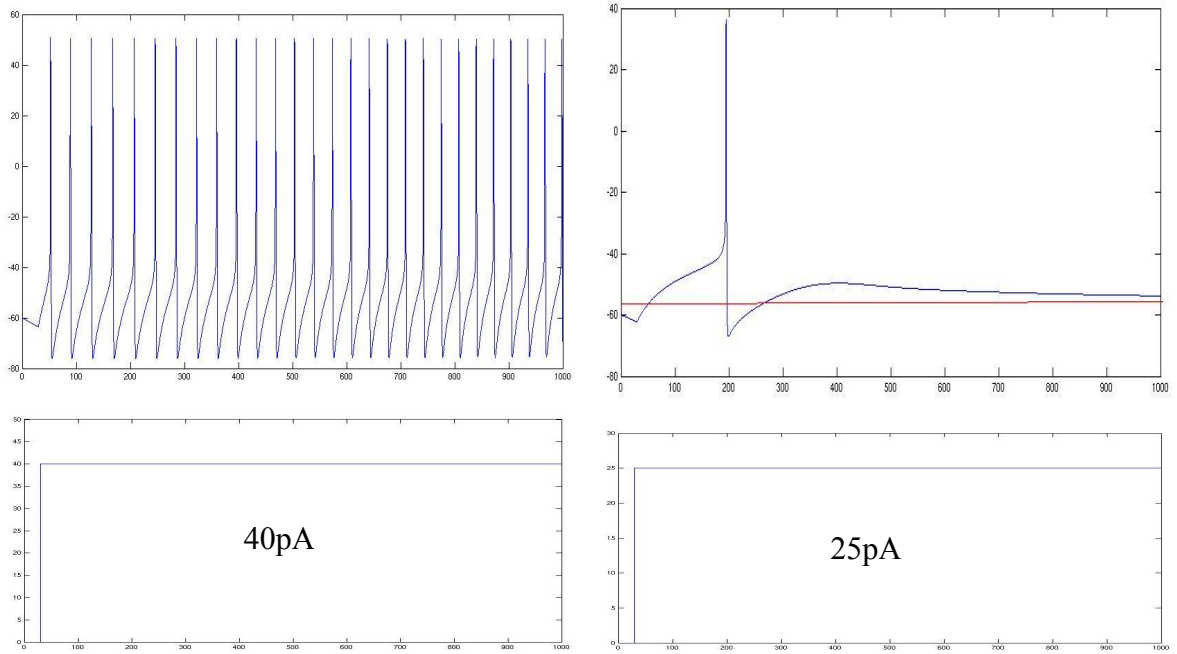


Figure A1: The figure on the left shows the response of the A type baroreceptor for a constant current injection of 40pA and the figure on the right shows the response of a C type baroreceptor for a constant current injection of 25pA.

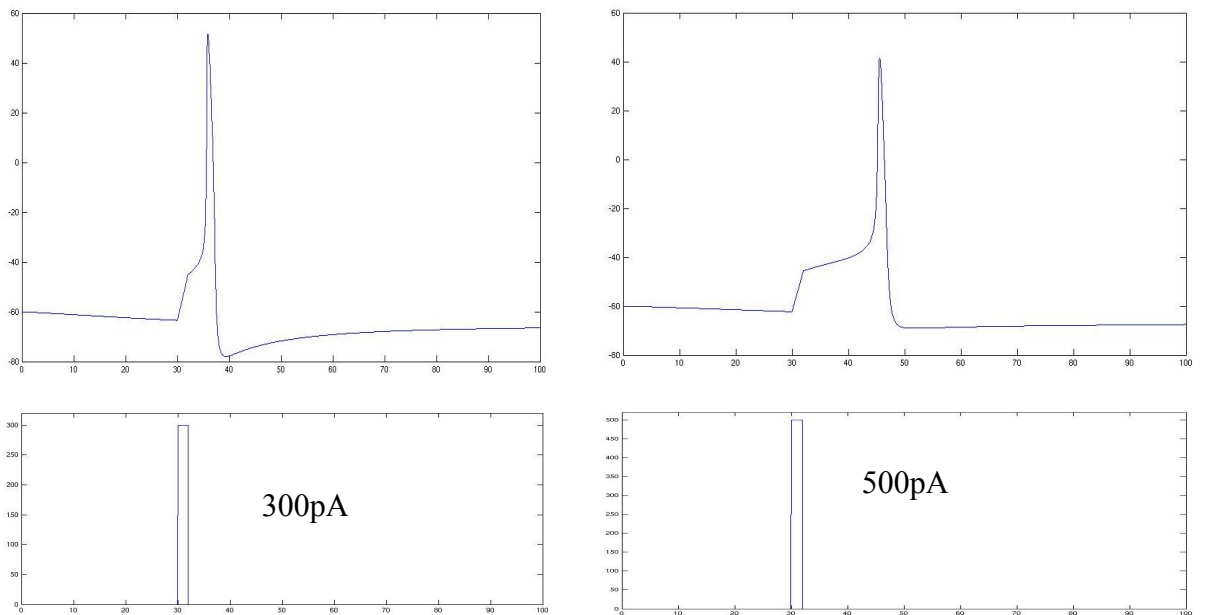


Figure A2: The figure on the left shows the response of the A type baroreceptor for an impulse current injection of 300pA and the figure on the right shows the response of a C type baroreceptor for an impulse current injection of 500pA.

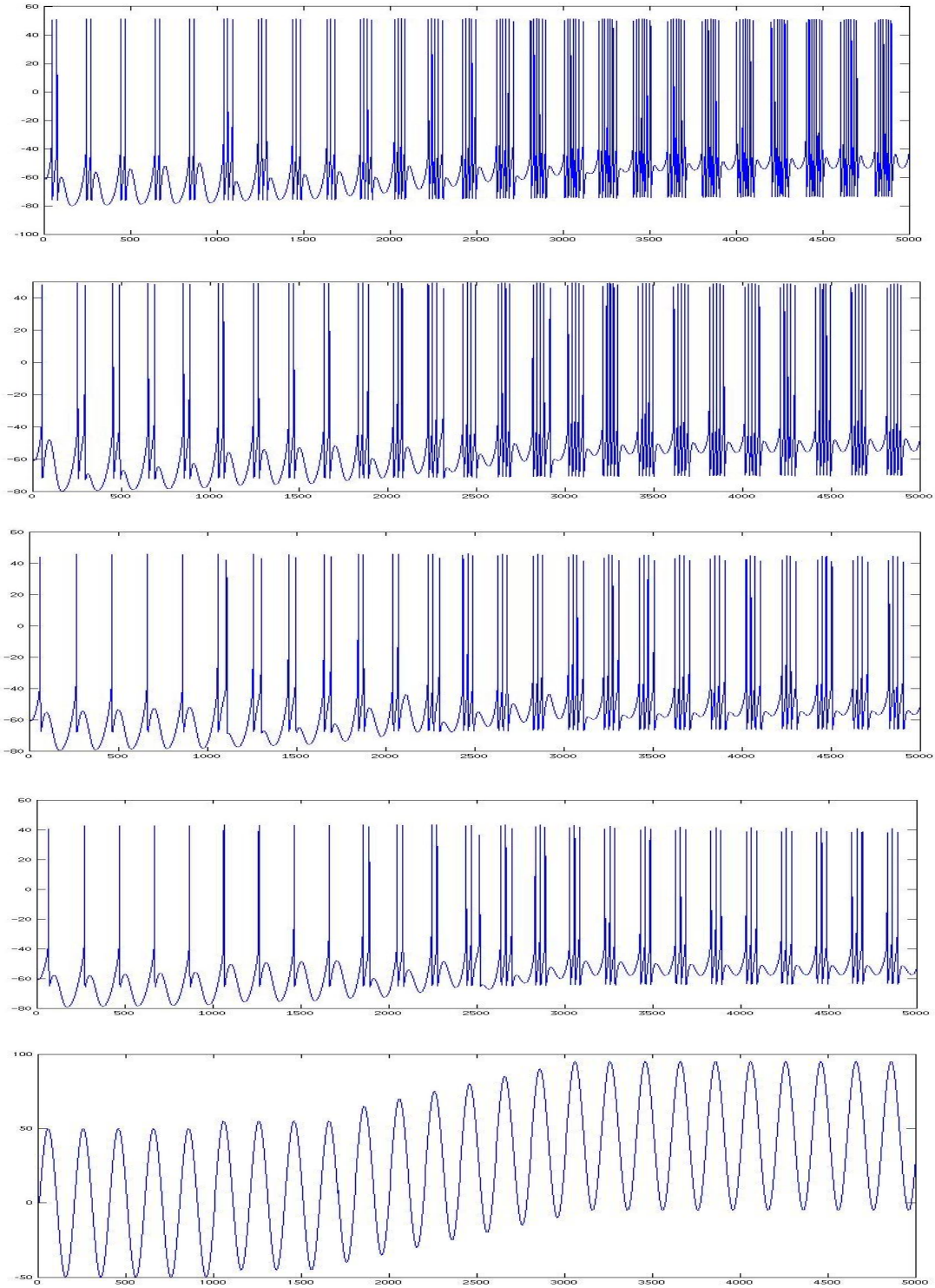


Figure A3: The top 4 figures show the response of the baroreceptor cells of membrane capacitance 33pF, 45pF, 60pF, 75pF respectively for a sinusoidal input of 5Hz frequency shown at the bottom.

PRESENTATIONS AND PUBLICATIONS

Presentations

- Presented at an International Conference, Experimental Biology 2007 (EB2007) held in Washington DC.
Gummadavalli, P, Kline, DD, Nair, S and Potts, JT (2007) Computational model of Nucleus Tractus Solitarius (NTS) sensory circuits transmitting arterial baroreceptor signals *FASEB J.* 21(5), abstract # 582.8

Papers in preparation

- **Pavan Gummadavalli**, Satish Nair, Jeffery T Potts "Transfer function analysis at the first synapse of the NTS transmitting arterial baroreceptor signals-A computational analysis"
- **Pavan Gummadavalli**, Satish Nair, Jeffery T Potts "Network Model of Baroreceptor-NTS pathway"
- **Pavan Gummadavalli**, Satish Nair, Jeffery T Potts "Neural Network Model"

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