

Proposal: Development of a Large Scale Model of the Mammalian Cochlear Nucleus

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Executive Summary:

This is a proposal to develop a large-scale network model of the mammalian cochlear nucleus. The cochlear nucleus is the first processing center for acoustic information after it is transduced into a neural code within the cochlea. This biologically inspired, 'neuromorphic' model is to be developed using transistor-based neurons that implement both the specific ion channels and local neural networks found in the biological tissue. A silicon-based format allows for several unique modeling features, most importantly this medium provides the ability to simulate large populations of neurons (thousands to tens of thousands) in real time. Acoustic stimuli will be delivered through a silicon model of the cochlea currently in development that has outputs modeling those of the auditory nerve. The proposed model will be the first real-time, large-scale model of the entire nucleus (including approximately ten characterized cell types), and as such will provide a powerful tool for testing hypotheses about the nature of cochlear nucleus response characteristics while providing the appropriate inputs for development of future silicon models of upstream auditory nuclei.

Aims and Objectives:

The aim of this proposal is to develop an integral piece to the puzzle of how the auditory system utilizes its diverse population of neuronal types and interconnections to cohesively process acoustic information. The auditory system's traditional ranking as "number two" behind the visual system in terms of sensory dominance and collective research interest has left significant gaps in our present understanding of its form and function. Anatomists and physiologists have described the various nuclei and cell types throughout the system, yet a cohesive understanding of the systems level information processing of acoustic information is lacking.

The objective of this proposal is to produce a biologically inspired, silicon-based large-scale model of the cochlear nucleus. Biologically inspired neuron models capture the output characteristics of the cell by modeling the important ion conductances and synaptic connectivity observed in actual tissue. Neuromorphic models of each of the roughly ten characterized cell types in the cochlear nucleus will be designed based on data cited from relevant literature. The ten types will be integrated together on a single chip adhering to the local connectivity observed in the biological system.

One of the most important characteristics of the auditory system is the preservation of timing information encoded by the phase locking spiral ganglia cells of the cochlea. This project will be the first large-scale model of the entire nucleus, where inputs from a silicon cochlea are simultaneously driving all cell types in real time. Therefore, this model will represent a major step in auditory system modeling and understanding, as issues arising from the real time simulation of entire populations of cells will invariably shed light on subtle complexities of auditory coding in the nervous system. Real-time delivery of acoustic information simultaneously across the cochlear nucleus provides the appropriate biological 'set-up' for all neural computations attributed to the auditory system as a whole. Based on intense timing requirements, the Inter-Aural Timing Difference (ITD) pathway will undoubtedly require this population level timing precision. Most likely, other auditory processing tasks have timing interdependencies in upstream auditory nuclei requiring synchronous stimulation of the down stream components. These processing tasks include but are not limited to inter-aural level difference calculations, pitch percept formation, and speech perception processing.

Therefore, the proposed model of the cochlear nucleus is scientifically important for two main reasons. More immediately, it will provide a substrate for testing hypothesis about the important biological parameters that define the observed outputs of the system. In the long term, this model will provide a real-time interacting population of cells that will ultimately drive future silicon models of the entire auditory system. The scientific understanding of the auditory system that comes from such a model has powerful implications not only in the neuroscience field, but may potentially lead to development of more sophisticated neural implants for those with hearing deficits.

Relevant Literature:

Neurons in the auditory system convey information about the acoustic stimulus. In contrast to the mammalian visual system in which all pre-thalamal/cortical processing occurs at the sensory epithelium, the auditory system utilizes a distributed set of up to five separate nuclei for acoustic pre-thalamal/cortical processing. Neural coding of auditory information initiated at the sensory cochlea propagates through the cochlear nucleus, where it is distributed to the contra lateral cochlear nucleus, the olivary complex (a set of three separate nuclei) and the inferior colliculus. Information processing occurs when the information content at the input of a cell is different than the information content at the output of the cell. The cochlear nucleus (CN) is the first stage of information processing after the conversion of acoustic stimuli into a neural code carried in the auditory nerve fiber (ANF). Two primary modalities of information processing occur in the mammalian CN, which I define as intrinsic and extrinsic. Neurons with intrinsic information processing properties utilize membrane characteristics and ANF synaptic connectivity to enhance the input signal's temporal and spectral representations. Neurons with extrinsic information processing properties utilize local inter-neuronal networks, which may receive both acoustic and non-acoustic inputs, in order to perform the tasks of spectral feature extraction and integration of multi-modal neuronal information. Anatomical descriptions of cell types and local networks are tightly coupled with the intrinsic/extrinsic classification I define. Please refer to appendix section Ia for diagrams and a brief description of cochlear nucleus innervation by the ANF, cell types, and local networks (for review of cochlear function see Geisler 1998, for review of the auditory system see Ehret & Romand 1997).

The preliminary investigations for this proposal include descriptions and simulations of transistor-based models for three intrinsic processing cell types of the cochlear nucleus. In the following section, more specific surveys of current literature regarding these intrinsic processing cochlear nucleus cells can be found. The models of these cells require a moderate degree of understanding of silicon neuron implementation. A brief description of transistor physics and the basic silicon neuron can be found in appendix section Ib of this proposal (for a review of transistor implementations of neurons and sub-threshold transistor physics see Mead 1989).

Preliminary Investigations:

As a preliminary investigation into the development of a cochlear nucleus model, I have engineered three intrinsic processing cells found in the ventral cochlear nucleus. Spherical bushy, globular bushy and octopus cells all receive primarily ANF innervations, and their response profiles are therefore a result of ANF synaptic connectivity and specific ion channel conductances. The following investigations consist of three parts: consolidation of relevant literature describing the inputs and channels associated with each cell, discussion of the design of specialized transistor model building blocks for each cell type inspired by the literature descriptions, and a brief comparison of the models' responses to the biological responses cited in the literature.

Spherical and Globular Bushy Cells

The bushy cells constitute a large population of cochlear nucleus cells, as there are approximately 36,000 spherical and 6,000 globular bushy cells in the cat cochlear nucleus (out of approximately 50,000 total cochlear nucleus cells). Spherical and globular bushy cells are specialized to preserve the timing of ANF responses. Their characteristic post-stimulus time histogram (PSTH) plots are called primary-like (PL) and primary-like-with-notch (PLN) respectively, as they closely resemble the PSTH of the incoming ‘primary’ ANF. In order to preserve the timing of the ANF and exhibit the two differing response profiles, these cells have several specializations:

- 1) Super threshold EPSPs via extra large surface area synapses
- 2) Brief EPSPs with rapidly desensitizing AMPA receptors (Trussell 1999)
- 3) Spherical bushy receives 1-3 and globular bushy receives 20-50 ANF inputs (Oertel et al 1990, Osen 1970)
- 4) Low threshold (Kv1 family) K^+ currents contributing to short membrane time constants preventing temporal summation and increasing EPSP decay (Perney 1997, Trussell 1999)
- 5) High threshold (Kv3.1) K^+ currents at the soma for re-polarization of large EPSP (Perney 1997)

All of the above specializations have been integrated into a transistor-based model of the bushy cells. The first three specializations have to do with the number, strength and timing of ANF synapses on the model bushy cell. Please refer to appendix section II, figure 1 for a diagram of the proposed circuit model for the bushy cell synapse.

The pulse to the left of the bushy cell synapse circuit diagram represents a voltage spike entering the cell from the ANF. This voltage is converted into a strong current that is mirrored onto a leaky integrating capacitor and the cell membrane. As this input current (divided by the attenuating deactivation threshold $e^{(\text{Deact Thresh})}$) increases above the ‘Deact Tau’ leak current, the capacitor charges up, and the deactivating transistor shuts off. The parameter ‘Deact Tau’ controls the timing of re-activation of the synapse, and ‘Deact Thresh’ controls the magnitude of deactivation. The result is a very short EPSP that deactivates quickly, and reactivates at a rate dictated by ‘Deact Tau’.

Beyond the rapidly deactivating AMPA synapse, the two potassium channels described by Perney (1997) are also included in the model. The Kv3.1 high threshold potassium channel is maximally activated at -30mV and is thought to sharpen the bushy cell action potential at higher frequency stimulation. It activates and deactivates quickly compared to the low threshold channel discussed below. The silicon neuron model described in appendix section 1 utilizes the response of digital architecture to perform a hard reset on the membrane voltage of the cell. This post-spiking, hyperpolarizing conductance is sufficient to bring the depolarized membrane potential back to ground in time for the next stimulation at rates in excess of biological firing rates. If necessary based on future simulations of the bushy cell response, this conduction can be made to appear slower with the addition of an adaptive $K(\text{Ca}, \text{Vm})$ channel to the cell (Hynna and Boahen 2001). The low threshold Kv1 channel described by Perney (1997) required an additional design component be added to the bushy cell model. The Kv1 channel provides a conductance that is active at rest (-70mV) and is responsible for decreasing the EPSP height and duration. This channel activates and deactivates slowly compared to the high threshold potassium channel, yet has a high maximal conductance that tends to hyperpolarize the membrane when fully active. Refer to appendix section II, figure 2 for a circuit diagram of the low threshold Kv1 model.

This low threshold model is a log-domain low pass filter that derives its input (activation) current from the membrane voltage. As the membrane voltage increases, the ‘Activation Current In’ increases beyond the current through the ‘Kv1 Tau’ transistor. At this point, charge collects on the capacitor, increasing the gate voltage of the two vertical output transistors on the left. The ‘Kv1 Thresh’ transistor is configured between the two output transistors such that the three may be viewed as a differential pair. Before the output gate voltages surpass ‘Kv1 Thresh’, current flows from Vdd at the drain of the ‘Kv1 Thresh’ transistor through to the ground of the bottom output transistor. As the gate voltages surpass ‘Kv1 Thresh’, current flows entirely from the membrane node through the ‘K Current Out’ pathway to ground. This threshold mechanism provides a mock delay in the onset of this Kv1 channel, as the low pass filtered version of the membrane current needs to overcome the threshold current before drawing from the membrane voltage.

Complete Bushy Cell Model Current Clamp and PSTH Response

To complete the bushy cell model, these two specialized components are added to the simple integrate and fire neuron described in appendix section 1. The complete model circuit diagram may be found in appendix section II, figure 3. The assembled model has been used to compare response profiles of the model bushy cell types to those profiles described in the literature. Example PSTHs of primary-like and primary-like-with-notch responses are shown below in figure 4. PLN shows a pronounced onset with a repeatable latency followed by a refractory notch generally lasting less than 2ms. After the refractory period, PLN neurons fire irregularly as do their ANF inputs (Rothman et al. 1993). The intracellular recording from a bushy cell is also shown in figure 1. A current clamp was used to pump both positive and negative current into the cell while recording the voltage across the membrane. Notice with positive current stimulation, the cell spikes immediately, followed by a second spike and a maintained depolarization of the membrane potential.

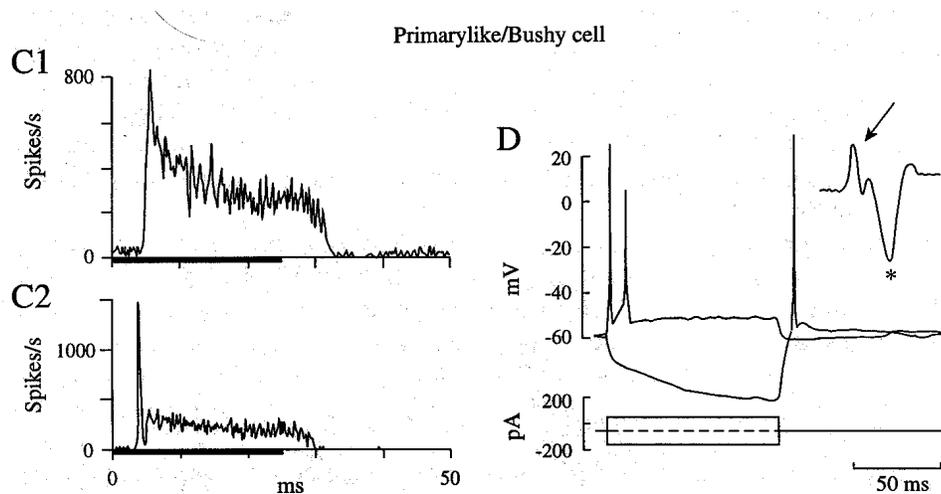


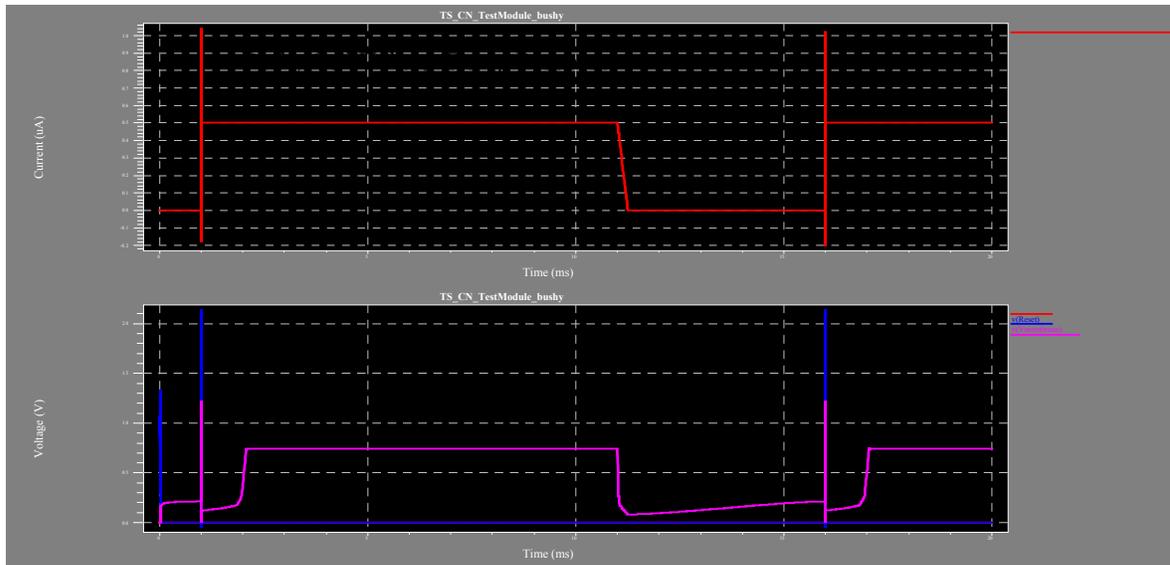
Figure 1: Primary-like and primary-like-with notch PSTH and intracellular recording with current clamp (from Manis and Marx 1991)

Below are simulations of bushy cell current clamp responses and PSTH. The bias values used to achieve the current clamp results are as follows:

Bias (see appendix for circuit diagram)	Bias Value (Voltage)
Vthresh	2
VkTau	0.13
VkThresh	0.6

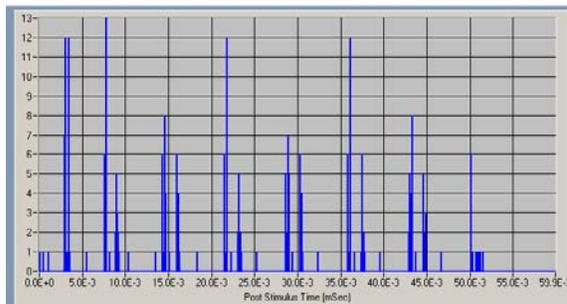
Vleak	0.1
Input Deactivation Tau	1.5
Input Deactivation Thresh	2.4

Current Clamp Results: The rough plot below shows an injected current step (top) and resulting membrane voltage (bottom). The input current was measured through a transistor that reacted to the spiking of the neuron; therefore the spikes observed in the upper graph are artifacts and were not injected into the cell by the stimulating source. The silicon model shows comparable current clamp response, as the onset of the current step lead to a rapid membrane depolarization and spike followed by an elevated membrane potential.

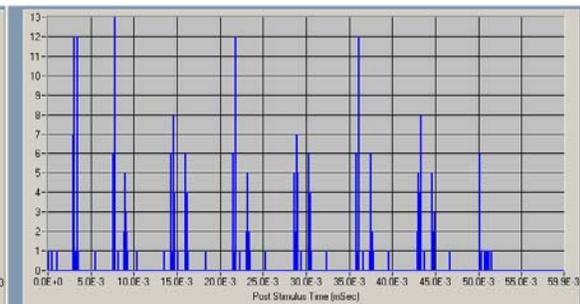


Comparison of ANF response of Spherical Bushy to model ANF (adaptive Si neuron with constant input): The mock ANF PSTH shown on the left is a poor representation of the expected biological response. To the right the silicon bushy cell model shows a similar PSTH response profile. Although this is inconclusive with respect to the ability of the bushy cell model to follow biological data, as a preliminary result this data indicates that the bushy cell is following the ANF input with good temporal resolution. As is addressed in the proposed investigations section of this report, a better model of the ANF PSTH is needed to fully asses the presented models.

Mock ANF PSTH to 50millisecond tone with 10 millisecond refractory period



PSTH of bushy cell with 1 ANF input (PSTH of input to left) PSTH characteristics match as is expected for primary response



Octopus Cell

The octopus cells are also specialized to preserve the timing of the ANF inputs. In the cat cochlear nucleus there are approximately 1500 octopus cells. Instead of locking to an ANF stimulus train like the bushy cells and producing a primary-like PSTH response profile, the octopus is a coincidence detector that fires once at the onset of a moderate intensity broadband sound (Golding, Robertson, and Oertel 1995). Anatomically, octopus cells have four to six large dendrites oriented perpendicular to the iso-frequency axis of the incoming ANF in the ventral cochlear nucleus. The octopus cell dendrites are usually oriented such that the distal ends of the dendrites are in contact with high frequency ANF while the proximal portion of the dendrites and the cell body are in contact with low frequency ANF. The temporal characteristics of the octopus are attributed to similar features found in the bushy cells such as the Kv1 low threshold potassium channel. Following is a list of specializations of octopus cells found in the literature that may contribute to their onset response:

- (1) Briefest EPSPs (sub threshold) found in any cell
- (2) Dendrites span 1/3 tonotopic map with >50 ANF inputs (dendrite tips receive higher frequency inputs) (Golding, Robertson, and Oertel 1995)
- (3) Mixed Cation I_h current that is active at hyper polarization and partially active at rest increasing resting conductance and cell threshold (Bal and Oertel 2000)
- (4) Low threshold (Kv1 family) K^+ currents contributing to short membrane time constants preventing temporal summation and increasing EPSP decay (Perney 1997, Trussell 1999, Bal and Oertel 2001)
- (5) AP seem small (in electrophysiological recordings) as they are initiated in Axon Hillock, not the soma

Overall the octopus cells have a high threshold and low input resistance (high conductance) from a combination of active I_h and Kv1 channels at rest. The hyper polarization activated inward rectifying I_h current has a reversal potential between -25 and -60 mV, and has been quantified as being 41% active at rest (Bal and Oertel 2000). The low threshold Kv1 channel described previously for the bushy cell is again used in my octopus cell model. A new feature for this cell is the I_h channel, which I have found through simulations to increase the firing threshold of the cell. Appendix section III, figure 1 shows a circuit diagram of this channel:

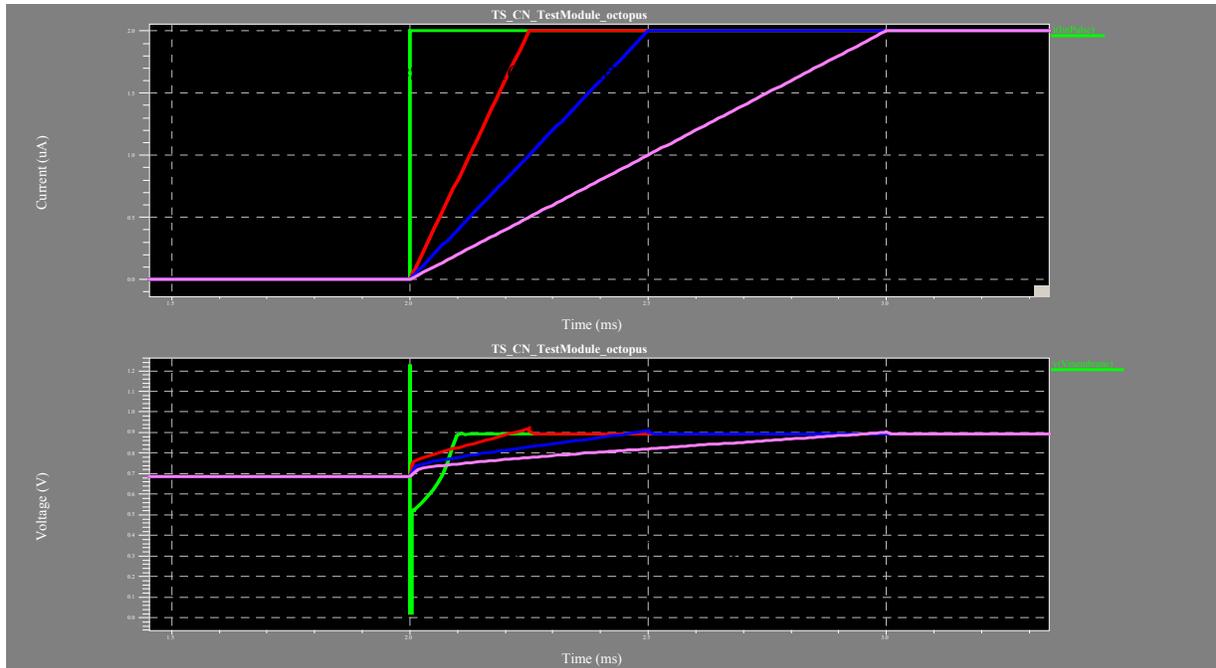
This channel is constructed from a simple log-domain low pass filter that is driven by the membrane voltage. When the membrane is hyperpolarized (ground), the ‘hyperpolarized-active current’ transistor will be turned on maximally, and the charge on the capacitor will decrease opening the ‘Inward Rectified Cation Current In’ transistor. As the membrane voltage increases beyond the threshold set by the ‘Deactivating Current In’ transistor’s gate voltage bias, the charge on the capacitor will increase such that the gate voltage on the output transistor approaches Vdd. The addition of this channel to the cell model increases the cell’s resting voltage, which is determined by the equilibrium achieved between the I_h channel and the Kv1 channel. Therefore, at rest, both the membrane voltage and the membrane conductance are increased. This effectively increases the threshold of the cell as greater EPSCs are required to achieve a significant change in EPSP.

Ferragamo and Oertel (2002), in addition to Cai et al (2000) have stated that octopus cells sense the rate of depolarization and produce their onset response only when depolarized sufficiently quickly. I have simulated current clamp experiments in which the rate of a current ramp increases until the model octopus cell fires an action potential. The results were obtained using the following parameters:

Bias Name (see appendix section 3)	Bias Value (Volts)
Vthresh	1.75
VkTau	0.15

VkThresh	0.6
Ih_Off_Thresh	0.6
Input Current Max	2microAmps
Input Current Rise Time	1, 250, 500, and 1000microSeconds

Below are low-resolution plots of input currents with differing rise times (top) vs the membrane voltage associated with each input (bottom). With the given bias settings, this octopus neuron only spikes when the input current has a rise time of 1 microsecond. At zero input current, the membrane voltage is stable at a depolarized voltage of 0.65 milliVolts above ground.



Proposed Investigations

Creating a large-scale silicon model of the cochlear nucleus presents several engineering challenges, although the driving force behind this modeling effort is to better understand the biological auditory system. Three stages of investigations are therefore proposed to address both the engineering and biological components of this work. The stages are as follows: 1) modeling of all components of the cochlear nucleus with transistors and fabrication of an actual cochlear nucleus chip, 2) validation of individual neurons of the chip against biological data, 3) hypothesis testing using the chip as a validated, large-scale model of the cochlear nucleus. These three stages are described in detail below.

Modeling all components of the chip is an engineering intensive stage of the proposed investigations and will follow the format described in the pilot study. The preliminary investigations described in the previous section represent first order approximations and evaluation of the intrinsic information processing units of the cochlear nucleus. These particular cell types were chosen as preliminary models to exemplify how the biologically inspired, neuromorphic design process can dictate an individual neuron's design. The three cell types explored constitute three of six cell types in the cochlear nucleus that have outputs to other parts of the auditory system. These three types were

chosen, because they are all strictly intrinsic information processors (only receiving synaptic input from the auditory nerve).

The preliminary results displayed in this proposal reveal there is more work to be done to accurately model the bushy and octopus cells. In particular, a more valid model of ANF output is necessary to qualitatively assess the PSTH of each of these cell types. The primary criticism of the work already done is that it has not been scrutinized against biological data enough at this point. What has been presented are early versions of cell models that will surely become revised to increase their accuracy in matching the responses found in biology.

The extension to the described pilot study is to design and test models of all intrinsic processing units in the cochlear nucleus. This modeling effort will include those cell types that do not provide output to other auditory nuclei and are only involved in local networks of the cochlear nucleus. After development, testing, and refinement of all intrinsic processing units, extrinsic processing units will be designed utilizing both ANF and local neuron synaptic inputs to shape the response profiles of those cell types. As stated in the aims and objective section, the proposed cochlear nucleus chip is to have local interconnections hard-wired onto the chip. After transistor models have been designed and simulated, the full cochlear nucleus large-scale model will be fabricated on silicon via a private company (MOSIS, Marina Del Ray, CA).

Validation of individual neurons of the chip against biological data provides opportunities for a greater understanding of the functioning of the engineered model as well as the biological cells that are being modeled. The primary tools for validation of the model are those tools used by neurobiologists to quantify the response properties of cells in the cochlear nucleus. In the preliminary investigations section, the Peri-Stimulus-Time Histogram and current clamp data were used to assess how well the intrinsic cell models captured features of their biological counterparts. Extrinsic processors, those that rely on local network connectivity to form their response profiles, are generally assessed using tuning curves that show the strength of the neuron's response for different intensities and frequencies of pure tones (Young 1980, Young and Voigt 1982). Therefore a significant amount of validation simply requires stimulation of the silicon cochlea with pure tones at various frequencies and intensities. A large variety of more sophisticated acoustic stimulants have also been used in the literature to study more specific aspects of various acoustic neurons. These studies utilize complex tones composed of two or more simple tones, amplitude modulated tones, frequency sweeps, spectrally filtered noise, and speech (Young 1998 discusses a wide range of these stimuli).

Whatever acoustic stimuli is used in the biological literature to create PSTHs, tuning curves, or other response assessments for the various cell types of the cochlear nucleus can be used to stimulate the silicon cochlea and silicon cochlear nucleus as well. Model validation is in general a comparison of the various reported biological responses versus silicon cochlear nucleus responses originating from the same acoustic stimuli. Validity may be quantified by statistical evaluation of the model's response against biological data. Initially, this statistical evaluation will be used to compare all features of the data sets under scrutiny (differences in peak amplitude, differences in plasticity, ect). As system level analysis of the cochlear nucleus chip and further auditory chips are made, identification of the important features of such a statistical evaluation can be made. This means that the statistical tests used in model validation will be refined as they become better understood in the context of overall auditory processing.

After being created and validated, this model will be used to test the following hypothesis: the cochlear nucleus enhances auditory information in a way that is crucial for later processing of four particular auditory processing tasks; vertical sound localization, ITD, ILD, and pitch perception. Sound localization (including ITD and ILD) and pitch perception are heavily researched topics in the auditory system that are addressed in the following reviews (Konishi 2000, Cariani 1999). Testing the above hypothesis involves evaluation of various aspects of cochlear nucleus information processing that are believed to be significant contributors to the formation of these two percepts. The cochlear nucleus chip alone can be used to test the above hypothesis as the outputs of the chip can be recorded and evaluated to extract out the information conveyed by various pathways on the chip.

Additionally, as further components to the auditory system are modeled in silicon, the functional relevance of the cochlear nucleus to these specific auditory tasks can be more directly assessed (for example by connecting the cochlea directly to upstream components associated with sound localization or pitch perception).

The stated hypothesis may be broken down into four more specific components that will be independently tested. 1) Specific dorsal cochlear nucleus neurons have “spectral notch filter” responses that are crucial for vertical sound localization as they process information imparted by the transfer function of the outer ear’s pinna. 2) Spherical and globular bushy cells of the ventral cochlear nucleus show enhanced phase-locking (over ANF) to the acoustic signal that is crucial for ITD sound localization. 3) Specific cochlear nucleus neurons enhance ANF input to create monotonic, non-saturating rate-intensity functions over a wide range of acoustic intensities that are crucial for ILD sound localization. 4) Various cochlear nucleus cells have enhanced responses to amplitude modulated acoustic stimulation that is crucial for pitch perception formed later in the auditory system. Theoretical testing of the above hypotheses involve information theory in conjunction with statistical assessment of what auditory processing functions are lost when various cells are omitted from the cochlear nucleus. As stated above, these theoretical analysis used to test the hypothesis will eventually be complimented with data collected from a more complete silicon auditory system model, one that has all the necessary components for sound localization and pitch perception.

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Appendix Contents:

Section Ia: Innervation of the cochlear nucleus, cell type distributions, and local networks

Section Ib: Basic overview of MOS-FET transistors and the silicon neuron:

Section II. Bushy Cell Circuit Diagrams and Response Profiles

Section III: Octopus Circuit diagrams and response plots

Section IV: Review of cochlear nucleus models in the literature

Section Ia: Innervation of the cochlear nucleus, cell type distributions, and local networks

The auditory nerve fiber (ANF) enters the CN between the anteroventral cochlear nucleus (AVCN) and posteriorventral cochlear nucleus (PVCN) where it bifurcates (Osen 1970). The caudal branch forms boutons and terminates in the AVCN. The dorsal branch innervates the PVCN via boutons then travels up to the dorsal cochlear nucleus (DCN) where it terminates. The cochlea is arranged tonotopically, as the base is most sensitive to high frequency acoustic stimuli and the apex is sensitive to low frequency acoustic stimuli. Tonotopic organization is preserved throughout the CN, as the more medial and dorsal fibers carry signals collected from the more basal parts of the cochlea. Figure 1 illustrates the CN and its innervation by the ANF.

The principle cells in the CN are defined as those whose outputs are the efferent connections of the CN to the next stages in the auditory system (Young 1998). A few principle cells double as interneurons as they have axon collaterals that terminate within the CN. All principle cells in the CN receive direct inputs from the ANF, and a few non-principle interneurons receive inputs from the ANF as well.

Figure 1 illustrates the distribution and diversity of cell types throughout the cochlear nucleus (from Osen 1970). The cell types may be loosely classified by their location in the various CN subdivisions. The AVCN principle cells are spherical and globular bushy cells. The PVCN principle cells are multipolar cells, and octopus cells. The DCN contains a variety of interneurons and two principle cells, the pyramidal cells and giant cells. The DCN interneurons include vertical, granule, cartwheel, unipolar, stellate, chestnut, and golgi cells. Throughout the CN, granule cells permeate the outer layers but are most numerous in the DCN. Small cells too are found throughout the entire CN.

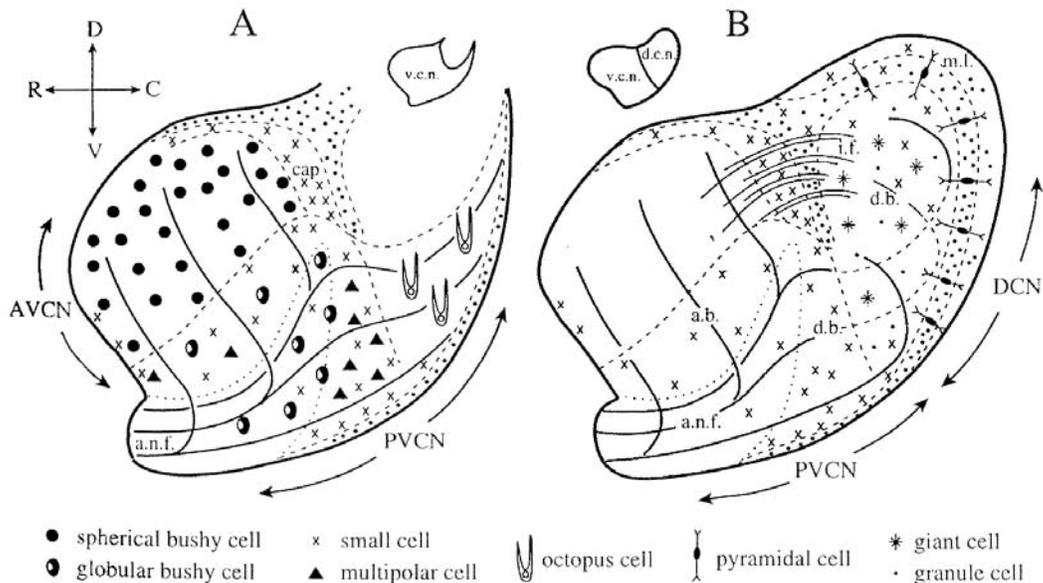


Figure 1: Cochlear nucleus schematic with ANF fibers and cell type locations (from Osen 1970)

Architecture of DCN

The DCN is partitioned into four anatomical layers. Figure 2 is a representation of an approximately isofrequency slice of the DCN showing the cell types and morphologies within (from Osen. et al 1990). The most dorsal layer (layer 1) is called the molecular or superficial layer. This layer contains the cell bodies of the cartwheel cells, the axonal projections of the granule cells, and apical dendritic branches of the pyramidal cells. The axonal projections of the granule cells make up what are called parallel fibers in this layer, which are orthogonal to the isofrequency sheet shown in figure 2. Layer II, the pyramidal layer, contains the cell bodies of the pyramidal cells of the DCN and most of the granule cell bodies. Granule cell bodies are also found in the other layers of the DCN. Layer III and layer IV are called the deep DCN. Vertical cell bodies are found in layer III, along with giant cell dendrites and pyramidal basal dendritic trees, which are relatively flat and contained with a narrow band of frequencies. Layer IV contains the giant cell bodies.

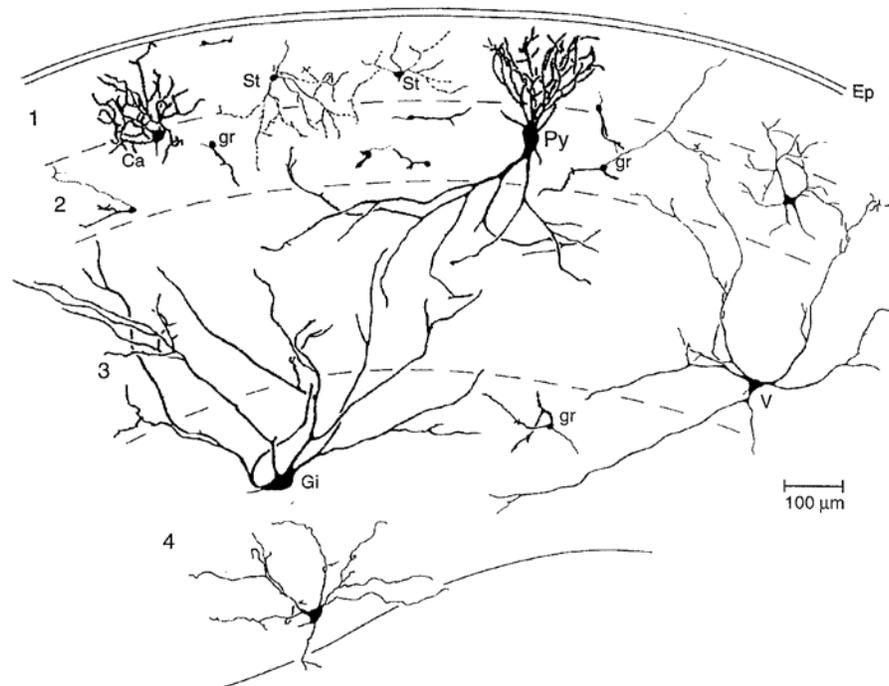


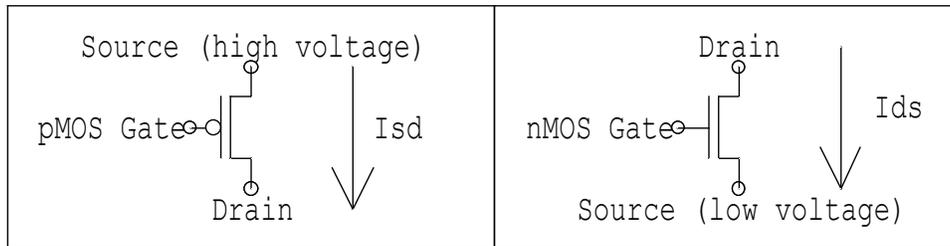
Figure 2: Dorsal cochlear nucleus layered structure and cell types in a plane approximately parallel to an isofrequency sheet; granule cell axons run perpendicular to the page in layer 1 and ANFs would run within the page mainly in layer 3. The free surface of the DCN is at the top (Ep); layers are numbered at the left. Abbreviations: Ca, cartwheel cell; Gi, giant cell; gr, granule cell; Py, pyramidal cell; St stellate cell; V, vertical cell. Some unidentified cell types are shown unlabeled (from Osen et al 1990)

Section Ib: Basic overview of MOS-FET transistors and the silicon neuron:

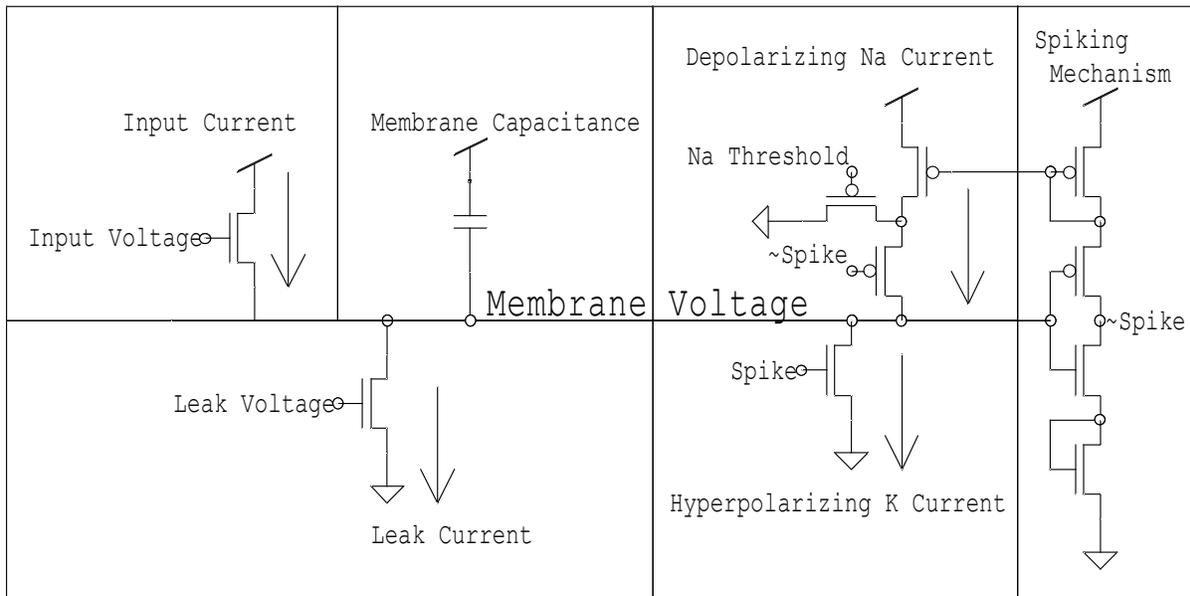
Complimentary Metal Oxide Semiconductor (C-MOS) design will be used to implement the neuron models making up the silicon cochlear nucleus. Two Metal Oxide Semiconductor Field Effect Transistors (MOS-FET) types are available with this process, n-MOS and p-MOS. These are three terminal devices in which the voltage applied to the gate (V_g) governs the amount of current that can flow between the drain and source (I_{ds} for nMOS and I_{sd} for pMOS). Given the voltage and current

levels dealt with in this design process, the I_{ds} currents are generally considered sub-threshold. An additional simplification can be made to the sub-threshold current equations by assuming that the transistor is in saturation, which for the purposes of this brief introduction is a reasonable assumption to make. The combination of these two operating ranges dictates that the relationship between I_{ds} , and the gate and source voltages follow an exponential equation as described below:

$$\begin{aligned} \text{nMOS:} \quad & I_{ds} = (w/l) * I_0 * \exp[(\kappa V_g - V_s)/u_T] \\ \text{pMOS:} \quad & I_{sd} = (w/l) * I_0 * \exp[-(\kappa V_g - V_s)/u_T] \end{aligned}$$



For nMOS transistors the source voltage, V_s , is low (frequently zero, or ground). As V_g increases from zero, the current flowing from the drain to the source increases exponentially. PMOS transistors have an opposite reaction. PMOS V_s is generally V_{dd} , or the highest voltage on the chip (2.5 volts for the .25 micron process used in the Neuroengineering Penn lab today). As the pMOS gate voltage *decreases* from V_{dd} , the current flowing from source to drain increases exponentially. The two figures above depict a pMOS transistor on the left and a nMOS transistor on the right. The difference in notation between the two is the pMOS gate has a circle above it while the nMOS gate does not.



Above is a diagram of a simple integrate-and-fire neuron in silicon. Included in this simple model is an input current, a membrane capacitance, a leak current, and a spiking mechanism complete with a depolarizing Na^+ conductance and hyperpolarizing K^+ conductance. Basic operation of the neuron is as follows: At rest, with the membrane voltage at ground, the output of the spiking mechanism is high (nMOS gate is closed and pMOS gate is open). When the input current exceeds the leak current, charge builds up on the membrane capacitor linearly increasing the membrane voltage. As the membrane voltage increases, current flows down through the spiking mechanism to the right. This is a result of the middle ground between the nMOS turning on and the pMOS turning off. This transition current is ‘mirrored’ into the depolarizing Na^+ current section and when overcoming the Na threshold onto the membrane capacitance. This causes a rapid increase in the membrane voltage completing the transition from rest (Gnd) to depolarized (some large fraction of Vdd). As a result of this transition, the node labeled ~Spike has gone from high (Vdd) to low (Gnd) and signals digital communication on the chip that this neuron has spiked. The chips response to this signal is to set the node labeled “spike” to Vdd, which quickly pulls charge from the membrane capacitor and returns the membrane voltage to the resting potential ground.

Section II. Bushy Cell Circuit Diagrams and Response Profiles

Figure 1: Bushy Cell Synapse Circuit Diagram

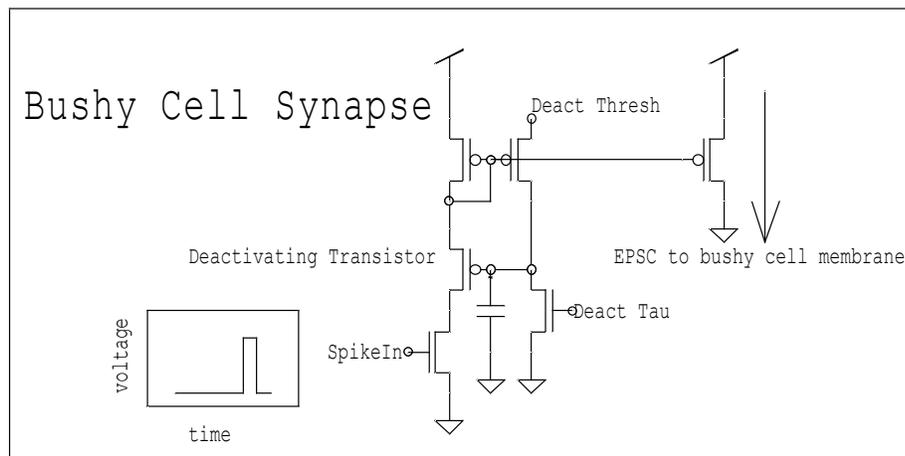


Figure 2: Low Threshold Kv1 Circuit Diagram

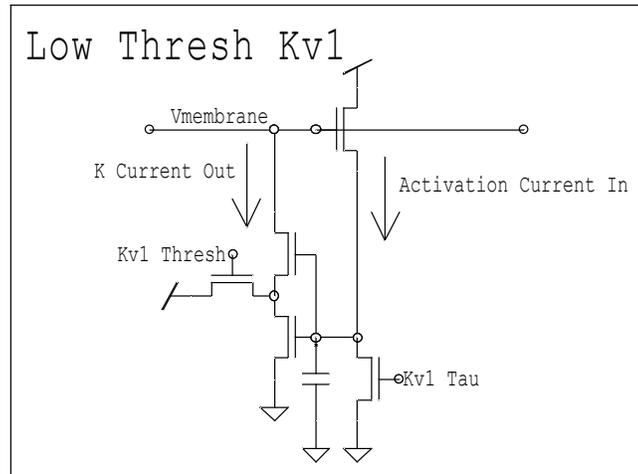
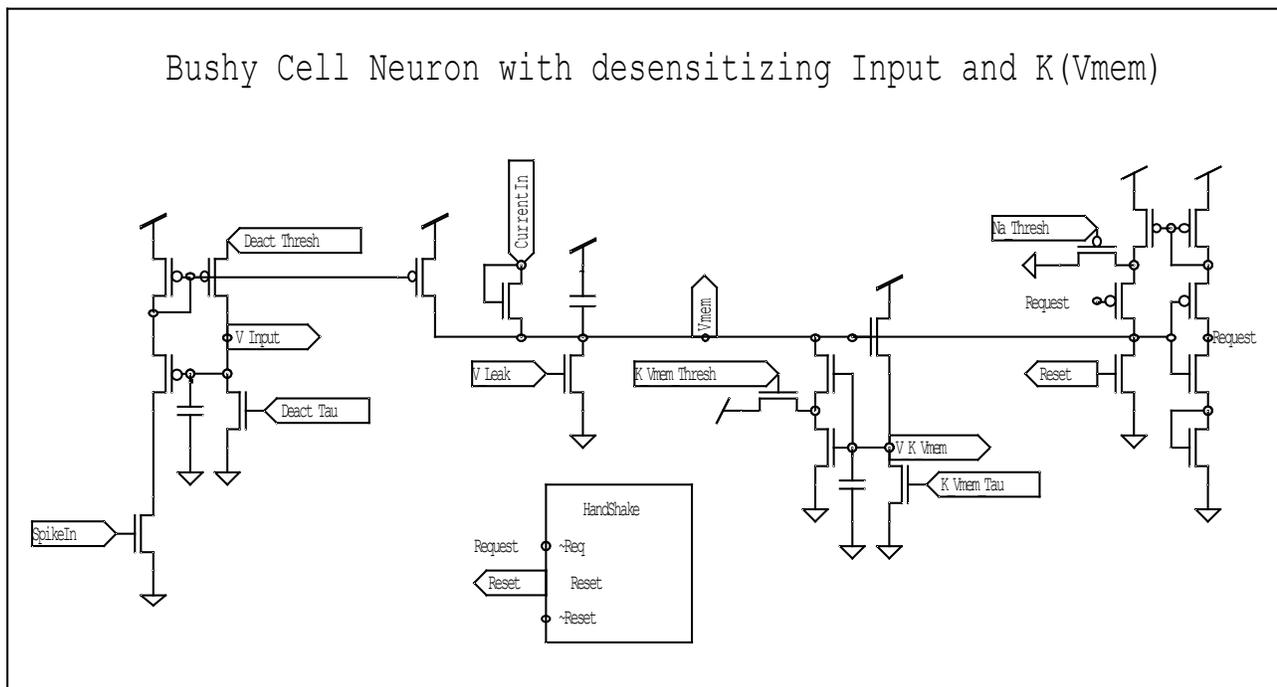


Figure 3: Complete Bushy Cell Circuit Diagram with Labeled Bias Nodes



Section III: Octopus Circuit diagrams and response plots

Figure 1: Hyperpolarized-active mixed cation Ih channel circuit diagram

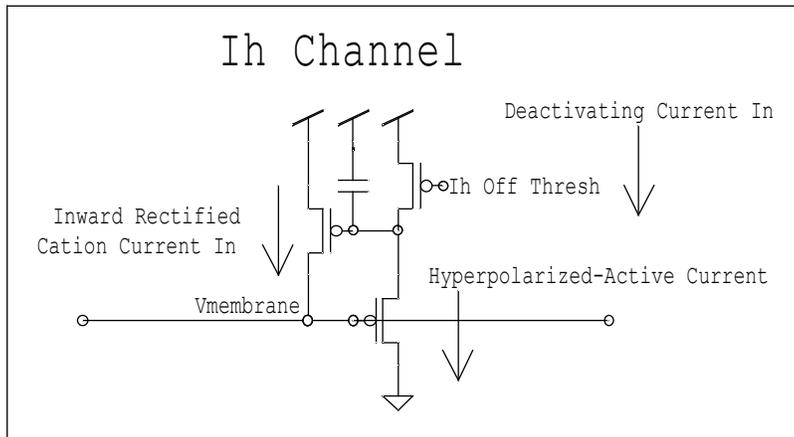
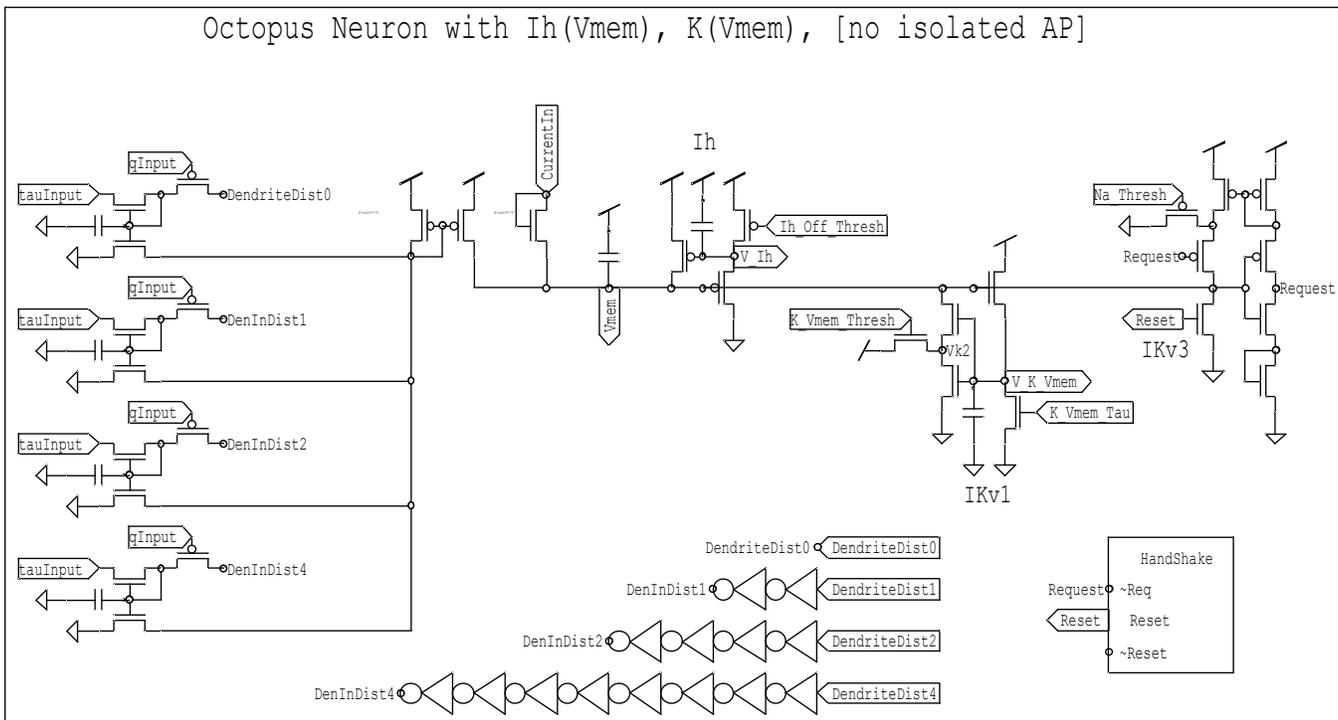


Figure 2: Complete Octopus Cell Circuit Diagram with Labeled Bias Nodes



Section IV: Review of cochlear nucleus models in the literature

This appendix section addresses the question of what previous modeling efforts have been cited in the literature. The types of models found may be categorized into three groups; channel models, cell models, and network models. The channel models generally come from electrophysiologists who are trying to fit a line to discrete points of patch clamp data from isolated

membrane channel types. Cell models are the most predominant model type of the cochlear nucleus. Generally these are computer-simulated models, and they are used to test hypothesis about the significance of synaptic strength and membrane channel conductances in shaping the cells overall output. Network models are used primarily to describe the output of dorsal cochlear nucleus cells. All the network models I have found in the literature use no more than three cells interacting together. One network model, consisting of 32 silicon neurons, uses a common input for all 32 neurons, and lacks interconnections between the cells (hence they are not interacting with each other). Therefore, the cochlear model that I propose, with parallel processing of different frequencies in populations of both ventral and dorsal cochlear nucleus cells is unique with regards to published work.

Channel models in the cochlear nucleus are primarily equations that are fit to biological patch clamp data. The current-voltage and current-time data recorded during patch clamp experiments are discrete points that show a certain degree of variability or noise due to limitations in equipment and/or experimental conditions. As such is it desirable to describe the relationship between current, voltage, and time using mathematical equations that can be used to extrapolate points not recorded during the experiment. Additionally, simplifying the data with a descriptive equation may provide insights into the nature of each channel, and how different conductances in the cell relate.

Two representative examples of channel modeling efforts may be found in Manis, P.B. and Marx, S.O. (1991), and Bal, R., and Oertel, D. (2000). Manis and Marx describe the low threshold potassium conductance found in several cell types of the cochlear nucleus. Figure 1 is a plot of current traces (left inset) that were used to construct the current-voltage curve found in the center. The data points are overlaid with three smooth traces that exemplify the modeling effort of this paper. Bal and Oertel (2000) similarly describe patch clamp data using mathematical equations. In particular, the I_h - inward hyperpolarizing mixed cation current found in octopus cells, is characterized by the sum of two exponentials during activation and a single exponential during inactivation. The time constants of activation and inactivation are then readily compared with respect to voltage as seen in the right side of figure 2. Both of these channel modeling papers fit patch clamp data with relatively simple mathematical expressions in order to both simplify the raw data, and gain insights into the channel functionality over a wide range of operating conditions.

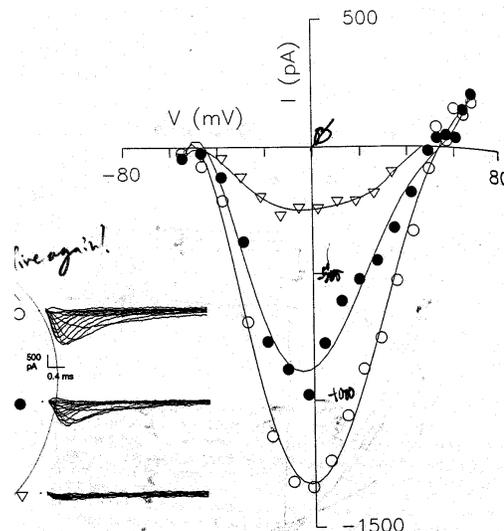


Figure 1: Current traces at different voltage steps on the left are used to construct the current – voltage plot shown on the right. Curves modeling the current – voltage relationship may be used to extrapolate values not observed in the data. From Manis and Marx (1991)

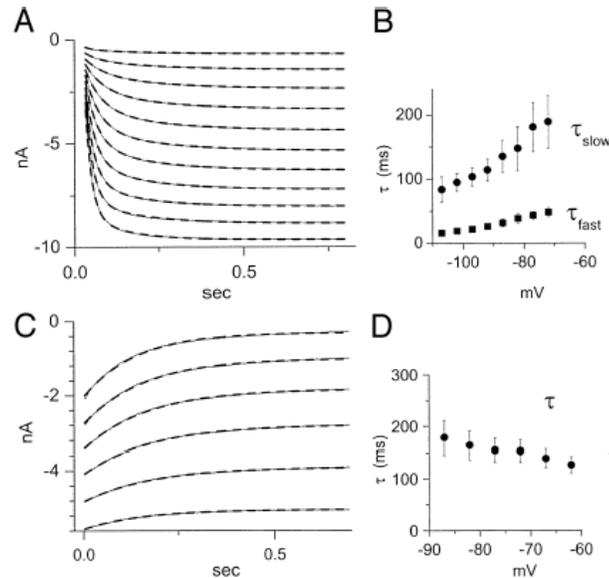


Figure 2: Fitting activation and inactivation of I_h current in octopus cells (A and C) that allows for visualization of time constant vs membrane voltage (B and D). From Bal and Oertel (2000)

The predominant modeling effort pertaining to ventral cochlear nucleus cells found in the literature is computational cell models. Computer models range in complexity from 1 to more than 80 compartments per cell. Generally, cell models are used to explore the contributions of various membrane conductances and dendritic low pass filtering to the overall output of different cell types. Anatomical and physiological data are used to define the primary components of the cells (i.e. what channels are found in a certain cell type and the predominance of dendritic vs somal synaptic inputs) but the conductances characterized with patch clamp data are not used directly. In addition to the variation in complexity of cell compartments, the cell models vary in their instantiation of synaptic input. Some models emulate stimulation of cell with direct depolarizations, where others use sound pressure inputs into detailed models of outer, middle and inner ear, connecting to the cochlear nucleus cell of interest via model spiral ganglion cells.

Two representative examples of computational cell models come from Banks and Sachs (1991) and Cai, McGee, and Walsh (2000). Banks and Sachs used 1 and 12 compartment models to test hypothesis about the primarylike and chopper responses respectively. Each compartment consisted of a simple membrane circuit model of a capacitor in parallel with several different conductances. Figure 3 shows the circuit schematic and computed outputs of these two cell types. By modulating the relative strengths synaptic inputs and membrane conductances, Banks and Sachs concluded that the primarylike response is heavily dependent on a strong depolarization to an incoming spike. Their chopper cell model, with a single-compartment axon, single-compartment soma, and ten-compartment dendrite, lead them to conclude the low pass filtering of the dendrite coupled with a regular firing mechanism in the soma created the chopper response despite the randomness of the inputs to the cell.

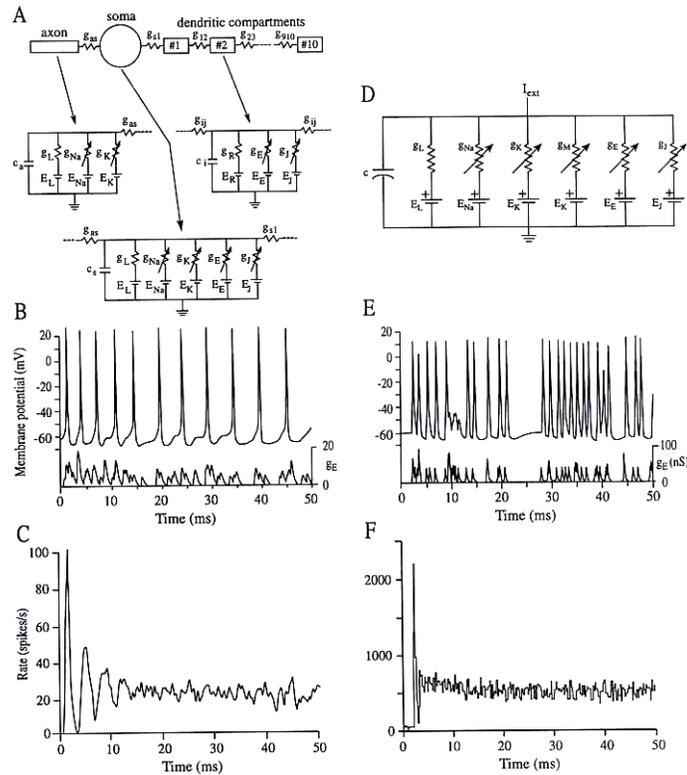


Figure 3: Chopper (left) and primarylike (right) cell models. The top images (A and D) show the circuit model for each cell type. The middle plots show membrane voltage versus time and excitatory conductance vs time for the model. The bottom plots are PSTHs from each of the models. From Banks and Sachs (1991)

Cai, McGee and Walsh used an 82 compartment octopus cell model to test hypothesis about the significant of the I_h (inward hyperpolarizing mixed cation) current to octopus cell characteristics. This modeling paper addresses observations of input depolarization rate vs octopus cell firing made by Bal and Oertel in 2000 (also addressed in the octopus cell model from this proposal). Cai, McGee and Walsh's model uses similar functional blocks as Banks and Sachs, a simple circuit model of the membrane, with a membrane capacitance and a set of conductances in parallel. These units are connected resistively in series in order to make up the four separate, twenty compartment dendrites of the model octopus cell. The primary variable that was tuned in this model was the I_h conductance, which was found to be necessary for the cell to function as a high pass, or onset response type, filter.

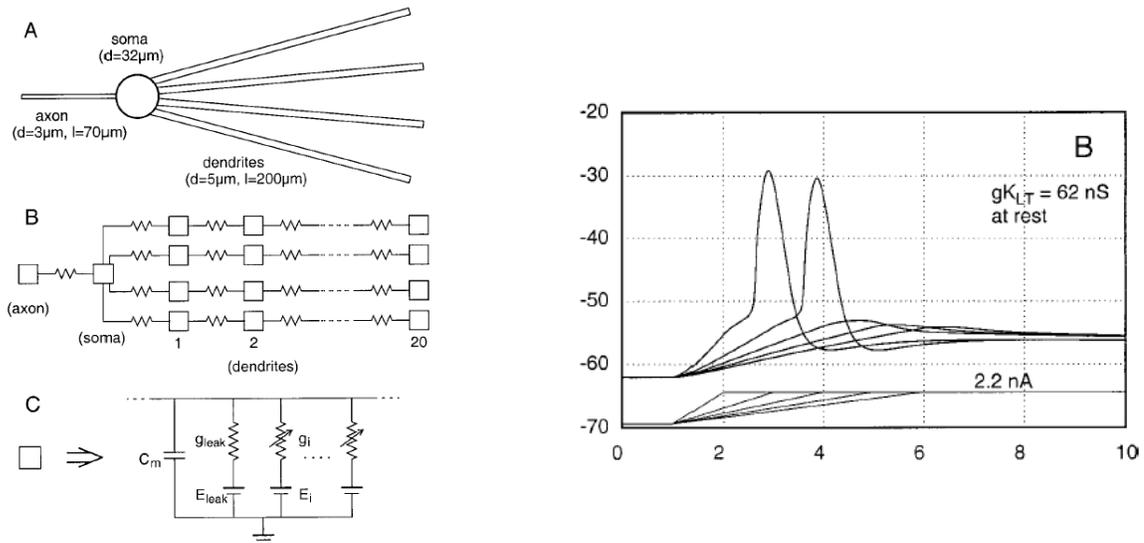


Figure 4: Octopus cell model components and response. Left images show abstractions of the model from anatomy (top) to the individual compartment circuit diagram (bottom). The right shows the model's performance in the depolarization rate vs firing experiment that was initially performed by Bal and Oertel (2000) during patch clamp experiments. From Cai, McGee, and Walsh (2000)

Network modeling is the category that my proposed cochlear nucleus chip falls into. Most of the network models proposed in the literature are used to describe the output characteristics of various dorsal cochlear nucleus cell types, although some ventral cochlear nucleus cell responses have been described using network models in the literature as well. For the most part the models are software simulations or just qualitative descriptions of possible connectivity, although one deviating network model was designed in silicon. I have not found a model in the literature that considers more than three different cochlear nucleus cell types at one time, or that simulates the response of a single cell type across multiple stimulation frequencies in parallel.

Two examples of network level models in the ventral cochlear nucleus are those of Schaik (1991) with 32 identical neurons in silicon, and Eriksson and Robert (1999) with a three cell type model explaining stellate cell responses. Because his model is in silicon, Schaik's model is particularly relevant to compare with the cochlear nucleus model that I propose. He has fabricated a set of 32 generic neurons in $1\mu\text{m}$ technology shown in figure 5 (as opposed to the $.25\mu\text{m}$ technology that Dr. Boahen's lab is currently using). The model does not include a cochlea, but does include inner hair cells that half wave rectify an incoming sinusoidal stimulation. The output of the hair cell is modeled as an EPSC that is distributed identically to all 32 neurons. Additionally, a single set of biases controls all of the neurons' conductances and time constants. The result is an array of identical neurons (less variation due to fabrication 'noise') that are stimulated by the same input. Schaik varies the excitatory, leak, potassium, and sodium maximum conductance amplitudes in order to make the output of the generic cell resemble that of chopper, primarylike, and onset cells. The ion channels and synaptic connectivity that are specific to each of these cell types (stellate, bushy, and octopus cells respectively) is not taken into account in the design of this chip. Only PSTHs, the averaged spike output, are compared between the model and biological responses. Much recent work has exemplified the importance of membrane channels on shaping the membrane voltage and spiking activity of various cochlear nucleus cells (Bal and Oertel 2000, Trussel 1999, Young 1998). As Schaik's model does not take into account the specialized conductances of the different ventral

cochlear nucleus cells, it can be expected that the membrane voltage of his model cells do not correspond well to that of the biological cells, which may ultimately effect the accuracy of the models spiking output when stimulus conditions are varied.

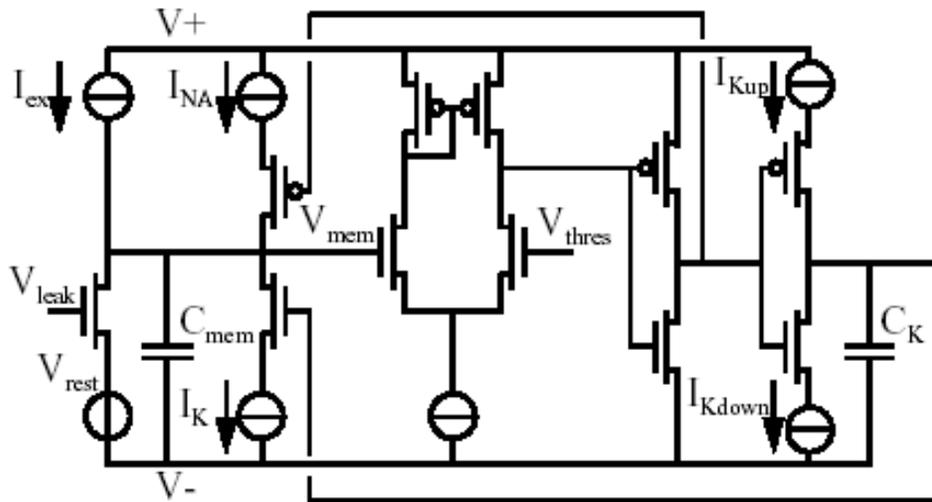


Figure 5: Generic silicon ventral cochlear nucleus cell model in silicon. As excitatory current dumps onto the membrane capacitance (C_{mem}), V_{mem} raises eventually passing V_{thres} . This causes the output of the first inverter to switch low, turning on the positive feedback of the sodium conductance while charging up the potassium capacitor (C_K). When the voltage on C_K becomes sufficiently high, I_K repolarizes the membrane by pulling down V_{mem} . The magnitude V_{leak} , I_{na} , I_K and I_{ex} are the primary variables used to adjust this generic neuron's PSTH to look like that of onset, chopper, and primarylike responses. From Schaik (1991).

In 1999, Erikson and Robert proposed a three cell network model to describe the output characteristics of ventral cochlear nucleus stellate cells. Their computational model includes sophisticated outer, middle, and inner ear components ultimately driving the auditory nerve inputs into stellate, multipolar-II and tuberculoventral cells types. As seen in figure 6, the auditory nerve drives all three cell types with excitatory synapses, while the multipolar-II and tuberculoventral cells drive the other two cells with inhibitory synapses. This model is used to explain the deterioration of the chopping response of stellate cells over time. Single cell models of choppers (such as that by Banks and Sachs described above) attribute the attenuation of the chopping response over the course of the 20 – 50 msec of a PSTH to the averaging out of minute variations in the chopping interval from one stimulus presentation to the next. The regularity is enough to see a clear chopping response initially, but as time goes on from the onset of the stimulus, minor variation in chopping frequency eventually get successive trails out of phase causing the PSTH to become flat. Erikson and Robert instead propose that the attenuation of the chopping response comes from inhibitory inputs that are delayed relative to the auditory nerve fiber input directly into the stellate cell. Two and three compartment models of multipolar-II and stellate cells respectively are used in the computational model that is based on the MacGregor model with added conductances. The network model is used to test hypotheses regarding the effects of noise on the tonal response of stellate cells. The primary variable adjusted in this model is the synaptic strength of the two inhibitory inputs onto the stellate cell. They concluded that this three cell circuit model could reasonably account for the noise tolerance observed in stellate cells of the ventral cochlear nucleus.

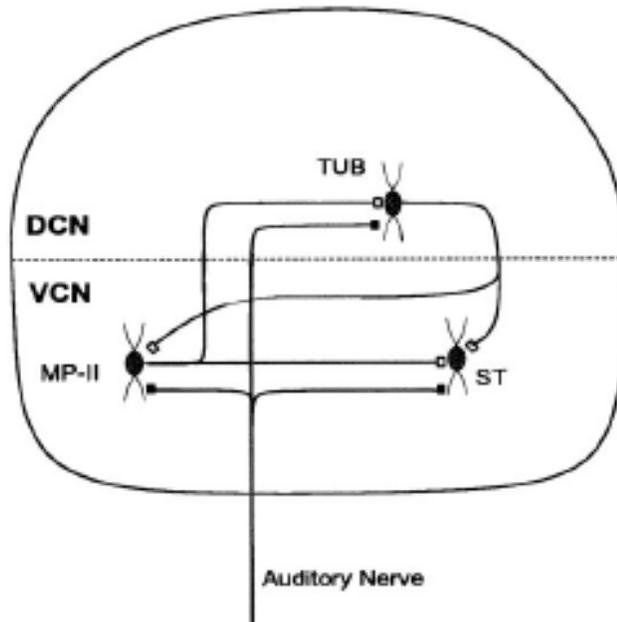


Figure 6: Network model used to describe stellate cell outputs. Auditory nerve fibers (ANF) synapse on all three cell types included (stellate, multipolar-II, and tuberculoventral) which form a recurrent network. Excitatory synapses are filled circles, and inhibitory synapses are open circles. From Eriksson and Robert (1999)

I have presented the three classes of cochlear nucleus models found in the literature today. All three classes of models provide insights to the working of cochlear nucleus neurons ultimately aiding in my design of the complete cochlear nucleus in silicon. The channel models that describe patch clamp data using mathematical expressions is paramount to the development of a individual cochlear nucleus cell models that I propose for my model. One flaw to these models is they are not formed from in vivo data, as patch clamps of cochlear nucleus cells is too challenging in vivo, and are thus preformed in slice preparations. As such, the dependence on temperature of the various membrane conductances described with these models needs to be considered carefully. The cell models are also elucidating in their use of dendrite synaptic connections and various channel conduction strengths. My silicon models are implemented in a substantially different form than these simple resistor cascaded membrane units (as in figure 3 and 4), and as such, it is more reasonable for me to base my design from raw data and membrane channel models rather than the current cell models described. Despite this, the cell models provide insight by exemplifying the relative significance of various components to the overall output of each cell type. The network models described above also aid in my design process, by indicating potential network connectivity to be implemented in my silicon model.

Overall, the model I propose is radically different than all existing models. The silicon cochlea currently in development in Dr. Boahen's laboratory can be used to address the details of the outer, middle and inner ear found in some models. The specific design of each cochlear nucleus cell type allows me to take advantage of what is known about cochlear nucleus membrane conductances so that I may more accurately model the membrane voltage of each cell type as opposed to just the PSTH (as is done by Schaik, 1991). Having multiple copies of each cell type being stimulated in parallel by their respective auditory nerve fiber inputs will provide the first large scale parallel view of cochlear nucleus function across the audible frequency range. The division of multiple frequencies

among the various cell types in parallel will likely be essential for computation of upstream auditory features such as pitch extraction, sound localization, and speech perception. Therefore my proposed model not only differs significantly from all forms of current models present, it will allow for development of the greater auditory pathway in silicon which itself will provide a large scale platform for understanding the functionality of this sophisticated neural system.