Modeling and Simulation of the Auditory Pathway

TECHNICAL REPORT

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1 Abstract

Our objective is to develop a detailed, physiologically-based cellular computational model of the human auditory pathway. The model, once fully developed and validated, will aid in studies that target underlying mechanisms of auditory processing disorders. Several cellular models do exist that describe an individual neuron response to auditory stimuli. A combination of these cellular models with synaptic interaction could accurately reproduce auditory brainstem responses similar to those previously recorded. This report briefly reviews the relevant cellular models and assesses the practical application and feasibility of each model to our project goals.

2 Introduction

Models of auditory processing are usually constructed to either represent the results of a variety of experiments or explain the function of a given system. These models aid in generating hypotheses that can be later tested experimentally. Several types of models exist: biophysical, physiological, and mathematical. Biophysical and physiological models attempt to replicate a given behavior through accurately modeled mechanisms, while mathematical and phenomenological models recreate observed behaviors through mathematical modeling schemes that not usually physiologically based. The former modeling scheme allows for better insight on the underlying mechanisms that drive these observed behaviors but relies on the accuracy of experimental data. Furthermore, these models can be computationally difficult to implement. The latter type of model can be designed to be faster and more efficient at the cost of anatomical and physiological accuracy. There are several auditory processing models that employ either or both schemes. However, most of the existing auditory processing models simulate experimentally observed behavior of the auditory system without explicitly modeling the intrinsic and synaptic mechanisms that underlie this behavior.

The goal of this research is to create a composite computational model that can recreate the experimentally observed behavior of the auditory system and accurately describe the underlying biophysical mechanisms. This can be achieved by integrating cellular models of various types of neurons. Cellular models are chosen by their anatomical and physiological features and are added accordingly. This is advantageous as existing cellular models can be easily modified to represent various processing centers of the auditory system.

The existence of accurate biophysical parameters and mechanisms at each processing stage of the auditory pathway allows one to easily modify or change certain parameters to reflect current and future experimental findings in literature. In addition, one can compare the model responses to changes in model parameters to those observed experimentally. In this way, the model may be useful in identifying the possible anatomical and physiological origins of certain auditory disorders. This could
lead to targeted experimental studies that could lead to more efficient and effective forms of treatment.

Prior to the construction of this model, an exhaustive review of the existing physiologically-based neuron models of the auditory system is needed. This study will compare and review the relevant modeling studies for each structure in the auditory pathway, and the practical application of each cellular model to the composite model will be assessed.

3 Background

Biophysical neuron models

Biophysical and physiological models attempt to replicate a given behavior through accurately modeled mechanisms. This allows for better insight on the underlying mechanisms that drive the experimentally observed behavior. For neuron modeling, there have been several modeling schemes that have been used and are described in the following review. A brief description of these neuron model types is given below.

Integrate and Fire

One of the earliest neuron models is the integrate-and-fire neuron. The neuron responses are represented by the time derivative of the membrane potential, the membrane capacitance, and the input current. The equation that governs the model is described as follows:

\[
I(t) = C_m \frac{dV_m}{dt}
\] (1.1)

When an input current is applied, the membrane potential increases until a constant threshold value \( V_{th} \) is reached and an action potential “spike” occurs. The voltage is then reset to its resting potential. A refractory period can be added to limit the firing frequency of the neuron by preventing any spiking to occur within this set period. In addition, a “leak” current is added to reflect the diffusion of ions that occurs within the cell membrane to reach equilibrium. While a useful model to investigate responses due to varied synaptic inputs, the integrate-and-fire model lacks intrinsic properties that can alter and modulate the neuron response.

Hodgkin-Huxley

The Hodgkin-Huxley model is one of the most successful neuron models. This model was originally developed in 1952 by Alan Lloyd Hodgkin and Andrew Huxley to explain ionic mechanisms that underlie the initiation and propagation of action potentials in a squid giant axon. The membrane potential is described as follows:
\[ C_m \frac{dV(t)}{dt} = -\sum I(t,V) \]  

(1.2)

Where \( C_m \) is the cell membrane capacitance. Voltage-gated ion channels are represented by equations that follow Ohm’s Law:

\[ I(t,V) = g(t,V) \ast (V - V_{eq}) \]  

(1.3)

Where \( g(t,V) \) is the time and voltage dependent conductance of the current. The conductance can be further described by a constant value and activation/inactivation variables, which govern the ion flow through available membrane channels. The conductance equations usually follow the form:

\[ g(t,V) = g_{\text{max}} \ast m(t,V)^p \ast h(t,V)^q \]  

(1.4)

Leak channels, which describe the natural permeability of ions through the neuron membrane, are usually described as voltage-gated channel with a constant conductance value \( g \).

**MacGregor Neuron**

The MacGregor Neuron model is a simplification of the Hodgkin-Huxley model\(^5\). It models the membrane potential and the potassium channel responses, but simplifies the remaining individual channels into an excitatory and inhibitory channel response. Neuron firing is governed by a binary spiking variable, which takes a value of 1 when the membrane potential exceeds a threshold and is 0 otherwise. Spiking threshold and neuron refractory period are governed by the following equations:

\[ \frac{dG_k}{dt} = \frac{(-G_k + B \ast S)}{\tau_{Gk}} \]  

(1.5)

\[ \frac{dV_{th}}{dt} = \frac{(-(V_{th} - V_{th0}) + c \ast V)}{\tau_{th}} \]  

(1.6)

Where \( G_k \) is the potassium capacitance, \( B \) is the post-spiking potassium increment, \( \tau_{GK} \) is the time constant decay of \( G_k \), \( V_{th} \) is the spiking threshold, \( V_{th0} \) is the resting threshold value, \( c \) is the rise value of threshold, \( \tau_{th} \) is the decay constant of the threshold and \( V \) is the membrane potential.
The primary auditory pathway transfers auditory signals from inner ear to the auditory cortex. This pathway can be divided into an ascending and descending pathway. In the ascending auditory pathway, information received through the ear is processed through the auditory brainstem, midbrain, and cortex. The descending auditory pathway provides any necessary feedback signals from higher brain structures to individual nuclei. The feedback mechanisms that underlie the descending pathway are not well understood. This review briefly mentions these connections; however, the bulk of this study will focus on modeling the ascending pathway mainly because these are the short latency pathways that are the generators of the auditory brainstem response (ABR) and mid-latency auditory evoked potential (MLAEP).

### Ascending Auditory Pathway

The ascending auditory pathway begins in the ear, where mechanical vibrations from the incoming sound are encoded into electrical stimuli through the inner hair cells (IHC) of the inner ear. These signals are converted to action potentials at the IHC synapse with spiral ganglion cells whose axons form the auditory nerve (AN) where they serve as inputs for the subdivisions of the cochlear nuclei. From the cochlear nuclei, neural signals are sent to either the superior olivary complex, lateral lemniscus, or the inferior colliculus. Nearly all ascending auditory pathways later converge at the inferior colliculus. Information from the inferior colliculus is then sent to the medial geniculate body and eventually, auditory cortex. This review will focus on modeling studies investigating the neural regions between, and including, auditory nerve and inferior colliculus.
4.1 Auditory Nerve

Spiral ganglion cells receive inputs from the inner hair cells and then relay these signals to the cochlear nucleus. The axons of these spiral ganglion cells collectively make up the auditory nerve (AN). The AN fibers are characterized by their spontaneous activity and their best or characteristic frequency, the frequency to which a fiber responds at minimal stimulus intensity. The fibers display a monotonic increase in their firing rate up to a maximum level at which the firing rate remains constant as the stimulus intensity is increased.

Initial model design included a phenomenological model of the auditory nerve response. The model describes the responses of high spontaneous activity auditory nerve fibers to stimulus waveforms. Due to the number of auditory nerve fibers and the necessary models needed to cover the typical frequency range of human hearing, phenomenological AN models can be used in lieu of a large number of spiral ganglion neuron models.

4.2 Cochlear Nucleus

The cochlear nucleus is the first major site of neural processing where the inputs are subdivided into multiple output pathways. The cochlear nucleus receives its inputs from the auditory nerve. Each auditory nerve fiber bifurcates upon entry into the cochlear nucleus, where they make synaptic connections with the various cells of each CN subdivision. Lower frequency axon fibers innervate the ventral portions of the dorsal cochlear nucleus (DCN) and ventrolateral portions of the anteroventral cochlear nucleus (AVCN). Axon fibers corresponding to higher frequency stimuli project to the dorsal portion of AVCN and some areas of DCN. Cells from each subdivision are described below.

4.2.1 Anteroventral Cochlear Nucleus, AVCN

**Spherical Bushy Cells**

One of the major cell types in the ventral cochlear nucleus is the bushy cells. Bushy cells are further classified by their location within the CN, their shape, and their projections to specific regions of the superior olivary complex. Based upon these criteria, they are subclassified as being either spherical or globular. Spherical bushy cells are located in the rostral AVCN, receive inputs from the auditory nerve and project their axons to the lateral superior olive. Each class of VCN neurons has also been associated with their differing responses to acoustic stimuli, and is believed to perform distinct processing functions. Spherical bushy cells respond to tone bursts with a “primary-like” response, which is similar to primary auditory nerve fiber responses.
A couple models have been designed to model the *in vivo* and *in vitro* responses of spherical bushy cells\(^7,\ 8\). Both models were able to successfully replicate the response properties of spherical bushy cells and follow high frequency trains of synaptic inputs. However, these models are not accurate in their descriptions of the \(K^+\) channel mechanisms that drive the cell responses. A comparison of the modeled currents to experimental data\(^9\) shows some differences in channel activation, current, and time constants.

A later modeling study by Rothman et al.\(^9\) improved upon their previous model to better describe the VCN cells’ differing response characteristics through more accurate descriptions of the potassium channel kinetics. The model is based upon voltage-clamp recordings of isolated neurons taken from the ventral cochlear nucleus of guinea pigs\(^10,\ 11\). An advantage of this study is the ability to accurately recreate the responses of spherical bushy, globular bushy and stellate cells through adjusting the conductance parameters of a few potassium conductance channels. However, this study provides different model parameter configurations that correspond to certain response types recorded experimentally through a voltage-clamp recording setup. The disassociation of the individually recorded neurons removed most of their dendritic and axonal processes, which made anatomical classification difficult. Instead, the neurons recorded from VCN were identified by their voltage clamp properties; notably, the presence of a low-threshold potassium current at a resting potential of \(-60\) mV (Type II) or lack of such a current (Type I). Currently, these identified response types do not correlate well with the morphology of cell type. The paper infers that bushy cells (globular and spherical) have a response indicative of what the authors refer to as a type II neuron. Thus, the model description below is based upon this inference.

The VCN spherical bushy cell model described by Rothman et al.\(^9\) is a single compartment model with the membrane potential \(V\) described by the following first-order differential equation:

\[
C_m \frac{dV}{dt} = I_A + I_{LT} + I_{HT} + I_{Na} + I_h + I_{hk} + I_E - I_{ext}
\]

Where \(C_m\) is the membrane capacitance, \(I_A\) is the fast-inactivating A-type \(K^+\) current, \(I_{LT}\) is the fast-activating slow-inactivating low-threshold \(K^+\) current, \(I_{HT}\) is the high threshold \(K^+\) current, \(I_{Na}\) is the fast-inactivating \(Na^+\) current, \(I_h\) is the hyperpolarization-activated cation current, \(I_{hk}\) is the membrane leak current, \(I_E\) is the excitatory synaptic current, and \(I_{ext}\) is an external current source. The equations describing the kinetics for the potassium channels are derived from experimental data and described in previous studies\(^11\). The sodium and hyperpolarization-activated currents are derived from other
studies and are described in the appendix. The model lists parameter setting for five different model configurations that correspond to different VCN cell type and response characteristics.

**Globular Bushy Cells**

The second class of bushy cell found in the ventral cochlear nucleus is the globular bushy cell. Globular bushy cells receive input from the auditory nerve and project its axons to medial nucleus of the trapezoid body (MNTB) and the lateral superior olive (LSO). Like the spherical cells, a globular bushy cell response is characterized as “primary-like with notch”, described as “primary-like” with the addition of a brief absence of neural spiking following onset (Figure 3).

The Rothman model, used to accurately model spherical bushy cells, has also been used to predict the responses of globular bushy cells. The model design is identical to the one used to describe the spherical bushy cells, and the model design is described in the previous section. Although the intrinsic mechanisms of each cell type may be similar, differences in the responses between globular and spherical bushy cells may be due to the synaptic connectivity. Two to four large nerve terminals called the endbulbs of Held innervate spherical bushy cells. Each endbulb contains multiple synaptic sites. Globular bushy cells, however, typically receive a larger number of smaller sized inputs. Spirou et al. used the Rothman 2003 model design, but made several changes to the synaptic inputs to the model bushy cell. The nerve terminals to the globular bushy cells were modeled anatomically and based on a model of the calyx of Held. Given these additions, the model is successfully verified through comparison of the model peri-stimulus time histograms (PSTH) to those measured experimentally.

4.2.2 **Posteroventral Cochlear Nucleus (PVCN)**

**Octopus Cells**

Octopus cells are neurons that are located within a distinct region of the PVCN. These cells named as such due to their unique shape and configuration of their dendrites. Octopus cells receive ascending inputs from the auditory nerve from a wide range of characteristic frequencies and projects to the ventral nucleus of the lateral lemniscus (VNLL). In addition, they are associated with having an onset-type response to tone bursts. The type of onset response further classifies the cells; the O₁ response is usually one or two precise timed action potentials following the tone onset, with no sustained spiking during the presentation of the stimulus, while the O₂ response has precisely timed onset spikes with sustained activity during stimulus presentation.
Several studies have investigated the mechanisms that underlie the octopus cells’ onset response\(^{15-18}\). These studies used compartmental models that were based on anatomical and physiological data\(^{19}\). Both were successful in reproducing the O\(_I\) and O\(_L\) response, but did so through differing mechanisms in their respective models. Kipke and Levy\(^{15-17}\) attributed the onset response to fast membrane dynamics and coincidence of excitatory synaptic signals, while Cai\(^{18}\) attributed the onset response to intrinsic mechanisms, namely specific voltage-gated ionic channels. It is possible that both studies are correct, as it is likely that the fast membrane dynamics arise in part because of the high conductances of voltage-gated channels at rest in octopus cells (Oertel et al., 2000; Ferragamo and Oertel, 2002). A later study by Cai\(^{20}\) modified the 1997 model design to further investigate the role of the ionic channels in shaping the onset response.

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<thead>
<tr>
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<tbody>
<tr>
<td><strong>Anatomical description of model</strong></td>
<td>Multi-compartmental model consisting of a soma, an axon, and four dendrites.</td>
<td>Multi-compartmental model consisting of a soma, an axon, and four dendrites.</td>
</tr>
<tr>
<td><strong>Model design/parameters</strong></td>
<td>Hodgkin-Huxley type Na(^+) and K(^+) channels, low-threshold potassium channel, hyperpolarization-activated cation channel.</td>
<td>Hodgkin-Huxley type Na(^+) and K(^+) channels, based on a model of hippocampal CA3 neurons(^{21}). No added potassium channels; slight modifications to membrane properties and time constants.</td>
</tr>
<tr>
<td><strong>Model verification</strong></td>
<td>Anatomical and physiological data for model taken from data from published experiments.</td>
<td>Model verification done by comparison of computed responses to physiologically recorded responses.</td>
</tr>
<tr>
<td><strong>Synaptic connectivit y and modeling of inputs.</strong></td>
<td>No synaptic conductances modeled; cell model driven with external current injection.</td>
<td>56 dendritic inputs represented with 14 independent, uniformly distributed, time-varying synaptic conductances. Inputs are modeled from high spontaneous rate auditory nerve fibers.</td>
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</table>
4.2.3 Dorsal Cochlear Nucleus (DCN)

**Fusiform Cells**

The fusiform, or pyramidal, cells are the principal cells found in the DCN. These cells also receive excitatory inputs from the auditory nerve and have a “build-up” and “pauser” response to tone stimuli (Figure 4). A “build-up” response refers to a delayed, long first spike latency response to the onset of a stimulus. A “pauser” response consists of a short latency onset response, followed a long first interspike interval preceding regular firing\(^2\). Fusiform cells project directly to the central nucleus of the inferior colliculus, providing ascending excitatory input to the IC.

Previous models have simulated the typical fusiform cell response through modifications of the original Hodgkin-Huxley model\(^4, 22, 23\). These models attempted to reproduce the *in vitro* results found by Manis\(^24\) taken from recorded fusiform cells taken from guinea pigs. While successful in reproducing the aforementioned results, these models used arbitrarily defined cell and channel parameters which may or may not have been physiologically accurate. A more accurate model, based on recent *in vitro* intracellular recordings\(^2\), was created by Kanold and Manis that was capable of reproducing the voltage-clamp responses characteristic of DCN fusiform cells\(^25\). The present model is thus physiologically accurate and consistent with experimentally observed results.

The model fusiform cell is a single compartment model containing five voltage-dependent ionic conductances and a leak conductance described by the following equation:

\[
-d\frac{V_m}{dt} = \frac{1}{C_m} \left( I_{KIF}(V,t) + I_{KIS}(V,t) + I_{KNI}(V,t) + I_{Na}(V,t) + I_{L}(V,t) + I_{L}(V,t) \right) \quad (2.2)
\]

Where \( I_{KIF} \) and \( I_{KIS} \) are the fast and slowly inactivating potassium currents, \( I_{KNI} \) is the non-inactivating potassium current, \( I_{Na} \) is the sodium current, and \( I_{L} \) is the leak current. The sodium current is modeled a Hodgkin-Huxley type sodium channel. The fast and slowly inactivating potassium currents are modeled using parameters determined from previous studies\(^2\). A description hyperpolarization-activated cation currents is taken from published studies and modified for use in the current model\(^26, 27\).
The model has accurate intrinsic properties that accurately reflect the properties of fusiform cells recorded in vitro. However, none of the models mentioned have accurately modeled the synaptic inputs to the fusiform cell. The cell models have all been driven by current pulses that are not a physiologically accurate representation of the synaptic inputs. Kanold and Manis mention that the fusiform cells do receive inhibitory inputs from several sources, and hypothesize that these inputs may alter the firing patterns of the cell to produce either the “pauser” or “build-up” responses described previously.

### 4.2.4 Multipolar/Stellate Cells (PVCN and AVCN)

A major subset of cochlear nuclei cells exists throughout both the ventral and dorsal cochlear nucleus. These cells are asymmetrical in shape and are known as either multipolar or stellate cells. Stellate cells that are found in the AVCN and PVCN exhibit “chopper” responses to tone stimuli and send excitatory inputs directly to inferior colliculus. The chopper response is characterized by a PSTH that has several distinct peaks, which indicates regular cell firing during presentation of the stimulus (Figure 5).

A few studies have attempted to model the chopper responses of the stellate neuron. The first model, designed by Banks and Sachs, is a multi-compartment model with Hodgkin-Huxley type conductances and synaptic inputs. The model does utilize experimental data from cat and mouse in the design of their model. However, the excitatory and inhibitory inputs and the membrane properties of these cells were not fully understood. Thus, several assumptions were made in the original model design that had not been verified. Eriksson and Robert designed a model using the MacGregor cell model with additional conductances added. Bahmer and Langner proposed a more complex input circuitry to the stellate cell: the cells receive inputs from both auditory nerve and onset (octopus) cells. The model used for their stellate cell in this particular study is an integrate-and-fire neuron model, which lacks several physiologically based voltage-dependent current mechanisms found in the other models. The study by Rothman provides model parameter configurations that result in model cell responses that are comparable to recordings from stellate cells. The cell includes voltage-dependent currents that have been shown to be physiologically accurate in comparison to experimental recordings. However, the cell lacks the anatomical precision that is present in the model by Banks and Sachs. A comparison of the listed models is shown in the table below.

![Figure 5. “Chopper” response to tone stimuli shown by regular peaks in recorded PSTH. Figure from Banks and Sachs.
](image-url)
| Anatomic  
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<tbody>
<tr>
<td>Model design/parameters</td>
<td>Hodgkin-Huxley modeled sodium and potassium conductances, modeled leak conductance.</td>
<td>Model characterized by transmembrane potential, after-spike hyperpolarization potassium conductance, threshold, spiking variable (digital). Stellate cell receives mixed input from circuitry that includes tuberculoventral cells and multipolar type II cells.</td>
<td>Integrate-and-fire neuron contains time constants for leakage currents of each compartment. Incoming postsynaptic currents from inputs are integrated to form the postsynaptic potential. A leakage current diminishes inputs. A set threshold determines spiking. Constants are set for absolute and relative refractory period.</td>
<td>Hodgkin-Huxley modeled sodium conductance, leak conductance, fast-inactivating A-type K⁺ current, fast-activating slow-inactivating low-threshold K⁺ current, high threshold K⁺ current, hyperpolarization-activated cation current. Model parameters correspond to configuration of a type I-c neuron response.</td>
</tr>
<tr>
<td>Model verification</td>
<td>Anatomical and physiological data taken from stellate cells from cats.</td>
<td></td>
<td>Potassium current kinetics modeled from experimental data. Sodium and hyperpolarization-activated current modeled from published sources.</td>
<td></td>
</tr>
<tr>
<td>Synaptic connectivity and modeling of inputs.</td>
<td>Excitatory and inhibitory inputs given to somatic and dendritic compartments. Modeled as non-stationary Poisson processes</td>
<td>Excitatory and inhibitory postsynaptic conductances modeled through linear differential equations.</td>
<td>Synaptic inputs (inhibitory and excitatory) modeled through equations governing neurotransmitter vesicle release, and transmitter concentration.</td>
<td>Excitatory synaptic input modeled from auditory nerve fiber driven excitatory postsynaptic currents (EPSCs)</td>
</tr>
</tbody>
</table>
4.3 Superior Olivary Complex (SOC)

The SOC is a group of nuclei located on either side of the brainstem. Each side receives and integrates inputs from both ears via the cochlear nucleus. The superior olive is the first auditory processing center to receive binaural inputs onto individual neurons. The integrated inputs are then transferred either within the SOC for further processing or to higher auditory centers such as the lateral lemniscus or inferior colliculus.

The SOC is composed of three major components that are well studied due to their roles in sound localization: The lateral superior olive (LSO), medial superior olive (MSO) and medial nucleus of the trapezoid body (MNTB). In mammals, the relative size of these structures varies greatly between species. Descriptions of function of these components and their respective modeling studies are described below. There is also a collection of other poorly understood SOC nuclei, including the ventral and lateral nucleus of the trapezoidal body (VNTB, LNTB), the superior paraolivary nucleus and a variety of other paraolivary nuclei. These nuclei are not discussed further in this review.

4.3.1 Lateral Superior Olive

The lateral superior olive (LSO) typically processes binaural inputs associated with mid- to high-frequency (>1 kHz) sounds. These neurons are excited by stimulation of the ipsilateral ear and inhibited by similar stimulation of the contralateral ear through input from the MNTB. The excitatory inputs are believed to originate from the spherical bushy cells of the AVCN and terminate on the distal dendrites of LSO cells. Inhibitory inputs are believed to originate from the principal cells of the MNTB, which are innervated from contralateral inputs from globular bushy cells in the AVCN. The inhibitory inputs from MNTB terminate on the soma and proximal dendrites. Integration of these inputs results in a “chopper” response typical of cells in the LSO.

A single neuron model designed by Zacksenhouse et al. took anatomical data from previous studies investigating LSO neurons in gerbils and mice. The model, while anatomically accurate, could have been better fine tuned with appropriate intracellularly recorded data to confirm the kinetics of the active membrane conductances.

Another neuron model, created and studied by Szaliszno investigated the role of two hyperpolarization activated conductances in the LSO. This study is motivated by an intracellular study of LSO neurons in rats. A single and double compartment model was created in this study. While the model parameters produce accurate response characteristics, the model kinetics are based on published studies of ionic channels from different neurons. Details and comparisons of both models are given in the table below.
<table>
<thead>
<tr>
<th><strong>Anatomical description of model</strong></th>
<th><strong>Zacksenhouse et al., 1998</strong></th>
<th><strong>Szalisznyo, 2006</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>A multi-compartment model consisting of a cylindrical soma, two cylindrical dendrites (proximal and distal), and a short cylindrical axon located at the center.</td>
<td>Two models, one single compartment and a dual (soma and dendrite) compartment model.</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th><strong>Model design/parameters</strong></th>
<th><strong>Zacksenhouse et al., 1998</strong></th>
<th><strong>Szalisznyo, 2006</strong></th>
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<tbody>
<tr>
<td>The dendrites are modeled as a passive membrane and its characteristics are based on physiological data from gerbils and mice. The somatic compartments consist of sodium, potassium, calcium, and calcium-dependent potassium channels. The axonal compartment consists of only the sodium and potassium channels. These channels are modeled as Hodgkin-Huxley type channels, and are modified from a VCN chopper (stellate) cell model by Banks and Sachs.</td>
<td>Voltage-dependent sodium and potassium channels are modeled as Hodgkin-Huxley type conductances with slight changes to parameter values; Inward-rectifier potassium channel and slowly activating, noninactivating channel kinetics are modeled from previously published studies.</td>
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<tr>
<th><strong>Model verification</strong></th>
<th><strong>Zacksenhouse et al., 1998</strong></th>
<th><strong>Szalisznyo, 2006</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Anatomical and physiological data taken from studies of LSO neurons from gerbils, mice and cats.</td>
<td>No synaptic connectivity is modeled; all model simulations are driven by injected currents.</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th><strong>Synaptic connectivity and modeling of inputs</strong></th>
<th><strong>Zacksenhouse et al., 1998</strong></th>
<th><strong>Szalisznyo, 2006</strong></th>
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<tbody>
<tr>
<td>The synaptic inputs are modeled as an alpha function conductance change with constants for maximum conductance and time constant. Excitatory inputs have a reversal potential of 0mV and innervate the dendritic compartments. Inhibitory inputs have a reversal potential of -75mV and provide IPSPs at the soma.</td>
<td>No synaptic connectivity is modeled; all model simulations are driven by injected currents.</td>
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### 4.3.2 Medial Superior Olive

The medial superior olive (MSO), like the LSO, receives and processing binaural inputs. The MSO is responsible for sound localization in the horizontal plane, through coincidence detection of inputs from the contra- and ipsilateral ear. The MSO measures the difference in arrival time of the binaural sounds to each ear, known as the interaural time difference (ITD). This time difference allows the MSO to code for location along the horizontal plane.

Several studies have investigated the function of MSO neurons and its ability to integrate binaural inputs. A later model based on those previous studies was designed by Zhou et al.
Zhou et al. studied two models of MSO neurons. The first is a single compartment point neuron, similar to the model used by Brand et al. and modified from Brughera et al. The second model is a bipolar neuron that takes an asymmetrical shape based on anatomical data from previous studies of MSO neurons from guinea pigs. The two models are described in the table below.

<table>
<thead>
<tr>
<th>Point MSO model: (Brughera et al., 1996; Brand et al., 2002, Zhou et al. 2005)</th>
<th>Bipolar MSO model: (Zhou et al., 2005)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anatomical description of model</strong></td>
<td>Single compartment model.</td>
</tr>
<tr>
<td><strong>Model design/parameters</strong></td>
<td>Single-compartment structure with ionic channels modeled previously by Rothman. Contains Hodgkin-Huxley modeled sodium and potassium currents, with a low-threshold potassium current modeled previously.</td>
</tr>
<tr>
<td><strong>Synaptic connectivity and modeling of inputs.</strong></td>
<td><em>Brughera et al.</em> Six excitatory and six inhibitory inputs are given per side (contra and ipsilateral). Each is modeled as alpha functions and synaptic events are timed by the output of model bushy cell. Zhou et al.* Bilateral excitatory and contralateral inhibitory inputs are derived from responses of an auditory nerve model.</td>
</tr>
</tbody>
</table>

4.3.3 Medial Nucleus of the Trapezoid Body

The third major region of cells that comprise the superior olive is the medial nucleus of the trapezoid body (MNTB). These cells are located medial to the MSO among the fibers of the trapezoid body. The size of the MNTB varies much with the frequency hearing range of the species. The MNTB has been found to be relatively large in species with large LSOs and a hearing ability in the high-frequency ranges (20-80 kHz), while small in species with small LSOs such as apes, monkeys and humans. MNTB neurons receive major inputs from globular bushy cells of the contralateral AVCN and provide inhibitory inputs to both contralateral LSO and MSO.
Currently, there are few physiologically based models of the MNTB\textsuperscript{44-46}. The latter two are iterations based upon the model by Wang\textsuperscript{44}. These studies focus on characterization of specific high-threshold potassium channels. The models are single compartments and lack modeled synaptic current inputs. However, the responses generated from the model do accurately produce typical firing patterns recorded from MNTB neurons. The model parameters are described below.

<table>
<thead>
<tr>
<th>Anatomical description of model</th>
<th>Wang et al., 1998</th>
<th>Macica et al. 2003</th>
<th>Johnston et al., 2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model design/parameters</td>
<td>Sodium, high-threshold potassium and low-threshold potassium currents modeled with membrane leak current. Parameters of high-threshold current modeled from Perney and Kaczmarek\textsuperscript{8}. Low-threshold current parameters modeled from direct fit to traces recorded from mouse MNTB neurons.</td>
<td>Sodium, high-threshold potassium and low-threshold potassium currents modeled with membrane leak current. Equations for the model were taken from Wang et al.\textsuperscript{44}. Parameters of high-threshold current modeled from direct fit to traces recorded from MNTB neurons and Kv3.1-transfected CHO cells.</td>
<td>Model design taken from Macica et al.\textsuperscript{45} with modifications to leak current conductance and the addition of a modeled A-type potassium current. Model simulations run in NEURON.</td>
</tr>
<tr>
<td>Synaptic connectivity and modeling of inputs.</td>
<td>No synaptic connectivity modeled; model driven by current pulses.</td>
<td>No synaptic connectivity modeled; model driven by current pulses.</td>
<td>Alpha function modeled excitatory synaptic currents.</td>
</tr>
</tbody>
</table>

4.3.3.1 Calyx of Held

The Calyx of Held is a particularly large synapse found in the auditory pathway. These synaptic terminals provide inputs to the MNTB from the globular bushy cells in the VCN. This large synapse is designed for quick, efficient transport of information to the MNTB. Due to its large size and rapid transport of information to the MNTB, there have been a number of experimental and modeling studies investigating its synaptic properties\textsuperscript{13, 47-50}. It would be feasible to implement these models to better generate synaptic inputs to the superior olive, thus improving accuracy of the MSO and LSO response.

4.3.4 Lateral Lemniscus

The lateral lemniscus receives and transmits information from various regions in the SOC and CN to the inferior colliculus. The lateral lemniscus is divided into two regions: ventral and dorsal nucleus (VNLL and DNLL, respectively).
The VNLL has been found to be a part of neural circuitry that mediates a short latency acoustic startle response. However, it is unclear of the purpose the VNLL has, if any, in the primary auditory pathway of primates and humans. The VNLL receives inputs from the octopus cells in the PVCN and projects an inhibitory input to the inferior colliculus.

The DNLL receives inputs from both ipsilateral and contralateral regions of the MSO and LSO and projects an inhibitory input to the inferior colliculus. It is believed that the DNLL provides a major source of inhibitory inputs to cells in the inferior colliculus.

Currently, there are no physiologically based modeling studies of either region of the lateral lemniscus. Two phenomenological modeling studies have investigated the responses of binaural stimuli in the DNLL. Models of the inferior colliculus, which include inhibitory inputs, assume these inputs originate from the lateral lemniscus. However, there have been no explicit cell models created for the lateral lemniscus. The anatomical and physiological data exists that could serve as a basis for a future cell model of both the DNLL and VNLL.

4.4 Inferior Colliculus

The inferior colliculus (IC) is a major integrative processing center in the auditory pathway; nearly all ascending and descending auditory pathways synapse in the IC. In addition, the IC receives inputs from both monaural and binaural pathways from the auditory brainstem. In addition, many of the neurons in the IC give off axonal collaterals within the IC. Therefore, in addition to the convergence of multiple ascending pathways, neurons within the IC also contribute to the neural response.

Due to the assumed integrative function of the inferior colliculus, several modeling studies have attempted numerous mathematical and physiological methods to better predict IC responses.

Several network simulation studies used a MacGregor point neuron to model the IC neuron response. While each model displayed accurate IC responses, the inputs to the model are constructed through mathematical modeling schemes and are not physiologically based. Furthermore, the IC model is based on a MacGregor point neuron, which includes a spiking variable to initiate action potential firing.

A modeling study by Cai et al. constructed a network to provide physiologically relevant inputs to a model IC neuron. The model incorporated models of the auditory periphery (AN fiber, spherical bushy cells, MSO). These periphery models are based on studies mentioned previously. The IC neuron model is based on equations from Rothman et al., with an additional potassium channel to simulate a calcium-activated potassium channel.

Borisyuk et al. created a similar network model to investigate IC responses. The network includes excitatory inputs from a model MSO neuron and inhibitory inputs modeled from a second MSO unit via the DNLL. It is assumed in both the Cai and
Borisyuk studies that the DNLL is a relay nucleus and is an instantaneous converter of excitation to inhibition\textsuperscript{54, 66}. The IC model, however, is an integrate and fire based model, with no sodium channels and a threshold that indicates neuron firing. Model design details for both models are described below.

<table>
<thead>
<tr>
<th>Anatomical description of model</th>
<th>Cai et al. 1998a,b</th>
<th>Borisyuk et al. 2002</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model design/parameters</td>
<td>Single compartment neuron model</td>
<td>Single compartment neuron model</td>
</tr>
<tr>
<td>Rothman\textsuperscript{7} model equations used for model design. Model includes Hodgkin-Huxley type sodium and potassium channels, low-threshold and calcium-activated potassium channels. Also includes leak membrane current and synaptic currents.</td>
<td>Model contains a membrane leak, adaptation, and post-inhibitory rebound currents. No sodium or delayed-rectifier potassium channels to produce action potentials. Spiking is indicated by membrane potential exceeding threshold set at $V_{th} = 10\text{mV}$. Model output is spike rate, given by the equation $r = k(V - V_{th})$ when $V &gt; V_{th}$ and $r = 0$ otherwise.</td>
<td></td>
</tr>
<tr>
<td>Synaptic connectivity and modeling of inputs.</td>
<td>Excitatory synaptic conductance is a modeled alpha function. Inhibitory conductance function is a linear summation of an alpha function and an exponential function. Inhibitory input is delayed by 1ms to simulate the presence of the DNLL in the modeled network.</td>
<td>Model IC cell receives binaural excitatory input from an ipsilateral MSO model and indirect inhibitory input (via DNLL) from a contralateral MSO modeled neuron. The existence of the DNLL is only implied in the network, as in Cai et al.</td>
</tr>
</tbody>
</table>
5 Model Validation

Once construction of our composite model and the design and parameters has been chosen based on the analysis given, the model should be validated for accuracy and its ability to faithfully recreate the response characteristics of the given neural region. Ideally, each region will require two steps of validation: first, each cellular model would be validated for its accuracy in reproducing neural outputs comparable to its physiological counterpart, and second, the output of an aggregate of cellular models that comprise a neural region should be compared to a population response recorded from a given region.

Cell Model Validation

A majority of the models described in this review are based on voltage-dependent ionic conductances that were based upon voltage-clamp recordings from single unit intracellular in vitro studies. Validation of these models would typically consist of comparison of model responses to current injection or physiologically based synaptic inputs to current-clamp responses recorded from intracellular recordings in vitro. Further validation would be a comparison of PSTHs from the cellular model and from intracellular in vitro or single-unit in vivo recordings. Comparison of PSTHs would be ideal for validation of models of neurons from cochlear nucleus as the PSTH response characteristics are well known and easily found in literature1, 2, 7, 9-11.

Population Validation

Validation of the population response of the aggregate model may be more difficult to assess. Population responses will differ by neural region and vary by the regions’ function. For example, neuron models from the LSO and MSO can be assessed by their sensitivity to interaural level difference and interaural time difference, respectively. Comparison of the aggregate response of the model to auditory brainstem responses (ABRs) and frequency following responses (FFRs) could serve as validation for the completed model.

6 Conclusion

A model of the ascending auditory pathway allows for better understanding of the underlying mechanisms that produce recorded neural responses to auditory stimuli. The model would also be advantageous in investigating hypotheses that may difficult or impossible to investigate in studies in vitro or in vivo. A review of the literature finds several cellular models at nearly all neural regions in the ascending auditory pathway.
from auditory nerve to inferior colliculus. These models will serve as a basis for construction of our model. However, there are several gaps in knowledge that can hinder model construction.

There is a lack of physiologically based cell models of neurons in the lateral lemniscus. While modeling studies have made certain assumptions to justify the omission of the lateral lemniscus\textsuperscript{54, 64}, an explicit model may provide better accuracy in our combined model response. Fortunately, anatomical and physiological studies of the lateral lemniscus are available and a simple model can be constructed through data taken from these studies.

A second obstacle is the relative number of neurons needed to produce a valid neural response to auditory stimuli. The number of neurons of any given region in the auditory pathway is unclear. Animal studies can give estimates of neuron population, but the relative sizes of each region vary between species. Initial iterations of the model will be simple and contain the minimum number of neurons required to drive an accurate response. Further model simulations and data from literature may give insight as to the number of individual neuron models to be constructed at a given region in the auditory pathway.

A third obstacle is the number of converging inputs each individual neuron model receive and the number of diverging axonal outputs from each neuron model. There are relatively few studies that give estimates of the number converging inputs or diverging outputs. A few of the models reviewed do have converging inputs and diverging outputs, but the numbers of each are adjusted to improve computational efficiency and model accuracy. For our model, a simple estimate of the number of inputs and outputs can be used, with adjustments made to improve accuracy of neural responses to physiological data.

The final obstacle is the accurate modeling of synaptic inputs to each individual cell model. A majority of the reviewed models either use simple external current injection or modeled alpha functions to as inputs. Our model can further expand on this convention and create synaptic currents that are accurately modeled based on experimental data. Thus, synaptic inputs to each cell model will have accurate physiologically based characteristics and will improve the accuracy of the composite model response.

The detailed aggregate physiologically based model can provide insight into the mechanisms that produce a given neural response to auditory stimuli. Predictions from this model can provide a basis for future experimental studies. Furthermore, the model can be used to investigate possible mechanisms that underlie several auditory processing disorders (APD).
7 Appendix

A list of parameters and equations for most of the reviewed models are given below. Other models use variations of rate equations taken from previous studies; only the original equations are given.

**Rothman and Manis 2003 Model Equations**

<table>
<thead>
<tr>
<th>Model Type</th>
<th>I-α</th>
<th>I-I</th>
<th>I-II</th>
<th>II-I</th>
<th>II</th>
</tr>
</thead>
<tbody>
<tr>
<td>(R_{Na})</td>
<td>1000</td>
<td>1000</td>
<td>1000</td>
<td>1000</td>
<td>1000</td>
</tr>
<tr>
<td>(R_{Kc})</td>
<td>150</td>
<td>80</td>
<td>150</td>
<td>150</td>
<td>150</td>
</tr>
<tr>
<td>(R_{L})</td>
<td>0</td>
<td>0</td>
<td>20</td>
<td>35</td>
<td>200</td>
</tr>
<tr>
<td>(R_{A})</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>(R_{h})</td>
<td>5</td>
<td>0.5</td>
<td>2</td>
<td>3.5</td>
<td>20</td>
</tr>
<tr>
<td>(R_{k})</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>(V_{rest})</td>
<td>-63.9</td>
<td>-64.2</td>
<td>-64.1</td>
<td>-63.8</td>
<td>-63.4</td>
</tr>
<tr>
<td>(E_{Kc})</td>
<td>473</td>
<td>453</td>
<td>212</td>
<td>244</td>
<td>71</td>
</tr>
<tr>
<td>(t_{Na})</td>
<td>7.0</td>
<td>4.0</td>
<td>5.7</td>
<td>2.9</td>
<td>0.5</td>
</tr>
<tr>
<td>(t_{K})</td>
<td>-38.3</td>
<td>-34.9</td>
<td>-31.2</td>
<td>-58.0</td>
<td>-02.7</td>
</tr>
<tr>
<td>(E_{Na})</td>
<td>0.3</td>
<td>0.3</td>
<td>0.5</td>
<td>12.6</td>
<td>49.5</td>
</tr>
<tr>
<td>(E_{Kc}) @ 22°C</td>
<td>26</td>
<td>22</td>
<td>2.8</td>
<td>5.2</td>
<td>8.4</td>
</tr>
<tr>
<td>(E_{a}) @ 38°C</td>
<td>11</td>
<td>12</td>
<td>15</td>
<td>17</td>
<td>34</td>
</tr>
</tbody>
</table>

**SODIUM CURRENT**

\[ I_{Na} = \frac{g_{Na} \cdot m^3 h \cdot (V - V_{Na})}{\tau_n} \]

\[ m_n = [1 + \exp(-(V + 38)/7)]^{-1} \]

\[ h_n = [1 + \exp((V + 65)/6)]^{-1} \]

\[ \tau_n = 10 \cdot [5 \exp((V + 60)/18) + 36 \exp(-(V + 60)/25)]^{-1} + 0.04 \]

\[ \tau_h = 100 \cdot [7 \exp((V + 60)/11) + 10 \exp(-(V + 60)/25)]^{-1} + 0.6 \]

**FAST TRANSIENT K+ CURRENT**

\[ I_{K} = g_{K} \cdot \alpha \cdot \beta \cdot (V - V_{k}) \]

\[ \alpha_n = [1 + \exp(-(V + 33)/6)]^{-1/4} \]

\[ \beta_n = h_n (1 - \xi) \cdot [1 + \exp((V + 66)/7)]^{-1/2} \]

\[ \tau_k = 100 \cdot [7 \exp((V + 60)/14) + 92 \exp(-(V + 60)/24)]^{-1} + 0.1 \]

\[ \tau_{c} = 1000 \cdot [14 \exp((V + 60)/27) + 29 \exp(-(V + 60)/24)]^{-1} + 1 \]

\[ \tau_{\alpha} = 90 \cdot [1 + \exp(-(V + 66)/17)]^{-1} + 10 \]

**LEAK CURRENT**

\[ I_{leak} = g_{leak} \cdot (V - V_{leak}) \]

**LOW-THRESHOLD K+ CURRENT**

\[ I_{LT} = \frac{g_{LT} \cdot \alpha \cdot \beta \cdot (V - V_{LT})}{\tau_L} \]

\[ \alpha_L = [1 + \exp(-(V + 48)/6)]^{-1/4} \]

\[ \beta_L = [1 + \exp((V + 71)/10)]^{-1} \cdot (1 - \xi) \]

\[ \tau_L = 100 \cdot [6 \exp((V + 60)/6) + 16 \exp(-(V + 60)/45)]^{-1} + 0.5 \]

\[ \tau_L = 1000 \cdot [exp((V + 60)/20) + exp(-(V + 60)/8)]^{-1} + 50 \]

**HIGH-THRESHOLD K+ CURRENT**

\[ I_{HT} = \frac{g_{HT} \cdot \alpha \cdot \beta \cdot (V - V_{HT})}{\tau_H} \]

\[ \alpha_H = [1 + \exp(-(V + 15)/5)]^{-1/2} \]

\[ \beta_H = [1 + \exp((V + 23)/6)]^{-1} \]

\[ \tau_H = 100 \cdot [11 \exp((V + 60)/24) + 21 \exp(-(V + 60)/23)]^{-1} + 0.7 \]

\[ \tau_H = 1000 \cdot [4 \exp((V + 60)/32) + 5 \exp(-(V + 60)/22)]^{-1} + 5 \]

**HYPERPOLARIZATION-ACTIVATED CATION CURRENT**

\[ I_{h} = g_{h} \cdot \alpha \cdot \beta \cdot (V - V_{h}) \]

\[ \alpha_h = [1 + \exp(-(V + 48)/6)]^{-1/4} \]

\[ \beta_h = [1 + \exp((V + 23)/6)]^{-1} \]

\[ \tau_h = 100 \cdot [237 \exp((V + 60)/12) + 17 \exp(-(V + 60)/14)]^{-1} + 25 \]
This work was supported in part by NSF award 0801119.

Cai et al., 2000 Model Equations

HYPERPOLARIZATION-ACTIVATED CURRENT

\[ gI_h = gI_{h_{max}} i_h S \]
\[ \alpha_{i_h} = \alpha_{i_h} 0 \exp((V + 62 - I_{h_{SP}}) / K_\alpha) \]
\[ \beta_{i_h} = \beta_{i_h} 0 / \{ \exp(-(V + 62 - I_{h_{SP}}) / K_\beta) + 1 \} \]
\[ \tau_p \frac{di_h}{dt} + i_h = i_{hx} \]
\[ \tau_{i_h} = I_{ih_{ac}} / (\alpha_{i_h} + \beta_{i_h}) \]
\[ i_{hx} = \alpha_{i_h} \tau_{i_h} / (\alpha_{i_h} + \beta_{i_h}) \]

HODGKIN HUXLEY MODELED SODIUM CURRENT

\[ gNa = gNa_n n^4 hS \]
\[ \alpha_n = -0.1(V + 37 + M_{St}) / \{ \exp[-(V + 37 + M_{St}) / 10] - 1 \} \]
\[ \beta_n = 4 \exp[-(V + 62 + M_{St})] / 18 \]
\[ \alpha_m = 0.07 \exp[-(V + 62 + H_{St}) / 20] \]
\[ \beta_m = 1 / \{ \exp[-(V + 32 + H_{St}) / 10] + 1 \} \]

HODGKIN-HUXLEY MODELED POTASSIUM CURRENT

\[ gK = gK_{LT} \max BS \]
\[ \alpha_B = \alpha_B 0 \exp[(V - V_{1/2} - B_{SP}) / K_\alpha] \]
\[ \beta_B = \beta_B 0 \exp[(V + V_{1/2} + B_{SP}) / K_\beta] \]

LEVY and KIPKE 1998 MODEL EQUATIONS

MEMBRANE POTENTIAL, DENDRITIC COMPARTMENTS

\[ c_{m} \frac{dV_{a}}{dt} = -g_L(V_{a} - E_{c}) - g_{Na}(V_{a} - E_{Na}) \]
\[ \frac{1}{r_a}(V_{a(t)} - V_{a}) - \frac{1}{r_a}(V_{a} - V_{a(t-1)}) \]

POTASSIUM CURRENT

\[ g_k(V_{a(t)}) = \alpha_{k} n^4 \]
\[ \frac{dn}{dt} = \alpha_n (1 - n) - \beta_n n \]
\[ \alpha_n (V_{a(t)}) = \frac{-0.064(V_{a(t)} - E_{Na} - 15)}{\exp[-(V_{a(t)} - E_{Na} - 15) / 5] - 1} \]
\[ \beta_n (V_{a(t)}) = 1.0 \exp[-(V_{a(t)} - E_{Na} - 10) / 40] \]

SODIUM CURRENT

\[ g_{Na}(V_{a(t)}) = \alpha_{Na} m^3 h \]
\[ \frac{dm}{dt} = \alpha_m (1 - m) - \beta_m m \]
\[ \alpha_m (V_{a(t)}) = \frac{-0.64(V_{a(t)} - E_{Na} - 13)}{\exp[-(V_{a(t)} - E_{Na} - 13) / 4] - 1} \]
\[ \beta_m (V_{a(t)}) = \frac{0.56(V_{a(t)} - E_{Na} - 40)}{\exp[(V_{a(t)} - E_{Na} - 40) / 5] - 1} \]
\[ \frac{dh}{dt} = \alpha_h (1 - h) - \beta_h h \]
\[ \alpha_h (V_{a(t)}) = 0.256 \exp[-(V_{a(t)} - 17) / 18] \]
\[ \beta_h (V_{a(t)}) = \frac{8.0}{\exp[-(V_{a(t)} - E_{Na} - 40) / 5] + 1} \]

LOW-THRESHOLD POTASSIUM CURRENT

\[ c_{m} \frac{dV_{a}}{dt} = -g_L(V_{a} - E_{c}) - g_{Na}(V_{a} - E_{Na}) - g_k(t)(V_{a} - E_{Na}) - g_{kLT}(t) \]
\[ \frac{1}{r_a}(V_{a(t)} - V_{a}) - \frac{1}{r_a}(V_{a} - V_{a(t-1)}) \]

MEMBRANE POTENTIAL, SOMATIC COMPARTMENT 1

\[ c_{m} \frac{dV_{a}}{dt} = -g_L(V_{a} - E_{c}) + \sum_{j} g_{Na}(t)(V_{a(t)} - E_{Na}) \]
\[ \frac{1}{r_a}(V_{a(t)} - V_{a}) - \frac{1}{r_a}(V_{a} - V_{a(t-1)}) \]

MEMBRANE POTENTIAL, SOMATIC COMPARTMENT 2

\[ c_{m} \frac{dV_{a}}{dt} = -g_L(V_{a} - E_{c}) - g_{Na}(V_{a} - E_{Na}) - g_k(t) \]
\[ \frac{1}{r_a}(V_{a(t)} - V_{a}) - \frac{1}{r_a}(V_{a} - V_{a(t-1)}) \]
SODIUM CURRENT

\[ I_{Na}(V_{m},t) = g_{Na}p_{Na}h_{Na}(V_{m} - V_{Na}) \]

\[ n_{Na}(V_{m}) = (1 + \exp[-(V_{m} + 38)/3])^{-1} \]

\[ h_{Na}(V_{m}) = (1 + \exp(V_{m} + 89.6)/6.7)^{-1} \]

FAST INACTIVATING POTASSIUM CURRENT

\[ I_{Kf}(V_{m},t) = g_{Kf}p_{Ka}h_{Ka}(V_{m} - V_{K}) \]

\[ m_{Ka}(V_{m}) = (1 + \exp[-(V_{m} + 53)/25.8])^{-1} \]

\[ h_{Ka}(V_{m}) = (1 + \exp[-(V_{m} + 89.6)/6.7])^{-1} \]

\[ \tau_{mf}(V_{m}) = (0.15 \times \exp[(V_{m} + 57)/10] + 0.3 \times \exp[-(V_{m} + 57)/10])^{-1} + 0.5 \]

\[ \tau_{mf}(V_{m}) = (0.015 \times \exp[(V_{m} + 87)/20] + 0.03 \times \exp[-(V_{m} + 87)/20])^{-1} + 1 \]

LEAK CURRENT

\[ I_{L}(V_{m}) = g_{L}(V_{m} - V_{L}) \]

SLOWLY INACTIVATING POTASSIUM CURRENT

\[ I_{Ks}(V_{m},t) = g_{Ks}p_{Ks}h_{Ks}(V_{m} - V_{K}) \]

\[ m_{Ks}(V_{m},t) = (1 + \exp[-(V_{m} + 40)/23.7])^{-1} \]

\[ h_{Ks}(V_{m},t) = (1 + \exp[(V_{m} + 38.4)/9])^{-1} \]

\[ \tau_{mf}(V_{m}) = (0.15 \times \exp[(V_{m} + 40)/10] + 0.3 \times \exp[-(V_{m} + 40)/10])^{-1} + 0.5 \]

\[ \tau_{mf}(V_{m}) = 200 \]

Zacksenhouse 1998 Model Equations

**MODEL PARAMETERS AND RATE EQUATIONS**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium activation</td>
<td>[ V + 37 + M_{Na} ] [ \exp[-(V + 37 + M_{Na})/10] - 1 ] [ M_{Na} = 2 \text{ mV} ]</td>
</tr>
<tr>
<td>Potassium activation</td>
<td>[ V + 52 + N_{Na} ] [ \exp[-(V + 52 + N_{Na})/10] - 1 ] [ N_{Na} = 10 \text{ mV} ]</td>
</tr>
<tr>
<td>Calcium activation</td>
<td>[ V + 17 ] [ \exp[-(V + 17)/12.5] - 1 ]</td>
</tr>
<tr>
<td>Calcium-dependent potassium activation</td>
<td>[ \alpha_{K} = 0.3 \text{ mV} ] [ \beta_{K} = 0.62 \text{ mV} ]</td>
</tr>
</tbody>
</table>

**CHANNEL EQUATIONS**

\[ i_{Na} = g_{Na}p_{Na}h_{Na}(V - E_{Na}) \]

\[ i_{K} = g_{K}h_{Na}(V - E_{K}) \]

\[ i_{Ca} = g_{Ca}h^{5}(V - E_{Ca}) \]

\[ i_{MHP} = g_{MHP}(V - E_{K}) \]

This work was supported in part by NSF award 0801119.
Szalisznyo 2006 Model Equations

MEMBRANE POTENTIAL EQUATION
\[ C \frac{dV}{dt} = -g_m(V - E_m) - G_k(V - E_k) - I_{leak(Na)} - I_{leak(K)} + I_{ext} \]

SODIUM CURRENT
\[ g_{Na} = g_{Na} m^h \]
\[ \alpha_\text{m} = -0.1 \cdot \frac{(V + 39.3)}{\exp((-V + 39.3)/10) - 1} \]
\[ \beta_\text{m} = 4 \cdot \exp\left(\frac{V + 64.3}{18}\right) \]

LEAK CURRENTS
\[ I_{leak(Na)} = g_{leak(Na)} (V - E_{Na}) \]
\[ I_{leak(K)} = g_{leak(K)} (V - E_K) \]

Borisyuk 2002 Model Equations

POTASSIUM CURRENT
\[ G_k = g_k n^4 \]
\[ \frac{dn}{dt} = \frac{n_{inf} - n}{\tau_n} \]
\[ n_{inf} = \frac{\alpha_n}{(\alpha_n + \beta_n)} \]
\[ \tau_n = 0.0625 \frac{\exp(V + 50.7)}{10} - 1 \]
\[ \beta_n = 0.125 \frac{\exp(-V + 60.7)}{80} \]

HYPERPOLARIZATION-ACTIVATED CURRENT
\[ G_h = g_h s \]
\[ \frac{ds}{dt} = s_{inf} - s \]
\[ s_{inf} = \frac{1}{(1 + \exp([V + 75]/5.5))} \]
\[ \tau_s = \frac{3900}{\exp([89.3 - V]/(-11.63)) + \exp([71.9 - V]/14.27)} \]

POTASSIUM INWARD RECTIFIER CURRENT
\[ G_{kIR} = g_{kIR} \frac{1}{1 + \exp((V - V_{IR})/\gamma)} \]
References