Modeling of Synchronization in Bushy Cells of Cochlear Nucleus

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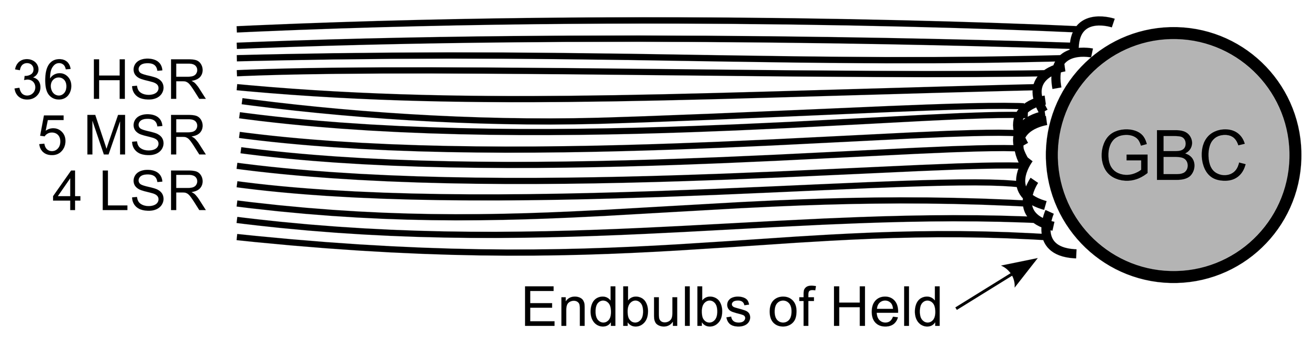
ABSTRACT

In the inner ear sounds are converted into action potentials and propagated to the central nervous system. The cochlear nucleus in the auditory brainstem is the first station that receives synaptic inputs from auditory nerve fibers (ANF) and consists of several neuron types. Here we focus on globular bushy cells (GBC) that are part of the sound localization pathway. One of the main properties of GBC is their excellent temporal firing precision in response to sounds. Our model of GBCs is a point neuron with Hodgkin-Huxley type ion channels (HPAC, Kht, Klt). It receives several excitatory inputs from an inner ear model simulating responses of ANFs. ANF activity drives endbulb of Held synapses located directly on the GBC soma. We modeled two types of synapses: with short-term depression as measured in many in-vitro studies (Yang and Xu-Friedman 2009) and without depression as reported by recent in-vivo studies (Borst 2010). The model is able to reproduce standard experiments involving pure tone stimulation. In particular the PSTH displays proper levels of spontaneous and driven rates as well as characteristic primary-like with notch shapes. Additionally, stimulation with low frequency tones shows improvement in synchronization that can be characterized as high-sync (SI > 0.9) according to Joris et al. (1994). Interestingly, high entrainment levels where achieved only by the model without synaptic depression. In summary, our model is able to reproduce the key features of GBC responses. Our results suggest that depression in-vivo is much lower compared to in-vitro conditions. In the future, the model will allow us to study the response of GBCs to complex natural stimuli like speech.

Introduction and Model Description

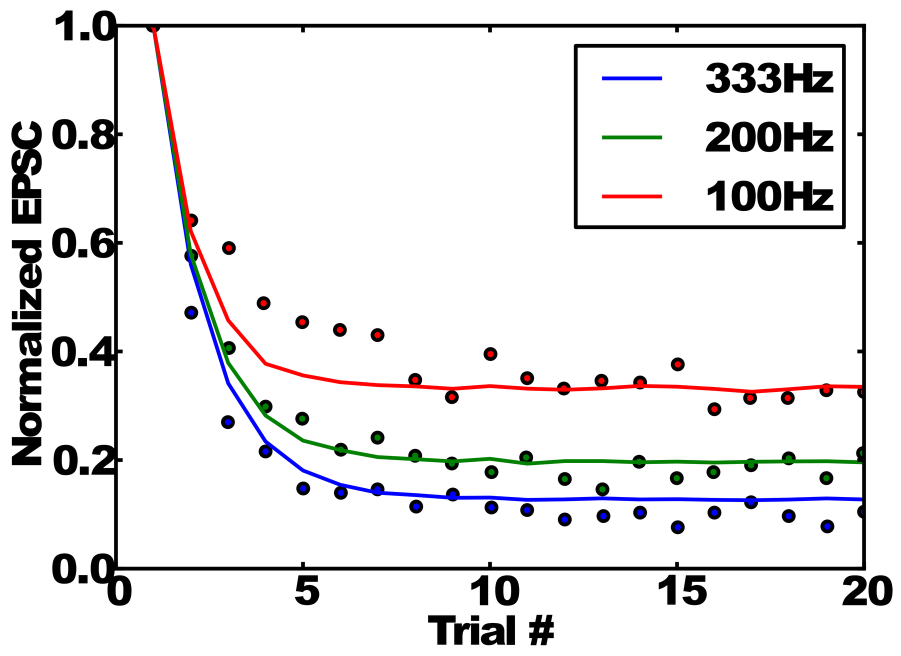
Globular bushy cells (GBC) are one of the principal cells in Cochlear Nucleus and receive direct excitatory input from auditory nerve fibers through giant synapses. It has been shown in previous studies that such synapses are chronically depressed under in-vivo like activity levels (Herman et al. 2007). However, it is still unclear what are the depression levels and their dependency on stimulation frequency. Virtually all in-vitro studies (Wand and Manis 2008, Yang and Xu-Friedman 2009) report a strong dependency of depression on stimulation frequency. On the other hand, only a few in-vivo studies (see Borst 2010 for review) suggest no significant changes in synaptic depression. The goal of this work is to develop a model of GBC that captures key features (high synchronization and entrainment) and compare how synapses with and without depression influence those properties.



Our model of GBC consists of multiple ANFs converging onto the soma, which was represented as a single compartment with Hodgkin-Huxley like ion channels described by Rothman and Manis (2003). In particular, low- and high-threshold potassium and hyperpolarization-activated cation currents have been implemented. It has been shown by Spirou et al. (2005) that the number of inputs greatly varies for individual GBCs in cats (9-69 for 12 studied cells). Our model has 45 ANF inputs from high-, medium- and low-spontaneous rate fibers. We examined two models of Endbulbs of Held: with and without synaptic depression.

Fitting Synapses

A depressing synapse was modeled phenomenologically with two recovery time constants and fitted to experimental data from Yang and Xu-Friedman (2009). In this experiment, ANF fibers were stimulated with electrical shocks at three different frequencies for 20 times. At the same time, EPSCs at the postsynaptic membrane (GBC cell) was measured as shown by dots in the Figure. Fitting was done with a least-squares method and the result is shown as solid lines. The slow recovery time constant was set to 1000 ms (experimental constraint) and the fast component was fitted (27 ms).



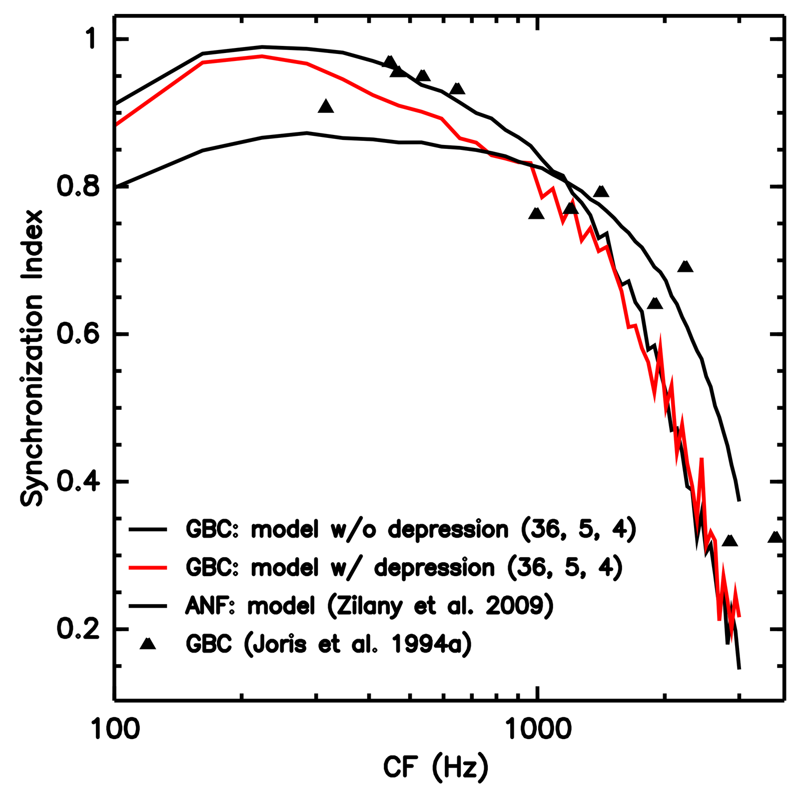
Synaptic weights for the Endbulbs of Held were fitted for a single cell (CF: 600Hz). It was stimulated 200 times by 50 ms pure tones at CF. This procedure was performed for each combination of weights corresponding to different ANF types. The optimum selection was based on assuring that spontaneous firing rate was <3 sp/s and maximizing synchronization and entrainment. It has been repeated for both depressing and non-depressing synapse models.

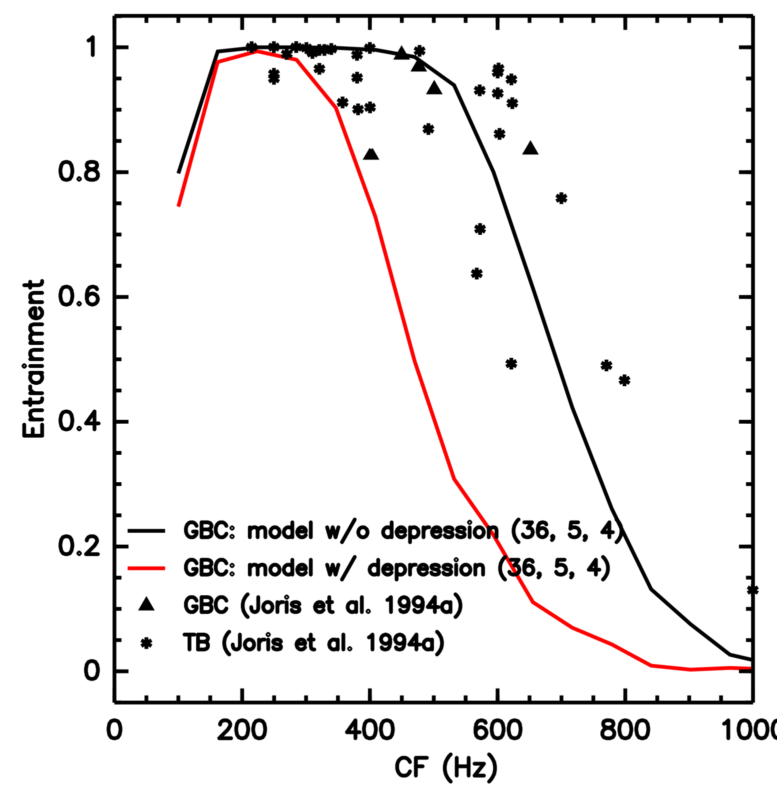
Conclusions

- A single compartment GBC model with multiple converging ANF inputs is able to reproduce basic properties.
- Including of synaptic depression is not necessary to model high synchronization and entrainment. In contrast, adding synaptic depression reduces entrainment to unrealistically low values at low frequencies.

Outlook:
- Examine various types of GBC by varying the number of ANF inputs (Rothman et al. 1993, Spirou and Manis 2005)
- Examine the influence of inhibition on synchronization and entrainment (Dehmel et al. 2010)
- Test complex sounds (e.g. speech) with the model

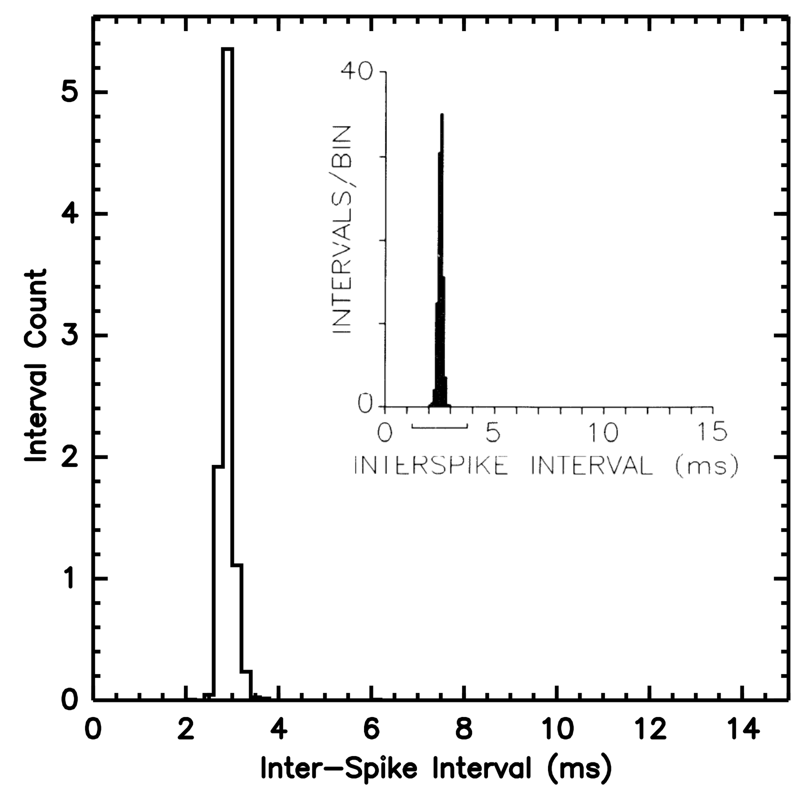
Synchronization and Entrainment

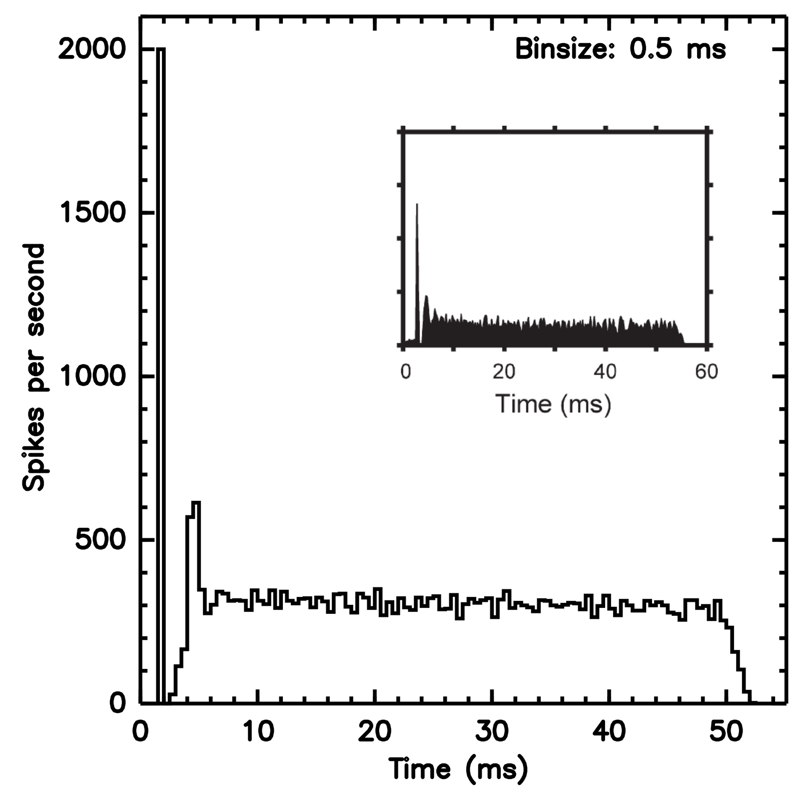




The synchronization index describes how precisely a neuron fires with respect to the phase of a periodic stimulus. Entrainment tells us if a neuron tends to fire every cycle or skips some periods of the input signal. GBC display extraordinary synchronization and entrainment as shown by points in the plots above. Both synapse models show very good and comparable synchronization. But when we look at entrainment, the model w/ depression shows unrealistically low entrainment. Model w/o synaptic depression reaches high entrainment for low CF cells, which is consistent with the data.

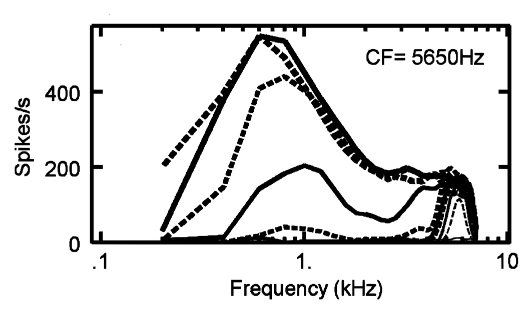
Pure Tone Stimulation

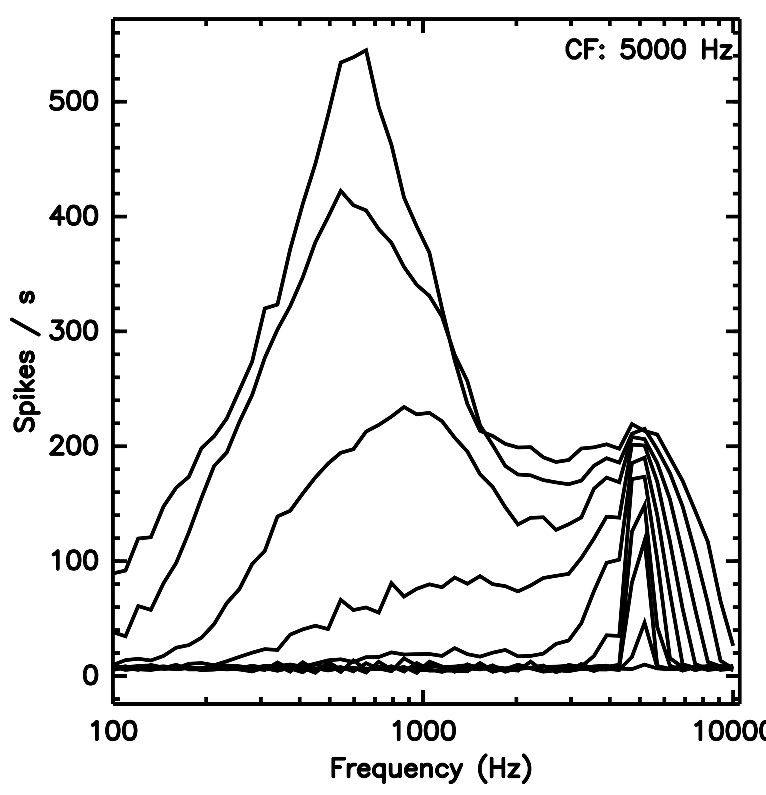




The model w/o synaptic depression agrees with experimental data from simple pure tone stimulation both for high and low CF cells. The left panel shows an inter-spike interval histogram from a simulated neuron driven by a pure tone at its CF (350Hz). The single bump in the ISIH means perfect entrainment and spike at every period of the input signal. The right panel shows a simulated GBC with a high CF, which displays a typical primary-like with notch response when stimulated at its CF.

Here we simulated an experiment done by Rhode (2008) where he measured rate response of a unit with a high frequency CF to a range of tones at various intensities. GBCs with high CFs tend to fire for low frequency high intensity stimuli, which is consistent with experiments from Joris et al. (1994).





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