SU 151

Refinement of Inner Hair Cell Dysfunction in a Phenomenological Auditory Nerve Model Using Physiological and Single-Unit Recordings following Selective IHC Dysfunction

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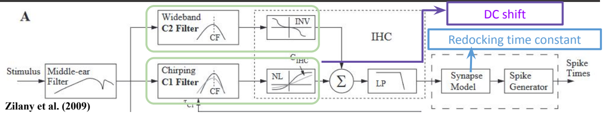
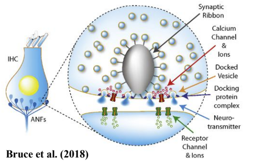
Introduction



- An existing line of phenomenological Auditory Nerve(AN) model have C1 and C2 filter components responsible for controlling tall and short stereocilia respectively. Inner Hair Cell (IHC) damage induced with carboplatin (CA) is shown to disrupt stereocilia organization in IHCs that are not lost [1] .



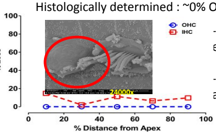
- The BEZ [3] model takes into account the synaptic depression caused by the decrease in the readily available neurotransmitter pool. The model introduces a delay time constant which corresponds to the synaptic redocking time of approximately ~60ms.

- However, the model's 'cihc' parameter fails to capture reduced spontaneous and driven rates which are key features of altered neural coding following IHC damage. [2]

Methods

Physiology (Axe 2017, [1]):

-**IHC Damage** induced using 38mg/kg carboplatin (CA) in chinchillas
Histologically determined : ~0% OHC loss, ~10% IHC loss with **stereocilia loss** in remaining fibers.



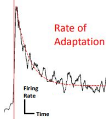
-**Single Unit AN characterization:** Temporal coding deficits after CA exposure quantified using spontaneous rates and driven rates

-**Evoked potential data (EFRs):** Used to study deficits in modulation and tone complex coding in presence of IHC damage

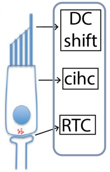
Graph from [1], SEM image from Vijaya Muthaiah

Modeling (BEZ 2018 [3]):

- PSTH responses were simulated using the BEZ 2018 model using tone at best frequency of fiber as stimulus.
- Exponential curve was fitted in the first 50 ms of response to calculate the time constant of adaptation of firing.



To account for IHC damage :
- A DC shift (reduction) term was added in the C1+C2 filter output to induce a shift in spontaneous rate as observed in physiology
- To compensate for reduced driven rates, an increased redocking time constant(RTC) was used.



Possible knobs for modeling IHC damage

Single-Unit

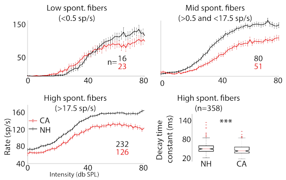
ANF model used to simulate and compare rate level curves(RLVs) and time constants of adaptation between physiology and simulated data

Physiology Results [1]

- RLVs from physiology shows reduction in spontaneous rates for only high spont fibers. Reduction of driven rate is observed across all types of fibers

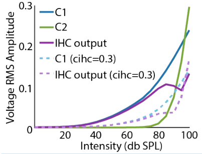
- CA induced fibers show a faster decay in response and hence a significant reduction in adaptation time constant

- Similar results of reduced adaptation time constant have been observed in noise induced hearing loss[4], suggesting possible similarities in synaptic transmission impairment .



- This suggests a longer synaptic depression. Hence, we targeted the redocking time constant (RTC) and increased it to 3X its original value to replicate observed reduction in driven rates.

Simulating IHC dysfunction



From existing model

- Outputs from C1 (dominating low and mid sound levels) and C2 (observed between 80-100 dB SPL) filters, and C1+C2(rms) output from low pass filter plotted against sound level.

- Both C1 and C2 show exponential increase with sound level.

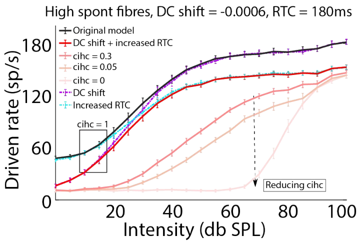
- Since only C1 pathway is affected by IHC damage (reduced cihc), physiology results of reduced driven rates observed at high sound levels cannot be explained by cihc alone.

Using additional parameters

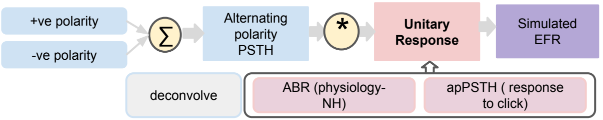
- Simulation results (without reducing cihc) show:
 - Introducing a DC shift in the IHC transduction function, we get reduced spontaneous rates
 - Increasing the RTC allows us to get reduced driven rates

- Results show that even with no change in cihc, effects similar to physiology can be simulated using the model.

- Reducing cihc shows change in curvature of the rate level curves with no effect on driven or spontaneous rates.



Evoked Potentials

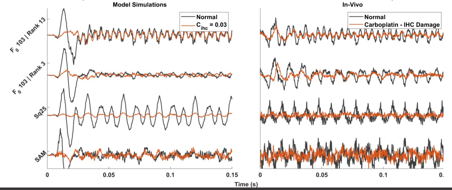


- Unitary response derived by deconvolving ABRs corresponding to clicks, obtained from normal hearing animals with the click stimulus PSTH generated using AN model. This unitary function was then convolved with the PSTH corresponding to complex temporal stimuli, giving simulated EFRS [5].

- This simulated EFRs were compared with corresponding EFRs obtained from physiology. This comparison was done to find the best set of parameters in the AN model, which would replicate the physiology EFRs.

- We found that mid-level EFRs did not show significant differences between the optimal current BEZ model (CIHC reduced to 0.03) and the refined model (added DC shift and RTC increase to the CIHC=0.03 model).

- Thus suggests that CIHC alone may capture some effects of CA in evoked EFRs, however, this should not be taken to support that CIHC alone is adequate to account for all effects of IHC damage given the single-unit data.



Conclusions

The proposed refinements in the model are able to capture in-vivo phenomenon observed following specific-IHC dysfunction

- As observed previously, cihc parameter in itself is not able to capture the observed changes in single unit physiology post IHC dysfunction

- The proposed changes in parameters in the model including a DC shift in the transduction function and increased redocking time constant allow the model to capture reduced driven and spontaneous rates (even with cihc=1).

- However, when using the same parameters for comparing physiology using simulated EFRs, we find that these parameters may not be sufficient to model CA damage without reducing cihc.

- This suggests that while a multi-parameter fit may be able to capture specific IHC damage for both single unit and evoked responses, a more biophysically inspired modification to the model may be required to capture the natural dependencies of spontaneous/driven rates and transduction-function slope on IHC damage.

Acknowledgements:

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References:

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