A single compartment model of intrinsic hair cell tuning to low-frequency stimuli.

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Outline

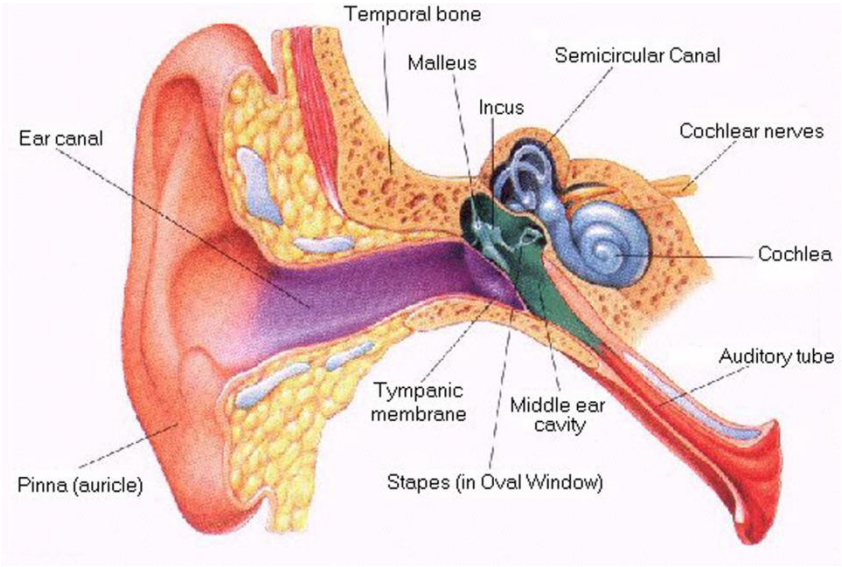
- Modeling Hair Cells – Why?
  → Biological Design & Structural Limitations

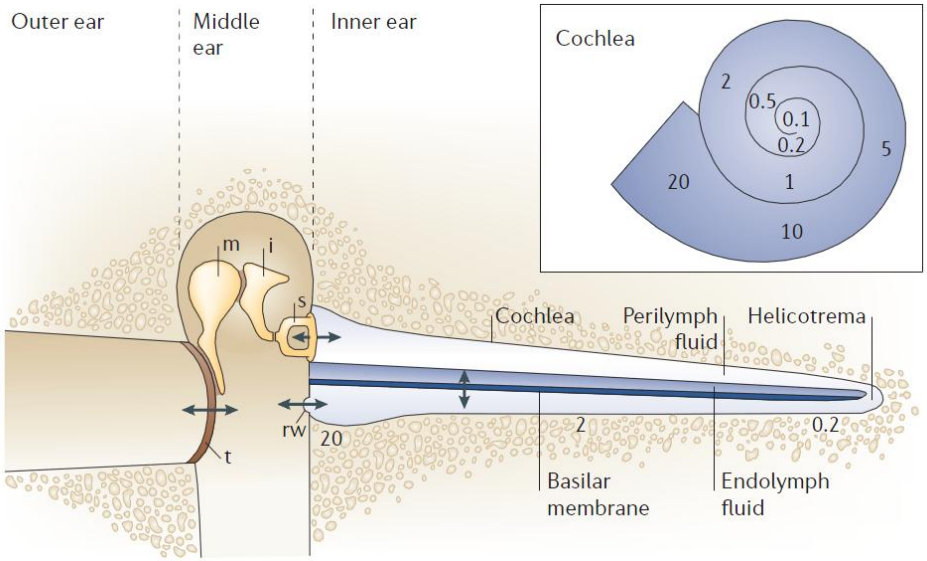
- Experimental Objectives
  → Model Design

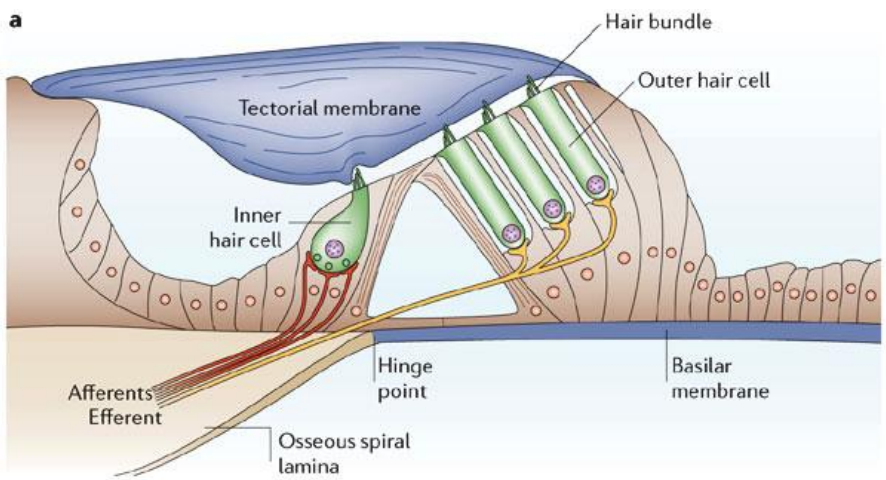
- Experimental Results
  → Good, Bad & Ugly

- Conclusions and future directions

Hair cell tuning in the mammallian cochlea

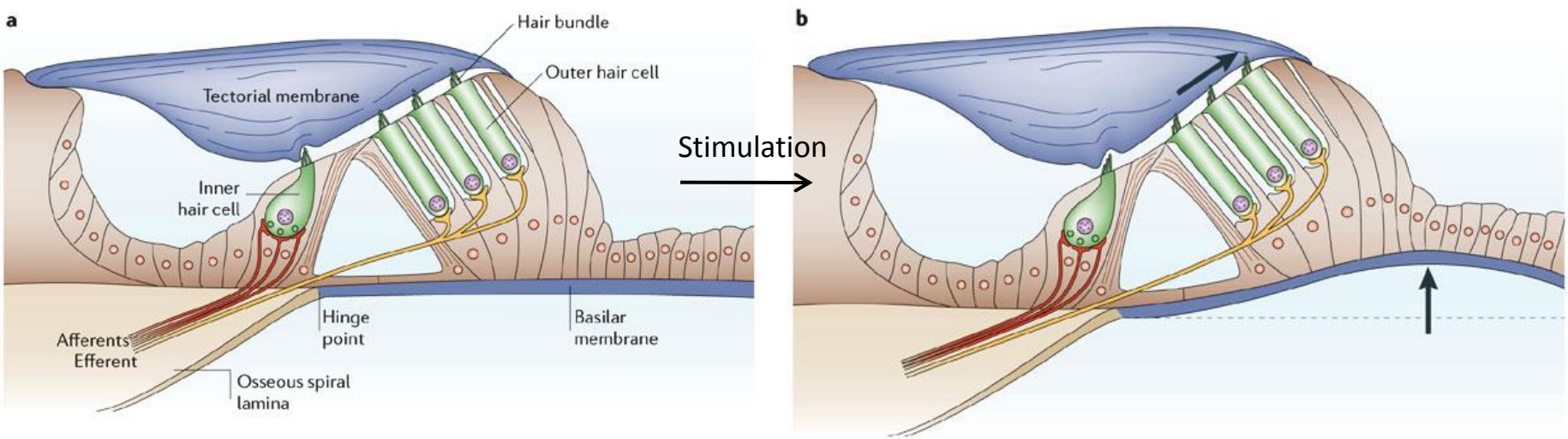


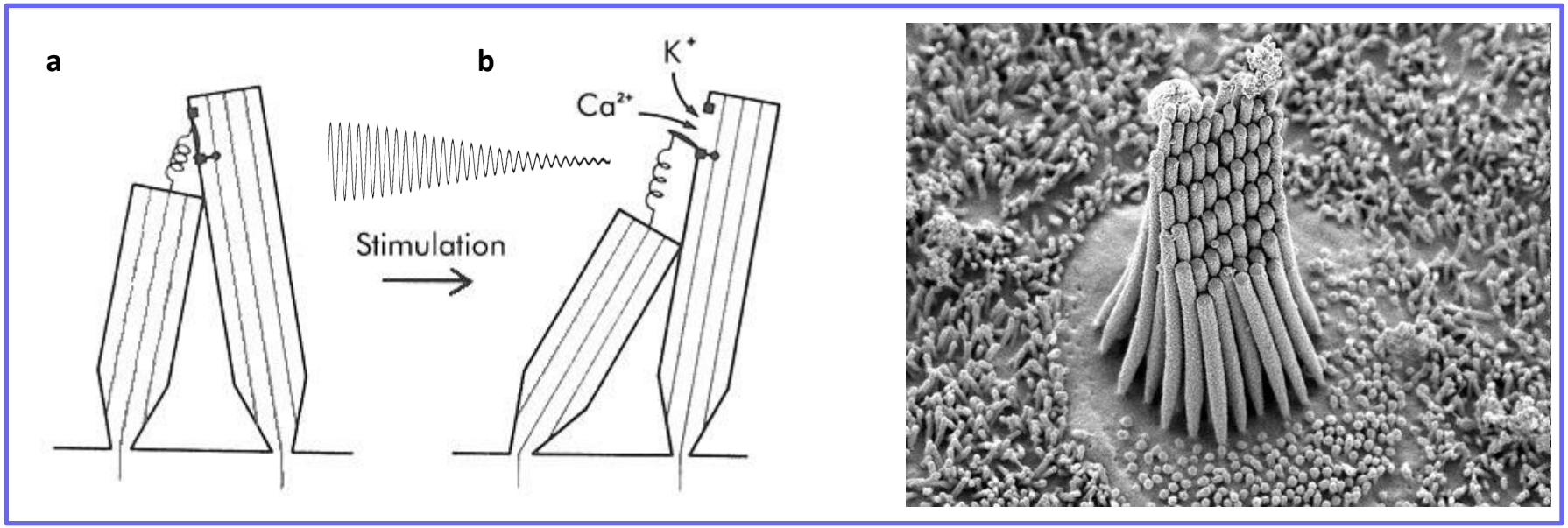




(Fettiplace & Mackney, 2006)

Hair cell tuning in the mammallian cochlea

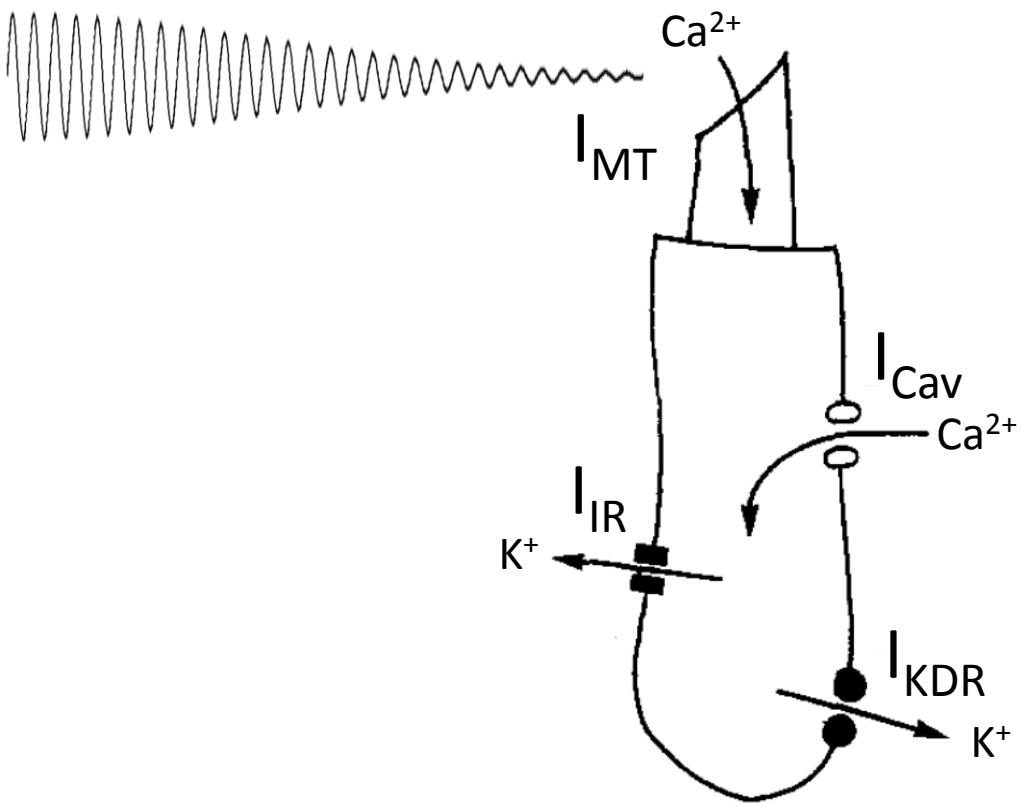




(Fettiplace & Mackney, 2006)

Biophysical mechanism of intrinsic tuning in nonmammals

Hair cell bundle height and density don't explain diversity of sensitivity at low frequencies … intrinsic oscillations?

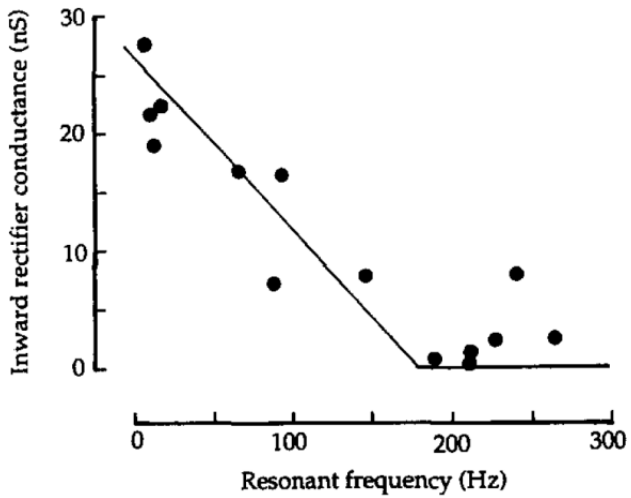


(Wu et al., 1995)

Experimental objectives

Expected Results

- Passive properties of hair cells match empirical data (R_m, V_{rest}, capacitance, size, …)
- Accurately model ionic currents
- Resonance and/or spiking in response to static current clamp
- As gIR increases, firing rate decreases.

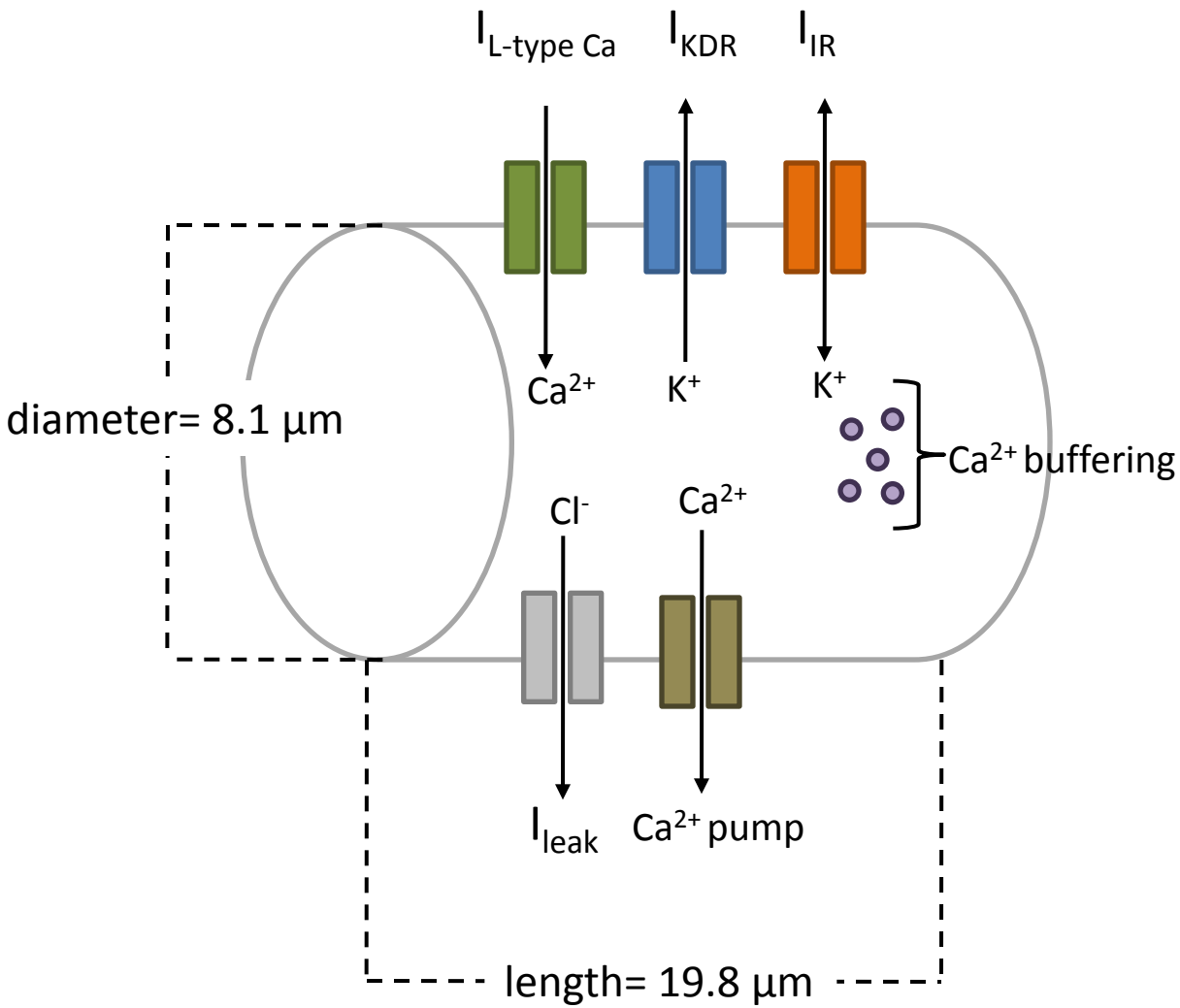


(Wu et al., 1995)

Additional questions

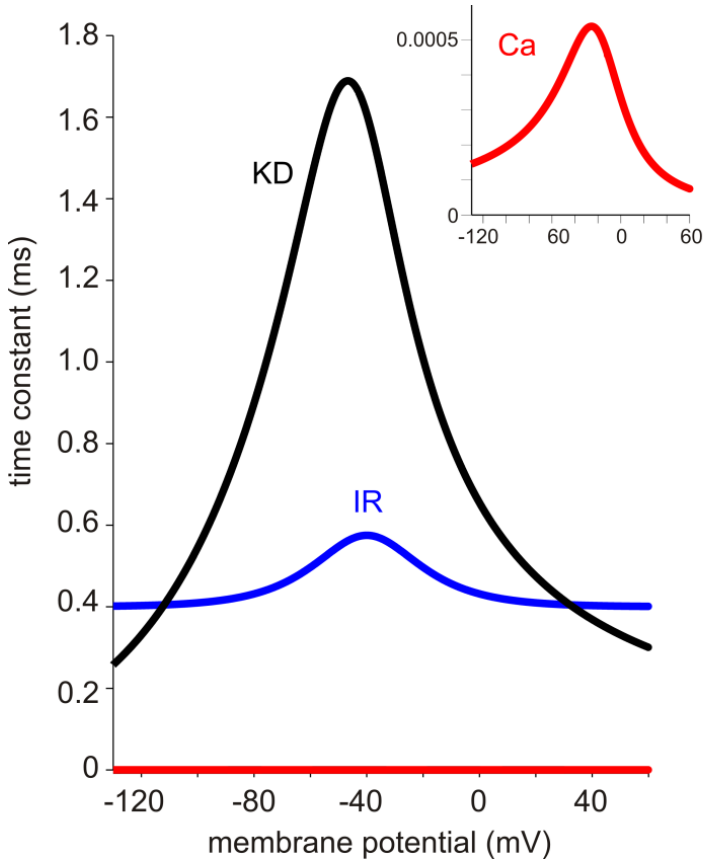
- How does firing rate depend on frequency and amplitude of current injection (for cells with different gIR)
- Can the firing rate of a cell be predicted from the frequency and amplitude of current input?
- How does the model respond to a complex current input?

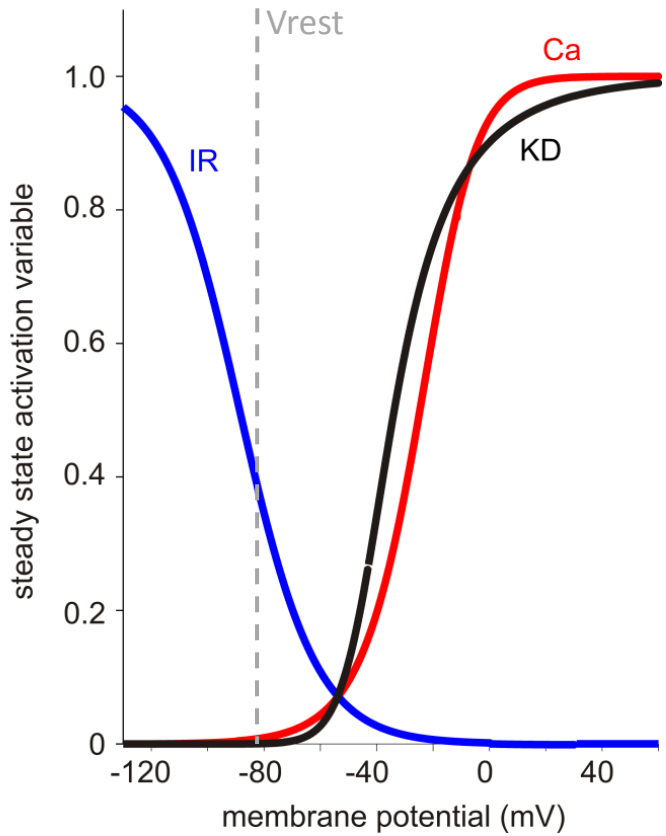
Hair Cell Model



Steady state activation curves of I_{KD}, I_{IR}, and I_{Ca}

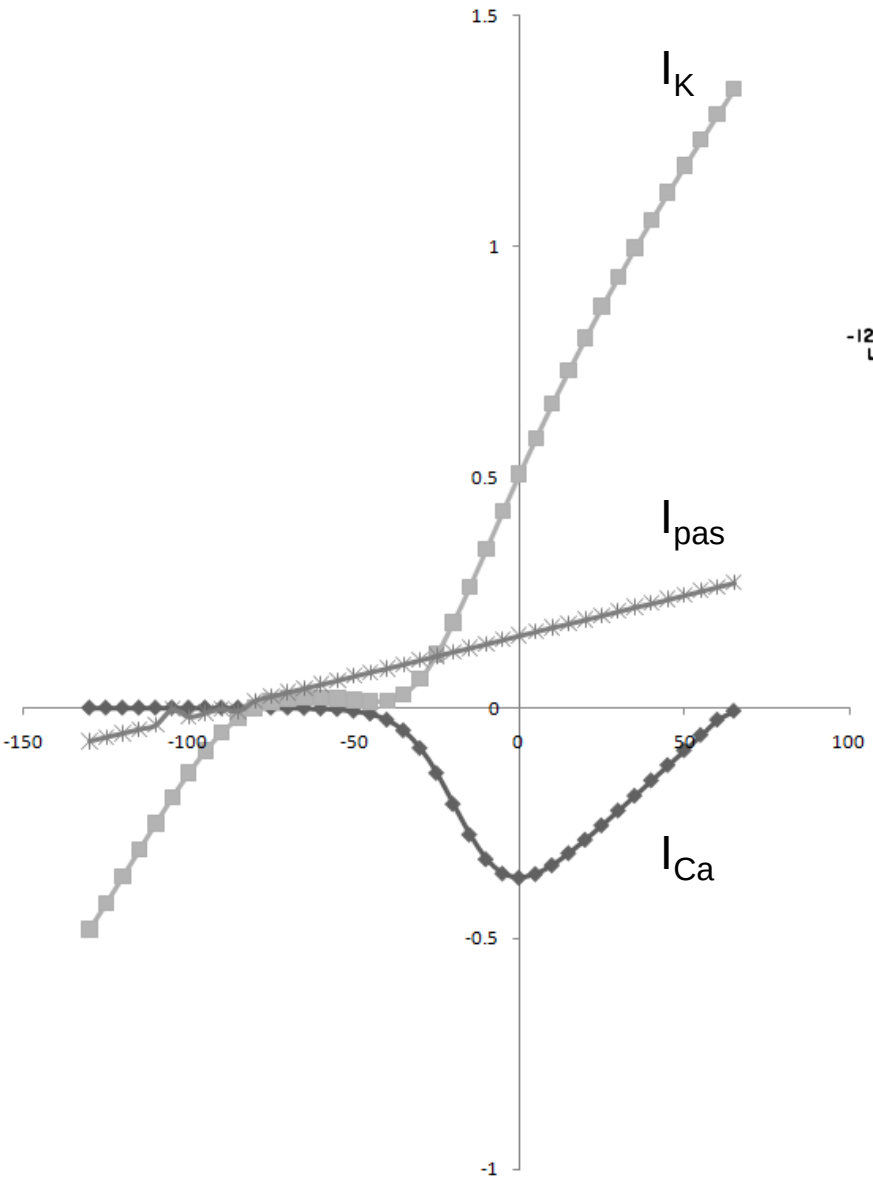
(ICa model based on Zidanic and Fuchs, 1995; IIR based on Goodman and Art, 1996)



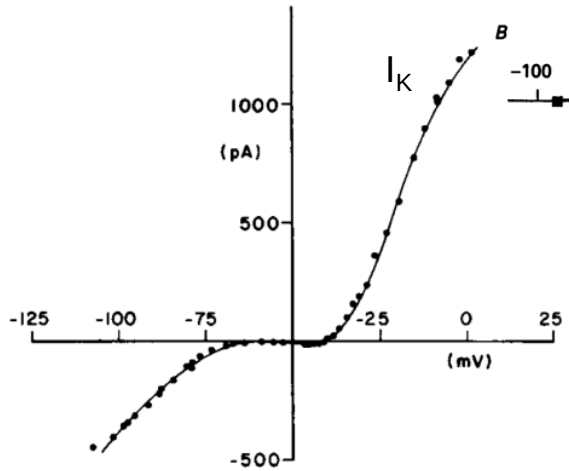


IR and Ca are both modeled on experimental observation of hair cells

Are current-voltage properties comparable with empirical data?



(Fuchs et al., 1988)



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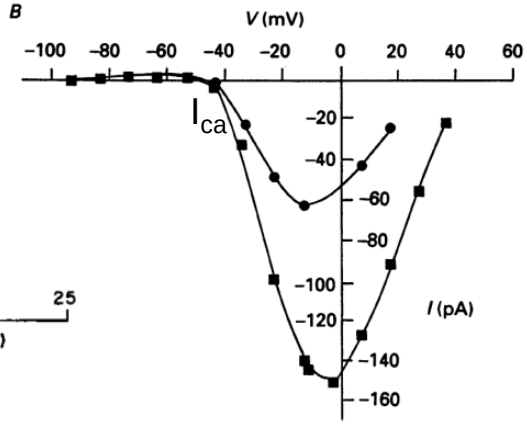
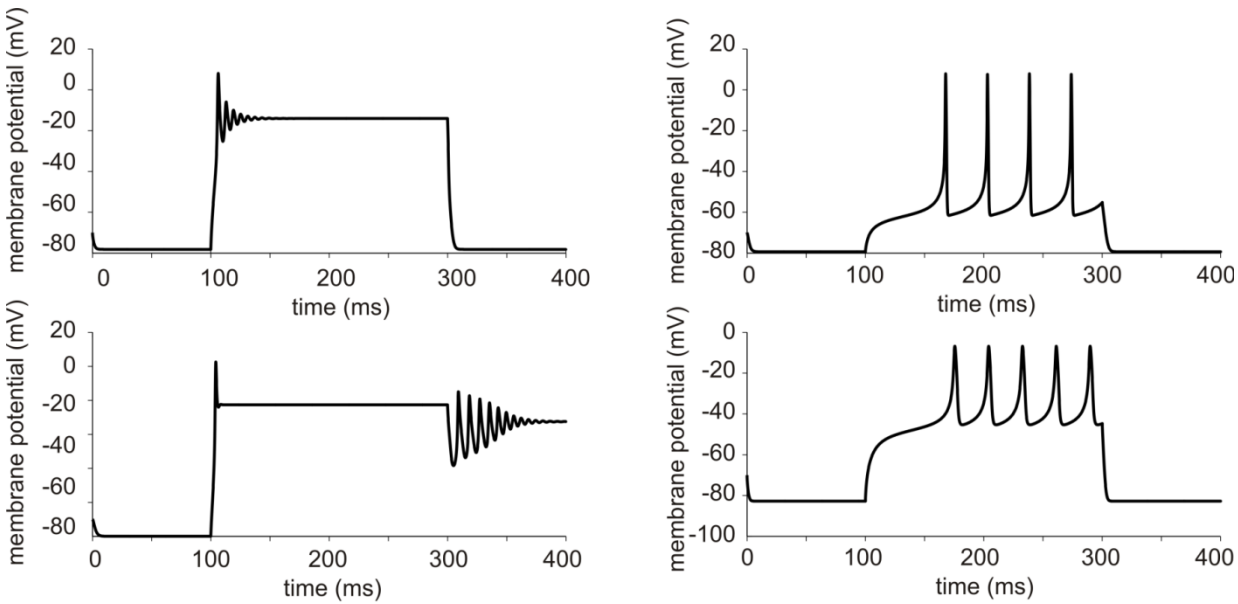


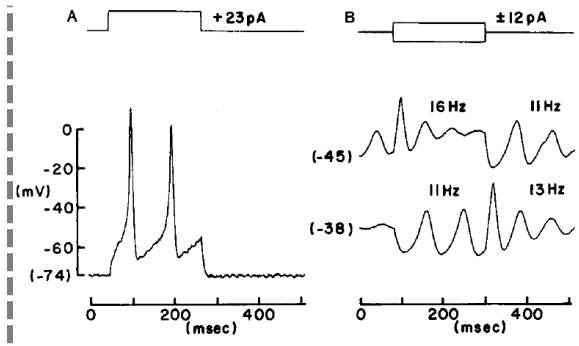
	Model	Experimental
Length x width (µm)	19.8 x 8.1	19.8 x 8.1
Resting potential (mV)	-82	-78
Thresh. Potential (mV)	-53	-60 (?)
Capacitance (pF)	5.8	6.4
Input resistance (MΩ)	**119**	**26 (?)**

Model membrane properties and IV curves are a good match with experimental observations.

Why the disparity in Ca^{2+} current? resistance?

What types of responses do we see?





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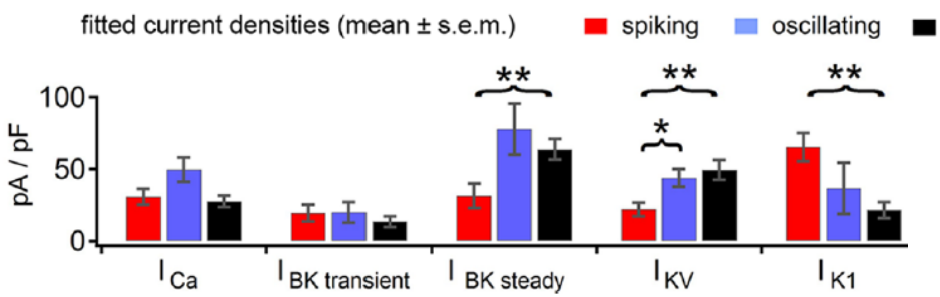
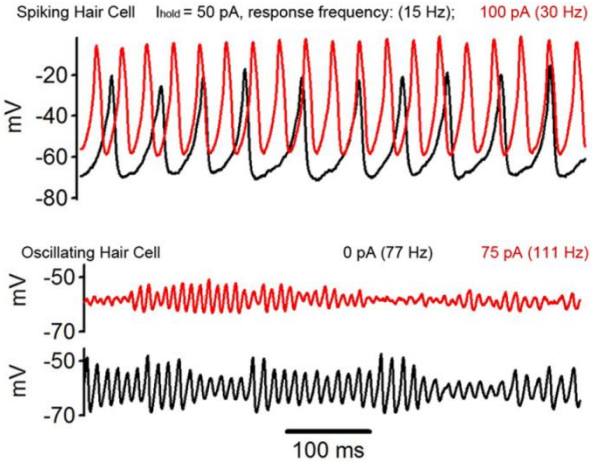


(Rutherford and Roberts, 2009)



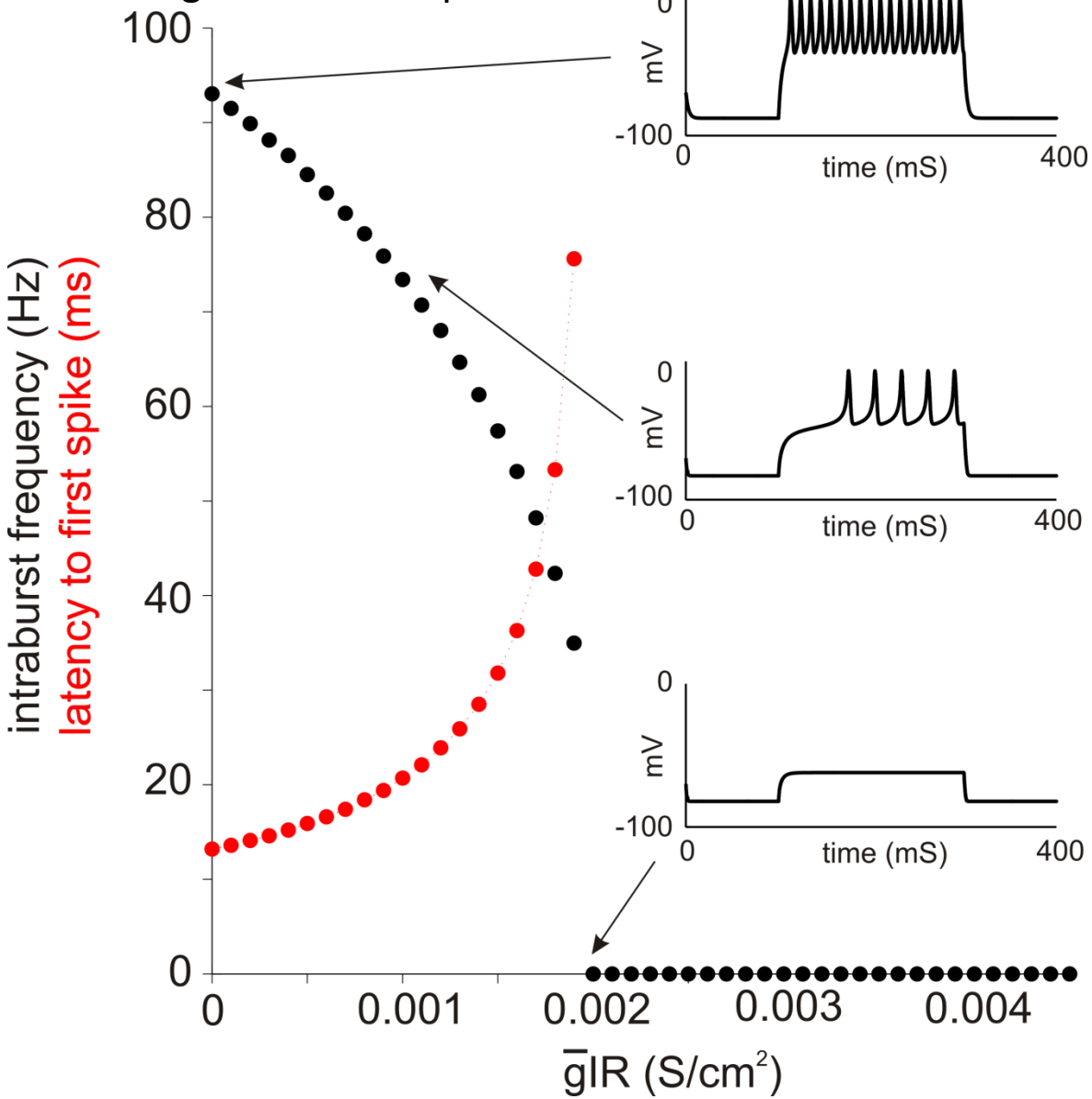
(Rutherford and Roberts, 2009)

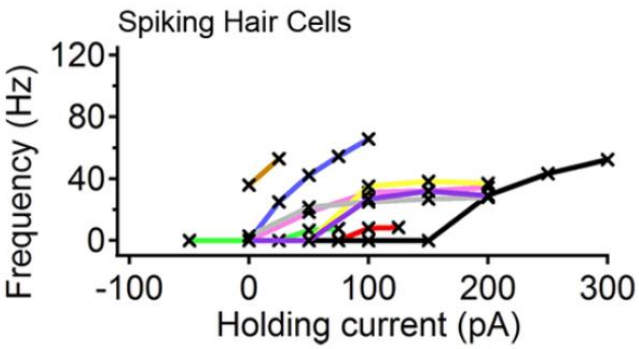
We see both resonance and spiking in different cells, which matches experimental observations.

Passive conductance level influences probability of spiking

Does firing rate vary with gIR for a **static** current clamp?

Holding current = 80 pA





(Rutherford and Roberts, 2009)

Cells with greater gIR have lower firing rates.

Describing a sound as a sum of sine waves

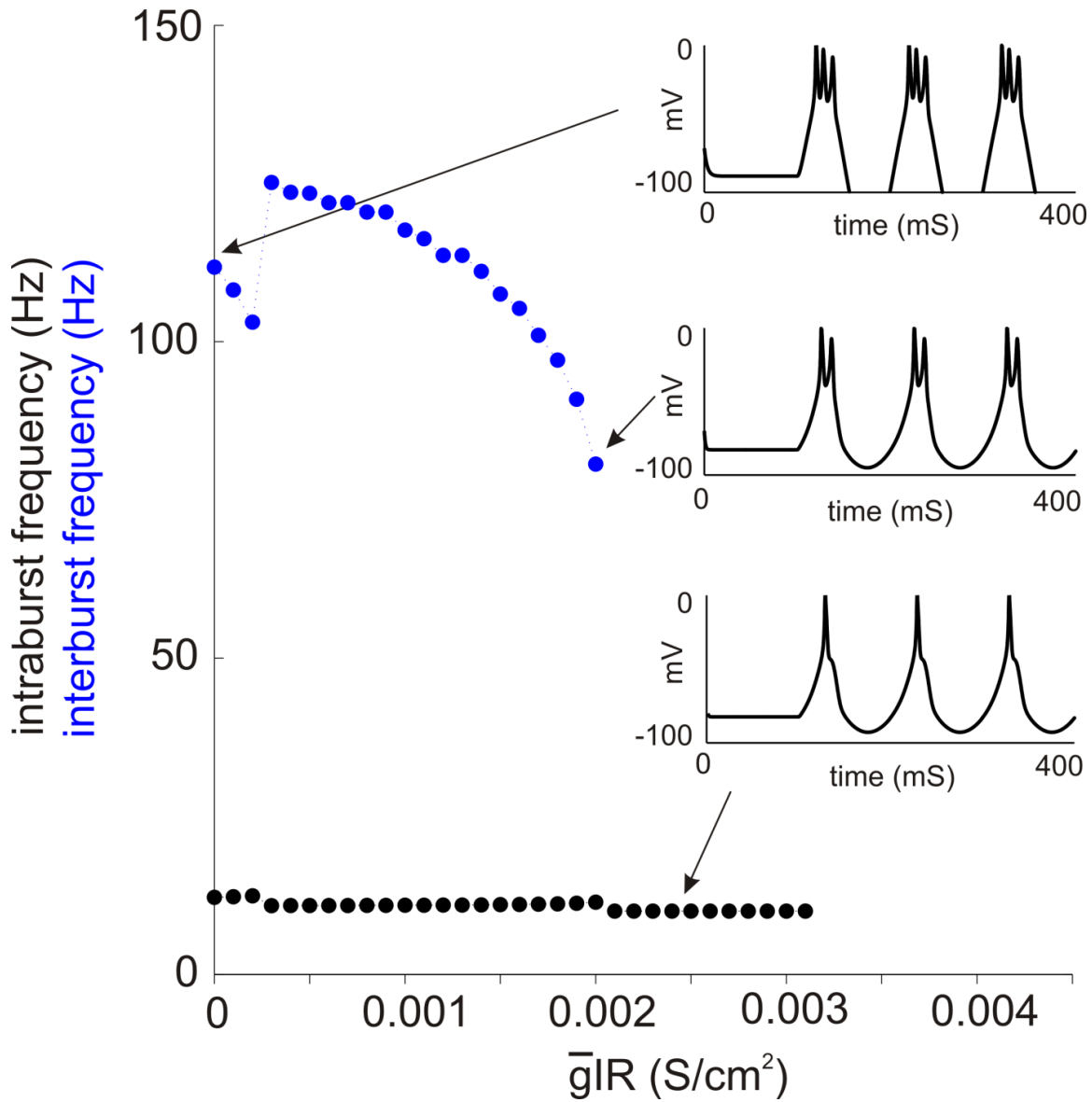
10 Hz (1)

30 Hz (2)

80 Hz (3)

all Hz (1+2+3)

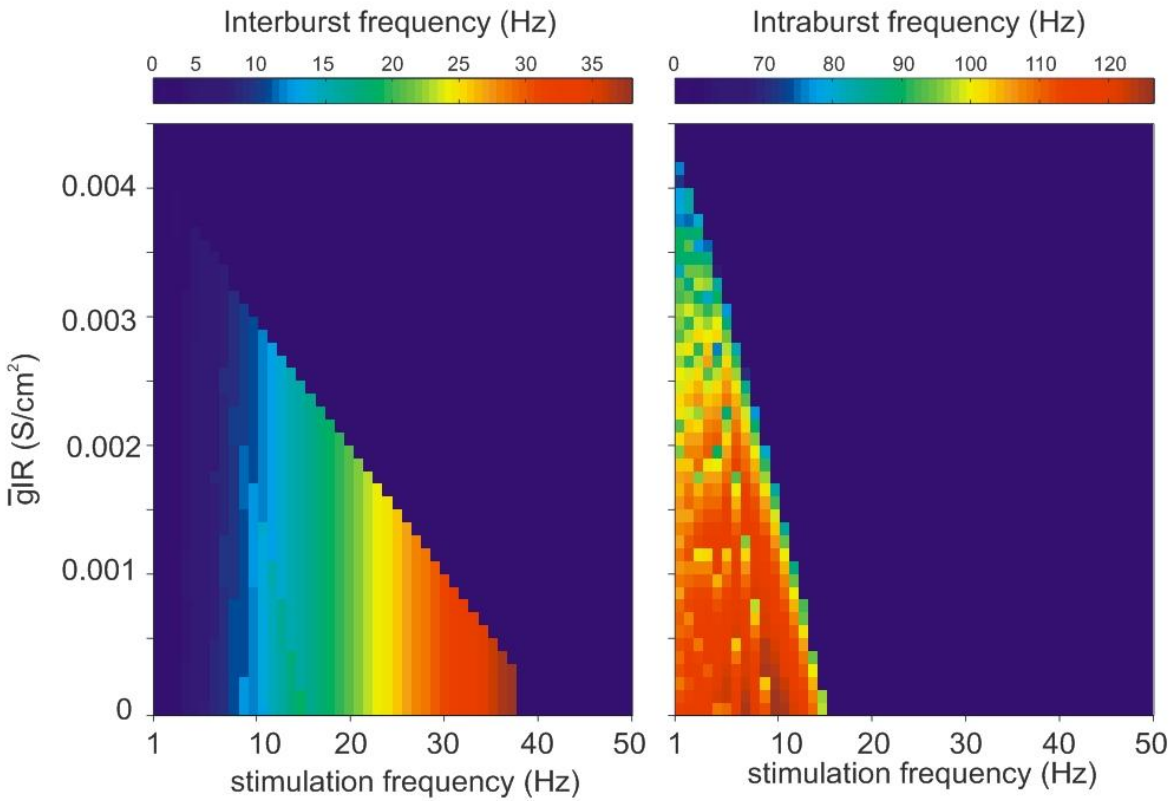
How does firing rate vary with gIR for an **oscillatory** current clamp?

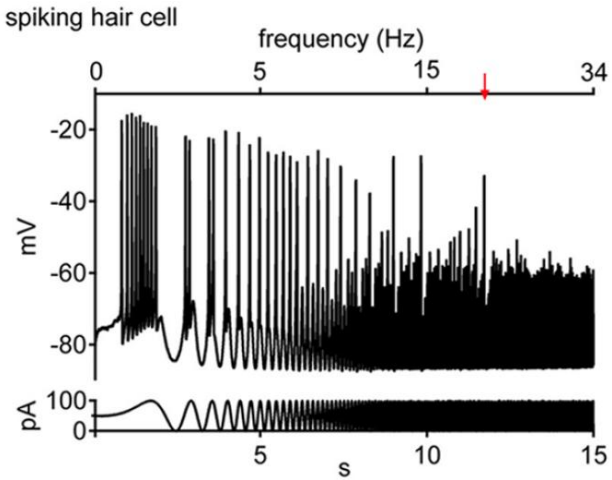


A neuron can code for a stimulus frequency by:
(1) **intra**burst frequency
(2) **inter**burst frequency

Cells with different gIRs respond with different intraburst frequencies.

How does firing rate vary with gIR and stimulus frequency?

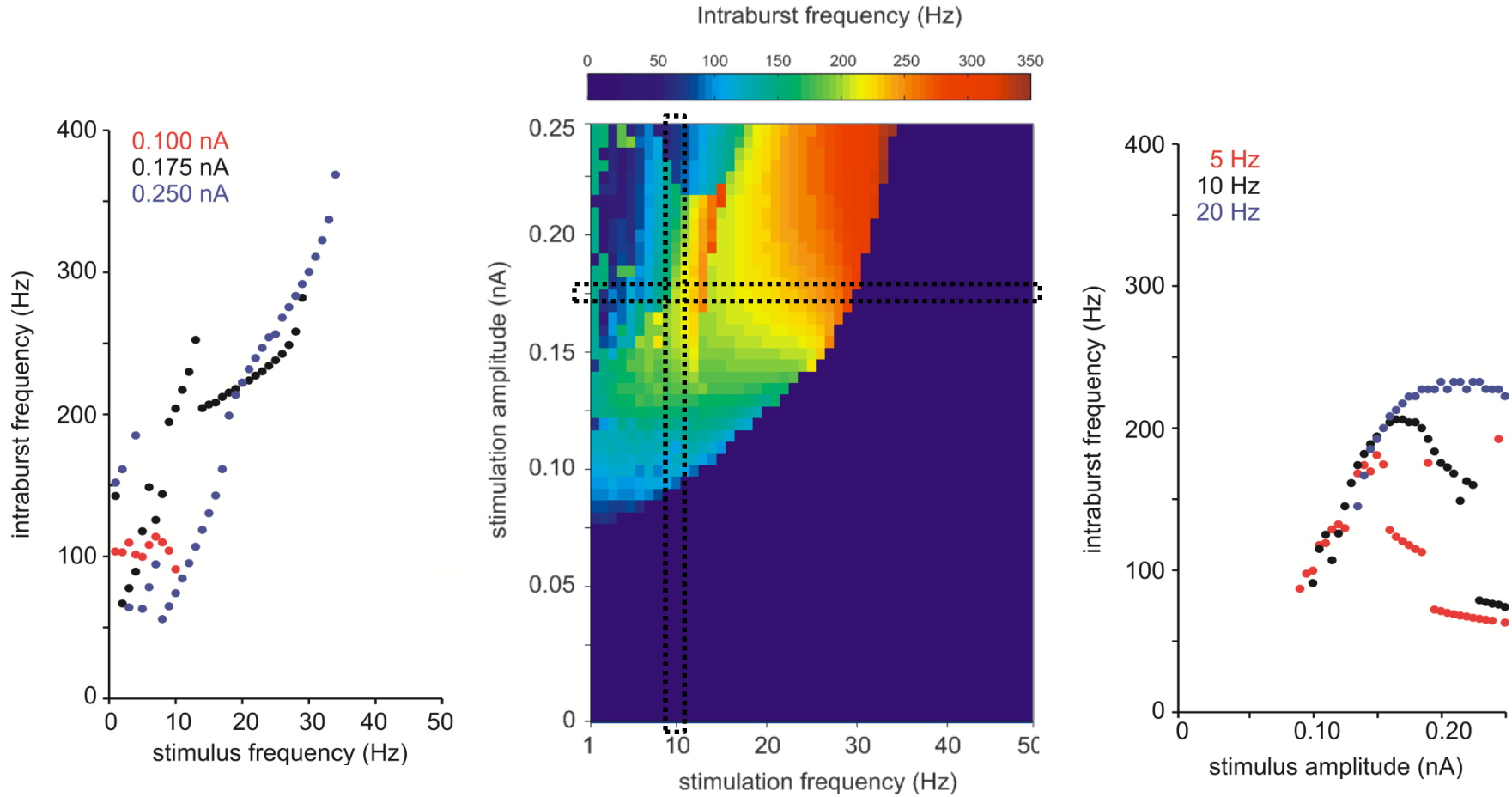




(Rutherford and Roberts, 2009)

gIR limits the range of frequencies to which a cell can respond

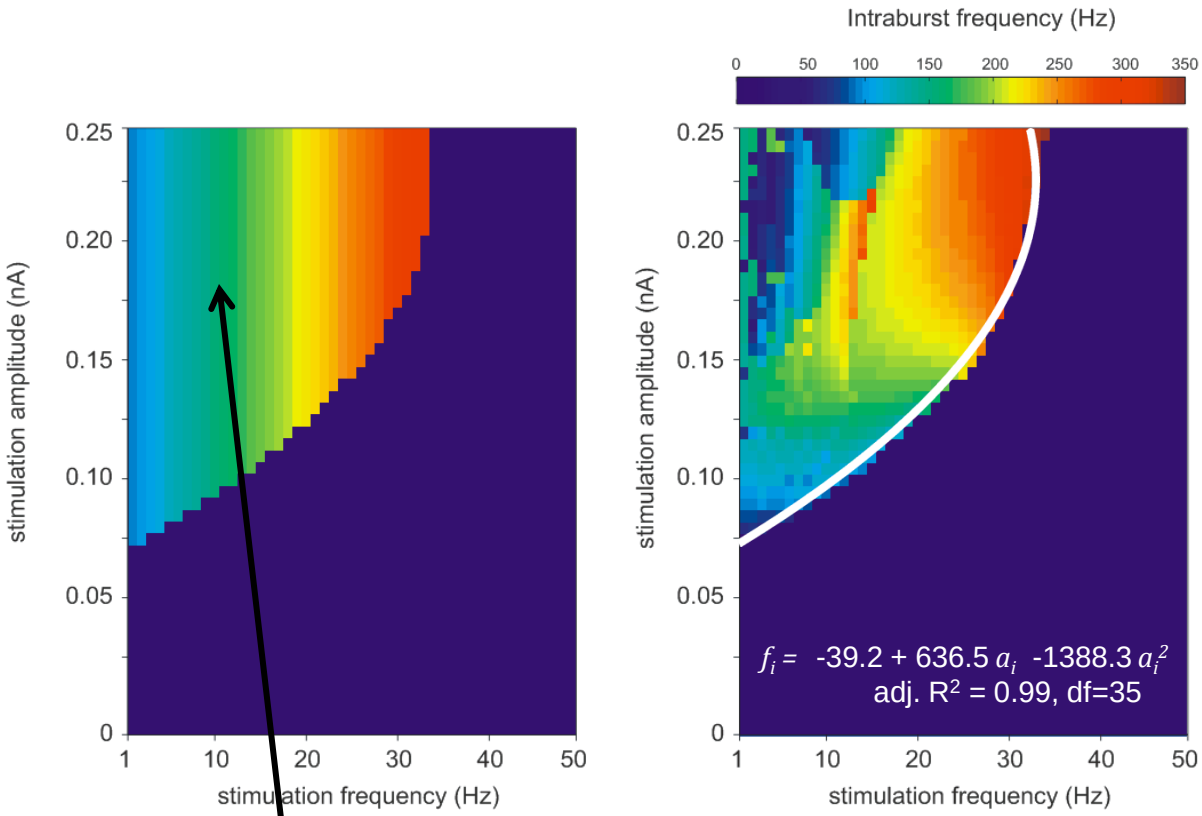
Does the firing rate of a cell depend on stimulus amplitude?



Keeping amplitude the same, firing rate increases with stimulus frequency (to a limit)

The model cell is tuned to a specific amplitude of a given frequency.

Can a single hair cell neuron code for stimulus frequency?



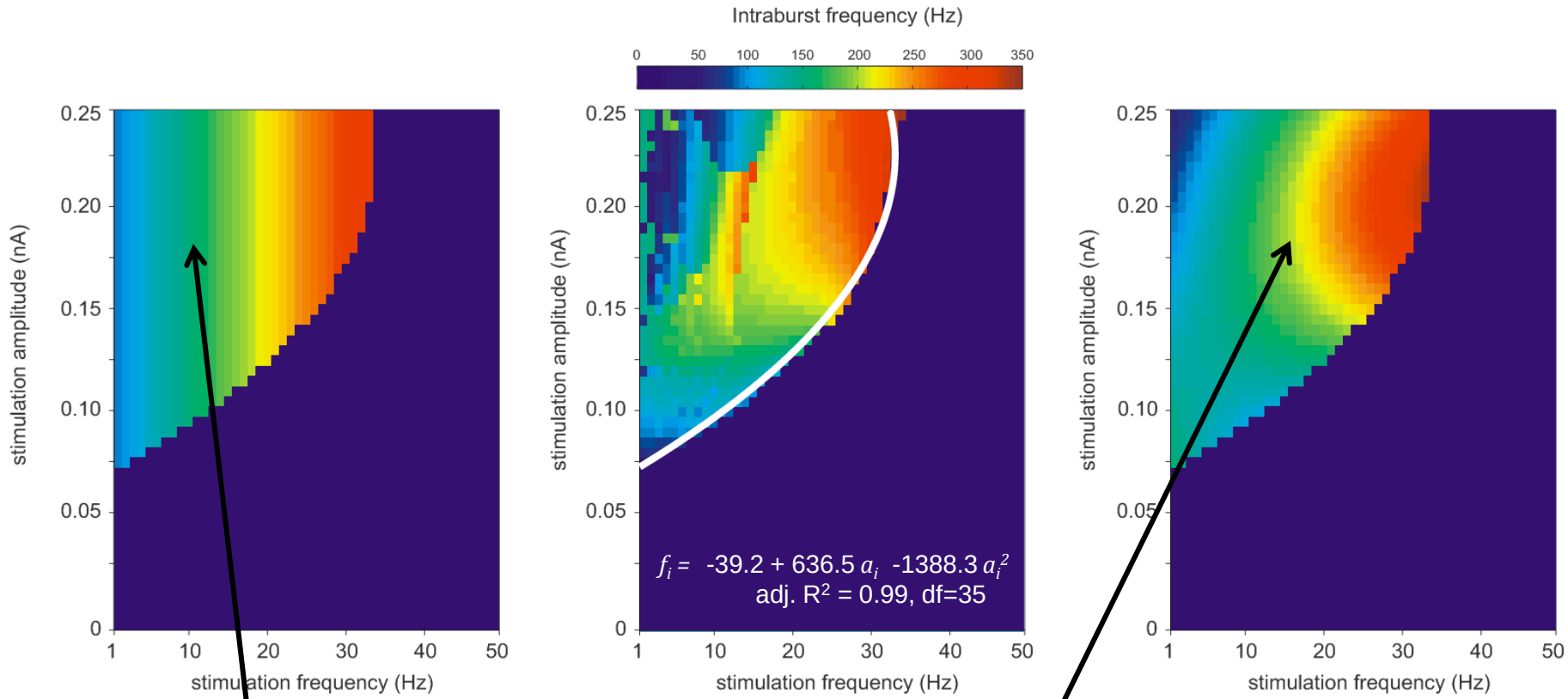
$$r_i = \beta_1 + \beta_2 f_i$$

	β_1	β_2
	88.3	6.6
	(0.000)	(0.000)

adj. R^2 = 0.72, df=823

Knowing the burst rate of a cell, we can make a good of the stimulus frequency.

Can a single hair cell neuron code for stimulus frequency? amplitude?



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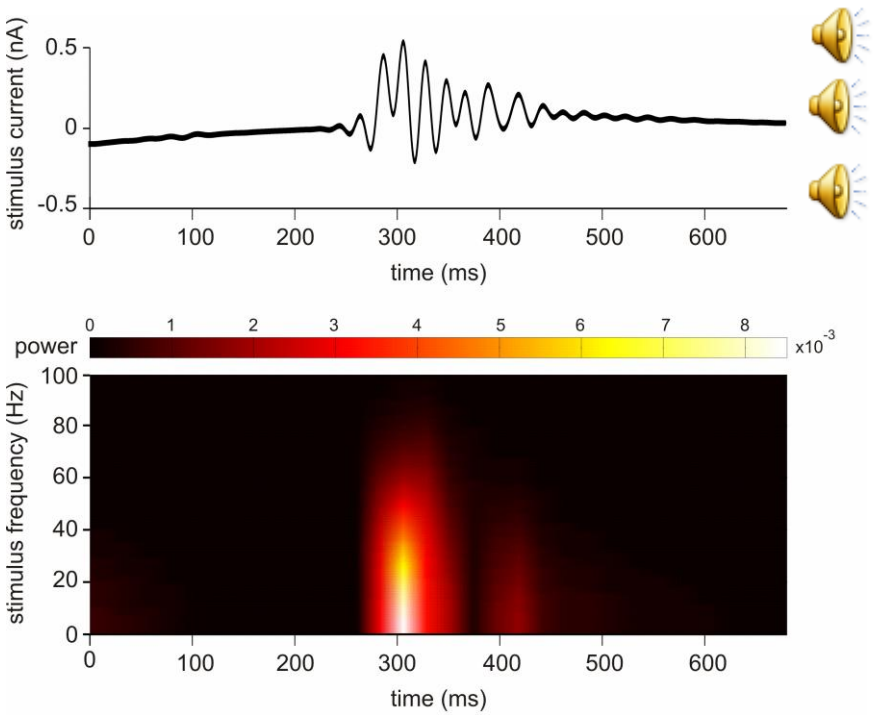
$$r_i = \beta_1 + \beta_2 f_i + \beta_2 a_i + \beta_2 f_i a_i + \beta_2 f_i a_i^2$$

	β_1	$\beta_2 f_i$	$\beta_2 a_i$	$\beta_2 f_i a_i$	$\beta_2 f_i a_i^2$
	213.0	-30.3	-638.4	343.6	-771.4
	(0.000)	(0.000)	(0.000)	(0.000)	(0.000)

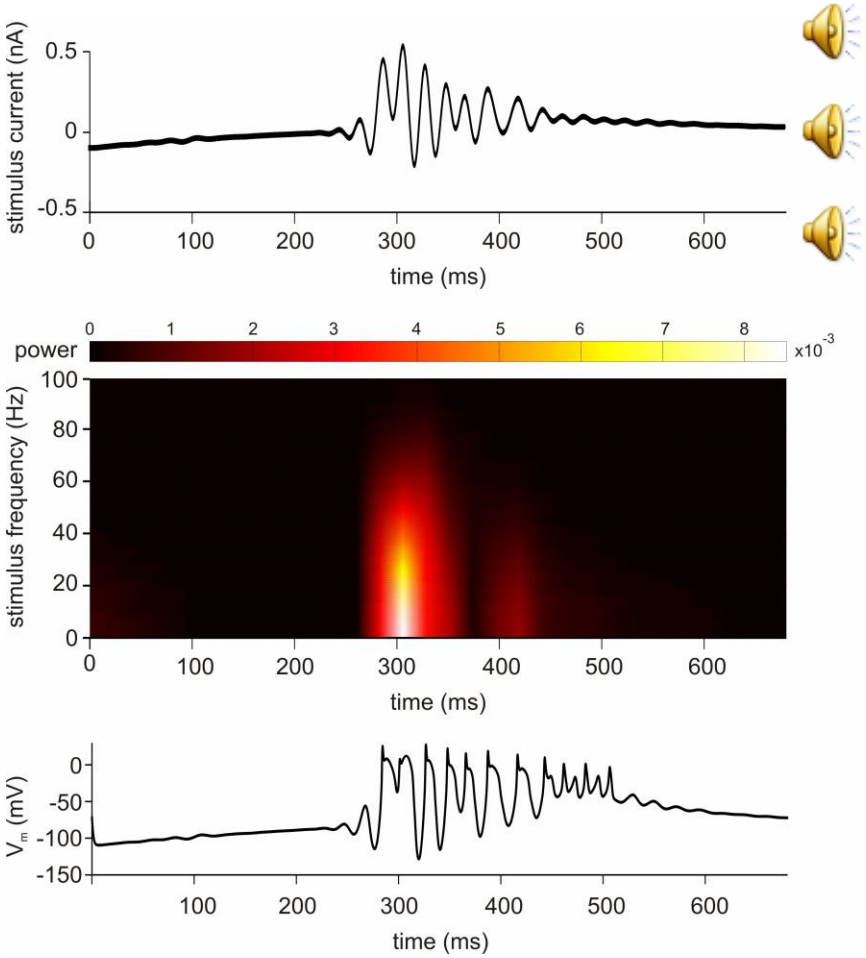
adj. R^2 = 0.80, df=823

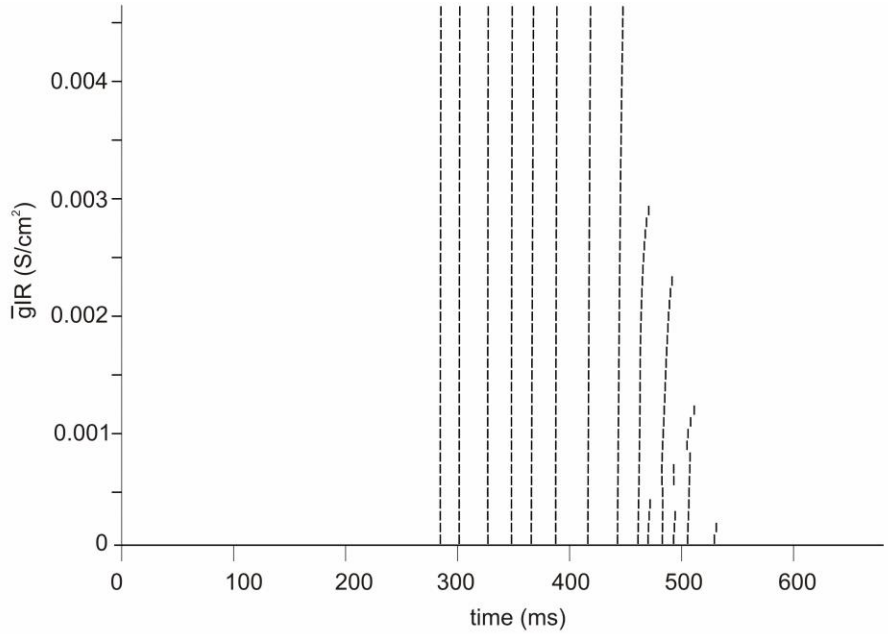
Knowing the burst rate of a cell, we can make a good of the stimulus frequency. Together, two cells can potentially code for both frequency and amplitude.

How does the model respond to a complex stimulus?



How does the model respond to a complex stimulus?





<u>Intra</u>burst frequency cannot entirely encode this complex sound.
How does variation of amplitude in time influence intraburst rate?

Conclusions

- Passive membrane and spiking properties of the model are a good match with experimental observations in hair cells.
  → Can differences in Ca^{2+} current be accounted for? Resistance?

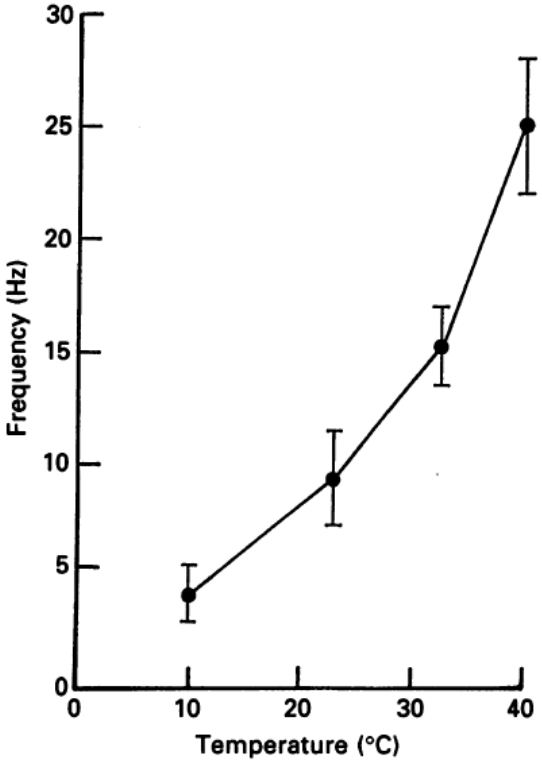
- Model cells with greater gIR have lower firing rate responses

- Cells respond with different rates to different frequencies and amplitudes. We propose a function by which two cells can discern both the frequency and amplitude of a simple stimulus. Can this function be tested in vitro?
  → lateral inhibition, multiple aferent

We propose how a hair cell might respond to a complex stimulus

Future Directions

- Fine tune model to correct for Ca^{2+} current in input resistance…?
- How does the model respond to a sine wave with a dynamic amplitude?
  → knowing this, can we use firing rate to predict a complex sound?
- Can latency of spiking code for the phase of a sinusoidal stimulus?
- How does temperature influence the hair cell's firing rate profile?



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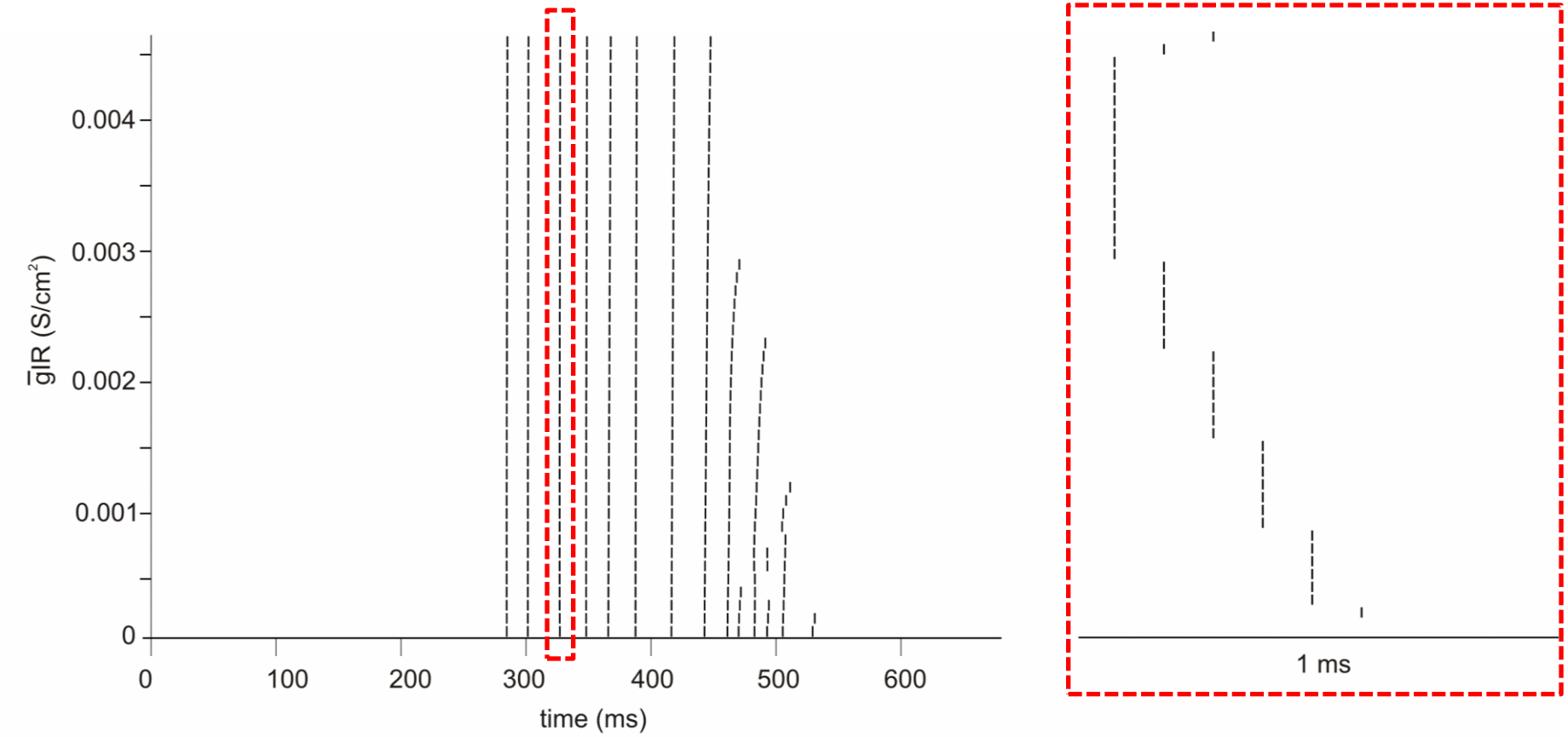
0.004
0.003
0.002
0.001
0
$\bar{g}$IR (S/cm^2)
0
100
200
300
400
500
600
time (ms)
1 ms