



Combined biophysical and statistical modeling pipeline for investigating roles of ion channels in stimulus encoding

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Introduction

To understand single neuron computation, it is necessary to know how specific ion channel conductances affect neural integration and output. Knowledge of these relationships is critical in understanding how changes in biophysical properties affect stimulus encoding. Here we present a computational pipeline combining biophysical and statistical models to provide a link between variation in functional ion channel expression and changes in single neuron stimulus encoding. Biophysical models provide mechanistic insight, whereas statistical models provide insight into what spiking actually encodes. We used published biophysical models of two morphologically and functionally distinct projection neuron cell types: mitral cells (MCs) of the main olfactory bulb, and layer V cortical pyramidal cells (PCs). We first simulated MC and PC responses to pink noise stimuli while scaling individual ion channel conductances and then fit point process regression models (generalized linear models; GLMs) to the resulting spike trains. This provides both stimulus effects (the stimulus filter) and spike-history effects (the history filter). Although we find interesting differences for several channel types in each model, we focus here on A-type K^+ channels (K_A) and high-voltage-activated Ca^{2+} channels (Ca_{HVA}) as examples of our pipeline. Increasing K_A decreases trial-to-trial correlations and vice-versa. Changing Ca_{HVA} conductance converts our PC models from burst firing to regular firing. These changes are reflected predominantly in changes of the GLM stimulus filter for K_A and the history filter for Ca_{HVA} . Stimulus reconstruction reveals that changes to each conductance results in changes in encoding of specific stimulus features. Thus, we can predict how differences in individual conductances affect encoding of specific stimulus features. Our computational pipeline provides a way of screening all channel types to identify those channels that most strongly influence single neuron computation in any cell type of interest.

Methods

Biophysical Models

- Models were programmed and run in NEURON v7.4^[2] via Python2.7 on a personal computer or the Pitt CRC cluster^[2]
- Mitral cell (MC) model from Bhalla and Bower, 1993^[3]
- Pyramidal cell (PC) model from Almog and Korngreen, 2014^[4]
- All channels modeled based on Hodgkin-Huxley-style kinetics
- Conductance densities for each channel type were scaled globally
- V_m responses to somatic injection of 100 correlated stimulus trials were recorded from the soma for each scaling factor and for each channel type

Stimulus Generation
- 3 s Gaussian white noise was generated and convolved with an alpha function: $\alpha(t) = (t/T)^{-\alpha} \exp(-t/T)$ with $T = 3$ ms^[5]

- To mimic trial-to-trial experimental noise in spike timing in deterministic models, we used 100 trials of correlated noise^[6]

- Noise was added to a constant step current yielding firing rates: MC, 500 pA and ~35 Hz; PC, 400 pA and ~20 Hz

Analysis
- All analyses were performed in python or Matlab using standard libraries, including elephant^[7], neo^[8], and custom scripts

- PSTH^[9]; correlation^[10]; STA features^[10]; stimulus reconstruction^[10]

Generalized Linear Models (GLMs)

- Models were fit and run in Matlab R2018a on a personal computer
- GLMs differed from canonical log link function^[7] (assuming the observations are in Poisson distribution) as it introduces bias, so we replaced it with the logistic link function
- The first 800 ms of each trial was ignored to allow neurons to reach steady state firing
- 70 noise trials were used for training the GLM, and the remaining 30 trials were used for testing
- For testing, each stimulus was simulated for 10 trials, and spike times were used to create a PSTH, then compared to biophysical model PSTH^[8]

Equations for GLM Fits with the Penalty Hyperparameter

$$\min_{\beta(g_i), \beta(g_{i+1})} \sum_{i=1}^B -\ell_i(\beta(g_i)) + \lambda \sum_{i=1}^{B-1} \frac{1}{g_i - g_{i+1}} \|\beta(g_i) - \beta(g_{i+1})\|_1 \quad (1)$$

$$\lambda^* = \arg \max_{\lambda \in \Lambda} \left\{ \lambda : \sum_{i=1}^{B-1} \frac{1}{g_i - g_{i+1}} |\beta(g_i, \lambda)| > -\zeta + \max_{g \in \mathcal{G}} |\ell_i(\beta(g, \lambda))| \right\} \quad (2)$$

$$A(\lambda)|_g = \begin{cases} 1 & \text{if } \sum_{i=1}^{B-1} \frac{1}{g_i - g_{i+1}} |\beta(g_i)| - |\beta(g_{i+1})| > 1 \\ 0 & \text{otherwise} \end{cases} \quad (3)$$

Acknowledgements

This work was supported by NSF Award (1622977) to AK, REK, and NNU and by NIH Grant F32 (DC016775) to NGG.

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Mitral Cell (MC) Model

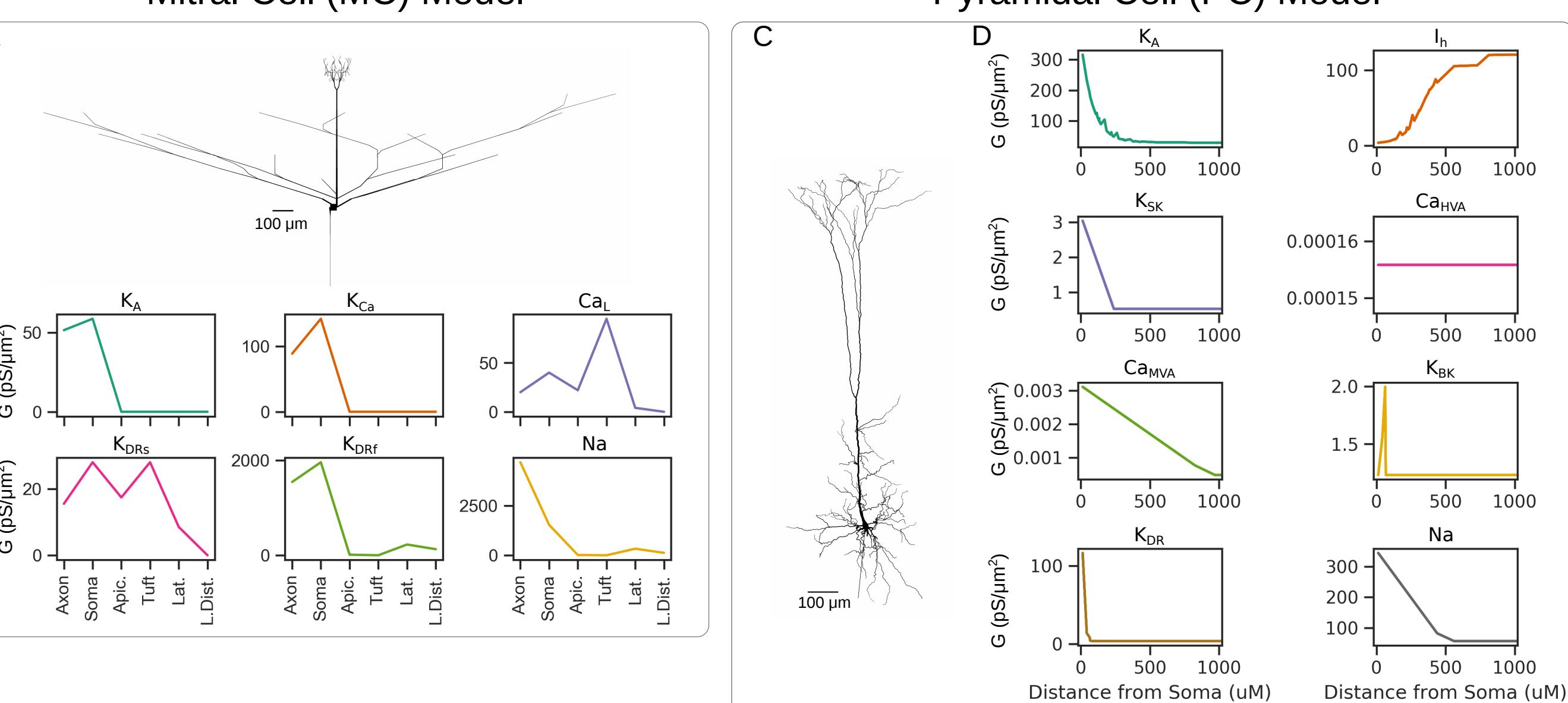
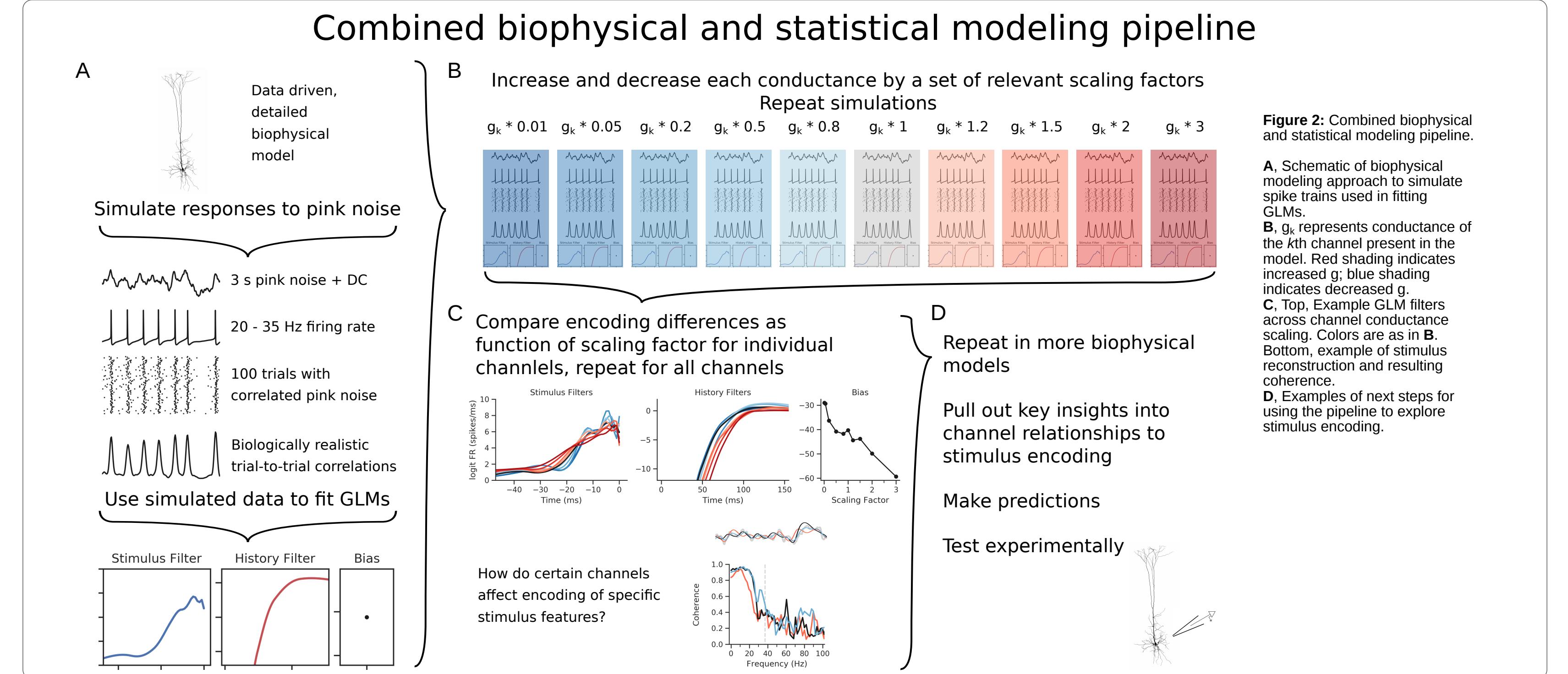


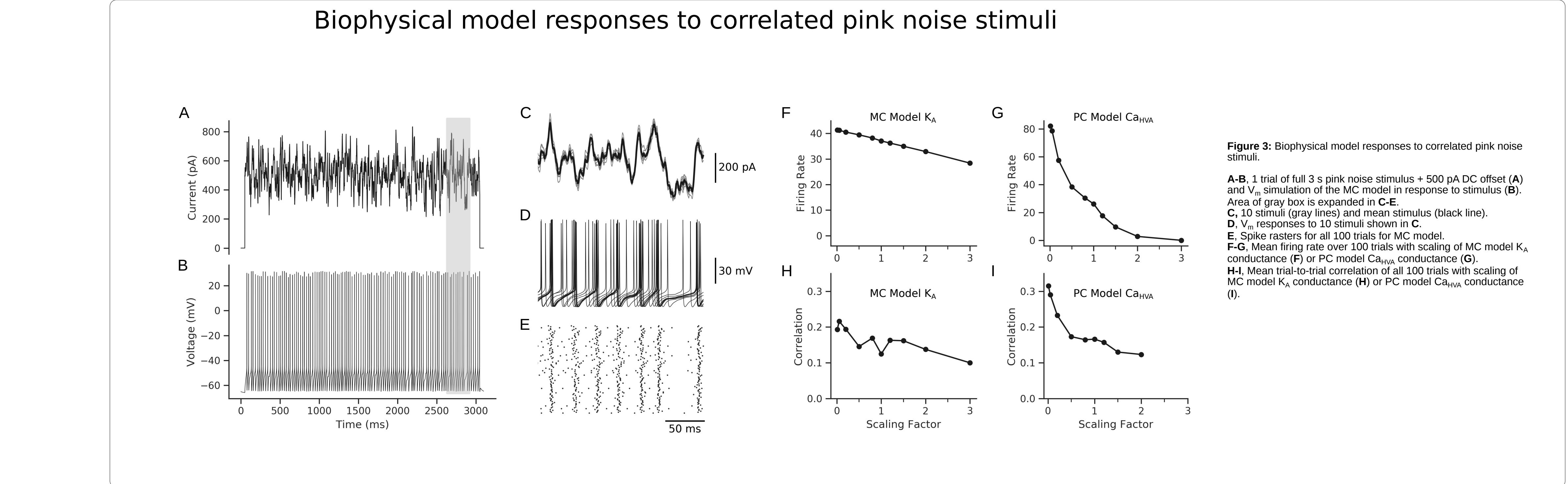
Figure 1: Model Descriptions

A-B, Depiction of the mitral cell (MC) biophysical model morphology (A) and distribution of channel conductances in different compartments (B). There are 6 distinct compartment-conductance density distributions: soma, apical dendrite, tuft, latitudinal dendrite (Lat.), distal latitudinal dendrite (Dist.). C-D, Depiction of the layer V pyramidal cell (PC) biophysical model morphology (C) and distribution of channel conductances as a function of distance from the soma in the apical dendrite. Conductance densities in the basal dendrites are equal to the soma. The axon was based off of Manen and Sejnowski (1998)^[10] model axon. E, Schematic of the GLM model architecture. Model parameters describe a stimulus filter, postspike history filter, and a constant bias term controlling spike rate. An exponential nonlinearity defines an instantaneous spike rate and is used to draw noisy spikes.



Combined biophysical and statistical modeling pipeline

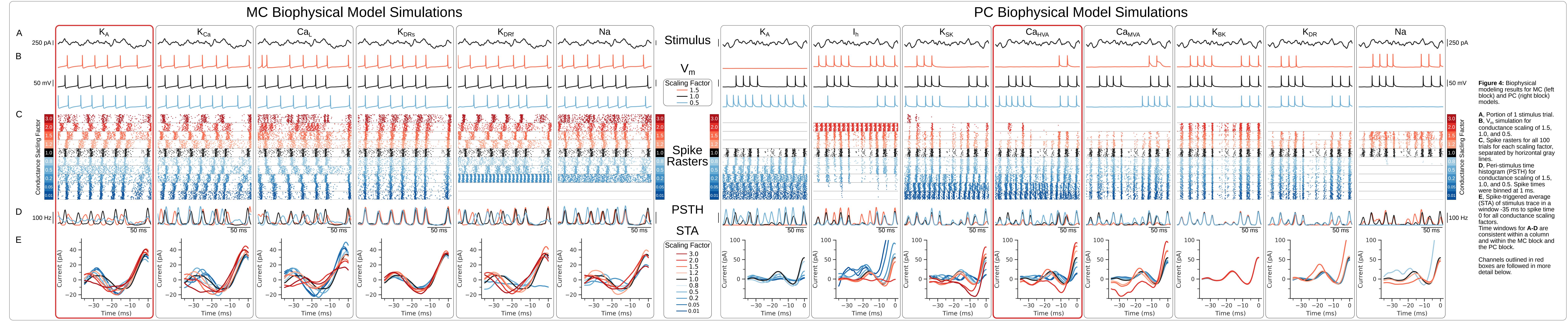
A Increase and decrease each conductance by a set of relevant scaling factors
B Repeat simulations
C Compare encoding differences as function of scaling factor for individual channels, repeat for all channels
D Repeat in more biophysical models
E Pull out key insights into channel relationships to stimulus encoding
F Make predictions
G Test experimentally



Biophysical model responses to correlated pink noise stimuli

A A trial of full 3 s pink noise stimulus + 500 pA DC offset (A) and V_m simulation of the MC model in response to stimulus (B). Area of gray box is expanded in C-E.
B V_m responses for all 100 trials for MC model (C). Top: Example GLM filters across channels and distance scaling. Colors are as in B. Bottom: example of stimulus reconstruction and resulting coherence.
C Examples of next steps for using the pipeline to explore stimulus encoding.

Figure 3: Biophysical model responses to correlated pink noise stimuli.



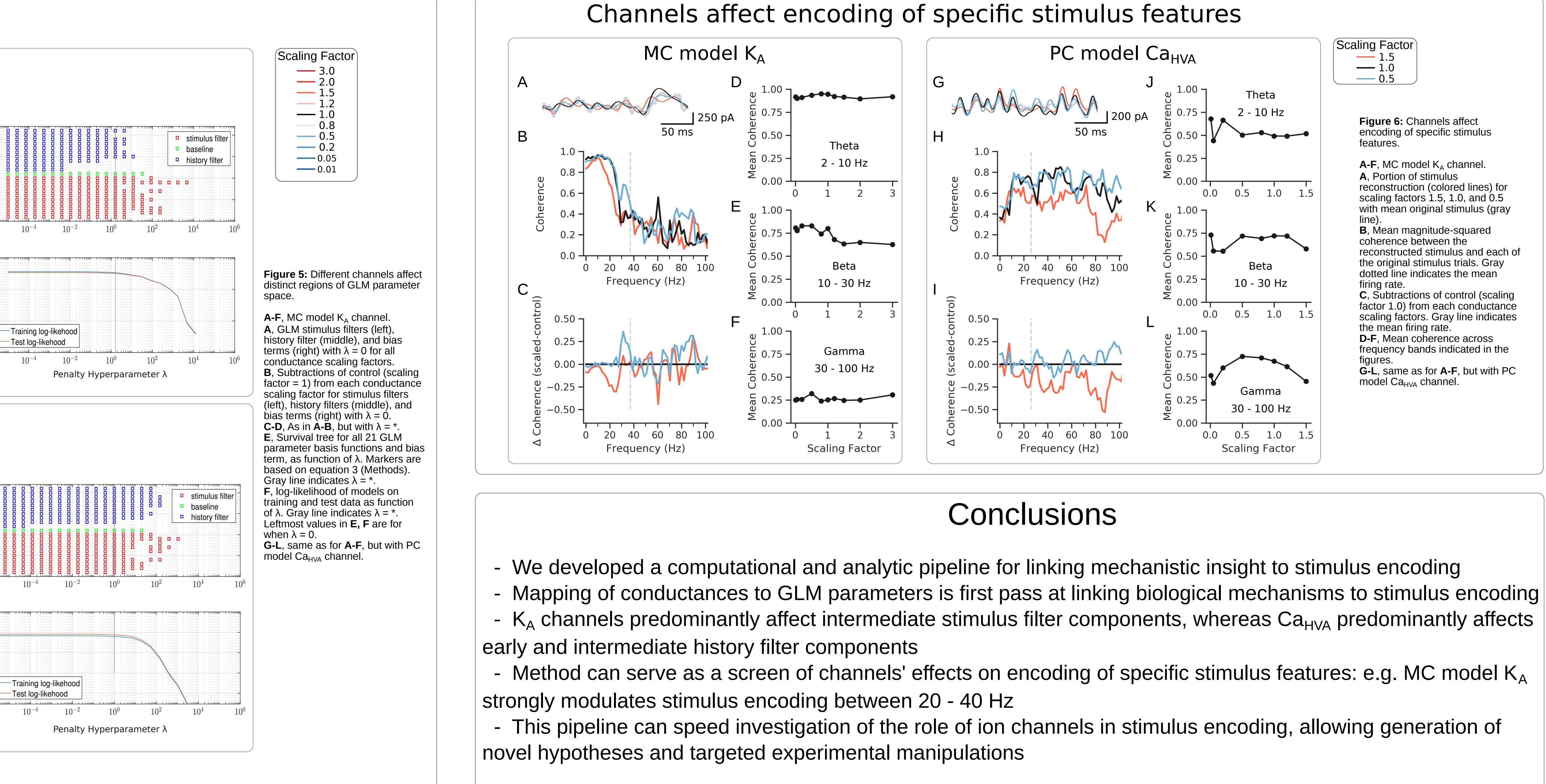
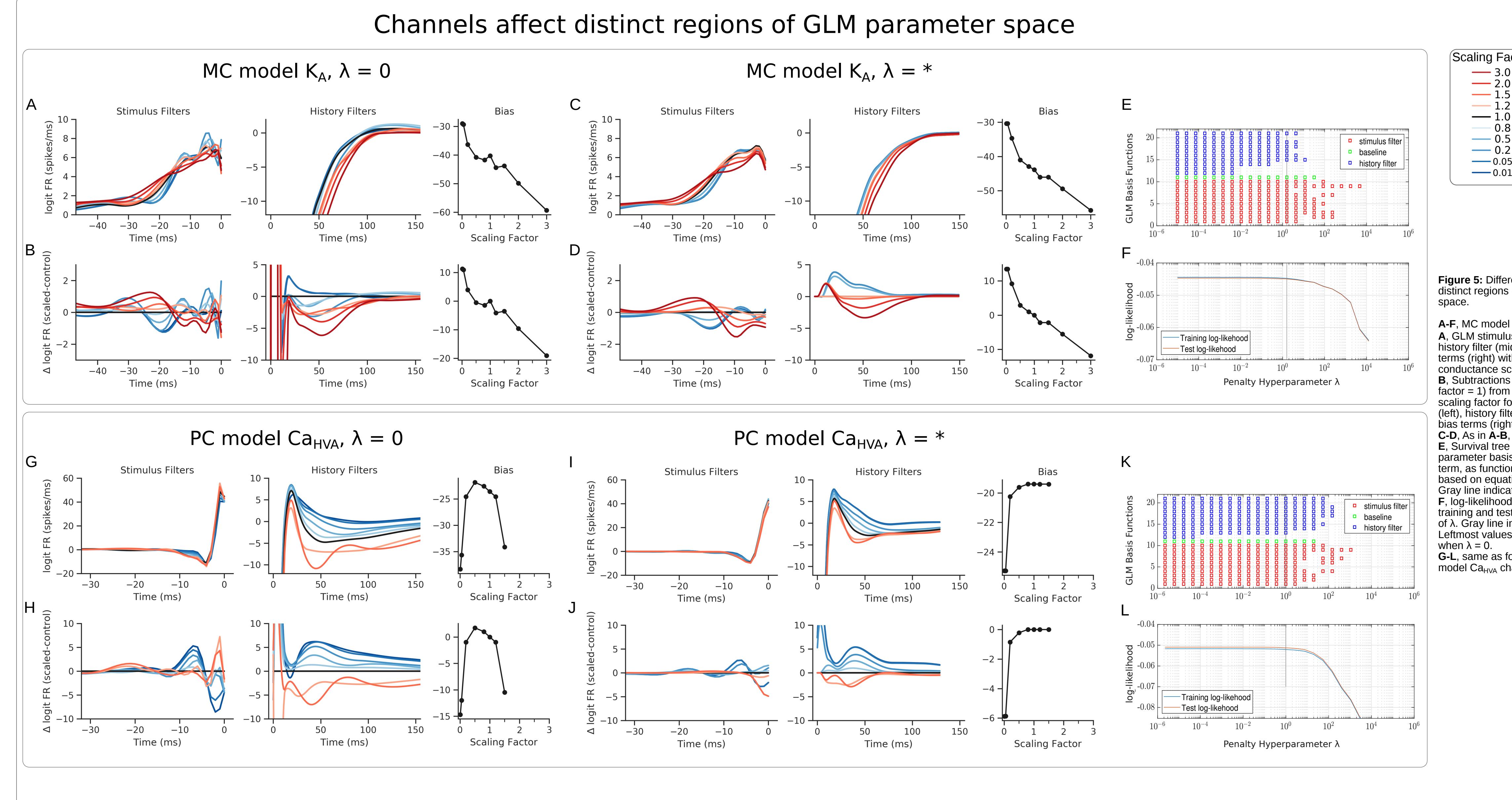
MC Biophysical Model Simulations

A K_A
B K_{Ca}
C Ca_L
D K_{DR}
E Na
F Stimulus
G K_A
H I_h
I K_{SK}
J Ca_{HVA}
K Ca_{MVA}
L K_{ek}
M K_{DR}
N Na

A K_A
B I_h
C K_{SK}
D Ca_{HVA}
E Ca_{MVA}
F K_{ek}
G K_{DR}
H Na

Figure 4: Biophysical modeling results for MC (left block) and PC (right block) models.

Channels affect distinct regions of GLM parameter space



Channels affect encoding of specific stimulus features

A MC model K_A , $\lambda = 0$
B MC model K_A , $\lambda = *$
C PC model Ca_{HVA} , $\lambda = 0$
D PC model Ca_{HVA} , $\lambda = *$
E Stimulus Filters
F History Filters
G Bias
H Log FR (scaled-control)
I Log FR (scaled-control)
J Log FR (scaled-control)
K Log FR (scaled-control)
L Log FR (scaled-control)
M Log FR (scaled-control)
N Log FR (scaled-control)
O Log FR (scaled-control)
P Log FR (scaled-control)
Q Log FR (scaled-control)
R Log FR (scaled-control)
S Log FR (scaled-control)

Figure 6: Channels affect encoding of specific stimulus features.

Conclusions

- We developed a computational and analytic pipeline for linking mechanistic insight to stimulus encoding
- Mapping of conductances to GLM parameters is first pass at linking biological mechanisms to stimulus encoding
- K_A channels predominantly affect intermediate stimulus filter components, whereas Ca_{HVA} predominantly affects early and intermediate history filter components
- Method can serve as a screen of channels' effects on encoding of specific stimulus features: e.g. MC model K_A strongly modulates stimulus encoding between 20 - 40 Hz
- This pipeline can speed investigation of the role of ion channels in stimulus encoding, allowing generation of novel hypotheses and targeted experimental manipulations