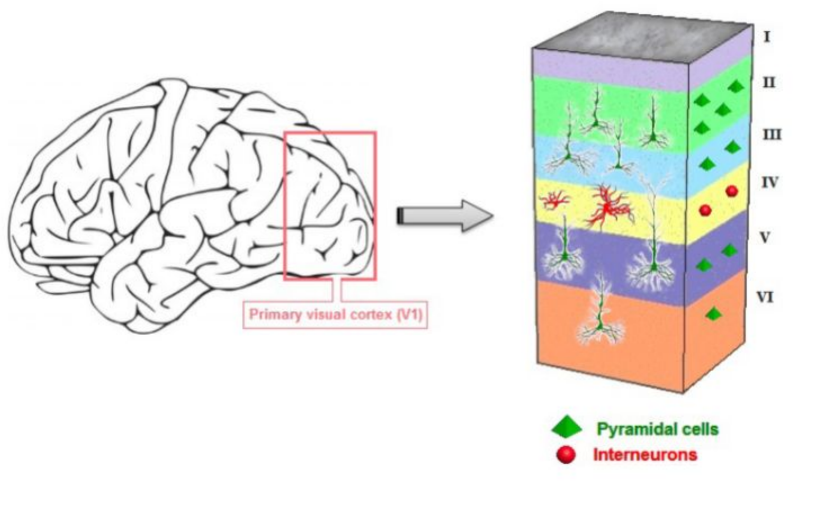
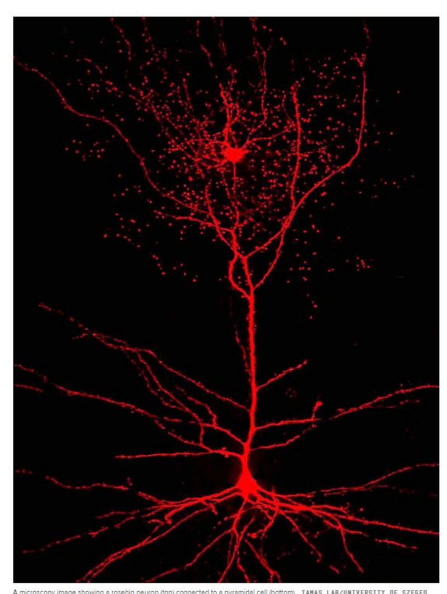
Modeling Pyramidal Neuron Excitability using 4D-Variational Data Assimilation

Rajeev Botadra, Soheil Saghafi, Casey Diekman, and students in the Math 451 Capstone course [1]
Department of Mathematical Sciences, New Jersey Institute of Technology, Newark NJ

Introduction

Pyramidal neurons are members of a family of excitatory neurons that release the neurotransmitter glutamate. Categorized as projector neurons, they typically have elaborate dendritic trees with pyramid-shaped somas. They posses a variety of voltage-gated ion channels that govern their excitable electrical behavior. To fit models of pyramidal cell excitability we used data assimilation (DA) techniques with current-clamp recordings of pyramidal cells originating from layers II and III of the visual cortex. This data was provided by Professor Jorge Golowasch (NJIT Biological Sciences) and includes the response of pyramidal cells to sets of square pulse current inputs along with ramp and sinusoidal currents. DA was used to estimate over 30 parameters of a conductance-based neuronal model, including maximal conductances and the kinetic parameters associated with the opening and closing of ion channels. This is a challenging fitting problem since most of the state variables of the dynamical system (i.e. the gating variables) are not directly observed.

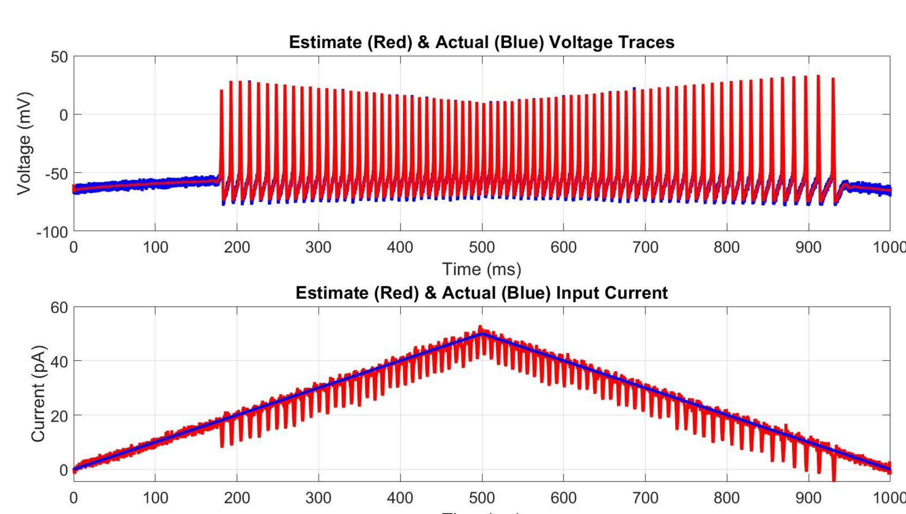


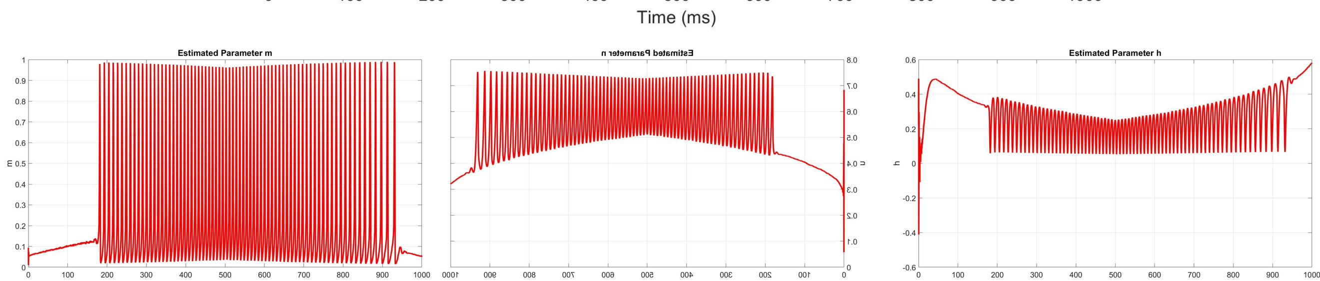


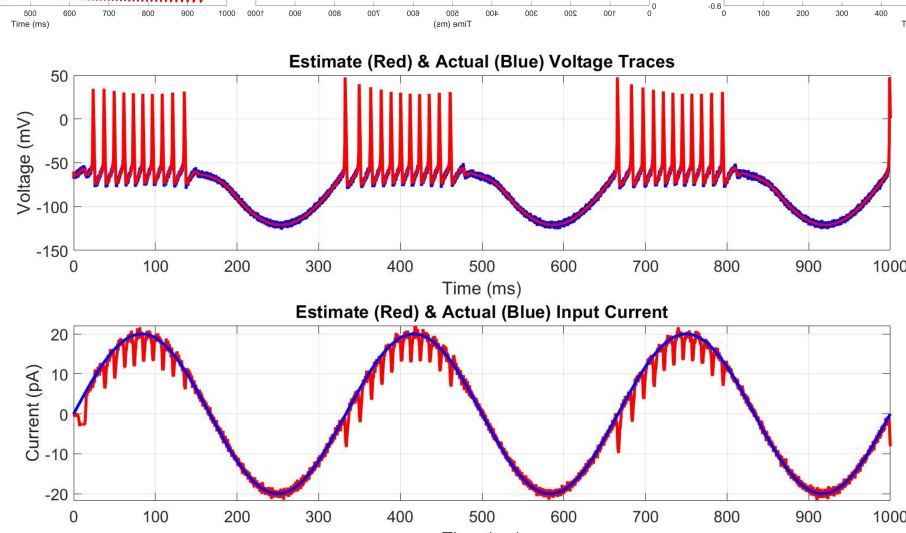
Background

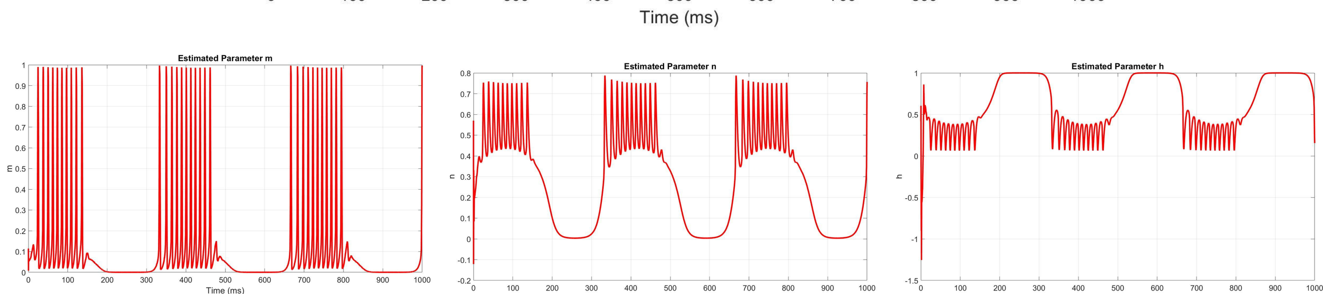
Data assimilation (DA) is an area of mathematics that seeks to optimally combine theory, in the form of a dynamical model, with experimental observations. In the Math 451 Capstone course this past semester, we learned and implemented two frameworks for data assimilation: Sequential DA such as the Unscented Kalman Filter (UKF), and a Variational DA method (4D-Var) based on the calculus of variations and optimal control theory.

Our goal was to use these methods to estimate the parameters of conductance-based neuronal models directly from voltage traces and then use the models to gain insight into the underlying electrophysiological properties of neurons. First, we created a UKF model attempting to approximate input current and the (m,n,h) gating variables described in the Hodgkin-Huxley model given a noisy synthetic input voltage.

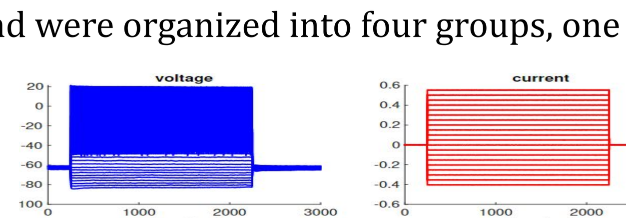




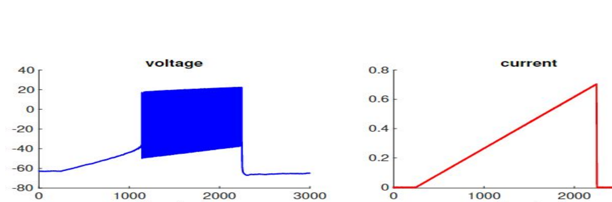




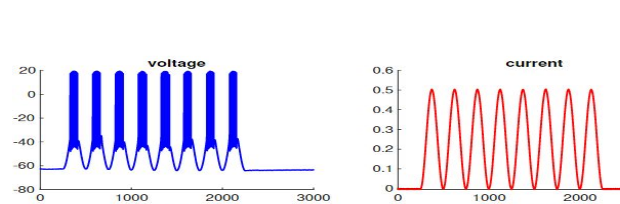
For our final project, we used 4D-Var to construct models of pyramidal neurons from current-clamp recordings provided by Jorge Golowasch (NJIT Biological Sciences). These recordings were collected from the pyramidal cells in the visual cortex of different animals and were organized into four groups, one for each animal.



Pulse Sweep Current Inputs



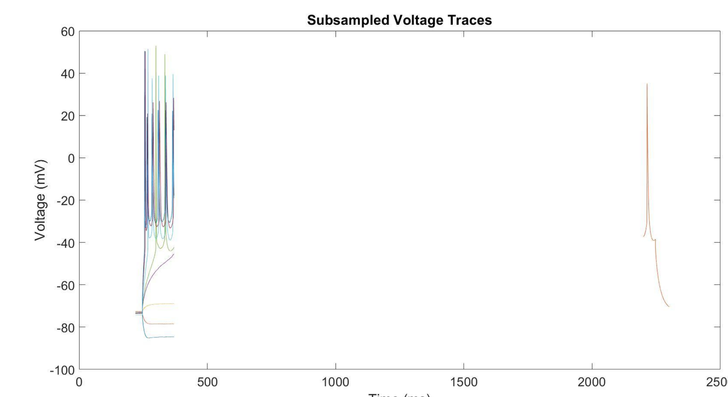
Ramp Current Input

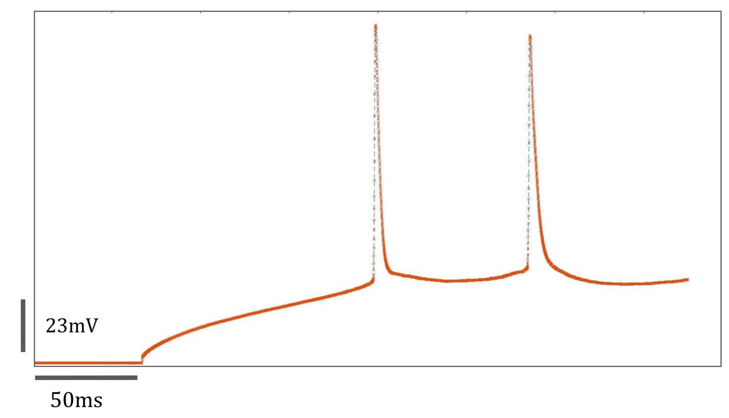


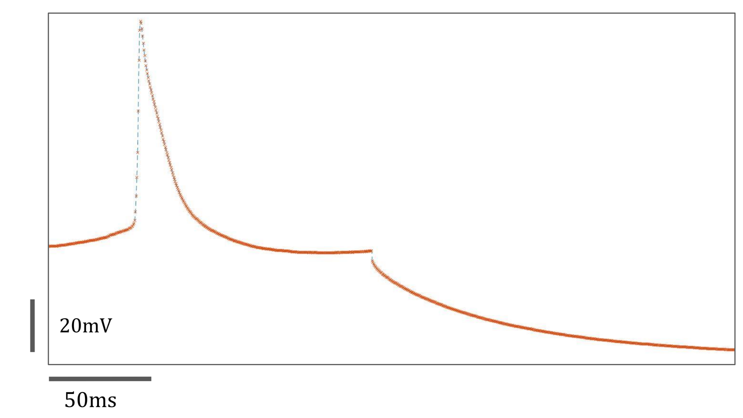
Sinusoidal Current Input

Objectives & Training Methodology

Using the in vitro pyramidal cell data, we train a model of the cell and gauge the accuracy of the model based on simulated voltage responses to sample input data. The 20 pulse sweep dataset was used to train the model while the ramp and sinusoidal data were used as test sets.







Optimization of the models was performed over a few dozen parameters resembling observed physical variables in neurons such as the Sodium, Potassium, and Leak channel gating variables. In addition, the models considered Sodium-leak and Potassium-leak variables.

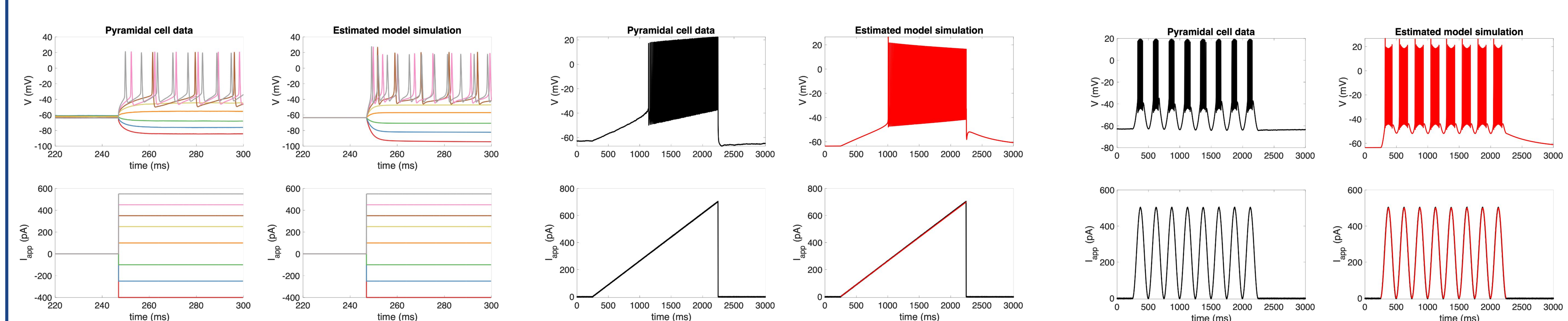
The optimization problem is highly non-linear, and thus solutions for optimal parameter values were highly susceptible to local minima. To account for this nearly 300 models were trained with varying initial estimates.

After a set of optimal parameters was found, the model was evaluated against the test data and the most optimal solutions were selected.

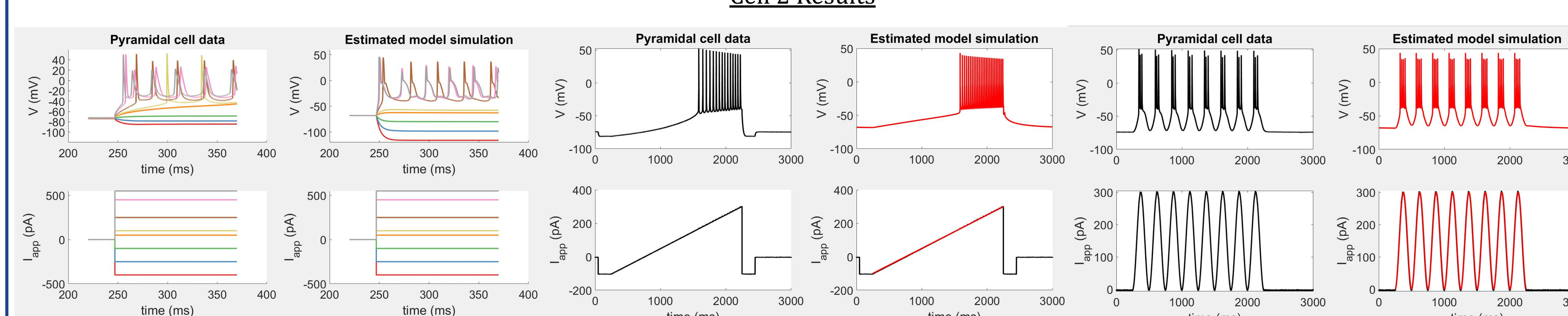
Training Results & Model Evaluation

A simulated voltage trace in response to the test data was generated using the optimal estimated parameters of each model. The best models were found to be those which replicated the firing rate, resting potential, depolarization behaviour, and hyperpolarization behaviour during simulation. The results of the best models for each group are shown below.

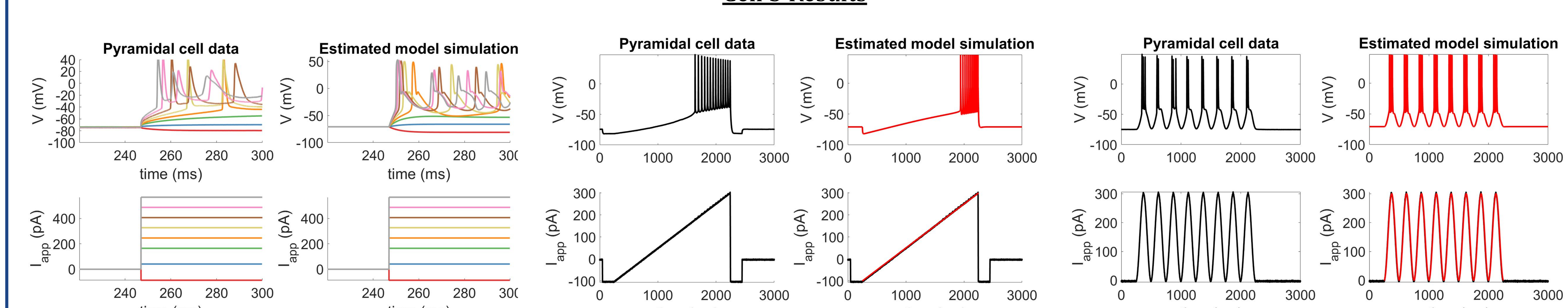
Cell 1 Results



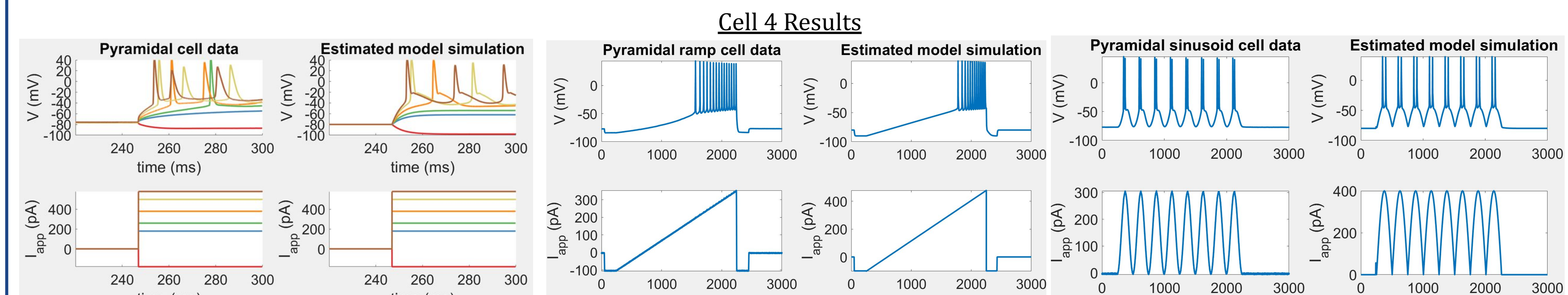
Cell 2 Results



Cell 3 Results



Cell 4 Results



Future Considerations

We have fit several different models to each cell. Our next step will be to compare the parameter estimates for a particular cell and across different cells to identify which parameters, in particular the maximal conductances shown below, are responsible for the variability in responses seen in the data.

Key Estimated Parameters

	Group 1	Group 2	Group 3	Group 0
C	40.1518	35.4	48.1	28.8
gNa	500	500	500	500
gCa	209.03	99.8	94.2	4.05
gK	300	255	300	300
gL_Na	1.6539	0.74	0.0001	3.08
gL_K	6.8097	7.68	10	10

References

1. Lucas Scalora, Nick Monticello, Kotaro Oi, Bryan Martinez, Cindy Tai, Mike Galanaugh, Sean Mackelvey, and Judy Zuo
2. Beatriz Bano-Otalora, Matthew J Moye, Timothy Brown, Robert J Lucas, Casey O Diekman, Mino DC Belle (2021) Daily electrical activity in the master circadian clock of a diurnal mammal. https://doi.org/10.7554/eLife.68179
3. GlobalCDA. (n.d.). Data assimilation (DA). Calibration & Data Assimilation. Retrieved May 18, 2022, from http://globalcda.de/projects/encda/data-assimilation/
4. Wan, E. A., & van der Merwe, R. (n.d.). *The unscented Kalman filter for nonlinear estimation*. Retrieved from https://groups.seas.harvard.edu/courses/cs281/papers/unscented.pdf
5. Kepert, J. (2009, May 17). *4D-var for dummies*. Retrieved from https://gmao.gsfc.nasa.gov/events/adjoint_workshop-8/present/Sunday/Kepert1.pdf
6. Small, S. (n.d.). *Data assimilation*. Data Assimilation - Asynch 1.0 documentation. Retrieved from https://asynch.readthedocs.io/en/latest/assim.html
7. Molteni, M. (2018, August 27). *Meet the Rosehip Cell, a new kind of neuron*. Wired. Retrieved May 19, 2022, from https://www.wired.com/story/meet-the-rosehip-cell-a-new-kind-of-neuron/
8. *J. Med. Chem.* 2015, 58, 18, 7093–7118. Publication Date:April 30, 2015. https://doi.org/10.1021/jm501981g