Novel approaches to optimize neuronal computational models.

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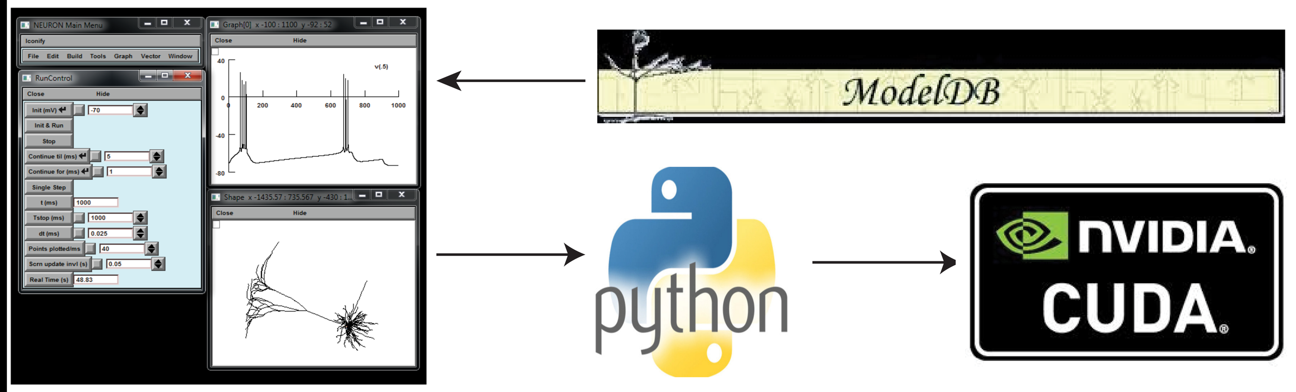
Abstract:

Compartmental modeling of neurons allows one to quickly and efficiently test how ion channels, distributed across neuronal compartments, contribute to activity. The quality of predictions generated from such models depends critically on the biophysical accuracy of the model. This accuracy can be improved through optimization, which constrains model parameters to best fit an empirical dataset. Depending on how optimization is implemented—both mathematically and experimentally—one can arrive at several solutions that all reasonably fit empirical datasets. Intuitively, as one increases the size and complexity of the target dataset, the number of models that accurately capture dataset properties decreases, theoretically leading to one unique solution that satisfies all aspects of the dataset. Identifying such a solution is a challenge.

Here we present detailed analytical approach to guide model optimization towards a **unique** set of parameter values that best represent experimental data. As a test bed, we began with Mainen and Sjenowski's 1996 model of a cortical pyramidal cell, which has 12 free parameters describing ion channel distribution along the different compartments of the neuron. Initially we used the original values of the free parameters (named the target parameters) to create a dataset of voltage responses that represents the ground truth target d ata. Given this target dataset, our goal was to determine whether we could use optimization to arrive at similar parameter values when these values were unknown.We tested over 260 different stimulation protocols and 20 score functions, which compares the simulated data to the ground truth dataset, to determine which combination stimulation and score functions creates datasets that reliably constrain the model. Then we checked how sensitive each parameter was to different score functions. We found that five of the twelve parameters were sensitive to many different score functions. While these five could be constrained, the other seven parameters were sensitive only to a small set of score functions.

The results here suggests that iterative, sensitivity analysis-based optimization could allow for more accurate fitting of model parameters to empirical data.

NeuroGPU, an intuitive platfom to accelerate neuronal simulations

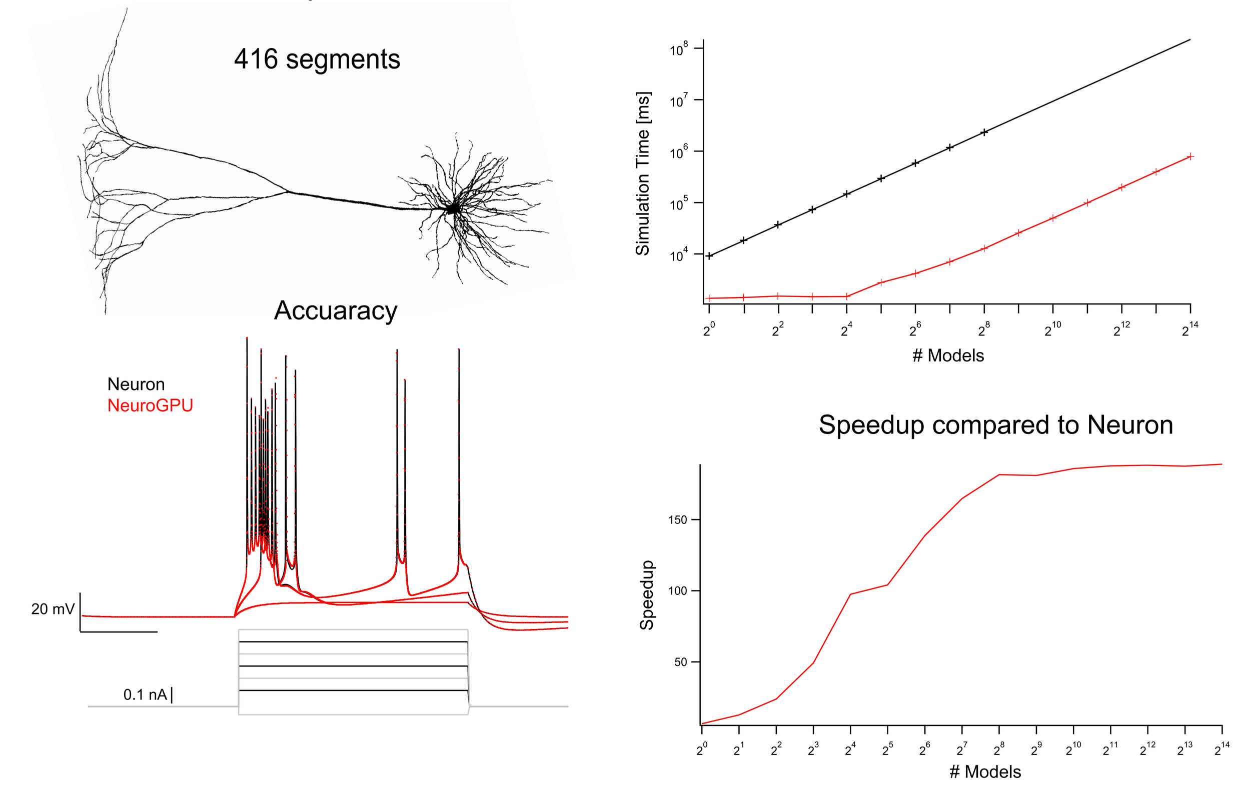


IPython Interactive Computing

Graphical user interface:
Porting model from neuron
Creating stimulation
Running optimization (DEAP)
Plotting output

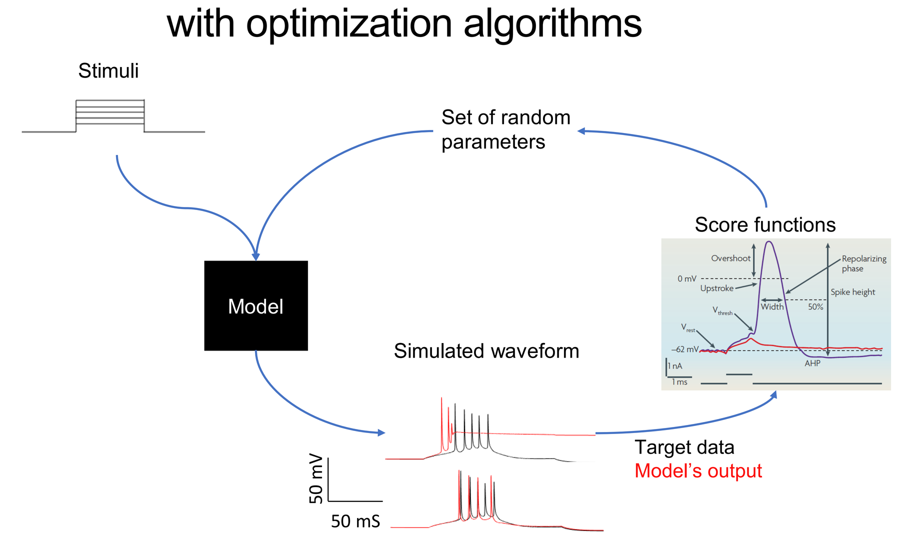
NeuroGPU accelerates neuronal simulation by 170x compared to CPU

Pyramidal Neuron
Mainen & Sejnowski 1996

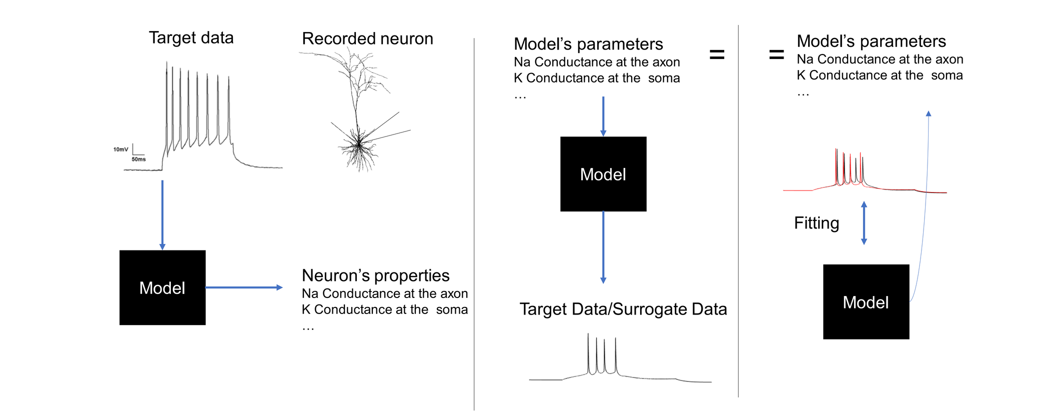


Predicting ion channel distributions in recorded neurons using compartmental models

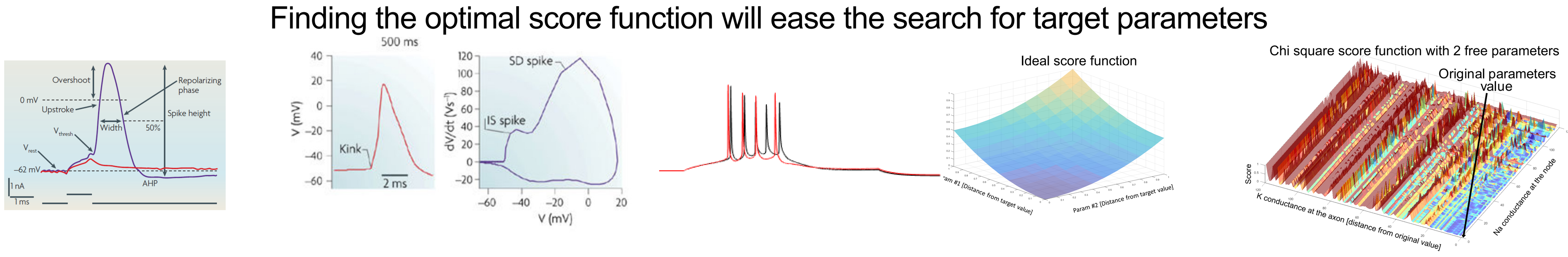
Models can be fitted to neuronal recording with optimization algorithms



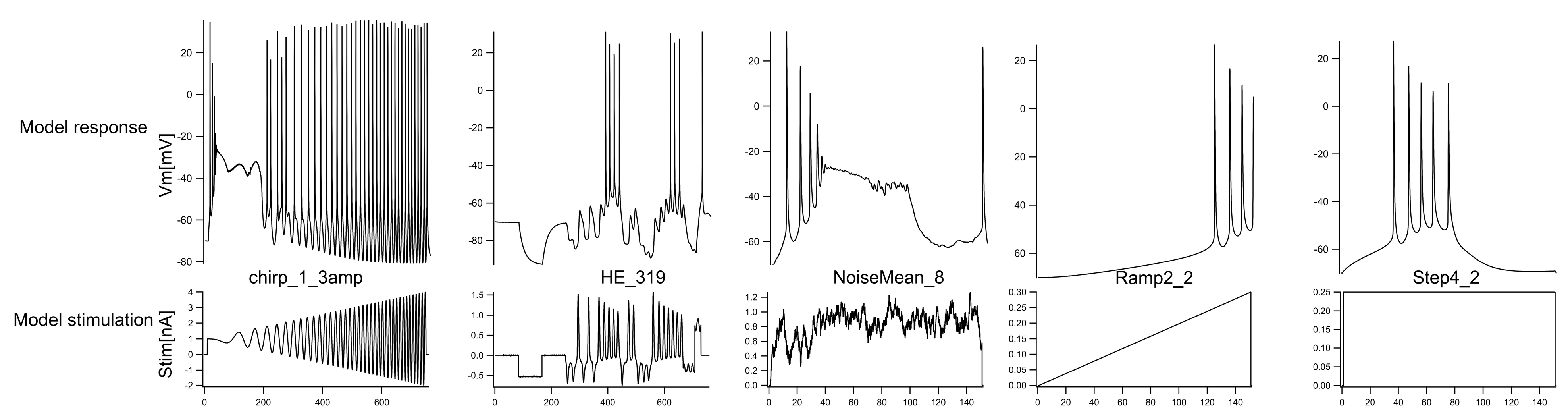
Surrogate data assess optimization algorithm preformance



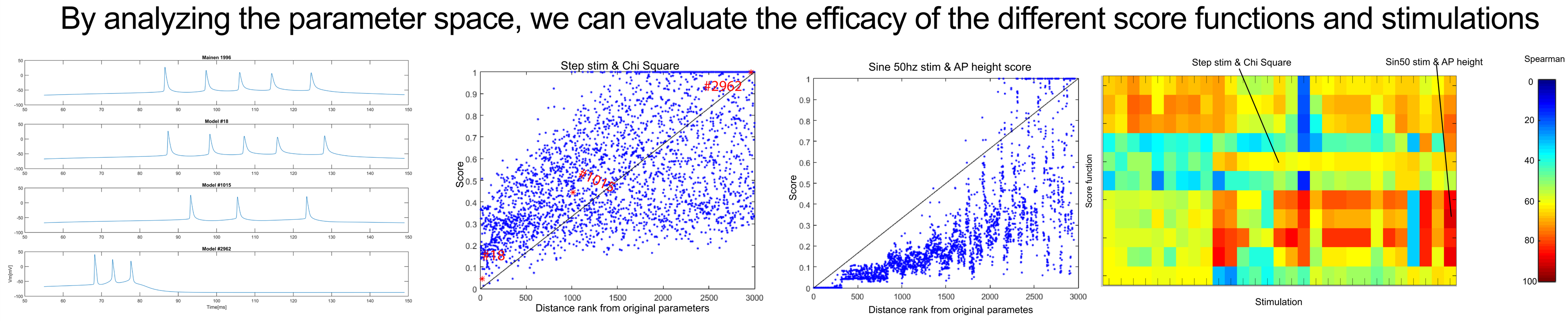
Finding the optimal score function will ease the search for target parameters



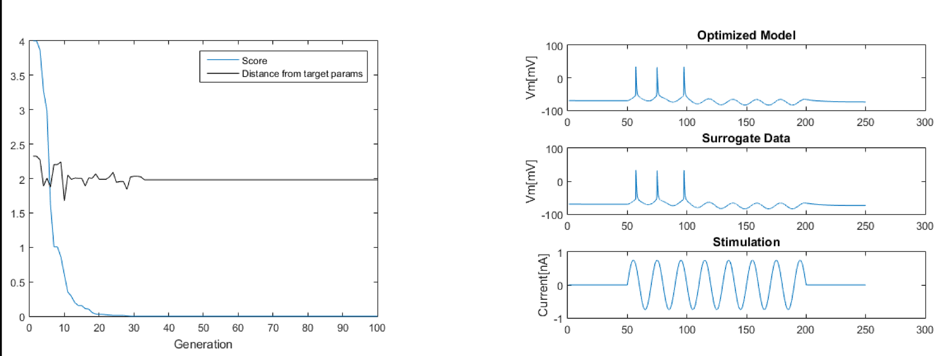
We used 260 different stimuli to generate rich target (surrogate data



By analyzing the parameter space, we can evaluate the efficacy of the different score functions and stimulations

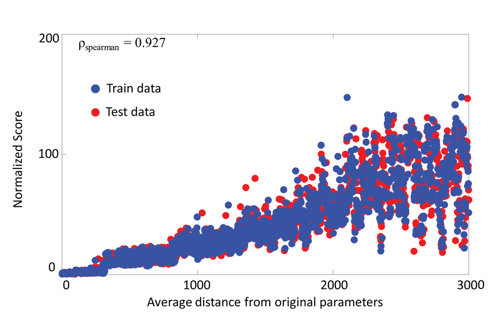


Several solutions can generate the target data when using only one stimulaion and score function

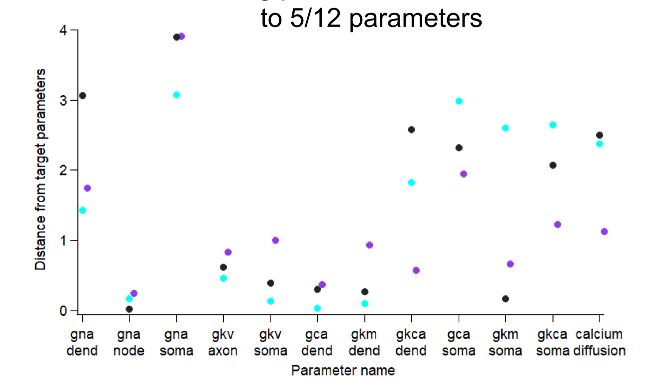


When combining several stimuli and score functions, the number of appropriate solutions decrease

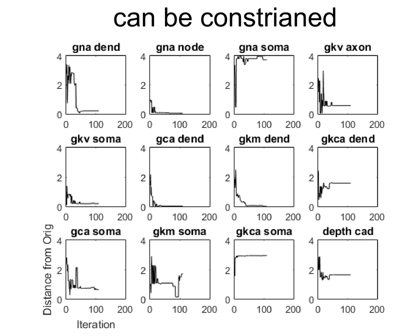
• F1 * W1 + F2 * W2 + … + F11 * W11 = CSF



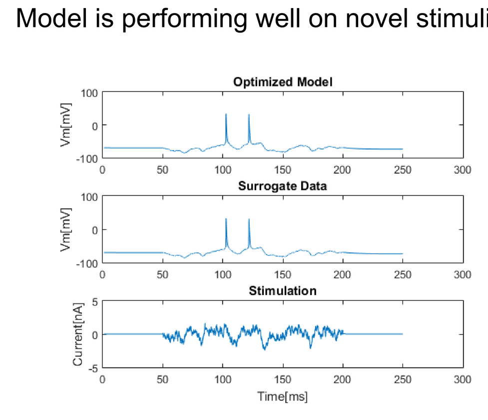
Different starting points results with similiar values to 5/12 parameters



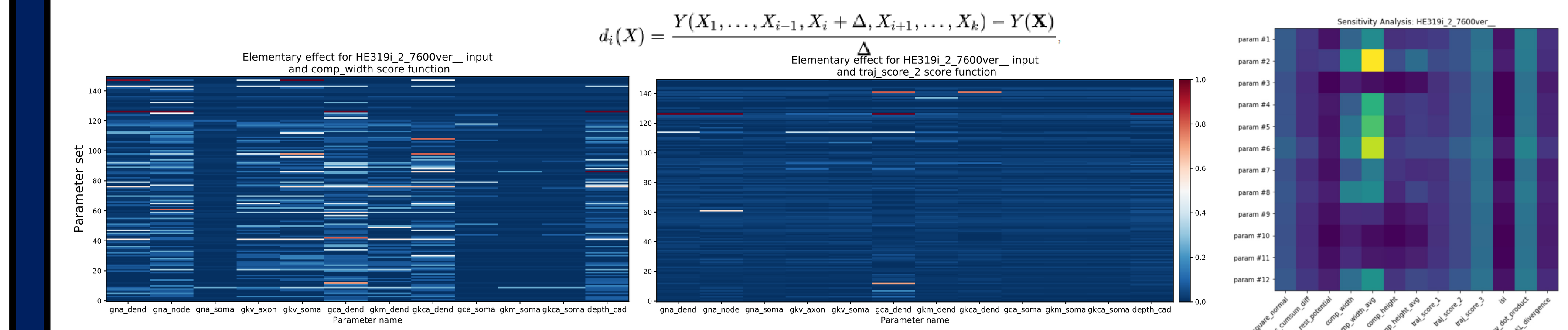
5/12 parameters can be constriained



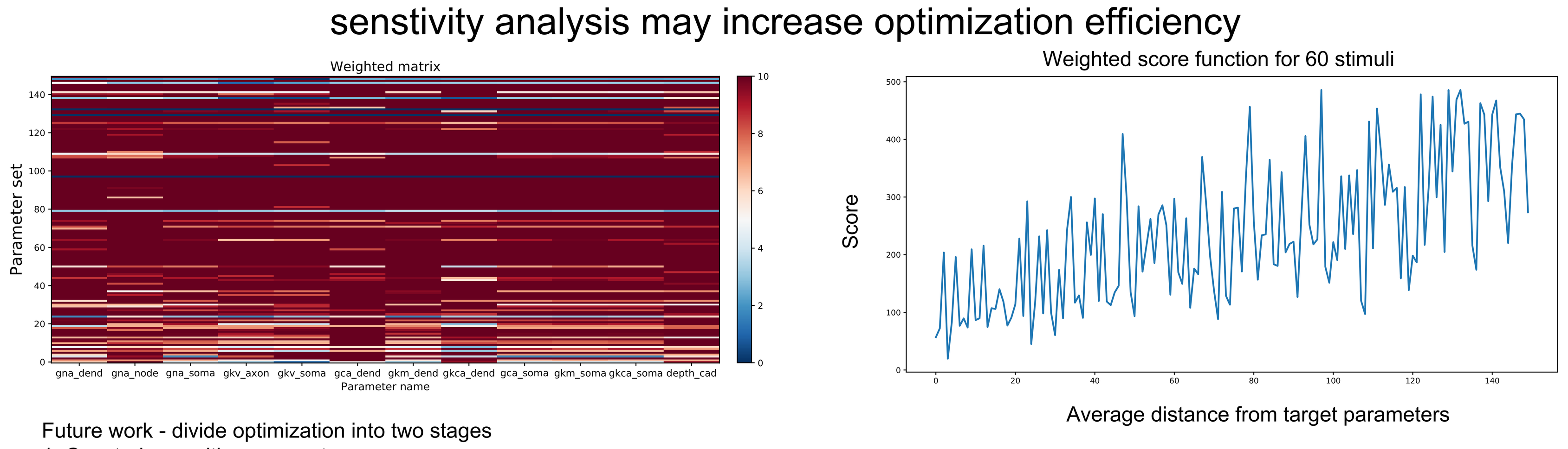
Model is performing well on novel stimuli



Analyzing the sensitivity of the models parameters can help us find better combinations of score functions



A combined score function that includes both spearman and senstivity analysis may increase optimization efficiency



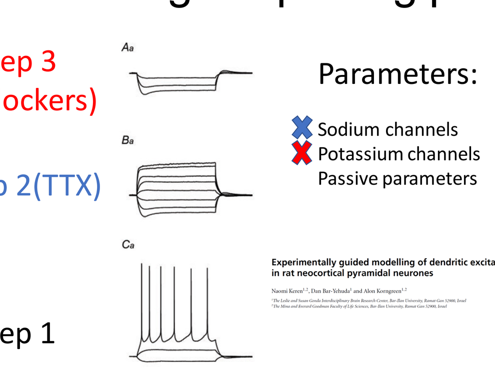
Future work - divide optimization into two stages
1. Constrain sensitive parameters
2. Fix parameters from 1
3. Constrain non-sensitive parameters

Future Work: divide optimization to several stages - peeling procedure

Step 3 (K-blockers)

Step 2(TTX)

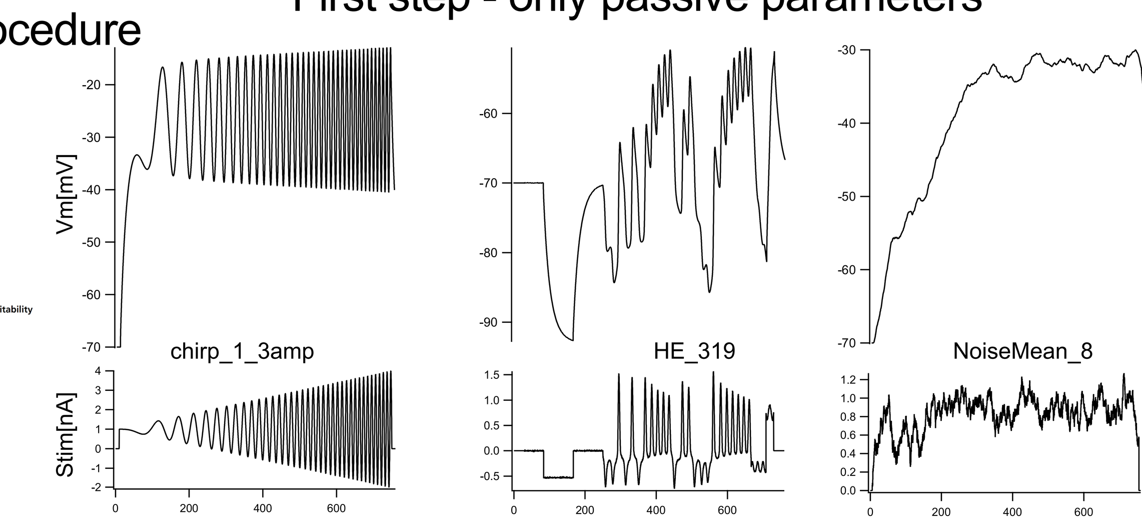
Step 1



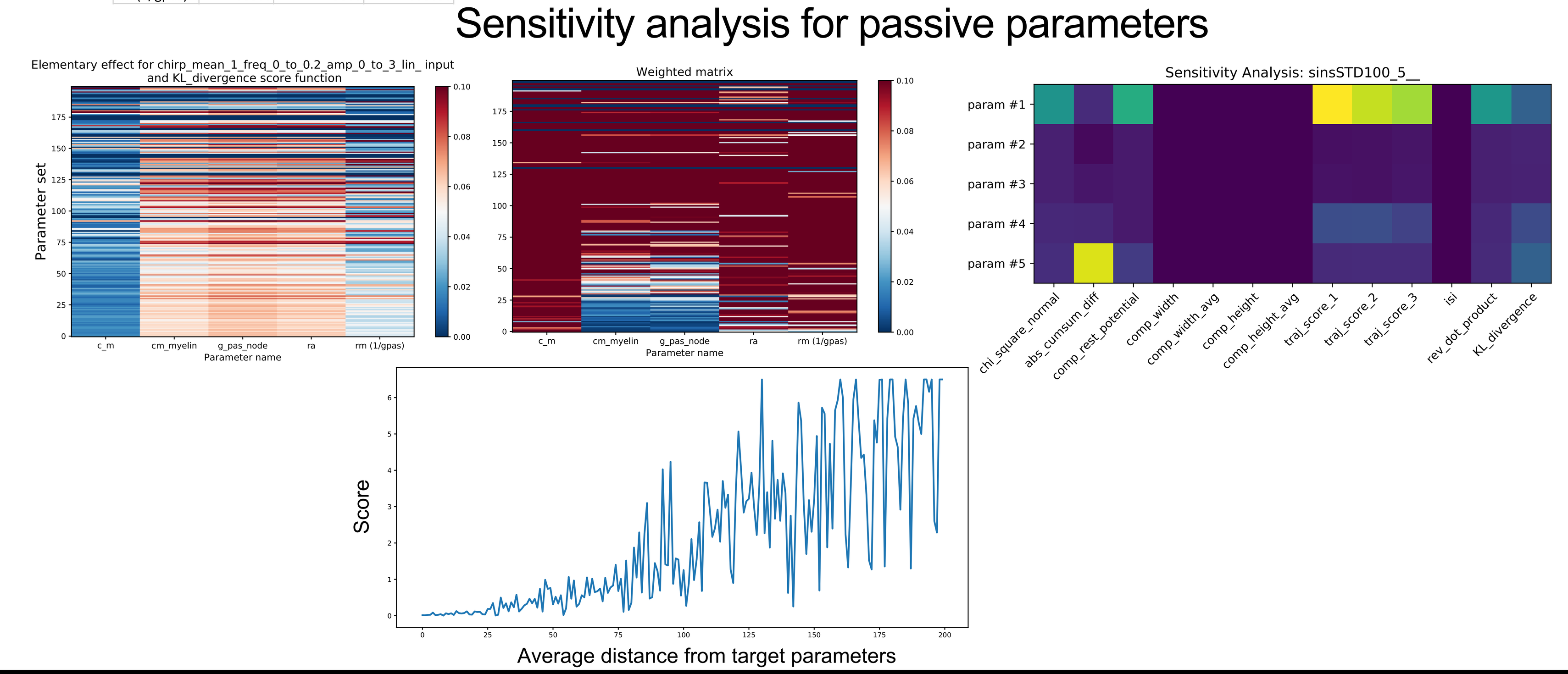
Parameters:
Sodium channels
Potassium channels
Passive parameters

Param name	Base value	Lower bound	Upper bound
c_m	0.75	0.25	4
cm_myelin	0.04	0.0001	0.1
g_pas_node	0.02	0.002	0.2
ra	150	75	225
rm (1/gpas)	30000	3000	300000

First step - only passive parameters



Sensitivity analysis for passive parameters



Conclusions:

• GPUs can accelerate neuronal simulation by 170 fold.
• Our unique method for fitting models to neuronal data identifies the most effective set of stimuli and score functions for optimization
• We can reliably constrain 5/12 parameters in Mainen's model
• Using sensitivty analysis we can divide optimization to several steps - focusing on constraining specific parameters

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