CoMParE: Conductance based Model Parameter Evaluation

Kyung Geun Kim

Electrical Engineering and Computer Sciences
University of California, Berkeley

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by Kyung Geun Kim

Research Project

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Approval for the Report and Comprehensive Examination:

Committee:

Kannan RAMCHANDRAN

Professor Kannan Ramchandran
Research Advisor

5/18/2020

(Date)

* * * * * * *

Professor Kristofer Bouchard
Second Reader

5/18/2020

(Date)

Abstract

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by

Kyung Geun Kim

Master of Science in Electrical Engineering and Computer Sciences

University of California, Berkeley

Professor Kannan Ramchandran,

Neurons are the most fundamental cells in the brain responsible for processing information. The most essential characteristic that discriminates neurons from other cells comes from their ability to produce electrical signals. The electrical activities are governed by the ion-channels distributed along the membrane of the neurons, making them a critical component to understand the complex neuronal behavior. Compartmental modeling allows us to efficiently model and simulate ion-channels connected to the activities in neurons. Although such models allow meaningful predictions, the quality, as well as the generalizability of the predictions depends heavily on the biophysical accuracy of the models. The accuracy of the model for each neuron recorded from could be improved with an optimization procedure by constraining the model parameters to best fit to the experimental datasets. Depending on both empirical and mathematical aspects of how the optimization procedure is implemented, it is not difficult to arrive at several solutions that fit reasonably well to the experimentally recorded target. However, there exists a single, unique solution that is an accurate description of the neuron recorded from due to the fact that it is a physical system. Current state-of-the-art methods to constraint these model parameters are not yet successful at recovering the unique solution. In this paper, we show that as more conditions are enforced, we could guide the optimization algorithm to eliminate inaccurate solutions and theoretically recover a unique solution that could best represent experimental data. We propose the **Co**nductance based **M**odel **Par**ameter **E**valuation (CoMParE) algorithm, which is an algorithmic framework for inferring ion-channel distributions of the neurons recorded from. In order to construct and test the CoMParE algorithm, we first began with Mainen and Sjenowski's 1996 model of a cortical pyramidal cell with 12 free parameters describing ion channel distribution within the dendritic, somatic, and axonal compartments. With the original parameters of Mainen's model predefined as the ground truth values, we first showed that the CoMParE algorithm is capable of recovering the ground truth values accurately. Next, we showed that our method could be generalized to other models as well as recover a general point in the parameter space. As a result, the CoMParE algorithm shows a wide potential and capability of fitting biologically detailed models to experimental datasets.

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Kyung Geun Kim
University of California, Berkeley
kyung4952@berkeley.edu

Abstract

Neurons are the most fundamental cells in the brain responsible for processing information. The most essential characteristic that discriminates neurons from other cells comes from their ability to produce electrical signals. The electrical activities are governed by the ion-channels distributed along the membrane of the neurons, making them a critical component to understand the complex neuronal behavior. Compartmental modeling allows us to efficiently model and simulate how ion channels module neuronal activities. Although such models allow meaningful predictions, the quality, as well as the generalizability of the predictions depends heavily on the biophysical accuracy of the models. The accuracy of the model for each neuron recorded from could be improved with an optimization procedure by constraining the model parameters to best fit to the experimental datasets. Depending on both empirical and mathematical aspects of how the optimization procedure is implemented, it is not difficult to arrive at several solutions that fit reasonably well to the experimentally recorded target. However, there exists a single, unique solution that is an accurate description of the neuron recorded from due to the fact that it is a physical system. Current state-of-the-art methods to constraint these model parameters are not yet successful at recovering the unique solution. In this paper, we show that as more conditions are enforced, we could guide the optimization algorithm to eliminate inaccurate solutions and theoretically recover a unique solution that could best represent experimental data. We propose the **Co**nductance based **M**odel **Par**ameter **E**valuation (CoMParE) algorithm, which is an algorithmic framework for inferring ion-channel distributions of the neurons recorded from. In order to construct and test the CoMParE algorithm, we first began with Mainen and Sjenowski's 1996 model of a cortical pyramidal cell with 12 free parameters describing ion channel distribution within the dendritic, somatic, and axonal compartments. With the original parameters of Mainen's model predefined as the ground truth values, we first showed that the CoMParE algorithm is capable of recovering the ground truth values accurately. Next, we showed that our method could be generalized to other models as well as recover a general point in the parameter space. As a result, the CoMParE algorithm shows a wide potential and capability of fitting biologically detailed models to experimental datasets.

1 Introduction

Neurons are excitable cells in the brain with a critical role in processing information. In response to an input stimulus, neuronal firing dynamics determine the behavior of complex neuronal networks. In single neurons, the response is mostly determined by its biophysical properties, including the distribution and density of ion-channels along the membrane of the neuron [1, 2]. Therefore, disruptions of these ion-channels can lead to diverse psychological and neurological conditions [3, 4].

Starting from the early works of Hodgkin & Huxley, there have been many approaches to model the biophysical mechanisms of neurons [5]. One of the major breakthroughs in neuronal modeling is the introduction of compartmental models that translate neurons to electrical circuits and can be simulated on computers [6, 7]. Using compartmental models, ion-channel densities and distributions could be modeled as conductances of resistors in electrical circuits. However, a critical but difficult task is inferring the conductances of different channels. The lack of a detailed biophysically accurate model that can predict the ion-channel conductances in recorded neurons presents a gap in our ability to understand and simulate neuronal behavior in experimental settings [8]. Bridging this gap will allow us to predict the behaviors of neurons under general conditions, for example, how neurons with neurological disorder conditions respond to pharmacological interventions.

Optimization algorithms (OA) have been utilized as one of the most promising approaches to solve this problem, but current results show critical limitations [8]. In the case of inferring ion-channel distributions in neuronal models, we optimize conductance parameters of a model to minimize the discrepancy between the model's response to the

experimental responses. This problem, therefore, can be tailored into a standard optimization problem given an adequate discrepancy measure for voltage traces as the algorithm's objective function. We defined elementary discrepancy measures as the score functions, which in general depend on electrophysiological features of neuronal membrane potential changes. However, these problems are generally highly nonconvex and nonsmooth, making it extremely difficult to avoid local minima. Specifically, many solutions may produce the same voltage responses [9]. Therefore, the existence of many local and global minima makes it very difficult to recover the conductance parameters that created the experimental, target data. The difficulty of recovering the unique solution is known as the solution degeneracy problem. We hypothesize that imposing more constraints will reduce the number of possible solutions because it becomes more difficult to satisfy many criteria at once. Ideally, with enough constraints, we will be able to recover a unique solution. One widely used method to tackle the solution degeneracy problem in fitting these kinds of models is the multi-objective optimization (MOO) method [10]. However, MOO has inherent limitations when aiming to find a unique solution because the Pareto optimality condition used to compare the solutions outputs many optimal solutions by design. Therefore, while the MOO approach has the right idea, it is still incapable of solving the degeneracy problem.

Here we present an algorithmic framework called **Co**nductance based **M**odel **Par**ameter **E**valuation (CoMParE) to provide a better method to solve the degeneracy problem and recover the unique solution for biologically detailed neuronal models. We developed a method to construct a single objective function with a significantly reduced number of local minima in the search space. In order to reduce the number of local minima, we combined diverse elementary score functions in an optimal way. We gradually combined more elementary score functions to construct the final objective function and used a genetic algorithm (GA) to find the solutions. We show that as we add more constraints by diversifying the pool of elementary score functions, we obtain better solutions for the model. Thus, with the CoMParE algorithm, we were able to reshape the search space by significantly reducing the number of local minima and construct an objective close to an ideal one. As a result, by showing that imposing more constraints will lead to a unique solution, we show the correctness of our initial hypothesis.

2 Results

2.1 Ion-channel distributions as conductance parameters

The goal of CoMParE algorithm is to be able to infer the ion-channel distributions of single biological neurons we record from. Many characteristics of a neuron could also be studied with compartmental models, but we are particularly interested in the ion-channel distributions because of the following two reasons. First, unlike other parameters such as the ion-channel kinetics, the ion-channel distributions cannot be measured directly from experiments. Second, the ion-channel distributions are variant from one neuron to another, while other properties of the model can be drawn from the literature due to the fact that they are invariant across individual instances of neurons. Therefore, the conductance parameters are our primary interest, and for simplicity, Mainen's model [11] is used for the purpose of designing the CoMParE algorithm.

2.2 Defining the parameter space

In Mainen's model, conductance parameters model how sodium, potassium, and calcium channels are distributed along the membrane for soma, dendrites, and axon of a neuron, which are described in detail in the Table 1 below.

With the chosen relevant conductance parameters for the Mainen's model, we seek to recover the unique parameter set that is a biologically accurate description of neurons. While the final goal is to recover the conductance parameters of biological neurons with experimental data, we first show the capability of the CoMParE algorithm using surrogate data for the scope of this paper. To elaborate, we first use the Base values of the Mainen's model given in Table 1 as the ground truth values and check against the solution given by the CoMParE algorithm. We will show that the CoMParE algorithm is able to constrain to the base values first then show that it can also constrain other points in the parameter space in the later sections.

To construct the CoMParE algorithm, it is critical to examine and analyze how each parameter is entangled in the model. Each parameter has different properties depending on electrophysiology, thus spanning different ranges shown as in the lower and upper bounds of Table 1. In order to consistently consider different ranges and interaction dynamics, we defined the notion of the parameter space as the feasible set of the optimization problem within the ranges of each parameter. Because the score functions are not mathematically analytic, the parameter space must be examined through sampling. While the goal is to explore the whole parameter space, we sample in a way that each sample can be sorted to have explicit ranks so that the ranks represent the distance from the original parameter set (Base value in the second column of Table 1). Since each parameter of the model has different ranges, we first sampled from a normalized domain of Mainen's model in order to assign unbiased ranks. After sampling, each normalized sample is assigned a rank

Parameter name	Base value	Lower bound	Upper bound	Unit	Description
gna_dend	20	0.2	2000	S/cm^2	Sodium conductance at the dendrites
gna_node	30000	300	3000000	S/cm^2	Sodium conductance at nodes of Ranvier
gna_soma	20	0.2	2000	S/cm^2	Sodium conductance at the soma
gkv_axon	2000	20	200000	S/cm^2	Kv conductance at the axon
gkv_soma	200	2	20000	S/cm^2	Kv conductance at the soma
gca_dend	0.3	0.003	30	S/cm^2	Calcium conductance at the dendrite
gkm_dend	0.1	0.001	10	S/cm^2	Km conductance at the dendrites
gkca_dend	3	0.03	300	S/cm^2	Calcium dependent potassium channel (CDPC) at the dendrite
gca_soma	0.3	0.003	30	S/cm^2	Calcium conductance at the soma
gkm_soma	0.1	0.001	10	S/cm^2	Km channel conductance at the soma
gkca_soma	3	0.03	300	S/cm^2	CDPC at the soma
depth_cad	0.1	0.001	10	μm	Depth parameter of the mechanism that sets the inner concentration of calcium

Table 1: Mainen's model conductance parameters. The Base values represents the values of the surrogate data of the model. The Lower bound and Upper bound are determined by multiplying 0.01 and 100 to the base values.

according to the distance from the normalized values of the original parameter set then reverted to the values in the standard parameter space (Methods). As a result, we created samples with ranks assigned to each set while exploring the full parameter space.

2.3 Objective with best pair of stimulus and score function

The OA minimizes the objective function, which is a combination of score functions, but our goal is to minimize the distance of the best solution from the original parameter. To achieve this, we computed Spearman's correlation coefficients between the scores and the ranks of the parameter sets. Because the Spearman's correlation coefficient computes correlations between ranks of the parameter sets and the score values, higher Spearman's correlations indicate a stronger monotonic relation between the two variables. Therefore, as it serves as a measure of how much local minima exists for a given score function, the maximization of Spearman's correlation coefficient can result in a better objective function with fewer local minima.

Initially, we computed the Spearman's coefficient for every single pair of 300 stimuli and 80 score functions. We took the best combination, which achieved the maximum Spearman's coefficient and used them as the objective of the genetic algorithm. The plot of score values versus the ranks of the parameter sets are shown in the Fig. 1A where the points with low score values with high parameter ranks represent local minima. To test the performance of the constructed objective, we first compared how well the parameters were constrained with respect to the surrogate data. Additionally, to check if the method provided an improvement to the degeneracy problem, we compared the voltage traces produced by the surrogate data and the optimized parameter set with stimulus used in training as well as novel stimuli. As a result, only one or two out of 12 parameters were constrained when compared against the base values as shown in Fig. 1B. The voltage response of the best solution shows a decent fit when tested with the training stimulus as shown in Fig. 1C. However, when tested with novel stimuli, it shows no improvement to the degeneracy problem as shown in Fig. 1D, E as the fit is not sufficiently close to the target.

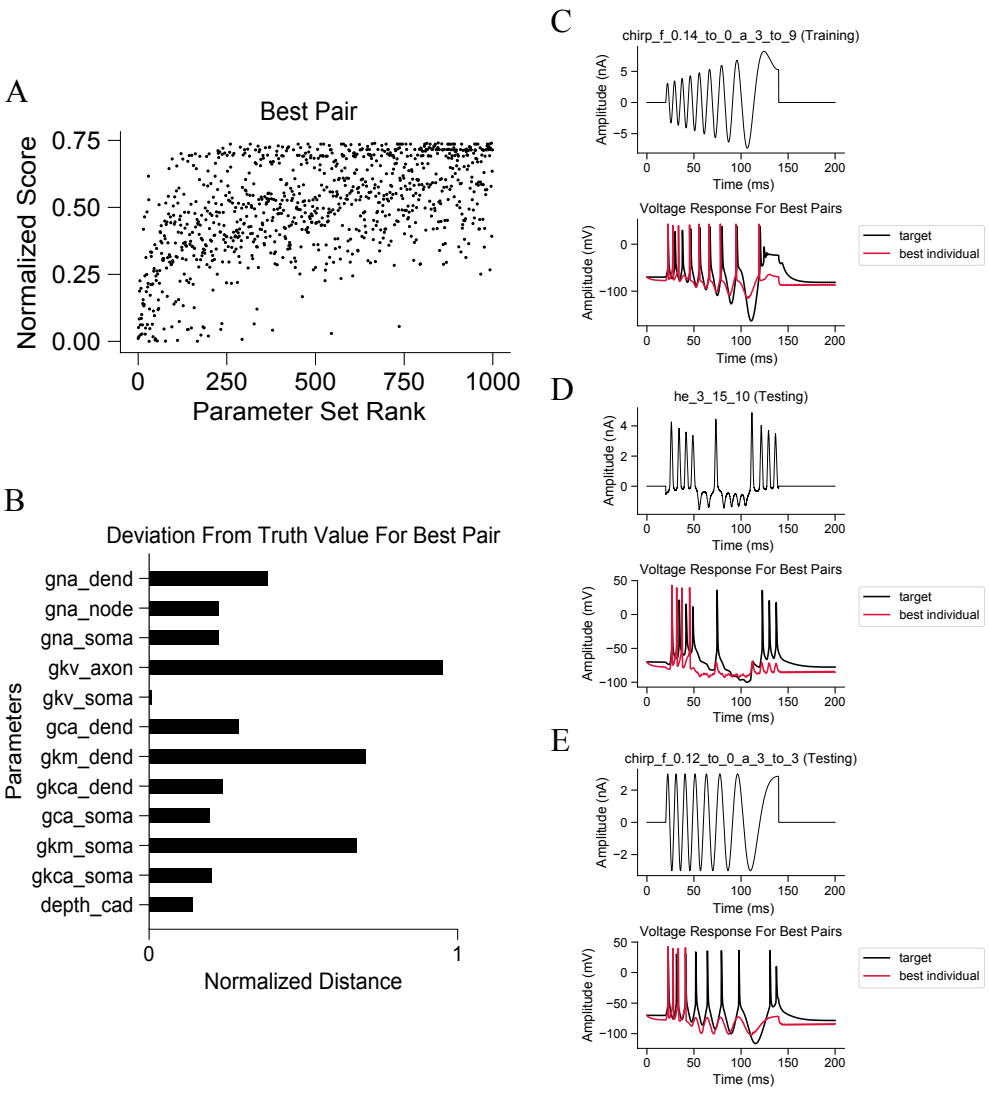

Figure 1: Best pair of stimulus and score function. **A**, Normalized score values versus parameter set ranks for the best pair of stimulus and score function. **B**, Deviations are computed by taking difference between the solutions and the base values (surrogate data) and dividing by the range to normalize. Determining constrained parameters is difficult and it requires expertise in electrophysiology. We selected a threshold of $< 10\%$ as a heuristic to determine the constrained parameters. Here only a single parameter of *gkv_soma* is considered constrained **C**, The target response and solution response are compared for the stimulus used in the optimization procedure (training). Almost all action potentials are matched. **D**, One of *HE* stimulus used as testing purposes. It is a novel stimulus the model has not seen during the optimization process. Many action potentials are missed compared to the training case. **E**, One of novel chirp stimulus for testing purposes. Many action potentials are missed here as well

2.4 Objective with single stimulus and multiple score functions

We next turned to our hypothesis that imposing more constraints will reduce the number of local minima. Specifically, we took a linear combination of every score function for the best stimulus solving the optimization problem of maximizing Spearman's coefficient (Methods). The score plot against parameter ranks shown in Fig. 2A suggests that the newly constructed objective function will have a reduced number of local minima than the case of the best pair. To elaborate, there are fewer points with low scores but high parameter ranks compared to Fig. 1A. With the improved objective, we verified this prediction by observing that about 4 of 12 parameters are constrained as shown in Fig. 2B. In addition, the voltage responses show improvement for the degeneracy problem as the solution's response to novel stimuli became more accurate compared to the best pair case as shown in Fig. 2C, D, E.

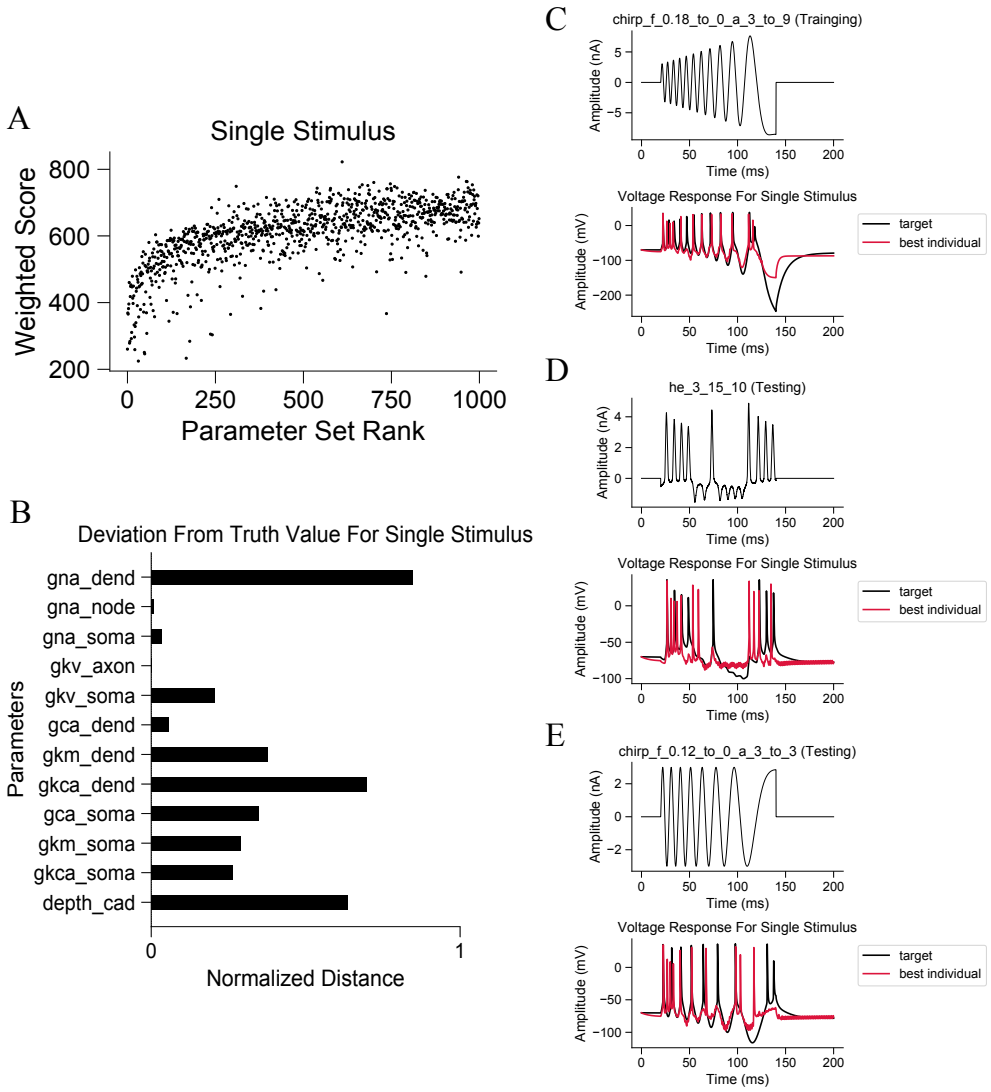

Figure 2: Single stimulus and multiple score functions. **A**, There are fewer points representing local minima than the best pair case suggesting improvement. **B**, Parameters *gna_node, gna_soma, gkv_axon, gkv_soma, gca_dend* are considered to be constrained. **C**, Similar to the best pair case, almost all action potentials are matched for the training case. **D**, Compared to the best pair case, more action potentials are aligned resulting in a better fit. However, some action potentials are missed compared to the training case. **E**, Similarly, more action potentials are aligned but it performs worse than the training case.

2.5 Objective with multiple stimuli and multiple score functions

It is important to note that for every different stimulus, the same score functions behave entirely differently. Therefore, the elements of the objective for the genetic algorithm should actually be pairs of stimulus and score function rather than just score functions alone. With this reasoning, we improved the objective by linearly combining objective elements of stimulus and score function pairs using the same optimization procedure. In other words, we took linear combinations of multiple stimuli and multiple score functions, getting the results represented in Fig. 3A. As a result, we were able to constraint about 7 to 8 out of 12 parameters as shown in Fig. 3B. We were also able to get very close to the target voltage responses matching all the action potentials for both training and testing stimuli as shown in Fig. 3C, D, E. At every stage of the improvement process, we have observed a reduction in the estimated number of local minima verifying that with more constraints we apply to the problem, we get closer to the unique desired solution.

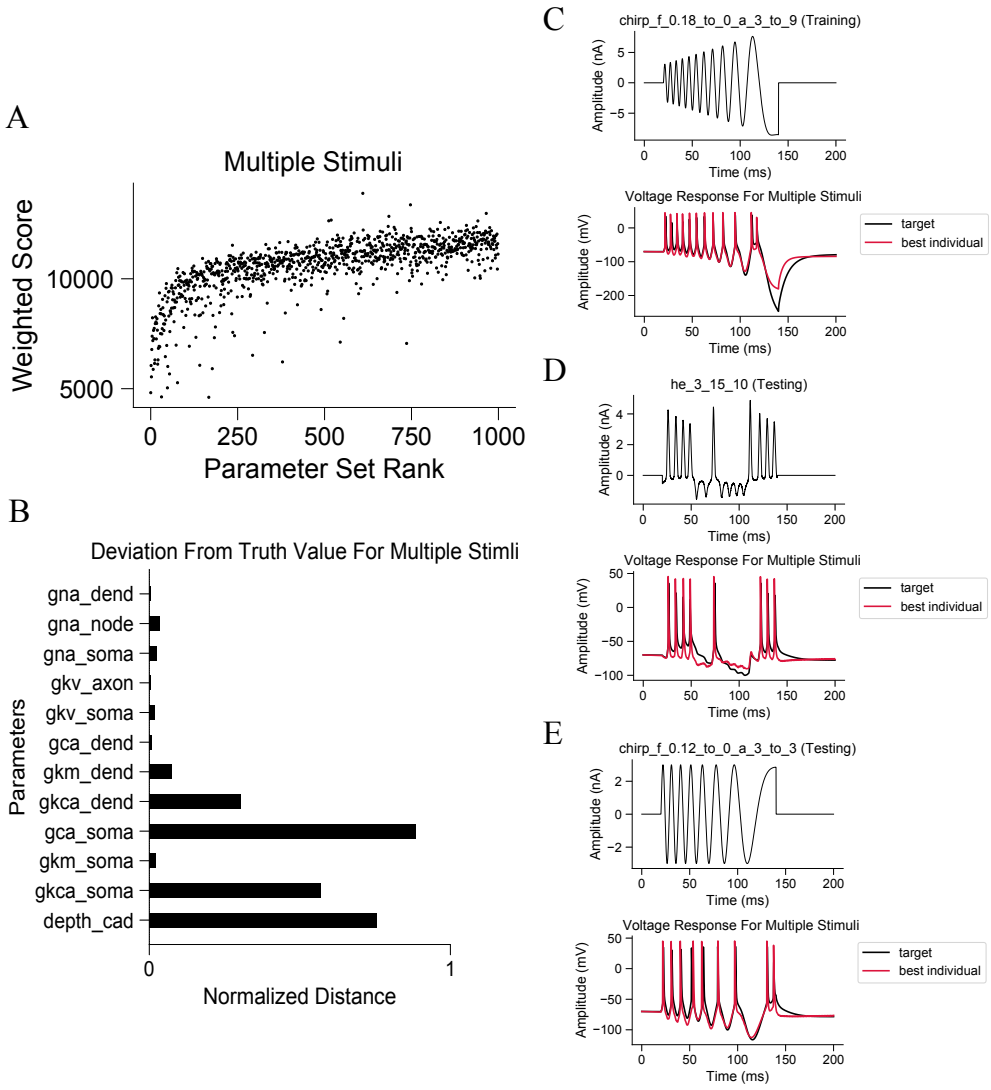

Figure 3: Multiple stimulus and multiple score functions. **A**, Even fewer local minima, and potential local minima are found than the single stimulus case. **B**, Parameters *gna_dend, gna_node, gna_soma, gkv_axon, gkv_soma, gca_dend, gkm_dend, gkm_soma* are considered to be constrained. **C**, Out of multiple stimuli used in the training procedure a chirp stimulus is picked as an example for evaluation. Here, not only all action potentials are matched, but the shapes of the spikes are aligned to the target as well. **D**, Every action potentials are aligned resulting a much better fit than the single stimulus case. However, some details of each spikes are not perfect. **E**, Similarly, much better alignment is observed compared to the single stimulus case.

2.6 Generalization results

In order for the CoMParE algorithm to succeed with the experimental data, it is important that the algorithm not only works for a specific setting with the surrogate data but in general settings as well. To test the CoMParE algorithm's ability to generalize, we tested if the genetic algorithm is able to converge to a parameter set that is not the surrogate data given different, corresponding target responses.

We first generated a random parameter set from a restricted range of 50-base ($[\frac{p_i}{50}, 50p_i]$ for all base values p_i) and checked if it produced reasonable voltage responses for multiple stimuli. With the previously constructed objective using multiple stimuli and multiple score functions, we ran the genetic algorithm. We were able to constraint a similar number of parameters of about 6 to 7 out of 12 as with the original experiment with surrogate data as shown in Fig. 4A. Also, to our surprise, the results show similar patterns when observing which parameters are constrained. For the voltage responses, the solution's response gets very close to the target response as well as described in Fig. 4B, C, D. The generalization results show that it is possible to recover most of the parameters from a randomly chosen point

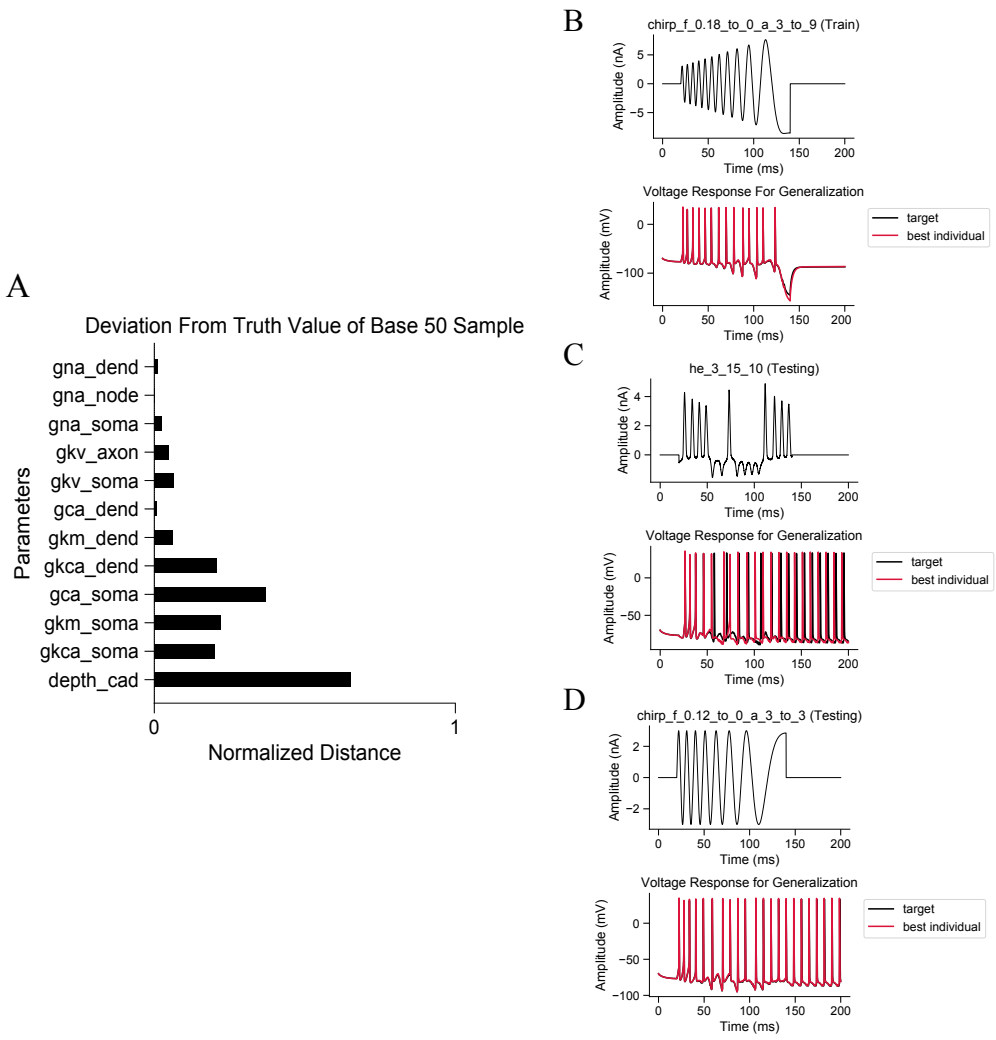

Figure 4: Generalization results on Mainen's model. **A**, Parameters *gna_dend, gna_node, gna_soma, gkv_axon, gkv_soma, gca_dend, gkm_dend* are considered to be constrained. **B**, The voltage response of the best solution almost perfectly matches the target response for the training case. **C**, There are some mismatch of positions of action potentials for the given *HE* stimulus but overall has very close fit. **D**, Surprisingly, the solution's voltage response is perfectly aligned to the target response.

from the parameter space. With this result, we conclude that the CoMParE algorithm could be used in settings with experimental data as the target responses and predict the conductance parameters of recorded biological neurons.

2.7 Testing with the Blue Brain Project model

We also tested the CoMParE algorithm using the Blue Brain Project (BBP) model [12, 13], which is the most physiologically accurate model of neurons up to date. The standard BBP model has 19 free conductance parameters opposed to 12 of the Mainen's model, making the optimization problem harder. Despite the difficulty of this problem, the results show that we were able to constrain 9 to 10 of 19 parameters and 9 to 10 as well for the generalization test (Fig. 5A, B). The voltage responses were also very close to the target for optimizing to surrogate data as well as for the generalization test (Fig. 5C, D, E, F, G, H). This result shows that the CoMParE algorithm can be used for general models that are more complex and sophisticated than the Mainen's model.

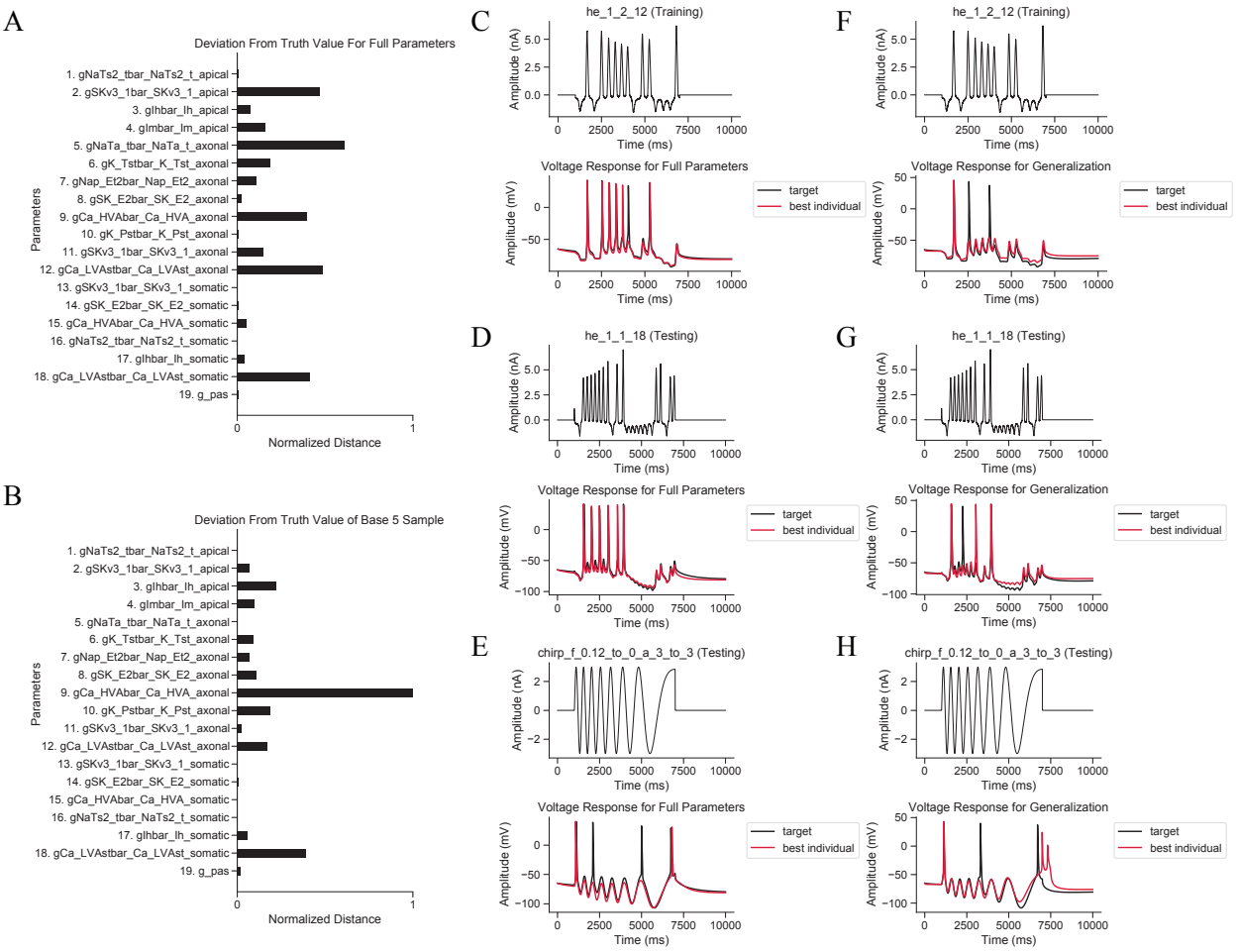

Figure 5: Results using BBP model. **A**, For the case where the target response is generated from the surrogate data, parameters 1, 3, 8, 10, 13, 14, 15, 16, 17, 19 are considered to be constrained. **B**, The random parameter sample was taken from range of base 5 for BBP model for the generalization test. Here, the parameters 1, 5, 7, 11, 13, 14, 15, 16, 17, 19 are considered to be constrained. **C**, Examination of fit using training HE stimulus for the base model fitting. **D**, Examination of fit using novel HE stimulus for the base model fitting. **E**, Examination of fit using novel chirp stimulus for the base model fitting. **F**, Examination of fit using training HE stimulus for the generalization test. The fit is slightly worse than the case of base model fitting. **G**, Examination of fit using novel HE stimulus for the generalization test. **H**, Examination of fit using novel chirp stimulus for the generalization test.

3 Discussion

3.1 Analysis and visualization of objective function

We have shown that the key to reaching the unique solution from surrogate data is imposing more constraints. This idea is intuitively reasonable because if a model is forced to meet many demanding criteria, it must find or get closer to the correct model representation that produced the target data. Specifically, imposing many similarity criteria for many different stimuli pushes the parameter set found by optimization more towards the ground truth values. This observation is also consistent with the idea of local minima reduction because a local minimum represents a solution that is able to produce accurate voltage responses for some stimuli but will fail eventually with different stimuli. We believe that the process of combining diverse score functions to guide the optimization algorithm to enforce many criteria is the underlying principle of the CoMParE algorithm.

To visualize the constructed objective function, we've selected the most dominant two directions in the parameter space from principal component analysis (PCA). We grid sampled the parameter space along the PC directions and evaluated the objective function for every point to plot them. While it is impossible to visualize the full objective function in high dimensions, the plot with the two most dominant directions in parameter space gives an adequate representation of the behavior of our objective functions. The optimized score function is mostly convex as observed in Fig. 6A.

However, the Spikecount score function, which is one of the elementary score functions, has many local minima even when observed in two-dimensional space as represented in Fig. 6B. In the full parameter space of high dimensions, we expect there to be even more local minima for a single score function.

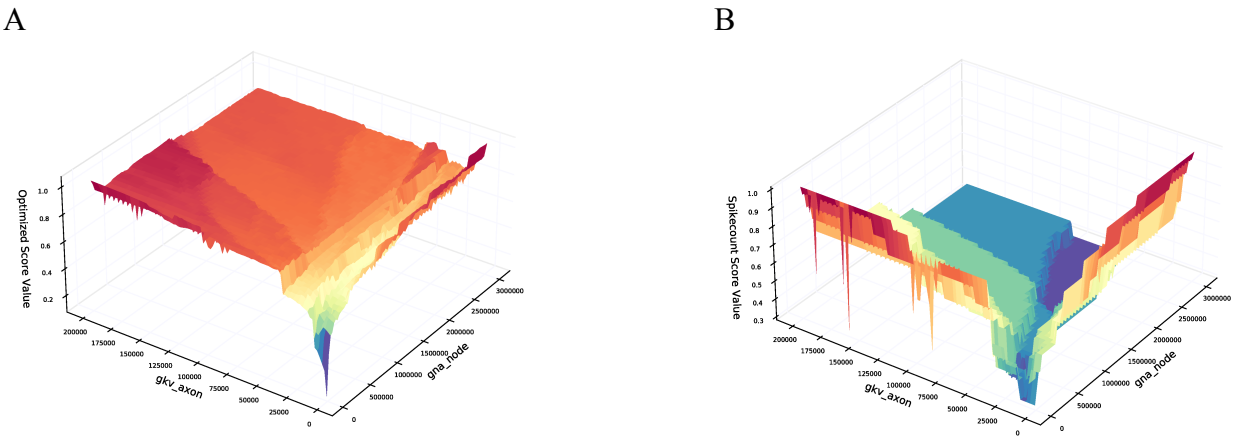

Figure 6: Visualization of objective functions in 3-dimensional space. **A**, The figure shows the optimized score function for the single stimulus case represented as a surface plot. The surface plot is created with grid samples along the most two dominant parameter directions *gkv_axon* and *gna_node*. **B**, The figure shows a single score function *Spikecount* with the same parameter samples as figure A.

3.2 Limitations and Future work

A limitation of the CoMParE algorithm is that although we have successfully reduced many local minima, this problem is still nonconvex. This is mainly due to the limited expressibility of feature-based score functions. Because of this limitation of expressibility, it becomes very difficult to fine-tune the details of voltage responses. Therefore, the genetic algorithm will not be guaranteed to find the perfect, unique solution but only a close one.

One potential solution to solve this problem is using machine learning to learn the relevant features of voltage responses. This way, it becomes possible to learn the relevant features of voltage responses necessary for a better fitting method. It would also be interesting to try an end to end approach with algorithms that can handle time series well.

Another potential solution is to use an experimentally inspired method called the Peeling Procedure [14]. The Peeling Procedure allows us to partially select parameters to optimize with the guide of experimental techniques. Therefore, with Peeling Procedure, the full optimization problem in a high dimension can be divided into many stages of optimization problems in lower dimensions.

4 Conclusion

The key training procedure where the score function weights are found relies on the rank information. Since the rank is determined relative to the surrogate data, the trained score function is vulnerable to overfitting to the surrogate datapoint. In other words, it is possible that the CoMParE algorithm is able to constrain many parameters because it inherently encodes information about the surrogate data. However, the generalization result suggests that if the solution exists in the parameter range, the CoMParE algorithm will be able to constrain the relevant parameters reasonably well. Therefore, the possibility of overfitting is eliminated by the generalization result.

With the CoMParE algorithm, we show the possibility of creating accurate neuronal models with biologically detailed ion-channel distributions. With the right experiments, the CoMParE algorithm allows us to reverse engineer the ion-channel distribution parameters of the neuron recorded from. As a result, we can provide critical information about neuronal excitability for both scientific and clinical research in identifying and treating neurodevelopmental diseases.

5 Methods

5.1 Score functions

A score function refers to a function that takes in two voltage responses and outputs a single scaler to measure the difference between the input traces. Each score functions are feature-based most of which are taken from Electrophys Feature Extraction Library (eFEL) [15]. There are also custom-designed functions such as KL-divergence and inner product between the two voltage vectors. We have defined around 80 score functions, but many of them are assigned zero weight during the optimization procedure. Since the functions have different units and characteristics, we normalized all the values to [0, 1] before doing any analysis.

5.2 Sampling parameter space

When sampling the parameter space, the samples are taken from the normalized domain of 12-dimensional hypercube for the Mainen's model and 19-dimensional hypercube for the BBP model. Specifically, for each parameter, we divided the normalized domain of [-1, 1] into subzones with gradually increasing range sampling uniformly randomly from them. After sampling, parameter sets are sorted according to l-100 norm to penalize the values that are very large compared to the other values in the parameter vector. Then we transformed parameter samples from normalized domain to the model's parameter space by using piecewise linear functions. We mapped -1 to the lower bound, 0 to the base value of surrogate data, and 1 to the upper bound. An important point to note is that by sorting the normalized parameter using the value of $l - 100$ norm in the normalized domain, it is sorted with respect to $l - 100$ norm distance from the surrogate data values in the scaled parameter domain. Finally, we assign ranks equal to the sorted ordering.

5.3 Choice of stimuli

We selected various stimulation protocols of ramps (increasing linear functions), normal sinusoids, chirps, and *HE* stimulations [16, 17]. For each class of stimulation protocols, we selected a wide range of different combinations of parameters. Specifically, stimuli with varying combinations of magnitude and frequency parameters for sinusoids, starting and ending amplitude for ramps, and starting and ending amplitudes and frequencies for chirps were generated. Then we ran wet-lab experiments to select out stimuli that are both stable and able to create sufficient action potentials.

The top stimuli chosen by the optimization algorithm as part of the GA objective turns out to have many chirps than other kinds of stimulation protocols. This result is consistent with the reasoning of choosing chirps as one of the stimulation protocol categories in the first place. We have reasoned that since chirps contain a wide range of frequency spectrum, it will extract more information than the other kinds of stimulations.

5.4 Score function weight optimization

In the case of MOO, the Pareto optimality condition is satisfied if not one objective can be improved without degrading other objectives. This means the Pareto optimal solutions will not be a single one, but a set called Pareto frontier. Therefore, MOO cannot be the right approach to the degeneracy problem.

The main goal of using many constraints is to reduce the number of local minima. To align with this goal, the weights of each score function is found by maximizing Spearman's correlation coefficient between scores and parameter distance ranks. Mathematically, we solved an optimization problem of $w^* = \text{argmax}_w(w^\top f(p), rank(p))$ where f is the score function vector, and p is the parameter vector. For implementation, we have used the pattern search algorithm in the Noisyopt [18] python library to optimize for the weights.

5.5 Genetic algorithm

We've implemented the genetic algorithm using Distributed Evolutionary Algorithms in Python (DEAP) library [19]. When running GA for the generalization experiments, we used 1200 offspring at each generation for 100 generations. For every other run, we used 1000 offspring at each generation for 100 generations. At every generation, each offspring (parameter set) is evaluated by the objective function, and the top-performing offspring go through random crossings and mutations to be passed to the next generation.

The objective of a genetic algorithm is a vector-valued function $f : R^d \to R$ where d is the dimension of the parameter space. This interpretation is the result of abstracting away the process of computing voltage responses and computing voltage-dependent features. Given one parameter set, voltage responses for given stimuli are computed using NEURON [20] then the voltage trance dependent features are extracted using eFEL to compute the final objective function.

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