

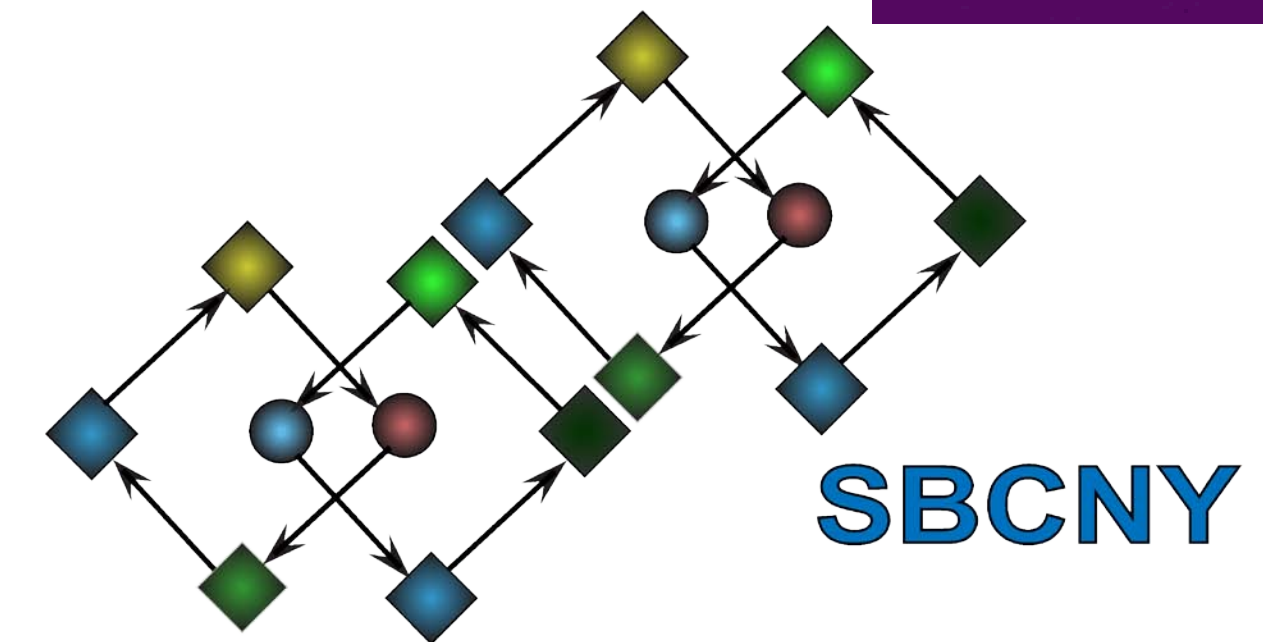


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# Parameter Sensitivity in a Model of the Ventricular Action Potential: Visualizing a Multi-Dimensional Conductance Space

Preet Minhas, Eric A. Sobie  
City College of New York, NY, USA

Department of Pharmacology and Systems Therapeutics, Mount Sinai School of Medicine, New York, NY, USA



## Abstract

The electrical behavior of the cardiac myocyte depends on the coordinated action of numerous voltage-dependent ion channels in the cell membrane. With each heartbeat, the orderly opening and closing of these ion channels results in membrane depolarization, which initiates an action potential, and subsequent membrane repolarization, which allows for myocyte relaxation. Computational models serve as an important tool to link ion channel behavior to action potential morphology. With most existing models, however, our understanding of how changes in ion channel expression lead to changes in cell behavior is limited.

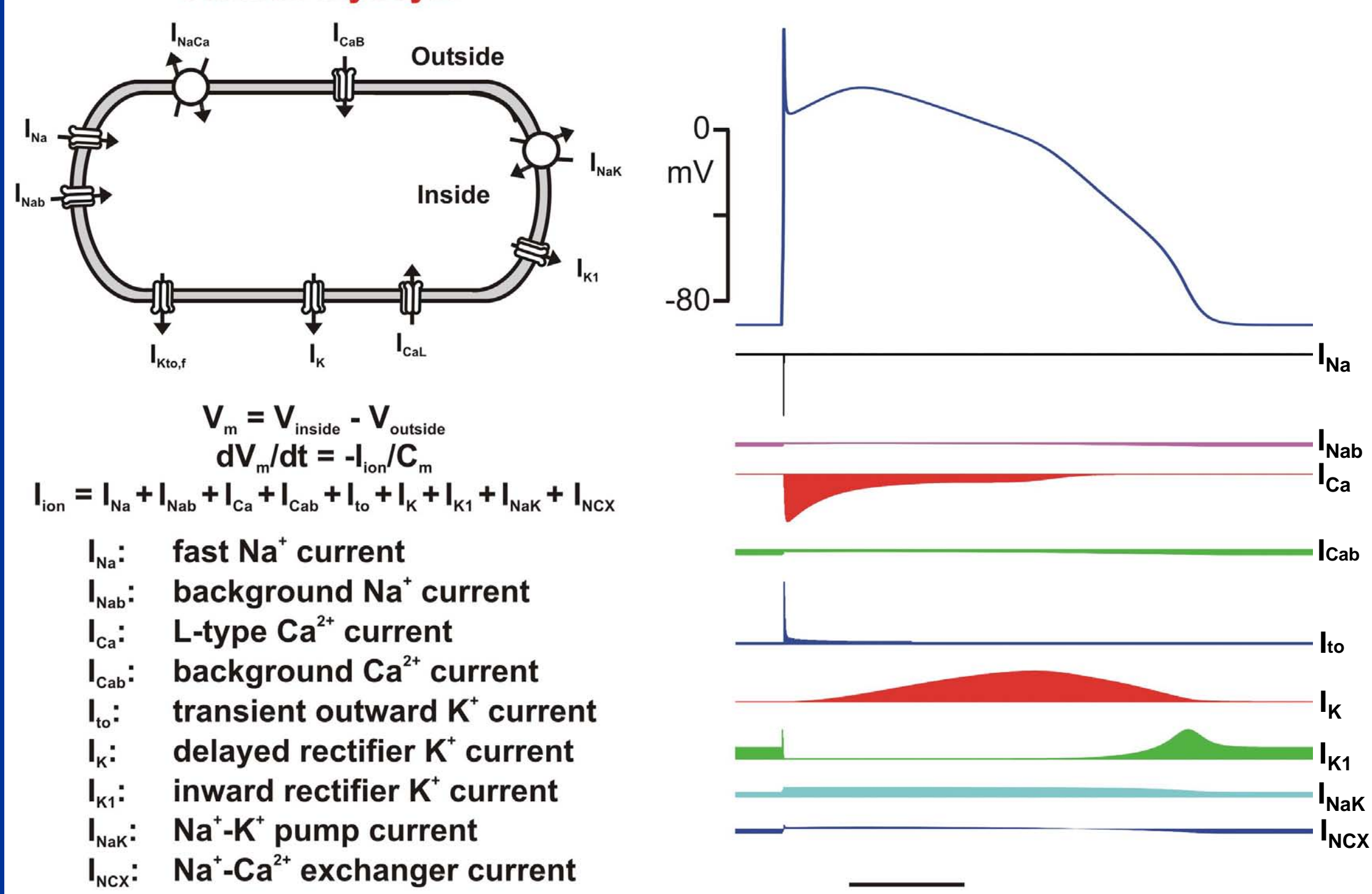
In this study we sought to explore thoroughly the parameter space of a mathematical model of the human ventricular myocyte. We systematically varied the nine maximal conductances that govern electrical behavior in this model and examined how changes in each conductance affected the action potential duration, an important physiological characteristic. Five values of each maximal conductance were tested, for a total of  $5^9 = 1,953,125$  action potential simulations.

In order to understand how changes in multiple parameters affect the action potential duration we used a technique called dimensional stacking. This technique allowed us to visualize multidimensional data in two dimensions. Pairs of dimensions are embedded within each other with each data point having a unique location on the resulting image. We generated five images, each displaying an eight dimensional space at a different conductance of  $G_{NaK}$ , and chose a color scale that most appropriately displays the changes in action potential duration across the multidimensional space. The order in which dimensions are stacked has a large impact on the "interpretability" of the resulting image. An optimal order is believed to be one that yields an image with a uniform distribution of solid color rather than patches of color. Furthermore, the order provides insight into which conductances have a larger effect on the action potential duration than others. The more significant parameters end up on the outer dimensions, while the less significant end up on the inner dimensions. The technique described here serves as a useful complement to PLS regression. The latter approach only provides insight into the neighborhood within a parameter space. Using dimensional stacking we can explore the parameter space more thoroughly.

## Background

### Mathematical model of human ventricular myocyte

#### Cardiac myocyte

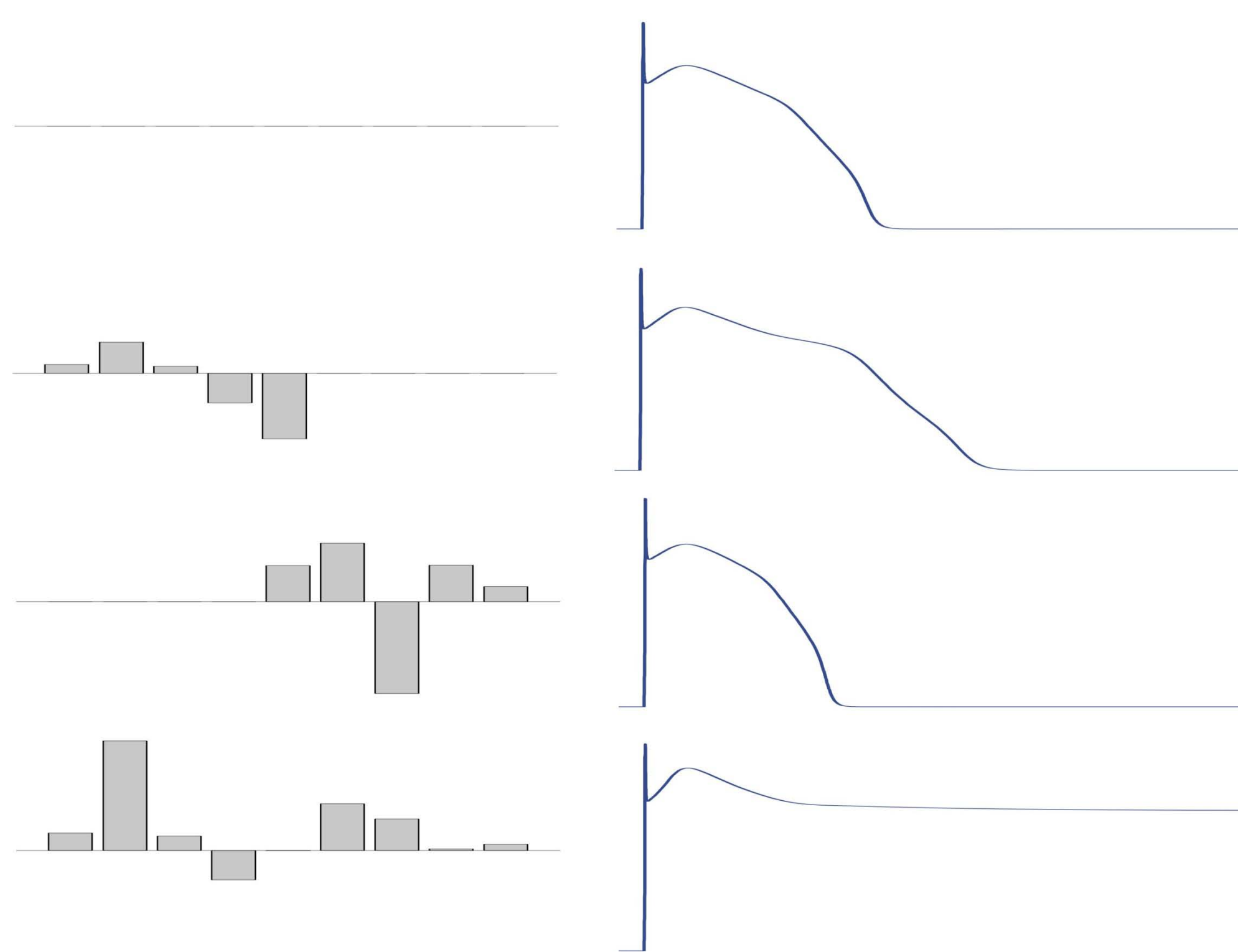


The magnitude of each current is proportional to its maximal conductance, e.g.  $I_{Na} = G_{Na} m^3 (V - E_{Na})$

The figure on the left is a schematic diagram of a cardiac myocyte showing different currents flowing through various channels and pumps. This figure on the right shows an action potential and time profile of different currents that give rise to it.

## Background

### Changes in maximal conductances cause changes in AP shape

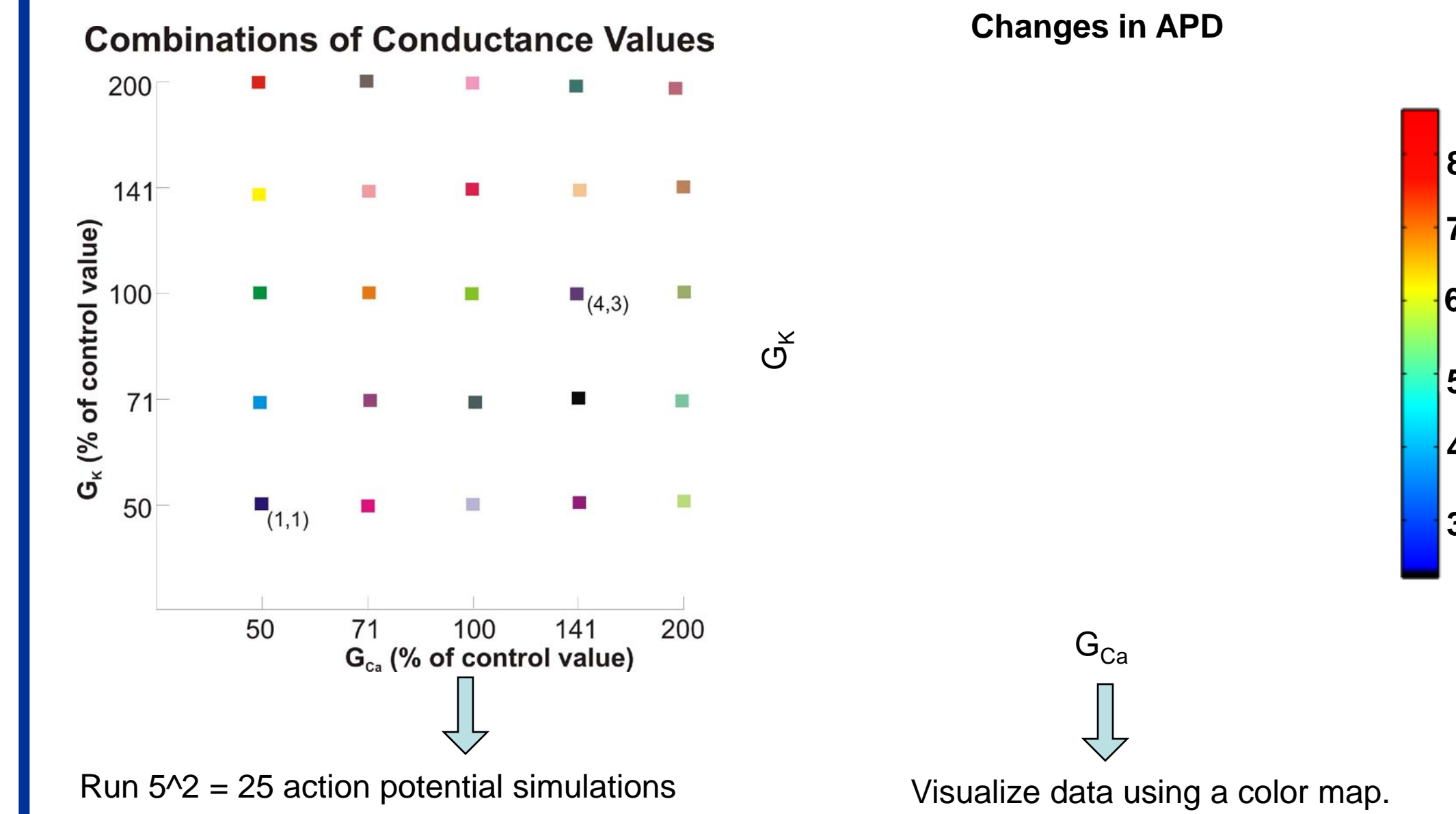


How can we characterize quantitatively the effects on AP shape caused by changes in maximal conductances of ionic currents?

## Approach

### How else can we quantify this relationship?

As an example of our method, here we show how we vary two maximal conductances for five different values.

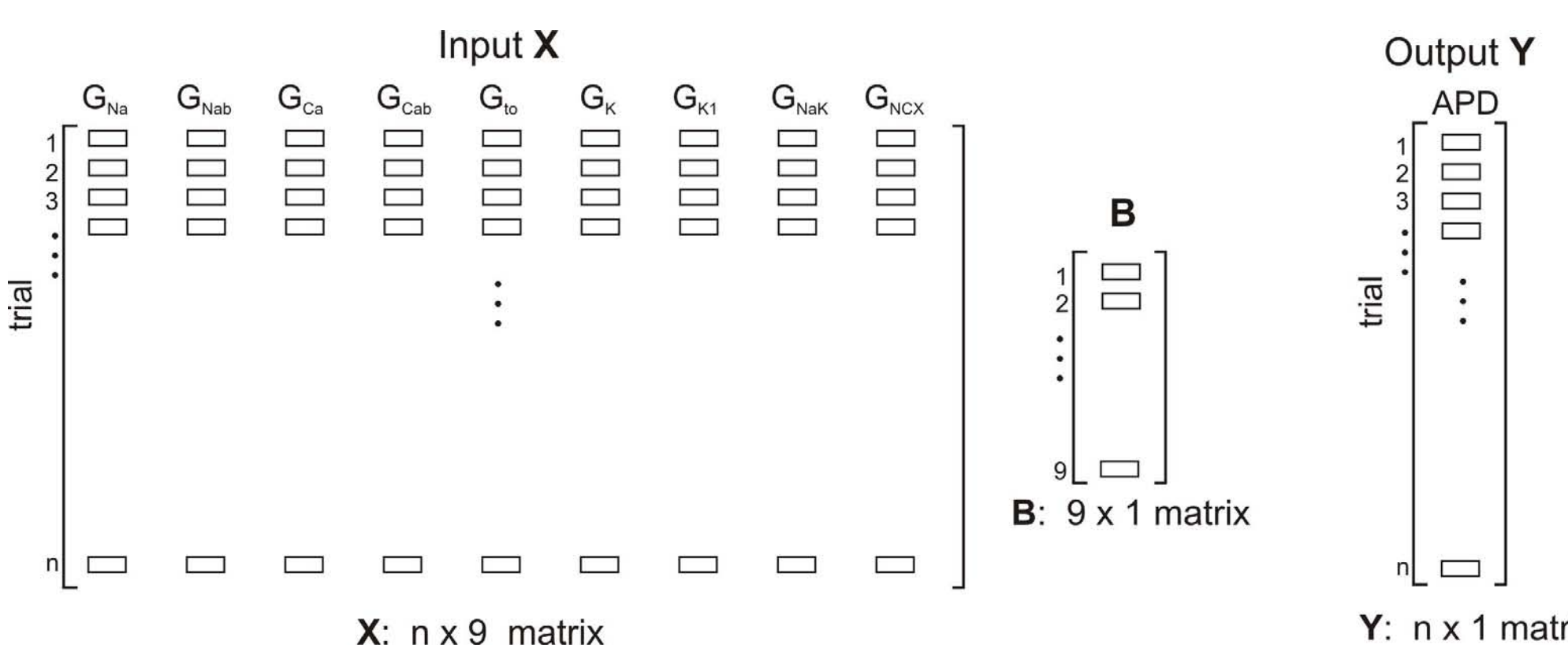


Run  $5^2 = 25$  action potential simulations  
To see how all 9 conductances contribute to changes in AP morphology run  $5^9 = 1,953,125$  action potential simulations.

How can we analyze such large-scale data?

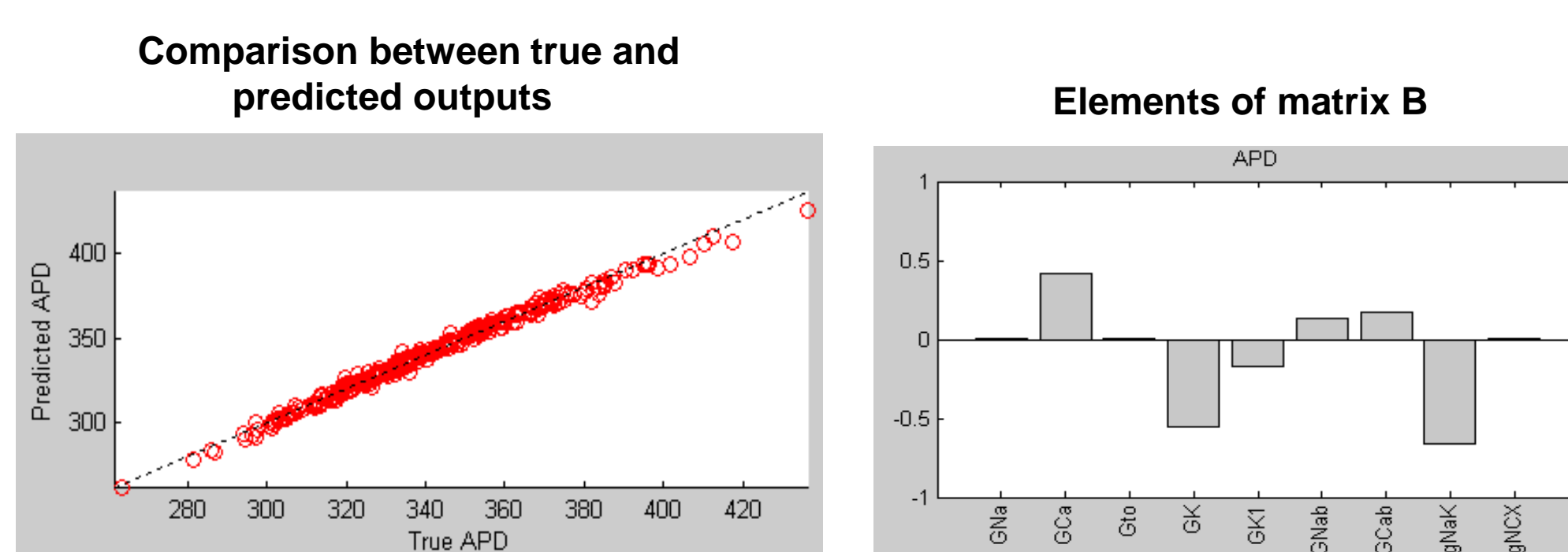
## Approach

One method is to use Partial Least Squares Regression.



- 1) Randomly vary the nine conductances, run repeated simulations, and collect the results as an output matrix **Y**.
- 2) Use partial least squares regression to determine a matrix **B** that can predict the output **Y** given the input matrix **X**.

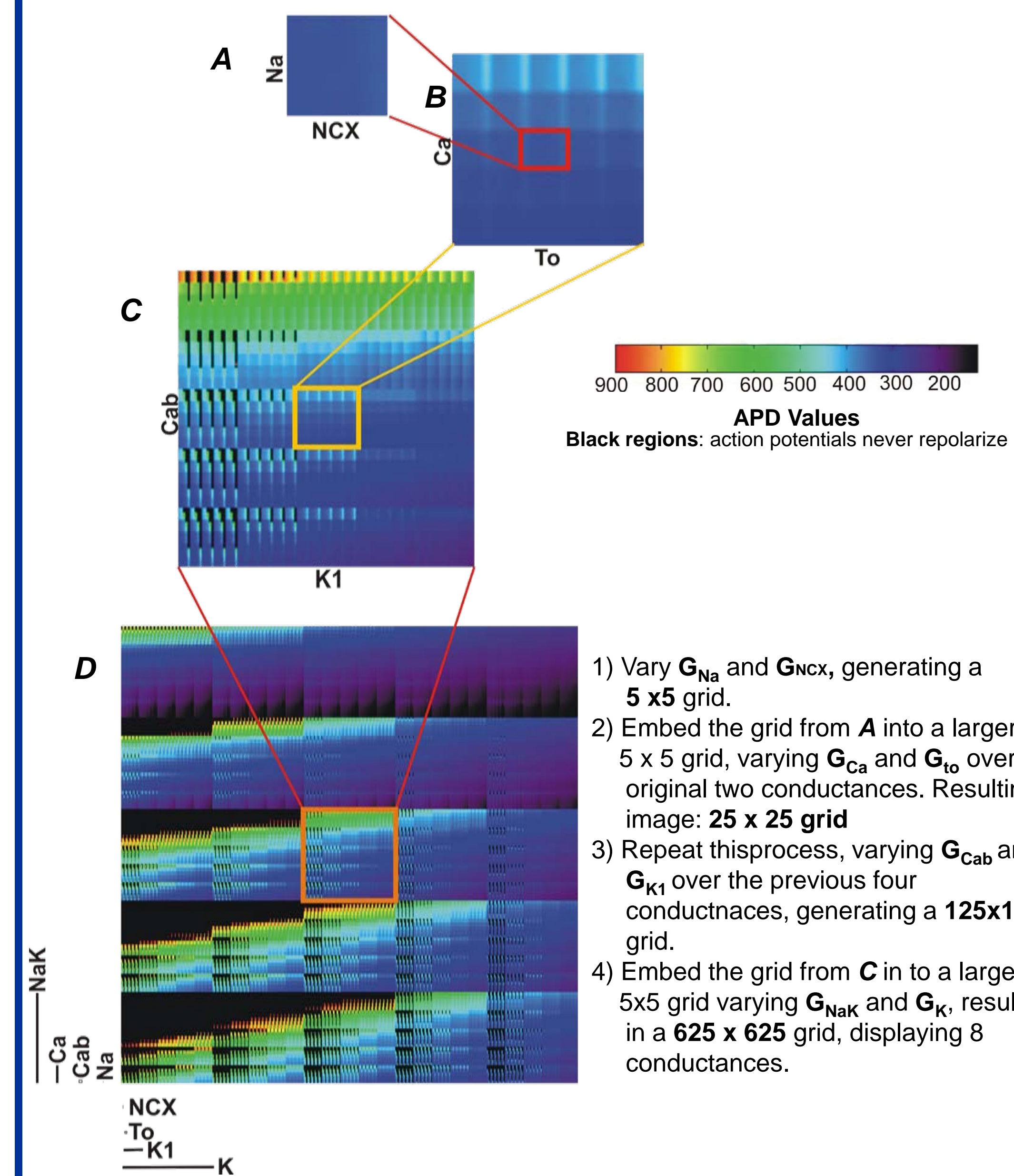
This technique has been shown to accurately predict how changes in ionic conductances affect AP morphology.



The regression coefficients in the matrix **B** indicate how changes in maximal conductances affect action potential duration.

## Results

We chose to analyze the data using Dimensional Stacking which is to embed dimensions within each other (Taylor et al. 2006)

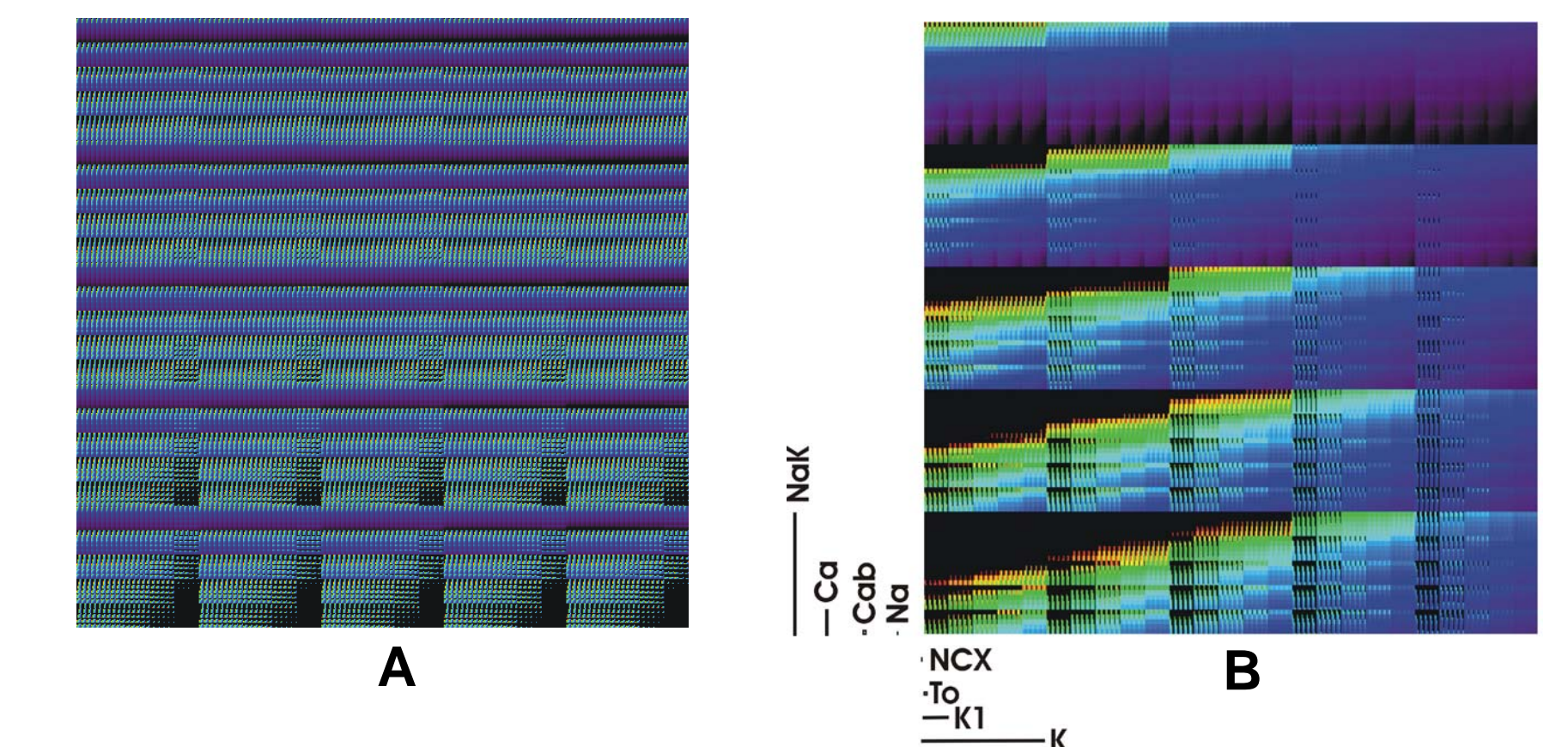


- 1) Vary  $G_{Na}$  and  $G_{NCX}$ , generating a  $5 \times 5$  grid.
- 2) Embed the grid from **A** into a larger  $5 \times 5$  grid, varying  $G_{Ca}$  and  $G_{CaT}$  over the original two conductances. Resulting image:  $25 \times 25$  grid
- 3) Repeat this process, varying  $G_{CaL}$  and  $G_{K1}$  over the previous four conductances, generating a  $125 \times 125$  grid.
- 4) Embed the grid from **C** in to a larger  $5 \times 5$  grid varying  $G_{NaK}$  and  $G_K$ , resulting in a  $625 \times 625$  grid, displaying 8 conductances.

## Results

"Interpretability" of resulting image depends on order in which dimensions are stacked.

### Random vs. Optimal Order



It is difficult to draw any conclusions from image **A**, however, from image **B** we learn :

- $G_{NaK}$  and  $G_K$  have the greatest effect on APD. Decreasing both  $G_{NaK}$  and  $G_K$  results in action potentials that never repolarize.
- Increasing  $G_{Ca}$  and decreasing  $G_K$  causes the APD to increase.
- $G_{CaL}$ ,  $G_{CaT}$ ,  $G_{Na}$ , and  $G_{NCX}$  have a minimal effect on APD

## Conclusion

- We have applied a novel method, dimensional stacking, to help us visualize a nine dimensional conductance space.
- The order in which the dimensions are stacked provides insight into which conductances have the greatest effect on APD.
- This method serves as a complement to PLS regression, which only considers a neighborhood within the parameter space.
- Although dimensional stacking provides valuable information it requires experience to interpret the resulting image

## Future Direction

- Use the data collected, here, to test the accuracy of PLS regression.
- Understanding what combinations of currents are responsible for arrhythmias can lead to the development of drugs targeting the specific currents.

## Acknowledgments

Special thanks to:

Dr. Eric A. Sobie, Dr. Hena Ramay, Dr. Young-Seon, Amrita Sarkar, Frank Fabris, Rushita Patel, Ona Liu

Supported by the Systems Biology Center in New York, National Institute of General Medical Sciences Grant P50 GM071558.