

# Mathematical Approaches to Understand Changes in Cardiac Action Potential Morphology

## Caused by Non-Specific Drugs

Kathleen McGovern, Eric A. Sobie

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



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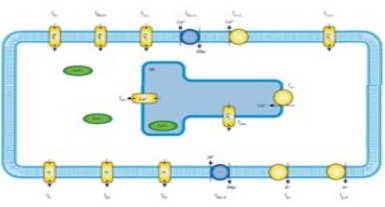
### Abstract

Changes to action potential duration and morphology are key factors in the development of cardiac arrhythmias. Torsades de pointes is a well-known arrhythmia that results from the prolongation of the QT interval. Prolongation of the QT interval is a direct result of extended action potential duration (APD) of cardiac myocytes. Action potential duration may be extended as a consequence of a congenital disorder, such as Long QT Syndrome, or it may be extended via pharmacological agents. Many drugs have been pulled off the market for causing toxic and sometimes lethal cardiac side effects. Terfenadine, an antihistamine, was removed from the market after exhibiting these types of lethal side effects. Prolongation of the action potential duration is not the only factor that can have potentially fatal consequences. Shortening of the action potential duration, when coupled with morphological changes, can lead directly to ventricular fibrillation. Unfortunately, some pharmacological agents are not shown to be lethal until the agent is exposed to a large enough population. Therefore, prediction of changes to action potential duration is of high importance for the development of safe drugs.

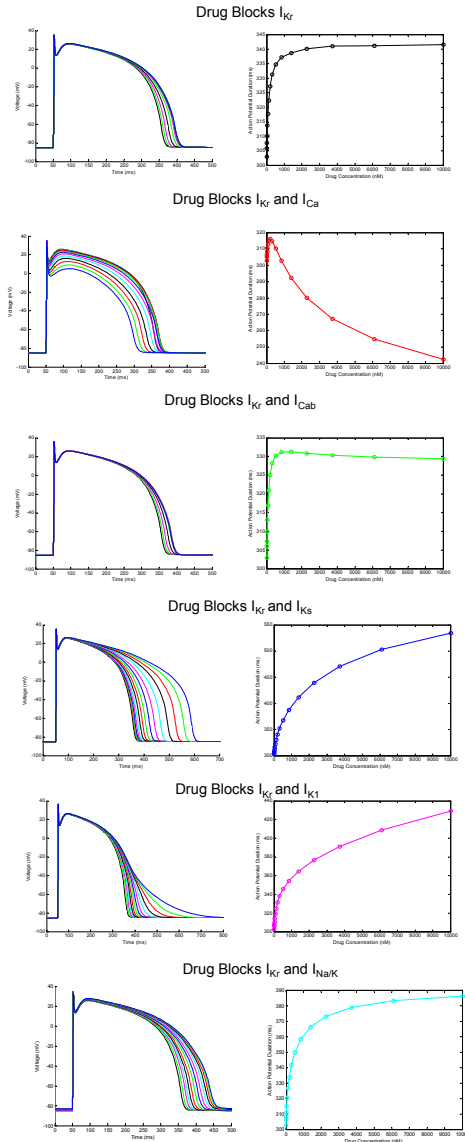
Action potential duration and morphology are a result of a delicate system of ionic currents which bridge the intracellular space to the extracellular space of ventricular myocytes. These currents run through a network of channels that allow and restrict the flow of different ions at key instances. Blocking one or more of these channels can therefore have a dramatic effect on the action potential. One channel that has been shown to be of high importance to the action potential duration is the channel through which the rapid delayed rectifier current ( $I_{Kr}$ ) flows. This current is responsible for the repolarization of the cellular membrane, so a pharmacological agent which blocks the  $I_{Kr}$  channel will extend the duration of the action potential. Some drugs may not be specific for  $I_{Kr}$  only and as a result may block other channels in addition to  $I_{Kr}$ . How combinatorial blocks affect the action potential is difficult and expensive to test experimentally. Moreover, if a pharmacological agent is affecting action potential duration and/or morphology, how can a drug developer determine the channels responsible for the change? Computational simulations can be used to address these issues. Using a model of a ventricular myocyte, one can block different channels and observe the changes to the action potential. Mathematical analysis of the results can then lead to an understanding of how to discover probable channel blocks which lead to changes to action potential duration.

### Methods

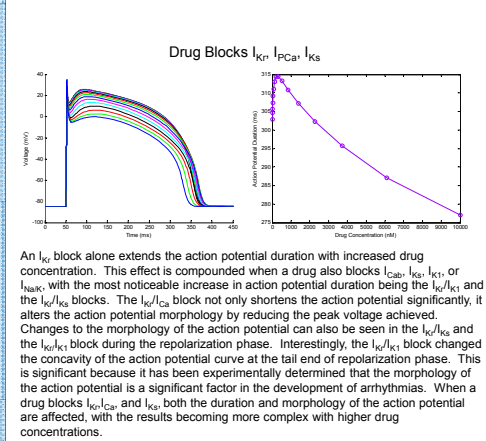
The TTNP (ten Tusscher et al, *American Journal of Physiology*, 2004) model of the ventricular myocyte was used in performing simulations of action potential generation. Beginning with an  $I_{Kr}$  block only, all sixteen channels of the model were blocked in addition to the  $I_{Kr}$  block and the results were observed. The drug affinity for  $I_{Kr}$  was set at 100 nM, and the affinity of the additional channel block was set at 1000 nM. The drug affinity was calculated using the drug dissociation constant ( $K_D$ ), which is the ratio of the concentration of independent ligands and independent receptors to the concentration of ligand-receptor complexes. Therefore, low  $K_D$  values correspond to higher drug affinity, and vice-versa. Action potential duration was plotted against drug concentration at scaled values of  $K_D$  on the significant channel blocks. In order to see how coupled  $I_{Kr}$  and other channel blocks changed the action potential duration compared to an  $I_{Kr}$  block alone, the ratio of the action potential durations from the coupled blocks to the  $I_{Kr}$  block was computed and plotted. From this plot the slopes of the various curves were extracted. A partial least squares linear regression was performed on the model to show the probabilistic relationship between ionic channel blocks and action potential duration. Finally, the extracted slopes of the ratio curves were plotted against and compared with the regression ( $B_{pls}$ ) coefficients.



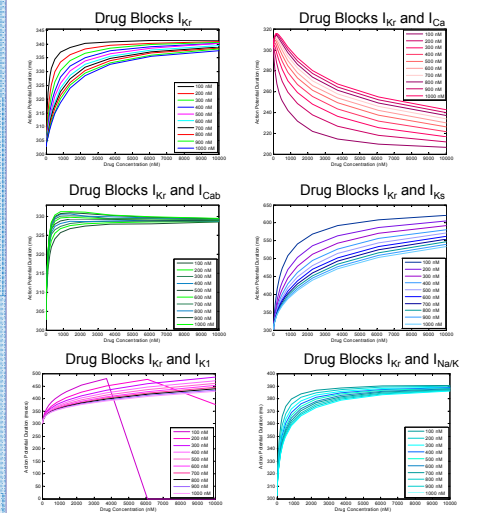
### Effects of Drug Block on APD



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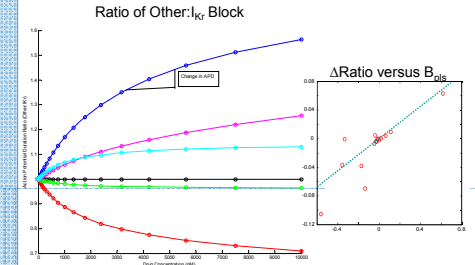


### Scaled $K_D$ Values for Drug Block

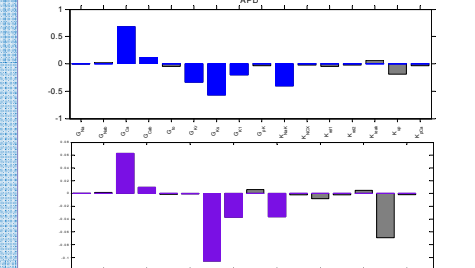


Different drug affinities produce altered action potential durations. Notably, at a high drug affinity for the  $I_{Kr}/I_{Ca}$  channel the action potential duration spiked at low drug concentrations before reducing as the drug concentration increased. When drug has a high affinity for both  $I_{Kr}$  and  $I_{K1}$ , an action potential will eventually fail to generate.

### Extracted Slopes



### $B_{pls}$ Coefficients vs. Ratio Slopes



There exists a strong correlation between the slopes of the ratio graphs, the  $B_{pls}$  coefficients, and the changes to the action potential duration. From this, if one were given data regarding the nature of the action potential duration, one could hypothesize which channels are involved.

### Conclusions

- The channels which have the greatest influence on action potential duration and morphology are the rapid delayed potassium rectifier current ( $I_{Kr}$ ), the L-type calcium current ( $I_{CaT}$ ), the inward calcium current ( $I_{CaL}$ ), the slow delayed potassium rectifier current ( $I_{Ks}$ ), the inward rectifier potassium current ( $I_{K1}$ ), and the sodium potassium pump current ( $I_{NaK}$ ). These results correspond with the largest regression coefficients.
- The rate of change of the action potential duration as a result of drug concentration shows a linear relationship between combinatorial channel blocks and action potential duration. Therefore, if the rate of change of action potential duration is known, the channel blocks responsible may be ascertained.
- Nonlinear relationships exist between channel blocks and action potential duration. A nonlinear regression analysis may unveil the nature of these relationships.
- The model failed to produce an action potential when the SERCA current ( $I_{SERCA}$ ) was blocked at high levels of drug concentration. The reported calcium levels in the cell at these high drug concentrations were roughly 100 times higher than they are currently known to be physiologically. This shows that there are flaws in the model in relation to the action of this pump and the model should be reexamined in this regard.

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