

A Global Sensitivity Tool for Cardiac Cell Modeling: Application to Ionic Current Balance and Hypertrophic Signaling

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Abstract— Cardiovascular diseases are the major cause of death in the developed countries. Identifying key cellular processes involved in generation of the electrical signal and in regulation of signal transduction pathways is essential for unraveling the underlying mechanisms of heart rhythm behavior. Computational cardiac models provide important insights into cardiovascular function and disease. Sensitivity analysis presents a key tool for exploring the large parameter space of such models, in order to determine the key factors determining and controlling the underlying physiological processes. We developed a new global sensitivity analysis tool which implements the Morris method, a global sensitivity screening algorithm, onto a Nimrod platform, which is a distributed resources software toolkit. The newly developed tool has been validated using the model of IP₃-calcineurin signal transduction pathway model which has 30 parameters. The key driving factors of the IP₃ transient behaviour have been calculated and confirmed to agree with previously published data. We next demonstrated the use of this method as an assessment tool for characterizing the structure of cardiac ionic models. In three latest human ventricular myocyte models, we examined the contribution of transmembrane currents to the shape of the electrical signal (i.e. on the action potential duration). The resulting profiles of the ionic current balance demonstrated the highly nonlinear nature of cardiac ionic models and identified key players in different models. Such profiling suggests new avenues for development of methodologies to predict drug action effects in cardiac cells.

I. INTRODUCTION

Mechanical contraction of the heart is closely interlinked with its electrical activity. Altered electrical behavior may lead to irregular heart function, causing tachycardia, ventricular fibrillation, and possibly sudden death. Furthermore, altered physical state of the heart (e.g. hypertrophy) is also a known risk factor for heart failure. The investigation of mechanisms underlying regular and irregular cardiac rhythms, as well as of biological pathways underlying cardiac disease is thus an active area of research.

Ultimately the dynamics of a single cell are responsible for the electrical activity of the heart. Moreover, to

understand risk factors associated with heart failure, it is important to characterize cardiac disease at cellular level, which involves untangling a complex interaction of signal transduction pathways. Thus, identifying the key cellular mechanisms involved in regulation of regular and irregular heart function on a beat-to-beat basis, as well as interaction of signal transduction pathways, is essential for understanding cardiac function under both normal and disease conditions.

Since their origin in 1962 (starting with Noble 1962 Purkinje cell model), computational models of electrical activity in cardiac myocytes have been providing additional insight into the underlying mechanisms of regulation of cardiac electrophysiological behavior at the cellular level. The models' complexity, however, has increased, and in recent years, cardiac modeling community has become more aware of challenges faced amidst the increased complexity of the models, where the number of parameters involved is on the order of hundreds. Such challenges include over-parameterization within the existing models, e.g. sloppiness and non-identifiability of parameters (e.g. Dokos & Lovell 2004, N. Gutenkunst et al. 2007, Fink & Noble 2009).

There are many sensitivity analysis and parameter estimation tools and methodologies (e.g. Morris 1991, Dokos & Lovell 2004, Fink & Noble 2009, Sobie 2009). Yet, there is a lack of a computationally efficient and user-friendly tool for rapidly assessing and characterizing how changes in parameters influence the outputs. Recent methods developed with a specific aim to assess the robustness of the cardiac single cell model parameters include: parameter variability analysis which examine the effect of varying one parameter at a time, local sensitivity analysis software (e.g. Fink & Noble 2009), techniques which assess the significance of parameters using multivariable regression over randomized set of input parameter values (e.g. Sobie 2009) and a global sensitivity analysis method called the Morris screening algorithm (e.g. Cooling 2007).

Given the high nonlinearity of cardiac models, global analysis is essential when assessing the structure, model robustness, and determining the key factors in a cardiac model. Moreover, it is also necessary to do this in an efficient manner since the models are typically very computationally intensive. We have developed a new global sensitivity analysis tool which implements the Morris screening algorithm (Morris 1991, Cooling 2007) within the Nimrod platform (Abramson et al. 2000) that enables the use of distributed computing resources for computations. Section II outlines the details of the newly developed tool. Section III presents results and discussion on validation and application of the tool and Section IV presents concluding remarks.

Manuscript received April 23, 2010

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This work was supported by preDiCT, the European Commission DG-INFO Grant. The Nimrod toolkit development has been funded by the Australian Research Council, the Cooperative Research Centre for Enterprise Distributed Systems, the Department of Communications, Information Technology and the Arts under a GrangeNet grant, and the Australian Partnership for Advanced Computing.

II. METHODOLOGY

A. The Morris Method (Morris 1991, Cooling 2007)

The Morris method is a global sensitivity screening algorithm, which ranks the parameters according to their average effect on a particular model output over a given range of parameter value. The Morris method is as efficient as commonly-used variance based techniques in detecting factors of low sensitivity, yet it is computationally cheaper. The method takes two parameters as inputs:

- p - number of partitions, based on which a random set of points in the n -dimensional parameter space (where n is the number of model parameters that are being ranked) is generated.
- r - number of trajectories. Morris trajectories start at a random point in the parameter space, where points are defined by p and the user-defined model parameter ranges. A trajectory is then defined by varying one parameter at a time by Δ where $\Delta = p/2 * 1/(p-1)$.

The Morris analysis yields the following measures of the sensitivity of the outputs to the model parameters:

- μ - a direction-independent global estimate measure of the mean change of the objective function on a change in parameter value by $\pm\Delta$.
- δ - standard deviation which estimates the second and higher order effects of the parameter on the objective function such as interactions with other parameters.

In summary, in the Morris method parameters are varied and their effect on objective functions is assessed. The Morris analysis yields a score for each parameter of the model estimating the partial differential of an objective function with respect to that parameter.

B. Nimrod Parameter Sweep Toolkit

Nimrod is a convenient, user-friendly framework of distributed computing software developed by Abramson et al. 2000 (<http://messagelab.monash.edu.au/Nimrod>). The Nimrod family of tools allow a user to specify large computational experiments and to execute these over a Grid of computational resources. Most users specify their problems in a simple declarative form called a 'plan' file, and submit these through a Web portal. Whilst Nimrod represents a variety of different search tools, the Nimrod/G component supports complete parameter enumeration and execution on the Grid.

C. Global Sensitivity Analysis Implemented via Nimrod Platform

The work flow of the newly developed tool is shown in Fig. 1. Importantly, the evaluations of the objective functions at different points in n -dimensional space, as required by the Morris method, are independent of each other. Therefore, by incorporating the Morris analysis onto the Nimrod platform, we take advantage of parallel batches of evaluations, and hence improve the computational cost required for the Morris analysis.

The work flow stages are: (1) input definition by the user,

(2) plan file submission via Nimrod Portal, (3) generation of set of parameters for which the function influence is measured, (4) running model via Nimrod G using grid middleware to generate the objective function values, (5) collecting the resulting outputs and performing the Morris analysis to calculate the resulting μ and δ , (6) output the resulting measures to the user.

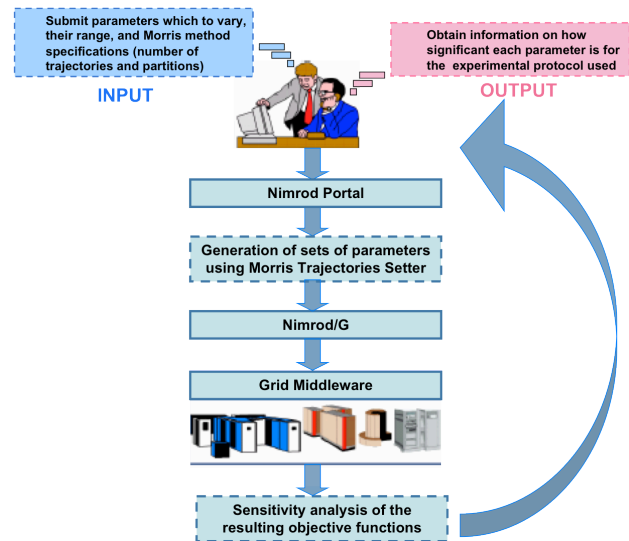


Fig. 1. Work flow diagram of the distributed software Nimrod toolkit which combines Morris Method and Nimrod G platform to perform Global Sensitivity Analysis for parameters in a given model within a chosen range.

D. Cardiac Models

For validation studies, the IP3 production model by Cooling et al. 2007 was simulated. The influence of 30 model parameters (each varied by 10-fold increase/decrease) on the peak value of IP3 transient was calculated. The Morris method parameters (i.e. $p=16$, $r=8000$) were also chosen as in Cooling et al. 2007.

Intra-species comparison was performed to assess the balance of ionic currents in human cardiac models. Three most recent models of human ventricular myocyte were examined: Ten Tusscher et al. 2006, Fink et al. 2008 and Grandi et al. 2010. Eleven parameters were varied by $\pm 30\%$. Objective function was calculated as the % change in the action potential duration (APD90) after 200 beats at 1Hz as compared to the APD90 of the control run with the original set of model parameter values.

All models were coded using MATLAB R2008a. The ordinary differential equations were solved using ode15s, with the maximum relative error tolerance of integration set to 10^{-6} . The simulations performed via remote processors used compiled version of the MATLAB code.

III. RESULTS AND DISCUSSION

In this work we applied a global sensitivity analysis (the Morris Method implemented on Nimrod/G platform) to determine the most influential parameters that determine the properties of the electrical signal (such as duration) in

ventricular myocytes and of the IP3 production system (such as peak level of IP3 transient) in atrial myocytes.

Cardiac hypertrophy at the cellular level is caused by a complex interaction of signal transduction pathways. Specifically, the IP3-calcineurin pathway (Fig. 2) plays an important role in cardiac hypertrophy. The IP3 production activates calcineurin, which stimulates the transcription factor NFAT. The latter has an ability to act as a signal integrator for hypertrophy, through binding to DNA cooperatively with other hypertrophic transcription factors and facilitating transcription. Cooling’s 2007 model of IP3 production system describes the detailed signal transduction pathway from extracellular agonist to the production of IP3, where two different agonists are used. It has been experimentally observed that the responses of IP3 to the two agonists differ, despite the signal transduction pathway being almost identical. Sensitivity analysis and re-parameterization of the system studies (Cooling 2007) allowed us to determine which parameters are significant in determining features of the IP3 transient. Specifically, it was found that differences observed in the IP3 system behavior upon stimulation by different agonists can be explainable by receptors kinetics, as opposed to, for instance, the ligand strength. Such insight, coming from mathematical models, on conflicting experimental data is essential for the development of practical therapeutic treatments.

To validate the newly developed tool, Cooling et al.’s 2007 model of IP3 transient was simulated. An agreement on sensitivity (i.e. in μ values) of the peak IP3 transient to the 30 model parameters (data not shown) was obtained. The Morris analysis was performed using 16 partitions and 8000 trajectories as in Cooling 2007. A total of 300,000 runs were simulated (taking 2.5 days, on approx 450 processors).

One of the advantages of the newly developed tool is that it can be applied easily to any model, by uploading the model of interest. Hence, once the tool was validated using an IP3 transient atrial cell model, we next investigated different models.

Identifying the key mechanisms involved in electrical signal (i.e. action potential, AP) generation on a beat-to-beat basis is essential for understanding regular and irregular heart function. We thus chose to investigate the effects of the ionic currents on the trans-membrane voltage in human ventricular myocytes.

Specifically, the two aims of this study were as follows. The first aim was to perform a global sensitivity analysis to demonstrate the potential use of this method in determining the key driving factors of a particular output for the purpose of informing future parameter estimation/optimization studies. In other words, the information on the most influential parameters can be used in informing the choice of parameters being used for optimization for instance during model development. Secondly, the Morris analysis suggests a way for assessing the underlying structure of the models such as of their ionic currents’ profiles. Hence, the aim was to characterize how changes in the expression of ion channels relate to alterations in physiological phenomena such as APD.

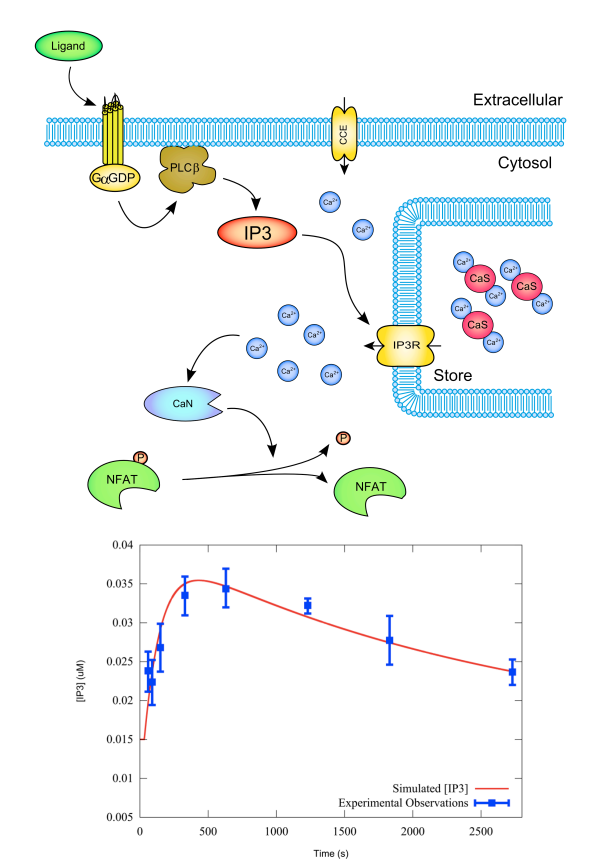


Fig. 2. The IP3-calcineurin pathway (top), IP3 transient (middle) and ten most significant parameters (bottom).

We ran single cell model (e.g. Ten Tusscher 2006) for sets of $r=500, 1000$ and 3000 trajectories. The number of trajectories was increased to check the results of two independent analyses for a given r were comparable. 1000 trajectories were found to be sufficient to give repeatable clustering and ordering results between sets.

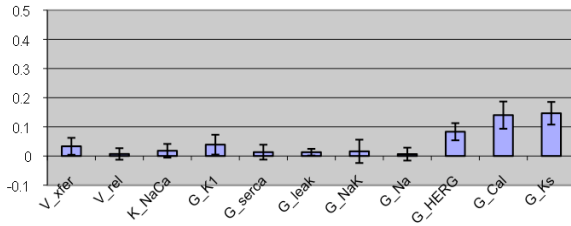
Fig. 3 shows the impact of conductances and maximum flux rates of different currents, pumps, exchangers and diffusive currents in a single cell on APD in three most recent human ventricular single cell models. Parameters ranged within $\pm 30\%$.

Further, Fig. 3 illustrates how the newly developed tool can help to characterize and assess computational models through comparison of their ionic currents’ profiles.

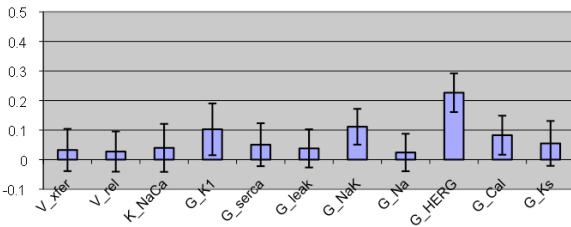
Results from all three human ventricular myocyte models show high standard deviation levels, which is indicative of highly nonlinear system under investigation with high interaction of parameters with each other. For some parameters high standard deviation implies that no definite conclusion can be made from the results on the significance of the parameter influence (e.g. for G_{Na}) on APD90 at 1Hz

with respect to other parameters. Yet from the results the most dominant parameters are apparent, for instance G_{HERG} in Fink 2008 model (Fig. 3 middle panel) and I_{CaL} in Grandi 2010 model (Fig. 3 bottom panel) are the most influential out of the 11 parameters studied.

A. Ten Tusscher 2006



B. Fink 2008



C. Grandi 2010

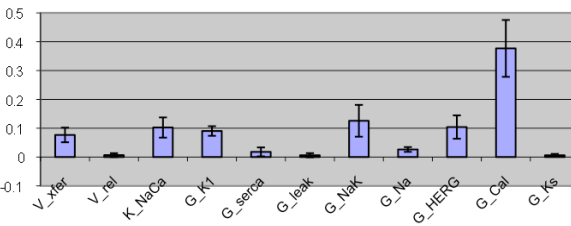


Fig. 3. Assessment of ionic currents composition in different human ventricular cell models. Parameters are varied by $\pm 30\%$. Objective function is defined as the change in APD90 recorded after 200 beats at 1Hz as compared to the control. The y-axis units are given as units of objective function over the parameter range. ($p=10$, $r=1000$).

Importantly, comparison between profiles of the balance of ionic currents in different models reveals the significant differences in structures of these models. For instance, the results show that Fink 2008 model, a modified version of TT06 model, as expected contains an altered I_{HERG} to I_{Ks} currents ratio as compared to TT06 model (compare top and middle panels in Fig. 3).

Moreover, the above intra-species comparison emphasizes that using these models for predicting drug effects would produce different results due to different balance of ionic currents. Most Ca^{2+} related drugs act on both L-type calcium currents (I_{CaL}) and K^{+} -related currents, therefore the balance of these currents is crucial for predicting I_{CaL} related drug action.

Specifically, Fig. 4 illustrates the effect of modelling BRL-32872 (10 μM) drug action in two human ventricular models: Ten Tusscher 2006 and Fink 2008. The BRL-32872 action is modeled by altering conductances of hERG and I_{CaL} according to the respective IC_{50} values (2800 nM for I_{CaL} and 28nM for hERG) using the following formula

$1/(1+[D]/\text{IC}_{50})^{n_H}$, where $[D]$ denotes drug concentration, and the hill coefficient (n_H) is assumed to be 1. Fig. 4 shows that the predicted effect of the drug action on APD from the two models is opposite.

Further, note that the results presented in Fig. 3 are for a particular output function, i.e. APD90 at 1Hz. Yet impact of parameters on other characteristic measures of the model can be investigated. In other words, the objective function instead of APD90 could be the Ca_i transient duration and peak, dynamic restitution curves, Na_i and K_i levels at different frequencies and/or other markers of cellular cardiac activity. Comparison of the results from influences on various objective functions would help to identify which parameters are more important for a particular model output. The latter is advantageous when developing drugs which would have an effect on one model characteristic but not on another. Thus, one immediate step for further development of the new tool is to incorporate the multi-objective functions into the Morris analysis software.

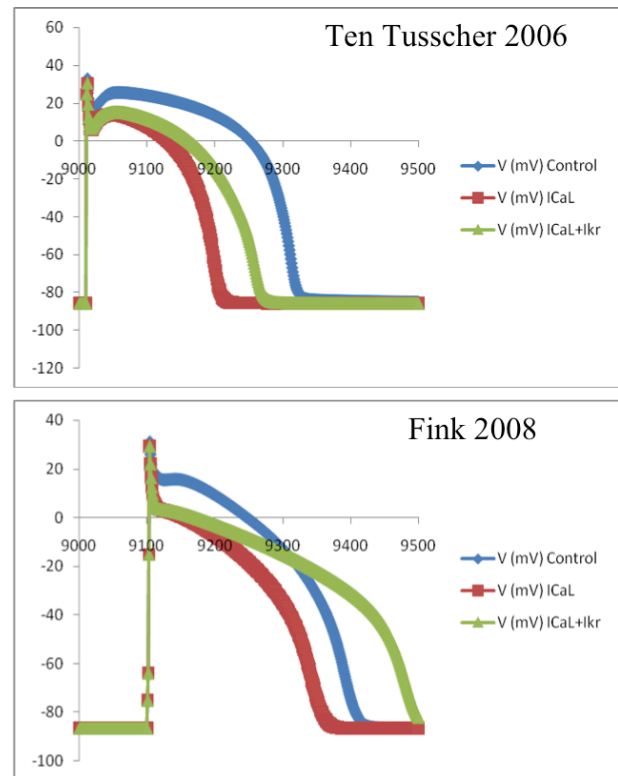


Fig. 4. Effect of different balance of currents in different human ventricular cells models on APD at 1Hz becomes apparent when modelling BRL-32872 drug action.

IV. CONCLUDING REMARKS

In summary, a global sensitivity analysis algorithm (the Morris method) has been implemented in the Nimrod tool family. This combination has allowed us to speed up the method significantly as compared to the previous implementation (Cooling et al. 2007). Further, the tool significantly simplifies the analysis of any new model, as the code is no longer model specific.

This new tool also helps to evaluate and characterize the effect of model parameters onto the model outputs in a systematic manner. Specifically, in this work we used the newly developed tool to demonstrate the influence of 30 parameters of IP3 production pathway on the peak of IP3 transient in the model of atrial myocyte, and to examine the profiles of the balance of ionic currents in the most recent human ventricular myocyte models. The resulting profiles of the ionic current balance demonstrated the highly nonlinear nature of the cardiac ionic models and identified key players in different models. Such profiling suggests new avenues for development of methodologies to predict drug action effects in cardiac cells. The newly developed tool can be used for intra-species and interspecies model structure assessment, can be applied to any model and is shown to be computationally cheaper as compared to the previously implemented global sensitivity analysis method.

As outlined throughout the paper, there is a number of important applications of the newly developed tool. These include studying the drug effects on behavior of cardiac cells, and identifying critical parameters which can be used in the estimation/optimization studies.

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