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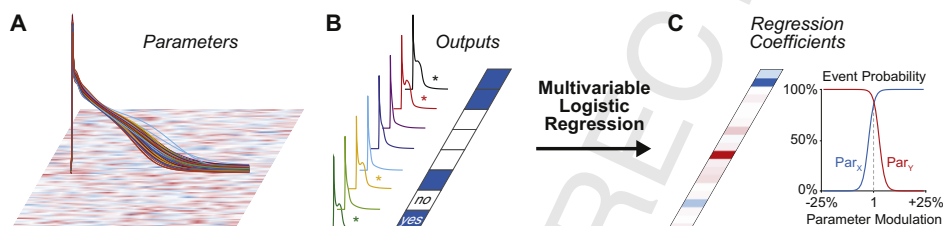
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Logistic regression analysis of populations of electrophysiological models to assess proarrhythmic risk

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GRAPHICAL ABSTRACT



ABSTRACT

Population-based computational approaches have been developed in recent years and helped to gain insight into arrhythmia mechanisms, and intra- and inter-patient variability (e.g., in drug responses). Here, we illustrate the use of multivariable logistic regression to analyze the factors that enhance or reduce the susceptibility to cellular arrhythmogenic events. As an example, we generate 1000 model variants by randomly modifying ionic conductances and maximal rates of ion transports in our atrial myocyte model and simulate an arrhythmia-provoking protocol that enhances early afterdepolarization (EAD) proclivity. We then treat EAD occurrence as a categorical, yes or no variable, and perform logistic regression to relate perturbations in model parameters to the presence/absence of EADs. We find that EAD formation is sensitive to the conductance of the voltage-gated Na^+ , the acetylcholine-sensitive and ultra-rapid K^+ channels, and the Na^+/Ca^{2+} exchange current, which matches our mechanistic understanding of the process and preliminary sensitivity analysis.

The described technique:

- allows investigating the factors underlying dichotomous outcomes, and is therefore a useful tool to improve our understanding of arrhythmic risk;
- is valid for analyzing both deterministic and stochastic models, and various phenomena (e.g., delayed afterdepolarizations and Ca^{2+} sparks);

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- is computationally more efficient than one-at-a-time parameter sensitivity analysis.

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Method details

Population-based approaches have been widely adopted in the recent years in the field of computational cardiac electrophysiology [1–8]. The classical analysis performed with a single action potential (AP) model has been extended to the study of the properties emerging in a broad group of models (called “population”). Each individual in the population is obtained from the same parent model (called “baseline”) by randomly perturbing several parameters. These differences in model parameterization reflect the natural variability among cells in a tissue (intra-subject variability) or among different individuals (inter-subject variability). Thus, by investigating a more realistic and comprehensive scenario, this approach allows obtaining new insights in several aspects of myocyte function in health and disease, including arrhythmia mechanisms and responses to drugs [9]. Moreover, the assessment of sensitivity of model predictions to parameter perturbations ensures enhanced robustness of the results of computational studies [10]. However, the choice of appropriate mathematical and statistical tools is fundamental when performing sensitivity analysis on a population of hundreds or thousands AP models. Here, we illustrate the use of multivariable logistic regression to analyze the factors underlying the occurrence of a dichotomous outcome (such as the development of cellular arrhythmogenic events).

Explanation of the methodology

Regression analysis is a statistical process used to estimate relationships among variables in a system [11,12]. It is usually applied to correlate modifications in independent variables (called “predictors”) to the consequent effect on dependent variables. The result of regression analysis is a function of the independent variables (called “regression function”), which is used to predict the values of the dependent variables (e.g., to estimate a certain outcome after changes in fixed system properties). More specifically, the result of this analysis is the set of regression coefficients used in the regression function. The general principles of regression analysis are formalized in the following equation:

$$\mathbf{X} * \mathbf{B} = \mathbf{Y} \approx \mathbf{Y}$$

where \mathbf{X} and \mathbf{Y} are the matrices of the independent and dependent variables, respectively. Based on \mathbf{X} and \mathbf{Y} , this technique allows the determination of the regression coefficients (in the matrix \mathbf{B}), which can be used to estimate \mathbf{Y} ($\mathbf{Y} \sim$) given \mathbf{X} .

In the field of computational cardiac electrophysiology, sensitivity analysis of population of AP models is usually performed to assess how variations in model parameters (e.g., conductances of ion channels) affect model outputs, such as AP duration (APD) or Ca^{2+} transient amplitude. In this case, when the outputs of interest are continuous variables, linear multivariable regression analysis can be performed, and the resulting regression function allows predicting how these outputs change (in a continuous range) upon modifications in model parameters [1]. In a population of n_m AP models, obtained by varying n_p parameters in a baseline model, the size of the matrix of the predictors \mathbf{X} is $n_m \times n_p$ (rows \times columns). The matrix \mathbf{Y} reports different outputs (n_o) identified in each model of the population (size $n_m \times n_o$). In general, the matrix \mathbf{B} contains a coefficient describing the effect of perturbation in each parameter on each output (size $n_p \times n_o$).

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