

In-silico Safety Pharmacology on Intersubject Variability Population of Models: A Regression Model Approach

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Introduction: Safety pharmacology aims towards identifying undesirable effect of drugs during its development phase. However, limitations are present in in-vitro and preclinical research because of its low detection efficacy during this process.

Aims: To study the effect of drugs at in-silico tissue level and evaluate inducibility in a multivariable scenario by using a regression model.

Methods: 127 mathematical models were tested for two different tissue sizes (basal: 15cm², dilated: 20cm²) during control and isoproterenol. Reentrant activity was induced with a S1S2 protocol. Proarrhythmic and antiarrhythmic effects of the drug on the tissue were studied, including AF maintenance duration (MD). Results of these simulations were compared with the predictions of a new regression model based on Canonical Correlation Analysis (CCA) (i.e. 80% of the models (N=101) were used as training set, whereas the remaining 20% samples were used as test set).

Results: Dilated atria resulted in a larger number of models with AF induction (basal: 80 models, dilated: 88 models) and with longer MDs (basal: 394ms, dilated: 681ms). Isoproterenol exhibited an overall proarrhythmic effect, increasing the mean AF MD on both tissue sizes. However, isoproterenol was antiarrhythmic in a part of the database (Fig 1). CCA analysis obtained 96% accuracy on the test set for basal size and 100% on the dilated one, allowing the identification of drug effect without the need of highly time-consuming simulations.

Conclusions: A new promising methodology was proposed for fast in-silico safety pharmacology including variability between patients, setting the base for improving the drug development process and precision medicine.

