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Quantitative assessment of the physiological parameters influencing QT interval response to medication - simulation study

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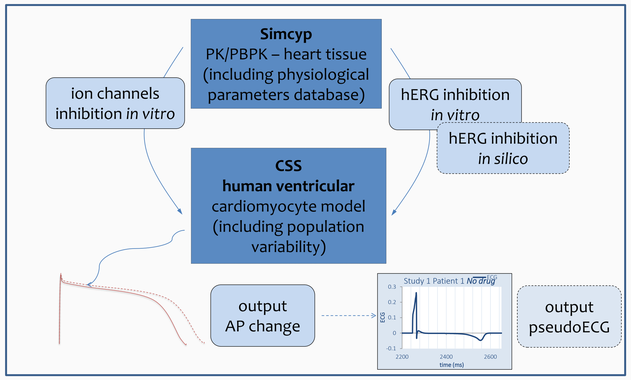
Introduction

Cardiac repolarization abnormalities can be triggered by a wide range of compounds and may lead to the development of the life-threatening ventricular arrhythmias (i.e. Torsade de Pointes -TdP) and sudden cardiac death. There is a substantial variability in response to drug administration at the level of ECG and its derivatives. It can be hypothesized that the variability at the level of physiological covariates influences the ECG.

Aim of the study

The aim of the current study was to analyse factors crucial for the observed variability and correlate them with QT interval length.

Figure 1. CSS – in vitro-in vivo extrapolation system.



Methods cont.

The dataset with reduced number of variables describing individual subjects was further used to build an empirical model correlating chosen input parameters with the single output (QTc value).
Artificial neural networks (monmlp [10]), random forest [11], rule-based regression (Cubist [12]) and multivariate adaptive regression splines (MARS [13]) were used as tested algorithms. Moreover, genetic programming (GP) was used to develop an equation describing correlation between covariates and ECG as a clinical endpoint (rgp [14]). The latter namely GP based algorithm allows to eliminate the black-box problem and provide an overt and analysable equation.

Table 1. Results of sensitivity analysis. Selected parameters describing simulated QTc dataset. **In bold** inputs included in the final QTc model.

INPUT No	1	2	3	4	5	6	7	8	9	**10**	**11**	12	**13**	**14**	15	16	**17**
description	CYP 1A2 abundance (pmol)	CYP 3A4 abundance (pmol)	Gut CYP 2C9 abundance (pmol)	Age (years)	Weight (kg)	Sex (F/M)	Body Surface Area (m^2)	Cardiac Outpu (L/min)	Cardiomyocyte volume (μm^3)	**String length (µm)**	**$[K^+]$ (mM)**	$[Na^+]$ (mM)	**$[Ca^{2+}]$ (mM)**	**IKr inhibition (fraction 0-1)**	IKs inhibition (fraction 0-1)	INa inhibition (fraction 0-1)	**ICa inhibition (fraction 0-1)**

Results

Normalized root mean squared errors (NMRSE) were calculated to assess the quality of the developed models. An 8-fold cross validation procedure was applied, and results are presented in Table 2. The lowest generalization error, 2.2%, was achieved for the model developed with GP algorithm. Moreover, the GP procedure allowed further input vector reduction (Equation 1). The resulting equation had four parameters (C1 - C4) and included 5 dependent variables: string length (µm), potassium and calcium concentration (mM), potassium and calcium inhibition (fraction of 0 to 1). This indicates that from the population characteristics point of view, the string length is the parameter which differentiates the individuals and allows predicting the QTc interval length. Figure 2 shows the results presented in the form of 3D plots.

Table 2. NMRSE for developed models – 8-fold cross validation procedure.

Algorithm	NMRSE
Cubist	2.5
GP	**2.2**
MARS	4.8
monmlp	2.3
Random Forest	5.4

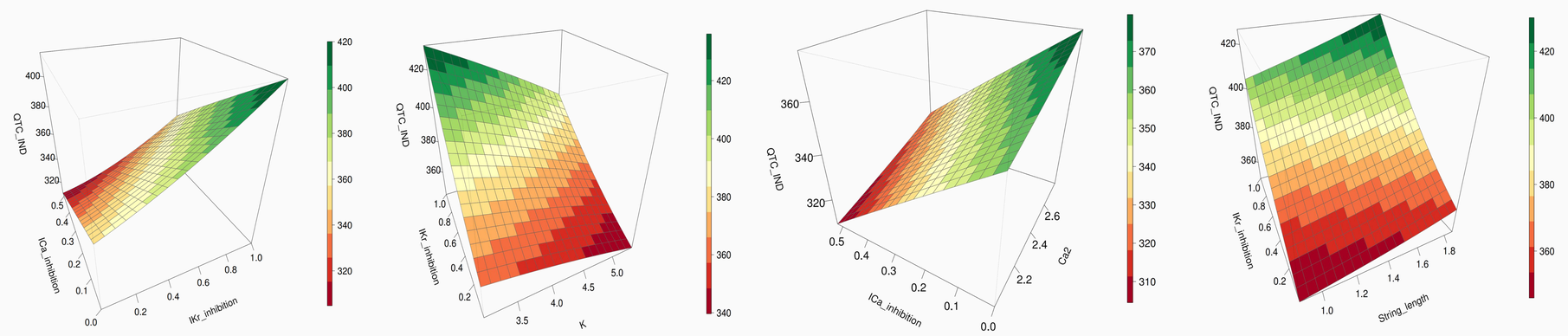
Equation 1. Empirical QTc model generated by genetic algorithm. IN_n – input variables, C_n – equation parameters (C1 = 5.87, C2 = -2.26, C3 = 6.56, C4 = -8.71).

$$QT_c = C_4 IN_{14}\sqrt{-C_2 IN_{17} + IN_{10}IN_{14} + \sqrt{IN_{13}}} - C_1 C_3 C_4 IN_{17} + \sqrt{IN_{10}}\left(\sqrt{2}C_8 C_9 - \sqrt{2}C_9 IN_{11} IN_{13}\right)IN_{14} + e^{IN_{13}} + IN_{11}^{\frac{3}{2}}\sqrt{IN_{13} + \sqrt{IN_{13}}} + \sqrt{IN_{11}}\left(e^{IN_{10}} - C_6 IN_{11} + (IN_{11}+1)IN_{13}\right) + IN_{10}IN_{11} + \sqrt{C_7}IN_{11} + e^{C_5}$$

Methods

Population of virtual patients exposed to terfenadine alone and in combination with various metabolic inhibitors (clarithromycin, erythromycin, itraconazole, ketoconazole, fluconazole, fluoxetine, and paroxetine) during the simulated clinical trials was used to analyse factors potentially responsible for the observed ECG variability [1-7]. Electrophysiological response to drug administration was simulated with the use of tenTusscher TNNP04 human ventricular cardiomyocyte model [8] implemented in Cardiac Safety Simulator (Figure 1).

A set of 48 factors influencing the obtained QTc values was analysed. This included human related parameters (demographic, anatomic and physiologic), drug related parameters (four main cardiac ion currents inhibition), and study dependent parameters (time of the day). The final data set consisted of 10 360 records. Sensitivity analysis and feature selection process was performed with use of fscaret R environment package [9]. 17 parameters with the greatest impact on QTc were selected: gender, weight, body surface area, cardiac output, CYPs abundance, electrolytes concentrations, ion currents inhibition (Table 1).



Conclusions

The current study allowed to select crucial for the QTc value parameters and build predictive, empirical model for the QTc assessment.

References

[1] Honig PK, et al. (1993), JAMA 269:1513-1518; [2] Honig PK, et al. (1992), Clin Pharmacol Ther 52:231-238; [3] Honig PK, et al. (1993), J Clin Pharmacol 33:1201-1206; [4] Honig PK, et al, (1993), Clin Pharmacol Ther 53:630-636; [5] Honig PK, et al. (1994), Drug Investigation 7:148-156; [6] Bergstrom RF, et al. (1997), Clin Pharmacol Ther 62:643-651; [7] Martin D, et al. (1997), J Clin Psychopharmacol 17:451-459; [8] H.W.J. Ten Tusscher et al., AJPhys Heart Circ Phys (2004) 286(4): H1573-H1589; [9] Szlęk J, et al., (2016) Computer Methods and Programs in Biomedicine, 134, 137-147; [10] Cannon AJ monmlp R package, (2005); [11] Breiman L, (2001), Mach Learn 5–32. doi: 10.1023/A:1010933404324, [12] Quinlan JR, (1992) Mach Learn 92:343–348. doi: 10.1.1.34.885; [13] Milborrow S., earth R package, (2016) [14] O. Flasch, et al., rgp R package, (2016)