An *in silico* population approach to study the effect of drugs on arrhythmia marker sensitivities of atrial cells

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MOTIVATION:

Flecanaide and Dofetilide are two commonly used drugs in the treatment of atrial arrhythmias. A recent study reported the effects of a cohort of drugs on the blockade of seven ion channels for the ventricular cell [3]. In this study, we simulate the effect of these two drugs on the action potential and restitution properties of a population of atrial cells.

ABSTRACT:

In this study, in silico populations of atrial cells were built to investigate the effects of drugs on markers of arrhythmia. The effect of two drugs routinely used to treat atrial fibrillation (Flecainide and Dofetilide) were incorporated into simulations to investigate their effects on AP morphology and APD restitution properties at three different concentrations. The effects of ion channel block were modeled by tuning the maximal conductance of seven ionic currents: INa_{fast}, INa_{late}, ICaL, IKr, IKs, IK1, and Ito, to match known properties of the drugs.

A population of cells in normal sinus rhythm was calibrated based on experimental data from literature. This guaranteed that all models tested presented normal AP morphologies before the drug effects were applied and thus exclude any model that showed unphysiological AP and calcium transient profiles. Furthermore, APD restitution curves were simulated under dynamic pacing. Biomarkers related to AP traces and APD restitution curves were extracted at 1 Hz pacing. We observed repolarization abnormalities with both Flecainide and Dofetilide, including repolarization failure and afterdepolarizations. Populations exposed to high drug concentrations of ten times Cmax showed an increase in predisposition for APD alternans, with alternans occurrence as high as 74% with Flecainide at 3 times Cmax and 76% with Dofetilide at 10 time Cmax. Sensitivity analysis showed that observed AP, CaT and alternans biomarkers were governed by similar parameters, with sensitivities being exacerbated at high drug concentrations.

This study showcases the potential for the use of in silico trials in the assessment of drug induced clinical arrhythmias.

RESULTS:

Table II. Percentage of models in the populations that showed abnormal AP shape, EADs, repolarization failure, and APD alternans.

	Abnormal AP	Repol. Failure	EADs	Alternans
Control	0.0	0.0	12.2	70.9
Flec 1	11.4	2.1	0.2	75.4
Flec 3	21.7	6.3	1.5	73.5
Flec 10	58.3	18.5	11.4	54.5
Dof 1	12.0	1.7	0.2	74.3
Dof 3	16.8	2.5	0.0	75.6
Dof 10	22.1	4.0	0.4	76.4

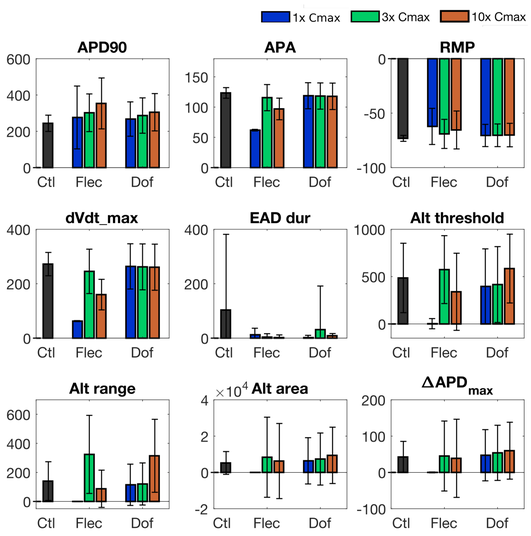


Fig 3. (*Right*) Mean values of biomarkers in control, Flecanaide and Dofaetilide populations. Error bars correspond to standard deviation.

METHODS:

Populations of models

Parameters varied

Maximum conductance: ICaL, INa, IK1, ICab, IKr, IKs, IKur, Ito, INaL

Maximum fluxes: INaK, INCX, ICaP

Ryanodine receptors: maximum conductance, time constants

Serca pump density

Calibration of control population

Calibration values [2]:

APD90: 190 — 440 ms

APA: > 75 mV

RMP: -85 — -65 mV

Upstroke velocity: 40 — 420 V/s

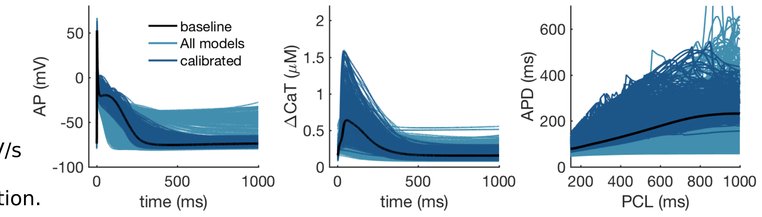
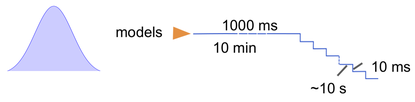


Fig1. *(Right)* Control population.

Dynamic pacing protocol



Application of drugs

Table I. Values of Cmax, IC50 and nh used to calculate dose dependent percentage block of ion channels [3].

		ICaL	IKr	IK1	Ito	IKs	INaL	INa
Defetilide	IC_{50}	∞	1.0	∞	∞	∞	∞	∞
$C_{max} = 2.1$	nh	1	0.6	1	1	1	1	1
Flecanide	IC_{50}	25599	692	∞	9266	∞	18870	6677
$C_{max} = 752.9$	nh	1.4	0.8	1	0.7	1	0.6	1.9

$$\%\,\text{block} = \frac{(C_{max} * \text{dose})^{nh}}{IC_{50}{}^{nh} + (Cmax * \text{dose})^{nh}}$$

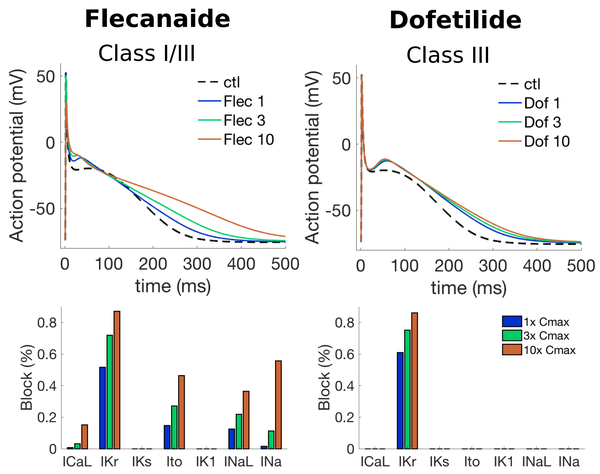


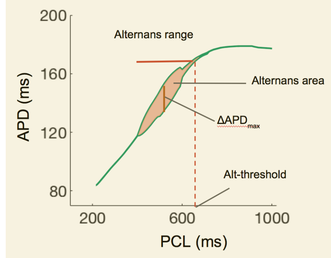
Fig 2. Ion channel block profile of Flecainide and Dofetilide [3].

Definition of Biomarkers

Action Potential
APD90
AP amplitude
Resting membrane potential
Upstroke velocity

Afterdepolarizations
EAD occurrence
EAD duration

APD Restitution Alternans [1]
Alternans threshold
Alternans range
Alternans area
Maximum long-short APD
Aternans occurrence



Sensitivity analysis

Multivariate linear regression

Input parameters — Regression coefficients — Output biomarkers

$$\mathbf{X} \cdot \mathbf{B} = \mathbf{Y}$$

(m x p) (p x n) (m x n)

Logistic regression

Probability

$$\mathbf{P(y|x)} = \frac{e^{(\mathbf{b_0} + \mathbf{B \cdot X})}}{1 + e^{(\mathbf{b_0} + \mathbf{B \cdot X})}}$$

Statistical significance of correlation coefficients

F-test, 90% confidence interval

Model selection [4]

Physiological AP (APD90, APA, RMP, time to peak)

Failed repolarization

Alternans occurrence

Afterdepolarizations occurrence

APD alternans

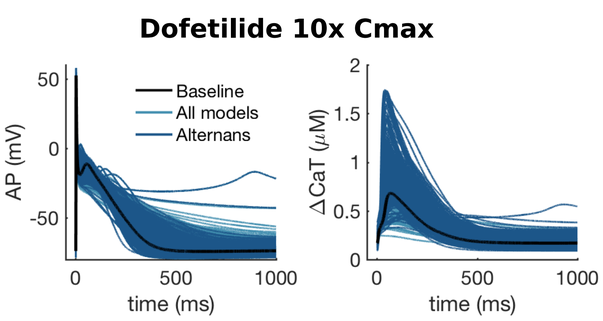


Fig 4. AP (left) and calcium transient (right) traces of Dofetilide 10x Cmax population. This population showed 76% incidence of APD alternans under dynamic pacing.

Afterdepolarizations

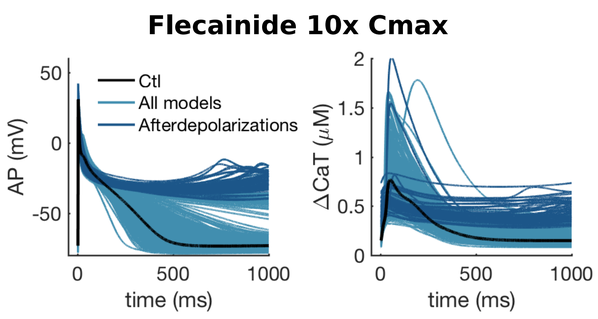


Fig 5. *(Left)* AP (left) and calcium transient (right) traces of Flecainide 10x Cmax population. This population showed 11% incidence of EADs at 1Hz pacing (one beat).

Sensitivity Analysis — Flecainide 10x Cmax

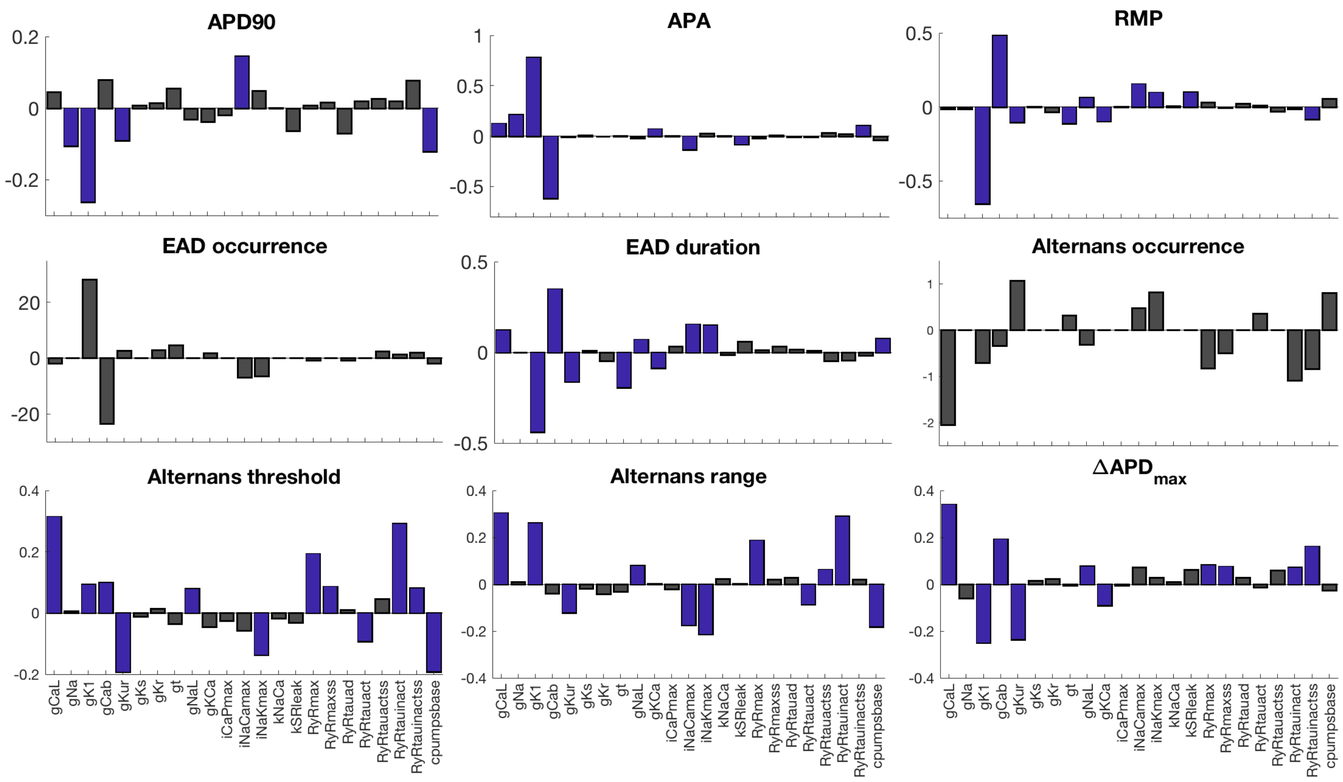


Fig 6. Sensitivity analysis of biomarkers of the Flecainide 10x Cmax population. Bars correspond to the regression correlection coefficients (B), and indicate the role of each model parameter in observed variability in the biomarkers. Positive/negative B means that an increase in the parameter results in an increase/decrease in the biomarker. Blue bars indicate correlation coefficients that showed statistic significance (*F*-test, p-value>0.1), and the gray bars represent coefficients with no statistical significance.

CONCLUSIONS:

This work showcases an application of the populations of models and sensitivity analysis approach for *in silico* drug screening for atrial fibrillation.

The results show altered electrophysiological behavior (particularly afterdepolarizations) when higher doses of Flecainide and Dofetilide are applied to a population of models of the normal atrial cell.

Sensitivity analysis results suggest that different model parameters drive alternans behaviour with Flecainide and Dofetilide, but method needs to be refined to reduce noise.

FUTURE WORK:

Replicate these simulations with a wider range of doses, and with additional drugs relevant for the treatment of atrial arrhythmias.

Perform a more mechanistic exploration of the effect of selected CiPA drugs on atrial electrophysiology at different stages of atrial remodeling.

Compare simulation results with available experimental data.

REFERENCES:

[1] Vagos et al, Chaos (2017);
[2] Sanchez et al, PLoS One (2014);
[3] W. Crumb Jr et al, J Pharmacol Toxicol Methods (2016); [4] E. Passini et al, Front. Physio. (2017)