Sensitivity analysis of populations of atrial cell models uncovers different mechanisms of APD alternans behavior in normal Sinus Rhythm and Atrial Fibrillation

Márcia Vagos[1,2], Hermenegild Arevalo[1], Bernardo de Oliveira[1],
Joakim Sundnes[1,2], Molly Maleckar[1]

[1] Simula Research Laboratory
[2] Department of Informatics, University of Oslo

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simula

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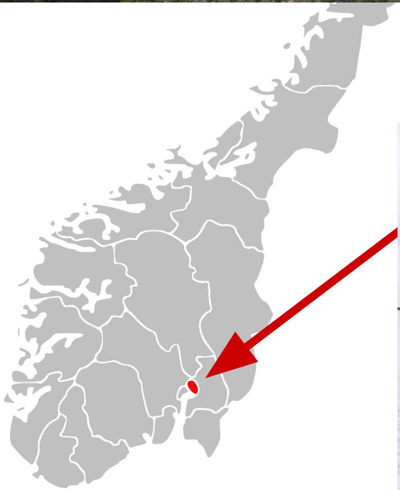
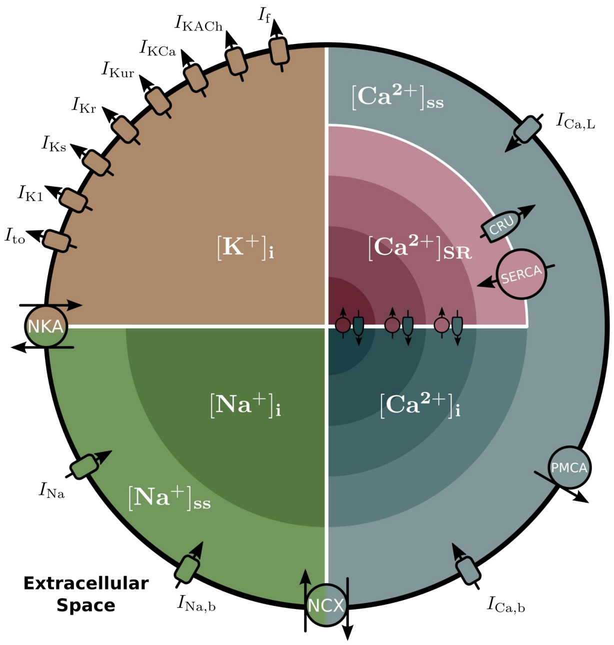


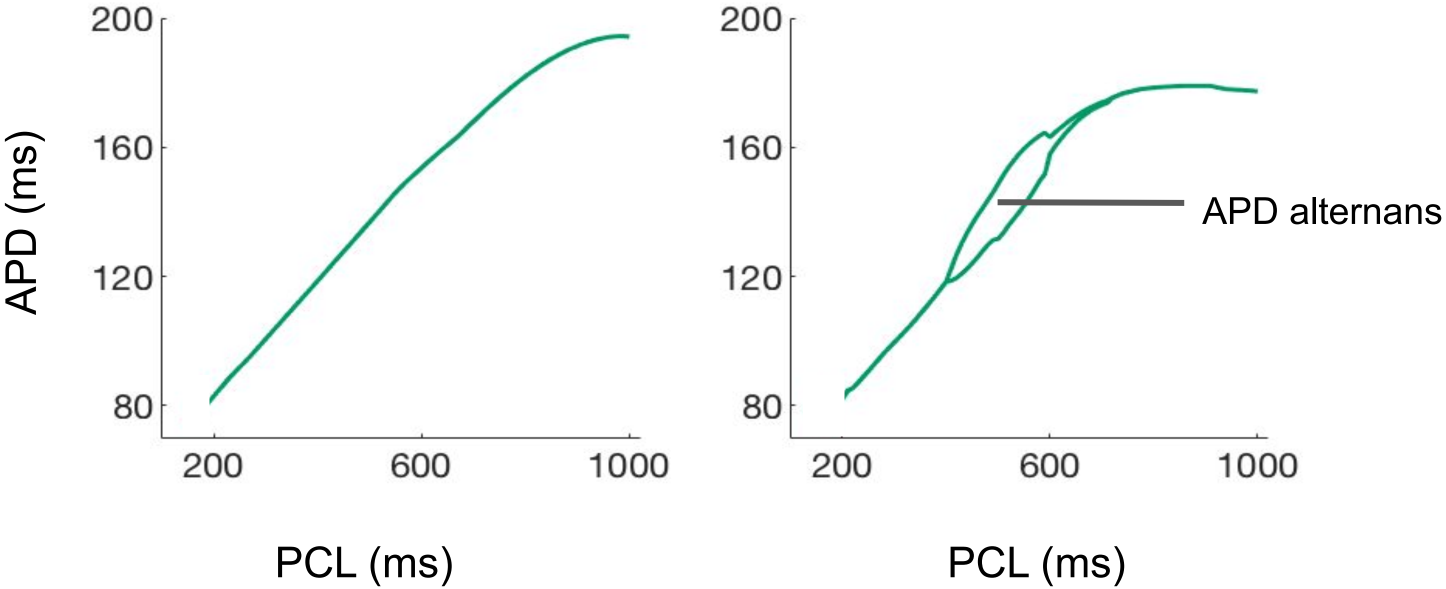
Oslo, Norway

The Koivumäki model of the human atrial cell showed APD alternans under dynamic pacing



- Spatial model with detailed calcium handling system
- Human ionic currents

APD restitution can be used to characterize APD alternans

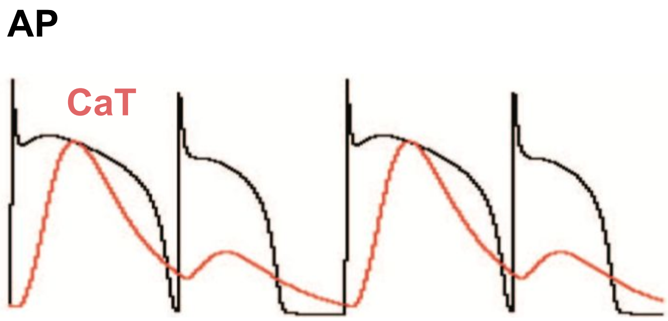


PCL: pacing cycle length

APD: Action potential duration

Cardiac alternans are correlated to AF episodes in patients and could serve as a marker for arrhythmia

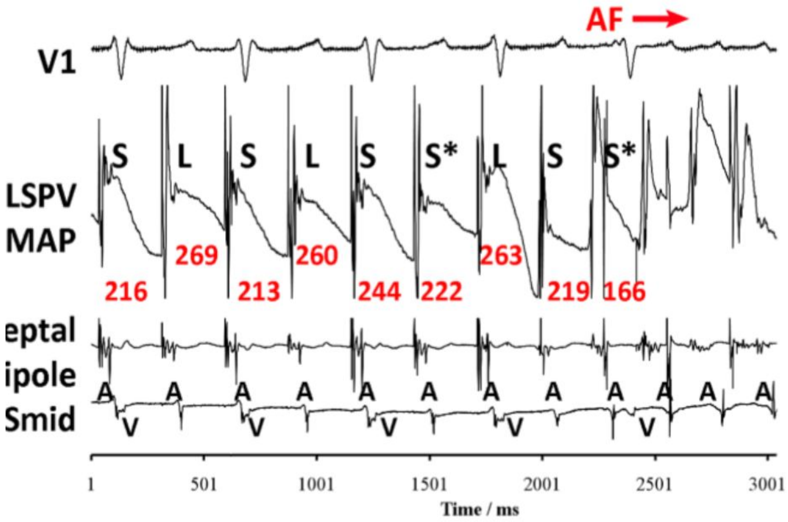
Cardiac alternans



AP: action potential → APD alternans

CaT: calcium transient → CaT alternans

Alternans precede AF



Narayan et al., Circulation, 2011

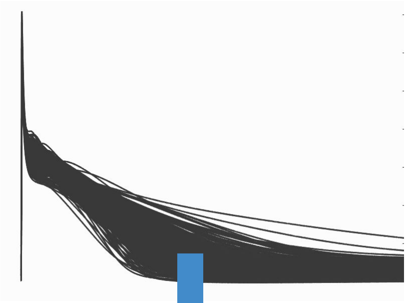
Objective

Get insight into the cellular mechanisms causing the observed APD alternans behavior in the Koivumäki model.

Data

Populations of models → Sensitivity analysis

Insight into model



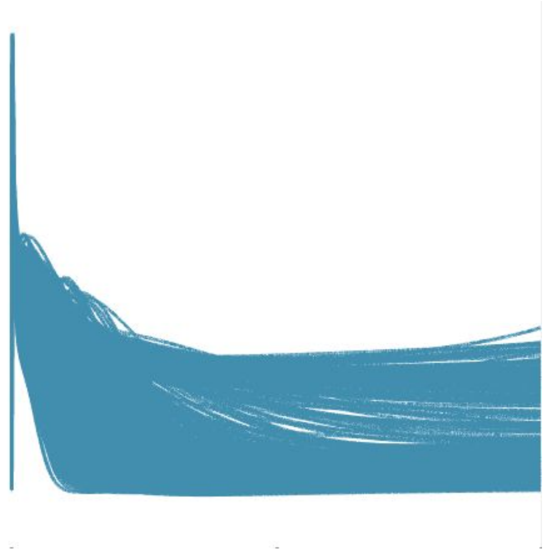
Large number of model instances that represent responses under different physiological conditions

Explore the role of individual model parameters in the observed model behavior

How did it start?

2009	**Parameter Sensitivity Analysis in Electrophysiological Models Using Multivariable Regression** Eric A. Sobie* Department of Pharmacology and Systems Therapeutics, Mount Sinai School of Medicine, New York, New York 10029	SA on a randomized set of models by using multivariate linear regression
2010	**Regression Analysis for Constraining Free Parameters in Electrophysiological Models of Cardiac Cells** Amrita X. Sarkar, Eric A. Sobie* Department of Pharmacology and Systems Therapeutics, Mount Sinai School of Medicine, New York, New York, United States of America	Extension by inversing the regression matrix to uniquely restrain model parameters
2013	**Experimentally calibrated population of models predicts and explains intersubject variability in cardiac cellular electrophysiology** Oliver J. Britton[a], Alfonso Bueno-Orovio[b], Karel Van Ammel[c], Hua Rong Lu[c], Rob Towart[c], David J. Gallacher[c], and Blanca Rodriguez[a,1]	Calibration of populations with experimental values of markers
2014	**Inter-Subject Variability in Human Atrial Action Potential in Sinus Rhythm versus Chronic Atrial Fibrillation** Carlos Sánchez[1,2,3], Alfonso Bueno-Orovio[3], Erich Wettwer[4], Simone Loose[4], Jana Simon[4], Ursula Ravens[4], Esther Pueyo[1,2], Blanca Rodriguez[3]*	Application of this methodology to populations of atrial cells

Populations of models simulate different model outputs



Incorporate natural **variability** observed in experimental data

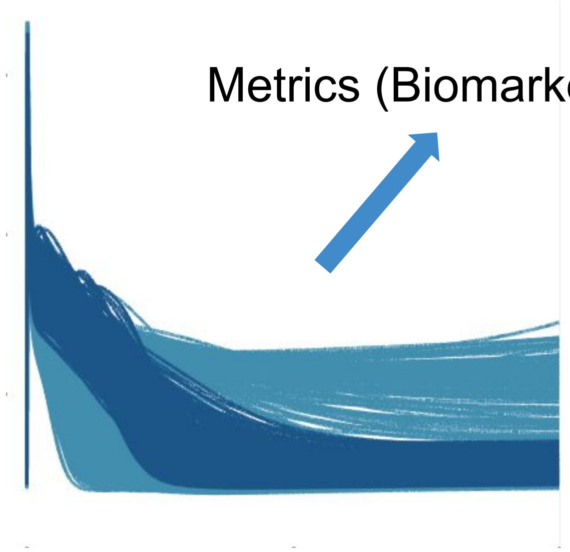
Simultaneously varying selected model parameters, related to the behavior of interest, plus “dummy” parameters.

Ion channels/pumps (maximum conductances, and gating variables)

RyR2 (time constants of close/open states)

Ionic buffering

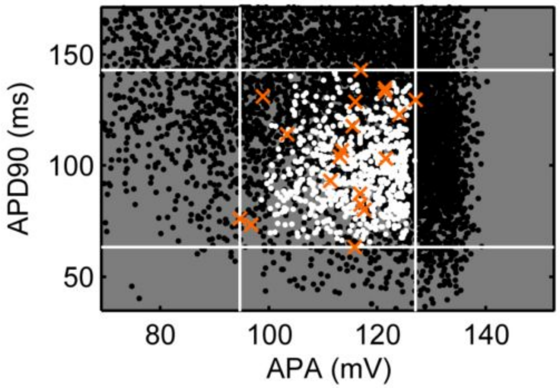
Parameters in population are calibrated by restricting biomarkers to within certain acceptable ranges



Data driven (eg, standard deviation)

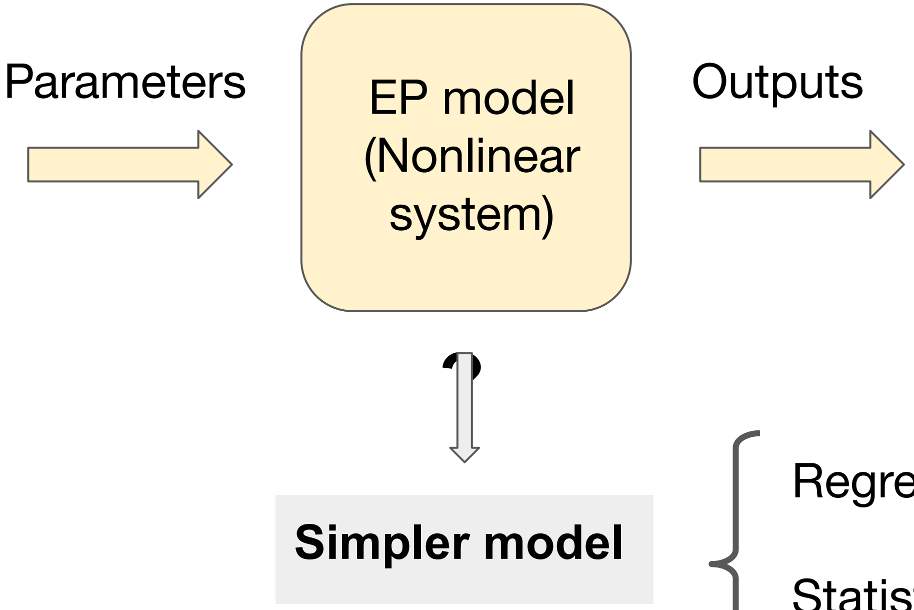
Experimental values

Restrain the parameter space



Muszkiewicz, A et al, 2014

Sensitivity analysis is useful for understanding the behaviour of a cell model



How much do model parameters influence observed model behavior?

Regression methods

Statistical learning methods (Genetic algorithm, bayesian methods)

Multivariate Linear Regression method

Input parameter

Regression coefficients

Biomarker

model

$$\underbrace{\begin{bmatrix} x_{11} & \cdots & x_{1p} \\ \vdots & & \vdots \\ x_{m1} & \cdots & x_{mp} \end{bmatrix}}_{(m \times p)} \times \underbrace{\begin{bmatrix} \beta_{11} & \cdots & \beta_{1k} \\ \vdots & & \vdots \\ \beta_{p1} & \cdots & \beta_{pk} \end{bmatrix}}_{(p \times k)} = \underbrace{\begin{bmatrix} y_{11} & \cdots & y_{1k} \\ \vdots & & \vdots \\ y_{m1} & \cdots & y_{mk} \end{bmatrix}}_{(m \times k)}$$

Multivariate Linear Regression method

$$Y_k = \beta_{0k} + \beta_{1k} \cdot x_{m1} + \beta_{2k} \cdot x_{m2} + \ldots + \beta_{pk} \cdot x_{mp}$$

$$\mathbf{Y} = \mathbf{X} \cdot \mathbf{B} + \boldsymbol{\epsilon} \;\Rightarrow\; \hat{\mathrm{Y}} = \mathrm{X} \cdot \hat{\mathrm{B}}, \qquad \hat{\mathrm{B}} = (\mathrm{X}'\mathrm{X})^{-1}\mathrm{X}'\mathrm{Y}$$

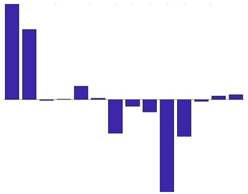
(m x k) (m x p) (p x k)

X → Model parameters

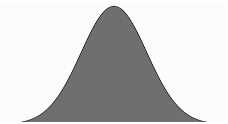
Y →Biomarkers

B → Regression coefficients (amount of variability in response explained by the parameter)

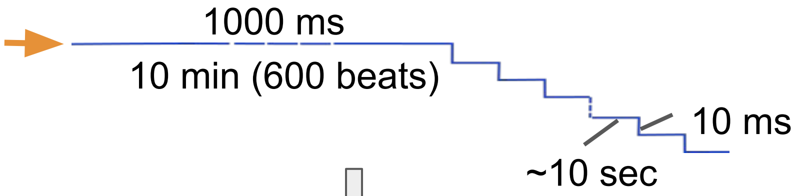
B represents the amount of variability in Y that is explained by each of the parameters x when considered to be **independent.**



Distributions of parameters



Dynamic pacing protocol



Action potential (AP) traces

Calcium transient (CaT) traces

Dynamic restitution curves

Parameters (X)

Maximum conductance:

ICaL, INa, IK1, ICab, IKr, IKs, IKur, Ito, INaL

Maximum fluxes:

INaK, INCX, ICaP

Ryanodine receptors:

Maximum conductance, gating variables

Biomarkers (X)

AP

APD90-50-20

AP amplitude

RMP

dVdt max

CaT

CaT amplitude

Diastolic $[Ca^{2+}]_i$

CaT time to peak

CaT time of decay

APD restitution

Alternans threshold

Alternans range

Alternans area

ΔAPD maximum

Alternans markers based on dynamic APD restitution

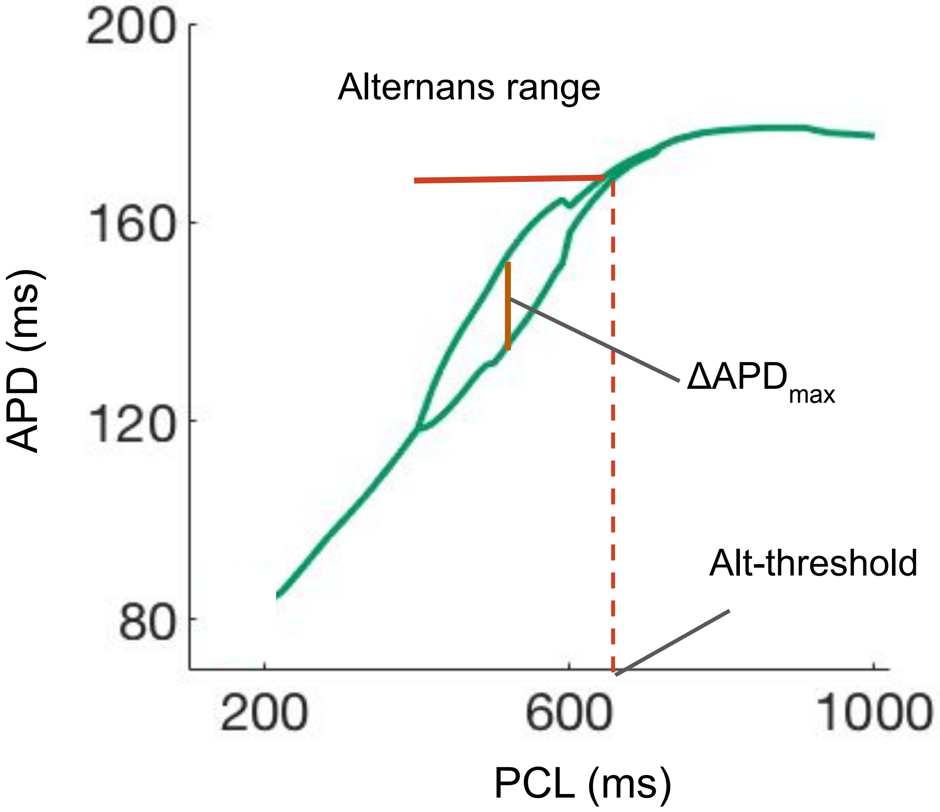
APD restitution

Alternans threshold

Alternans range

Alternans area

ΔAPD maximum



Alternans markers based on dynamic APD restitution

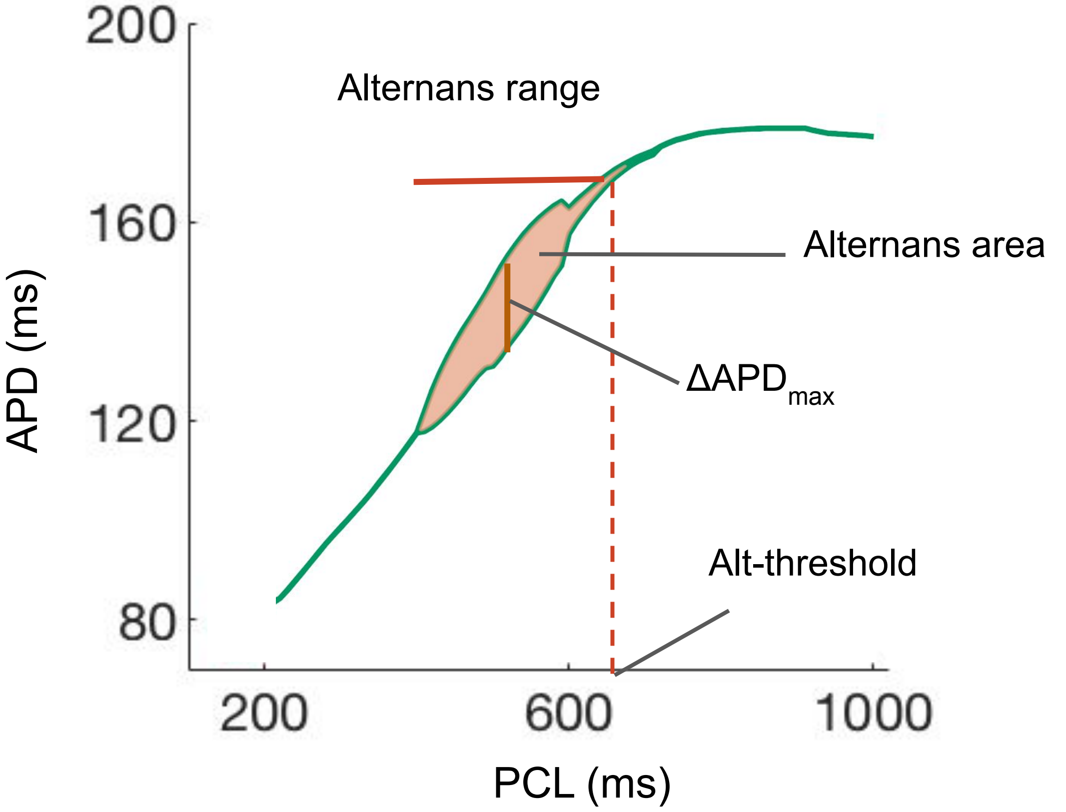
<u>APD restitution</u>

Alternans threshold

Alternans range

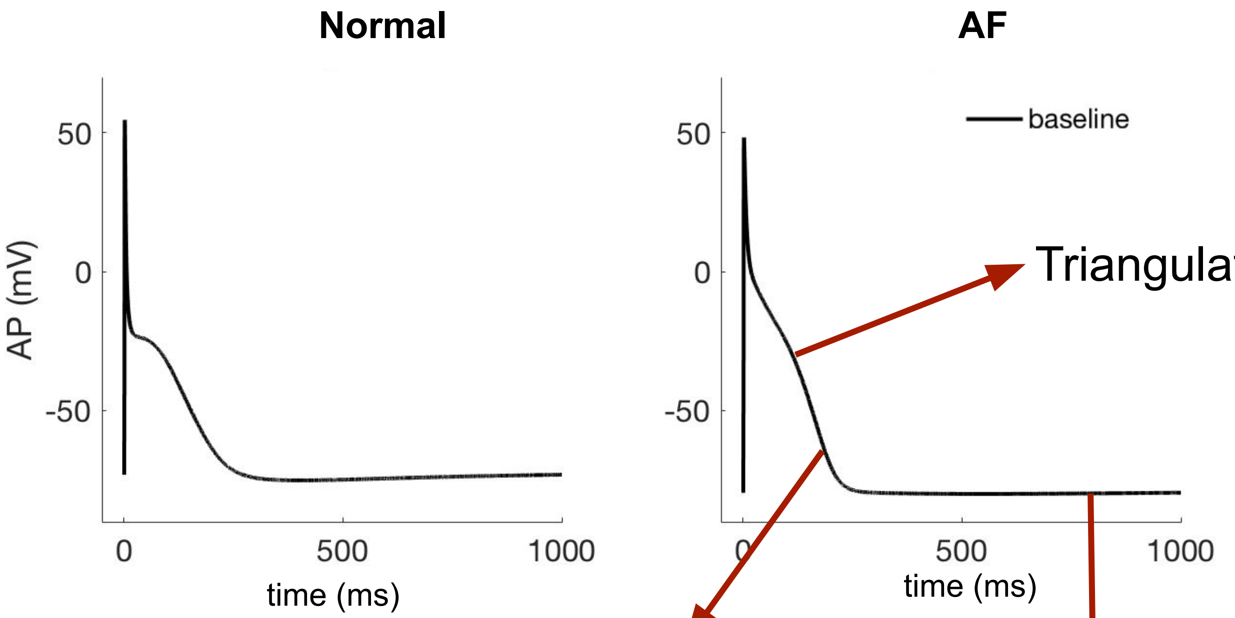
Alternans area

ΔAPD maximum



Results

Baseline of Normal and AF models



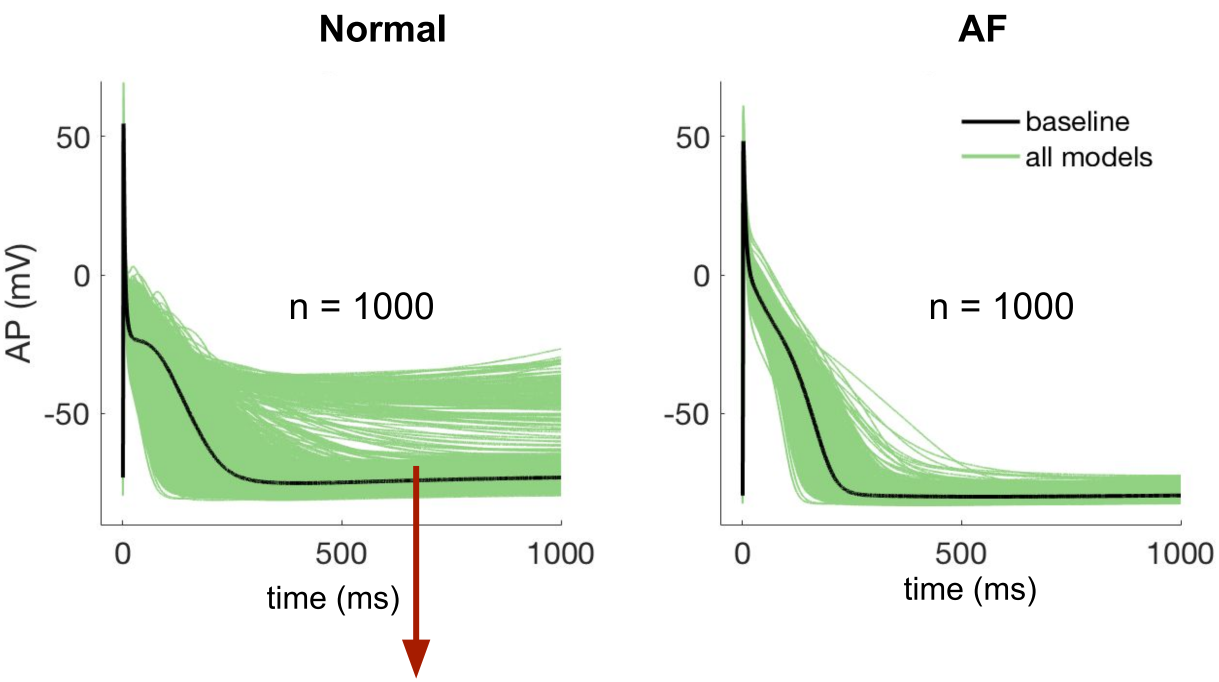
Triangulation

APD shortening

Lower resting membrane potential

gCaL	45% ↓
gK1	68% ↑
gNa	82% ↓
gKs	145% ↑
gKur	62% ↓
gto	38% ↓
gKCa	50% ↓
RyR	100% ↑

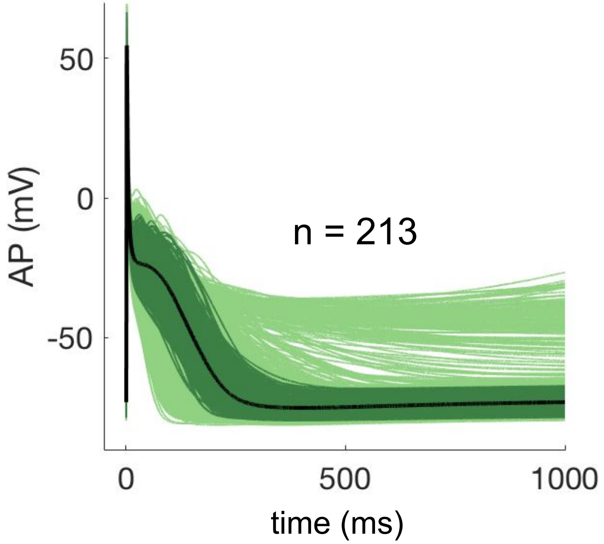
Populations of Normal and AF models



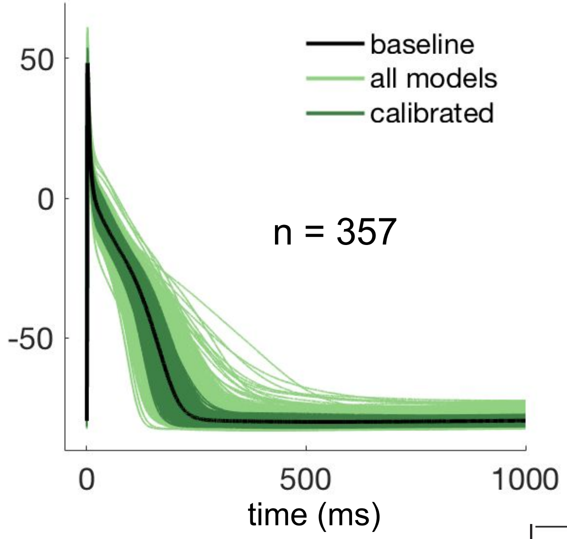
Higher intra-population variability

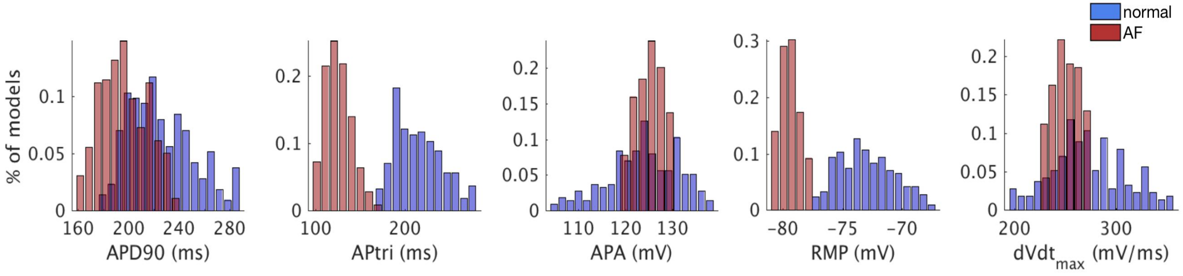
Populations of Normal and AF models

Normal



AF





Functional Calibration

Based on experimental data on human atrial cell by Sánchez et al (2014)

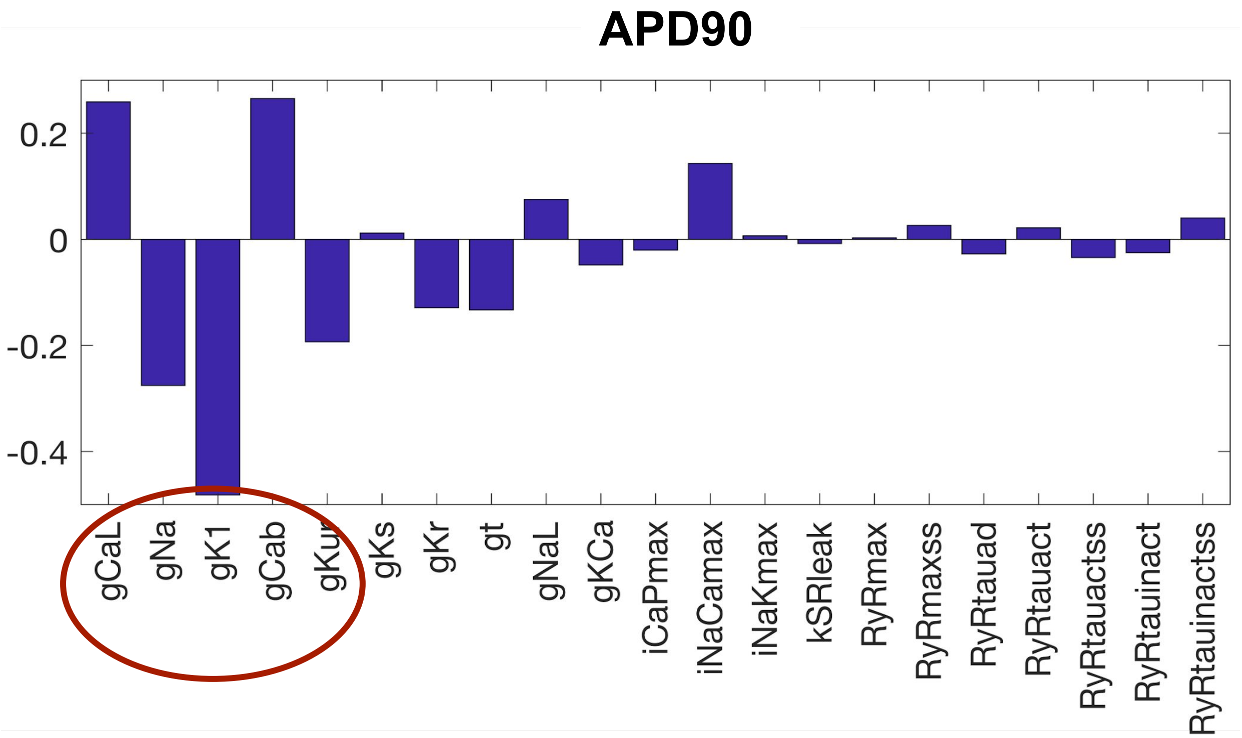
- APD90
- APA
- RMP
- Upstroke velocity

- Maximum and minimum APD in restitution curves

	SR		cAF	
	Minimum Value	*Maximum Value*	*Minimum Value*	*Maximum Value*
APD_{90} (ms)	190	440	140	330
APD_{50} (ms)	6	200	30	180
APD_{20} (ms)	1	60	1	75
APA (mV)	75	120	80	130
RMP (mV)	−85	−65	−85	−65
V_{20} (mV)	−35	10	−30	20
dV/dt_{max} (V/s)	40	420	40	420

Sánchez et al (2014)

Sensitivities of AP and CaT markers of normal population were consistent with literature



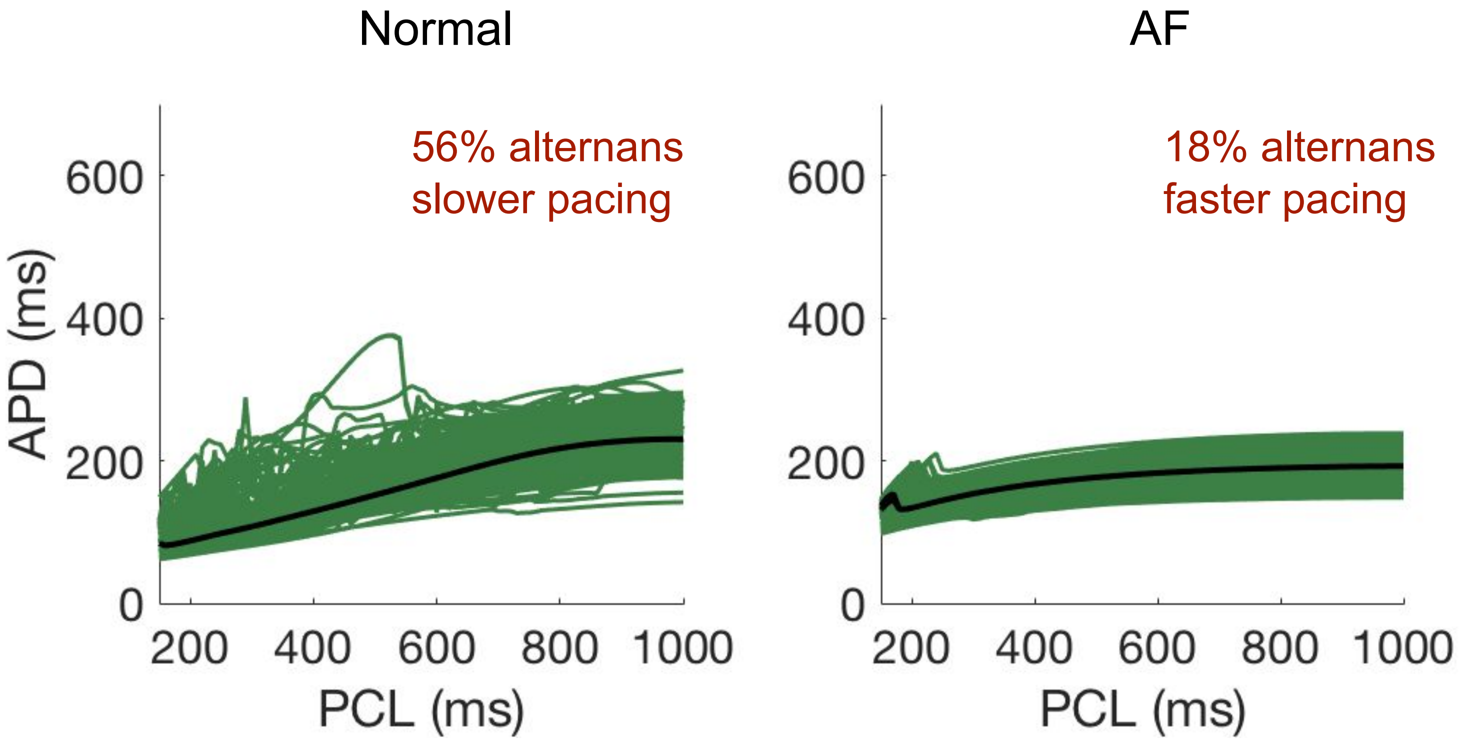
ICaL

IK1

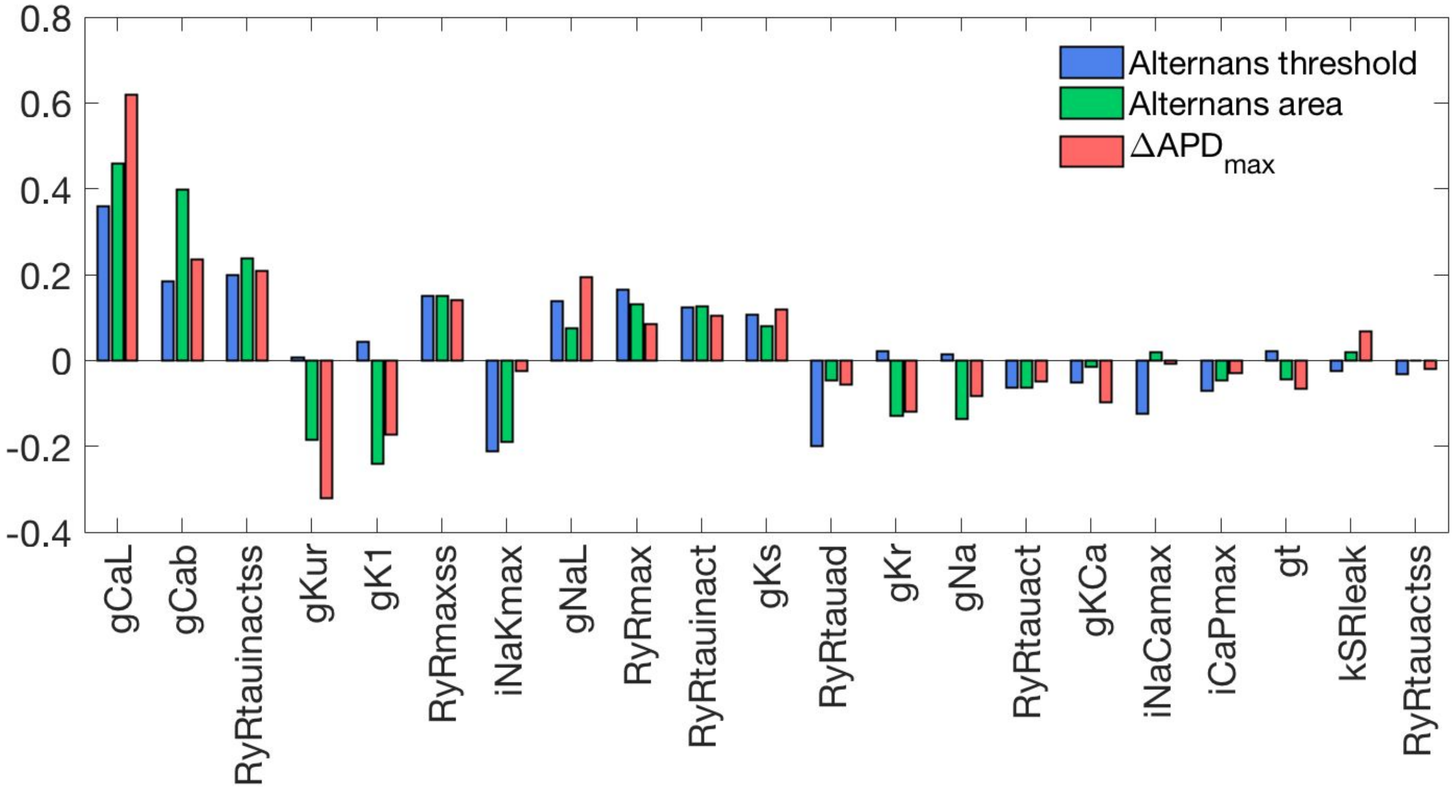
INa

IKur

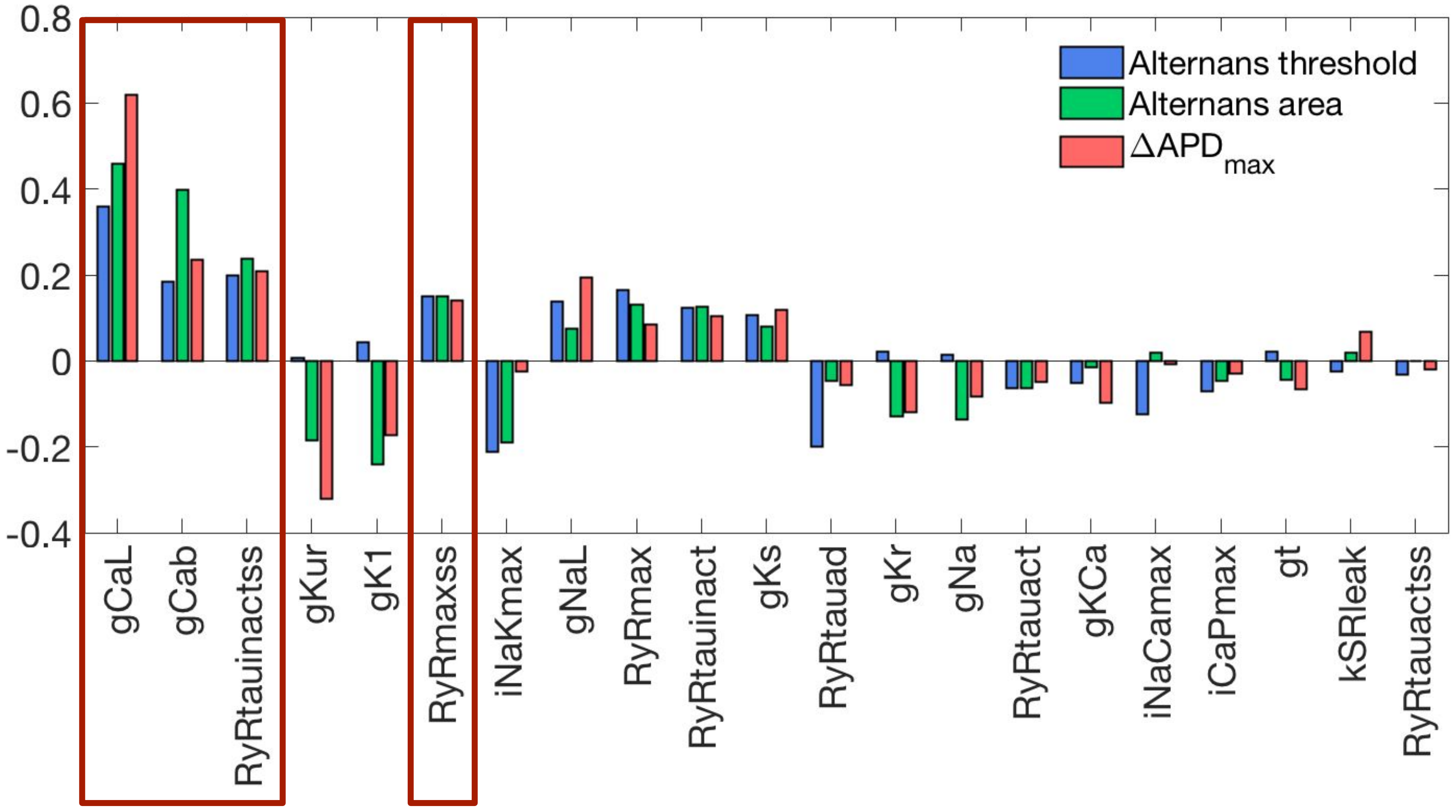
APD restitution of Normal cells revealed greater propensity to APD alternans compared to the AF cells



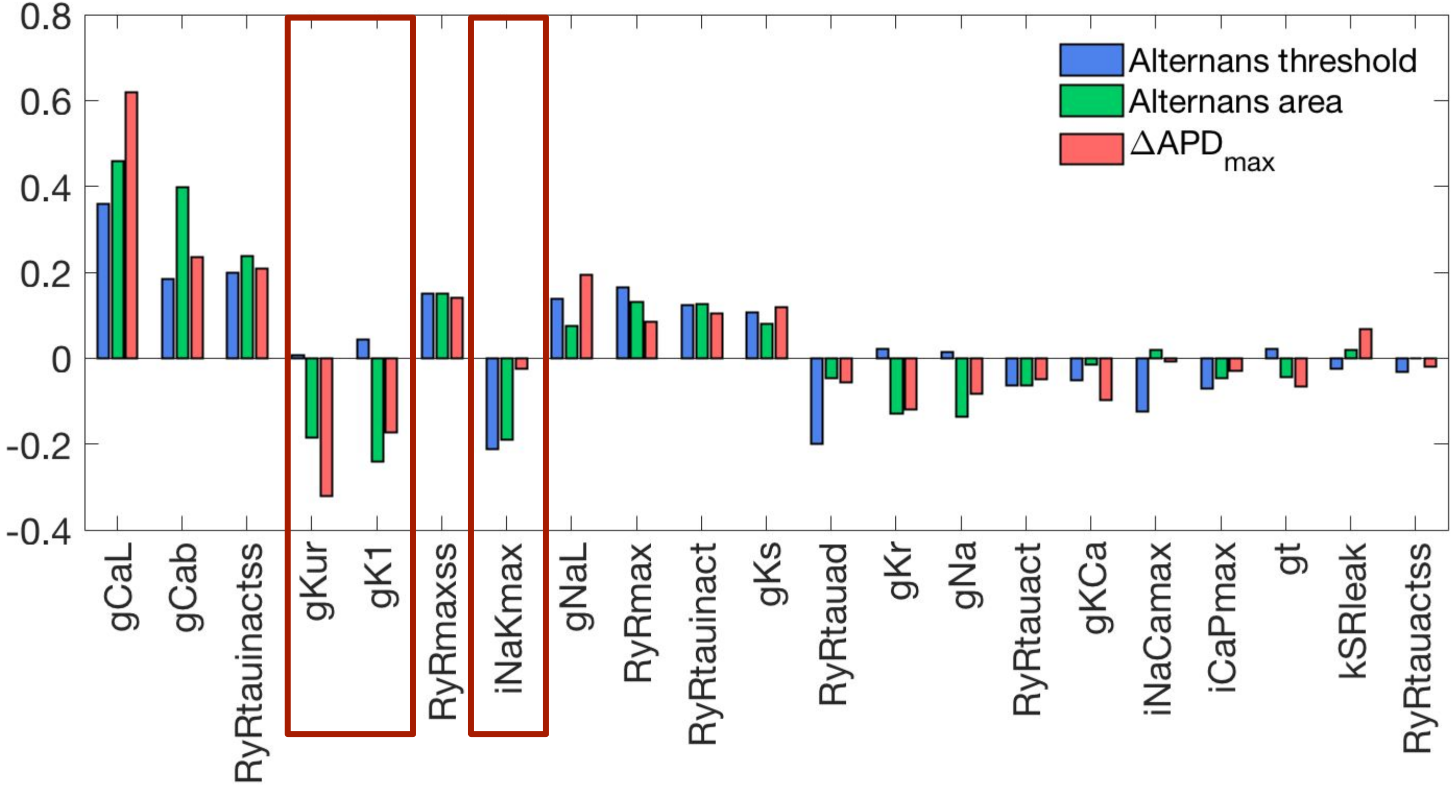
Alternans markers in Normal population



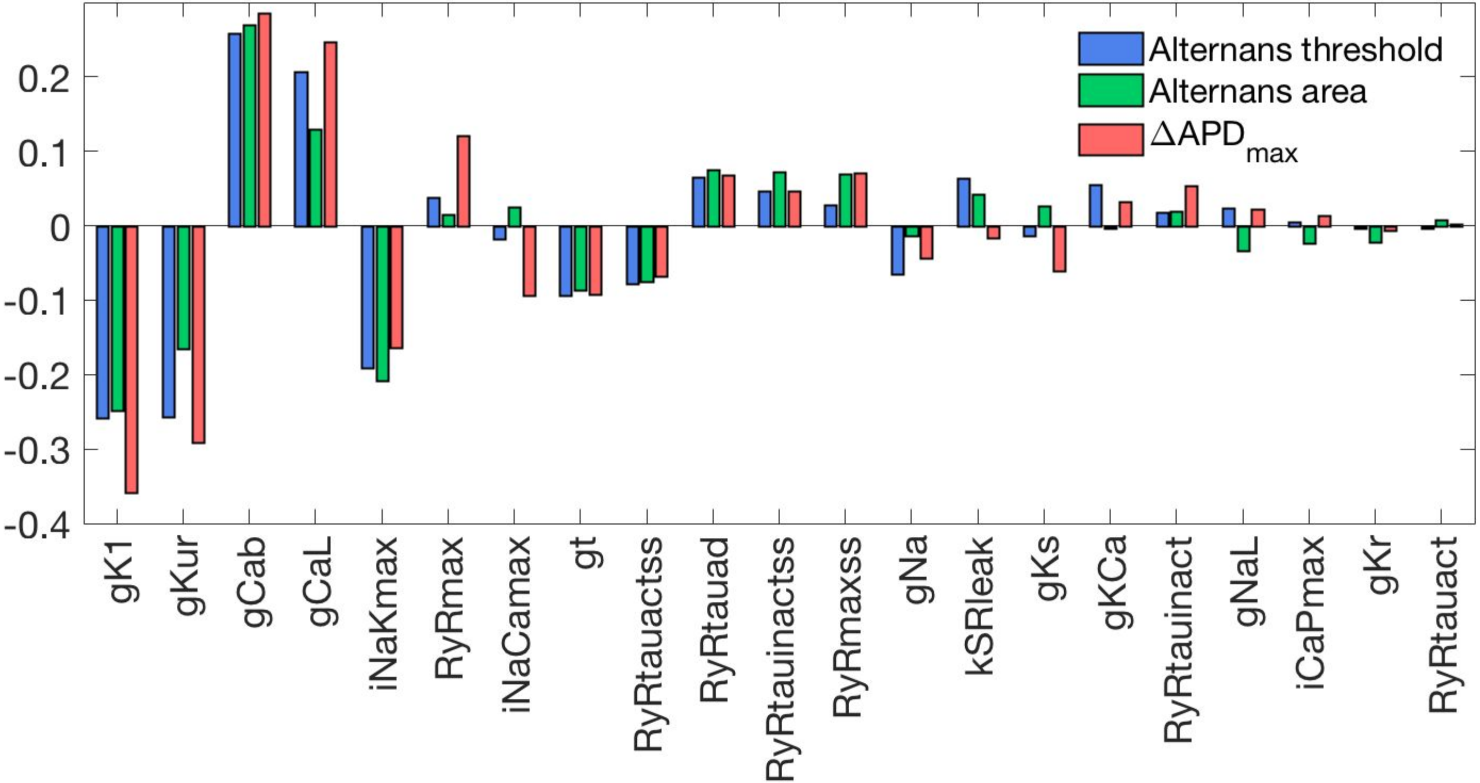
Alternans markers in Normal population showed known parameter dependencies



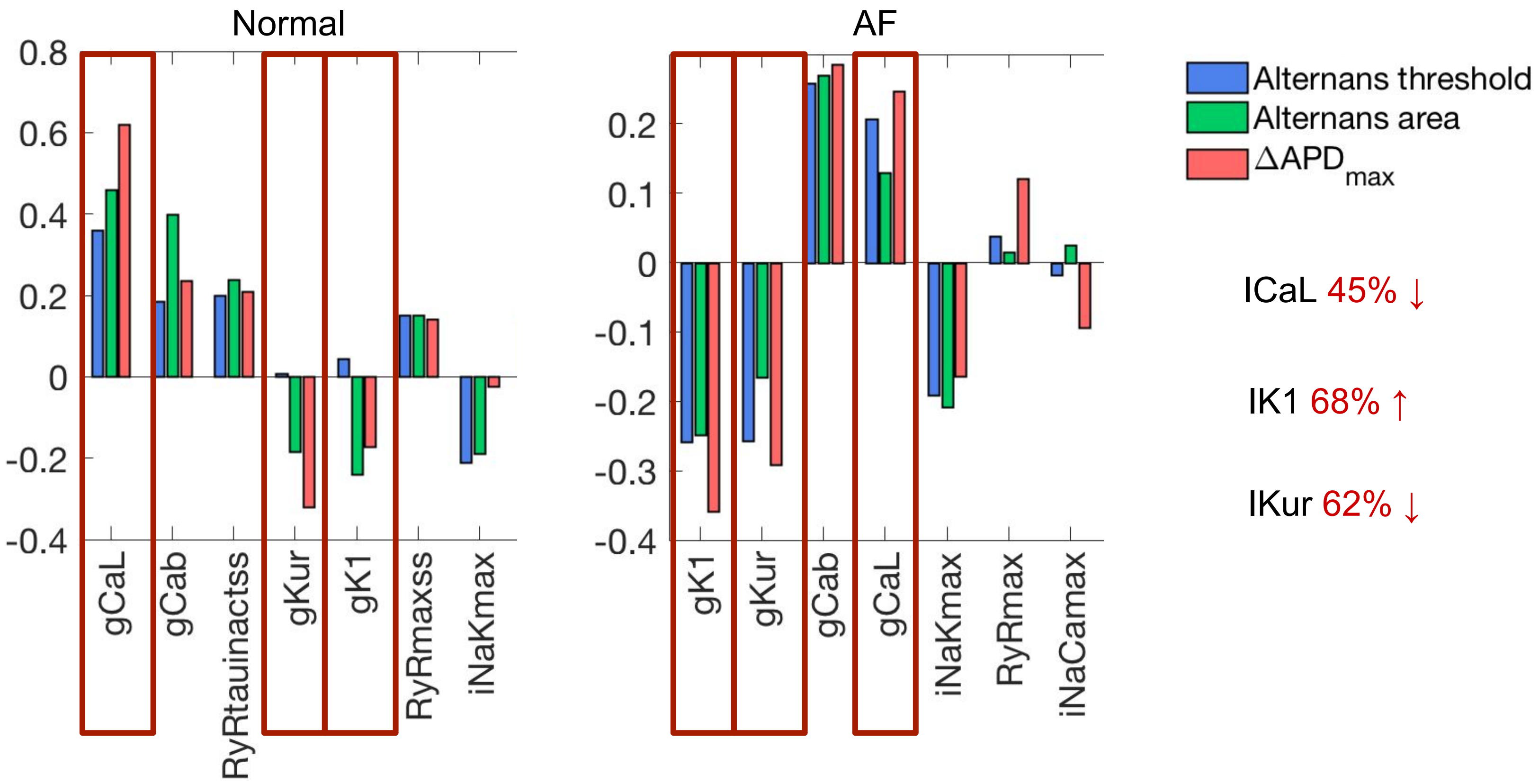
Alternans markers in Normal population provided new insights into role of IKur, IK1 and INaK



AF population showed highest sensitivities of alternans markers to IK1, IKur, ICaL and INaK



Normal and AF populations showed different sensitivities of alternans markers



ICaL 45% ↓

IK1 68% ↑

IKur 62% ↓

Conclusions and insights

Populations of Normal cells showed higher variability and propensity for APD alternans than the AF population

Normal and AF populations showed differences in the sensitivities of alternans to gCaL, gK1, gKur, and INaK conductance

Framework developed is a useful tool for studying mechanisms of cardiac alternans in single cells, and can be extended to tissue/organ simulations

This methodology can be applied to study other electrophysiology mechanisms related to arrhythmia

Limitations

Calculated B are sensitive to choice of parameters, since the coefficients represent the “relative” role of each parameter in explaining the variability in the observed response/biomarker

The simple regression model assumes no interactions between independent variables, which sometimes cannot be neglected. Use, eg, Partial Correlation.

Method can be extended to include nonlinear and interaction terms, but a more complicated model is also harder to interpret.

Method is also sensitive to the calibration step, so this has to be done with a rationale keeping in mind the what are the model behaviors we want to study.

Future work

- Incorporate variable interactions in the regression model, and reduce error by defining different a priori distributions of the parameters.
- Perform mechanistic analysis of alternans, by analysis individual components of the calcium release system (eg, function of RyR and NCX).
- Move to 2D simulations (populations of tissues), and try and find relationships between observed alternans behavior at the cellular and tissue level.
- Incorporate the effect of ion channel blockade effect of drugs commonly used in the treatment of Atrial Fibrillation.
- Derive an arrhythmia score based on cellular biomarkers that works as a surrogate of pro-arrhythmic risk.

Thank you

Joakim Sundnes

Hermenegild Arevalo

Molly Maleckar

Bernardo de Oliveira

Jussi Koivumäki