Sensitivity analysis of populations of cardiac models in healthy and diseased states

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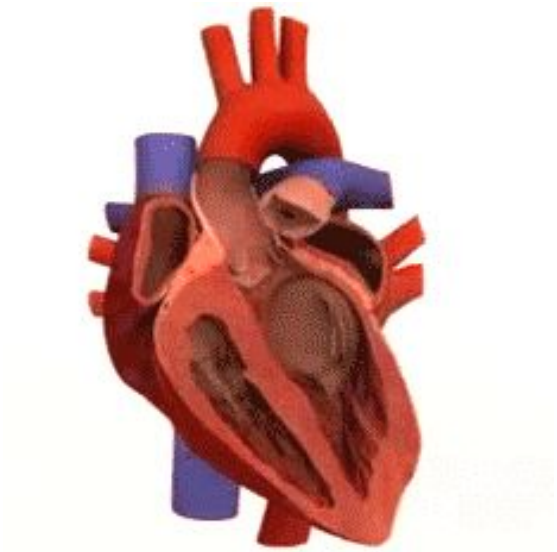
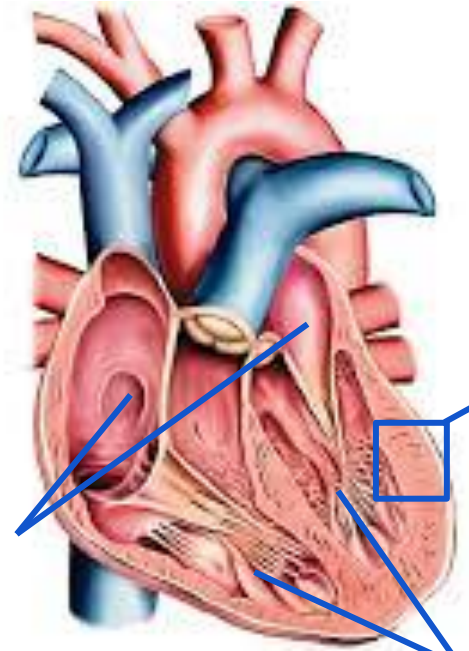
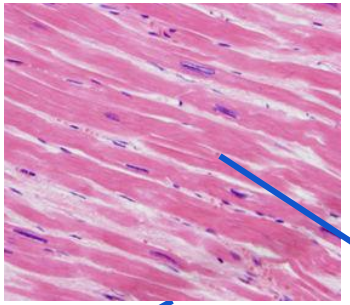
The normal heart contracts and relaxes at a regular beat

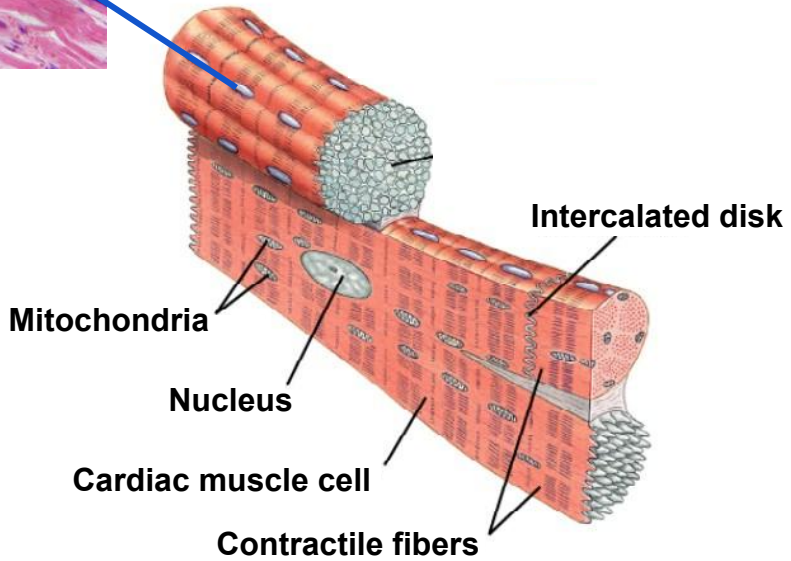


The myocardium is a muscle composed of tightly packed cardiomyocytes beating as a syncytium

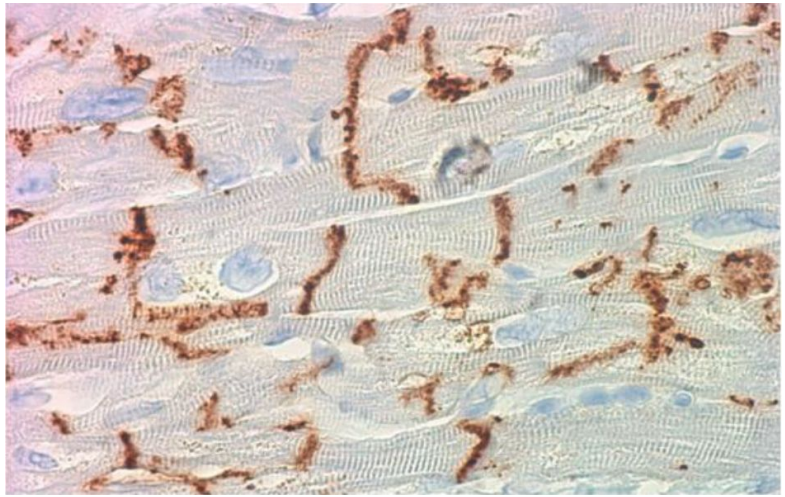




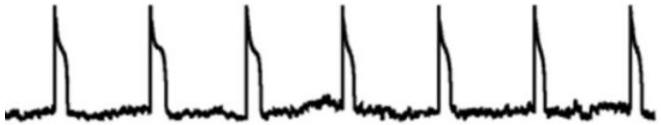
Ultrastructure of cardiac tissue



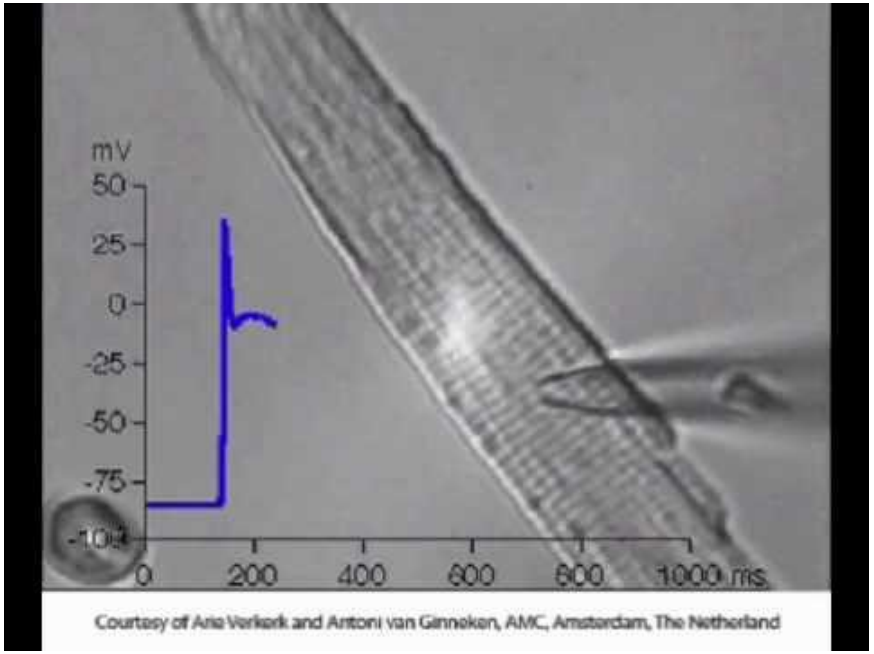
Cardiomyocyte electrical activity can be recorded *in vitro*



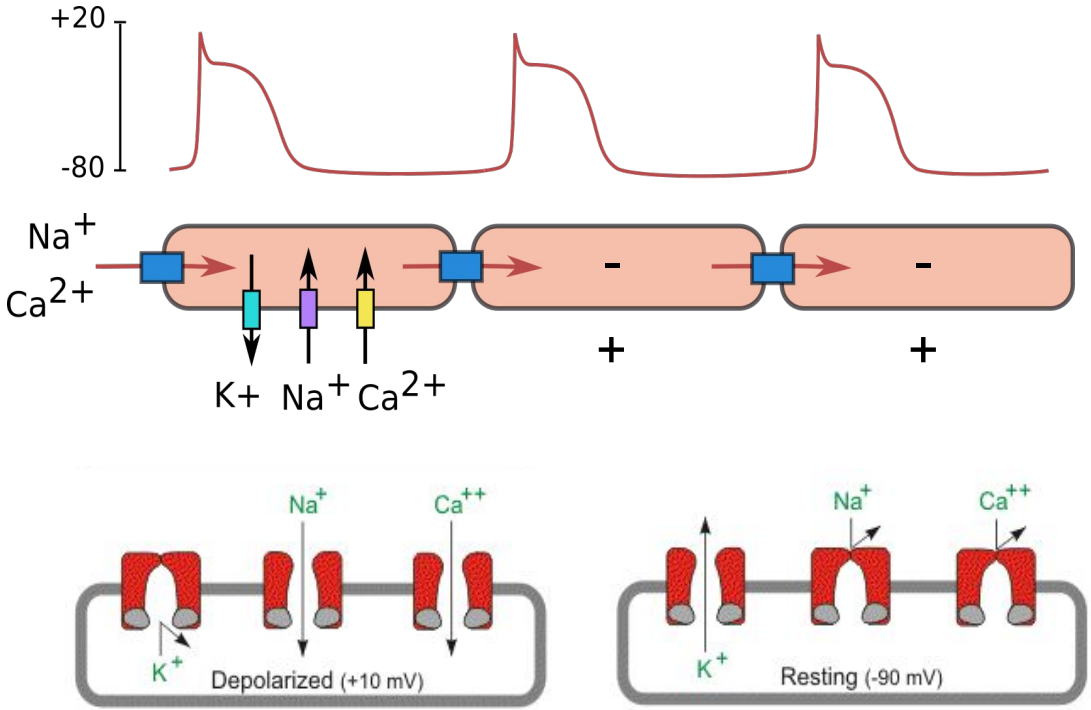
M. Lemoine et al., Scientific Reports, 2017

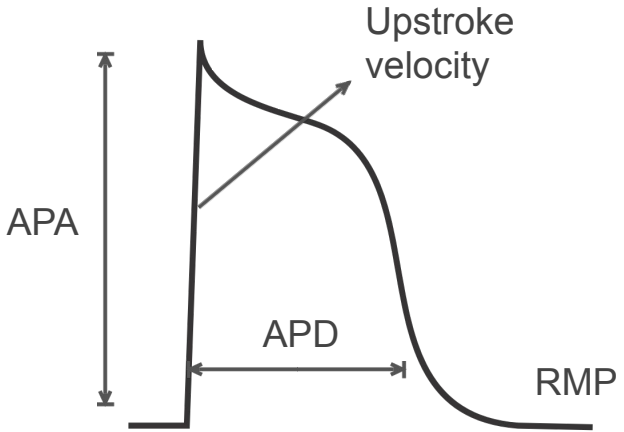


Y. Xie et al., Circulation, 2015

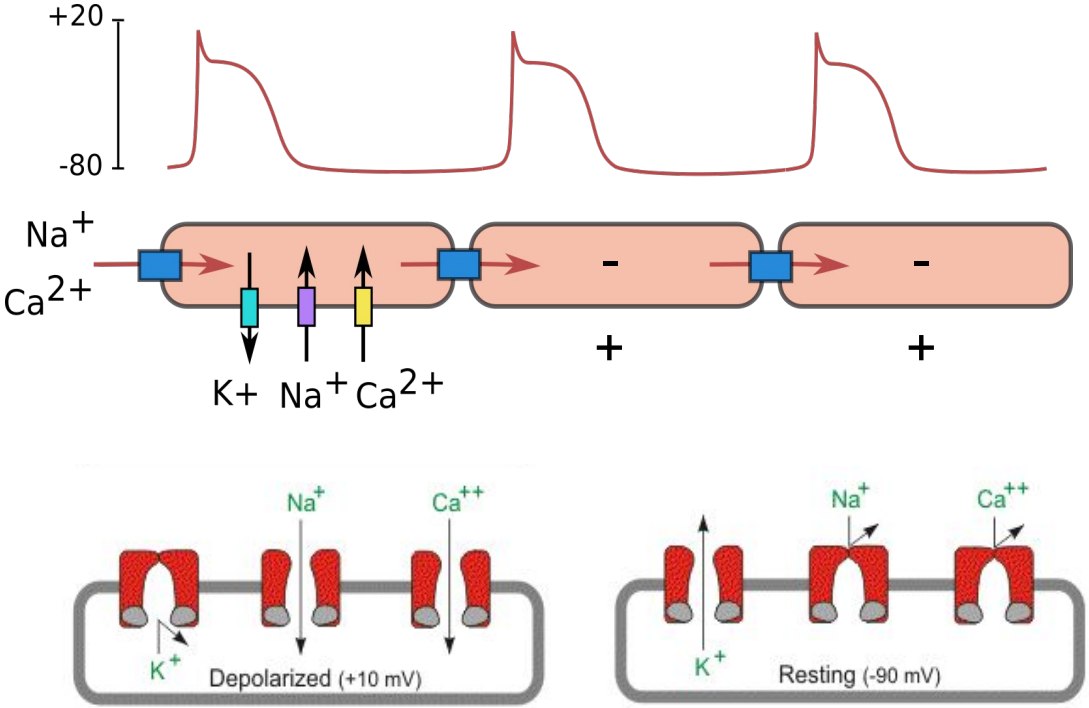


The heart contracts because of the propagation of electrical signals throughout the myocardium in the form of action potentials (AP)





Single cell models describe in mathematical terms the biological processes that occur during electrical activation of a cardiomyocyte



$$I(t) = I_C(t) + \Sigma I_{ion}(t)$$

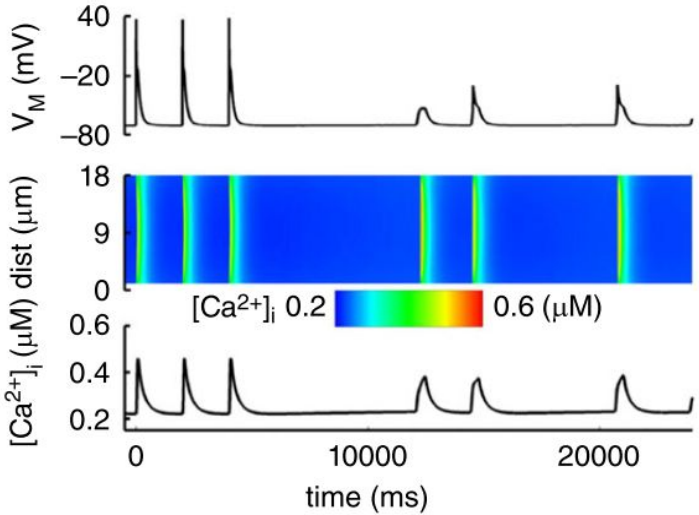
$$I(t) = C\frac{dV_m}{dt} + \Sigma I_{ion}(t)$$

$$I_{Na} = \bar{g}_{Na} m^3 h (V_m - E_{Na})$$

$$\frac{dm}{dt} = \alpha_m(1-m) - \beta_m$$

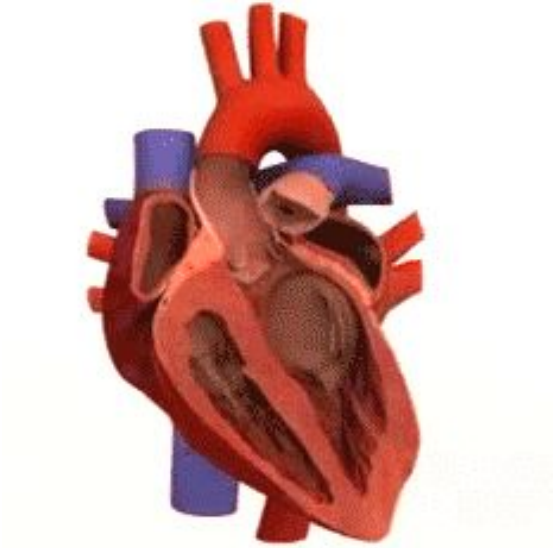
Computational models of the heart allow to simulate the cardiac function in normal and diseased conditions

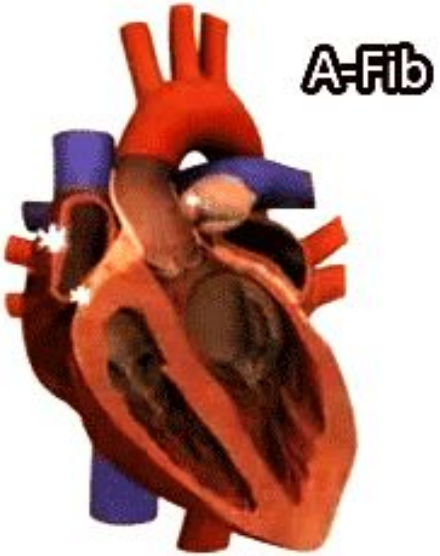
Simulate aspects of electrophysiology, such as APs, intracellular ionic concentrations, dynamic behavior



- Study mechanisms of initiation and maintenance of disease
- Test new treatment strategies
- Interpret experimental findings
- Simulate experimental conditions/protocols, sometimes not feasible in the lab.
- Reduce animal experiments

In **Atrial Fibrillation** is the fast irregular beating of the atria due to chaotic electrical activity





Atrial Fibrillation is a heart condition that causes the heart to beat in a fast irregular rhythm

Most common form of irregular heartbeat, or arrhythmia

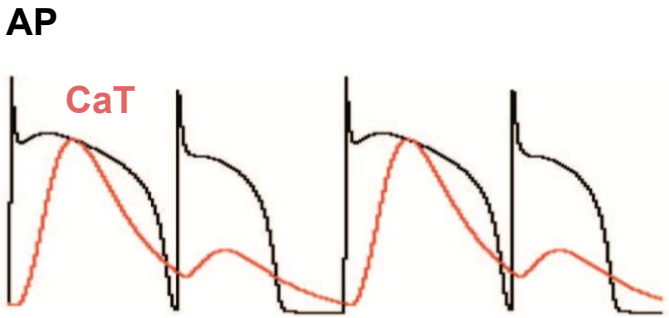
Affects 10 million people in Europe and 2.5 million people in the US

Increases the risk of heart failure, stroke and death

AF is a progressive disease → **Electrical & Structural Remodelling**

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

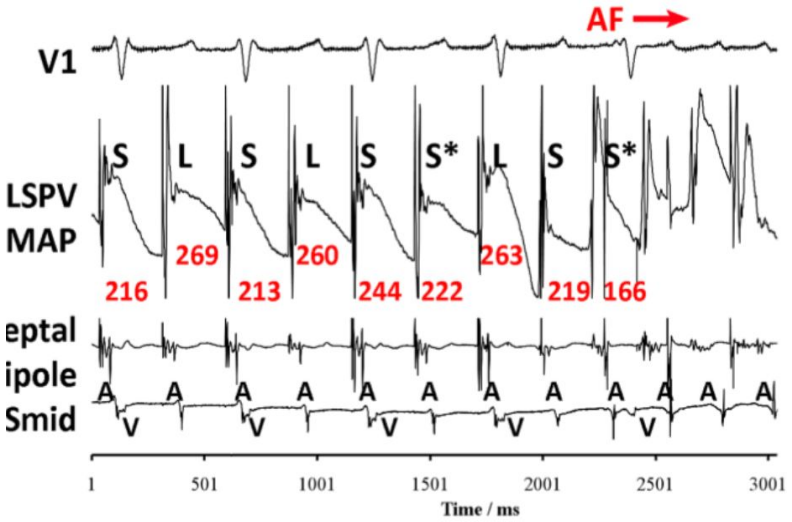
Cardiac alternans



AP: action potential → APD alternans

CaT: calcium transient → CaT alternans

Alternans precede AF

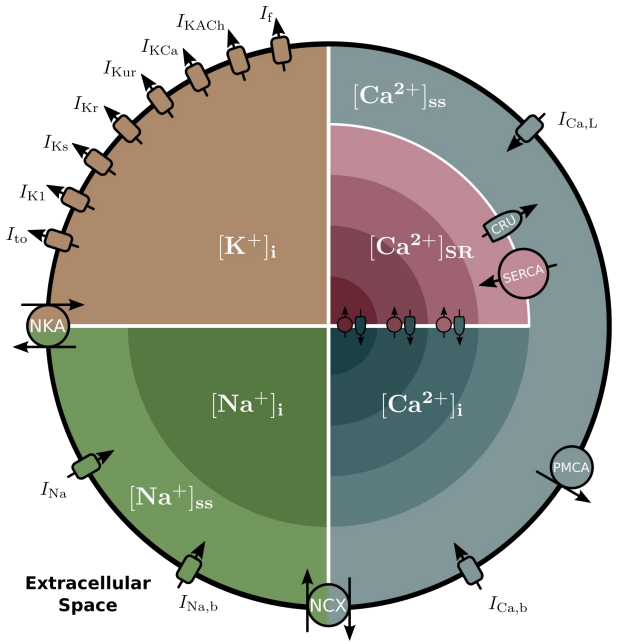


Narayan et al., Circulation, 2011

Main goal:

To use populations of models and sensitivity analysis to find which parameters of a single cell atrial model are causing the observed APD alternans behavior

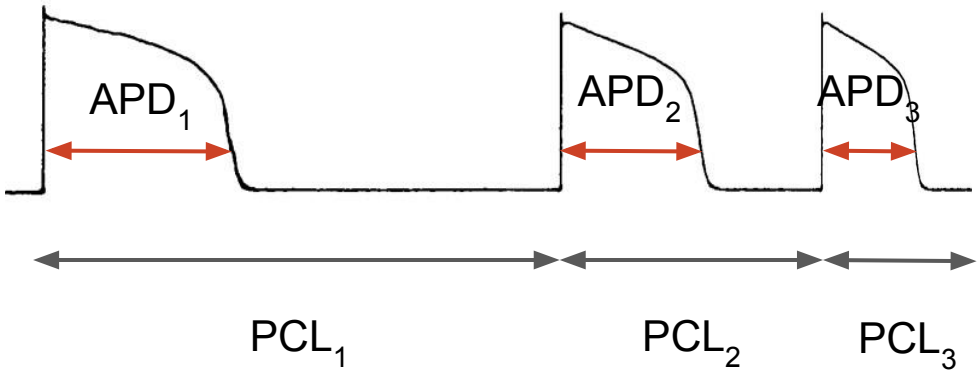
The Koivumäki model of the human atrial cell showed APD alternans under dynamic pacing



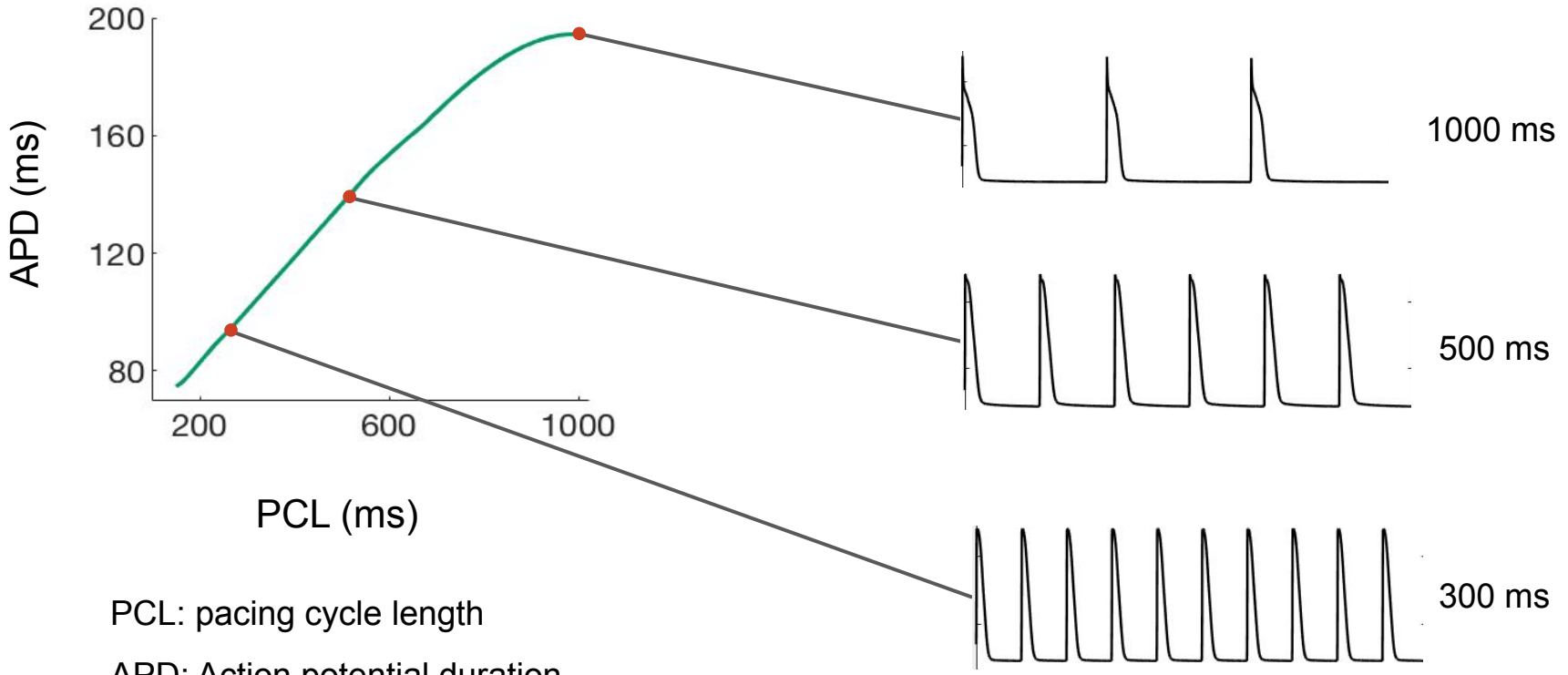
J. van den Brink, Master Thesis, 2016

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

AP duration (APD) depends on the pacing cycle length (PCL)



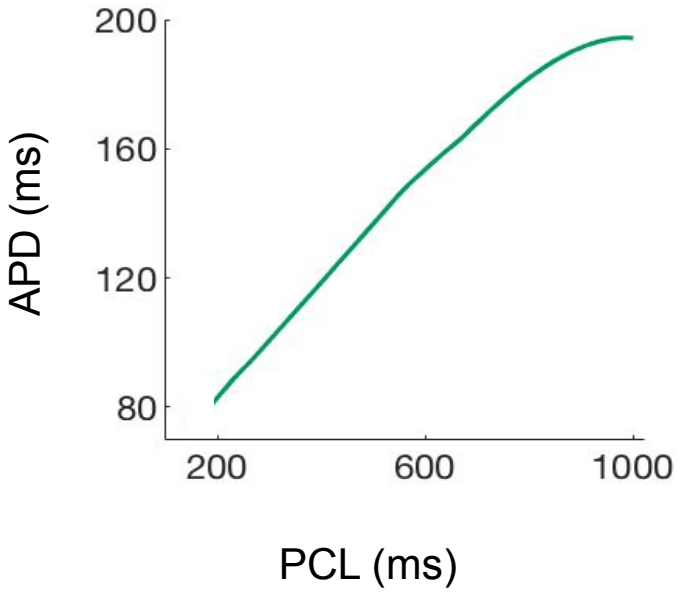
The relationship between APD and pacing rate is represented through restitution curves

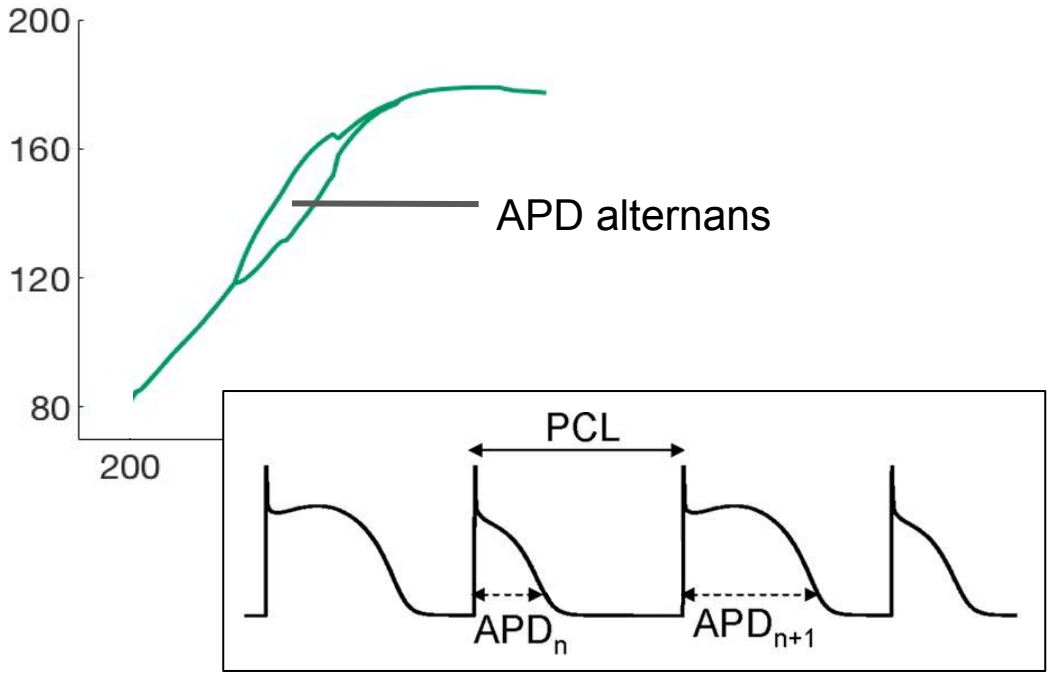


PCL: pacing cycle length

APD: Action potential duration

APD restitution can be used to characterize APD alternans





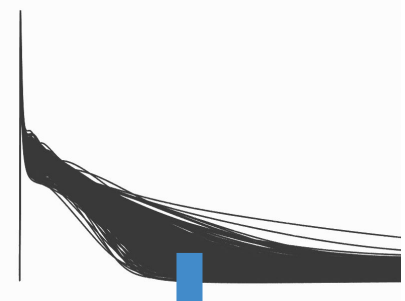
PCL: pacing cycle length

APD: Action potential duration

What are the cellular and molecular mechanisms underlying APD alternans in single cell models?

Data

Populations of models → Sensitivity analysis

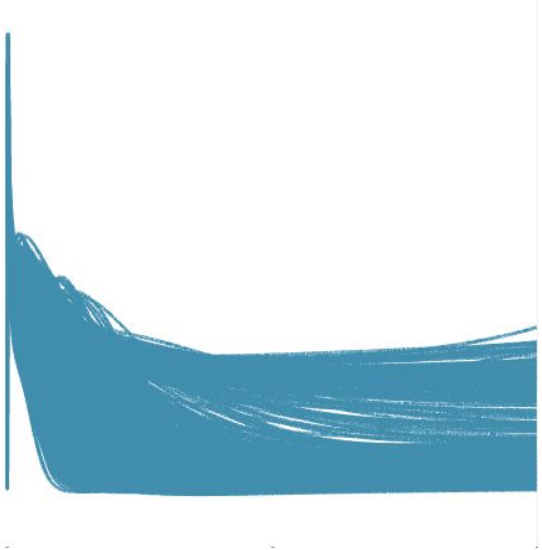


Insight into model

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

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

Populations of models simulate different model outputs

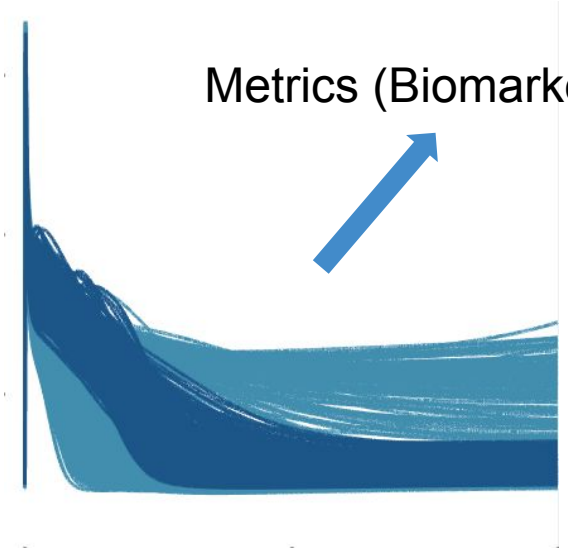


Incorporate natural **variability** observed in experimental data

Simultaneously varying selected model **parameters** related to electrophysiology mechanisms (eg, ion channels, transporters, ionic buffering, etc.)

Simulate electrical activity and extract output measure, such as AP duration (APD), AP amplitude, resting membrane potential, APD restitution curves, etc.

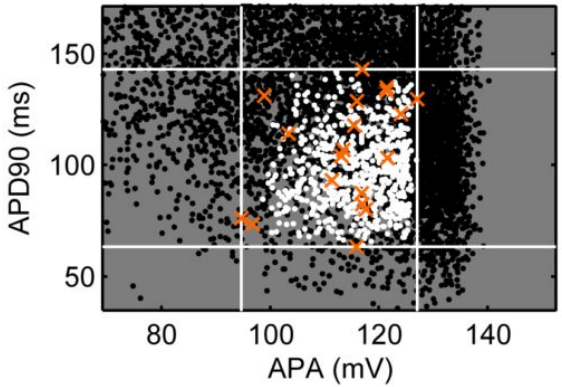
Parameters in population are calibrated by restricting biomarkers to within certain acceptable ranges



Data driven (eg, standard deviation)

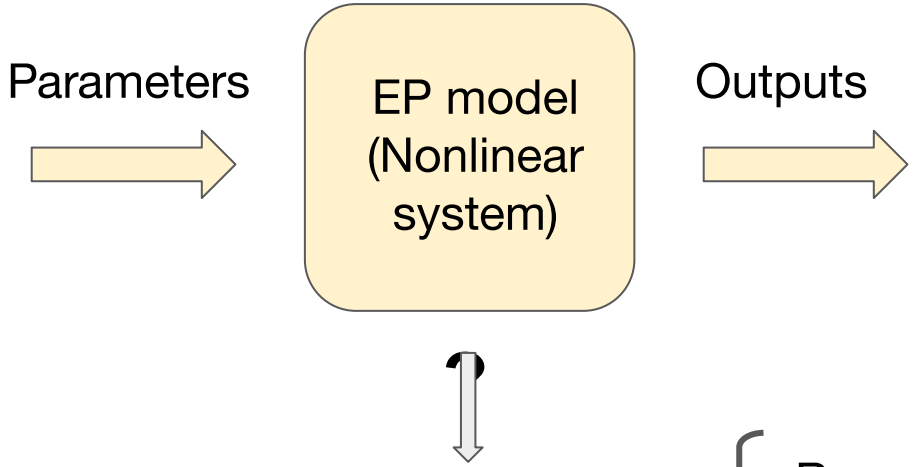
Experimental values

Restrain the parameter space

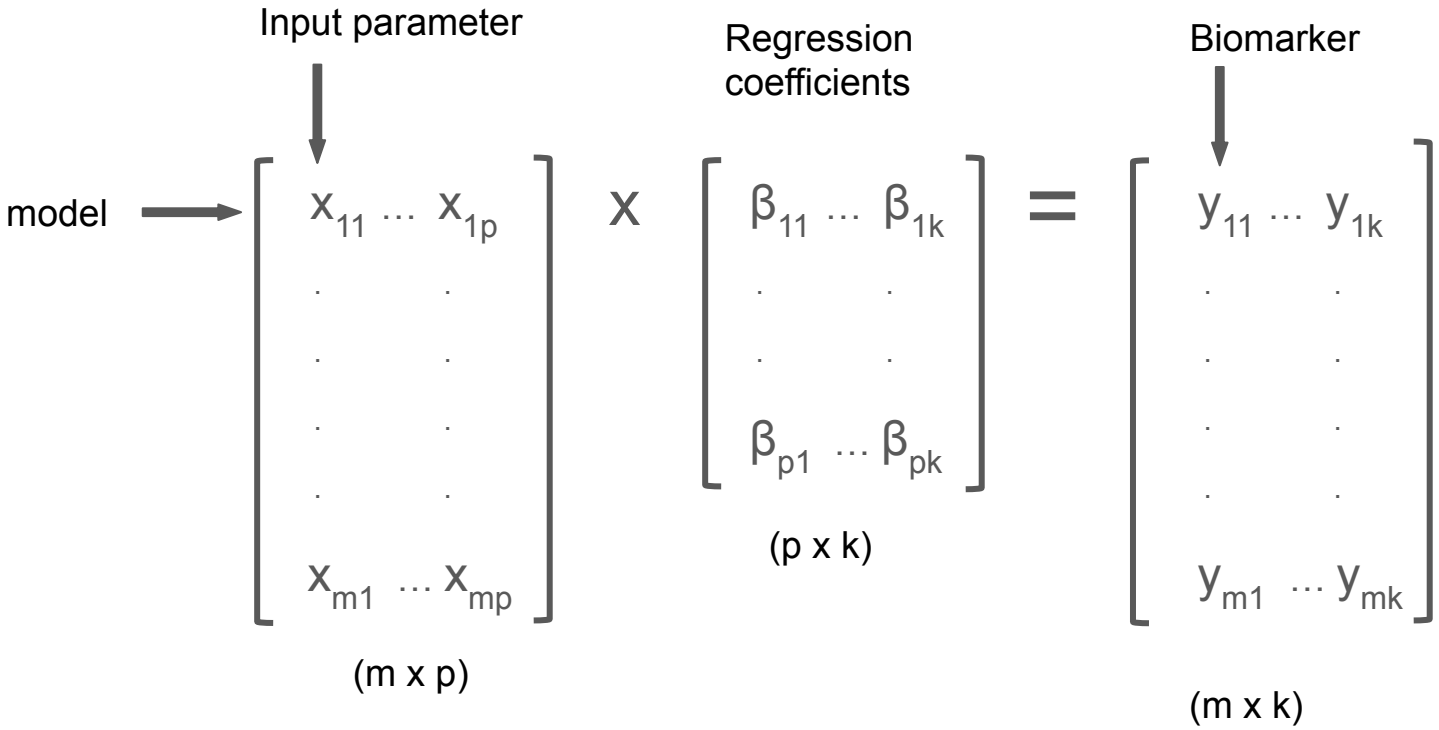


Muszkiewicz, A et al, 2014

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



Multivariate Linear Regression method



Multivariate Linear Regression method

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

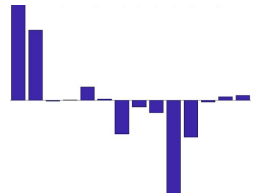
$$\mathbf{Y} = \mathbf{X} \cdot \mathbf{B} + \boldsymbol{\epsilon} \;\Rightarrow\; \hat{\mathrm{Y}} = \mathrm{X} \cdot \mathrm{B}, \qquad \mathrm{B} = (\mathrm{X}'\mathrm{X})^{-1}\mathrm{X}'\mathrm{Y}$$

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.**



Alternans markers based on dynamic APD restitution

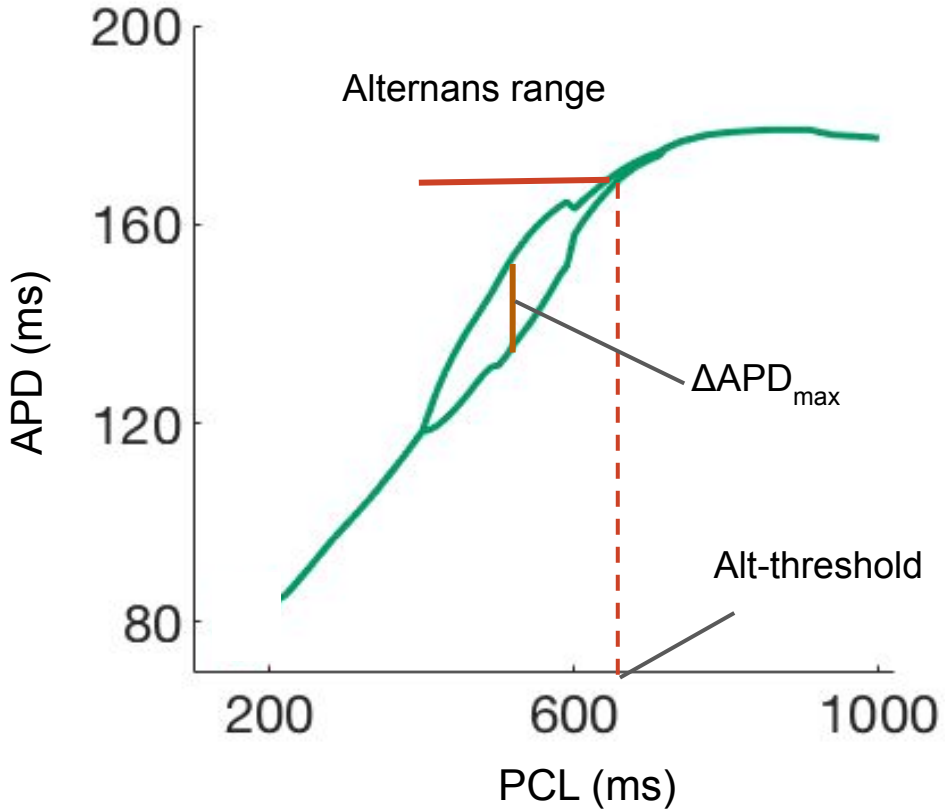
APD restitution

Alternans threshold

Alternans range

Alternans area

ΔAPD maximum



Alternans markers based on dynamic APD restitution

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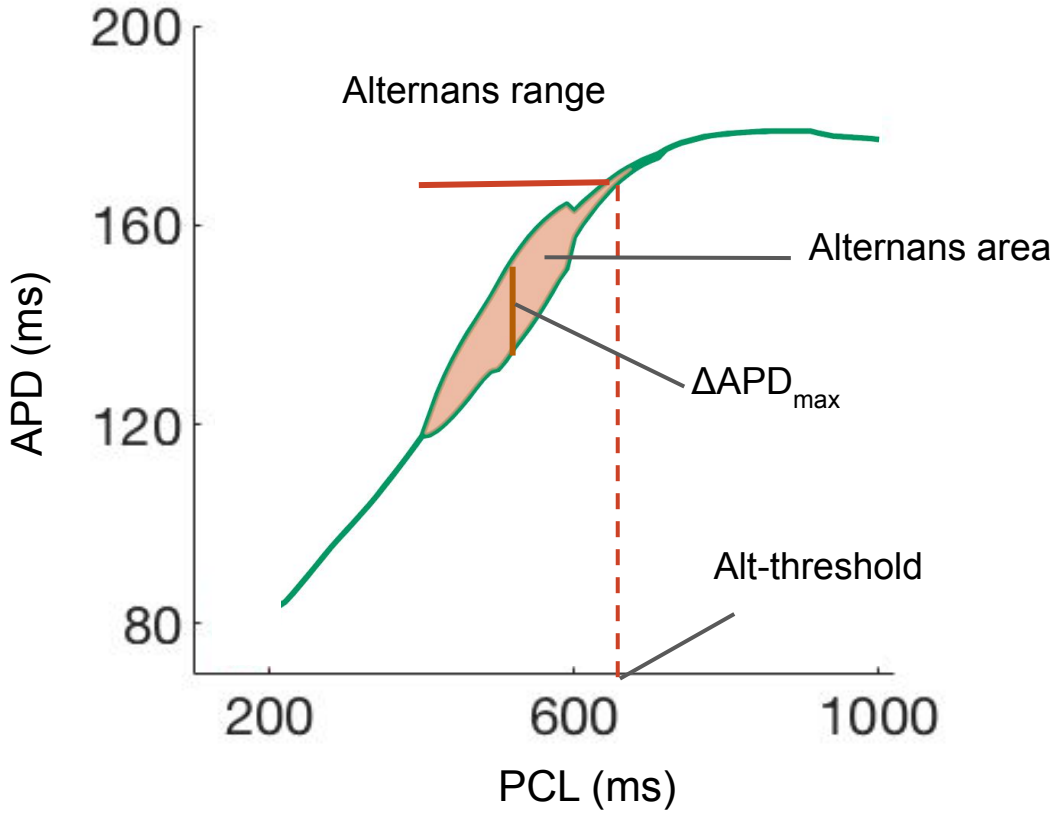
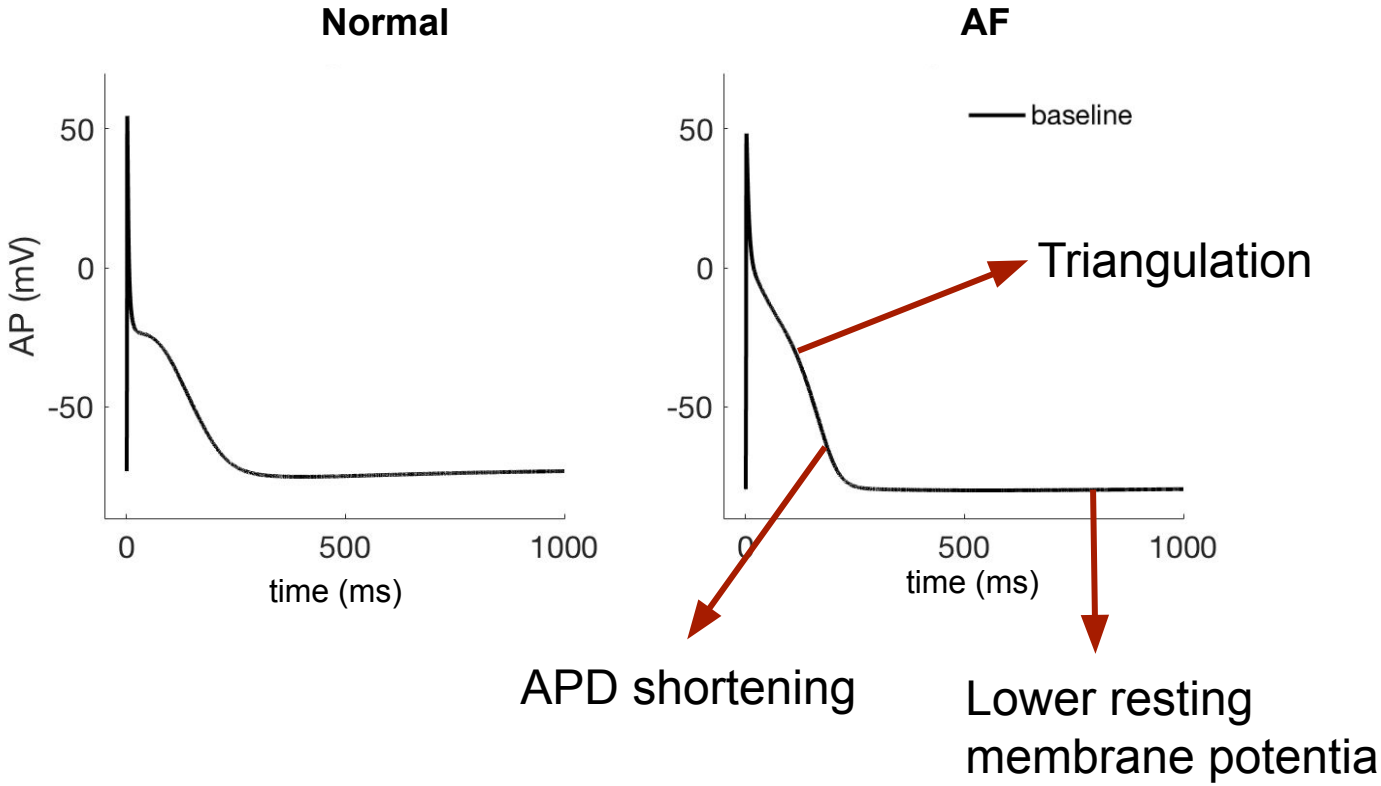


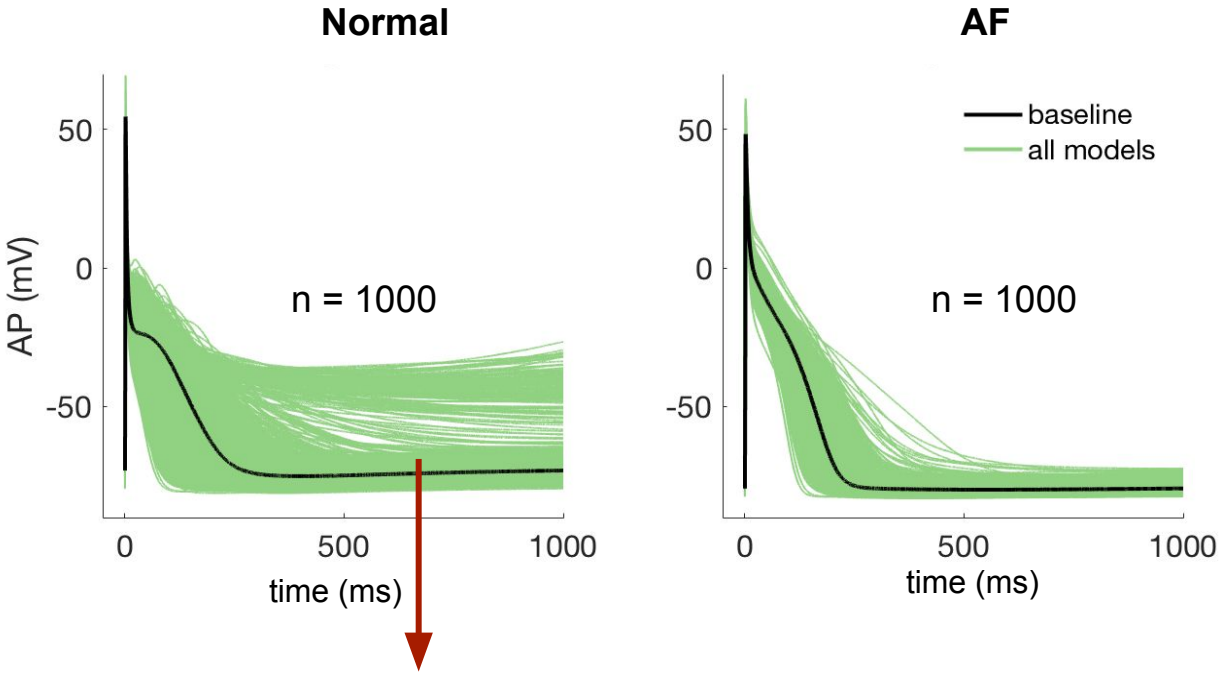
Results

Baseline of Normal and AF models



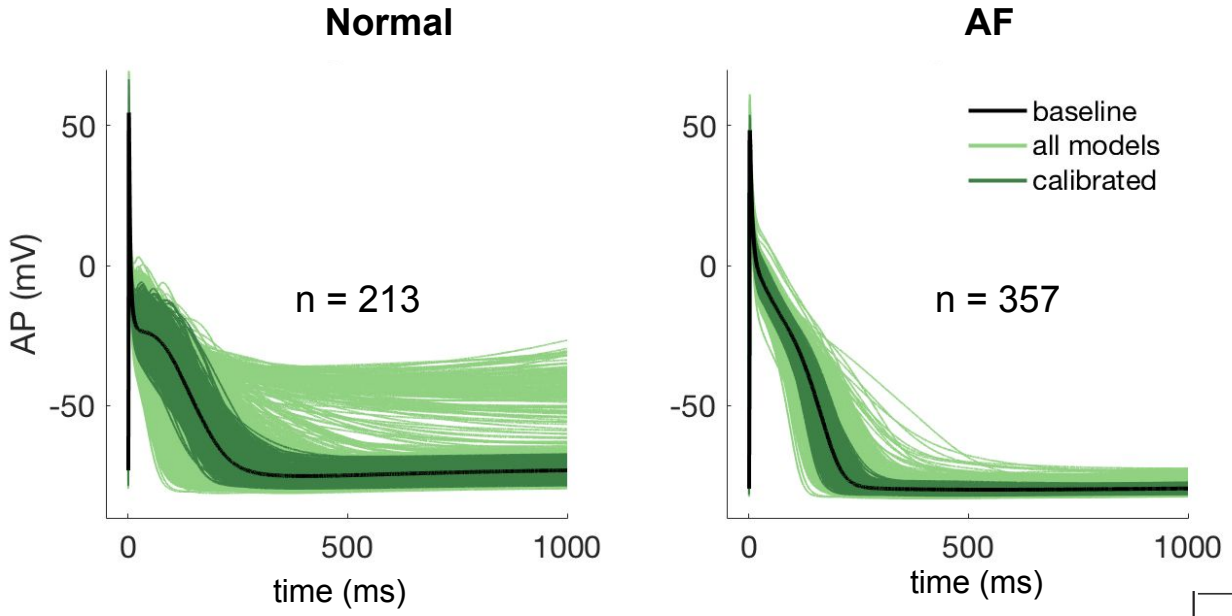
gCaL	45% ↓
gK1	68% ↑
gNa	82% ↓
gKs	145% ↑
gKur	62% ↓
gto	38% ↓
gKCa	50% ↓
RyR	100% ↑

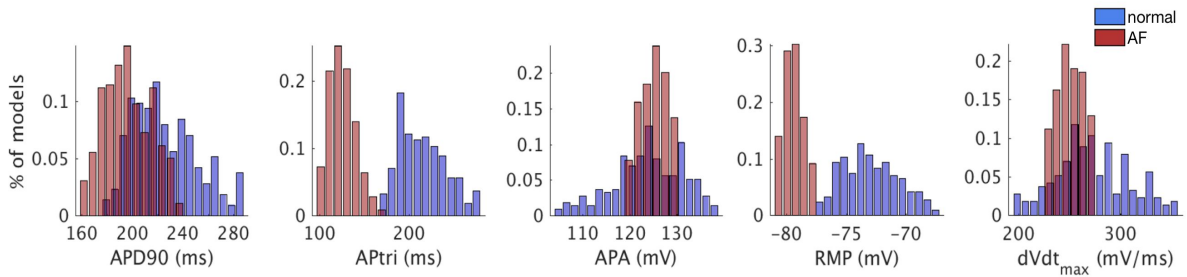
Populations of Normal and AF models



Higher intra-population variability

Populations of Normal and AF models





Functional Calibration

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

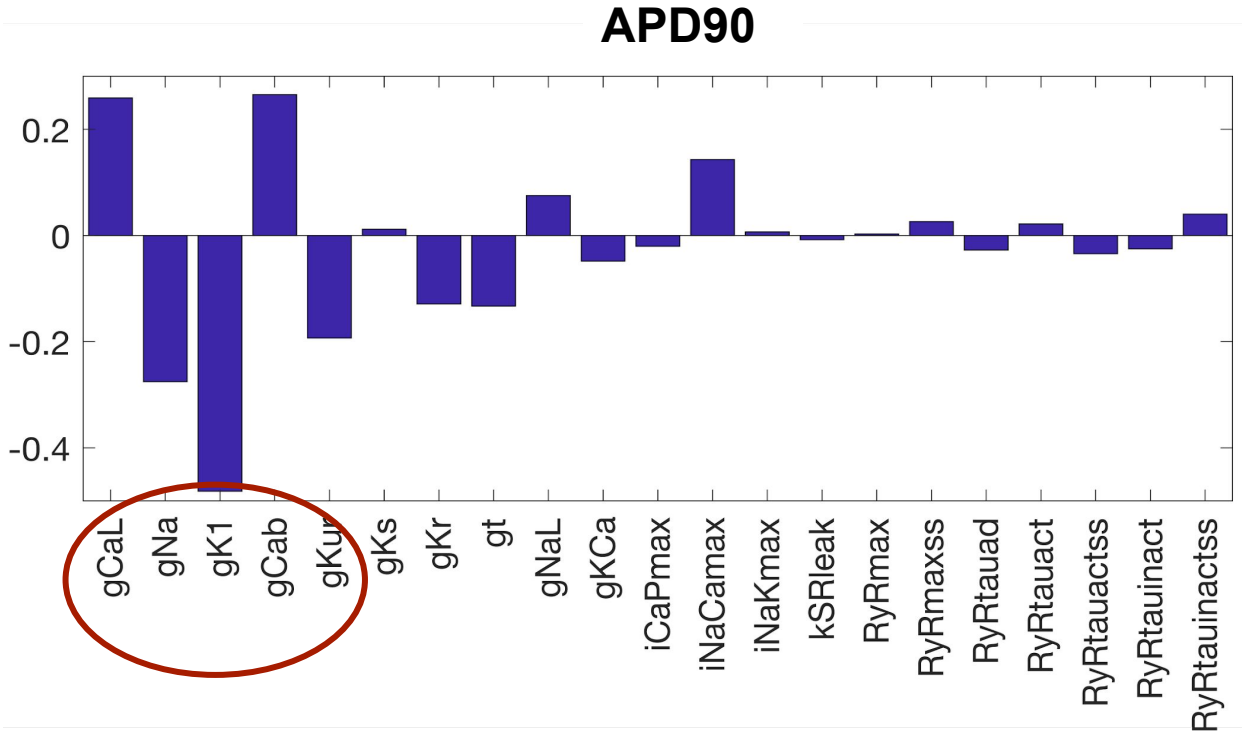
APD90
APA
RMP
Upstroke velocity

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



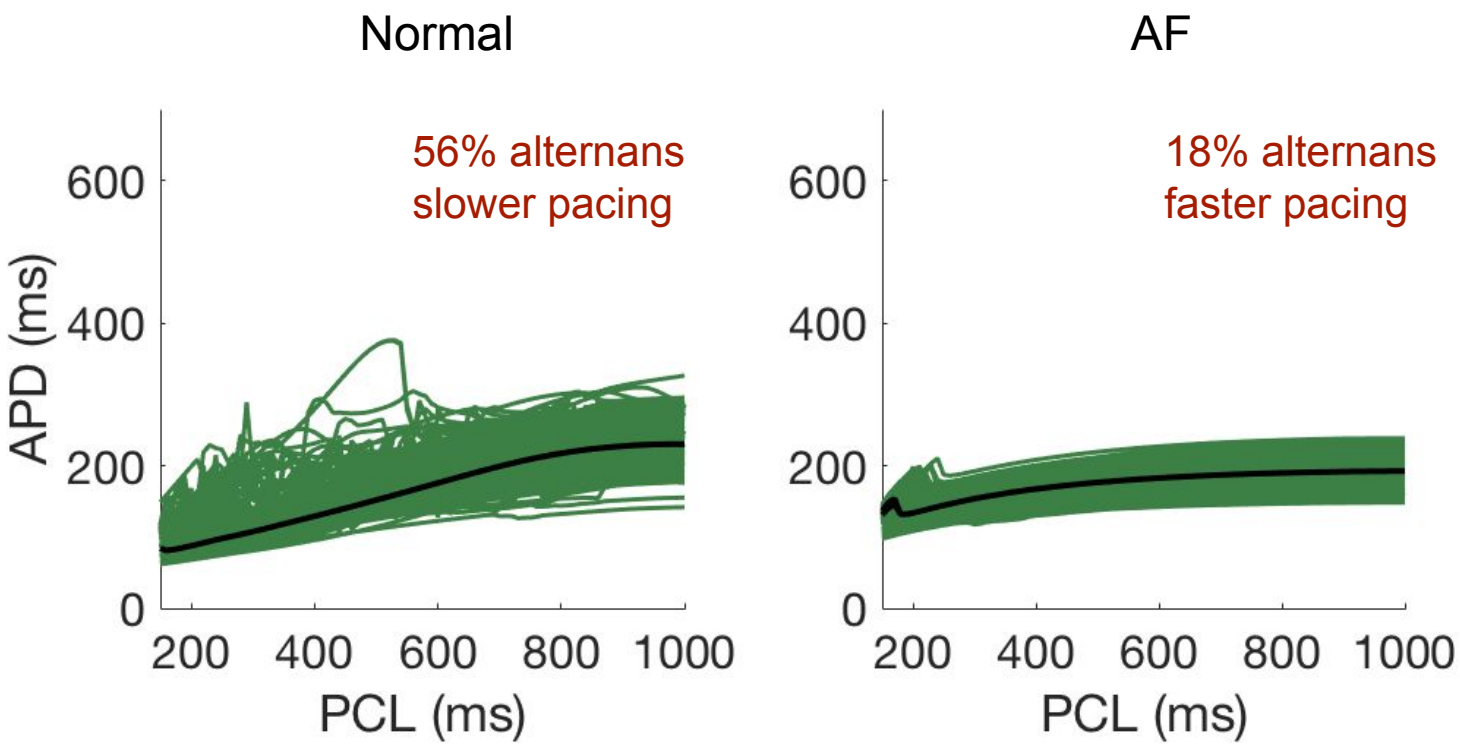
ICaL

IK1

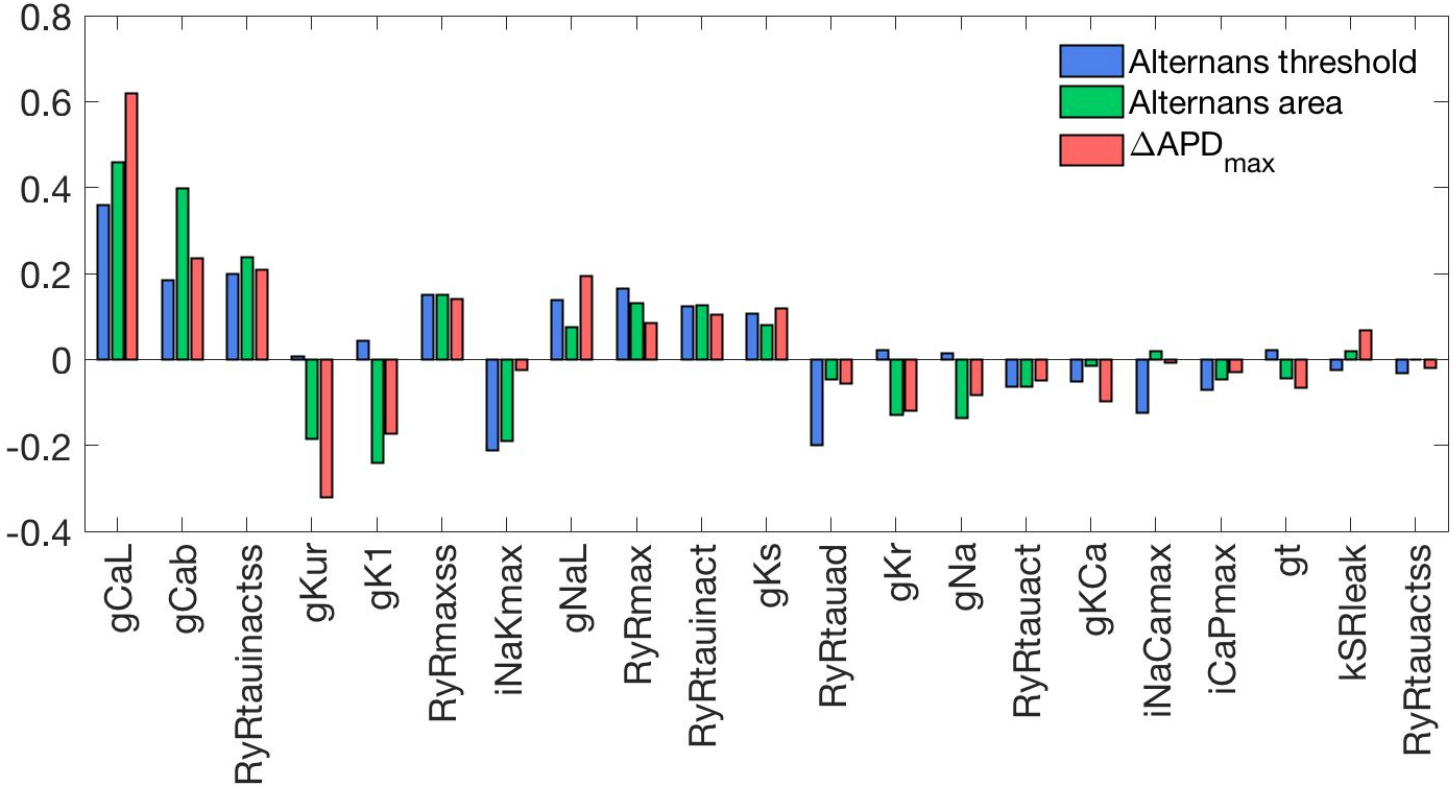
INa

IKur

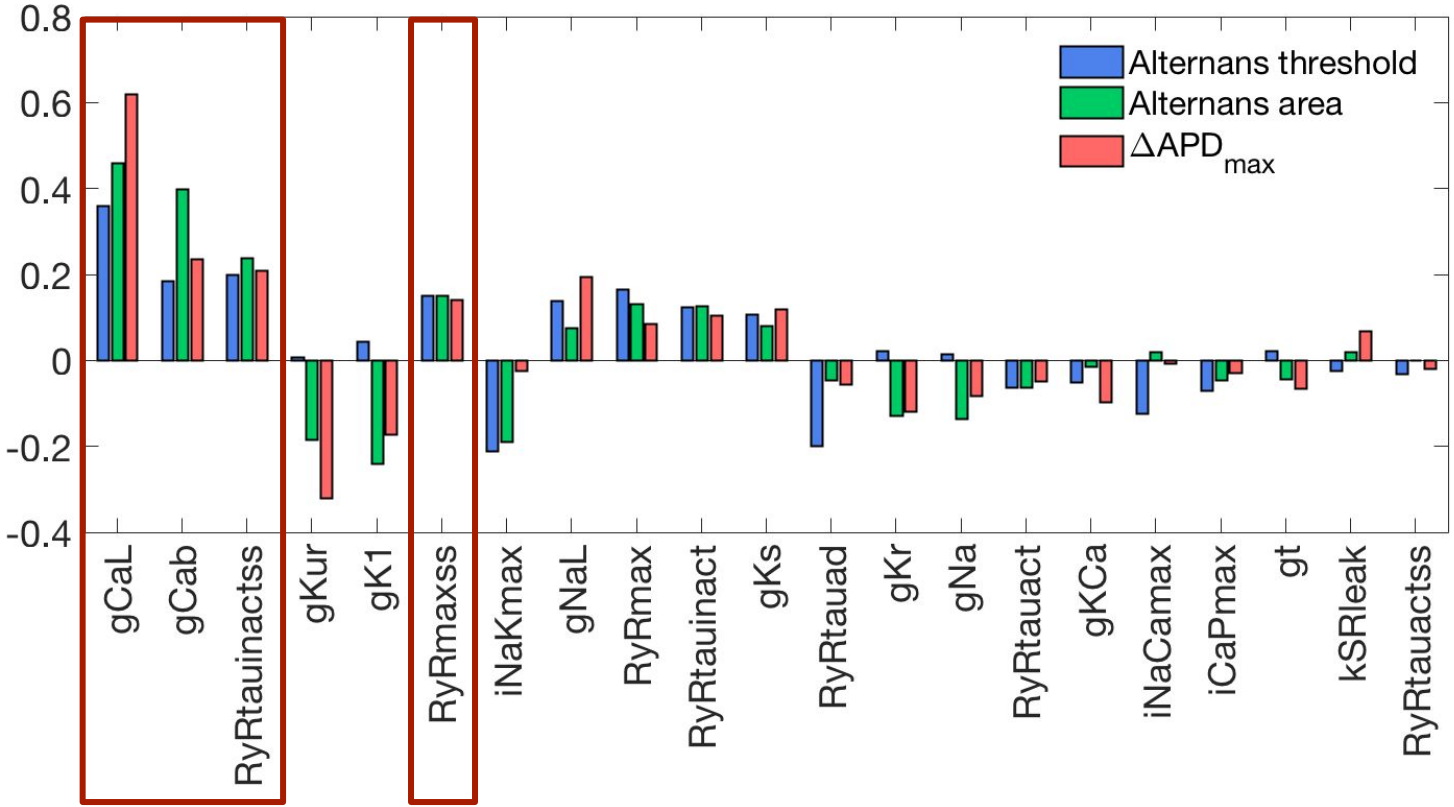
APD restitution of Normal cells revealed greater propensity to APD alternans compared to the AF cells



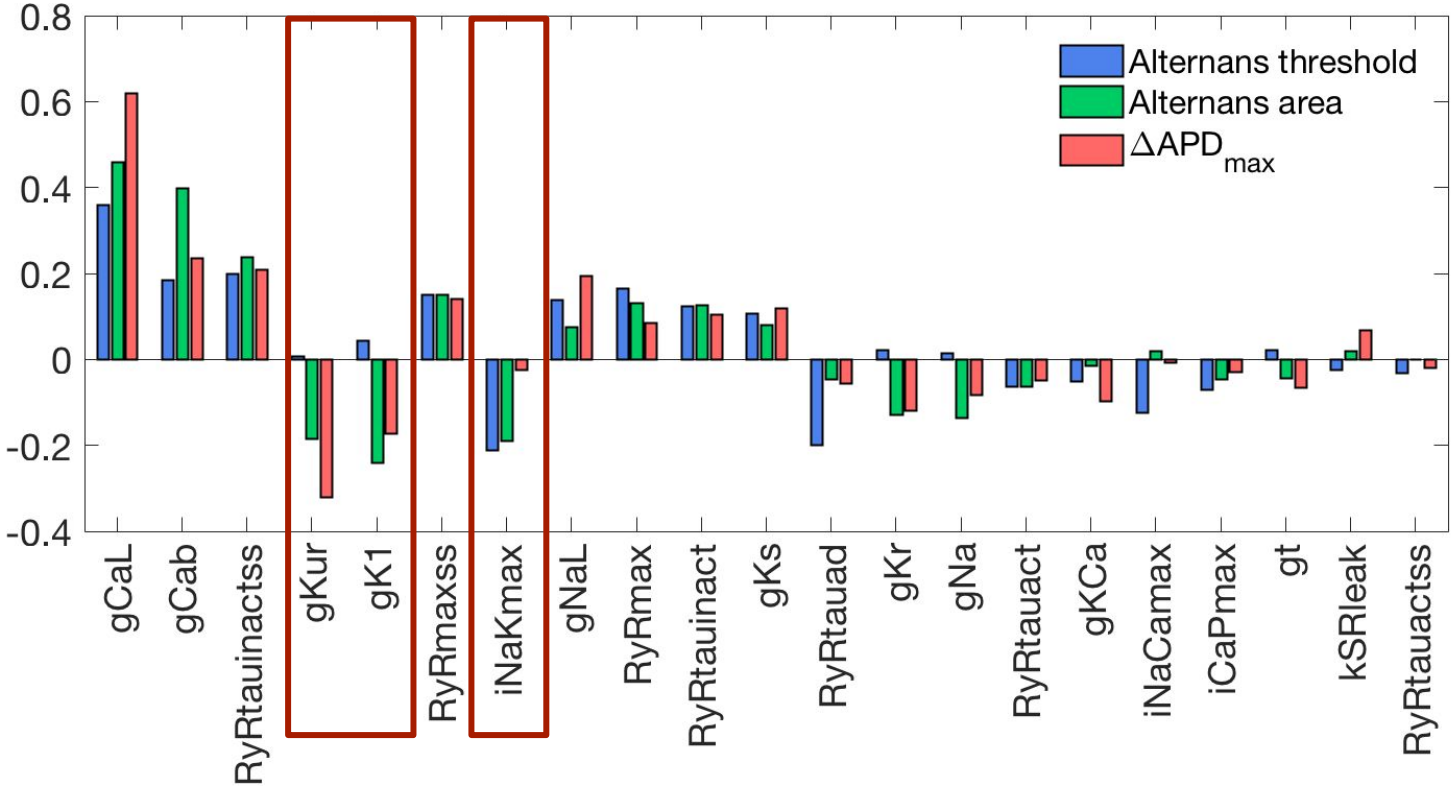
Alternans markers in Normal population



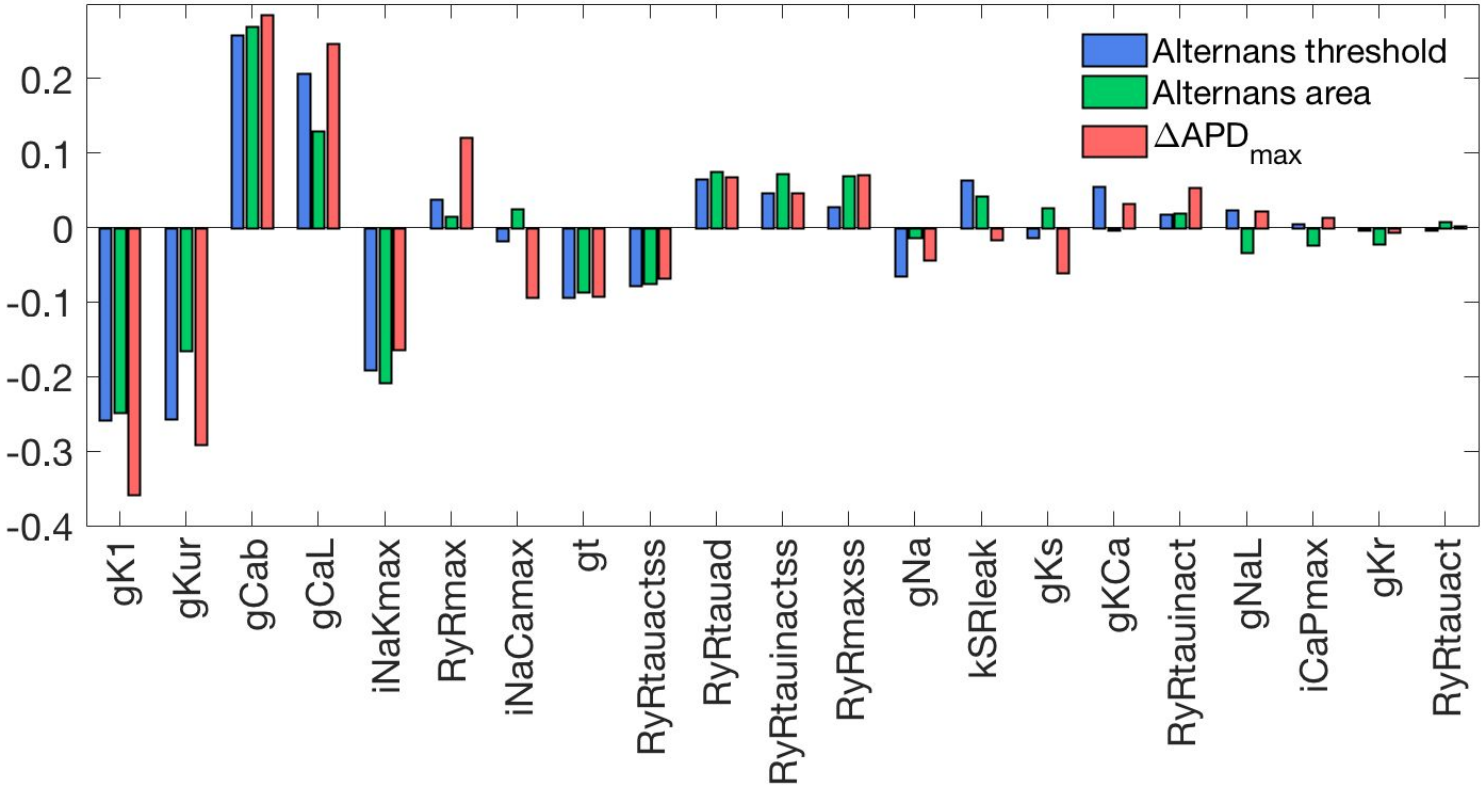
Alternans markers in Normal population showed known parameter dependencies



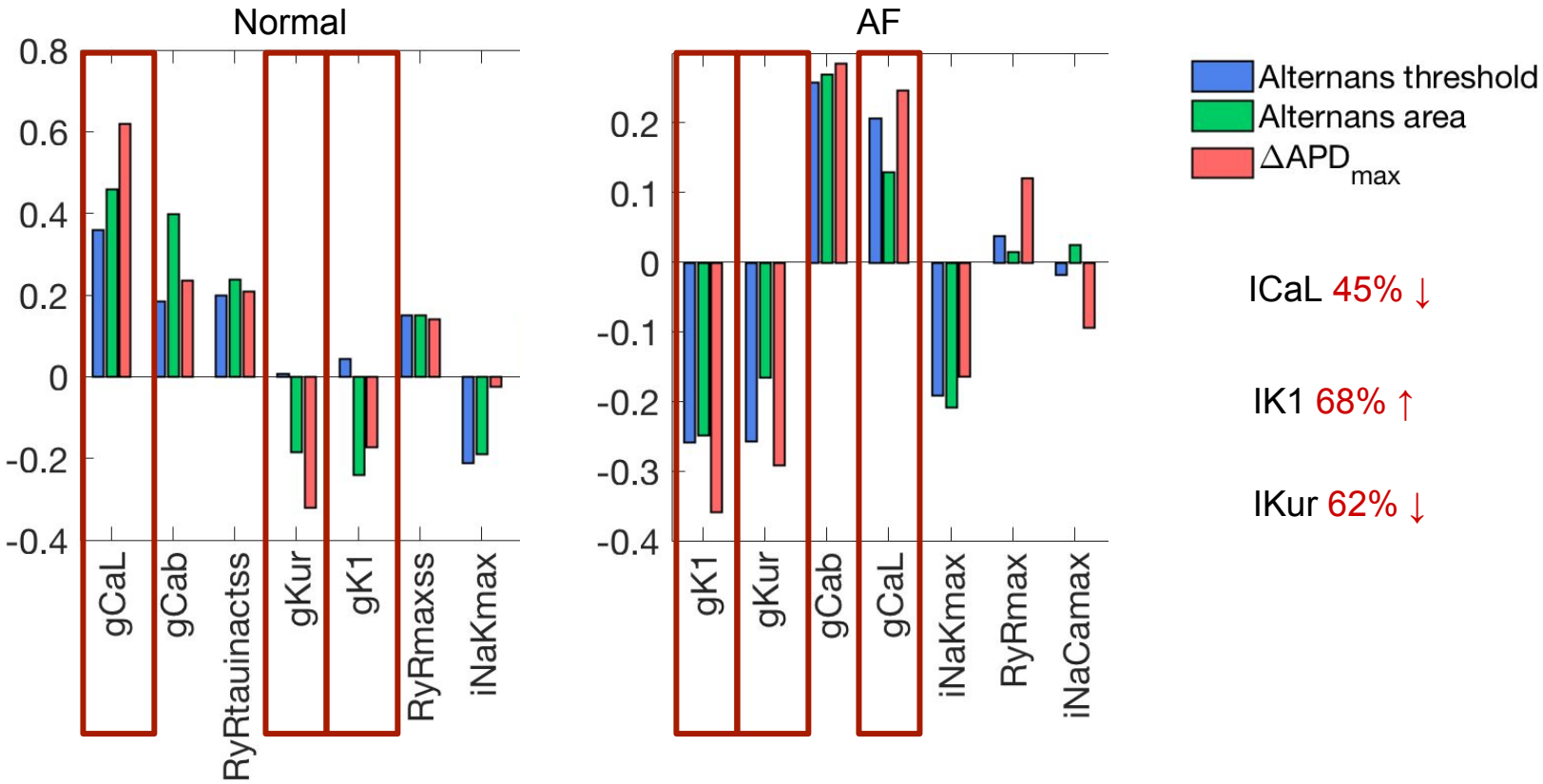
Alternans markers in Normal population provided new insights into role of IKur, IK1 and INaK



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



Normal and AF populations showed different sensitivities of alternans markers



Alternans pro-arrhythmicity

Results

AP duration	ICaL, INa, IK1, IKur
AP amplitude	INa, INaK, IK1
Resting membrane potential	IK1
Upstroke velocity	INa, IK1, INaK
Calcium transient (CaT) amplitude	ICaL, Ito, RyRtauinact
Diastolic calcium level	NCX, INaK
CaT time to peak	ICaL, IKur, INaL, INaK, RyRtauact
CaT time constant	INCX, INaK

Positive correlation

Negative correlation

Alternans pro-arrhythmicity

Results

Alternans threshold	ICaL, IK1 and IKur (AF), INaK, RyRmax and RyRtauinact (nSR)
Alternans range	ICaL, INaK, RyRtauinact (nSR)
Alternans area	ICaL (nSR), IK1, INaK, RyRtauinact (nSR)
ΔAPD_{max}	ICaL, IK1, IKur, RyRtauinact (nSR)

Positive correlation

Negative correlation

Publication in Chaos

A computational framework for testing arrhythmia marker sensitivities to model parameters in functionally calibrated populations of atrial cells

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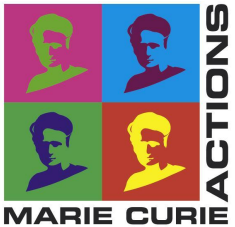
Conclusions and insights

- 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

Future work

- Incorporate variable interactions in the regression model, and reduce error by defining different a priori distributions of the parameters.
- Perform simulations on populations of models in 2D tissues to uncover relationships between alternans at the cellular and tissue level
- Simulate drug binding on the populations of models to simulate the effect drug therapies
- Derive an arrhythmia score based on cellular biomarkers that works as a surrogate of pro-arrhythmic risk.

Thank you



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