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Differential sensitivities of functionally calibrated populations of atrial cells to pro-arrhythmia markers in normal sinus rhythm versus chronic 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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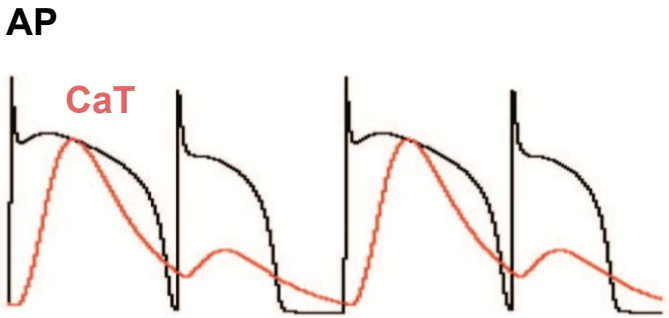
Cardiac alternans are correlated to AF episodes in patients and could serve as a marker for arrhythmia

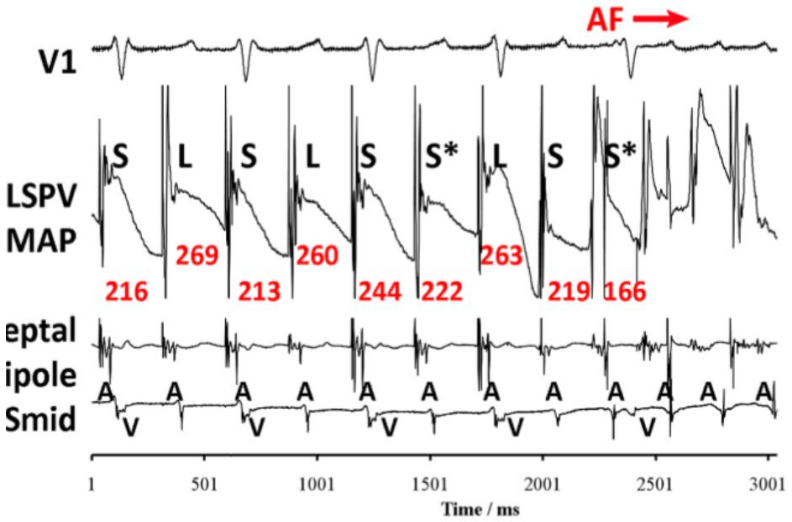
Cardiac alternans



AP: action potential → APD alternans

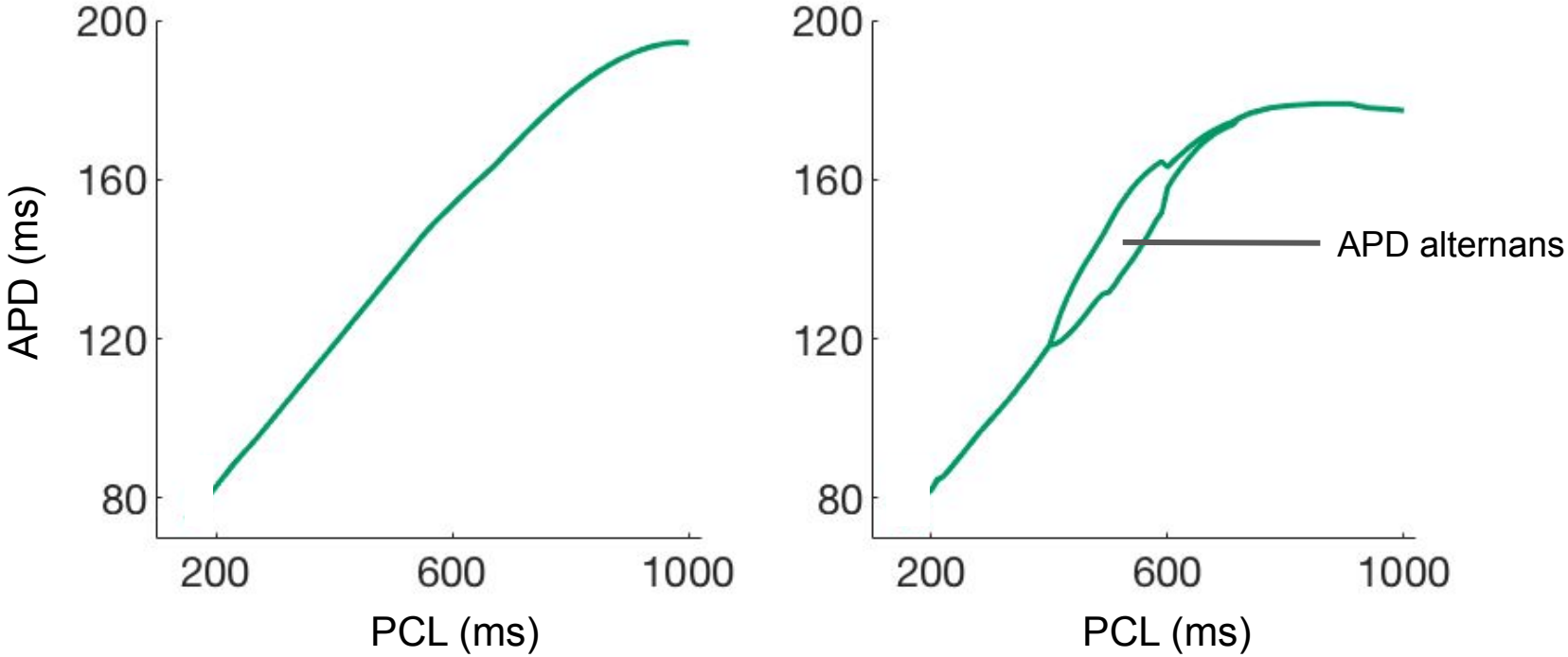
CaT: calcium transient → CaT alternans

Alternans precede AF



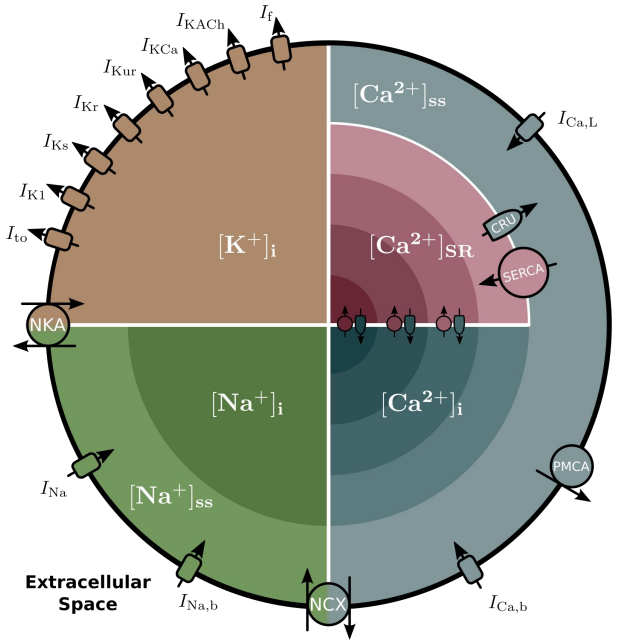
Narayan et al., Circulation, 2011

APD restitution can be used to characterize APD alternans



PCL: pacing cycle length

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

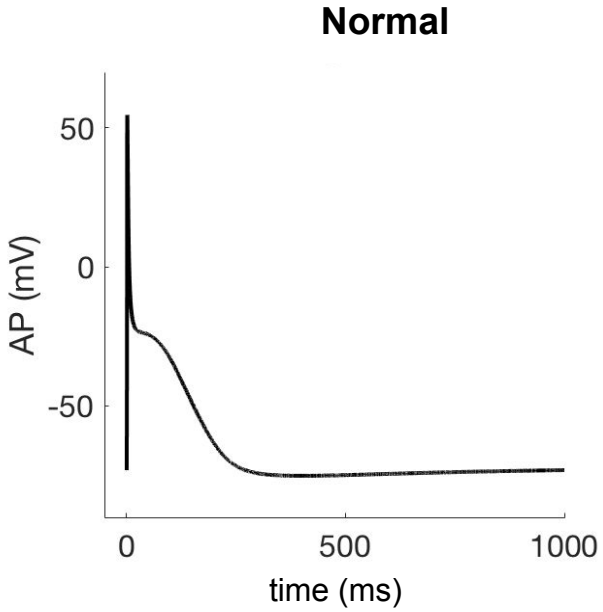


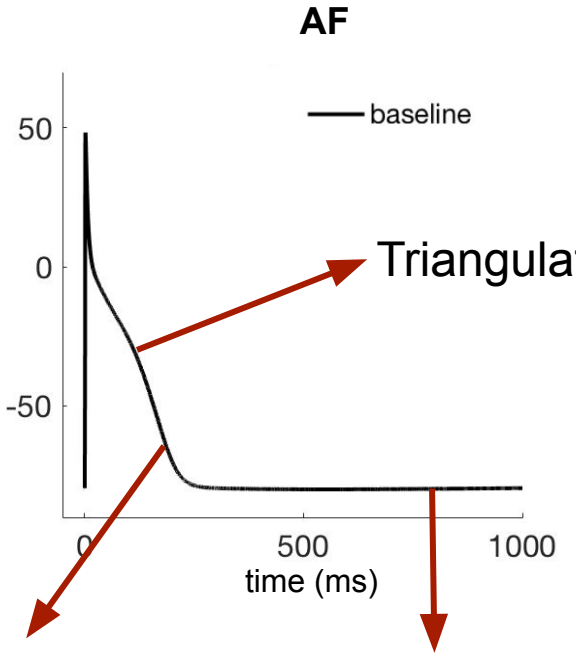
- Spatial model with detailed calcium handling system
- Human ionic currents

Goal:

To use Populations of models and Sensitivity analysis to find which parameters of the Koivumäki model are causing the observed APD alternans behavior.

Populations of Normal and AF cells

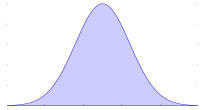


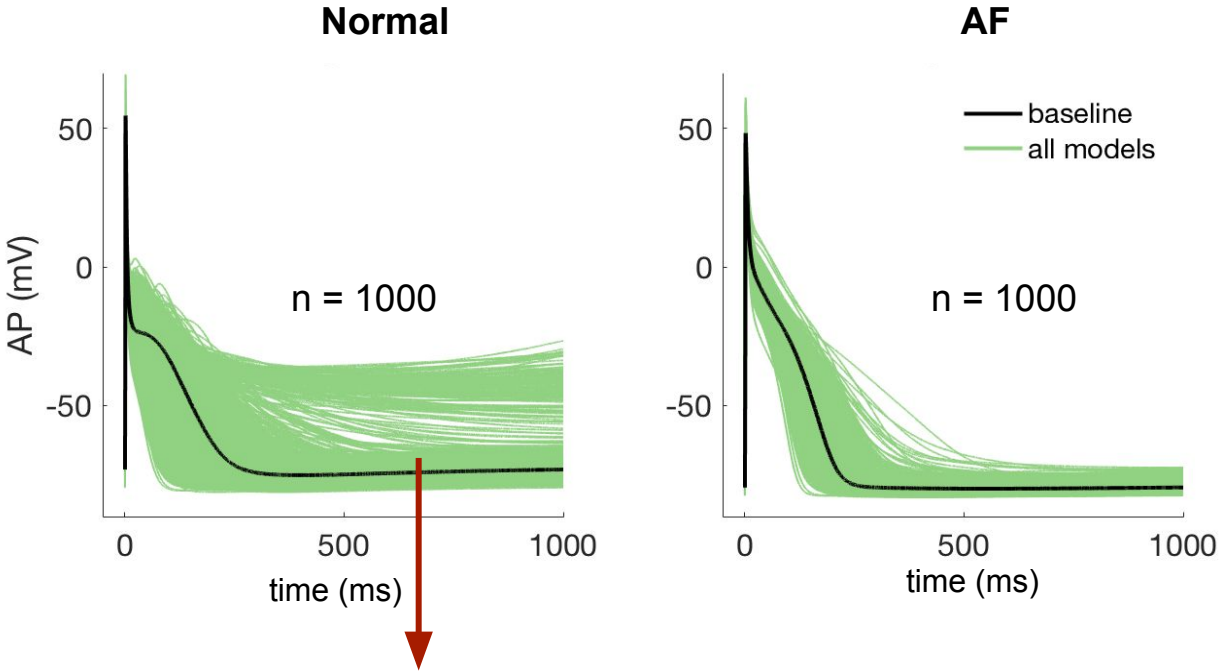


gCaL	45% ↓
gK1	68% ↑
gNa	82% ↓
gKs	145% ↑
gKur	62% ↓
gto	38% ↓
gKCa	50% ↓
RyR	100% ↑

Populations of Normal and AF cells

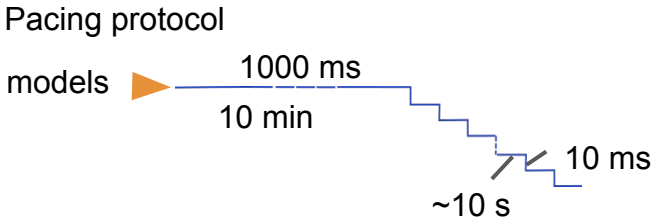
Distributions of *model parameters*



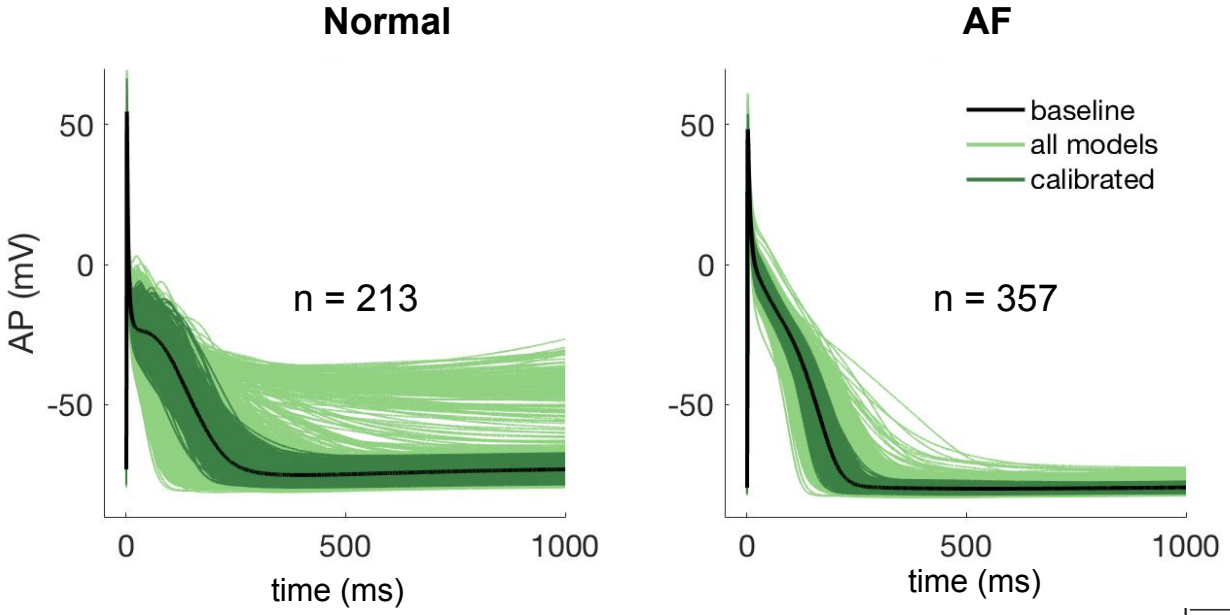


- Maximum conductance:
  ICaL, INa, IK1, ICab, IKr, IKs, IKur, Ito, INaL
- Maximum fluxes:
  INaK, INCX, ICaP
- Ryanodine receptors:
  Maximum conductance
  Time constants

Higher intra-population variability



Populations of Normal and AF cells

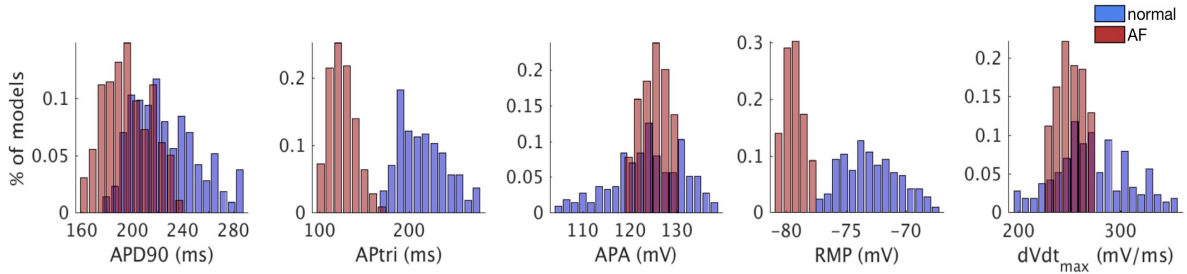


Functional Calibration

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

APD90
APA
RMP
Upstroke velocity

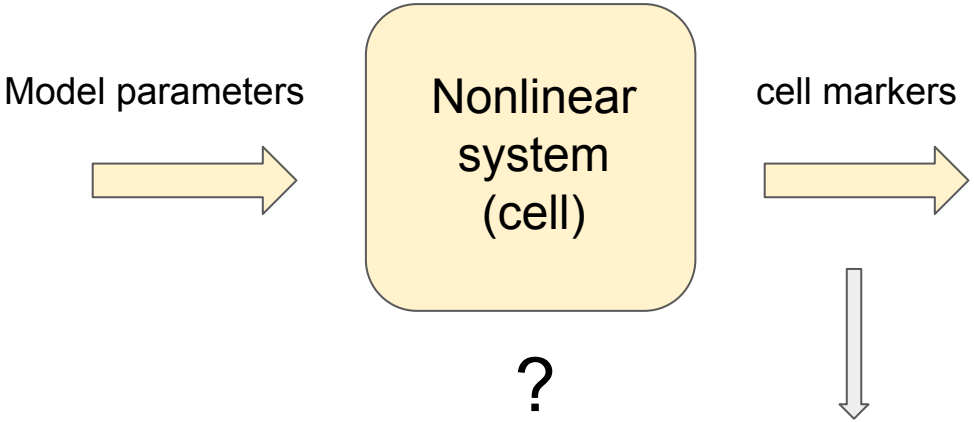
Maximum and minimum APD in restitution curves



	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)

Sensitivity analysis is useful for understanding the behaviour of a nonlinear system



How much do model parameters influence resulting EP properties?

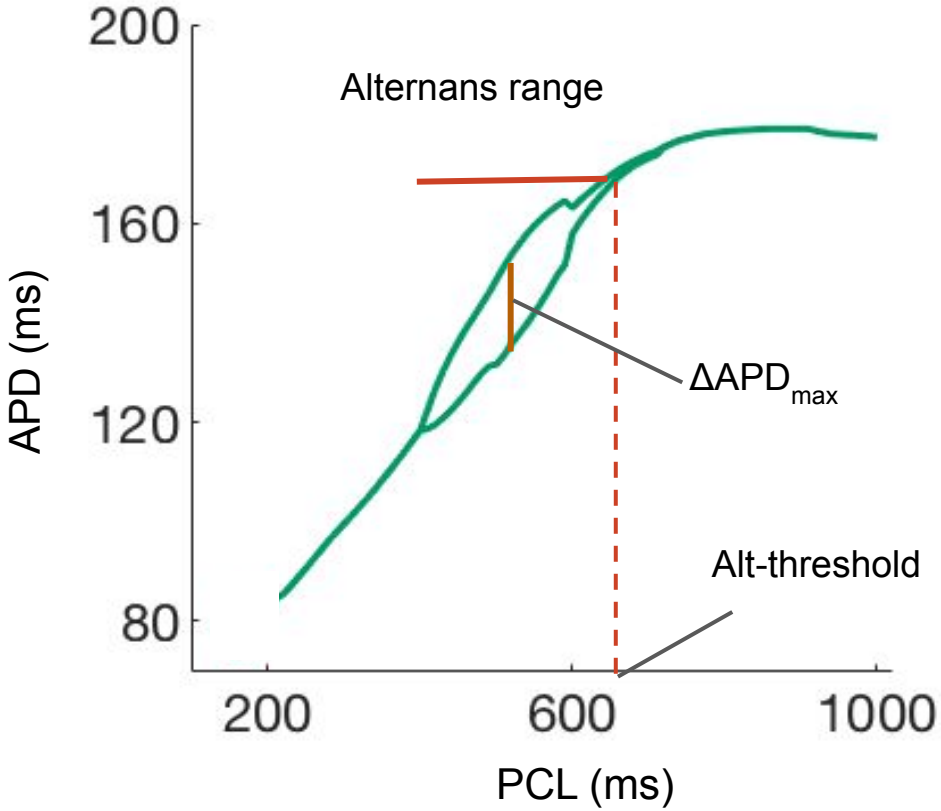
<u>AP</u>
APD90-50-20
AP amplitude
RMP
dVdt max

<u>CaT</u>
CaT amplitude
Diastolic $[Ca^{2+}]_i$
CaT time to peak
CaT time of decay

<u>APD restitution</u>
Alternans threshold
Alternans range
Alternans area
ΔAPD maximum

Input parameters		Regression coefficients		output markers
X	·	**B**	=	**Y**
(m x n)		(n x k)		(m x k)

We defined 4 different alternans markers



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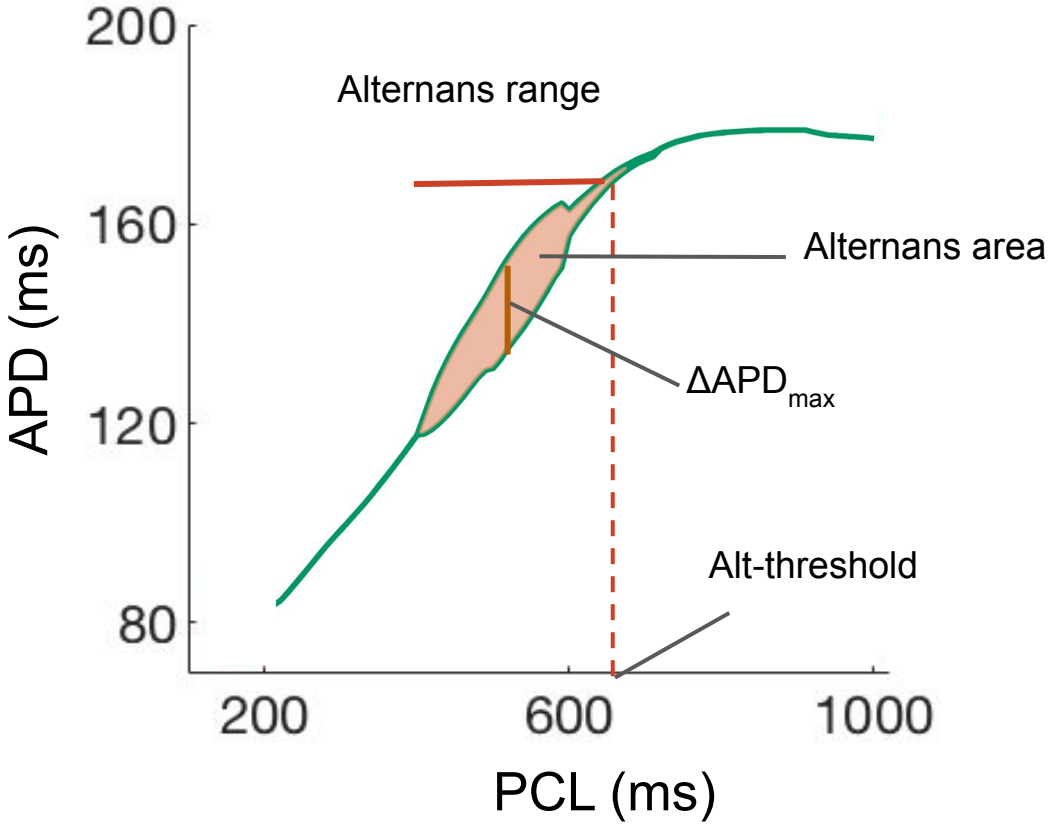
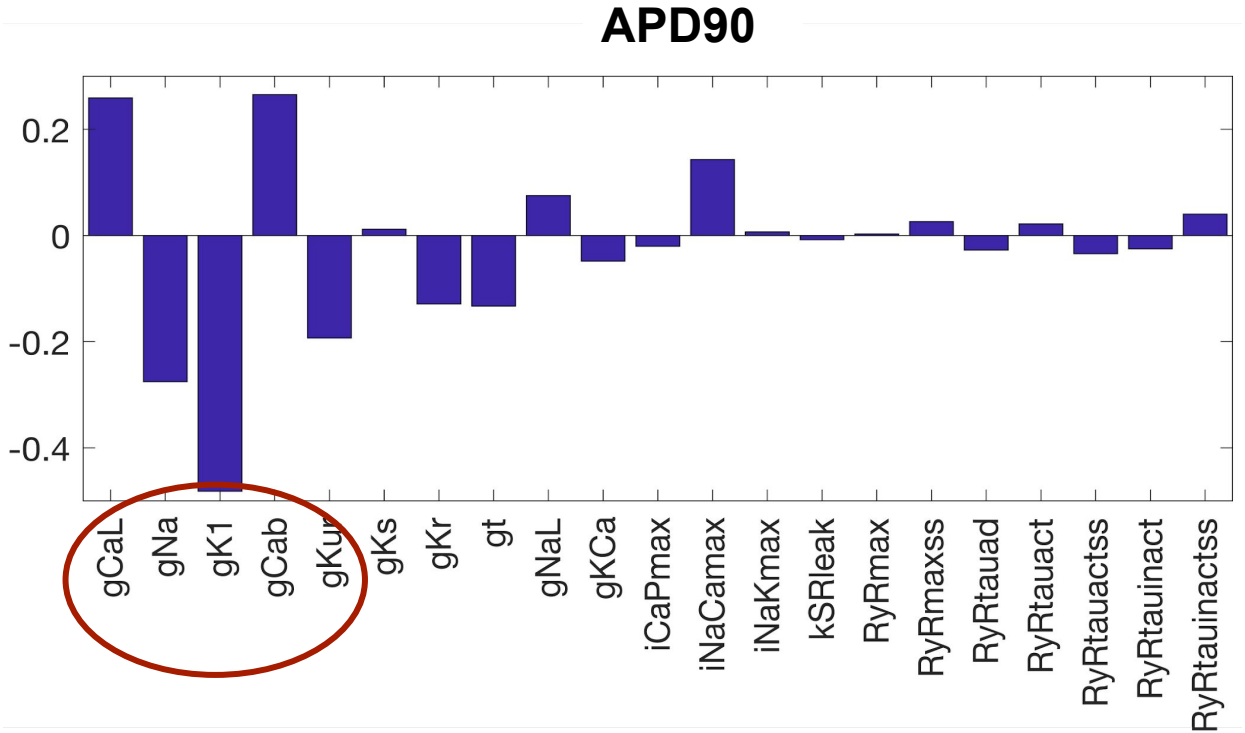


Results

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



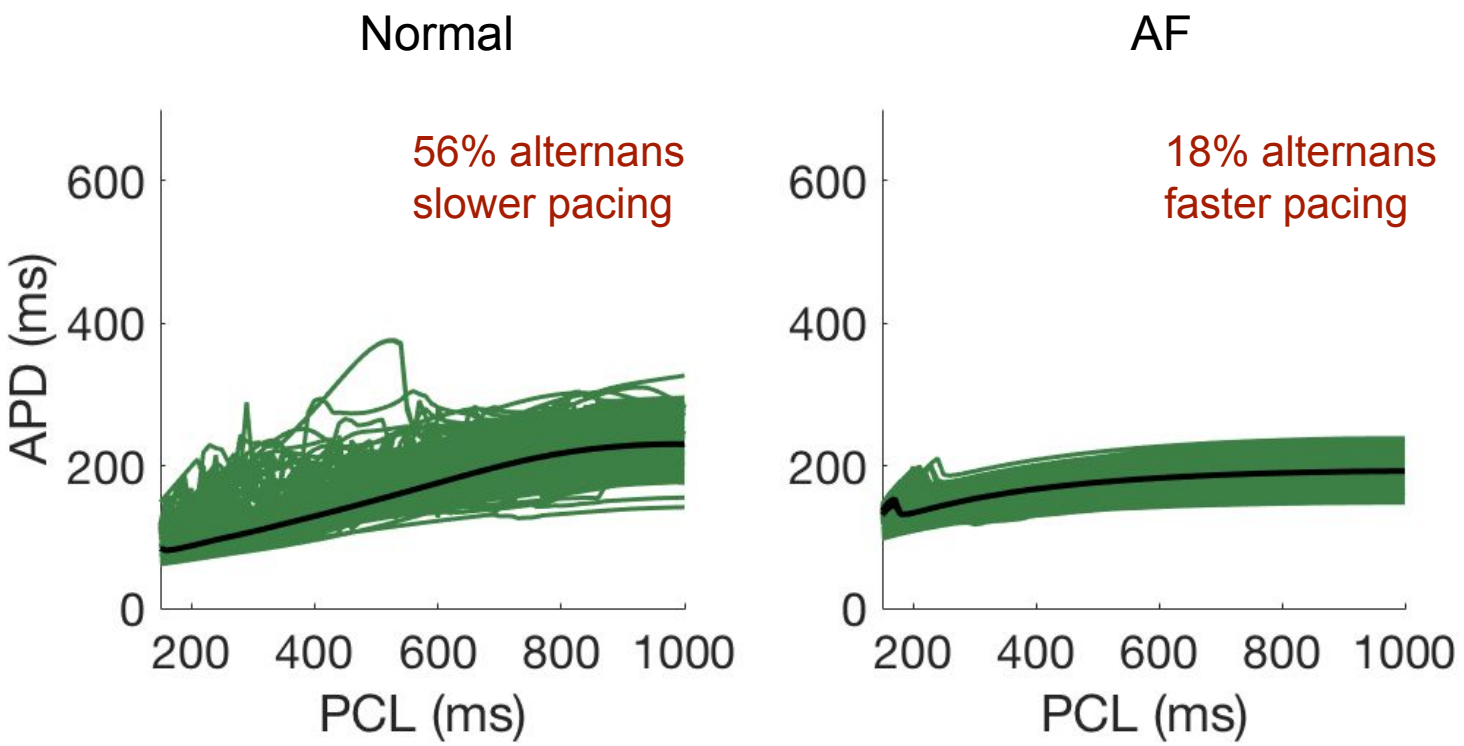
ICaL

IK1

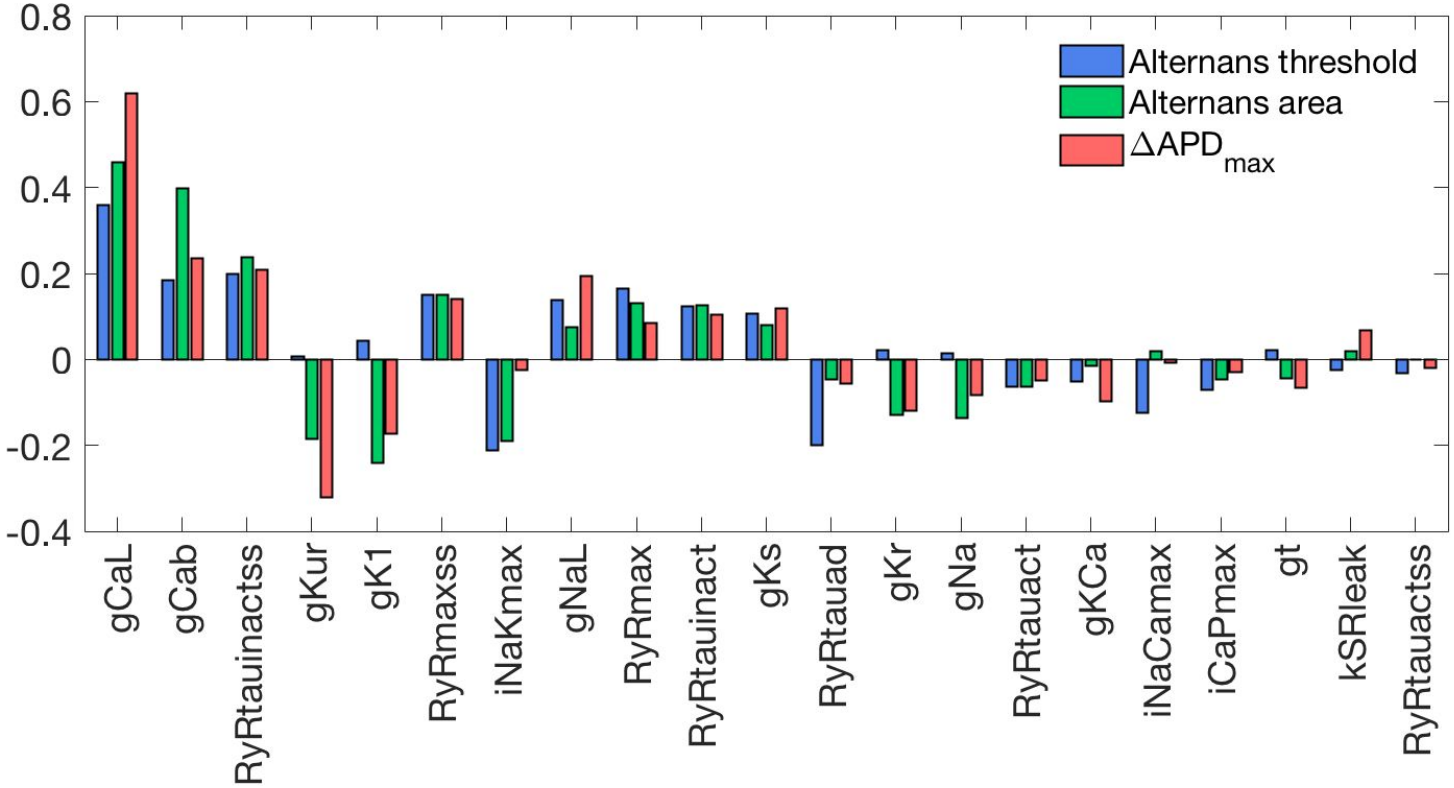
INa

IKur

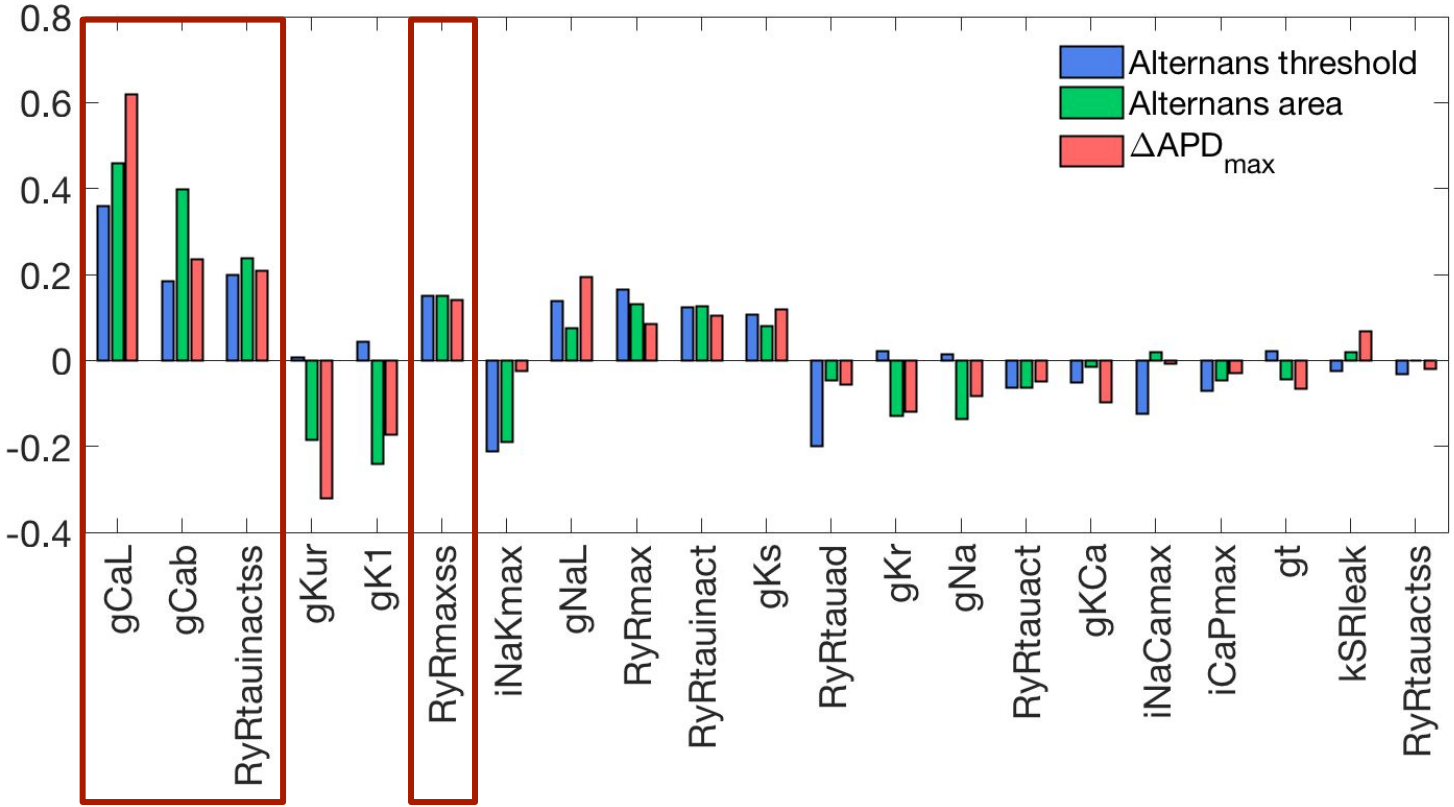
APD restitution of Normal cells revealed greater propensity to APD alternans compared to the AF cells



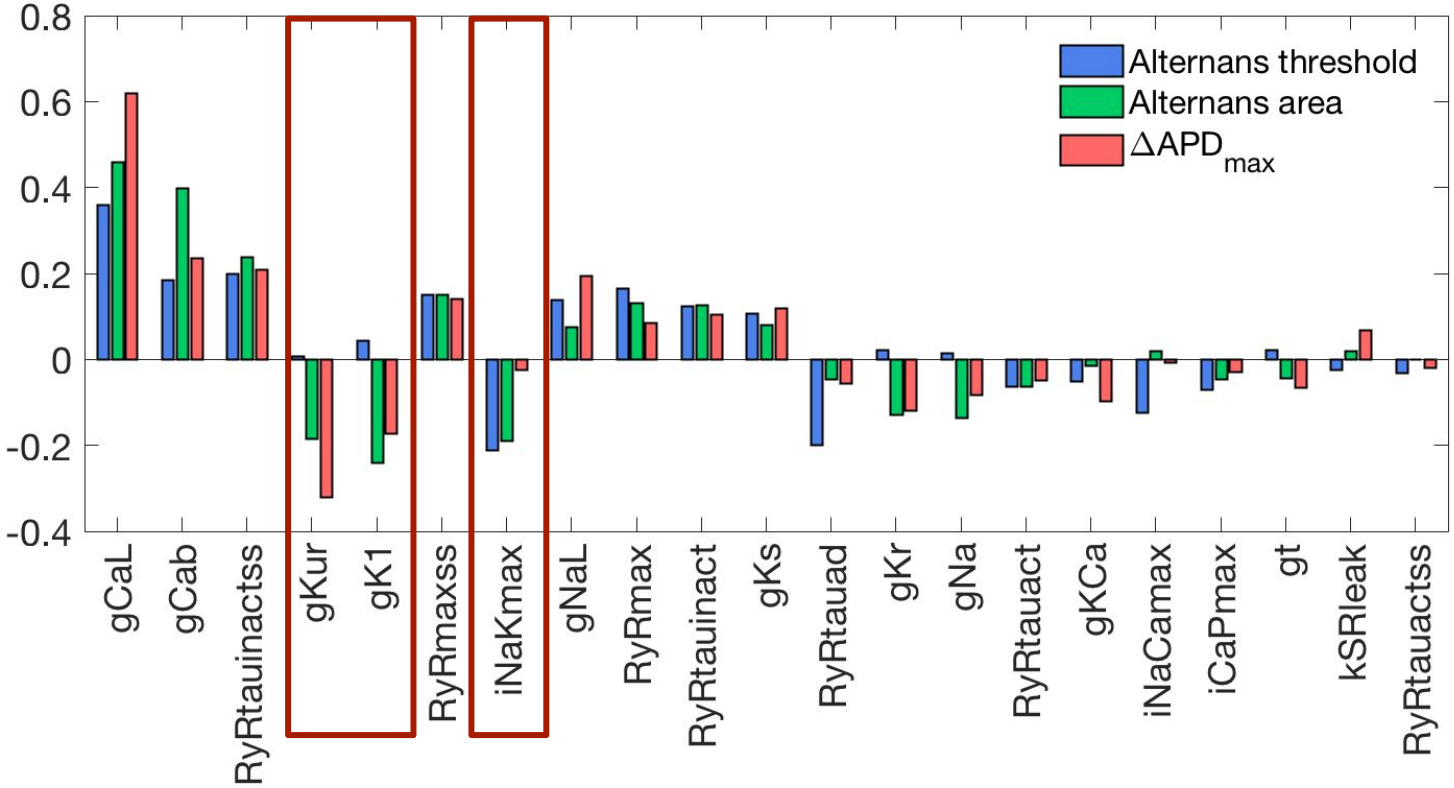
Alternans markers in Normal population



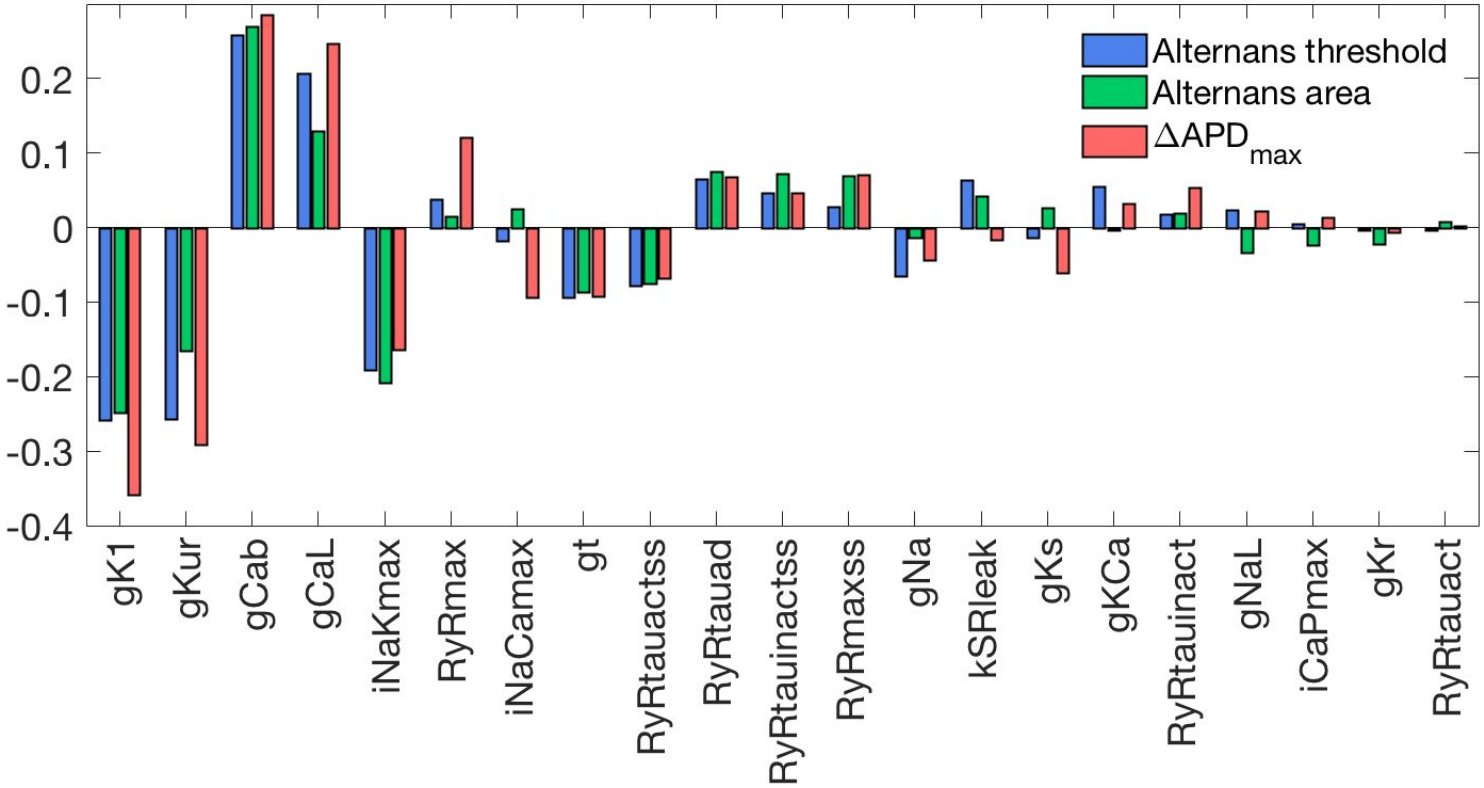
Alternans markers in Normal population showed known parameter dependencies



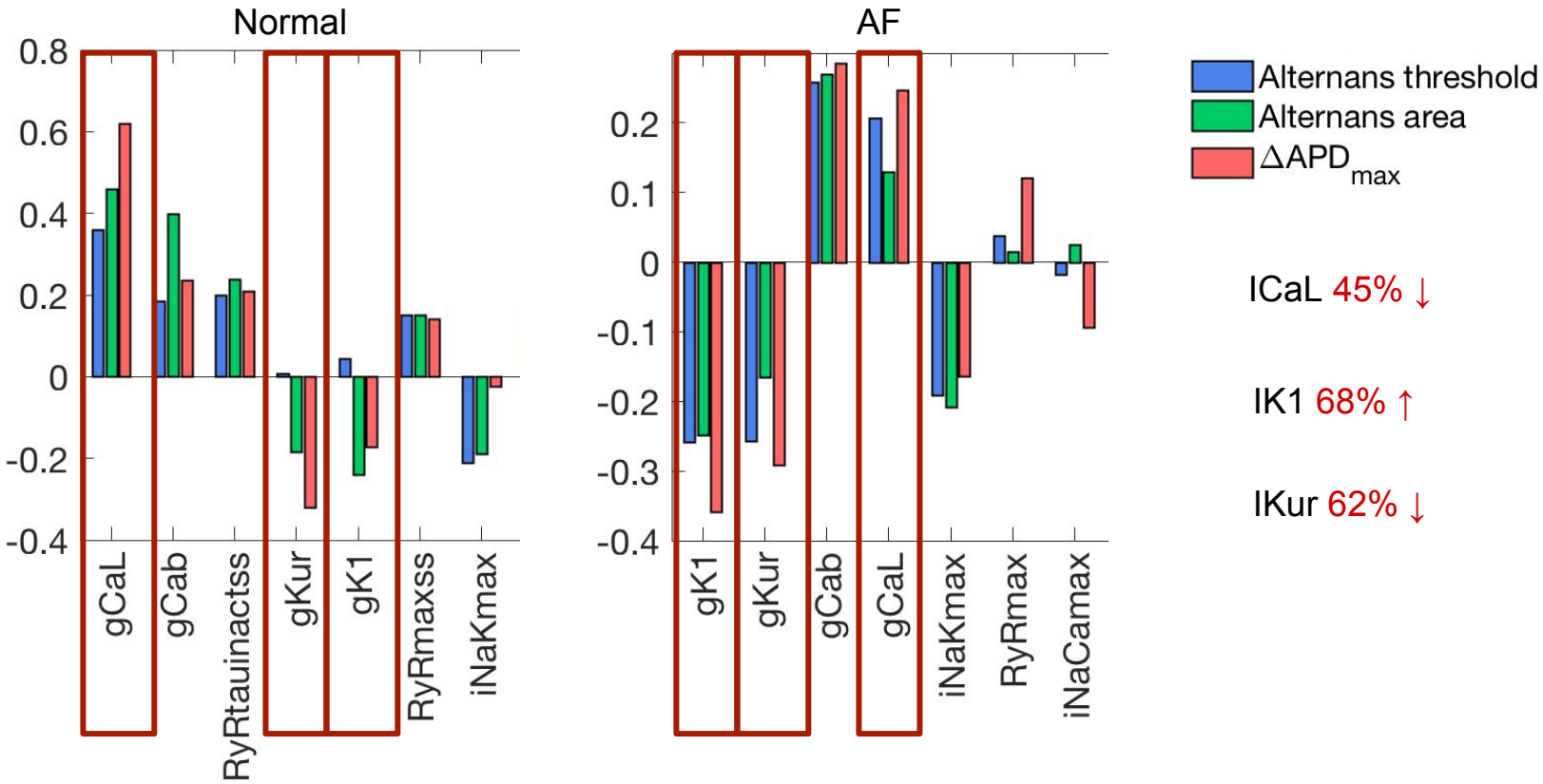
Alternans markers in Normal population provided new insights into role of IKur, IK1 and INaK



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



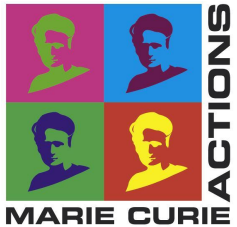
Normal and AF populations showed different sensitivities of alternans markers



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

Thank you



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UiO : University of Oslo

UNIVERSITY
OF EASTERN
FINLAND

Joakim Sundnes
Hermenegild Arevalo
Molly Maleckar
Bernardo de Oliveira

Jussi Koivumäki