Population modeling approach to study age-related effects on the excitation-contraction coupling in human cardiomyocytes

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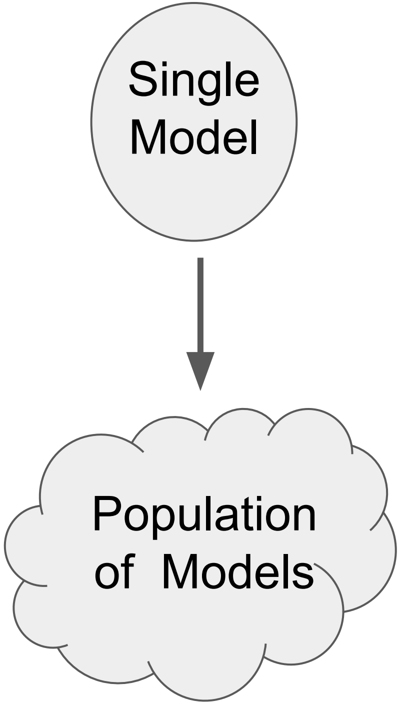
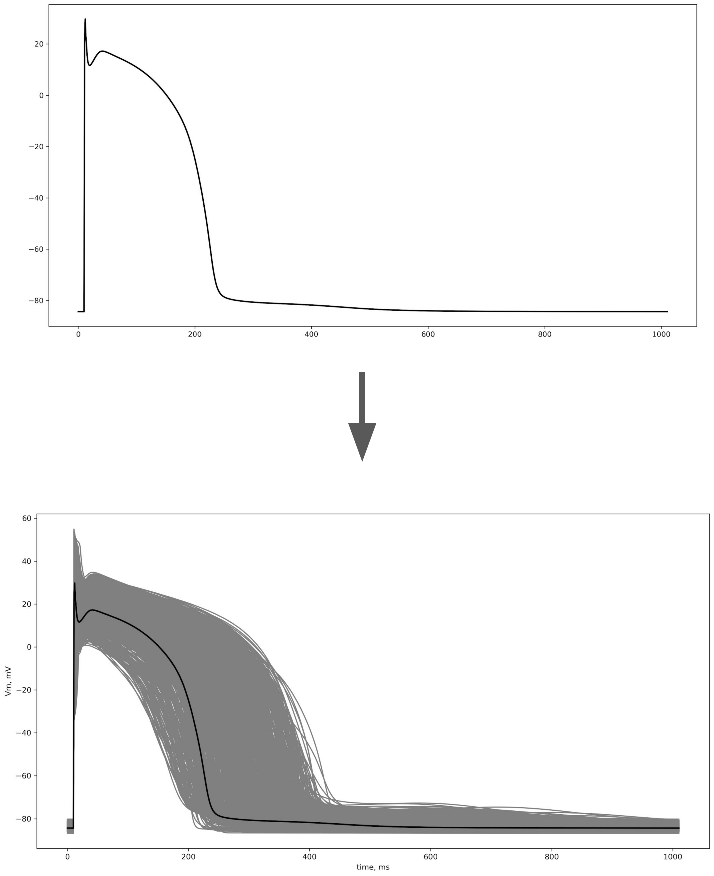
Motivation

Identify the dominant factors in the progress of heart disease during aging

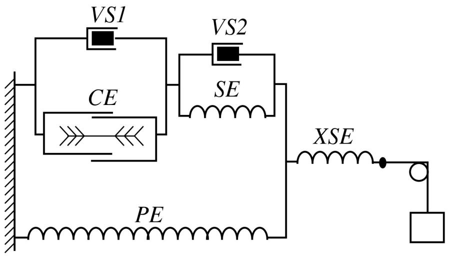
Population-based approach





TNNP+M electromechanical model of cardiomyocyte

Mechanical model [1]



$$F_{XSE} = F_{PE} + F_{CE} + k_{P\_vis} v$$

$$F_{XSE} = F_{PE} + F_{SE} + k_{S\_vis}(w - v)$$

$$F_{CE} \sim p(v) \cdot [Xb]$$

$$\frac{d[Xb]}{dt} = k_+(v) M(A) n_1(l_1) L_{oz}(1-[Xb]) - k_-[Xb]$$

Calcium kinetics [3]

[Xb] →

← [CaTnC]

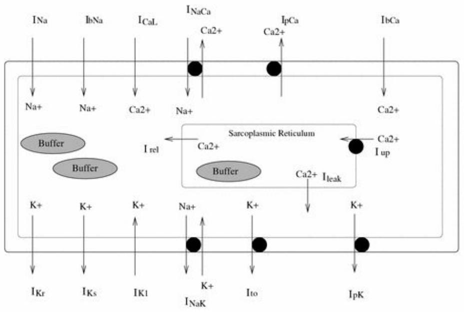
$$Ca^{2+} + TnC \underset{a_{off}}{\overset{a_{on}}{\rightleftharpoons}} CaTnC$$

[Ca^{2+}] →

← [i_{CaL}]

$$\frac{d[CaTnC]}{dt} = a_{on} \cdot ([TnC]_{tot} - [CaTnC]) \cdot [Ca^{2+}]_i - a_{off} \cdot ([CaTnC],[Xb]) \cdot [CaTnC]$$

Electrical model [2]



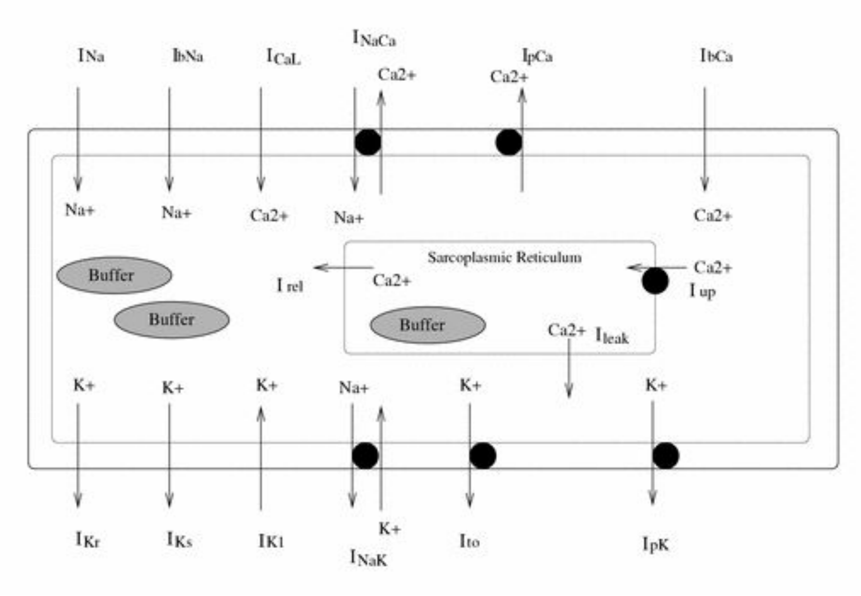
$$\frac{dV}{dt} = \frac{-I_{ion} + I_{stim}}{C_m}$$

$$I_{ion} = I_{Na} + I_{K1} + I_{to} + I_{Kr} + I_{Ks} + I_{CaL} + I_{NaCa} + I_{NaK} + I_{pCa} + I_{pK} + I_{bCa} + I_{bNa}$$

1. Katsnelson, L. B., Solovyova, O., Balakin, A., Lookin, O., Konovalov, P., Protsenko, Y., … Markhasin, V. S. (2011). Contribution of mechanical factors to arrhythmogenesis in calcium overloaded cardiomyocytes: Model predictions and experiments. Progress in Biophysics and Molecular Biology, 107(1), 81–89. https://doi.org/10.1016/j.pbiomolbio.2011.06.001
2. ten Tusscher, K. H. W. J. (2006). Alternans and spiral breakup in a human ventricular tissue model. AJP: Heart and Circulatory Physiology, 291(3), H1088–H1100. https://doi.org/10.1152/ajpheart.00109.2006
3. N. Balakina-Vikulova, O. Solovyova, A. Panfilov, L. Katsnelson. Mechano-Electric Feedbacks in a New Model of the Excitation-Contraction Coupling in Human Cardiomyocytes. Computing in Cardiology, V.45, 2018.

Model population generation

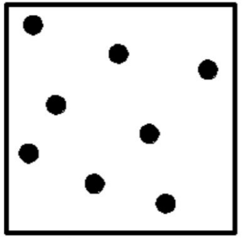
- 9 parameters in range of 0-200%:
  - gNa
  - gCaL
  - gK1
  - gto
  - gKr
  - gKs
  - SERCA
  - NaCaX
  - NaKX
- 20000 models, LHS sampling
- 200 isometric cycles for each model to reach steady-state + 1 isotonic cycle



Sampling methods

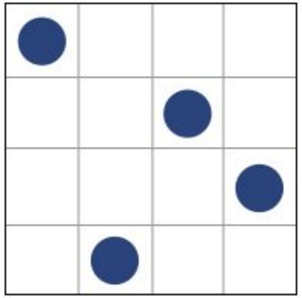
Monte Carlo sampling (MC)

- \+ simplicity
- \+ normal distribution (more "natural")
- \- low coverage rate 1/√(N)
- \- normal distribution (clustering)

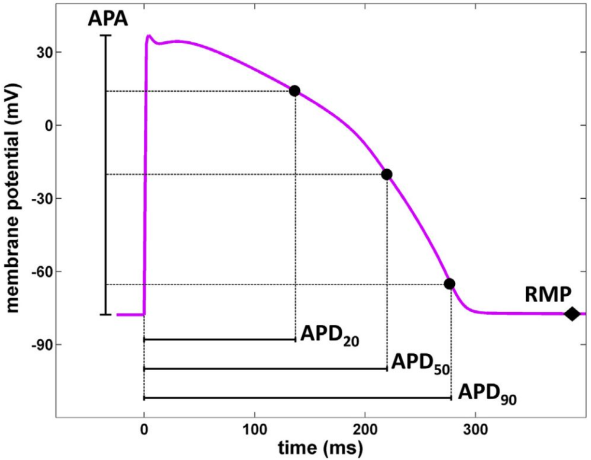


Latin Hypercube Sampling (LHS)

- \+ coverage rate ~ 1/N
- \+ cover full range of parameters
- \+ no clustering



Models filtering



$85\ \text{ms} \le \mathbf{APD_{40}} \le 320\ \text{ms}$

$110\ \text{ms} \le \mathbf{APD_{50}} \le 350\ \text{ms}$

$180\ \text{ms} \le \mathbf{APD_{90}} \le 440\ \text{ms}$

$10\ \text{mV} \le \mathbf{V_{peak}} \le 55\ \text{mV}$

$100\ \text{V/s} \le \mathbf{dV/dt_{max}} \le 1000\ \text{V/s}$

$50\ \text{ms} \le \mathbf{Tri_{90\text{-}40}} \le 150\ \text{ms}$

$-95\ \text{mV} \le \mathbf{RMP} \le -80\ \text{mV}$

$0.0005\ \text{mM} \le \mathbf{Ca_{i\_max}} \le 0.025\ \text{mM}$

$150 \le \mathbf{F_{max}}$

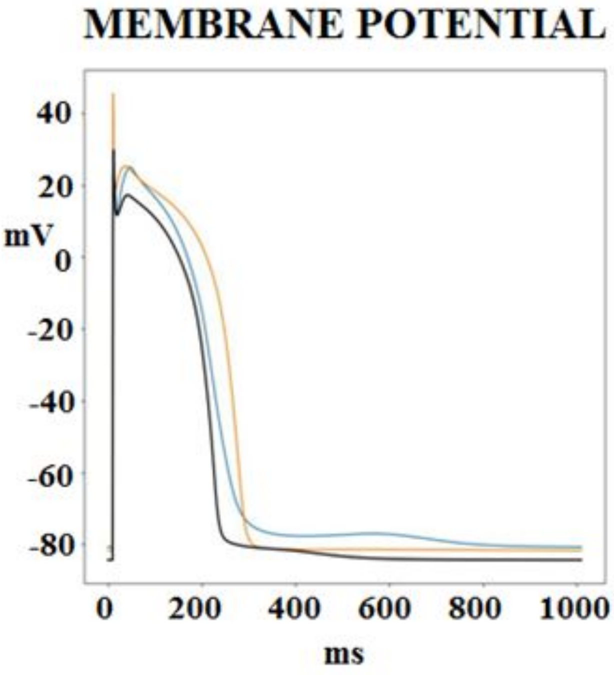
$\mathbf{F_{diastolic}} \le 10$

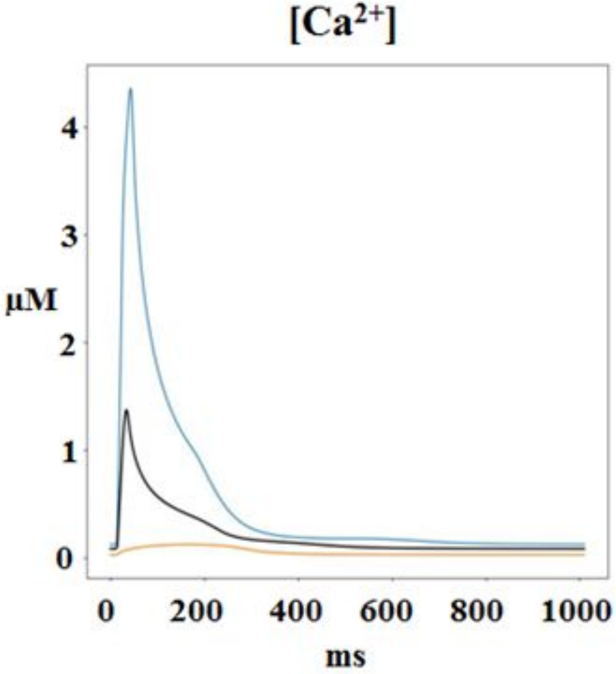
$10 \le \mathbf{F_{max}/F_{diastolic}} \le 50$

Britton, O. J., Bueno-Orovio, A., Virág, L., Varró, A., & Rodriguez, B. (2017). The electrogenic Na+/K+ pump is a key determinant of repolarization abnormality susceptibility in human ventricular cardiomyocytes: A population-based simulation study. Frontiers in Physiology, 8(MAY), 1–13. https://doi.org/10.3389/fphys.2017.00278

Population filtering

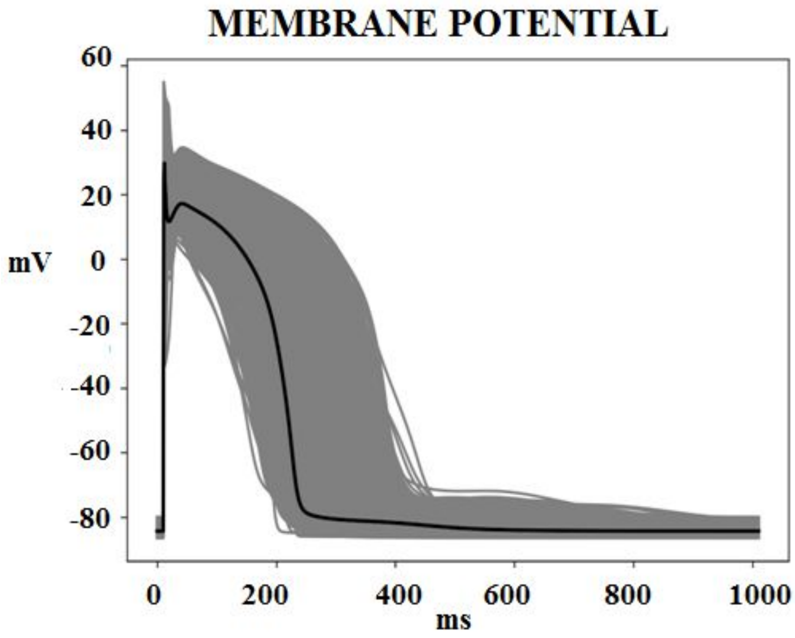
- AP filtering 4096 models

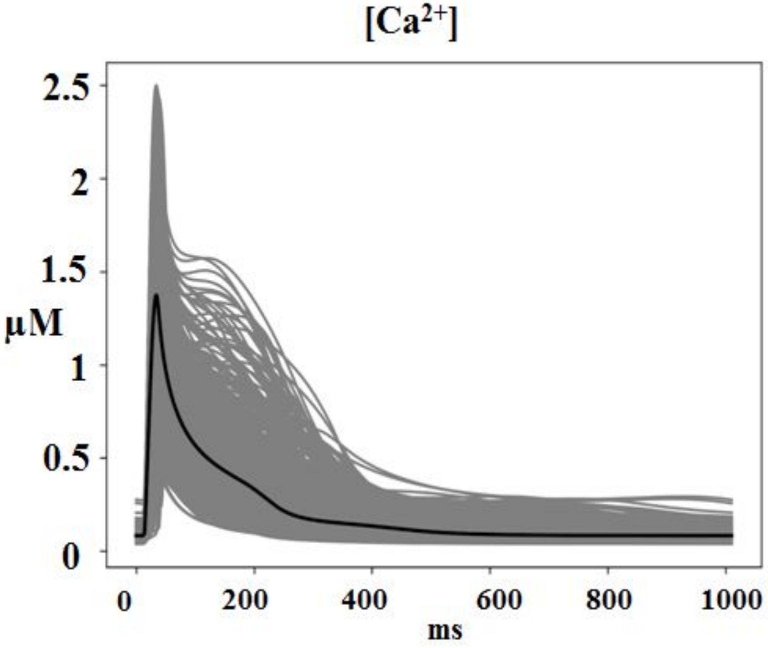




Population filtering

- AP+Ca filtering **1028 models**





Software

- Sampling

pyDOE
Design of Experiments for Python

A	B	C
0	0	1
1	0	0
0	1	0
1	1	1

Latin-Hypercube(pyDOE.lhs())

- Computation

sundials

SUNDIALS: SUite of Nonlinear and DIfferential/ALgebraic Equation Solvers

Numba

@jitclass()

- Postprocessing and data storage

HDF

pandas
$y_{it} = \beta' x_{it} + \mu_i + \epsilon_{it}$

SciPy

scikit learn

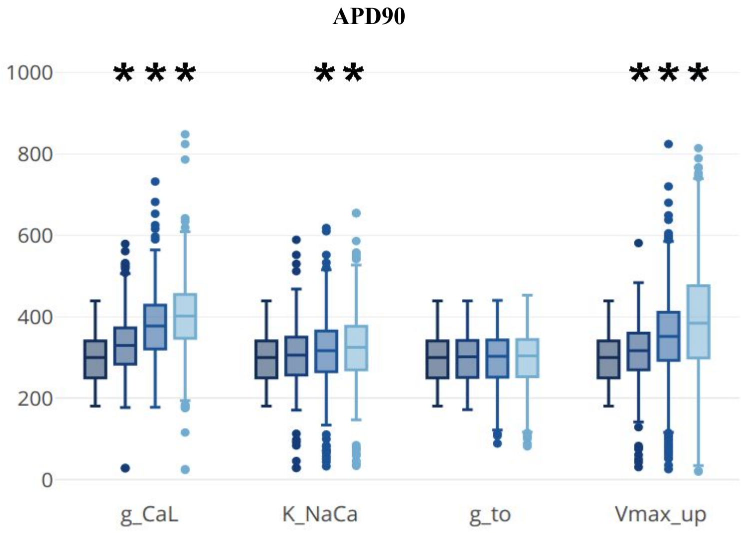
plotly

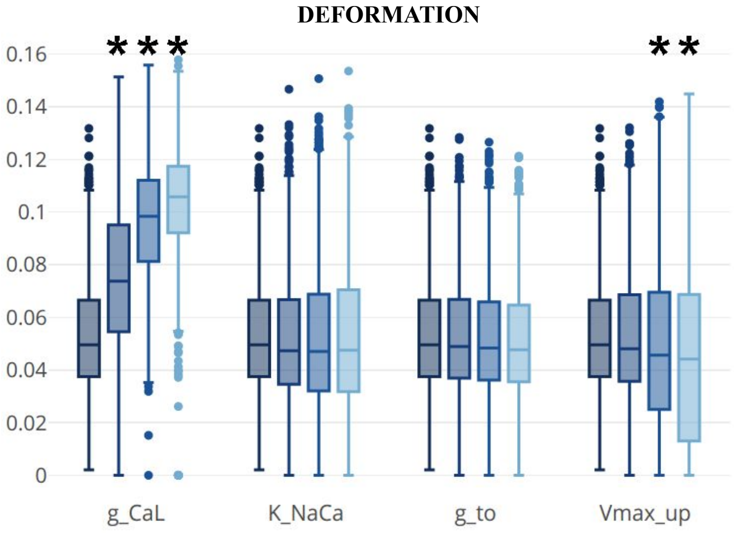
Studying the effects of aging

- **I_{to}** ↓ [1]
- **V_{max} SERCA** ↓ [2]
- **I_{CaL}** ↑ [3]
- **I_{NaCa}** ↑ [4]

1. Bassani R.A., (2006) Braz J Med Biol Res 39(3): 393-403
2. Taffet, G.E., et al., (1993) Am J Physiol Heart Circ Physiol; 264(5): p. H1609-H1614.
3. Isenberg, G., et al., (2003) Cell Calcium. 34(3): p. 271-280.
4. Wong, K., et al., (1998) Cardiovasc. Res. 37, 115–122.

The sensitivity for parameter modulation



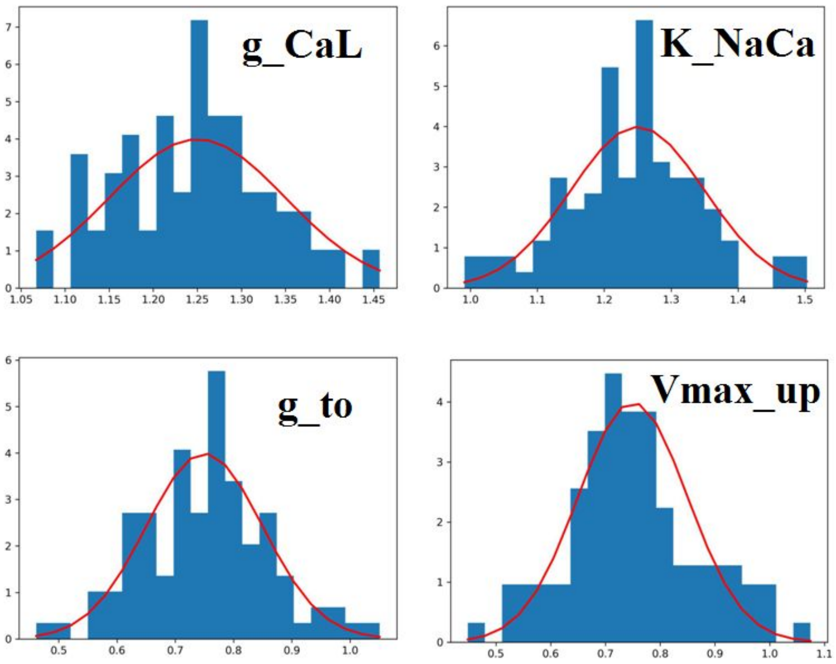


0% 20% 50% 70%

$\mathbf{I_{CaL}}\uparrow$ $\mathbf{I_{NaCa}}\uparrow$ $\mathbf{I_{to}}\downarrow$ $\mathbf{V_{max}}$SERCA$\downarrow$

Building an Aged Population

- 60 age-related sets
- normal distributions for parameter deviation
  - SD 0.1
  - Mean:
    - **1.25** for g_CaL and K_NaCa
    - **0.85** for g_to and V_max SERCA

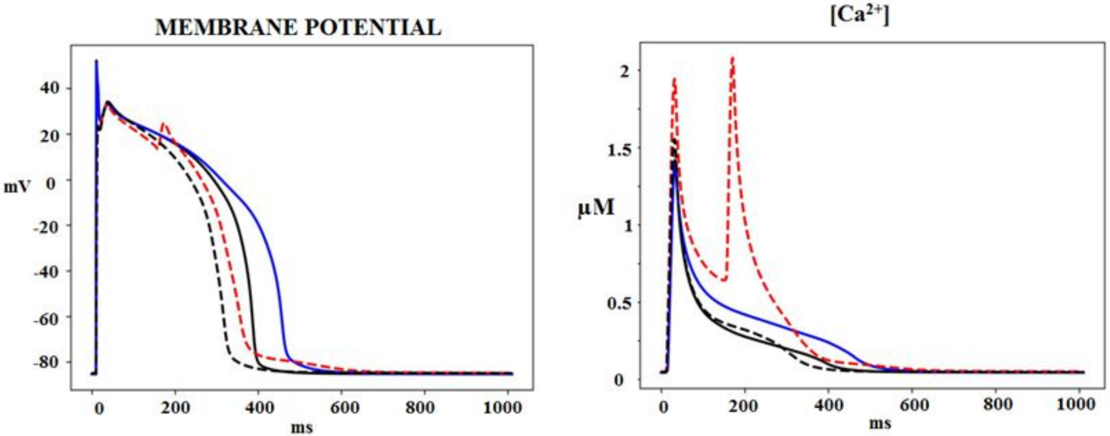


Arrhythmogenicity in aging

For each aged population:

- Detect the EAD cases
- Identify models with a prolonged AP >10%
- Calculate the score

$$W = \frac{N_{EAD}}{N_{total}}$$



Linear model

$$score = w_0 + w_1 g_{CaL} + w_2 P_{NaCa} + w_3 g_{to} + w_4 V_{max_{up}}$$

coefficient	value
w_0	-0.92
w_1	0.71
w_2	0.07
w_3	0.03
w_4	-0.25

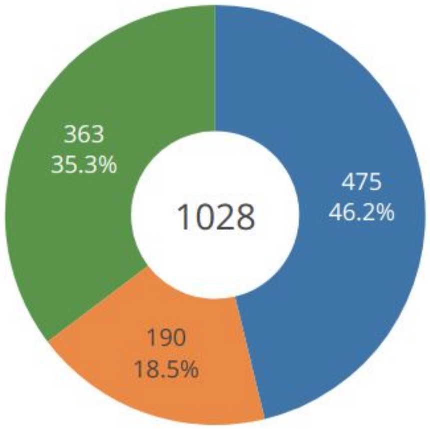
Determination coefficient = 0.986

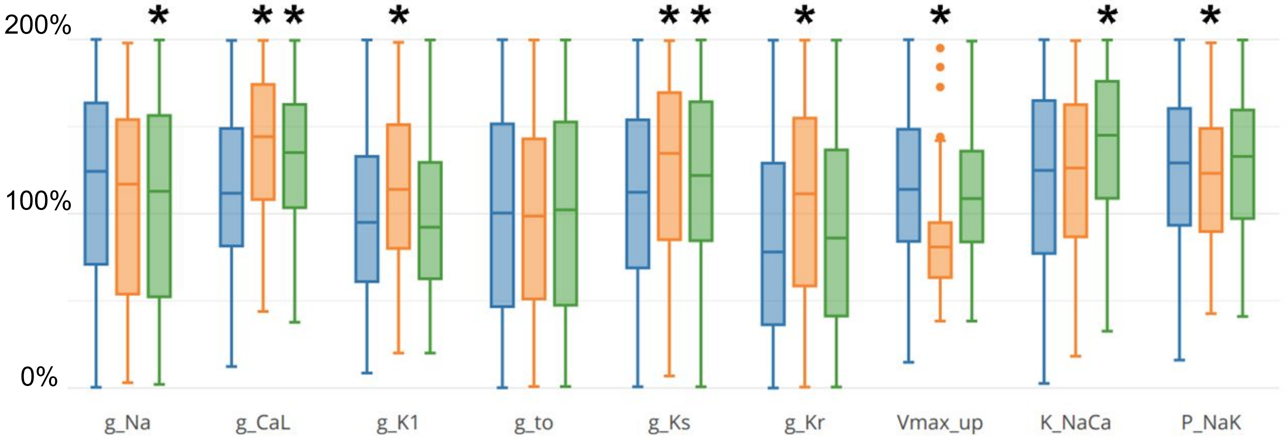
Model parameters distribution

blue: subpopulation without changes in AP

orange: subpopulation vulnerable to EAD after aging

green: subpopulation vulnerable to AP prolongation after aging





Conclusion

- Age-related changes in the cellular ionic currents may lead to an arrhythmogenic increase in APD and the emergence of EAD in human cardiomyocytes.
- The population based analysis allows one to classify age-related effects on different ECC mechanisms.
- An increase in the I_CaL current and a decrease in the SERCA flow is shown to be the significant factors of age-related cellular remodeling.
- An upregulation of I_CaL, IKs, IKr and downregulation of SERCA uptake increase risks of arrhythmias

Acknowledgements

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