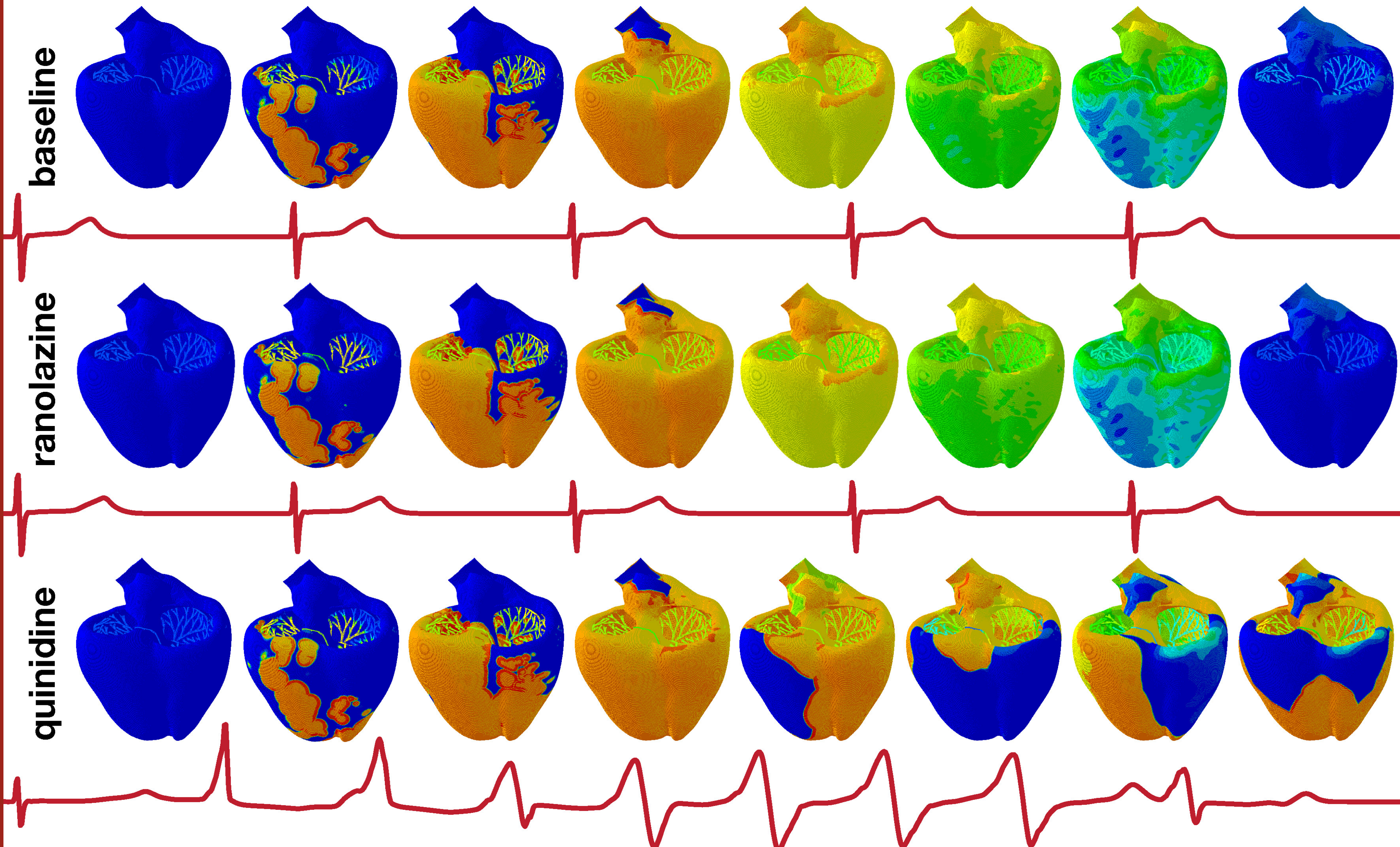


machine learning in drug development

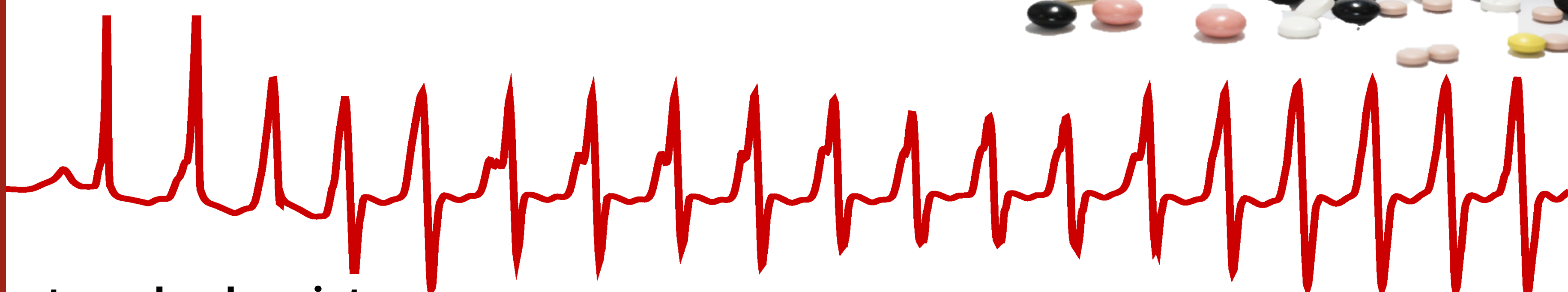
FRANCISCO SAHLI COSTABAL • JIANG YAO • KINYA SEO • PARIS PERDIKARIS • ANNA SHER • EUAN ASHLEY • ELLEN KUHL

multiscale modeling consortium meeting • march 6-7, 2019

advania
UberCloud
Pfizer
hp
DASSAULT SYSTEMES

drug development

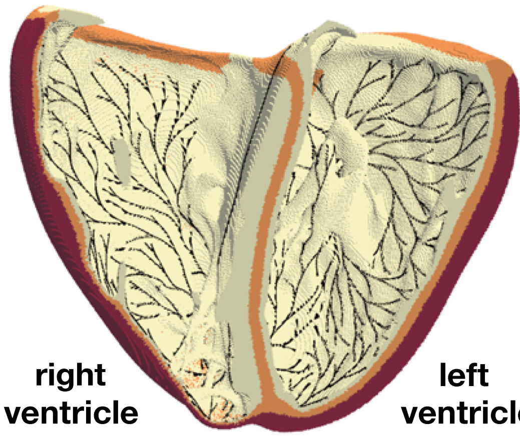
- numerous drugs have **serious side effects on the heart**
- gold standard safety test **action potential** and **QT interval** lengths
- criteria are **non-specific** / useful drugs are **falsely screened out**
- new drug - average cost **$2.5 billion** /average time **> 10 years**
- CiPA initiative by FDA – **new paradigm for drug safety evaluation**



torsades de pointes

colatsky et al. [2016], crumb et al. [2016], gintant et al. [2016], johannesen et al. [2014], mirams et al. [2011], sager et al. [2014], stockbridge et al. [2013], wang et al. [2017], vincente et al. [2016,2018]

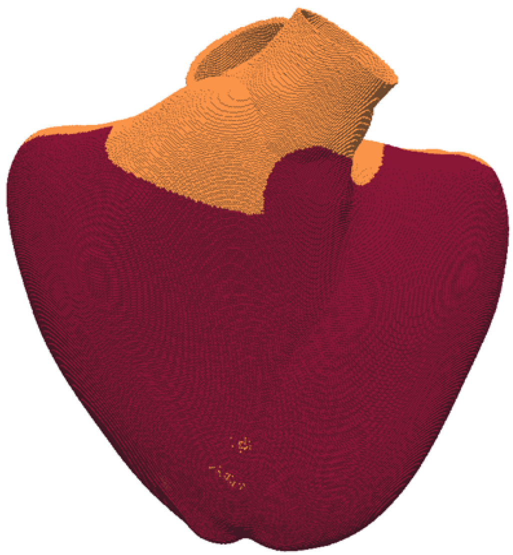
organ model - the living heart



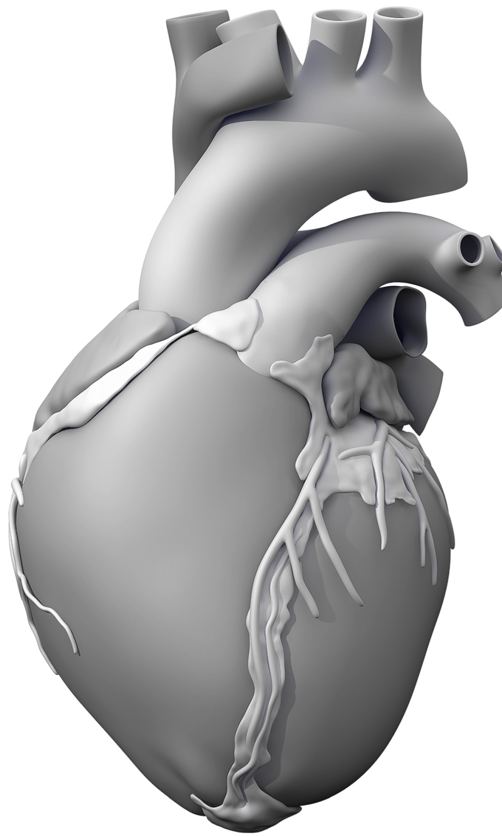
right ventricle

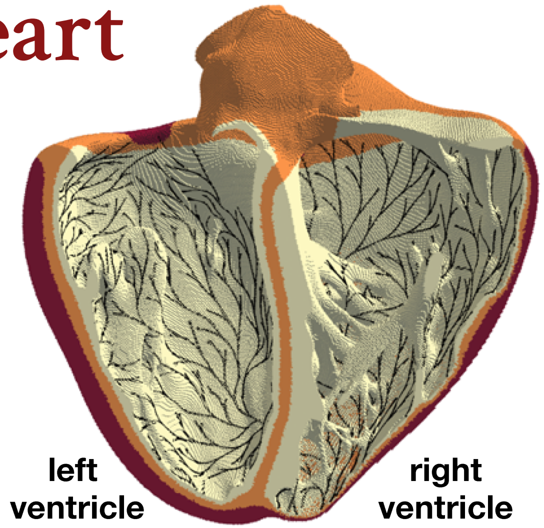
left ventricle

anterior view



endocardium
mid wall
epicardium
purkinje cells

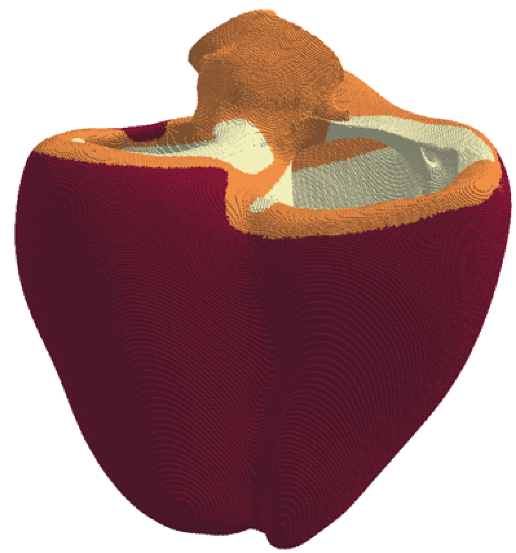




left ventricle

right ventricle

posterior view

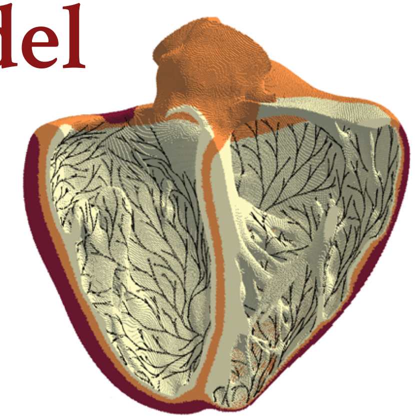


spatial discretization: 0.3mm, 7M linear hexahedral elements, 8M nodes, 250M internal variables; temporal discretization: 0.005ms, 1M steps, 5 beats.

sahli costabal, hurtado, kuhl [2016], https://github.com/fsahli/fractal-tree

GitHub

tissue model - monodomain model



- monodomain model - **action potential**

$$\dot{\phi} = \mathrm{div}(\boldsymbol{D} \cdot \nabla \phi) + f^{\phi}$$

- flux term - second order **conductivity tensor**

$$\boldsymbol{D} = D_{\mathrm{iso}} \, \boldsymbol{I} + D_{\mathrm{ani}} \, \boldsymbol{f} \otimes \boldsymbol{f}$$

- source term - **ionic currents**

$$f^{\phi} = -I_{\mathrm{ion}} / C_{\mathrm{m}} \qquad \text{with} \qquad I_{\mathrm{ion}} = I_{\mathrm{ion}}(\phi, \boldsymbol{q}(\phi); t)$$

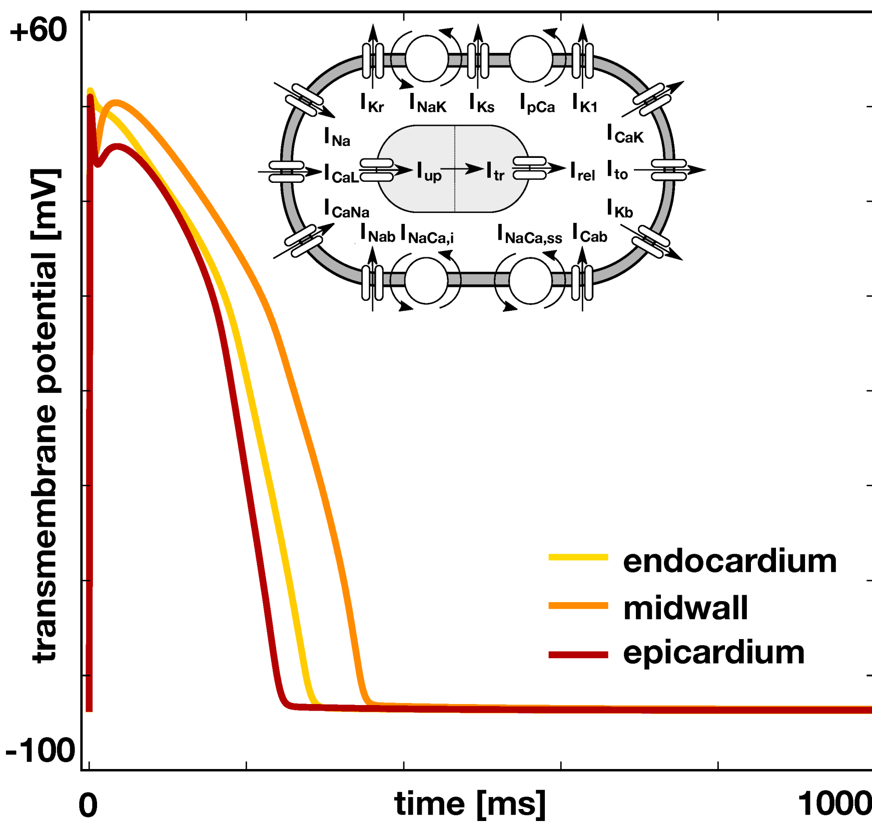
- ordinary differential equations for **state variables**

$$\dot{\boldsymbol{q}} = \boldsymbol{g}(\phi, \boldsymbol{q}(\phi); t)$$

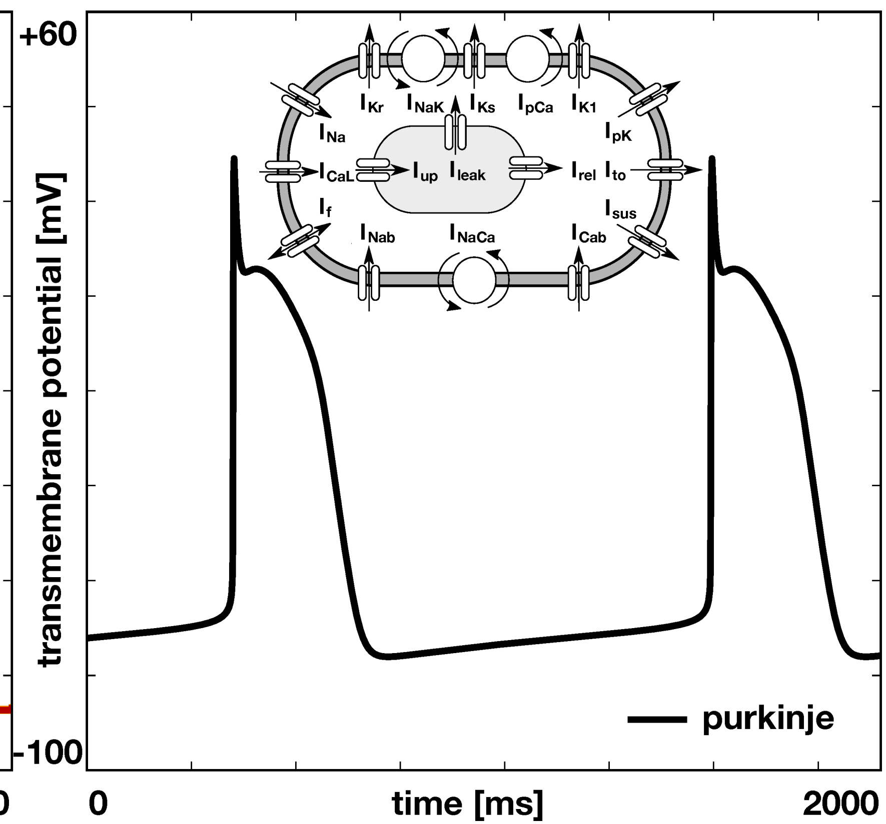
- ventricular cells - **o'hara rudy model** - 15 currents / 39 state variables
- purkinje cells - **stewart model** - 14 currents / 20 state variables

cell model - ventricular and purkinje cells

ventricular cells



purkinje cells

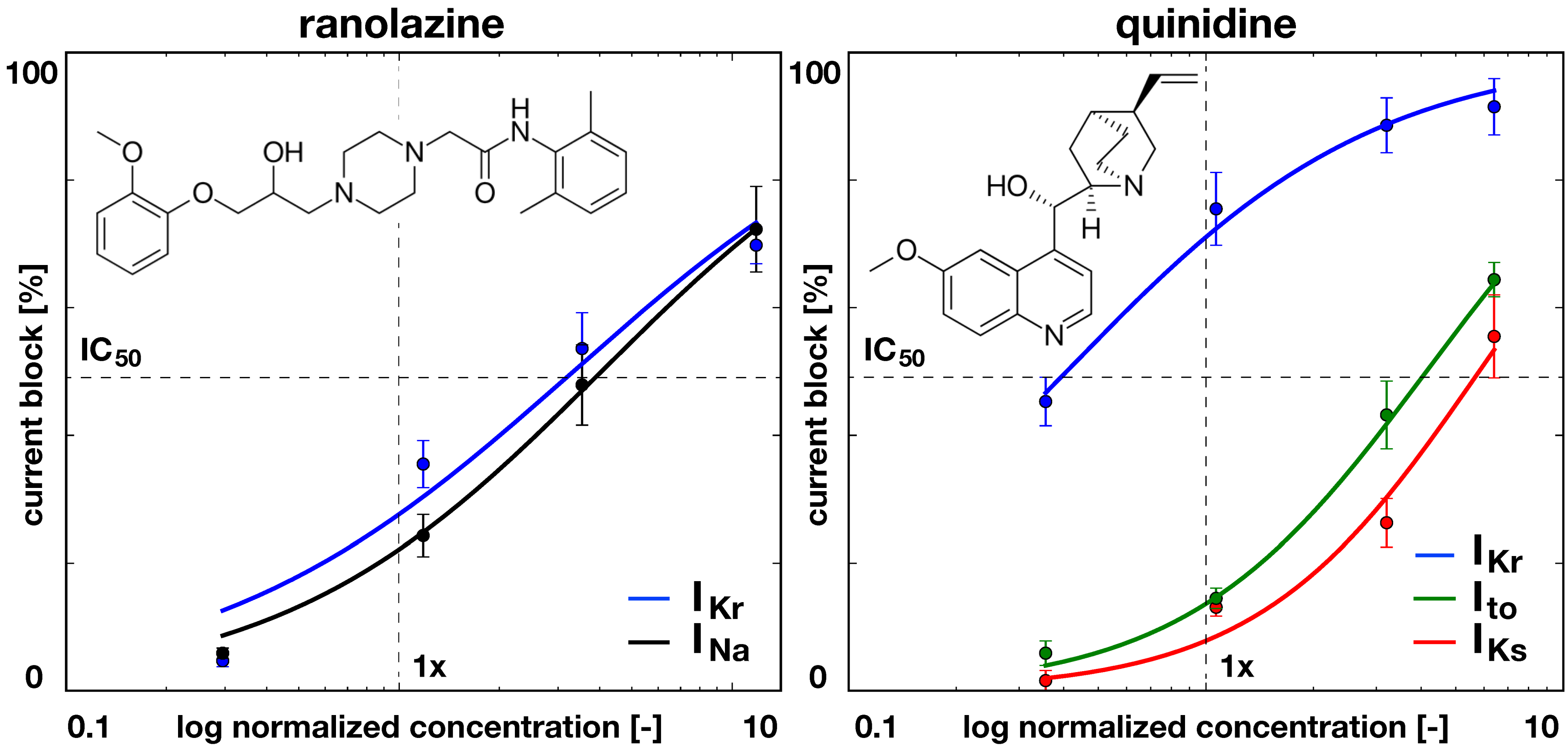


$$
\begin{aligned}
I_{\mathrm{ion}} = {} & I_{\mathrm{CaL}} + I_{\mathrm{Na}} + I_{\mathrm{Cab}} + I_{\mathrm{Nab}} \\
& + I_{\mathrm{Kr}} + I_{\mathrm{Ks}} + I_{\mathrm{K1}} + I_{\mathrm{to}} \\
& + I_{\mathrm{f}} + I_{\mathrm{sus}} \\
& + I_{\mathrm{NaK}} + I_{\mathrm{pCa}} + I_{\mathrm{pK}} + I_{\mathrm{NaCa}}
\end{aligned}
$$

$$
\begin{aligned}
I_{\mathrm{ion}} = {} & I_{\mathrm{CaL}} + I_{\mathrm{Na}} + I_{\mathrm{CaNa}} + I_{\mathrm{CaK}} \\
& + I_{\mathrm{Cab}} + I_{\mathrm{Nab}} + I_{\mathrm{Kb}} \\
& + I_{\mathrm{Kr}} + I_{\mathrm{Ks}} + I_{\mathrm{K1}} + I_{\mathrm{to}} \\
& + I_{\mathrm{NaK}} + I_{\mathrm{pCa}} + I_{\mathrm{NaCa,\,i}} + I_{\mathrm{NaCa,\,ss}}
\end{aligned}
$$

o'hara, virag, varro, rudy [2011], stewart, aslanidi, noble, noble, boyett, zhang [2009]

drug model - ranolazine and quinidine



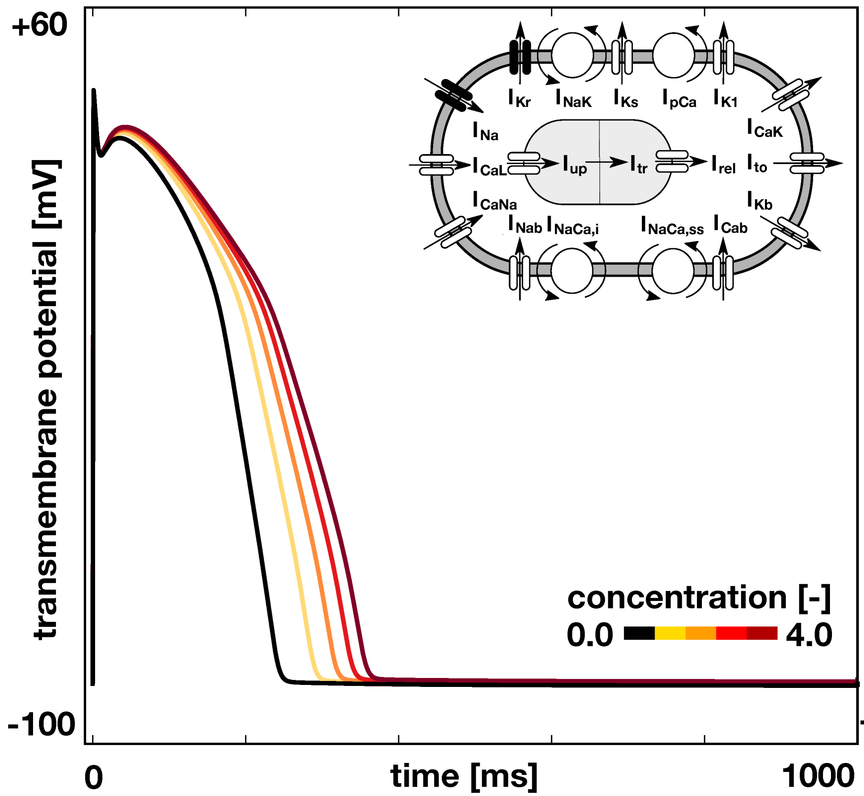
- calculate **ionic current**
- two-parameter **Hill-type model**
- calculate drug-specific block

$$I_{\text{ion}} = I_{\text{ion}}(\phi, \boldsymbol{q}(\phi); t)$$
$$\beta = C^h / [IC_{50}^h + C^h]$$
$$I_{\text{drug}} = [\, 1 - \beta \,]\, I_{\text{ion}}$$

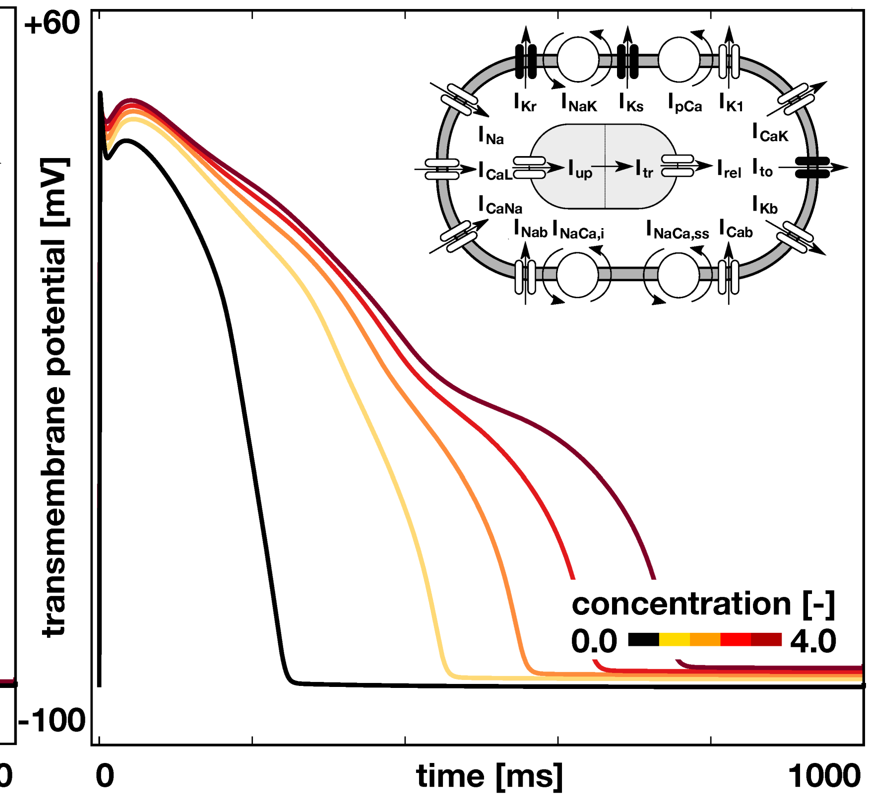
mirams, cui, sher, fink, cooper, heath, mc mahon, gavaghan, noble [2011], colatsky, fermini, gintant, pierson, sager, sekino, strauss, stockbridge[2016], crumb, vicente, johannesen, strauss[2016]

drug model - effects on the cell level

ranolazine



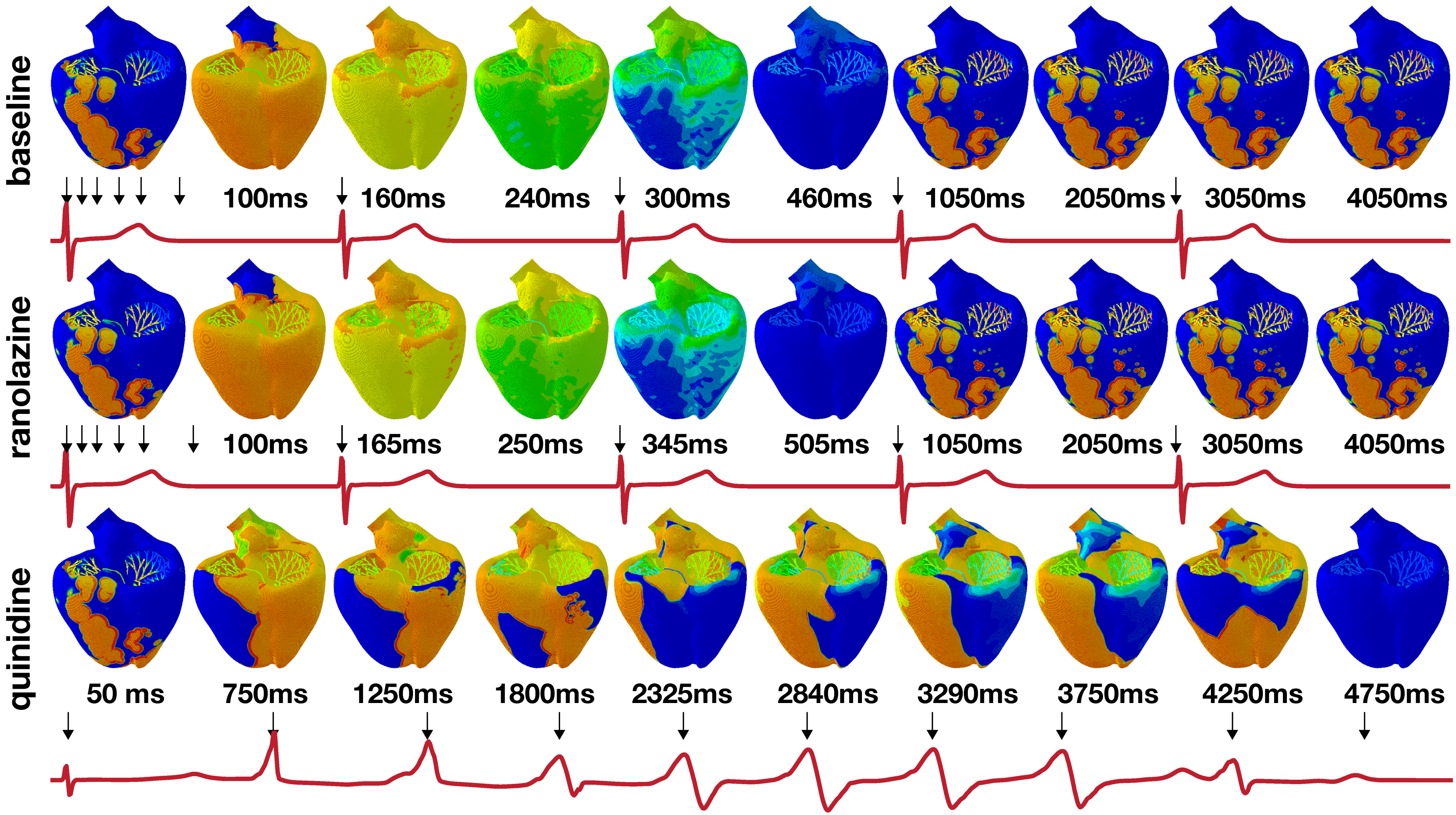
quinidine



- **ranolazine** chronic angina drug
- blocks $\mathbf{I_{Kr}}$ and $\mathbf{I_{Na}}$
- **mildly prolongs** APD and QT
- **low** torsades de pointes **risk**

- **quinidine** antiarrhythmic agent
- blocks $\mathbf{I_{Kr}}$ and $\mathbf{I_{Ks}}$ and $\mathbf{I_{to}}$
- **severely prolongs** APD and QT
- **high** torsades de pointes **risk**

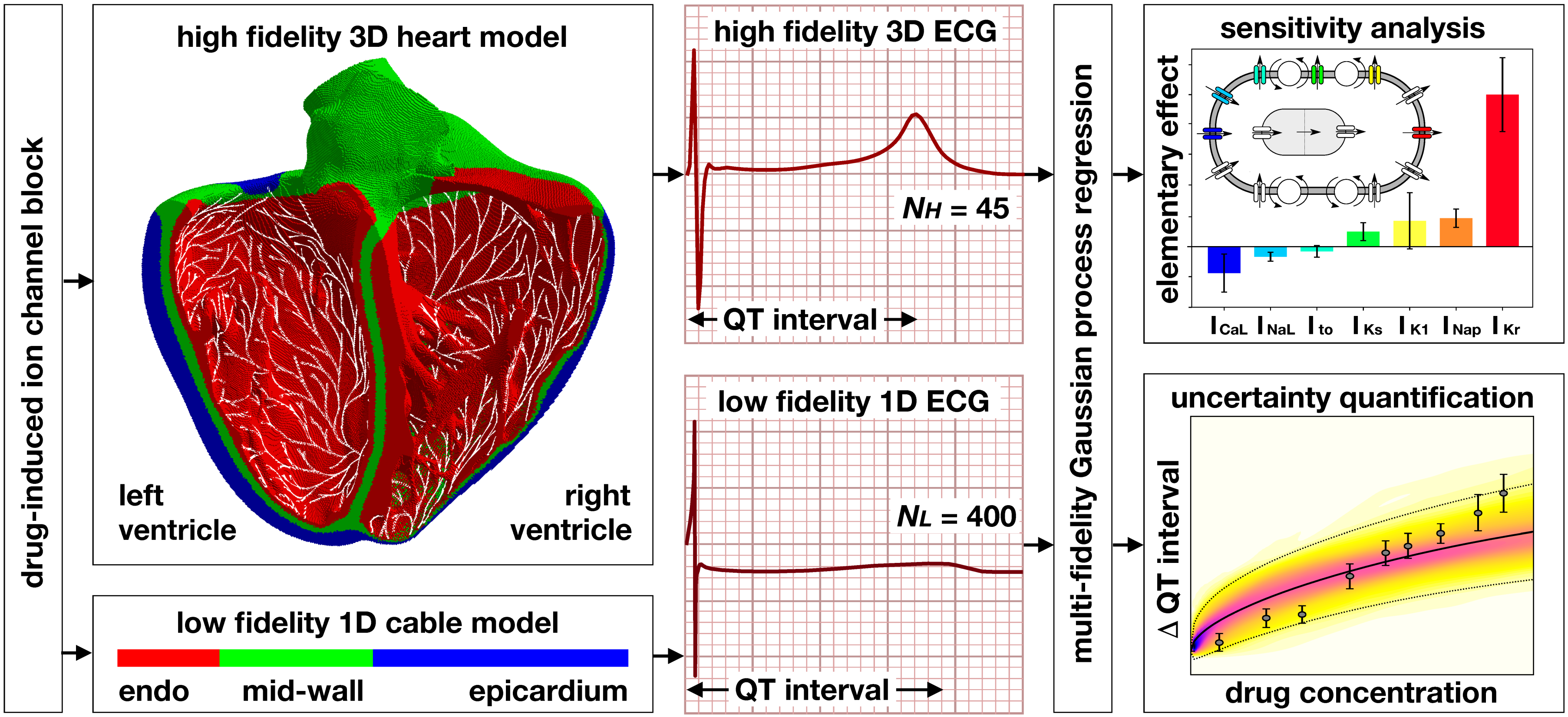
drug model - effects on the organ level



sahli costabal, yao, kuhl [2018]

Stanford University

using machine learning in drug development

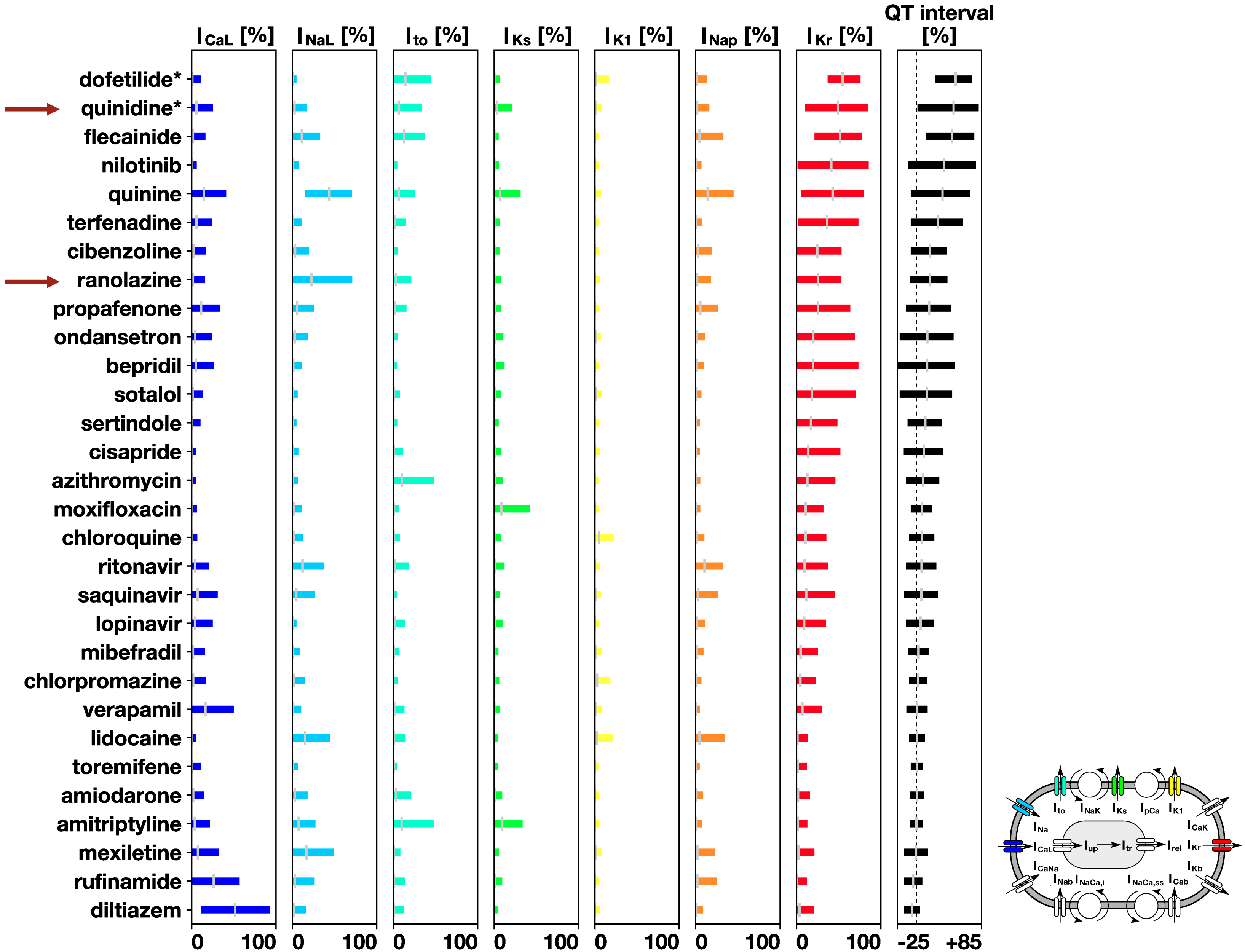


characterizing effect of 30 drugs on the QT interval using gaussian process regression, surrogate model for sensitivity analysis and uncertainty quantification

sahli costabal, matsuno, yao, perdikaris, kuhl [2019]

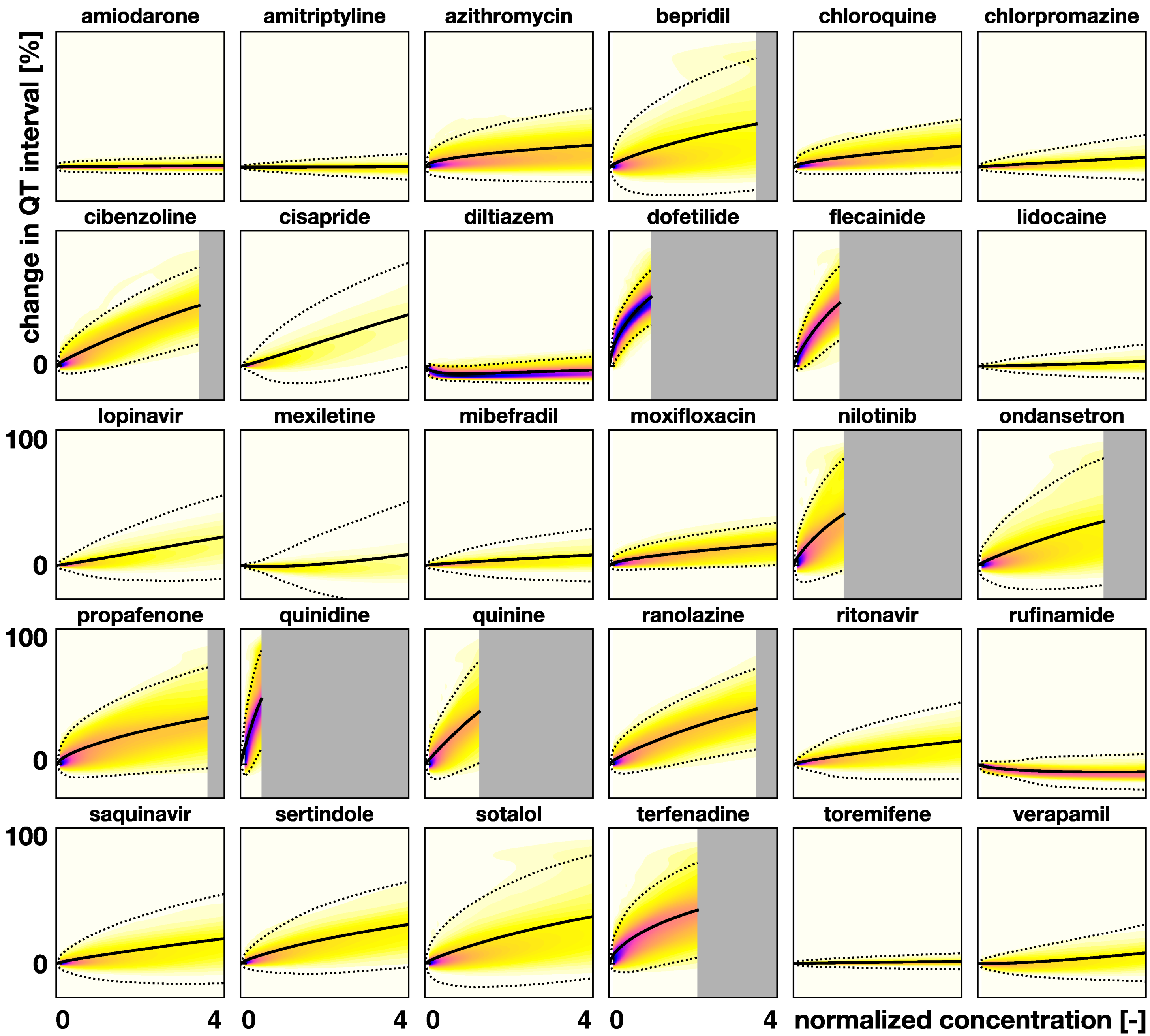
Stanford University

uncertainty quantification for 30 drugs

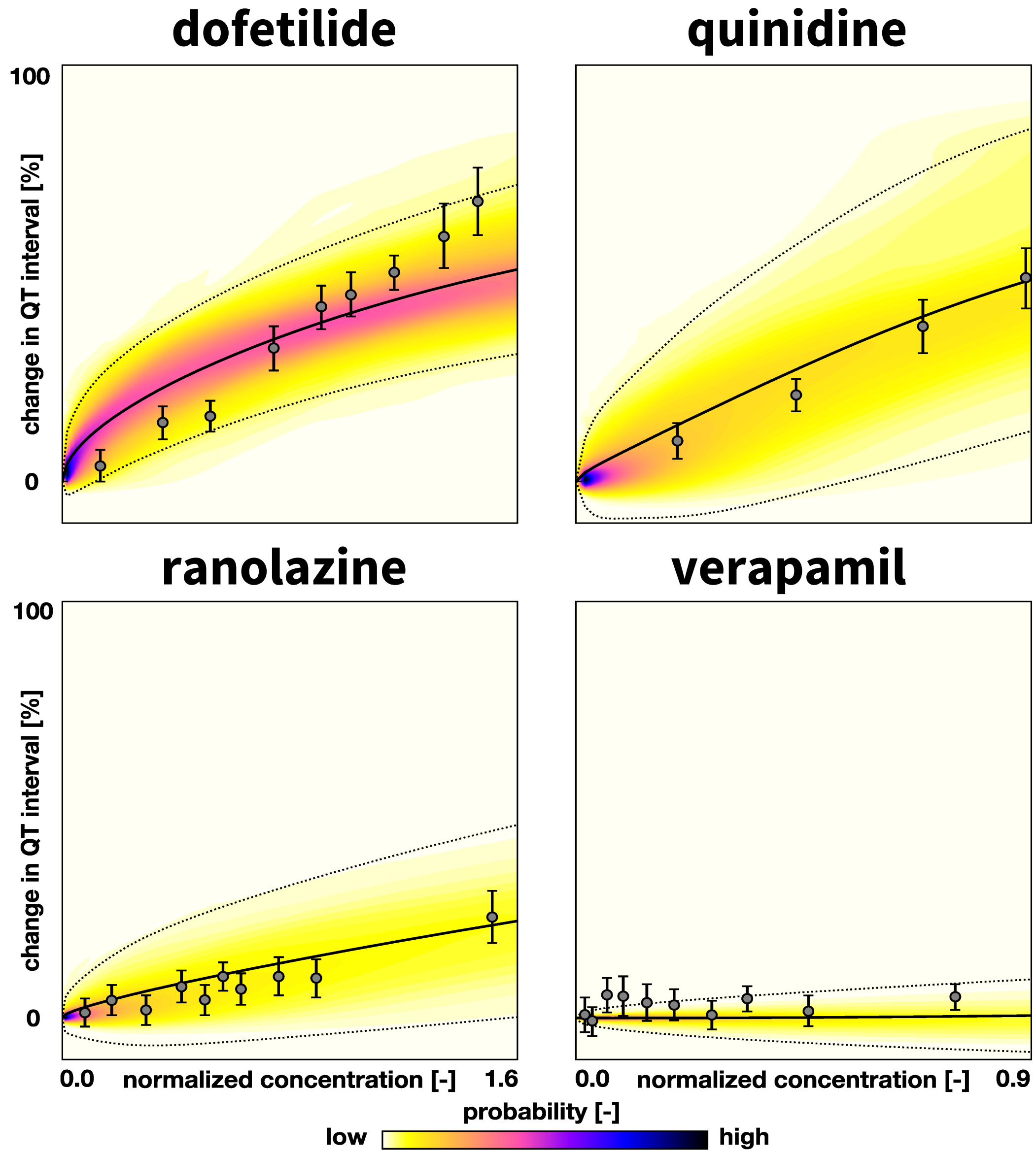


propagate uncertainties of drug-concentration measurements through surrogate model

uncertainty quantification for 30 drugs

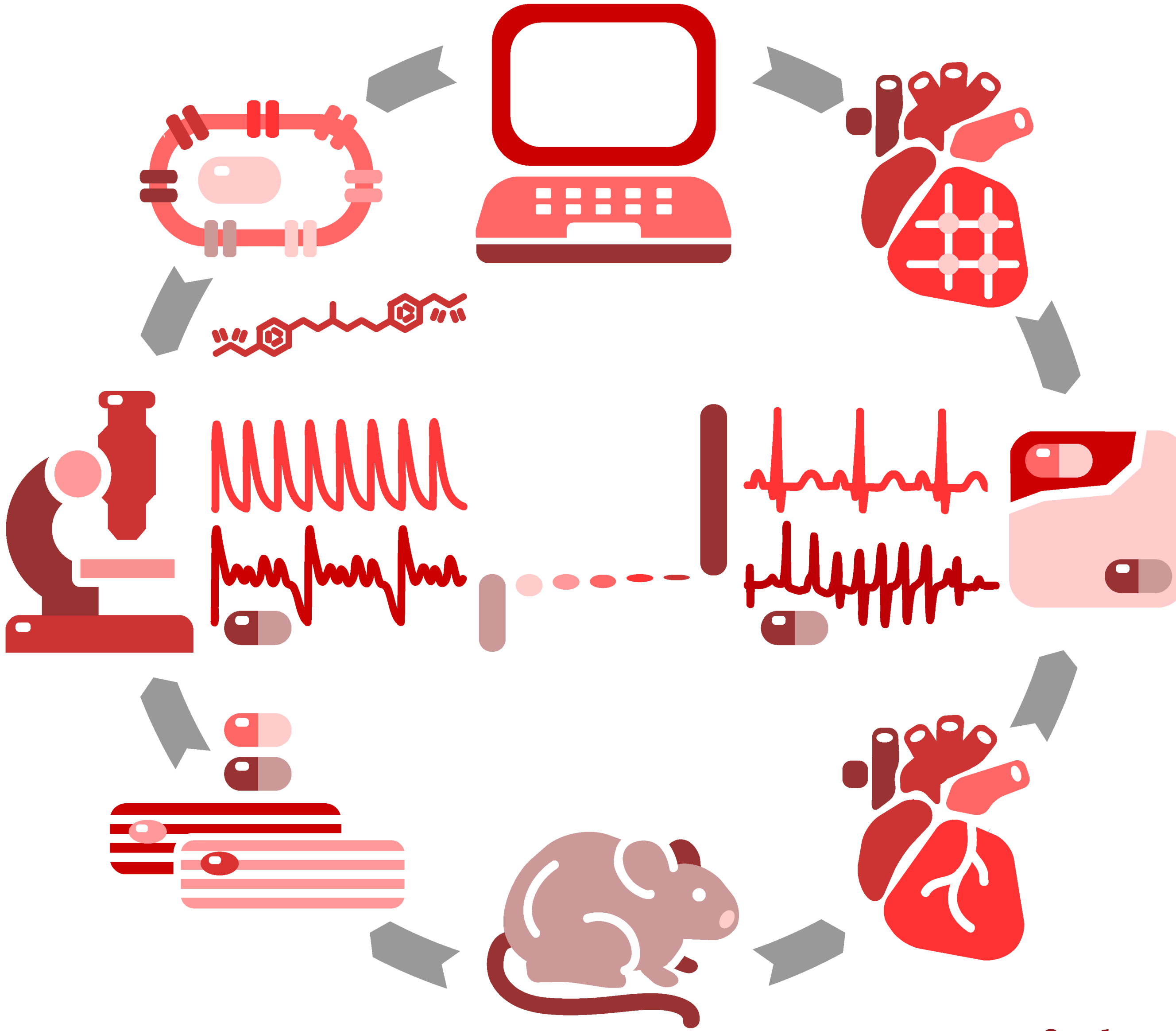


validation of uncertainty quantification



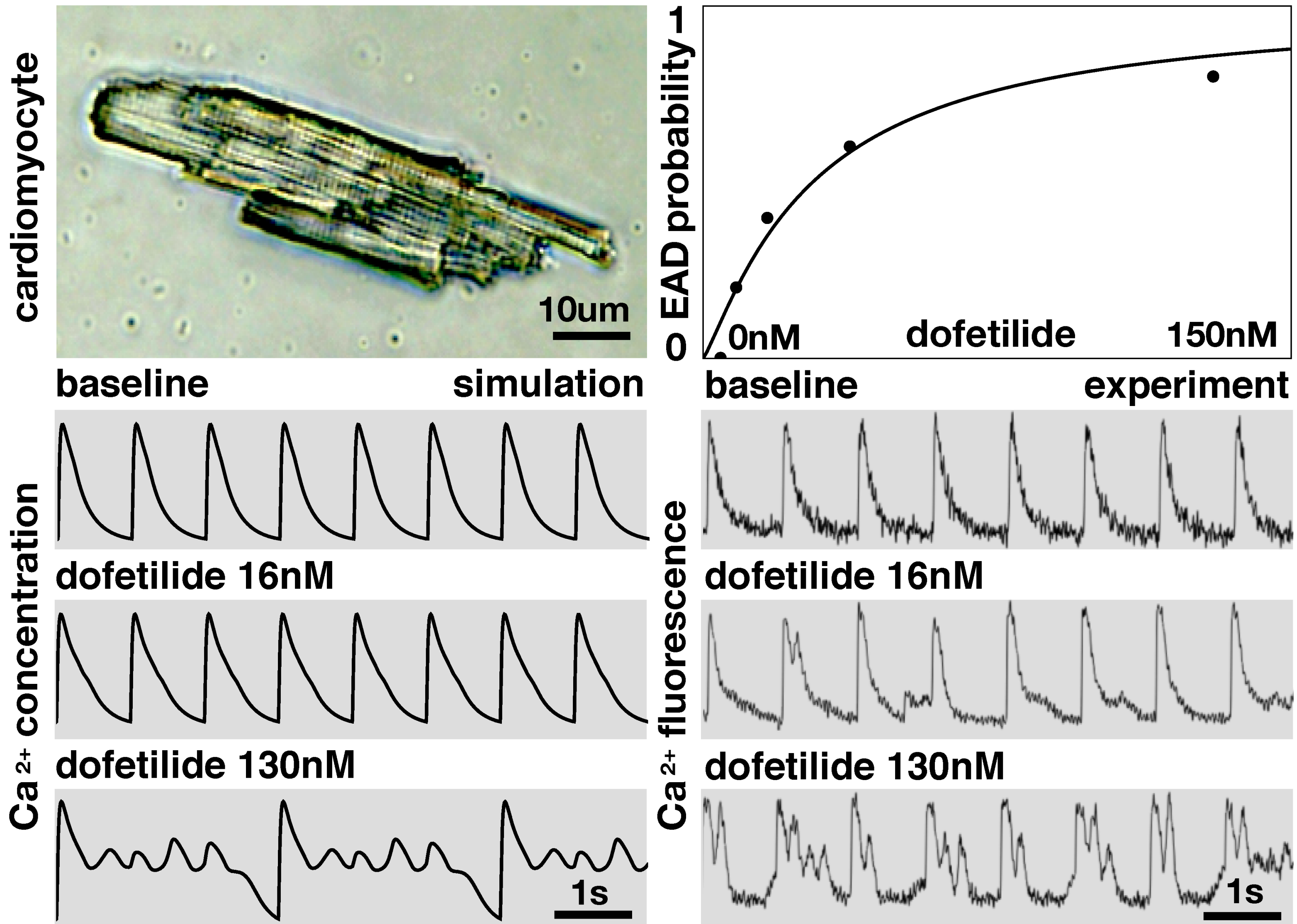
validation of QT interval change for drugs dofetilide, quinidine, ranolazine, and verapamil data from randomized clinical trial, error bars 95% confidence; johannesen et al. [2014]

validation on cell and organ levels



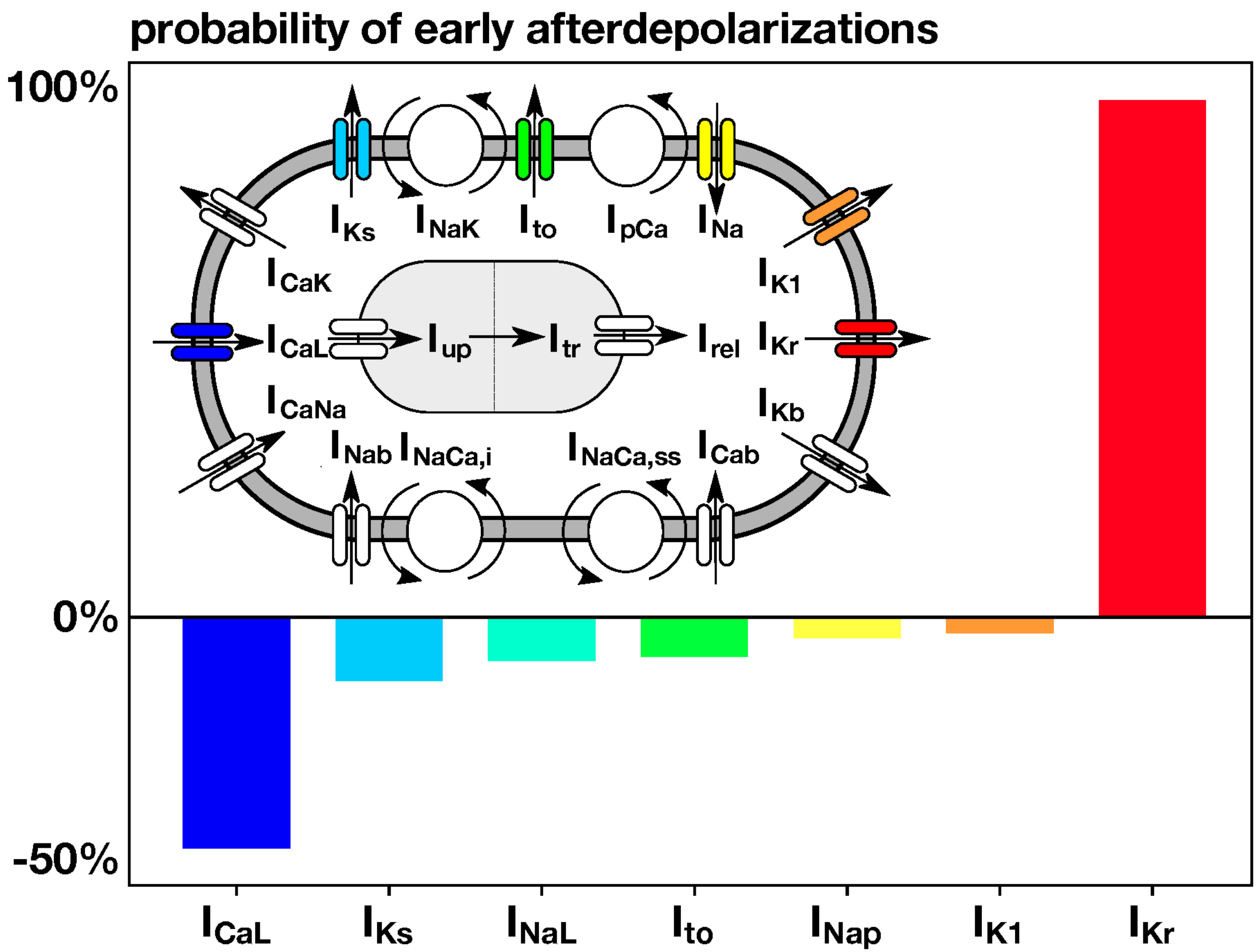
sahli costabal, seo, ashley, kuhl [2019]

cell level validation - early afterdepolarizations



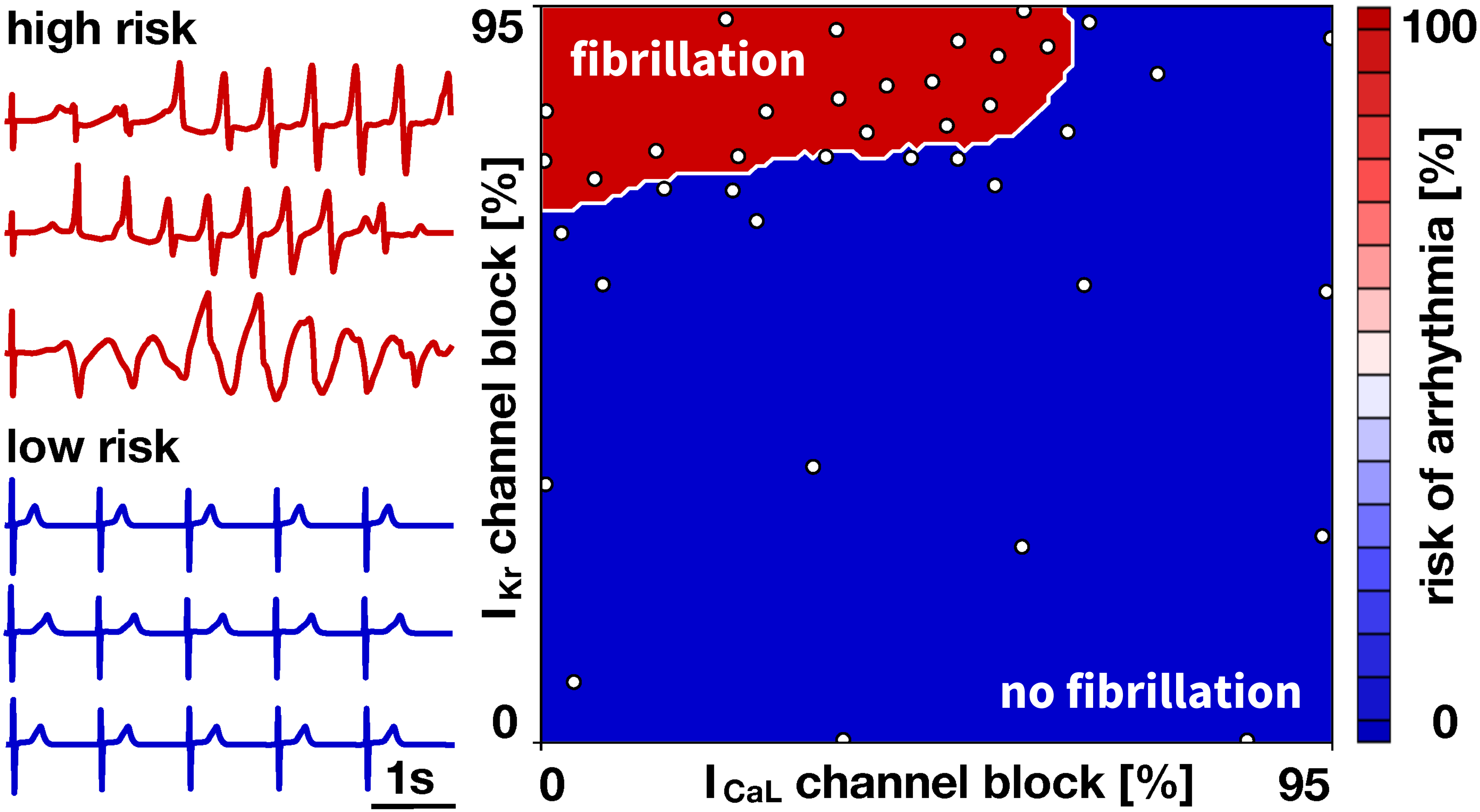
early afterdepolarizations. simulation and isolated rat cardiomyocytes at dofetilide concentrations of 4nM,8nM,16nM,38nM,130nM (n=6 cells each).

cell level sensitivity analysis - ion channels



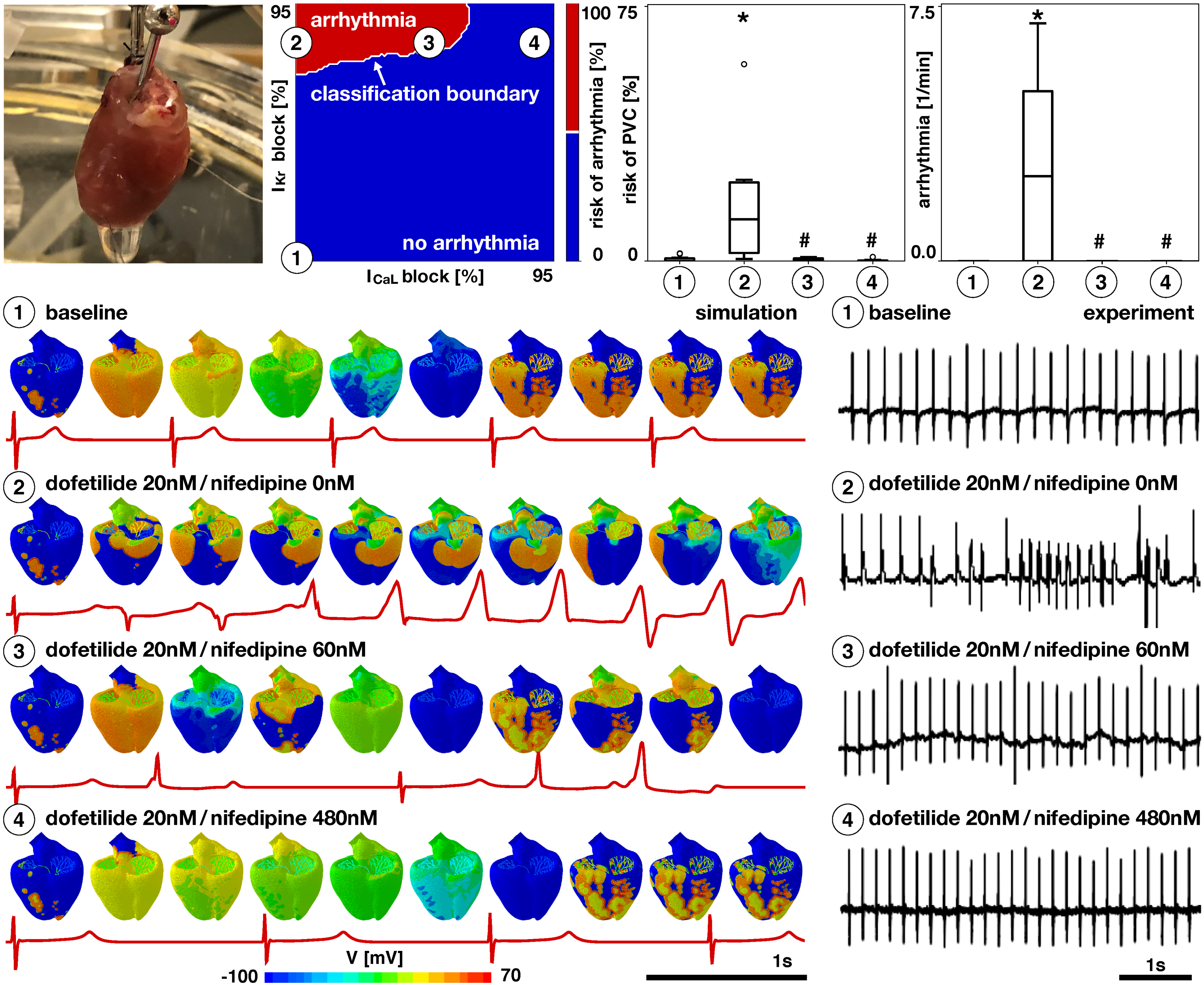
n = 500 single cell simulations > EAD > logistic regression > marginal effects.
blocking I_{Kr} and I_{CaL} increases and reduces risk of early afterdepolarizations

new pro-arrhythmic risk classifier

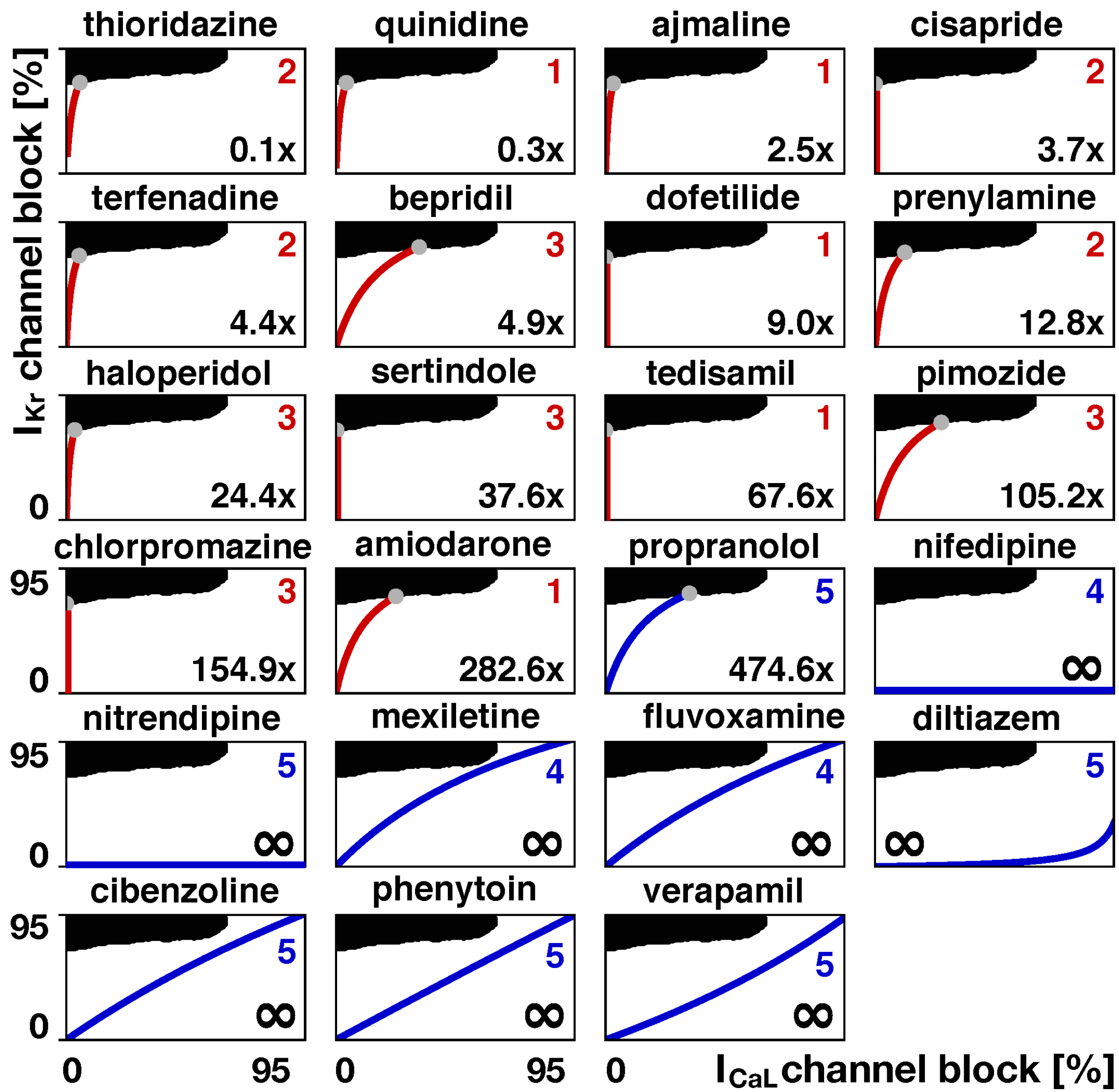


particle learning method to sample classification boundary within IKr / ICaL space, gaussian process classifier, adaptively sample of point of maximum entropy, create n = 10 samples from latin hypercube design, sample n = 30 samples adaptively

organ level validation - arrhythmogenic risk



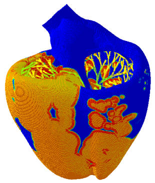
new paradigm for drug safety evaluation?



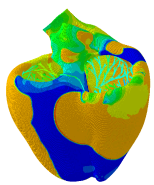
risk stratification of 23 drugs using our pro-arrhythmic risk classifier. numbers x indicate critical concentration; 1-5 risk category; red = torsadogenic, blue = safe.

mirams, cui, sher, …noble [2011], lancaster, sobie [2016]

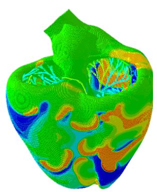
machine learning in drug development



multi fidelity **gaussian process regression** - sensitivities $\mathbf{I_{CaL}}$ / $\mathbf{I_{Kr}}$



uncertainty quantification – effect of variations on **QT interval**



gaussian process **classification** – risk classifier in **polypharmacy**

Francisco Sahli Costabal • Paris Perdikaris • Jiang Yao • Anna Sher • Kinya Seo • Euan Ashley

NSF CAREER award the virtual heart
BioX interdisciplinary seed grant 2018
NIH U01HL119578 multi-scale laws of myocardial growth and remodeling

Pfizer

Best Use of HPC in the Cloud
HPCwire Editors' Choice Awards 2017

Hyperion Research
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