multiscale modeling consortium meeting • march 6-7, 2019

machine learning in drug development

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numinous 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

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
tissue model - monodomain model

- monodomain model - **action potential**
  \[ \dot{\phi} = \text{div}(D \cdot \nabla \phi) + f^\phi \]

- flux term - second order **conductivity tensor**
  \[ D = D_{\text{iso}} I + D_{\text{ani}} f \otimes f \]

- source term - **ionic currents**
  \[ f^\phi = -\frac{I_{\text{ion}}}{C_m} \text{ with } I_{\text{ion}} = I_{\text{ion}}(\phi, q(\phi); t) \]

- ordinary differential equations for **state variables**
  \[ \dot{\mathbf{q}} = \mathbf{g}(\phi, q(\phi); t) \]

- 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

\[ I_{ion} = I_{CaL} + I_{Na} + I_{Cab} + I_{Nab} + I_{Kr} + I_{Ks} + I_{K1} + I_{to} + I_{f} + I_{sus} + I_{NaK} + I_{pCa} + I_{pK} + I_{NaCa} \]

purkinje cells

\[ I_{ion} = I_{CaL} + I_{Na} + I_{CaNa} + I_{CaK} + I_{Cab} + I_{Nab} + I_{Kr} + I_{Ks} + I_{K1} + I_{to} + I_{f} + I_{sus} + I_{NaK} + I_{pCa} + I_{pK} + I_{NaCa, i} + I_{NaCa, ss} \]

o’hara, virag, varro, rudy [2011], stewart, aslanidi, noble, noble, boyett, zhang [2009]
drug model - ranolazene and quinidine

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

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

mirams, cui, sher, fink, cooper, heath, mc mahon, gavaghan, noble [2011], colatsky, fermini, gint-ant, pierson, sager, sekino, strauss, stockbridge[2016], crumb, vicente, johannesen, strauss[2016]
drugs model - effects on the cell level

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

**Quinidine** antiarrhythmic agent
- blocks $I_{Kr}$ and $I_{Ks}$ and $I_{to}$
- severely prolongs APD and QT
- **high** torsades de pointes risk
drug model - effects on the organ level

sahli costabal, yao, kuhl [2018]
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]
uncertainty quantification for 30 drugs

propagate uncertainties of drug-concentration measurements through surrogate model
uncertainty quantification for 30 drugs
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]

Stanford University
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 $I_{Kr} / I_{CaL}$ 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
is a new paradigm for drug safety evaluation?

<table>
<thead>
<tr>
<th>Drug</th>
<th>I_kr channel block [%]</th>
<th>L_Ca,L channel block [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>thioridazine</td>
<td>0.1x</td>
<td>2</td>
</tr>
<tr>
<td>quinidine</td>
<td>0.3x</td>
<td>1</td>
</tr>
<tr>
<td>ajmaline</td>
<td>2.5x</td>
<td>1</td>
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<td>cisapride</td>
<td>3.7x</td>
<td>2</td>
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<tr>
<td>terfenadine</td>
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<td>2</td>
</tr>
<tr>
<td>bepridil</td>
<td>4.9x</td>
<td>3</td>
</tr>
<tr>
<td>dofetilide</td>
<td>9.0x</td>
<td>1</td>
</tr>
<tr>
<td>prenylamine</td>
<td>12.8x</td>
<td>2</td>
</tr>
<tr>
<td>haloperidol</td>
<td>24.4x</td>
<td>3</td>
</tr>
<tr>
<td>sertindole</td>
<td>37.6x</td>
<td>3</td>
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<td>tedisamil</td>
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<td>pimozide</td>
<td>105.2x</td>
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<tr>
<td>chlorpromazine</td>
<td>154.9x</td>
<td>3</td>
</tr>
<tr>
<td>amiodarone</td>
<td>282.6x</td>
<td>1</td>
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<tr>
<td>propranolol</td>
<td>474.6x</td>
<td>5</td>
</tr>
<tr>
<td>nifedipine</td>
<td>∞ ε</td>
<td>4</td>
</tr>
<tr>
<td>nitrendipine</td>
<td>∞ ε</td>
<td>5</td>
</tr>
<tr>
<td>mexiletine</td>
<td>∞ ε</td>
<td>4</td>
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<tr>
<td>fluvoxamine</td>
<td>∞ ε</td>
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<tr>
<td>diltiazem</td>
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<td>cibenzoline</td>
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<td>phenytoin</td>
<td>∞ ε</td>
<td>5</td>
</tr>
<tr>
<td>verapamil</td>
<td>∞ ε</td>
<td>5</td>
</tr>
</tbody>
</table>

Risk stratification of 23 drugs using our pro-arrhythmic risk classifier. Numbers x indicate critical concentration; 1-5 risk category; red = torsadogenic, blue = safe.
machine learning in drug development

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

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

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

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