Complex versus Simple Models: ion-channel cardiac toxicity prediction

David versus Goliath: Long Live David!

Outline

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  - Define inputs and question
- Data:
  - 3 data-sets from 2011, 2013 and 2016 (latest)

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    - Designated the "**Gold-Standard**" model by Zhou et al.
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    - **Certara scientists refer to it as "Cardiac Safety Simulator"**


Circulation Research

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INTEGRATIVE PHYSIOLOGY

In Vivo and In Silico Investigation Into Mechanisms of Frequency Dependence of Repolarization Alternans in Human Ventricular Cardiomyocytes

Xin Zhou, Alfonso Bueno-Orovio, Michele Orini, Ben Hanson, Martin Hayward, Peter Taggart, Pier D. Lambiase, Kevin Burrage, Blanca Rodriguez

QTc modification after risperidone administration – insight into the mechanism of action with use of the modeling and simulation at the population level approach

Anna Glinka & Sebastian Polak

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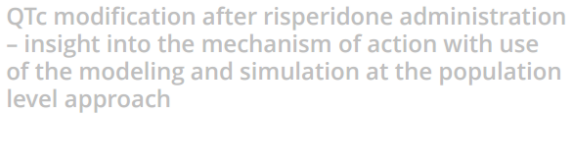
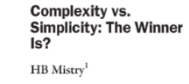
    - Certara scientists refer to it as "Cardiac Safety Simulator"
  - "Inet": addition & subtraction (simple mechanism)
    - Sum up block against depolarisation (D)
    - Sum up block against repolarisation (R)
    - Calculate: D-R

    Article showed: combine machine learning/biophysical model no better than above linear model





Question: in-vitro to in-vivo translation

Can we predict Torsadegenic risk of a compound based on in-vitro potency data at relevant drug exposure?

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Options (all categorical):

1. Redfern et al.
   - Developed by AstraZeneca: biased?
2. CiPA consortium (FDA/HESI etc.)
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3. CredibleMeds
   - Independent dedicated team with no conflict of interest
   - Extensive analysis of both literature and adverse event databases

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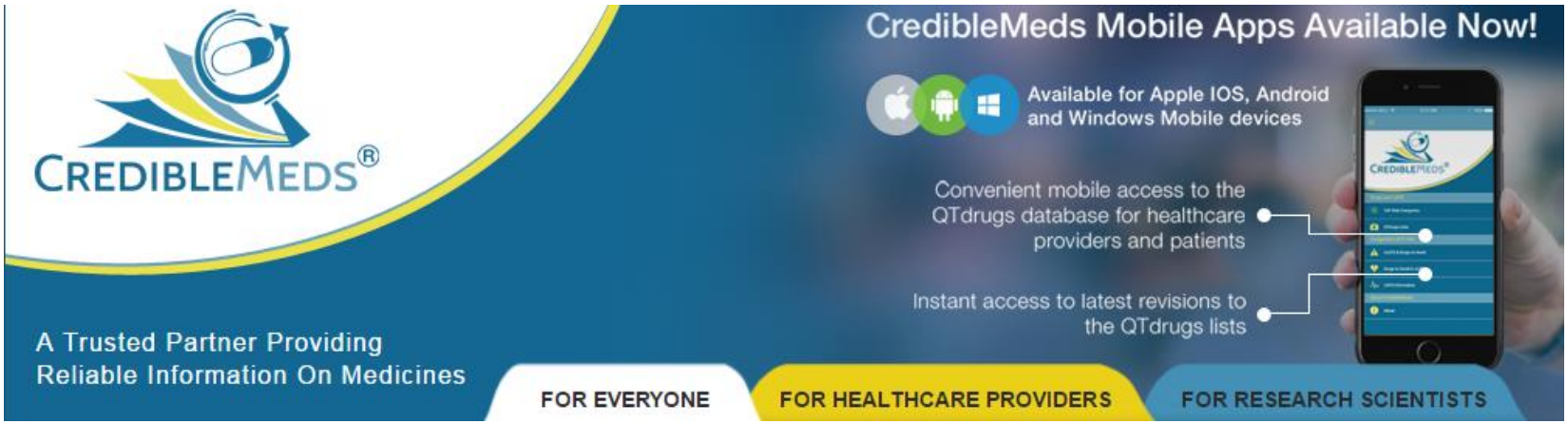

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Credible Meds is the only one known to most clinicians

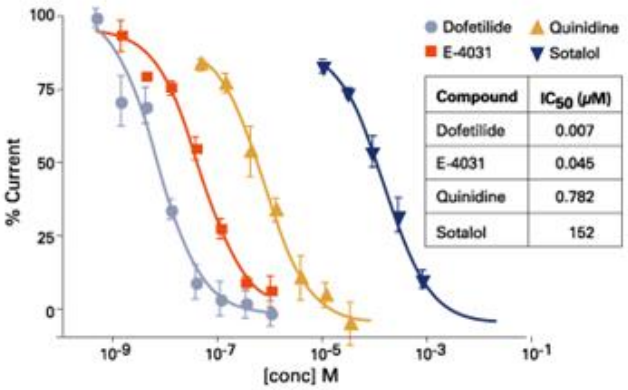
In-vitro Data

High-throughput screens:

- Dose-response isolated ion-channel
- Typically measured just hERG (single ion-channel)
- No. ion-channels measured is growing
  - May not need many though – prevalence?

Block

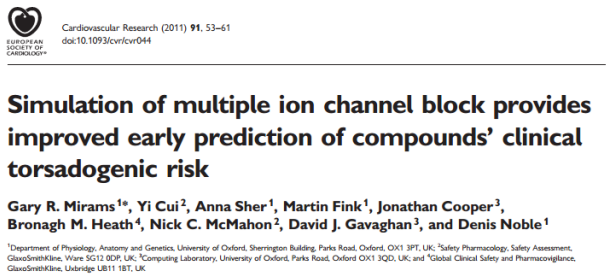
$$S_x = 1 - \frac{1}{1 + \left(\frac{IC_{50}}{[D]}\right)^n}$$



Compound	IC_{50} (μM)
Dofetilide	0.007
E-4031	0.045
Quinidine	0.782
Sotalol	152

Input Data

Collected % block at relevant clinical concentrations from 3 lit. studies:



Cardiovascular Research (2011) **91**, 53–61
doi:10.1093/cvr/cvr044

Simulation of multiple ion channel block provides improved early prediction of compounds' clinical torsadogenic risk

Gary R. Mirams[1]*, Yi Cui[2], Anna Sher[1], Martin Fink[1], Jonathan Cooper[3], Bronagh M. Heath[4], Nick C. McMahon[2], David J. Gavaghan[3], and Denis Noble[1]

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Mirams et al. (2011) - GSK

- 1st study looked at multi-channel effects
- Categorisation: Redfern – 4 and 2 categories
  - We replace this with CredibleMeds
- No. ion-channels screened: 3

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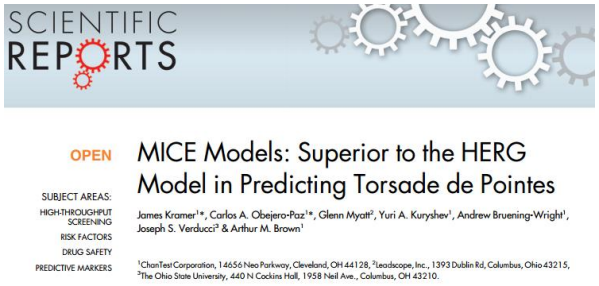

SCIENTIFIC REPORTS

OPEN

MICE Models: Superior to the HERG Model in Predicting Torsade de Pointes

SUBJECT AREAS:
HIGH-THROUGHPUT SCREENING
RISK FACTORS
DRUG SAFETY
PREDICTIVE MARKERS

James Kramer[1]*, Carlos A. Obejero-Paz[1]*, Glenn Myatt[2], Yuri A. Kuryshev[1], Andrew Bruening-Wright[1], Joseph S. Verducci[2] & Arthur M. Brown[1]

[1]ChanTest Corporation, 14656 Neo Parkway, Cleveland, OH 44128, [2]Leadscope, Inc., 1393 Dublin Rd, Columbus, Ohio 43215, [3]The Ohio State University, 440 N Cockins Hall, 1958 Neil Ave., Columbus, OH 43210.

Kramer et al. (2013) - Chantest

- Largest study – 55 compounds
- Categorisation: mix of databases – 2 categories
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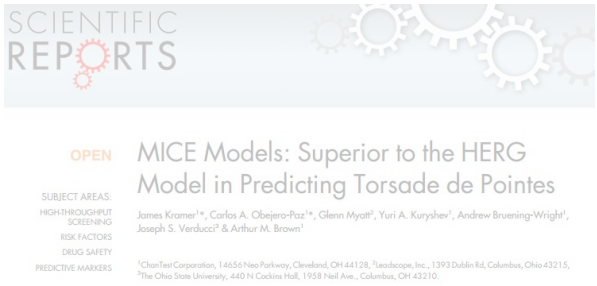

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ELSEVIER

Journal of Pharmacological and Toxicological Methods

Volume 81, September–October 2016, Pages 251-262

An evaluation of 30 clinical drugs against the comprehensive *in vitro* proarrhythmia assay (CiPA) proposed ion channel panel

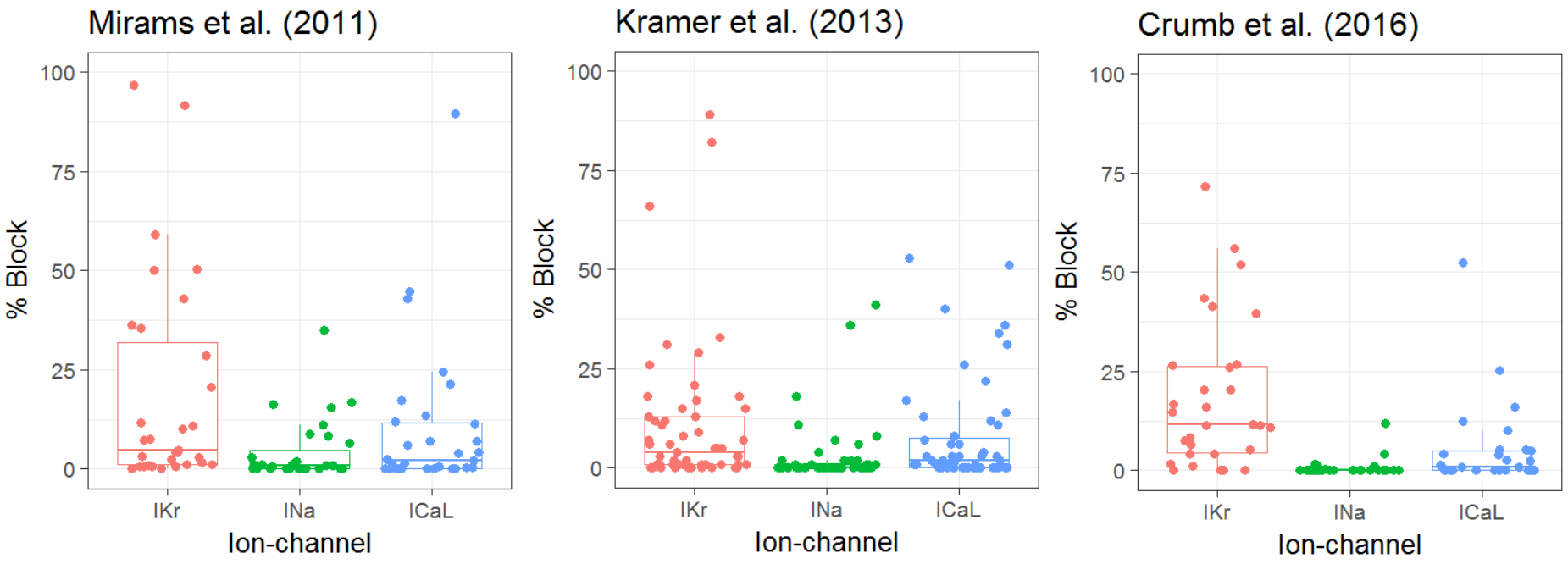
William J. Crumb Jr.[a], Jose Vicente[b], Lars Johannesen[b], David G. Strauss[b]

Crumb et al. (2016) - FDA commissioned

- No modelling
- Categorisation: none
  - We replace this with CredibleMeds
- No. ion-channels screened: 7

Input Data

Boxplots show the distribution of block across the compounds in each study – notice anything?



In the 1st instance we focus just on 3 ion-channels for the Crumb et al. data-set

Model Outputs

For each compound at concentration stated in original article calculate:

Cardiac models:

- Time taken to re-polarise action-potential by 90% (APD90)
- Compare treated versus control: ΔAPD90

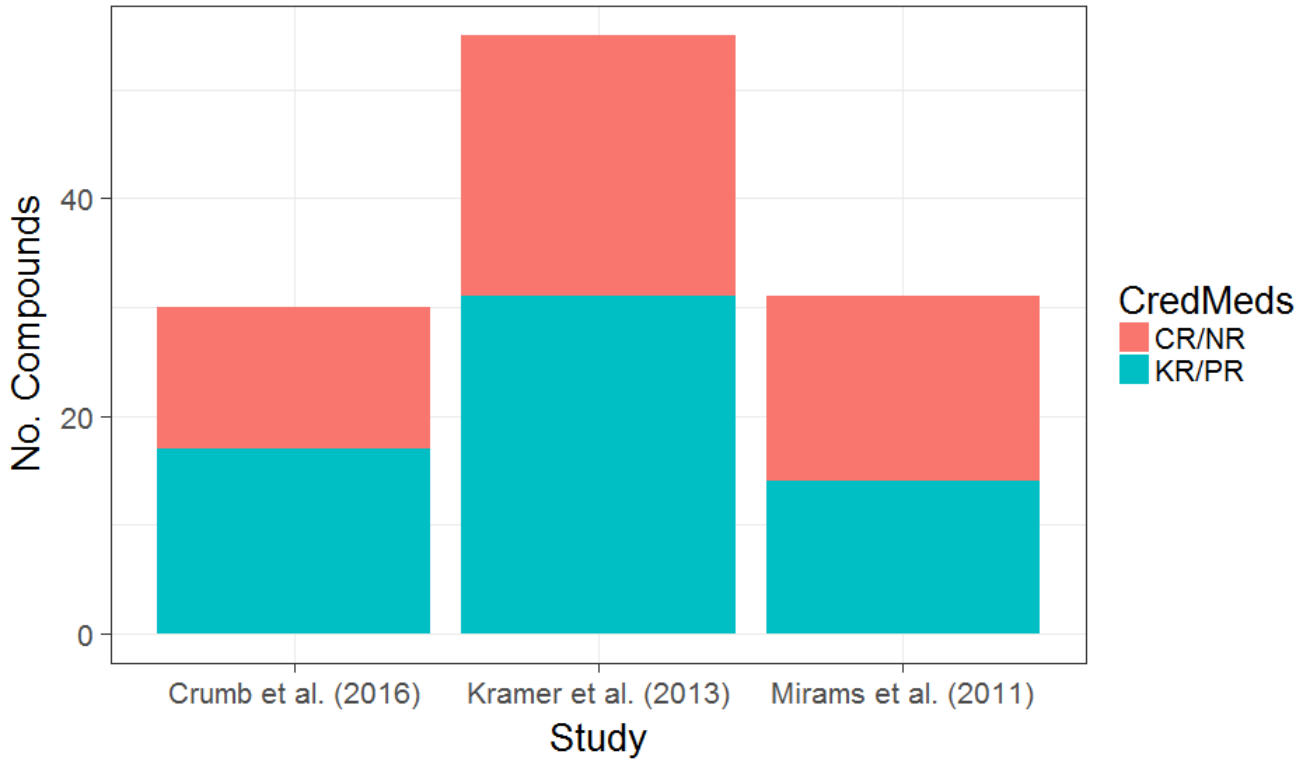
Inet:

- Sum up block against repolarisation (R)
- Sum up block against depolarisation (D)
- Calculate R-D

Output Data

Bar-chart showing the no. compounds classed as Torsadegenic (pink) versus safe (blue) – based on CredibleMeds

Key observation: data-sets are reasonably balanced

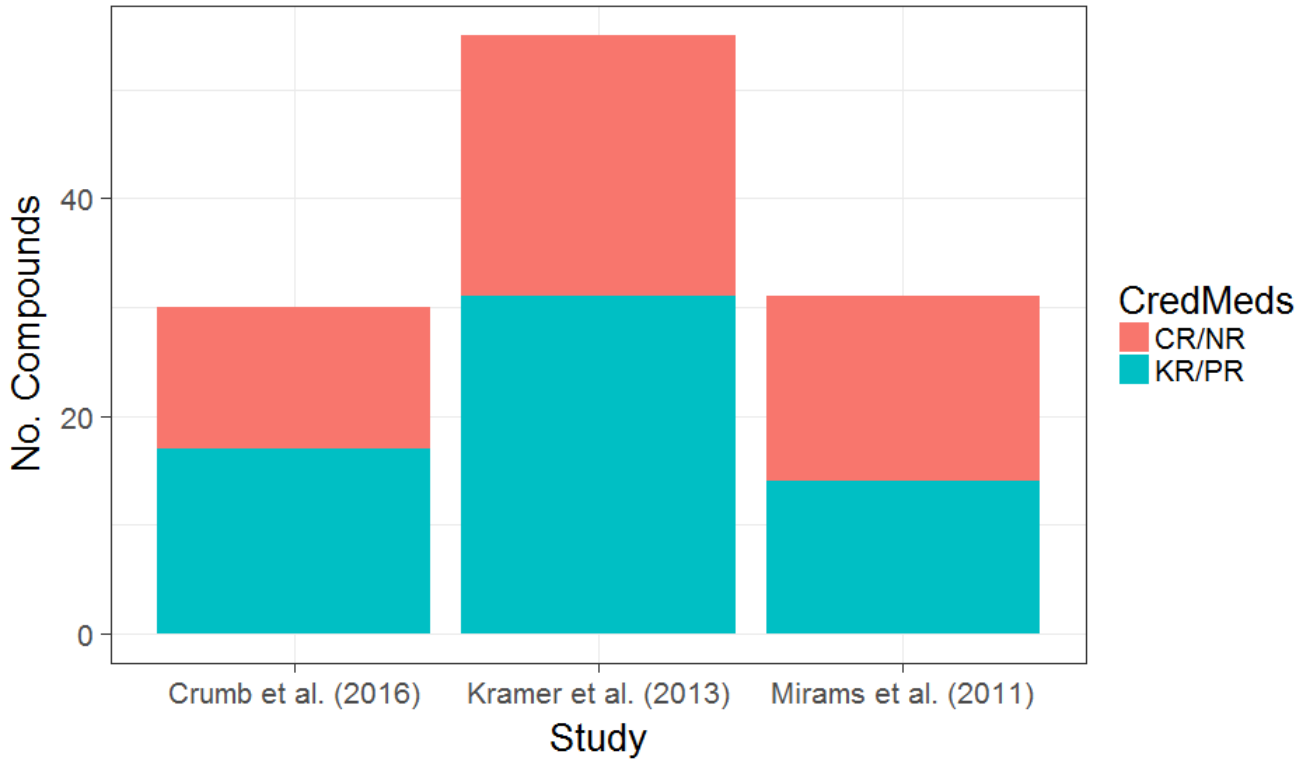


Output Data

Simple classification problem inputs are:

1. Change in APD90 from "Gold Standard" model (FDA/CiPA)
2. Change in APD90 from "Cardiac Safety Simulator"
3. Inet – a simple subtraction

Action Potential Simulations done using AP Predict (Oxford)



Results

A leave one-out cross validation is performed – report ROC AUC

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Leave One Out Cross Validation				
Data-Set	3 ion-channels			hERG
	I_{net}	Gold-Standard: ΔAPD90	Cardiac Safety Simulator: ΔAPD90	% Block IKr
Mirams (2011)	0.71	0.53	0.68	0.51

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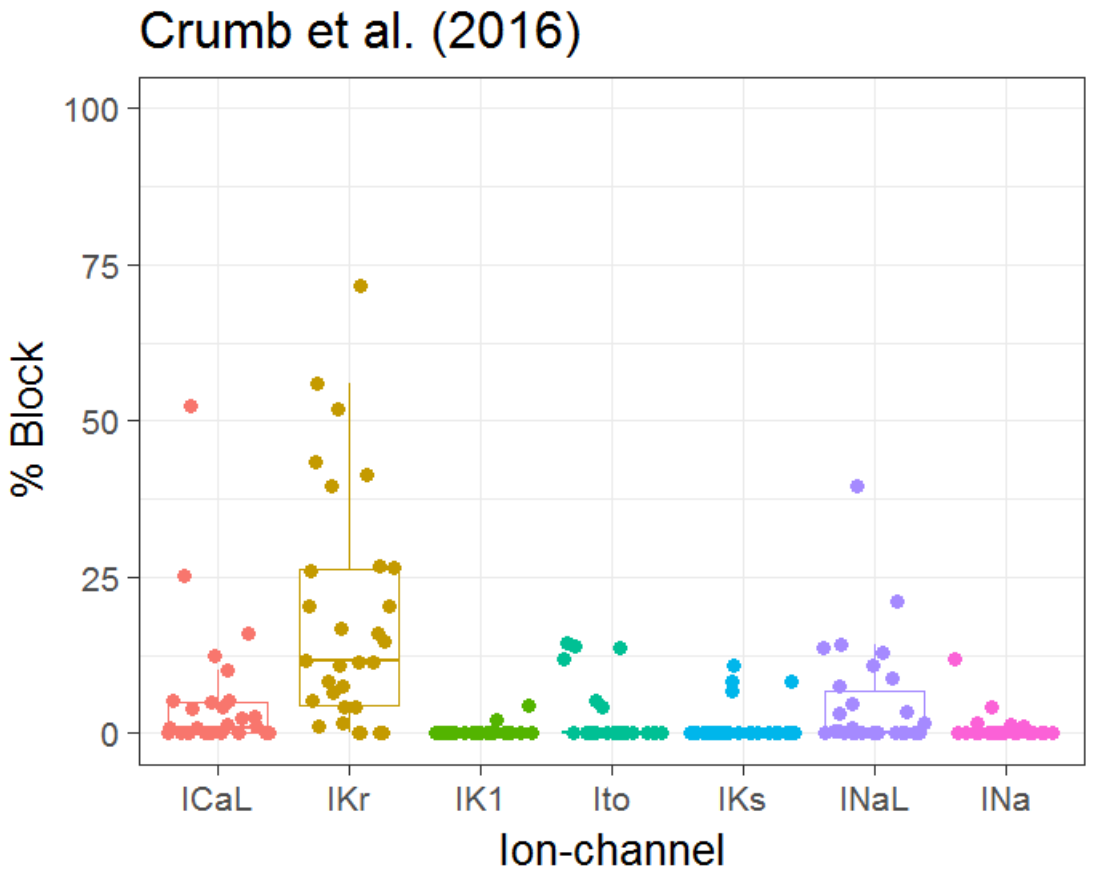
In Crumb we had 7 ion-channels: what happens if we use them all?

Crumb et al. – 7 ion-channels

What do you see?



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In Crumb we had 7 ion-channels: what happens if we use them all?
Easy to incorporate more in Inet
"Gold-Standard" contains all 7 ion-channels
"Cardiac Safety Simulator" cannot use info on INaL (only use 6)
Would you invest in building INaL model for the Cardiac Safety Simulator?

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	7 ion-channels			
Crumb (2016)	0.82	0.67	0.60*	

*based on 6 ion-channels – INaL not modelled by TenTusscher et al.; ΔAPD90: percentage change in APD90

Are these results surprising?

The M3-Competition: results, conclusions and implications

Spyros Makridakis, Michèle Hibon*

INSEAD, Boulevard de Constance, 77305 Fontainebleau, France

M-competitions: Simple methods perform better than complex approaches

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Simple versus complex forecasting: The evidence

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[a] *University of South Australia Business School, and Ehrenberg-Bass Institute, GPO Box 2471, Adelaide, SA 5001, Australia*
[b] *The Wharton School, University of Pennsylvania, 700 Huntsman Hall, 3730 Walnut Street, Philadelphia, PA 19104, USA*
[c] *Ehrenberg-Bass Institute, University of South Australia*

Key conclusions:
Complexity does not improve forecast accuracy
Complexity increases forecast error
Evidence for favouring complex approaches:

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Evidence for favouring complex approaches:

1. **Researchers awarded for publishing in highly cited journals**
2. **Modellers use complex methods to support clients plans**
3. **Clients reassured by incomprehensibility**

Summary

Ion-channel cardiac toxicity prediction - simple models perform better than complex models

Implications:

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- Can we trust poor performing complex models for extrapolation?

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- Should we invest more in improving complex models?
- Why apply model reduction to a poor performing complex model? Amplify the poor performance?
  - Rather than use model reduction – just build a simpler model - good old math. biology

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- Can we trust poor performing complex models for extrapolation?
- Should we invest more in improving complex models?
- Why apply model reduction to a poor performing complex model? Amplify the poor performance?
  - Rather than use model reduction – just build a simpler model - good old math. biology
- Academia incentivises complexity – is this the right place to find solutions to problems?

Blog: http://systemsforecasting.com/blog/