In silico prediction of the emergent effects of drugs on cardiac electrical activity

Colleen E. Clancy Lab

UCDAVIS HEALTH SYSTEM

UCDAVIS

"In few specialties of medicine are new promising drugs shown to be so much inferior to placebo, and even worse, to increase mortality."

-Sanderson, 1996 [Editorial on SWORD and CAST trials]

…But this doesn't mean that these drugs can't be useful in ***some*** situations

*There is currently no **reliable** method to predict when antiarrhythmic drugs will **succeed** or **fail**.*

NEW technologies for pharmacology

PatchExpress and Ionworks

NMR Screening

Synthetic biology

Novel Reagents

Biosensors

Patient-derived pluripotent stem (iPS) cells

It's EXCITING!

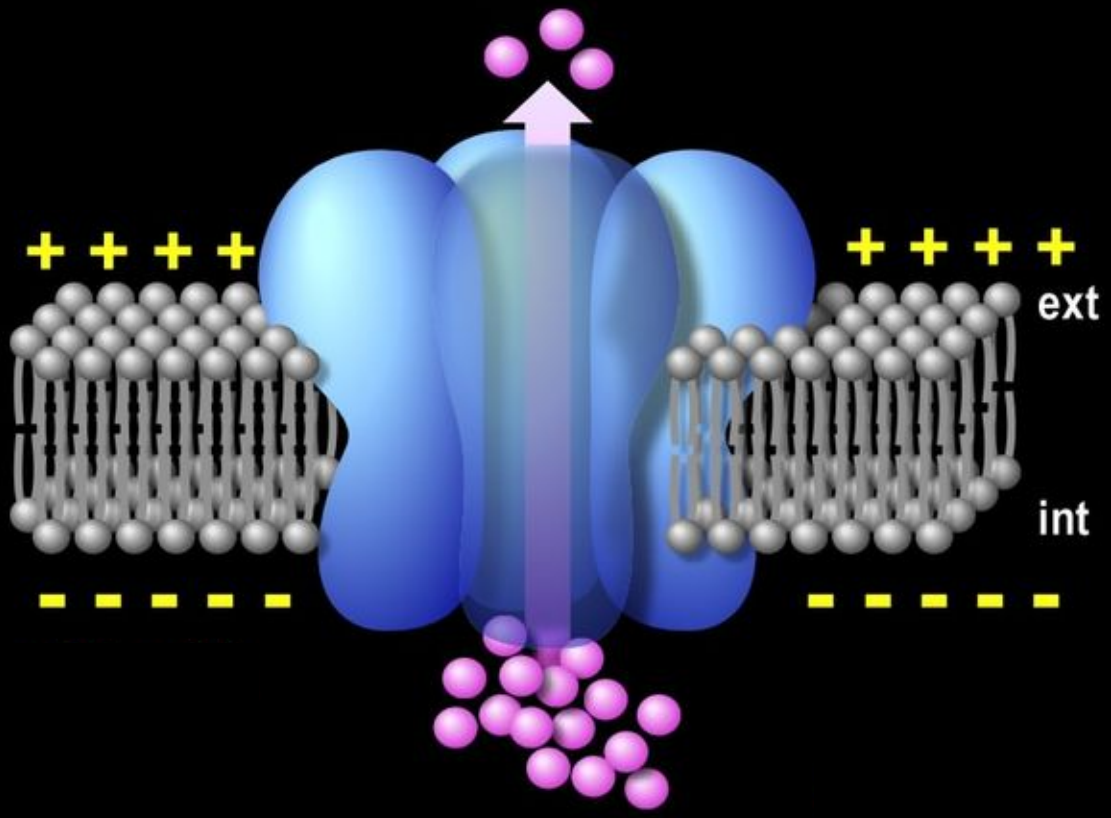
BUT……

While all of these developing technologies are innovative and needed, they ***focus only on constituent elements*** of the system. They can't each alone solve the fundamental problem – that the effects of multifaceted drug interactions are ***emergent***.

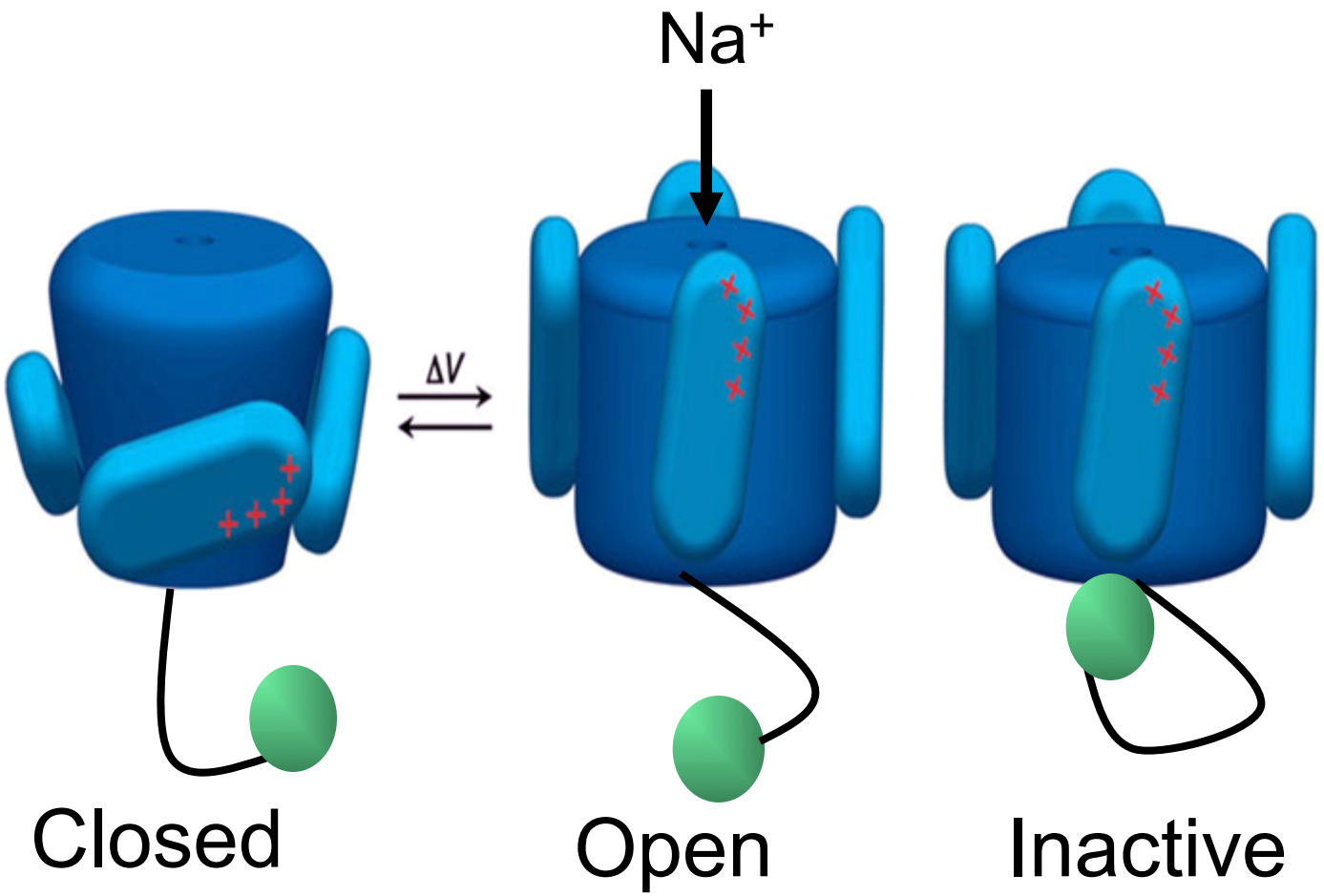
Our goal

Develop a *computational processes* for **SCREENING** for drug and disease, determination of MECHANISMS of success and failure and prediction of THERAPY

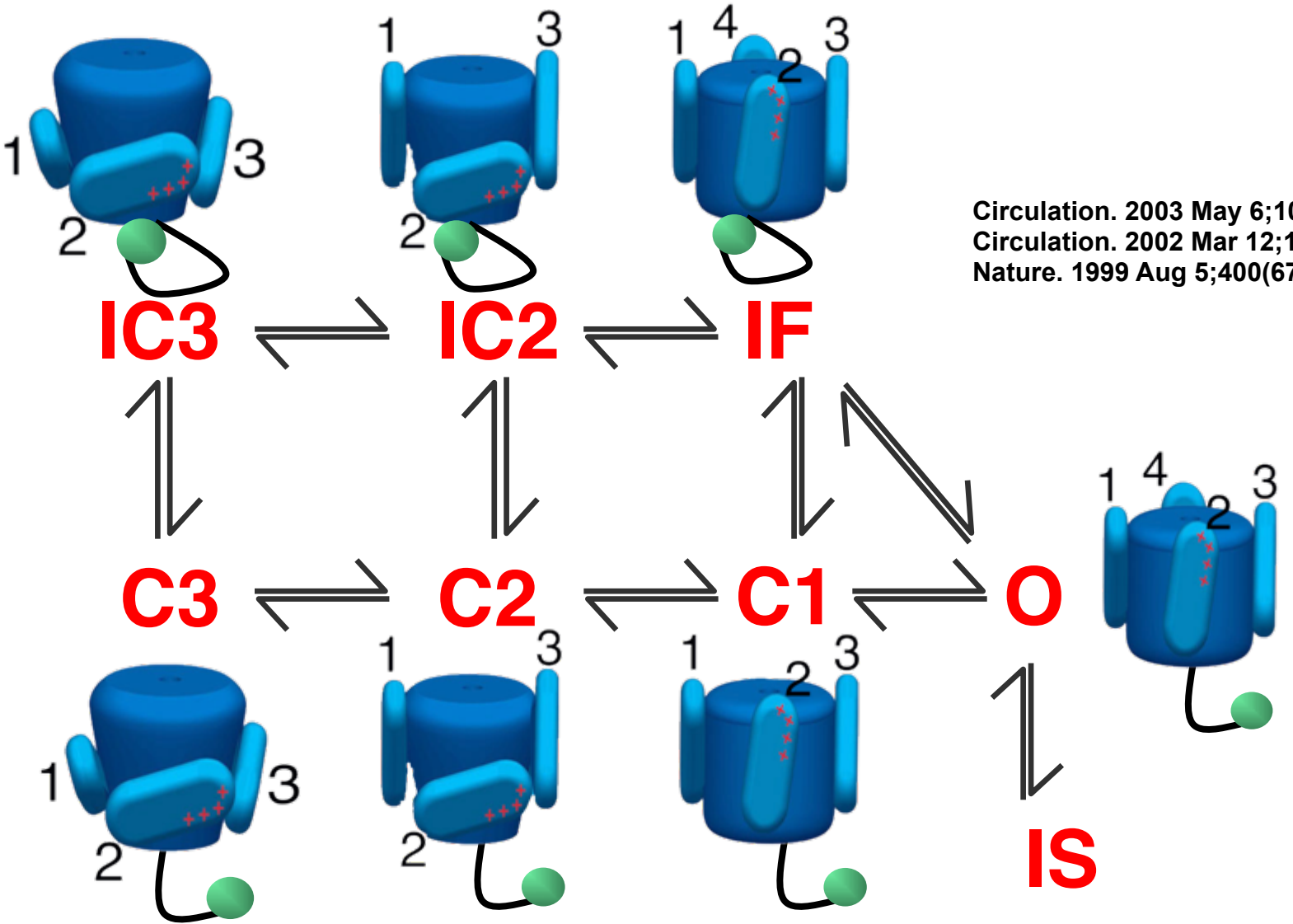
Most drugs intended to treat cardiac arrhythmia block voltage gated ion channels



Modeling drug free cardiac I_{Na} (encoded by *SCN5A*)

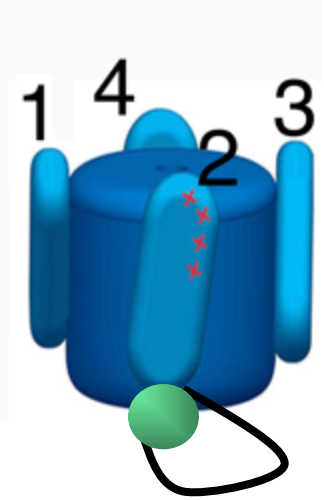


A computational model that predicts Na^+ channel kinetics



Circulation. 2003 May 6;107(17):2233-7.
Circulation. 2002 Mar 12;105(10):1208-13.
Nature. 1999 Aug 5;400(6744):566-9.

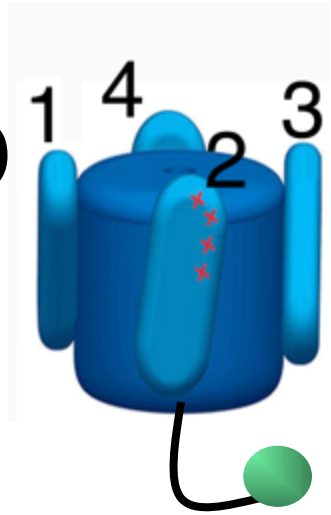
Extracting model parameters from experimental data

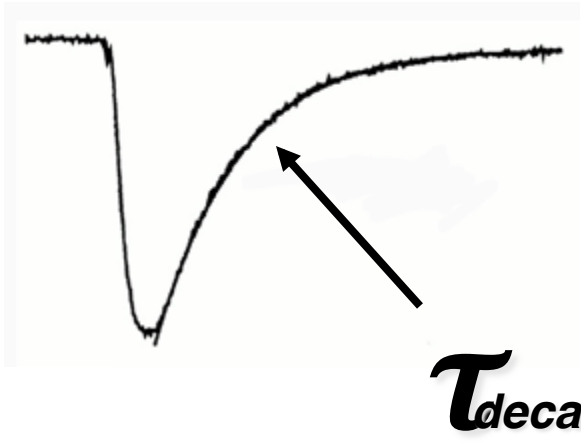


IF

α

O

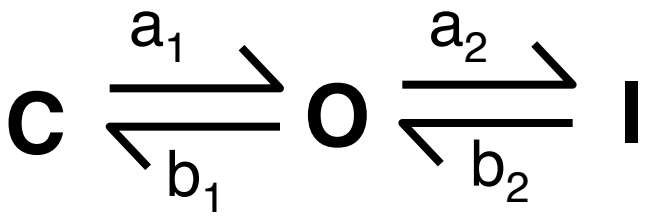




τ_{decay}

$\tau_{decay} = 1 / \alpha$

Computation of state probabilities



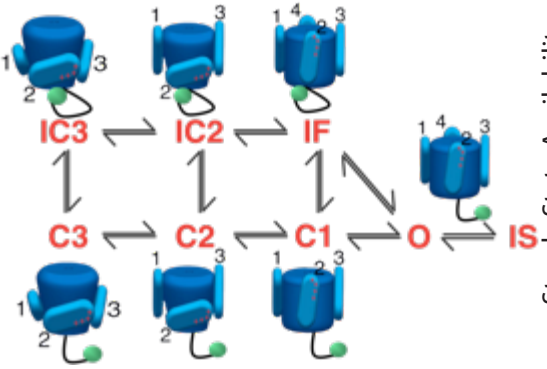
$$dP_i/dt = \sum_{j=1}^{N}[k_{ji} \bullet P_j(t,V_m)] - \sum_{j=1}^{N}[k_{ij} \bullet P_i(t,V_m)]$$

$dC/dt = P(O) \bullet b_1 - P(C) \bullet a_1$

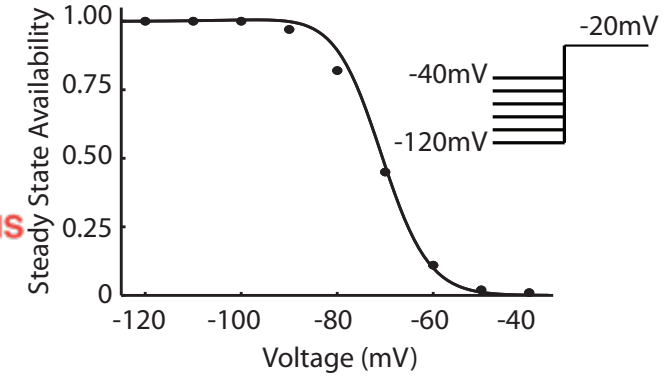
$dO/dt = P(C) \bullet b_1 + P(I) \bullet b_2 - (P(O) \bullet (a_2 + b_1))$

$dI/dt = P(O) \bullet a_2 - P(I) \bullet b_2$

Wild-type Drug Free Model - *Postoptimization*



a.



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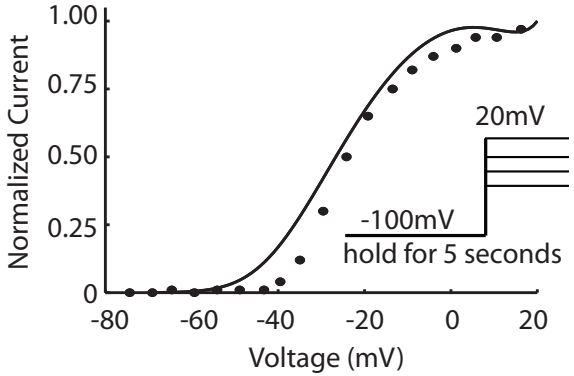
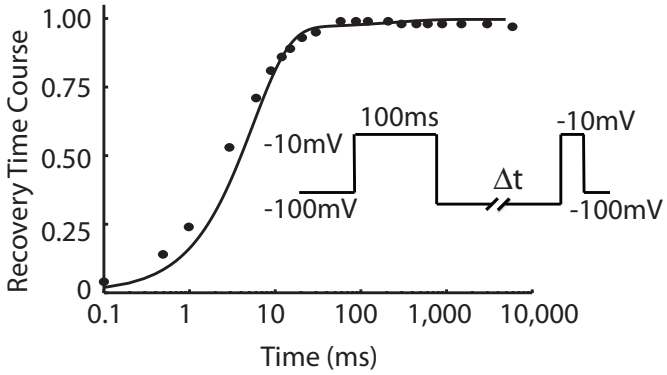
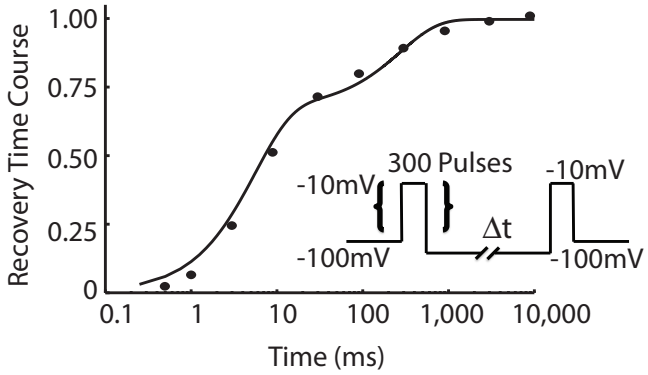


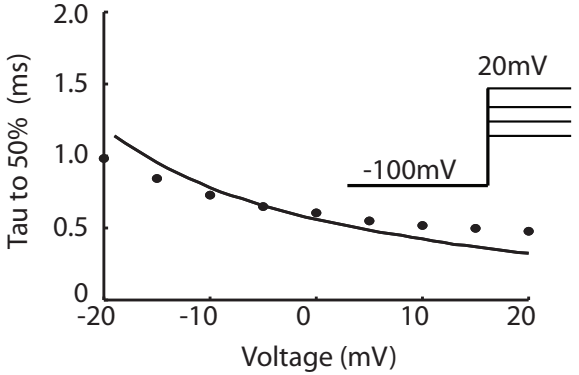
c.



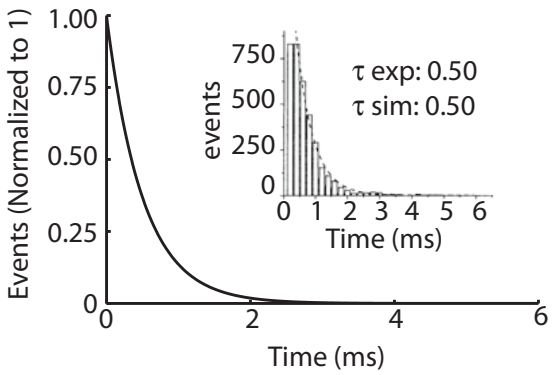
d.



e.

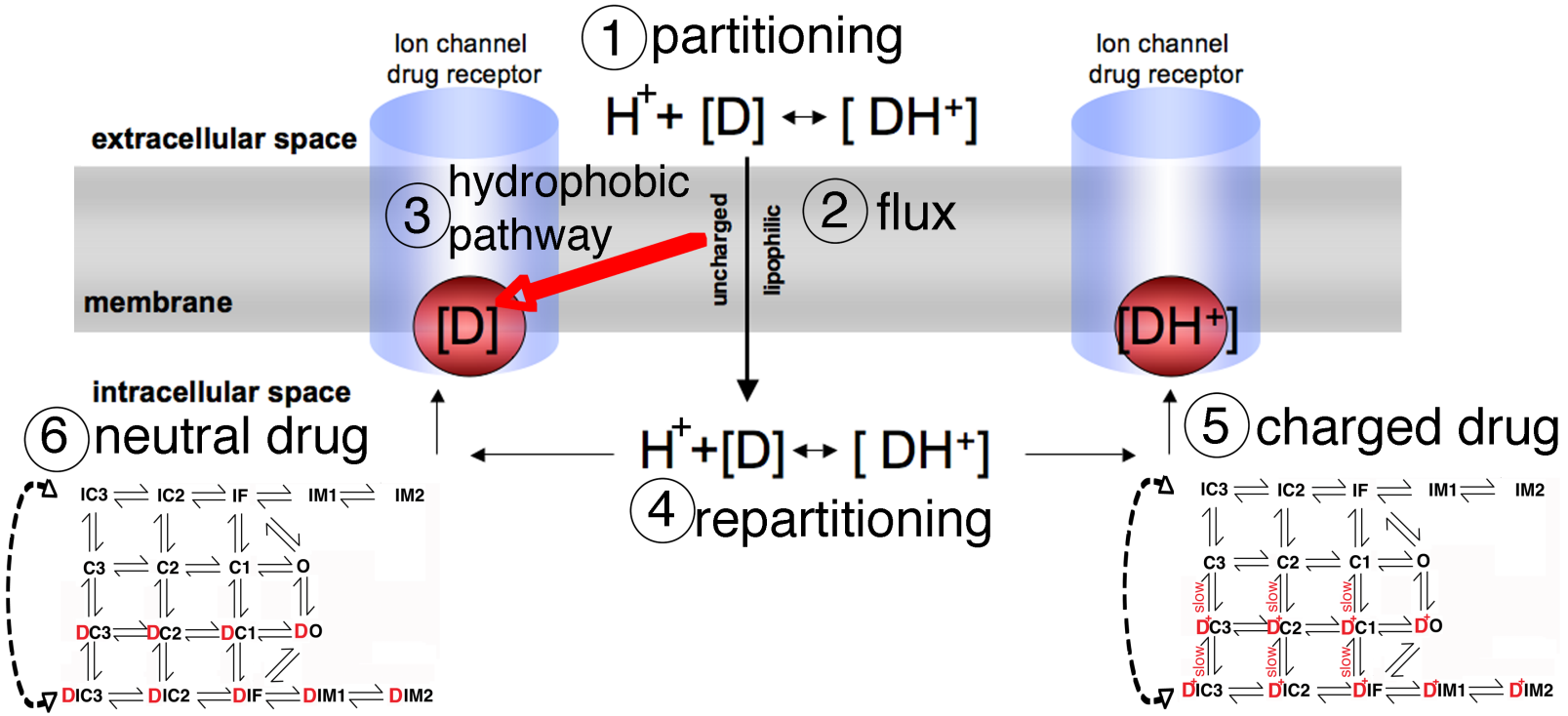


f.

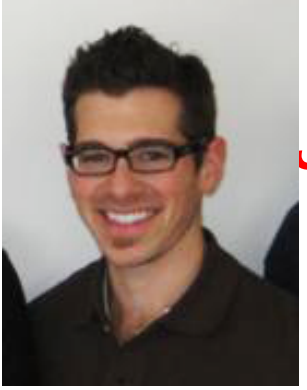


Pharmacodynamics is Complex

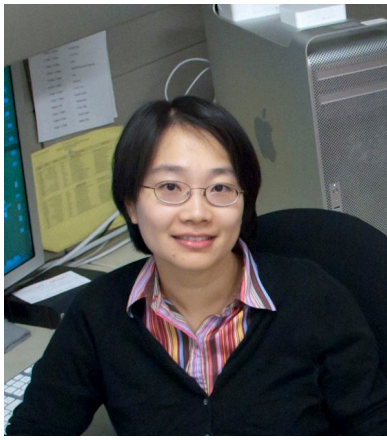
and determined by numerous factors including:



If we consider these properties in our model, can we begin to make predictions about functional effects of drug in higher dimensions?



Jonathan D. Moreno, M.D, Ph.D.



Pei-Chi Yang, Ph.D.

RESEARCH ARTICLE

Science Translational Medicine

AAAS

DRUG DEVELOPMENT

A Computational Model to Predict the Effects of Class I Anti-Arrhythmic Drugs on Ventricular Rhythms

Jonathan D. Moreno,[1,2] Z. Iris Zhu,[2] Pei-Chi Yang,[3] John R. Bankston,[4] Mao-Tsuen Jeng,[3] Chaoyi Kang,[3] Lianguo Wang,[3] Jason D. Bayer,[5] David J. Christini,[2] Natalia A. Trayanova,[5] Crystal M. Ripplinger,[3] Robert S. Kass,[4] Colleen E. Clancy[3]*

Circulation Research

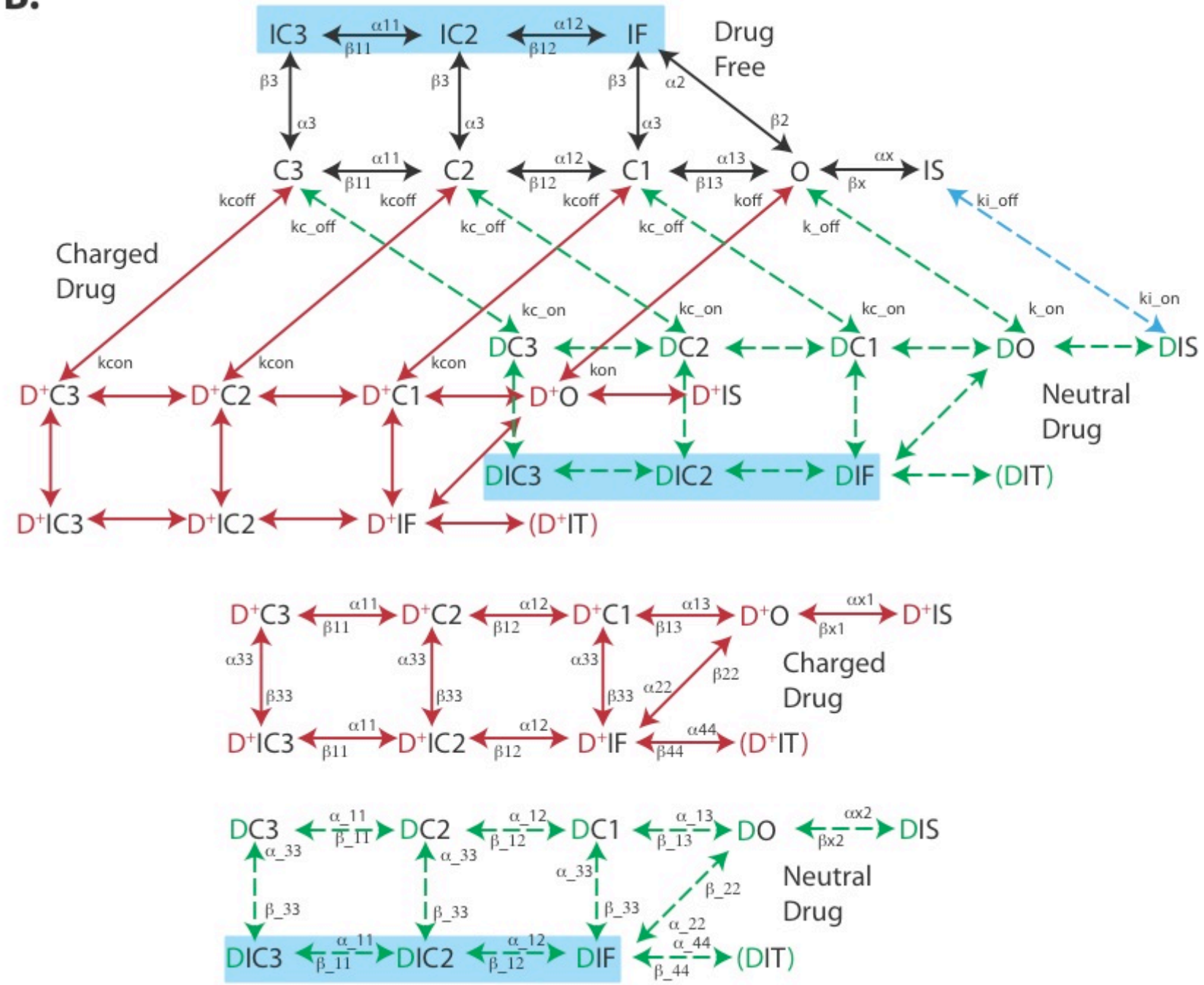
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association

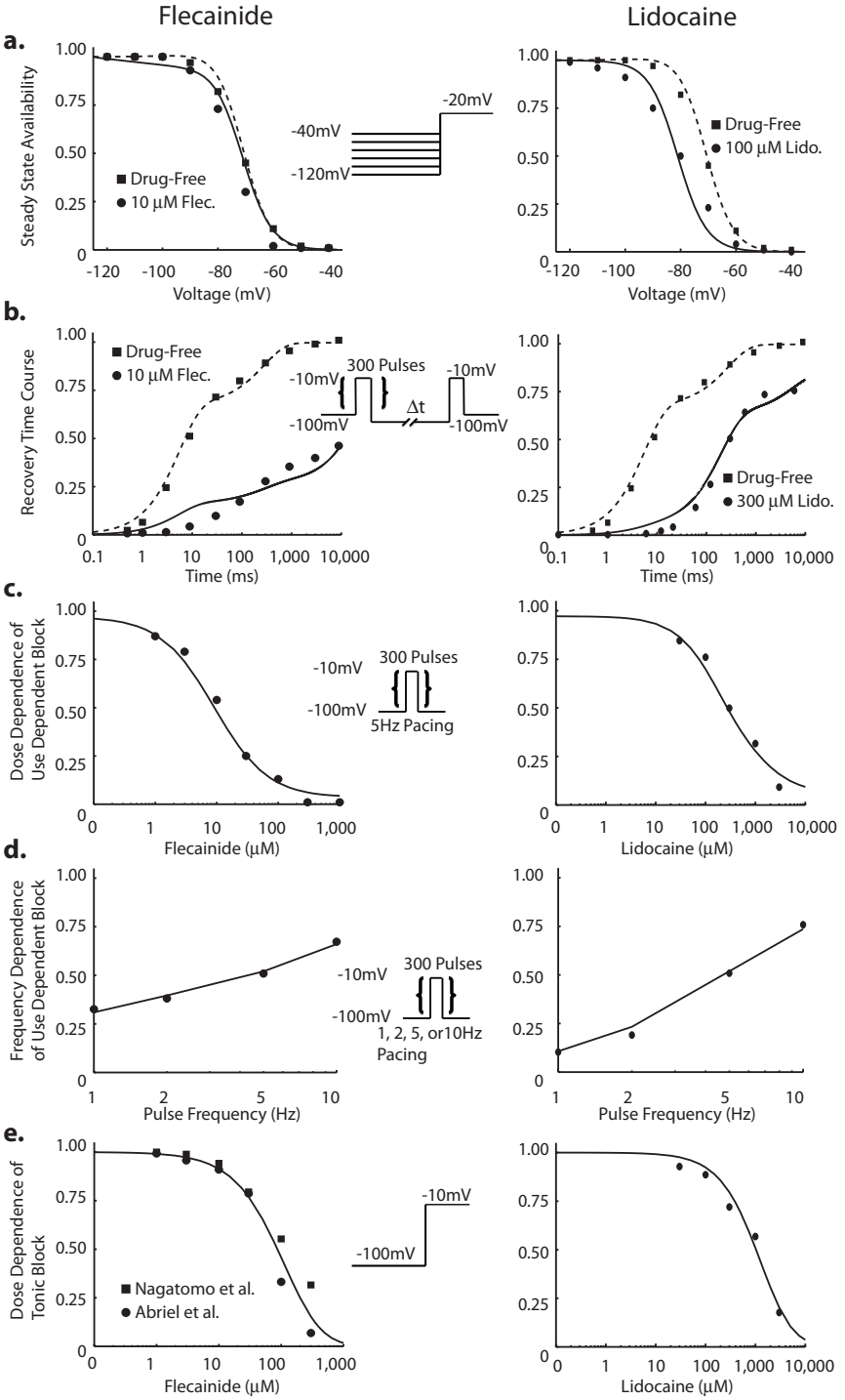
Ranolazine for Congenital and Acquired Late I_{Na}-Linked Arrhythmias: In Silico Pharmacological Screening

Jonathan D. Moreno, Pei-Chi Yang, John R. Bankston, Eleonora Grandi, Donald M. Bers, Robert S. Kass and Colleen E. Clancy

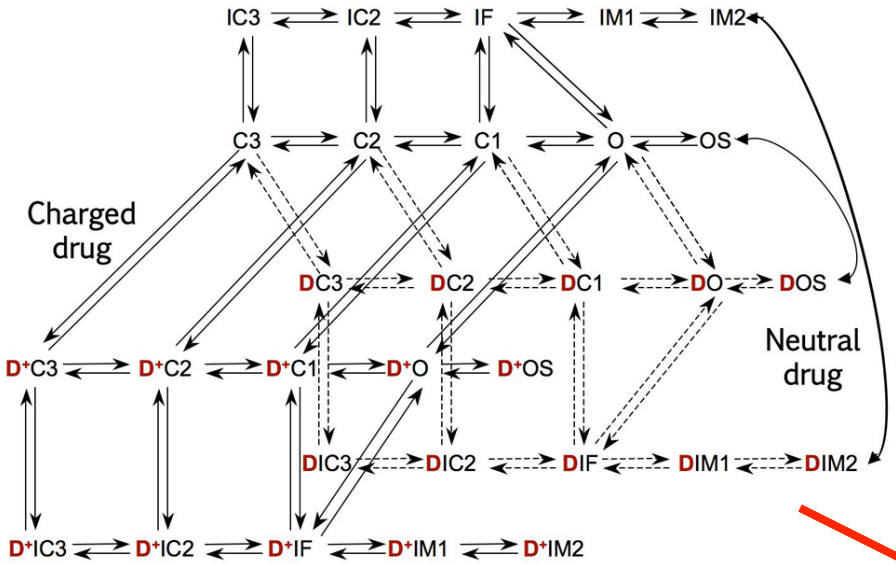
B.


IC3
α11
β11
IC2
α12
β12
IF
Drug Free
β3
α3
α2
β2
C3
C2
C1
O
αx
βx
IS
α13
β13
kcoff
koff
kc_off
k_off
ki_off
ki_on
Charged Drug
kc_on
k_on
DC3
DC2
DC1
DO
DIS
kcon
kon
D+C3
D+C2
D+C1
D+O
D+IS
Neutral Drug
DIC3
DIC2
DIF
(DIT)
D+IC3
D+IC2
D+IF
(D+IT)
α33
β33
α22
β22
α44
β44
αx1
βx1
α_11
β_11
α_12
β_12
α_13
β_13
α_33
β_33
α_22
β_22
α_44
β_44
αx2
βx2

Model fits to drug bound channel data

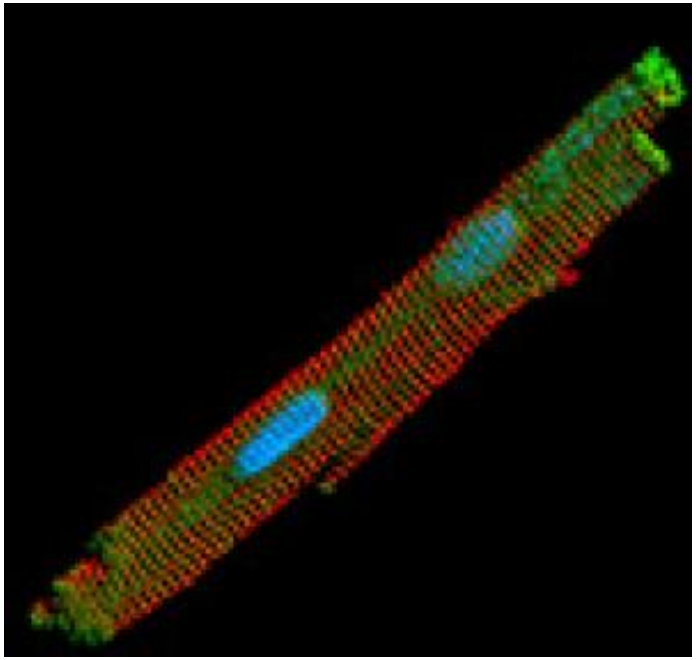


Drug Bound Channel



Simulations

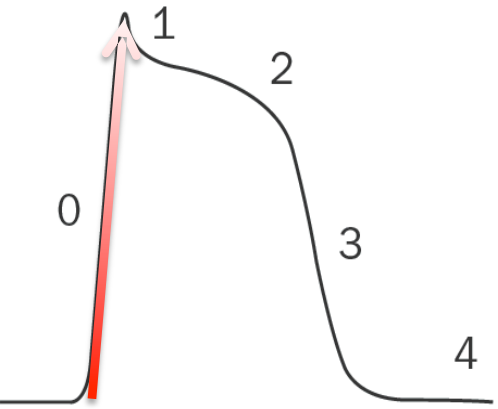
Cardiac Cell Model



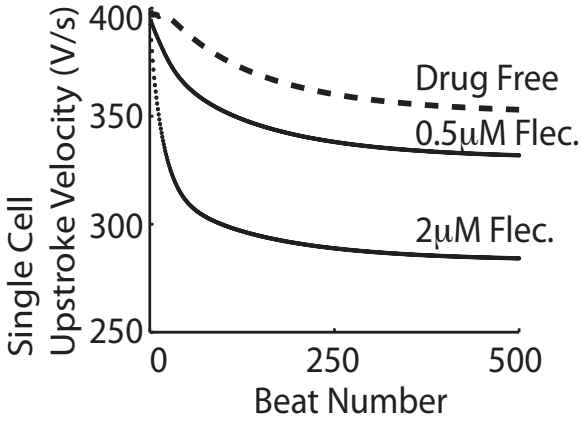
Predictions

Picture from *ScienceDaily* - University of Iowa (2008, May 5). Heart Disease Discovery: New Mechanism Links Activation Of Key Heart Enzyme And Oxidative Stress.

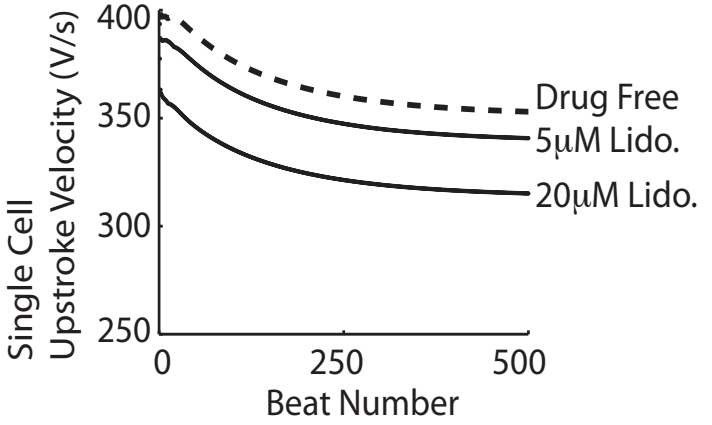
Effects of drugs on ***cell*** excitability

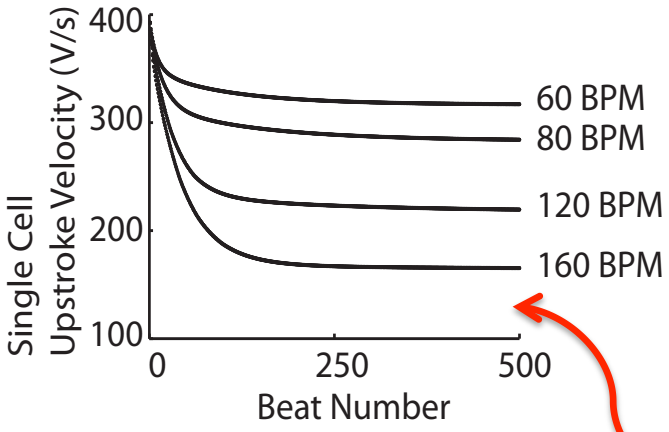


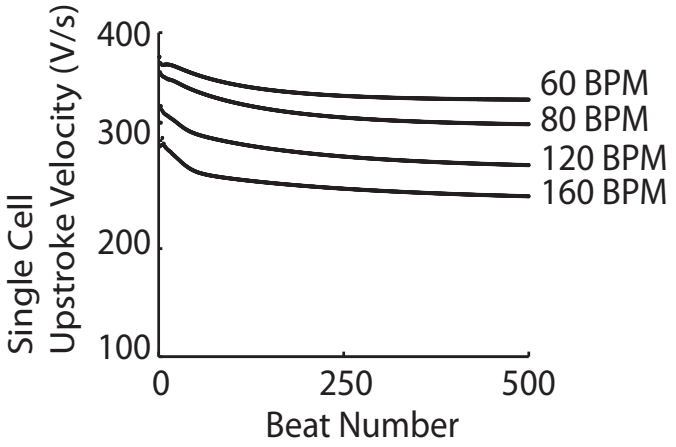
Flecainide



Lidocaine

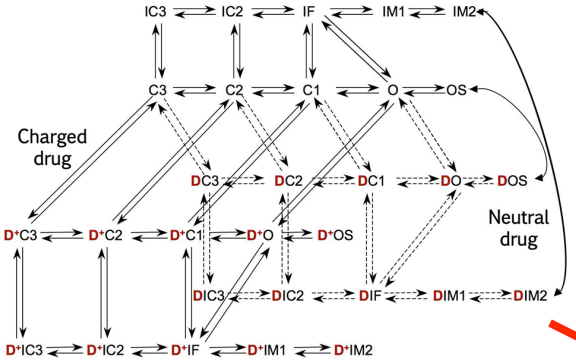




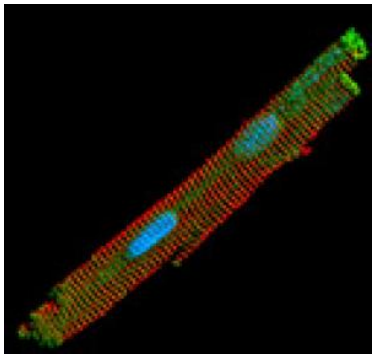


Increased ***Use-Dependent Block***

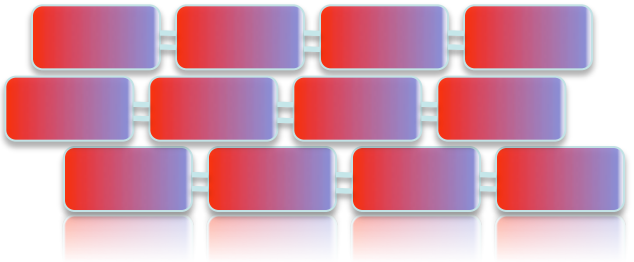
Drug Bound Channel



Cardiac Cell Model

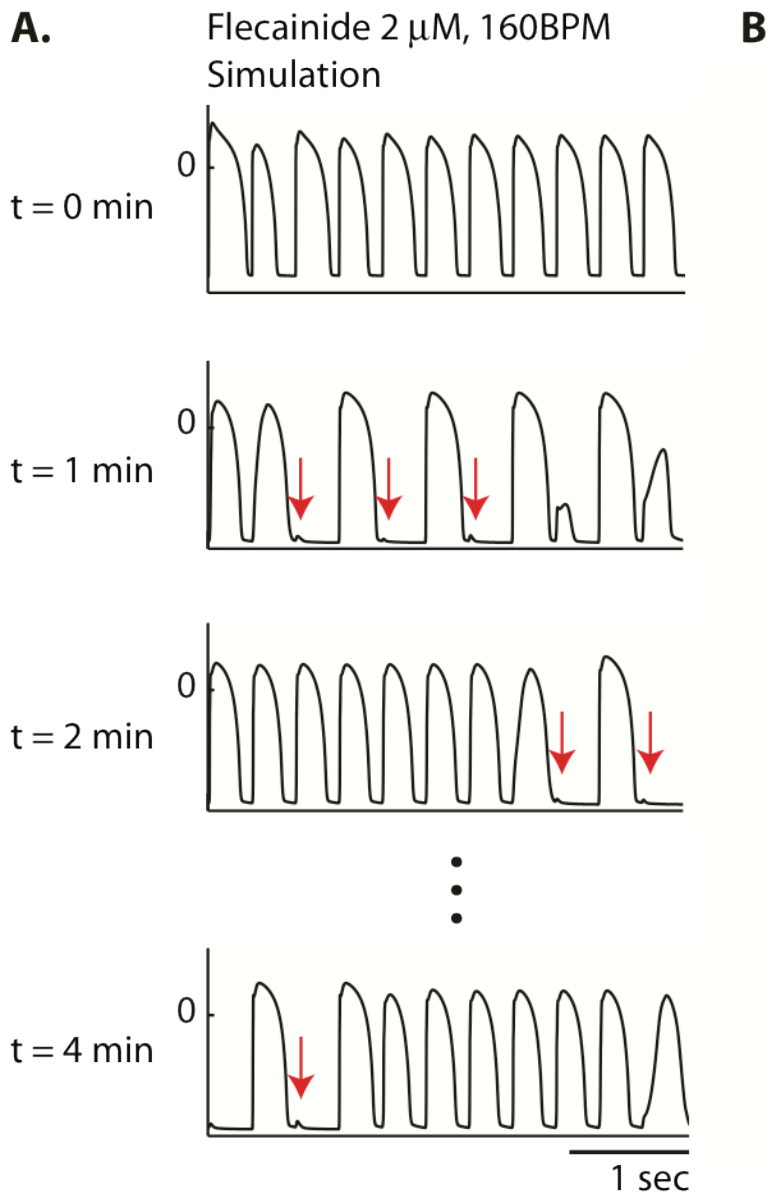


Multicellular Tissue



Picture from *ScienceDaily* - University of Iowa (2008, May 5). Heart Disease Discovery: New Mechanism Links Activation Of Key Heart Enzyme And Oxidative Stress.

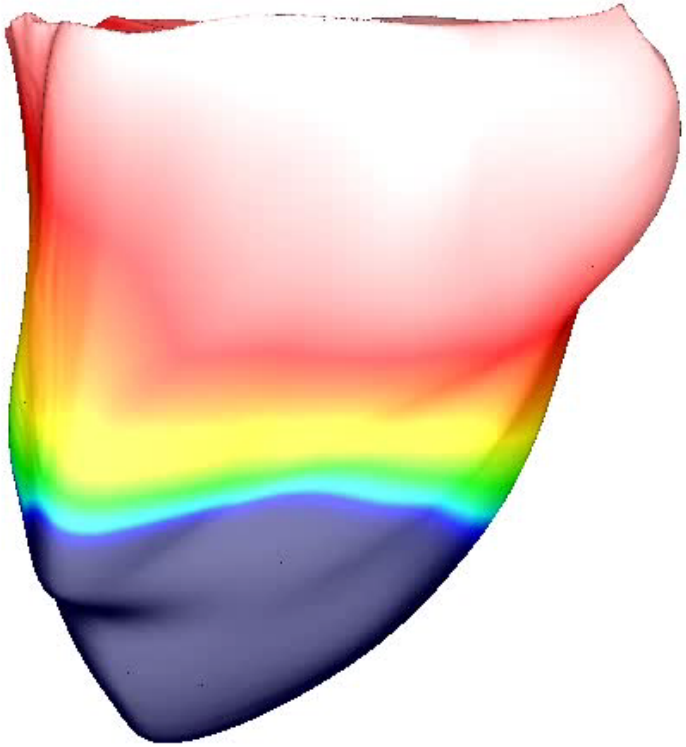
Tissue level proarrhythmic conduction blocks: prediction and validation



Drug effects on tissue dynamics

Persistent reentry with flecainide

No reentry with lidocaine



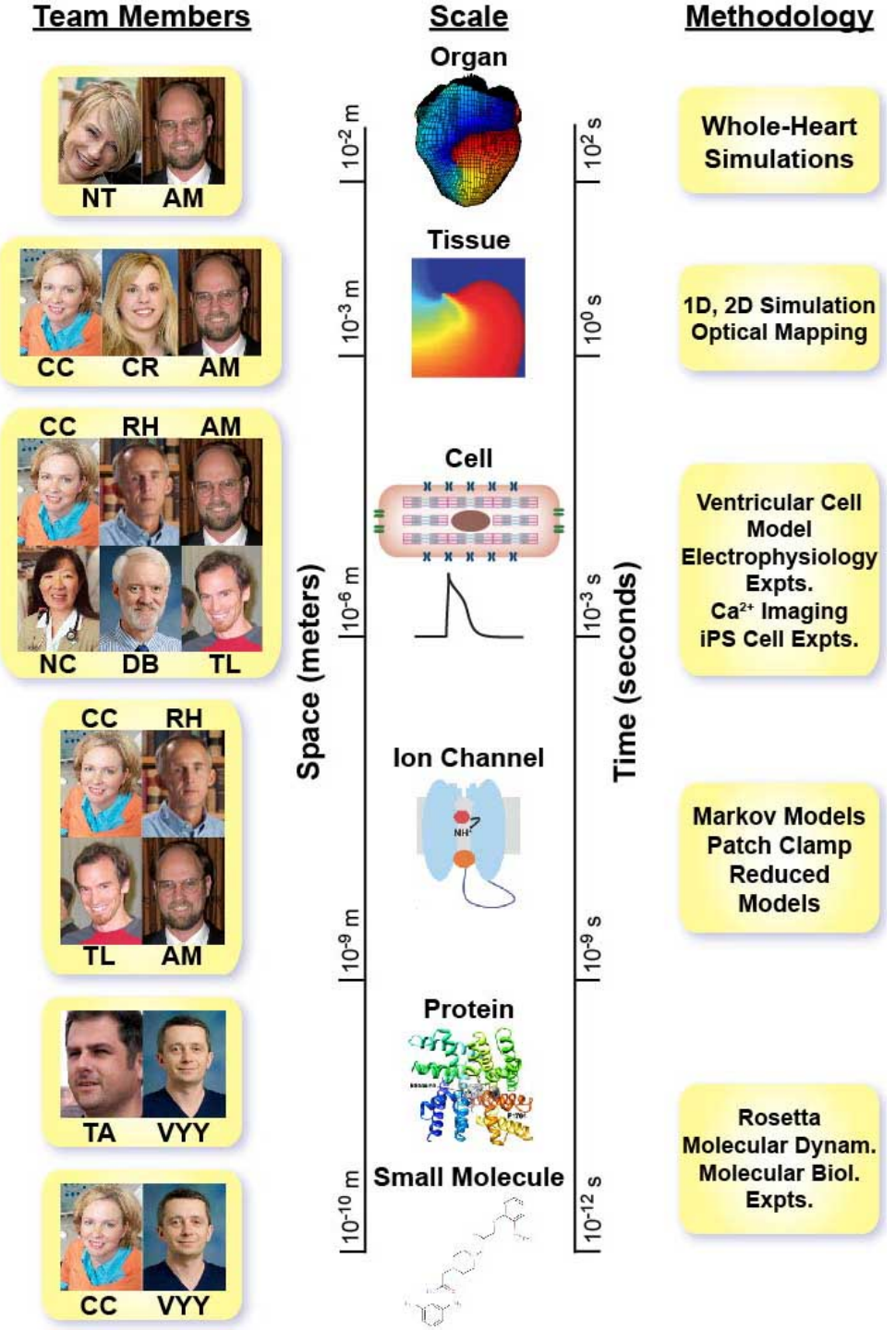
TRAYANOVA LAB (Johns Hopkins)

What's next?

Predictive multiscale computational pharmacology

Atomic to Organ

Computational EXPERIMENTS



What's next?

Development of a computational pharmacology working group as part of the MSM consortium.

ACKNOWLEDGEMENTS

National Institute of General Medical Sciences

NIH National Heart, Lung, and Blood Institute

Alfred P. Sloan Foundation

PhRMA Foundation

American Heart Association. Learn and Live.

GILEAD Advancing Therapeutics. Improving Lives.

Epilepsy Foundation. Not another moment lost to seizures.

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