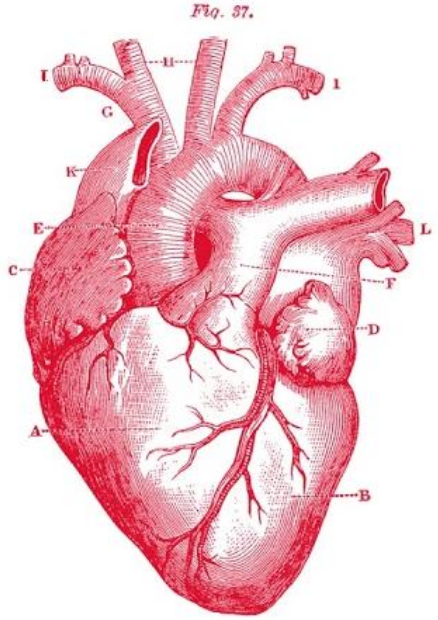
ROSA Worldwide Webinar Series

Cross-species translation of drug-induced electrophysiological response in cardiac myocytes



Stefano Morotti
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University of California Davis

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@MorottiLab

Outline

- Inter-species differences in cardiac electrophysiology
- Impact on drugs' cardiotoxicity screening
- Development of cross-species translators
- Experimental validation
- Future directions

All source codes are freely available for download at github.com/drgrandilab

Acknowledgements

Ele Grandi

Haibo Ni

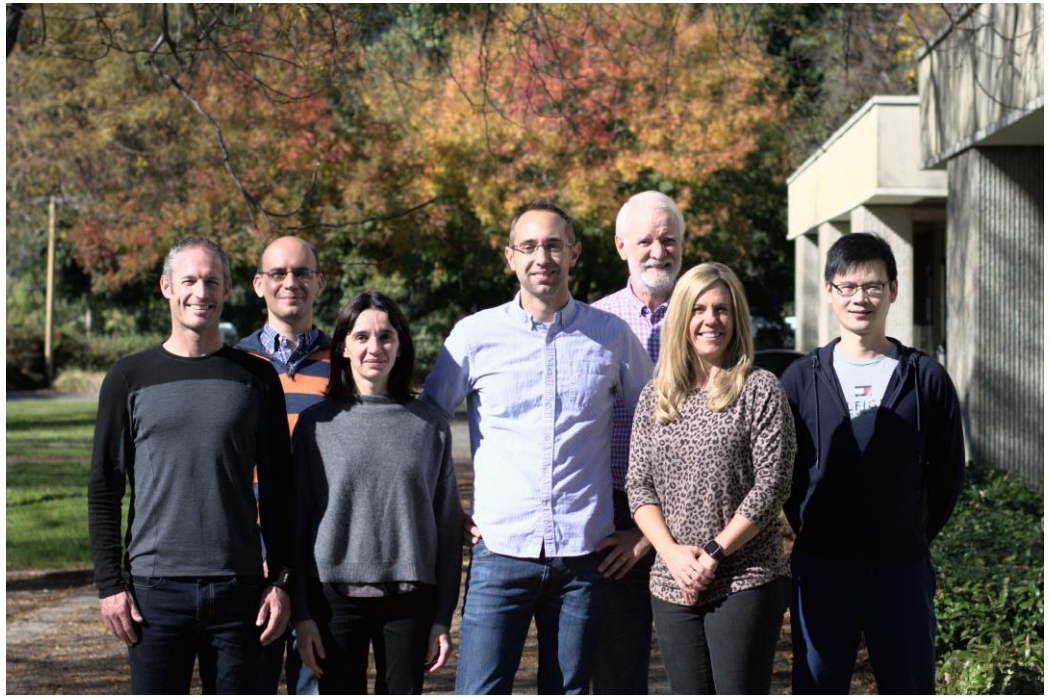
Alex Fogli Iseppe

Xianwei Zhang

Lin-Lin Liu

Andy Edwards

UC DAVIS HEALTH



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Bence Hegyi

Kim Hellgren

BERKELEY LAB

Marco Pritoni

NIH National Heart, Lung, and Blood Institute

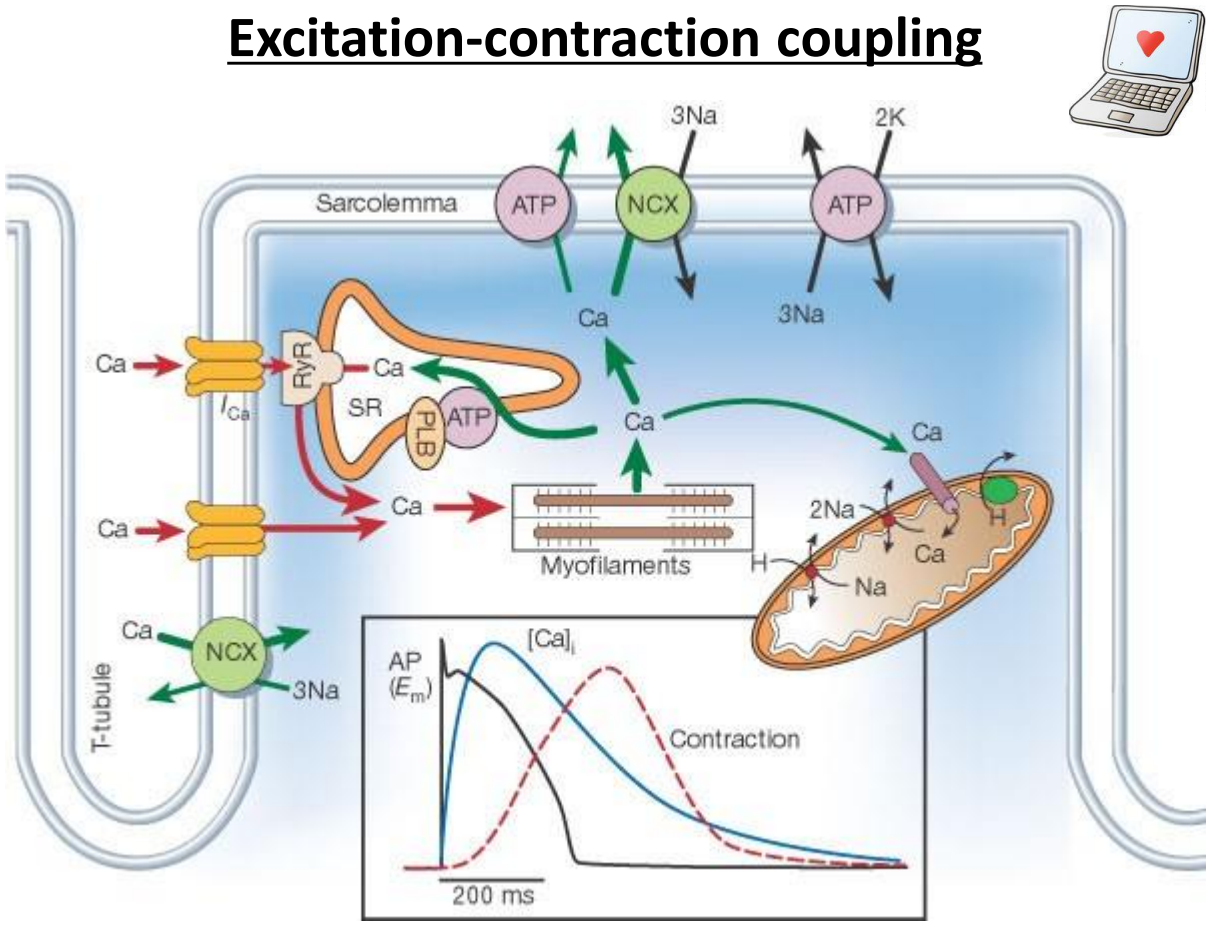
SPARC

BURROUGHS WELLCOME FUND

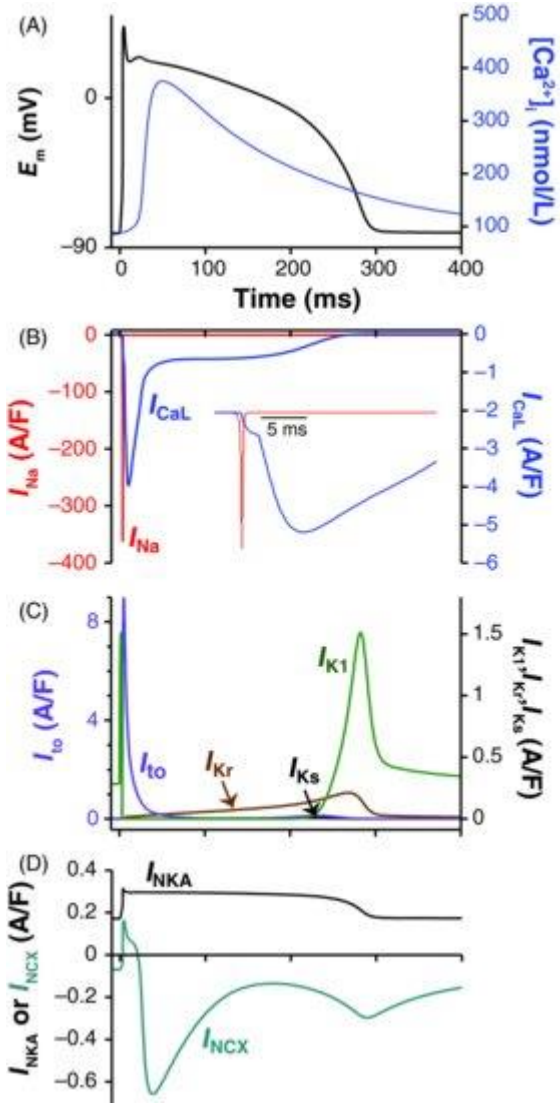
DORIS DUKE CHARITABLE FOUNDATION

Cardiomyocyte electrophysiology

Excitation-contraction coupling



Action Potential (**AP**) – Ca Transient (**CaT**) – Myofilament Contraction

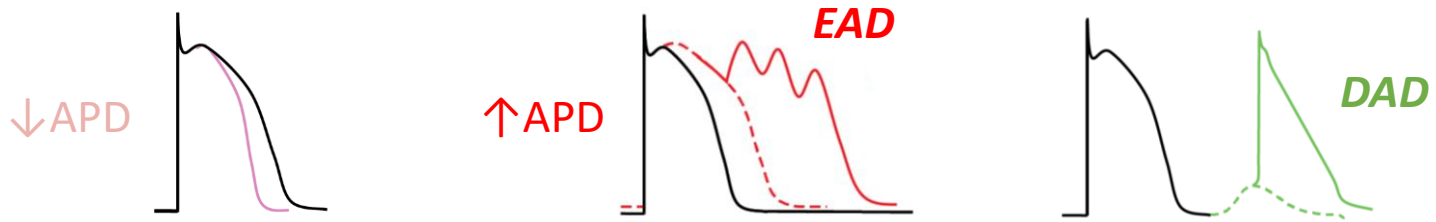


Bers, *Nature*. 2002

Grandi & Bers, in *Cardiac Electrophysiology: From Cell to Bedside*. 2013

AP regulation & arrhythmias

- Impaired AP regulation facilitates both development & maintenance of arrhythmias

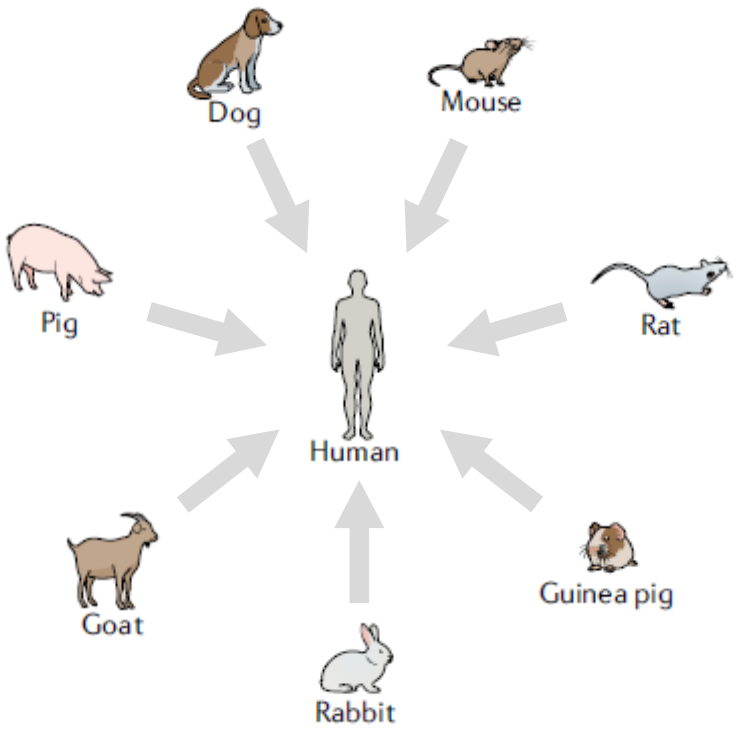


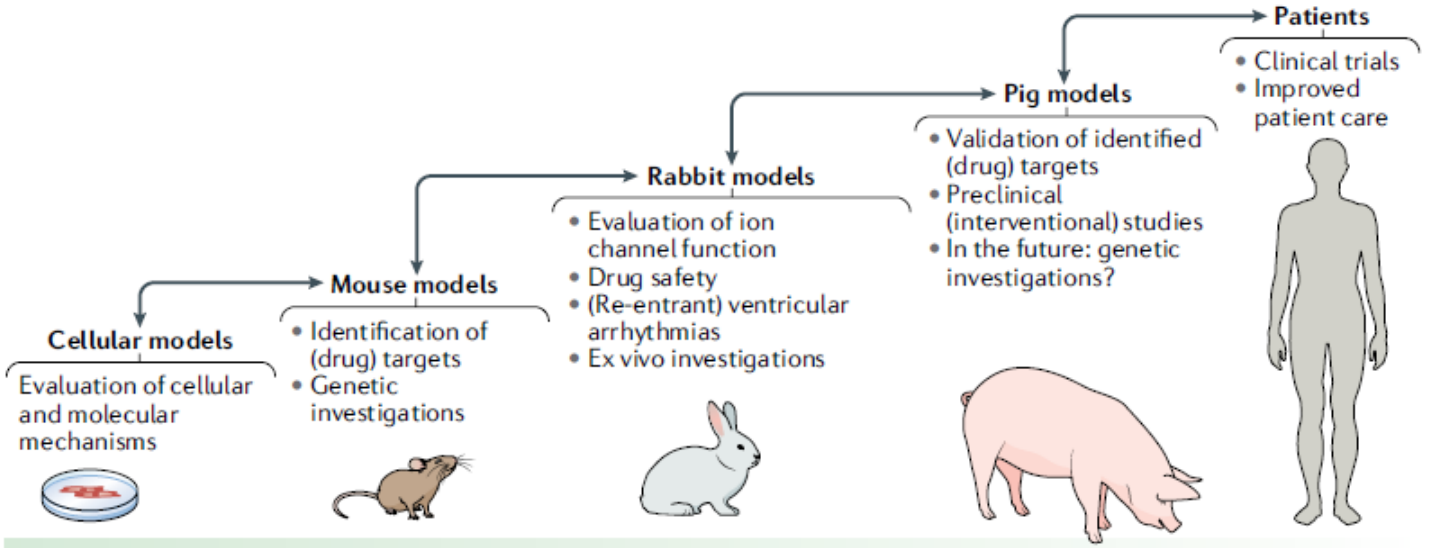
Vulnerable substrate *Ectopic activity*

- Inherited conditions
  (long QT, Brugada, etc.)
- Acquired conditions
  (heart failure, atrial fibrillation, etc.)
- Drug-induced
  (Torsade de Pointes, brady-arrthyhmias, etc.)

Cardiotoxicity screening of novel compounds (pre-clinical trials)

Animal models in arrhythmia research

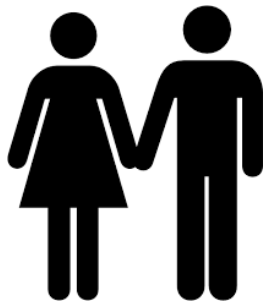


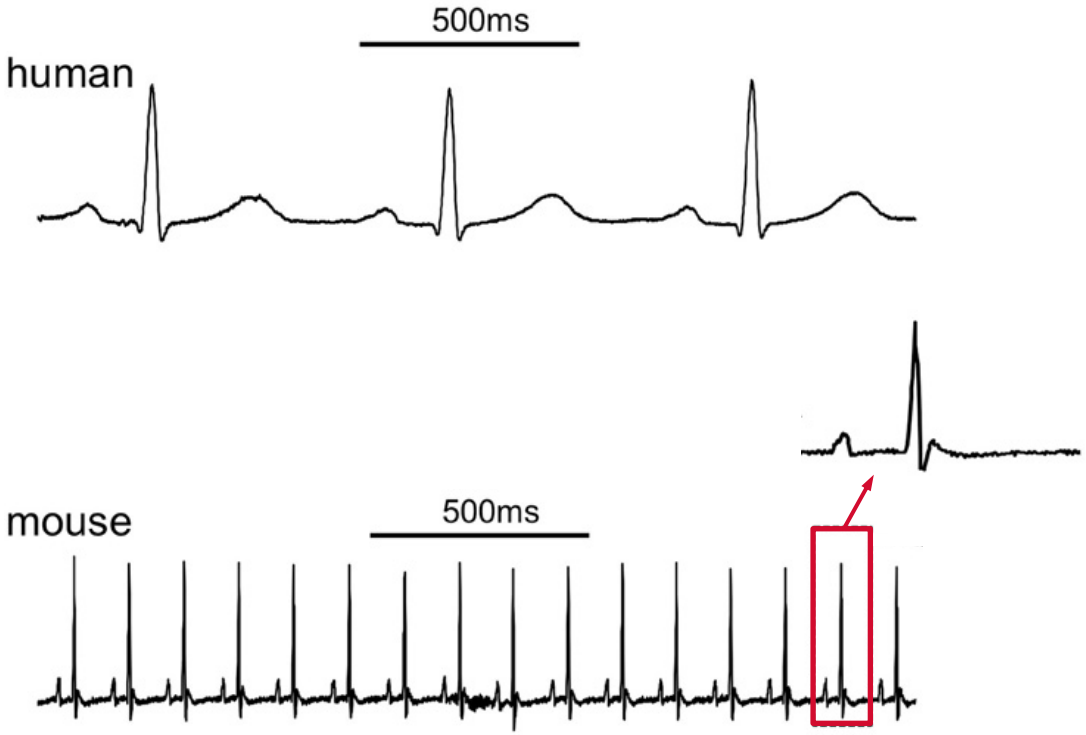


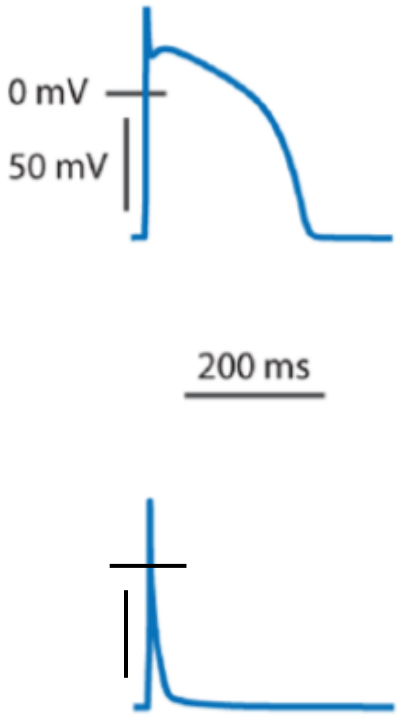
	Mouse models	Rabbit models	Pig models
Advantages	• Availability • Transgenic mice • Housing and breeding at most institutions • Low costs • High societal acceptance	• Availability • Housing and breeding at most institutions • Relatively low costs • Vetricular electrophysiology • Ideal for ex vivo studies • High societal acceptance	• Availability • Cardiovascular anatomy • Electrophysiology • Instrumentation (regular electrophysiology study is possible and human equipment can be used) • Growing number of transgenic pigs • Relatively high societal acceptance
Disadvantages	• Cardiovascular anatomy • Electrophysiology • Not every model or experiment is possible	• Only a few transgenic rabbits • Atrial electrophysiology • Not every model or experiment is possible	• Housing and breeding possible only at a few institutions • High costs • Time-consuming and labour-intensive

Clauss et al., *Nat Rev Cardiol.* 2019

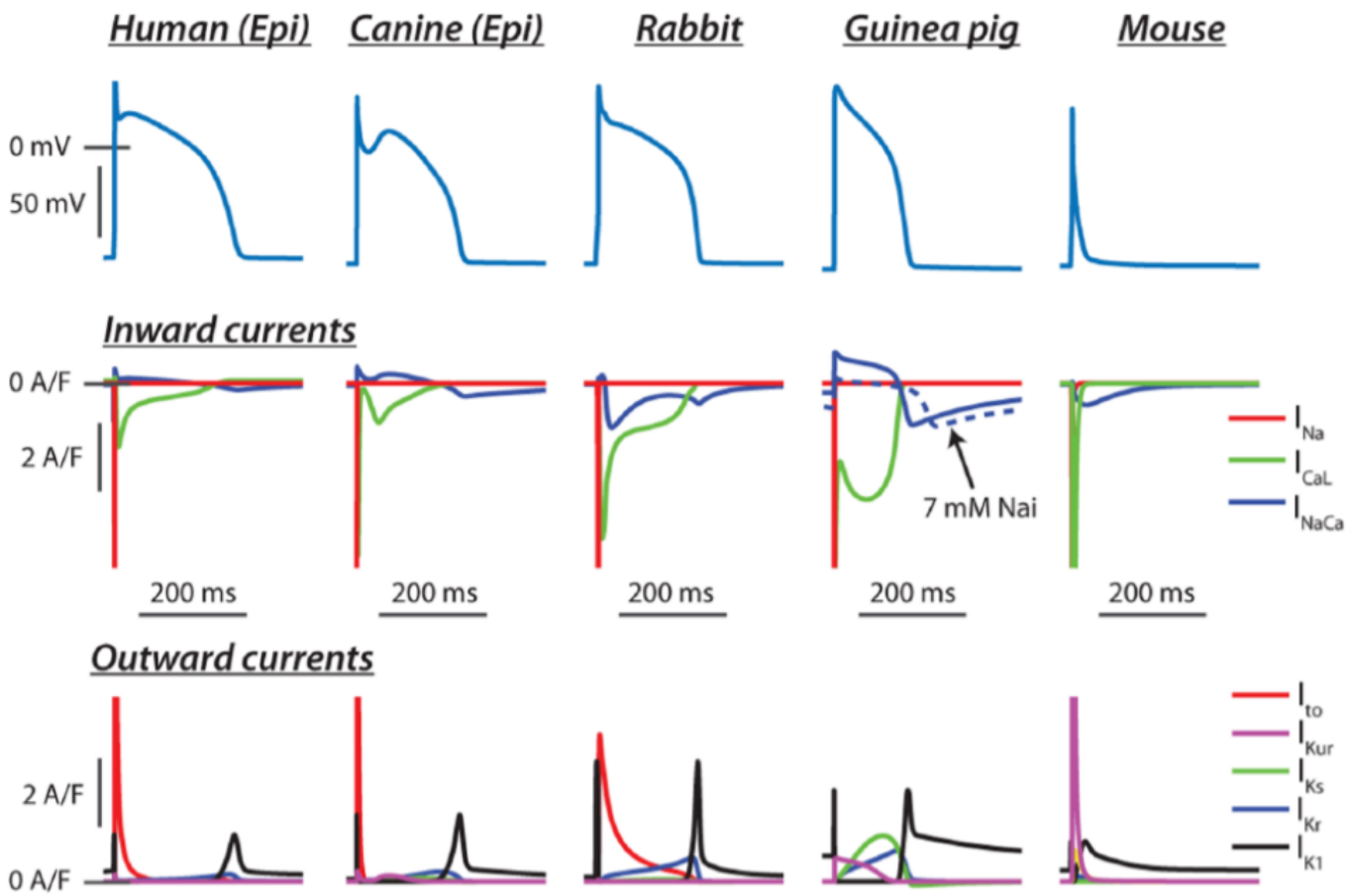
Inter-species differences in cardiac electrophysiology



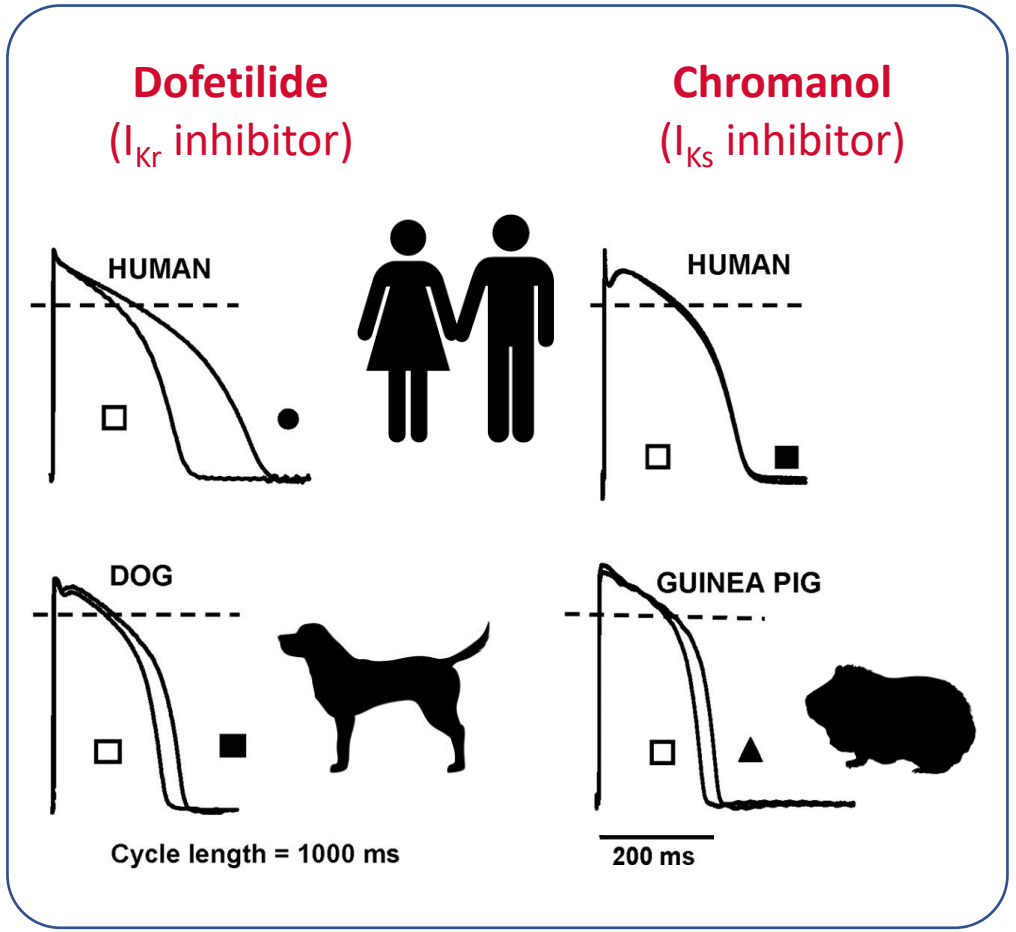




Inter-species differences in ventricular electrophysiology



Edwards & Louch, *Clin Med Insights Cardiol.* 2017



Rudy et al., *Circulation.* 2008

Impact on drugs' cardiotoxicity screening

JACC: BASIC TO TRANSLATIONAL SCIENCE

VOL. 4, NO. 7, 2019

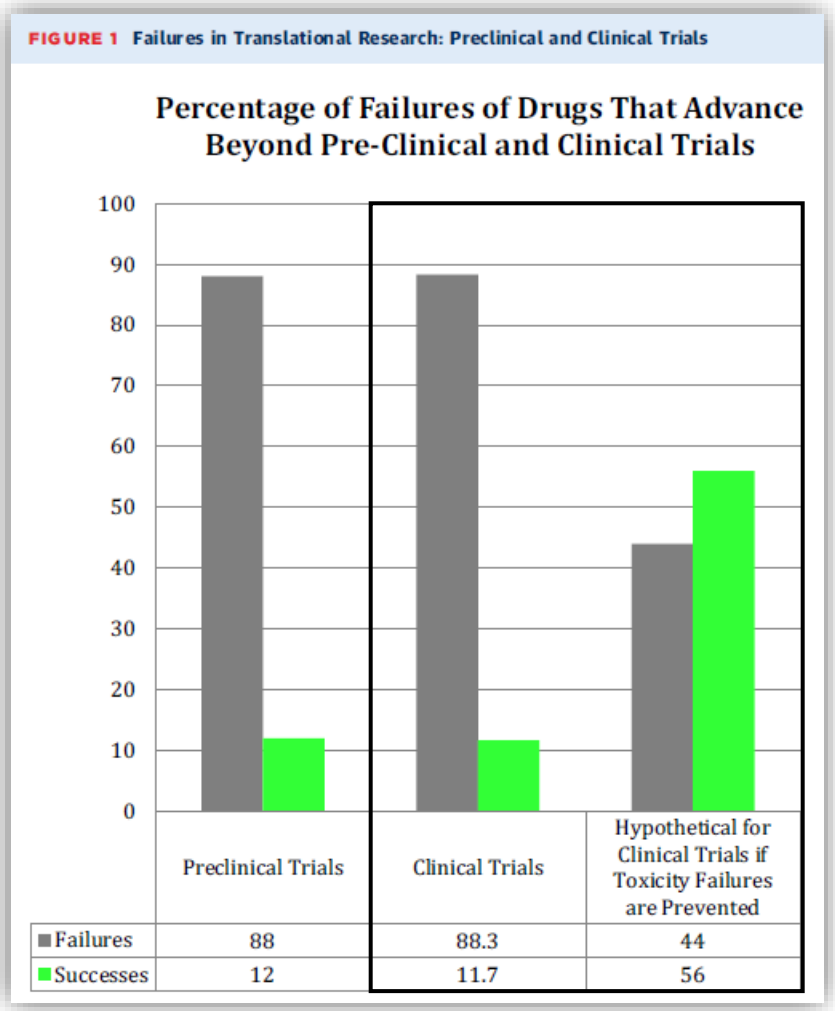
TRANSLATIONAL PERSPECTIVE

Limitations of Animal Studies for Predicting Toxicity in Clinical Trials

Is it Time to Rethink Our Current Approach?

Gail A. Van Norman, MD

FIGURE 1 Failures in Translational Research: Preclinical and Clinical Trials



Van Norman, *JACC Basic Transl Sci.* 2020

Impact on drugs' cardiotoxicity screening

JACC: BASIC TO TRANSLATIONAL SCIENCE

VOL. 4, NO. 7, 2019

TRANSLATIONAL PERSPECTIVE

We must systematically characterize species-differences in the regulation of cardiomyocyte electrophysiology

FIGURE 1 Failures in Translational Research: Preclinical and Clinical Trials

Percentage of Failures of Drugs That Advance Beyond Pre-Clinical and Clinical Trials

	Preclinical Trials	Clinical Trials	Hypothetical for Clinical Trials if Toxicity Failures are Prevented
Failures	88	88.3	44
Successes	12	11.7	56

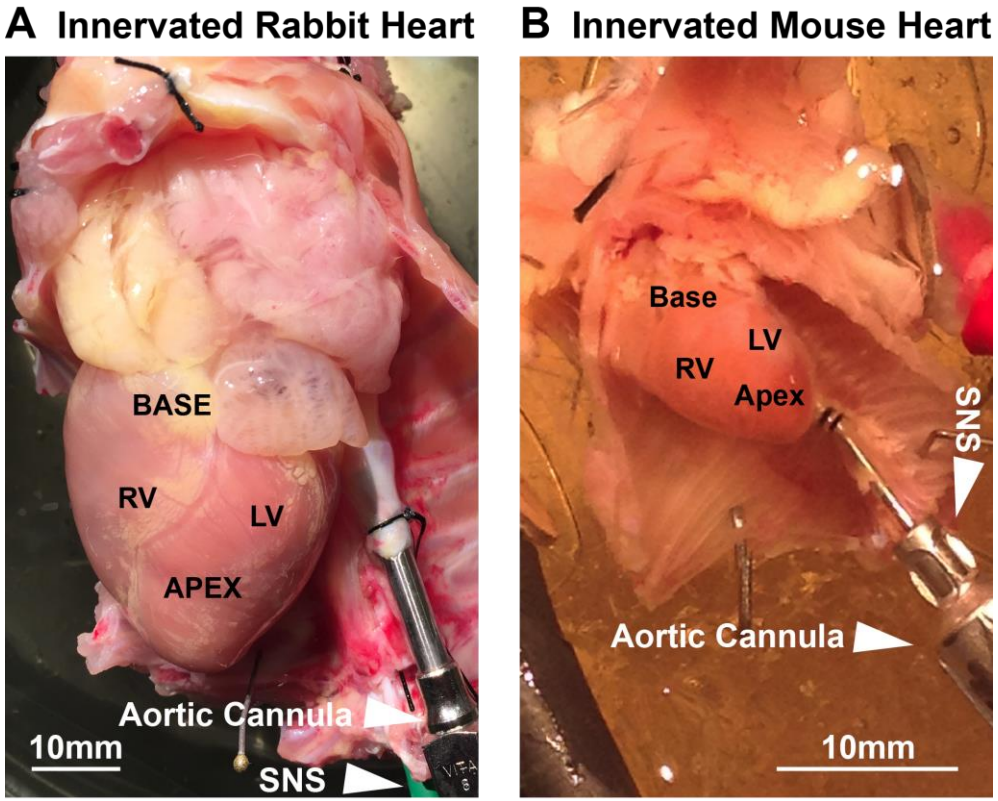
Van Norman, *JACC Basic Transl Sci.* 2020

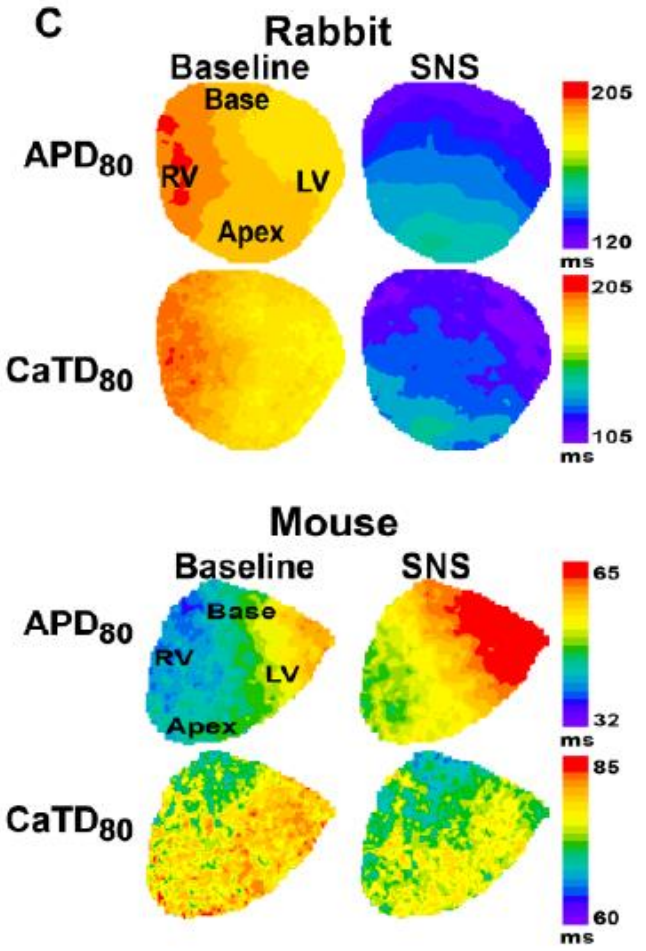
Species-differences in response to β-adrenergic stimulation

i) β-AR signaling mediates the well-known *fight-or-flight* response, a conserved mammalian behavior

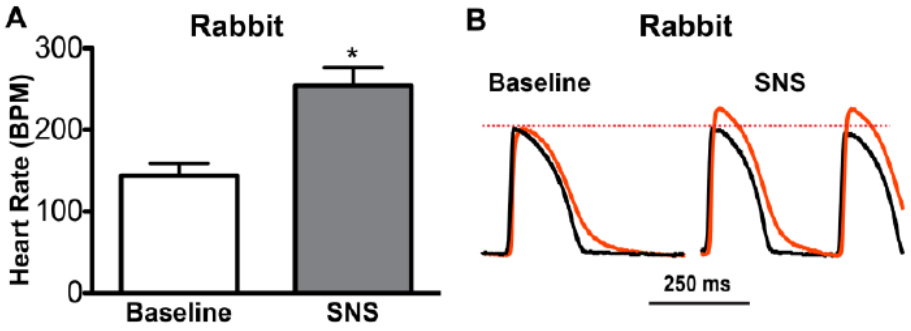
ii) β-AR stimulation is associated with increased propensity for cardiac arrhythmias

Sympathetic nerve stimulation (SNS) in whole-heart preparations

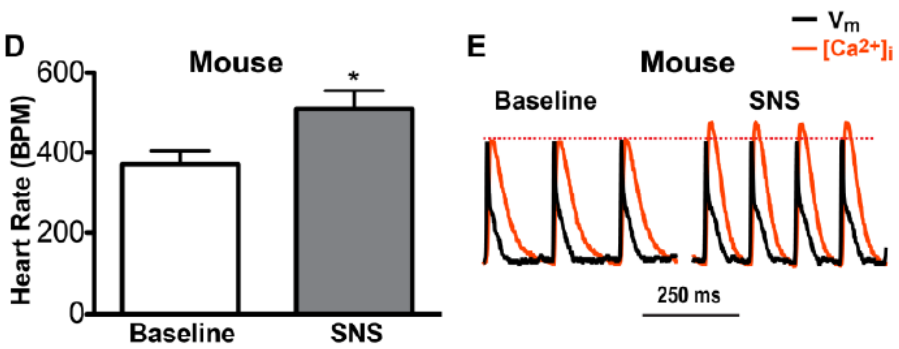


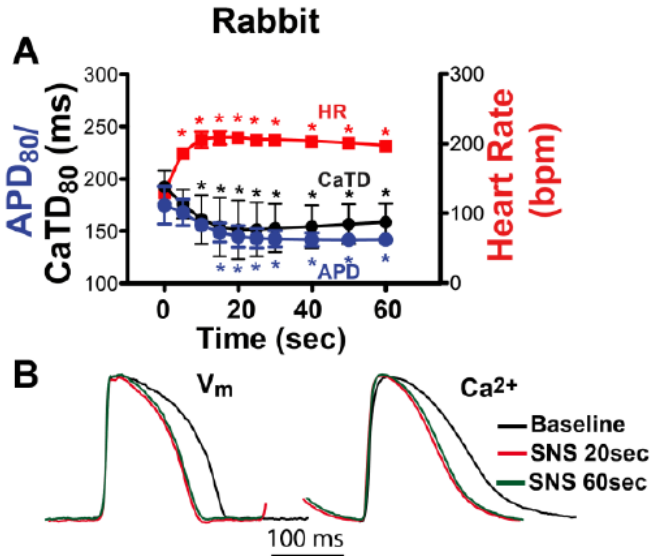


Consequences of SNS in rabbit vs. mouse

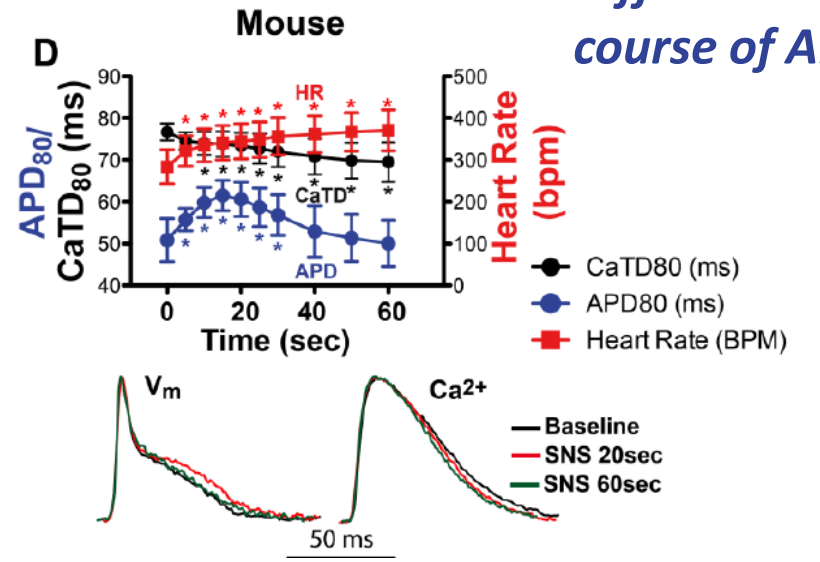


Conserved chronotropic & inotropic response





Different time course of APD



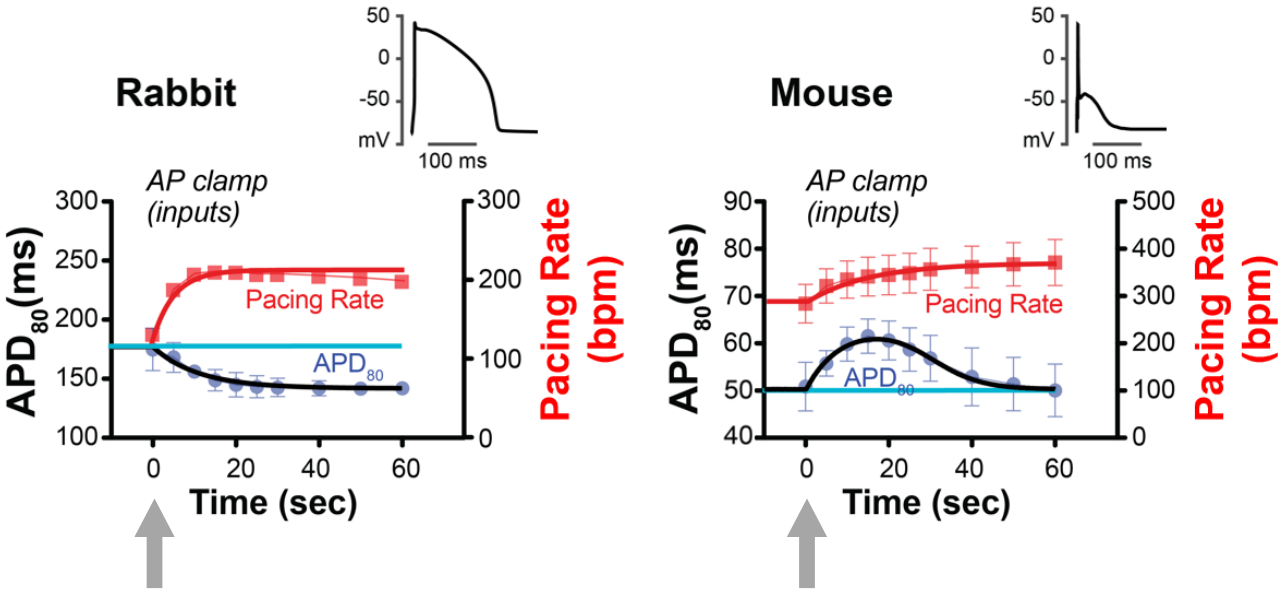
Wang et al., *J Physiol.* 2019

Ripplinger Lab, UC Davis

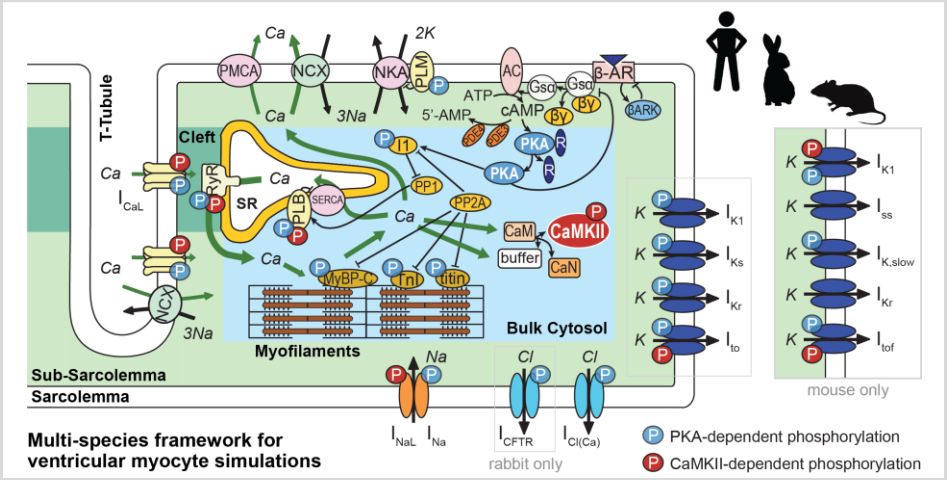
AP-clamp simulations reveal inter-species differences

Input:
time-dependent modulation of pacing rate and APD + ISO administration

Output:
time course of CaT amplitude (*inotropy*) and time constant of CaT decay (*lusitropy*)



Deterministic ODE models of AP, Ca transient, & myofilament contraction in ventricular myocytes



Based on
Grandi et al., 2010, Moreno et al., 2013 (**Human**);
Shannon et al., 2004, Soltis & Saucerman, 2012, Negroni et al., 2015, Bartos et al., 2017 (**Rabbit**);
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Wang et al., *J Physiol.* 2019

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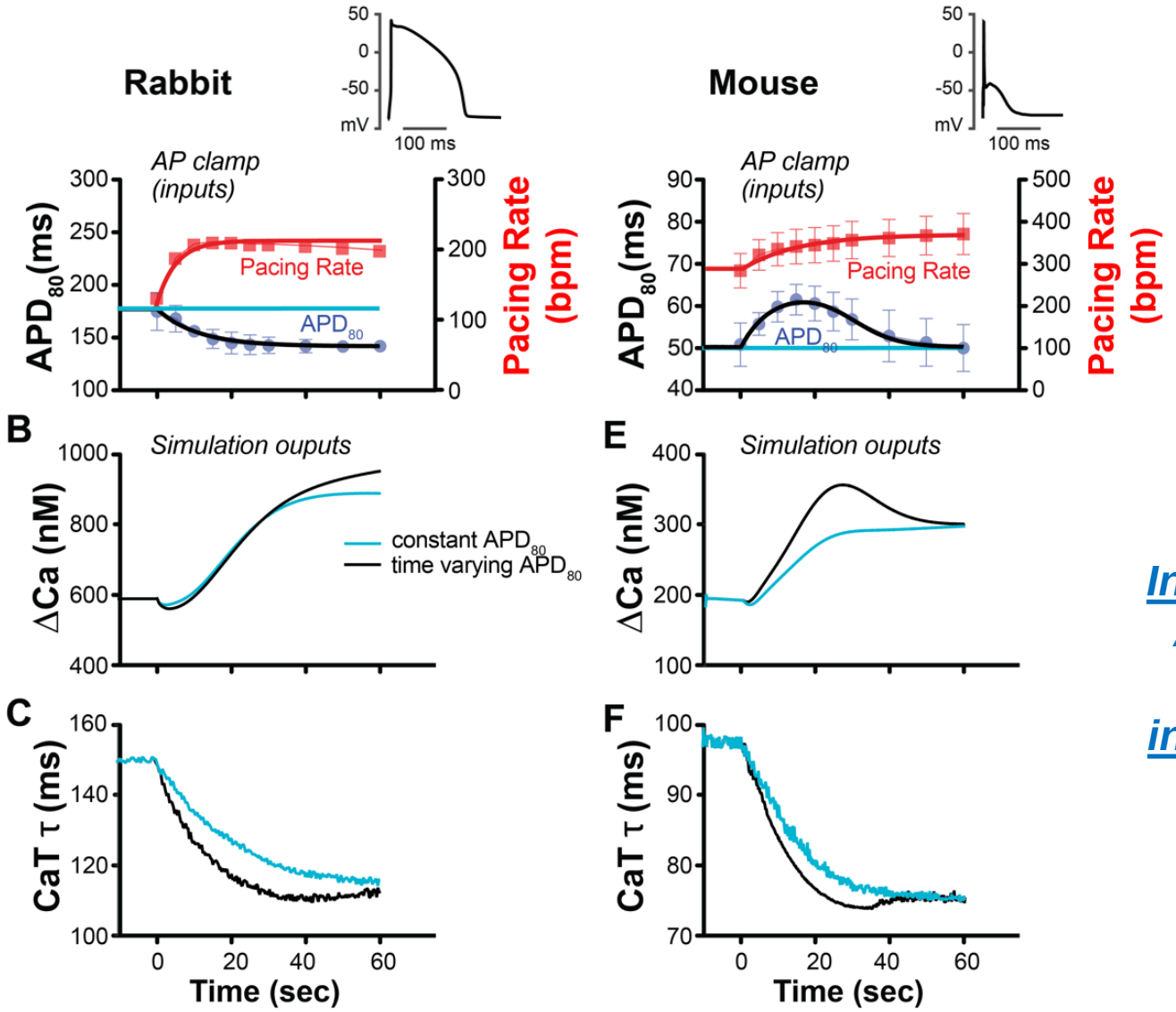

Inter-species differences in AP repolarization lead to optimal enhancement of inotropy & lusitropy during fight-or-flight response

Wang et al., *J Physiol.* 2019

AP-clamp simulations reveal inter-species differences

Input:
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+ ISO administrat

Output:
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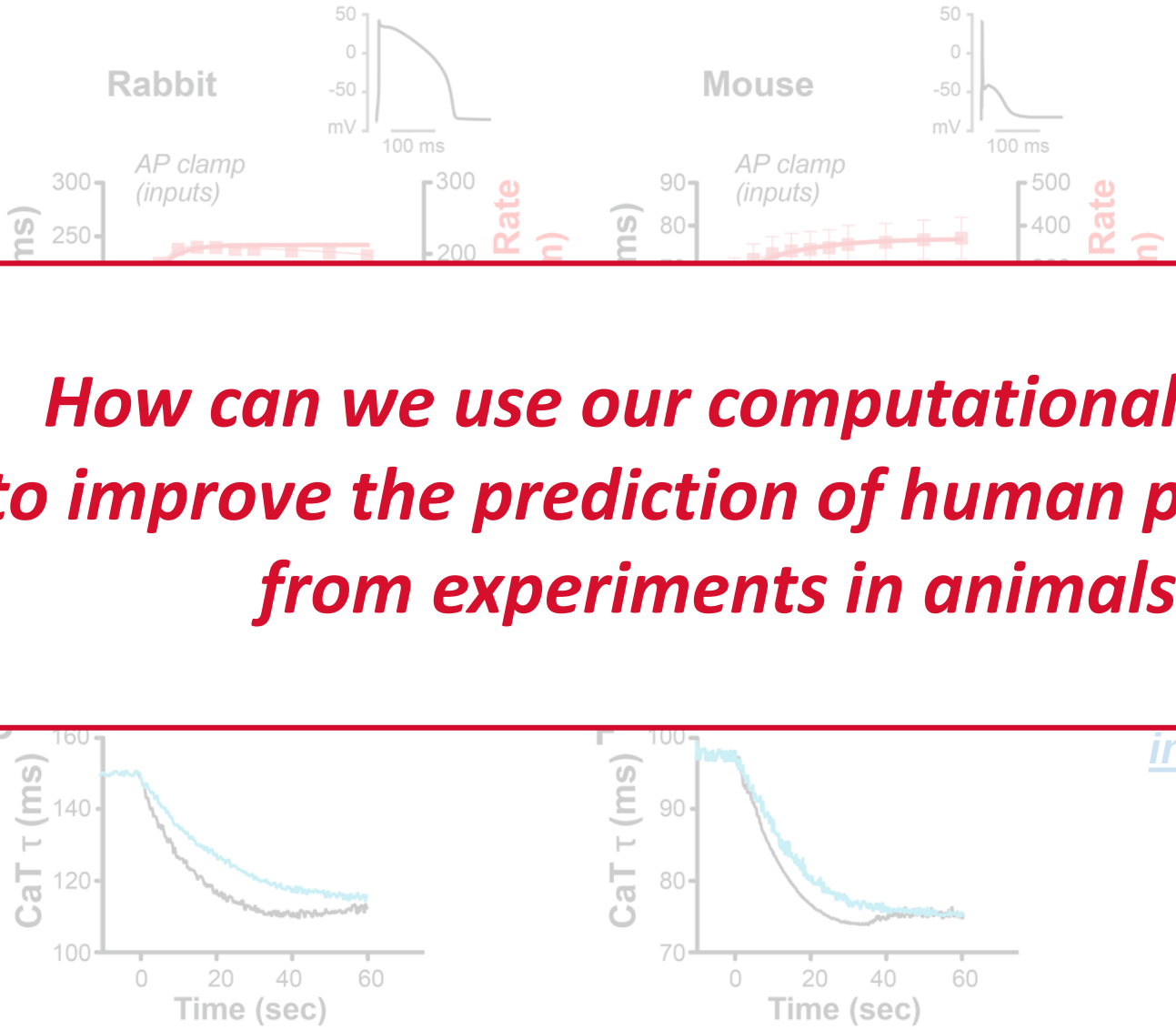

How can we use our computational models to improve the prediction of human physiology from experiments in animals?

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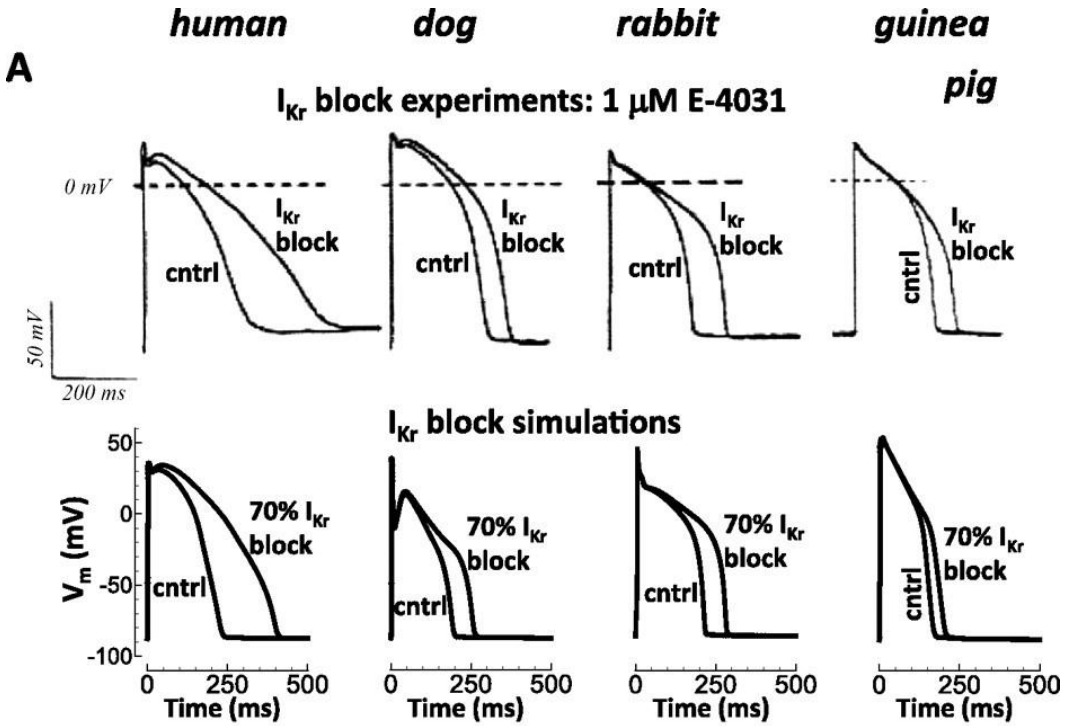
inotropy & lusitropy during
fight-or-flight response

Wang et al., *J Physiol.* 2019

Existing computational approaches

- Comparing simulations performed in different species

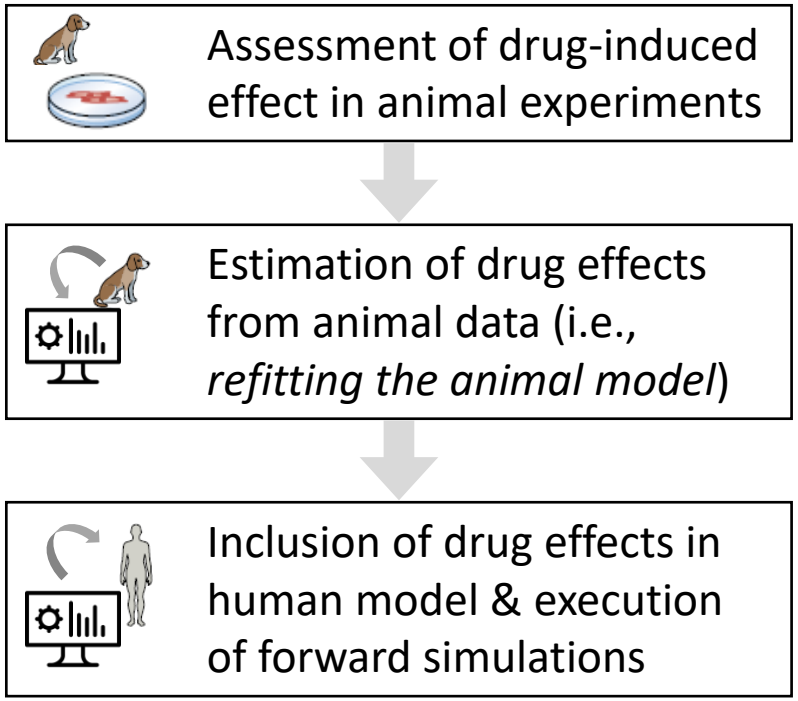


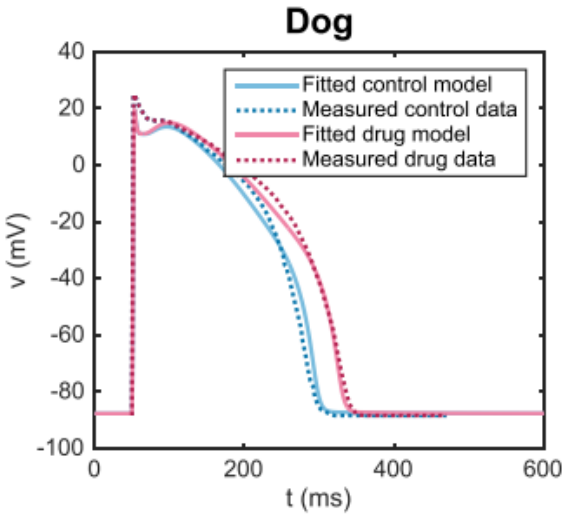
O'Hara & Rudy, *Am J Physiol Heart Circ Physiol.* 2012

Existing computational approaches

- Comparing simulations performed in different species

- Cross-species translation based on estimation of drug effects from animal experiments, and execution of new simulations with human model





SCIENTIFIC REPORTS
nature research
Check for updates

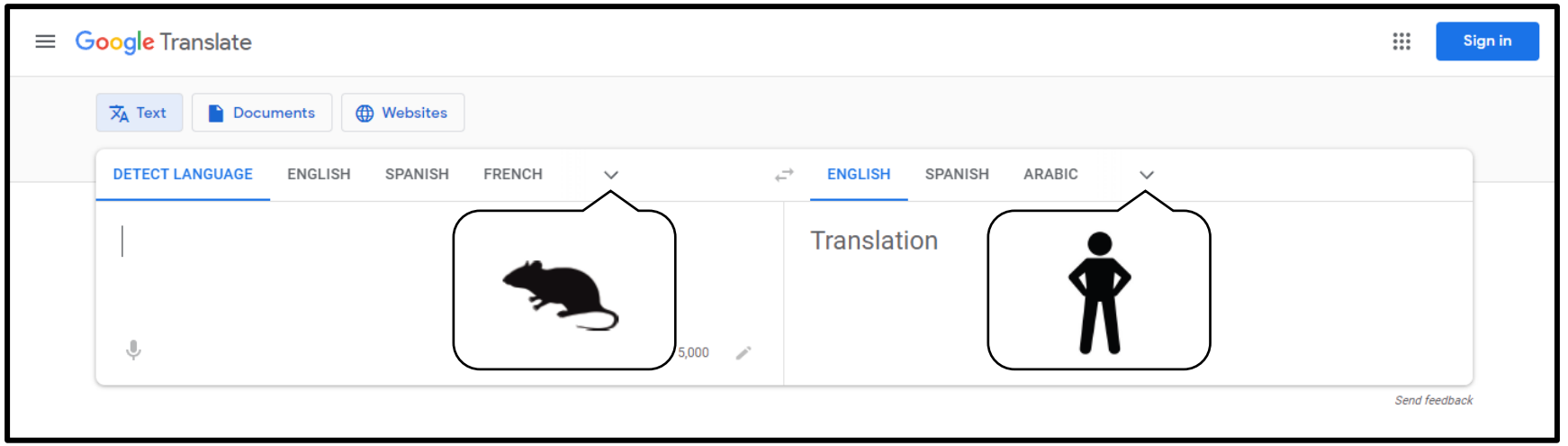
Computational translation of drug effects from animal experiments to human ventricular myocytes

Aslak Tveito[1]✉, Karoline Horgmo Jæger[1], Mary M. Maleckar[1], Wayne R. Giles[2] & Samuel Wall[1]

Tveito et al., *Sci Rep.* 2020

Goal: to develop an *immediate* cross-species translator

Assessment of drug-induced effect in animal experiments



Quantitative prediction of drug-induced effect in human

A previously developed *immediate* translator

ARTICLE OPEN

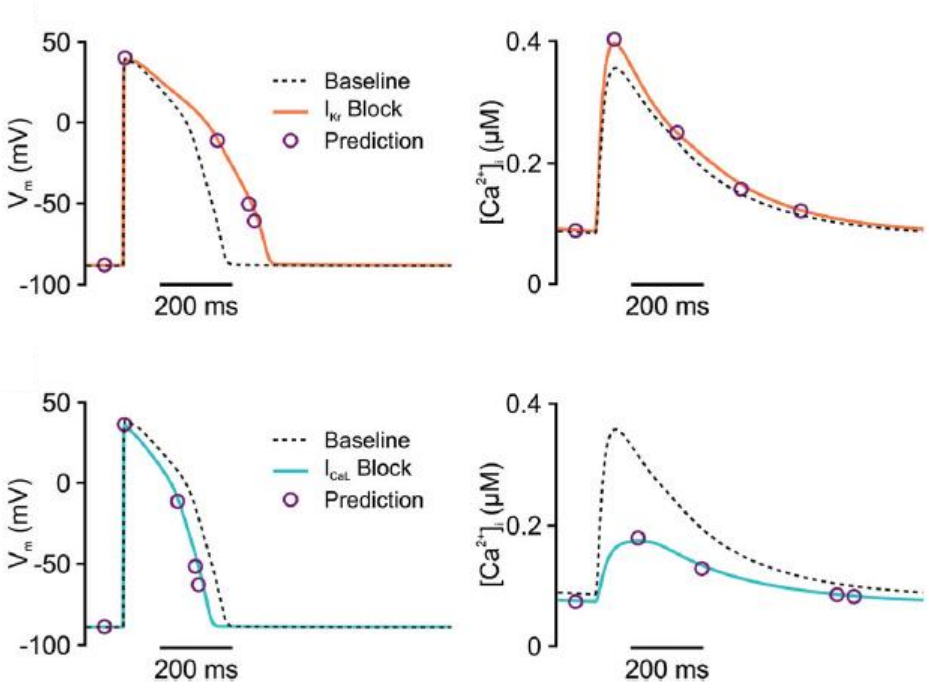
Population-based mechanistic modeling allows for quantitative predictions of drug responses across cell types

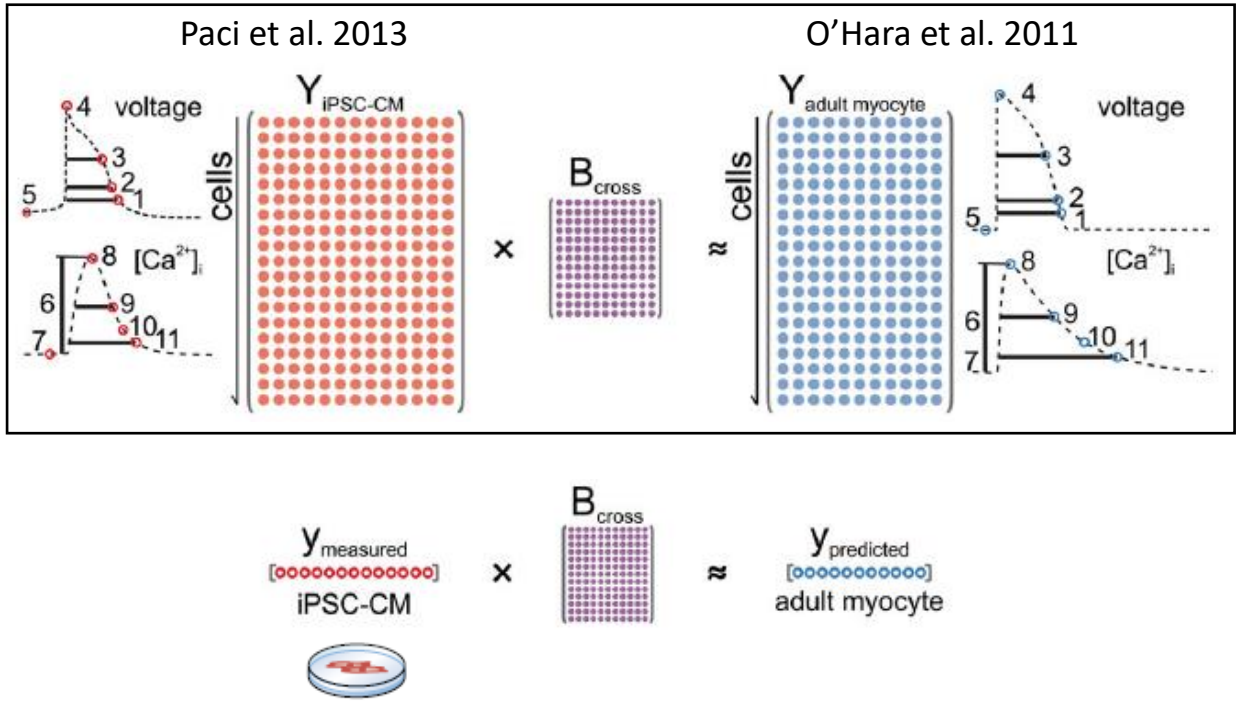
Jingqi Q. X. Gong[1] and Eric A. Sobie[1]

[1]Department of Pharmacological Sciences, Icahn School of Medicine at Mount Sinai, New York, NY, USA
Correspondence: Eric A. Sobie (eric.sobie@mssm.edu)

npj | Systems Biology and Applications

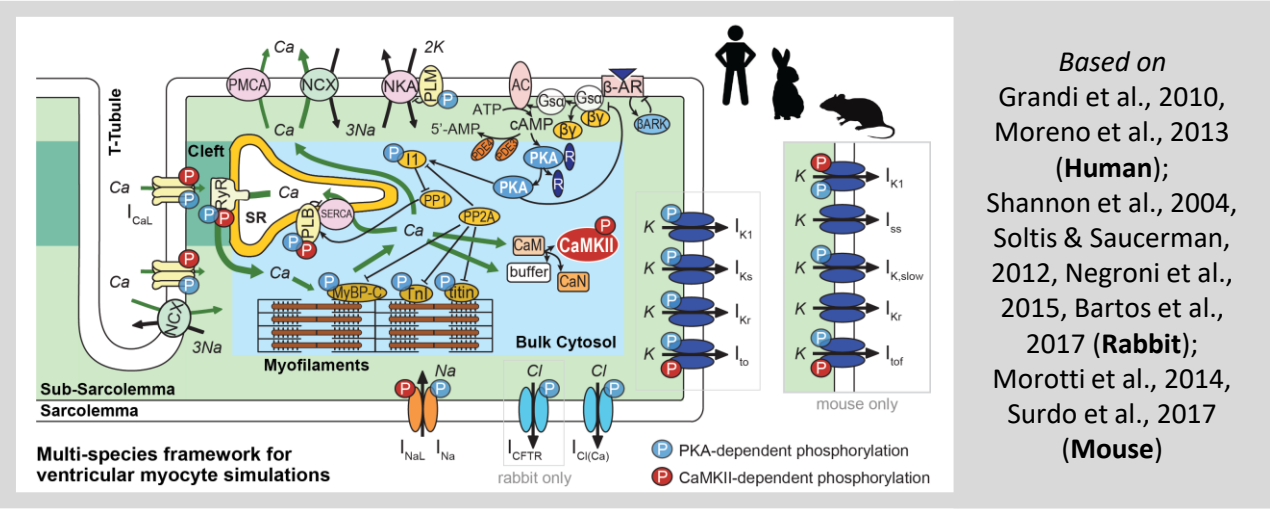
Response in **hiPSC-CM** → Response in adult **HVM**



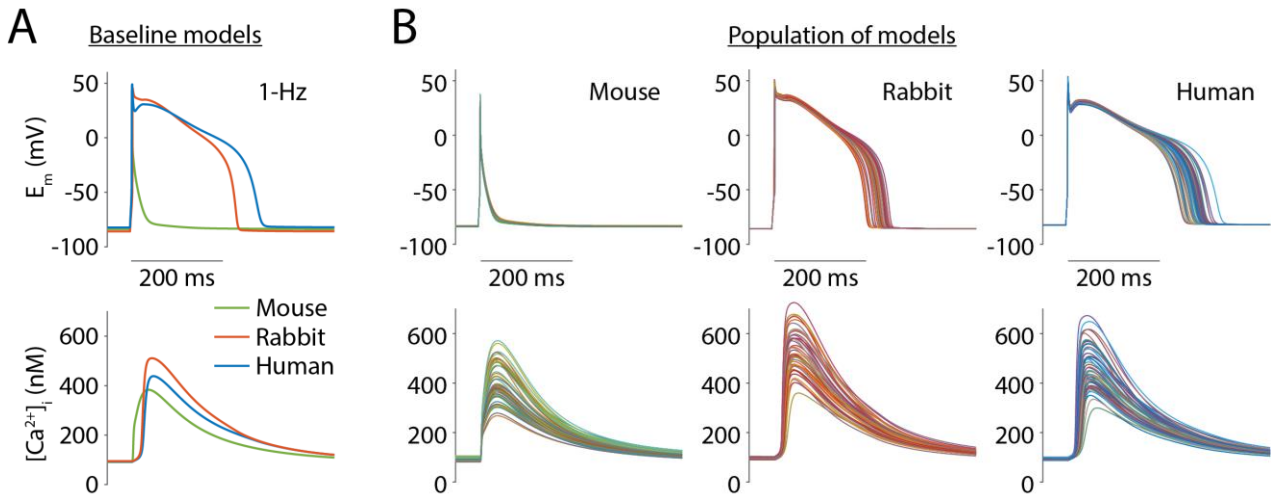


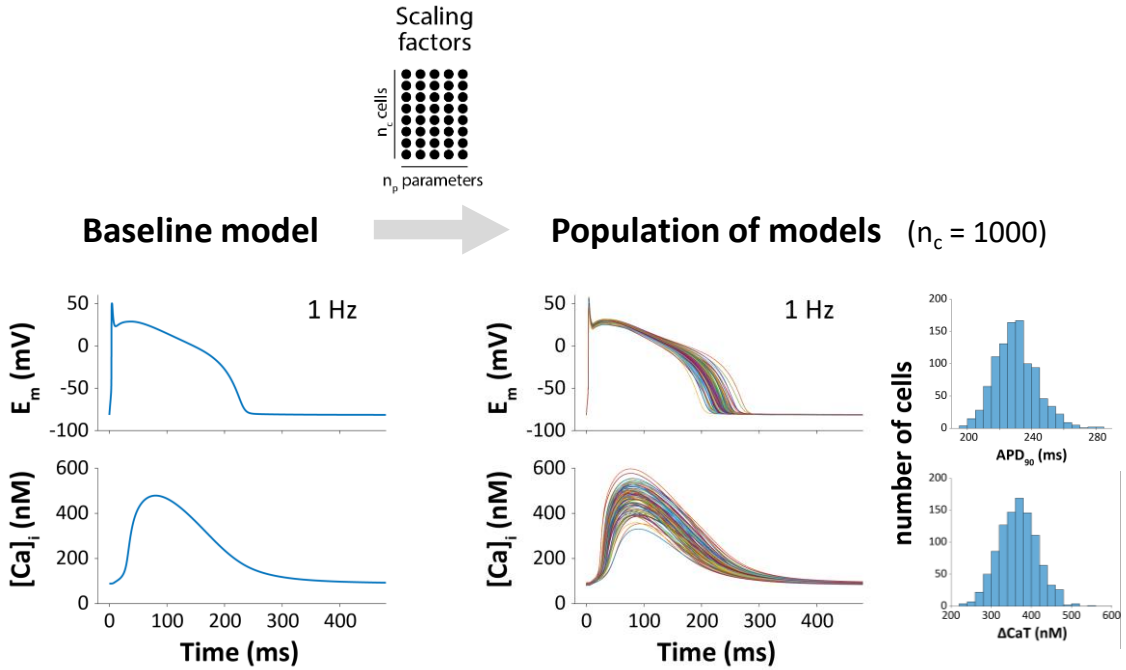
Gong & Sobie, *NPJ Syst Biol Appl*. 2018

Methods: building populations of models



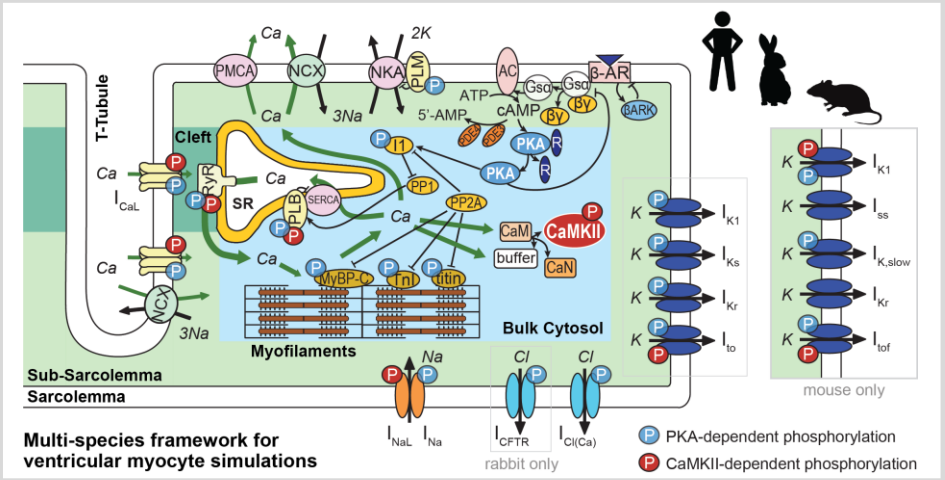
Based on Grandi et al., 2010, Moreno et al., 2013 (**Human**); Shannon et al., 2004, Soltis & Saucerman, 2012, Negroni et al., 2015, Bartos et al., 2017 (**Rabbit**); Morotti et al., 2014, Surdo et al., 2017 (**Mouse**)





Morotti et al., *Sci Adv*. 2021

Methods: performing sensitivity analysis



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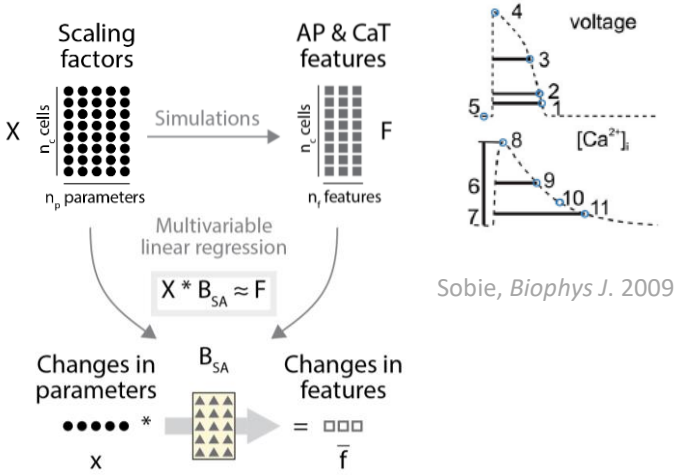
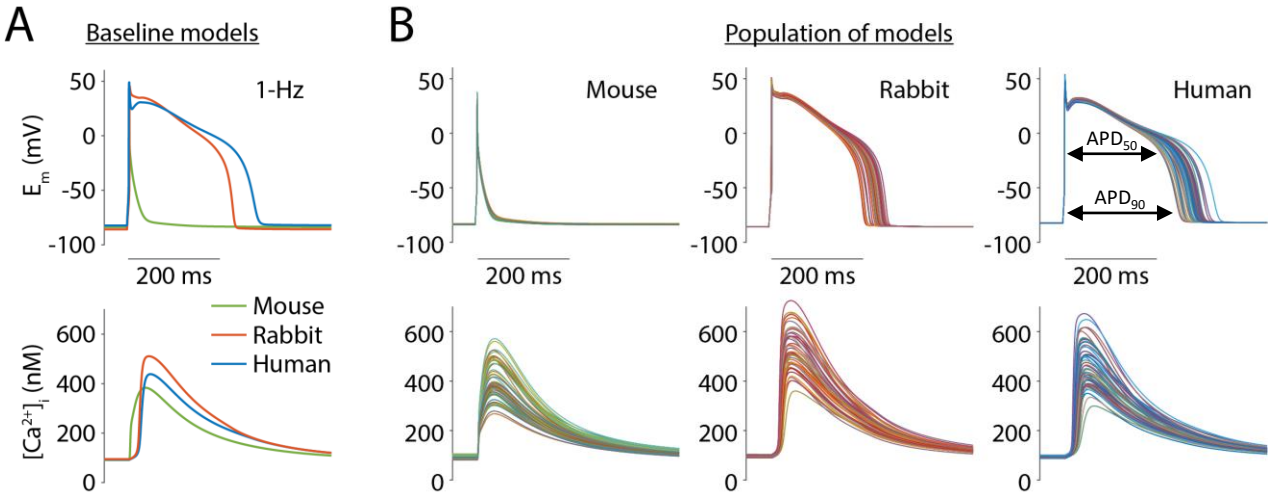
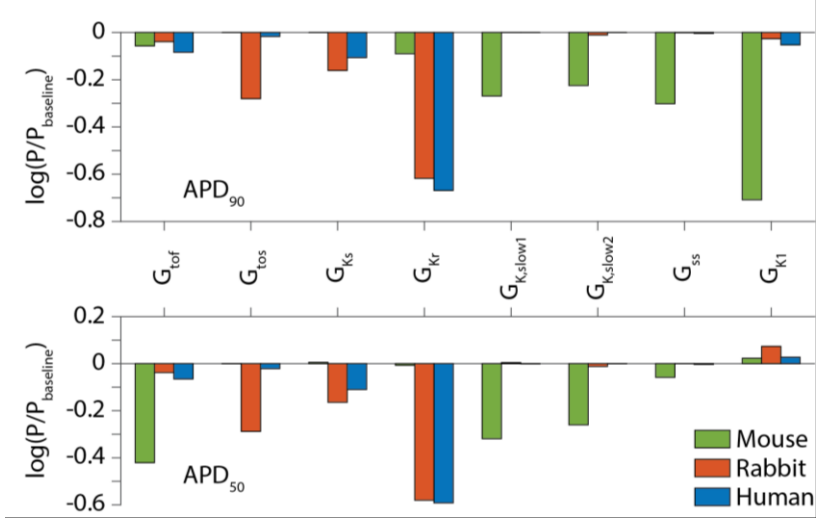


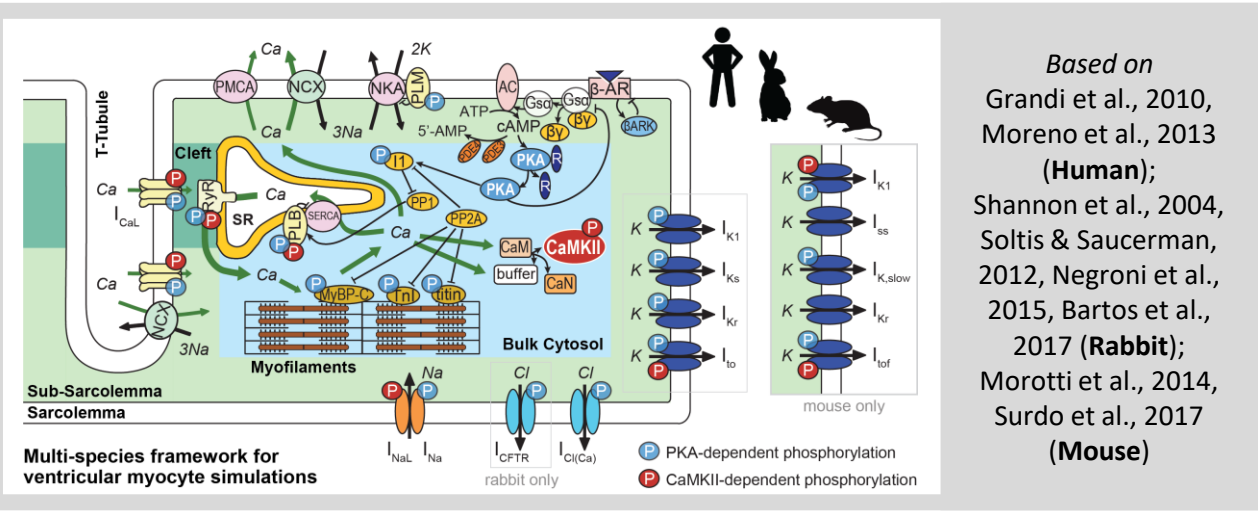
Sobie, *Biophys J*. 2009





Morotti et al., *Sci Adv*. 2021

Methods: constructing the translators



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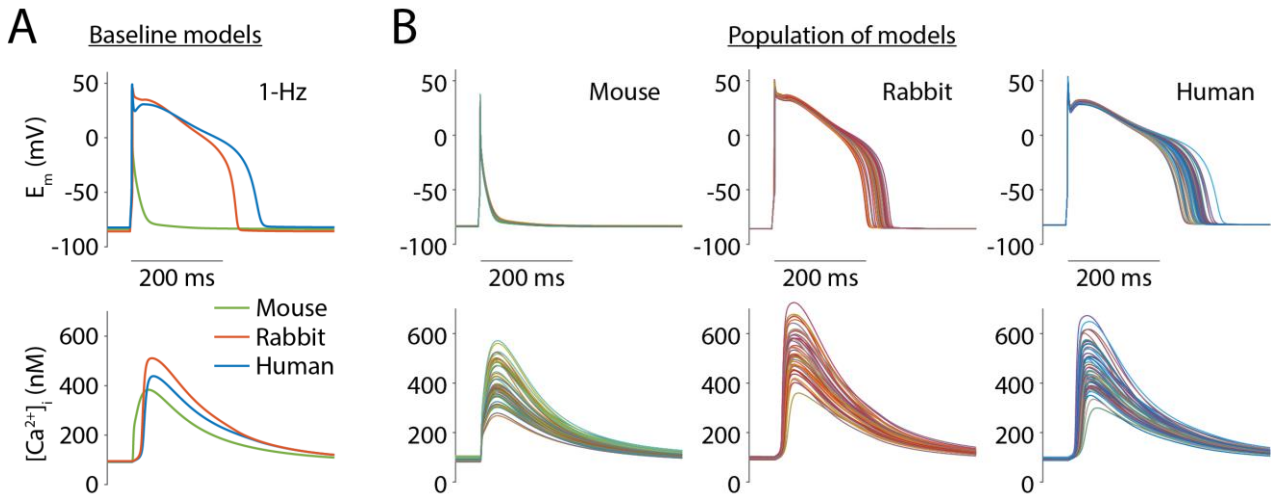
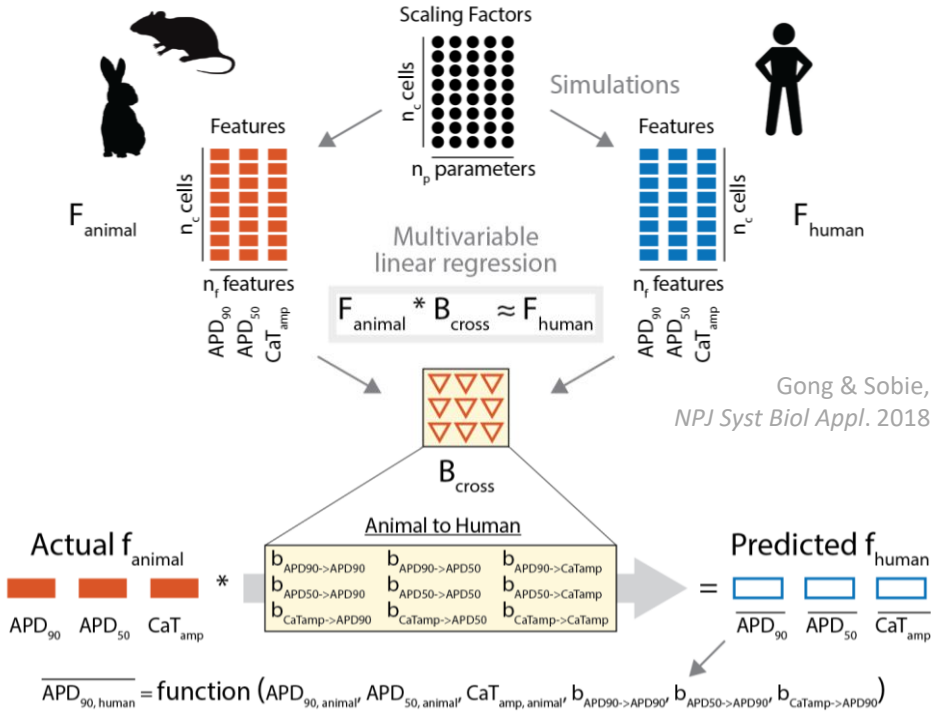
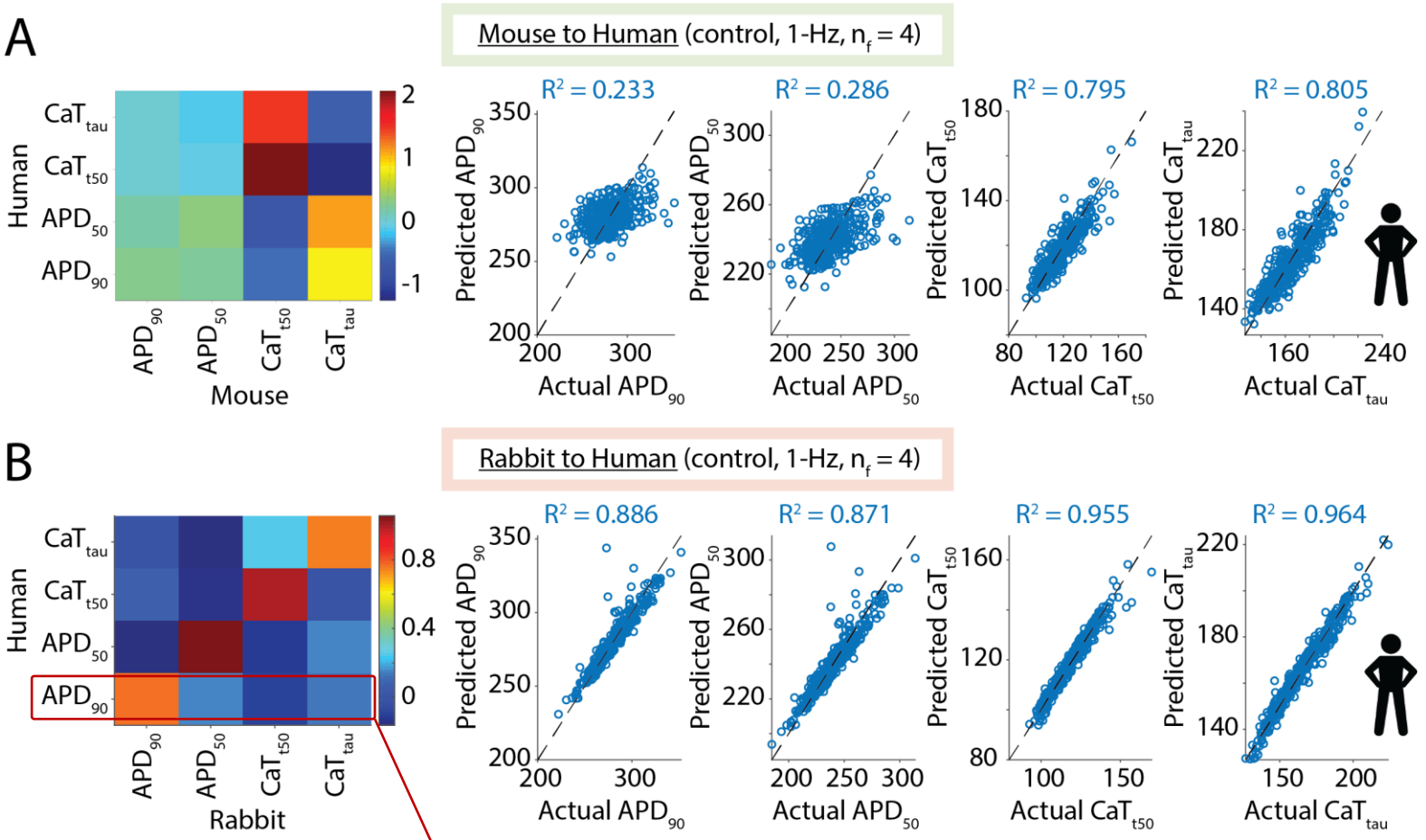




Gong & Sobie, *NPJ Syst Biol Appl*. 2018

Morotti et al., *Sci Adv*. 2021

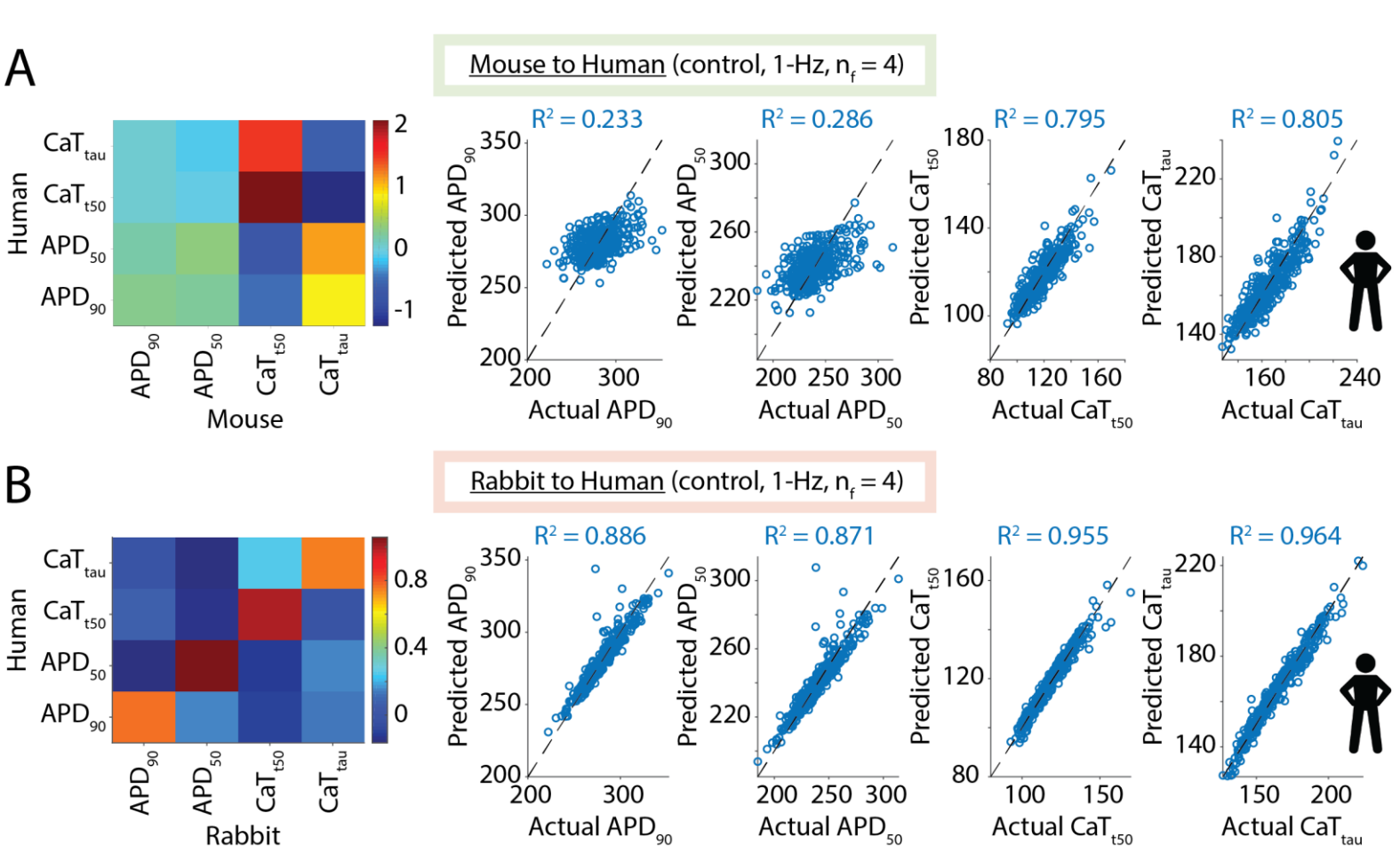
Development of cross-species translators

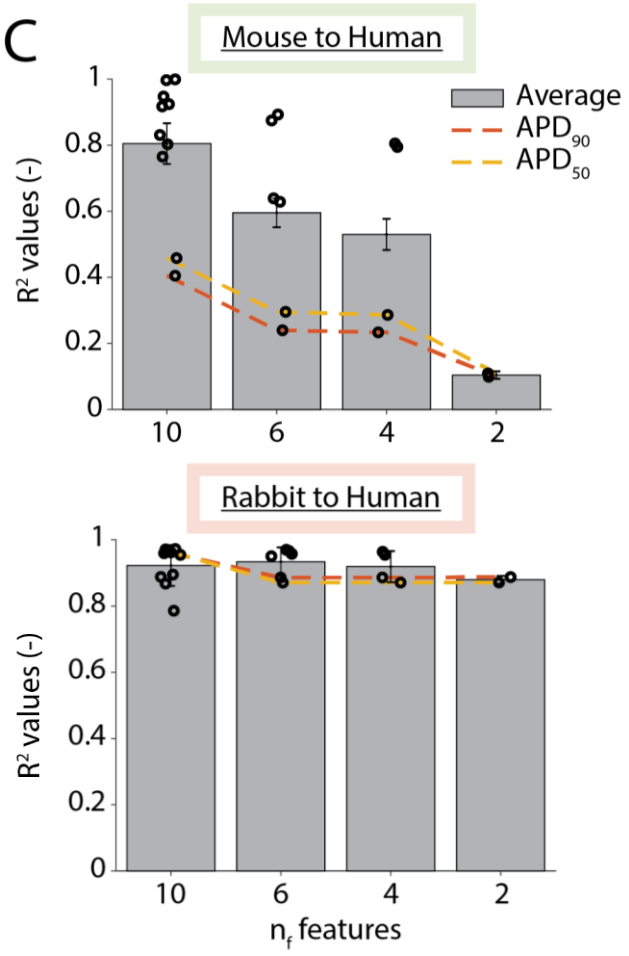


$$\boldsymbol{APD_{90,human}} = function\left(B_{APD90\rightarrow APD90}, \boldsymbol{APD_{90,rabbit}}, B_{APD50\rightarrow APD90}, \boldsymbol{APD_{50,rabbit}}, B_{CaTt50\rightarrow APD90}, \boldsymbol{CaT_{t50,rabbit}}, B_{CaTtau\rightarrow APD90}, \boldsymbol{CaT_{tau,rabbit}}\right)$$

Morotti et al., *Sci Adv*. 2021

Development of cross-species translators





10 AP & CaT features
UV, MDP, AP_{amp}, APD_{90}, APD_{50}, CaT_{min}, CaT_{amp}, CaT_{ttp}, CaT_{t50}, CaT_{tau}

6 AP & CaT features
APD_{90}, APD_{50}, CaT_{min}, CaT_{amp}, CaT_{t50}, CaT_{tau}

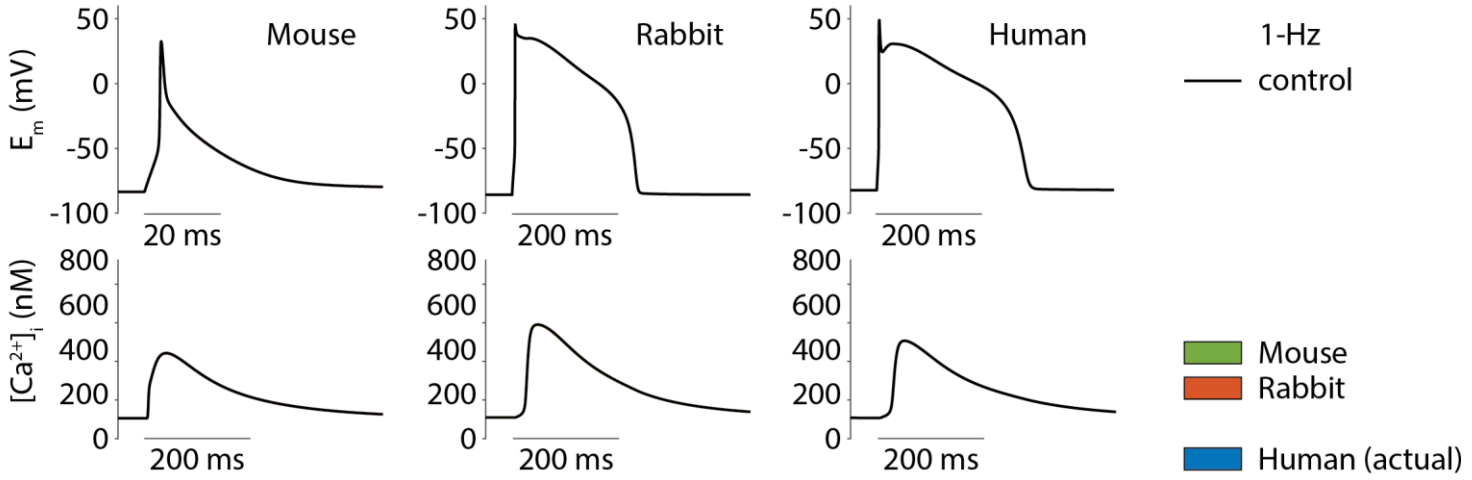
4 AP & CaT features
APD_{90}, APD_{50}, CaT_{t50}, CaT_{tau}

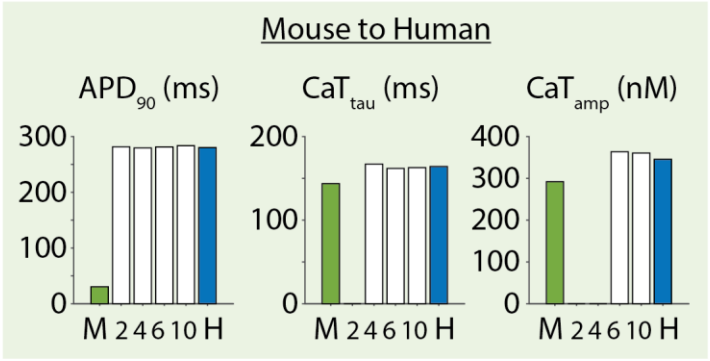
2 AP features
APD_{90}, APD_{50}

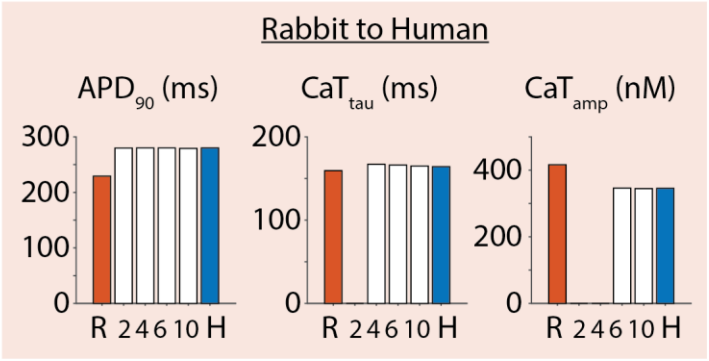
Morotti et al., *Sci Adv*. 2021

Validation against simulated data

- *Control*







2 AP features
APD_{90}, APD_{50}

4 AP & CaT features
APD_{90}, APD_{50}, CaT_{t50}, CaT_{tau}

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APD_{90}, APD_{50}, CaT_{min}, CaT_{amp}, CaT_{t50}, CaT_{tau}

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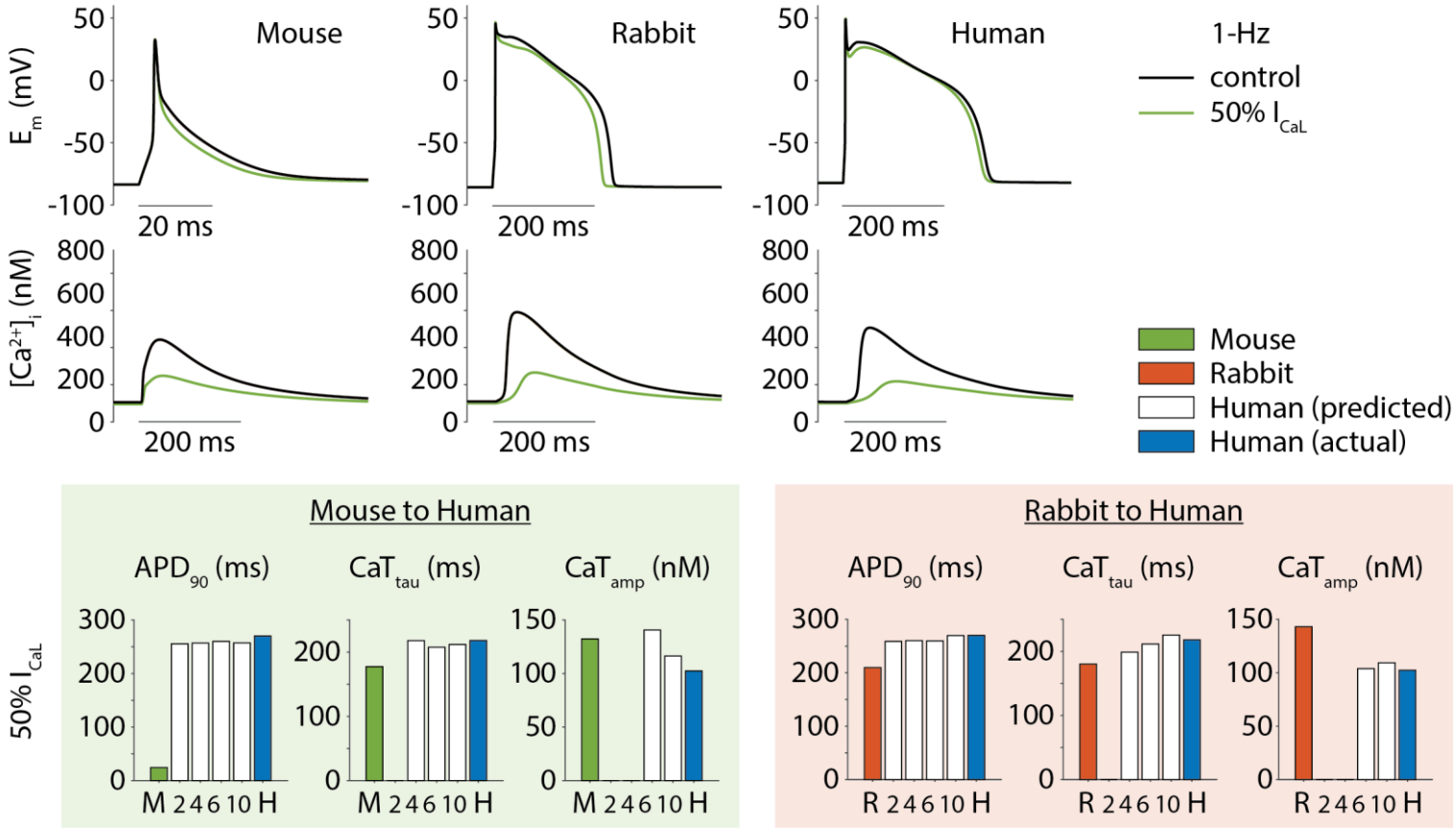
UV, MDP, AP_{amp}, APD_{90}, APD_{50}, CaT_{min}, CaT_{amp}, CaT_{ttp}, CaT_{t50}, CaT_{tau}

Morotti et al., *Sci Adv*. 2021

Validation against simulated data

- *Selective ion channel block*

I_{CaL} block



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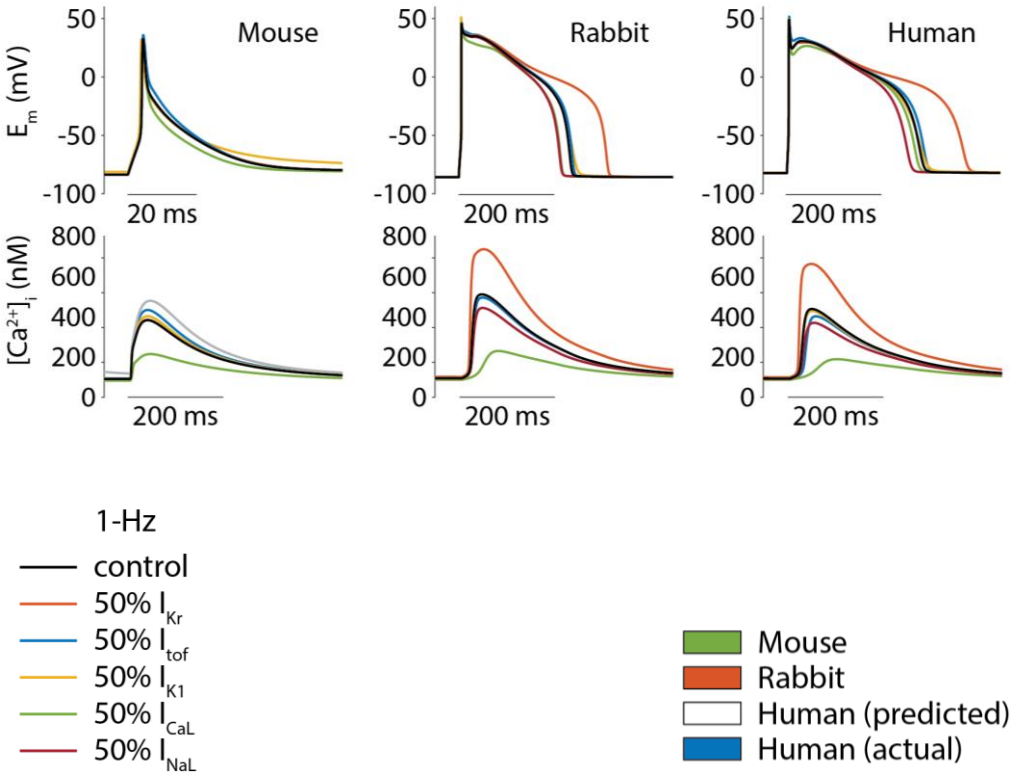
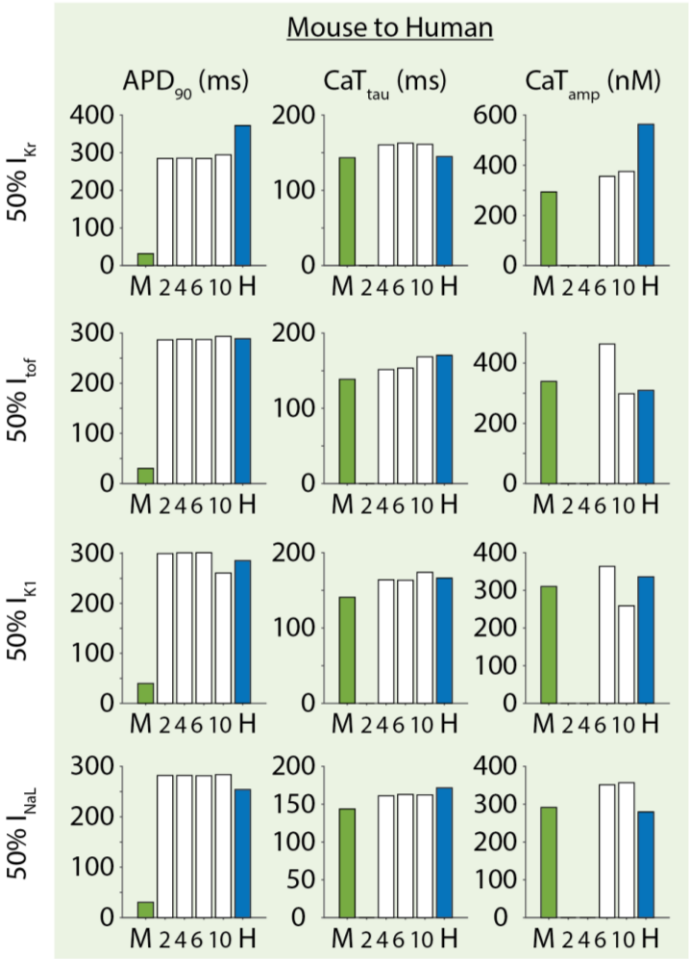
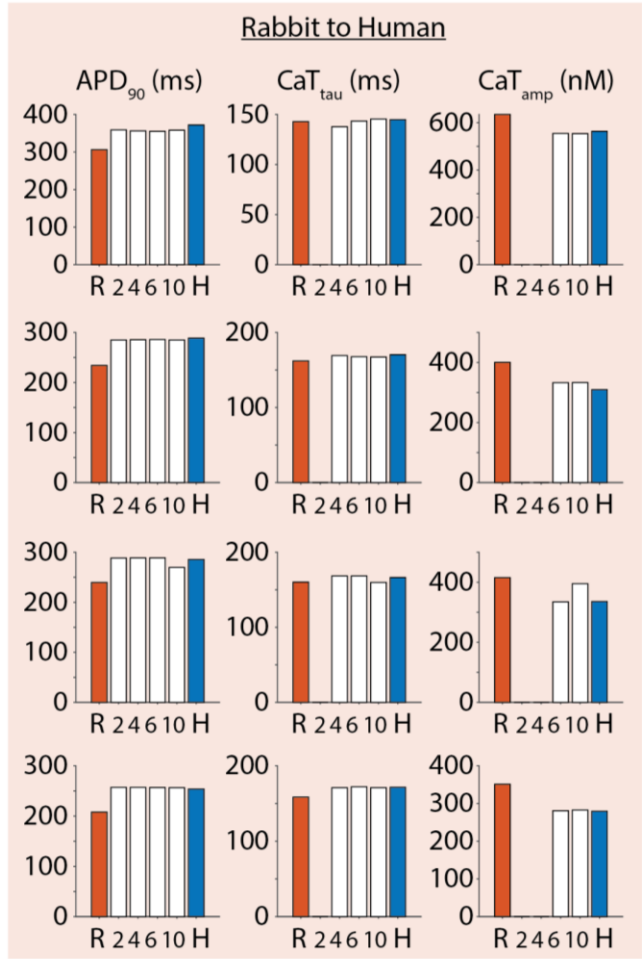
Morotti et al., *Sci Adv*. 2021

Validation against simulated data

- *Selective ion channel block*







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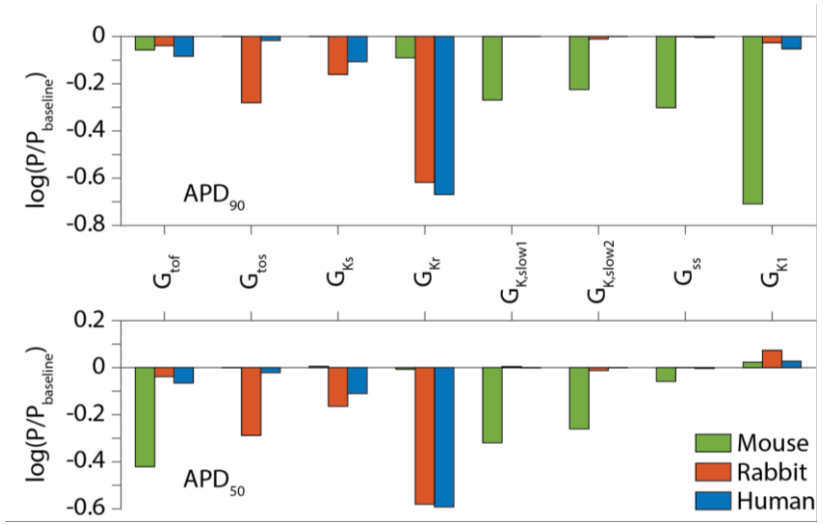
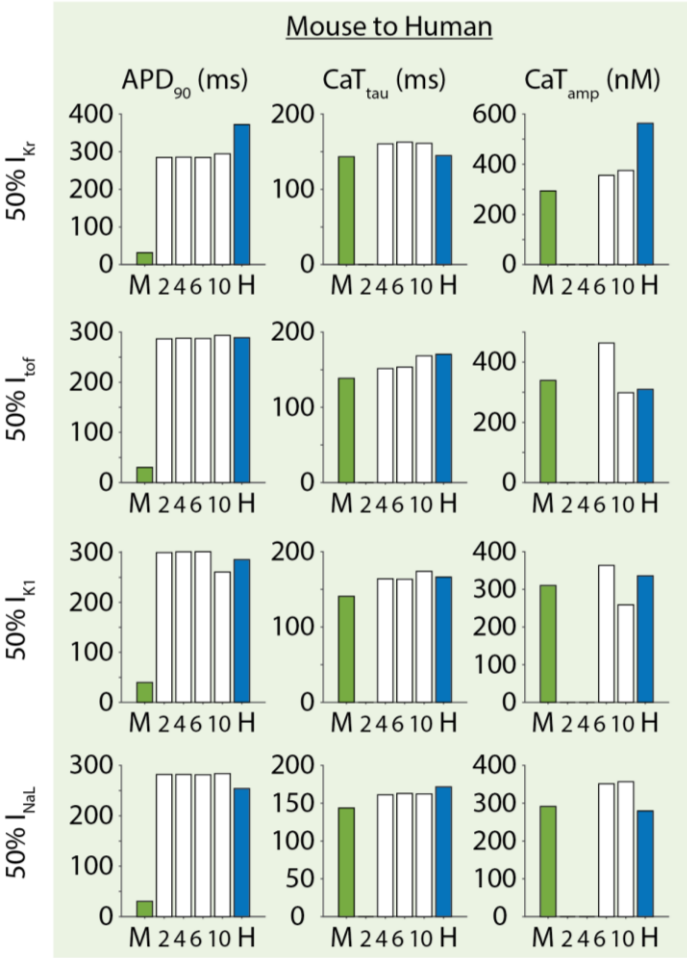
Morotti et al., *Sci Adv*. 2021

Validation against simulated data

Limitations of mouse-to-human translation

i) Very different sensitivity to changes in some model parameters (e.g., I_{NaL}, I_{Kr}, I_{K1})





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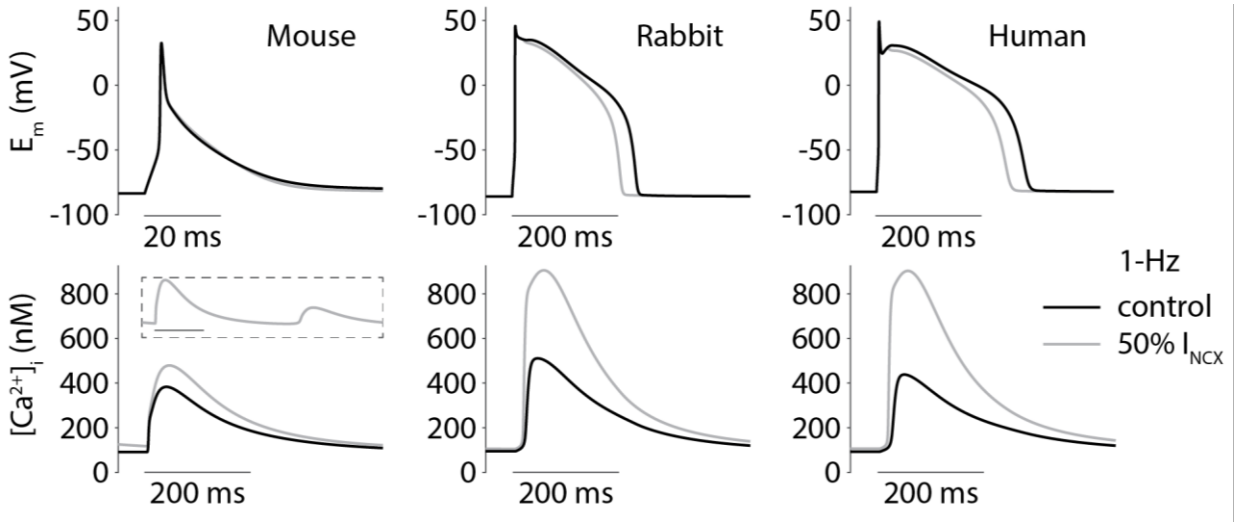
Morotti et al., *Sci Adv*. 2021

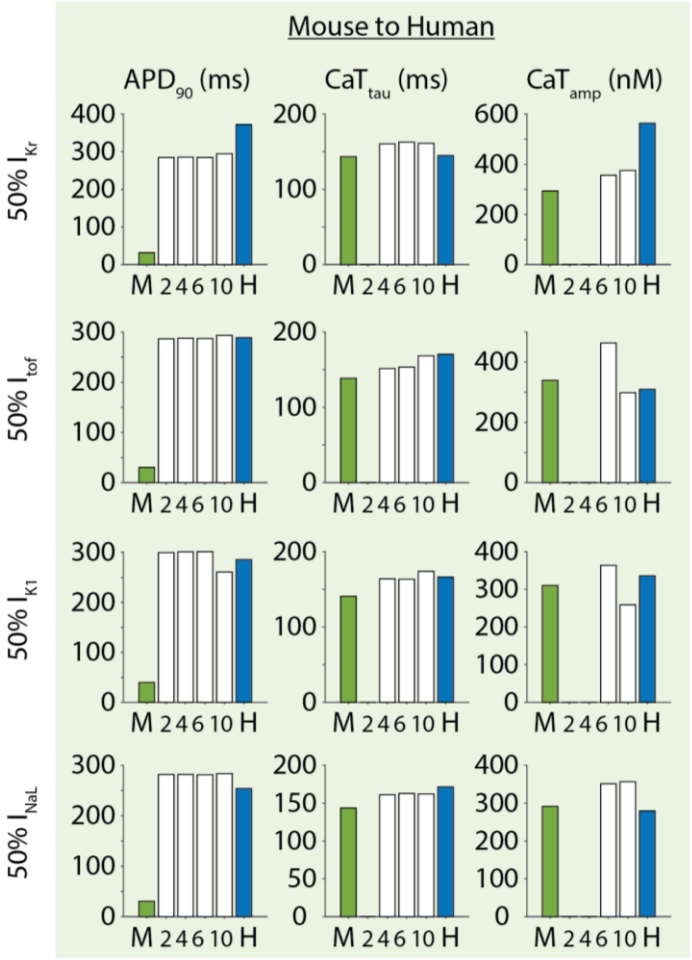
Validation against simulated data

Limitations of mouse-to-human translation

i) Very different sensitivity to changes in some model parameters
(e.g., I_{NaL}, I_{Kr}, I_{K1})

ii) Different propensity for membrane potential and/or Ca instabilities





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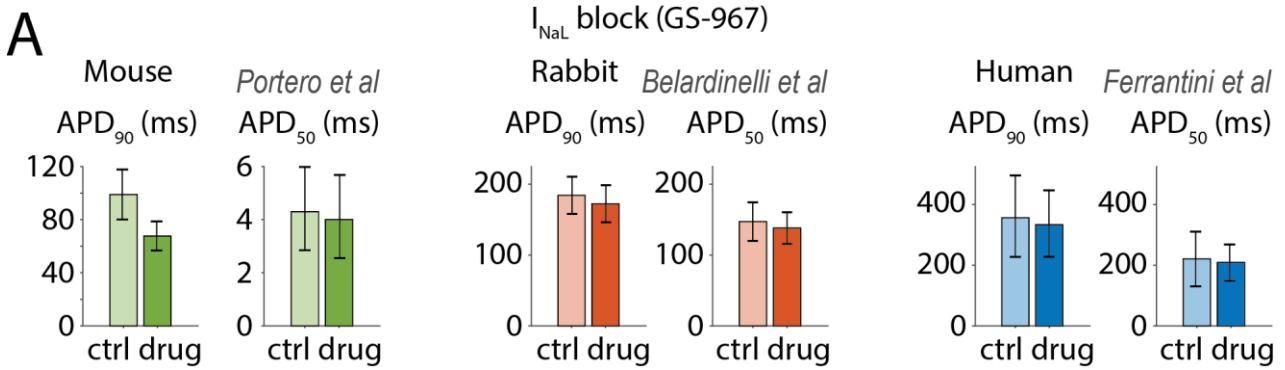
UV, MDP, AP_{amp}, APD_{90}, APD_{50}, CaT_{min}, CaT_{amp}, CaT_{ttp}, CaT_{t50}, CaT_{tau}

Morotti et al., *Sci Adv*. 2021

Experimental validation

I_{NaL} block



To account for variability among experimental datasets, when applying our translators to experimental data, we use the **relative changes** in the measured AP & CaT properties induced by a perturbation (rather than the absolute values)

$$\text{Actual } f_{\text{animal, drug}} * B_{\text{cross}} = \text{Predicted } f_{\text{animal, drug}}$$

$$\overline{APD_{90,\text{human, drug}}} = \text{function}\left(APD_{90,\text{animal, drug}}, APD_{50,\text{animal, drug}}, CaT_{\text{amp, animal, drug}}, b_{APD90\text{->}APD90}, b_{APD50\text{->}APD90}, b_{CaTamp\text{->}APD90}\right)$$

with

$$APD_{90,\text{animal, drug}} = APD_{90,\text{baseline animal model, ctrl}} * APD_{90,\text{exp, drug}} / APD_{90,\text{exp, ctrl}}$$
$$APD_{50,\text{rabbit, drug}} = APD_{50,\text{baseline animal model, ctrl}} * APD_{50,\text{exp, drug}} / APD_{50,\text{exp, ctrl}}$$
$$CaT_{\text{amp, rabbit, drug}} = CaT_{\text{amp, baseline animal model, ctrl}} * CaT_{\text{amp, exp, drug}} / CaT_{\text{amp, exp, ctrl}}$$

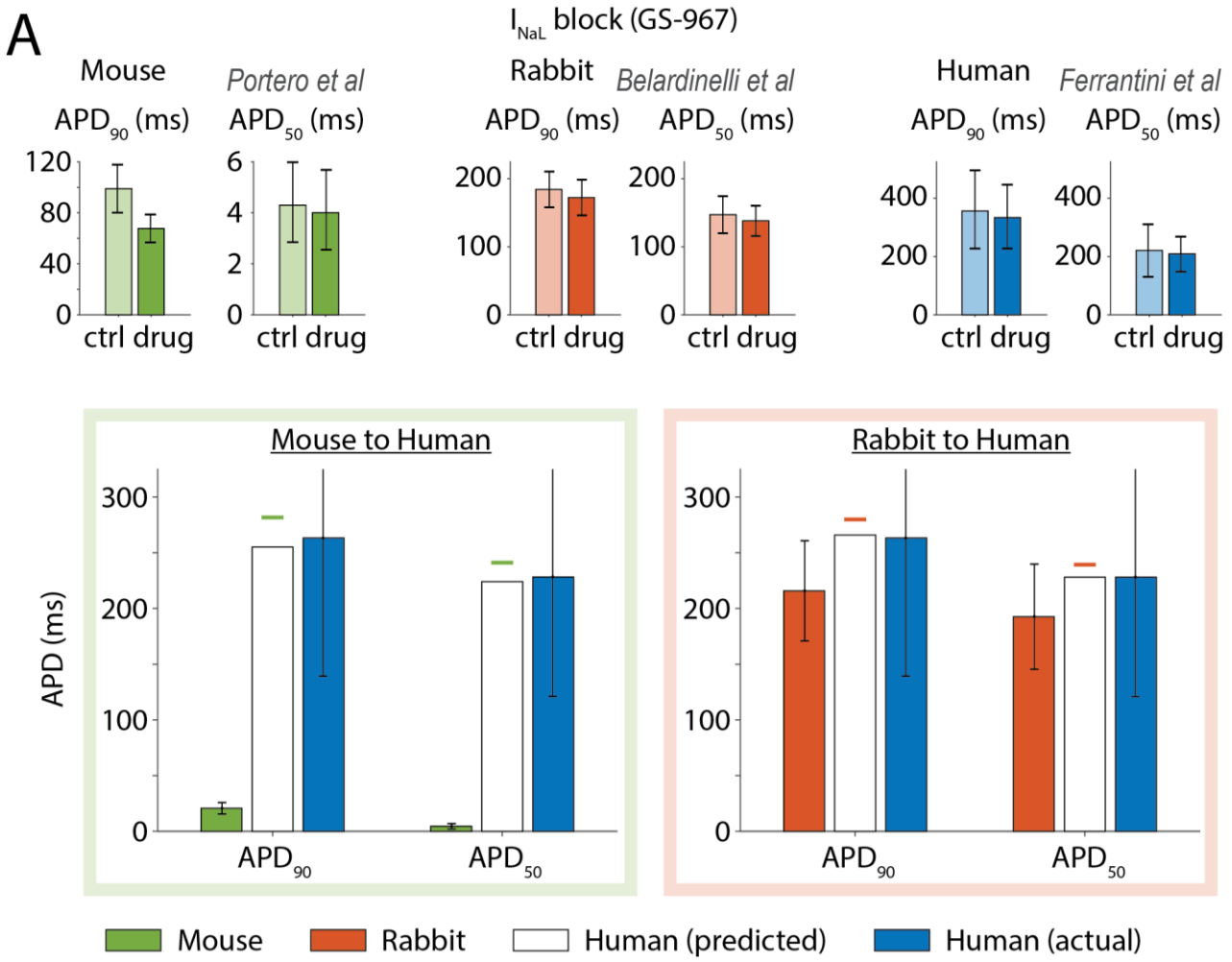
Simulations with baseline model

Experiments

Morotti et al., *Sci Adv*. 2021

Experimental validation

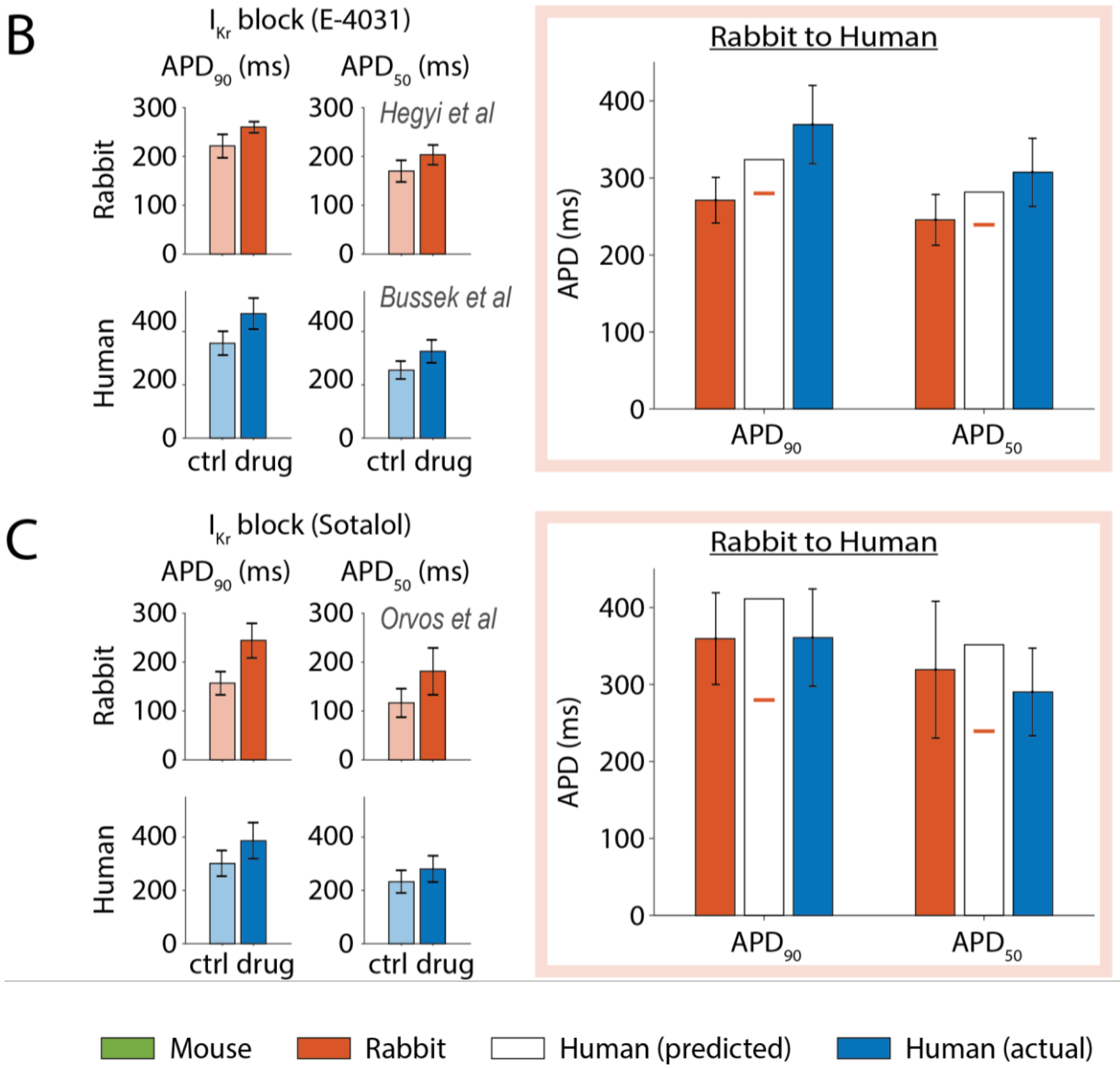
I_{NaL} block



Morotti et al., *Sci Adv*. 2021

Experimental validation

I_{Kr} block

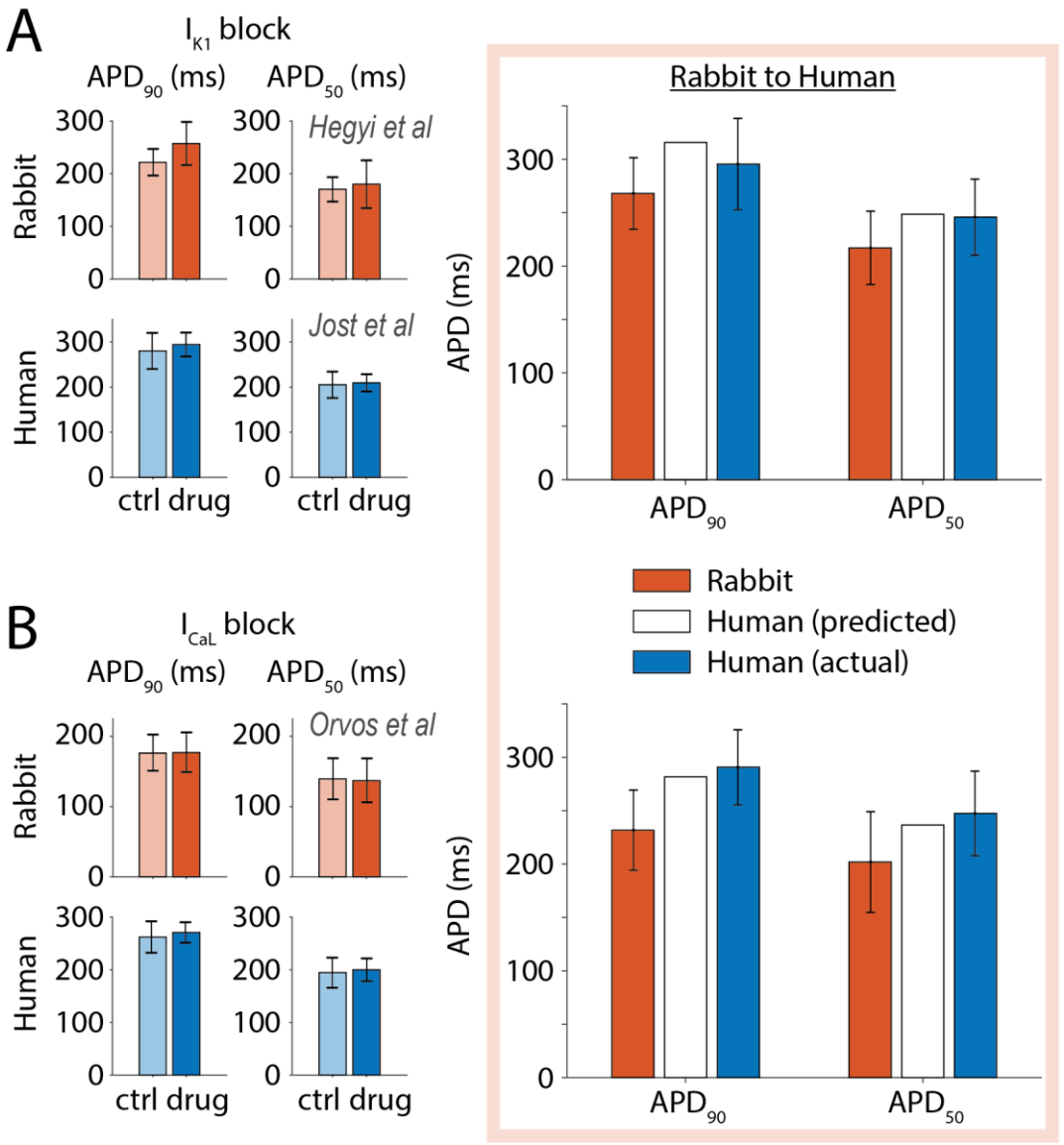


Morotti et al., *Sci Adv*. 2021

Experimental validation

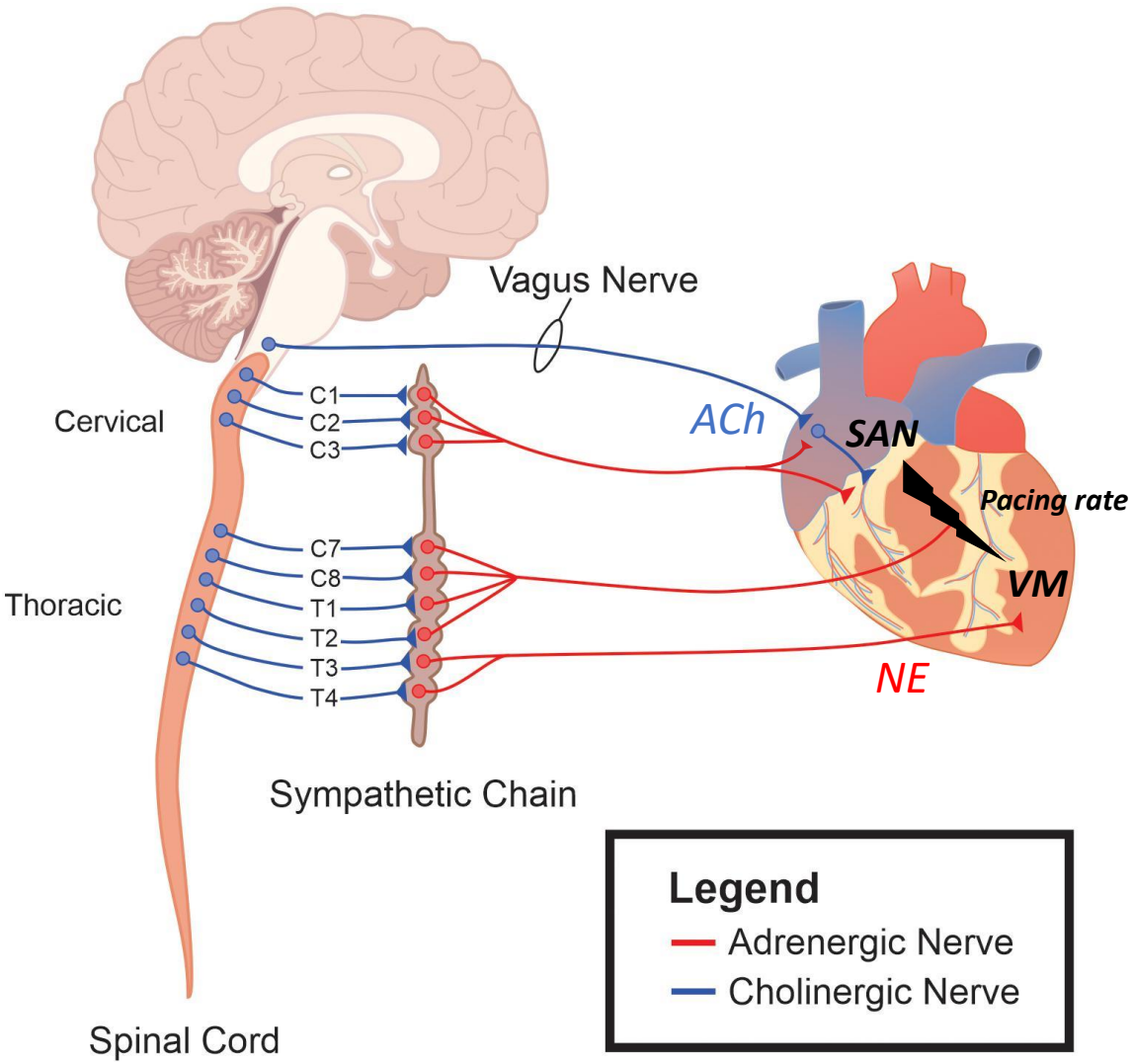
I_{K1} block

I_{CaL} block

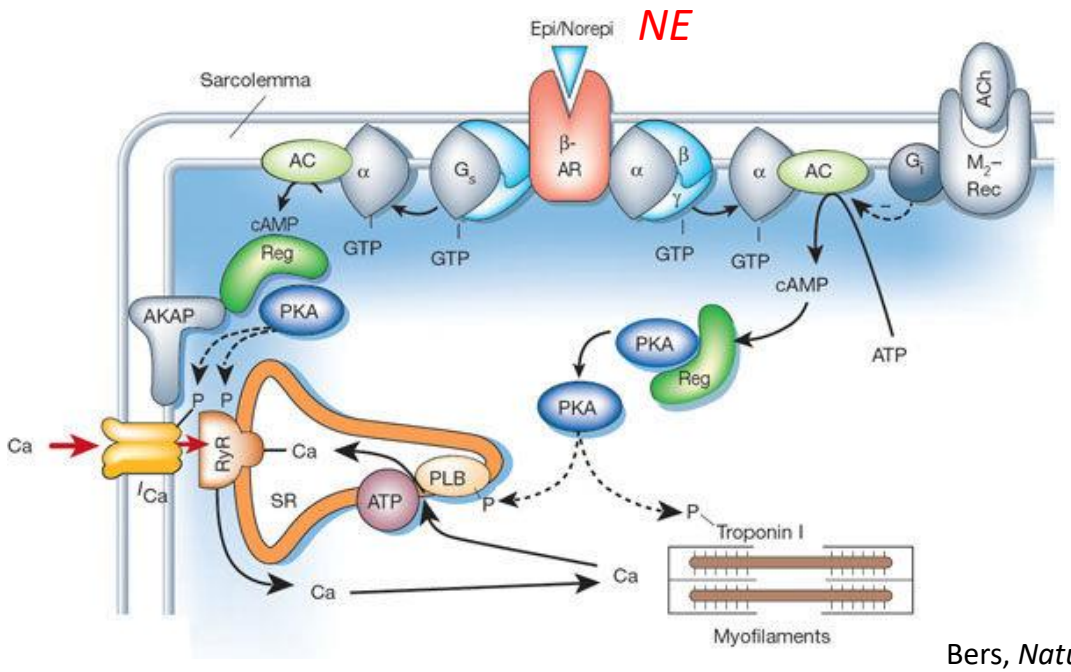


Morotti et al., *Sci Adv*. 2021

Prediction of response to sympathetic stimulation



- Ventricular activity is influenced by:
  - Increased beating rate (via SAN)
  - Altered activity of the targets of the β-adrenergic (β-AR) signaling cascade

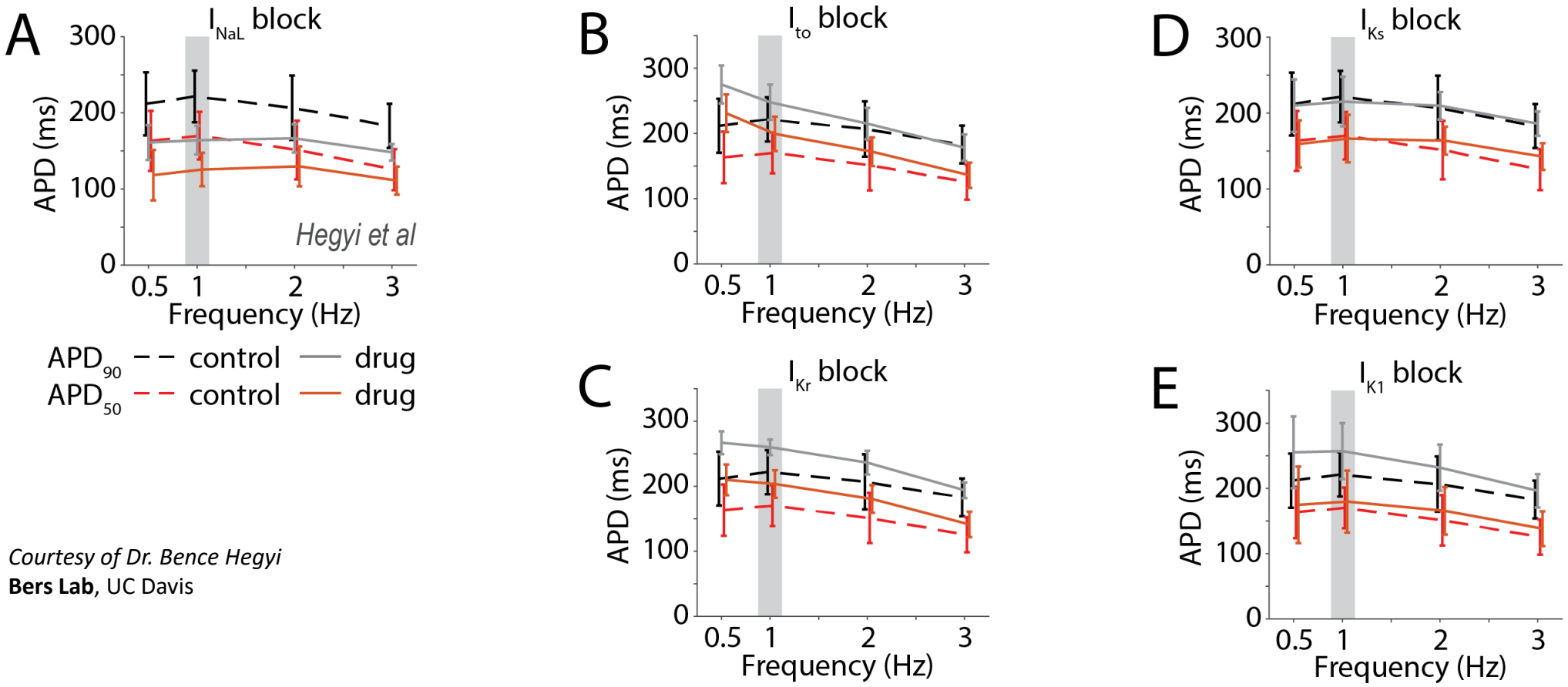


Espinoza et al., *Front Physiol*. 2021

Bers, *Nature*. 2002

Cross-frequency prediction of drug-induced effect

- Frequency-dependence of ion channel block in rabbit ventricular myocytes

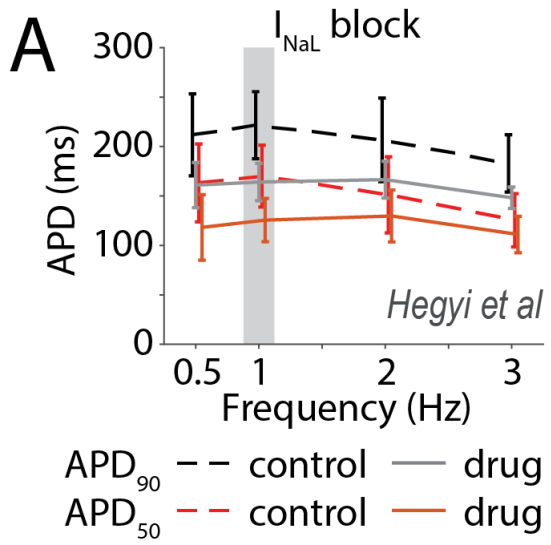


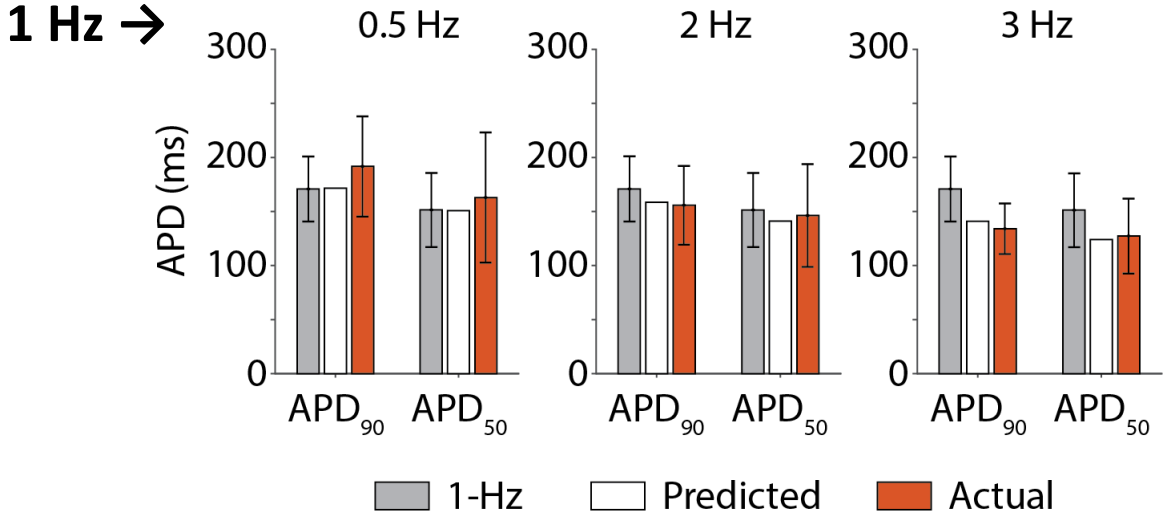
Courtesy of Dr. Bence Hegyi
Bers Lab, UC Davis

Morotti et al., *Sci Adv*. 2021

Cross-frequency prediction of drug-induced effect

- Predicting the effect of block of I_{NaL} on APD from 1 to 0.5, 2 & 3 Hz data

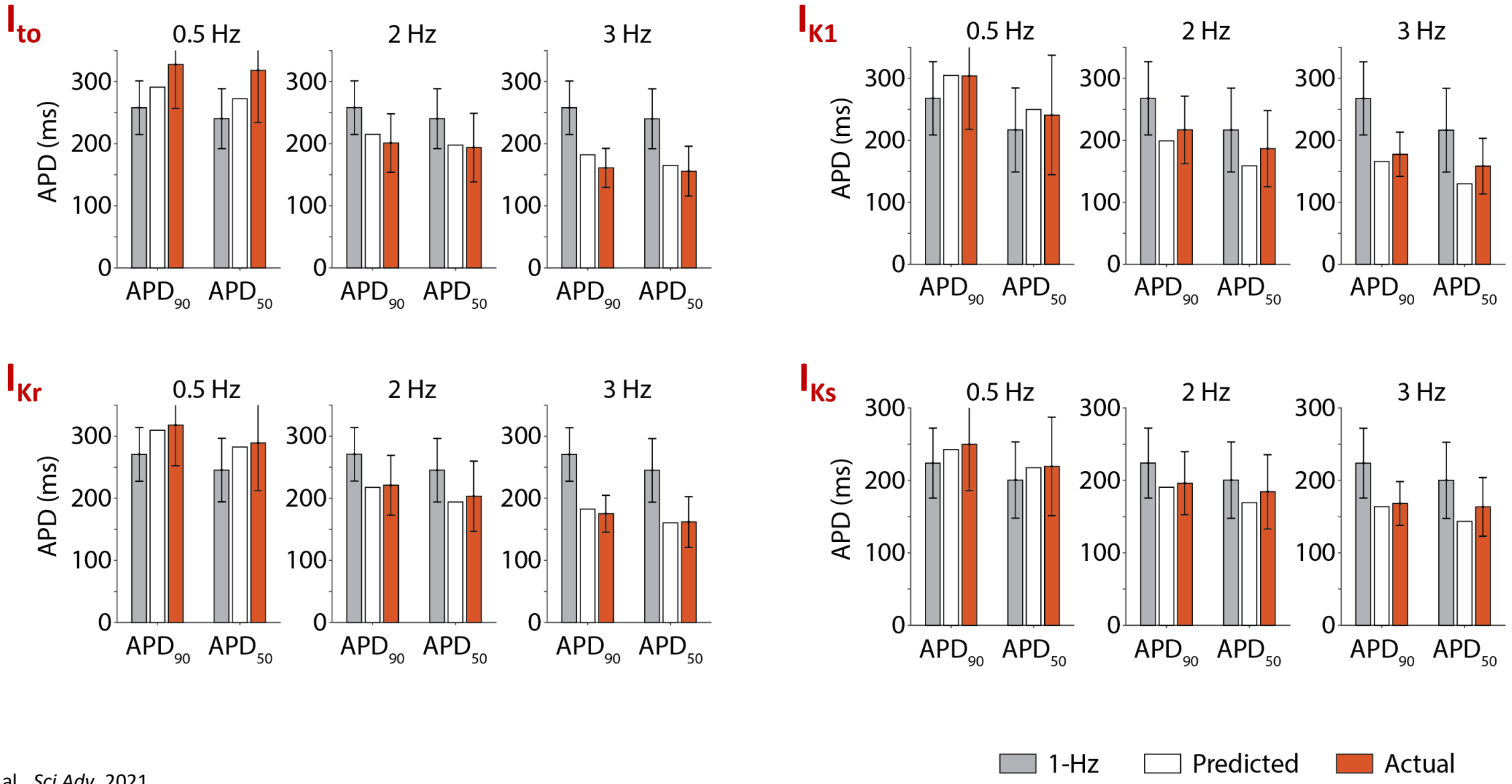




Courtesy of Dr. Bence Hegyi
Bers Lab, UC Davis

Morotti et al., *Sci Adv*. 2021

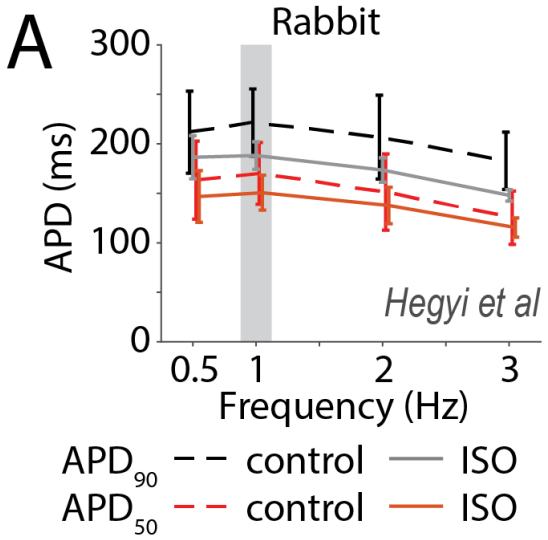
Cross-frequency prediction of drug-induced effect



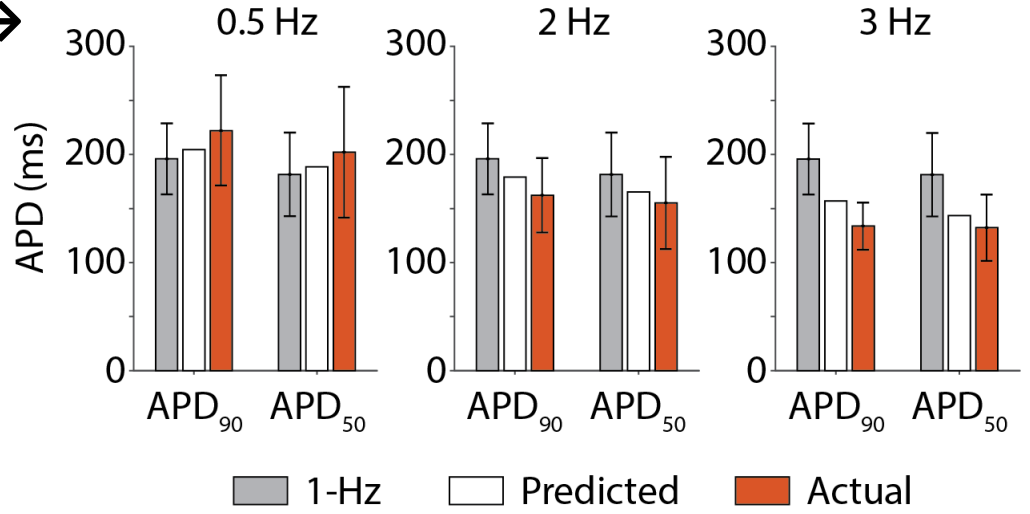
Morotti et al., *Sci Adv*. 2021

Cross-frequency prediction of ISO-induced effect

- Predicting the effect of Isoproterenol (**ISO**) on APD from 1 to 0.5, 2 & 3 Hz data



1 Hz →

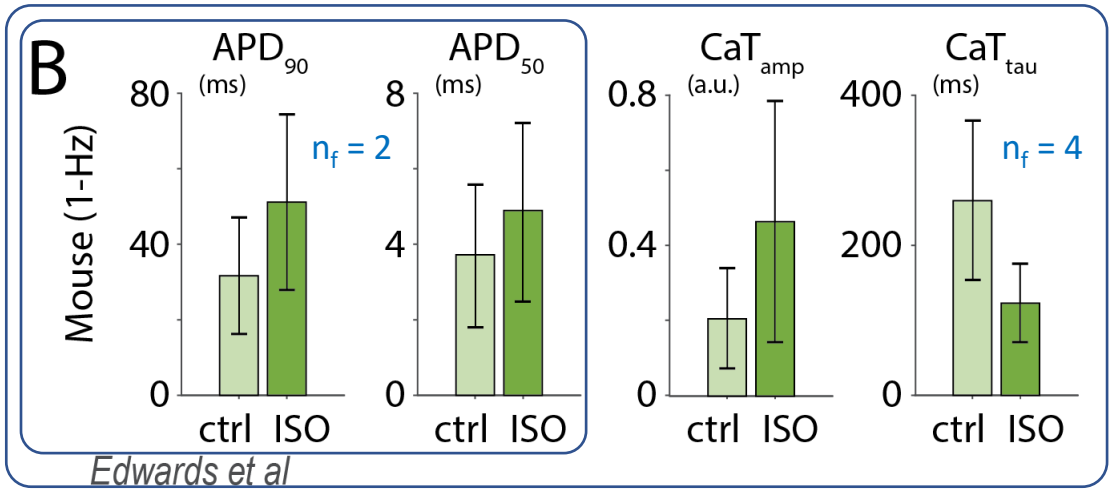


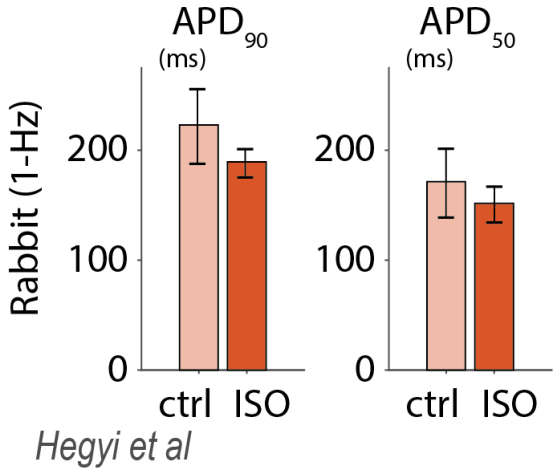
Courtesy of Dr. Bence Hegyi
Bers Lab, UC Davis

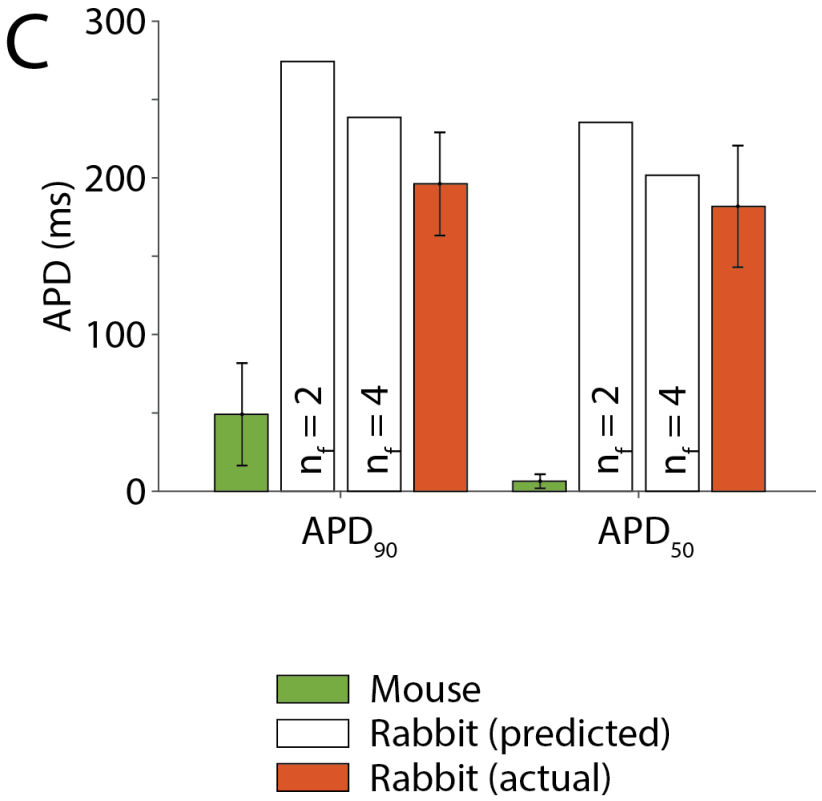
Morotti et al., *Sci Adv*. 2021

Cross-species prediction of ISO effect at fixed pacing rate

- Predicting the effect of **ISO** administration on rabbit APD from mouse data (1 Hz)

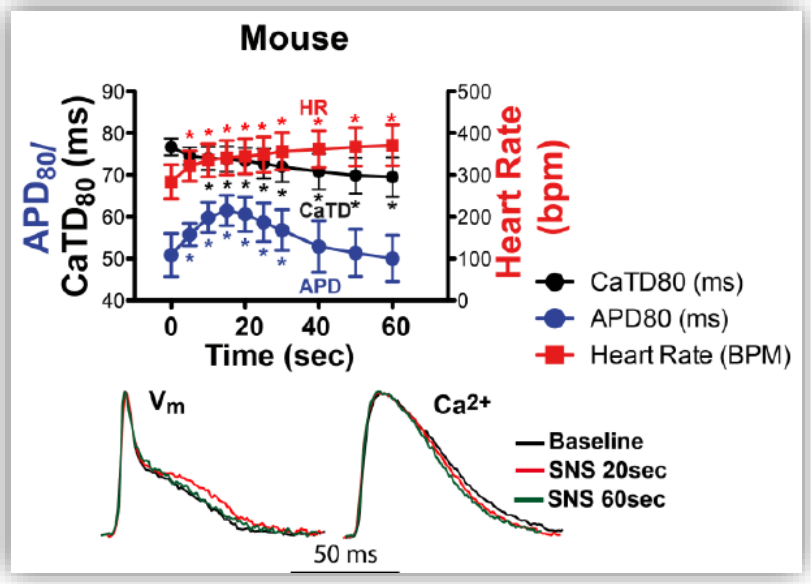




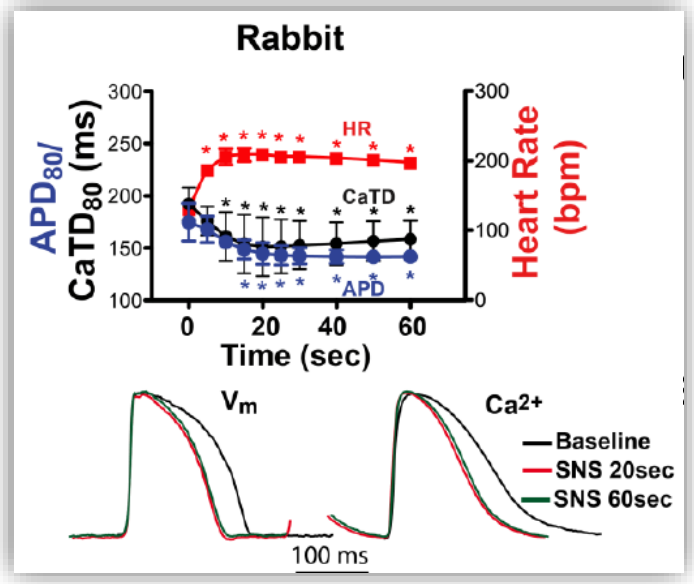


Morotti et al., *Sci Adv*. 2021

Sympathetic stimulation in quasi-physiological conditions



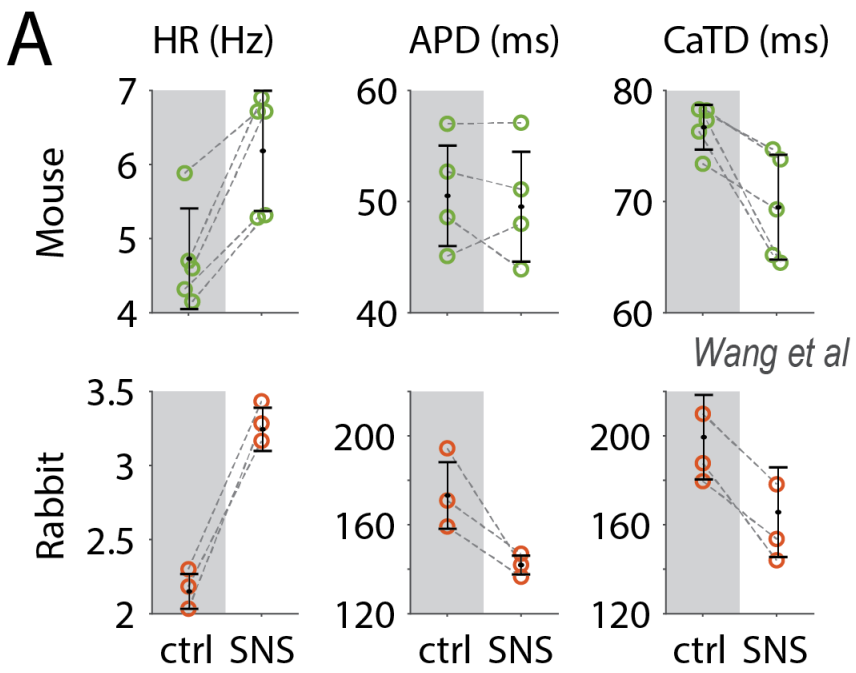
?

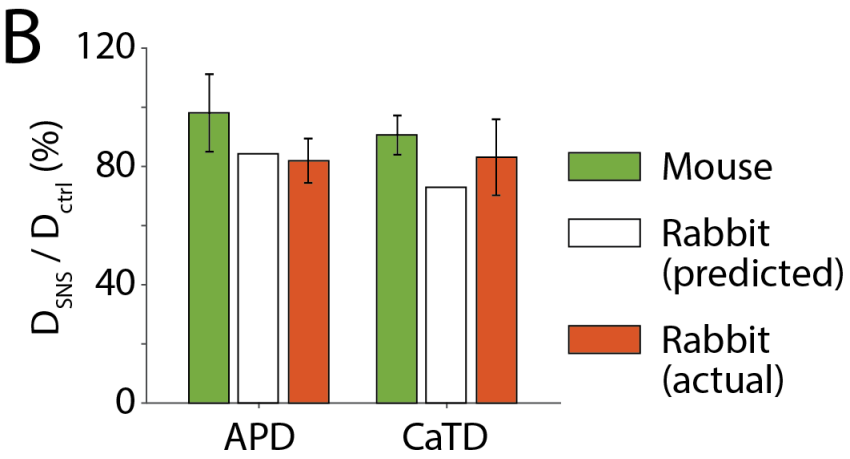


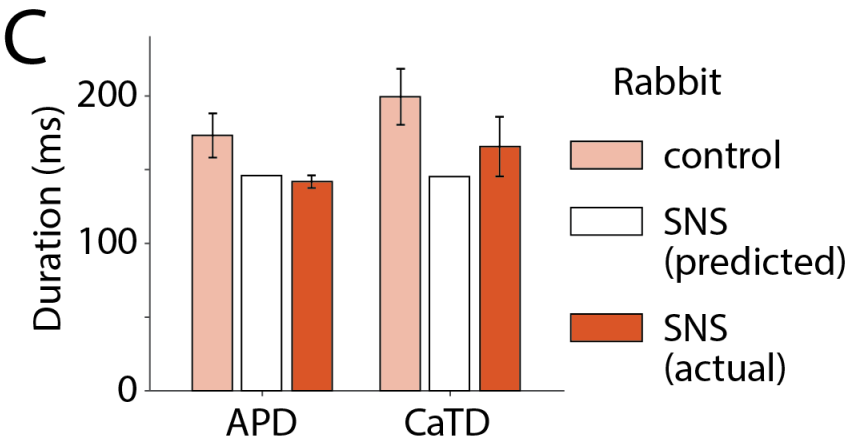
Wang et al., *J Physiol.* 2019

Sympathetic stimulation in quasi-physiological conditions

SNS-specific cross-species translators
of the relative effect induced by sympathetic activation
(accounting for change in beating rate)







Morotti et al., *Sci Adv*. 2021

Experimental validation summary

- Cross-species prediction of drug-induced effect (mouse & rabbit to human) ✓
- Cross-frequency prediction of drug-induced effect (rabbit) ✓
- Cross-frequency prediction of ISO-induced effect (rabbit) ✓
- Cross-species prediction of ISO-induced effect at fixed pacing rate (mouse to rabbit) ✓
- Cross-species prediction of sympathetic stimulation effect with concomitant change in heart rate (mouse to rabbit) ✓

Morotti et al., *Sci Adv*. 2021

Conclusions

- We constructed a suite of translators for quantitatively mapping electrophysiologic responses across species and experimental conditions
- We trained these statistical operators using a broad dataset obtained simulating populations of our models of mouse, rabbit, and human ventricular myocytes
- We tested our translators against experimental data describing the response to various stimuli (ion channel block, change in beating rate, β-adrenergic challenge)
- **Our work demonstrates that this approach is well suited for predicting the effects of perturbations across different species, thereby suggesting its integration into mechanistic studies and drug development pipelines**

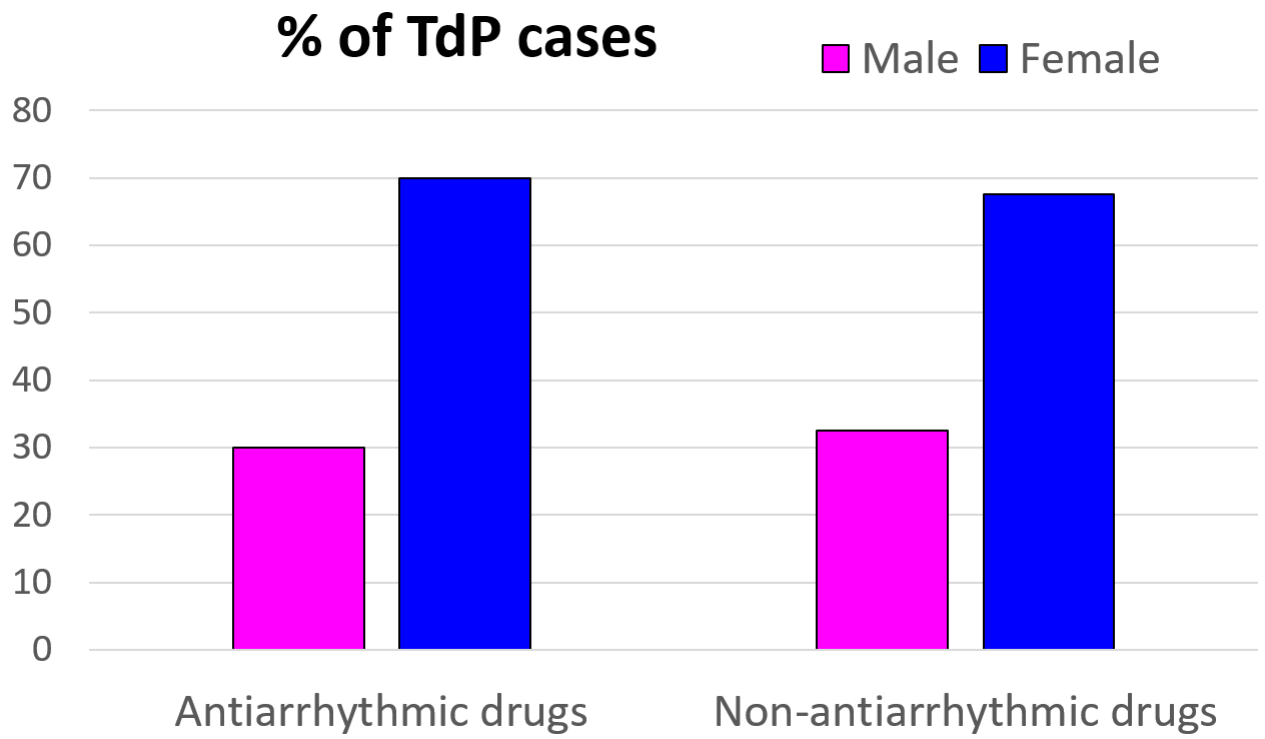
Morotti et al., *Sci Adv*. 2021

Future directions

- Further refinement/validation
- Inclusion of more species
- Cross-regional translation (atria⇔ventricles)
- **Cross-sex translation**

Cross-sex translation

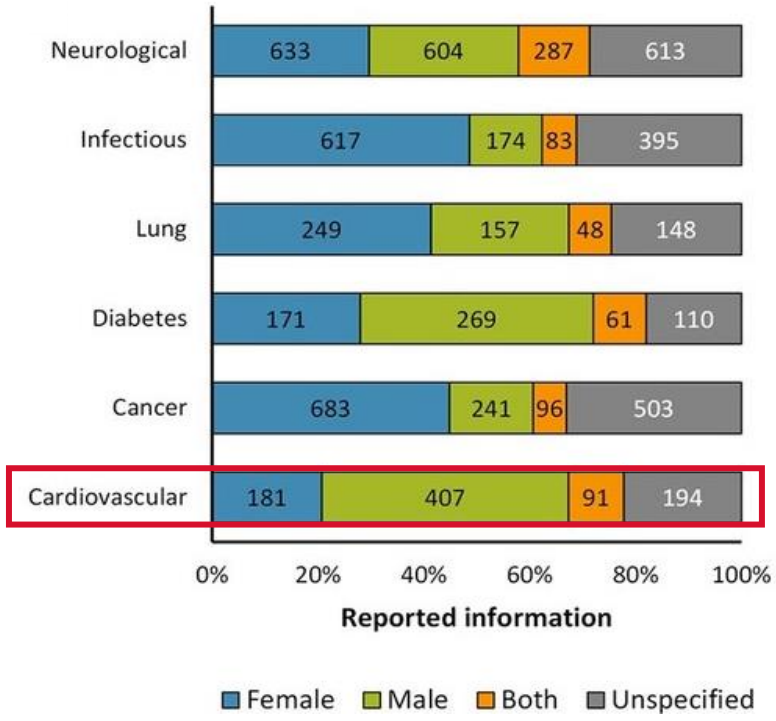
- Female sex is an independent risk factor for Torsade de Pointes (TdP)

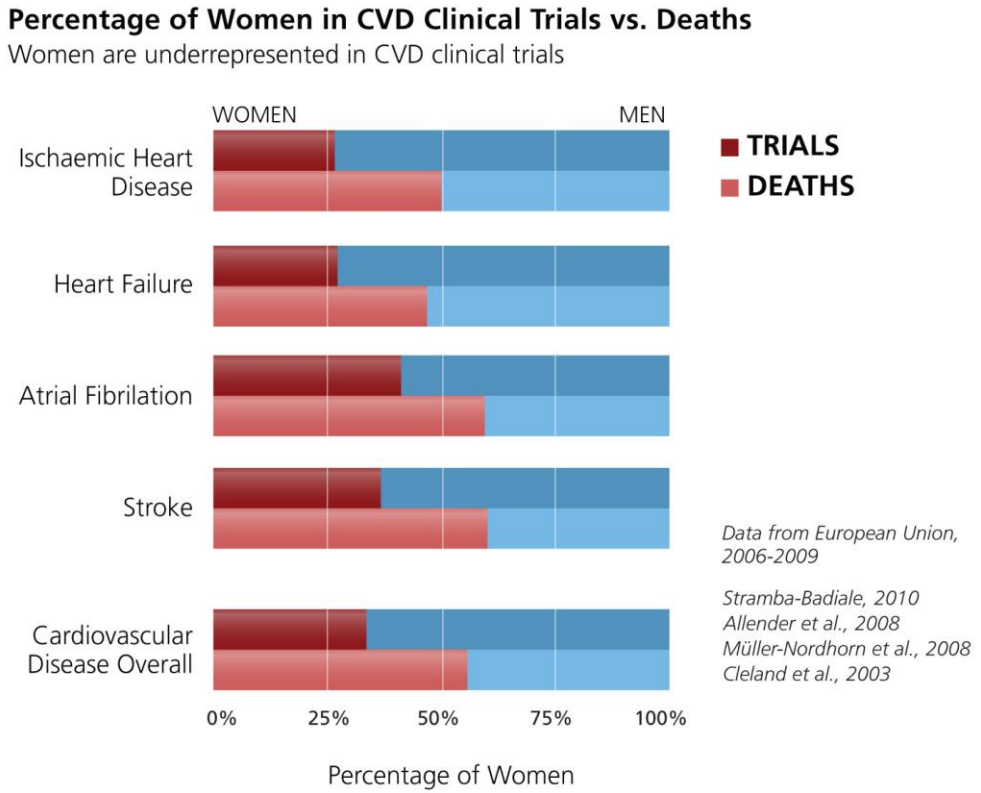


Adapted from Bednar et al., *Am J Cardiol.* 2007

Cross-sex translation

- Female sex is an independent risk factor for Torsade de Pointes (TdP)
- Female sex is underrepresented in both experimental & clinical studies





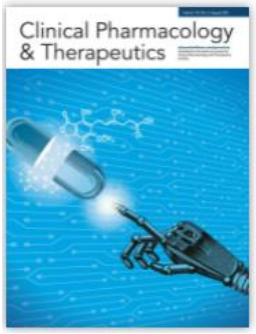
Adapted from Florez-Vargas et al., *eLIFE*. 2016

Cross-sex translation

ARTICLE

Sex-Specific Classification of Drug-Induced Torsade de Pointes Susceptibility Using Cardiac Simulations and Machine Learning

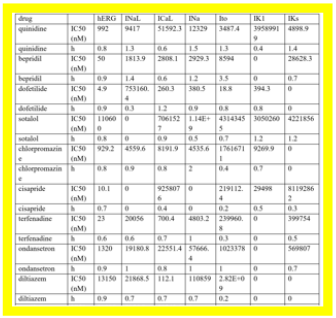
Alex Fogli Iseppe[1], Haibo Ni[1], Sicheng Zhu[1], Xianwei Zhang[1], Raffaele Coppini[2], Pei-Chi Yang[3], Uma Srivatsa[4], Colleen E. Clancy[1,3], Andrew G. Edwards[1], Stefano Morotti[1] and Eleonora Grandi[1,*]



Volume 110, Issue 2
August 2021
Pages 380-391

We combined **mechanistic modeling** & **machine learning** to develop sex-specific TdP classifiers (based on AP & CaT features)

- TdP classifiers require different features in females vs. males
- if applied to female data, male-based classifiers perform poorly and lead to a systematic underestimation of arrhythmic risk

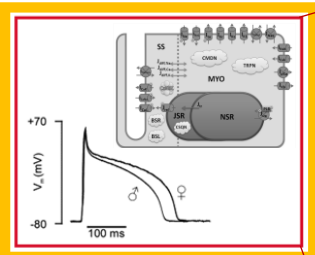


Experimental Data
Ion channel block by drugs

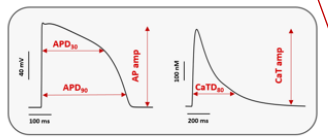
Clinical Data on drug toxicity

CREDIBLEMEDS®

Simulations using mechanistic sex-specific models of human cardiac electrophysiology
- Various drug concentrations
- Various heart rates
- Various conditions



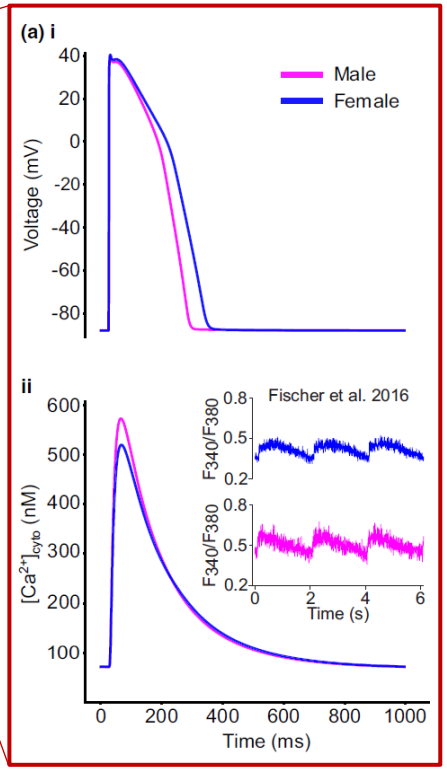
Simulated Features
APD, Ca^{2+} transient properties



Statistical Models
Using machine learning or logistic regression analysis

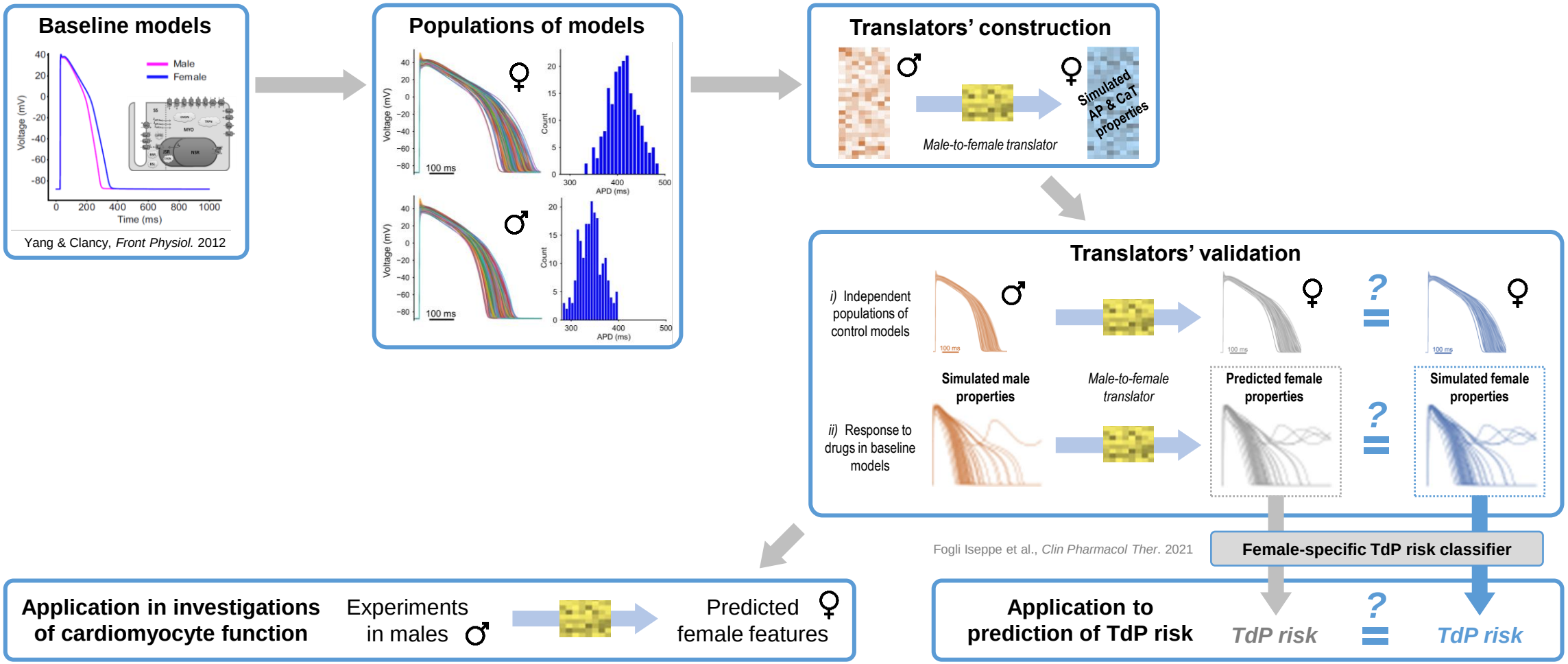
♀♂

TdP risk?



Fogli Iseppe et al., *Clin Pharmacol Ther.* 2021

Cross-sex translation



Hellgren et al., *in preparation*

Acknowledgements

Ele Grandi

Haibo Ni

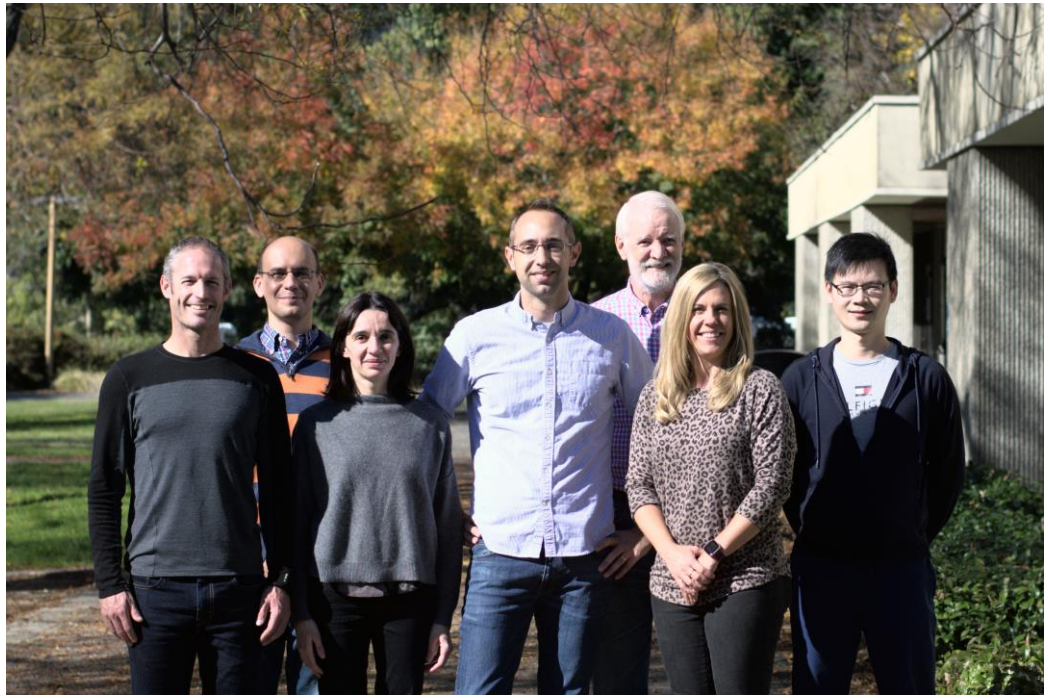
Alex Fogli Iseppe

Xianwei Zhang

Lin-Lin Liu

Andy Edwards

UC DAVIS HEALTH



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Lianguo Wang

Don Bers

Bence Hegyi

Kim Hellgren

BERKELEY LAB

Marco Pritoni

NIH National Heart, Lung, and Blood Institute

SPARC

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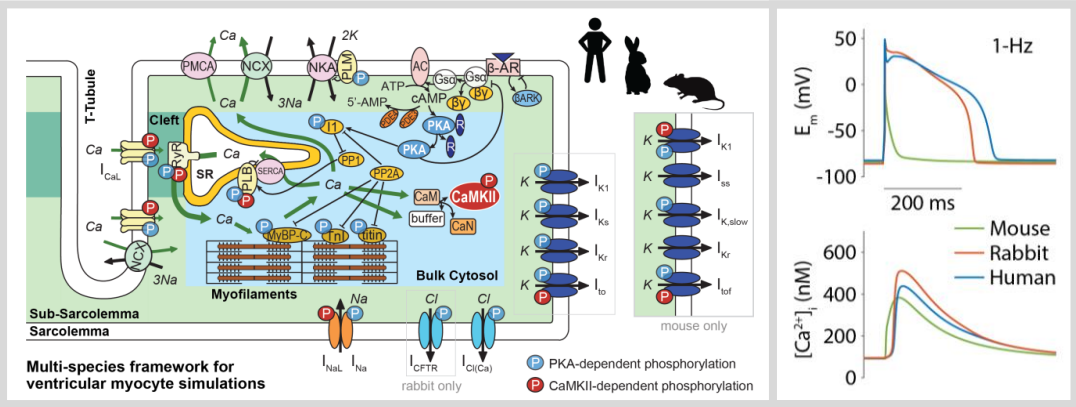
DORIS DUKE CHARITABLE FOUNDATION

Thank you!

Cross-species translation of drug-induced electrophysiological response in cardiac myocytes



Species-differences

Experiments in animal models

Translator of electrophysiological response

Predicted human features

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