The Potential Impact of Physiological Computer Models in Medicine: Regulation and Considerations for Ensuring Patient Safety

March15, 2018

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U.S. Food and Drug Administration

Disclaimer

The opinions expressed in this presentation are mine and do not necessarily reflect the official views of the U.S. Food and Drug Administration (FDA)

Utilization of Computer Modeling

- Hypotheses Development & Testing
- Design of Medical Products
- Personalized Medicine
- In-Silico Clinical Trials
- Regulatory Submissions & Evaluation

FDA & Computer Modeling

- Examples
  - marketed devices
  - clinical research
  - internal use
- Partnerships
- Other
  - Standards
  - Guidances
  - MDDT
  - Evaluation

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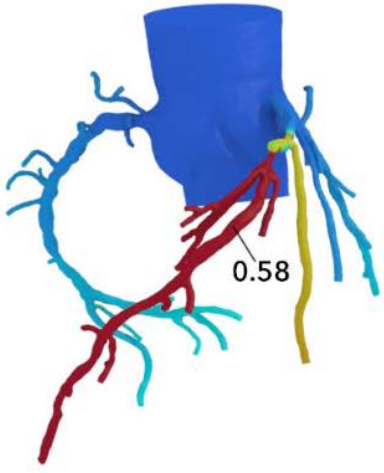
HeartFlow®

Sophisticated Analysis, Delivered Simply

- HeartFlow creates a **personalized, digital 3D model of the arteries.**
- **Powerful computer algorithms** solve millions of complex equations to assess the impact that blockages have on blood flow.
- The result is a **color-coded map** that aids clinicians in determining, vessel-by-vessel, if sufficient blood is reaching the heart.



Information regarding the Indications and Limitations of the HeartFlow Analysis can be found here.

cleared January 2016 https://www.accessdata.fda.gov/cdrh_docs/pdf15/K152733.pdf

CardioInsight Medtronic

www.medtronic.com/us-en/healthcare-professionals/products/cardiac-rhythm/cardiac

CARDIOINSIGHT MAPPING VEST

The CardioInsight™ Mapping Vest is a single use, disposable, multi-electrode vest that works with the CardioInsight Workstation to gather cardiac electrophysiological data from the body surface.

Indications, Safety, and Warnings

Read More

CARDIOINSIGHT WORKSTATION

The CardioInsight™ Workstation takes the ECG signals collected by the CardioInsight Mapping Vest and combines them with CT scan data to produce and display simultaneous, multi-chamber, 3-D cardiac maps.

Indications, Safety, and Warnings

Read More

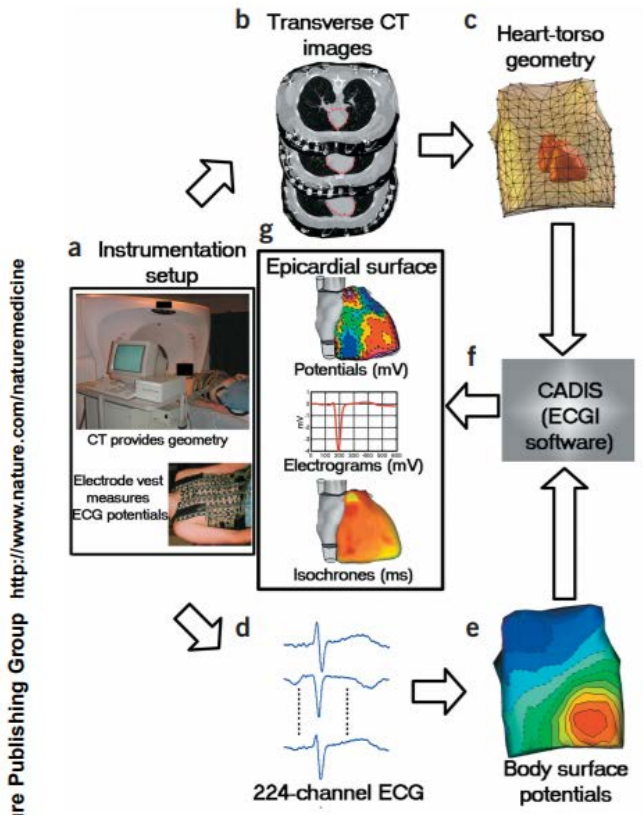


Figure 1 Block diagram of the ECGI procedure. (**a**) Photographs of instrumentation setup. (**b**) CT transverse slices showing heart contours (red) and body-surface electrodes (shiny dots). (**c**) Meshed heart-torso geometry. (**d**) Sample ECG signals obtained from mapping system. (**e**) Spatial representation of BSPM. (**f**) ECGI software package (CADIS). (**g**) Examples of noninvasive ECGI images, including epicardial potentials, electrograms and isochrones.

Ramanathan et al., Nature Med., 2004

cleared November 2016 https://www.accessdata.fda.gov/cdrh_docs/pdf16/k162440.pdf

Clinical Research

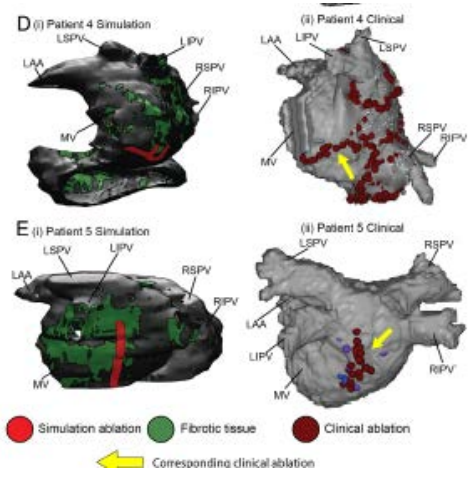
Heart Rhythm, Vol 13, No 8, August 2016

Feasibility of using patient-specific models and the "minimum cut" algorithm to predict optimal ablation targets for left atrial flutter

Sohail Zahid, BS,[*] Kaitlyn N. Whyte,[*] Erica L. Schwarz,[*] Robert C. Blake III, MS,[†] Patrick M. Boyle, PhD,[*] Jonathan Chrispin, MD,[‡] Adityo Prakosa, PhD,[*] Esra G. Ipek, MD,[‡] Farhad Pashakhanloo, BS,[*] Henry R. Halperin, MA, MD, FHRS,[‡] Hugh Calkins, MD, FHRS,[‡] Ronald D. Berger, MD, PhD, FHRS,[‡] Saman Nazarian, MD, PhD, FHRS,[‡§] Natalia A. Trayanova, PhD, FHRS[*‡]

From the [*]Institute for Computational Medicine, Department of Biomedical Engineering, Johns Hopkins University, Baltimore, Maryland, [†]CardioSolv Ablation Technologies Inc, Baltimore, Maryland, [‡]Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland, and [§]Department of Epidemiology, Johns Hopkins University School of Medicine, Baltimore, Maryland.

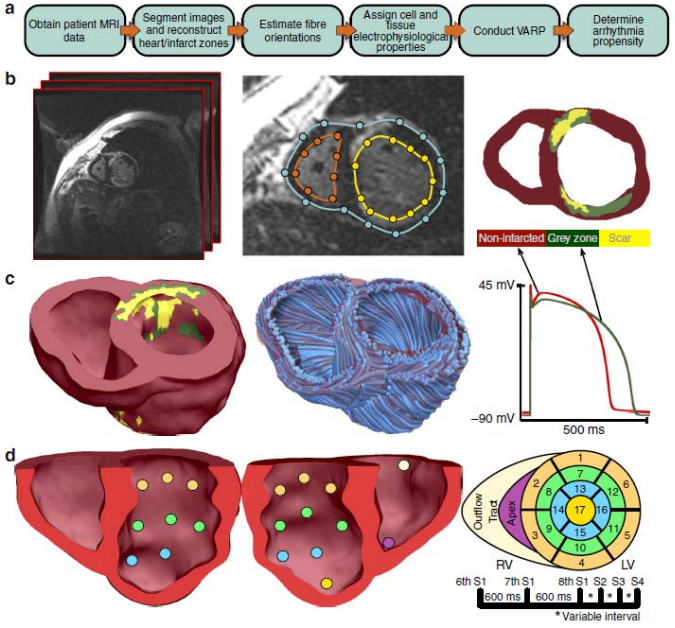
pre-procedure ablation targeting



ARTICLE NATURE COMMUNICATIONS | DOI: 10.1038/ncomms11437

Arrhythmia risk stratification of patients after myocardial infarction using personalized heart models

Hermenegild J. Arevalo[1,*], Fijoy Vadakkumpadan[1,*], Eliseo Guallar[2], Alexander Jebb[1], Peter Malamas[1], Katherine C. Wu[3] & Natalia A. Trayanova[1]



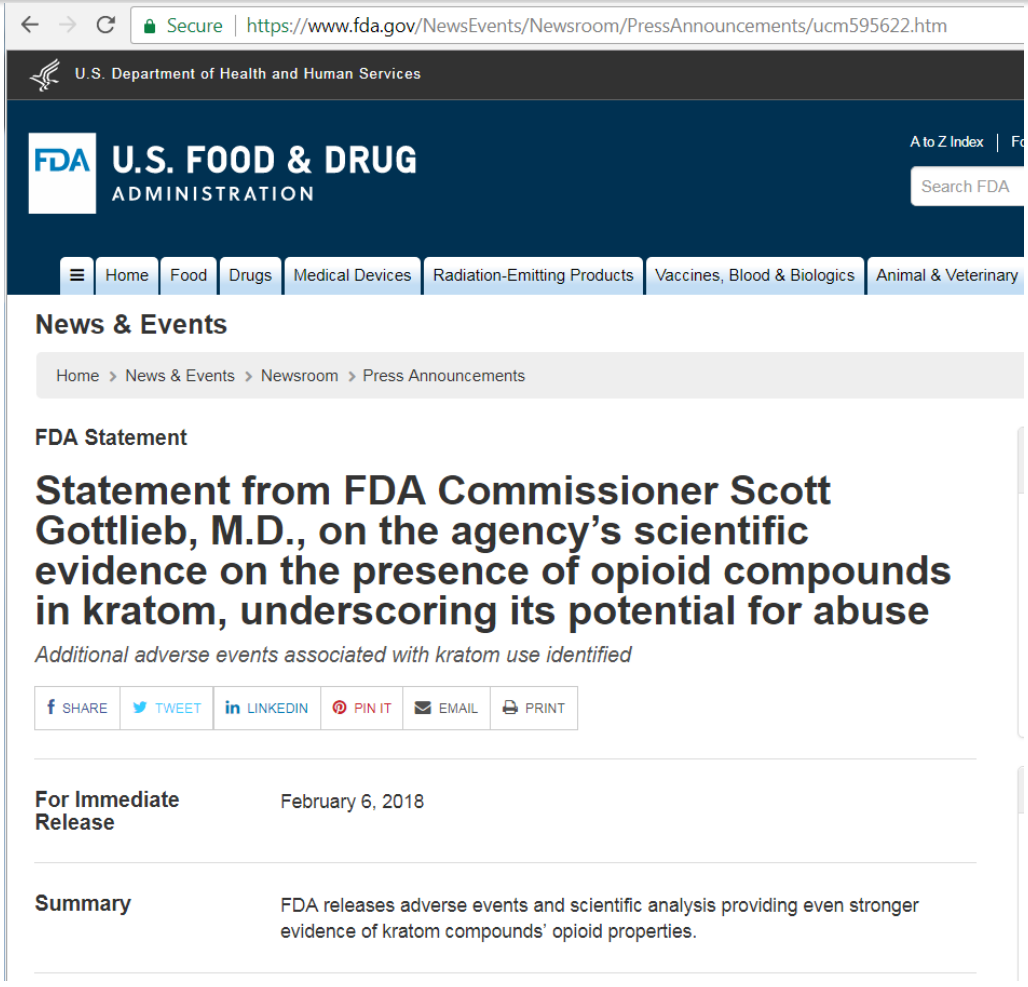
risk stratification

Examples of FDA Partnerships

- European Joint Initiatives/Global Collaborations
- Medical Device Innovation Consortium (MDIC)
- Interagency Modeling and Analysis Group (IMAG)
- Health and Environmental Science Institute (HESI)
- Avicenna Alliance

https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm595622.htm

FDA Modeling



Secure | https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm595622.htm

U.S. Department of Health and Human Services

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News & Events

Home > News & Events > Newsroom > Press Announcements

FDA Statement

Statement from FDA Commissioner Scott Gottlieb, M.D., on the agency's scientific evidence on the presence of opioid compounds in kratom, underscoring its potential for abuse

Additional adverse events associated with kratom use identified

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For Immediate Release	February 6, 2018
Summary	FDA releases adverse events and scientific analysis providing even stronger evidence of kratom compounds' opioid properties.

FDA developed the Public Health Assessment via Structural Evaluation (PHASE) methodology – a tool to help us simulate, using 3-D computer technology, how the chemical constituents of a substance (such as the compounds alkaloids found in kratom) are structured at a molecular level, how they may behave inside the body, and how they can potentially affect the brain. In effect, PHASE uses the molecular structure of a substance to predict its biological function in the body.

https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm595622.htm

FDA Modeling

VICTRE: Virtual Imaging Clinical Trials for Regulatory Evaluation

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Contact:

Aldo Badano, Ph.D.

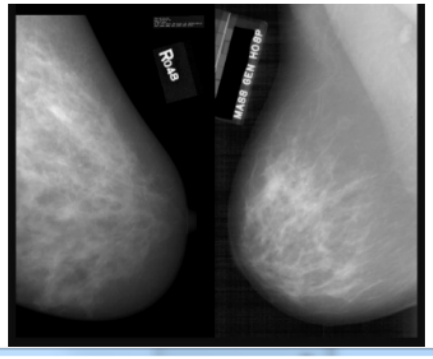
VICTRE in 3

1. What is VICTRE? VICTRE is a research program aiming at demonstrating that computational modeling can play an increasingly predominant role in the regulatory assessment of imaging products.
2. Rationale: Expensive and lengthy clinical trials delay regulatory evaluation. This burden can stiffle innovation affecting patient access to novel, high-quality imaging technologies.
3. Strategy: We propose an in silico replication of an existing clinical trial with demonstration of savings and benefits for stakeholders.

Summary

Powerful and open-source radiation imaging system simulation and image analysis tools are now becoming available to industry, academia, and government researchers, allowing for a greater understanding of the effect of system design and modifications on the performance of new imaging technologies. These tools have the potential to facilitate less-burdensome regulatory evaluation and rapid deployment of meritorious imaging devices while demonstrating significant pitfalls in defective designs.

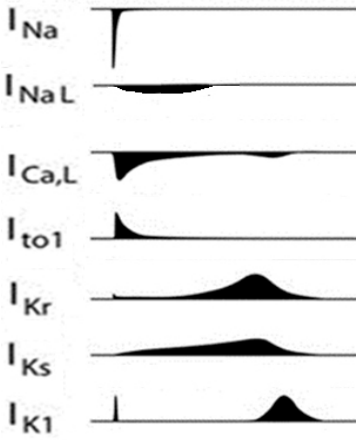
In this program, we aim to demonstrate the benefits of computational modeling for entire imaging chains in comparison to traditional methods that rely on burdensome



https://www.fda.gov/medicaldevices/scienceandresearch/researchprograms/ucm477418.htm

Comprehensive in vitro Proarrhythmia Assay (CiPA)

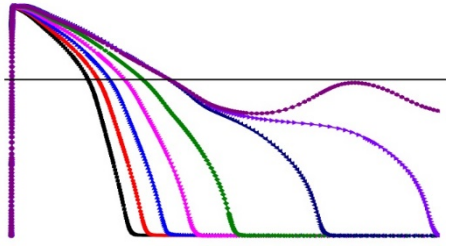
1. High Throughput Assessment of Effects on Multiple Ionic Currents



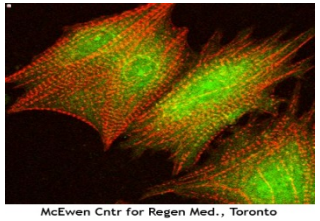
modified from Hoekstra et al., 2012

2. *In silico* Reconstruction of Human Ventricular Cardiomyocyte Electrophysiology

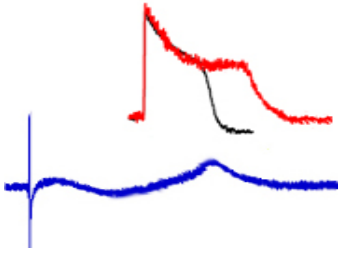
$$I_{stim} = C\frac{dV_m}{dt} + I_m$$



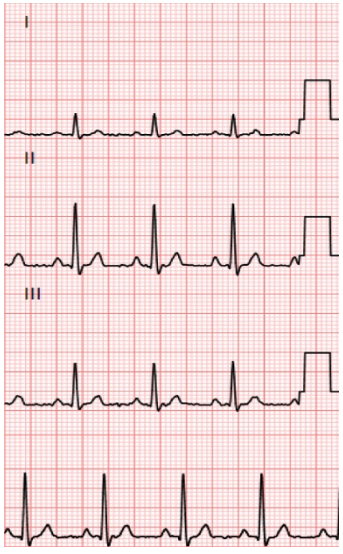
3. *In vitro* Effects on Human Stem-Cell Derived Ventricular Cardiomyocytes



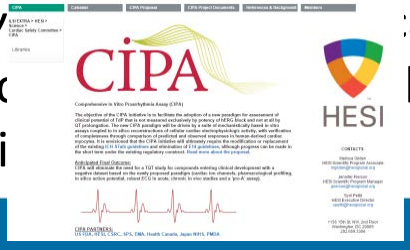
McEwen Cntr for Regen Med., Toronto



4. Evaluation of Unanticipated Effects in Clinical Phase 1 Studies

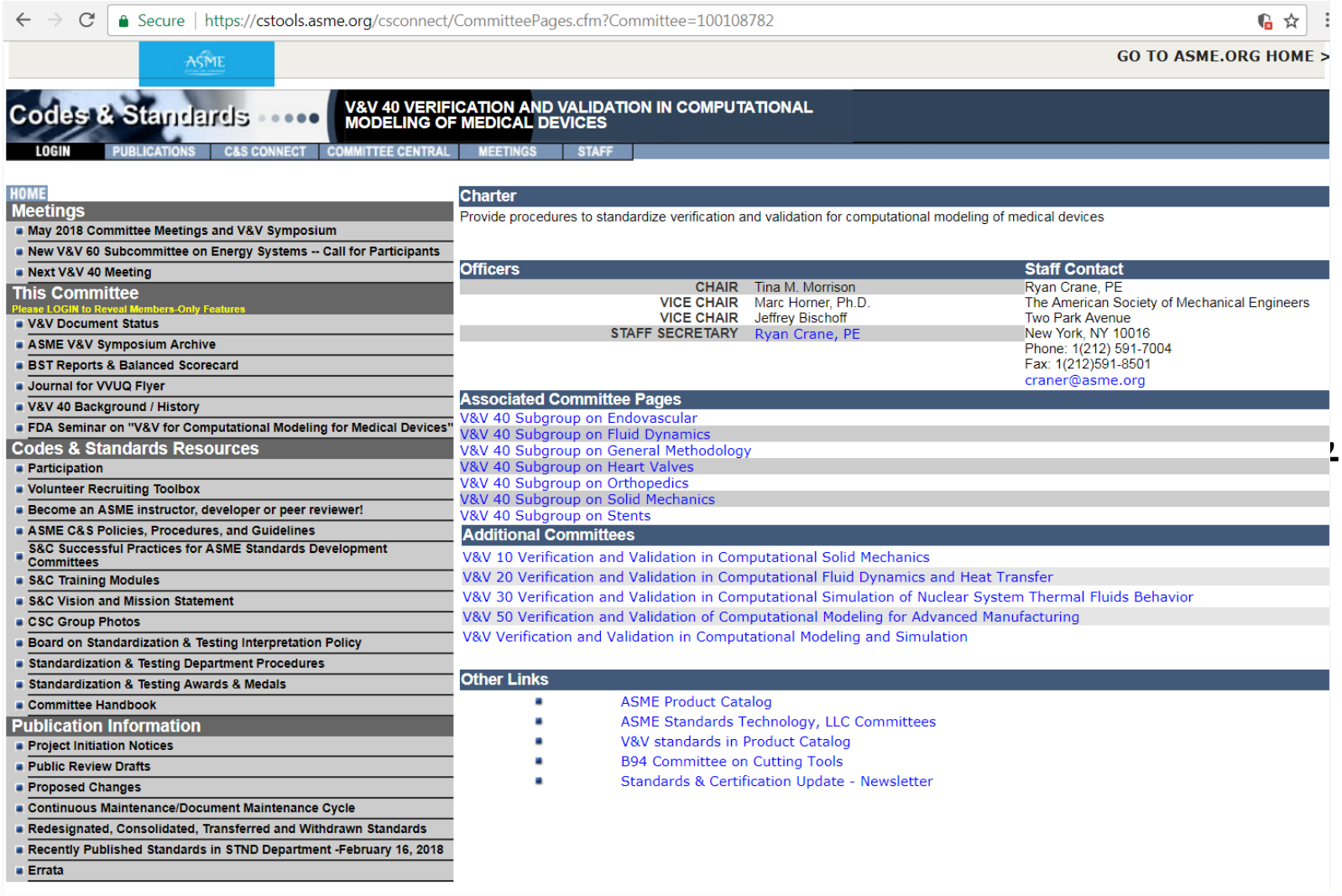


Goal: Develop a new *in v* ...*ca*...*n* that provides a more acc ...*he*...*as* of proarrhythmic potenti



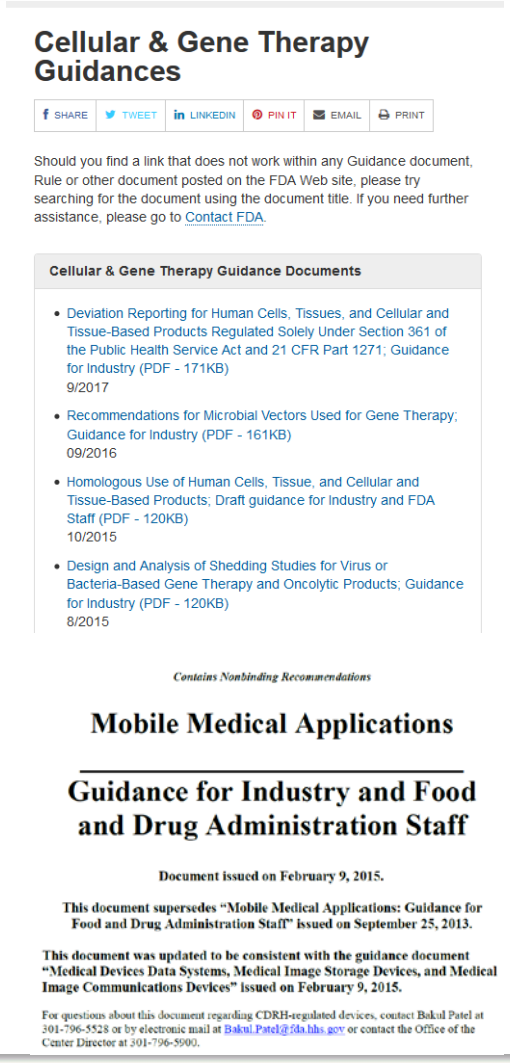
slide courtesy off David Strauss, FDA

Standards



http://www.fda.gov/regulatoryinformation/standards/default.htm

Guidances



Cellular & Gene Therapy Guidances

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Should you find a link that does not work within any Guidance document, Rule or other document posted on the FDA Web site, please try searching for the document using the document title. If you need further assistance, please go to Contact FDA.

Cellular & Gene Therapy Guidance Documents

- Deviation Reporting for Human Cells, Tissues, and Cellular and Tissue-Based Products Regulated Solely Under Section 361 of the Public Health Service Act and 21 CFR Part 1271; Guidance for Industry (PDF - 171KB)
  9/2017
- Recommendations for Microbial Vectors Used for Gene Therapy; Guidance for Industry (PDF - 161KB)
  09/2016
- Homologous Use of Human Cells, Tissue, and Cellular and Tissue-Based Products; Draft guidance for Industry and FDA Staff (PDF - 120KB)
  10/2015
- Design and Analysis of Shedding Studies for Virus or Bacteria-Based Gene Therapy and Oncolytic Products; Guidance for Industry (PDF - 120KB)
  8/2015

Contains Nonbinding Recommendations

Mobile Medical Applications

Guidance for Industry and Food and Drug Administration Staff

Document issued on February 9, 2015.

This document supersedes "Mobile Medical Applications: Guidance for Food and Drug Administration Staff" issued on September 25, 2013.

This document was updated to be consistent with the guidance document "Medical Devices Data Systems, Medical Image Storage Devices, and Medical Image Communications Devices" issued on February 9, 2015.

For questions about this document regarding CDRH-regulated devices, contact Bakul Patel at 301-796-5528 or by electronic mail at Bakul.Patel@fda.hhs.gov or contact the Office of the Center Director at 301-796-5900.

Guidance for Industry

E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs

Additional copies are available from:

Office of Training and Communication
Division of Drug Information, HFD-240
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857
(Tel) 301-827-4573
http://www.fda.gov/cder/guidance/index.htm

Office of Communication, Training and Manufacturers Assistance, HFM-40
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike, Rockville, MD 20852-1448
http://www.fda.gov/cber/guidelines.htm.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

October 2005
ICH

Guidance for Industry

S7B Nonclinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals

Additional copies are available from:

Office of Training and Communication
Division of Drug Information, HFD-240
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857
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1401 Rockville Pike, Rockville, MD 20852-1448
http://www.fda.gov/cber/guidelines.htm.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

October 2005
ICH

http://www.fda.gov/forindustry/fdabasicsforindustry/ucm234622.htm

Reporting of Computational Modeling Studies in Medical Device Submissions

Contains Nonbinding Recommendations

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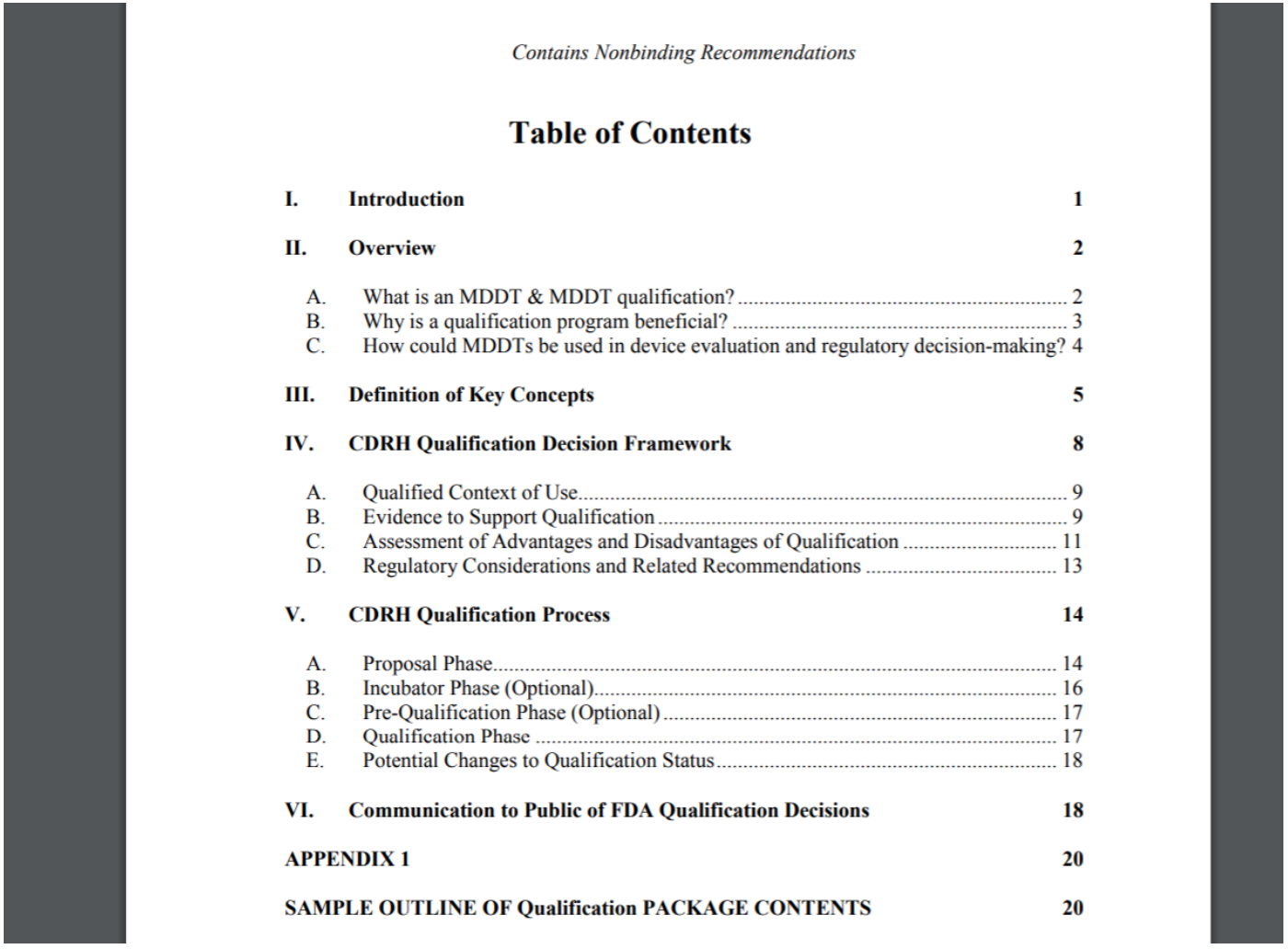
http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm381813.pdf

Medical Device Development Tools



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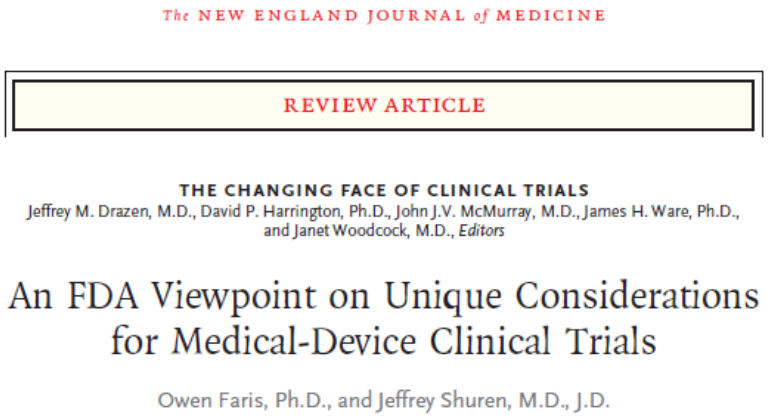
http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM374432.pdf

Evaluation of Computer Modeling at FDA



The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

THE CHANGING FACE OF CLINICAL TRIALS

Jeffrey M. Drazen, M.D., David P. Harrington, Ph.D., John J.V. McMurray, M.D., James H. Ware, Ph.D., and Janet Woodcock, M.D., *Editors*

An FDA Viewpoint on Unique Considerations for Medical-Device Clinical Trials

Owen Faris, Ph.D., and Jeffrey Shuren, M.D., J.D.

"In some circumstances, a clinical trial is not able to answer the most critical questions related to the safety and effectiveness of a device…"

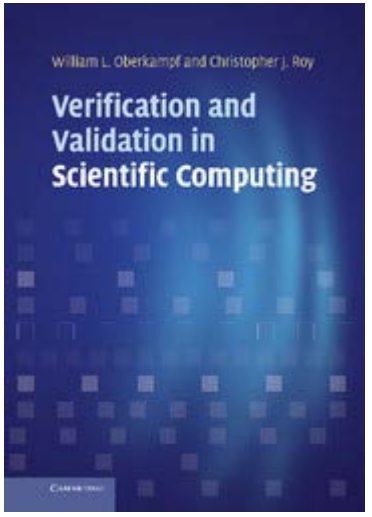
"The greatest safety concern for pacemakers in the MRI environment is the potential for a cardiac lead to act as an antenna and to direct radiofrequency energy from the MRI scanner to the lead tip, heating the tip and potentially ablating cardiac tissue."

"Given that heating would be most likely to occur in rare, worst-case conditions that would be difficult to predict clinically, relying on a clinical trial as the primary validation of safety would have required many thousands of participants. Instead, FDA approval rested primarily on robust mathematical modeling that was validated with bench studies and studies in animals. The modeling data, which simulated thousands of combinations of device and patient geometries and MRI scan conditions, provided strong evidence that even worstcase conditions would be very unlikely to result in detrimental lead heating."

http://www.nejm.org/doi/full/10.1056/NEJMra1512592

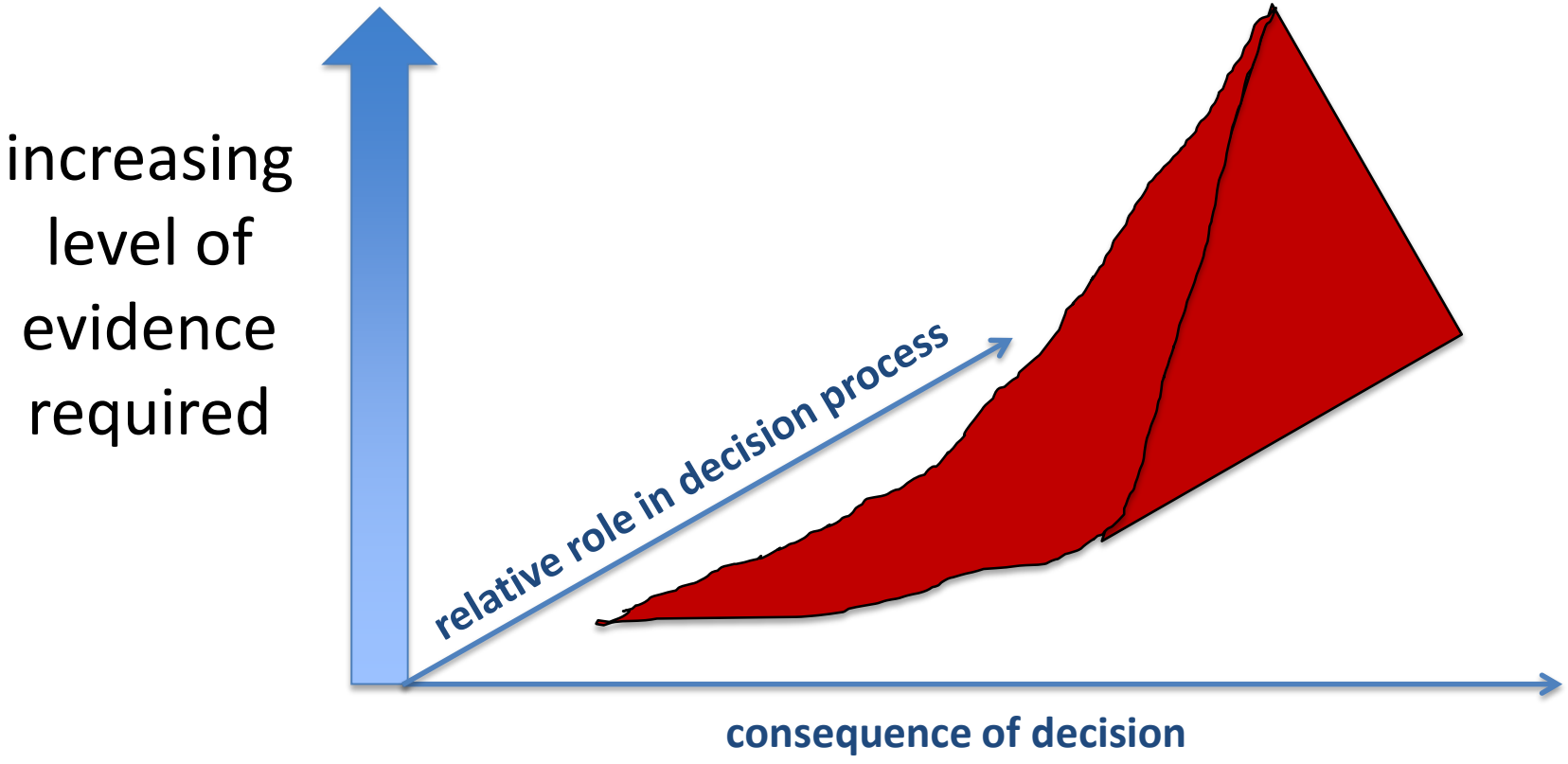
Evaluation of Computer Models

- Verification
- Validation
- Uncertainty Quantification (VVUQ)
- Calibration
- Parameter Sensitivity Analysis
- Implementation (numerical solvers)
- Emulators
- Optimal Experimental Design
- Credibility/Applicability
- Risk Assessment



Evaluation of Computer Models

depends on the context of use (COU)!

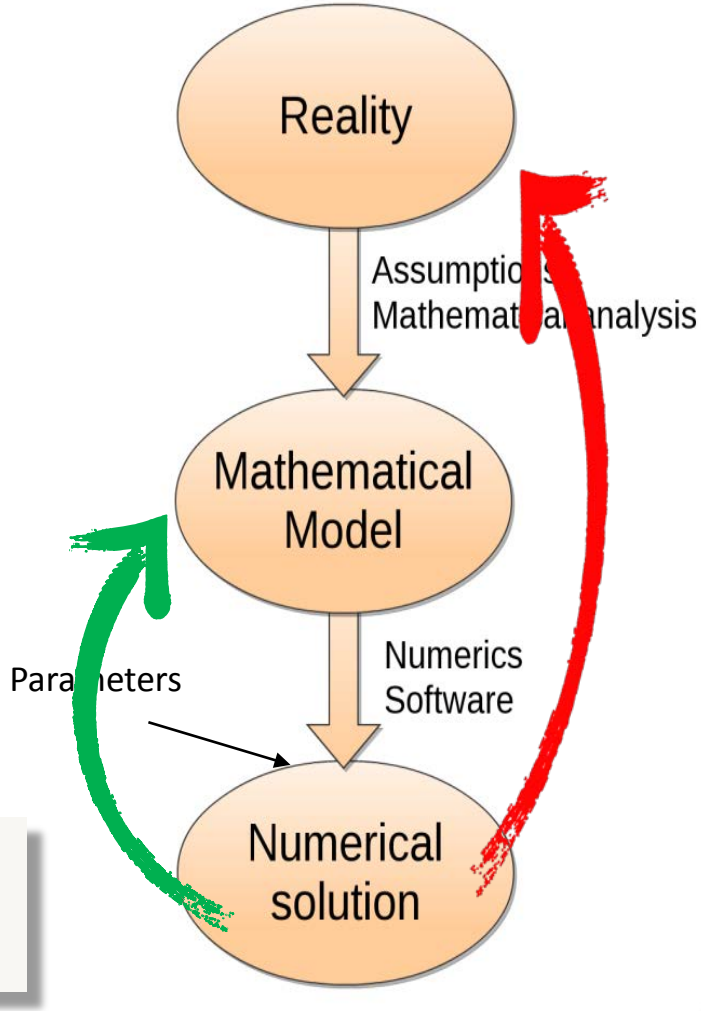


Verification, Validation and Uncertainty Quantification (VVUQ)

Verification:
Does the computational model accurately solve the underlying mathematical model?

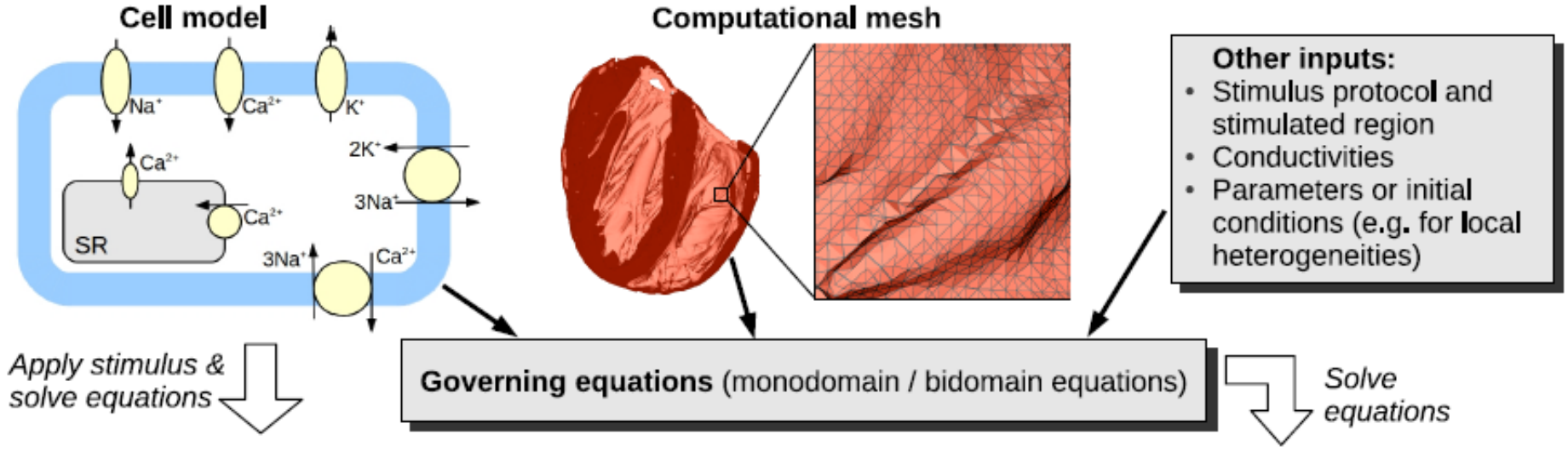
Validation:
How well does the computational model approximate 'reality'?

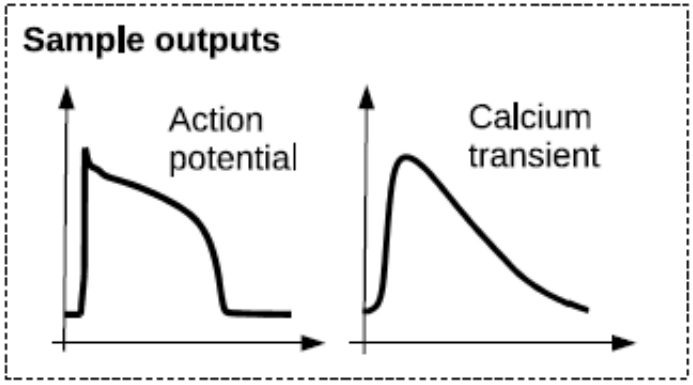
Uncertainty Quantification (UQ):
How much does uncertainty in parameters / initial conditions affect the results?

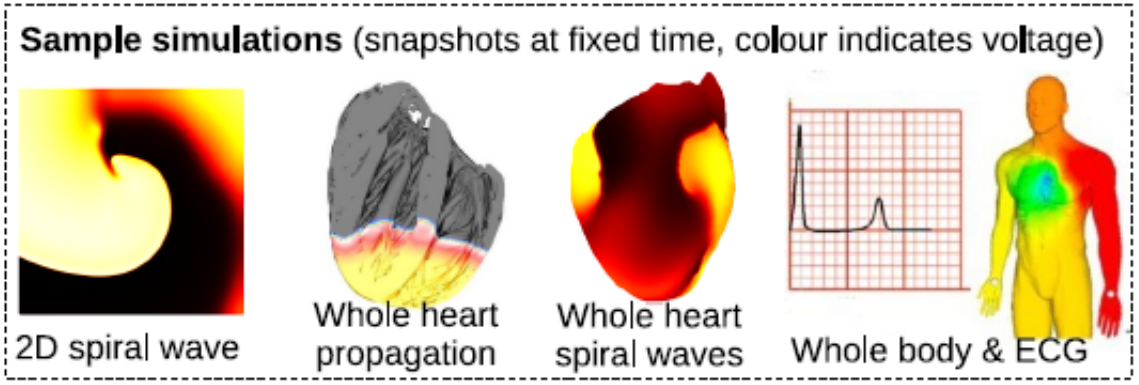


examples of are provided for each in the following slides

Modeling of Cardiac Electrophysiology

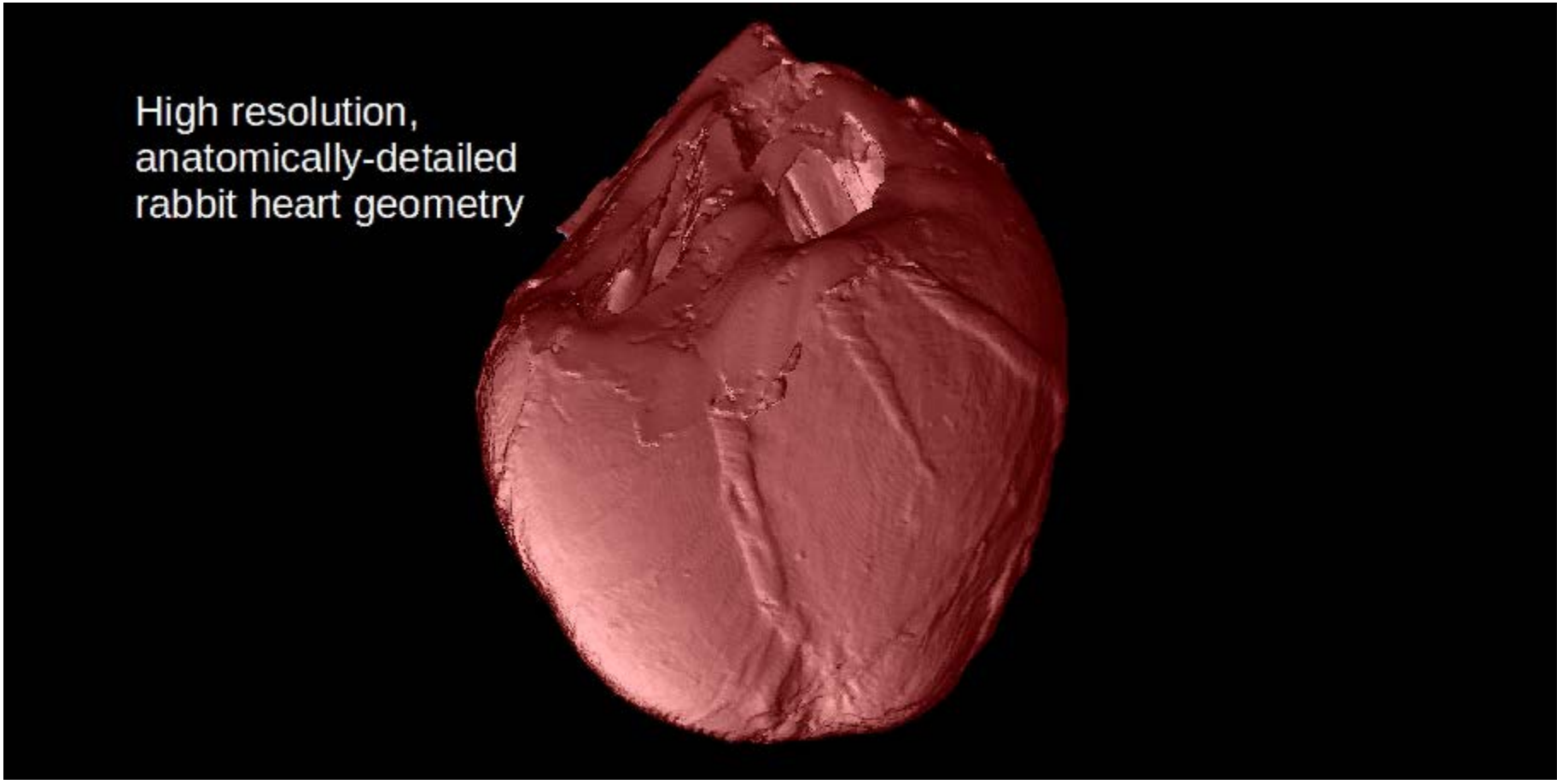






Pathmanathan & Gray. Ensuring reliability of safety-critical clinical applications of computational cardiac models. Front. Physiol. 2013

Modeling of Cardiac Electrophysiology



special thanks to Brian Fitzgerald et al. at FDA HPC

http://tinyurl.com/VFsim

Verification of Electromechanical Computer Simulations

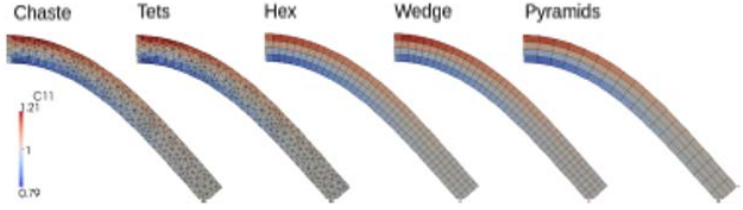
First tool for strongly verifying 'bidomain' solvers –
can be used by anyone to demonstrate correctness of their solvers

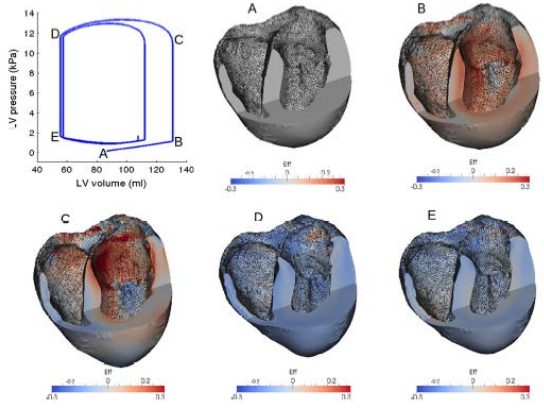
- "method of manufactured solutions" -> analytical result
- high confidence in solver correctness
- exact-error convergence analyses

Pathmanathan & Gray, *Verification of computational models of cardiac electrophysiology*, IJNMBE, 2014

Verification test problems for cardiac mechanics solvers

	P1	P2	P3	P4
Max displacement magnitude (Chaste)	5.2791	6.0839	0.9998	2.7867
Max difference: Cardioid-tet versus Chaste	0.0038	0.0039	0.0020	0.0120
Max difference: Cardioid-hex versus Chaste	0.0072	0.0073	0.0025	0.0208
Max difference: Cardioid-wedge versus Chaste	0.0071	0.0071	0.0025	0.0218
Max difference: Cardioid-pyramid versus Chaste	0.0166	0.0223	0.0031	0.0345

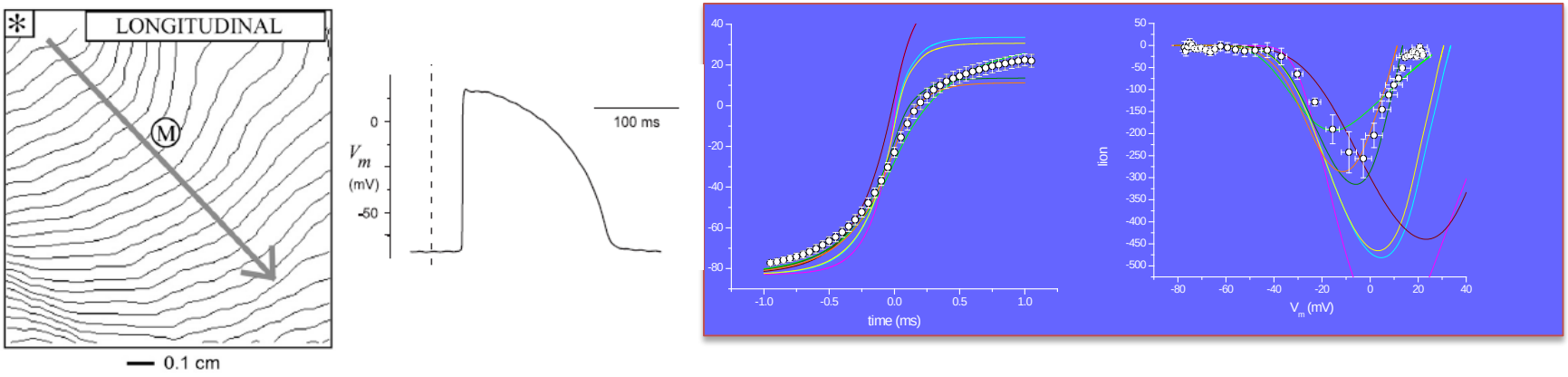




Gurev, Pathmanathan et al., A computational model of the deforming human heart, BMMB, 2015

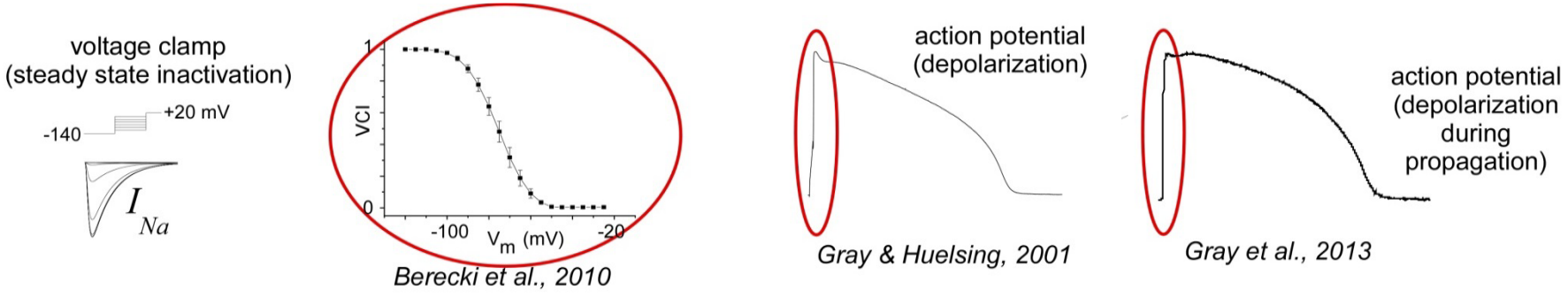
Validation of Electrophysiological Computer Models

Existing models do not represent the action potential upstroke during propagation!



Gray et al., Quantification of transmembrane currents during action potential propagation in the heart. *Biophysical Journal*, 2013

Model Development

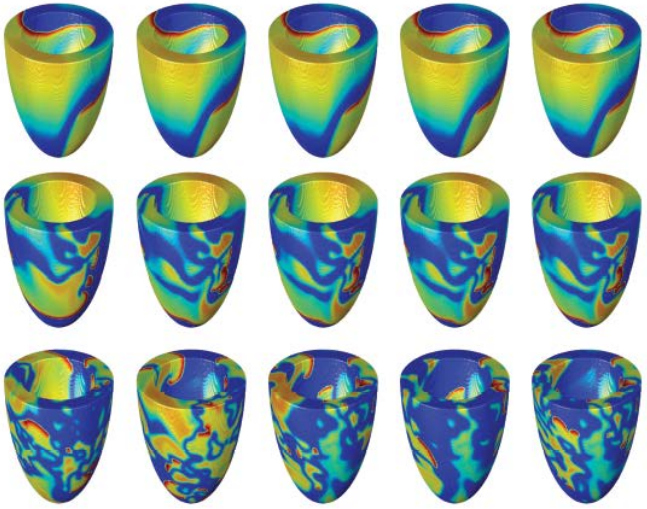


Gray RA, Pathmanathan P. A Parsimonious Model of the Rabbit Action Potential Elucidates the Minimal Physiological Requirements for Alternans and Spiral Wave Breakup. *PLOS Computational Biology*, 2016, 12(10): e1005087.

Uncertainty Quantification

The Journal of Physiology

Volume 594 / Number 23 / 1 December 2016



The Cardiac Physiome Project

A publication of The Physiological Society

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WHITE PAPER

Uncertainty and variability in computational and mathematical models of cardiac physiology

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Abstract The Cardiac Physiome effort is one of the most mature and successful applications of mathematical and computational modelling for describing and advancing the understanding of physiology. After five decades of development, physiological cardiac models are poised to realise the promise of translational research via clinical applications such as drug development and patient-specific approaches as well as ablation, cardiac resynchronisation and contractility modulation therapies. For models to be included as a vital component of the decision process in safety-critical applications, rigorous assessment of model credibility will be required. This White Paper describes one aspect of this process by identifying and classifying sources of variability and uncertainty in models as well as their implications for the application and development of cardiac models. We stress the need to understand and quantify the sources of variability and uncertainty in model inputs, and the impact of model structure and complexity and their consequences for predictive model outputs. We propose that the future of the Cardiac Physiome should include a probabilistic approach to quantify the relationship of variability and uncertainty of model inputs and outputs.

How does uncertainty affect model results?

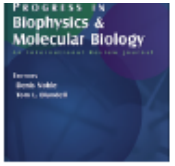
http://onlinelibrary.wiley.com/doi/10.1113/JP271671/full

Uncertainty Quantification

ELSEVIER

Progress in Biophysics and Molecular Biology

journal homepage: www.elsevier.com/locate/pbiomolbio



Uncertainty quantification of fast sodium current steady-state inactivation for multi-scale models of cardiac electrophysiology

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ARTICLE INFO

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ABSTRACT

Perhaps the most mature area of multi-scale systems biology is the modelling of the heart. Current models are grounded in over fifty years of research in the development of biophysically detailed models of the electrophysiology (EP) of cardiac cells, but one aspect which is inadequately addressed is the

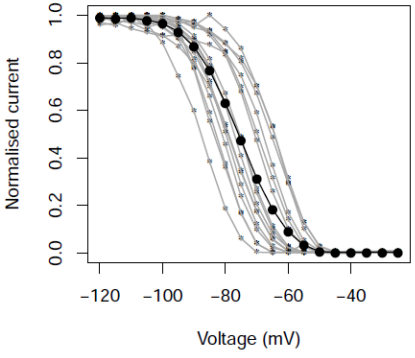
methodology to assess voltage clamp data. Advantages of this approach over a more traditional 'population-averaged' approach are highlighted. The method was used to characterise variability amongst cells isolated from canine epi and endocardium, and this variability was then 'propagated forward' through a

"To our knowledge this article is the first to quantify population variability in membrane dynamics in this manner, and the first to perform formal UQ for a component of a cardiac model."

Uncertainty Quantification

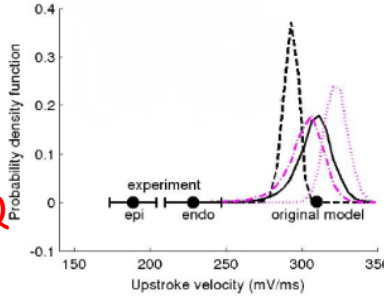
Single-cell level: significant variability including model failure

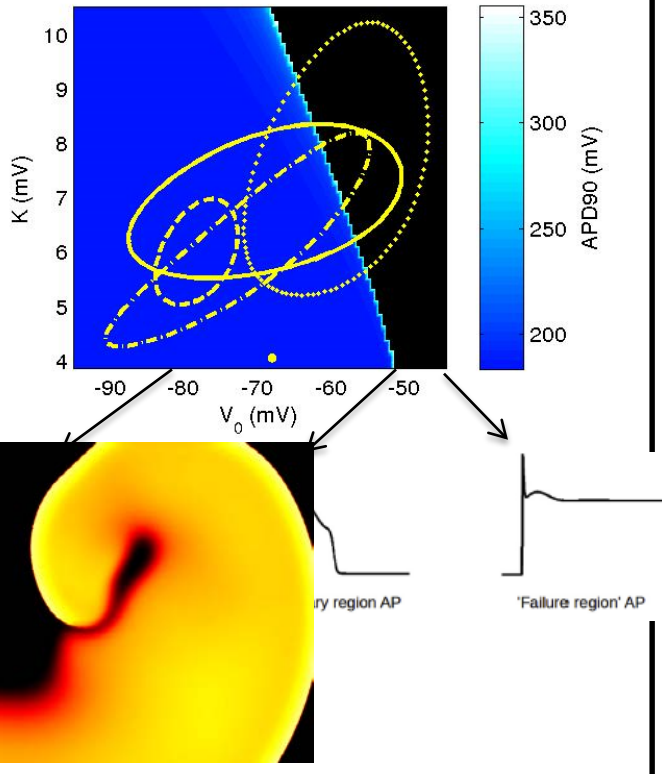
experimental variability (ion-channel level)



NOT parameter sensitivity!

"propagate" UQ through the model





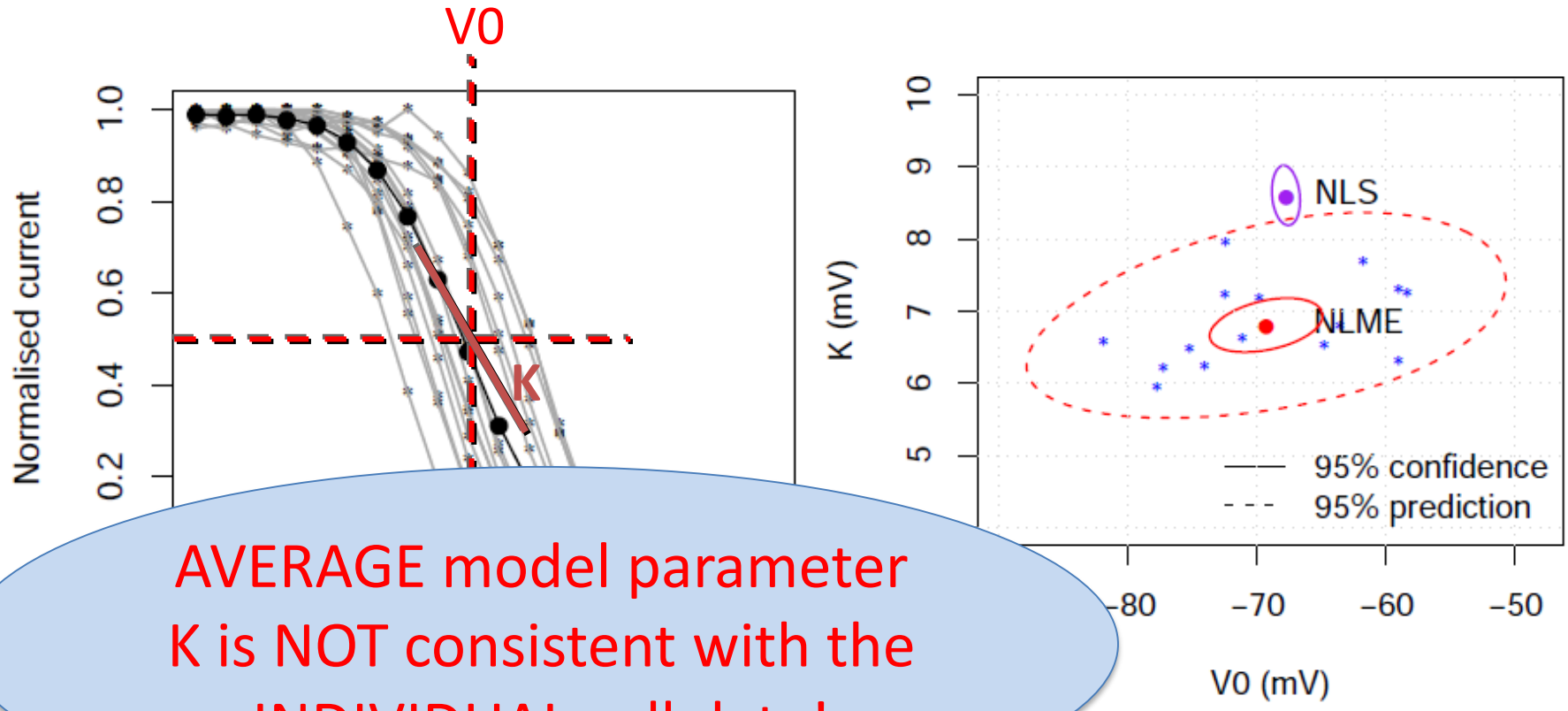
Tissue level: almost no variability

"Emergent Robustness"

Pathmanathan et al., *Uncertainty quantification of fast sodium current steady-state inactivation for multi-scale models of cardiac electrophysiology*, Progress in Biophysics and Molecular Biology, 2015.

Uncertainty Quantification

steady state inactivation of sodium current (INa)



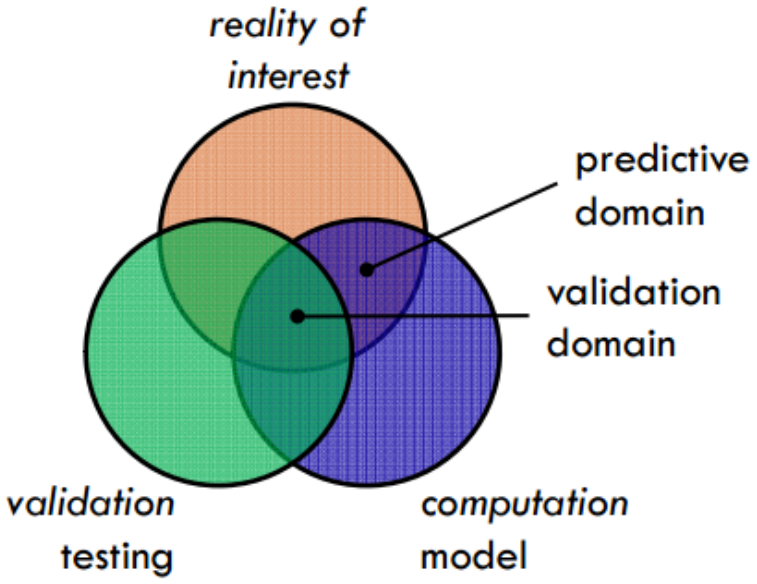
AVERAGE model parameter K is NOT consistent with the INDIVIDUAL cell data!

Pathmanathan et al., *Uncertainty quantification of fast sodium current steady-state inactivation for multi-scale models of cardiac electrophysiology,* Progress in Biophysics and Molecular Biology, 2015.

Model Validation Paradox

10

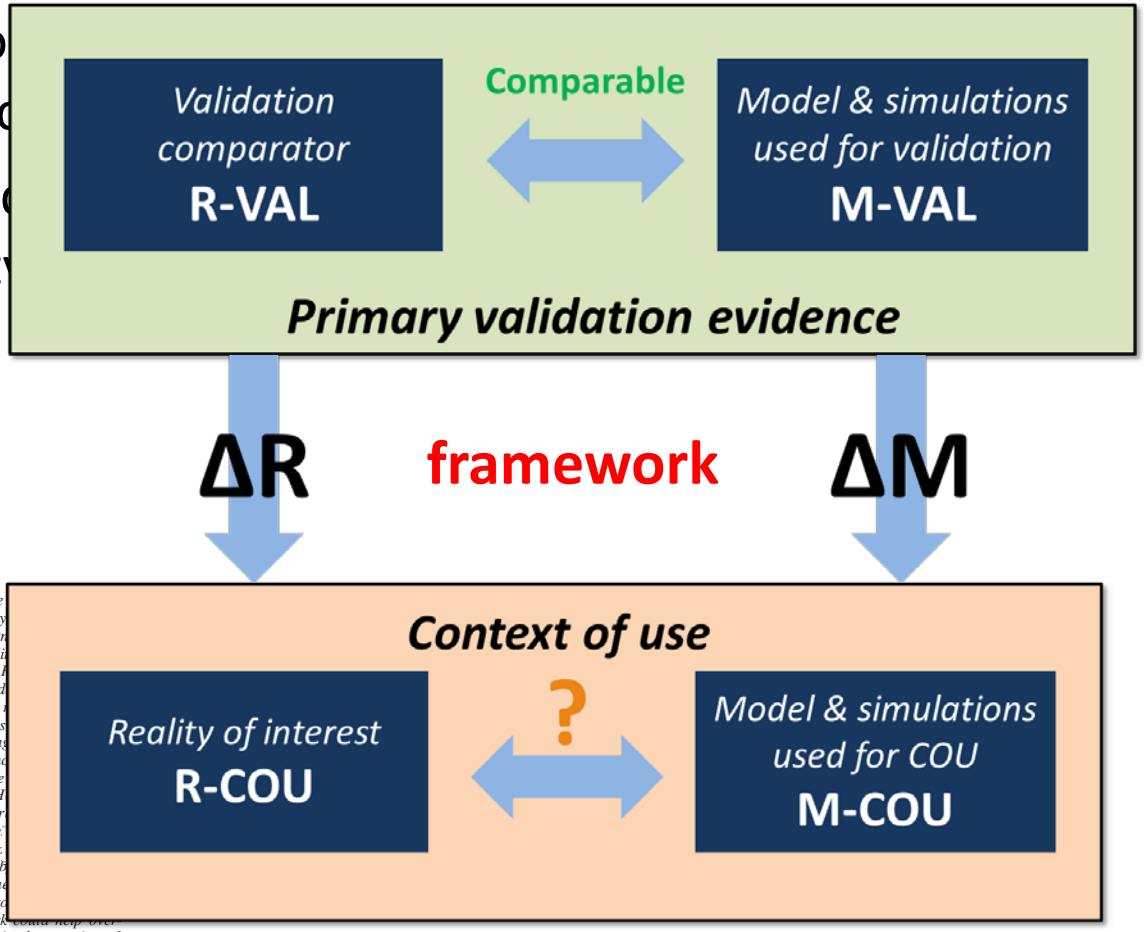
- Models developed to make predictions where no experimental data can or will be obtained
  - Models only approximate a portion of entire reality of interest
  - Similarly, validation testing only replicates portions of the reality of interest
  - Model use is desired beyond the domain of validation where no validation exists (extrapolation)



http://www.fda.gov/downloads/MedicalDevices/NewsEvents/WorkshopsConferences/UCM358733.pdf

Evaluation of Credibility of Computer Models

- The *context of use* of mo
  usually involves the clinic
- The inability to perform
  acceptance and reliabilit



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Applicability Analysis of Validation Evidence for Biomedical Computational Models

Computational modeling has the potential to revolutionize medicine formed engineering. However, despite decades of work, there has only gress to successfully translate modeling research to patient care. Or which often occurs with biomedical computational models is an inabili dation in a setting that closely resembles how the model will be used. biomedical model that makes in vivo clinically relevant predictions, d predictions may be impossible for ethical, technological, or financial able limitations inherent to the validation process lead to challenges credibility of biomedical model predictions. Therefore, when evaluatin els, it is critical to rigorously assess applicability, that is, the relevan tional model, and its validation evidence to the proposed context of use there are no well-established methods for assessing applicability. H novel framework for performing applicability analysis and demonstr medical device computational model. The framework provides a syste method for breaking down the broad question of applicability into a questions, which may be addressed using supporting evidence and sub tise. The framework can be used for model justification, model assessm planning. While motivated by biomedical models, it is relevant to a bro plines and underlying physics. The proposed applicability framework come some of the barriers inherent to validation of, and aid clinical implementation of, biomedical models. [DOI: 10.1115/1.4037671]

Journal of Verification, Validation and Uncertainty Quantificatio JUNE 2017, Vol. 2 / 021005-1

Pathmanathan et al., Applicability Analysis of Validation Evidence for Biomedical Computational Models, JVVUQ, 2017.

Applicability Framework for Biomedical Models

Our approach to assess the applicability of the model for the COU involves considering differences listed in ΔR and the modifications listed in ΔM.

Step 1: **Describe the Aim of the Computational Modeling.**

Step 2: Describe the Reality and Model Elements of the COU.

Step 3: Describe the Sources of Validation Evidence.

Step 4: Describe the Reality and Model Elements of the Primary Validation Evidence.

Step 5: Describe the Aspects of the Computational Model that are the Identical in M-VAL and M-COU.

Step 6: Describe the Aspects of the Computational Model that are Different Between M-VAL and M-COU.

Step 7: Describe the Relevant Differences Between R-VAL and R-COU.

Applicability Framework for Biomedical Models

Our approach to assess the applicability of the model for the COU involves considering differences listed in ΔR and the modifications listed in ΔM.

Step 8: Is It Appropriate to Use the Model Aspects Listed in Step 5 to Make Predictions About R-COU? Provide Rationale, Evidence, or Discussion.

Step 9: Do the Modifications to the Computational Model (Listed in Step 6) Result in Trustworthy Predictions for the COU? Provide Rationale, Evidence or Discussion.

Step 10: Provide Rationale for Trustworthiness If the COU QOIs Differ From Validation QOIs.

Step 11: Consider the Overall Computational Model M-COU, in the Context of Differences Between R-VAL and R-COU.

Step 12: Assess the Overall Applicability of the Computational Model for the COU.

Credibility Evidence (examples)

TABLE 1 | Different types of evidence relevant to the credibility of a cardiac EP model, with ion channel, cell, and organ-level examples.

Category	Type of credibility evidence	Examples		
		Ion channel	**Cell model**	**Organ-level model**
Category 1	Evidence regarding validity of model assumptions or supporting the model formulation	Successes of Hodgkin-Huxley formulation for modeling ion channels—see section Ion channel models	Evidence supporting the formulation of cell membrane as a parallel resistor-capacitor electric circuit	The successes of the bidomain equations, in particular predictions made that were later experimentally observed—see section Organ-level models
	Evidence regarding accuracy/fidelity of model parameters/inputs	Evidence supporting accuracy of steady-state inactivation parameters—see section Ion Channel Models	Rationale behind standard choice of membrane capacitance equal to 1 uF/cm^2.	Evidence on fidelity of geometry used and on fidelity of fiber/sheet specification—discussed in section Organ-Level Models.
Category 2	Calibration results	Results showing agreement between ion channel model and experimentally recorded current-voltage relationship when ion channel parameters are calibrated using this data	Results showing agreement between the model action potential and experimental recordings when maximal conductances are tuned to achieve the match	Results showing activation patterns match experiment if fast sodium current maximal conductance (which controls conduction velocity) chosen to maximize agreement
Category 3	Reproduced (emergent) phenomena	Simulation results demonstrating that a rapid sodium current model can exhibit damped oscillations	Simulation results demonstrating that a cell model reproduces action potential spike and dome morphology	Simulation results demonstrating that ECG predicted by a heart and torso model exhibits realistic-looking QRS complex and T wave
	General validation results	Comparison of a general-purpose ion channel model predictions to new voltage-clamp data not used in the construction of the model.	Comparisons of model results with experimental data for a novel general-purpose cell model, e.g., all such results in O'Hara et al. (2011). Discussed in detail in section Cell Models	Excitation patterns of general purpose bi-ventricular model compared to experimental/clinical data. ECG of general-purpose heart and torso model compared to experimental/clinical data.
	COU-driven validation results	Evaluation of a hERG model to predict pharmaceutical pro-arrhythmic risk	Evaluation of a cell model-based biomarker to predict pharmaceutical pro-arrhythmic risk (e.g., CiPA, discussed in section Cell Models)	Number of phase singularities during ventricular fibrillation (VF) compared to clinical data, when the model will be used to understand mechanisms behind VF—see section Organ-Level Models. Clinical evaluation of a whole-heart model which uses patient-specific information to predict optimal ablation targets to terminate arrhythmias—see section Organ-Level Models

Pathmanathan & Gray, Validation and Trustworthiness of Multiscale Models of Cardiac Electrophysiology. Front. Physiol. 2018

Patient-Specific Modeling

Journal of Cardiovascular Translational Research
https://doi.org/10.1007/s12265-018-9792-2

REVIEW

Patient-Specific Cardiovascular Computational Modeling: Diversity of Personalization and Challenges

Richard A. Gray[1,2] · Pras Pathmanathan[1]

Received: 13 December 2017 / Accepted: 2 February 2018

Abstract
Patient-specific computer models have been developed representing a variety of aspects of the cardiovascular system spanning the disciplines of electrophysiology, electromechanics, solid mechanics, and fluid dynamics. These physiological mechanistic models predict macroscopic phenomena such as electrical impulse propagation and contraction throughout the entire heart as well as flow and pressure dynamics occurring in the ventricular chambers, aorta, and coronary arteries during each heartbeat. Such models have been used to study a variety of clinical scenarios including aortic aneurysms, coronary stenosis, cardiac valvular disease, left ventricular assist devices, cardiac resynchronization therapy, ablation therapy, and risk stratification. After decades of research, these models are beginning to be incorporated into clinical practice directly via marketed devices and indirectly by improving our understanding of the underlying mechanisms of health and disease within a clinical context.

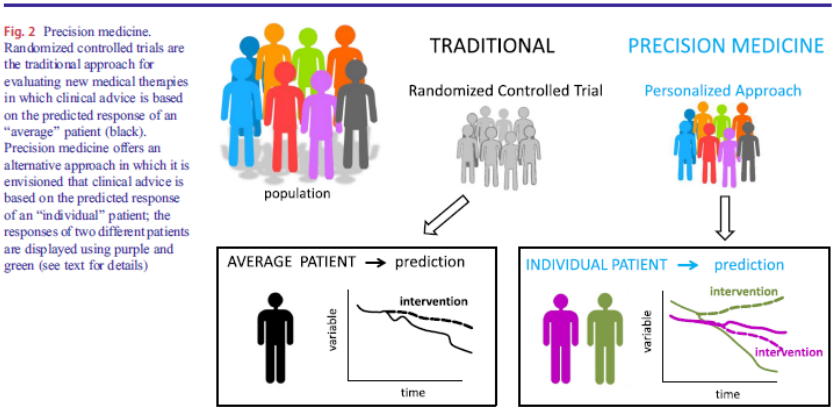

Fig. 2 Precision medicine. Randomized controlled trials are the traditional approach for evaluating new medical therapies in which clinical advice is based on the predicted response of an "average" patient (black). Precision medicine offers an alternative approach in which it is envisioned that clinical advice is based on the predicted response of an "individual" patient; the responses of two different patients are displayed using purple and green (see text for details)

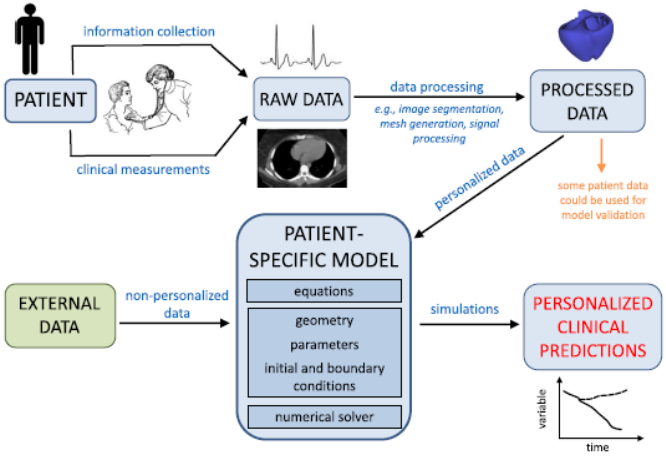

Fig. 3 Patient-specific modeling workflow involves collecting and processing data from an individual patient and incorporating that data into a mathematical model represented digitally in a computer. The model incorporates the governing equations and parameters as well as mathematical representations of the patient's geometry and boundary and initial conditions. Data collected from the patient can also be used for model validation (see the "Challenges" section for a discussion). Note that data used for model validation should be distinct to data used for model development

- clinical utilization involves addressing two very complex approaches
  - individualized therapy
  - computer modeling
- some evaluation of patient-specific modeling is unique
- we argue for the need for model transparency and robust evaluation frameworks that consider the risk to the patient and limitations in acquiring clinical data

Gray & Pathmanathan, Patient-Specific Cardiovascular Computational Modeling: Diversity of Personalization and Challenges, JCTR, 2018

Summary

- Existing VVUQ methods are not often applicable for *mechanistic physiological computer models in medicine* because of a variety of reasons, e.g.:
  - biological variability
  - limitations of human experimentation
  - complexity of models that are multi-scale in time and space.
- Research of VVUQ for *mechanistic physiological computer models in medicine* is in its infancy.
- Model evaluation is dependent upon the context of use (COU).
- Global validation (e.g., ECGs, PV loops) for some COU's will not be adequate.
- Credibility (Applicability) evaluation of models for clinical use is of paramount importance for high-risk COU's.
- Patient-Specific models involve two very complex approaches (individualized therapy and computer modeling), and the appropriate implementation(s) and evaluation(s) of these approaches remain largely unknown and a matter of ongoing discussion.

Thank you!

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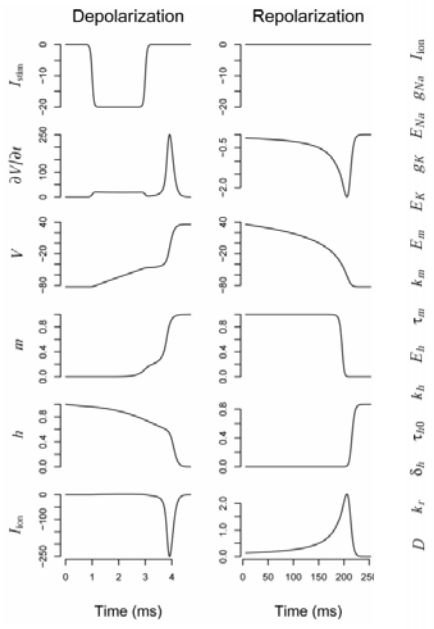
Model Identifiability

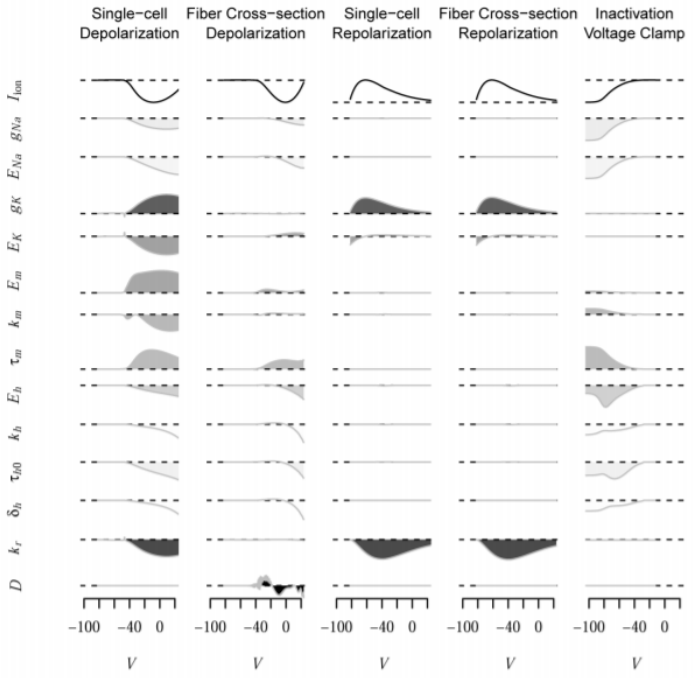
Estimability Analysis and Optimal Design in Dynamic Multi-scale Models of Cardiac Electrophysiology

Matthew S. Shotwell and Richard A. Gray

We present an applied approach to optimal experimental design and estimability analysis for mechanistic models of cardiac electrophysiology, by extending and improving on existing computational and graphical methods. These models are 'multi-scale' in the sense that the modeled phenomena occur over multiple spatio-temporal scales (e.g., single cell vs. whole heart). As a consequence, empirical observations of multi-scale phenomena often require multiple distinct experimental procedures. We discuss the use of conventional optimal design criteria (e.g., D-optimality) in combining experimental observations across multiple scales and multiple experimental modalities. In addition, we present an improved 'sensitivity plot'—a graphical assessment of parameter estimability—that overcomes a well-known limitation in this context. These techniques are demonstrated using a working Hodgkin–Huxley cell model and three simulated experimental procedures: single-cell stimulation, action potential propagation, and voltage clamp. In light of these assessments, we discuss two model modifications that improve parameter estimability, and show that the choice of optimality criterion has a profound effect on the contribution of each experiment.
Supplementary materials accompanying this paper appear on-line.

Key Words: Cardiac cell model; Identifiability; Sensitivity plot; Voltage clamp.





Shotwell & Gray, Front. J Agric Biol Environ Stat. 2016

FDA Scientific Priority Areas

- Modernize Toxicology to Enhance Product Safety
- Stimulate Innovation in Clinical Evaluations and Personalized Medicine to Improve Product Development and Patient Outcomes
- Harness Diverse Data through Information Sciences to Improve Health Outcomes

CDRH Science Priorities

- Leverage “Big Data” for regulatory decision making
- Modernize biocompatibility and biological risk evaluation of device materials
- Develop methods and tools to improve and streamline clinical trial design
- Develop computational modeling technologies to support regulatory decision making
- Enhance the performance of Digital Health and strengthen medical device cybersecurity
- Leverage precision medicine and biomarkers for predicting medical device performance, disease diagnosis, and progression.

State-of-the-Art Scientific Modelling

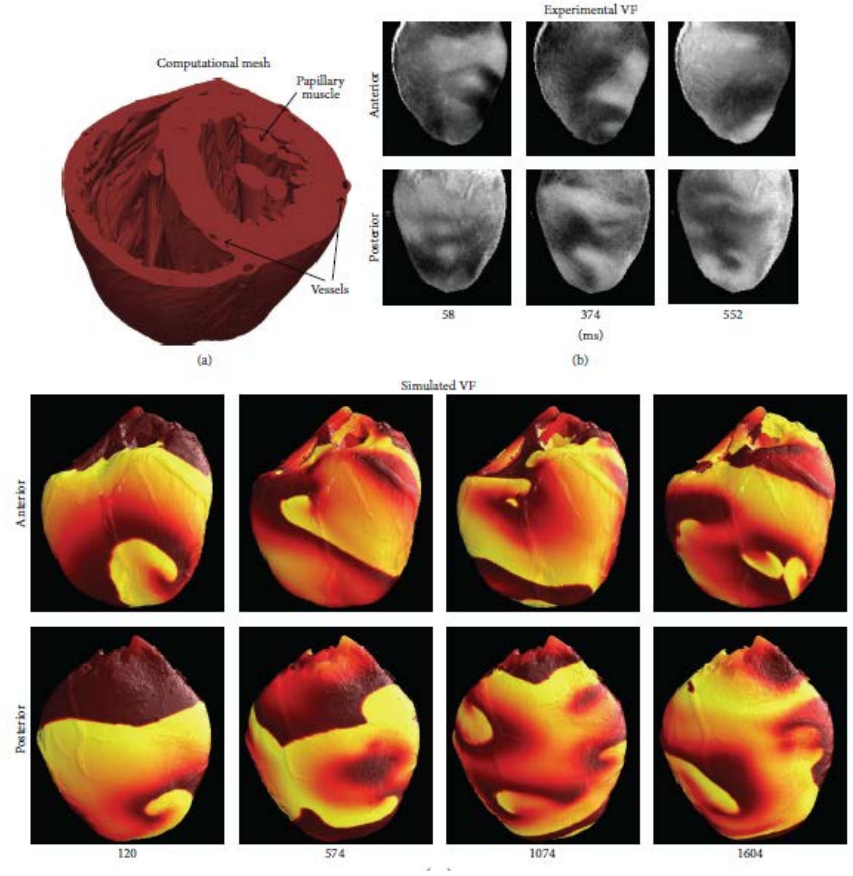
- How well can models reproduce the *phenomenon of interest?*

  – *Cardiac Examples*
    - *fibrillation*
    - *defibrillation*

Filament Dynamics during Simulated Ventricular Fibrillation in a High-Resolution Rabbit Heart

Pras Pathmanathan and Richard A. Gray

U.S. Food and Drug Administration, 10903 New Hampshire Avenue (WO 62), Silver Spring, MD 20993, USA

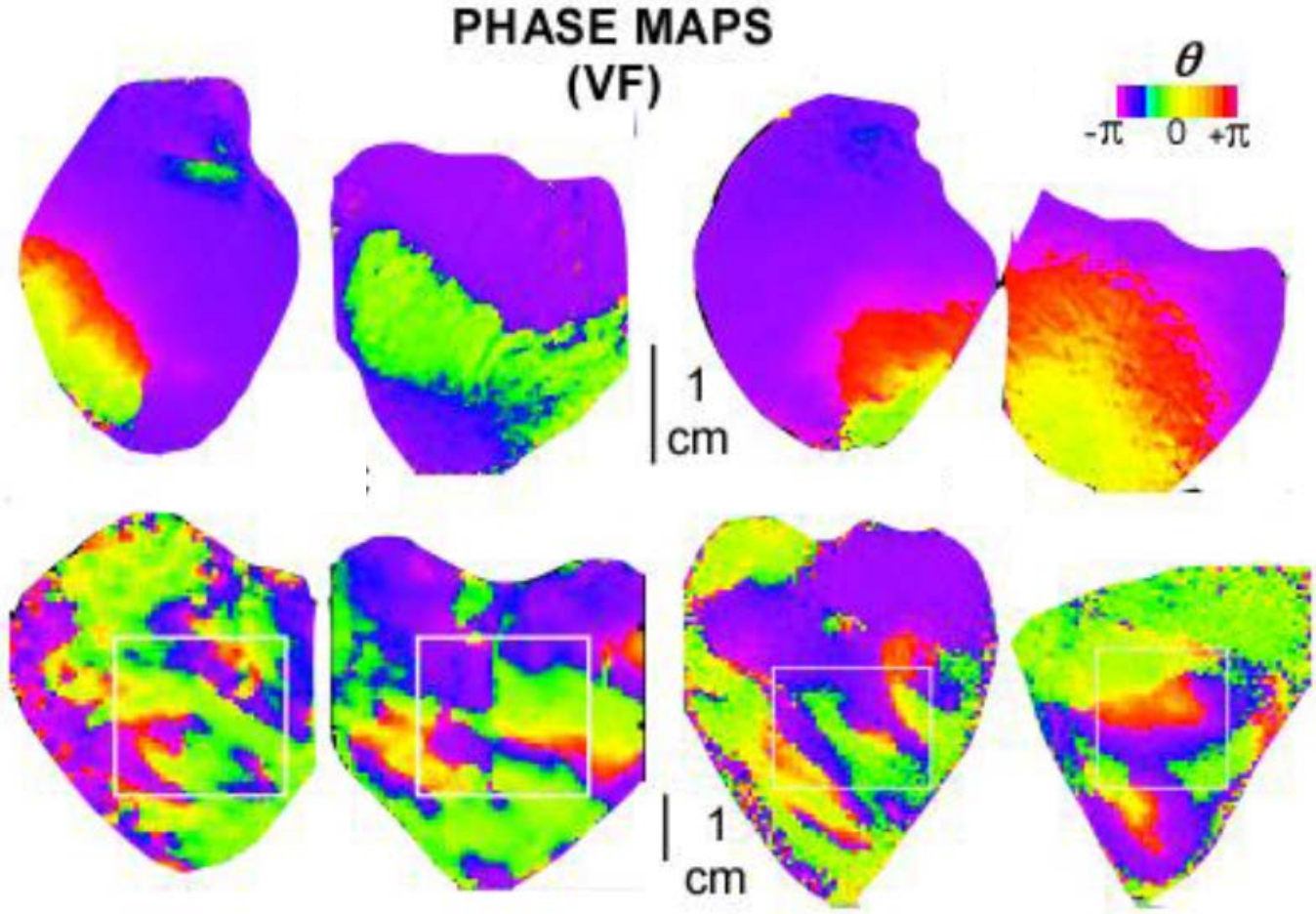


Pathmanathan P, Gray RA. Filament Dynamics during Simulated Ventricular Fibrillation in a High-Resolution Rabbit Heart. *BioMed Research International*, 2015: 720575

Validation of Fibrillation Simulations

RABBIT

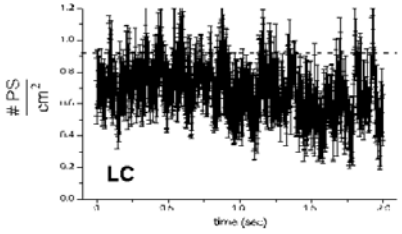
SWINE



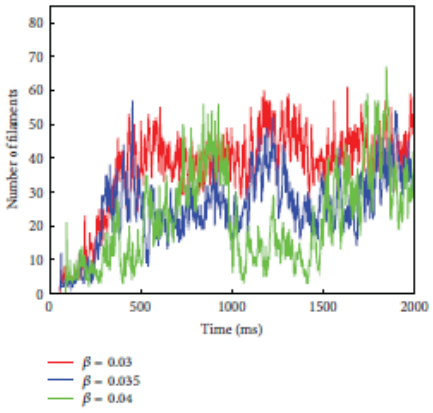
cytochalasin D

diacetyl monoxime

experimental results



simulation results



Park S, Gray RA. Optical Mapping of Ventricular Fibrillation Dynamics. In: Adv Exp Med Biol. Springer, Ltd, 2015.

Biomech Model Mechanobiol
DOI 10.1007/s10237-014-0639-8

ORIGINAL PAPER

A high-resolution computational model of the deforming human heart

	P1	P2	P3	P4
Max displacement magnitude (Chaste)	5.2791	6.0839	0.9998	2.7867
Max difference: Cardioid-tet versus Chaste	0.0038	0.0039	0.0020	0.0120
Max difference: Cardioid-hex versus Chaste	0.0072	0.0073	0.0025	0.0208
Max difference: Cardioid-wedge versus Chaste	0.0071	0.0071	0.0025	0.0218
Max difference: Cardioid-pyramid versus Chaste	0.0166	0.0223	0.0031	0.0345

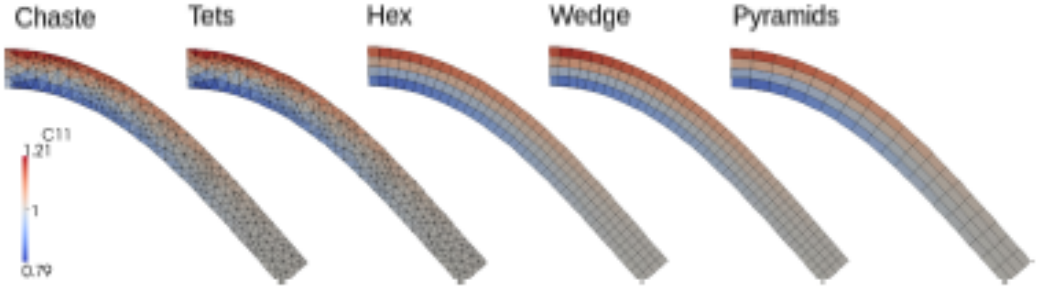
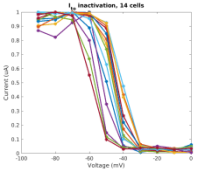


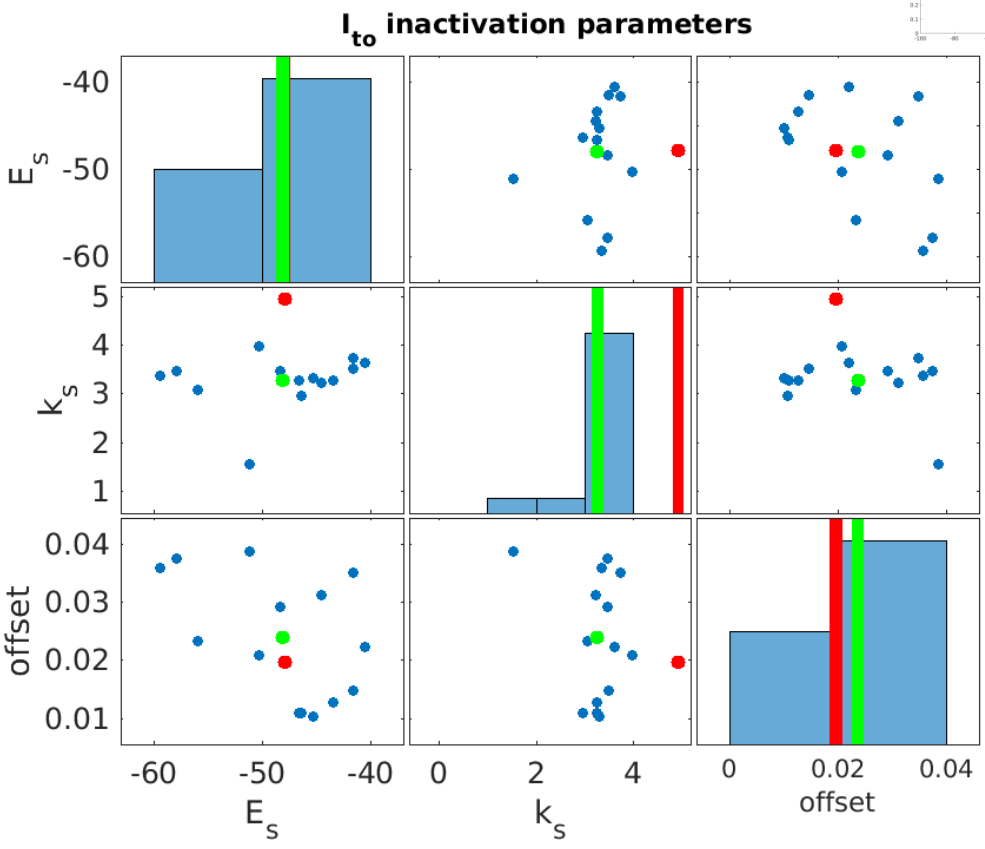
Fig. 6 Solution of problem P2 (bending under pressure) with Chaste and different finite elements in Cardioid, as labeled. The same tetrahedral mesh was used in Chaste and the Cardioid tetrahedral mesh simulation. Strain is calculated in the center (point at average coordinates of the vertexes) of every finite element. Non-vertex nodes of the finite elements are dropped for visualization proposes

Uncertainty Quantification: Multiple Currents

The 'average cell' is not well-represented by averaged data

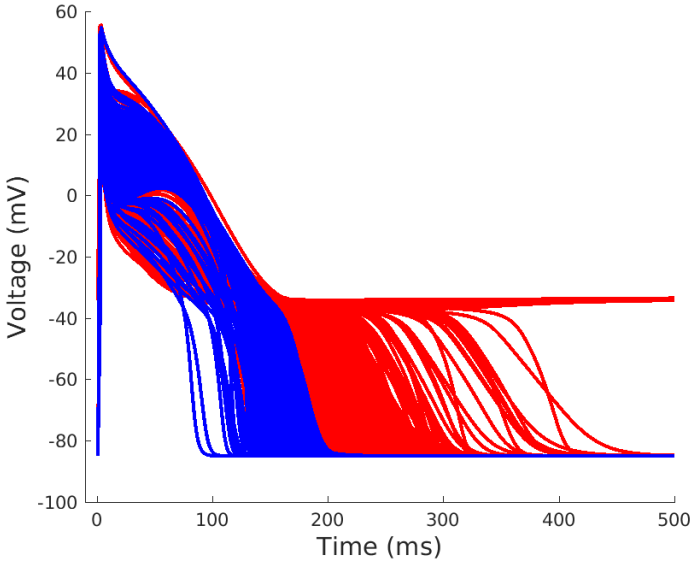


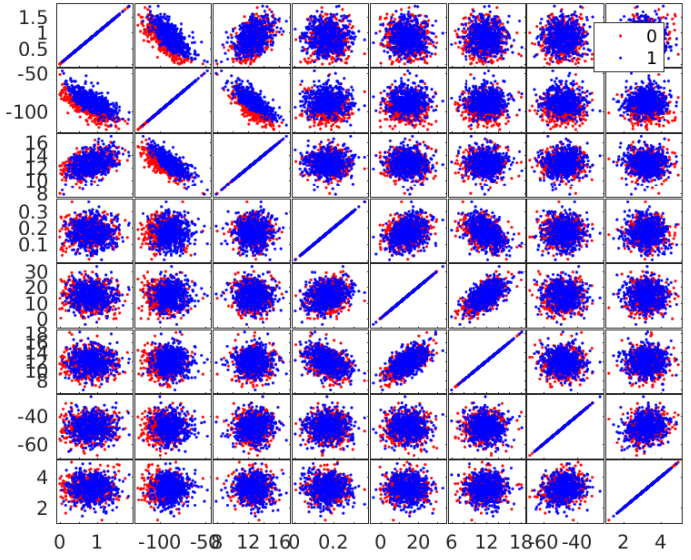
- **Aim: fit all parameters possible (avoid ad-hoc methods)**
- Some correlation observed
- Green: 'average cell'
- Red: result of using averaged data (I-V curves)



Impact of correlation between parameters

- We **only** have any information regarding correlation between parameters from the **same** currents.





accounting for correlation among parameters may be important