Verification and Validation of Complex Physiological Mathematical Models

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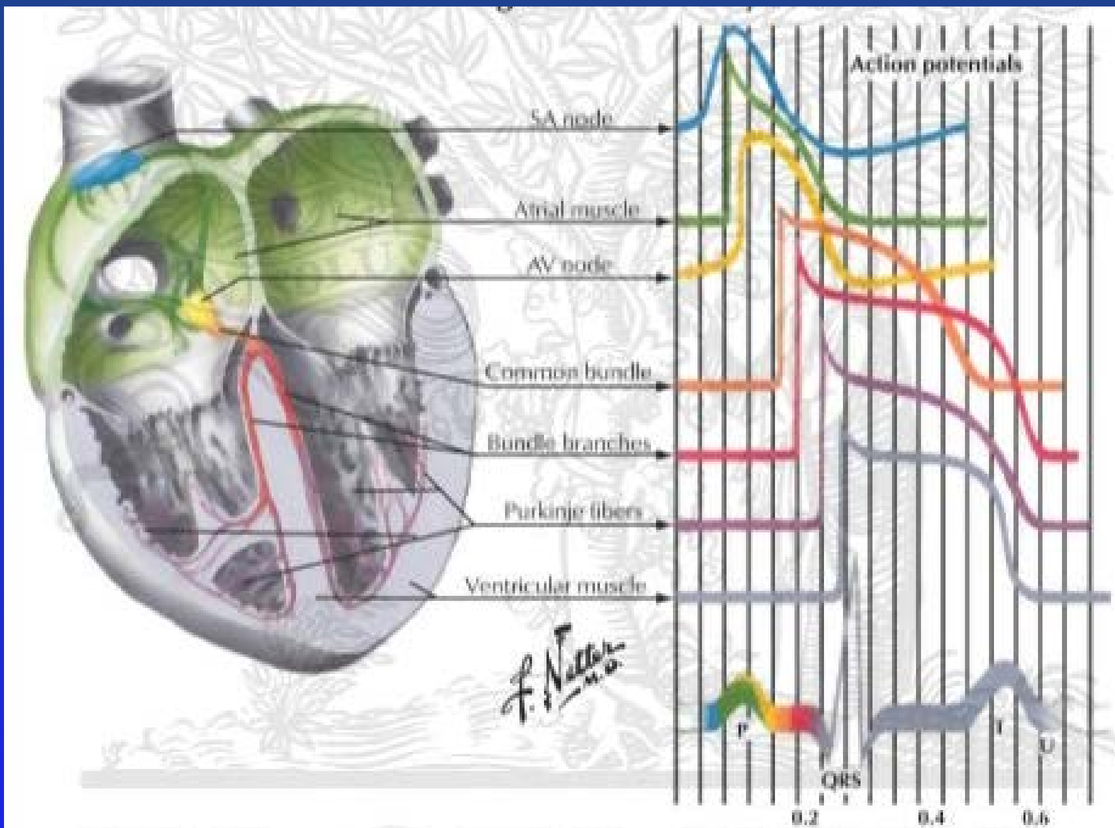
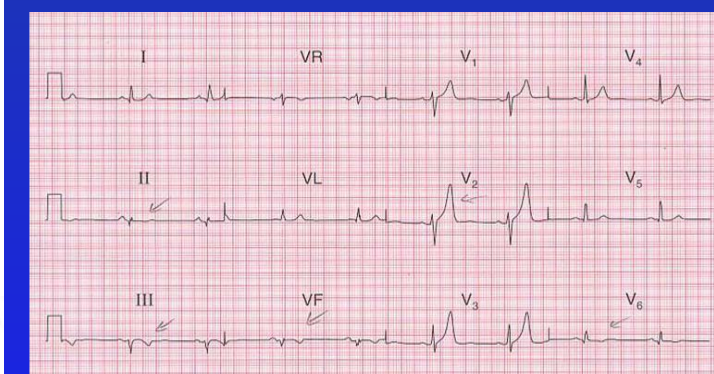
Whole Heart Electrophysiology Is Inherently Multi-scale



transmembrane (V_m) signal
i.e. action potential



electrocardiogram (ECG)

artist: Frank Netter
image courtesy of Elsevier, Inc

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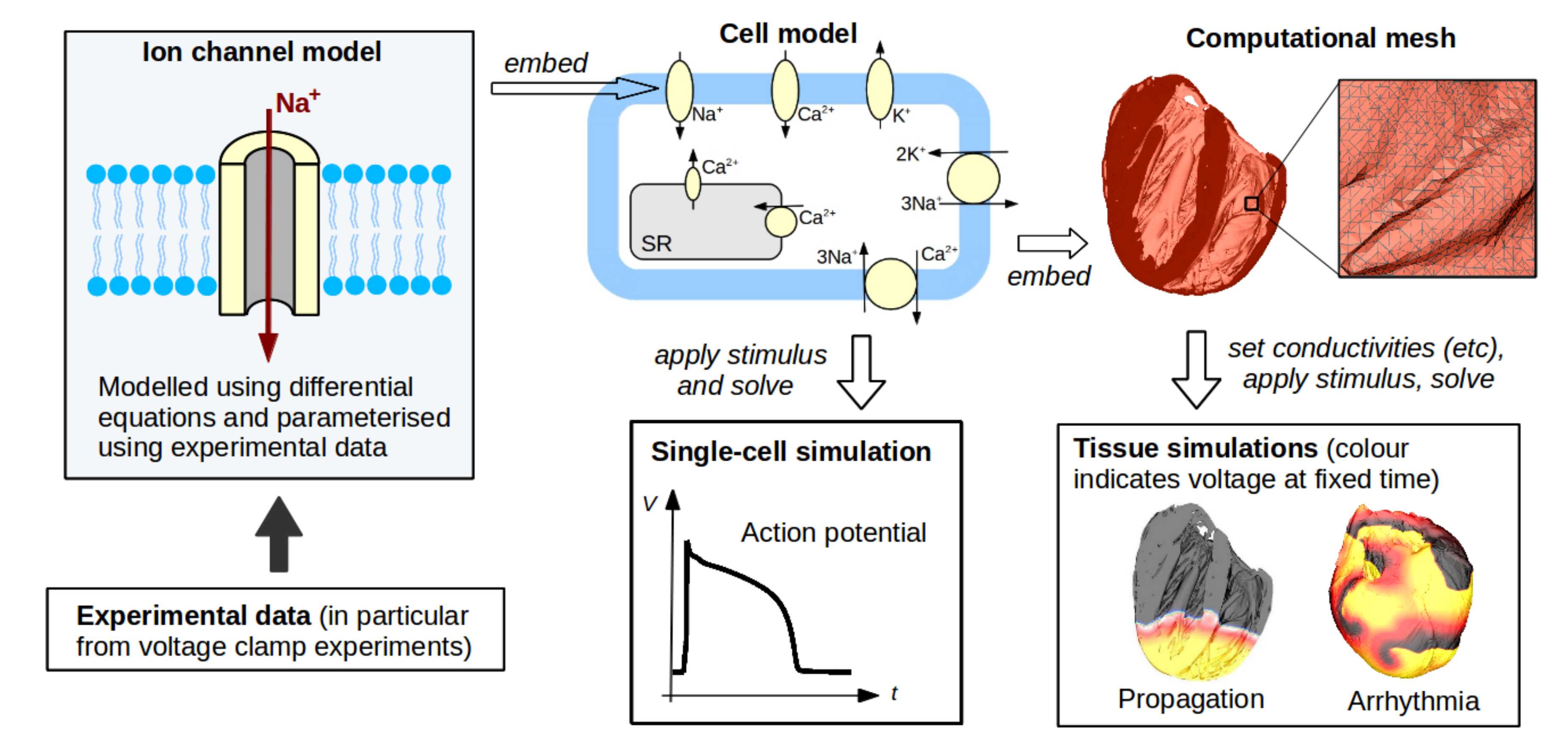
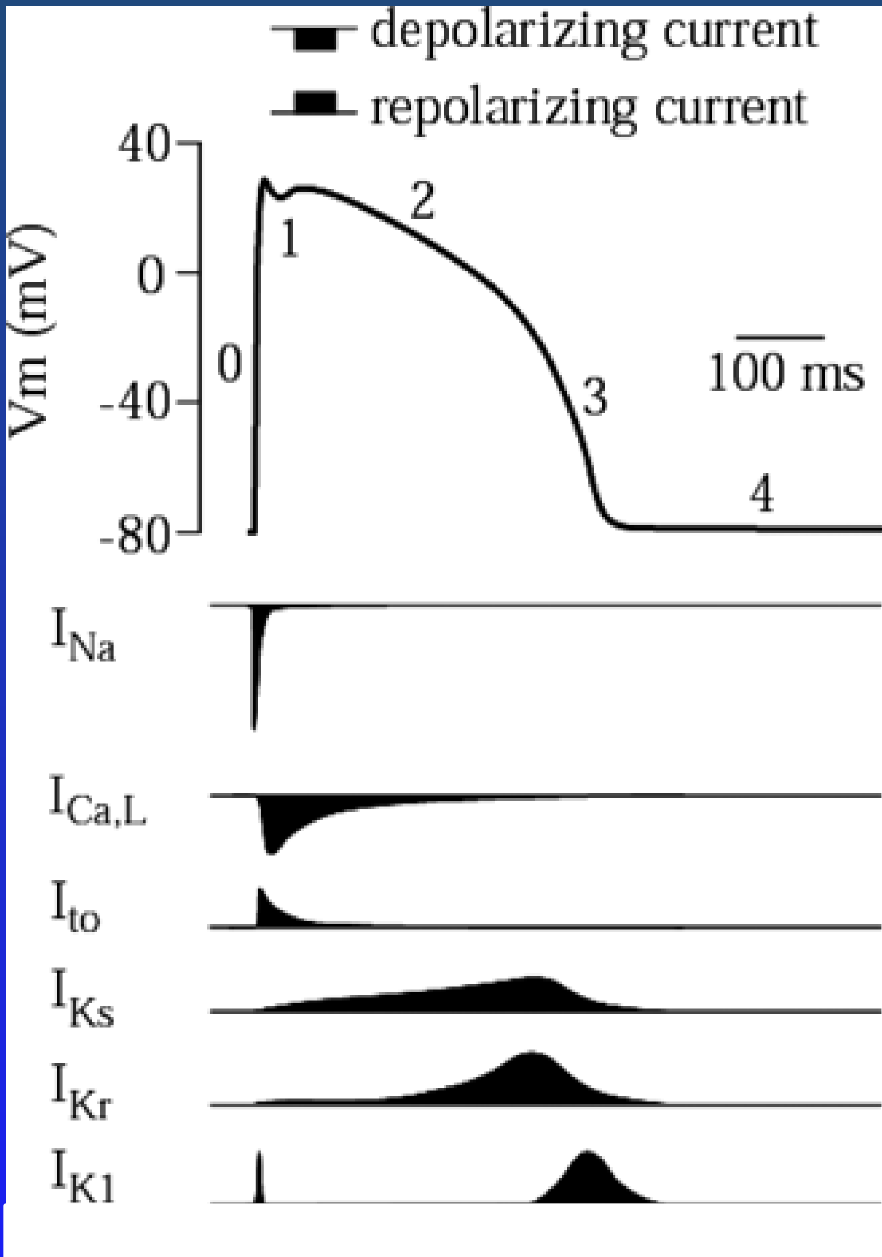


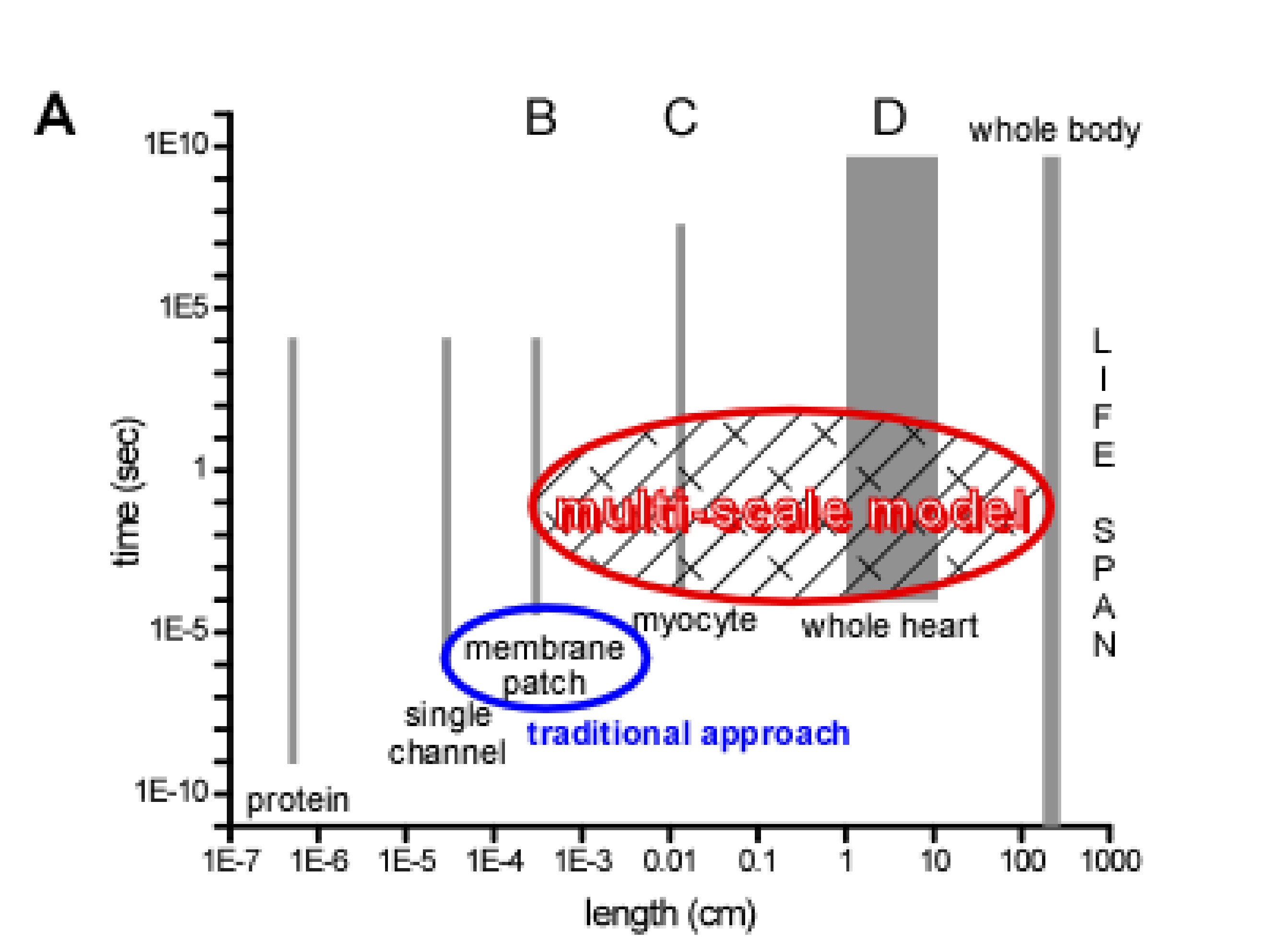


"I believe very strongly that the fundamental unit, the correct level of abstraction, is the cell and not the genome."

Syndey Brenner

Noble Prize winner for Physiology or Medicine (2002) for his work on molecular biology

We are developing models using experimental data from multi-scale



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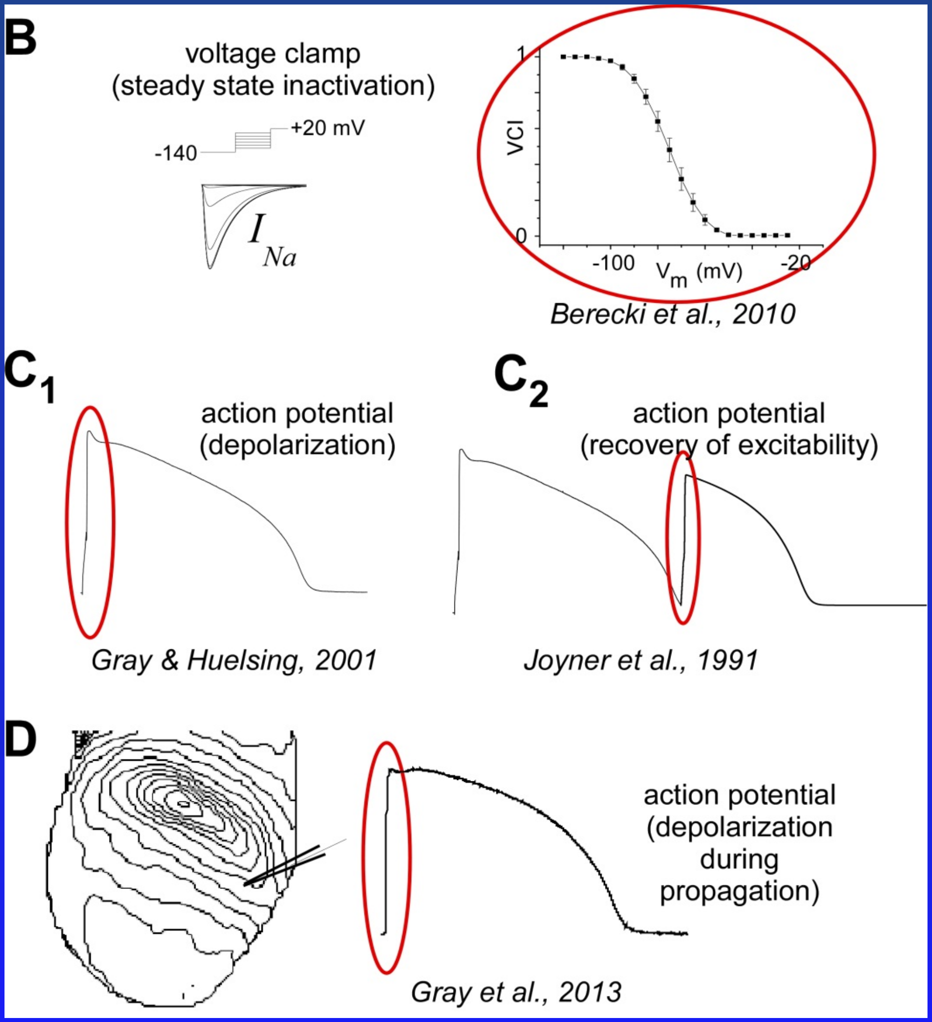
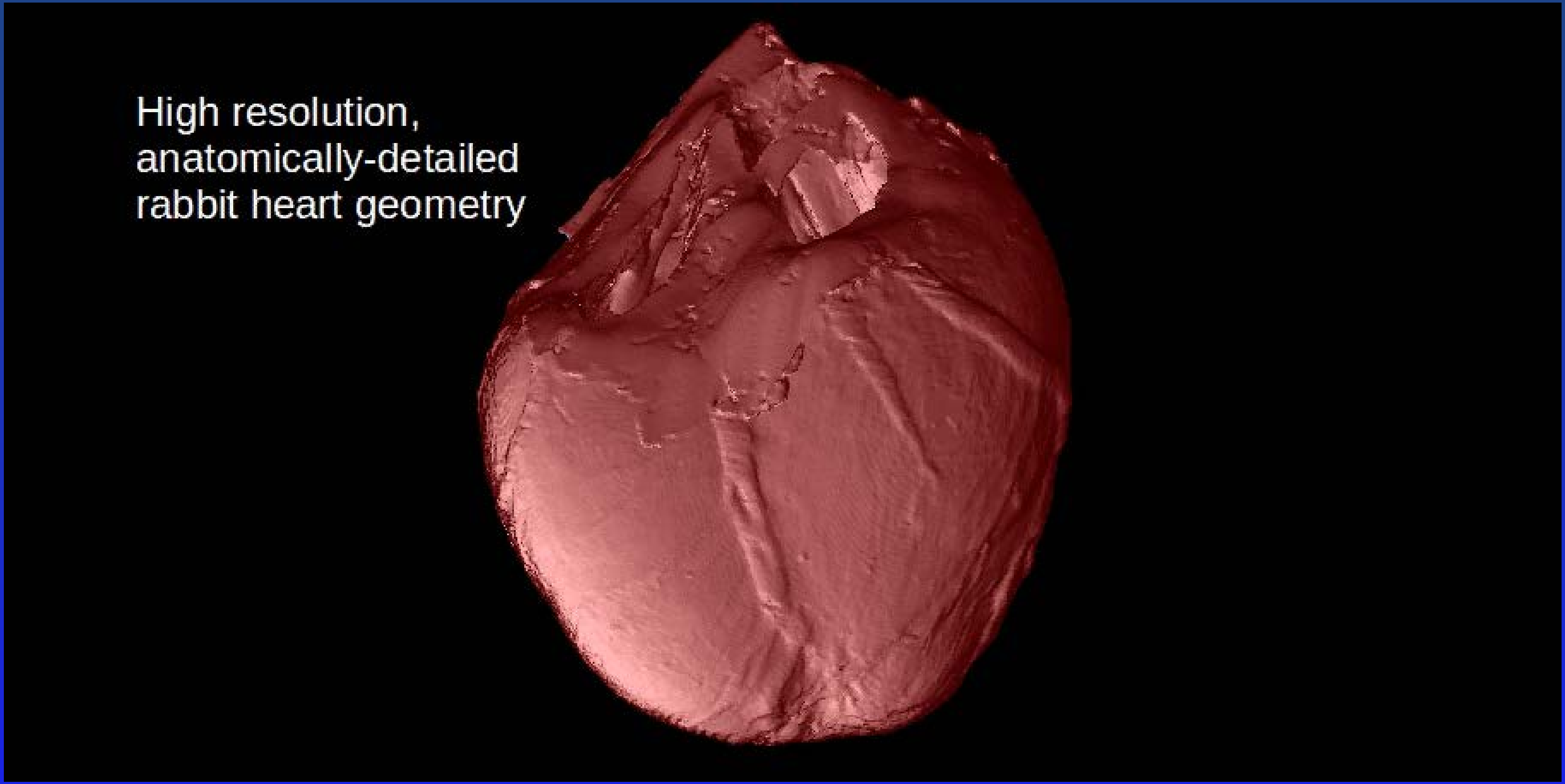


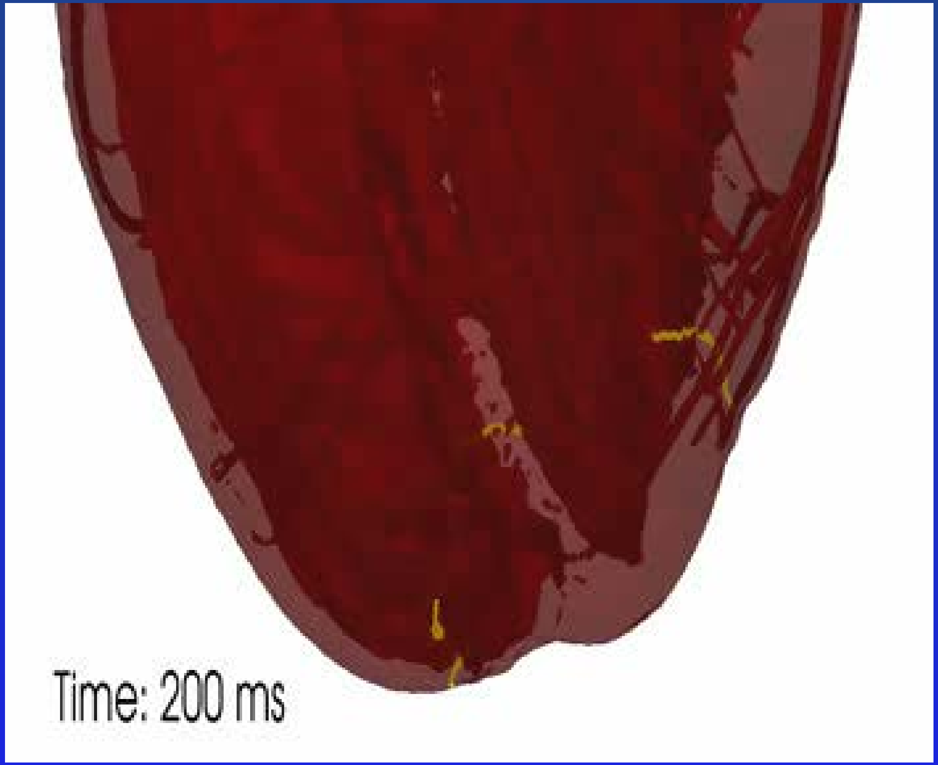
same species, same physiological environment (e.g. temperature, extracellular ion concentrations, etc.)

Simulation of Ventricular Fibrillation



http://tinyurl.com/VFsim

These Simulations Allow us to Look Inside the Virtual Heart



behavior results from a combination of
function (cell dynamics)
AND
structure (heart geometry)

Pathmanathan & Gray, Filament dynamics during simulated ventricular fibrillation in a high-resolution rabbit heart, *BioMed Research, in press.*

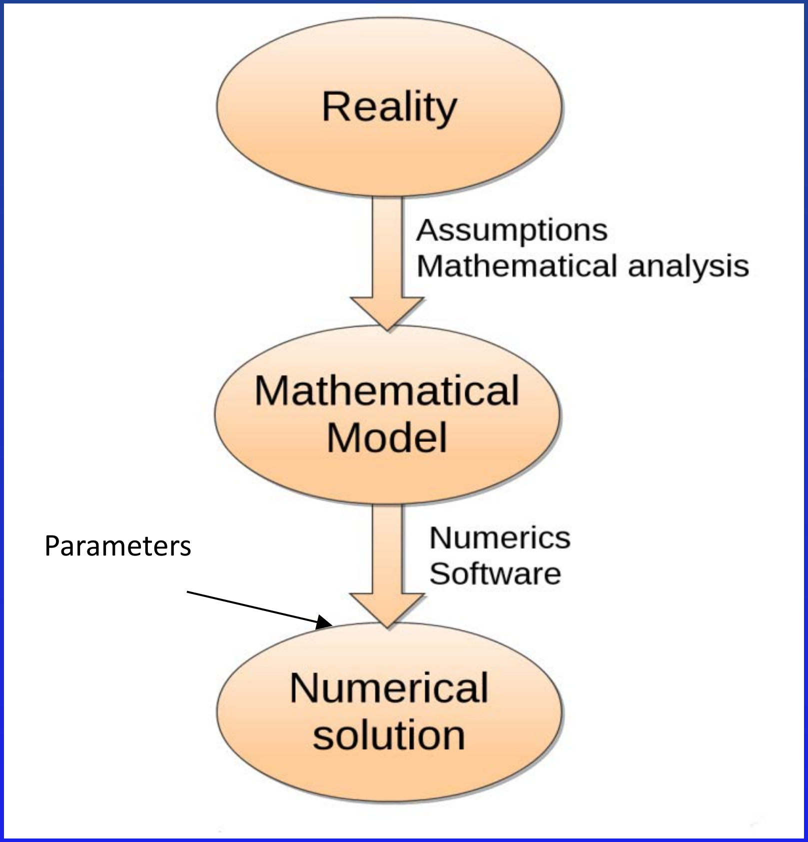
FDA

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?



Verification Examples

First tool for strongly verifying 'bidomain' solvers –

can be used by anyone to demonstrate correctness of their solvers (method of manufactured solutions).

- high confidence in solver correctness
- exact-error convergence analyses

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

Developed verification test problems for cardiac mechanics solvers

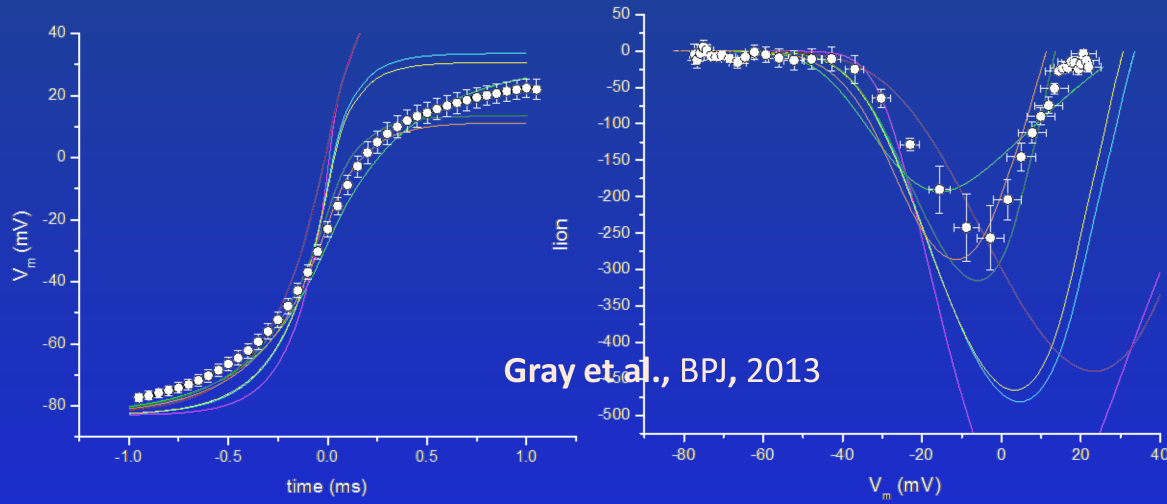
used to verify two independently-written solvers, and can be applied to others

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

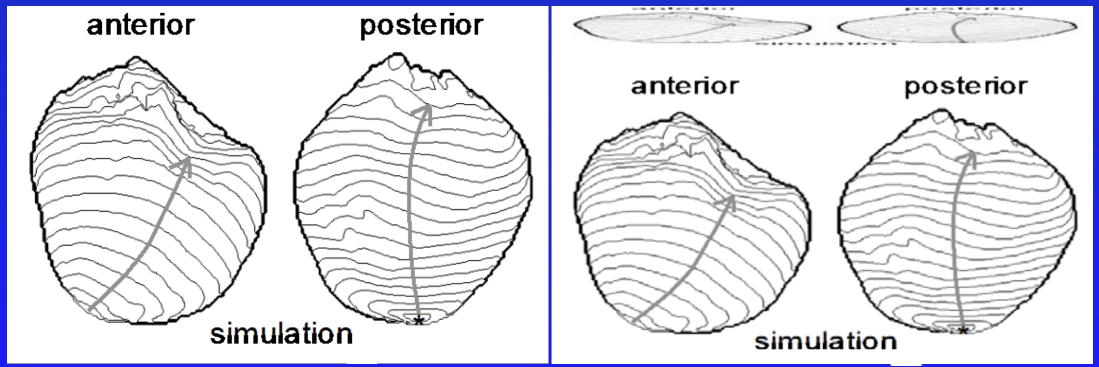
Validation of Physiological Models

Extremely difficult and linked to context of use (COU)!

How well do existing models represent new data?



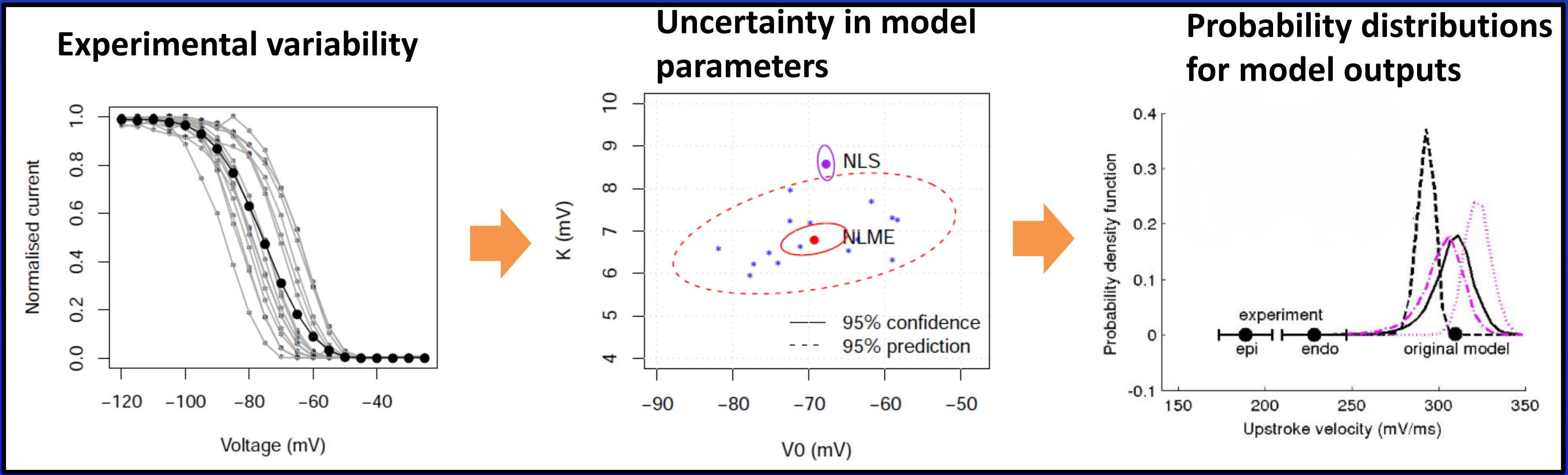
How does one validate complex models of complex phenomenon that are multi-scale in time and space?



Uncertainty Quantification

maybe the biggest challenge in rigorous credibility assessment!

Example: Using a novel statistical approach for assessing voltage-clamp data, we have quantified population variability in a sodium channel sub-component



Pathmanathan et al., *Uncertainty quantification of fast sodium current steady-state inactivation for multi-scale models of cardiac electrophysiology,* PBMB 2015

Summary

VVUQ of physiological/mechanistic models is

1) more complicated than for physics-based models
2) in its infancy

This presents unique challenges!

1) Can we reduce complexity?
2) Are models "identifiable"?
3) Is there a need for general VVUQ, not just COU?
4) Should/can we develop physiological based models with a COU in mind?