SPARC 2020 Ideas Lab

Predictive Modeling to Inform Development of Bioelectronic Medicine Therapies

15 January 2020

Tyler Best, PhD; NIH-OSC

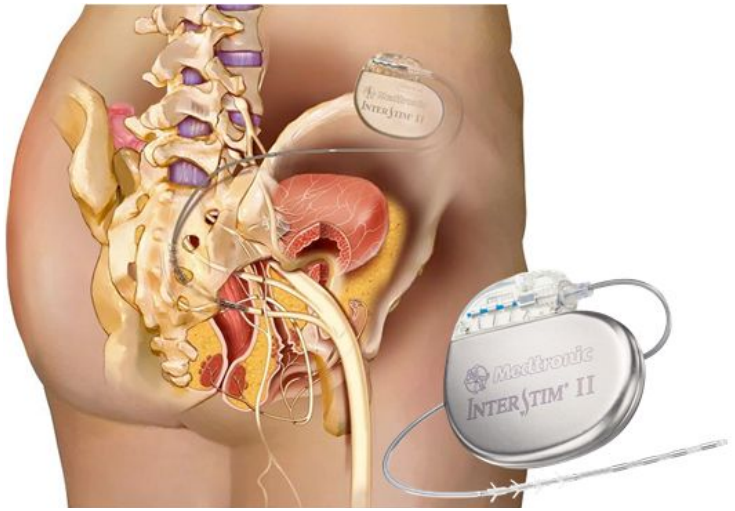
Colleen Clancy, PhD; UC Davis

Esra Neufeld, PhD; IT'IS Foundation

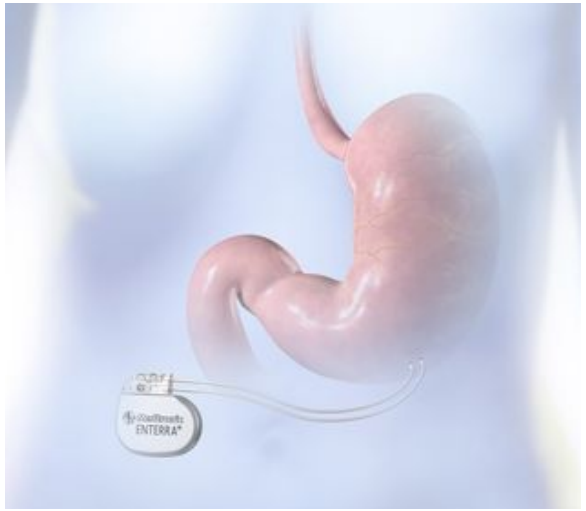
Andrew Weitz, PhD; NIH-NIBIB

SPARC and Bioelectronic Medicine

- What is Bioelectronic Medicine?
  - Aka: Electroceuticals; Neuromodulation
- Interacting with peripheral (autonomic) nerves to treat disease or disorder
- Why not drugs?
  - Targeting precision
  - Timing
  - Potential for feedback control
- Examples:
  - Urinary Incontinence
  - Gastroparesis



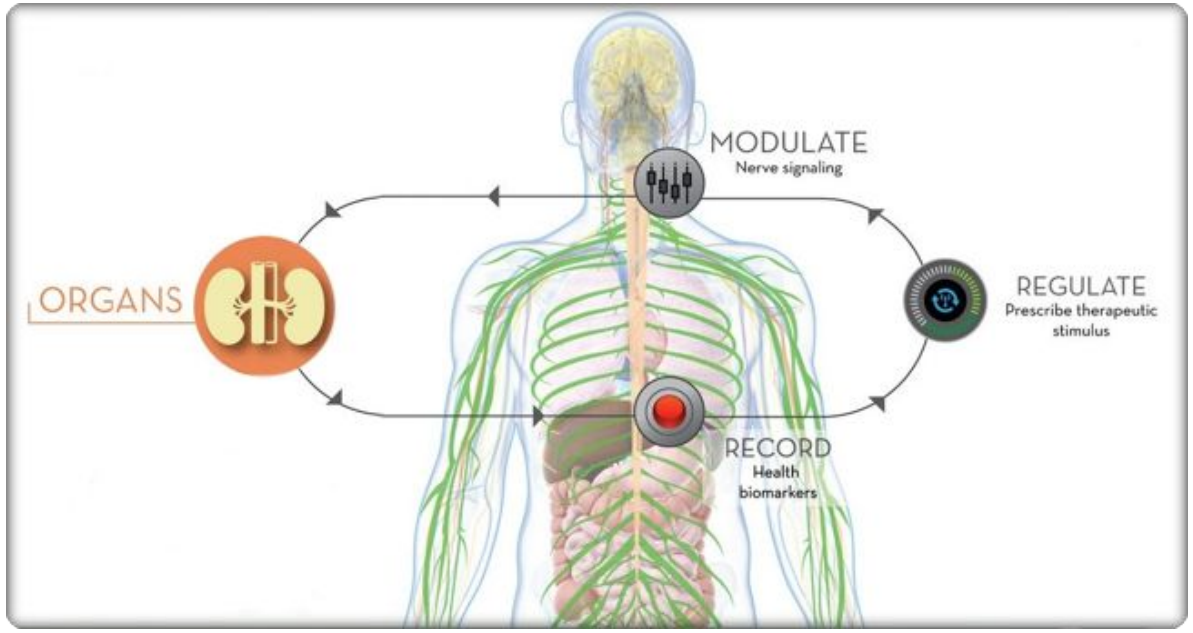
Medtronic InterStim II



Medtronic Enterra II

Stimulating Peripheral Activity to Relieve Conditions (SPARC)

The Common Fund



Opportunity: Neuromodulation of end-organ function holds promise in treating many diseases/conditions.

Challenge: The mechanisms of action for neuromodulation therapies remain poorly understood.

SPARC program goals:

- Capitalize on recent advances in technology to deliver detailed, integrated functional and anatomical neural circuit maps for organs.
- Provide the scientific foundation necessary to pilot new and improved neuromodulation devices and stimulation protocols that are more advanced and effective.

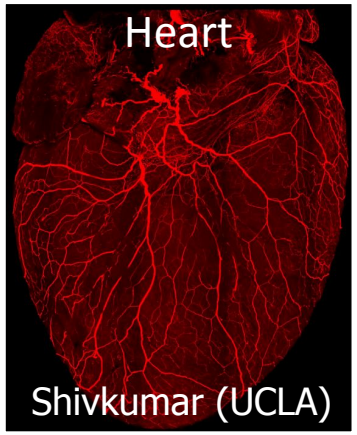
Improve targeting for more specifically designed neuromodulation therapies by providing access to high-value datasets, maps, and predictive simulations

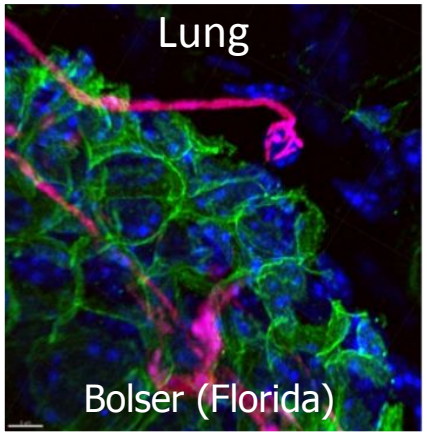
Stimulating Peripheral Activity to Relieve Conditions (SPARC)

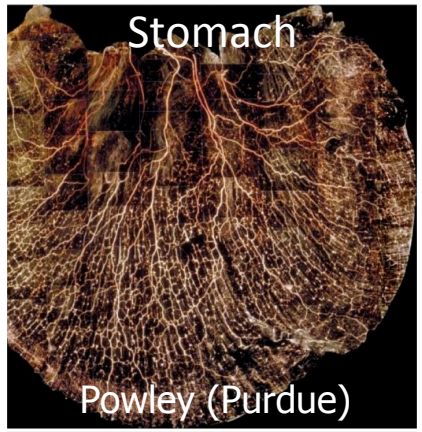
NIH The Common Fund

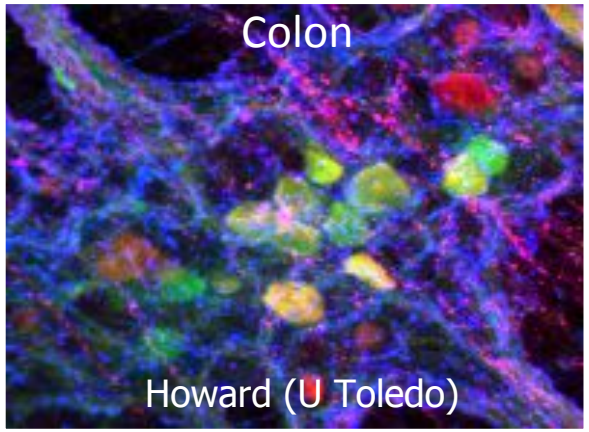
Experimental data generation: High-resolution anatomical tracing, *in vivo* electrophysiology, live cell imaging, and transcriptomics for mapping peripheral neural networks in a variety of species

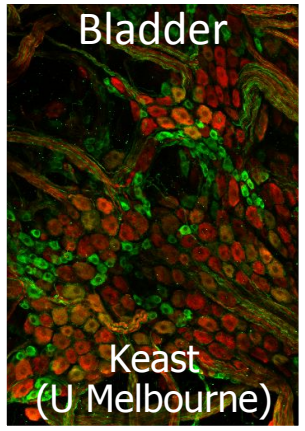
Software tools to support the data: Integrative online hubs to synthesize and share map data and build predictive multiscale simulations









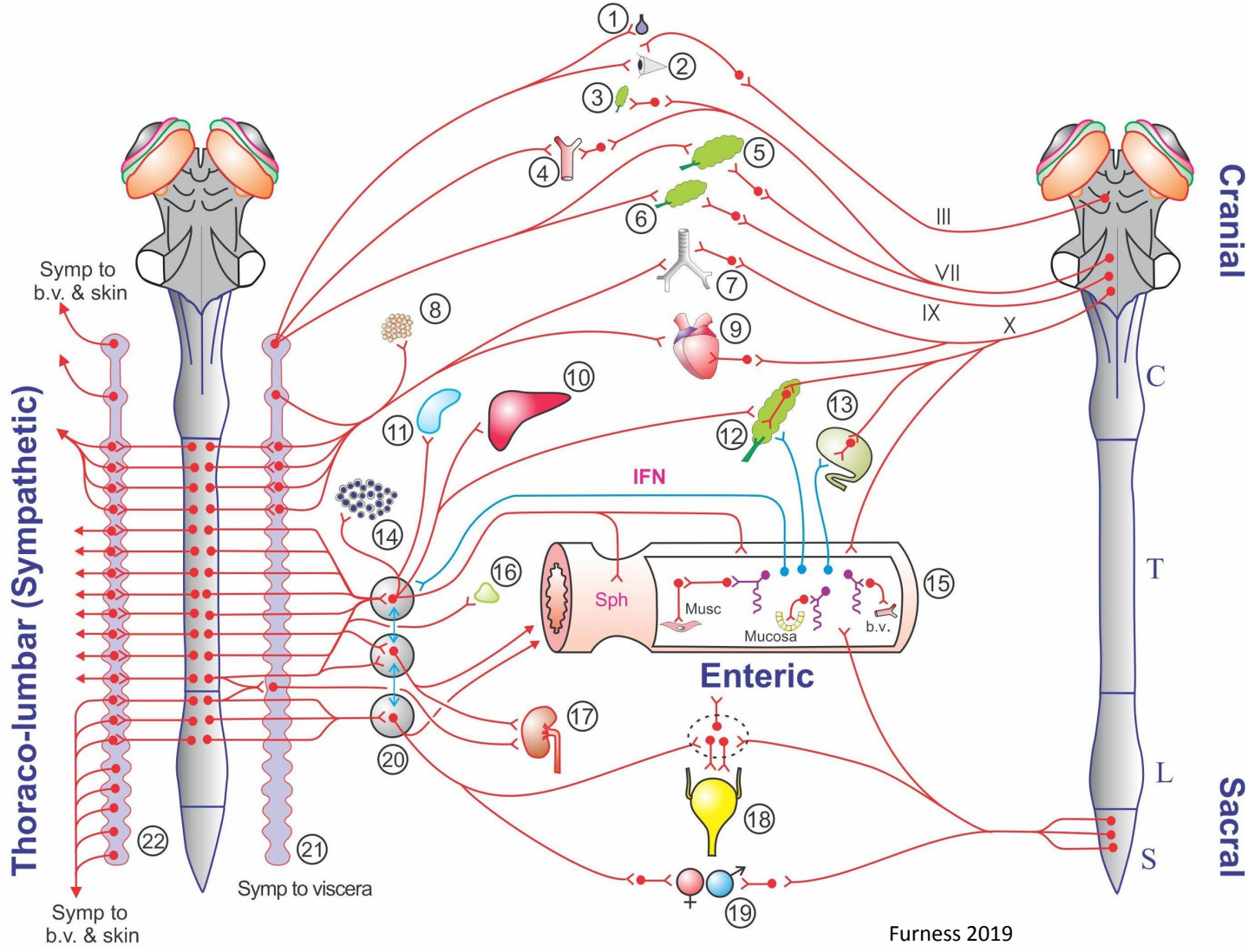


Bioelectronic Medicine Possibilities

What if we could tap into the peripheral nerves to target the organs that SPARC is studying?

What conditions could we treat?

What do we need to know to treat these conditions?



SPARC Ideas Lab

NIH The Common Fund

Five-day workshop that brings together multidisciplinary groups of researchers to stimulate thinking and collaboration

1. Learn about each other, the purpose of the Ideas lab, and the goals of SPARC
2. Identify opportunities/ideas (~500 are generated)
3. Prune the ideas to create candidate project options (~30 are selected)
4. Refine the projects
5. Develop pre-proposals and present results (~8 pre-proposals)

Modelers
Data Scientists
Experimentalists
Physician-Scientists

The output of an Ideas Lab is a set of ideas that form the basis for scientific proposals

The Challenge: Despite the vast amounts of data being generated by SPARC and other autonomic neuroscience researchers, the field currently lacks a comprehensive effort to incorporate these data into models that predict how modulation of a given neural target impacts organ functional responses

- Few existing organ models explicitly consider the role of the autonomic nervous system and electrophysiological signaling in function
- Experimentation and interactive computational model development are often isolated; data sciences are rarely involved
- Collection of experimental data is not driven by the parameter needs of model developers
- Integration across species, spatial and temporal scales, and organs is technically challenging
- Existing neuroscience knowledge-bases and computational resources are underutilized

Ideas Lab

Goal: Facilitate the generation of innovative research project concepts aimed at building interoperable, extensible, and personalizable simulations to inform bioelectronic medicine development.

- Focus on diseases and conditions that impact the **stomach**, **colon**, **lungs**, **heart**, or **lower urinary tract**.
- To be clinically relevant, the simulations will need to **account for variability and uncertainty** across **species, individuals, and sexes**, and will need to **predict off-target effects**.

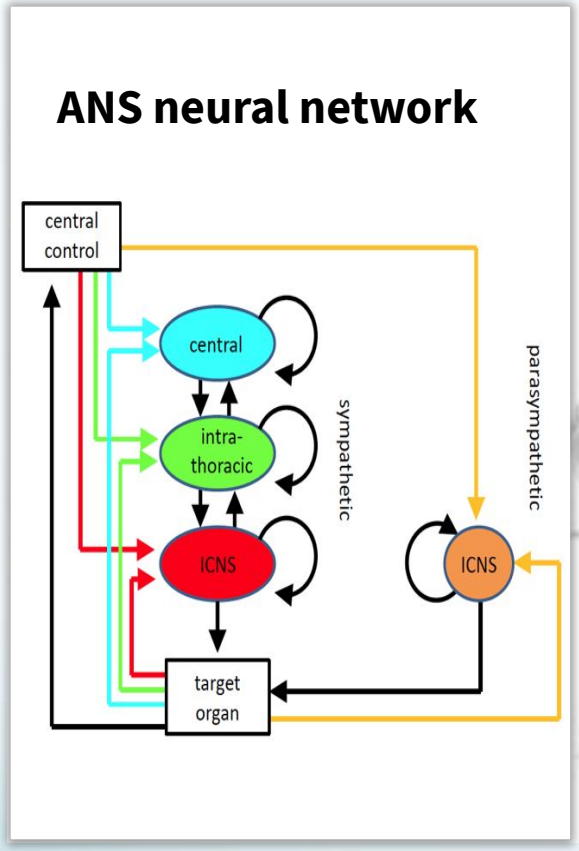
Requirements: All projects must leverage existing data and/or knowledge

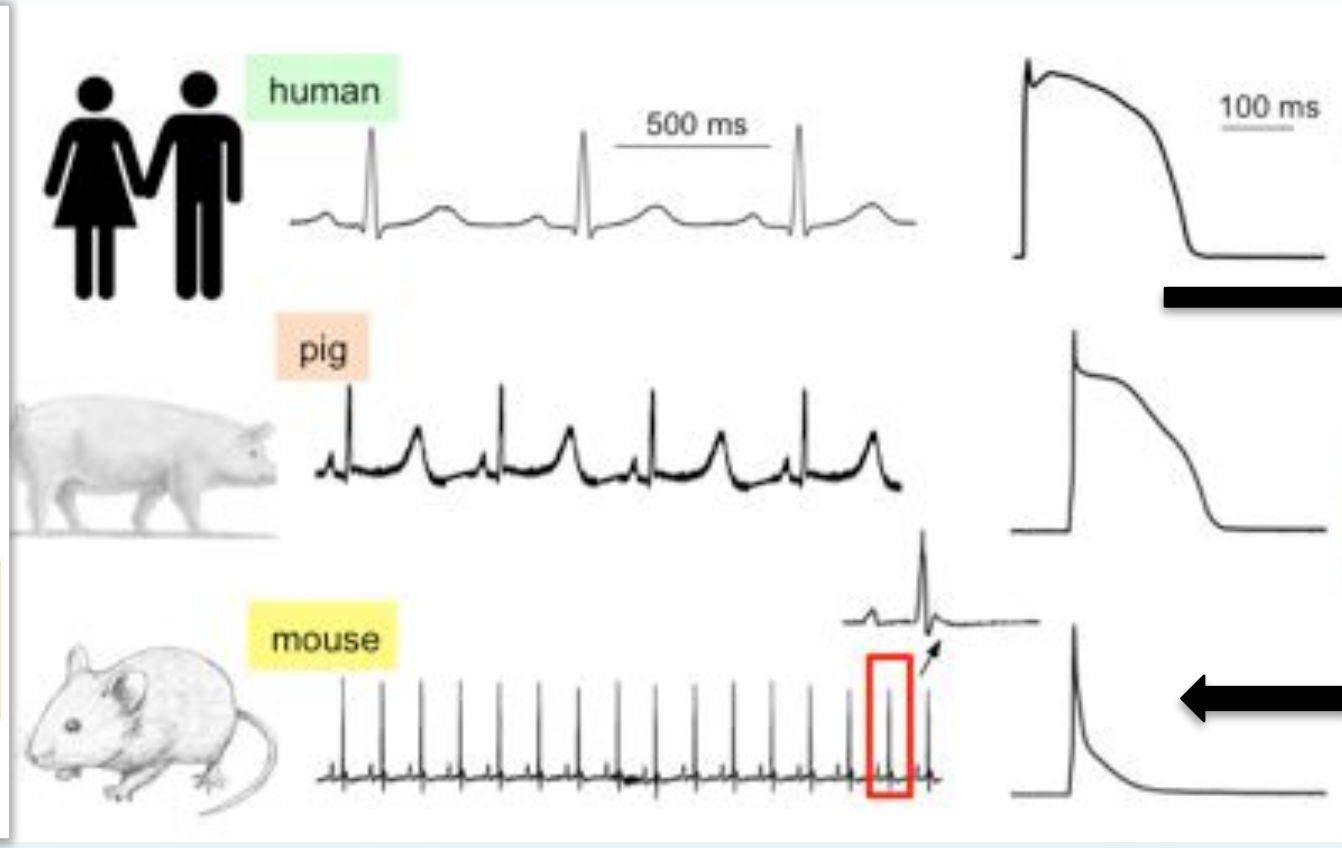
- From SPARC, the literature, or other resources (e.g., data repositories or knowledgebases)
- All projects must utilize SPARC's online computational platform, o^2S^2PARC

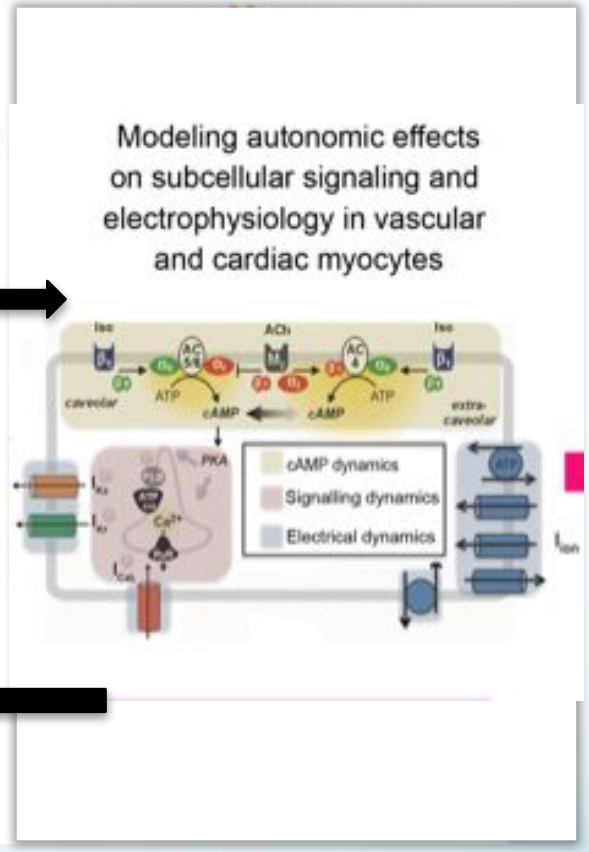
Example Project for SPARC: Development of the Predictive NeuroCardiovascular Simulator

UC DAVIS
UNIVERSITY OF CALIFORNIA

Goal: To develop a neurocardiovascular simulator







*Simulator suite will be **multiscale**, **multimodal** **and** **multispecies**. Simulator will predict the effects of stimulating or blocking peripheral nerve circuits on murine, porcine and human cardiovascular function. Inter subject variability from humans will be incorporated.*

UC Davis group
Predictive Neuro Cardiovascular Simulator ORG

TOOLS
SIMULATION THEORY

Clancy/Yang
Multiscale models
intersubject variability
Neurotransmitter modeling
Smooth muscle cell modeling

Grandi/
Cardiac region- and
species-specific cell models
Kinase signaling models
Population-based approaches

Lewis/
Neural network & feedback
Model reduction
Dynamical mechanisms

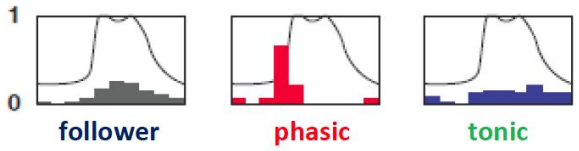
EXPERIMENTS

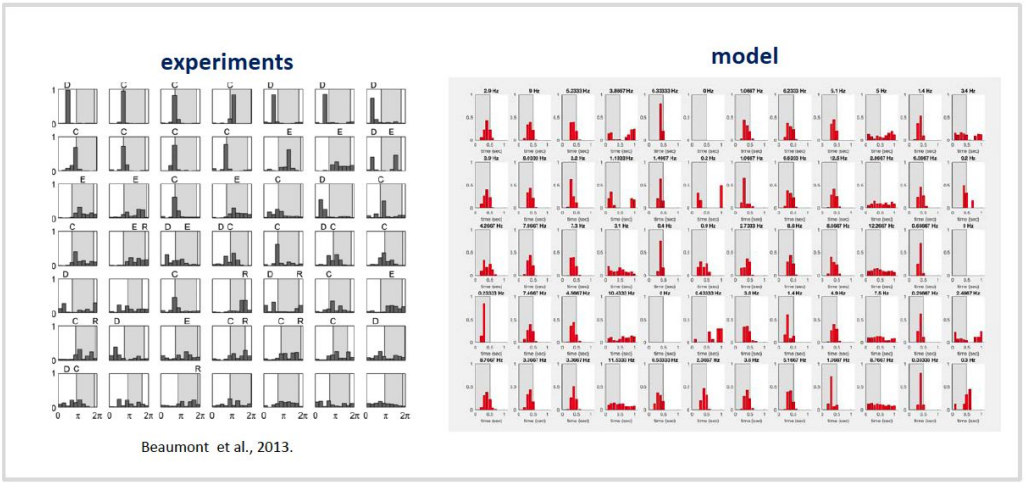
Ripplinger/
Whole heart functional mapping
Intact nerve stimulation

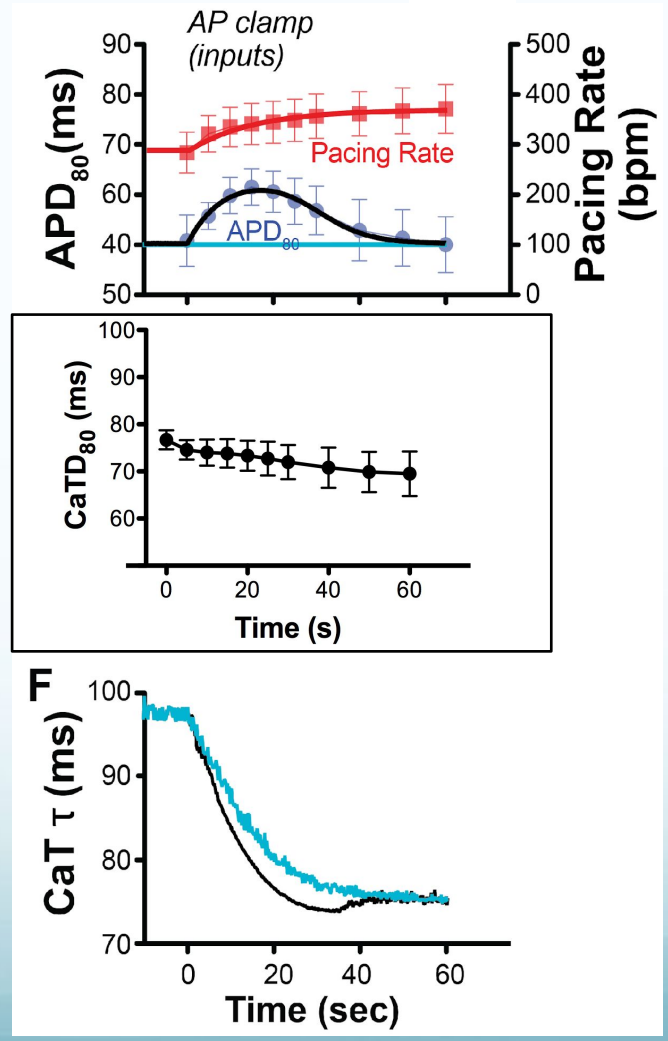
Santana/
Smooth muscle experiments
Autonomic control
cellular & subcellular

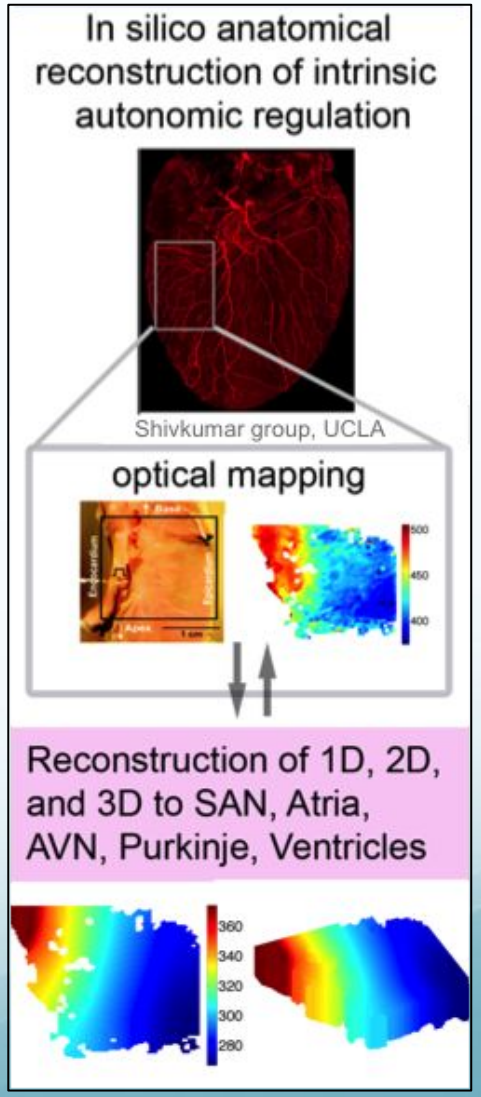
Chen/
Central control feedback

Data to **inform** model development



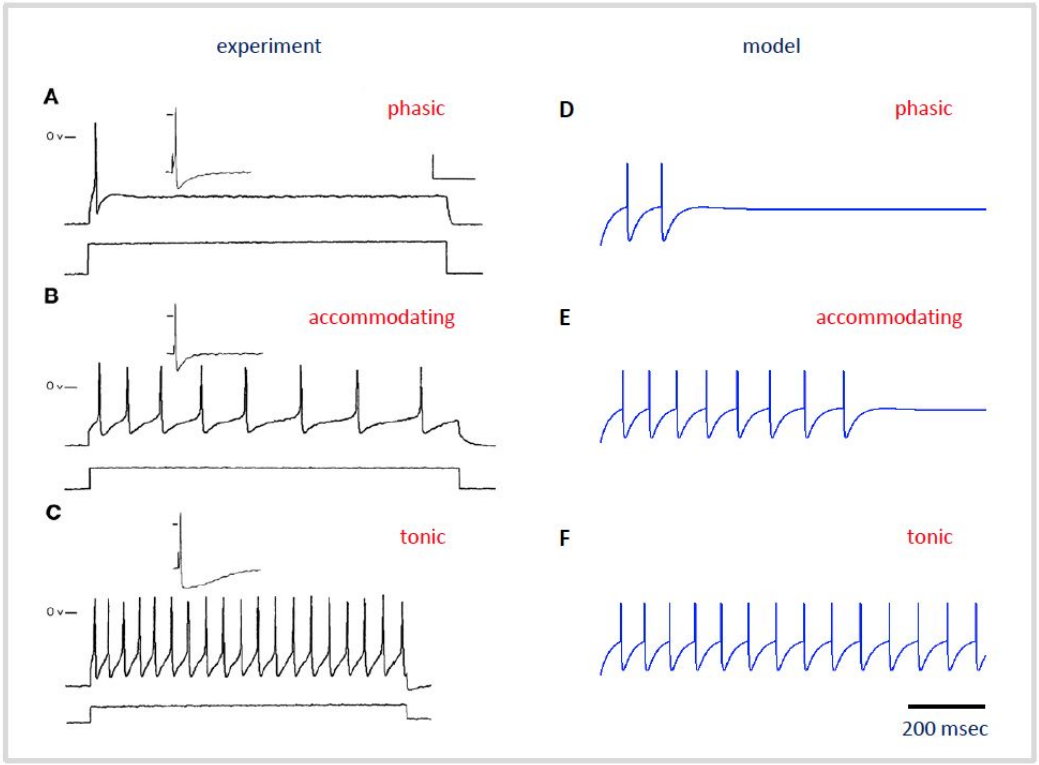




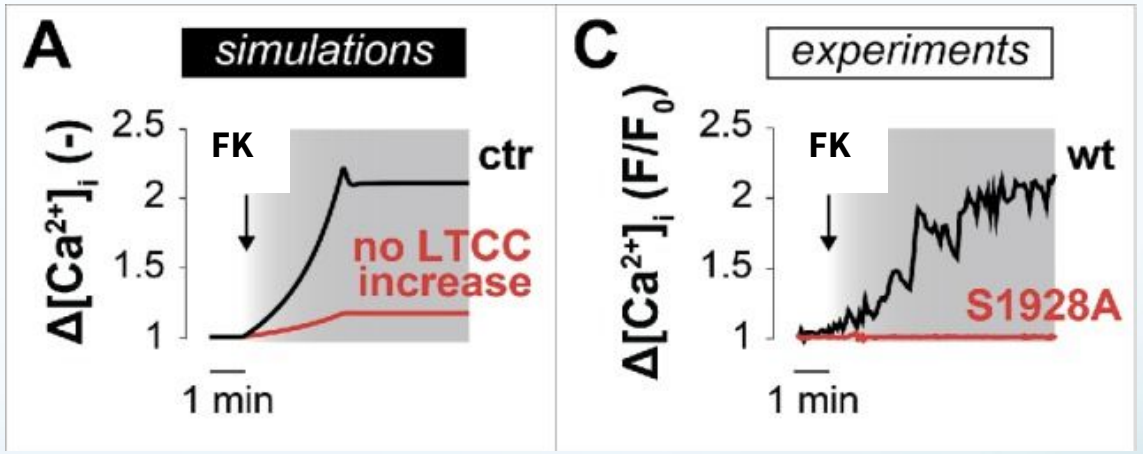


Data to **validate** model development

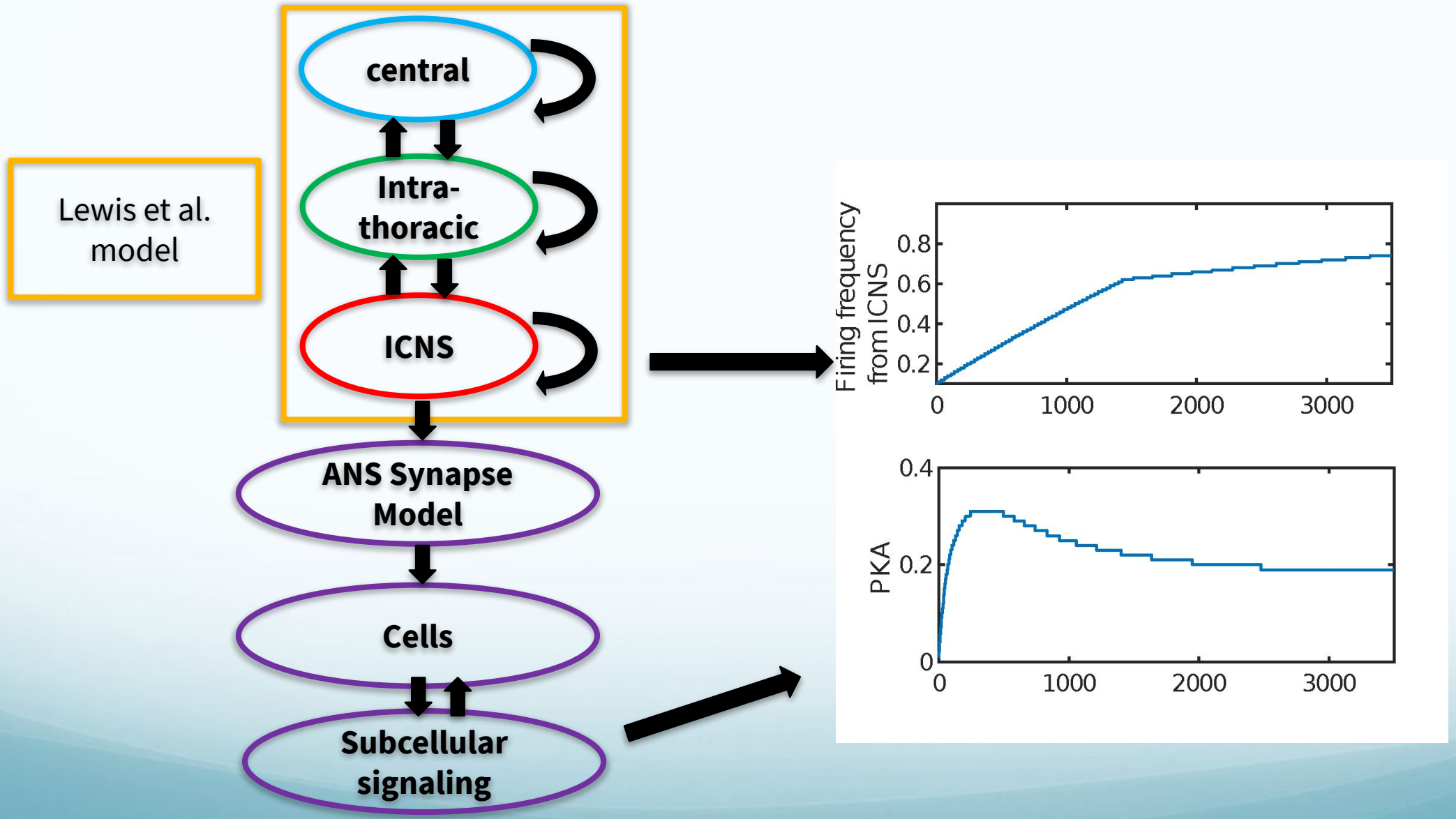
intrinsic neuronal properties:



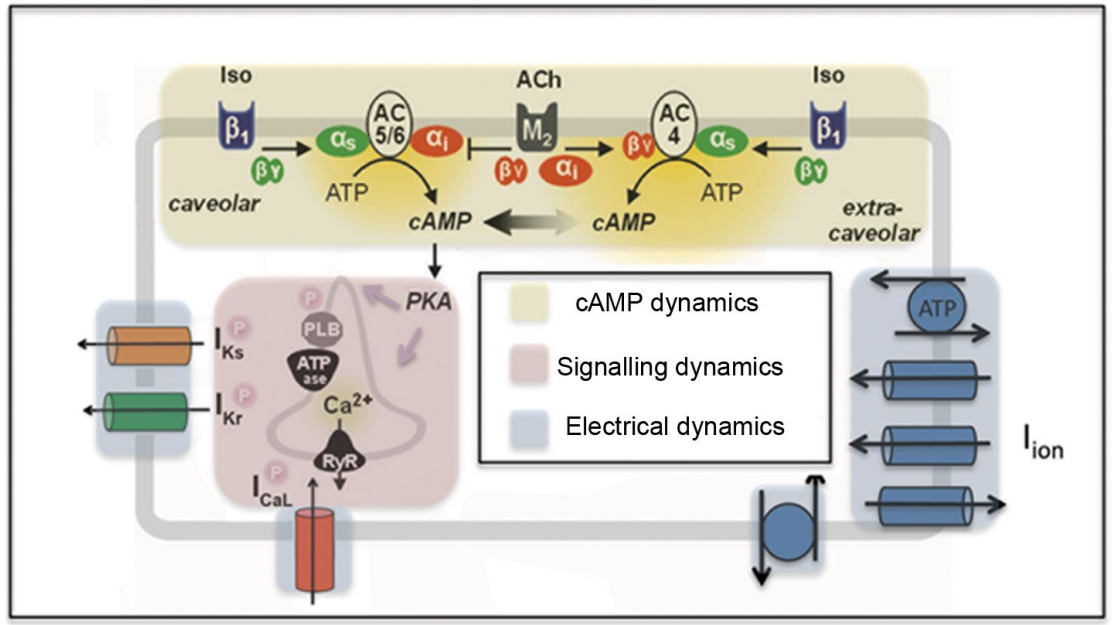
A-C: Examples responses of (porcine) ICNS neurons to intracellular depolarizing current (Smith, 1999). **D-F:** Conductance-based integrate-and-fire model response to depolarizing current. Top-to-bottom: applied current is 100, 150, and 200 pA. Note that same transition in firing pattern can be seen in response to decreasing the magnitude of the M-current.



From the ANS neural network to the subcellular signaling



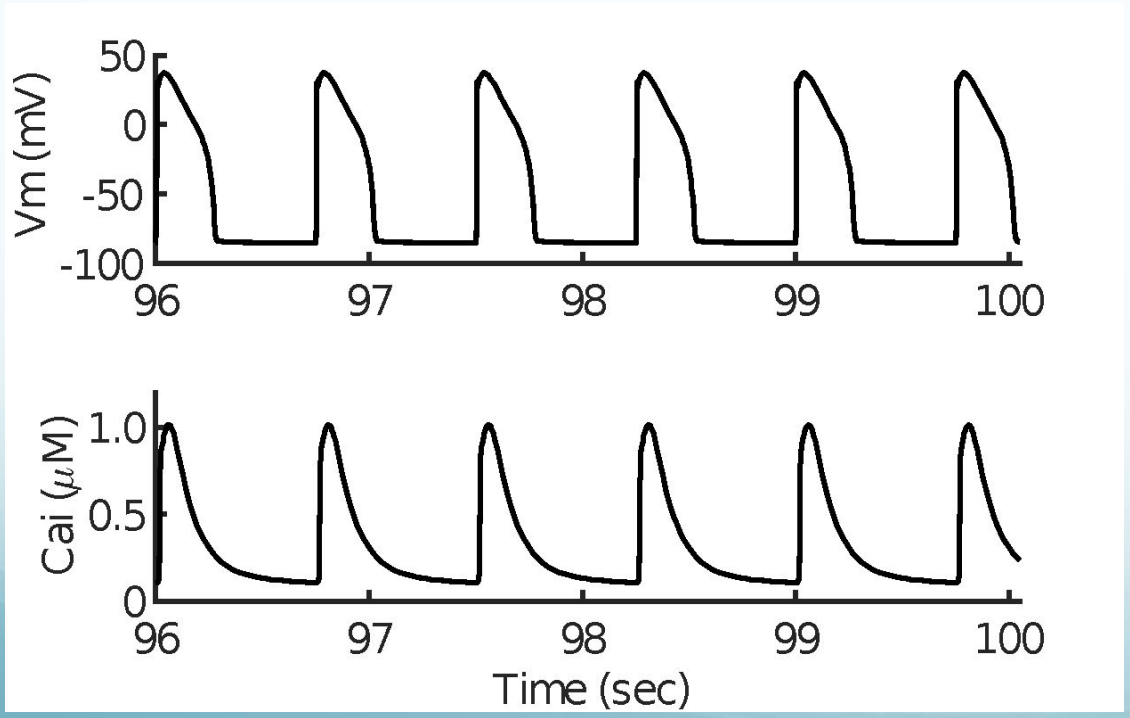
Compartmentalization of cAMP model connect to cell model



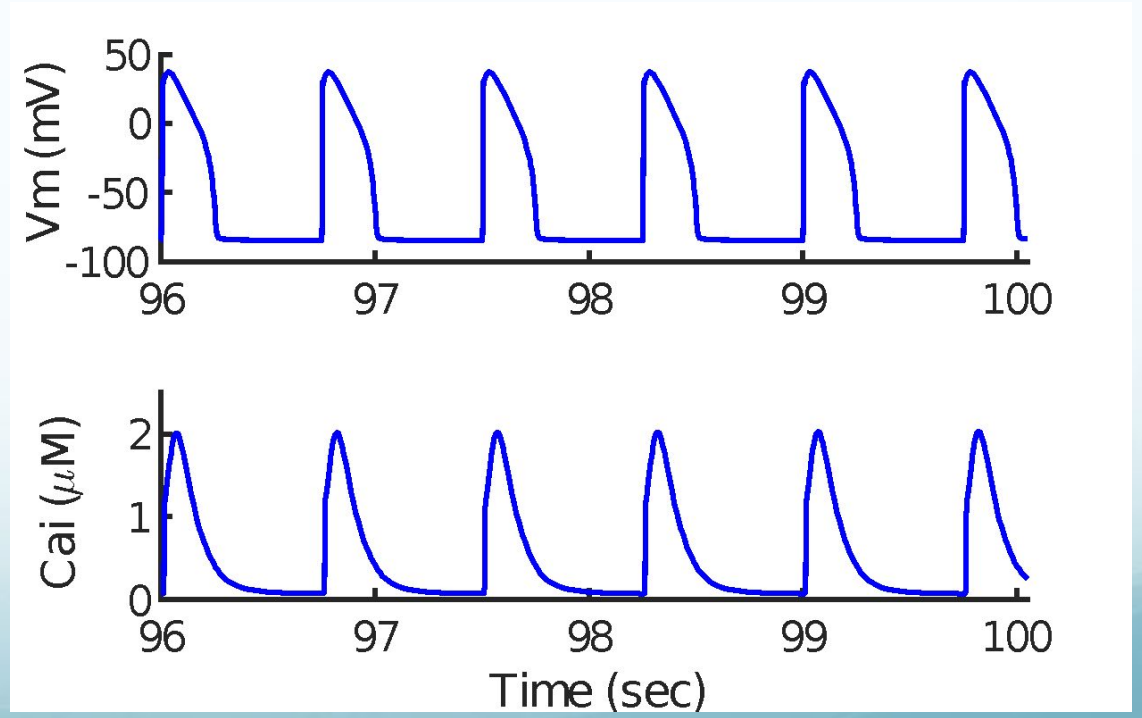
Modeling autonomic effects on subcellular signaling and electrophysiology in cardiac myocytes

From the ANS to subcellular signaling and resultant impact in simulated human ventricular myocytes

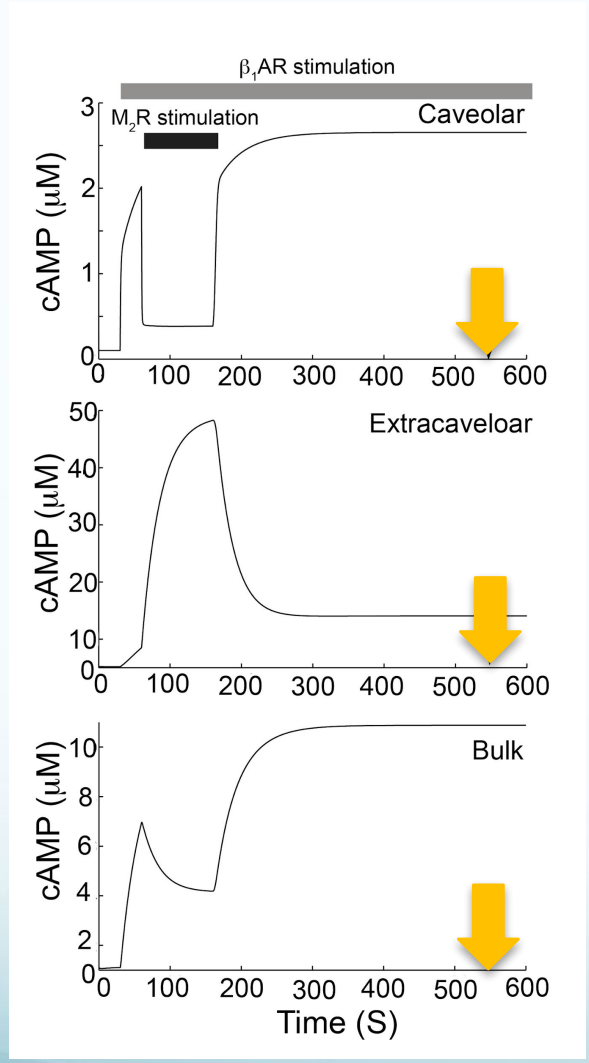
NO ICNS



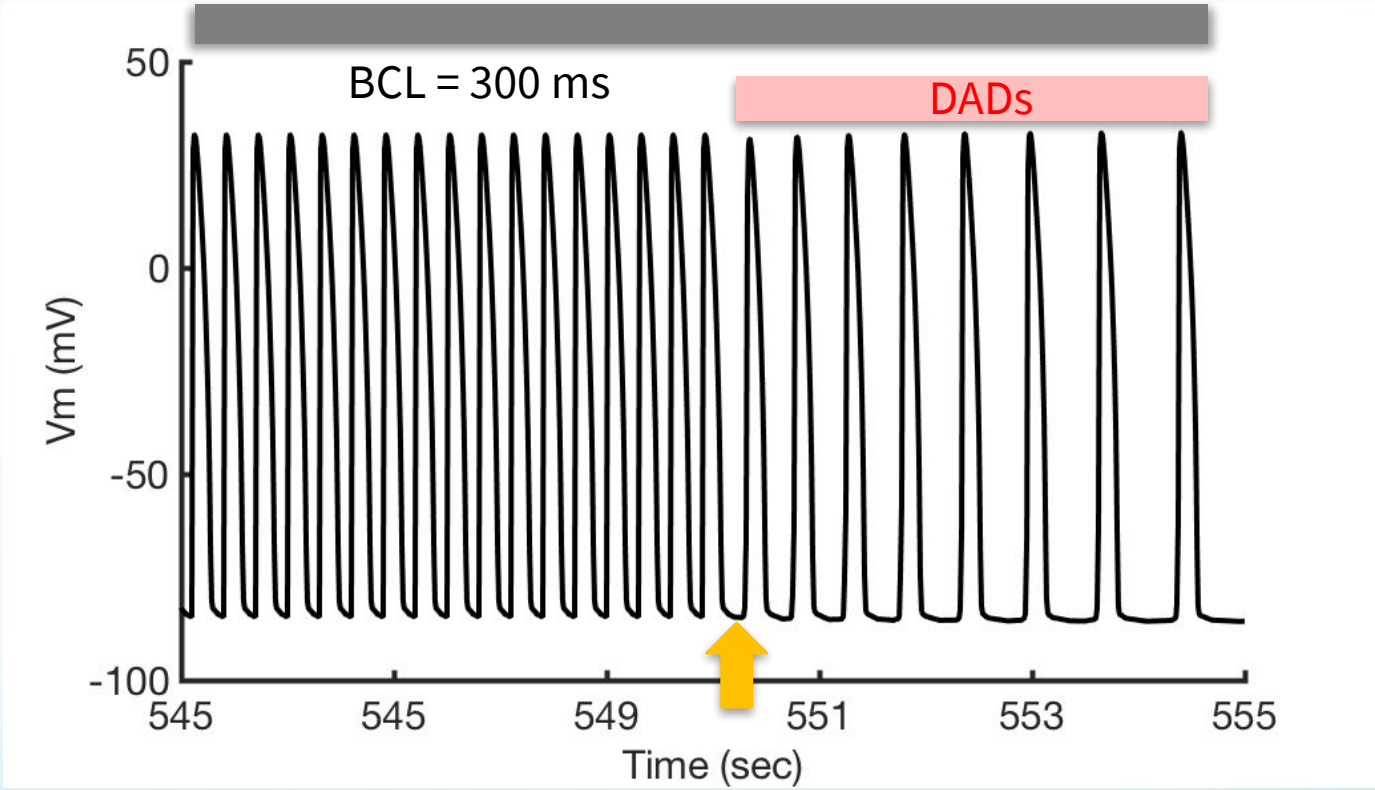
ICNS



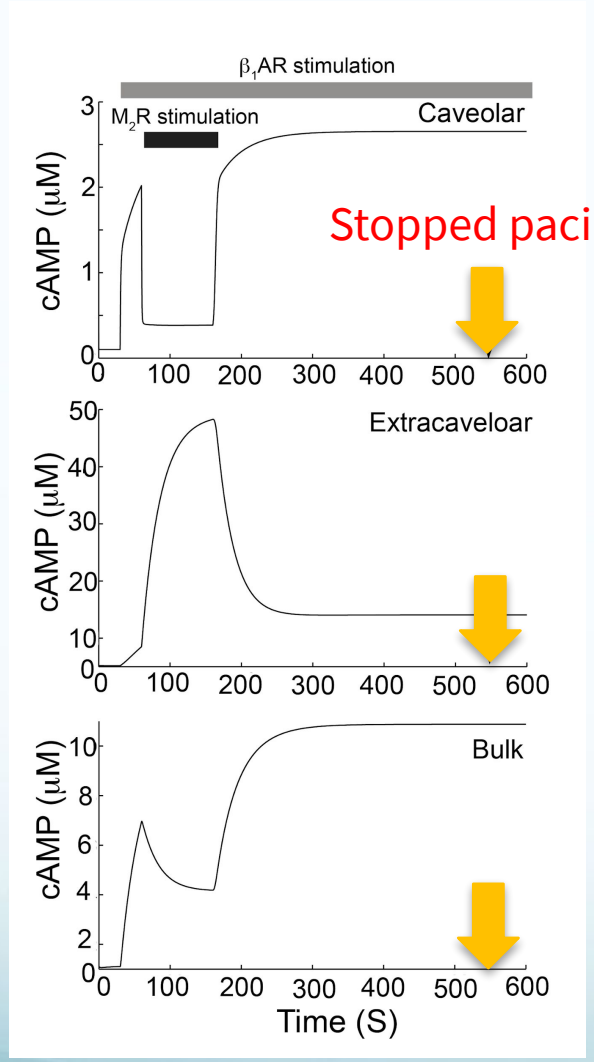
Simulated Action potential during sympathetic after muscarinic withdrawal

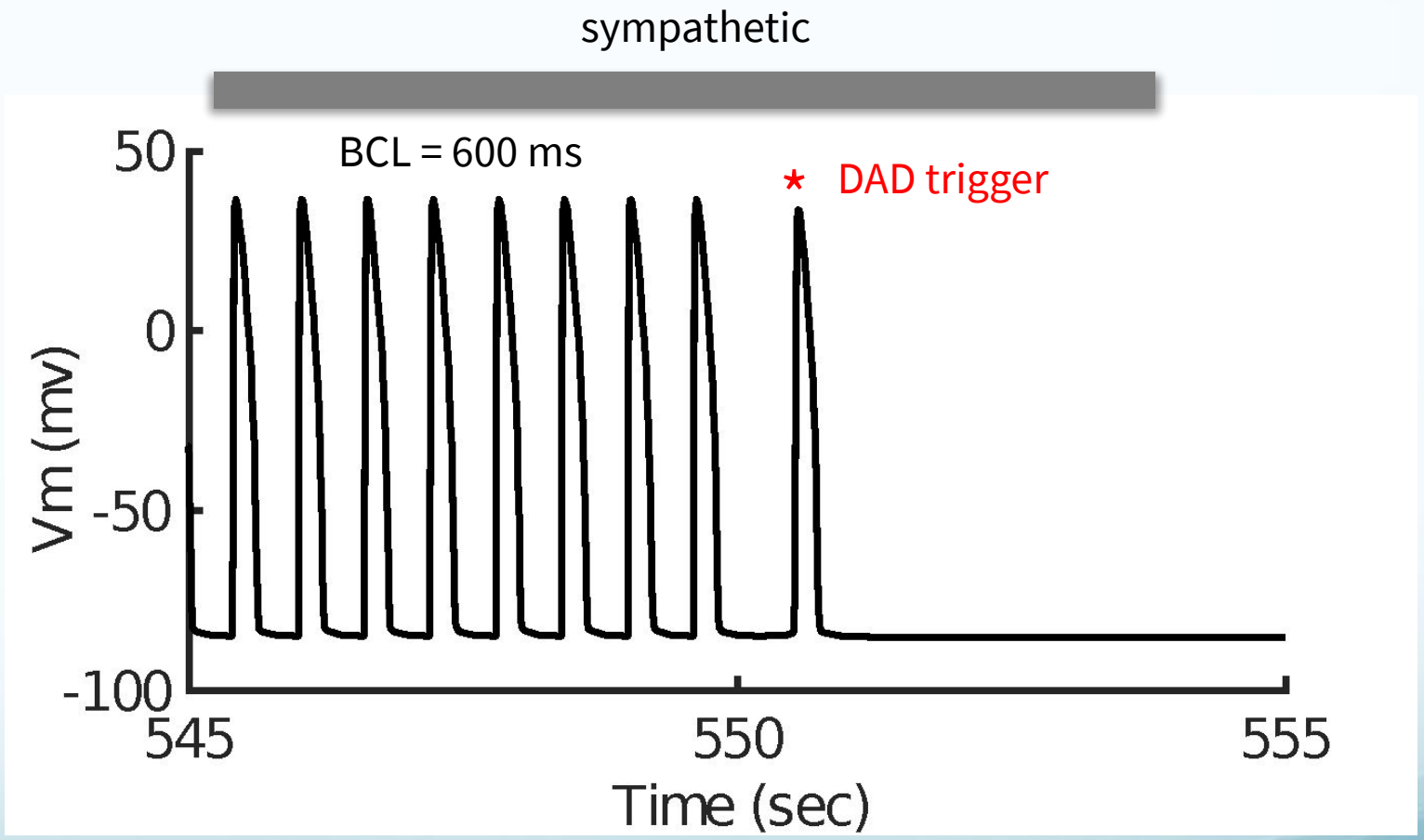


sympathetic



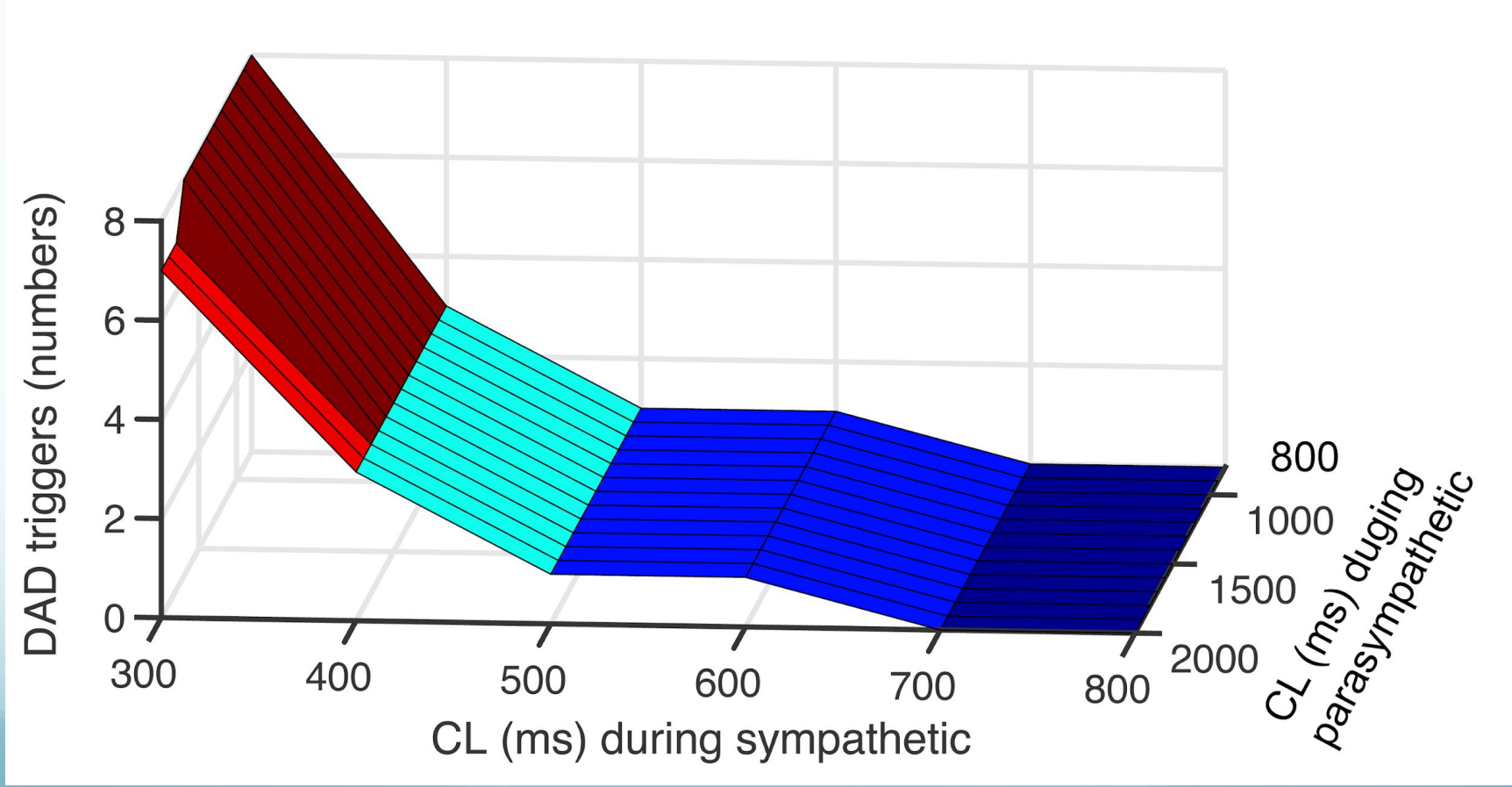
Simulated Action potential during sympathetic after removed M_2R activation



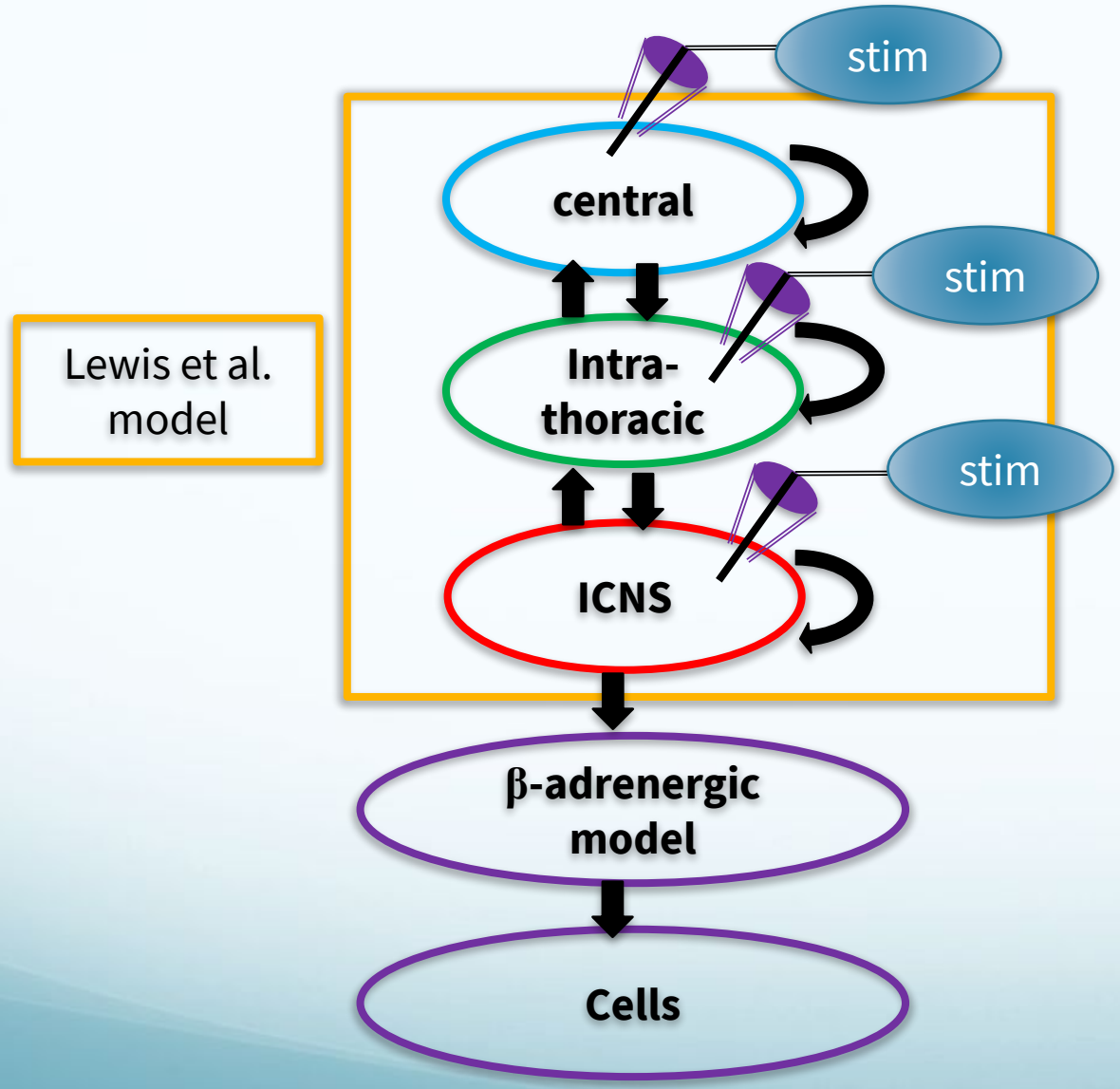


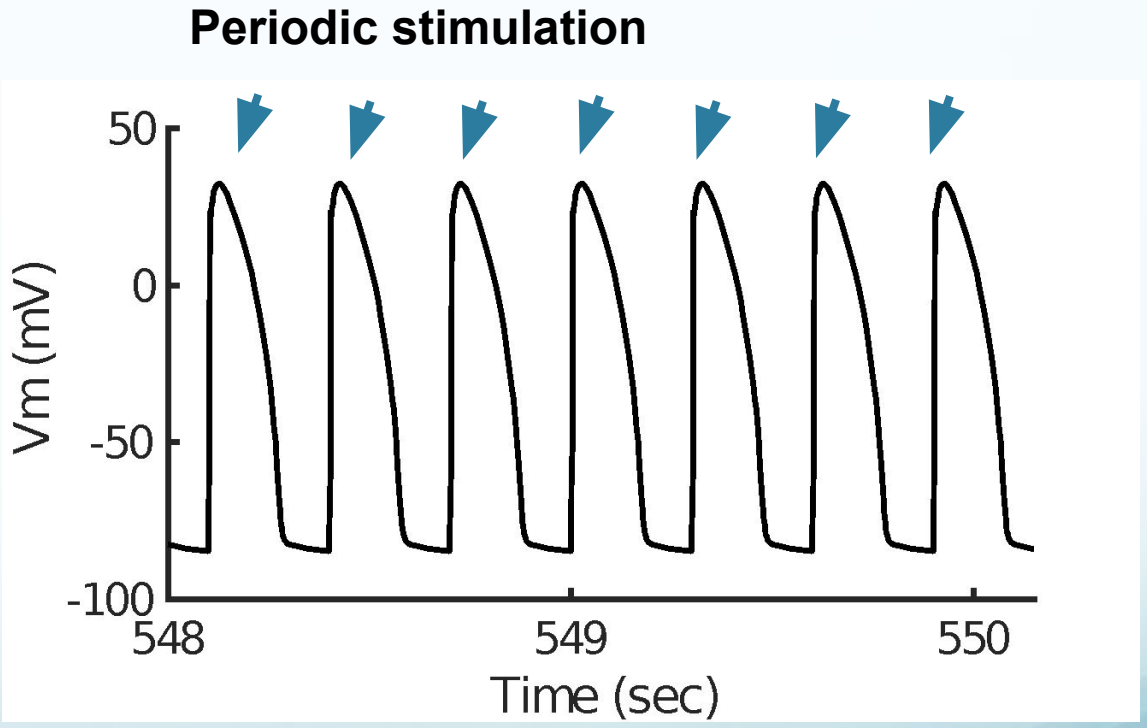
Testing parasympathetic mediated arrhythmia mechanisms in the setting of elevated sympathetic tone

Testing all possible combinations to identify the cycle length where triggered activity

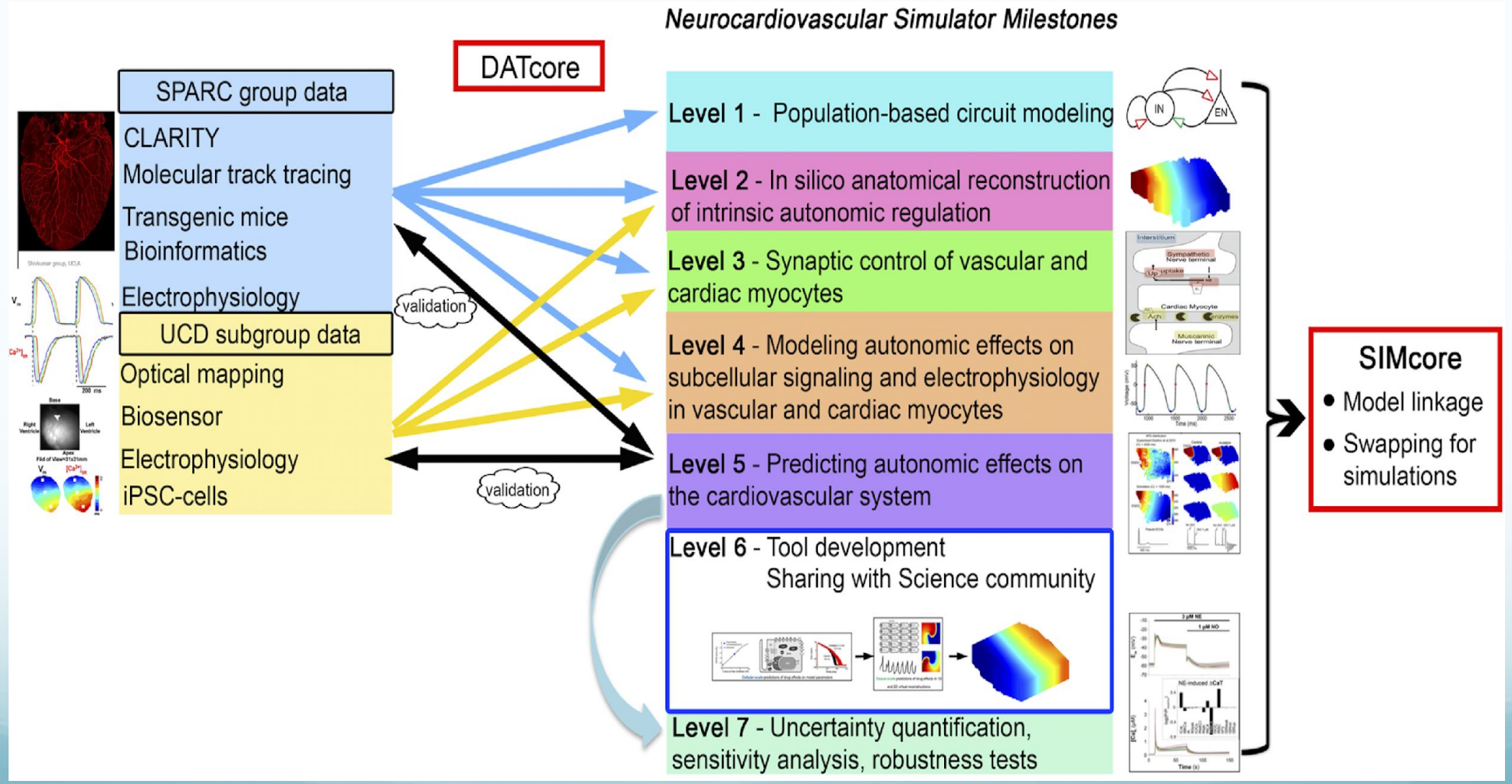


To be Tested


Lewis et al. model
stim
central
stim
Intra-thoracic
stim
ICNS
β-adrenergic model
Cells

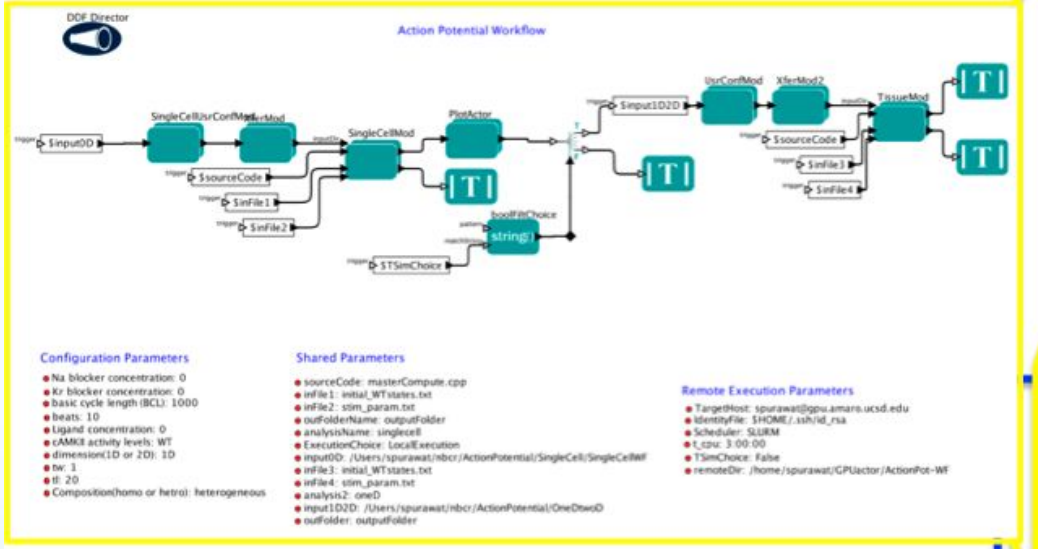

Periodic stimulation
50
0
-50
-100
Vm (mV)
548
549
550
Time (sec)

Integration of the UC Davis modeling group with SPARC consortium



Up next! Interaction with SIM Core

UC Davis/NBCR Workflow:
Functional level simulations



Cell simulations

Markov model into cell
& validations
(Generates
"populations" cells)

Kepler

Tissue simulations

Cable/tissue maps
Compare to experiments

Kepler

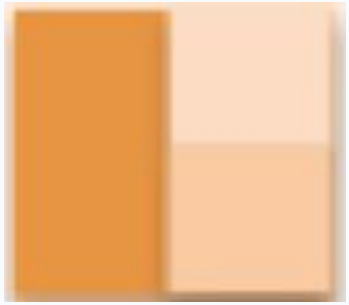
Pseudo ECG: Workflow in Progress

Compare to clinical ECG

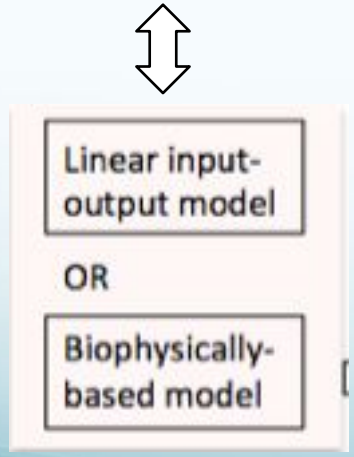
UC Davis proposed

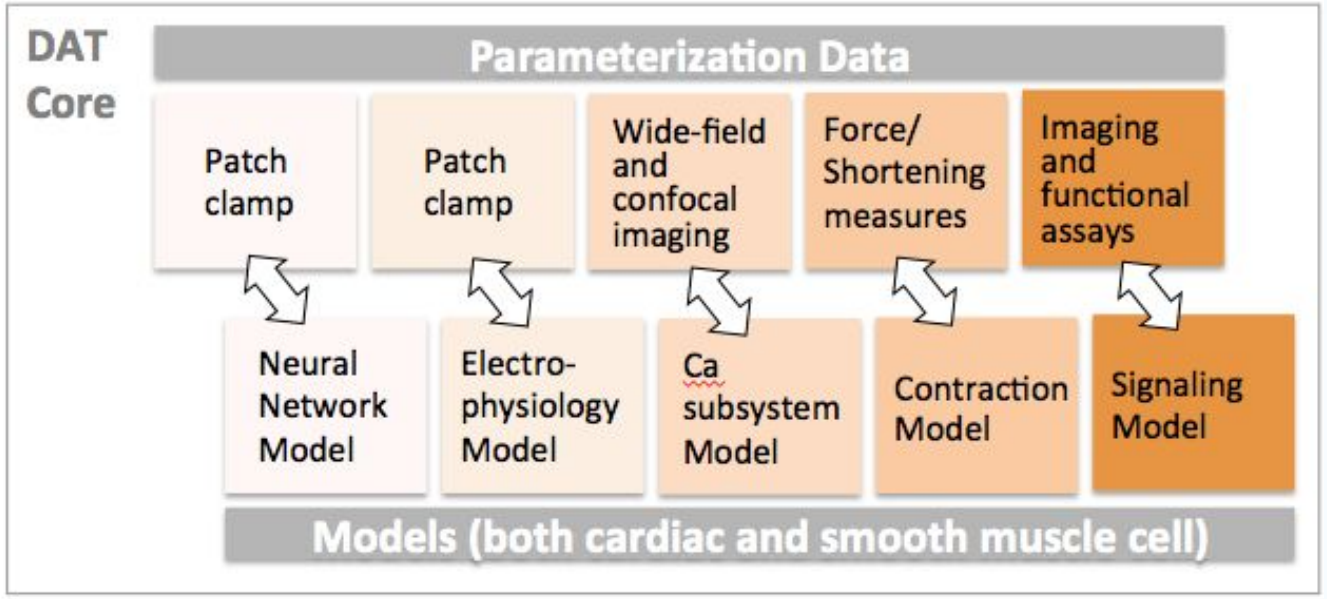
Minimal Viable Product

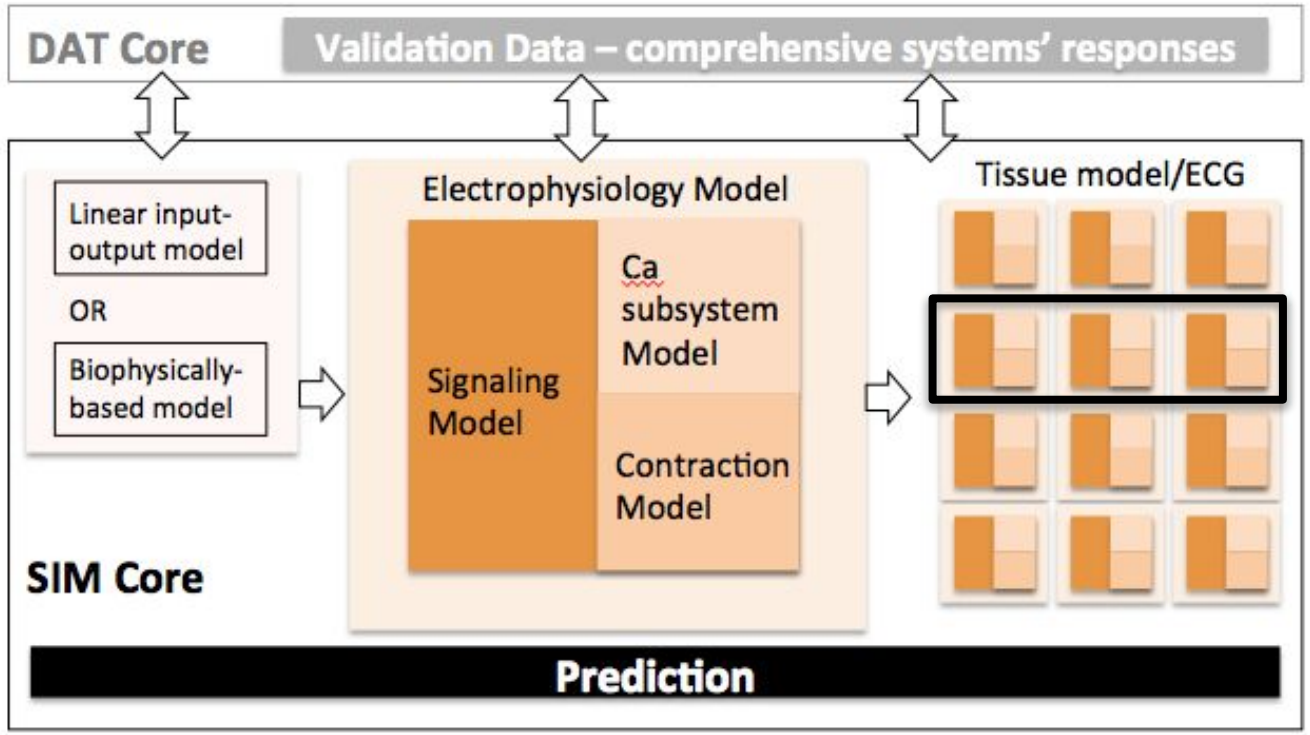
Use Case



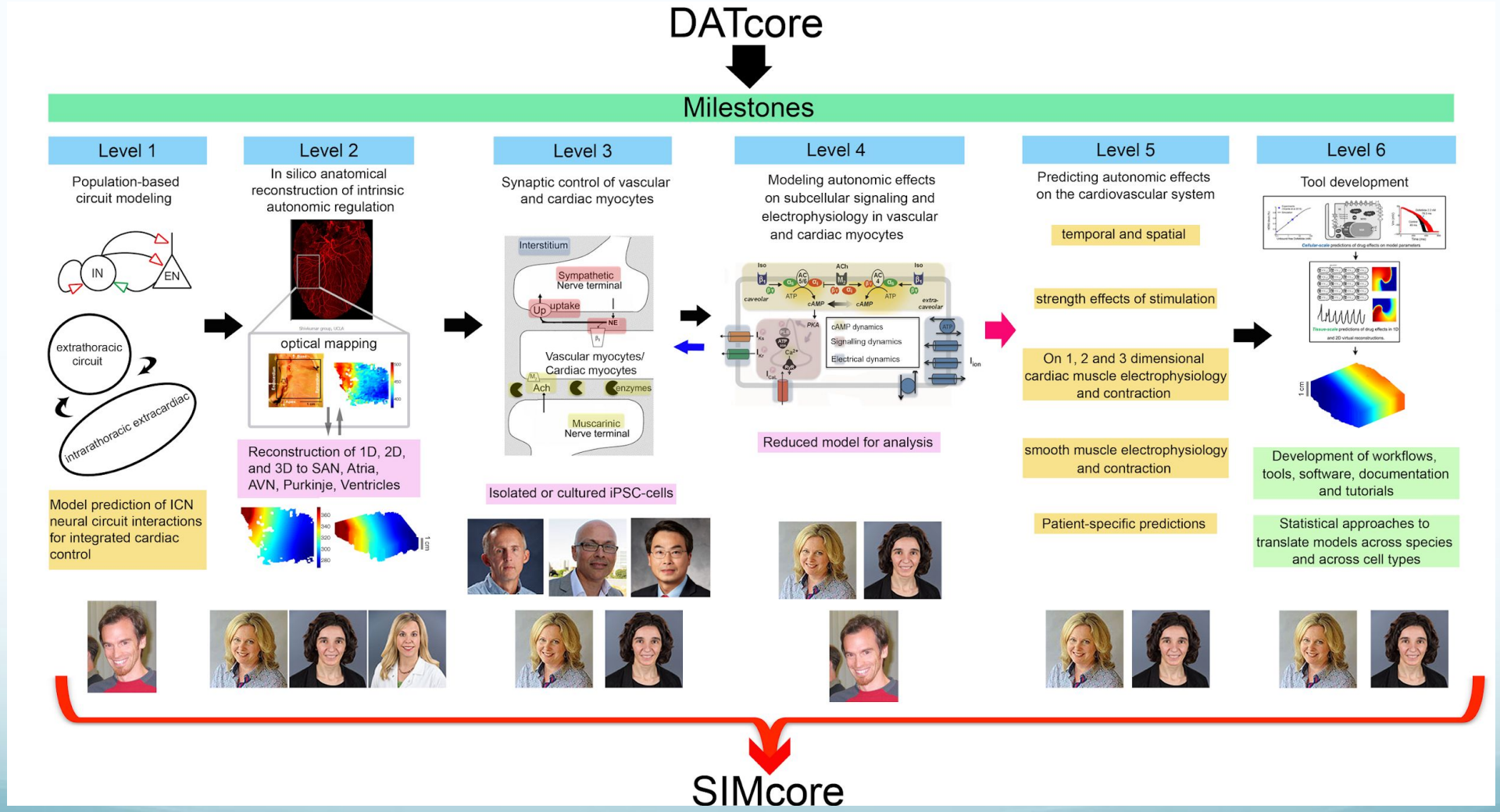
Flexible Components



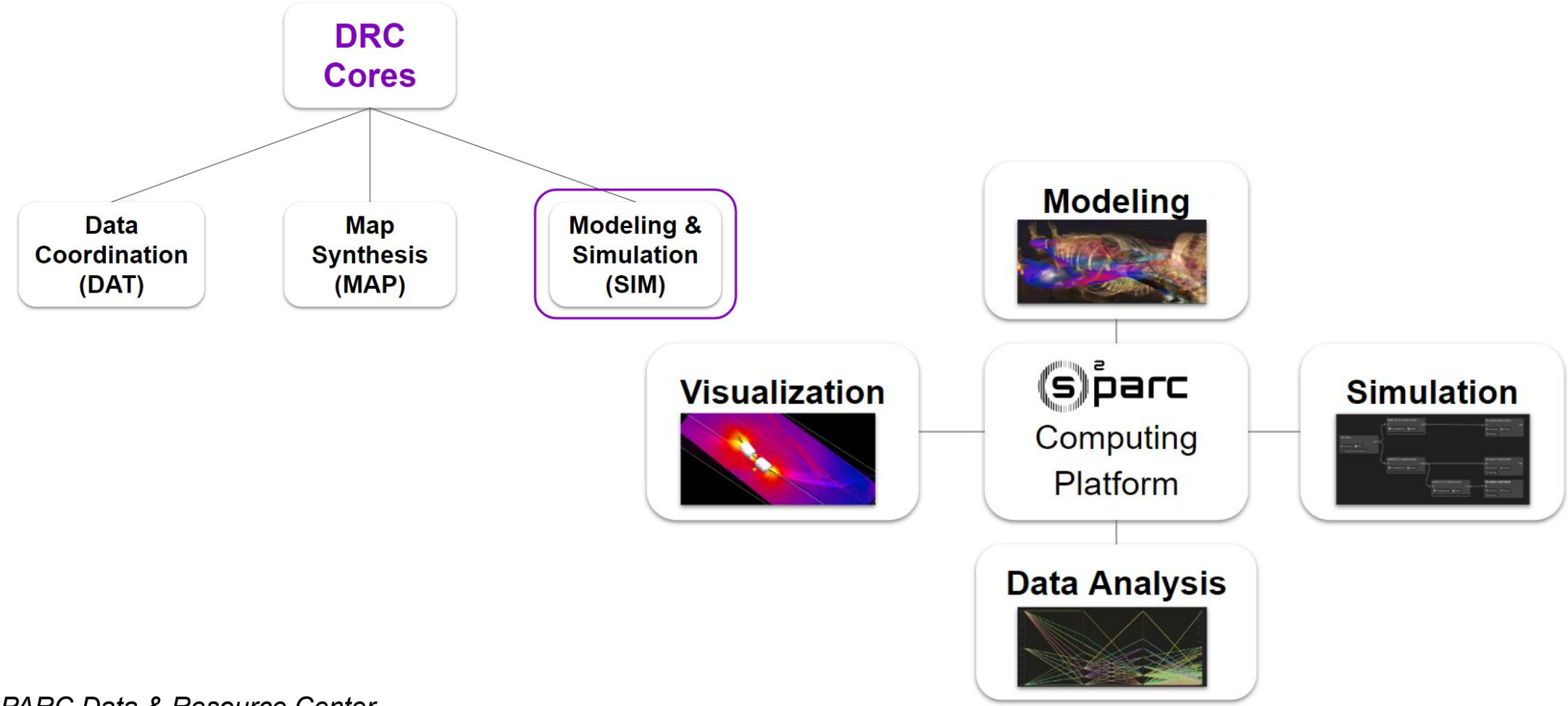




Development Strategy



SPARC's Central Sharing Hub for neuromodulation of the body's organs.

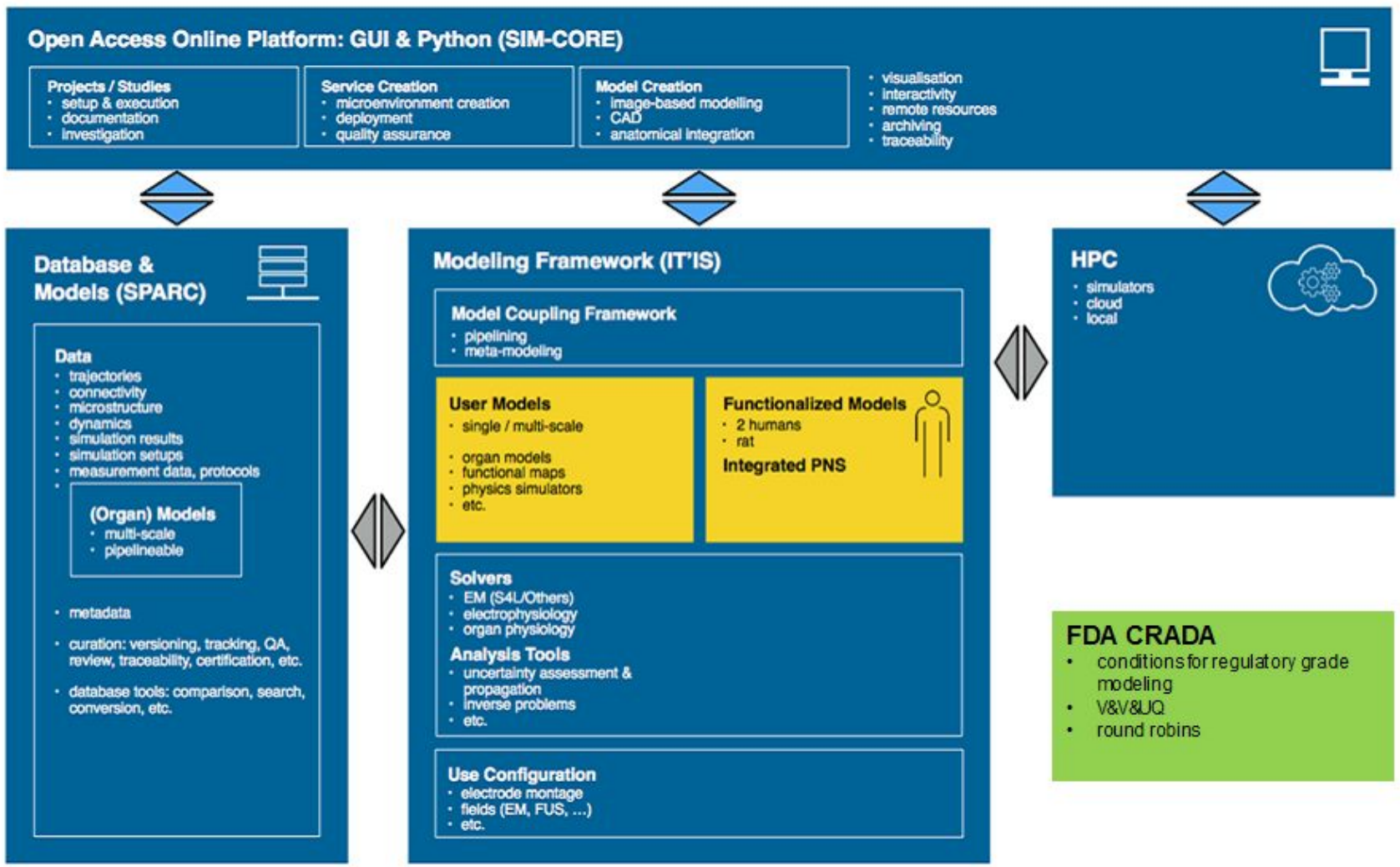


DRC: SPARC Data & Resource Center

The SPARC Platform for Computational Studies

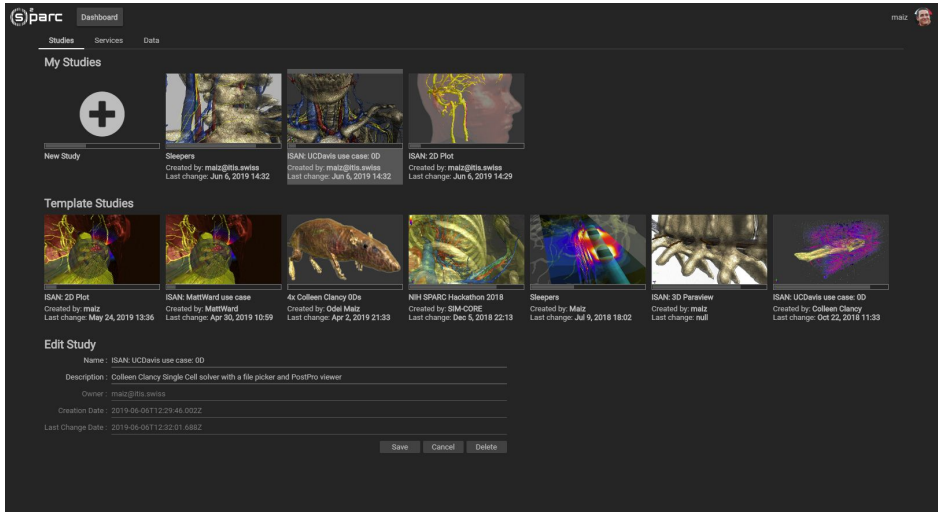
- An online, cloud-based, open, extensible platform for computational (neuro-)sciences
- A place to host, share, execute, document, and couple your computational models, analyses, and projects with others'
- A functionalized anatomical model-centered hub for computational model integration
- A collection of
  - detailed anatomical models
  - SPARC codes/models
  - data analysis and visualization tools
  - and (coming soon) powerful physics and physiology simulators
  - as well as (later) parameterization, uncertainty analysis, and optimization functionality
- An integral part of the DRC that interfaces with the Data Coordination & Map Synthesis Cores

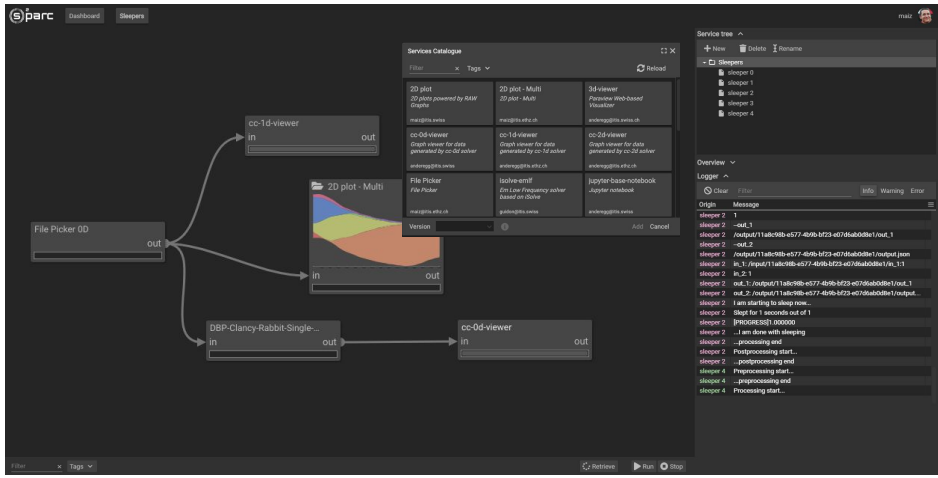
o²S²PARC – Platform for Computational Studies



Why use o²S²PARC?

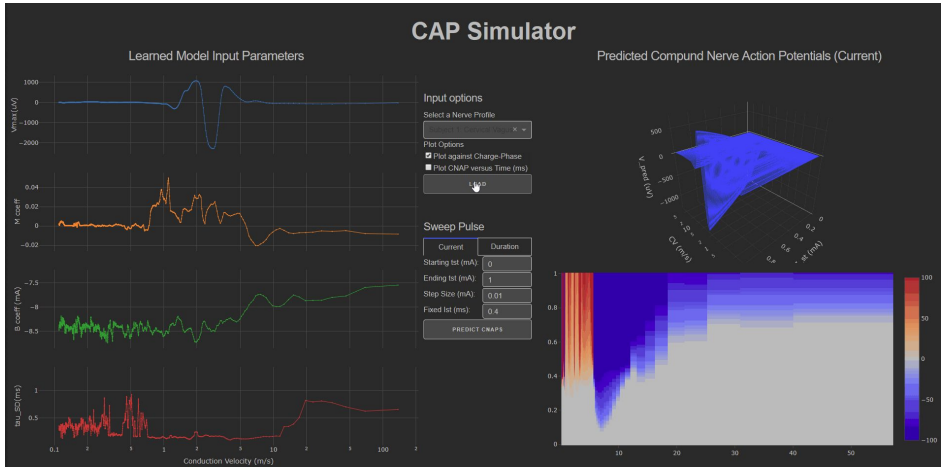
- Obviously because
  - the NIH says so (if you are SPARC funded)
  - it is awesome
- But most importantly because
  - it provides valuable tools (simulators, anatomical models, etc.)
  - it helps sustainably preserve models
  - models become shareable and reproducible
  - it includes extensive quality assurance functionalities
  - it allows models to run in the cloud through a user-friendly GUI
  - models become part of something that is bigger than the single contributions
  - it enables sharing and accessing predefined workflows that reflect extensive expertise
  - ir provides access to scalable computational resources
  - it permits to enhance paper/publication/grant application/etc. with an interactive demonstrator (supplementary data)
  - contributors can receive credit when others use their modules
  - it allows you to perform your work using the tools and approaches you are used to, **with minimal perturbation**

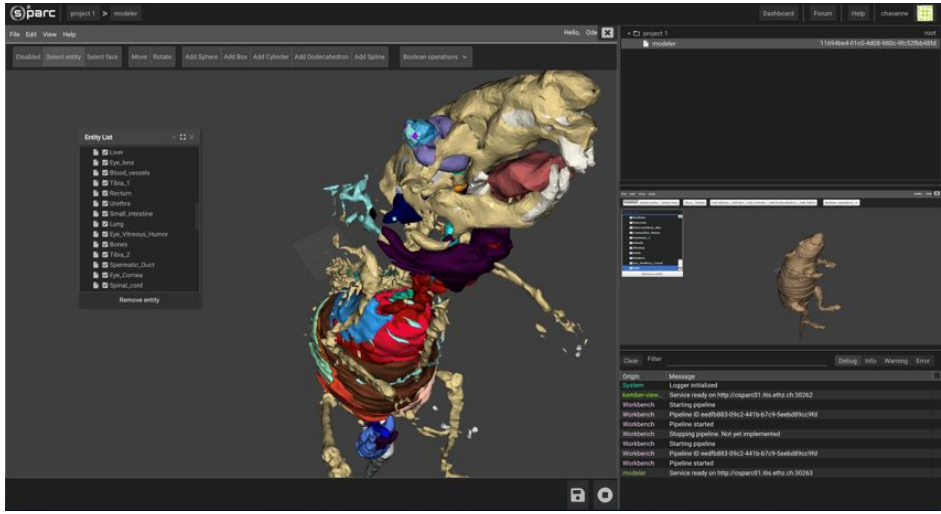




Why should SPARC teams use o²S²PARC?

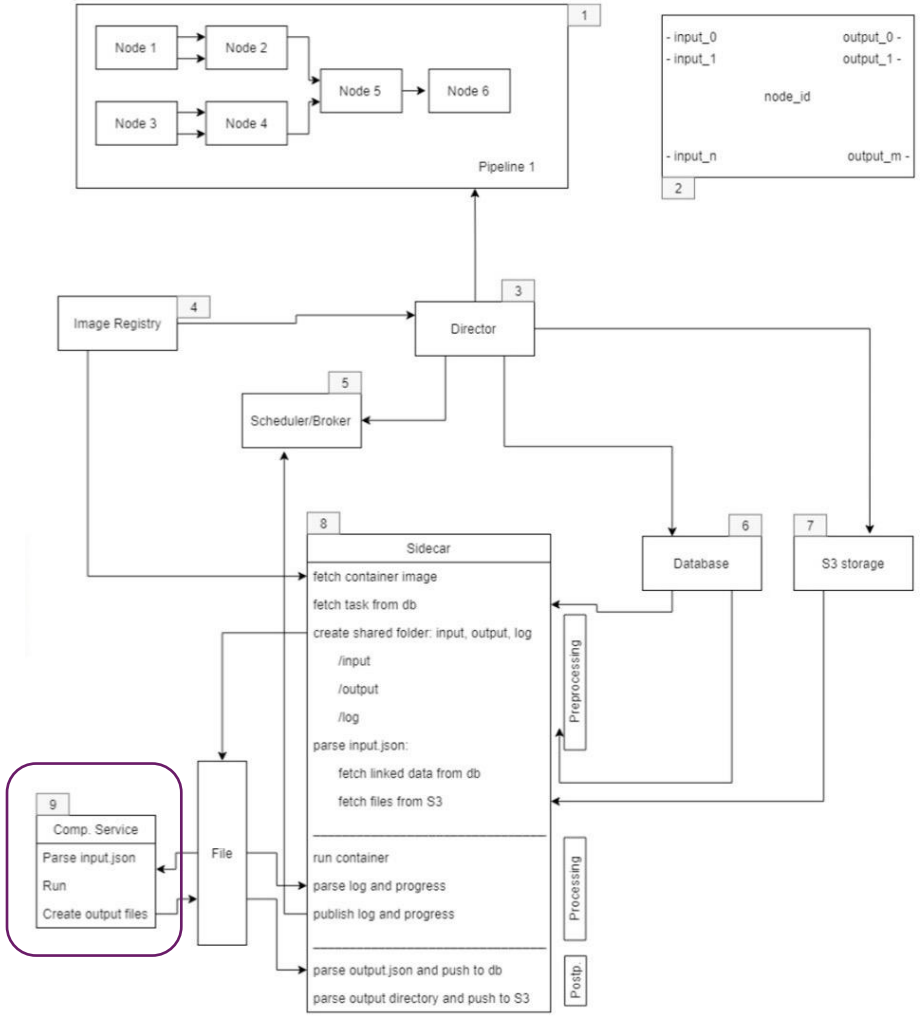
- Obviously because
  - the NIH says so (if you are SPARC funded)
  - it is awesome
- But most importantly because
  - it provides valuable tools (simulators, anatomical models, etc.)
  - it helps sustainably preserve models
  - models become shareable and reproducible
  - it includes extensive quality assurance functionalities
  - it allows models to run in the cloud through a user-friendly GUI
  - models become part of something that is bigger than the single contributions
  - it enables sharing and accessing predefined workflows that reflect extensive expertise
  - ir provides access to scalable computational resources
  - it permits to enhance paper/publication/grant application/etc. with an interactive demonstrator (supplementary data)
  - contributors can receive credit when others use their modules
  - it allows you to perform your work using the tools and approaches you are used to, **with minimal perturbation**





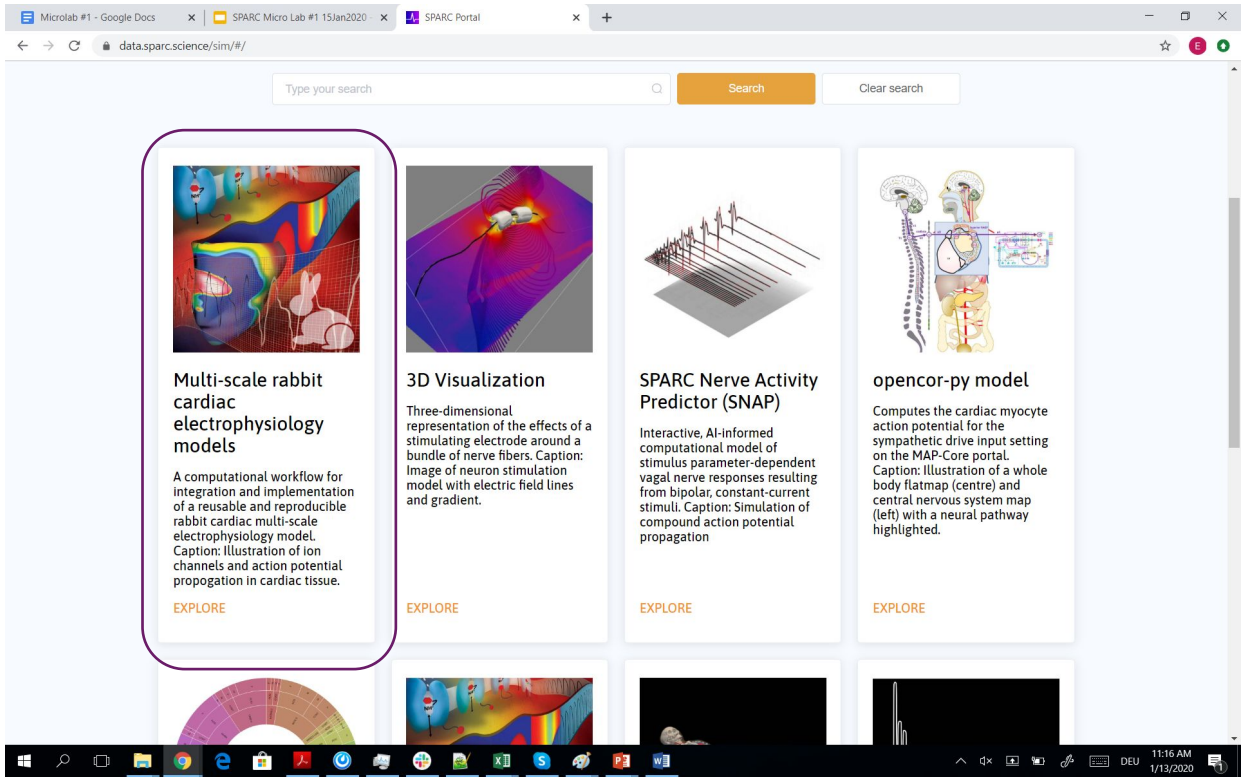
Why should SPARC teams use o²S²PARC?

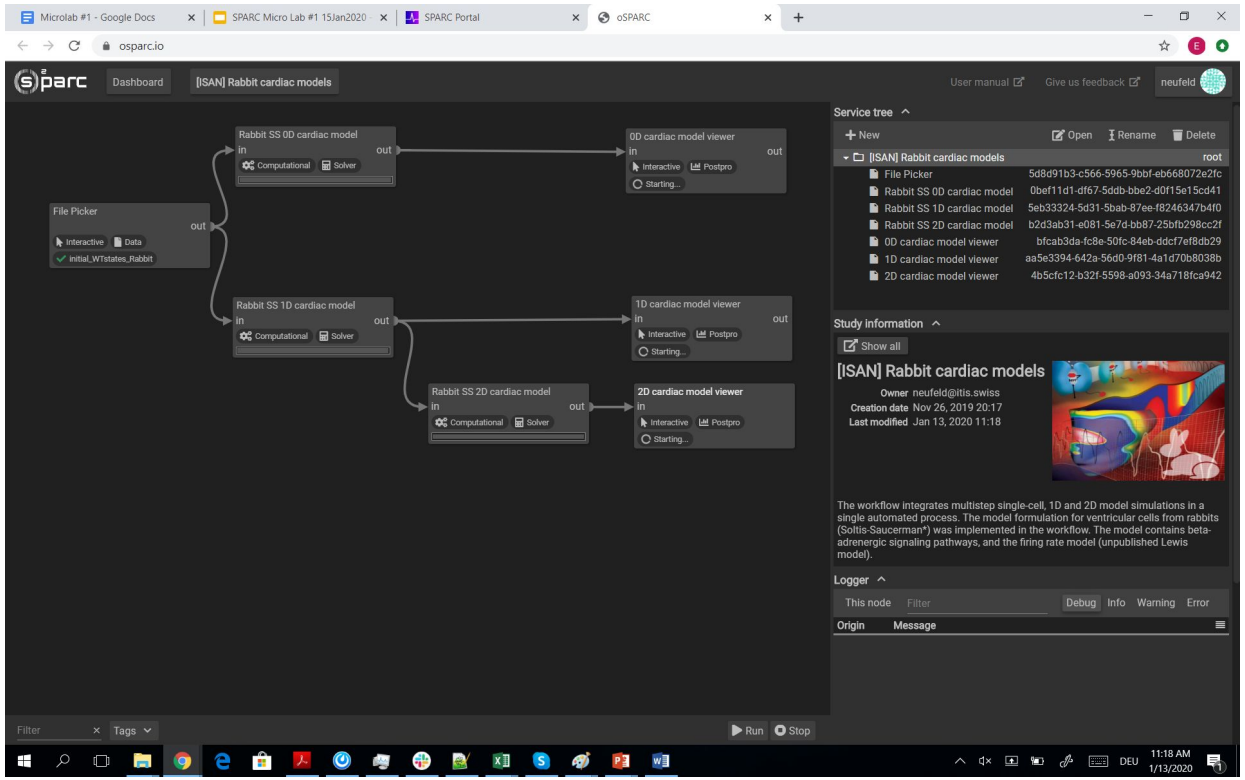
- Obviously because
  - the NIH says so (if you are SPARC funded)
  - it is awesome
- But most importantly because
  - it provides valuable tools (simulators, anatomical models, etc.)
  - it helps sustainably preserve models
  - models become shareable and reproducible
  - it includes extensive quality assurance functionalities
  - it allows models to run in the cloud through a user-friendly GUI
  - models become part of something that is bigger than the single contributions
  - it enables sharing and accessing predefined workflows that reflect extensive expertise
  - ir provides access to scalable computational resources
  - it permits to enhance paper/publication/grant application/etc. with an interactive demonstrator (supplementary data)
  - contributors can receive credit when others use their modules
  - it allows you to perform your work using the tools and approaches you are used to, **with minimal perturbation**



o²S²PARC Demo

Interactive DEMO: integration of models from Dr. Colleen Clancy's team:





Ideas Lab

Application deadline: 31 January 2020 @ 5pm ET

Event dates: April 20-24, 2020 (*must attend entire duration*)

Location: Washington, DC metro area (*travel and lodging expenses are covered*)

Funding: Following the Ideas Lab, full proposals can be submitted to a future NIH SPARC Funding Opportunity for potential funding. Participation in the Ideas Lab is **not** a requirement for proposal submission.

Visit http://bit.ly/35gacuL to learn more and apply!

Breakout Discussions

Questions to Answer - Use this URL to access » go.hub.ki/SPARCulab

1. What are the most exciting opportunities and possibilities for predictive modeling in bioelectronic medicine?
2. What are the challenges that if overcome would speed up progress in bioelectronic medicine?
3. Why is there so much (neuro-)physiological measurement data and so few computational models? Could we change that?
4. What type of non-obvious potential collaborator would you like to work with in this area, and why? (a statistician, an AI expert, a zoologist, a science-fiction writer …?)
    a. Thinking of someone specific? Feel free to invite them to apply 

Breakout Discussions

http://go.hub.ki/SPARCulab