IMAG 20yr anniversary celebration

A Vision for the Future of IMAG

A multiscale modeling framework for computational physiology

Peter Hunter

29th June 2023

THE UNIVERSITY OF AUCKLAND
Te Whare Wānanga o Tāmaki Makaurau
NEW ZEALAND

AUCKLAND BIOENGINEERING INSTITUTE

Historical perspective on Physiome Project (1997 ..)

IUPS Physiome Project


Denis Noble


Jim Bassingthwaighte


Marco Viceconti


Stig Omholt

EU & the VPH Institute

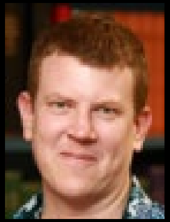
NIH IMAG

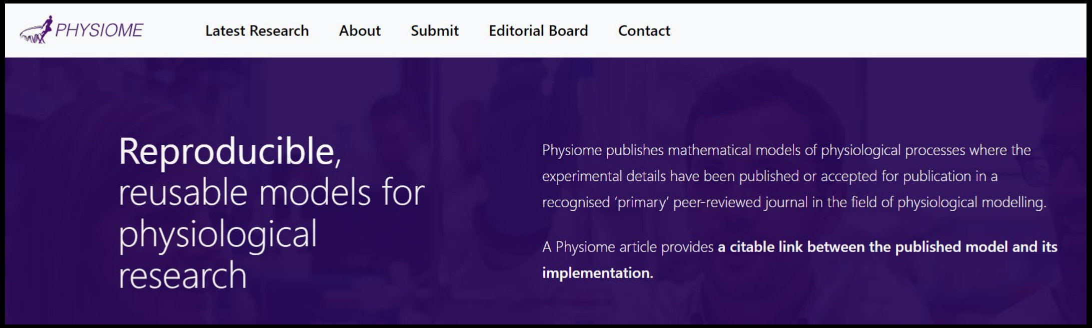

Grace Peng

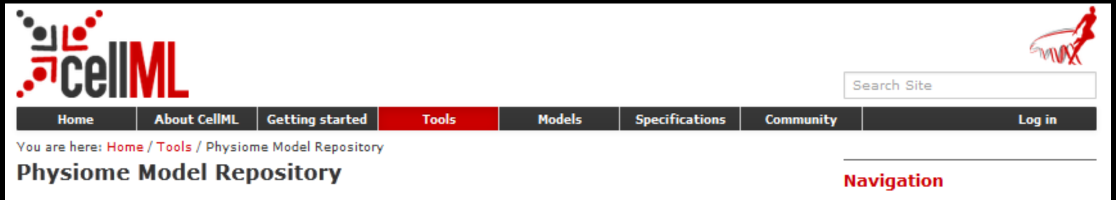
CellML & PMR

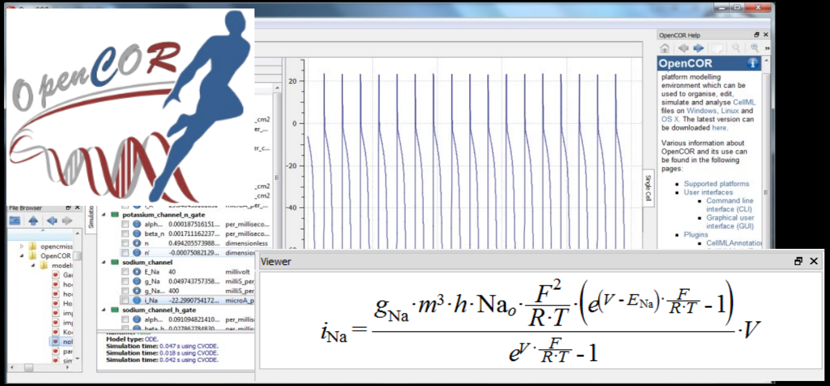

Poul Nielsen

Physiome journal


Andre (David Nickerson)



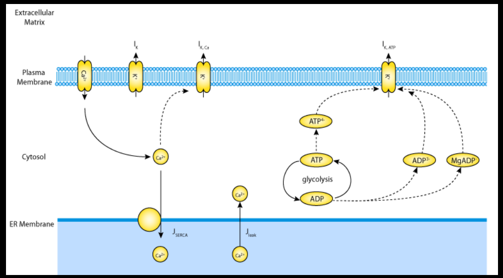




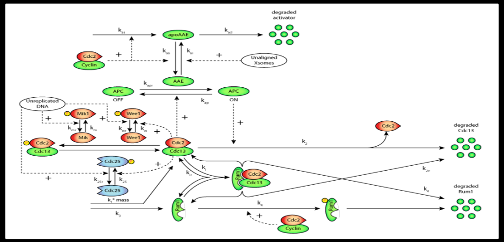
www.opencor.ws

The Physiome Model Repository (~1500 models)

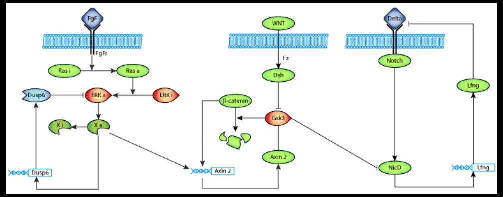
Calcium dynamics



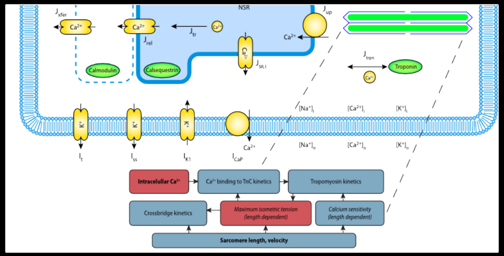
Cell cycle



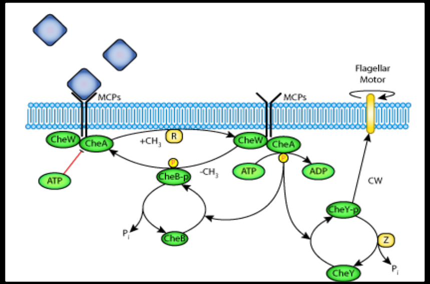
Circadian rhythms



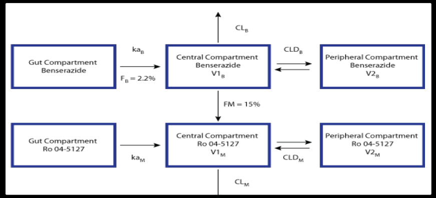
Excitation-contaction



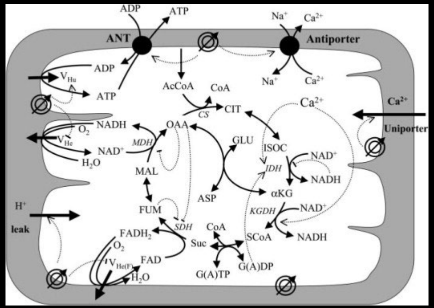
Cell migration



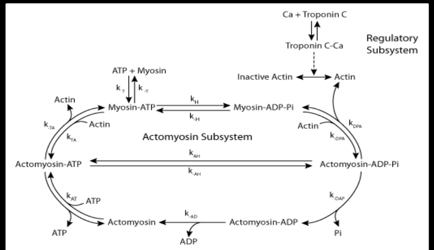
PKPD models



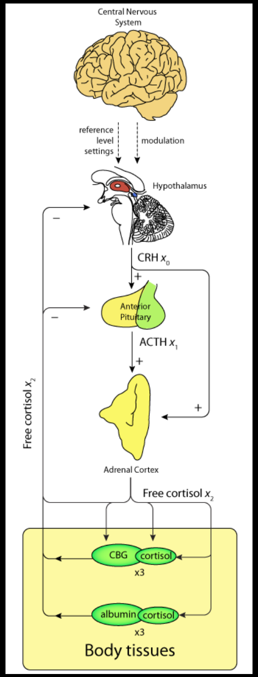
Metabolism

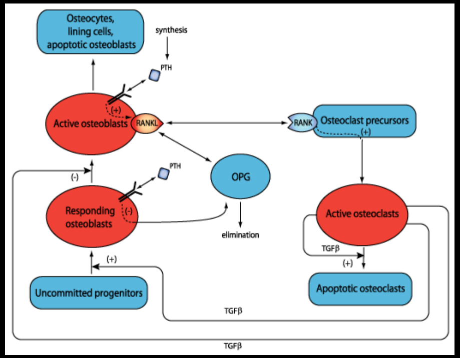


Myofilament mechanics

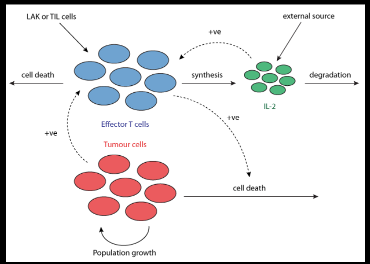


Endocrine system

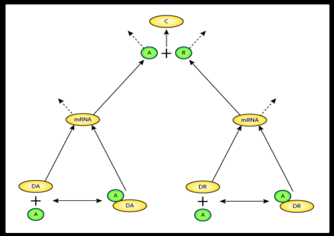


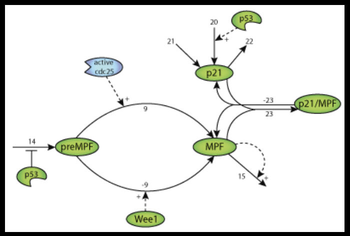


Immunology

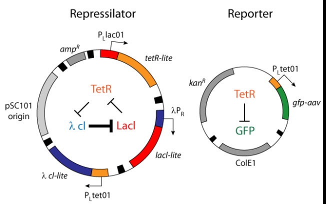


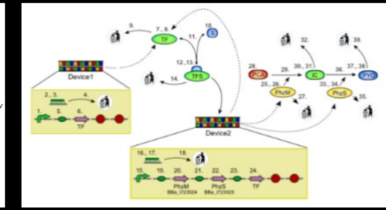
Gene regulation DNA repair



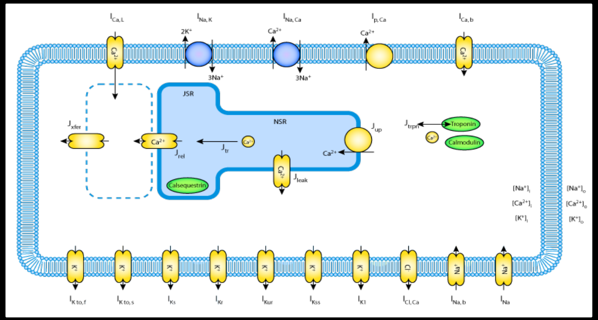


Synthetic biology

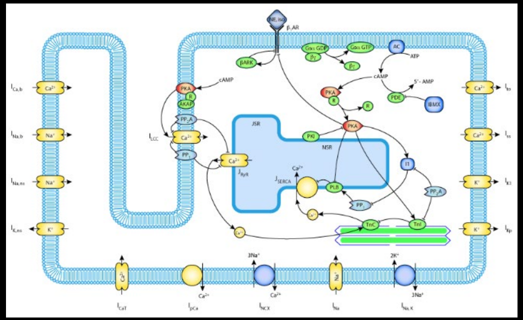


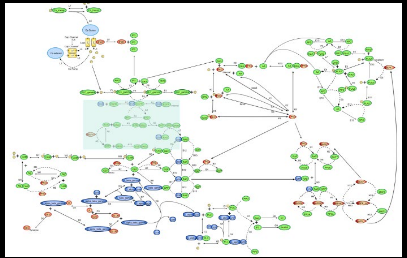


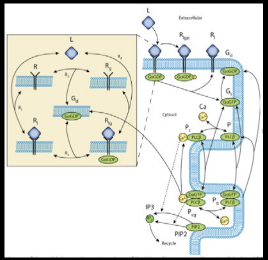
Electrophysiology

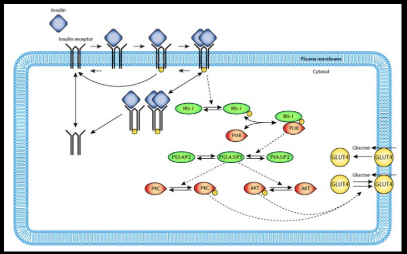


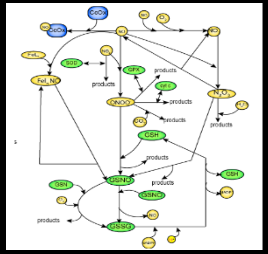
Signal transduction











Physiome journal

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Reproducible, reusable models for physiological research

Physiome publishes mathematical models of physiological processes where the experimental details have been published or accepted for publication in a recognised ‘primary’ peer-reviewed journal in the field of physiological modelling.

A Physiome article provides **a citable link between the published model and its implementation.**

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AUCKLAND BIOENGINEERING INSTITUTE

DIGITAL science

VPH Institute Building the Virtual Physiological Human

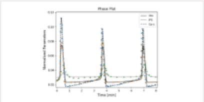
Curvenote

Original
Jan 20, 2023

A theoretical model of slow wave regulation using voltage-dependent synthesis of inositol 1, 4, 5-trisphosphate

The system of equations and figures presented in Imtiaz *et al.* (2002) are verified and reproduced in the current curation paper.

Leyla Noroozbabaee, Mohammad Imtiaz, Dirk Van Heldenn, Peng Du, David P. Nickerson

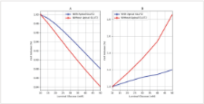


Original
Jan 19, 2023

Reproducibility Study of Computational Modelling of Glucose Uptake by SGLT1 and GLUT2 in the Enterocyte

Afshar *et al.* (2021) generated a computational model of non-isotonic glucose uptake by small intestinal epithelial cells. The model incorporates apical uptake via SGLT1 and GLUT2, basolateral efflux into the blood via GLUT2 and cellular volume changes in response to non-isotonic conditions.

Nima Afshar, Soroush Safaei, David P. Nickerson, Peter J. Hunter, Vinod Suresh

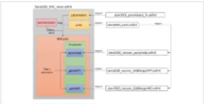


Original
Jan 11, 2023

Reproducibility Study for a Computational Model of the Neurovascular Coupling Unit

The mechanistic model of neurovascular coupling was developed and studied by Sten *et al.* (2020). This model describes and predicts the arteriolar dilation data of mice under various stimulations while anaesthetised and awake. We reconstructed the model in CellML, using a modular approach for each neuronal pathway, and successfully reproduced the original experiments.

Sergio Dempsey, Gunnar Cedersund, Maria Engström, Gonzalo Maso Talou, Soroush Safaei

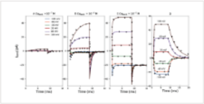


Original
Jan 11, 2023

Computational modeling of anoctamin 1 calcium-activated chloride channels as pacemaker channels in interstitial cells of Cajal

Lees-Green *et al.* (2014) describes a biophysical computational model of anoctamin 1 calcium-activated chloride channels. The system of equations and simulation results are verified and reproduced.

Leyla Noroozbabaee, David P. Nickerson, Peng Du

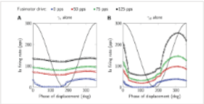


Retrospective
Jan 27, 2022

Spindle Model Responsive to Mixed Fusimotor Inputs: an updated version of the Maltenfort and Burke (2003) model

The muscle spindle model presented in Maltenfort & Burke (2003) calculates muscle spindle primary afferent feedback depending on the muscle fibre stretch and fusimotor drive.

Laura Schmid, Thomas Klotz, Utku Ş. Yavuz, Mitchell Maltenfort, Oliver Röhrle

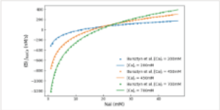


Original
Oct 19, 2021

Mathematical model of excitation-contraction in a uterine smooth muscle cell

The model incorporates processes of intracellular Ca^{2+} concentration control, myosin light chain (MLC) phosphorylation and stress production.

Weiwei Ai, Limor Freifeld, David P Nickerson

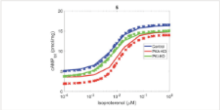


Original
Sep 23, 2021

A kinetic model of β-adrenergic control in cardiac myocytes

The system of equations and figures presented in Saucerman *et al.*, 2003 are verified and reproduced in this paper's curation effort.

Shelley Fong, Jeffrey J. Saucerman

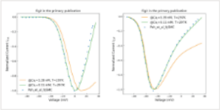


Original
Sep 9, 2021

A Quantitative Model of Human Jejunal Smooth Muscle Cell Electrophysiology

The Poh *et al.* (2012) paper describes the first biophysically based computational model of human jejunal smooth muscle cell (hJSMC) electrophysiology. The ionic currents are described by either a traditional Hodgkin-Huxley (HH) formalism or a deterministic multi-state Markov (MM) formalism.

Weiwei Ai, David P. Nickerson

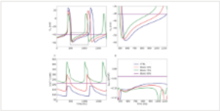


Original
Sep 1, 2021

Reproducibility study of the Fabbri *et al.* 2017 model of the human sinus node action potential

The sinoatrial node (SAN) is the natural pacemaker of the mammalian heart. It has been the subject of several mathematical studies, aimed at reproducing its electrical response under normal sinus rhythms, as well as under various conditions.

Nima Afshar, Alan Fabbri, Stefano Severi, Alan Garny, David Nickerson

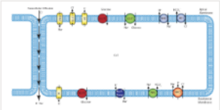


Original
Oct 1, 2020

Computational Modelling of Glucose Uptake in the Enterocyte

An implemented model of glucose absorption in the enterocyte, as previously published by Afshar *et al.* (2019).

Nima Afshar, Soroush Safaei, David P. Nickerson, Peter J. Hunter, Vinod Suresh

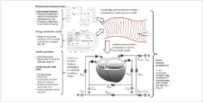


Original
Sep 15, 2020

Computational Modeling of Coupled Energetics and Mechanics in the Rat Ventricular Myocardium

A multi-scale model computational model of myocardial energetics—oxidative ATP synthesis, ATP hydrolysis, and phosphate metabolite kinetics—and myocardial mechanics used to analyze data from a rat model of cardiac decompensation and failure.

Bahador Marzban, Rachel Lopez, Daniel A. Beard

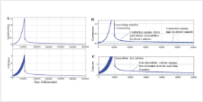


Letter
Aug 28, 2020

Model of skeletal muscle cramp and its reversal

We reproduce muscle cramp, as well as its prevention and reversal, by investigating muscle contraction and cramp, in which calcium regulatory networks are involved, using the extended model in comparison with the original model.

Kazuyo Tasaki, Penelope J. Noble, Alan Garny, Paul R. Shorten, Nima Afshar, Denis Noble

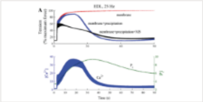


Retrospective
Aug 28, 2020

Incorporation of sarcolemmal calcium transporters into the Shorten *et al.* (2007) model of skeletal muscle: equations, coding and stability

We describe a major development of the Shorten *et al.* (2007) model of skeletal muscle electrophysiology, biochemistry and mechanics.

Penelope J. Noble, Alan Garny, Paul R. Shorten, Kazuyo Tasaki, Nima Afshar, Denis Noble

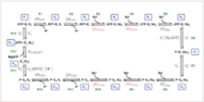


Retrospective
Aug 27, 2020

The cardiac Na^{+}/K^{+} ATPase: An updated, thermodynamically consistent model

The Na+/K+ATPase is an essential component of cardiac electrophysiology, maintaining physiological Na+ and K+ concentrations over successive heart beats. Terkildsen et al. (2007) developed a model of the ventricular myocyte Na+/K+ ATPase to study extracellular potassium accumulation during ischaemia, demonstrating the ability to recapitulate a wide range of experimental data, but unfortunately there was no archived code associated with the original manuscript.

Michael Pan, Peter J. Gawthrop, Joseph Cursons, Kenneth Tran, Edmund J. Crampin

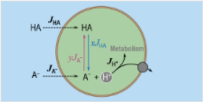


Review
Aug 27, 2020

The Boron & De Weer Model of Intracellular pH Regulation

The classic Boron & De Weer (1976) paper provided the first evidence of active regulation of pH in cells by an energy-dependent acid-base transporter. This Physiome paper seeks to make that model, and the experimental conditions under which it was developed, available in a reproducible and well-documented form, along with a software implementation that makes the model easy to use and understand.

Rossana Occhipinti, Soroush Safaei, Peter J. Hunter, Walter F. Boron



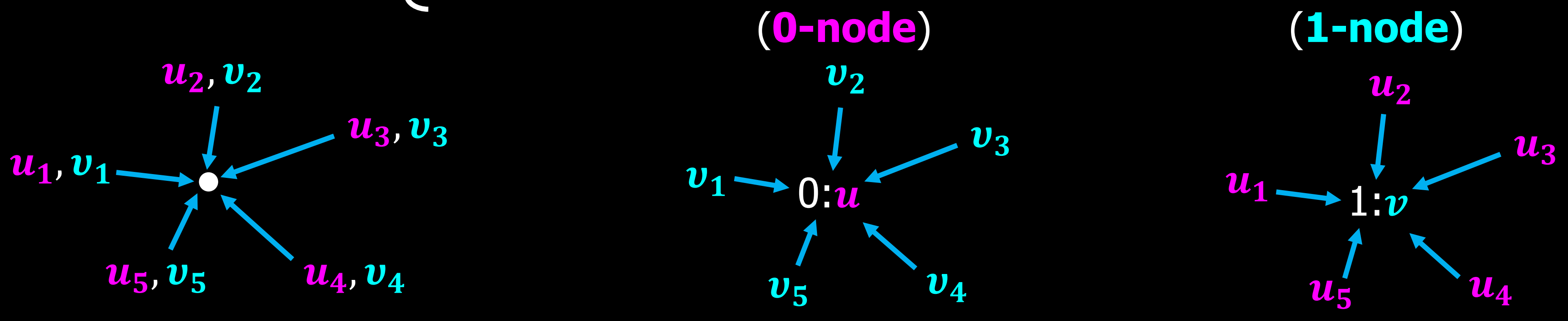
Now need a maths/physics framework that links models across all spatial & temporal scales …

1. Energy based modeling: Port-Hamiltonians … 0D version is Bond Graphs
2. Use BG/CellML/SBML for all proteins to create a generic cell (.`.. Reactome)
3. FTUs and Functional Connectivity (FC) maps (... all of physiology)
4. Organ scaffolds and whole-body 3D models (… SPARC)
5. Reduced models via physics-constrained AI (… surrogate models)
6. Systems physiology (control for homeostasis, etc) ... bond graphs etc
7. A single knowledgebase (probably federated … e.g. Proto-OKN)

… and we need new instrumentation & new software engineering

Bond graphs: Energy & Power transmission

$$\sum u_i v_i = 0 \begin{cases} \text{If } u_1 = u_2 = u_3 = u_4 = u_5 \Rightarrow \sum v_i = 0 & \textbf{Conservation of Mass, Charge, etc} \\ \text{If } v_1 = v_2 = v_3 = v_4 = v_5 \Rightarrow \sum u_i = 0 & \textbf{Conservation of Energy} \end{cases}$$



where $v = \frac{dq}{dt}$

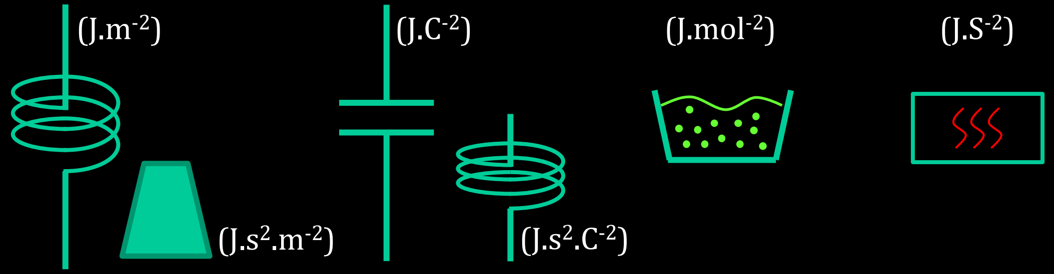
and q is measured in

meters (m; or m^3)
Coulombs (C), Candela (Cd),
moles (mol) or entropy (S)

	Mechanical	Electrical	Chemical	Heat	
$u.v$ has units:	J.m^{-1}.m.s^{-1} (N)	J.C^{-1}.C.s^{-1} (V)	J.mol^{-1}.mol.s^{-1}	J.S^{-1}.S.s^{-1} (K)	(= J.s^{-1})

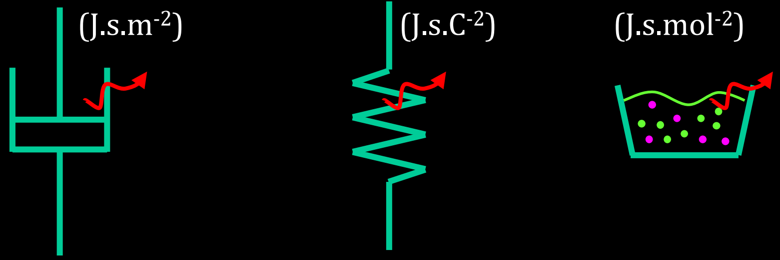
Energy storage

Mechanical **Electrical** **Chemical** **Heat**



Energy dissipation

Mechanical **Electrical** **Chemical**



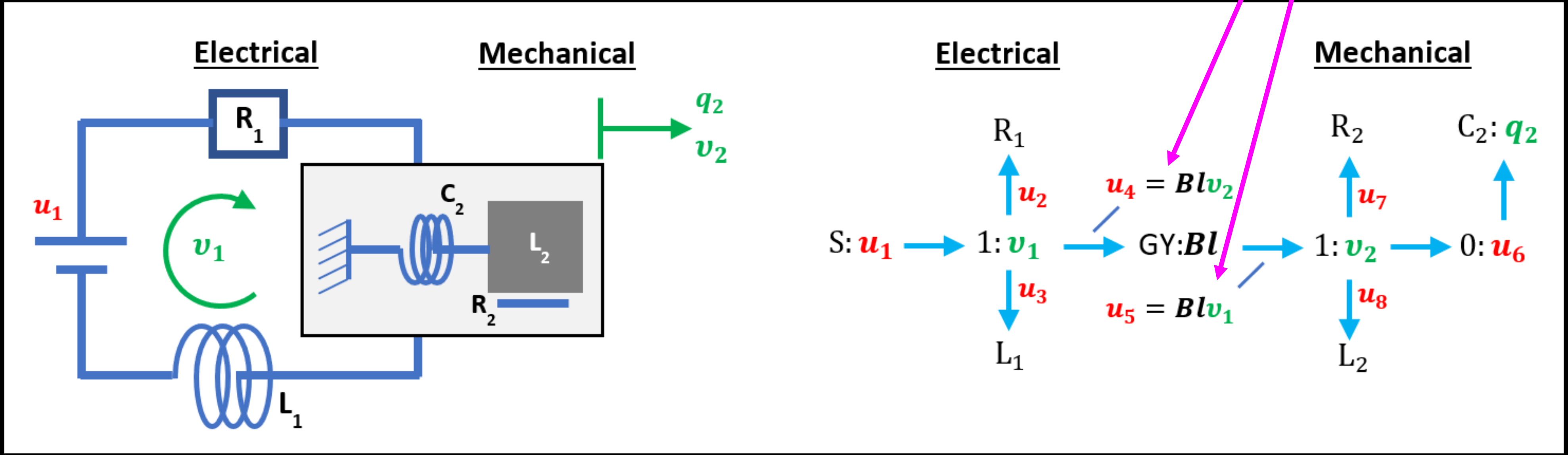
Gawthrop PJ and Crampin EJ. Energy based analysis of biochemical cycles using bond graphs. *Proc. R. Soc. A* 470:20140459, 2014.
Gawthrop PJ and Crampin EJ. Modular bond-graph modelling and analysis of biomolecular systems. *IET Systems Biology*, 2015.
Gawthrop PJ, Cursons J and Crampin EJ. Hierarchical bond graph modelling of biochemical networks. *Proc. R.* Soc *A*, 471(2184), 2015.

Examples

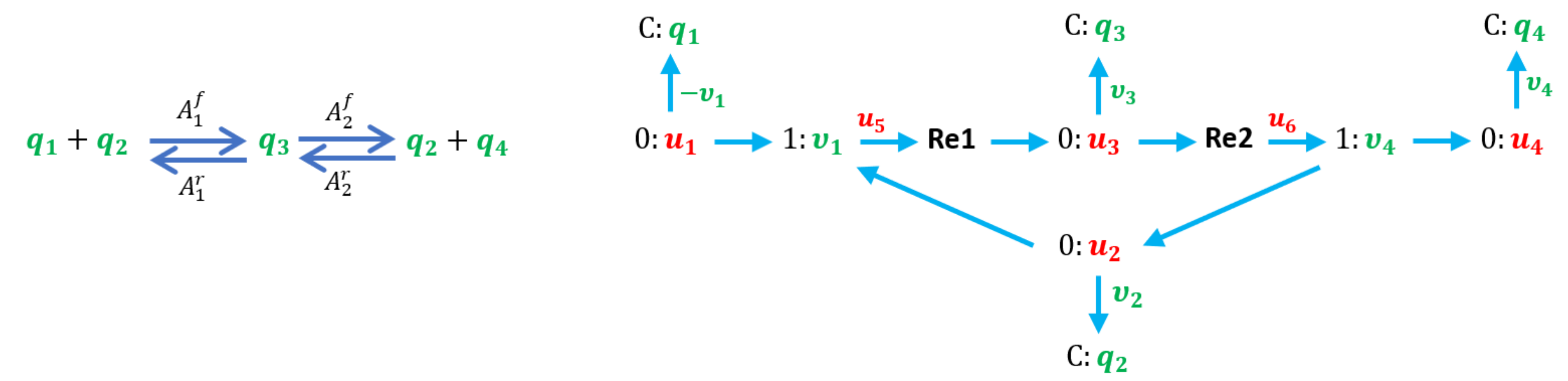
A coupled electromechanical system

Faraday's law of induction

Lorentz force



An enzyme-catalyzed reaction



For 3D continuum problems: BG → Port-Hamiltonians

constitutive constants or relationships

Meter
- **Solid mechanics** (Finite elasticity): $det\boldsymbol{F}^T\boldsymbol{F} = 0;\ \tau^{ij}\big|_i = f^j;\ \boldsymbol{\tau^{ij}} = f\left(\boldsymbol{e_{ij}}\right)$
- **Fluid mechanics** (Navier-Stokes eqns): $\nabla.\boldsymbol{u} = 0;\ \dfrac{D\boldsymbol{u}}{Dt} = \dfrac{\partial \boldsymbol{u}}{\partial t} + \boldsymbol{u}.\nabla\boldsymbol{u} = -\dfrac{1}{\rho}\nabla p - \nabla.(-\nu\nabla\boldsymbol{u})$

Entropy
Mole
- **Heat flow**
- **Reaction-diffusion**

$$\frac{DC}{Dt} = \frac{\partial C}{\partial t} + \boldsymbol{u}.\nabla C = f_s - \nabla.(-k\nabla C)$$

Coulomb
Candela
- **Electromagnetics** (Maxwell's eqns)

$$\boldsymbol{\nabla}.\boldsymbol{E} = \frac{\rho}{\epsilon};\quad \boldsymbol{\nabla}.\boldsymbol{B} = \boldsymbol{0}$$

$$\boldsymbol{\nabla}\times\boldsymbol{E} = -\frac{\partial \boldsymbol{B}}{\partial t};\quad \boldsymbol{\nabla}\times\boldsymbol{B} = \mu\left(\boldsymbol{J} + \boldsymbol{\epsilon}\frac{\partial \boldsymbol{E}}{\partial t}\right)$$

Energy-based equivalent to bond graphs is port-Hamiltonians

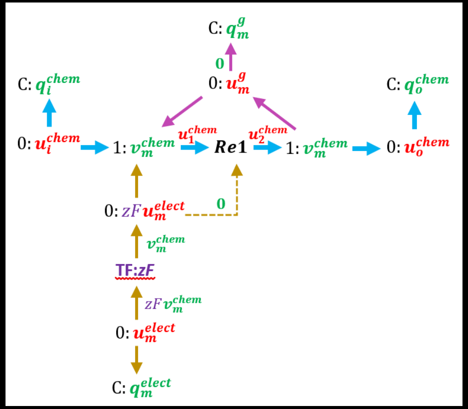
For skew symmetric matrix J, $\boxed{\boldsymbol{a}^T\boldsymbol{J}\boldsymbol{a} = 0}$ and hence $\boldsymbol{b} = \boldsymbol{J}\boldsymbol{a} \Rightarrow \boldsymbol{a}^T\boldsymbol{b} = 0$

J is connectivity matrix for 0D system, or $J = \begin{bmatrix} \boldsymbol{0} & -\boldsymbol{Div} \\ \boldsymbol{Grad} & \boldsymbol{0} \end{bmatrix}$ for continuum field

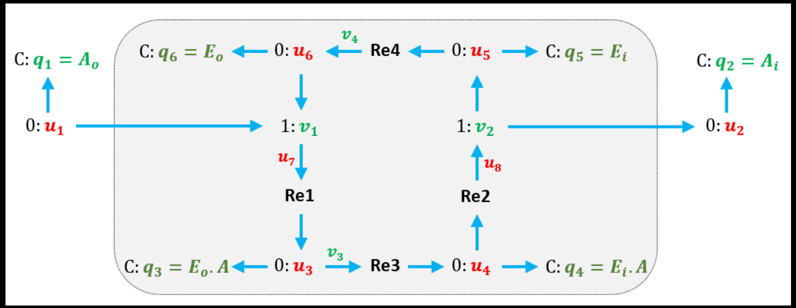
Argus, Bradley, Hunter (2021) Theory and implementation of coupled port-Hamiltonian continuum and lumped parameter models. *J. Elasticity* ISSN: 0374-3535, 1573-2681; 1-44. 10.1007/s10659-021-09846-4

Bond graph physiological models

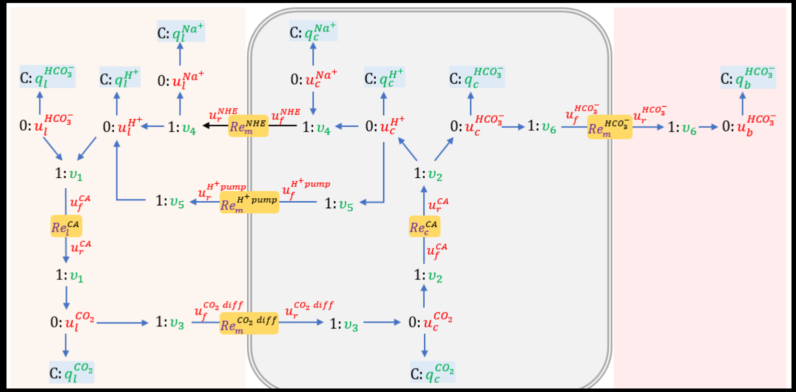
Gated ion channel



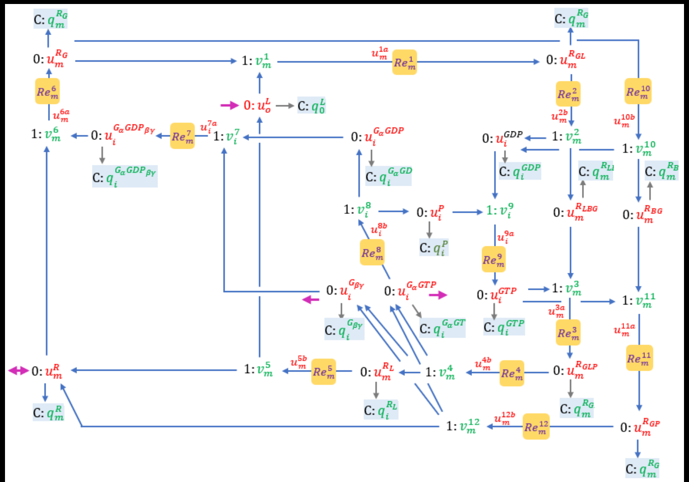
GLUT glucose transporter



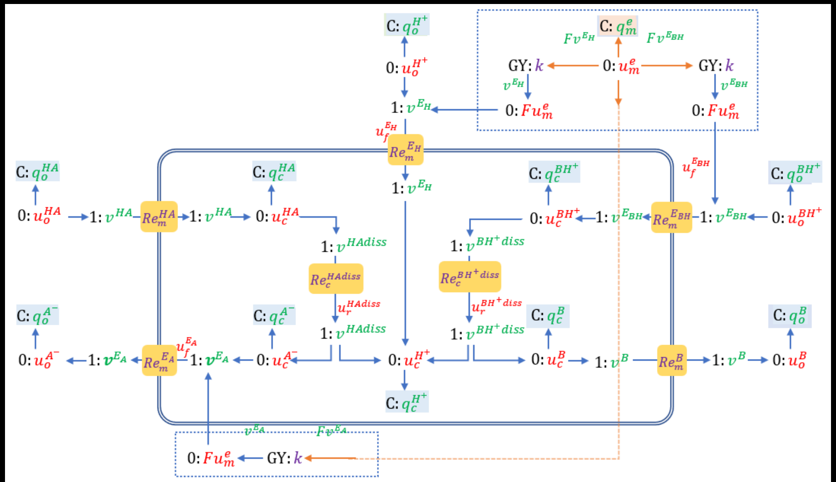
H⁺ extrusion in the renal tubule



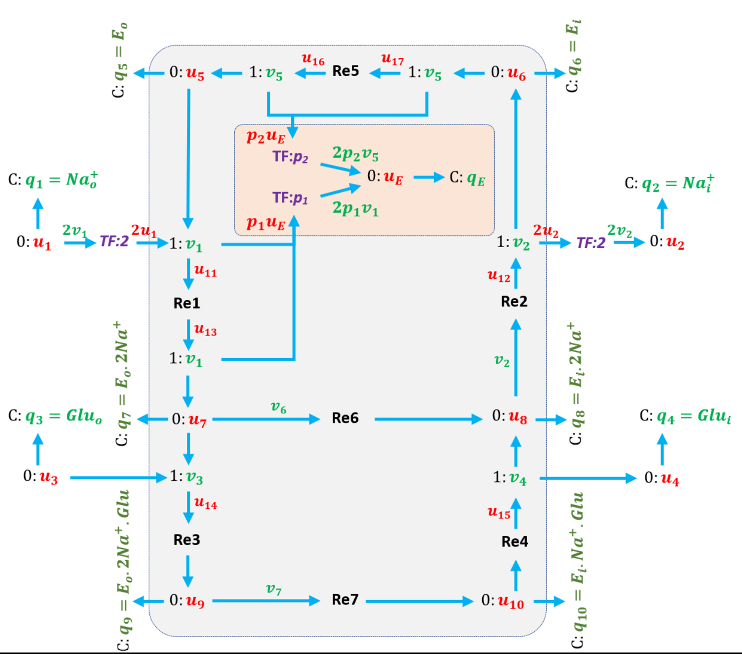
GPCR



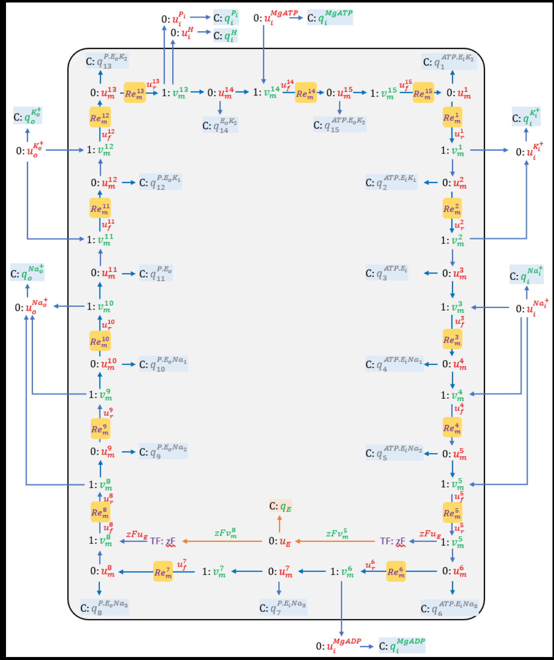
pH buffering with weak acids & bases



Na⁺/glucose co-transporter



Na/K ATPase exchanger

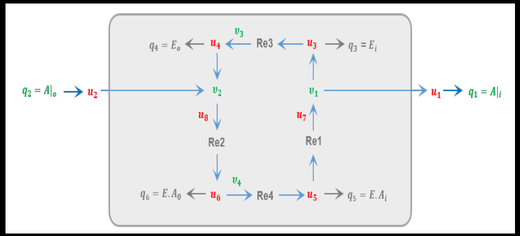


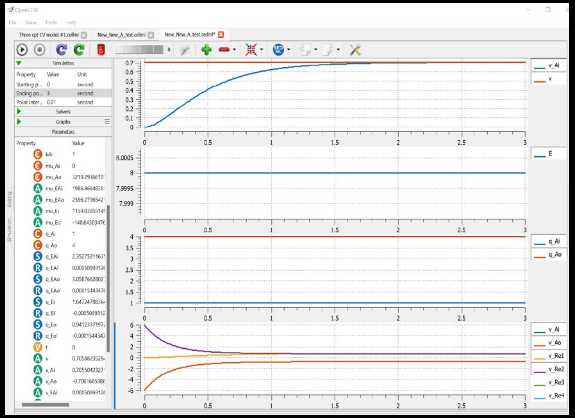
Project with CWRU on SLC transporters (458 genes in 65 gene families)

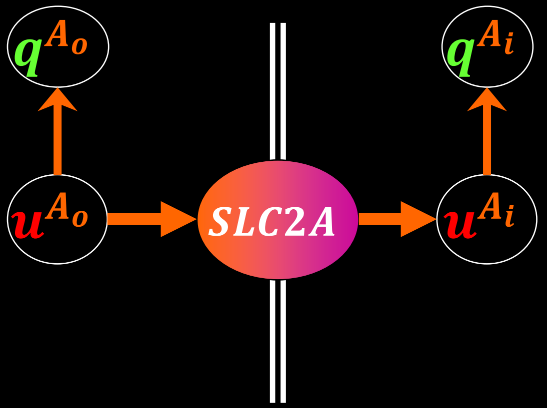
SLC1: High-affinity glutamate and neutral amino acid transporters
SLC2: Facilitative GLUT transporters
SLC3: Heavy subunits heterodimeric amino acid transporters
SLC4: Bicarbonate cotransporters
SLC5: Na^+/glucose cotransporters
SLC6: Na^+- and Cl^--dependent neurotransmitter symporters
SLC7: Cationic AA transporter/glycoprotein - assoc AA transporters
SLC8: Na^+/Ca^{2+} exchangers
SLC9: Na^+/H^+ exchangers
SLC10: Na^+/bile salt co-transporters
SLC11: Proton-coupled metal ion transporters
SLC12: Electroneutral cation/Cl^- co-transporters
SLC13: Na^+/SO_4^{2-}/carboxylate co-transporters
SLC14: Urea transporters
SLC15: Proton-driven oligopeptide cotransporters
SLC16: Monocarboxylate transporters
SLC17: Type I Na^+/phosphate cotransporters
& vesicular glutamate transporters
SLC18: Vesicular amine transporters
SLC19: Folate/thiamine transporters
SLC20: Type-III Na^+/phosphate co-transporters
SLC21: Organic anion and cation transporters
SLC22: Organic cation/anion/zwitterion transporters
SLC23: Na^+-dependent ascorbic acid transporters
SLC24: Na^+/(Ca^{2+}–K^+) exchangers
SLC25: Mitochondrial carriers
SLC26: Multifunctional anion exchangers
SLC27: Fatty acid transporters
SLC28: Na^+-coupled nucleoside transporters
SLC29: Facilitative nucleoside transporters
SLC30: Zinc efflux transporters
SLC31: Copper transporters
SLC32: Vesicular inhibitory amino acid transporters
SLC33: Acetyl-CoA transporters
SLC34: Type II Na^+-phosphate cotransporters
SLC35: Nucleoside-sugar transporters
SLC36: Proton-coupled amino acid transporters
SLC37: Sugar-phosphate/phosphate exchangers
SLC38: System A and System N Na^+-coupled neutral AA transporters
SLC39: Metal ion transporters
SLC40: Basolateral Fe^{2+} transporters
SLC41: MgtE-like magnesium transporters
SLC42: $NH_3/NH_4^+, CO_2$ channels
SLC43: Na^+-independent, system-L-like amino acid transporters
SLC44: Choline-like transporters
SLC45: H^+/sugar cotransporters
SLC46: Folate transporters
SLC47: Multidrug and toxin extrusion (MATE) transporters
SLC48: Heme transporters
SLC49: FLVCR-related transporters
SLC50: Sugar efflux transporters
SLC51: Steroid-derived molecules transporters
SLC52: Riboflavin transporters
SLC53: Phosphate carriers
SLC54: Mitochondrial pyruvate carriers
SLC55: Mitochondrial cation/proton exchangers
SLC56: Sideroflexins
SLC57: NiPA-like magnesium transporters
SLC58: MagT-like magnesium transporters
SLC59: Sodium-dependent lysophosphatidylcholine symporters
SLC60: Glucose transporters
SLC61: Molybdate transporters
SLC62: Pyrophosphate transporters
SLC63: Sphingosine-phosphate transporters
SLC64: Golgi Ca^{2+}/H^+ exchangers
SLC65: NPC-type cholesterol transporters

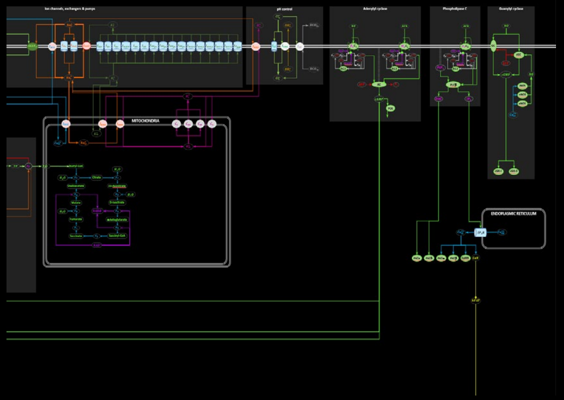
Solution of BG/CellML model in OpenCOR and model reduction

SLC2A1









Steady state flux

$$v_1 = v_2 = v_3 = v_4 = v$$

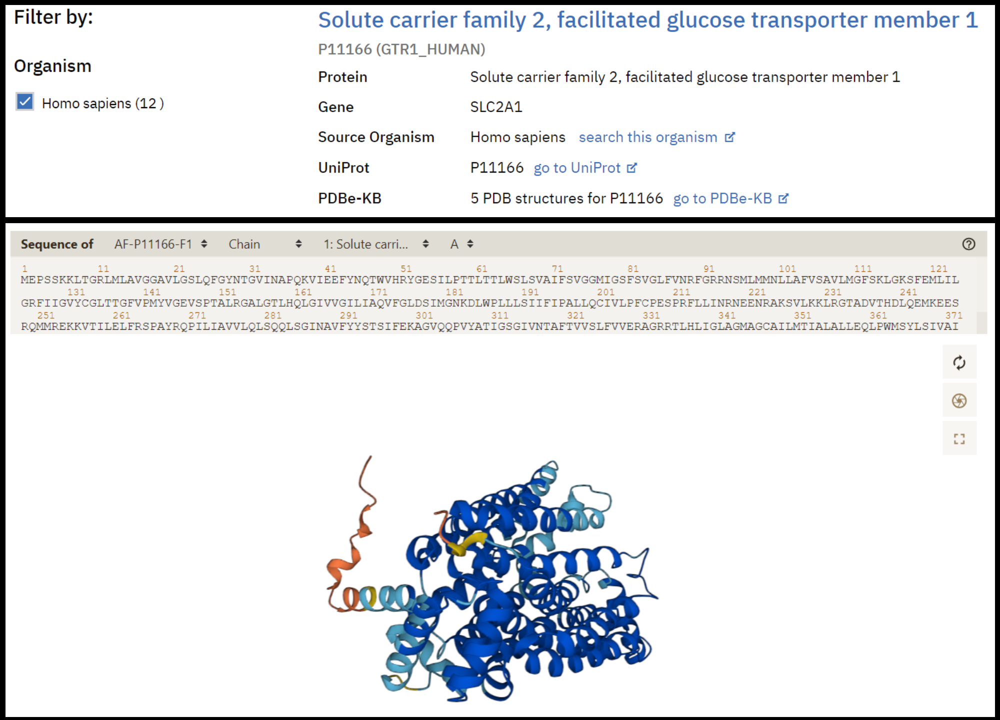
$$\dot{q}_3 = \dot{q}_4 = \dot{q}_5 = \dot{q}_6 = 0 \quad \text{and} \quad \dot{q}_1 = -\dot{q}_2 = v$$

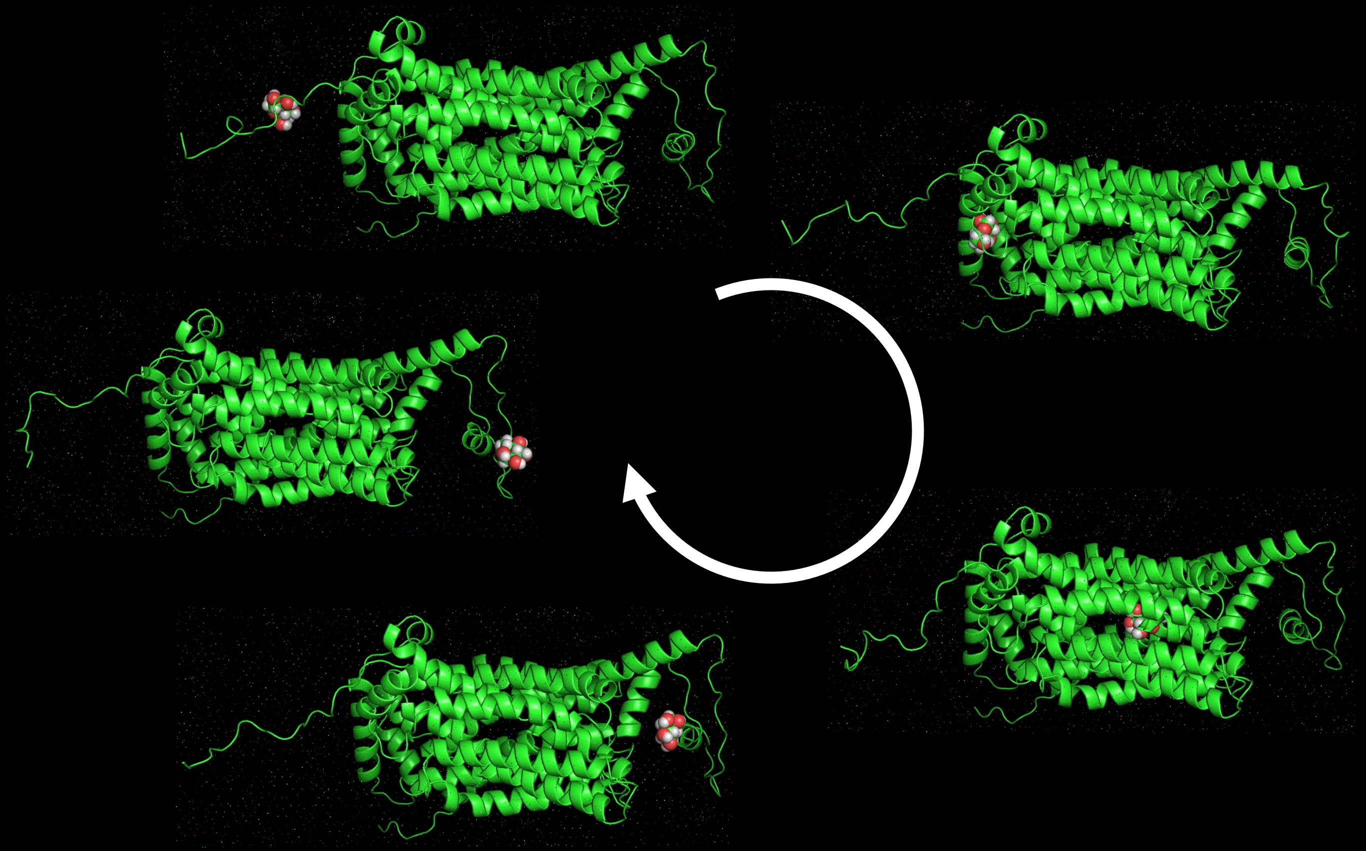
$$v = \left(\left(k_1^f k_2^f k_3^f k_4^f q^{A_o} - k_1^r k_2^r k_3^r k_4^r q^{A_i}\right) E_{tot}\right) / \{ k_1^f k_3^f k_4^f + k_1^f k_3^f k_2^r + k_1^f k_4^f k_3^r + k_1^f k_2^r k_3^r + k_3^f k_2^r k_4^r + k_2^r k_3^r k_4^r$$
$$+ (k_1^f k_2^f k_3^f + k_1^f k_2^f k_4^f + k_2^f k_3^f k_4^f + k_2^f k_3^f k_4^r) q^{A_o}$$
$$+ (k_4^f k_1^r k_3^r + k_1^r k_2^r k_3^r + k_1^r k_2^r k_4^r + k_1^r k_3^r k_4^r) q^{A_i}$$
$$+ (k_2^f k_4^f k_1^r + k_2^f k_1^r k_4^r)\, q^{A_o} q^{A_i} \}$$

or $v = E_{tot}\left(A^f q^{A_o} - A^r q^{A_i}\right) / \left(B_1 + B_2 q^{A_o} + B_3 q^{A_i} + B_4 q^{A_o} q^{A_i}\right)$

Molecular modeling: SLC2A1 (GLUT1)

SLC2A1 structure from AlphaFold





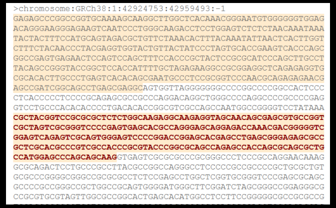
Molecular computations by Sina Safaei.

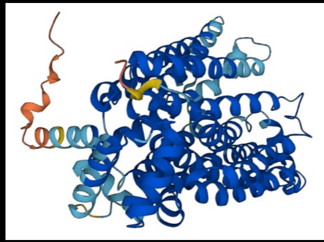
Kastner J, Thiel W. Bridging the gap between thermodynamic integration and umbrella sampling provides a novel analysis method: "Umbrella integration". *J Chem Phys* 2005, 123:144104(1–5).

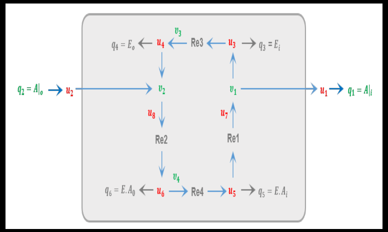
SLC transporters: 458 genes in 65 gene families, 20 BG templates

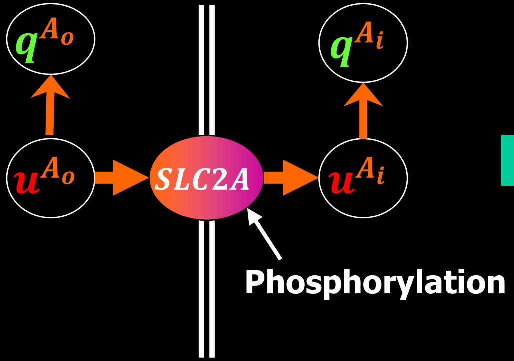
Genetic sequence | **Protein structure** | **Bond graph model** | **Component of cell model** | ***Physiome* journal**

(Umbrella sampling)







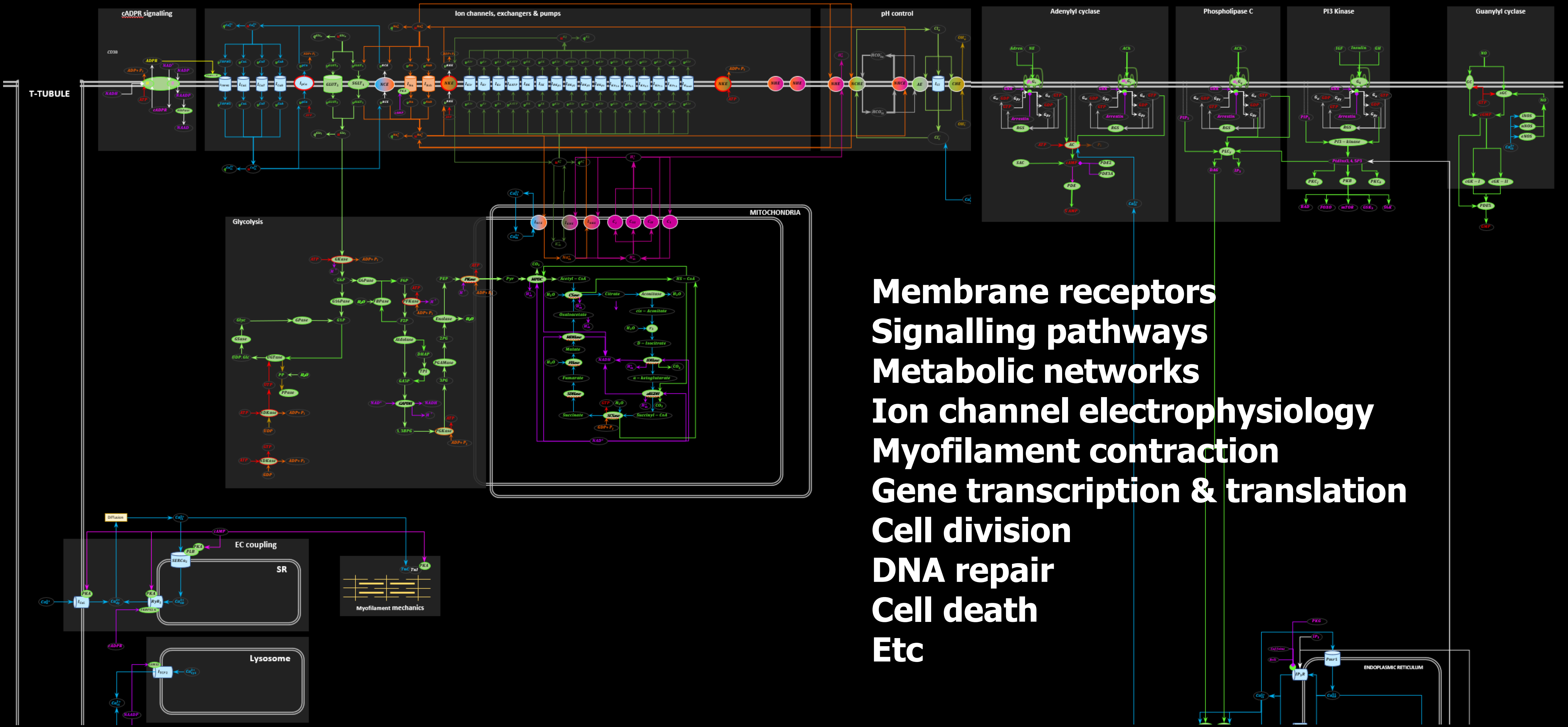


HUGO | **AlphaFold** | **PMR** | **PMR** | ***Physiome***

Molecular modelling

FAIR DO (NIDDK) project with CWRU & UCSD

A generic whole-cell BG modelling tool?



Membrane receptors
Signalling pathways
Metabolic networks
Ion channel electrophysiology
Myofilament contraction
Gene transcription & translation
Cell division
DNA repair
Cell death
Etc

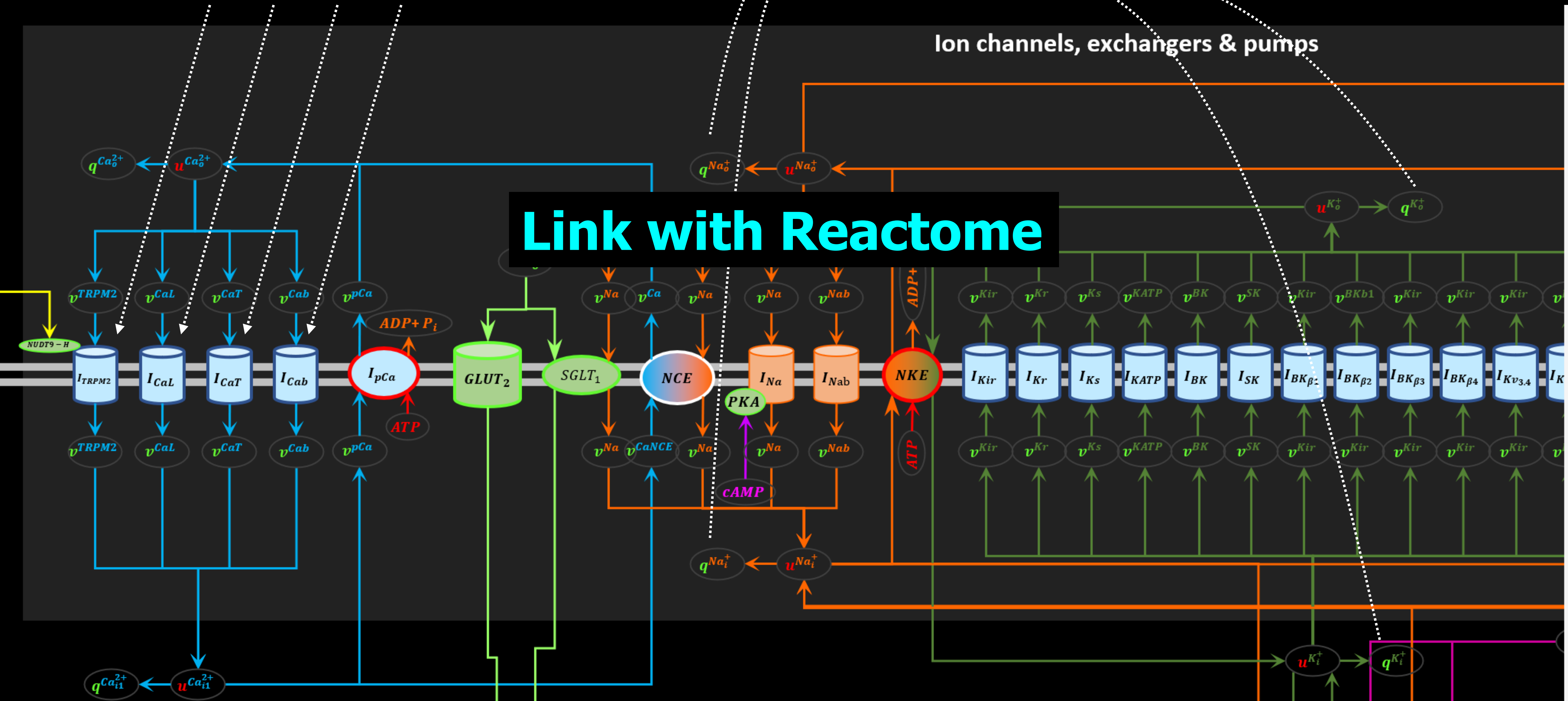
CellML model for each reaction

$$v_i = f(r_i, K_j, q_j)$$

One system equation for all solutes

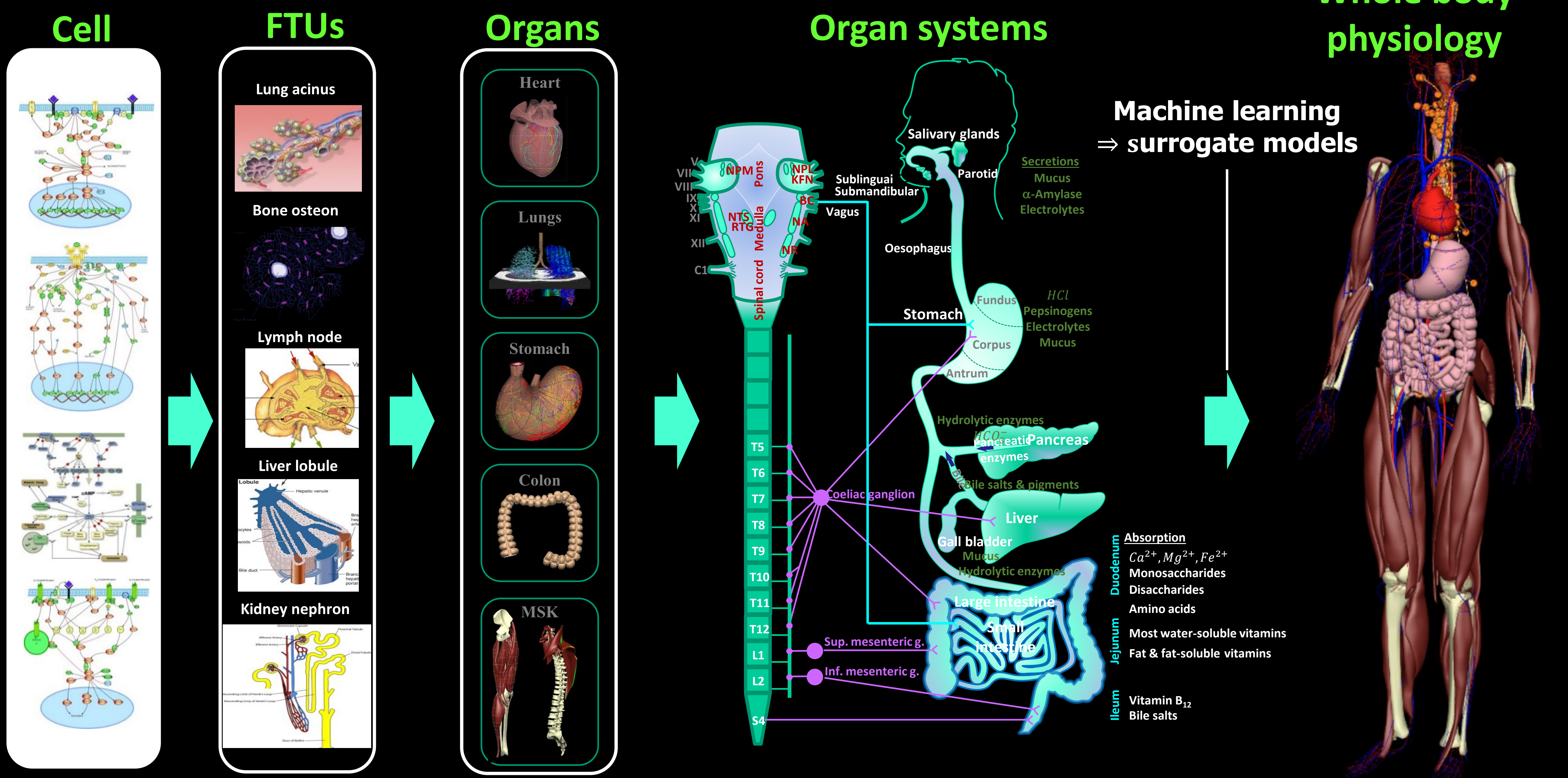
$$\left[\frac{dq_j}{dt}\right] = N \times [v_i]$$

$$\Rightarrow \frac{dq_j}{dt} = \phi(r_i, K_j, q_j)$$



The tissue/organ/whole-body scales

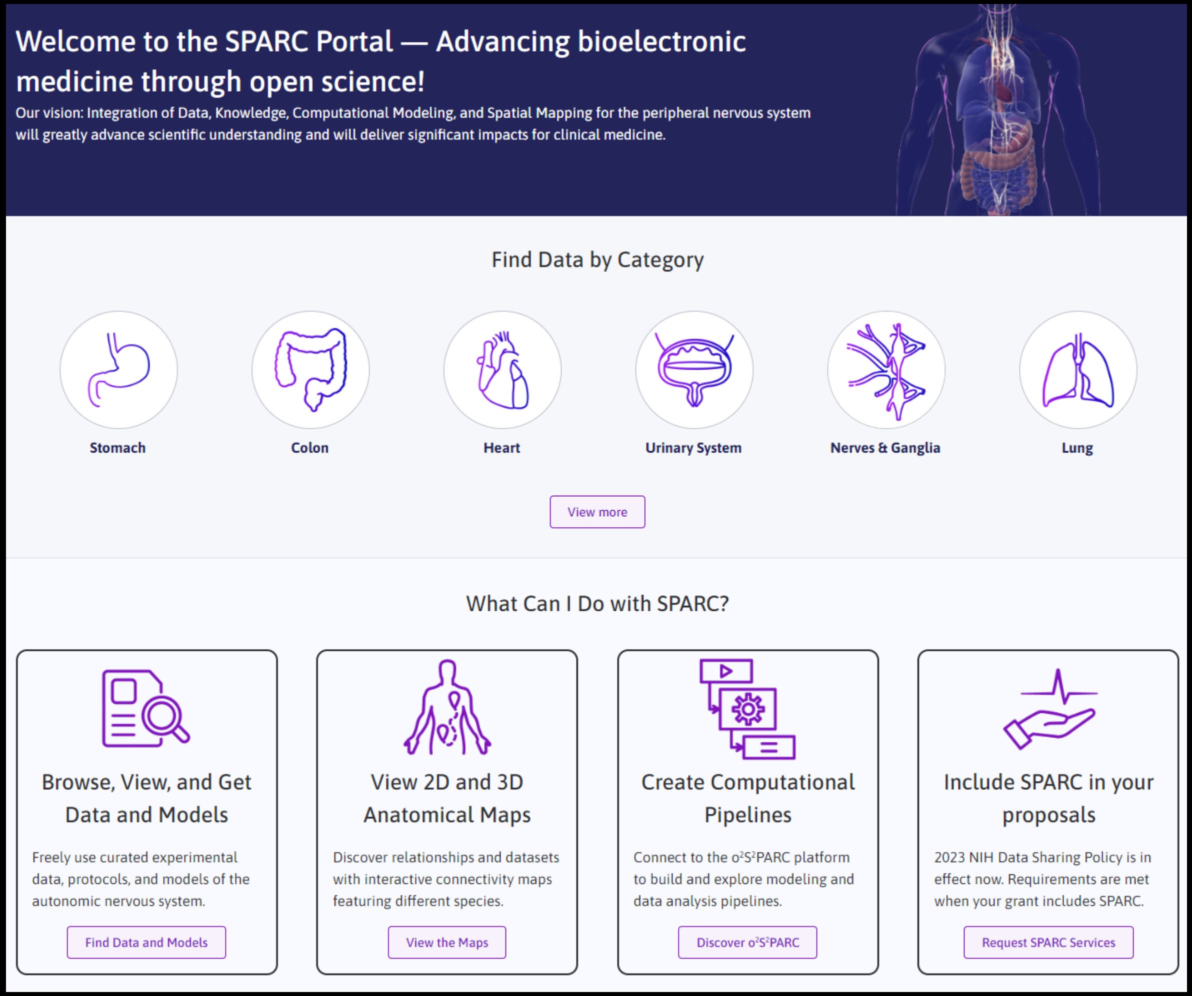
Functional Tissue Units (FTUs)

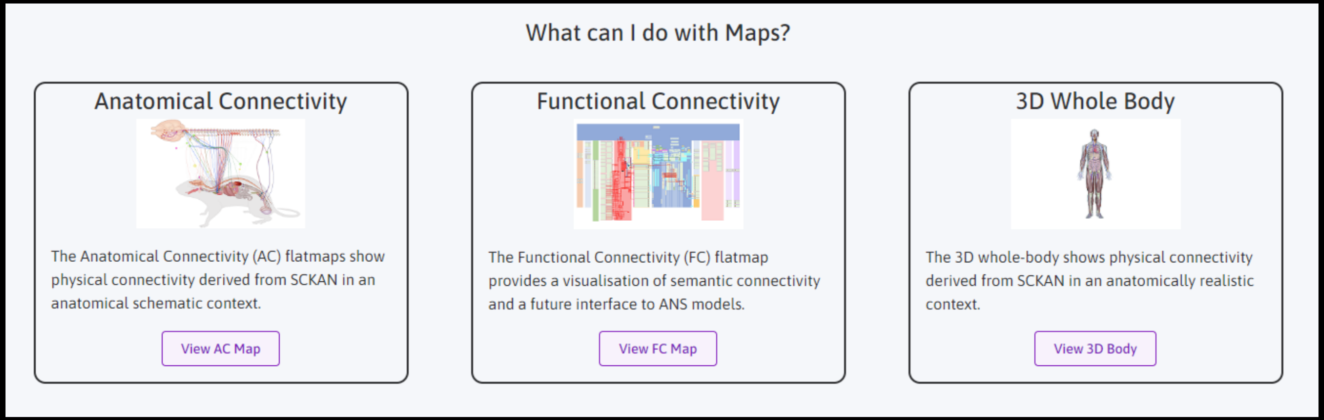


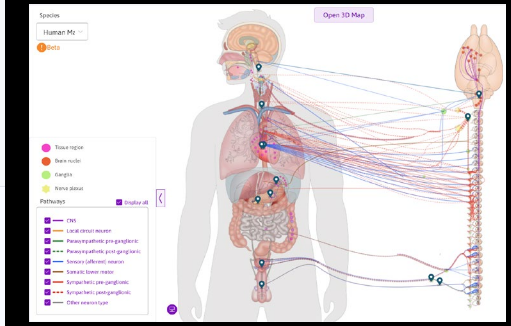
de Bono, Grenon, Baldock, Hunter (2013). **Functional tissue units** and their primary tissue motifs in multiscale physiology. *J Biomed Semantics*, *4*(1), 22 doi:10.1186/2041-1480-4-22

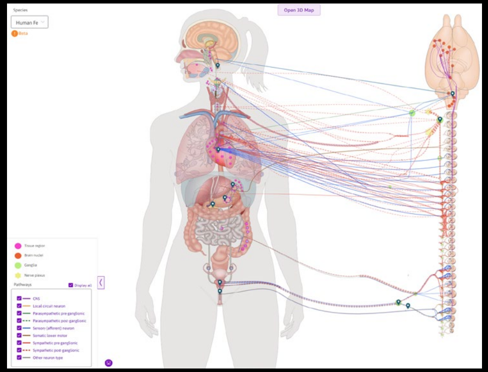
Neural connectivity: The NIH SPARC project

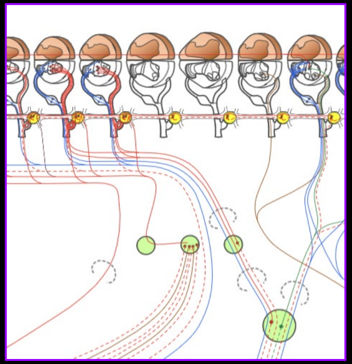
https://sparc.science

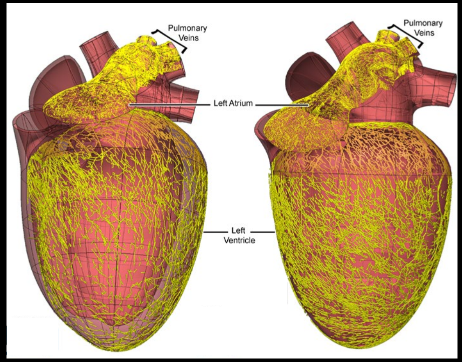




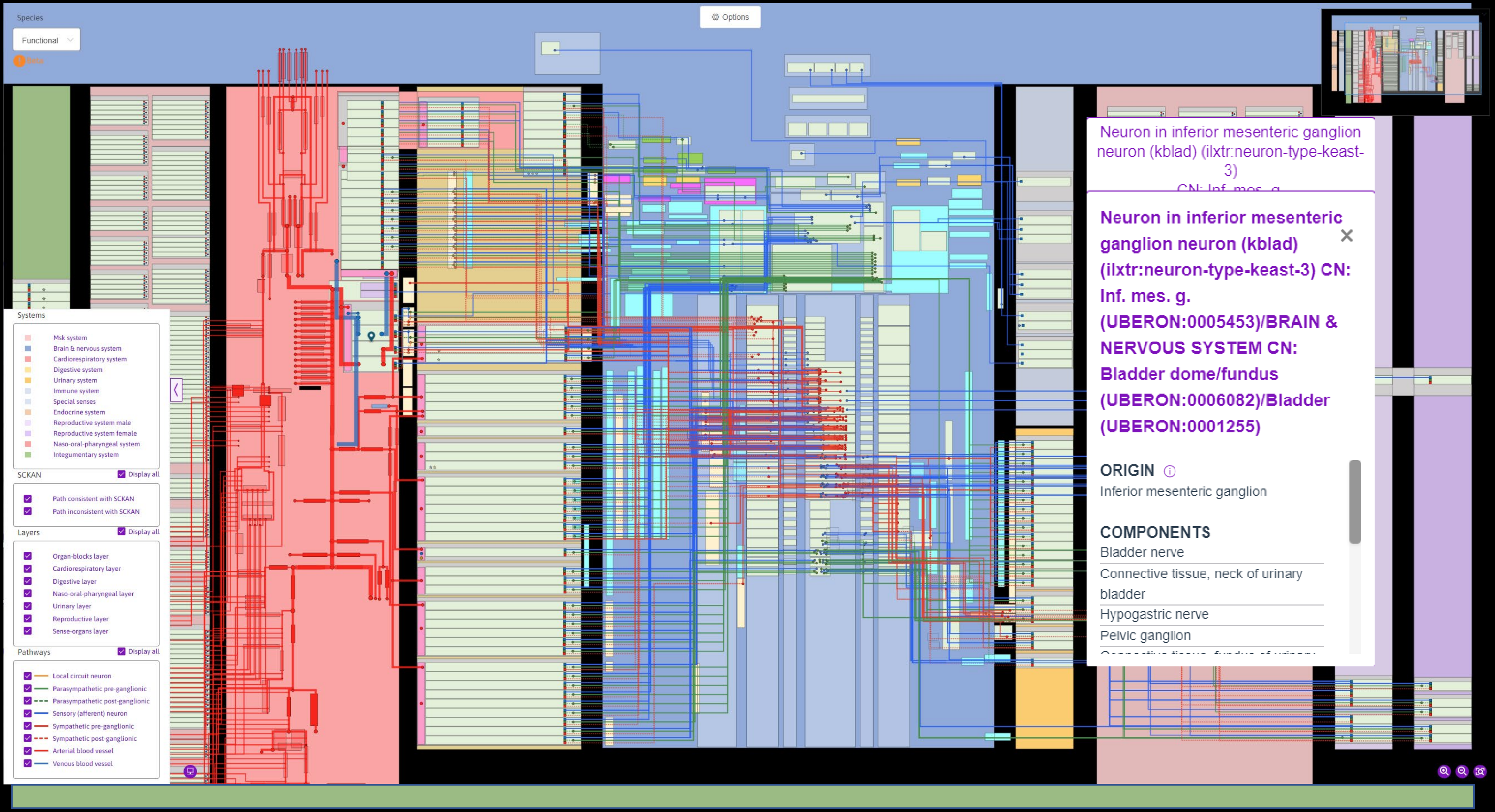




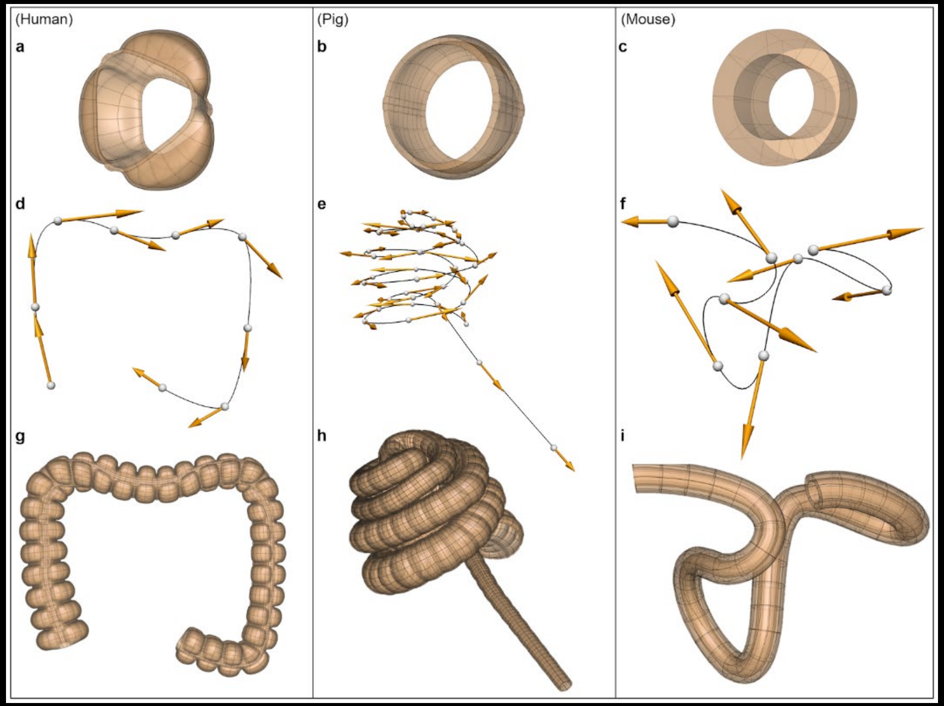


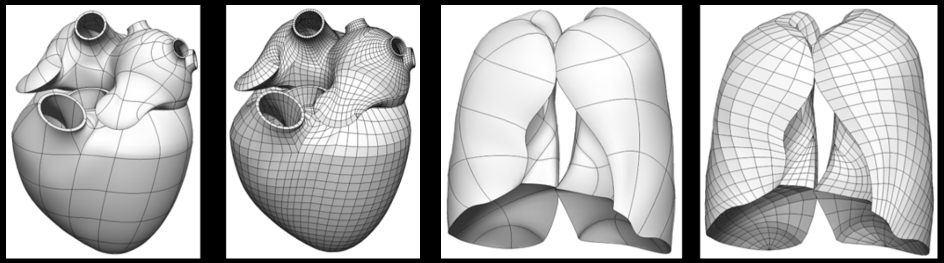


Functional Connectivity (FC) map

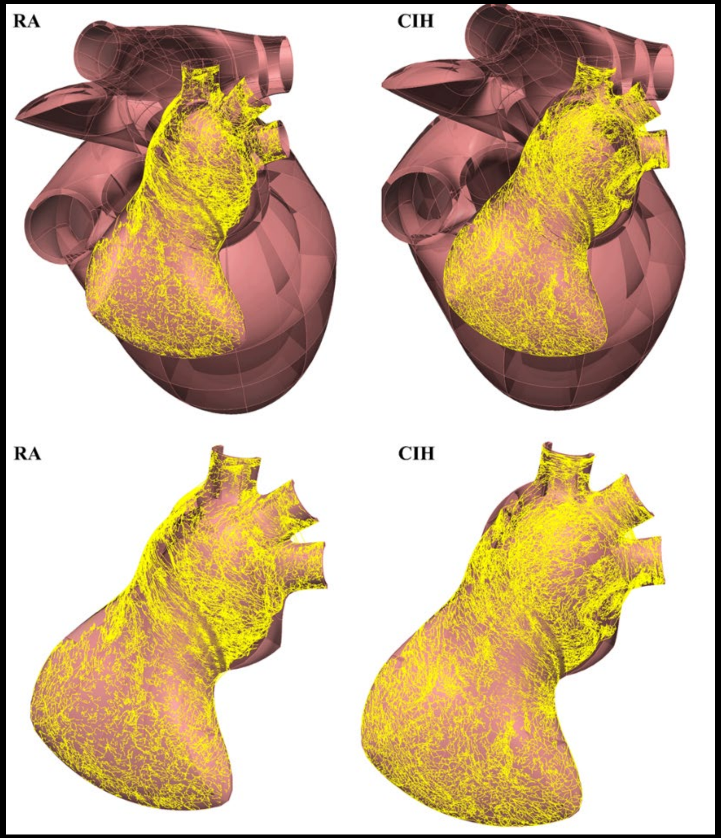


Scaffolds

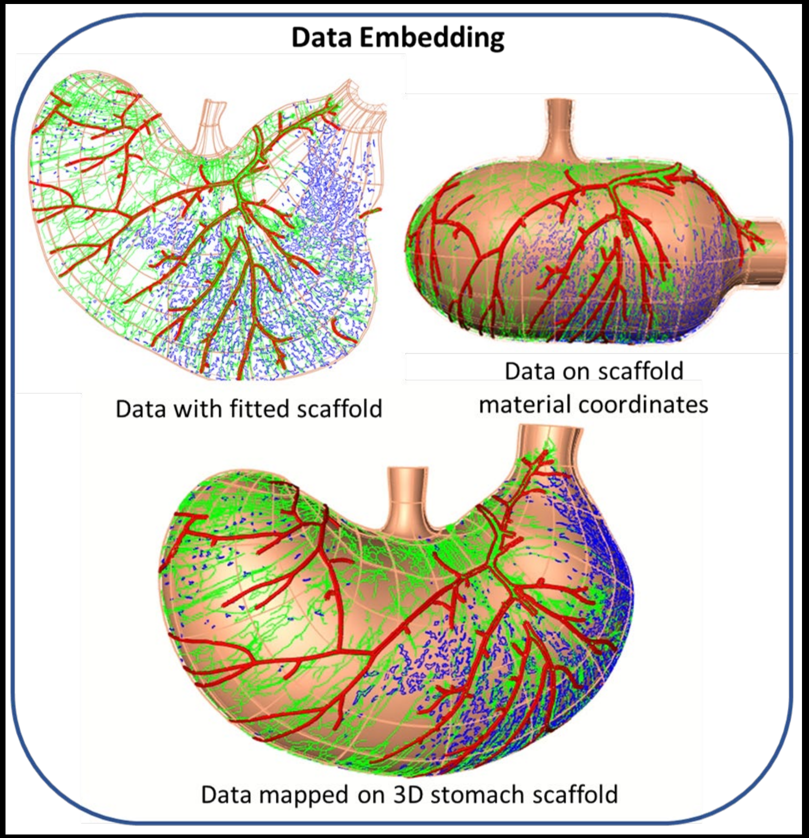




Mapping TH-IR innervation of the whole left atrium on the 3D heart scaffold



Mapping of CGRP-IR axon innervation on mouse stomach

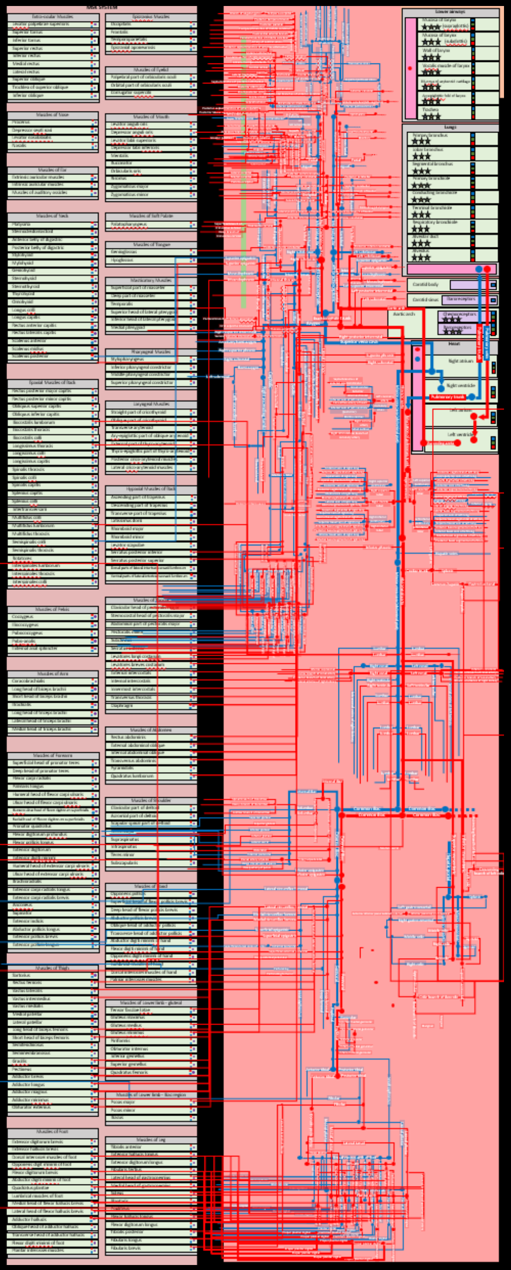


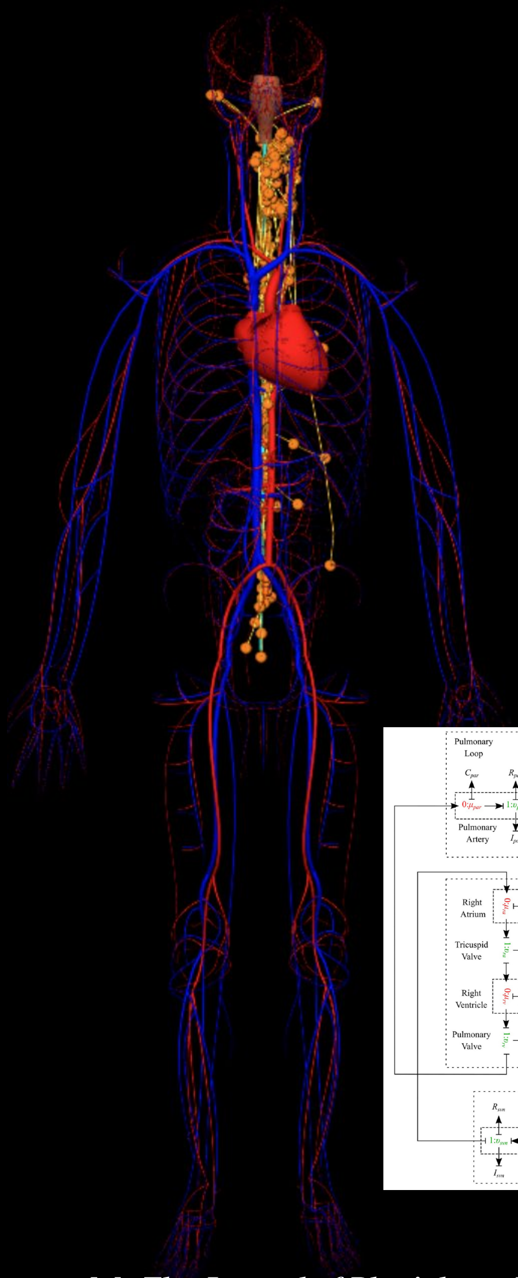
The 3D reference coordinate system for each organ is consistent across multiple species, to facilitate cross-species comparisons and the analysis of variation within a population.

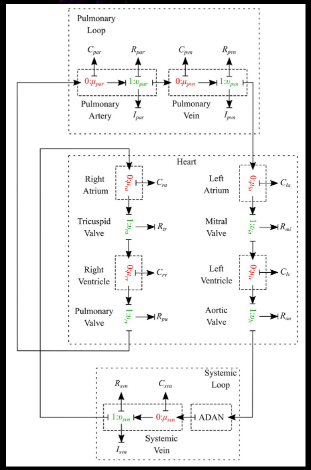
[ABI Mapping Tools — ABI Mapping Tools 0.1.0 documentation (abi-mapping-tools.readthedocs.io)](abi-mapping-tools.readthedocs.io)

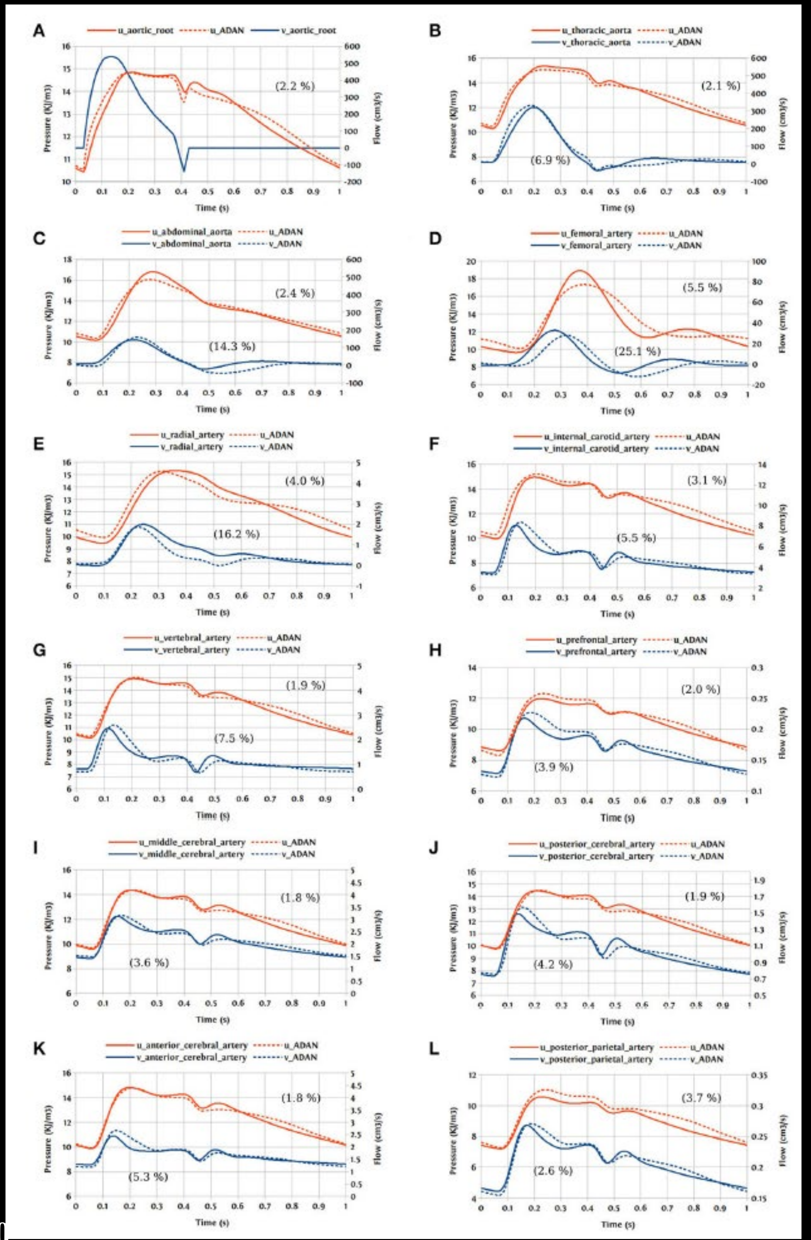
3D body scaffold

FC maps → BG network models → physiological function



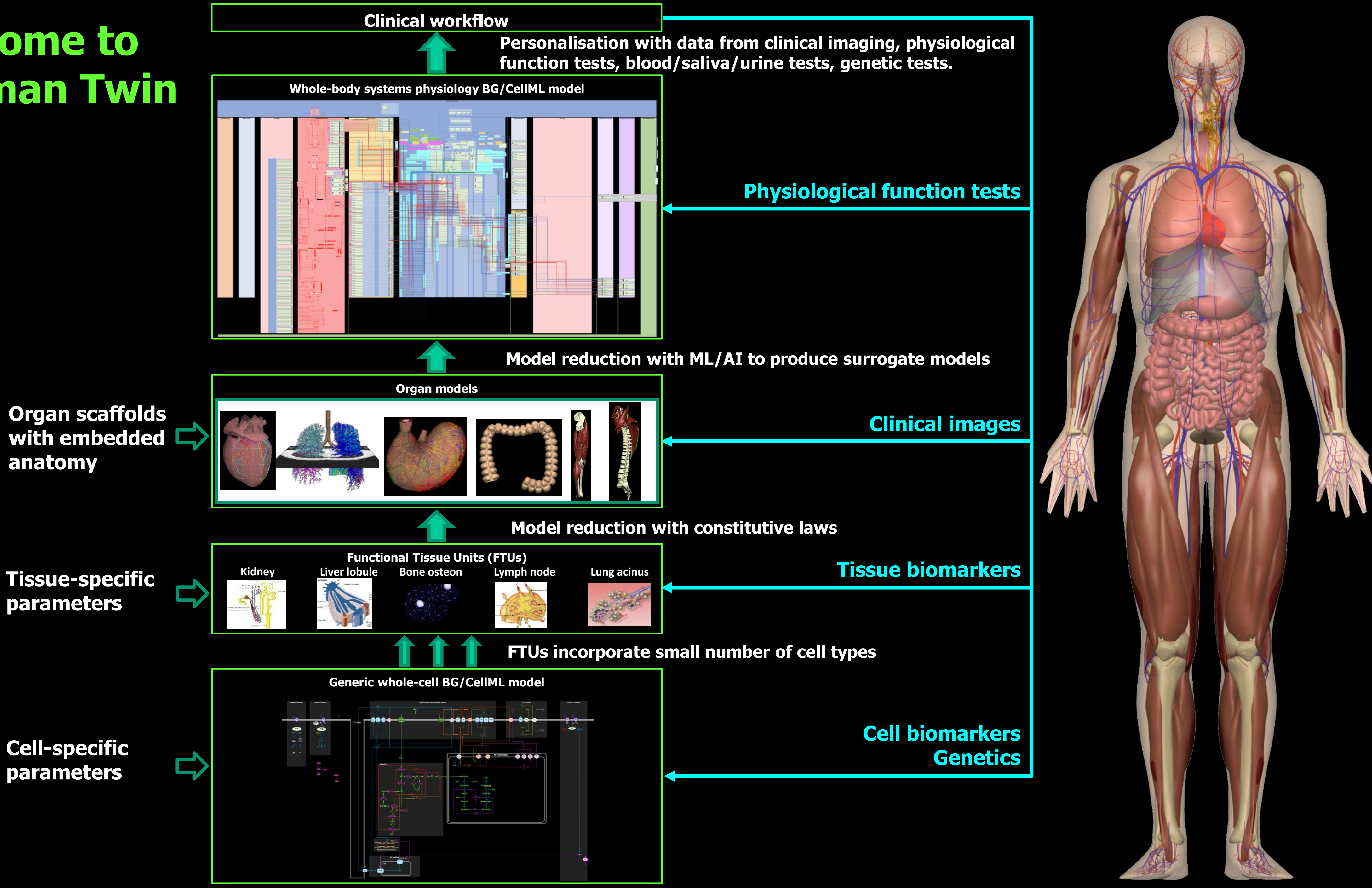




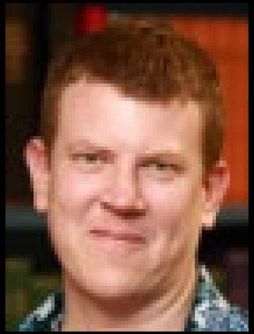


Safaei S, et al (2016). Roadmap for cardiovascular circulation model. *The Journal of Physiology*. doi:10.1113/JP272660

From Physiome to Virtual Human Twin



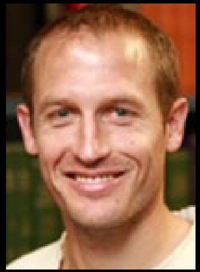
Acknowledgements



Andre
(David Nickerson)

Dave
Brooks

Richard
Christie

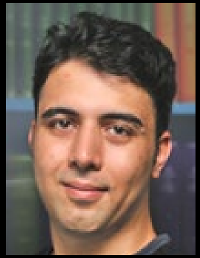


Hugh
Sorby

Mabelle
Lin

Finbar
Argus

Vickie
Shim

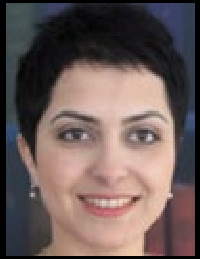


Elias
Soltani

Alan
Wu

Massoud
Alipour

Niloofar
Shahidi



Naz
Ebrahimi

Weiwei
Ai

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Thank you!