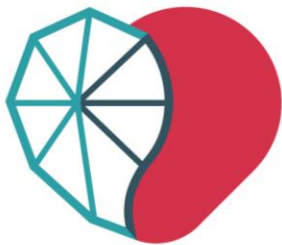


Reproducibility, reuse, and standards: interoperable model sharing.

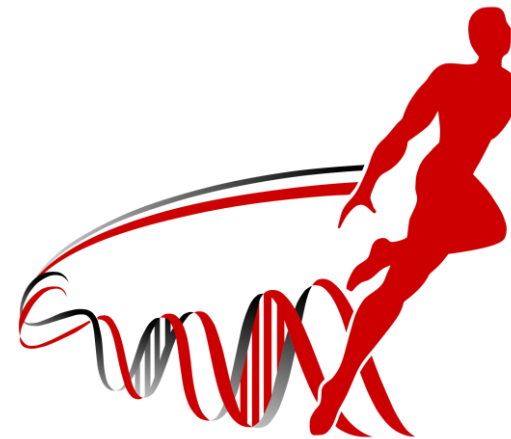
David Nickerson
Auckland Bioengineering Institute
Auckland, New Zealand



**SIM
CARDIO
TEST**

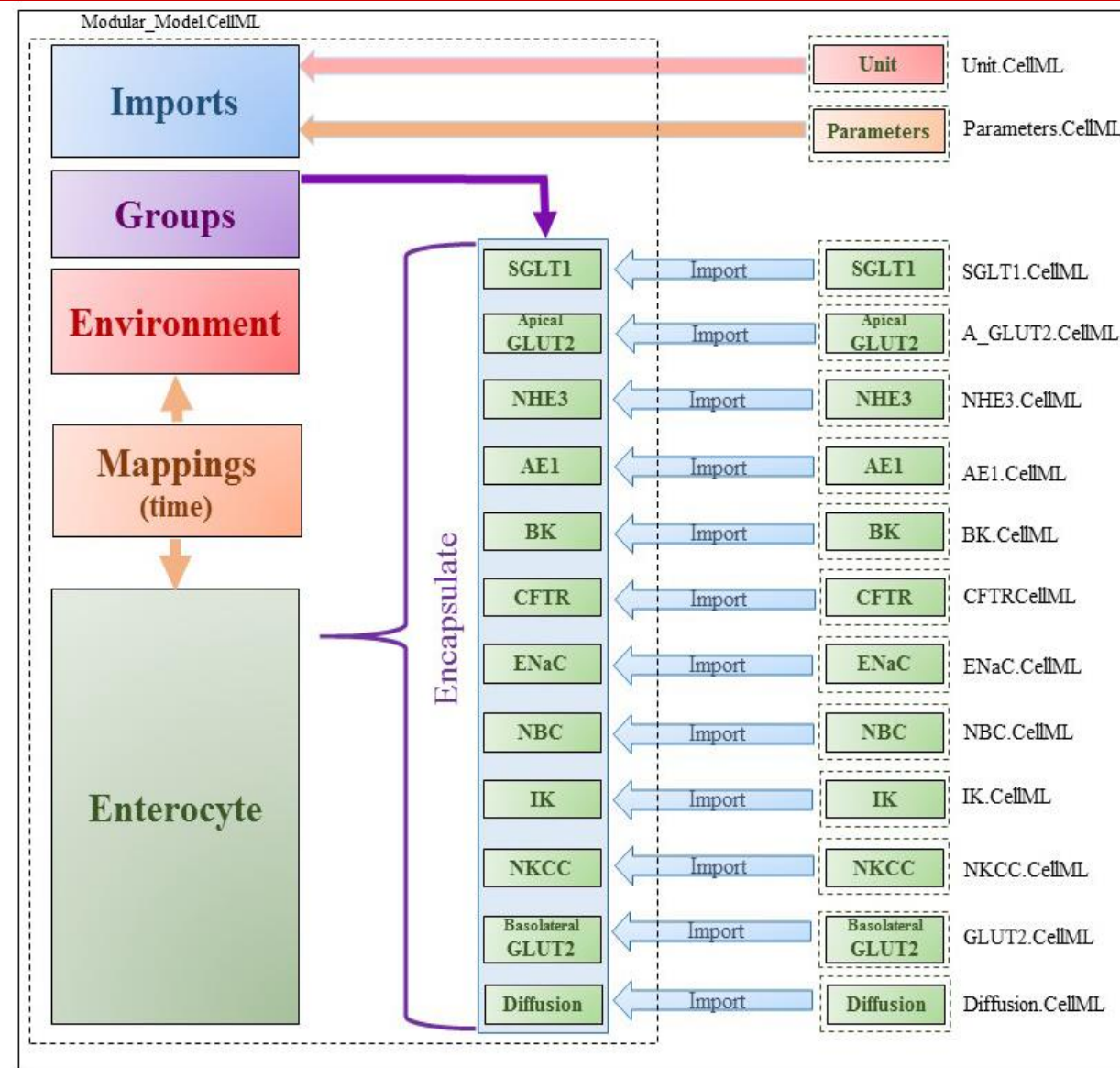
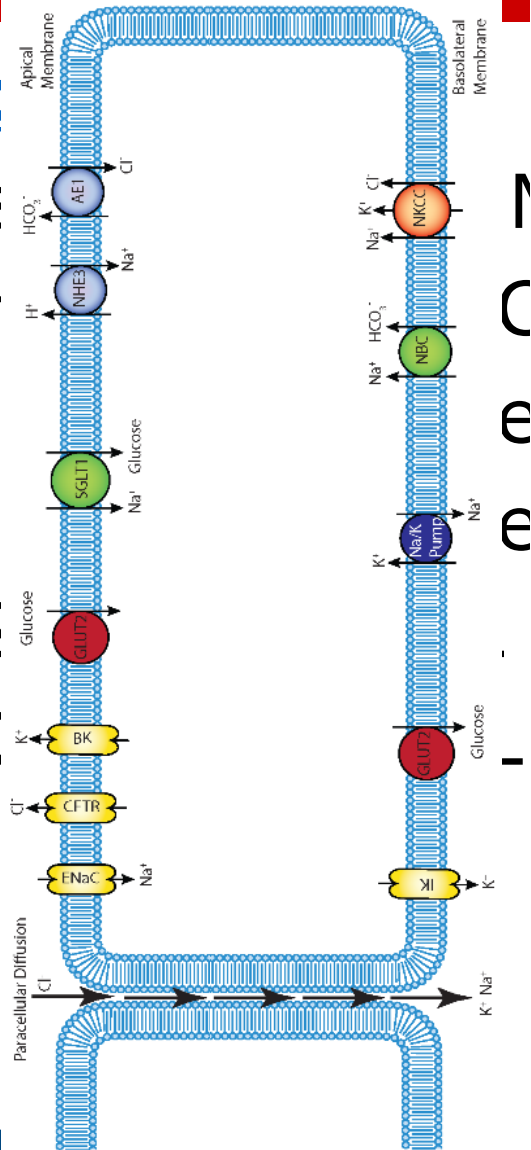
**SimCardioTest Workshop
on Standardisation**

Logo page



The evolution of CellML....

- <https://doi.org/10.17608/k6.auckland.16884799>
- August 2017
- November 2017
- February 2018
- February 2018
- May 2018
- April 2019



CellML 2.0

- Normative specification
- Only CellML allowed in the XML document
 - No metadata, annotations, cmeta:id
 - No extension elements
- XML syntax simplifications
 - Grouping replaced with only encapsulation
 - No more map_components
- Improved reusability
 - Connections no longer have direction
 - Single interface attribute controlling scope: public, private, public_and_private, none

CellML 2.0

- Units clarifications
 - No need to specify `base_units` explicitly
 - Units with offsets removed
 - “celsius” removed from built-in units
 - Component-scope unit definitions removed
- New and compulsory MathML subset
 - No more “recommended” subset to support
 - Well defined, no confusion
- Reset rules
 - Arbitrary rules to “reset” variables

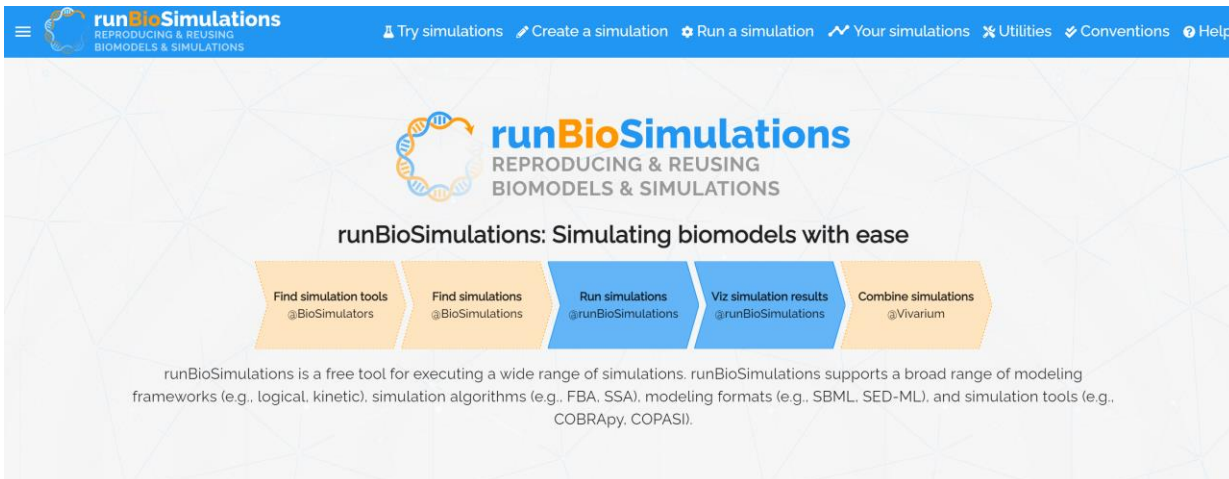
libCellML

- New C++ library to meet the needs of users
- Supporting CellML 2.0 and beyond
- Much more streamlined and maintainable
- Better suited for testing out new features and extensions to the specification
 - Allowing rapid prototyping
 - Exploring alternatives
 - Testing model exchange and reproducibility

SED-ML

- <https://sed-ml.org>
- What needs to be done to reproduce a result in a publication
 - Model manipulations/pre-processing
 - Algorithms to apply
 - Analyses to perform
 - Post-processing of resultant data
 - Presentation of results
- Designed for XML-based model encoding formats (e.g., CellML, SBML) but now “working” for other model types
 - As long as there is a way to identify things in a model

SED-ML enables...



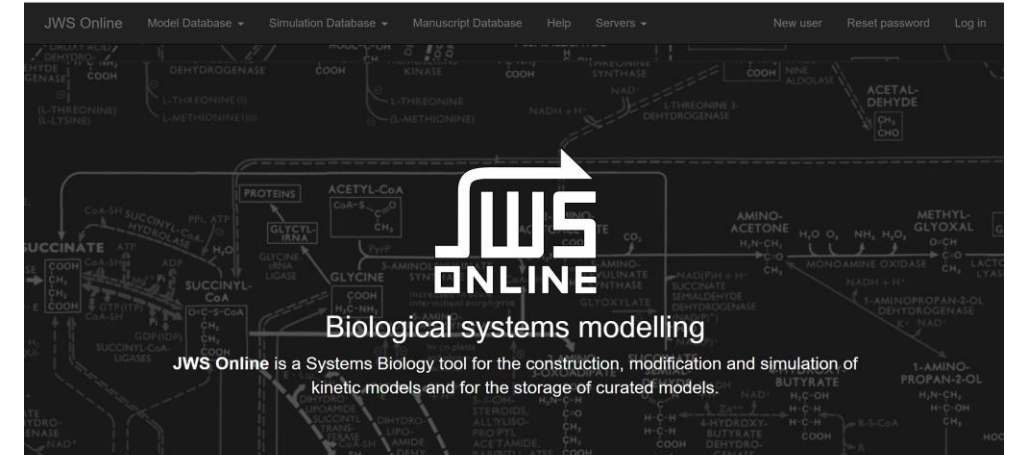
The image shows the header and main content of the runBioSimulations website. The header is blue with the logo and navigation links. The main content area has a light blue background with a geometric pattern. It features the runBioSimulations logo and a central banner with five steps: Find simulation tools, Find simulations, Run simulations, Viz simulation results, and Combine simulations. Below this, a paragraph describes the tool's capabilities.

runBioSimulations
REPRODUCING & REUSING
BIOMODELS & SIMULATIONS

runBioSimulations: Simulating biomodels with ease

Find simulation tools @BioSimulators | Find simulations @BioSimulators | Run simulations @runBioSimulations | Viz simulation results @runBioSimulations | Combine simulations @Vivarium

runBioSimulations is a free tool for executing a wide range of simulations. runBioSimulations supports a broad range of modeling frameworks (e.g., logical, kinetic), simulation algorithms (e.g., FBA, SSA), modeling formats (e.g., SBML, SED-ML), and simulation tools (e.g., COBRAPy, COPASI).



The image shows the header and main content of the JWS Online website. The header is dark with the logo and navigation links. The main content area has a dark background with a complex metabolic pathway diagram. It features the JWS Online logo and a central banner with the text 'Biological systems modelling' and 'JWS Online is a Systems Biology tool for the construction, modification and simulation of kinetic models and for the storage of curated models.'

JWS ONLINE
Biological systems modelling

JWS Online is a Systems Biology tool for the construction, modification and simulation of kinetic models and for the storage of curated models.

Helping investigators **execute** biomodeling studies


Simulate studies
Execute many formalisms & algorithms
runBioSimulations is a central application for executing simulations of a broad range of


Vis simulation results
Analyze predicted trajectories
runBioSimulations provides a simple web interface for interactively plotting the results of


Reuse published studies
Evaluate new hypotheses
By making it easier to execute simulations, runBioSimulations makes it easier to reuse

Construct your own model

With the new **JWS Online model builder** you can build a model from scratch using a simple interface. Models can be simulated directly in the **JWS Online simulator**. The builder adheres very closely to the **SBML** model specification and

Simulate models

Simulate curated kinetic models from the **JWS Online** database, or non-curated models built or uploaded to **JWS Online**. **JWS Online** supports **time evolutions, steady-state simulations, structural analysis, metabolic-control analysis,**

SBML compliant

JWS Online now uses a database implementation with a native format that mirrors the **SBML** specification. This minimises changes in SBML structure during the upload-edit-save cycle. **JWS Online** supports uploading and modification of

<https://run.biosimulations.org>

<http://jjj.biochem.sun.ac.za/>

You are here: [Home](#) / [Exposures](#) / [O'Hara-Rudy-CiPA-v1.0 \(2017\)](#) / O'Hara-Rudy CiPA v1.0 (2017)

Model Status

Model Structure.

The diagram illustrates the complex ion transport and signaling pathways in a cardiac myocyte. Key components include:

- Cell Membrane:** Features several ion channels and transporters: I_{Na} , I_{to} , I_{Kr} , I_{Ks} , I_{Ks} , I_{NaCa} , and I_{NaK} .
- Sarcoplasmic Reticulum (SR):** Contains $NaCa_2^+$, Ca_2^+ , $CaNa^+$, and Ca_2^+ transporters. It is associated with BSR and BSL regions.
- Nucleus:** The NSR (nuclear envelope) is shown with a PLB (phospholamban) transporter. The $CSQN$ (calcium store) is located within the nucleus.
- Cytoplasm:** Contains $CMDN$ (mitochondria), $TRPN$ (transient receptor potential), MYO (myofibrils), and $CaMK$ (calcium/calmodulin-dependent kinase).
- Calcium Signaling:** Ca^{2+} is released from the SR into the cytoplasm, where it can be taken up by the nucleus or used by $CaMK$.

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SED-ML lessons

- Easy to share simple analyses
 - Analyses that all tools support
 - When tools implement things in very similar manner
- Hard to share complex analyses
 - i.e., the novel analyses that will finally get that Nature paper!
- Range of tools supporting different aspects of the “standard”
- Reproducibility within compatible tools works well
 - But hard to know which tools are compatible
- Interoperability between tools possible for experts

One solution



Registry of biosimulation tools

Find simulation tools
@BioSimulators

Find simulations
@BioSimulations

Run simulations
@runBioSimulations

Viz simulation results
@runBioSimulations

Combine simulations
@Vivarium

BioSimulators is a free **registry of biosimulation tools**. The simulators support a broad range of frameworks (e.g., logical, kinetic), simulation algorithms (e.g., FBA, SSA), and formats (e.g., BNGL, CellML, NeuroML/LEMS, SBML, Smoldyn). Many of the simulators provide Docker images that support a consistent interface that builds on SED-ML, COMBINE, and other standards. Together, BioSimulators makes it easier to execute simulations. BioSimulators is powered by several **standards** for specifications, interfaces, and images of simulators and reports of simulation results.

<https://biosimulators.org/>

<https://doi.org/10.1093/nar/gkab411>

SED-ML v2

- (current ideas)
- Clear definition of simulator capabilities
 - Common API?
- Workflow-like composition of computation tasks
 - Pre-processing of models
 - Analysis and simulation algorithms
 - Post-processing of resultant data
 - Visualisation of results
- Standard tools for interpreting the workflows
 - Serializable into traditional workflow engines, Python scripts, etc.
 - Modularity and reuse

OpenCOR

- <https://opencor.ws>
 - CellML 1.0 and 1.1 editor and simulator
 - Supports parts of SED-ML
 - Embedded Python interpreter for custom analyses
-
- libOpenCOR
 - Separate simulation core from the desktop application
 - Enable reuse of high-performance simulation module



Semantics are key



Harmonizing semantic annotations for computational models in biology

Maxwell Lewis Neal , Matthias König , David Nickerson , Göksel Mısırlı , Reza Kalbasi, Andreas Dräger , Koray Atalag, Vijayalakshmi Chellia Sharon Crook , Migu John H. Gennari, Padr Nick Juty, Chris Myers, Jacky L. Snoep, Vasun Dagmar Waltemath

DE GRUYTER

Journal of Inte

John H. Gennari*, Matthias König, Goksel Misirli, Maxwell L. Neal
David P. Nickerson and Dagmar Waltemath

OMEX metadata specification (vers

<https://doi.org/10.1515/jib-2021-0020>

Received August 7, 2021; accepted August 27, 2021; published online October 20, 2021

CORRECTED PROOF

libOmexMeta: enabling semantic annotation of models to support FAIR principles

Ciaran Welsh, David P Nickerson, Anand Rampadarath, Maxwell L Neal, Herbert M Sauro, John H Gennari

Bioinformatics, btab445, <https://doi.org/10.1093/bioinformatics/btab445>

Published: 16 June 2021 Article history ▼

<https://doi.org/10.1093/bib/bby087>
<https://doi.org/10.1515/jib-2021-0020>

<https://doi.org/10.1093/bioinformatics/btab445>
<https://github.com/sys-bio/libOmexMeta>

Standards = Reproducibility?

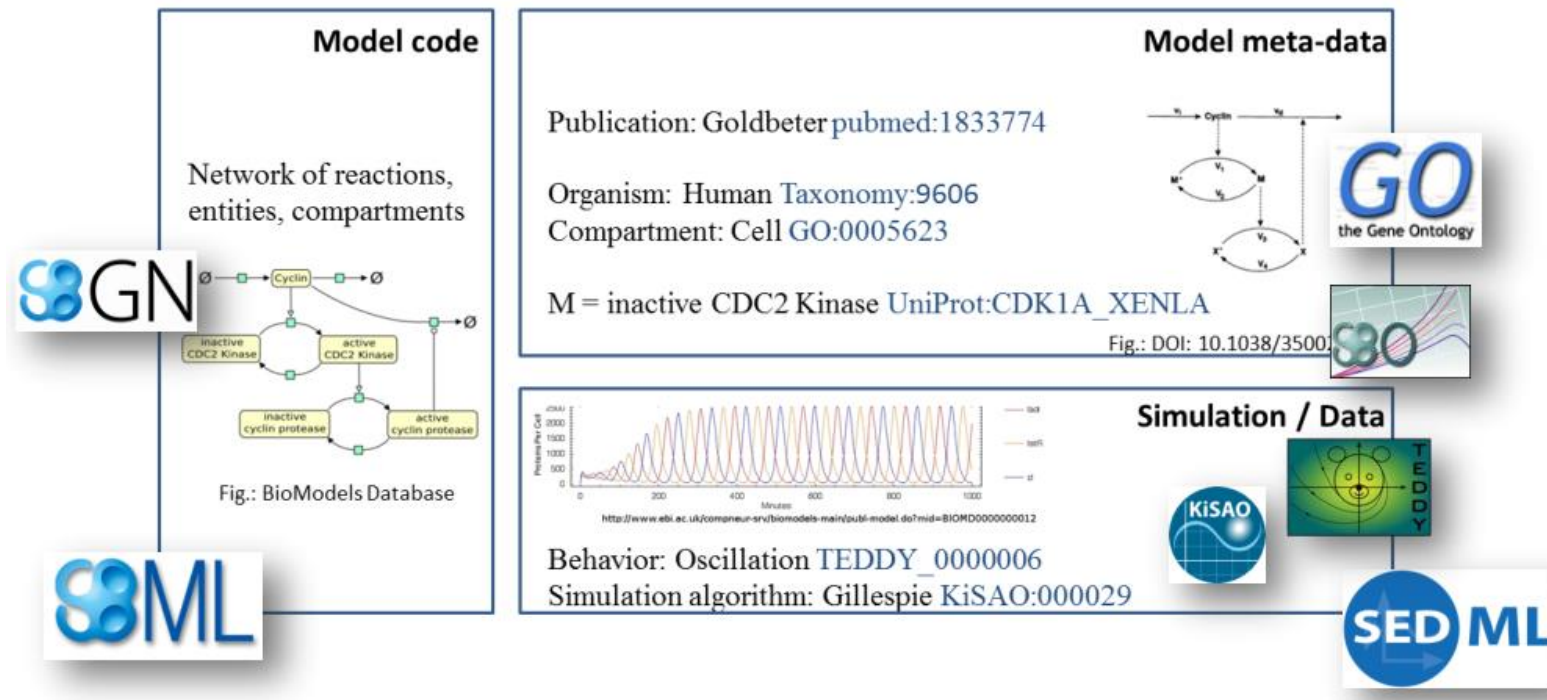
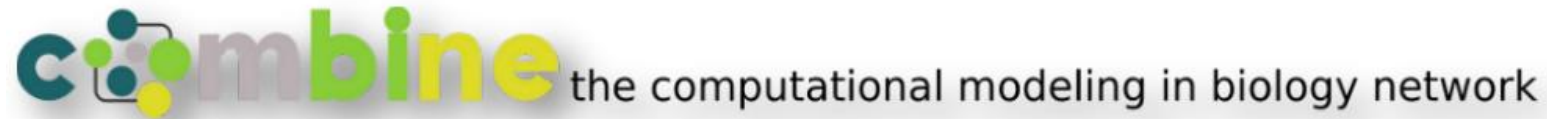


Figure from **Dagmar Waltemath**



You are here: Home / Physiome Repository

Physiome Repository

Main model listing

The list of processed model exposures (formats: 100 per page | full list), which are models that have documentation pages generated from the metadata they contain. Alternatively, you may start browsing via the categories that are listed below:

Please note: Comments about the functional status or curation status of the models within this repository are the opinions of the CellML Model Repository curators. We do our best to accurately represent these models, but please contact us if you have a query or issue with comments made on this site.

CellML models by category

- Calcium Dynamics
- Cardiovascular Circulation
- Cell Cycle
- Cell Migration
- Circadian Rhythms
- Electrophysiology
- Endocrine
- Excitation-Contraction Coupling
- Gene Regulation
- Hepatology
- Immunology
- Ion Transport
- Mechanical Constitutive Laws
- Metabolism
- Myofilament Mechanics
- Neurobiology
- pH Regulation
- PKPD
- Protein Modules
- Signal Transduction
- Synthetic Biology

FieldML models

Searching

Searching of models can be done anywhere on the site using the search box on the upper right hand corner.

Alternative search options for models in this repository:

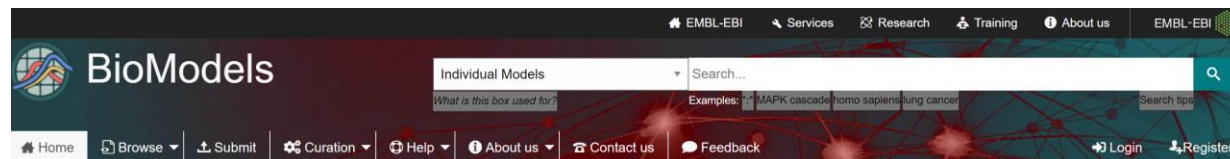
- Ontology based search engine
- Morre CellML search engine

Search Site

Navigation

Physiome Repository

Over 90% of models could not be reproduced on initial attempt based on published information



BioModels is a repository of mathematical models of biological and biomedical systems. It hosts a vast selection of existing literature-based physiologically and pharmaceutically relevant mechanistic models in standard formats. Our mission is to provide the systems modelling community with reproducible, high-quality, freely-accessible models published in the scientific literature. More information about using BioModels such as [model submission](#), [update](#), [publication](#) can be found in the [FAQ](#).



Submission /
Update



Manually Curated
1,039 models



Non-curved
1,282 models



Auto generated
833 models



GO Chart
1,132 classes



BioModels
Parameters
228,842 records

Model of The Month

August, 2021

Creemers2021 - Tumor-immune dynamics and implications on immunotherapy responses

A mechanistic ordinary differential equation model simulating tipping points in cancer-immune dynamics, which govern tumor responses and clinical outcomes to immunotherapy.

Model(s) associated with this Model of the Month:

Browse by Organism

This shows models distribution based on organisms. Click on a bubble to display models.



Find us on Twitter

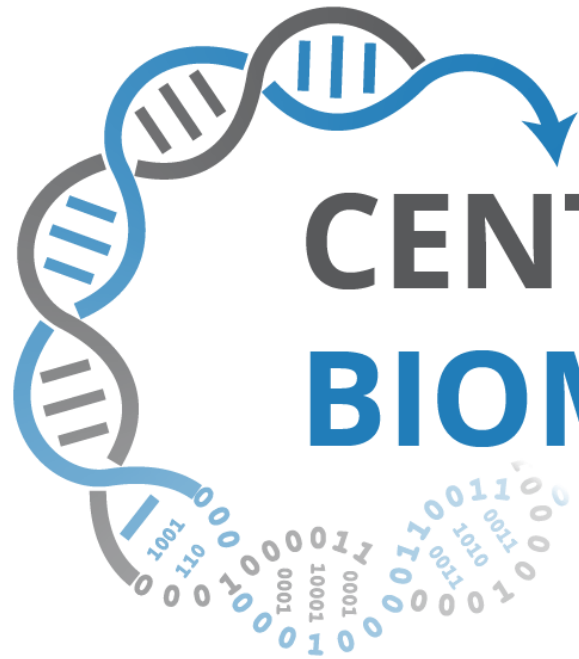
Tweets by @biomodels



The deadline for application to our Mathematics of Life 2021 virtual course is 2nd July, coming Friday! We have excellent speakers and tutors from academia and industry! Ideal for [More about this page](#)

<https://models.physiomeproject.org/>

<https://www.ebi.ac.uk/biomodels/>



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<https://reproduciblebiomodels.org/>



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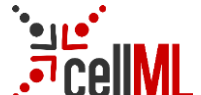
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<https://doi.org/10.17608/k6.auckland.16884799>



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Working with journals

PLOS COMPUTATIONAL BIOLOGY

EDITORIAL

Improving reproducibility in computational biology research

Jason A. Papin^{1*}, Feilim Mac Gabhann², Herbert M. Sauro³, David Nickerson^{4*},
Anand Rampadarath⁴

1 Department of Biomedical Engineering, University of Virginia, Charlottesville, Virginia, United States of America, **2** Department of Biomedical Engineering, Johns Hopkins University, Baltimore, Maryland, United States of America, **3** Department of Bioengineering, University of Washington, Seattle, Washington, United States of America, **4** Auckland Bioengineering Institute, University of Auckland, Auckland, New Zealand

* jap8r@virginia.edu (JAP); d.nickerson@auckland.ac.nz (DN)

<https://doi.org/10.1371/journal.pcbi.1007881>

Encouraging collaboration and reuse

- Needs to be easy
- Harmonising annotations
- “Rules” for how we construct models
- Reproducibility is key!
- Track and recognise contributions



PHYSIOME

<https://journal.physiomeproject.org/>



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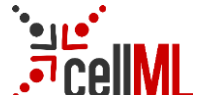
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<https://doi.org/10.17608/k6.auckland.16884799>



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What is a *Physiome* publication?



Modularity is also key

- Manage complexity
- Enable reuse

FCUs: Functional Cell Units

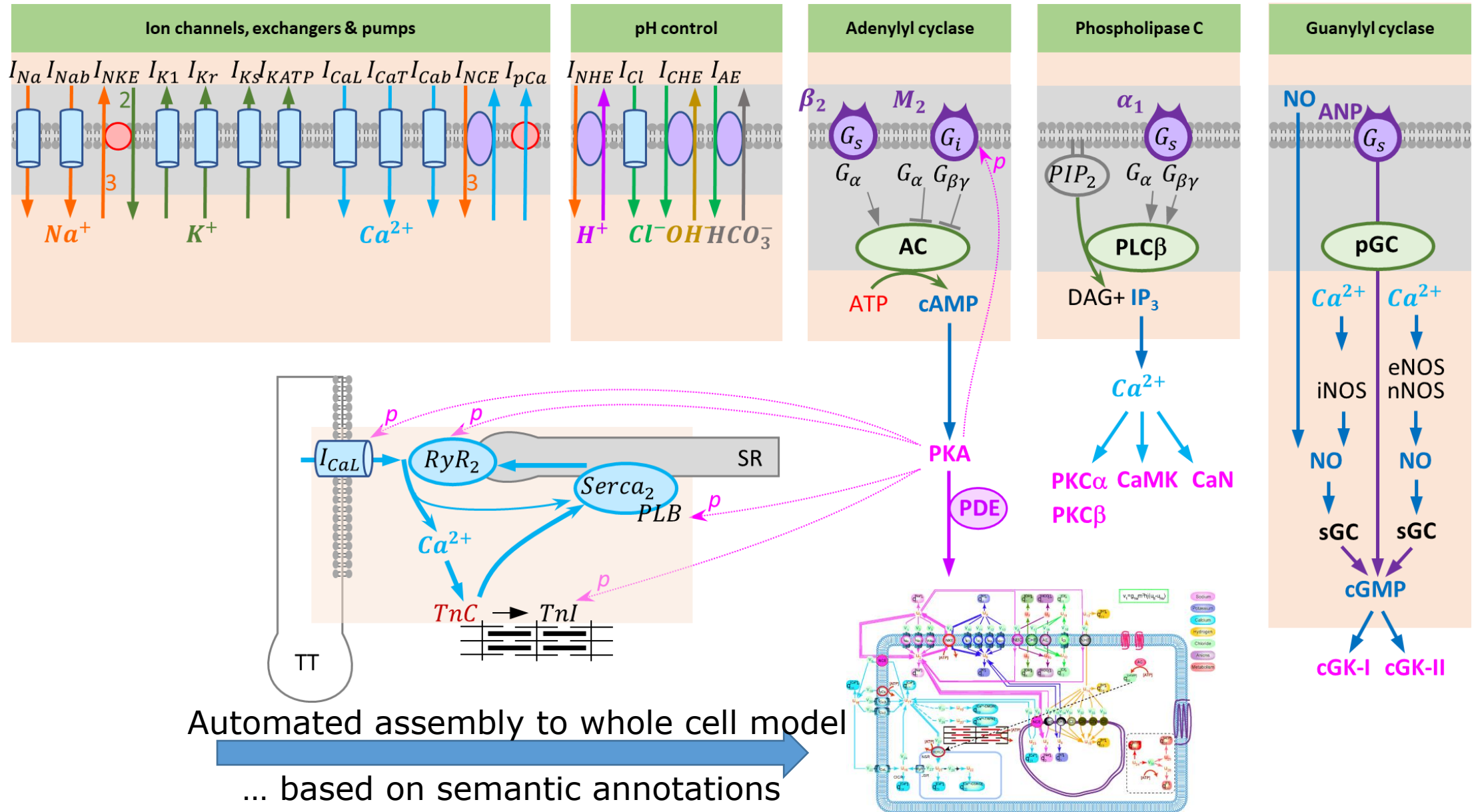
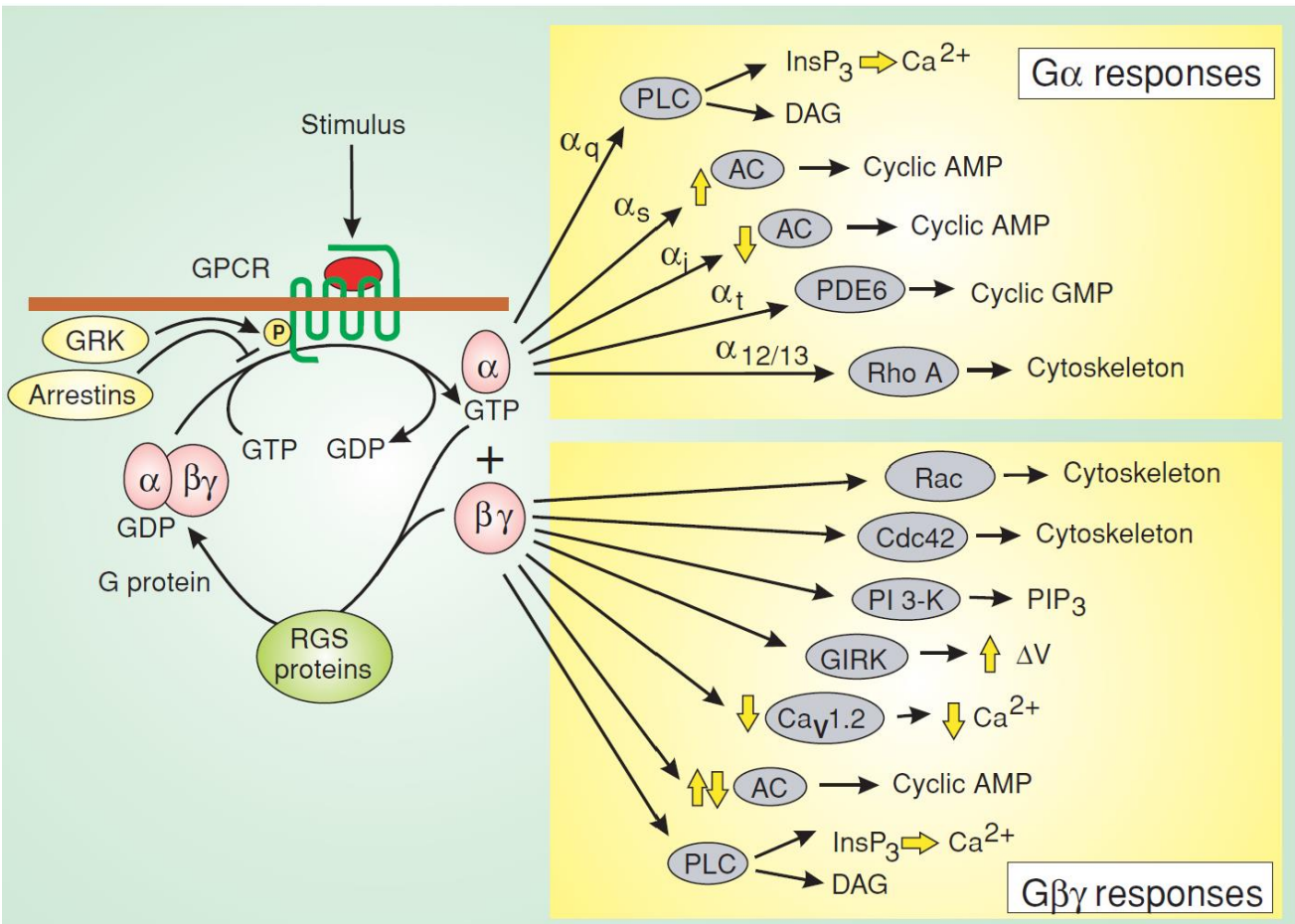
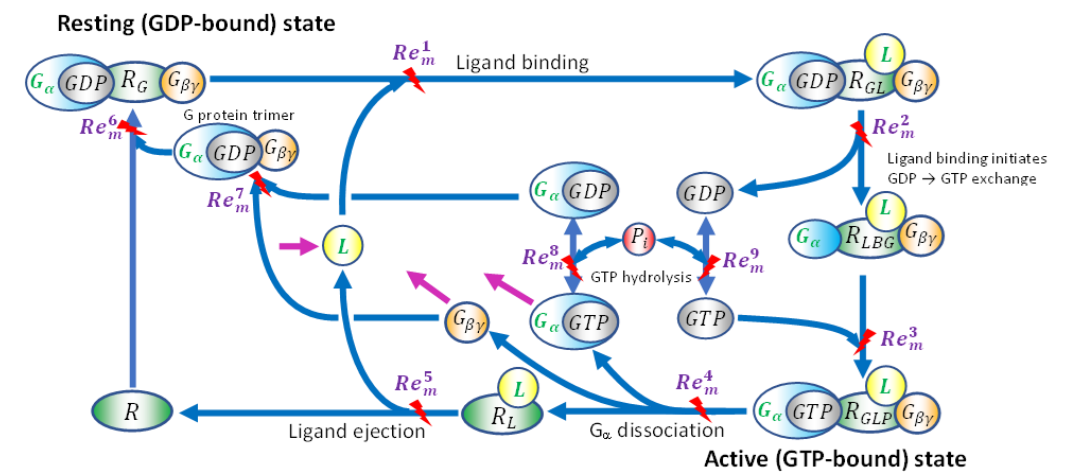


Figure from Peter Hunter

FCU Example: GPCR



(Berridge 2009)



Bond graph model

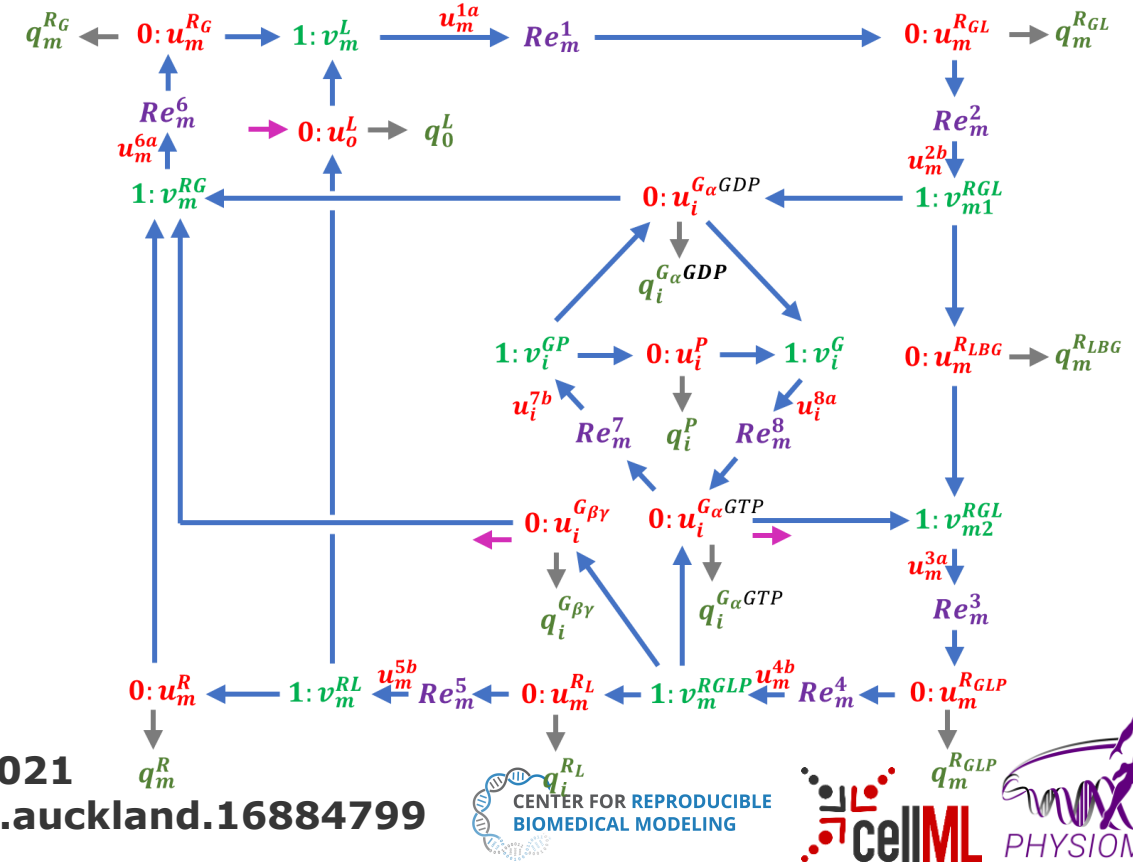


Figure from **Peter Hunter**

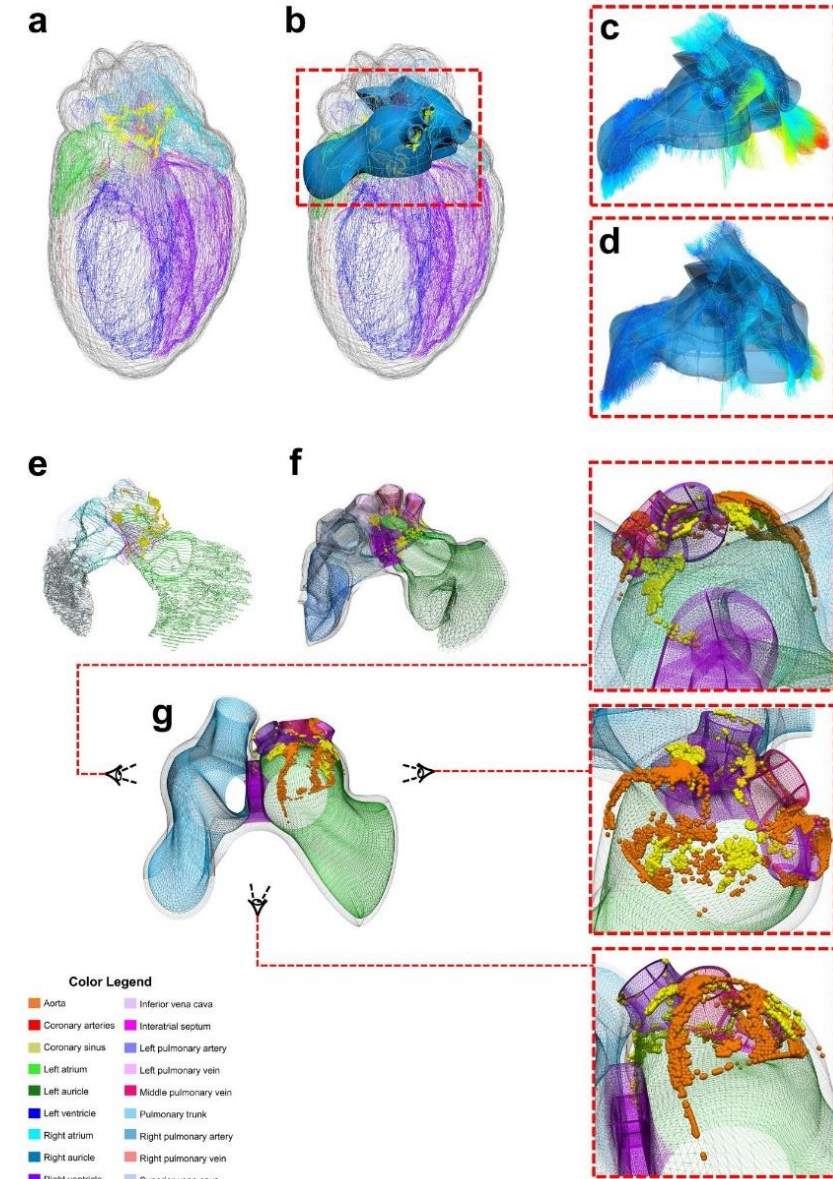
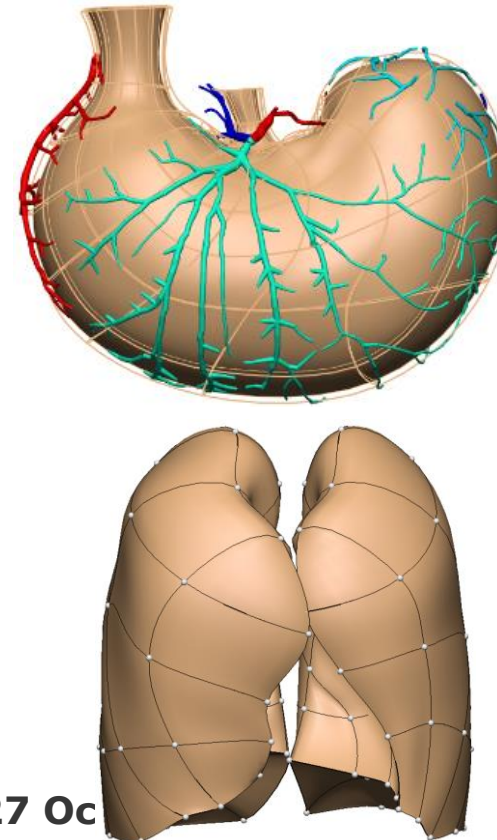
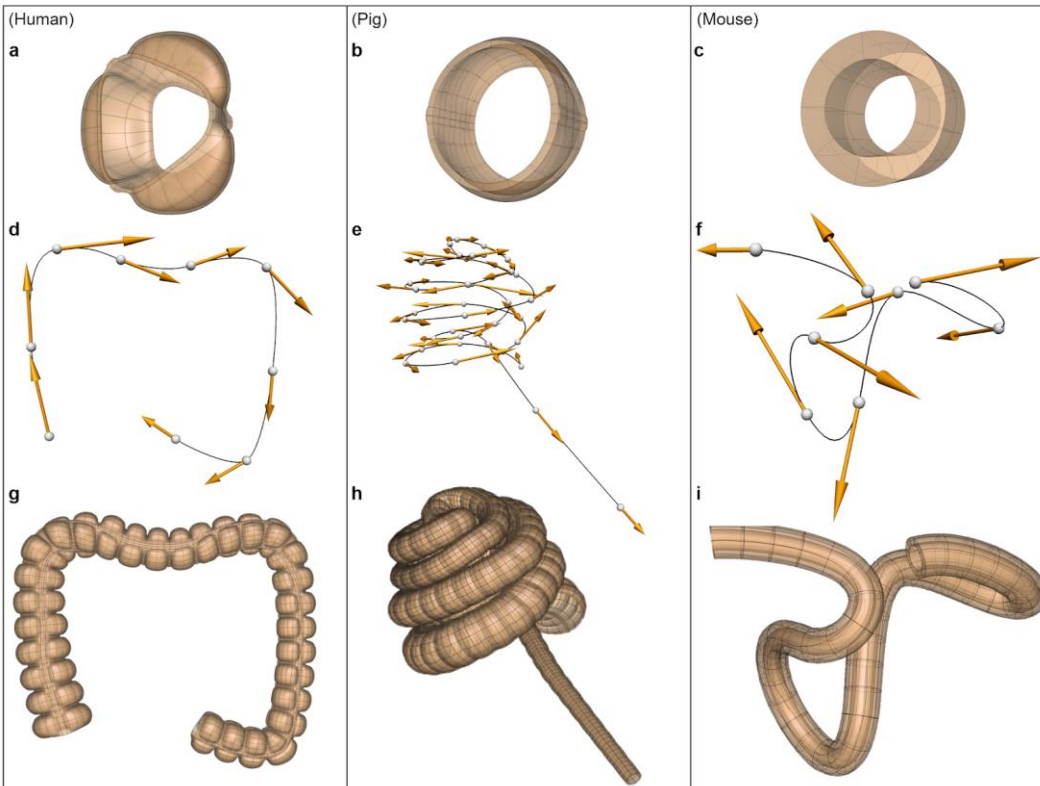
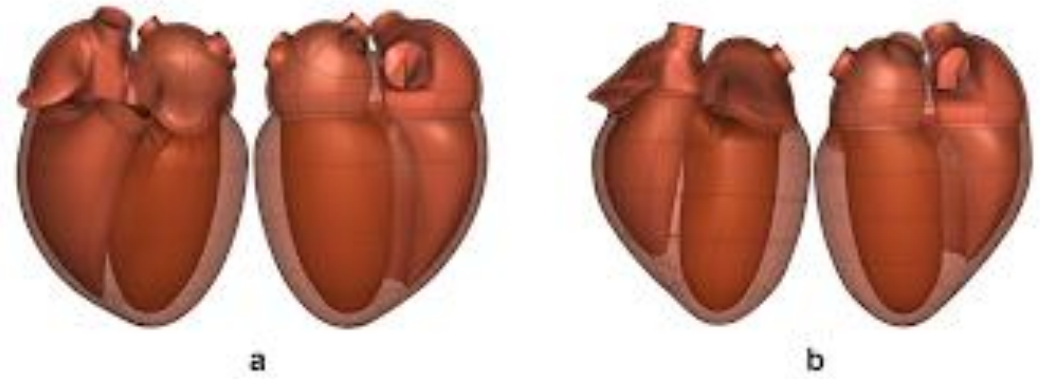
Database for physiological data and models



A semantic knowledgebase underlying all data and models: sparc.science/maps

The screenshot displays the SPARC MultiFlatmap interface. On the left, a 'Species' dropdown is set to 'Human', and a 'Pathways' section shows various neural pathways with checkboxes, all of which are checked. The central part of the interface features a detailed anatomical diagram of a human torso and head, with colored lines representing different neural pathways connecting the brain, heart, lungs, and digestive system. On the right, a search bar is present, and below it, a list of search results is shown. The first result is titled 'Sources of off-target effects for vagus nerve stimulation using the LivaNova clinical lead in swine' by Ludwig et al. (2021), with 1 sample (pig) and id: 163. The second result is 'Quantification of the relationship between rat gastric nerve fibers and enteroendocrine cells (EEC)' by Hunne et al. (2019), with 1 sample (rat) and id: 21. The third result is 'Mapping of ICN Neurons in a 3D Reconstructed Rat Heart' by Leung et al. (2019), with 1 sample (rat) and id: 37. Each result includes a thumbnail image and a 'View dataset' button.

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



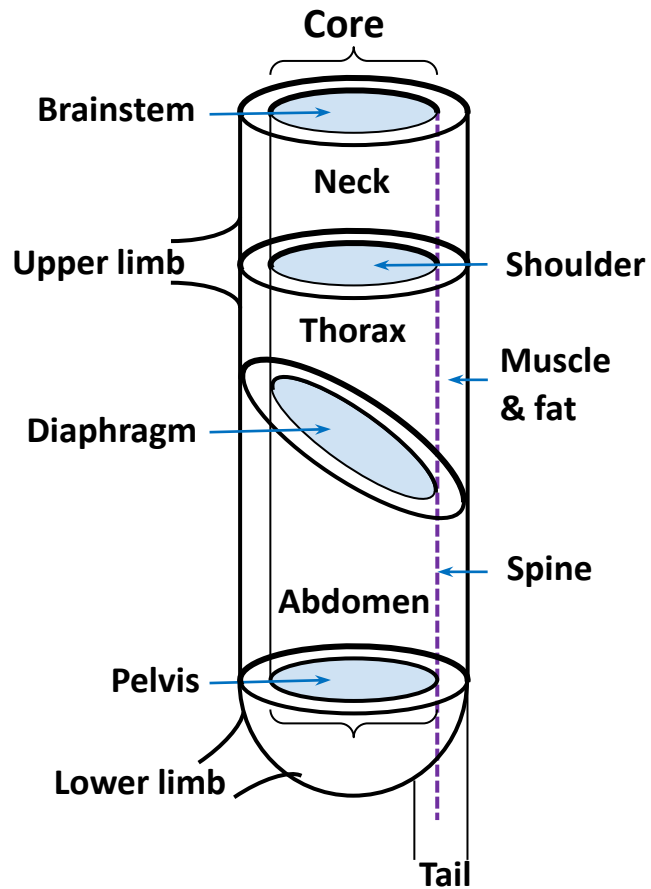
27 Oc

<https://doi.org/10.17608/k6.auckland.16884799>

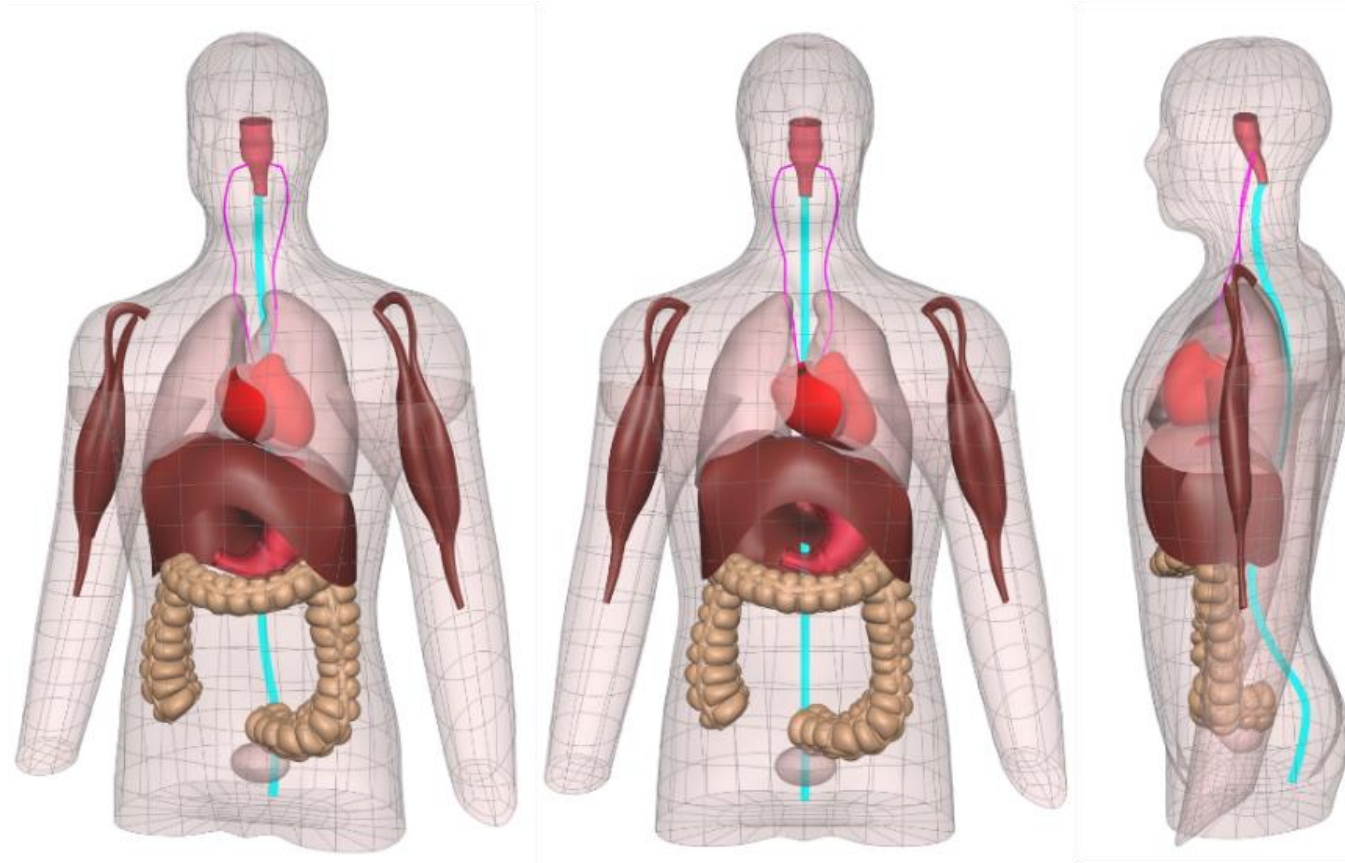
Whole body scaffolds

We are building a workflow in which organs and organ systems can be automatically assembled into the whole body reference coordinates. This will allow us to create both personalised models and population models for virtual clinical trials.

Reference coordinates



A pipeline for automated assembly



Database



27 October 2021

<https://staging.physiomeproject.org/e/653/>

<https://doi.org/10.17608/k6.auckland.16884799>

Acknowledgements

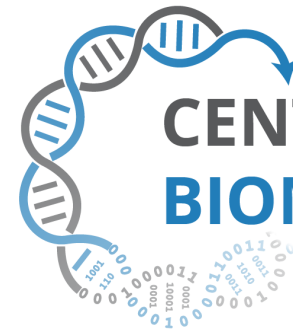
- Hugh Sorby
- Alan Garry
- Anand Rampadarath
- Tommy Yu
- Poul Nielsen
- Peter Hunter
- ABI Physiome Group



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