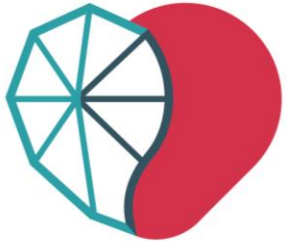
Reproducibility, reuse, and standards: interoperable model sharing.

David Nickerson
Auckland Bioengineering Institute
Auckland, New Zealand



SIM CARDIO TEST

SimCardioTest Workshop on Standardisation

27 October 2021
https://doi.org/10.17608/k6.auckland.16884799

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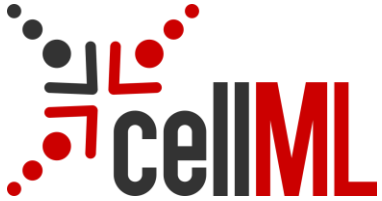
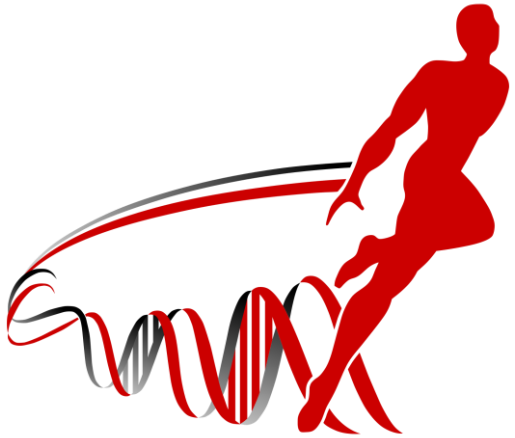
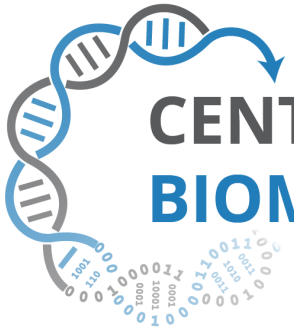
Logo page







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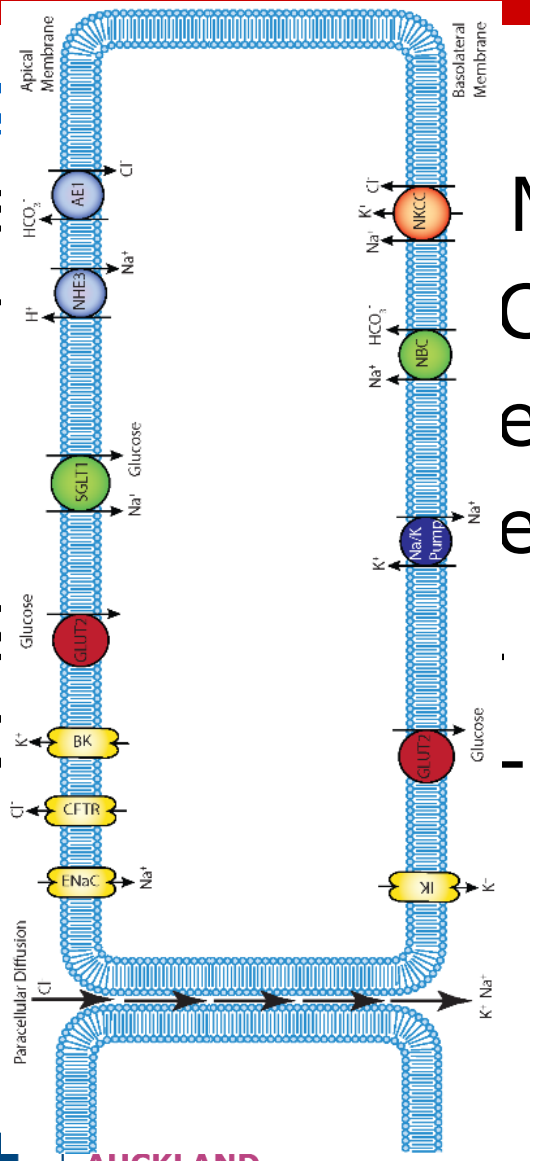
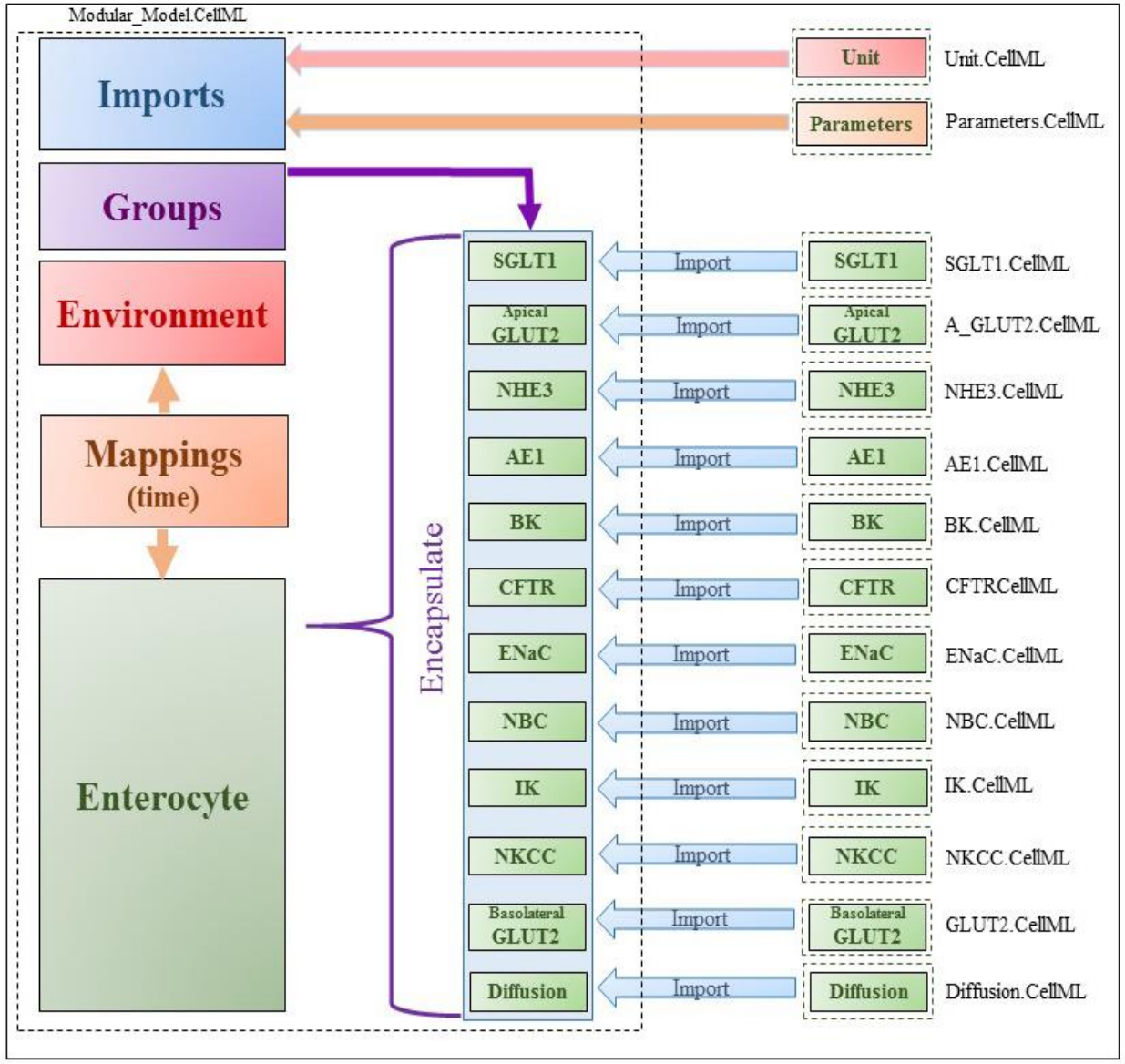
The evolution of CellML...

- https:
- Augus
- Nover
- Febru
- Febru
- May 2
- April





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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

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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

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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

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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

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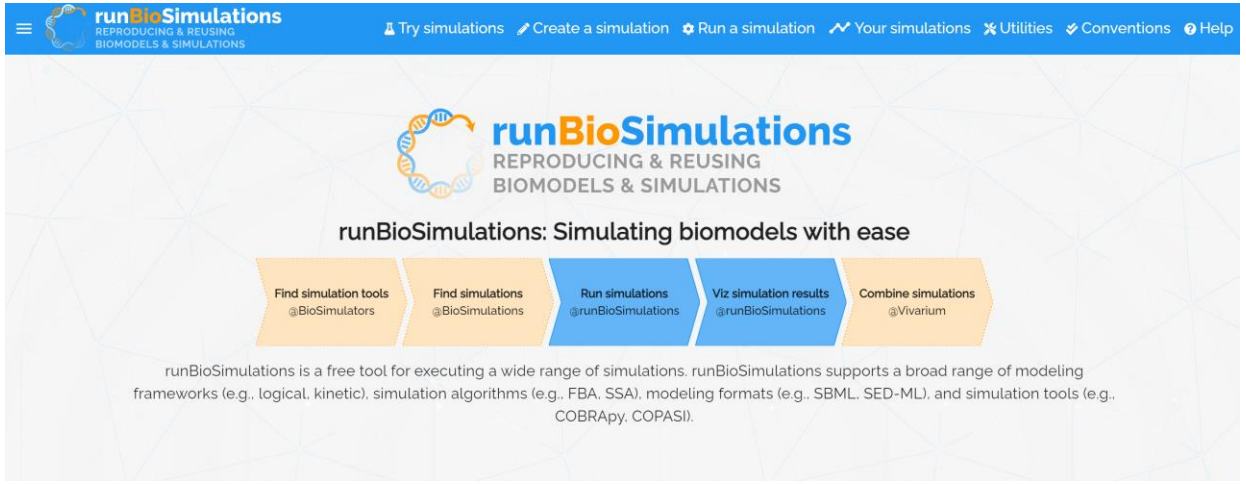
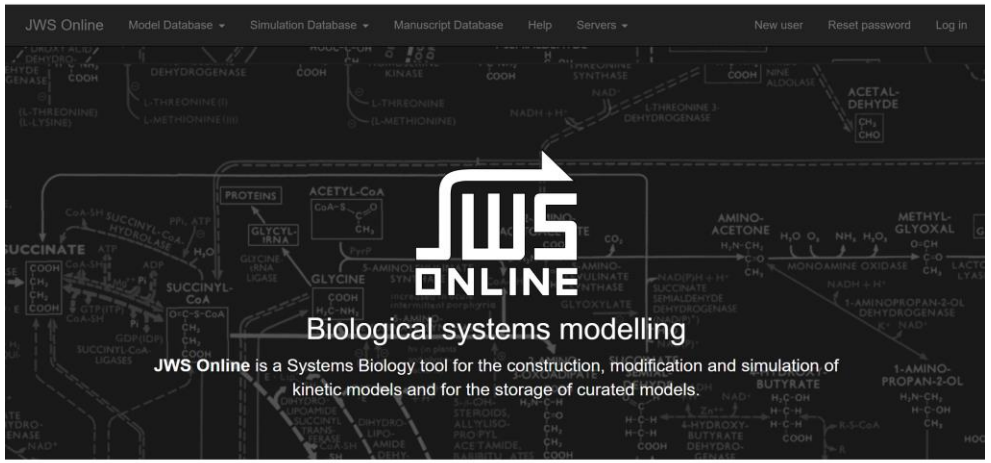
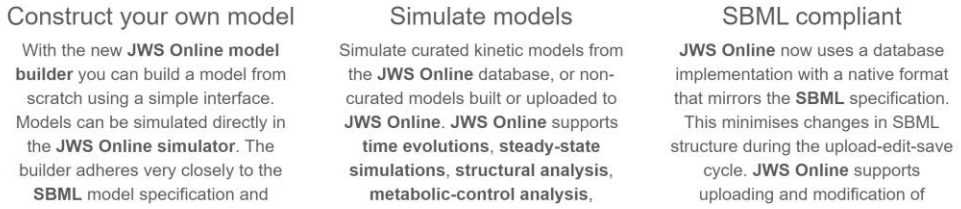
SED-ML enables...



https://run.biosimulations.org

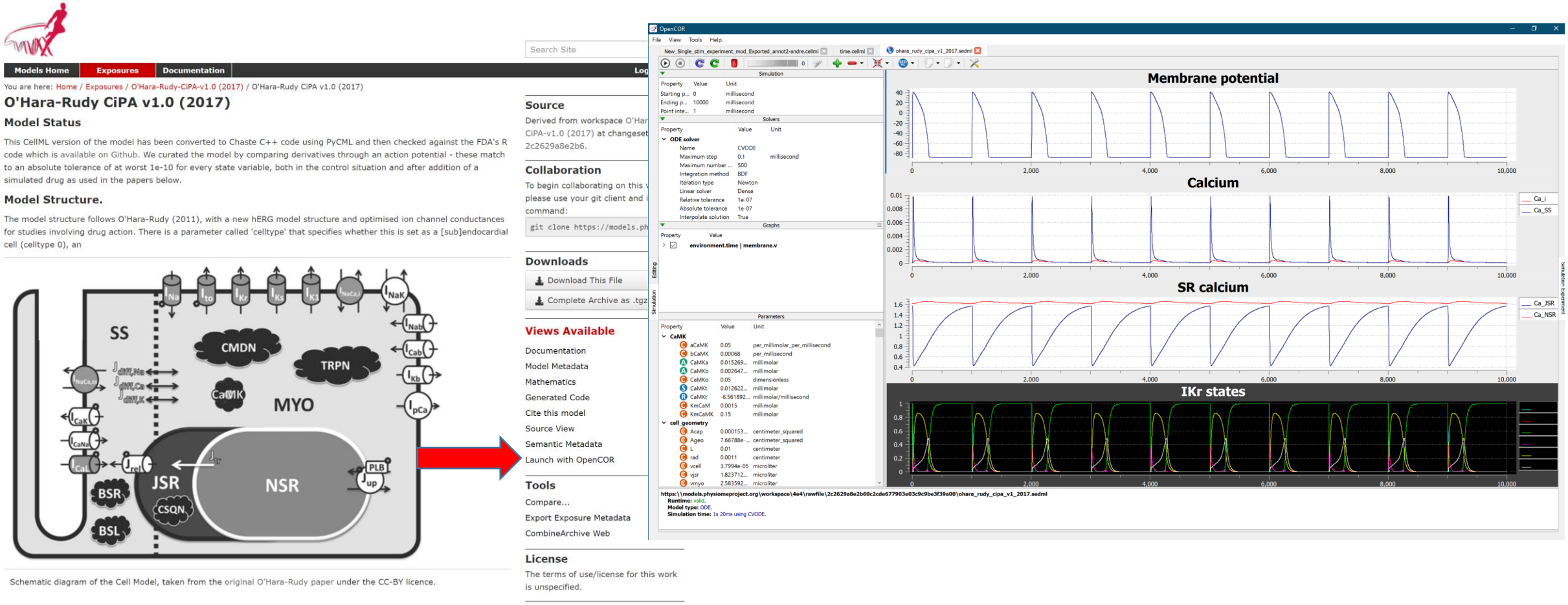




http://jjj.biochem.sun.ac.za/

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

SED-ML enables...



https://models.physiomeproject.org/e/5a0/

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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

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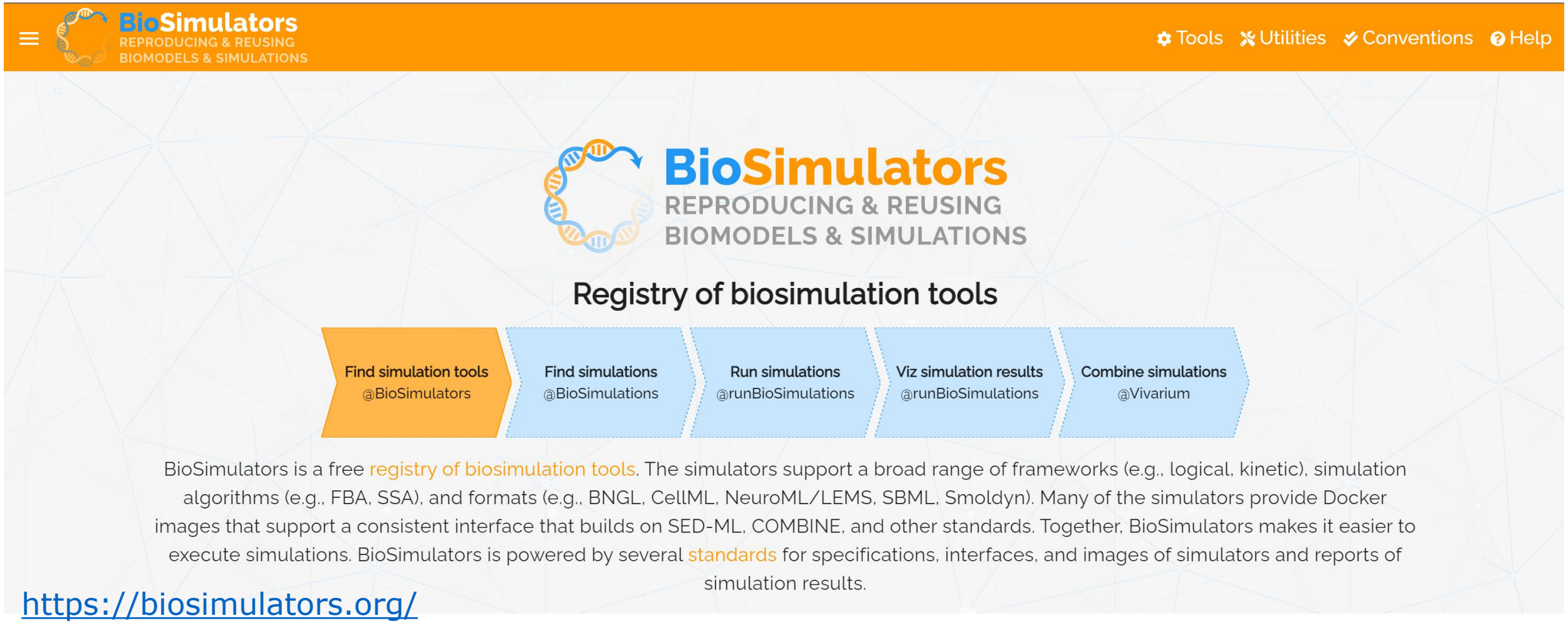
One solution



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

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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

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Semantics are key

combine

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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

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DE GRUYTER Journal of Inte

John H. Gennari*, Matthias König, Goksel Misirli, Maxwell L. Nea
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

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Standards = Reproducibility?

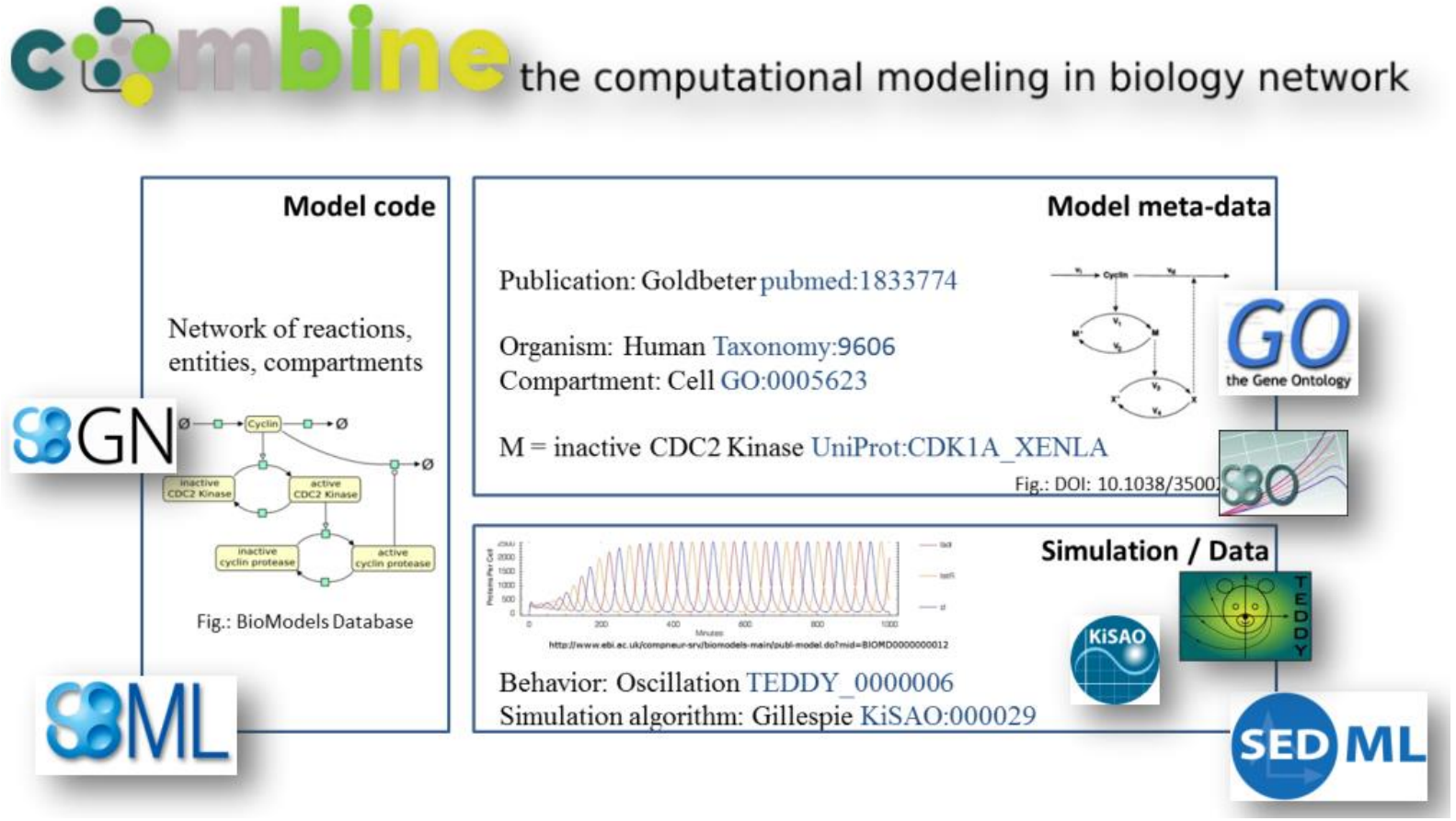
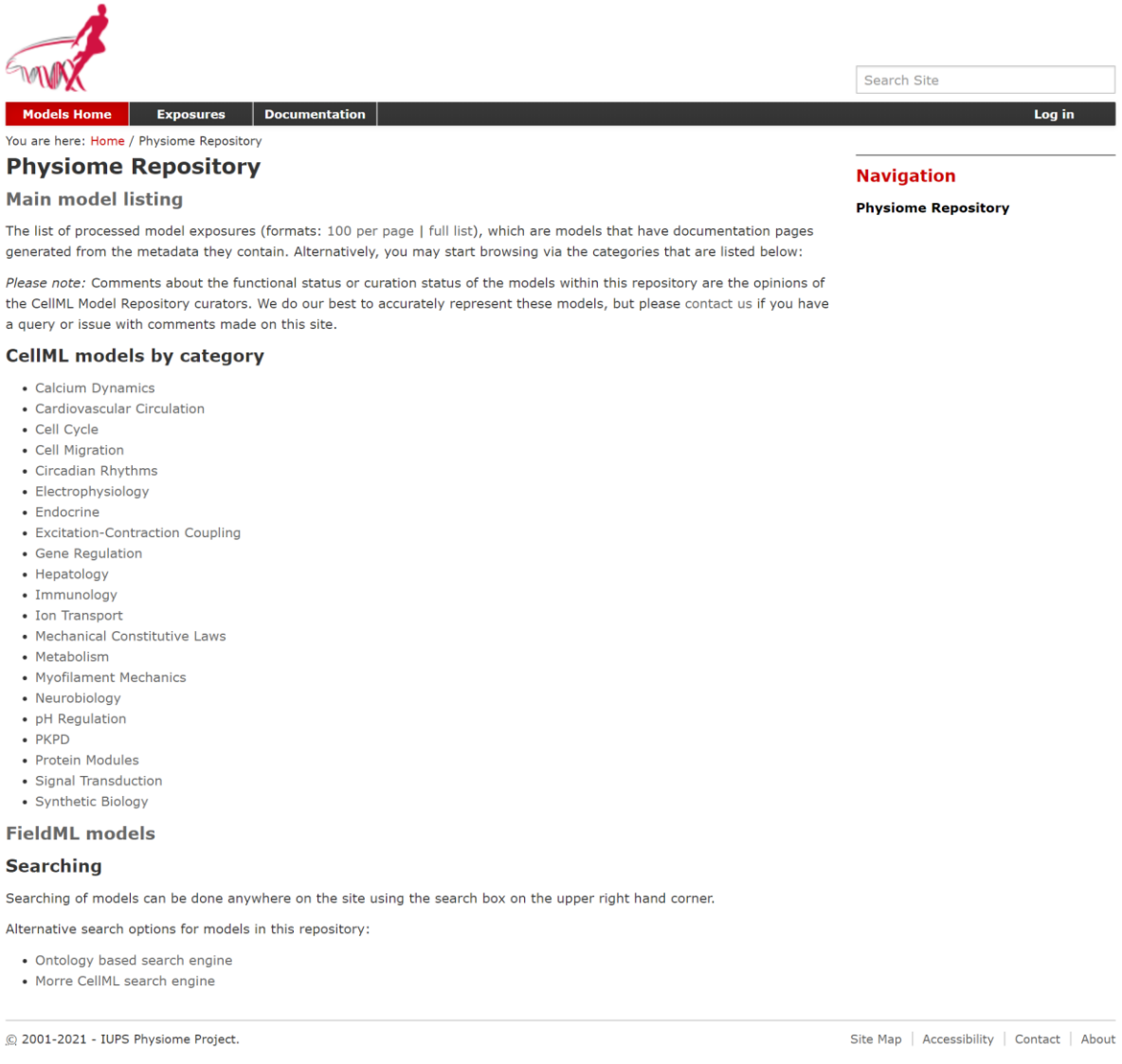
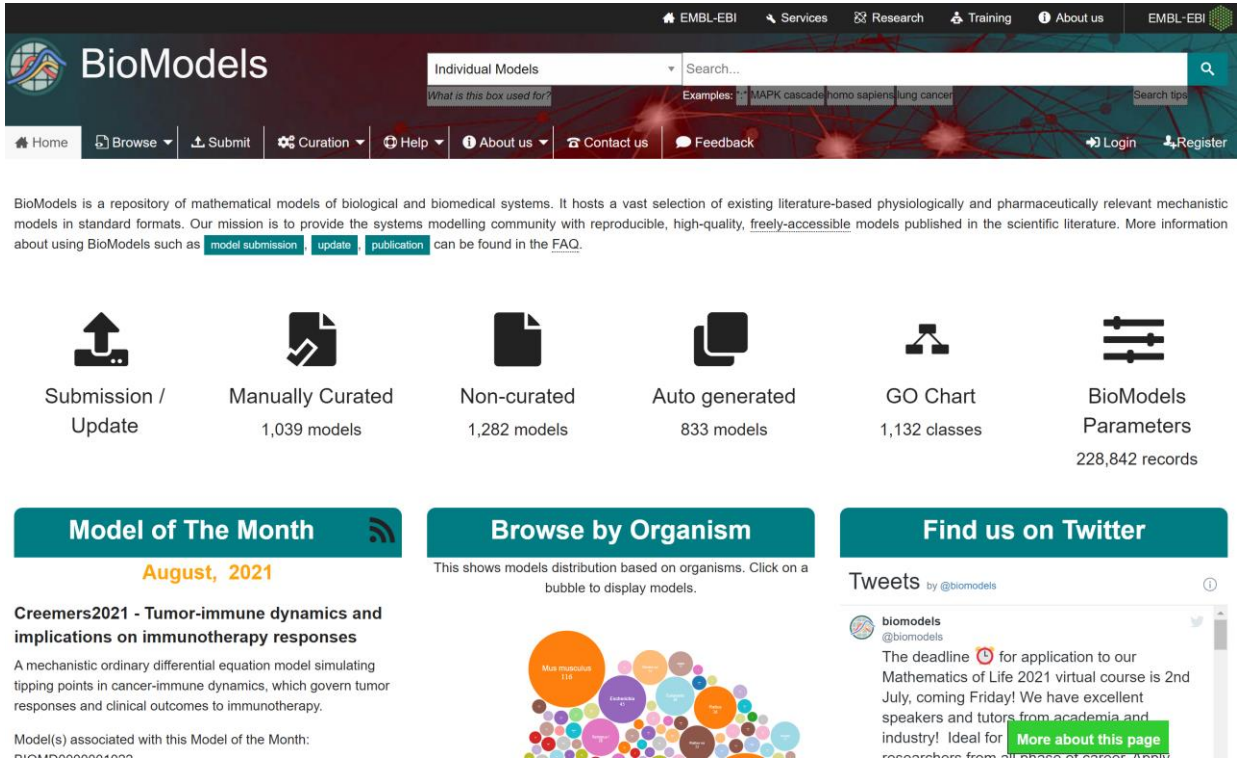


Figure from **Dagmar Waltemath**

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





https://models.physiomeproject.org/

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

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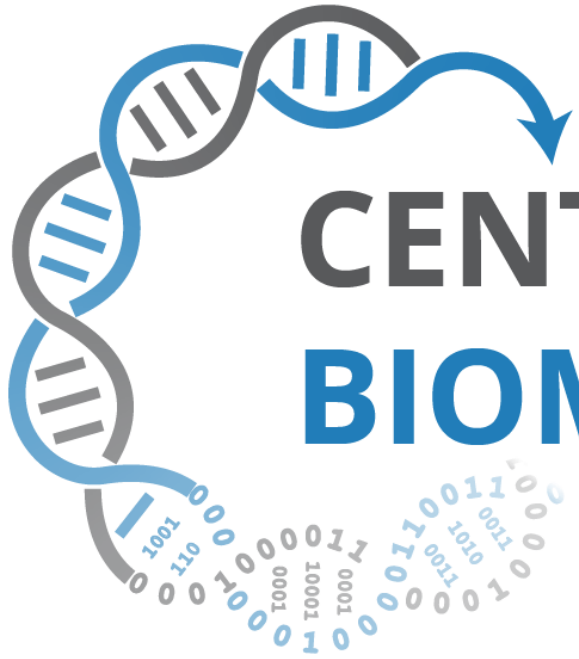

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https://reproduciblebiomodels.org/

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Working with journals

PLOS COMPUTATIONAL BIOLOGY

EDITORIAL

Improving reproducibility in computational biology research

Jason A. Papin[1]*, Feilim Mac Gabhann[2], Herbert M. Sauro[3], David Nickerson[4]*, Anand Rampadarath[4]

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

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

https://journal.physiomeproject.org/

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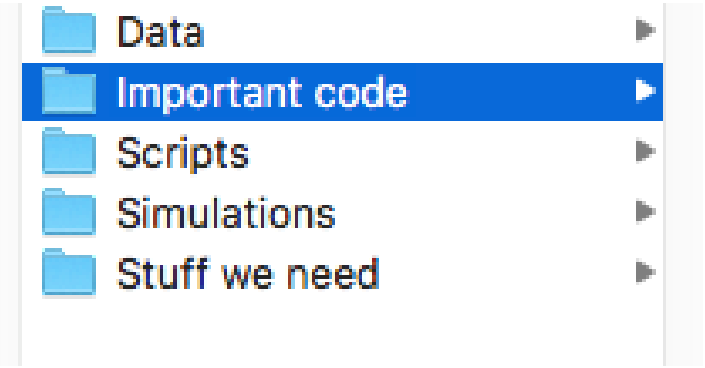
What is a *Physiome* publication?



Code + Primary publication + Descriptive summary

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Modularity is also key

- Manage complexity
- Enable reuse

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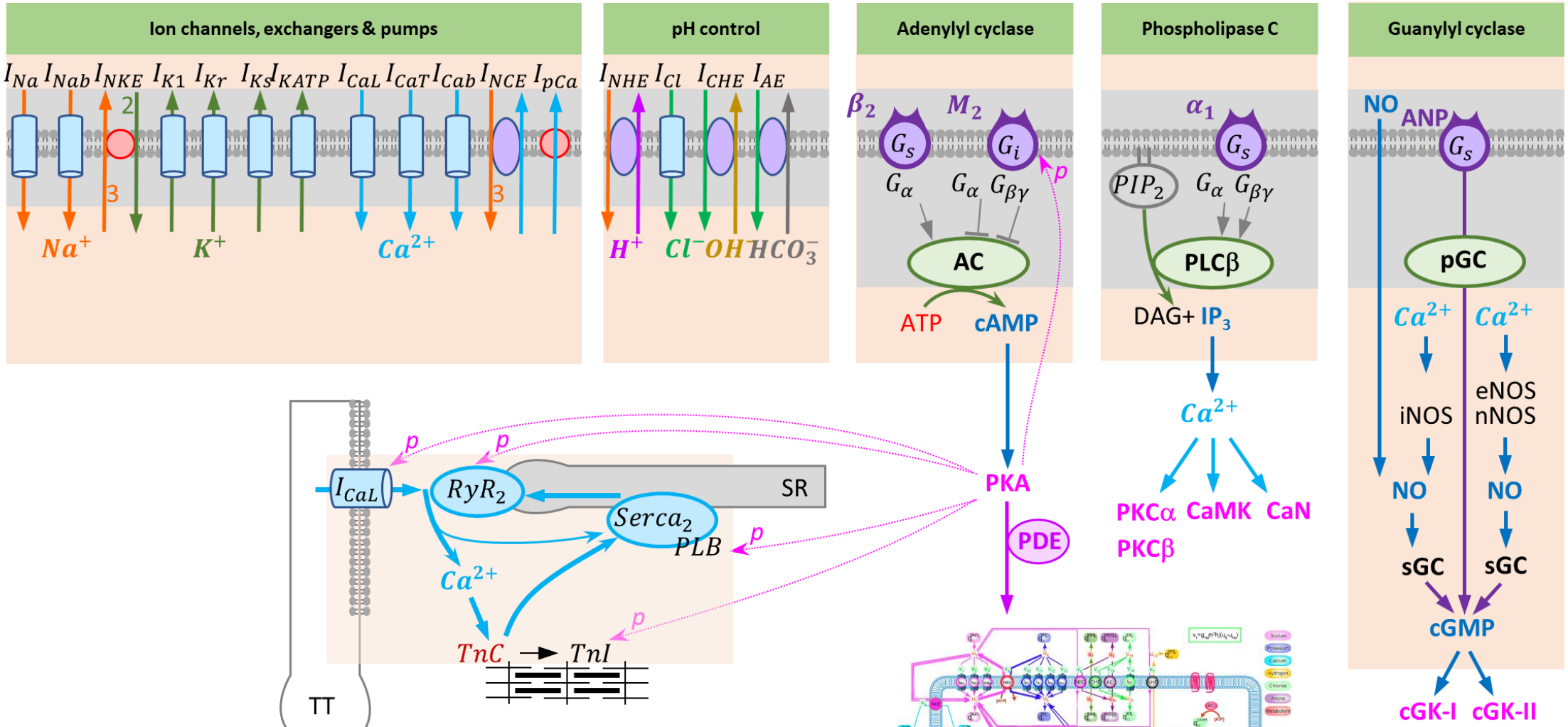
FCUs: Functional Cell Units



Automated assembly to whole cell model

… based on semantic annotations

Figure from **Peter Hunter**

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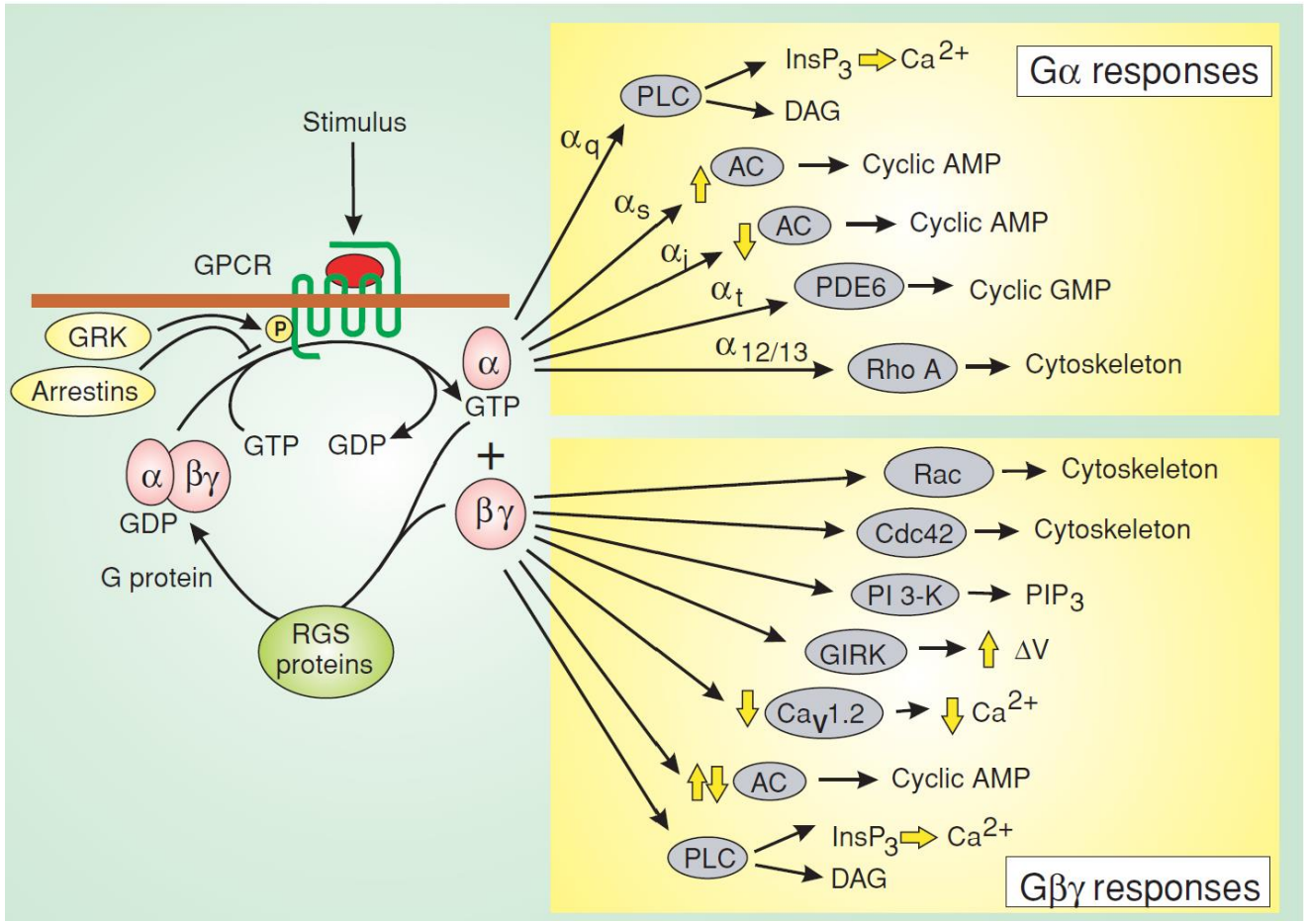
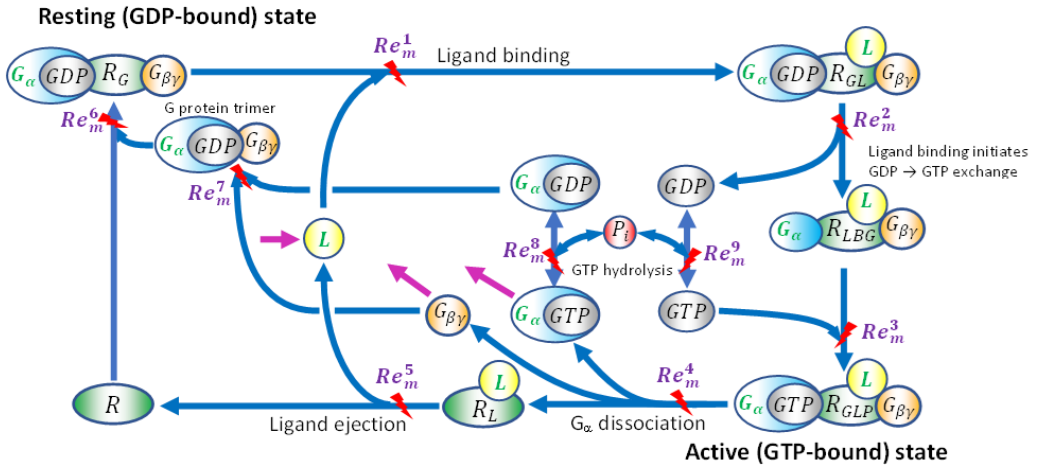
FCU Example: GPCR



(Berridge 2009)



Bond graph model

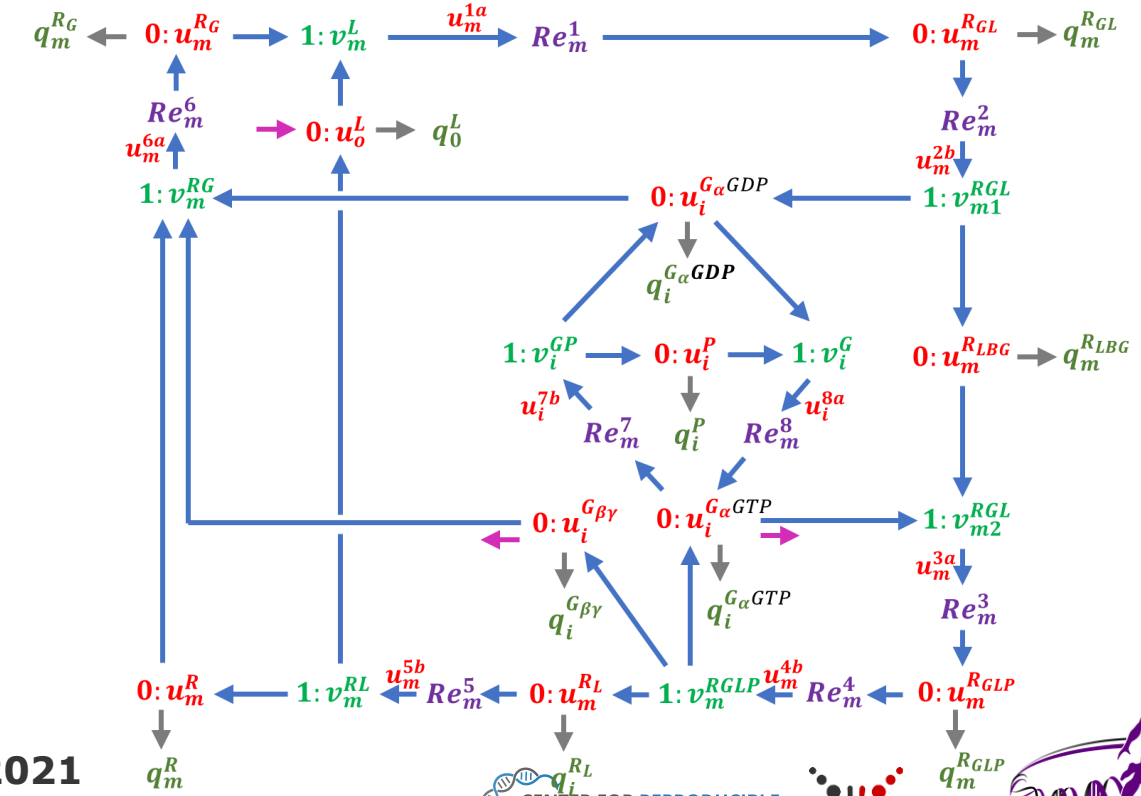


Figure from **Peter Hunter**

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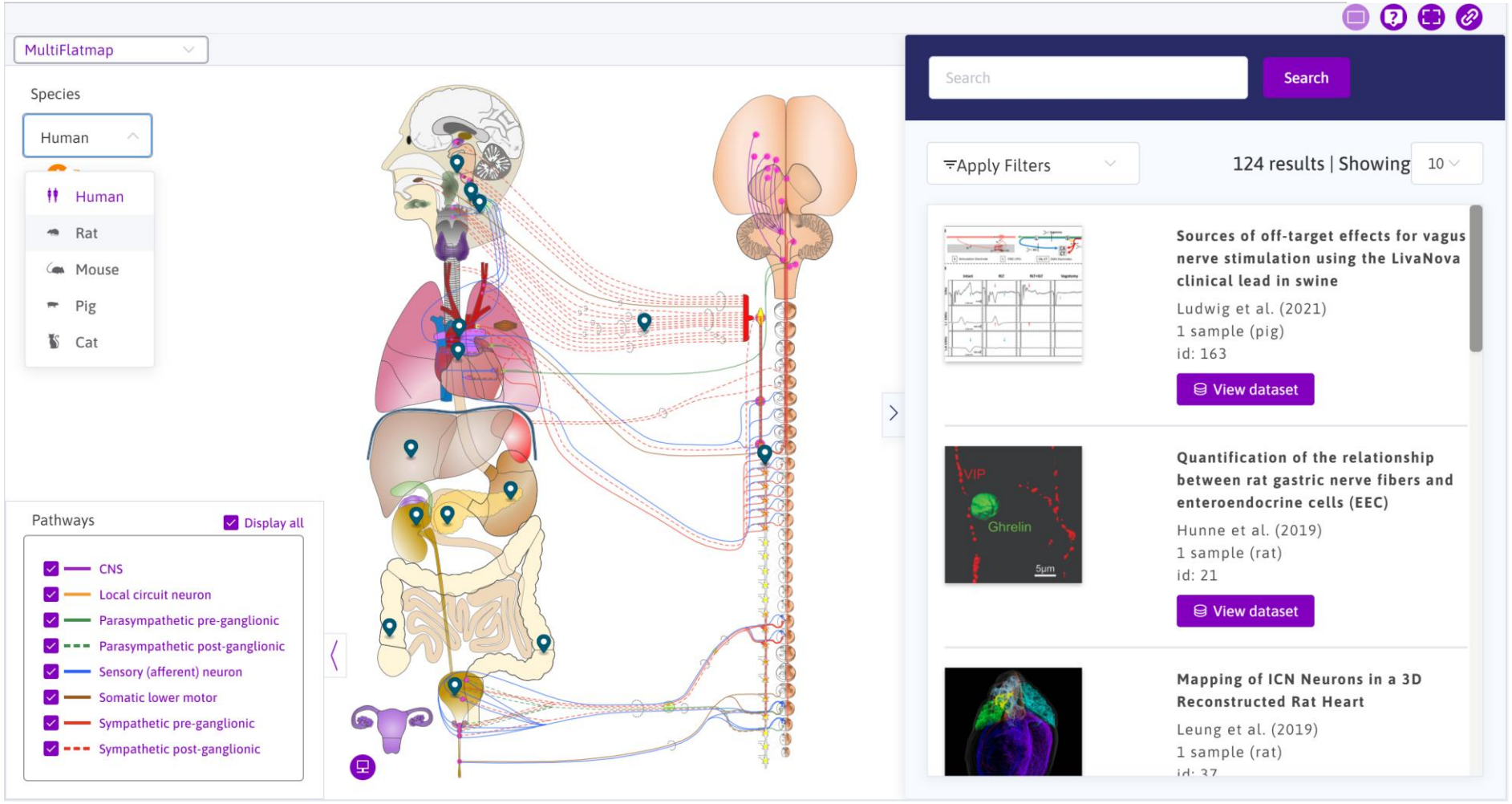
Database for physiological data and models

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



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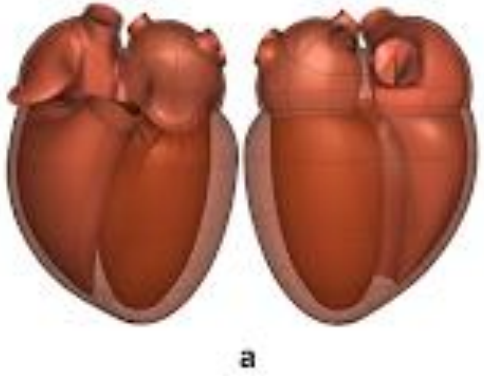
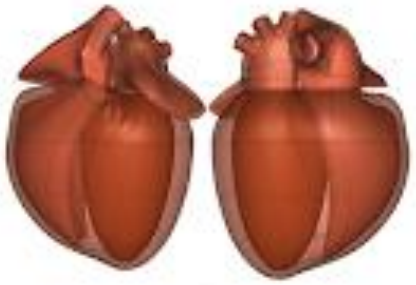
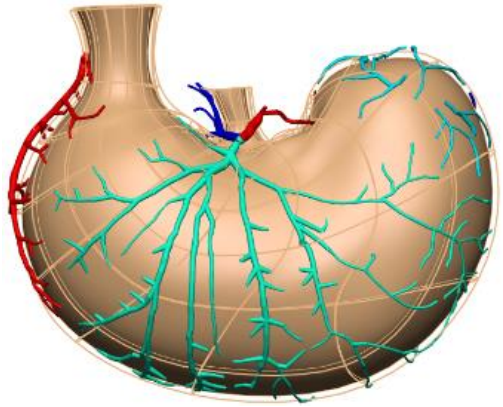
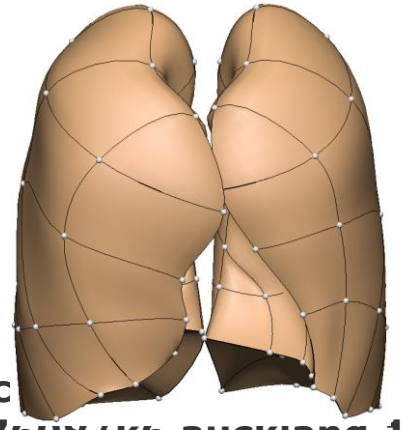
Scaffolds

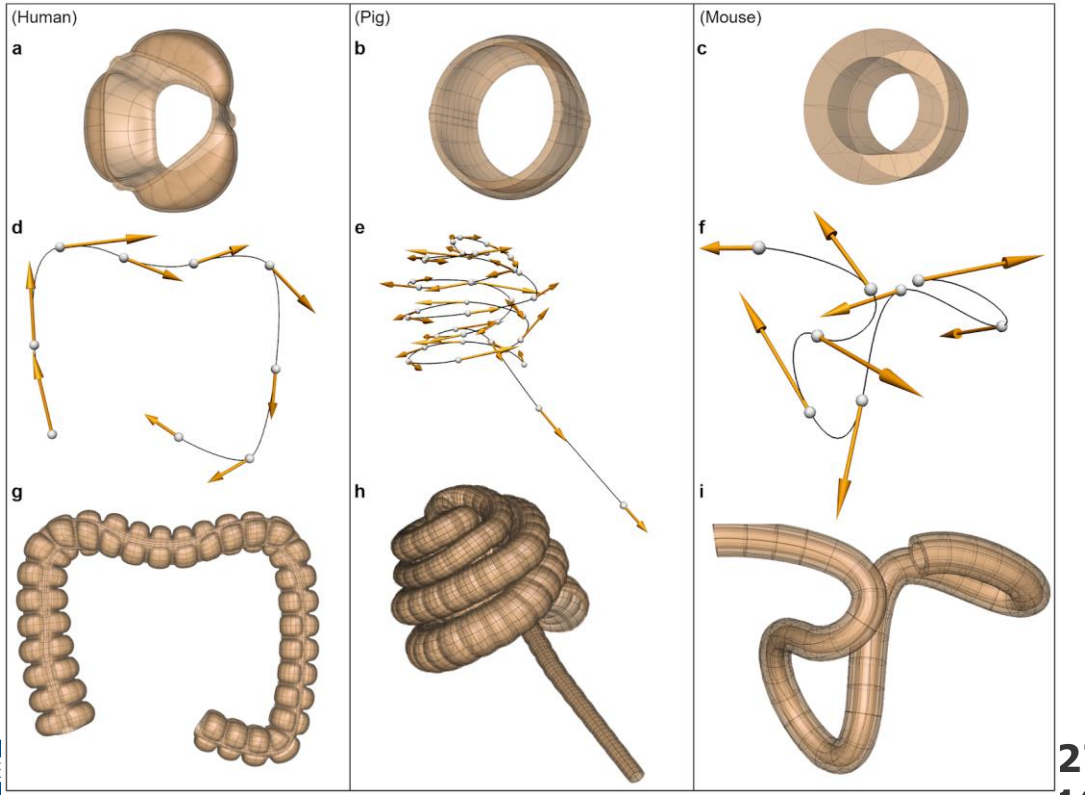
The 3D reference coordinate system for each organ is consistent across multiple species, in order to facilitate cross-species comparisons and the analysis of variation within a population.

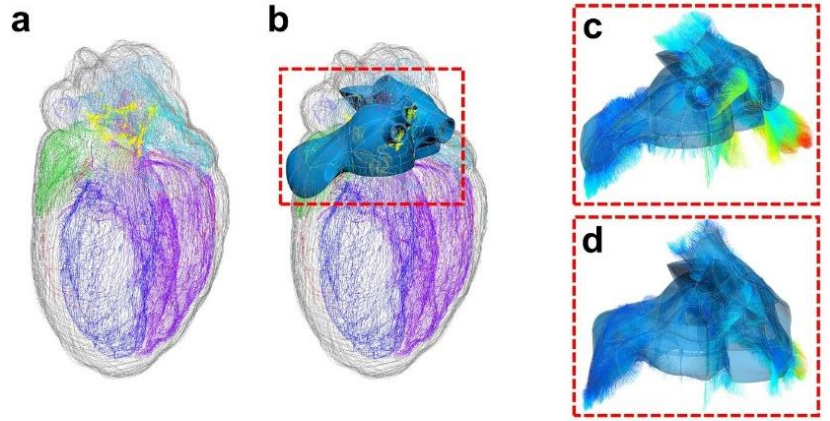


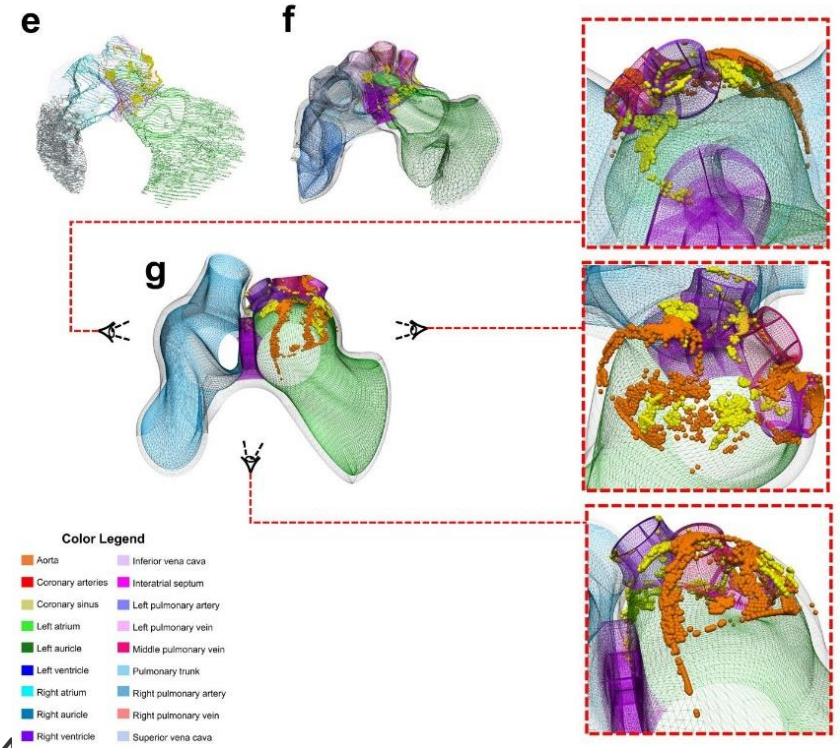












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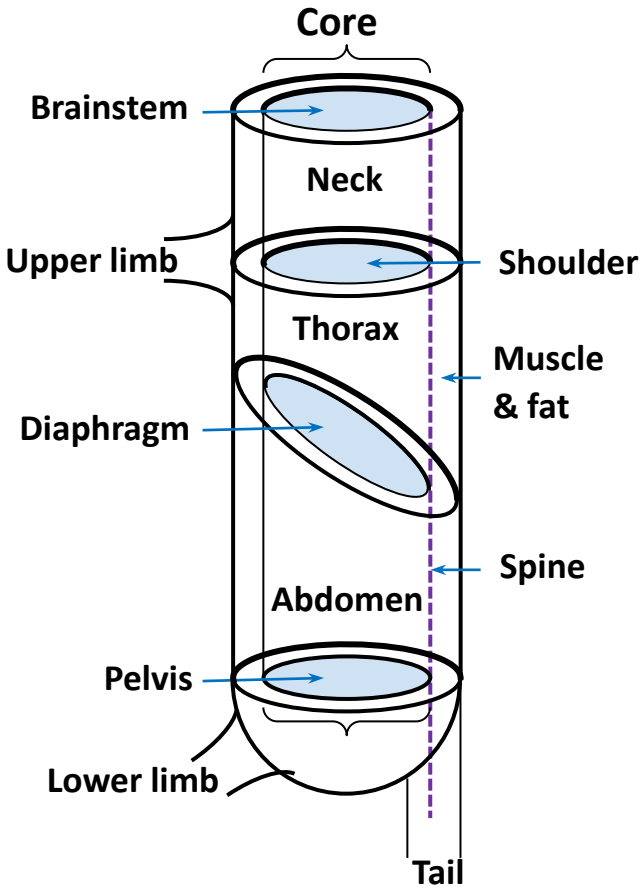
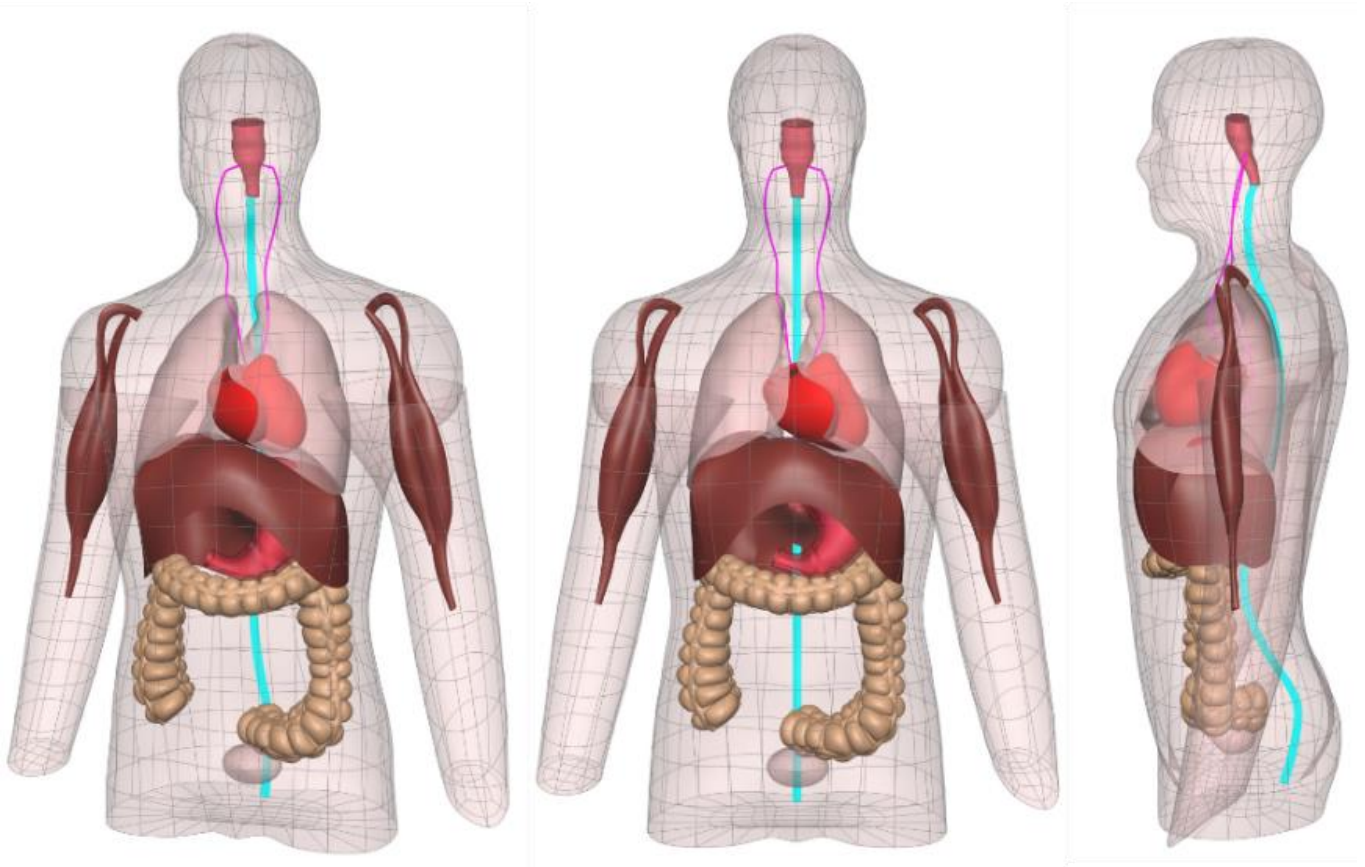
Whole body scaffolds

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.

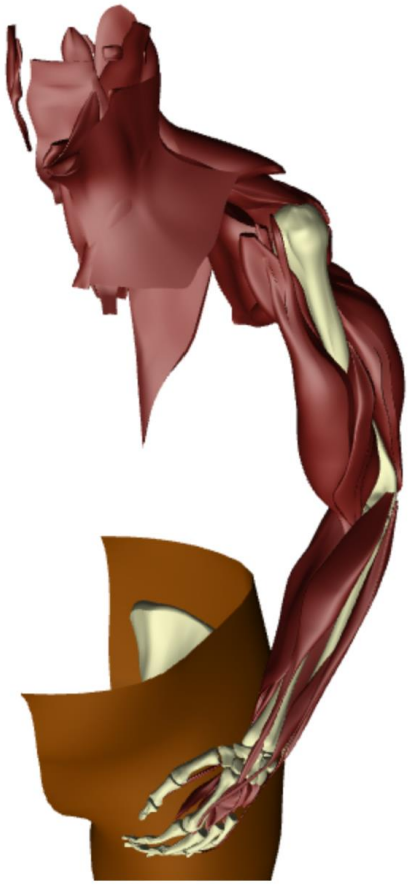
Reference coordinates



A pipeline for automated assembly



Database



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

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Acknowledgements

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

Aotearoa Foundation

SPARC

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