Towards ML-agnostic modeling

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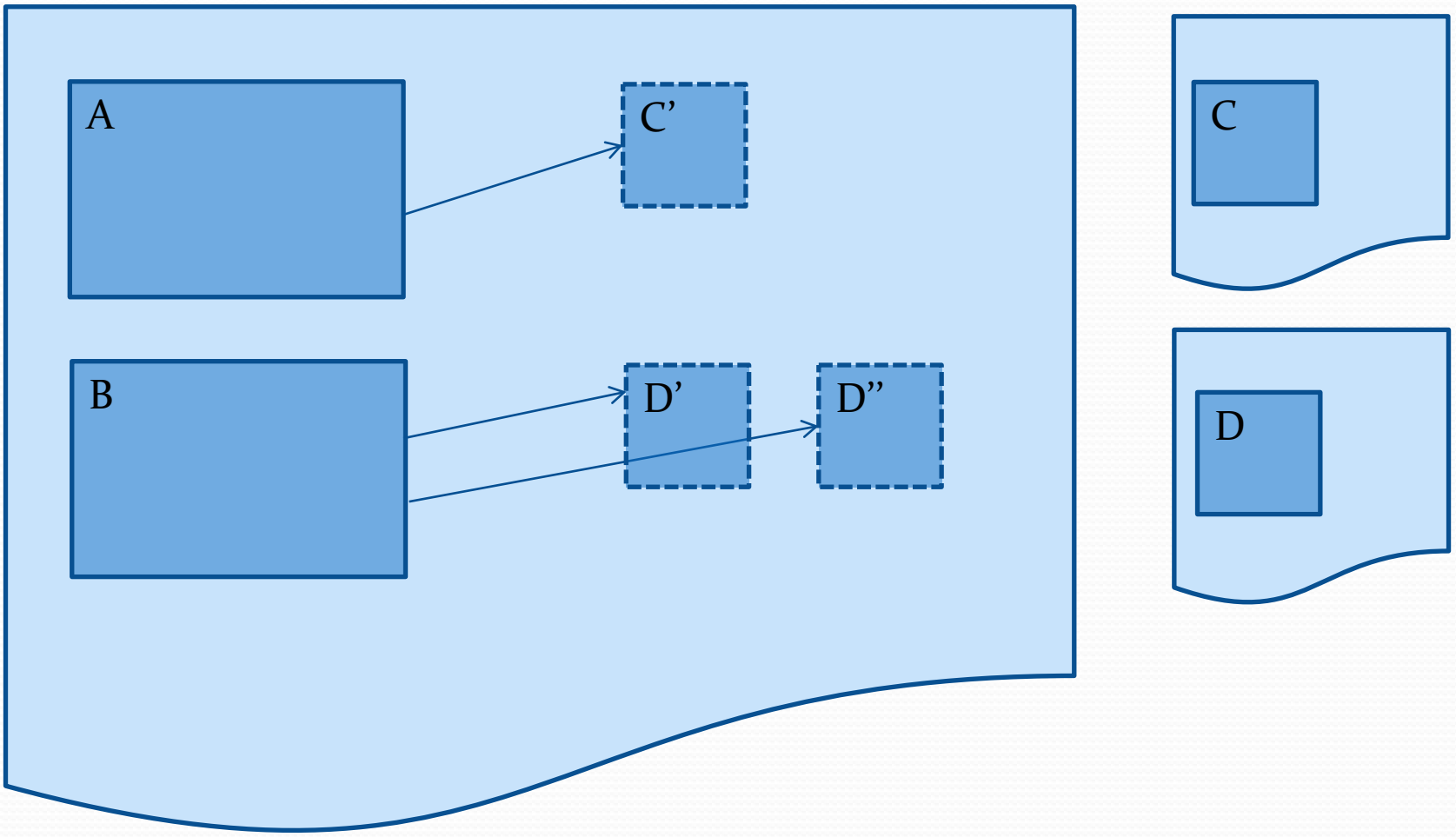
Model composition

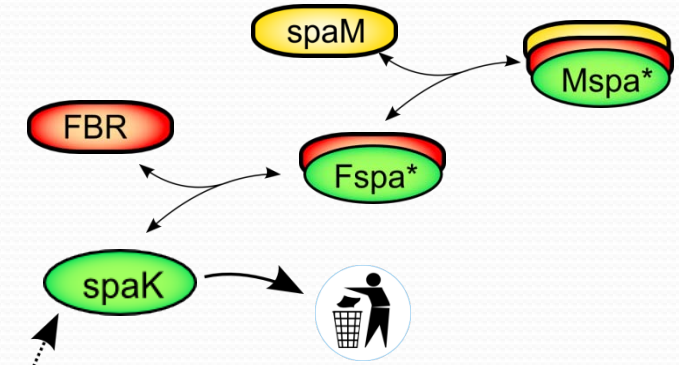
Hedley et al. (2001), Cuellar et al. (2003)

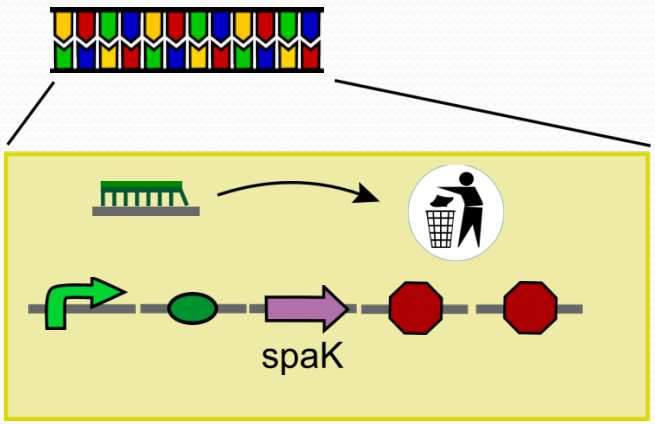
- Wrapper for MathML (which encodes maths)
- Partitioning the maths, variables into reusable pieces: ‘components’
- Domain inspecific - Systems biology, synthetic biology, physiology
- Inherent support for modularity

Importing



Example





'System Models'

'SVPs' -Physical things or processes

'Bioenvironment'

'Templates' – Mathematical structures

Adapted from Cooling et al. (2010) Bioinf. Fig 1.

Vascular (mal-)adaptation

Image courtesy of The Internet Encyclopedia of Science

Cummins et al. (2007) *Am J Physiol Heart Circ Physiol:292*, Fig 1.

- 3 interacting cell types, extracellular matrix
- Narrow focus to: shear stress -> NO production in endothelial cells….
  - Regulated by 6-10 signalling pathways
  - 100s of components….

(models.cellml.org)

Modelling Hypertrophic IP3 Transients in the Cardiac Myocyte (Cooling, Hunter, Crampin, 2007)

Model Status

This CellML model is the model which was used to produce the original results in the paper, and therefore it is known to be completely accurate.

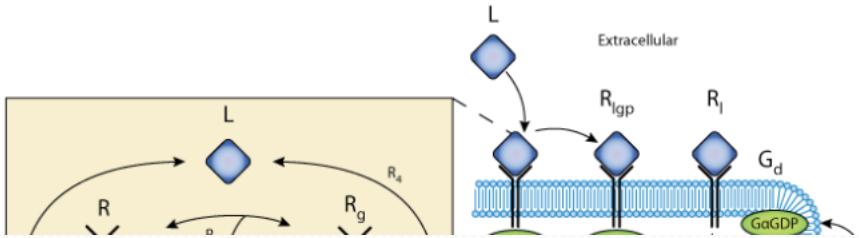
Model Structure

ABSTRACT: Cardiac hypertrophy is a known risk factor for heart disease, and at the cellular level is caused by a complex interaction of signal transduction pathways. The IP3 - calcineurin pathway plays an important role in stimulating the transcription factor NFAT which binds to DNA cooperatively with other hypertrophic transcription factors. Using available kinetic data we construct a mathematical model of the IP3 signal production system after stimulation by a hypertrophic {alpha}-adrenergic agonist (endothelin-1), in the mouse atrial cardiac myocyte. We use a global sensitivity analysis to identify key controlling parameters with respect to the resultant IP3 transient; including the phosphorylation of cell-membrane receptors, the ligand strength and binding kinetics to precoupled (with G{alpha}GDP) receptor, and the kinetics associated with precoupling the receptors. We show that the kinetics associated with the receptor system contribute to the behaviour of the system to a great extent, with precoupled receptors driving the response to extracellular ligand. Finally, by reparameterising for a second hypertrophic {alpha}-adrenergic agonist, angiotensin-II, we show that differences in key receptor kinetic and membrane density parameters are sufficient to explain different observed IP3 transients in essentially the same pathway.

Abstract reproduced from Cooling et al., Biophysical Journal 93, 2007, with permission.

This model of the NFAT cycling system is described in more depth in the original paper which is cited below:

Modeling hypertrophic IP3 transients in the cardiac myocyte, Michael Cooling, Peter Hunter and Edmund J. Crampin, 2007, *Biophysical Journal*, 93, 3421-3433. PubMed ID: 17693463



Model Curation

Curation Status: ★★★
OpenCell: ★★★
JSim: ☆☆☆
COR: ★★★

Source

Derived from workspace Cooling, Hunter, Crampin, 2007 at changeset b1ad010d41a7.

Downloads

Complete Archive as .tgz

Download This File

Views available

Model Metadata

Mathematics

Generated Code

Cite this model

Source View

Simulate using OpenCell

License

Reuse can happen, but…

- Goal: to make it easier to build and understand large models from reusable components.
- 'Integrated Services' (2010, IWBDA)
  1. Search and Retrieval
  2. Automated / assisted model composition
  3. Visualisation
  4. Analysis
- Consider the above 'services' in the context of SBML, perhaps Matlab, whatever-language
- Does the modeller care what ML the model is written in?
- Level of reuse – semantic level?

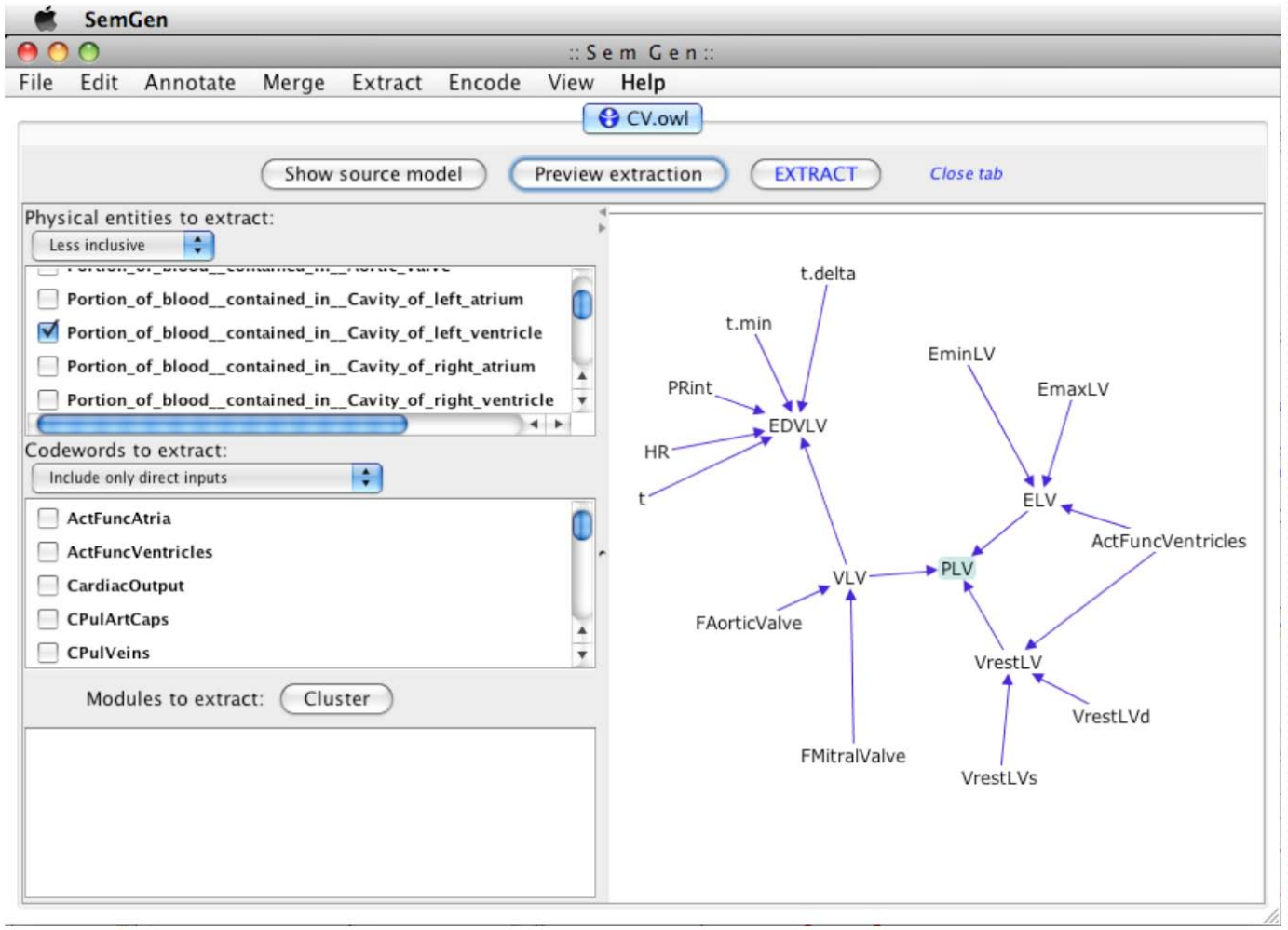
SemSim

- Maxwell Neal, John Gennari, Dan Cook

  University of Washington, Seattle, USA
- Modular, multi-domain, multi-scale platform for enabling reuse
- Describe models semantically
  - OWL
  - Separation
    - Computational_model_component
    - Physical_model_component

SemGen

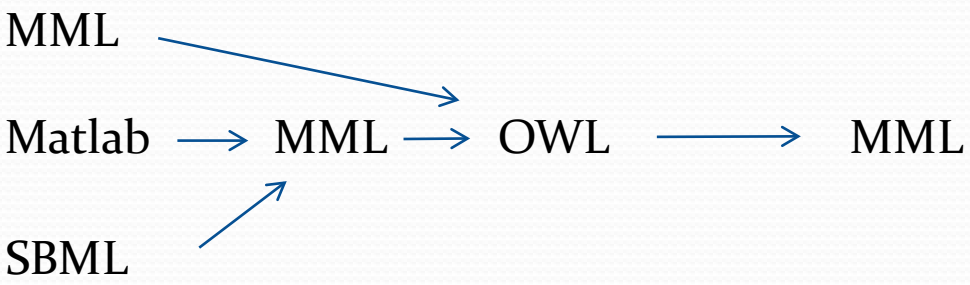
Fig. 7 from Neal M., 'Modular, semantics-based composition of biosimulation models', PhD dissertation (2010)



SemSim - Examples

- Coupling systemic arterial model to a wider model of the cardiovascular system (multiscale, making a component more realistic)
  - Neal, Gennari, Arts, Cook, Pac. Sym. Bio. (2009)
- Three interlinked models
  - Baroreceptor (blood pressure to heart rate)
  - CV model (heart rate, system resistance to blood pressure and flow)
  - VSM (calcium to arterial resistances)
    - Neal's PhD thesis (2010)

Under the hood

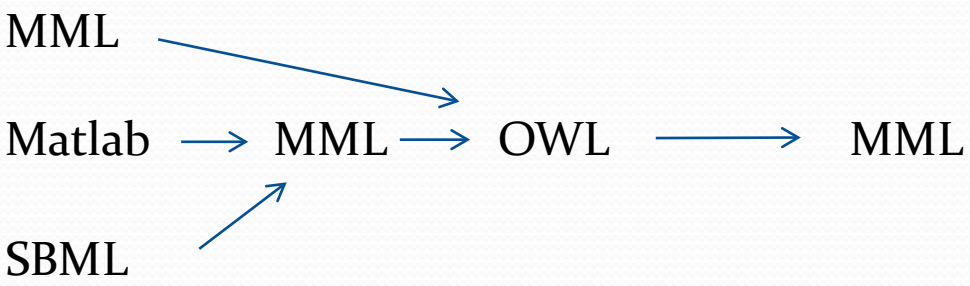


- MML (JSim) – Bassingthwaighte, UoWashington
- Two opportunities: extend for
  - Composition
  - Interoperability

Monolithism

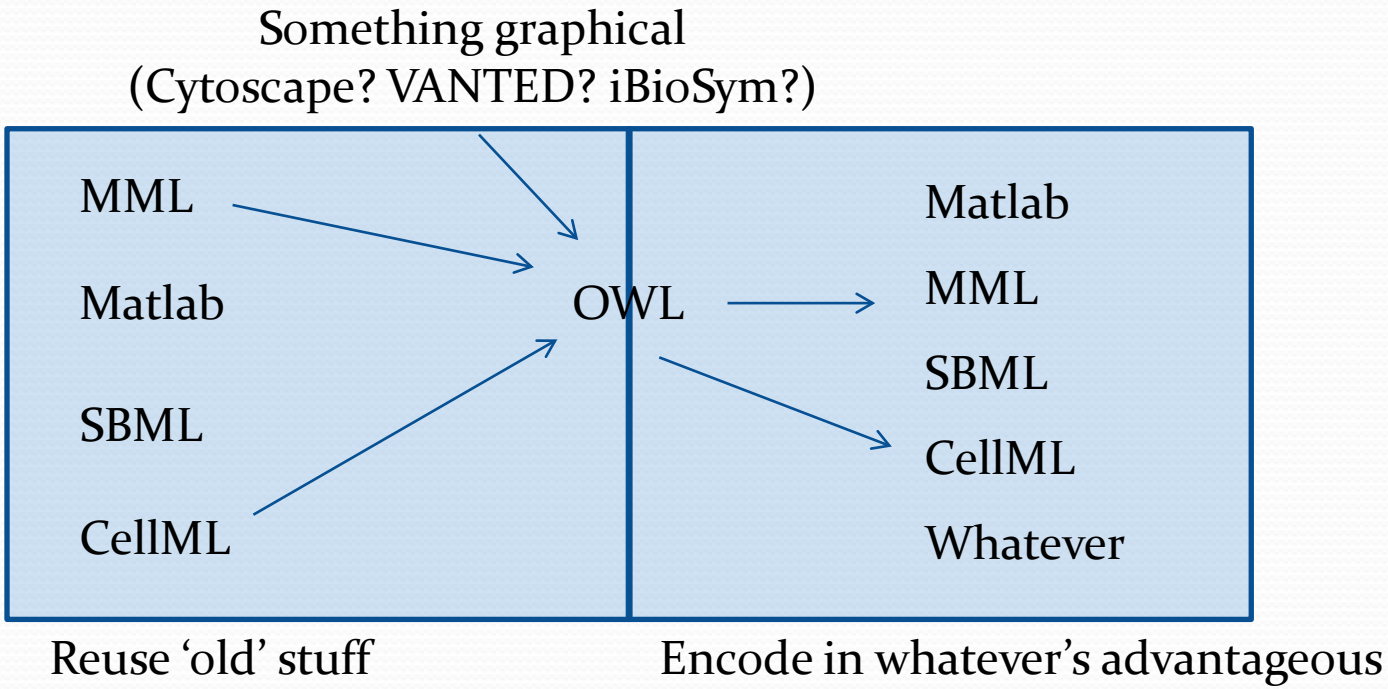
- Simple case: the monolithic model (flattened)
  - Quickly prove a point
  - Most models monolithic to start with
  - For simulation, structure not very important
- Structures (eg CellML components, ‘sub models’) lost
- Lost opportunity- want internal structures preserved

Conversion via MML



- Limited by the expressivity of MML
  - CellML Imports != MML templates
- OWL level is not specific to MML
  - Underlying abstraction…

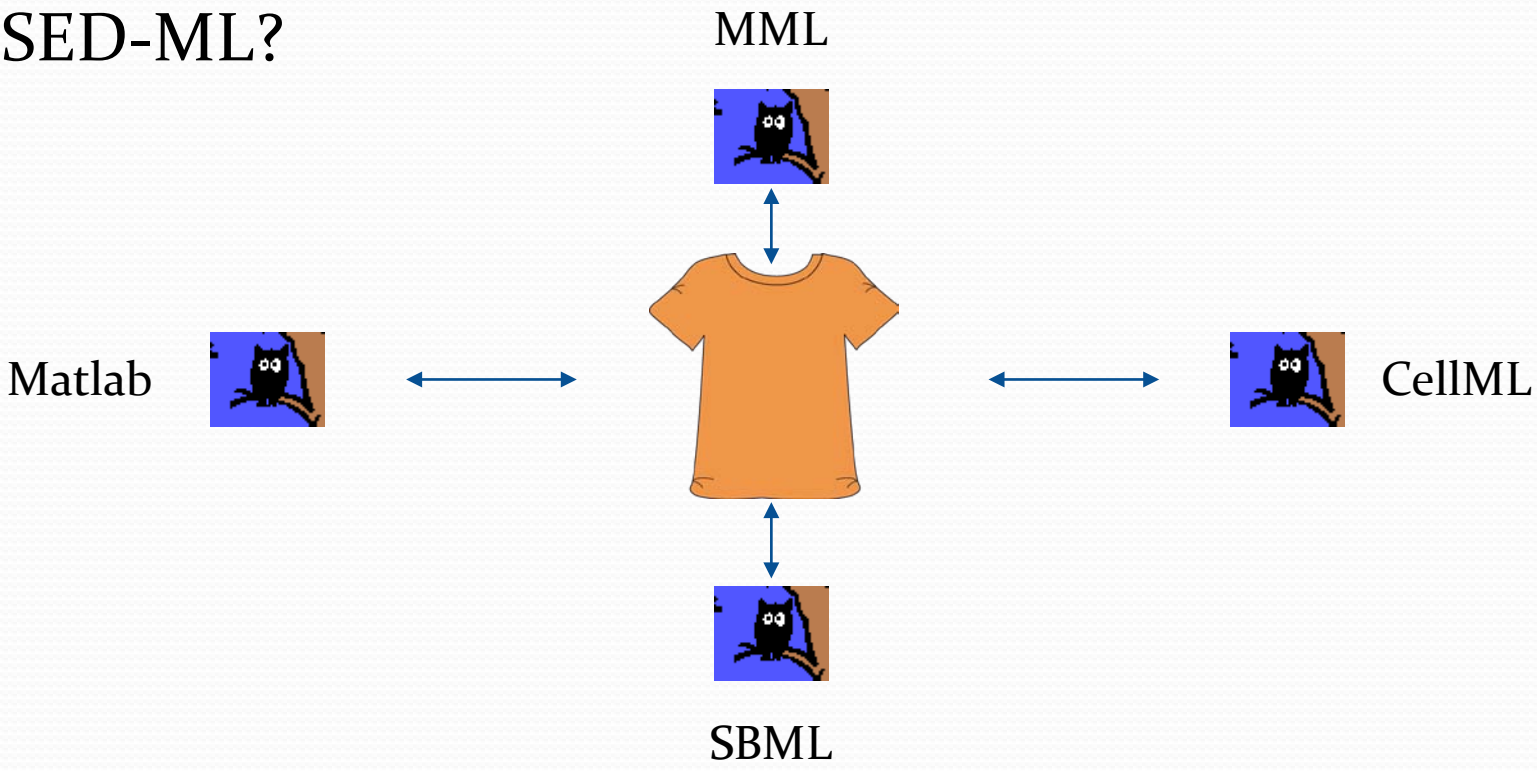
Multi-language Conversion



- Language <-> language interconversion
- Preserving structure where possible
- ML-agnostic composition
- (also, summary of abstractions for modelling)

True interoperability?

- Think about SOAP…
- Annotate interfaces
- SED-ML?



Grateful to


SEVENTH FRAMEWORK
PROGRAMME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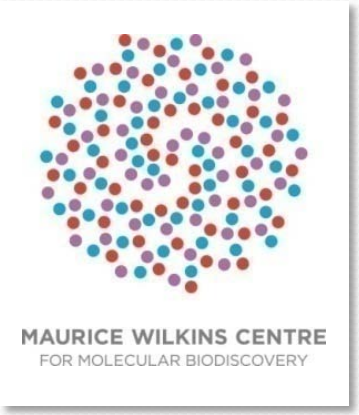
Te Whare Wānanga o Tāmaki Makaurau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