Towards a Modelling Ecosystem for Libraries of Modular, Reusable Components

Mike Cooling, September 2011

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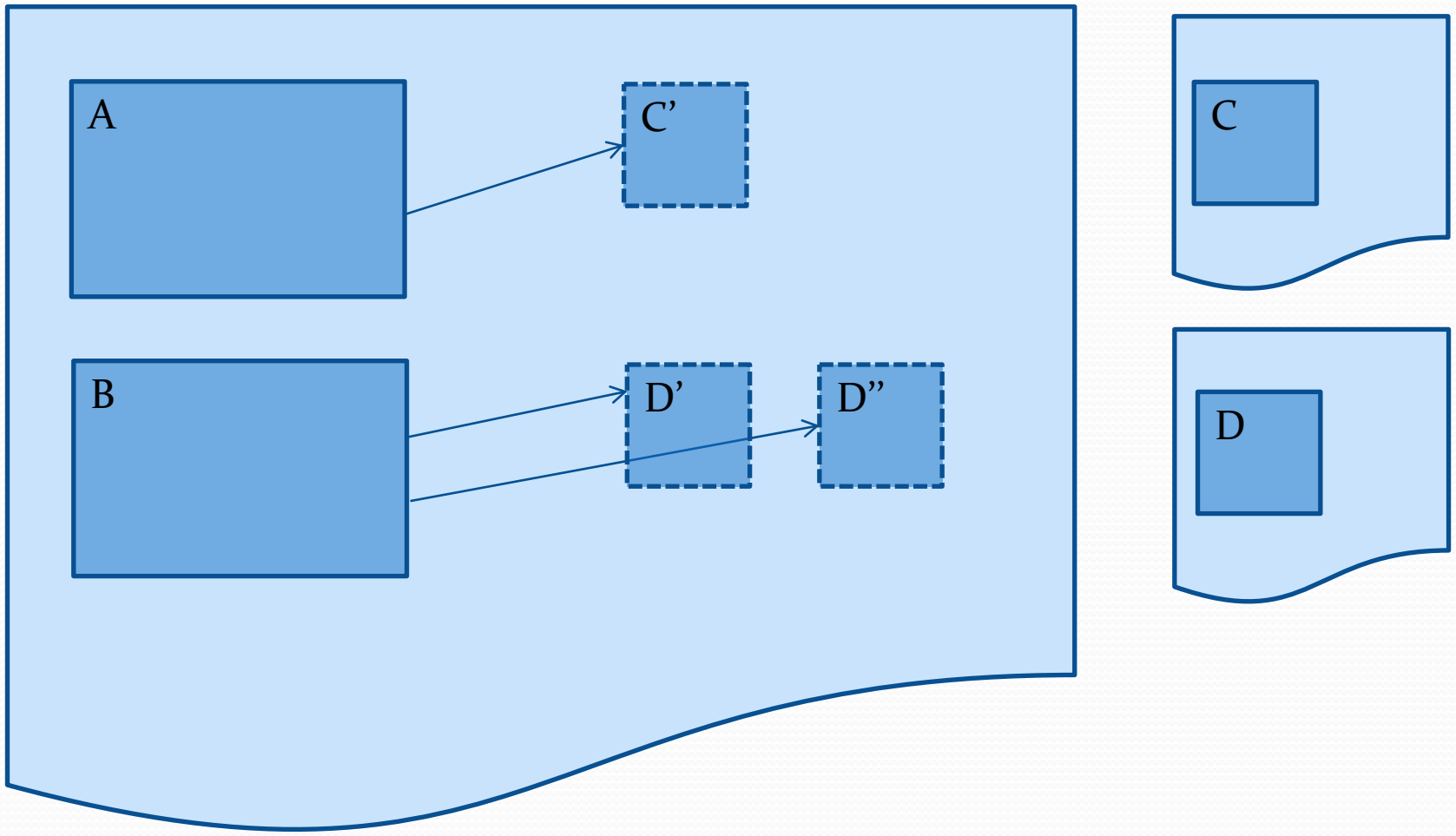
I want to make models…

- Primarily interested in how cells work
- A ‘user’ (a hopeful one)

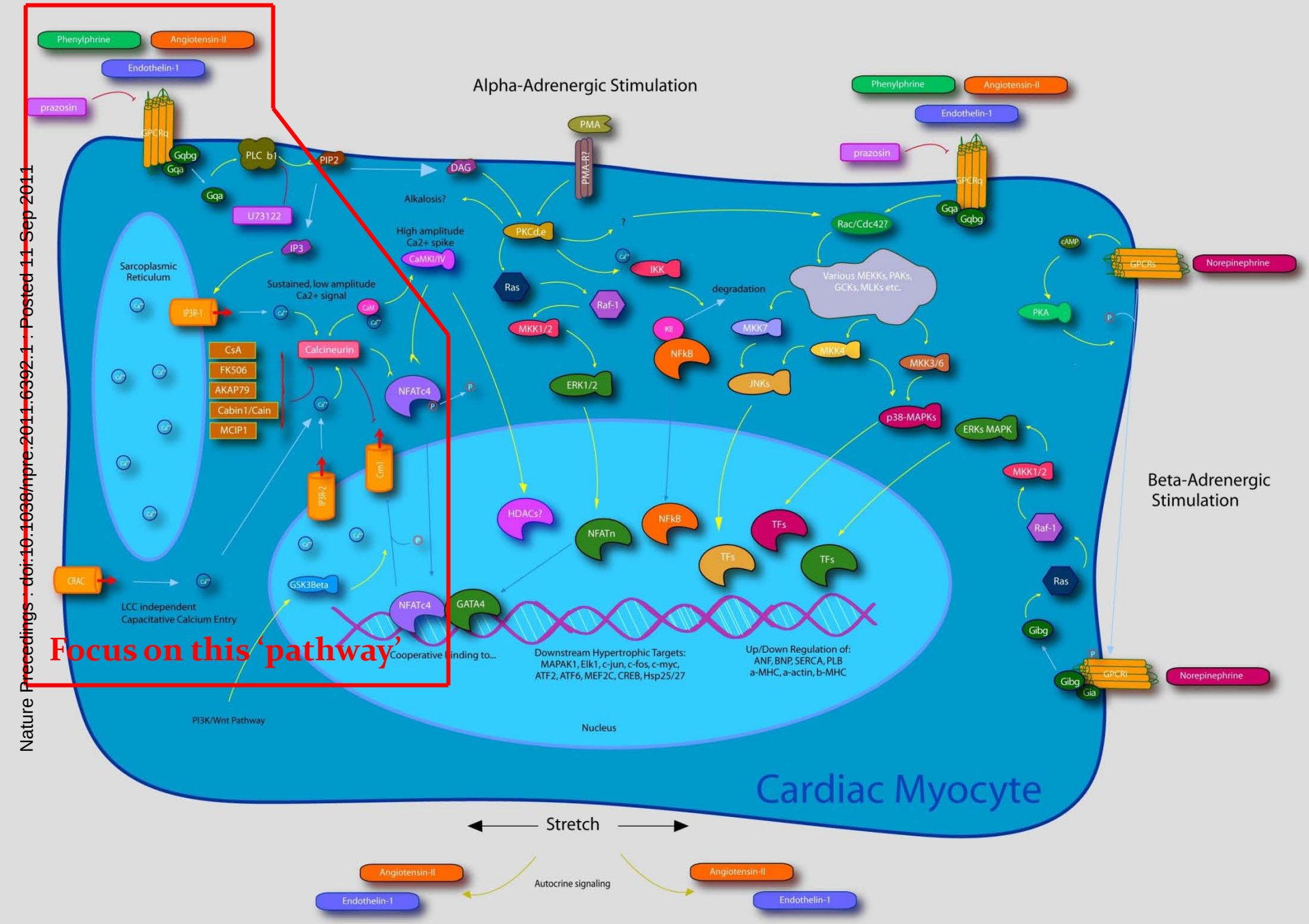
Hedley et al. (2001), Cuellar et al. (2003)

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

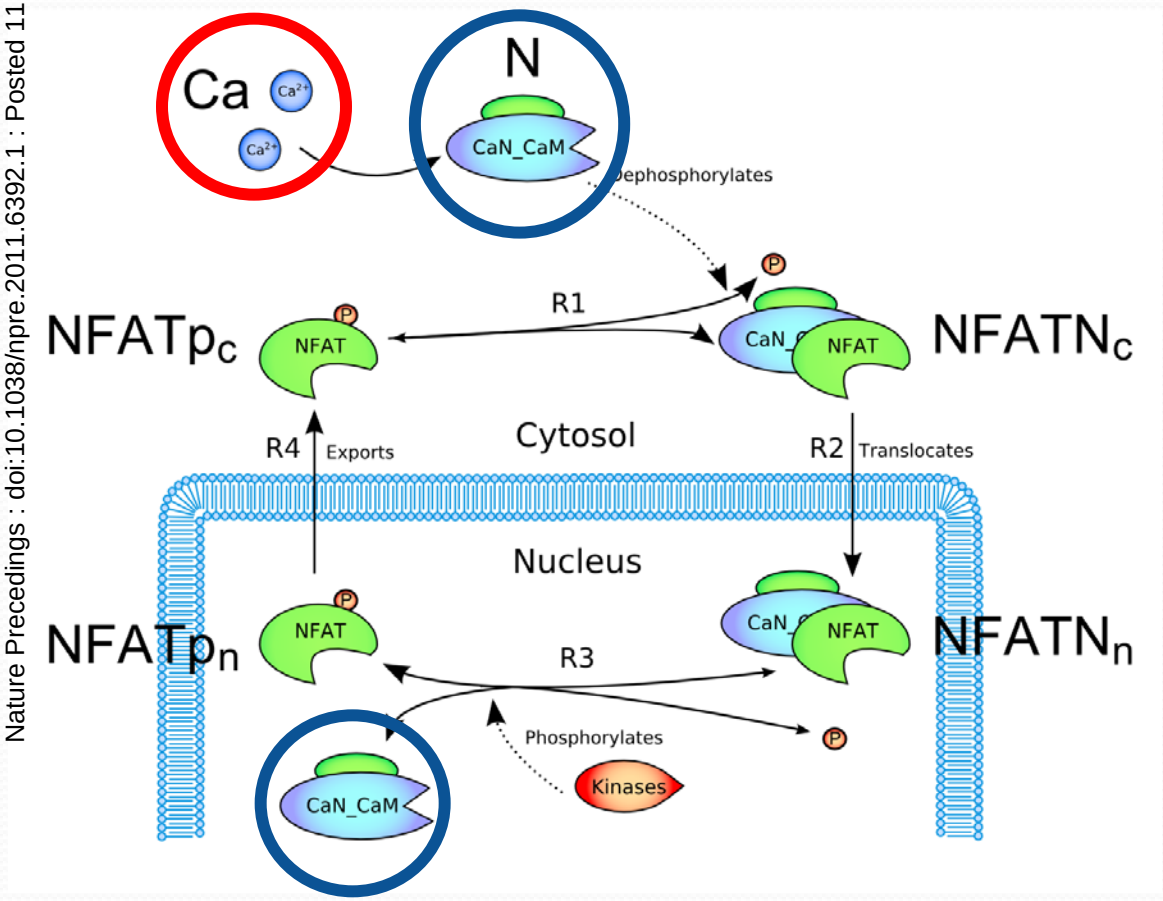
Importing



Nature Precedings : doi:10.1038/npre.2011.6392.1 : Posted 11 Sep 2011



Importing allows 'modules'



Cooling et al. (2009) Biophys. J. Fig 1.

- Variable Calcium
  - Oscillating pulses
  - Peak then plateau
  - Step changes
- Variable Calcineurin
  - Inhibition
- Virtual Experiments
- SED-ML?

(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.

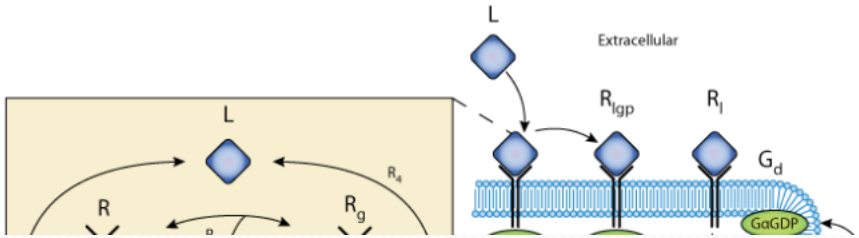
Model Structure

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

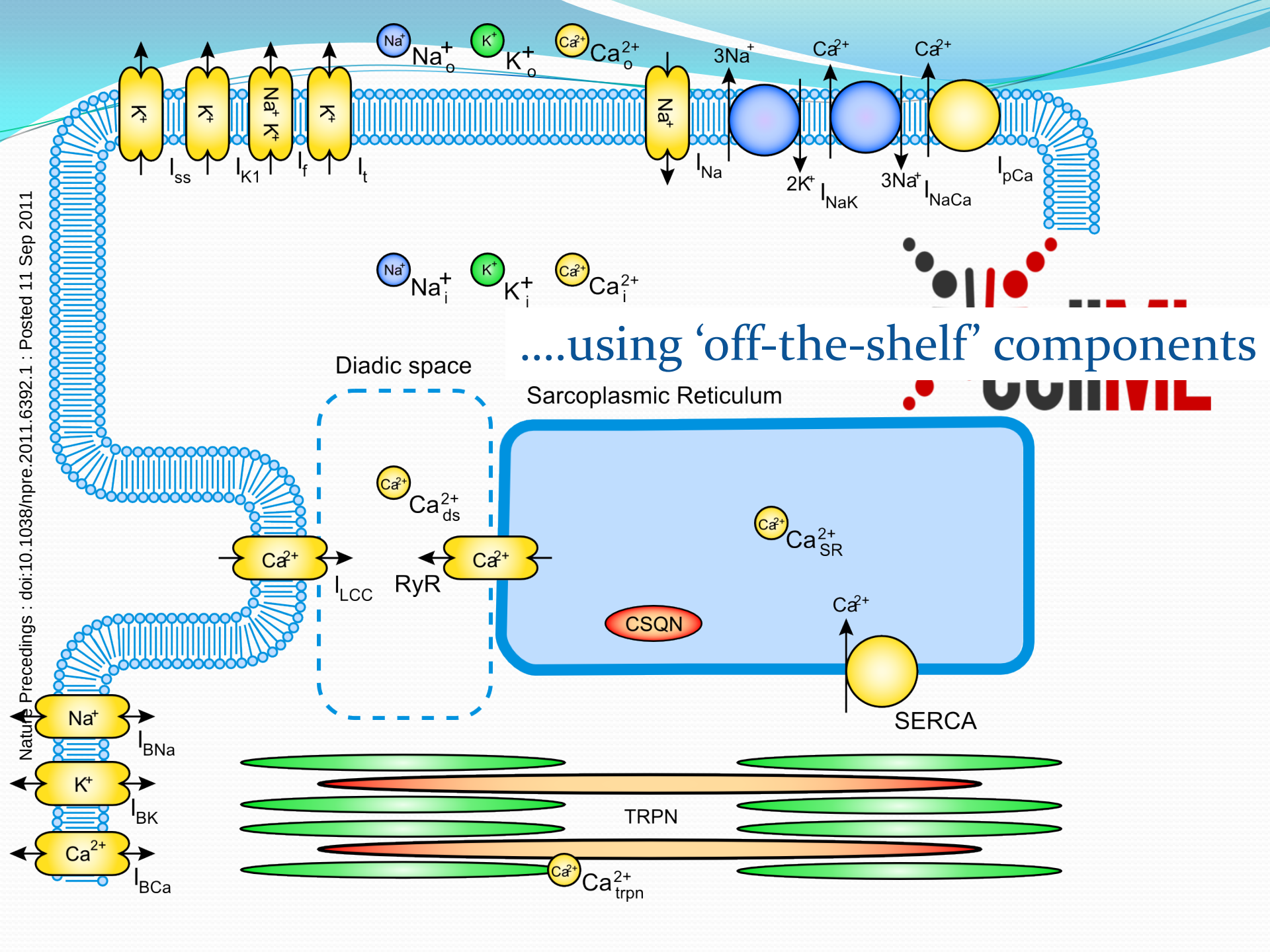
Generated Code

Cite this model

Source View

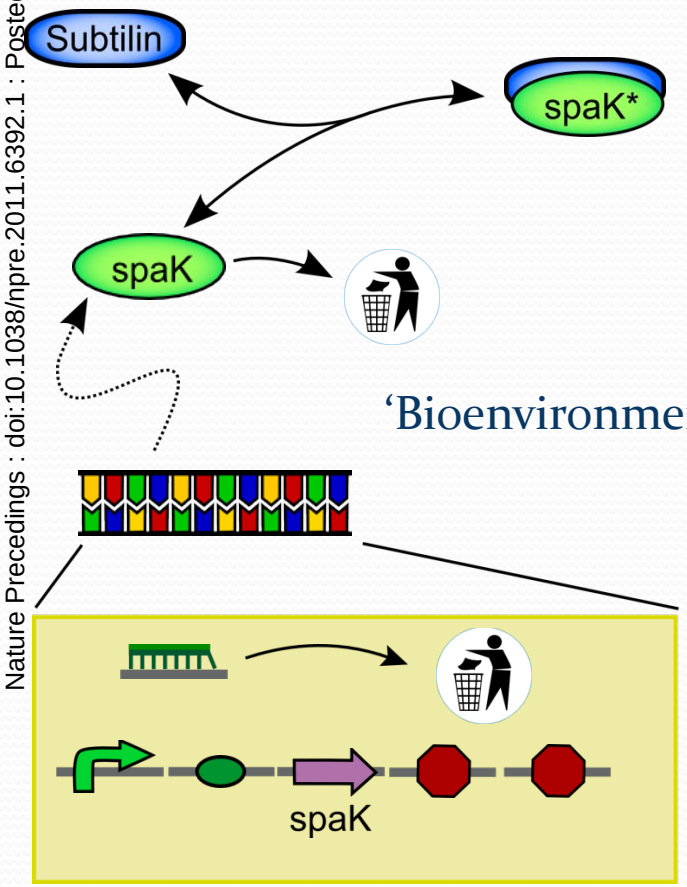
Simulate using OpenCell

License



....using 'off-the-shelf' components

Example



'Bioenvironment'

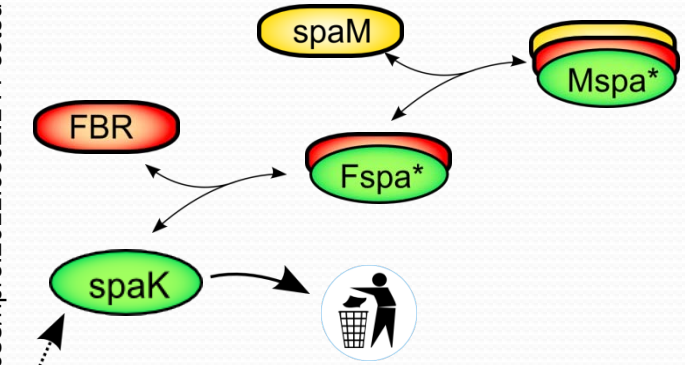
'System Models'

'SVPs' -Physical things or processes

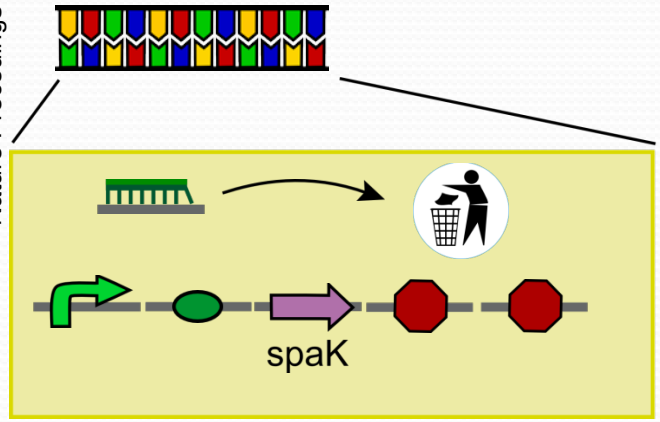
'Templates' – Mathematical structures

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

Example

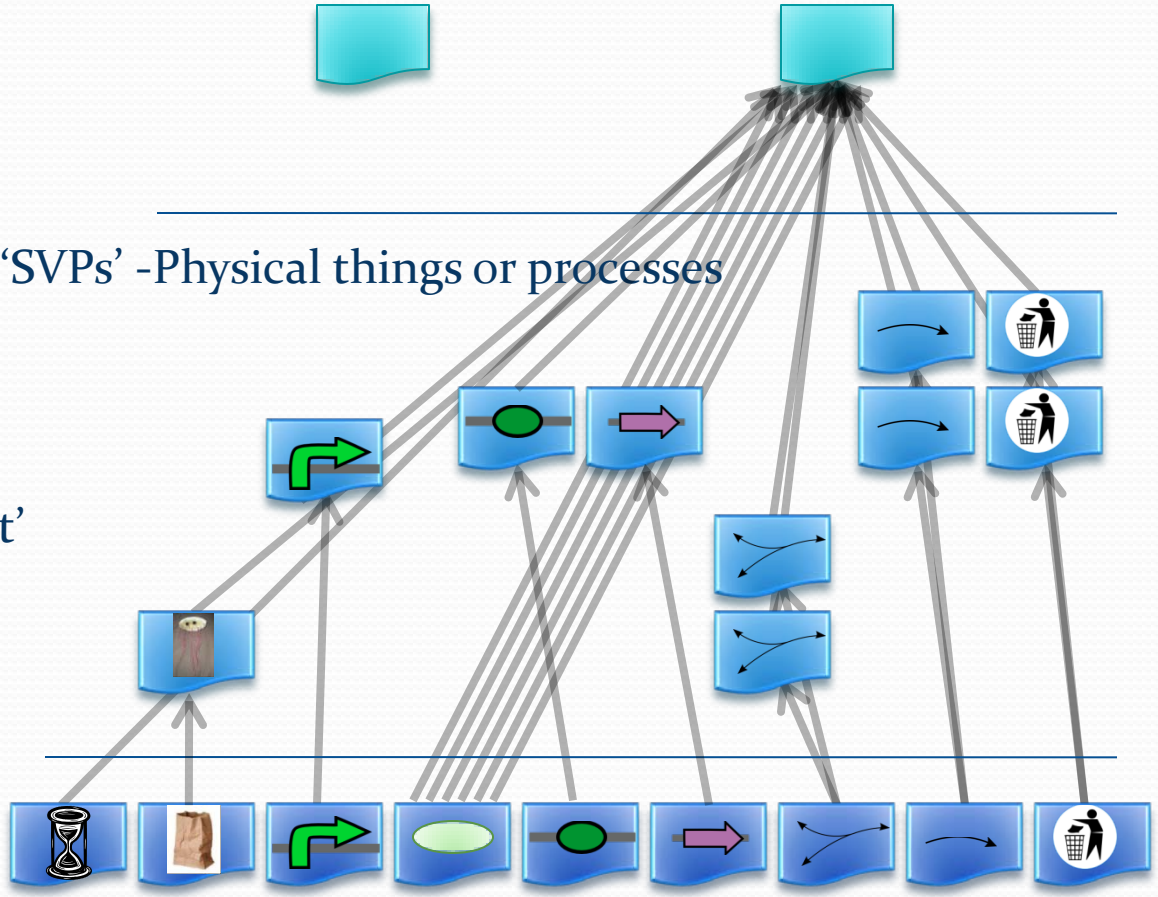


‘Bioenvironment’



‘System Models’

‘SVPs’ -Physical things or processes



‘Templates’ – Mathematical structures

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

Vascular (mal-)adaptation

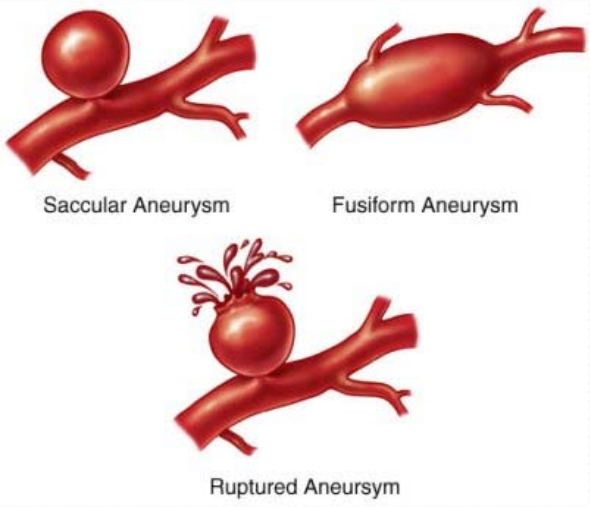
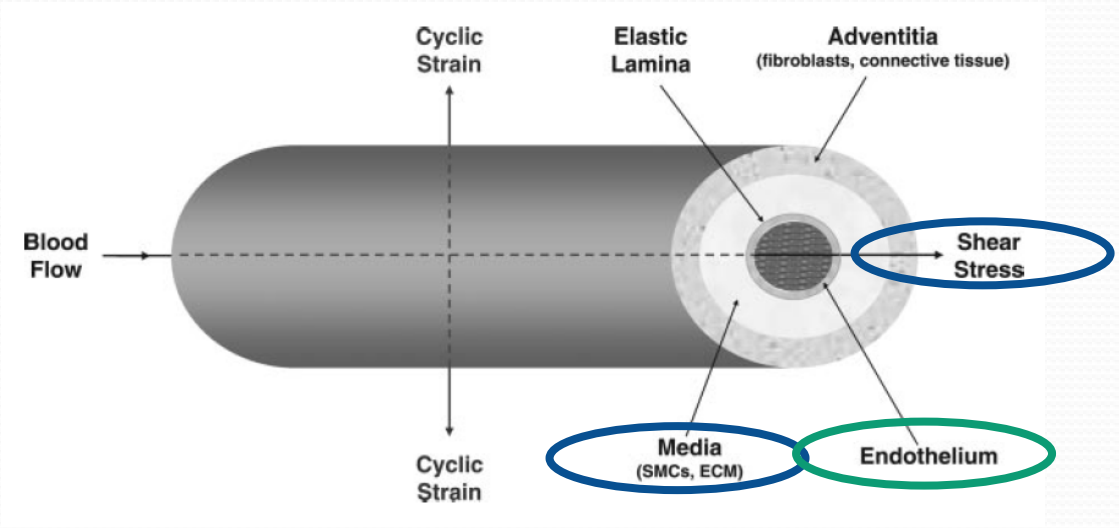


Image courtesy of The Internet Encyclopedia of Science



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

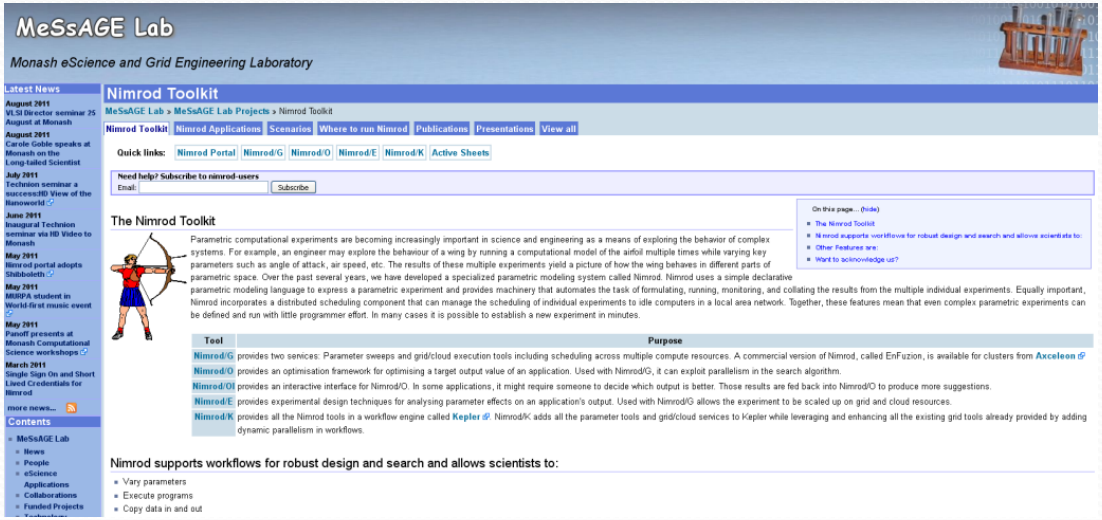
- 3 interacting cell types, extracellular matrix
- Narrow focus to: shear stress -> NO production in endothelial cells….
  - Regulated by 6-10 signalling pathways
  - 100s of components….

Modules are being reused, but…

- Concentrated on the 're' of 'reusable'…what about the 'usable'?
- 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
- Progress?

Analysis

- Sensitivity analysis services deployed on 'Nimrod' (Abramson et al. 1995)



- BeSTGRID (2010/2011)
  - CellML Simulator (not Matlab) - Nickerson
- MIASE
  - SED-ML

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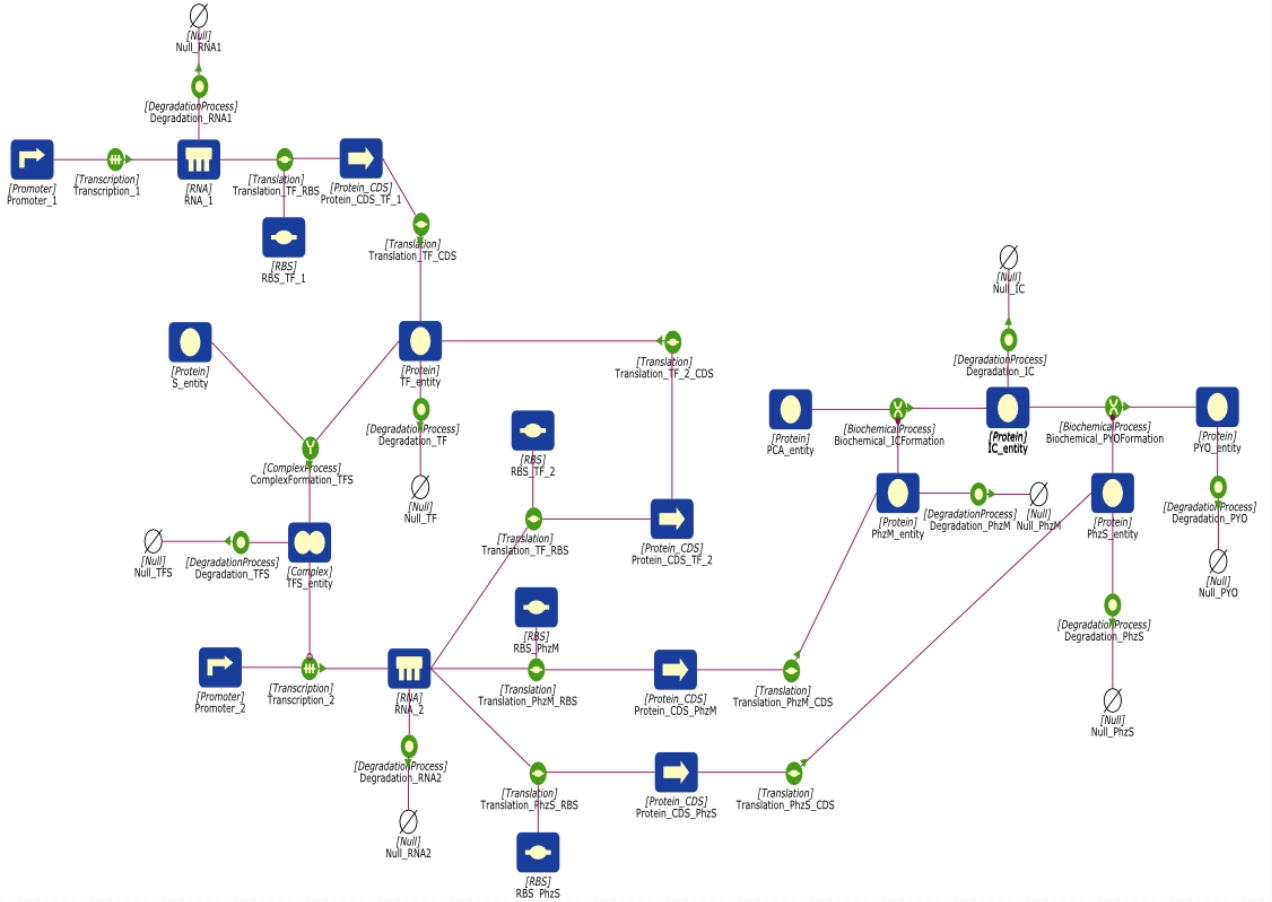
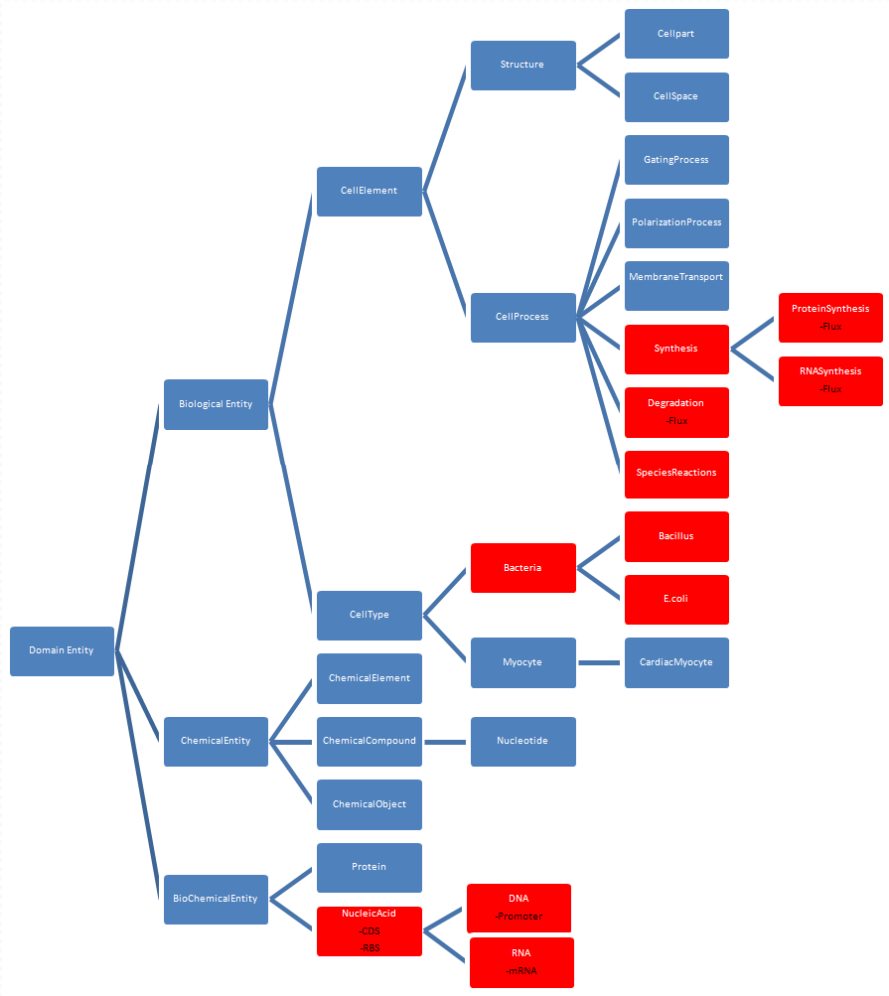
(Semi-Automated) Visualisation



Visualisation

- SBGN
  - Biological view
- Extension 1: Model structure view
  - Reusing other people's modules
  - One can easily make models that one needs time to re-understand 6 months later
- Extension 2: Presentation versus Action Language (Bennett J. "Building Decision Support Systems", Addison-Wesley 1983)
  - How to move between levels of abstraction (how well can it scale?), and views
- Prototype development pending…
- Semantic annotation to avoid idiosyncratic development

(Semi-Automated) Composition



(Semi-Automated) Composition

- Model structure important
- Several different approaches
  - Electrophysiology (Nickerson)
  - Visualisation (Wimalaratne)
  - Systems and Synthetic Biology (Cooling)
- ‘Best Practices’ (poster ICSB 2010)

Search

- Repositories or tombs?
- CellML Repository – keywords
- Annotation supporting
  - UI -> SPARQL? -> nice presentation
- Metadata specification 2.0 (poster)

Ecosystems

- (Tiwana et al. Info. Sys. Res. Dec 2010)
  - Platform – core services and interfaces
  - Modules – developed by many over time
- Examples
  - Firefox, Android, Eclipse
  - Not new to this group: exchange protocols, SBW
- Imagine the 'CellML Ecosystem'
  - Connect the services with 'standard' protocols…. use CellML API…. applications communicate via webservices….

Is that really the best we can do?

- Consider the above 'services' in the context of SBML, perhaps MatlabML, whatever-ML
- Who really cares what 'ML' the models are in?
  - Modellers?
  - Biologists?
  - Co.mbine participants?

Interoperability (future direction)

- I want to find, compose, visualise and analyse a mix of models no matter what format each is in
- What is the 'platform' really?
  - Not <some>ML + API
    - Makes software dev easier, user experience more complex
  - Semantic layer
- The more interesting question…
- Metadata Specification 2.0 <-> Annotation Package
- Try it with some 'real' models

Grateful to