

# Towards a Modelling Ecosystem for Libraries of Modular, Reusable Components

Mike Cooling, September 2011



# I want to make models...

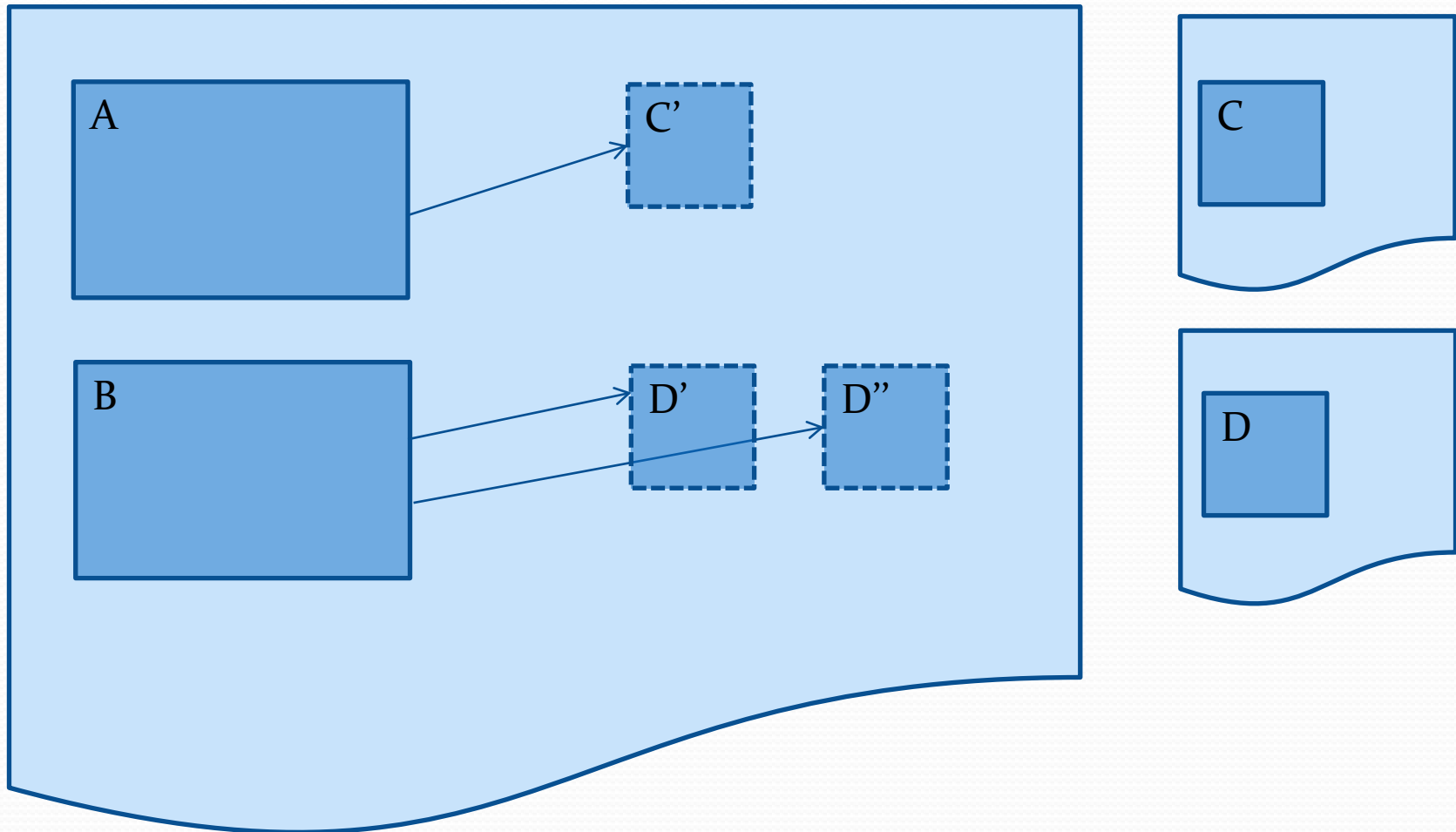
- Primarily interested in how cells work
- A 'user' (a hopeful one)

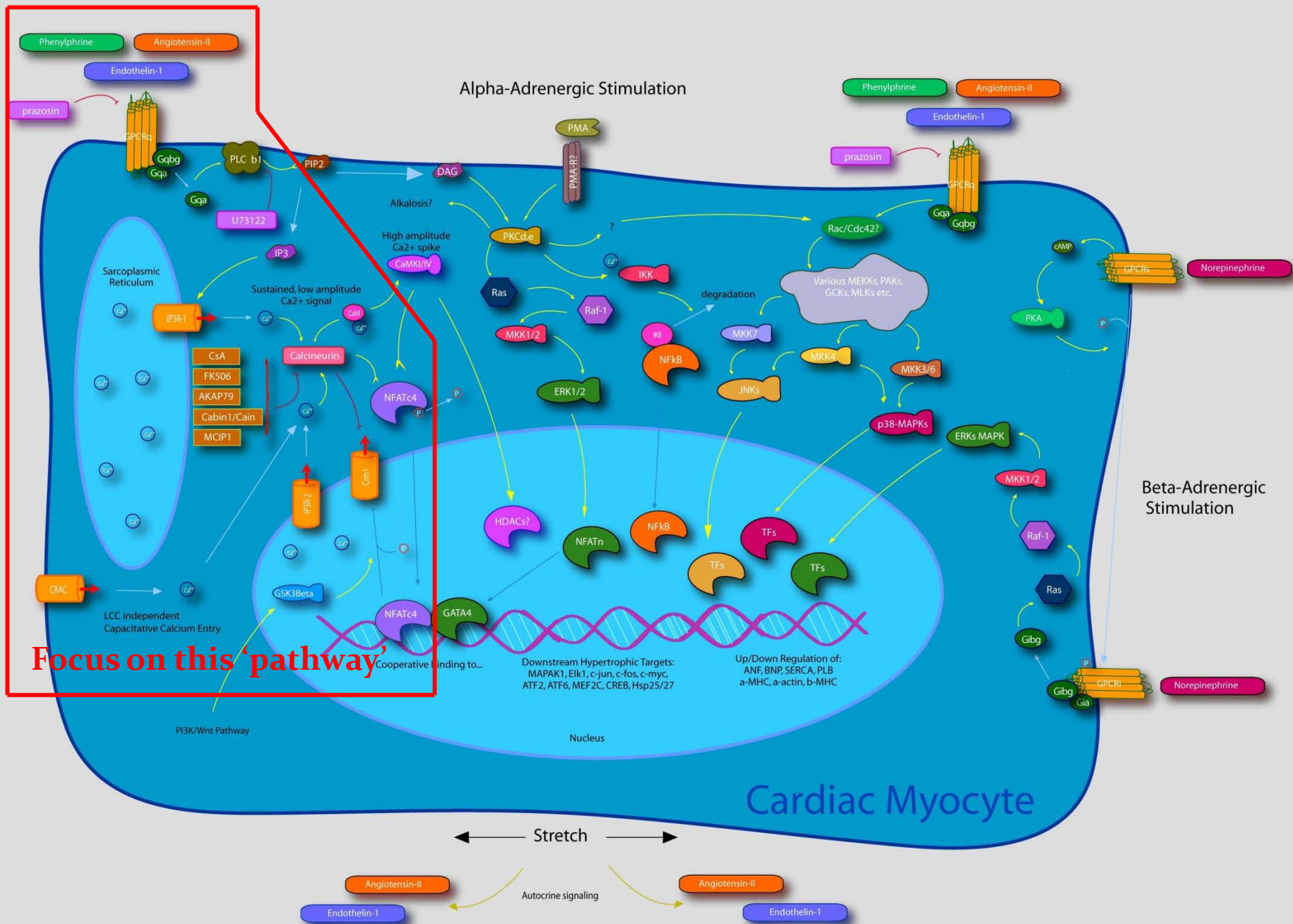


Hedley et al. (2001), Cuellar et al. (2003)

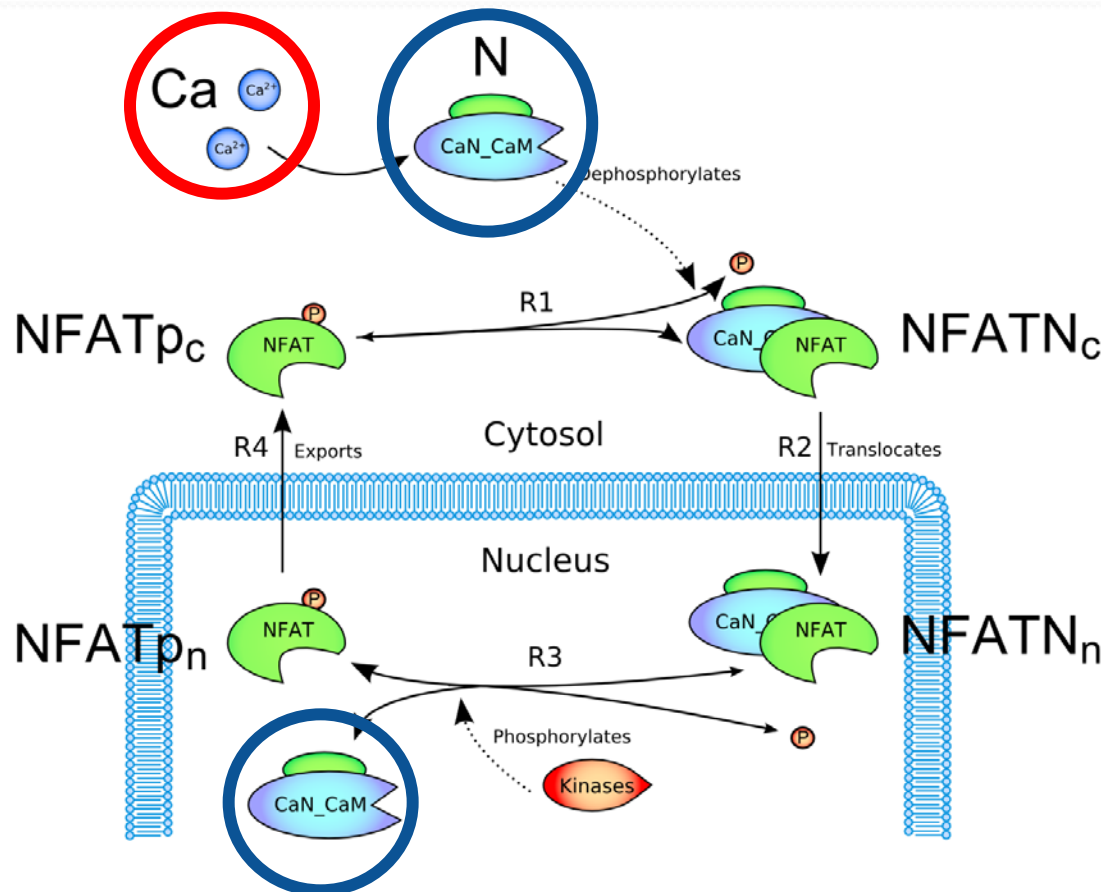
- Wrapper for MathML (which encodes maths)
- Partitioning the maths, variables into reusable pieces: 'components'
- Domain inspecific constructions
- Systems biology, synthetic biology, physiology
- Inherent support for modularity

# Importing





# Importing allows 'modules'



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



## Modelling Hypertrophic IP<sub>3</sub> 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.

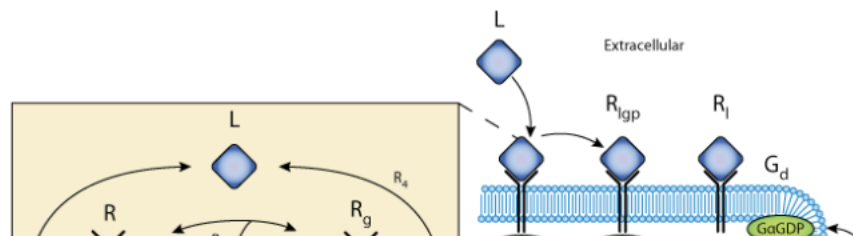
### Model Structure

**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 IP<sub>3</sub> - 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 IP<sub>3</sub> 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 IP<sub>3</sub> 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 IP<sub>3</sub> 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 IP<sub>3</sub> 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 [blad010d41a7](#).

### Downloads

[Complete Archive as .tgz](#)  
[Download This File](#)

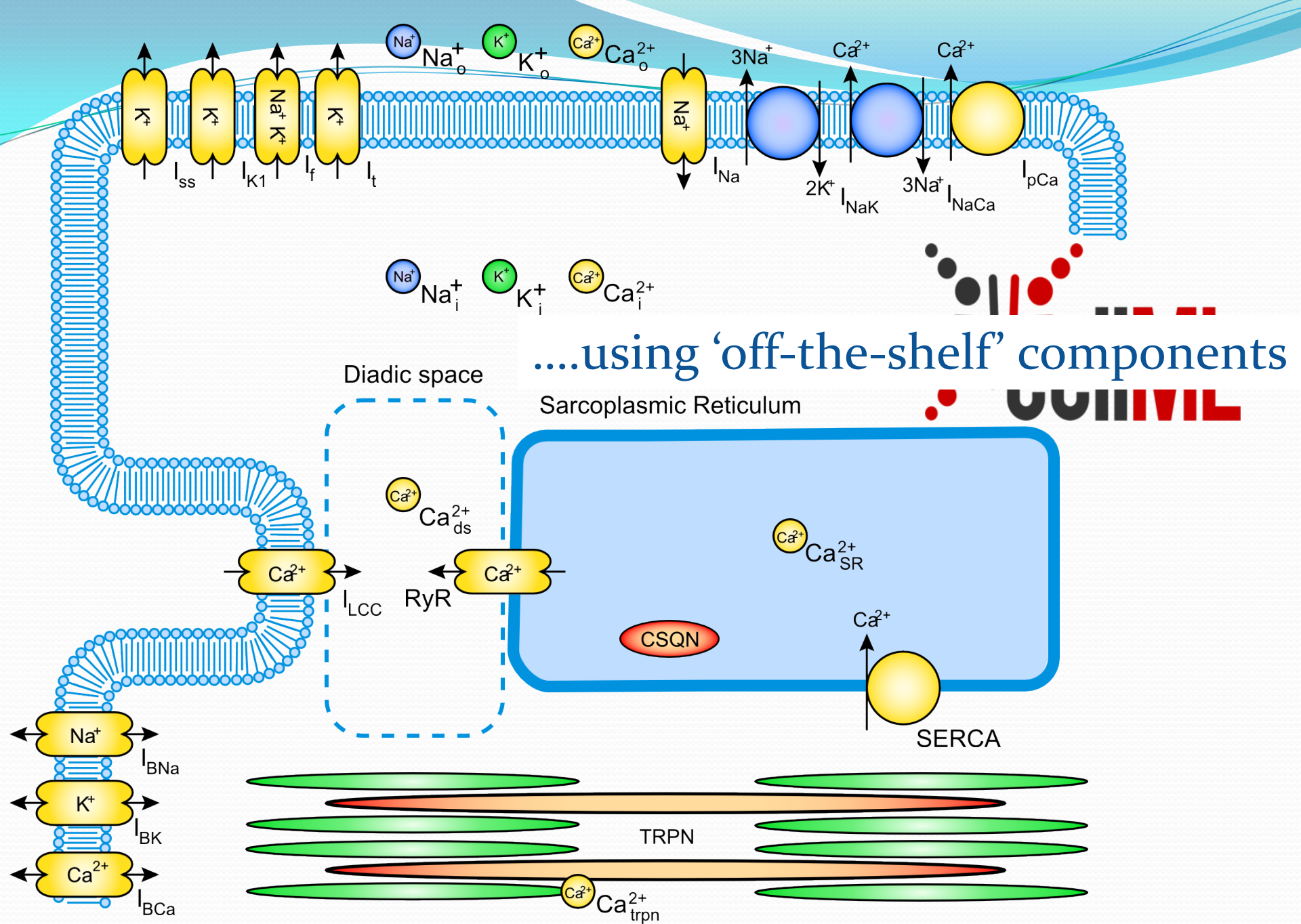
### Views available

[Model Metadata](#)  
[Mathematics](#)  
[Generated Code](#)  
[Cite this model](#)  
[Source View](#)  
[Simulate using OpenCell](#)

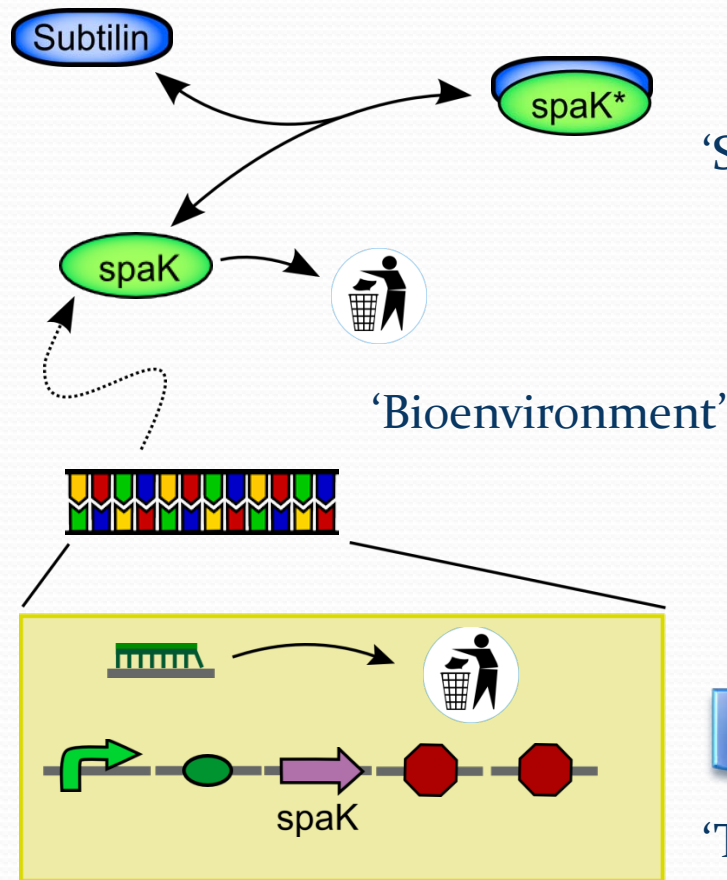
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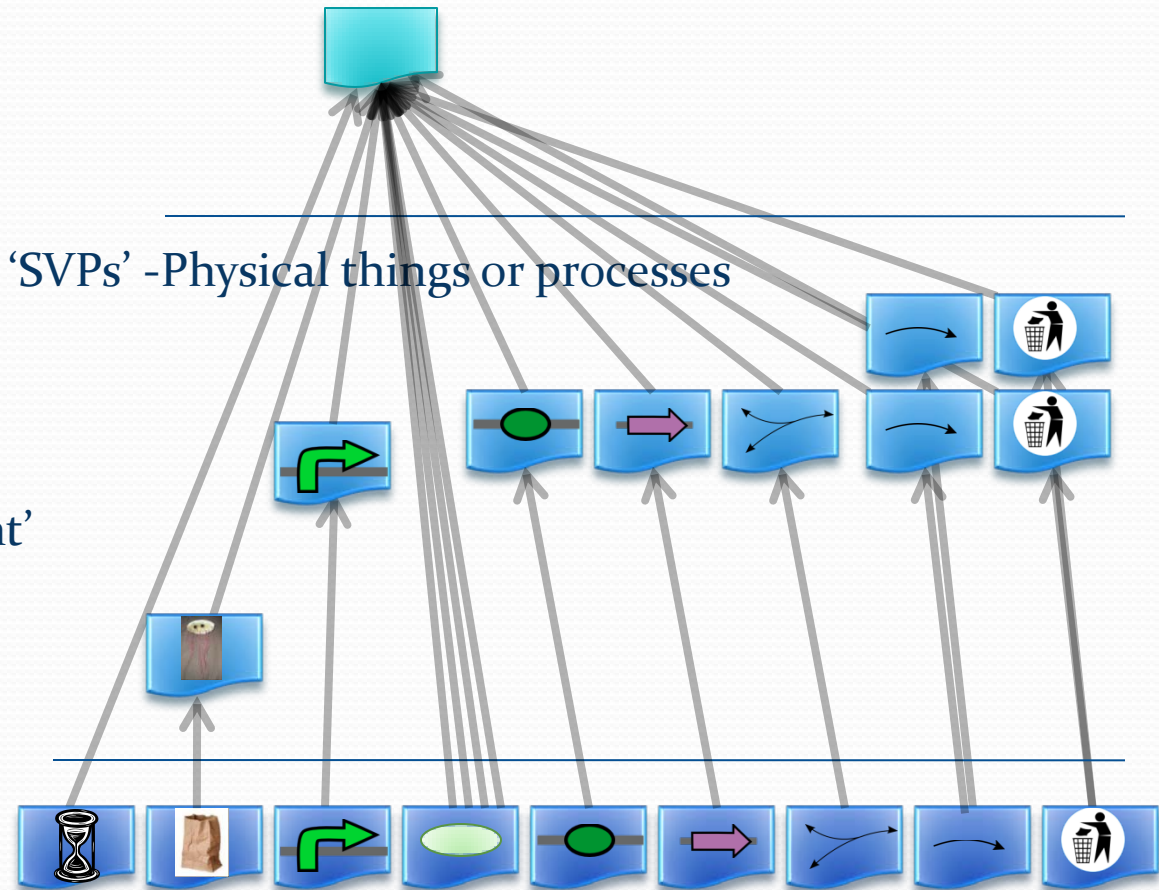


# Example



'System Models'

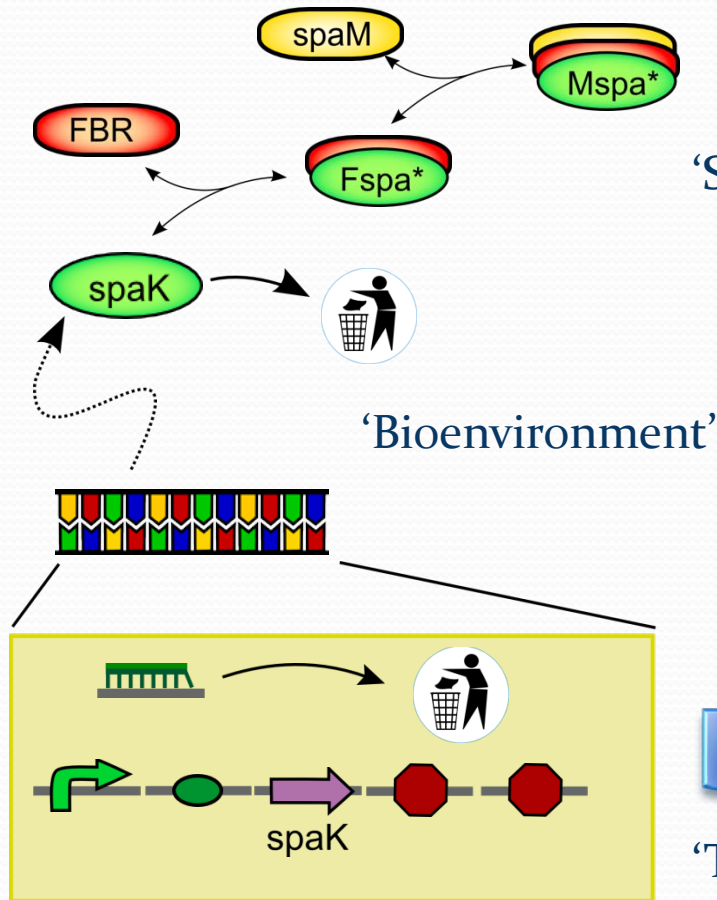
'SVPs' -Physical things or processes



'Templates' – Mathematical structures



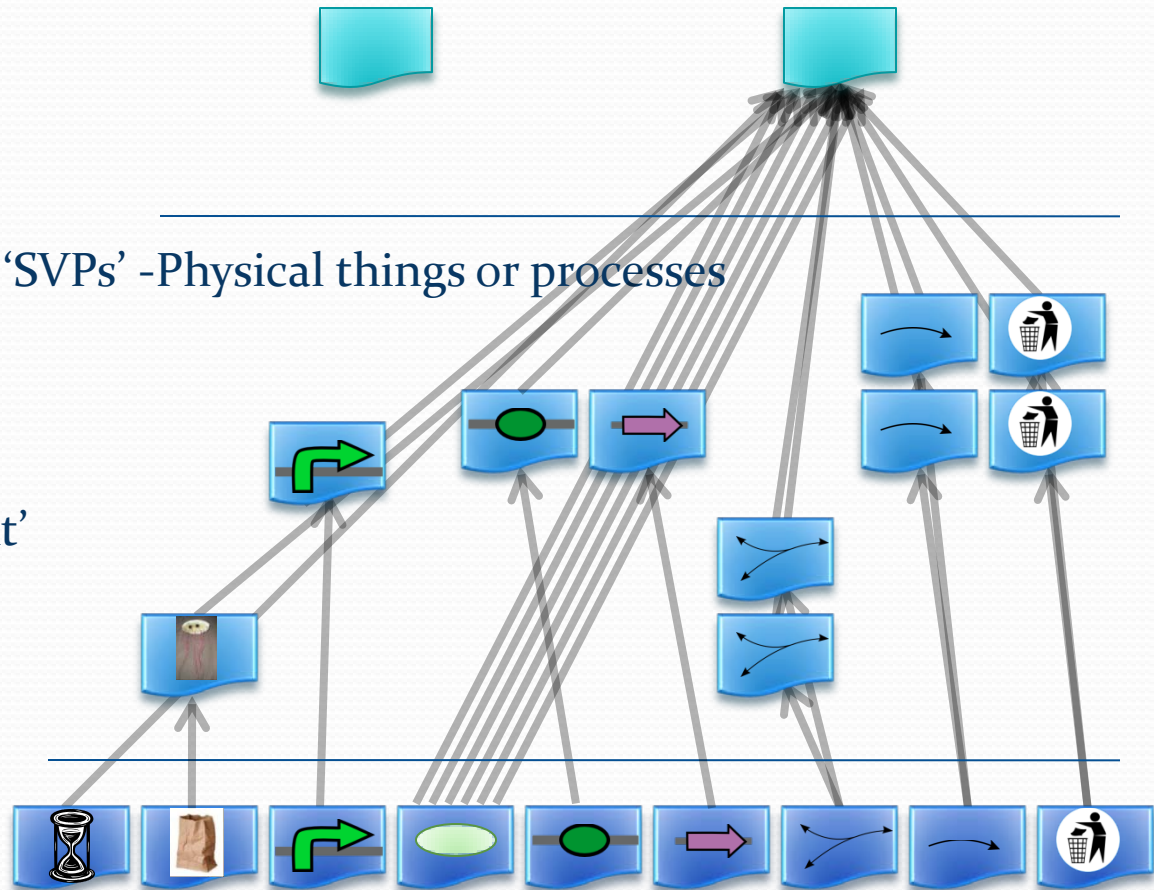
# Example



'System Models'

'SVPs' -Physical things or processes

'Templates' – Mathematical structures



# Vascular (mal-)adaptation

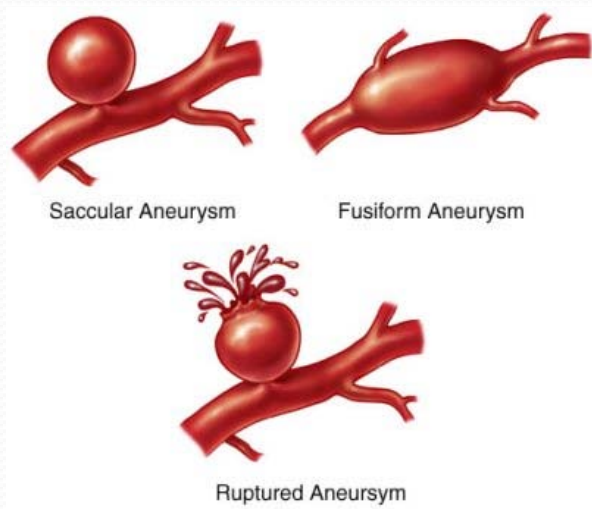
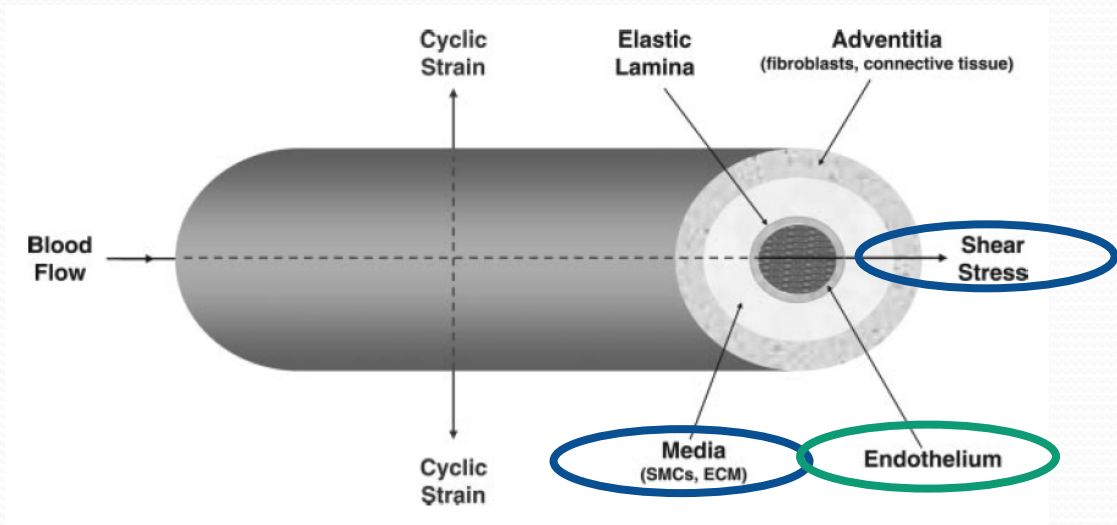


Image courtesy of The Internet Encyclopedia of Science



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

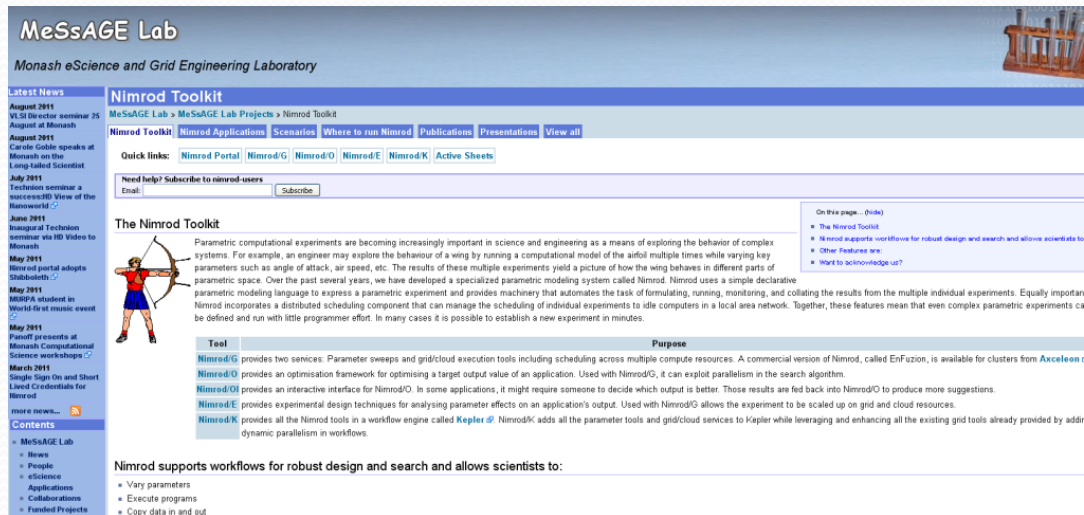
- 3 interacting cell types, extracellular matrix
- Narrow focus to: shear stress -> NO production in endothelial cells....
  - Regulated by 6-10 signalling pathways
  - 100s of components....

# 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, IWBD A)
  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)



The screenshot shows the MeSSAGE Lab website, which is part of the Monash eScience and Grid Engineering Laboratory. The page features a sidebar with 'Latest News' and a main content area titled 'Nimrod Toolkit'. The 'Nimrod Toolkit' section includes a navigation bar with links to 'Nimrod Applications', 'Scenarios', 'Where to run Nimrod', 'Publications', 'Presentations', and 'View all'. Below this, there are 'Quick links' to 'Nimrod Portal', 'Nimrod/G', 'Nimrod/O', 'Nimrod/E', 'Nimrod/K', and 'Active Sheets'. A 'Need help? Subscribe to nimrod-users' section is also present. The main text describes the Nimrod Toolkit as a specialized parametric modeling system that automates the task of formulating, running, monitoring, and collating the results from multiple individual experiments. It includes a table with the following content:

Tool	Purpose
Nimrod/G	provides two services: Parameter sweeps and grid/cloud execution tools including scheduling across multiple compute resources. A commercial version of Nimrod, called EnFuzion, is available for clusters from <a href="#">Axcelion</a> .
Nimrod/O	provides an optimisation framework for optimising a target output value of an application. Used with Nimrod/G, it can exploit parallelism in the search algorithm.
Nimrod/E	provides an interactive interface for Nimrod/O. In some applications, it might require someone to decide which output is better. Those results are fed back into Nimrod/O to produce more suggestions.
Nimrod/K	provides experimental design techniques for analysing parameter effects on an application's output. Used with Nimrod/O allows the experiment to be scaled up on grid and cloud resources.

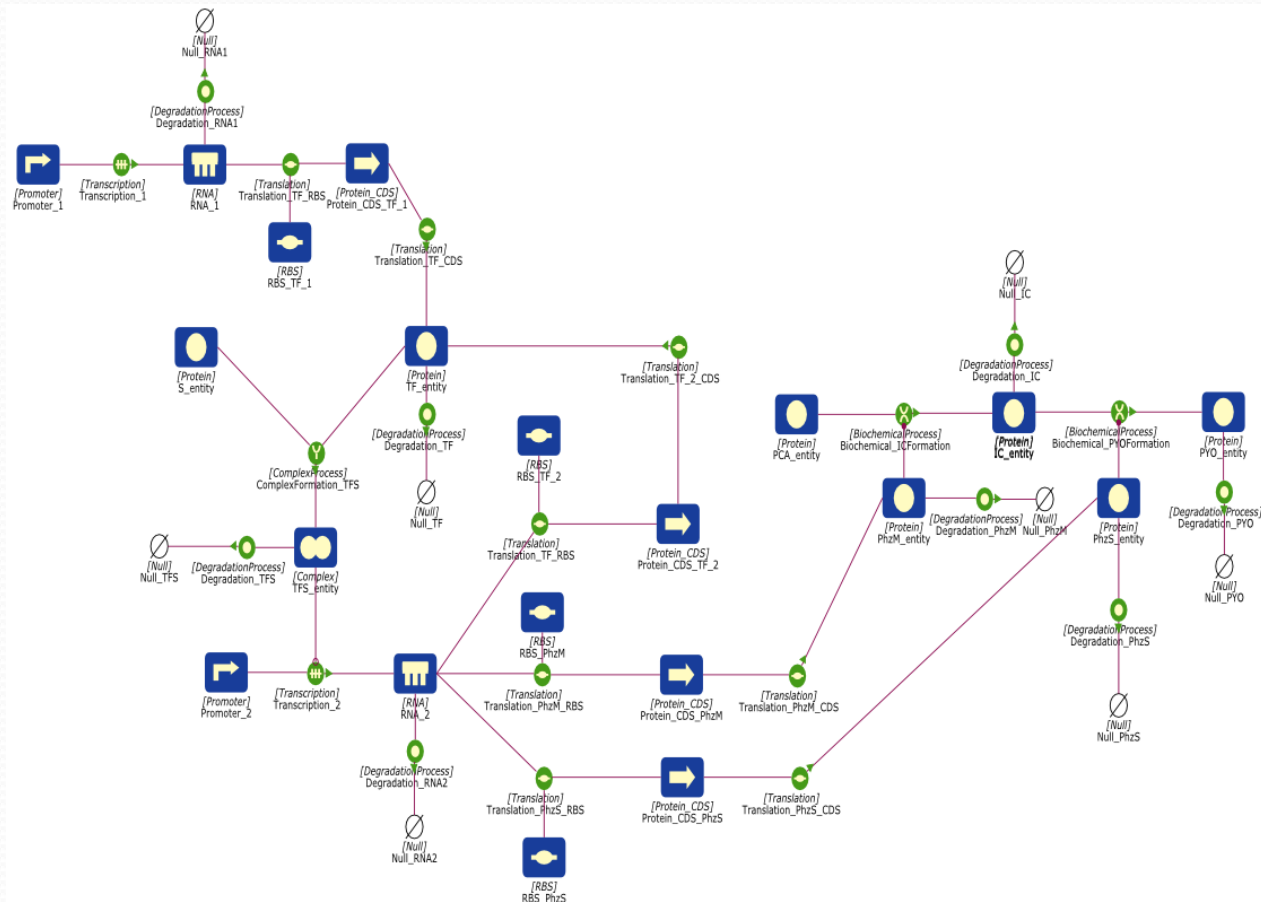
Below the table, it states: 'Nimrod/K provides all the Nimrod tools in a workflow engine called [Kepler](#). Nimrod/K adds all the parameter tools and grid/cloud services to Kepler while leveraging and enhancing all the existing grid tools already provided by adding dynamic parallelism in workflows.'

The page also mentions: 'Nimrod supports workflows for robust design and search and allows scientists to:'

- Vary parameters
- Execute programs
- Copy data in and out

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

# (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

