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The JigCell Model Builder and Run Manager

Marc Vass[1], Nicholas Allen[1], Clifford A. Shaffer[1,*],
Naren Ramakrishnan[1], Layne T. Watson[1] and John J. Tyson[2]

[1] Department of Computer Science and [2] Department of Biology, Virginia Polytechnic Institute and State University, Blacksburg, VA 24061-0106, USA

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ABSTRACT

Summary: We describe the JigCell Model Builder (JCMB), a tool for creating biochemical reaction network models. JCMB is designed for ease of use and its interface uses the standard spreadsheet metaphor. The JigCell Run Manager (JCRM) is a tool for organizing the large collections of simulation runs typically required by reaction network modeling activities.

Availability: JCMB and JCRM are part of the JigCell suite available at http://jigcell.biol.vt.edu

Contact: shaffer@cs.vt.edu

JCMB IMPLEMENTATION

Fundamental activities for modelers of biochemical reaction networks are to create a model, edit the model and execute simulations of the model. We describe two tools for doing these tasks: the JigCell Model Builder (JCMB) and the JigCell Run Manager (JCRM). Both use a standard spreadsheet metaphor for their user interface. Spreadsheets are familiar to typical users of the system and match their mental model for biochemical reaction networks. Spreadsheets are efficient in their use of screen space and provide information in a compact form. Our implementations scale well with model size. JCMB has been tested and found to be reasonably efficient with models containing hundreds of reactions, far larger than any hand-generated models currently in use.

JCMB users define models as a set of reaction equations (Fig. 1). Model definitions are saved in the Systems Biology Markup Language (SBML) (Hucka *et al*., 2003). A design goal of JCMB is to reduce the number of errors in the modeling process. The spreadsheet interface allows modelers to visualize the entirety of many current models on one screen, and to express models in the language of the domain. Modelers can see and specify a chemical equation, its associated rate law and constants on the same line.

When models are built by hand, the user types in the reaction equations while frequently consulting a wiring diagram. This process is error prone for many reasons. Typos and copy-paste mistakes are inevitable because of the tedium and repetitiveness of the process. Other common errors are incorrectly specifying the reaction rate law, leaving off terms from the right-hand side of the fundamental equation and incorrectly applying conservation conditions. If a conservation condition is overlooked, then the set of differential equations contains redundancies, and round-off errors in simulations can lead to violations of mass conservation. More seriously, modelers may mistakenly identify conservation conditions, which lead to differential equations that are incorrect.

JCMB attempts to reduce these errors by adopting a reaction-centered approach that separates a reaction from its rate law specification. This allows the computer to apply the specified rate law to discover the velocity for a particular reaction, which is then shown to the user in a separate column. Errors are shown to users by coloring inconsistent cells in orange.

Output formats. The native file format of JCMB is SBML. JCMB also supports other output formats: xpp for the simulation engines XPPAUT (Ermentrout, 2002) and WinPP, Fortran90 for use with LSODAR (Hindmarsh, 1980) and tab-delimited text.

JCRM IMPLEMENTATION

JCRM organizes related simulation specifications into a collection. A single simulation specification can be run to view the output of a model or for matching against a biological experiment. The purpose of a collection is to organize information stored by the biologist in many different files and in his or her head. Storing simulation run settings in multiple files allows for changes that make the specification inconsistent or invalid. JCRM seeks to prevent that problem.

JCMB stores specifications in sets. These sets can be derived from other sets, forming a tree. This allows a set to inherit changes in parameters and initial conditions, avoiding repeated entry. Inheritance is defined in a column called '`derived from`', which allows a user to see at a glance the relationships between sets.

To specify a simulation run, the user must provide a model, a parameter set, an initial condition set and a simulator

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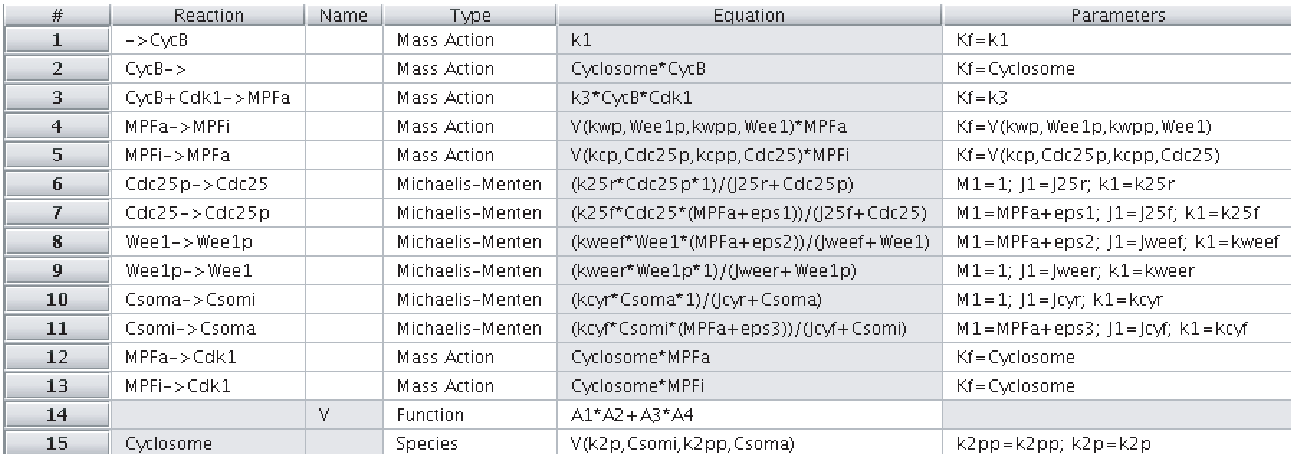
[*] To whom correspondence should be addressed.



#	Reaction	Name	Type	Equation	Parameters
1	->CycB		Mass Action	k1	Kf=k1
2	CycB->		Mass Action	Cyclosome*CycB	Kf=Cyclosome
3	CycB+Cdk1->MPFa		Mass Action	k3*CycB*Cdk1	Kf=k3
4	MPFa->MPFi		Mass Action	V(kwp,Wee1p,kwpp,Wee1)*MPFa	Kf=V(kwp,Wee1p,kwpp,Wee1)
5	MPFi->MPFa		Mass Action	V(kcp,Cdc25p,kcpp,Cdc25)*MPFi	Kf=V(kcp,Cdc25p,kcpp,Cdc25)
6	Cdc25p->Cdc25		Michaelis-Menten	(k25r*Cdc25p*1)/(J25r+Cdc25p)	M1=1; J1=J25r; k1=k25r
7	Cdc25->Cdc25p		Michaelis-Menten	(k25f*Cdc25*(MPFa+eps1))/(J25f+Cdc25)	M1=MPFa+eps1; J1=J25f; k1=k25f
8	Wee1->Wee1p		Michaelis-Menten	(kweef*Wee1*(MPFa+eps2))/(Jweef+Wee1)	M1=MPFa+eps2; J1=Jweef; k1=kweef
9	Wee1p->Wee1		Michaelis-Menten	(kweer*Wee1p*1)/(Jweer+Wee1p)	M1=1; J1=Jweer; k1=kweer
10	Csoma->Csomi		Michaelis-Menten	(kcyr*Csoma*1)/(Jcyr+Csoma)	M1=1; J1=Jcyr; k1=kcyr
11	Csomi->Csoma		Michaelis-Menten	(kcyf*Csomi*(MPFa+eps3))/(Jcyf+Csomi)	M1=MPFa+eps3; J1=Jcyf; k1=kcyf
12	MPFa->Cdk1		Mass Action	Cyclosome*MPFa	Kf=Cyclosome
13	MPFi->Cdk1		Mass Action	Cyclosome*MPFi	Kf=Cyclosome
14		V	Function	A1*A2+A3*A4	
15	Cyclosome		Species	V(k2p,Csomi,k2pp,Csoma)	k2pp=k2pp; k2p=k2p

Fig. 1. Frog egg extract model in JCMB.

configuration. The model must be in the SBML format. JCRM lets the user specify parameters, initial conditions and the simulation configuration. JCRM automatically discovers potential simulator configuration values by sending at runtime a network query asking for all simulators currently available to JCRM within the JigCell system. The list of available simulators and their associated parameters are then presented to the user.

Once a user is satisfied with their run settings, he or she can make a run by clicking the 'Plot' button. User may choose the species to plot against the time axis. To see a detailed view of the data, user clicks on the 'View' button to view a table of the simulation points.

DISCUSSION

JCMB and JCRM are used as a part of the JigCell problem solving environment, a component of the DARPA BioSPICE project. Each application can be used individually. JCRM can communicate directly with other BioSPICE components through the use of an OAA interface. The software is written in Java and supported platforms at this time are Windows, Linux and Solaris. Models of the cell cycle in fission yeast, budding yeast and frog eggs have been entered into JCMB. Runs matching experiments on budding yeast and frog eggs have been entered into JCRM. Figure 1 shows a current version of a frog egg extract model in JCMB.

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