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Web-based kinetic modelling using JWS Online

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Abstract

Summary: JWS Online is a repository of kinetic models, describing biological systems, which can be interactively run and interrogated over the internet. It is implemented using a client-server strategy where the clients, in the form of web-browser based Java applets, act as a graphical interface to the model servers, which perform the required numerical computations.
Availability: The JWS online website is publicly accessible at http://jjj.biochem.sun.ac.za/ with a mirror at http://www.jjj.bio.vu.nl/
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Overview

Kinetic models are powerful tools for describing and understanding the behaviour of complex cellular systems. Since the 1960's and especially in the last decade a large number of these models have been constructed and today form the basis for projects such as the Silicon Cell, SiC! (http://www.siliconcell.net/). However, key problems are often encountered by biologists who would like to study these models. For example, no central model database exists for kinetic models, making it difficult to find all the relevant information needed to build and study published models. Even when models are publicly available they often require a specific software environment to run in. This environment typically includes software that might be either operating system dependent, expensive to obtain or difficult to set up and maintain. New initiatives, such as the one by the System Biology Markup Language (SBML) Working Group (http://www.sbml.org/), are beginning to address the problem of model interchange by creating a standard language for describing biochemical reaction networks. Using SBML, modelers may easily exchange models between compatible applications such as Gepasi (Mendes 1997) or Jarnac (Sauro 2000). Currently, only a limited number of models are available in SBML format. A need, therefore, exists for both a central repository of kinetic models as well as a freely accessible, platform independent and user-friendly modelling interface that allows these models to be run using the Internet.

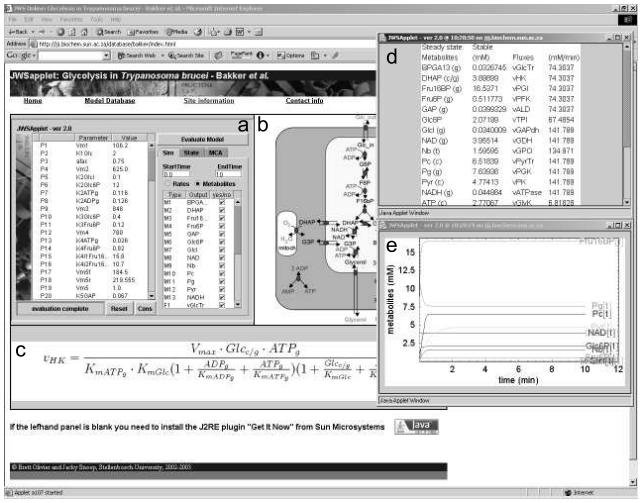

Figure 1: A typical `model` page showing: a. interactive applet, b. model reaction scheme, c. a highlighted rate equation d. steady-state output and e. time simulation result.

On visiting the JWS Online sites, which are freely available from a growing number of international locations, the `database` page contains all the currently available online models. These range in type from those built with realistic parameters - so called 'silicon cell' models typically obtained from literature e.g. (Helfert et al. 2001) - to 'core' models useful for teaching purposes. The database page also contains links to any relevant bibliographic information and we have established a collaboration with the SBML working group to make SBML versions of the models in the database available for download.

Once requested from the database the `model` page is

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displayed, as shown in Fig. 1. It consists of two main sections: the client applet Fig. 1a and its metabolic reaction scheme Fig. 1b. The applet acts as a graphical interface to the server and three types of analyses are available: a time simulation, steady-state analysis and metabolic-control analysis. The model parameters may easily be changed by setting their values in an input table situated on the left side of the applet. The type of analysis to be performed may be selected using the tabbed panel on the applet's righthand side. Each analysis type has various sub-options that become available on its selection. The time simulation allows either selected metabolite concentrations or enzyme rates to be output as required. Metabolic Control Analysis (MCA) is used to study the control properties of the system at steady state (Kacser and Burns 1973). The steady-state solution of the system may be calculated as well as various structural properties of the system (such as the K and L matrices) (Hofmeyr 2001), elasticities and control coefficients. If the mouse cursor is moved over an enzyme on the reaction scheme the selected step's rate equation is displayed in the lower window, Fig. 1c. All results are returned to the applet and displayed individually as shown in Fig. 1d and Fig. 1e.

Implementation

In order to make the JWS Online system as widely accessible and platform independent as possible the clients were written as Java™ applets (http://java.sun.com). Using Sun Microsystems Java Runtime Environment (J2RE) plugin a stable, cross-platform environment is created for running the client applets. Using the J2RE 1.4 plugin the applets have successfully run under: Microsoft Windows 98, 2000 and XP with Internet Explorer 5+ or Netscape 6+; Mandrake Linux 9.1 using Mozilla; MacOS X and Safari. The server acts as a communications gateway and interfaces with Wolfram Research's Mathematica™ (http://www.wolfram.com). Using the Mathematica Kernel for numerical processing allows access to industry standard algorithms, extensive numerical libraries and seamless integration with Java using the J/Link toolkit, also available from Wolfram Research. The model servers are able to handle multiple, simultaneous connections and for ODE based models the process of generating the applets and models is almost completely automated.

Hopefully, we have shown that JWS Online is a useful tool for the study of cellular systems. In order to keep the database up to date we are collaborating with various journals in order to facilitate the swift addition of published models into the database. We also welcome submissions by email. As our database expands and we can begin piecing models together, we hope JWS Online will make a meaningful contribution towards building the Silicon Cell.

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