SYCAMORE—a systems biology computational analysis and modeling research environment

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In order to facilitate the set-up, simulation and analysis of new biochemical models, particularly by non-expert users, we developed SYCAMORE. SYCAMORE is a web-based system that integrates different online applications as well as locally installed software. It provides user guidance for the sequence of steps associated with model building (especially based on database knowledge), model checking, simulation and analysis of results. Moreover, it offers some unique features, e.g. access to protein structure-based parameter estimation (Gabdoulline \textit{et al.}, 2007). Thus, it does not compete with web-based applications like WebCell (Lee \textit{et al.}, 2006), VCell (Schaff \textit{et al.}, 1997) or JSim (Raymond \textit{et al.}, 2003) which are online simulation and analysis tools, but rather should serve as a kind of expert system facilitating the setting up of the models. To really analyse a final model in detail SYCAMORE interfaces with locally installed tools like COPASI (Hoops \textit{et al.}, 2006) and does not intend to substitute or compete with this class of tools.

SYCAMORE aids the user in ensuring that their files are compatible with the SBML (Hucka \textit{et al.}, 2003) file standard for biochemical models. This facilitates the exchange and re-useability of kinetic models in systems biology. SYCAMORE also facilitates the searching of enzymatic reaction kinetics databases such as BRENDA (Schomburg \textit{et al.}, 2004) and SABIO-RK (Wittig \textit{et al.}, 2006) which contain kinetic parameters and kinetic equations that are required for setting up a kinetic model.

1 INTRODUCTION

Finding answers to the complexity of questions emerging in modern biology requires the use of quantitative, computational approaches. For example, the experimental and mathematical modelling of biochemical networks in systems biology has a strong theoretical component. However, the use and applicability of computational methods in systems biology is often hampered by the complexity of the software tools available to support the modelling tasks. One effort towards offering a better support to the user in the application of several different tools available is the Systems Biology Workbench (SBW; Sauro \textit{et al.}, 2003). SBW provides the seamless integration of different local software tools allowing the user to carry out several types of analysis with one or several models. However, the system does not provide any support for non-expert users in the task of model definition and analysis. Databases of models such as BioModels (Le Novère \textit{et al.}, 2006) and JWSOnline (Olivier and Snoep, 2004) offer certainly another important aspect of support for the community by providing models and in the latter case the option to simulate and analyse these online.

|ABSTRACT|

\textbf{Summary:} SYCAMORE is a browser-based application that facilitates construction, simulation and analysis of kinetic models in systems biology. Thus, it allows e.g. database supported modelling, basic model checking and the estimation of unknown kinetic parameters based on protein structures. In addition, it offers some guidance in order to allow non-expert users to perform basic computational modelling tasks.

\textbf{Availability:} SYCAMORE is freely available for academic use at http://sycamore.eml.org. Commercial users may acquire a license.

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2 DESCRIPTION

SYCAMORE is a web-browser-based application (see the screenshot in Fig. 1) running on Tomcat and currently supporting the Internet Explorer, Firefox, Mozilla web browsers running on Linux, Mac and Windows operating systems. It is mainly based on Java Server Pages (JSP) technology.

In the following, we describe SYCAMORE by a typical use case scenario in some detail.

2.1 Use case

Suppose the user is interested in simulating the first two steps of glycolysis in human hepatocytes. First a model has to be set-up.
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3 OUTLOOK

Currently, SYCAMORE interfaces with online tools, such as databases containing kinetic data, as well as with locally installed tools if these are SBML compatible and possess a command line version. Currently, support is offered for COPASI and ProMoT. We will extend SYCAMORE to interface with additional tools. Furthermore, tools will be added to transfer data back to SYCAMORE in a seamless fashion. User guidance is planned to be improved further by including wizards and other help functions.

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REFERENCES


Fig. 1. A screenshot of SYCAMORE showing parameter sensitivity analysis of the steady state concentrations of metabolites in an example system with respect to altering reaction parameters. The panel on the left allows the user to navigate through the functionalities of SYCAMORE. Thus, one may Load Existing Model from disk or from the SYCAMORE server, Build New Model within SYCAMORE, e.g. in a database supported manner, View and Edit Model, Refine and Analyze Model to check for model completeness, perform a sensitivity analysis, start a simulation on the SYCAMORE server or locally, perform a parameter estimation based on protein structural data or locally using experimental data and Save Model.

Fig. 2. Workflow in SYCAMORE.

For this, SYCAMORE provides an interface to the SABIO-RK database to permit the user to locate and select the relevant kinetic data for these two reaction steps. Once the data have been selected and sent to SYCAMORE, the parameters can be adjusted in the SYCAMORE editor, e.g. to make the units used consistent. SYCAMORE also allows the user to add further reactions, e.g. to make the system open and define an influx of glucose and an efflux of fructose-6-phosphate. SYCAMORE will then enable the user to check the model for completeness as regards the kinetic equations and their parameters. If parameters are missing, SYCAMORE provides search tools to locate relevant data for parameter estimation and the ability to estimate parameters using protein structural data or perform a classical parameter estimation using experimental data and locally installed software. In the case of the protein structural data, electrostatic distances between related proteins are computed and the kinetic parameters for the electrostatically most similar protein can be chosen (for details of the method see Gabdoulline et al., 2007). A parameter sensitivity analysis can also be performed (Figure 1). Once the model is complete, a simulation can be carried out on the SYCAMORE server using COPASI (Hoops et al., 2006) with SYCAMORE displaying a plot of the resulting time course or by launching locally installed software, e.g. COPASI or ProMoT (Ginkel et al., 2003). Figure 2 shows the workflow in SYCAMORE, highlighting the steps through which the user is guided.

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