Modeling biological systems using Dynetica—a simulator of dynamic networks

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ABSTRACT

Summary: We present Dynetica, a user-friendly simulator of dynamic networks for constructing, visualizing, and analyzing kinetic models of biological systems. In addition to generic reaction networks, Dynetica facilitates construction of models of genetic networks, where many reactions are gene expression and interactions among gene products. Further, it integrates the capability of conducting both deterministic and stochastic simulations.

Availability and supplementary information: Dynetica 1.0, example models, and the user’s guide are available at http://www.its.caltech.edu/~you/Dynetica/Dynetica_page.htm

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Despite its potential benefits for fundamental and applied biological research, application of kinetic modeling has been hindered by the lack of powerful and easy-to-use software tools for model construction and analysis. This is particularly true for experimental biologists who are often unfamiliar with numerical methods and programming. Recently, several programs, such as Gepasi (Mendes, 1993), DBsolve (Goryanin et al., 1999), E-Cell (Tomita et al., 1999), SCAMP (Sauro, 1993) STELLA (Hargrove et al., 1993), Virtual Cell (Schaaf et al., 1997), StochSim (Morton-Firth and Bray, 1998), and STOCKS (Kierzek, 2002), have been developed to facilitate model construction and analysis. Extensive discussion of progress in the development of modeling tools can be found in excellent recent reviews (Arkin, 2001; Loew and Schaff, 2001).

Here we present Dynetica (a simulator of dynamic networks), a general-purpose computational framework for creating, visualizing, and analyzing mathematical models of biological networks. Dynetica is distinct from other programs in three aspects: (1) it facilitates the construction of kinetic models of genetic networks where most reactions are expressions of genes; (2) it provides a visual representation of each model for interactive manipulation and interrogation; (3) it allows time-course simulations using both deterministic and stochastic algorithms. We anticipate that Dynetica will contribute significantly to advancing broader application of kinetic modeling in biological systems.

A reaction network in Dynetica consists of substances that interact with one another via a list of reactions (Fig. 1). Kinetics of these reactions may be specified by a list of parameters. A reaction in Dynetica is characterized by two attributes: its stoichiometry, which specifies the quantitative relationship between the substances in a reaction, and its kinetics, which specifies how fast (for non-equilibrated reactions) or to what extent (for equilibrated reactions) the reaction occurs. Dynetica employs two modules to describe generic reaction networks: a reaction parser and a mathematical expression parser. The reaction parser can interpret conventional chemical reaction formulas that specify the stoichiometry of reactions. The expression parser can interpret mathematical expressions composed of basic operations and functions, which describe reaction kinetics. The kinetics of most chemical reactions can be easily formulated within this framework.

Moreover, Dynetica allows easy representation of a genetic network, which is treated as a special reaction network that contains one or more genomes. Here a genome is defined as an array of genetic elements, such as genes, promoters, and transcription terminators. Examples of genomes include genomes of cells and viruses, and plasmids. Dynetica can automatically generate four reactions for each gene specified by the user: transcription and translation, and two degradation reactions for the resulting mRNA and protein. These automatically generated reactions are essentially educated guesses based on the user input, and can be refined as needed.

Dynetica allows simulations by both deterministic and stochastic algorithms with the same model (Fig. 1). Currently we have implemented three algorithms: a fixed time-step 4th order Runge–Kutta algorithm, a variable time-step 4th order Runge–Kutta algorithm, and the Gillespie algorithm (Gillespie, 1977). Deterministic algorithms include the traditional numerical algorithms for solving coupled differential equations, such as the fixed or variable time-step Runge–Kutta algorithms implemented.

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Fig. 1. A hypothetical reaction network in Dynetica. (a) The screen shot shows the tree-structure view and the graphic representation of the network. In the graph a green (red) line indicates the production (consumption) of the connected substance by the connected reaction, and a gray dashed line indicates that the connected substance affects the kinetics of the connected reaction. Also shown are the typical results from (b) deterministic and (c) stochastic simulations. See supplementary information for details of this network. See supplementary data for colour figure.

in Dynetica. They are appropriate when the continuity of the system can be justified. The Gillespie algorithm is applicable for a spatially homogeneous system where interacting molecules are so few that fluctuations in their levels are significant. In addition to time-course simulations, Dynetica provides the basic functionality to explore the sensitivity of the system dynamics to the perturbations to the model parameters. This capability is desirable for simulating dosage curves and for identifying key system parameters that are important in determining overall behaviors of the system.

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SUPPLEMENTARY DATA

For Supplementary data, please refer to Bioinformatics online.

REFERENCES


