Modeling biological systems using Dynetica – a simulator of dynamic networks

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ABSTRACT

Mathematical modeling and computer simulation may deepen our understanding of complex systems by testing the validity and consistency of experimental data and mechanisms, by generating experimentally testable hypotheses, and by providing new insight into the integrated behaviors of these systems. However, the application of this approach in biology has been hindered by the lack of software tools to build and analyze models. To meet this need, we have developed Dynetica – a simulator of dynamic networks – to facilitate model building for systems that can be expressed as reaction networks. A distinguishing feature of Dynetica is that it facilitates easy construction of models for genetic networks, where many reactions are the expression of genes and the interactions among gene products. In addition, it provides users the flexibility of performing time-course simulations using either deterministic or stochastic algorithms. Finally, since it is written in Java, Dynetica is platform-independent, allowing models to be easily shared among researchers. We anticipate that Dynetica will dramatically speed up the process of model construction and analysis for a wide variety of biological systems.

Availability: Dynetica 1.0 and the example models are freely available on request.

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INTRODUCTION

Over the past several decades, mathematical modeling has arguably become an important tool in biological research. Owing to the lack of detailed information for many biological systems, past efforts in modeling have relied on relatively simple approaches, such as Boolean network modeling (Glass and Kauffman 1973; Thomas 1973; Glass 1975) and stoichiometric modeling (Clarke 1988; Fell 1992). In Boolean representations of gene networks, each gene is treated as having two states, ON or OFF, and the dynamics describes how genes interact to change one another's states over time (Hasty et al. 2001). Although a Boolean model can provide insight into the qualitative behavior of the underlying system, it is usually overly simplified and tends to give ambiguous predictions (Kuipers 1986). A stoichiometric model represents the underlying system as a series of coupled chemical reactions. It does not require any information on the kinetics of the reactions, and as such is particularly attractive for systems where only sparse kinetic data are available or when steady-state assumptions can be justified (Varner and Ramkrishna 1999; Bailey 2001). Coupled with a technique called metabolic flux analysis (Fell 1992), stoichiometric models have played an instrumental role in shaping the field of metabolic engineering, by providing theoretic guidance for experimental manipulation of metabolic networks (Stephanopoulos et al. 1998). Recently, stoichiometric models have proven powerful in characterizing the underlying structure of metabolic networks by determining the elementary flux modes (Schuster et al. 2000) or the null space base vectors (Schilling and Palsson 1998) and in predicting steady-state metabolic capabilities of several model organisms, such as *E. coli* (Schilling et al. 1999; Edwards et al. 2001) and *H. influenzae* (Edwards and Palsson 1999). But their applications are limited by their

inability to predict the temporal evolution of these networks. To make such predictions, the stoichiometric structure of the reaction networks needs be supplemented with detailed kinetic information, resulting in kinetic models. Thanks to the rapid expansion of our knowledge in biology, kinetic modeling has become a realistic goal, particularly for the experimentally well-characterized systems. For example, kinetic models have recently been successfully applied to the analysis of a wide variety of biological systems, including bacterial chemotaxis signaling networks (Barkai and Leibler 1997; Spiro et al. 1997), developmental pattern formation in *Drosophila* (Reinitz et al. 1998; von Dassow et al. 2000), aggregation stage network of *Dictyostelium* (Laub and Loomis 1998), viral infection (Shea and Ackers 1985; Eigen et al. 1991; McAdams and Shapiro 1995; Endy et al. 1997; Reddy and Yin 1999; You et al. 2002), circadian rhythms (Barkai and Leibler 2000; Smolen et al. 2001), single cell growth (Shuler et al. 1979), and physiological processes (Quick and Shuler 1999; Winslow et al. 2000; Noble 2002).

A kinetic model essentially represents a mathematical integration of existing data and mechanisms on a particular system, and may be useful in a number of ways. By providing a global view of the underlying system, a kinetic model can be used to test the consistency in the experimental data or mechanisms (von Dassow et al. 2000) or provide mechanistic explanations for counter-intuitive observations (Fallon and Lauffenburger 2000), to facilitate the formulation of experimentally testable hypotheses (Abouhamad et al. 1998; Endy et al. 2000; You et al. 2002) or to test hypotheses that are difficult, expensive, or even impossible to explore experimentally with current technology (You and Yin 2002), and to provide insight into emergent properties, such as robustness (Barkai and Leibler 1997; Alon et al. 1999; von Dassow et al. 2000), which may be

otherwise difficult to grasp intuitively. As models become more "realistic" by incorporating more detailed data and mechanisms, they may be treated as *in silico* organisms and used to explore applied or fundamental questions that are beyond the underlying system per se. For example, a phage T7 model has been employed to explore anti-viral strategies using anti-sense mRNAs (Endy and Yin 2000), to elucidate the nature of genetic interactions by in silico mutagenesis at the population level (You and Yin 2002), and to test data-mining strategies for identifying potential protein-protein interactions from gene expression data (You and Yin 2000). Moreover, advances in high-throughput biotechnologies for genome-wide gene expression profiling at the transcription and translation level provide additional challenges and opportunities for mathematical modeling, which may accelerate the characterization of whole organisms by allowing the understanding of gene expression data (at the mRNA level or the protein level) in their natural context. This point is demonstrated in a recent work where kinetic formulation of DNA microarray data was used to determine the timing of transcriptional onsets and cessation in *Dictyostelium* (Iranfar et al. 2001).

Despite its potential benefits for fundamental and applied biological research, broader 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. This aspect is probably best evidenced by the fact that the majority of mathematical models of biological systems have been developed by researchers trained in disciplines other than biology. Further, because of the lack of such tools, most published models were developed from scratch, which can be a tedious and error-prone process.

To address this issue, a number of programs that aim to facilitate the model construction and analysis have been developed in the last several years. These programs include Gepasi (Mendes 1993; Mendes 1997), DBsolve (Goryanin et al. 1999), E-Cell (Tomita et al. 1999; Tomita 2001), SCAMP (Sauro 1993), STELLA, Virtual Cell (Schaff et al. 1997; Schaff and Loew 1999; Schaff et al. 2000), StochSim (Morton-Firth and Bray 1998), and STOCKS (Kierzek 2002). It would go beyond the scope of this current work to give a detailed account of these tools. Briefly, Gepasi, DBsolve, and SCAMP focus on the analysis of biochemical and metabolic networks. In addition to basic time-course simulations, these programs provide additional modules to explore the properties of metabolic networks. E-Cell aims to construct whole-cell models, and it has been applied to model a self-sustaining hypothetic cell (Tomita et al. 1999) and a human erythrocyte (Tomita 2001). Virtual Cell is advantageous in that it accounts for the diffusion of molecules in addition to their reactions in describing cellular processes. Distinct from other programs, StochSim and STOCKS simulate the system dynamics using stochastic algorithms instead of deterministic algorithms. These two differ in that StochSim employs a semi-empirical algorithm, while STOCKS uses the Gillespie algorithm (Gillespie 1977), which is rigorous for spatially homogenous systems. More extensive discussion of recent progress in the development of modeling tools may be found in excellent recent reviews (Arkin 2001; Loew and Schaff 2001).

We present here a unique, general-purpose computational framework for creating, visualizing, and analyzing mathematical models of biological networks, including biochemical, metabolic, signaling, and genetic networks. We call this program Dynetica, or a simulator of *dy*namic *net*works. Dynetica is distinct from other software packages in

three aspects: (1) it facilitates the construction of kinetic models of genetic networks where most reactions are expression 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. Furthermore, because it is written in Java, a platform-independent, object-oriented programming language, Dynetica can be run on most modern computers, which will facilitate the sharing of models among researchers. We anticipate that Dynetica will contribute significantly to advancing broader application of kinetic modeling in biological systems.

MODELING IN DYNETICA

Representation of generic reaction networks

A reaction network in Dynetica consists of a list of substances that interact with one another via a list of reactions. Kinetics of these reactions may be specified by a list of parameters (Figure 1). In addition to a tree structure, Dynetica provides a graphic representation of each reaction network. Figure 2 shows a hypothetical reaction network in Dynetica that consists of two reactions (Table 1). Each reaction is characterized by two basic 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 (using "$\rightarrow$" as the separator between reactants

and products), which specify the stoichiometry of reactions. The mathematical expression parser is used to interpret conventional mathematical expressions, which describe the kinetics of reactions. In Dynetica expressions both substances and parameters have values associated with them. The expression parser distinguishes between these entities by enclosing substance names with brackets. For example, the rate expression for reaction R1 in Table 1 is k_1 [A] [E], which means the value of parameter k_1 times the level of substance A and the level of substance E. The expression parser can interpret mathematical expressions composed of the operations and functions shown in Table 2. The kinetics of most chemical reactions can be formulated easily within this framework.

Representation of genetic networks

Genetic networks can be loosely defined as reaction networks involving gene expression processes, such as transcription of genes and translation of mRNAs. In Dynetica, a genetic network is treated as a special reaction network that contains one or more genomes (Figure 3A). Here a genome is defined as an entity composed of an array of genetic elements, such as genes, promoters, and transcription terminators. Examples of genomes include genomes of cells and viruses, as well as plasmids.

Each genetic element is characterized by two attributes, namely, its starting and ending positions (in base-pair number) along the genome. A gene in Dynetica is a special genetic element characterized by several additional attributes: the RNA polymerase responsible for its transcription, the ribosome responsible for its translation, the name of its RNA, and the name of its protein (if the gene is to be translated), the relative transcription activity, and the relative translation activity. The relative transcription activity is essentially a weighting factor by which RNA polymerases are allocated to

different genes, and the relative translation activity is the weighting factor by which ribosomes are allocated to different genes (more precisely, to different mRNAs). Genetic reactions can easily be formulated in Dynetica. Figure 3B demonstrates the Dynetica formulation of the central dogma of molecular biology. Essentially, the information transfer process from gene to mRNA to protein can be represented by two reactions. The transcription reaction specifies the conversion of nucleoside triphosphates (NTP) into mRNA, and is catalyzed by the gene and RNA polymerase (RNAP). The translation reaction specifies the conversion of amino acids (AA) into the protein, and is catalyzed by the mRNA and the ribosome.

Because expression of most genes follows the pattern as specified by the central dogma, Dynetica automatically creates a transcription reaction and a translation reaction for each gene that the user specifies in a genome. In addition, it also generates two reactions to represent the degradation of the gene products, the mRNA and the protein. In setting up the transcription reaction, we assume that the limiting step is the elongation of the RNAP, and the transcription follows Michaelis-Menten kinetics with NTP as the substrate. For the translation reaction, we assume that the limiting step is the elongation of the ribosome, and the reaction follows Michaelis-Menten kinetics with AA as the substrate. Note that these automatically generated reactions are essentially "first-order approximations" by the program based on the genetic information provided by the user. These approximations are useful because they provide an initial estimate of gene expression dynamics. The user can then refine the stoichiometry and kinetics of such reactions as needed.

Simulation

A model in Dynetica gives a schematic representation of the corresponding system, but it does not specify how the system evolves over time. The latter will be determined by an algorithm. Here, an algorithm is defined as the scheme by which the system represented by the model will be updated as a function of time. It can be either deterministic or stochastic. Deterministic algorithms include all the traditional numerical algorithms that are designed to solve coupled differential equations, such as fixed or variable time-step Runge-Kutta algorithms. A deterministic algorithm is appropriate when the continuity of the system can be justified.

Stochastic algorithms focus on updating reactions in the system. For example, a widely used stochastic algorithm proposed by Gillespie (Gillespie 1977) updates a reactive system by determining, at each step, which and when the next reaction will occur. A stochastic algorithm is appropriate for a spatially homogeneous system where the interacting molecules are few that fluctuations in their numbers are significant. A number of researchers have strongly advocated the use of stochastic algorithms for modeling biological systems, especially for intracellular processes (Arkin et al. 1998; Goss and Peccoud 1998; Morton-Firth and Bray 1998; Kierzek 2002).

The structure of a reaction network model in Dynetica is flexible enough to allow simulations by either deterministic or stochastic algorithms. Currently we have implemented three different algorithms: a fixed time-step 4^{th} order Runge-Kutta algorithm, a variable time-step 4^{th} order Runge-Kutta algorithm, and Gillespie's algorithm. By applying an algorithm to a model, we can generate the dynamics of the underlying system. Shown in Figure 4 are the results of deterministic and stochastic

simulations with the model in Figure 2. In this particular case, both approaches generate qualitatively the same result: substance A is gradually converted into substance B until equilibrium is reached, whereas the level of substance E remains constant over time. However, the details of the dynamics generated from these different approaches are quite different. For instance, there are no fluctuations in the substance concentrations as predicted by the deterministic simulation, but fluctuations are evident in the result from the stochastic simulation. In addition, because of the stochastic aspect of the Gillespie algorithm, every new simulation starting from the same initial condition will generate different dynamics (Gillespie 1977).

In addition to simulating the temporal evolution of a reaction network, Dynetica provides the basic functionality to explore how the dynamics of the network responds to the perturbations to the network, in terms of variations in parameter values or the initial levels of substances. This feature is desirable for simulating dosage curves and for identifying key system parameters that are important in determining overall behaviors of the system.

APPLICATIONS

To demonstrate the application of Dynetica we use it to build two models: one for the *Dictyostelium* aggregation stage network, and the other for the intracellular growth cycle of phage T7. The aggregation stage network model is shown here as an example of a general reaction network. The phage T7 model shown as an example of a genetic network.

A Dictyostelium aggregation stage network model

Amoebae of *Dictyostelium discoideum* grow as independent cells in the soil, but aggregate and develop as a multicellular organism under starvation. It has been proposed that the aggregation stage network, which consists of seven interacting components, is responsible for regulating the expression of developmental genes in homogeneous populations of *Dictyostelium* shortly after starvation (Loomis 1998; Soderbom and Loomis 1998). Previously, a kinetic model was developed to analyze the dynamics of this signaling network (Laub and Loomis 1998). The model accounted for the interactions among seven molecular species, and was shown to be able to predict the oscillations in the enzyme activities during *Dictyostelium* development.

Based on (Laub and Loomis 1998), we used Dynetica to reconstruct the aggregation stage network model (Figure 5A, Table 3). Figure 5B shows a representative simulation result demonstrating stable oscillations in levels of the interacting components.

A phage T7 model

Phage T7 is a lytic virus that infects bacterium *E. coli*. By incorporating the existing experimental data and mechanisms of T7 biology, we previously developed a genetically structured kinetic model to account for the intracellular life cycle of phage T7 (Endy et al. 1997; Endy et al. 2000; You et al. 2002). Various versions of this model were employed to explore anti-viral strategies (Endy et al. 1997; Endy and Yin 2000), effects of host physiology on phage development (You et al. 2002), design principles of phage T7 (Endy et al. 2000; You and Yin 2001), genetic interactions among deleterious

mutations (You and Yin 2002), and data-mining strategies for identifying potential protein-protein interactions from gene expression data (You and Yin 2000).

The model presented here is a simplified version of the previous models (Figure 6). The major difference between the current model and the previous ones is that a simplified genome is used here (Figure 6A). This simplified genome contains 20 essential T7 genes. The regulatory effect of promoters and transcription terminators is accounted for by specifying the relative transcription activity of each gene. As a result, RNA polymerases are allocated to different genes based on their relative transcription activities, whereas in the complete model RNA polymerases are allocated based on the relative strengths of promoters (You et al. 2002). The resulting T7 reaction network contains 91 reactions and 55 substances, excluding genes (Figure 6B). In this network, the reactions describing expression of genes and degradation of gene products are automatically generated by Dynetica. Although the network diagram is overall complex, it highlights several features of the system. First, most substances are involved in two reactions, one for production (green line) and the other for consumption (red line). Second, several nodes (as labeled) are highly connected. For example, the nodes for amino acid and NTP are highly connected because these two substances are used as precursors for transcription and translation reactions, respectively. Likewise, the nodes for T7 RNAP and ribosome are highly connected because they are used as catalysts for transcription and translation reactions, respectively.

Like the more comprehensive model, the current model accounts for the major steps of T7 infection: transcription of viral genes, translation of the resulting mRNAs, interactions between regulatory proteins, host DNA degradation and T7 DNA replication,

procapsid assembly, and eventually production of phage progeny. A representative simulation result showing the time courses of three viral components is presented in Figure 6c. It illustrates the synthesis of T7 DNAs and procapsids, and the packaging of T7 DNAs into procapsids to form viral progeny. Overall, this simplified model captures the main features of viral growth as predicted by the more comprehensive model.

DISCUSSION

We have developed Dynetica to facilitate the construction, visualization and analysis of mathematical models for biological systems that can be formulated as a coupled system of reactions. With Dynetica, the user need only specify the chemistry of this system, that is, what components are in the system and how they interact. Throughout the model-building process, the user need not write any differential equations, or formulate numerical algorithms to conduct simulations. Instead, the numerics is automatically handled by the program. Thanks to this feature, the user can focus on the model itself and its practical relevance rather than the technical aspects of computer simulation. Furthermore, by providing a graphic view of the underlying reaction network Dynetica will facilitate the interactive manipulation and analysis of each model.

Dynetica's ability to perform both deterministic and stochastic simulations on the same model may facilitate comparative studies of these two approaches. Deterministic algorithms have been traditionally used to simulate the dynamics of a system of coupled reaction network. However, the small numbers of interacting components in some intracellular processes may become an issue. First, the continuity of these systems is no longer warranted. Second, fluctuations in the concentrations of the reacting components

may significantly impact the system dynamics. Because of these issues, some researchers have questioned the use of deterministic algorithms in simulating the behaviors of biological systems, and suggested using stochastic algorithms instead (Arkin et al. 1998; Goss and Peccoud 1998; Morton-Firth and Bray 1998; Kierzek 2002). They have shown that stochastic simulations often produce dynamics drastically different from what is predicted by deterministic simulations. Moreover, they have argued that a stochastic simulation more accurately and more completely accounts for the temporal evolution of a well-stirred chemical reaction network than does a deterministic algorithm (Gillespie 1977; McAdams and Arkin 1998). Nonetheless, since a stochastic algorithm only gives accurate solutions for a well-stirred system, it may not be applicable for intracellular processes. It is unclear whether it is more appropriate than a deterministic approach in modeling such processes. To this end, Dynetica may be employed to simulate a system using both deterministic and stochastic approaches and explore which approach is more appropriate in a particular situation.

With its present underlying software structure, Dynetica can easily be extended in its functionality and flexibility. It has a software module that automates the construction of a genetic network model based on the organization of genetic elements along the genome. In achieving this functionality, we made simplifying assumptions regarding the organization of the genome. For each gene, Dynetica will automatically generate a transcription reaction, a translation reaction, and degradation reactions for the resulting mRNA and protein. However, in reality, there are also genes for tRNA and rRNA that do not have protein products. Future modifications of the program will be needed to represent and distinguish different kinds of genes. New numerical algorithms can be

implemented, so that the user will have the freedom in choosing the most appropriate one for a given situation. Further, we are developing model templates for different types of biological systems, such as signaling pathways, viruses, and single cells. Like the document templates one may encounter in many word-processing programs such as Microsoft® Word, these templates will further facilitate the model-building process, particularly for new users. An emerging challenge for the modeling community lies in the interchange of models constructed using different software tools, as listed in the introduction section. Recently, there have been many efforts toward developing modeling standards for biology modeling, such as the SBML (Systems Biology Markup Language) project (http://www.cds.caltech.edu/erato) and the CellML (Cell Markup Language) project (http://www.cellml.org). To provide exchangeable mathematical models, we plan to implement software modules to import models constructed with other tools, or written in standard modeling languages. Finally, we plan to implement software modules to annotate models; we expect this functionality will further facilitate the communication of mathematical models as a representation of the underlying biological systems.

The evolution of biological network modeling can be compared to that of the molecular dynamics simulation, which uses physical principles to compute the structure and dynamics of biological molecules. Although the development and use of molecular dynamics simulation programs were initially much restricted to researchers with strong background in theoretic physics and mathematics, it is the development of powerful and user-friendly tools that has established this computational approach as a routine tool for structural studies of natural or synthetic biological molecules (Loew and Schaff 2001). Similarly we envision that, Dynetica, together with other emerging modeling tools, will

promote a broader application of mathematical models in cell biology by serving as a computational platform to create, analyze and exchange such models.

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FIGURE LEGENDS

Figure 1. Representation of reaction networks in Dynetica. Each reaction network is represented as three lists: substances, reactions through which substances interact with one another, and parameters that specify the kinetics of the reactions.

Figure 2. Screenshot of a hypothetical reaction network in Dynetica. The left panel shows the tree-structure view of the network, and the right panel gives a graphic representation. In the graph a green line indicates the production of the connected substance by the connected reaction, a red line represents the 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. See text for details of the reactions.

Figure 3. Formulation of genetic networks in Dynetica. (A) A genetic network in Dynetica is represented as a special reaction network that contains one or more genomes. (B) The central dogma represented in Dynetica.

Figure 4. The simulation results from the reaction network in Figure 2 using both (A) deterministic and (B) stochastic algorithms.

Figure 5. Aggregation stage network model. (A) The graphic representation of the reaction network. (B) A representative simulation result. The network was constructed based on the reference (Laub and Loomis 1998). The reactions involved in this network are shown in Table 3. The parameter values for the simulation are: k_1 =1.4, k_2 = 0.9, k_3 =

2.5, k_4 = 1.5, k_5 = 0.6, k_7 = 2.0, k_8 = 1.3, k_9 = 0.3, k_{10} = 0.8, k_{11} = 0.7, k_{12} = 4.9, k_{13} = 18, k_{14} = 1.5 (W. Loomis, personal communication). The initial levels of all substances were set to be 1.0, and the variable time-step 4^{th} order Runge-Kutta algorithm was used for the simulation.

Figure 6. Phage T7 model. (A) The simplified T7 genome. The left panel shows a list of genes in the genome (not all genes are shown); the right panel shows the attributes of the currently selected gene. (B) The graphic representation of the reaction network. The reactions describing transcription and translation of genes were automatically generated by Dynetica. (C) A representative simulation result showing the time courses of three viral components.

Table 1. The reactions in the simple reaction network shown in Figure 2.

Reaction name	Stoichiometry	Kinetics
R1	$A \rightarrow B$	k_1 [A] [E] [a]
R2	$B \rightarrow A$	k_2 [B]

[a] The rate expression is actually written as k_1 [A] * [E] in Dynetica.

Table 2. The mathematical operations and functions that are supported by Dynetica

	Symbols or expressions	Note
Basic operations	+, -, *, /, ^	'^' represents to the power of.
Basic functions [a]	sin(a), cos(a), tan(a), sqrt(a), log(a)	log(a) returns the natural logarithm value of a
Special functions [a]	step(a, b)	returns 1 if a ¥ b, and 0 otherwise
	compare(a, b)	returns 1 if a > b, 0 if a = b, and –1 if a < b
	pulse(a, x, b)	returns 1 if a < x < b, 0 otherwise
	random(a, b)	returns a random value between a and b
	rand()	returns a random value between 0 and 1
	min(a, b, c, …)	returns the minimum value from the list of arguments
	max(a, b, c,…)	returns the maximum value from the list of arguments

[a] Each of the symbols (a, b, c and x) may represent a simple variable or a mathematical expression.

Table 3. The production reactions in the aggregation stage network [a]

Reaction	Stoichiometry	Kinetics	Notes
p_ACA	$\rightarrow$ ACA	k_1 [ERK2]	activation of ACA by ERK2
d_ACA	ACA $\rightarrow$	k_2 [ACA]	degradation of ACA
p_PKA	$\rightarrow$ PKA	k_3 [cAMPi]	activation of PKA by cAMPi
d_PKA	PKA $\rightarrow$	k_4 [PKA]	degradation of PKA
p_ERK2	$\rightarrow$ ERK2	k_5 [CAR1]	activation of ERK2 by CAR1
d_ERK2	ERK2 $\rightarrow$	k_6 [ERK2] [REGA]	degradation of ERK2 (catalyzed by REGA)
p_REGA	$\rightarrow$ REGA	k_7	constant production of REGA
d_REGA	REGA$\rightarrow$	k_8 [REGA] [ERK2]	degradation of REGA (catalyzed by ERK2)
p_cAMPi	$\rightarrow$ cAMPi	k_9 [ACA]	activation of cAMPi by ACA
d_cAMPi	cAMPi $\rightarrow$	k_{10}[REGA][cAMPi]	degradation of cAMPi (catalyzed by REGA)
p_cAMPe	$\rightarrow$ cAMPe	k_{11} [ACA]	activation of cAMPe by ACA
d_cAMPe	cAMPe$\rightarrow$	k_{12} [cAMPe]	degradation of cAMPe
p_CAR1	$\rightarrow$ CAR1	k_{13} [cAMPe]	activation of CAR1 by cAMPe
d_CAR1	CAR1$\rightarrow$	k_{14} [CAR1][PKA]	degradation catalyzed by PKA

[a] Although recent studies have suggested a slightly revised reaction network (http://www.biology.ucsd.edu/labs/loomis/network/laubloomis.html), the published model suffices to illustrate the usage of Dynetica.

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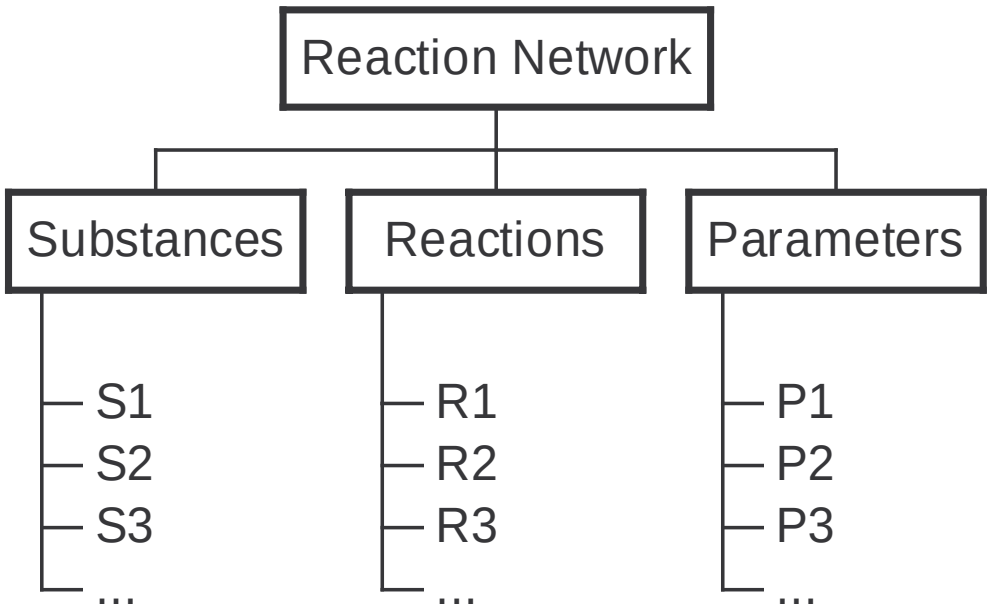
Figure 1


Reaction Network
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Reactions
Parameters
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S2
S3
...
R1
R2
R3
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P1
P2
P3
...

Figure 2

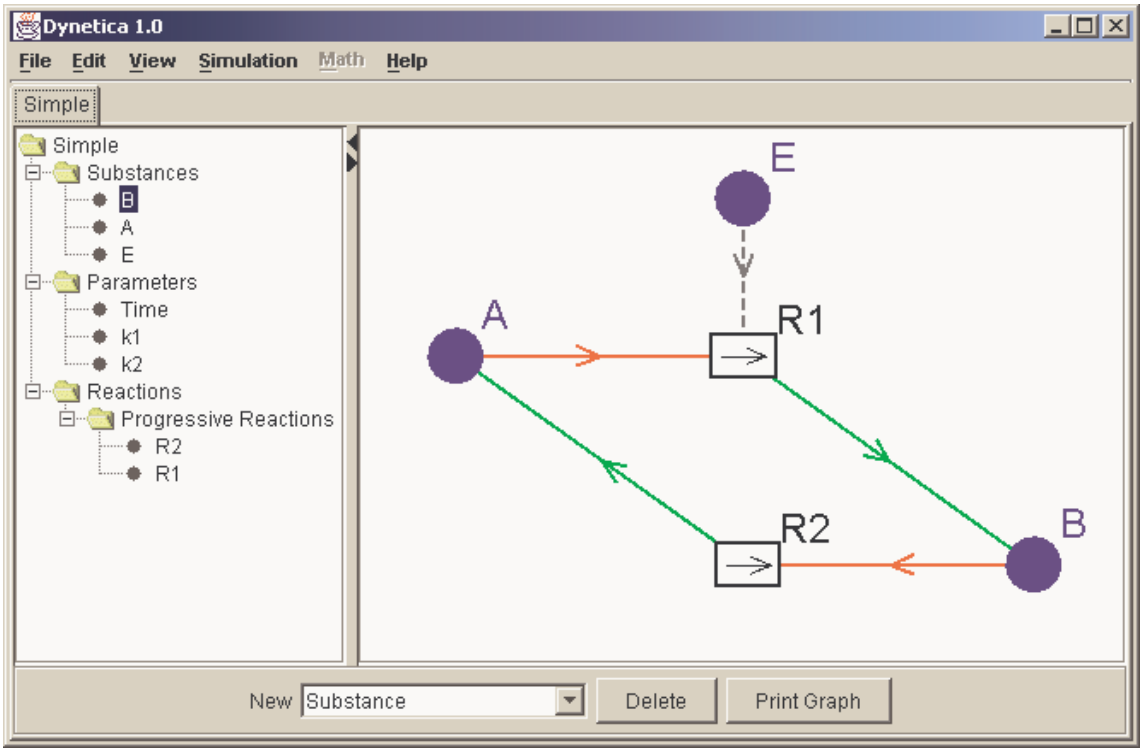

Dynetica 1.0
File Edit View Simulation Math Help
Simple
Simple
Substances
B
A
E
Parameters
Time
k1
k2
Reactions
Progressive Reactions
R2
R1
E
A
R1
R2
B
New Substance
Delete
Print Graph

Figure 3

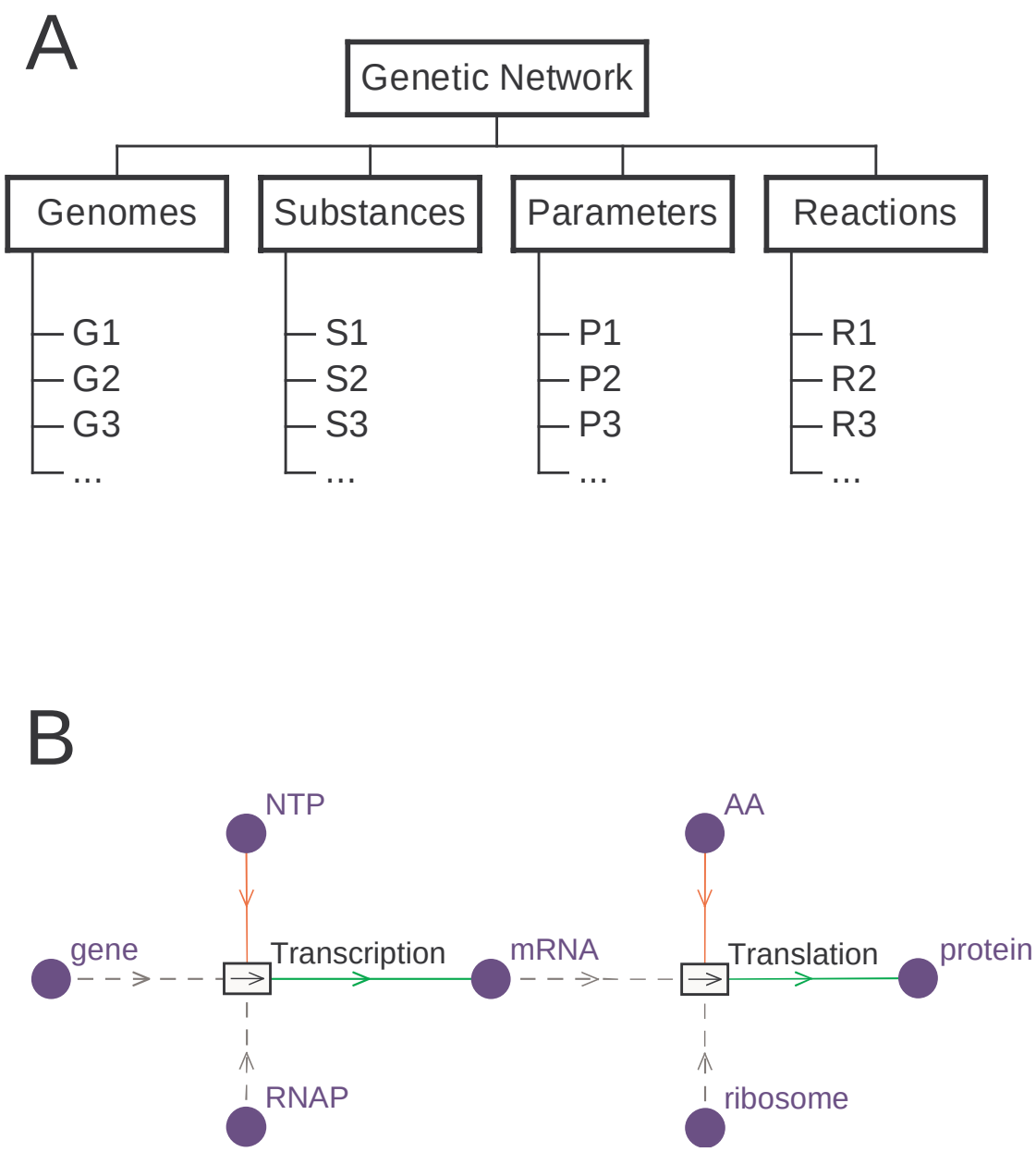
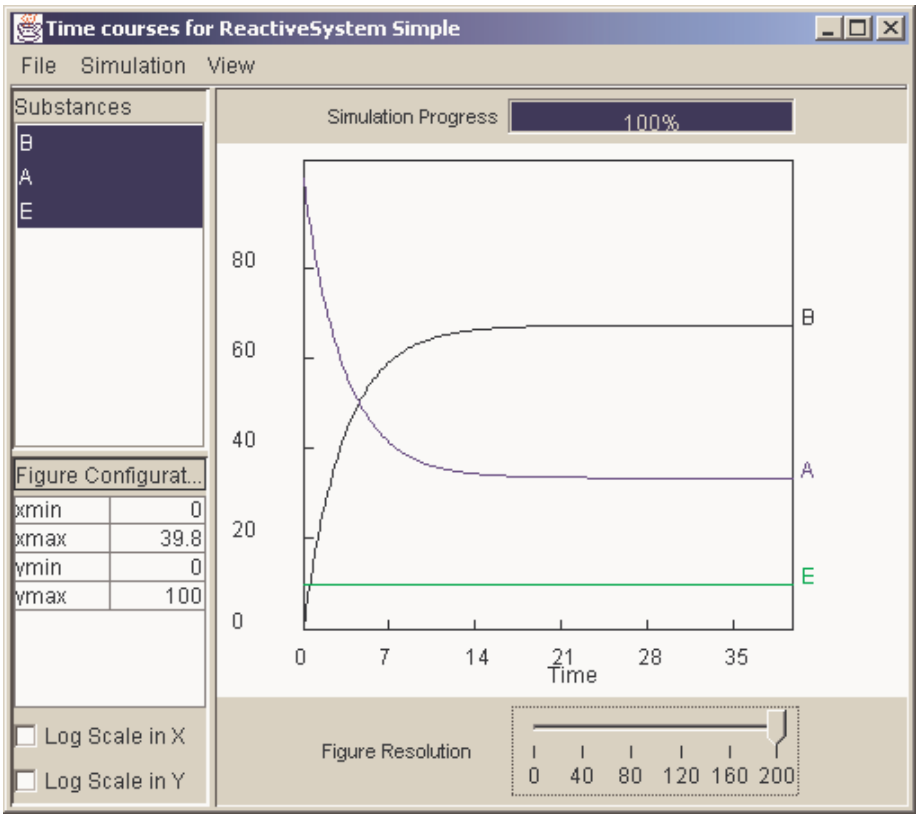

A
Genetic Network
Genomes
Substances
Parameters
Reactions
G1
G2
G3
...
S1
S2
S3
...
P1
P2
P3
...
R1
R2
R3
...
B
NTP
AA
gene
Transcription
mRNA
Translation
protein
RNAP
ribosome

Figure 4

A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File Simulation View
Substances
B
A
E
Simulation Progress
100%
80
60
40
20
0
B
A
E
0 7 14 21 28 35
Time
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Log Scale in X
Log Scale in Y
Figure Resolution
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B

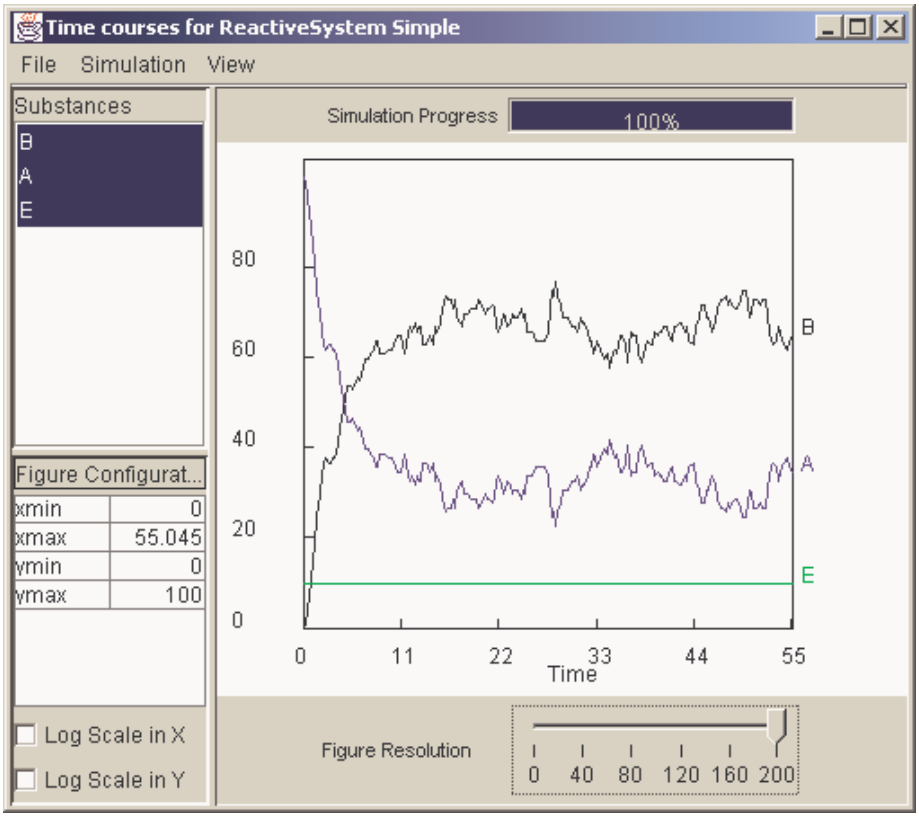
Time courses for ReactiveSystem Simple
File Simulation View
Substances
B
A
E
Simulation Progress
100%
80
60
40
20
0
B
A
E
0 11 22 33 44 55
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Figure Configurat...
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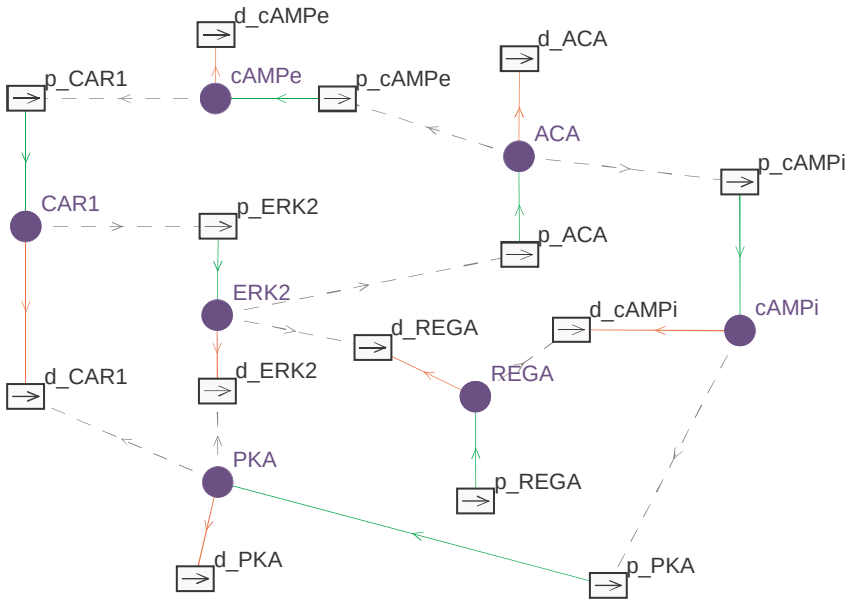
Log Scale in X
Log Scale in Y
Figure Resolution
0 40 80 120 160 200

Figure 5

A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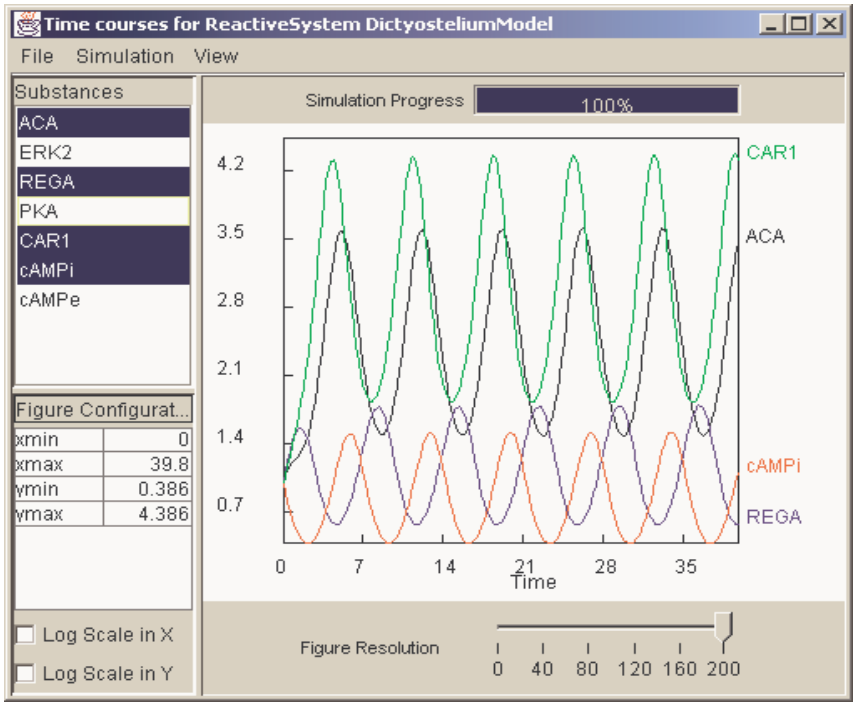
PKA
p_REGA
d_PKA
p_PKA

B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File
Simulation
View
Substances
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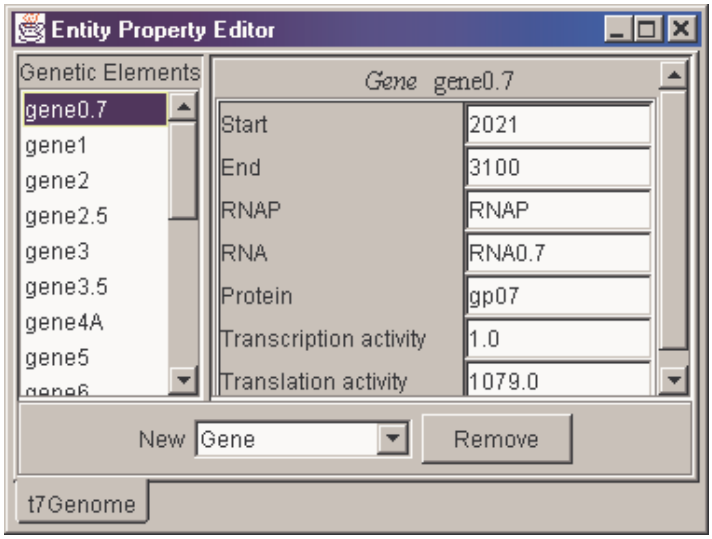
ERK2
REGA
PKA
CAR1
cAMPi
cAMPe
Figure Configurat...
xmin 0
xmax 39.8
ymin 0.386
ymax 4.386
Log Scale in X
Log Scale in Y
Simulation Progress
100%
4.2
3.5
2.8
2.1
1.4
0.7
0
7
14
21
28
35
Time
CAR1
ACA
cAMPi
REGA
Figure Resolution
0
40
80
120
160
200

Figure 6

A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gene3.5
gene4A
gene5
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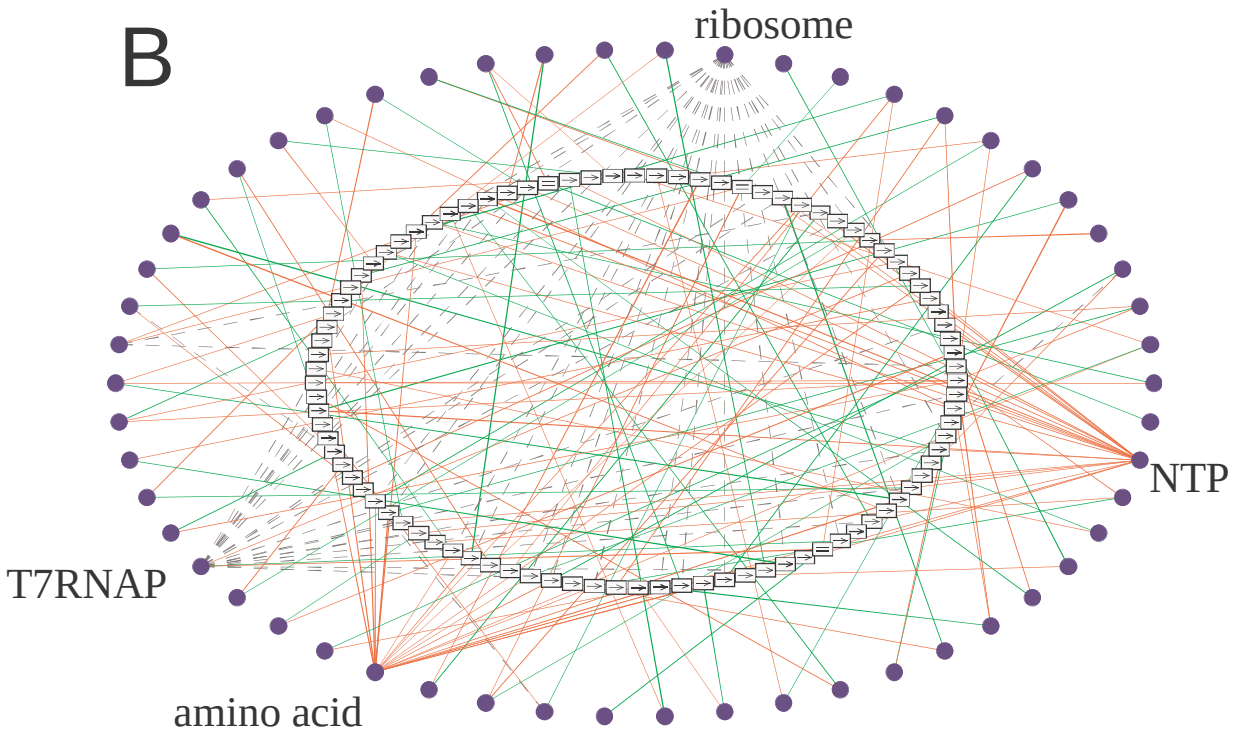
Translation activity 1079.0
New Gene
Remove
t7Genome

B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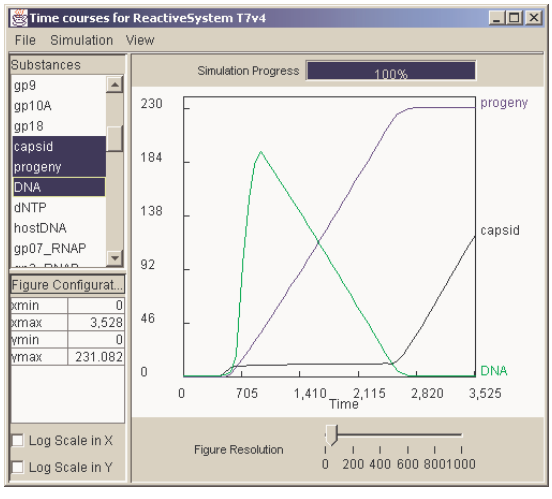
amino acid

C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hostDNA
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ymin 0
ymax 231.082
Log Scale in X
Log Scale in Y
Simulation Progress 100%
230
184
138
92
46
0
progeny
capsid
DNA
0 705 1,410 2,115 2,820 3,525
Time
Figure Resolution
0 200 400 600 8001000