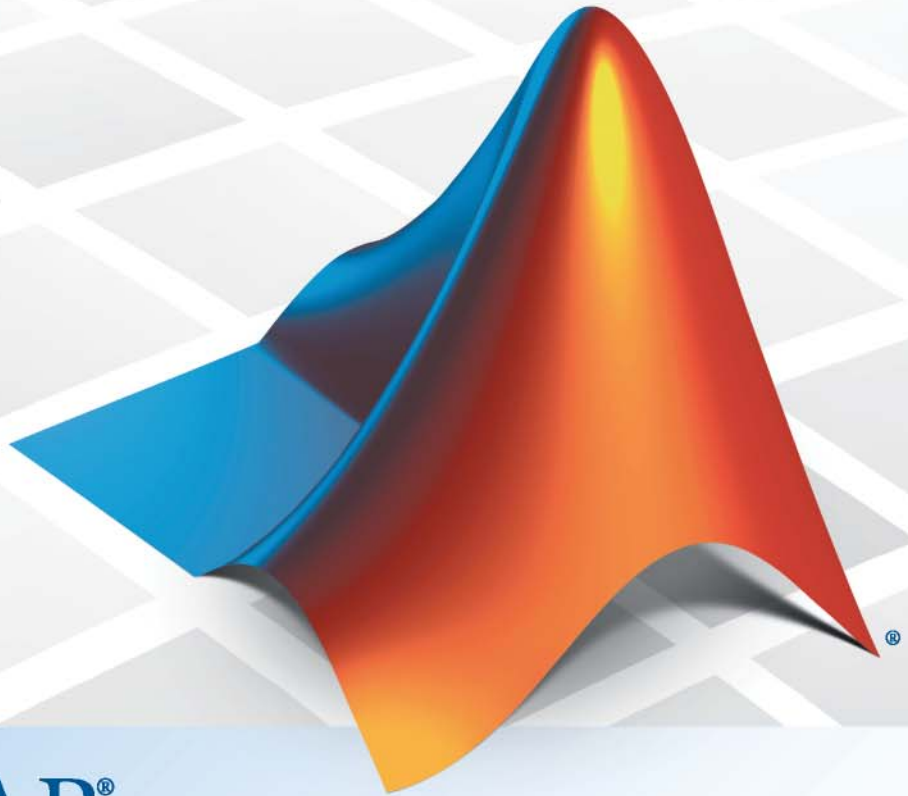


SimBiology[®] 3

Getting Started Guide



MATLAB[®]

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SimBiology[®] *Getting Started Guide*

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Introduction

1

Product Overview	1-2
Integrated Environment	1-2
Expected Users	1-3
Required Software	1-4
Optional Software	1-4
Related Software	1-5
Integrating SimBiology Models into Your Existing Workflow	1-6
Existing Workflow in Experimental Research	1-6
Workflow Incorporating Mathematical Modeling	1-7
Workflow Using SimBiology Models for Mathematical Modeling	1-9
Getting Started in the SimBiology Desktop	1-11
Overview	1-11
Creating or Opening a Model Using the New Project Wizard	1-11
Opening a SimBiology Project	1-15
Features and Functions	1-16
Using the Command Line versus the SimBiology Desktop	1-16
Graphical User Interface	1-17
Command-Line Interface	1-22
Data Formats and Projects	1-22
Modeling	1-23
Simulation	1-24
Analysis	1-25
SimBiology Support and SBML	1-26
What Is SBML?	1-26
SBML Support	1-26
Importing SBML Files	1-27

Building SimBiology Models

2

Gene Regulation Model	2-2
Model Diagram	2-2
Model Reactions	2-3
Opening the Gene Regulation Model in the SimBiology Desktop	2-6
Modeling Using the SimBiology Graphical User Interface	
About the Model Used in This Tutorial	2-8
Creating a Model	2-8
Saving Your Work as a SimBiology Project File	2-9
Adding Reactions to a Model	2-10
Simulating a Model	2-15
Modeling Using the SimBiology Diagram View	
About This Example	2-16
Creating a Model	2-16
Saving Your Work as a SimBiology Project File	2-20
Adding Species and Reactions to a Model Diagram	2-20
Simulating a Model	2-25
Setting Block Appearance and Diagram Layout	2-26
Printing and Exporting the Diagram	2-37
Modeling Using the Command-Line Interface	
About This Example	2-40
Creating a SimBiology Model	2-40
Adding the Reaction for Transcription	2-42
Adding the Reaction for Translation	2-43
Adding the Reactions for Gene Regulation	2-43
Adding the Reactions for mRNA and Protein Degradation	2-44
Simulating the Model	2-44
Simulating the Model with a Stochastic Solver	2-46

Introduction

This chapter introduces SimBiology® functions and features to help you develop a conceptual model for working with the software and your biochemical data.

- “Product Overview” on page 1-2
- “Integrating SimBiology Models into Your Existing Workflow” on page 1-6
- “Getting Started in the SimBiology Desktop” on page 1-11
- “Features and Functions” on page 1-16
- “SimBiology Support and SBML” on page 1-26

Product Overview

In this section...
“Integrated Environment” on page 1-2
“Expected Users” on page 1-3
“Required Software” on page 1-4
“Optional Software” on page 1-4
“Related Software” on page 1-5

Integrated Environment

SimBiology software provides an integrated environment for modeling biological processes, simulating the dynamic behavior of these processes, and analyzing the model with simulation and experimental data. Biological processes include metabolic, genetic, and signaling pathways with transform, binding, and transport reactions.

You can also create and analyze pharmacokinetic models. For more information see “Pharmacokinetic Modeling” in the SimBiology documentation.

- **Model** — Design and build models by entering reactions, species, parameters, kinetic laws, rules, and events with a graphical user interface, a block diagram editor, or using the MATLAB® Command Window. Verify that the model can be simulated, and use the verification results to fix any incompatibilities in the model.

Import SBML models created with the SimBiology software or other modeling software that is compliant with the Systems Biology Markup Language (SBML) standard.

Export models created with the SimBiology desktop to MATLAB and continue your simulations and analysis with command-line functions. For more information, see “Modeling” on page 1-23.

- **Simulate** — Observe changes in species amounts and parameter values over time. Convert your model to a system of differential equations and simulate the model numerically with various differential equation solvers.

The deterministic solvers include stiff and nonstiff ordinary differential equation (ODE) solvers. The stochastic solvers include a stochastic simulation algorithm with implicit and explicit tau variations. Perform multiple stochastic ensemble runs. For more information, see “Simulation” on page 1-24.

- **Analyze** — Save data from a simulation, compare simulation and experimental data, perform sensitivity analysis, species or parameter scans, parameter estimation, and search for conserved moieties. For more information, see “Analysis” on page 1-25.

Expected Users

The people who use SimBiology software come from a wide range of areas including biology, systems biology, pharmacology, computer science, and engineering. This product is intended for research scientists, computational biologists, and students who need to develop and study biological pathways at the molecular and systems level, develop custom analysis applications, or implement published ones, and visualize results.

Industry and Professional — SimBiology software allows you to model, simulate, and analyze biochemical and system pathways for applications in drug discovery and design, target identification, and pharmacokinetic modeling.

Modeling, simulating, and analyzing a biological system can test hypotheses for a pathway, identify side effects caused by drug interactions with a target compound, and identify biochemical pathways that lead to disease.

Academia — Build rigorous, dynamic, quantitative models that allow you to understand and predict system behavior at the molecular level. Build models to explore enzyme kinetics. Leverage the MATLAB foundation to easily manipulate large data sets.

Simulating the dynamic behavior of a model can confirm the validity of the models and identify behaviors and control mechanisms not apparent from studying static models. Validate models experimentally and use the model to predict *in vitro* and *in vivo* behavior.

Required Software

To use SimBiology software, you must first install the following MathWorks® product:

MATLAB

Provides a command-line interface and an integrated software environment. For instructions, see the MATLAB installation documentation for your platform.

If you have installed MATLAB and want to check which other MathWorks products are installed, enter `ver` in the MATLAB Command Window.

Optional Software

Statistics Toolbox™ (Version 7.0 (R2008b) or later)

Provides fitting tools including functions used to analyze nonlinear mixed effects.

Note This toolbox is required for analyzing nonlinear mixed effects.

Global Optimization Toolbox

Solve optimization problems using genetic and direct search algorithms. If this toolbox is installed, you can use various genetic and direct search algorithms for parameter estimation. If this toolbox is not installed, the software uses the optimization algorithms available in MATLAB.

Optimization Toolbox™

Optimization Toolbox extends the MATLAB technical computing environment with tools and widely used algorithms for standard and large-scale optimization. These algorithms solve constrained and unconstrained continuous and discrete problems. If the Optimization Toolbox product is installed, you can use some algorithms included this product for parameter estimation in SimBiology software. If the Optimization Toolbox product is not installed, the software uses the optimization algorithms available in MATLAB.

C Compiler

Required to prepare the model for accelerating simulations. For list of supported compilers, see Supported and Compatible Compilers .

Related Software**Bioinformatics Toolbox™**

Read, analyze, and visualize genomic, proteomic, and microarray data.

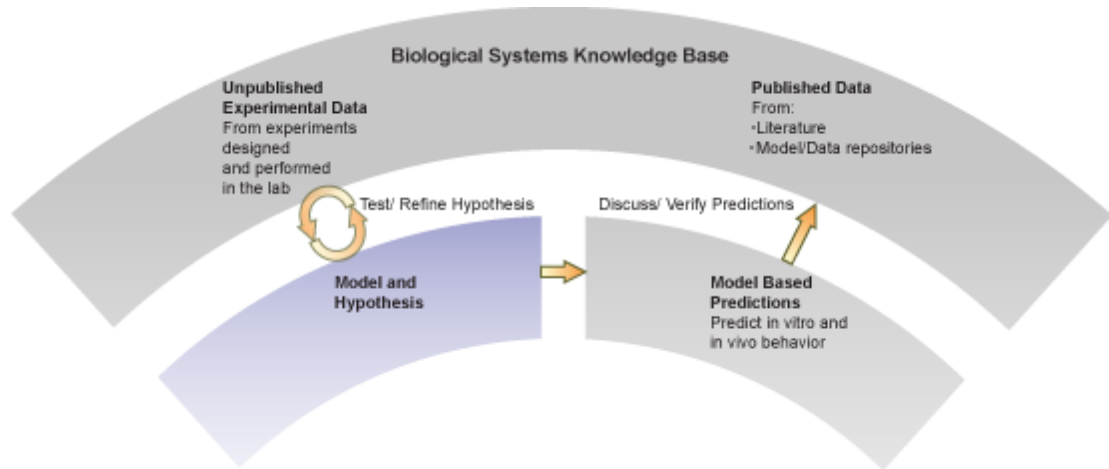
Integrating SimBiology Models into Your Existing Workflow

In this section...
“Existing Workflow in Experimental Research” on page 1-6
“Workflow Incorporating Mathematical Modeling” on page 1-7
“Workflow Using SimBiology Models for Mathematical Modeling” on page 1-9

Existing Workflow in Experimental Research

Consider the following typical workflow in research. The subsequent figure shows these general steps in experimental research.

- 1** Use preliminary results and published data to develop a model and hypothesis in your area of interest.
- 2** Validate your model by making predictions and designing experiments to test your model and hypothesis.
- 3** Make further predictions based on your model.
- 4** Publish results and predictions.
- 5** Continue to test predictions experimentally.

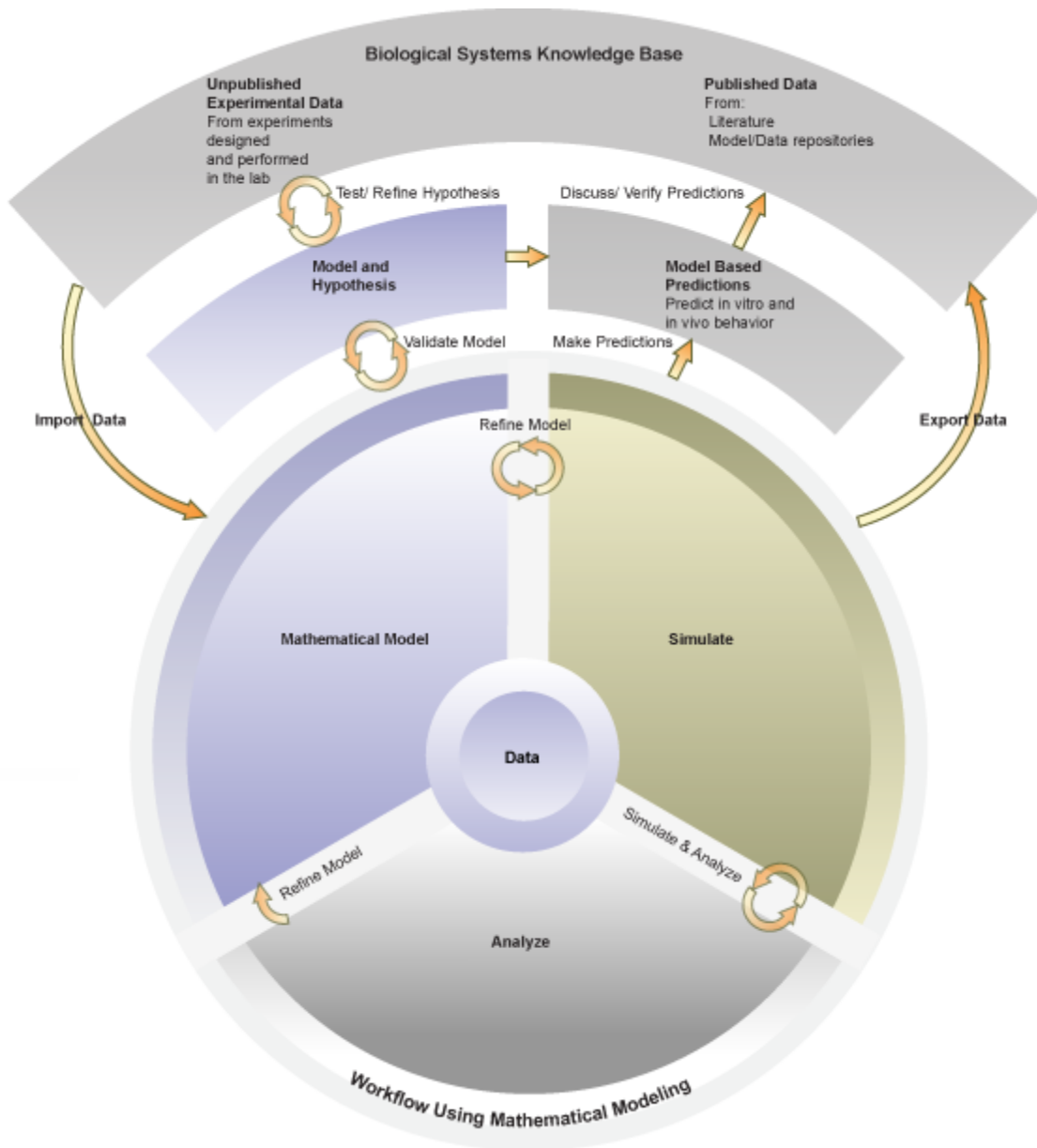


Typical Workflow in Experimental Research

Workflow Incorporating Mathematical Modeling

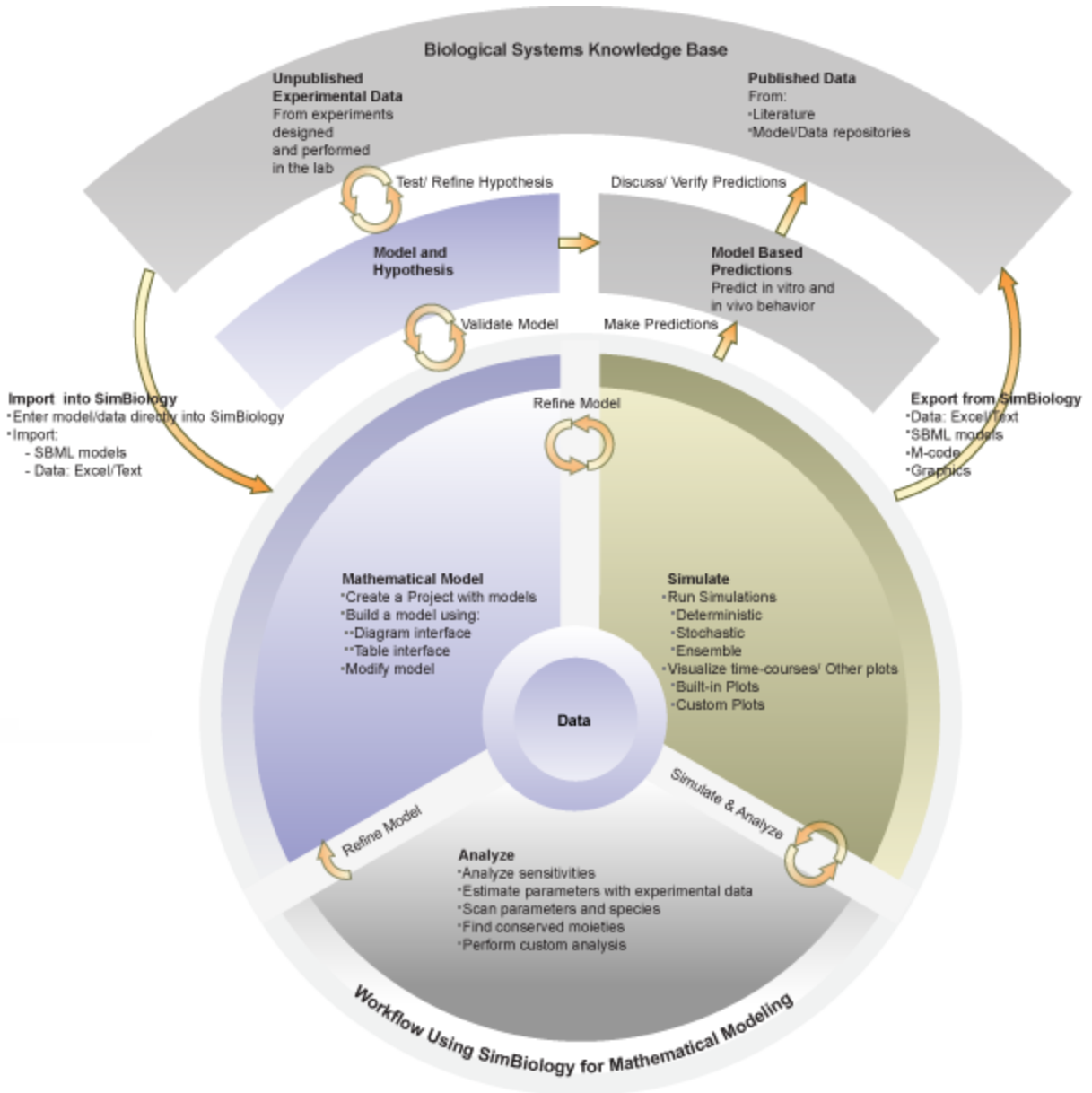
Mathematical modeling integrates into the preceding workflow by providing the means to:

- Consolidate quantitative data into the model.
- Represent large pathways and networks and lay them out in meaningful ways using a software application.
- Study emergent properties of pathways and use these predictions to guide the direction of experimental research in ways that can save time and development costs.



Workflow Using SimBiology Models for Mathematical Modeling

The SimBiology software provides an integrated environment for mathematical modeling and analysis of biological and biochemical pathways. The following diagram shows you an overlay of features and tasks in the product pictured in the context of the complete workflow in experimental research.



Getting Started in the SimBiology Desktop

In this section...

“Overview” on page 1-11

“Creating or Opening a Model Using the New Project Wizard” on page 1-11

“Opening a SimBiology Project” on page 1-15

Overview

Depending on your application area and the extent of the existing knowledge base for your area of interest and ease of data availability, you might choose various different paths into, within, and out of the product. For example:

- Build the model using SimBiology software; use published or unpublished kinetic data that you directly enter into the product or import the kinetic data using Microsoft® Excel® or text files, and then perform simulation and analysis.
- Build a pharmacokinetic model using the New Project Wizard, and analyze the model.
- Open and work with a SimBiology model (project) that you have obtained.
- Import an SBML format model into the product and perform simulation and analysis.

Creating or Opening a Model Using the New Project Wizard

The New Project Wizard lets you import data, add a model, and select the analysis tasks you want to add to the model:

- 1** In the MATLAB Command Window, type:

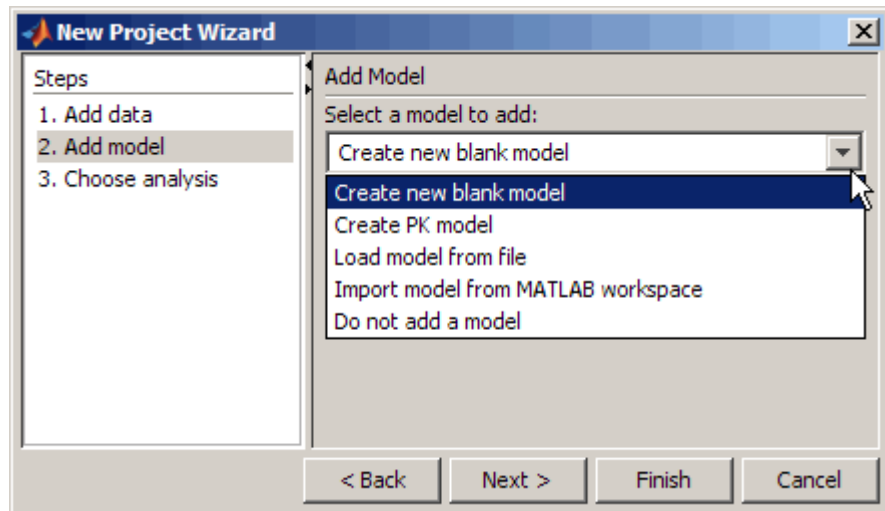
```
simbiology
```

The SimBiology desktop opens.

- 2** Select **File > New Project**. The New Project Wizard opens.

- 3** Choose to add data using the **Add Data** pane, or click **Next**. To add data:
 - a** In the **Add Data** pane, from the **Source** list, select **File** or **MATLAB Workspace**.
 - b** Depending on the selection in the previous step, specify the name of the file or the **MATLAB** variables to import and click **Next**.
- 4** In the **Add Model** pane, from the **Select a model to add** list, select one of the following:

Model Selection	Description
Create new blank model	Creates a model containing one compartment (at least one compartment is required for all models). You can later add model components such as species, reactions, rules, and events to the model.
Create PK model	Automatically generates pharmacokinetic (PK) models by specifying number of compartments, dosing type, and method of elimination.
Load model from file	Open a model from another project, or open an SBML model.
Import model from MATLAB workspace	Imports a model already in the MATLAB workspace.
Do not add a model	Lets you work with imported data without adding a Model Session .



5 Depending on the selection in the previous step, do one of the following:

If you chose ...	Do the following ...
Create new blank model	(Optional, but recommended) In the Model Name box enter a name for the model.
Create PK Model	Specify number of compartments, dosing type, and method of elimination. For more information see, “Fitting Pharmacokinetic Model Parameters in the SimBiology Desktop” in the SimBiology User’s Guide.
Load model from file	Browse to, or specify the name of the project or SBML file.
Import model from MATLAB workspace	Select from a list containing models from the workspace.
Do not add a model	Go to the next step.

6 Click **Next**.

7 In the **Choose analysis** pane, select the analysis tasks to add to the model and click **Finish**.

A new project with the selected specifications opens.

Opening a SimBiology Project

To open a SimBiology project that you received:

- 1 In the MATLAB Command Window, type:

```
simbiology
```

The SimBiology desktop opens.

- 2 Select **File > Open Project** to open the Open SimBiology Project dialog box.
- 3 Browse to and select the `.sbproj` format file containing the project.

Features and Functions

In this section...
“Using the Command Line versus the SimBiology Desktop” on page 1-16
“Graphical User Interface” on page 1-17
“Command-Line Interface” on page 1-22
“Data Formats and Projects” on page 1-22
“Modeling” on page 1-23
“Simulation” on page 1-24
“Analysis” on page 1-25

Using the Command Line versus the SimBiology Desktop

SimBiology extends MATLAB and lets you access functionality at the MATLAB command line and the graphical SimBiology desktop.

Use the command line to write and save scripts for batch processing, and to automate your workflow.

Use the SimBiology desktop to interactively change and iterate through the model workflow. The SimBiology desktop also lets you encapsulate models, data, tasks, task settings, and diagnostic plots into one convenient package, namely a SimBiology project.

Further, if you are using the SimBiology desktop and want to learn about working at the command line the code capture feature in the desktop lets you visualize the commands and export files for further scripting in the MATLAB editor.

Two tutorials in the Getting Started Guide walk you through building models through the desktop:

- “Modeling Using the SimBiology Graphical User Interface” on page 2-8
- “Modeling Using the SimBiology Diagram View” on page 2-16

Another tutorial in the Getting Started Guide walks you through building models at the command line:

- “Modeling Using the Command-Line Interface” on page 2-40

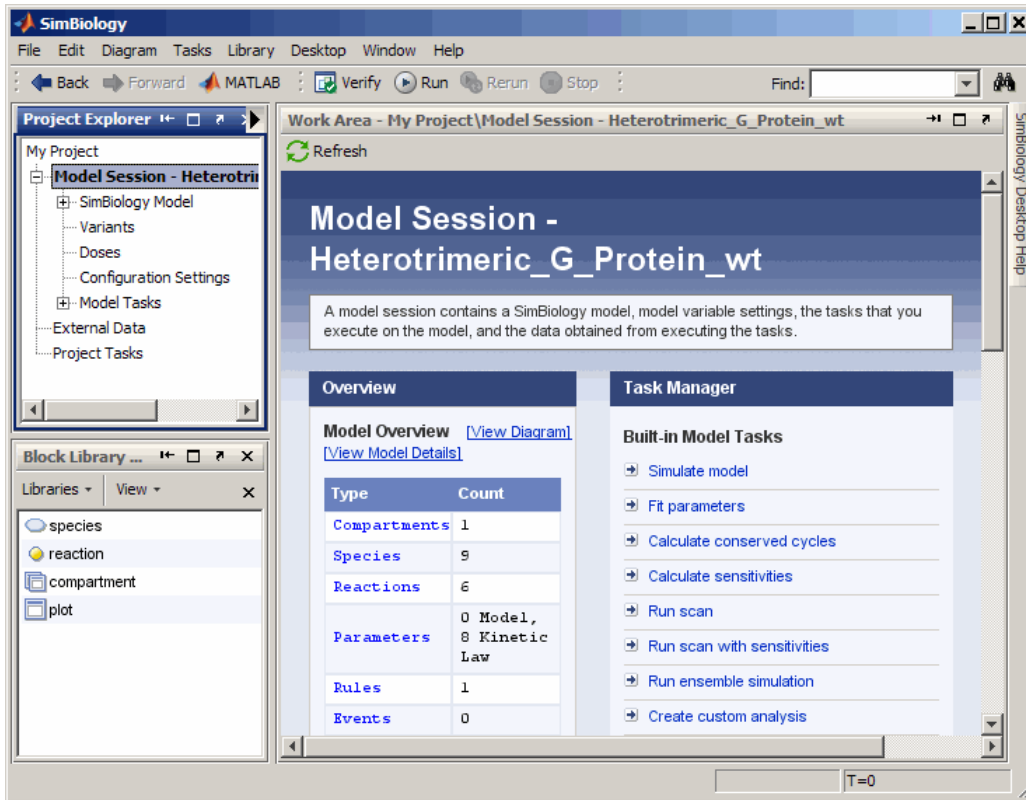
If you want to learn about pharmacokinetic modeling features see “Pharmacokinetic Modeling”.

There are video demos that show you how to work in the desktop and demos that show you how to programmatically build a model, simulate, and analyze. To access SimBiology demos, type the following at the MATLAB command line:

```
demo matlab simbiology
```

Graphical User Interface

The SimBiology desktop provides access to command-line functionality through a graphical user interface. The interface lets you model, simulate, and analyze biological pathways and reactions. Export your model to the MATLAB workspace and perform further analysis using the command line.



The graphical user interface (SimBiology desktop) is organized with the following set of integrated tools:

- **Project Explorer** — View projects and the organization of models, and navigate to components and subcomponents using a hierarchical tree view. The project branch is divided into separate model sessions.
- **Library Explorer** — View and modify libraries, which contain built-in and user-defined components, namely kinetic laws, plot types, units, unit prefixes, and blocks.
- **Component Palette** — View all available parameters, species, and compartments. You can drag and drop components from the Component Palette to panes in the SimBiology software.

- **Diagram View** — Enter model data using block representations for compartments, species, and reactions. Use the Plot block to visualize simulation data during a simulation.
 - **Block Library Browser** — View and use blocks from the built-in Basic library, and add custom blocks to user-defined block libraries for use in the diagram.
 - **Alignment Tool** — Align blocks in a diagram.
- **Table View of Model Components** — Enter data for model components such as reactions, species, or parameters, using a familiar spreadsheet format, forms, comma-separated files, or previously saved SBML models. Model and simulate biological processes as reactions with reactants, products, and reaction rates. Reactions include processes that transform species, and processes such as transport, and binding.
- **Verify Models** — Verify that the model does not generate any warnings or errors that would prevent simulation or analysis.
- **Simulation** — Simulate a model with deterministic or stochastic solvers, save simulation data, and export data to the MATLAB workspace.
- **Analysis Tasks** — Calculate sensitivities, scan species or parameters, fit parameters (analyze nonlinear mixed effects), find conserved moieties, perform ensemble simulations, or create custom analysis tasks.
- **Plotting** — Generate plots to visualize simulation and analysis results, and create and save custom plots.
- **Block Library Browser** — Use the Basic library for blocks in the diagram.
- **Diagram Overview** — Pan through large models using the miniaturized view of the model in this tool.
- **Diagram Table View** — Tools like hiding, pinning, splitting, and cloning for model layout in the Diagram, and generate a histogram for degree of connectivity of species in a model.
- **Searches** — Create custom searches for object properties with specific values within a project.
- **Find** — Use the **Find** feature for simple searches within a project. The results are shown in the **Search Results** pane.

- **Generate Reports** — Create reports for your project, include diagrams, figures, and data in the reports, and save them as HTML files.
- **Kinetic Law Manager** — View built-in kinetic laws and define your own kinetic laws.
- **Unit Manager** — View built-in units or define your own units composed from basic physical quantities.
- **Table Column Manager** — Customize the desktop spreadsheets using the Table Column Manager to display or hide the properties you are interested in viewing or editing.
- **MATLAB Code Capture Tool** — Convert interactive GUI actions with the SimBiology desktop to MATLAB scripts, and load them into MATLAB.
- **Embedded help** — The embedded help pane is context sensitive to the tasks you are performing while you build, simulate and analyze your model. As you select component branches in the **Project Explorer** pane or optional panes, the topics that support your current tasks appear in the embedded help pane on the right.

The Help browser supplements the embedded help information with detailed reference material for command-line functions; object methods and properties; tutorials to help you get started; and more details about modeling, simulation, and analysis.

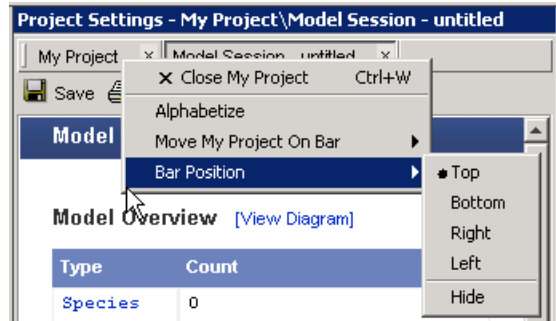
Customizing Desktop Views and Preferences

You can arrange the desktop layout according to your preferences.

- **Changing preferences** – Select **File > Preferences** to open the SimBiology Preferences dialog box. You can change preferences for the following:
 - **Desktop Display** — Specify which toolbars to display and which properties to display in model component tables.
 - **Project Explorer** — Specify whether to double-click or single-click to open each pane from the **Project Explorer**.
 - **Diagram** — Specify **Indicator** options, and whether to always warn when there are disallowed block actions.

- **Search** — Specify whether double-clicking a search result should open the selected component in the table view or the diagram.
- **Report Generator** — Specify the default format for report output, stylesheet to use when generating the report, default image formats, size, and location.
- **History** — Specify the number of recently used models, projects, help queries, searches, and libraries to display.
- **Confirmation Dialogs** — Specify whether dialog boxes should open for confirmation of various deletions, parameter reordering, or defining undefined variables.
- **Changing pane location** — Click the title bar of a pane, drag it to the desired location, and drop. The diagram shows you an outline of the pane during drag and drop. If the dropped location is on top of another pane, click the tabs at the bottom to navigate between the panes.
- **Obtaining default layout** — From the **Desktop** menu, select **Desktop Layout** and select **Default Layout**.
- **Organizing tables** — You can also add or delete the properties listed in the table columns on each pane using the **Table Column Manager**.

If the **Table Column Manager** does not appear on your SimBiology desktop, from the **Desktop** menu, select **Table Column Manager**. The **Table Column Manager** opens in the desktop, and if the context-sensitive help pane is open, the help updates with more information.
- **Changing pane title bar position** — You can open multiple panes from the **Project Explorer**. Each pane has a title bar in the **Project Settings** pane. You can change the location of the title bar. Right-click the title bar and then select **Alphabetize** or select **Bar Position** and select the location.



Command-Line Interface

You can access all features interactively or programmatically.

You can either create your models in the SimBiology desktop and export to the workspace or create your models directly in MATLAB.

- **Functions** — Use functions to create projects, manage the unit and kinetic law libraries, and simulate and analyze models.
- **Methods** — Use methods to create objects and specify object property values.
- **Code capture** — In the SimBiology desktop, you can record and save your actions as a script. After loading the script into MATLAB, you can then run the script programmatically and observe what you created interactively.

Data Formats and Projects

Store your models in project files. Projects group related models and simulation data into project files.

- **Projects** — Organize projects with related models, simulation data, and analysis results.

A *project* combines models, simulations, analysis, and results. Each project is divided into one or more *model sessions*.

- **Model session** — In the SimBiology desktop, a project can contain one or more model sessions. Each model session contains a model, all its configuration settings, and any saved data.

The configuration settings include simulation settings, units, kinetic laws, tags, notes, and annotations.

- **Kinetic Law library** — Use built-in kinetic laws or create your own kinetic laws for defining reaction rates.
- **Units library** — Use built-in units or create your own units for species and parameters.

In addition, SimBiology software supports SBML Level 2 Version 1. Systems Biology Markup Language (SBML) is becoming the standard language for documenting and sharing mathematical models for biological systems. You can save your models to an SBML-formatted file or read an SBML file created with SimBiology or other modeling software. For more information, see “SimBiology Support and SBML” on page 1-26.

When you save a project, the model definition is saved with the project. However, you can independently export a SimBiology model to an SBML file. Use this SBML file to import your model into SBML Level 2 Version 1-compliant modeling and simulation software.

When you import an SBML file created with other software, the model definition is translated into SimBiology objects.

Modeling

You can use SimBiology software to design and build pathway models.

- **Model** — A SimBiology *model* is a collection of interrelated reactions, rules, and events that transform, transport, and bind species. The model components are compartments, species, reactions, parameters, rules, and events. After creating a model, add a compartment. Then you can add reactions to the model, define a kinetic law for each reaction, and add the parameters for the reaction.
- **Model properties** — Properties define the characteristics of a component. For example, a reaction includes properties for reactions such as reaction rates, and links to associated species, parameters, and kinetic laws. You can interactively change these properties in the graphical user interface.

At the command line, all model components are represented as objects. Use the `get` and `set` commands to list object properties and change their values at the command line.

- **Notes** — The **Notes** property allows HTML-formatted text. This property lets you link to journal articles in PDF and other formats, Web pages, databases, graphic files, experimental data, and verbose project notes that do not fit into a text box.

Simulation

SimBiology software includes both stochastic and deterministic solvers.

- **Stochastic simulation** — Genetic and signaling pathways often have a small number of molecules that are simulated more accurately with stochastic algorithms. The stochastic solvers are based on Daniel Gillespie’s exact solution algorithm with variations for implicit and explicit tau leaping.

Gillespie, D., (1977), “Exact Stochastic Simulation of Coupled Chemical Reactions,” *The Journal of Physical Chemistry*, 8(1):2340–2361.

The implicit tau-leaping solver works optimally with large, numerically stiff systems. When solving numerically stiff systems, this solver remains stable for large time intervals (tau) where the explicit tau-leaping solver might not.

While stochastic simulations might accurately reflect the actual processes in a cell, they might not be practical for models with a large number of reactions or higher species amounts. Metabolic and signaling transduction pathways fall into this category. In this case, mass-action kinetics and ODE solvers can be a reasonable approximation.

- **Deterministic simulation** — You can choose from the list of stiff and nonstiff deterministic simulation solvers that are included with MATLAB. These solvers are reliable and robust.
- **Dimensional analysis and unit conversion** — Dimensional analysis compares the physical quantities for parameters and species in mathematical expressions (reaction rates, algebraic rules, assignment rules, and rate rules) and verifies that they are in consistent dimensions. Unit conversion scales the parameter values and species amounts to have the same units before simulation.

- **Plotting simulation results** — At the end of the simulation, the software plots the results in a figure window, or you can change plot settings and replot selected species yourself. In the SimBiology desktop, insert and configure a Plot block in the **Diagram** pane to view the results in a plot while the simulation runs.
- **Simulations settings** — Configuration set objects define the properties needed for simulation. These properties include the simulation time, absolute and relative tolerances, and controls for dimensional analysis and unit conversion.

Analysis

SimBiology software is closely integrated with MATLAB.

- **Getting simulation data into MATLAB** — During a simulation, the software saves (logs) the values for parameters and the amounts of species to the MATLAB workspace.
- **Plotting simulation data and analyzing results** — Using the functions in MATLAB, you can select and scale species for plotting.
- **Parameter estimation and optimization** — Estimate parameters that are unknown in the model.
- **Sensitivity analysis** — Calculate sensitivities of species with respect to species and parameter input factors.
- **Moiety conservation** — Calculate a complete set of linear conservation relations for the species in a SimBiology model.
- **Ensemble runs** — Perform iterative simulation runs to compare and analyze simulation results from stochastic solvers. Find the mean and variance as a function of time.

SimBiology Support and SBML

In this section...
“What Is SBML?” on page 1-26
“SBML Support” on page 1-26
“Importing SBML Files” on page 1-27
“Converting a SimBiology Model to SBML Format” on page 1-27

What Is SBML?

Systems Biology Markup Language (SBML) is an information standard for sharing, evaluating, and developing systems biology models cooperatively.

Its purpose is to provide a structure for creating models and sharing those models among various modeling and simulation software tools. The current specification is available on the Web at <http://sbml.org/documents/>.

SBML Support

SimBiology software supports a subset of the SBML Level 2 Version 1 specification. You can import from and export to SBML-compatible .xml files.

Unsupported features include:

- Piecewise kinetics — Models with piecewise kinetics are loaded in, but the definitions for piecewise kinetics are ignored.
- Function definitions — Models containing functional definitions are loaded, and you see a warning and the function definitions are ignored.
- MATLAB incompatible variable names in `UnitDefinition` — Models that have variable names incompatible with MATLAB in `UnitDefinition` are not loaded and you see an error message.
- The `hasOnlySubstanceUnits` field does not have a corresponding property in the SimBiology species object. For more information on dimensions for SimBiology species, see `DefaultSpeciesDimension`.

Importing SBML Files

To import an SBML file in the SimBiology desktop, use the **New Project Wizard**.

- 1 In the MATLAB Command Window, type:

```
simbiology
```

The SimBiology desktop opens.

- 2 Select **File > New Project**. The New Project Wizard opens.
- 3 Choose to add data using the **Add Data** pane, or click **Next**.
- 4 In the **Add Model** pane, from the **Select a model to add** list, select Load model from file
- 5 Browse to, or specify the name of the project or SBML file.
- 6 Click **Next**.
- 7 In the **Choose analysis** pane, select the analysis tasks to add to the model and click **Finish**.

A new project with the selected specifications opens.

Converting a SimBiology Model to SBML Format

To convert a SimBiology model to SBML format,

- 1 Select **File > Export Model to SBML**. The Save Systems Biology Markup Language File (SBML) dialog box opens.
- 2 Enter a path and file name.
- 3 Click **Save**.

The following information is included in the saved SBML format file:

- Compartments, events, parameters, reactions, rules, and species that are defined in the model.

Note Rules, reactions, and events that have their `Active` property set to `false` (inactive) are not exported.

- All unit definitions in SBML-compliant form
- The reaction rate equation, but not the kinetic law definition

Example

In SimBiology kinetic laws, the Henri-Michaelis-Menten equation, $V_m * S / (K_m + S)$ is a kinetic law definition stored in the kinetic law library.

Specifically, for a one-substrate enzyme-catalyzed reaction, if you assign $V_m = V_a$, $K_m = K_a$, and $S = A$, the reaction rate equation is $V_a * S / (K_a + A)$

- Model component properties with SBML equivalents, such as **Annotation**, species, and parameter unit values will be exported. Features and properties specific to SimBiology software, such as **Tag** and **Active**, cannot be exported.

The following SimBiology features are not supported by SBML and not included in the saved SBML format file:

- Projects — SimBiology software creates and stores all your models in project files with the `.sbproj` extension. You can store multiple models in one project file.
- Kinetic law — You can store kinetic law information such as the kinetic law name and a kinetic law definition.
- Dosing information — If the model contains dosed compartments, dosing information is not included in the SBML format file.

Building SimBiology Models

- “Gene Regulation Model” on page 2-2
- “Modeling Using the SimBiology Graphical User Interface” on page 2-8
- “Modeling Using the SimBiology Diagram View” on page 2-16
- “Modeling Using the Command-Line Interface” on page 2-40

Gene Regulation Model

In this section...

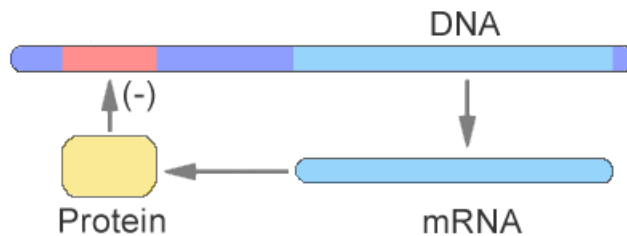
“Model Diagram” on page 2-2

“Model Reactions” on page 2-3

“Opening the Gene Regulation Model in the SimBiology Desktop” on page 2-6

Model Diagram

You can visualize a systems biology model with various levels of detail. One view sketches only the major species and processes. This model is an example of simple gene regulation, where the protein product from translation controls transcription. You could create a more complex model by adding the enzymes, coenzymes, cofactors, nucleotides, and amino acids that are not included in this model. The gene regulation example simplifies the regulatory mechanism by not showing the contributions of RNA polymerase and any cofactors. The protein product from gene expression binds to a regulatory region on the DNA and represses transcription.



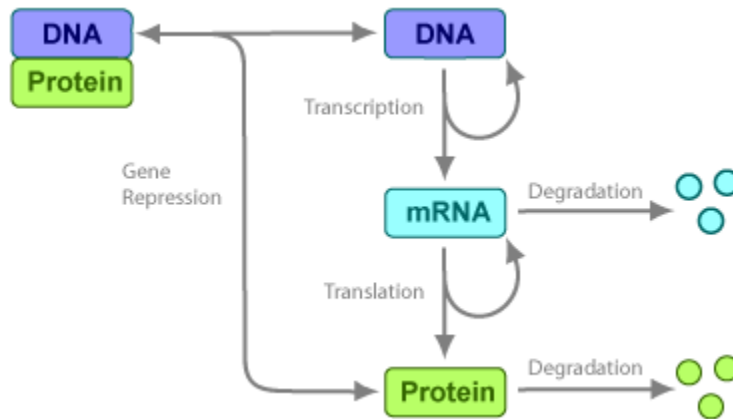
Another way of looking at a systems biology model is to list the reactions in a model with the processes they represent.

```

DNA -> DNA + mRNA           (transcription)
mRNA -> mRNA + protein       (translation)
DNA + protein -> DNA_protein (binding)
DNA_protein -> DNA + protein (unbinding)
mRNA -> null                 (degradation)
protein -> null              (degradation)

```

Drawing the reaction pathways will help you visualize the relationships between reactions and species. In the gene regulation example, as the amount of a protein increases, the protein forms a complex with the gene responsible for its expression, and slows down protein production.



Model Reactions

Reaction equations define a systems biology model at the level of detail needed for a software program to simulate the dynamic behavior of the model. The following reactions for transcription, translation, binding, and degradation describe a simple gene-regulating mechanism. For additional information about this model, see “Gene Regulation Model” on page 2-2.

Transcription

Transcription is where RNAPolymerase and cofactors bind with a DNA molecule. The RNAPolymerase then moves along the DNA and combines nucleotides to create mRNA. A simple model of transcription shows only the DNA and mRNA.



This model simplifies the transcription and the synthesis of mRNA by using a single reaction.

```
Reaction: DNA -> DNA + mRNA
Reaction rate: v = k1*DNA molecule/second
Species: DNA = 50 molecule
          mRNA = 0 molecule
Parameters: k1 = 0.2 1/second
```

Translation

After the mRNA moves from the nucleus to the cytoplasm, it can bind with ribosomes. The ribosomes move along the mRNA and create proteins with the help of tRNAs bound to amino acids. A simple model of translation shows only the mRNA and protein product.



The synthesis of the protein is modeled as a single reaction.

```
Reaction: mRNA -> mRNA + protein
Reaction rate: v = k2*mRNA molecule/second
Species: mRNA = 0 molecule
          protein = 0 molecule
Parameters: k2 = 20 1/second
```

Gene Repression

Transcription of DNA to mRNA is regulated by the binding of the protein product from translation to the DNA. As more protein is produced, the DNA is bound with the protein more often and less time is available for transcription with the unbound DNA.



Forward Reaction (Binding)

Reaction: DNA + protein -> DNA_protein
 Reaction rate: $v = k_3 \cdot \text{DNA} \cdot \text{protein}$ molecule/second
 Species: DNA = 50 molecule
 protein = 0 molecule
 Parameters: $k_3 = 0.2$ 1/(molecule*second)

Notice how the units are described for the parameter k_3 . In the literature, some of the common ways to display second-order rate constants are $\text{mole}^{-1}\text{second}^{-1}$ or $1/\text{mole}\cdot\text{second}$. However, software evaluations of these common ways are sometimes ambiguous.

Reverse Reaction (Unbinding)

Reaction: DNA_protein -> DNA + protein
 Reaction rate: $v = k_{3r} \cdot \text{DNA_protein}$ molecule/second
 Species: DNA_protein = 0 molecule
 Parameters: $k_{3r} = 1$ 1/second

For this tutorial, model the binding and unbinding reactions as one reversible reaction.

Reaction: DNA + protein <-> DNA_protein
 Reaction rate: $v = k_3 \cdot \text{DNA} \cdot \text{protein} - k_{3r} \cdot \text{DNA_protein}$ molecule/second
 Species: DNA = 50 molecule
 protein = 0 molecule
 Parameters: $k_3 = 0.2$ 1/(molecule*second)
 $k_{3r} = 1$ 1/second

Degradation

Protein and mRNA degradation are important reactions for regulating gene expression. The steady-state level of these compounds is maintained by a balance between synthesis and degradation reactions. Proteins are hydrolyzed to amino acids with the help of proteases, and nucleic acids are degraded to nucleotides.



mRNA degradation is modeled as a transformation to the null species.

```
Reaction: mRNA -> null
Reaction rate: v = k4*mRNA molecule/second
Species: mRNA = 0 molecule
Parameters: k4 = 1.5 1/second
```

Likewise, protein degradation is also modeled as a transformation to the null species. The species null is a predefined species name in SimBiology models.



```
Reaction: protein -> null
Reaction rate: v = k5*protein molecule/second
Species: protein = 0.0 molecule
Parameters: k5 = 1.0 1/second
```

Opening the Gene Regulation Model in the SimBiology Desktop

A project containing the model built in the gene regulation example is available with the product. To skip the sections on model building and to learn about simulations in the SimBiology desktop, you can access the completed model in the SimBiology desktop.

- 1 In the MATLAB Command Window, type:

```
simbiology
```

The SimBiology desktop opens.

- 2 Select **File > Open Project** to open the Open SimBiology Project dialog box.

- 3 Navigate to:

```
matlabroot/toolbox/simbio/simbiodem
```

- 4 Select `gene_reg.sbproj`, and click **Open**.

The project opens with two models: `cell1` and `cell2`. These two models are identical except for the graphical representation of the blocks in the **Diagram View** pane.

- 5** To explore the models, click an item in the **Project Explorer** to open individual panes.
- 6** See “Simulating a Model” on page 2-15 for procedures on simulating a model in the SimBiology desktop.

Modeling Using the SimBiology Graphical User Interface

In this section...
“About the Model Used in This Tutorial” on page 2-8
“Creating a Model” on page 2-8
“Saving Your Work as a SimBiology Project File” on page 2-9
“Adding Reactions to a Model” on page 2-10
“Simulating a Model” on page 2-15

About the Model Used in This Tutorial

This section shows how to mathematically model a simple gene-regulation pathway using the SimBiology desktop. The example uses the model described in “Gene Regulation Model” on page 2-2 and shows you how to build this model using a spreadsheet-style interface in the SimBiology desktop.

If you prefer to interact with diagrammatic representations of pathways, see “Modeling Using the SimBiology Diagram View” on page 2-16.

Alternatively, you can use the MATLAB command-line interface (see “Modeling Using the Command-Line Interface” on page 2-40). A comparison of these methods will help you understand the model objects that MATLAB creates behind the SimBiology desktop, and how to access and edit a model through the MATLAB Command Window.

Creating a Model

A SimBiology model is a collection of objects that are structured hierarchically. At least one model object is needed to contain all the other objects.

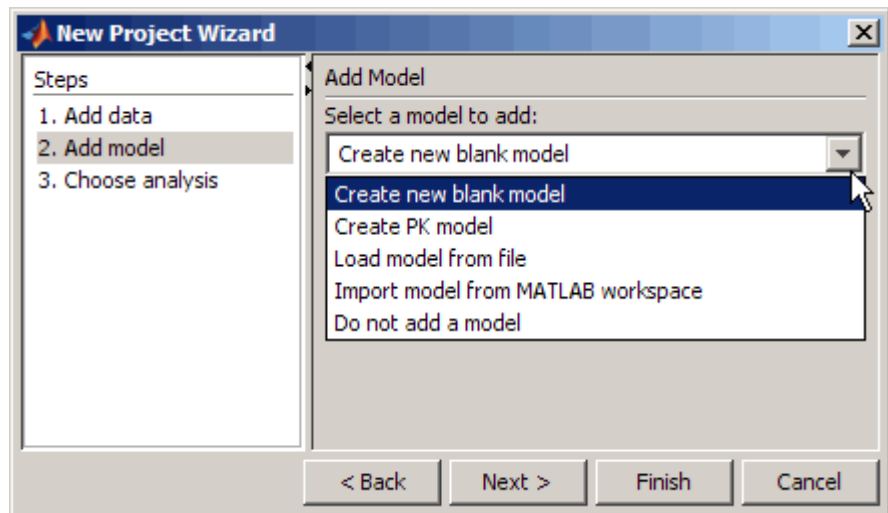
1 In the MATLAB Command Window, type:

```
simbiology
```

The SimBiology desktop opens.

2 Select **File > New Project**. The New Project Wizard opens.

- 3 Skip the **Add Data** step for this example and select **Add Model**.
- 4 In the **Add Model** pane, from the **Select a model to add** list, select **Create new blank model**. This selection creates a **Model Session** containing one compartment (at least one compartment is required for all models). You will later add model components such as species, reactions, rules, and events to the model.



- 5 In the **Model Name** box, type the name for your model.

cell
- 6 Click **Next**.
- 7 In the **Choose Analysis** pane, leave the default selection (**Simulate model**) selected for the analysis tasks to add to the model and click **Finish**.

A new project with the selected specifications opens.

Saving Your Work as a SimBiology Project File

Project is the file format that the SimBiology software uses to save one or more model sessions. The file extension is `.sbproj`. Projects let you save

custom settings, notes, and data associated with your models. For more information on projects, see “Data Formats and Projects” on page 1-22.

Save your work as a project now so that you can access this file later.

- 1 Select **File > Save Project as** to open the Save SimBiology Project dialog box.
- 2 Browse to the folder in which you want to save your projects, and enter a name for the project file, such as:

gene_regulation.sbproj

- 3 Click **Save**.

Adding Reactions to a Model

SimBiology models are defined by connected reactions representing transformation, binding, and transport.

- 1 In the **Project Explorer**, expand **SimBiology Model** and click **Reactions** to open the **Reactions** pane.
- 2 In the **Enter Reaction** box, enter the reactants and products, separated by a hyphen and right angle bracket. For example, enter the following simple reaction for transcription:

DNA -> DNA + mRNA

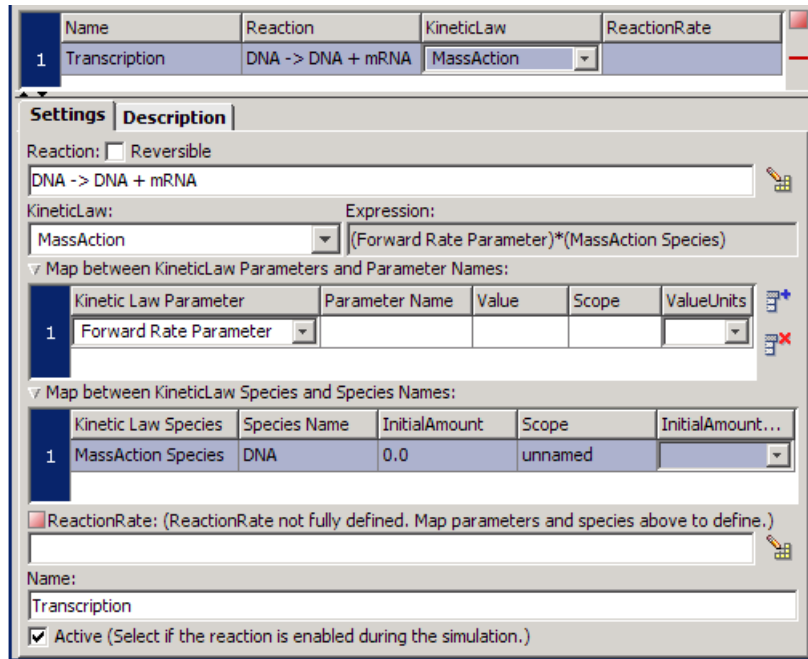
- 3 Click **Add**.

A red indicator appears to the right of the table (and in the **Project Explorer**). Move the pointer over the indicator for the reaction to get more information about the reason for the indicator. In this case, the indicator shows that the reaction rate is as yet undefined. Beginning in step 5, you will learn how to define the reaction rate.

- 4 Double-click the **Name** cell, enter a name for the reaction and press **Enter**. For example, enter the following:

Transcription

- 5 From the **KineticLaw** list, select **MassAction**. Your screen should resemble this one.



Note Species names are automatically populated for Mass Action. In this example notice that **MassAction Species** lists DNA.

- 6 In the **Map between KineticLaw Parameters and Parameter Names** section, locate the **Forward Rate Parameter** row, double-click the **Parameter Name** cell, type **k1** and press **Enter**.

The SimBiology desktop updates **ReactionRate** for the reaction to show $k_1 * \text{DNA}$.

Your reaction table should resemble the following.

Name	Reaction	KineticLaw	ReactionRate
Transcription	DNA -> DNA + mRNA	MassAction	k1*DNA

The indicator is green, showing that the reaction rate is now defined. The red indicator in the **Project Explorer** also disappears.

7 Double-click the **Value** cell and enter a new value.

0.2

8 From the **ValueUnits** list, select the units for this parameter. The rate constant k1 is a first order constant with units 1/second.

Your parameters table should resemble the following.

Map between KineticLaw Parameters and Parameter Names:					
	Kinetic Law Parameter	Parameter Name	Value	Scope	ValueUnits
1	Forward Rate Parameter	k1	0.2	DNA -> DNA + mRNA	1/second

About Scope

Notice that the **Scope** box for the parameter lists the reaction, indicating that the parameter is only available for reference at the level of the reaction.

If you set the scope of a parameter to the model (*Model Name*), you can use this parameter in rules, other reactions, and events. All the parameters for this example are scoped to their respective kinetic laws.

Scoping lets you overload parameters, that is you can have parameters with the same name at the kinetic law and at the model level. Because the desktop searches up from the kinetic law to the model level, when a parameter is overloaded, a reaction uses the parameter and parameter value in its kinetic law; however rules and events use the parameter value at the model level.

A reaction uses a parameter at the model level only if a corresponding parameter is not defined at the kinetic law level for the reaction.

9 In the **Map between KineticLaw Species and Species Names** section, locate the **MassAction Species** row (DNA), double-click the **InitialAmount** cell, type 50 and press **Enter**.

10 From the **InitialAmountUnits** list, select molecule.

The **Scope** of the species indicates the compartment that the species is within, and this is still *unnamed*. The next steps show you how to name the compartment.

11 In the **Project Explorer**, click **Compartments** to open the **Compartments** pane.

In the SimBiology desktop, models contain a compartment by default. The process of adding a reaction automatically adds the reaction species to a compartment in the model. If there are multiple compartments in the model, you must specify the reactants and products using qualified names (*compartmentName.speciesName*). For example, nucleus.DNA denotes the species DNA in the compartment nucleus.

12 This example contains only one compartment. Rename the compartment by doing the following:

In the **Name** cell, double-click and type a name such as contents for the compartment and press **Enter**. The compartment table updates with the new entry.

13 From the **Capacity Units** list select liter.

Leave other compartment properties such as **Owner** and **Capacity** in the default settings, for the purposes of this example.

14 In the **Project Explorer**, expand **Compartments** and click **contents Species**. The species you entered in the reaction are automatically added to the species table.

The default value for a species is 0.0.

15 In the row containing mRNA, from the **InitialAmountUnits** list, select molecule. Leave the **InitialAmounts** value at 0.0.

- 16 Enter the remaining reactions. For a list of reactions and parameters, see “Model Reactions” on page 2-3.

Notice that the ValueUnits for the second-order rate constant k3 is not a default unit in the list. However, molecule and second are default units and you can enter this unit directly by typing the following:

1 / (molecule*second)

Your reaction, species, and parameter panes should resemble the following ones.

Name	Reaction	KineticLaw	ReactionRate
Transcription	DNA -> DNA + mRNA	MassAction	k1*DNA
Translation	mRNA -> mRNA + protein	MassAction	k2*mRNA
Binding/Unbinding	DNA + protein <-> DNA_protein	MassAction	k3*DNA*protein - k3r*DNA_protein
mRNA Degradation	mRNA -> null	MassAction	k4*mRNA
Protein Degradation	protein -> null	MassAction	k5*protein

Name	Scope	InitialAmount	InitialAmountUnits
DNA	contents	50.0	molecule
mRNA	contents	0.0	molecule
protein	contents	0.0	molecule
DNA_protein	contents	0.0	molecule

Name	Scope	Value	ValueUnits
k1	DNA -> DNA + mRNA	0.2	1/second
k2	mRNA -> mRNA + protein	20.0	1/second
k3	DNA + protein <-> DNA_protein	0.2	1/(molecule*second)
k3r	DNA + protein <-> DNA_protein	1.0	1/second
k4	mRNA -> null	1.5	1/second
k5	protein -> null	1.0	1/second

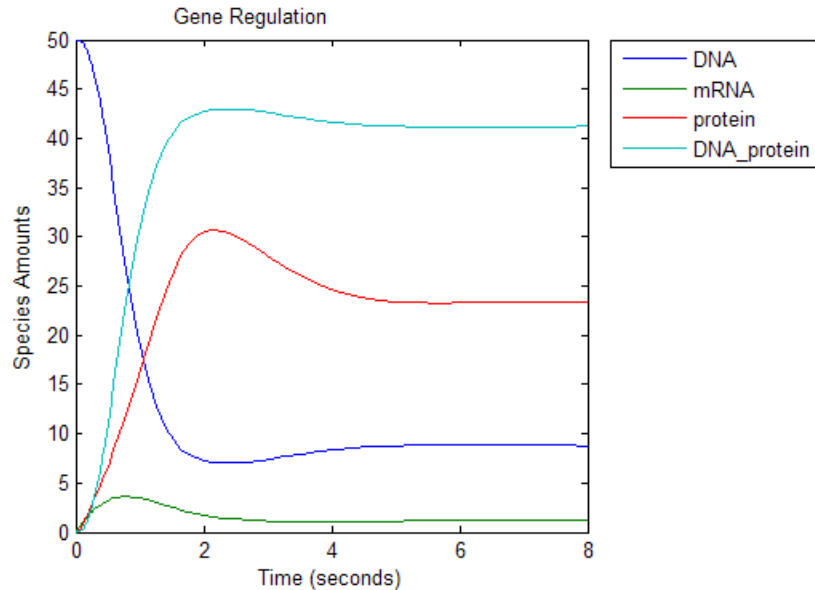
For more detailed information about the reactions in this model, see “Gene Regulation Model” on page 2-2.

Simulating a Model

After you enter the reactions for your model, you can simulate its dynamic behavior and plot the results.

- Click  (Run).

The simulation uses the default configuration settings, runs to completion, and then plots the results in a figure window. You can annotate your plot in the figure window. The following figure shows you an annotated version of the plot:



Modeling Using the SimBiology Diagram View

In this section...
“About This Example” on page 2-16
“Creating a Model” on page 2-16
“Saving Your Work as a SimBiology Project File” on page 2-20
“Adding Species and Reactions to a Model Diagram” on page 2-20
“Simulating a Model” on page 2-25
“Setting Block Appearance and Diagram Layout” on page 2-26
“Printing and Exporting the Diagram” on page 2-37

About This Example

This section shows how to mathematically model a simple gene-regulation pathway using the Diagram View in the SimBiology desktop. The example uses the model described in “Gene Regulation Model” on page 2-2.

If you prefer to interact with a tabular representation of reaction pathways, see “Modeling Using the SimBiology Graphical User Interface” on page 2-8.

Alternatively, you can use the MATLAB command-line interface (see “Modeling Using the Command-Line Interface” on page 2-40). A comparison of these methods will help you understand the model objects that MATLAB creates behind the SimBiology desktop, and how to access and edit a model through the MATLAB Command Window.

Creating a Model

This section shows how to model a simple gene-regulation pathway using the SimBiology Diagram View. For more information about this model, see “Gene Regulation Model” on page 2-2.

A SimBiology model is a collection of objects that are structured hierarchically. At least one model object is needed to contain all the other objects. The SimBiology Diagram View lets you work with the familiar graphical representation of biological pathways and processes.

This section shows you how to build your model using block representations for each compartment, species, and reaction. The model reactions are shown in “Gene Regulation Model” on page 2-2.

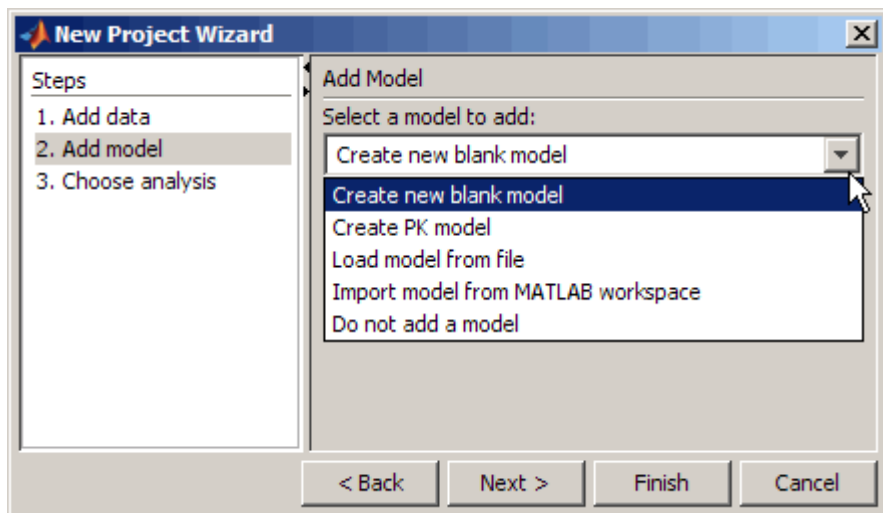
- 1 In the MATLAB Command Window, type:

```
simbiology
```

The SimBiology desktop opens.

All the procedures in this section refer to the SimBiology desktop in the default layout. To set the desktop to the default layout, select **Desktop > Desktop Layout > Default Layout**.

- 2 Select **File > New Project**. The New Project Wizard opens.
- 3 Skip the **Add Data** step for this example and select **Add Model**.
- 4 In the **Add Model** pane, from the **Select a model to add** list, select **Create new blank model**. This selection creates a **Model Session** containing one compartment (at least one compartment is required for all models). You will later add model components such as species, reactions, rules, and events to the model.



5 In the **Model Name** box, type the name for your model.

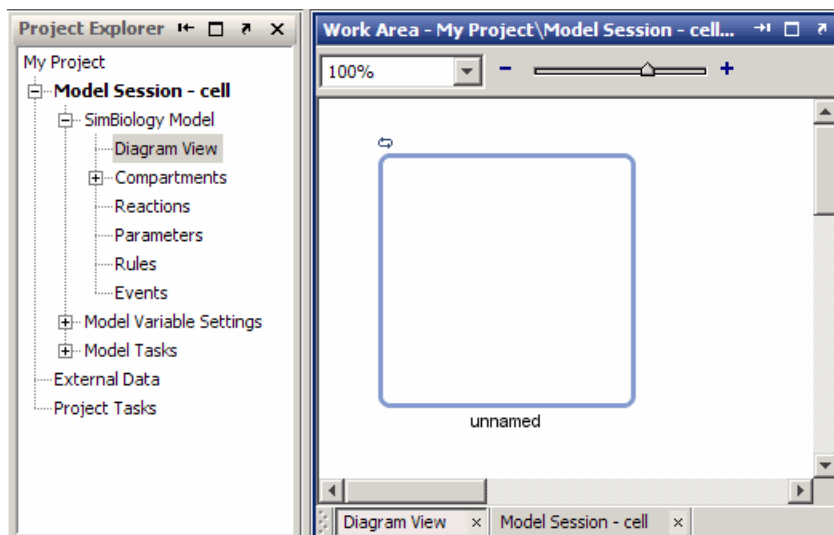
cell

6 Click **Next**.

7 In the **Choose Analysis** pane, leave the default selection (**Simulate model**) selected for the analysis tasks to add to the model and click **Finish**.

A new project with the selected specifications opens.

8 In the **Project Explorer**, expand **SimBiology Model** and click **Diagram View**. The **Diagram View** pane opens.



Notice the Compartment block (*unnamed*) in the model. In the desktop, all models contain a compartment by default.

9 Select **Diagram > Tools > Block Property Editor**.

Tip The **Block Property Editor** lets you enter or change block properties. Select a block in the diagram to access its properties in the **Block Property Editor**



All models created in the desktop contain a compartment by default. The process of adding a reaction automatically adds the reaction species to the compartment in the model. If there are multiple compartments in the model, you must specify the reactants and products using qualified names (*compartmentName.speciesName*). For example, nucleus.DNA denotes the species DNA in the compartment nucleus.






- 10** Select the model's compartment. The **Block Property Editor** updates to show the compartment properties.
- 11** In the **Name** box, type a name such as contents for the compartment and press **Enter**.
- 12** From the **Capacity Units** list select liter.

Leave other compartment properties such as **Owner** and **Capacity** in the default settings, for the purposes of this example.

Icons in the Diagram View

In the Diagram View, the following icons appear next to the block representations of compartments, species, and reactions, based on the settings for these blocks.

Icon	Meaning	Block in Diagram View
	Constant capacity	Compartment
	Constant amount	Species
	Pinned	Compartment
		Species
		Reaction

Icon	Meaning	Block in Diagram View
	Boundary condition	Species
	Cloned	Species
	Reversible	Reaction
	Inactive	Reaction
	Error	Reaction

Saving Your Work as a SimBiology Project File

Project is the file format that the software uses to save one or more model sessions; the file extension is `.sbproj`. Projects let you save custom settings, notes, and data associated with your models. For more information on projects, see “Data Formats and Projects” on page 1-22.

Save your work as a project now so that you can access this file later.

- 1 Select **File > Save Project as** to open the Save SimBiology Project dialog box.
- 2 Browse to the folder in which you want to save your projects, and enter a name for the project file, such as:

`gene_regulation.sbproj`

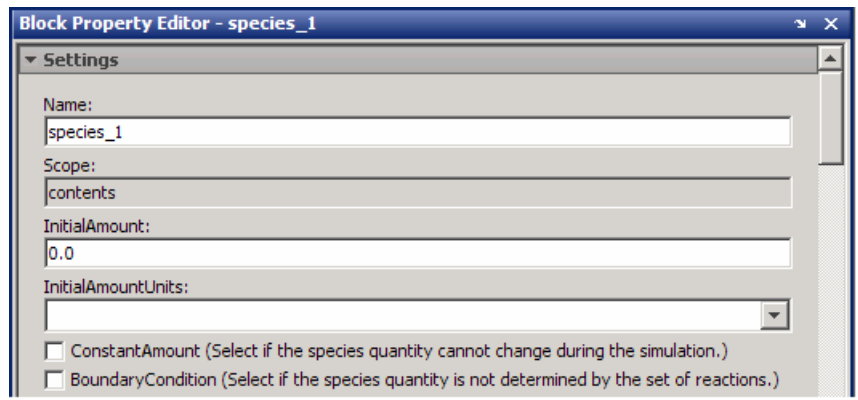
- 3 Click **Save**.

Adding Species and Reactions to a Model Diagram

SimBiology models are defined by connected reactions representing transformation, binding, and transport. You can graphically represent the reactions in the diagram. This section shows you how to add, connect, and

configure blocks in a diagram. For this example, use the **ModelBuilding** block library.

- 1 From the **Block Library Browser**, click-drag a species block into the compartment in the diagram.
- 2 Select the newly added species block to view the properties in the **Block Property Editor**.



- 3 In the **Name** box, enter the species name. For this example, enter DNA.

- 4 In the **InitialAmount** box, enter a new value.


50

- 5 From the **InitialAmountUnits** list, select the units for this species.

molecule

- 6 From the **Block Library Browser**, click-drag another species block into the diagram. Name this species mRNA. The **InitialAmount** for mRNA is the default (0.0). From the **InitialAmountUnits** list, select molecule as units for this species.

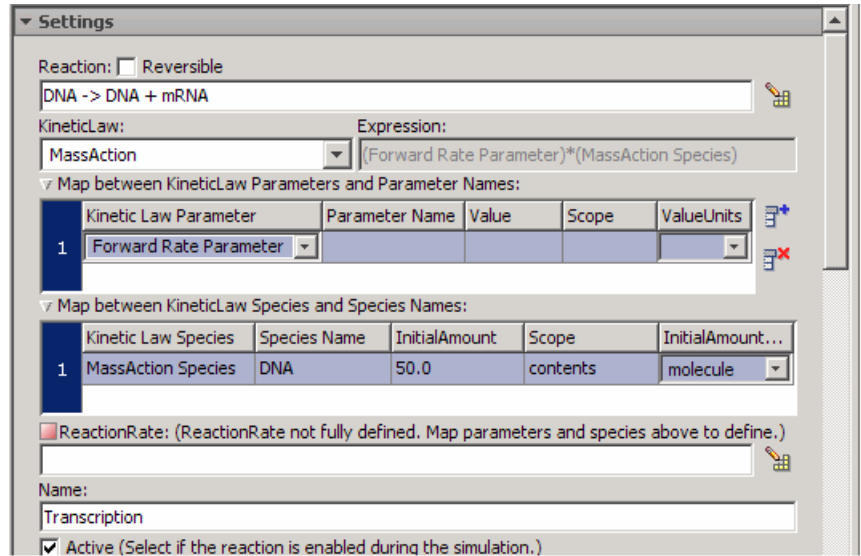
- 7 From the **Block Library Browser**, click and drag a reaction block into the diagram.

Note The newly added reaction has a  icon, indicating the reaction has not been fully defined. Once you define the reaction, as shown later in this example, the icon disappears.

- 8 Press and hold the **Ctrl** key (Windows® and Linux®) or the **Option** key (Macintosh®), click the DNA species block, drag the line to the reaction, and then release the mouse. The diagram assigns DNA as a reactant and displays a solid line.

Because DNA is also a product of the reaction, connect a line from the reaction block to DNA. The diagram draws a dashed line, indicating that DNA is a modifier for the reaction.

- 9 Draw a line from the reaction block to the mRNA species block.
- 10 Select the reaction block to view the block properties in the **Block Property Editor**. Notice that the **Reaction** box shows the reaction (DNA -> mRNA + DNA) to which the block applies.
- 11 In the **Name** box, at the bottom of the Settings section, enter a reaction name. For example, enter Transcription.
- 12 From the **KineticLaw** list, select MassAction. **The Block Property Editor** should resemble the following:



Note Species names are automatically populated for Mass Action. In this example notice that **MassAction Species** lists DNA.

- 13** In the **Map between KineticLaw Parameters and Parameter Names** section, locate the **Forward Rate Parameter** row, double-click the **Parameter Name** cell, type **k1** and press **Enter**.

The SimBiology desktop updates **ReactionRate** for the reaction to show **k1*DNA**.

The indicator is green, showing that the reaction rate is now defined.

- 14** Double-click the **Value** cell and enter a new value.

0.2

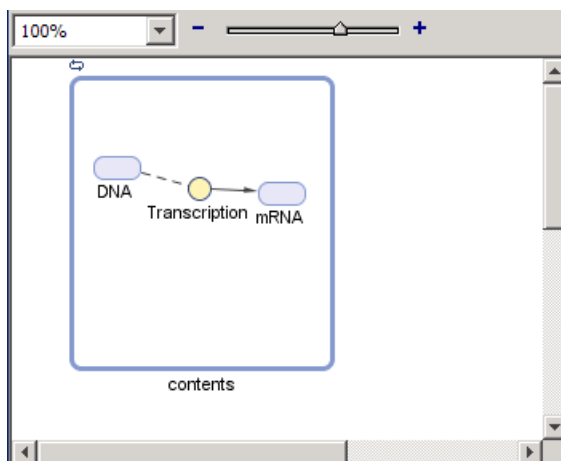
- 15** From the **ValueUnits** list, select the units for this parameter. The rate constant **k1** is a first order constant with units **1/second**.

Your parameters table should resemble the following.

Map between KineticLaw Parameters and Parameter Names:

	Kinetic Law Parameter	Parameter Name	Value	Scope	ValueUnits
1	Forward Rate Parameter	k1	0.2	DNA -> DNA + mRNA	1/second

Your diagram should resemble this one:

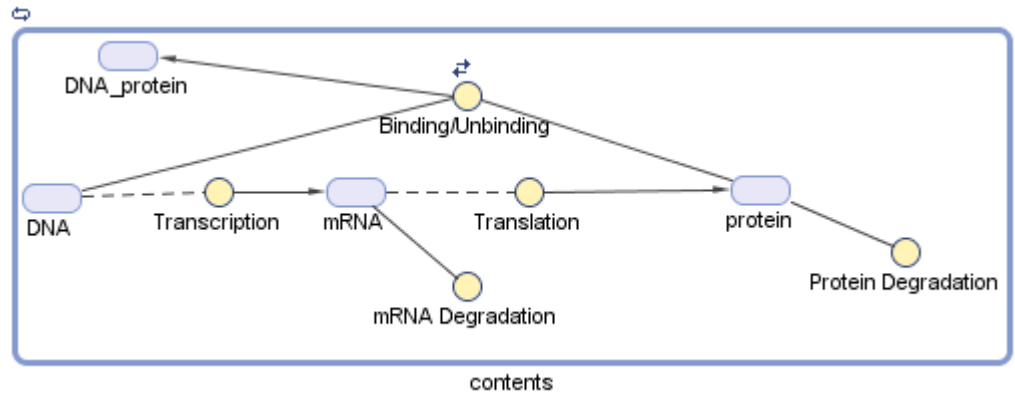


- 16** Add the other species and reactions blocks, and create parameters for each reaction as shown in the previous steps. For a list of reactions and parameters, see “Model Reactions” on page 2-3. To set a reversible reaction, select the **Reversible** checkbox in the Block Property Editor. Verify that the reaction rate is determined for each reaction.

Notice that the ValueUnits for the second-order rate constant k3 is not a default unit in the list. However, molecule and second are default units and you can enter this unit directly by typing the following:

`1/(molecule*second)`

After creating the model, the diagram should resemble this one.



Notice the use of dashed lines for species that are both reactants and products in a reaction (modifiers). Note the \rightleftharpoons icon for the reversible reaction associated with the Binding/Unbinding reaction.

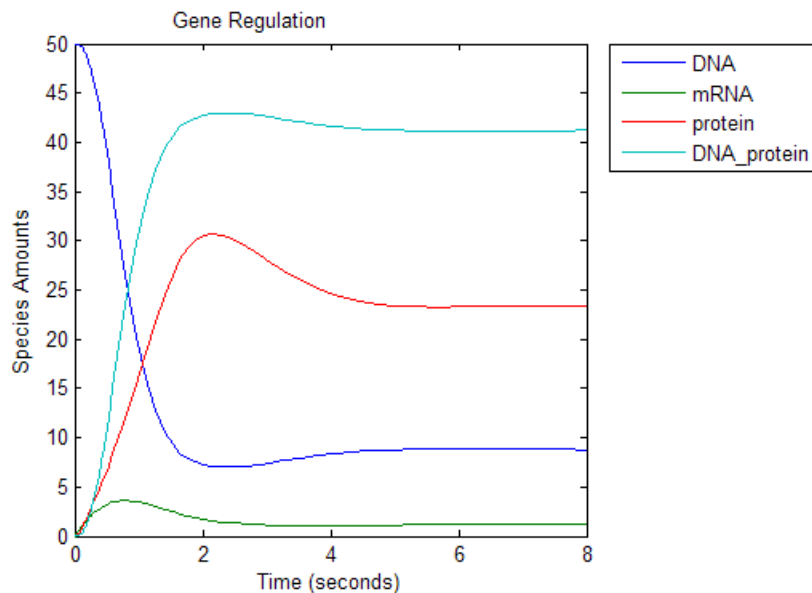
You can change the layout and appearance of the blocks any time. Double-click a block and click the **Appearance** tab to change the color, text font, size, and location. See “Changing Block Appearance” on page 2-26 for more information.

Simulating a Model

After you enter the reactions for your model, you can simulate its dynamic behavior and plot the results.

- Click  (**Run**).

The simulation uses the default configuration settings, runs to completion, and then plots the results in a figure window. You can annotate your plot in the figure window. The following figure shows you an annotated version of the plot:



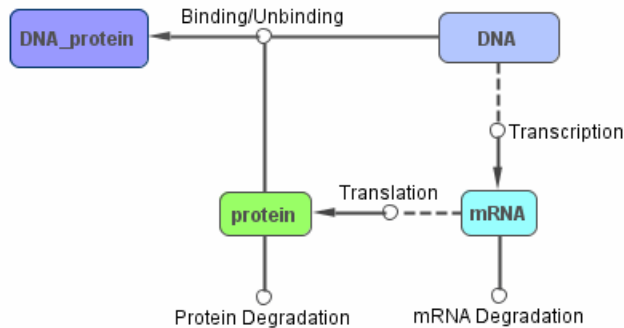
Setting Block Appearance and Diagram Layout

This section shows you how to change the appearance and layout of a SimBiology diagram.

- “Changing Block Appearance” on page 2-26
- “Applying Block Appearance Styles” on page 2-29
- “Changing the Diagram Layout Manually” on page 2-30
- “Changing the Diagram Layout Automatically” on page 2-33
- “How the SimBiology Desktop Does Diagram Layout” on page 2-36

Changing Block Appearance

You can change the appearance of blocks, text, lines, and indicators in the diagram. The following figure is one example.




This example uses the DNA species block and the Binding/Unbinding reaction block to show you how to change the color of the blocks, the location of the text, the appearance of the reversible indicator, and line appearance as shown in the previous figure.

- 1** Select **Diagram > Tools > Block Property Editor**. The **Block Property Editor** opens.
- 2** Select the species block or the reaction block to view the selected block property in the **Block Property Editor**. Perform the next steps in the **Appearance** section.
- 3** Change the following values to affect position and size of the block:
 - **X**– Position of block relative to the X axis of the diagram. For example, for the reaction block, try 260
 - **Y**– Position of block relative to the Y axis of the diagram. For example, for the reaction block , try 30
 - **Width** and **Height**– Horizontal and vertical size of the block respectively. For example, for the reaction block, try 25 and 40 respectively
- 4** From the **Text Location** list, select where the text should be positioned in the diagram. The default is **bottom**. For example:
 - For the DNA Species block, select **center** to position the text within the center of the Species block.

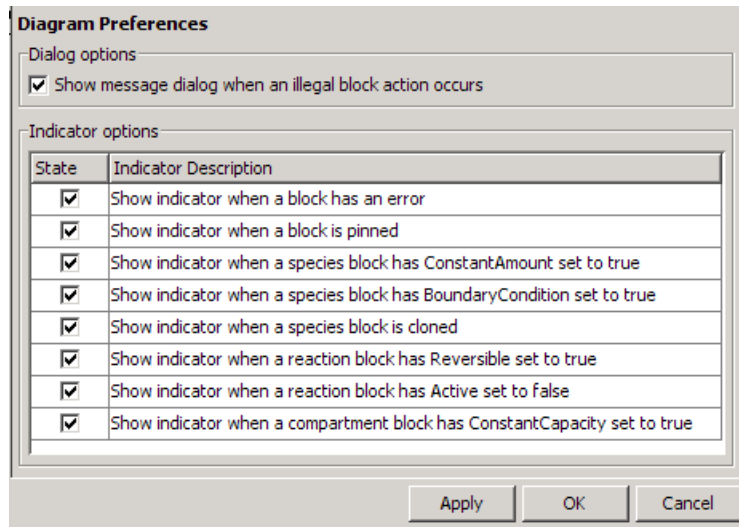
- For the **Binding/Unbinding Reaction** block, select top.

5 From the **Text Font**, **Block Appearance**, **Text Color**, **Edge Color**, and **Face Color** lists, select the text font, block appearance, text color, edge color, and block fill color.

Tip Select **Face Color > No Face Color** to obtain the result shown for reaction blocks in the diagram figure above.

Tip Select **Block Appearance > Image** to insert an image for the block. The SimBiology desktop opens a dialog box that lets you browse to the image location. If you change the image, click  (**Refresh**) to reload the updated image.

- 6** Double-click a line to open the Line Properties dialog box. The default line width is 1.0 pixels. The line width in the previous example diagram is 2.0.
- 7** Select **File > Preferences**. The SimBiology Preferences dialog box opens.
- 8** Select **Diagram**.



- 9 Clear or select an indicator check box to turn off or turn on the display of the indicator in the diagram. For example, clear the **Reversible** property indicator, and click **Close**.

Notice that the reversible indicator is now off for the **Binding/Unbinding Reaction** block in the diagram.

- 10 Right-click the diagram and select **Layout Diagram** to automatically change the layout of the diagram. You can manually lay out the diagram using the pin, split, clone, and hide features in the diagram.

For more information on the pin, split, clone, and hide features in the diagram, see “Changing the Diagram Layout Manually” on page 2-30. For information on automatic layout in the SimBiology desktop, see “Changing the Diagram Layout Automatically” on page 2-33.

Applying Block Appearance Styles

To replicate the appearance style of a block to other blocks by copying and applying the style on selected blocks:

- 1 Select a species block, for example, the DNA species block.

- 2 Right-click the block and select **Copy Block Style**.
- 3 Select another block, for example, the DNA protein species block.

You can also select multiple blocks to apply the style to all selected blocks.

- 4 Right-click the block and select **Apply Block Style**. The SimBiology desktop changes the appearance of the block to match the selected style.

Changing the Diagram Layout Manually

You can manually lay out the diagram using the pin, split, clone, and hide features in the diagram. Use the **Diagram Table View** pane or a block's right-click context menu to change the properties discussed next. To access **Diagram Table View**, select **Diagram > Tools > Diagram Table View**.

Tip While you are working on the diagram layout, remember to select **File > Save Project** to save the desired layout of your diagram. The SimBiology desktop saves the layout in the project.

To manually lay out the model diagram:

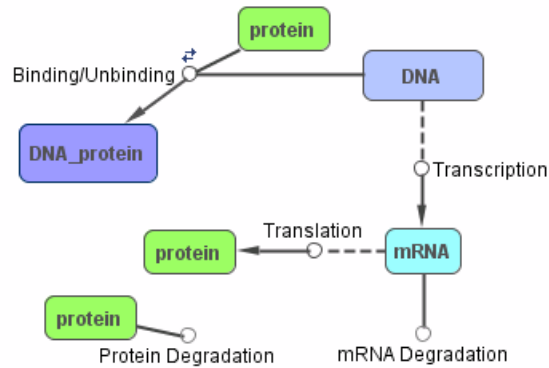
- 1 Right-click a species block, and select **Split Block**. For example, split the protein Species block.

The SimBiology desktop provides a representation of the split block for each instance of the species in the model. Notice that although there could be multiple split blocks, there is only one species.

If you change any block properties for any of these split blocks, the change will propagate to each split block. For example, if you change the appearance of the block, the change affects all split blocks.

Note You can split only species blocks.

- 2 Manually move the split blocks to the desired position.



- 3** From the **Diagram** menu, select **Tools > Diagram Table View** to open the **Diagram Table View** pane.

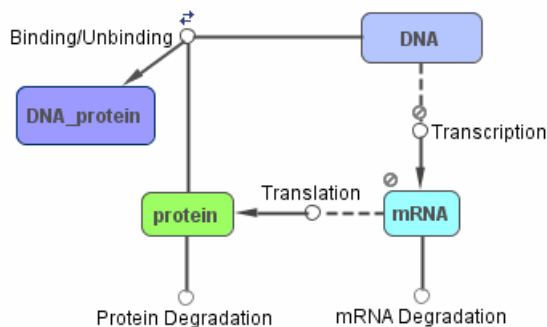
	Name	Split	Hide	Pin	Degree
1	DNA	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	3
2	protein	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	3
3	DNA_protein	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	1
4	mRNA	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	4
5	Protein Degradation	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	1
6	mRNA Degradation	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	1
7	Translation	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	3
8	Transcription	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	3
9	Binding/Unbinding	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	3

Diagram Table View is a tool that lets you hide or show blocks, split or combine blocks, and pin or unpin blocks. You can select a single block or perform the action on multiple selected blocks. Diagram Table View also shows you the degree of connectivity in your diagram and also lets you view a histogram of the degree of connectivity.

- 4** In the row for the protein Species block, clear the **Split** check box. The diagram combines the split blocks. Alternatively, you can right-click the Species block and select **Combine Split Blocks**.
- 5** Press and hold the **Ctrl** key (Windows and Linux) or the **Command** key (Macintosh). While holding the key down, select the row for the


Transcription reaction block and the row for the mRNA species block.
Pressing and holding **Ctrl** or **Command** lets you select discontinuous rows.

- 6 Right-click and select **Pin Selected Blocks**. The diagram pins the blocks. You cannot move pinned blocks manually or with automatic layout. Note the indicator for pinned blocks in the following diagram.

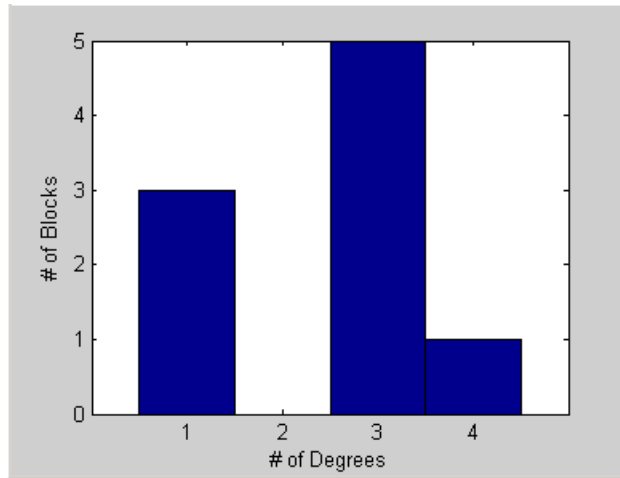


- 7 Select the row for the Protein Degradation reaction and press **Shift**+left-click to select the row for the mRNA Degradation reaction.
- 8 Right-click and select **Hide Selected Blocks**. The diagram hides the two reactions in the diagram. The reaction rows are visible in the **Diagram Table View** pane.

Note Hiding a block only hides it graphically. The block is still represented in the mathematical model.

- 9 Select a block, right-click and select **Rotate Clockwise** to rotate the selected block.
- 10 Select **Diagram > Show All Hidden Blocks and Lines** to see all blocks.
- 11 Click  in the Diagram Table View toolbar.

The SimBiology desktop opens a figure window with a histogram of the degrees of connectivity plotted as the number of connections versus the number of blocks.



You can also see the degree of connectivity in the **Degree** column.

Changing the Diagram Layout Automatically

From the **Diagram** menu, select **Layout All Elements or Only the Selected Elements** to use the automatic layout feature. Select blocks and use the automatic layout feature to lay out only the selected blocks in the diagram.

Automatic layout works only on blocks that are not pinned. You can right-click and select **Unpin Block** if you want to lay out all blocks. Leave blocks pinned if you do not want the position of the block to change during layout.

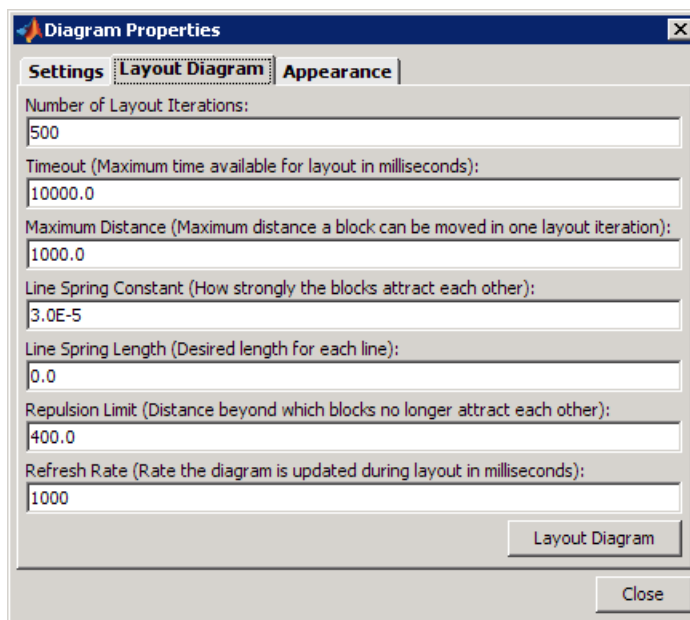
This example starts with the blocks for mRNA and Transcription pinned.

The default settings for automatic layout should work well for many models. You can optionally change the automatic layout settings in the SimBiology desktop.

To change the settings for automatic layout:

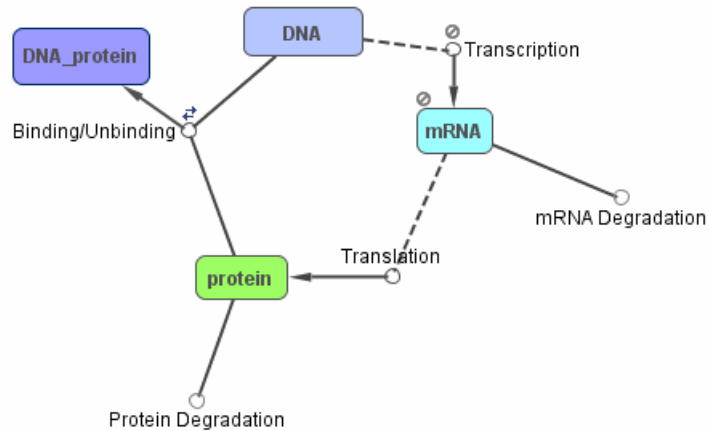
- 1 Right-click the diagram background and select **Properties**. The Diagram Properties dialog box opens.

2 Click the **Layout Diagram** tab.



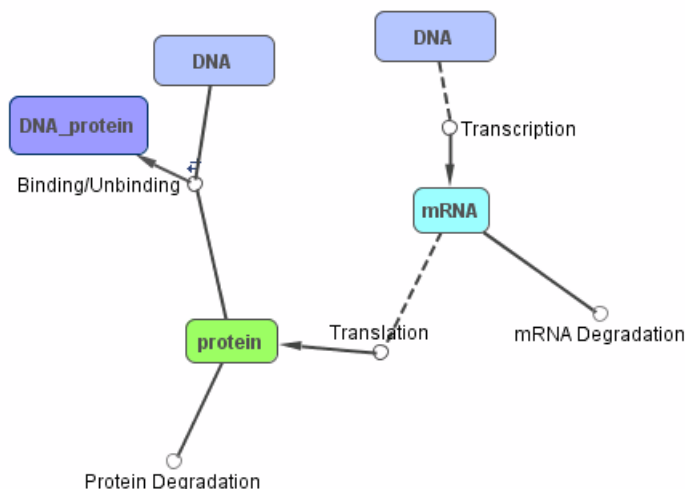
- 3 In the **Number of Layout Iterations** box, enter the number of iterations to include in the layout. The default is 500. More iterations give you a better layout, but also take more time. For example, enter 700.
- 4 In the **Timeout** box, enter the maximum amount of time available for layout. The default is 10000.0 milliseconds.
- 5 In the **Maximum Distance** box, specify the distance that a block moves in one iteration. The default is 1000.0. If you enter a smaller value, layout is slower. Large values can also cause oscillation in the layout. For example, enter 50.
- 6 In the **Line Spring Constant** box, specify the strength with which the lines between blocks pull blocks together. The default is 3.0E-5. Increasing the spring constant creates more compact diagrams by increasing the spring attraction. For example, enter 2.0E-6 and click **Layout Diagram** to apply the settings.

The layout should resemble the following diagram.



- 7** In the **Line Spring Length** box, specify the length for each line. The default is 0.0, indicating that force due to the spring is 0 at this length. Compress this length to push the blocks further apart. For example, enter 10.
- 8** In the **Repulsion Limit** box, specify the maximum repelling distance that limits the distance at which blocks repel each other. The default is 400.0. Setting this to a large distance causes all blocks to repel each other. This spreads the diagram out. A smaller value allows only nearby blocks to repel, creating a more uniformly filled diagram. For example, enter 200.
- 9** In the **Refresh Rate** box, enter the rate (in milliseconds) at which the diagram is updated during layout. The default is 1000. For example, enter 500 and click **Layout Diagram** to apply the settings.
- 10** Click **Close** to close the Diagram Properties dialog box.
- 11** In the **Diagram View** pane, right-click the DNA species block and select **Split Block**.
- 12** In the **Diagram Table View** pane, clear the **Pin** check boxes for the Transcription Reaction block and the mRNA Species block.

- 13** From the **Diagram** menu, select **Layout All Elements** or **Only the Selected Elements**. Your diagram should resemble the following diagram, but may be different depending on the diagram layout before you applied automatic layout.



How the SimBiology Desktop Does Diagram Layout

The automatic layout feature in the SimBiology desktop arranges blocks using a simple “force directed” algorithm.

Every block is affected by three forces:

- Edges of the diagram repel blocks.
- Blocks repel each other.
- Lines between blocks act as springs that draw blocks toward each other.

The algorithm tries to minimize the sum of these forces. In each iteration, the SimBiology desktop calculates the total force on each block. The diagram then moves each block in the direction of and proportional to the force acting on it. Two adjustable parameters control the dynamics of the layout:

- The number of iterations that are taken determines how long the layout takes and thereby how well it can do.
- The maximum distance constrains the distance that any block will be moved in one iteration. A small value makes layout progress go slowly. A large value may cause oscillation in the layout.

Three adjustable parameters influence the layout of the diagram:

- The spring constant controls how strongly the lines between blocks pull blocks together. Increasing the spring constant creates more compact diagrams as the spring attraction dominates the repulsion between blocks.
- The spring length controls the “natural length” of the lines between blocks. The force due to the spring is zero at this length. When a spring is compressed to less than this length, it pushes the blocks apart.
- The maximum repelling distance limits the distance at which blocks repel each other. Setting this value to a large distance causes all blocks to repel each other. This spreads the diagram out. A smaller value allows only nearby blocks to repel, creating a more uniformly filled diagram.

Printing and Exporting the Diagram

You can annotate and print your pathway diagram, or you can export the diagram to .svg, .jpeg, or .pdf file formats. For example, you can annotate the diagram with the name of the author, the date, notes, and name of the organization. You can choose to place the content as a header or footer on the diagram page.

Printing a Diagram

Right-click in the SimBiology diagram and select **Print** to open the Print dialog box and print the diagram. By default there are no annotations. However, if you previously annotated the diagram using **Diagram Print Setup**, the printed document contains the annotations. You can access **Diagram Print Setup** from the diagram’s right-click (context) menu.

To annotate and print a diagram:

- 1 In the **Diagram View** pane, right-click the background of the diagram and select **Diagram Print Setup**.

The Diagram Print Setup dialog box opens.

- 2** In the **Diagram Options** tab, do the following:
 - a** In the **Scale** box, select the size to adjust the diagram to (100% is the default size). Alternatively, click the **Fit diagram to** button and specify the desired width and height.
 - b** Clear the **Print frame around diagram** check box if you do not want a frame in the printed document.
- 3** Click the **Page Annotation** tab.
- 4** Click **Edit**. The Customize Page Annotation dialog box opens. This dialog box lets you enter and store customized information for print annotation.
 - a** In the relevant fields, enter the name of your organization and your name.
 - b** From the **Date Format** and **Page Format** lists, select the date and page formats respectively.
 - c** Click **OK**.
- 5** Place the cursor in a **Header** or **Footer** box and click **Author**, **Organization**, **Model**, or **Date**.

The SimBiology desktop inserts the information entered in the Customize Page Annotation dialog box. Alternatively, you can type information into each field.

- 6** In the **Diagram Notes** box, enter notes to be included.
- 7** From the notes location list, select whether to include notes in the printout, and the location. You can also choose to include the notes only on the first page.
- 8** Click **Close** to exit the Diagram Print Setup dialog box.

Alternatively, click **Print** to open the Print dialog box and print the diagram.

Exporting a Diagram Image

You can export the image of a pathway diagram in a portable file format for use by other software such as the Microsoft® PowerPoint® application. The SimBiology desktop exports the graphical representation of the model.

- 1** In the **Diagram View** pane, right-click the background of the diagram and select **Export Diagram As**.

The Export Diagram As dialog box opens.

- 2** From the **File type** list, specify the type of file to export.
- 3** Click ... (Browse) to choose the file location.
- 4** In the **File name** box, specify the file name.
- 5** Keep the default selection for the **Preserve aspect ratio** check box to preserve the width and height ratio of the diagram.
- 6** (Optional) Specify the desired width and height of the image in inches, in the **Width** and **Height** boxes respectively.
- 7** Click **OK** to export the file.

Modeling Using the Command-Line Interface

In this section...

“About This Example” on page 2-40

“Creating a SimBiology Model” on page 2-40

“Adding the Reaction for Transcription” on page 2-42

“Adding the Reaction for Translation” on page 2-43

“Adding the Reactions for Gene Regulation” on page 2-43

“Adding the Reactions for mRNA and Protein Degradation” on page 2-44

“Simulating the Model” on page 2-44

“Simulating the Model with a Stochastic Solver” on page 2-46

About This Example

This section shows how to model a simple gene-regulation pathway using the command-line interface. For more information about this model, see “Gene Regulation Model” on page 2-2.

You can also use a graphical user interface (see “Modeling Using the SimBiology Graphical User Interface” on page 2-8 and “Modeling Using the SimBiology Diagram View” on page 2-16). A comparison of the three methods will help you understand the model objects that are created and how to access and edit a model through the MATLAB Command Window.

Creating a SimBiology Model

A SimBiology model is a collection of objects that are structured hierarchically. At least one model object is needed to contain all the other objects.

- 1 Create a model object. For example, to create a model with the name `cell`, in the MATLAB Command Window, type

```
Mobj = sbiomodel('cell')
```

MATLAB creates a model object (`Mobj`) in the workspace and displays a summary of the objects in the model.

```
SimBiology Model - cell
```

```
Model Components:
  Compartments:      0
  Events:            0
  Parameters:        0
  Reactions:         0
  Rules:             0
  Species:           0
```

- 2** Display all the model object properties by typing

```
get(Mobj)
```

MATLAB displays a list of properties for the model object and their current values.

```
Annotation: ''
  Events: [0x1 double]
  Name: 'cell'
  Notes: ''
  Parameters: [0x1 double]
  Parent: [1x1 SimBiology.Root]
  Species: [0x1 handle]
Compartments: [0x1 double]
  Reactions: [0x1 double]
  Rules: [0x1 double]
  Tag: ''
  Type: 'sbiomodel'
  UserData: []
```

Some of the model properties are themselves objects or arrays of objects.

- 3** Add a compartment named `contents` to the model.

```
compObj = addcompartment(Mobj, 'contents');
```

All models must contain a compartment. You can either add a compartment and specify its name (as shown here), or you can let the process of adding a reaction automatically create a default compartment (*unnamed*) and add the

reaction species to that compartment. You can rename the compartment later.

If there are multiple compartments in the model, you must specify the reactants and products using qualified names (*compartmentName.speciesName*). For example, `nucleus.DNA` denotes the species DNA in the compartment nucleus.

This example contains only one compartment.

Adding the Reaction for Transcription

A simple model of transcription shows only the DNA and mRNA. For more details, see “Transcription” on page 2-3.

- 1 Enter the reaction `DNA -> DNA + mRNA` with reaction rate equation `v=k*DNA`.

```
Robj1 = addreaction(Mobj, 'DNA -> DNA + mRNA');  
Kobj1 = addkineticlaw(Robj1, 'MassAction');
```

The `Kobj1` property `KineticLawName` is set to `'MassAction'`. Because the reaction is enough information to determine the rate equation, the property `Expression` is set to `'MassAction'` and the reaction rate expression is assumed to be `'k*DNA'`.

Note Because this example has only one compartment, you need not specify the compartment to which each species belongs. If there are multiple compartments, here is an example of the reaction syntax:

```
Robj1 = addreaction(Mobj, 'nucleus.DNA -> nucleus.DNA + cytoplasm.mRNA');
```

`nucleus` and `cytoplasm` are the names of the compartments.

- 2 Define the reaction rate constant `k1 = 0.2`. For a first-order reaction, the property `ParameterVariableNames` has a single rate constant that needs defining. First create a parameter object named `k1`, and then use the parameter object name to set the rate constant in `ParameterVariableNames` to that object.

```
Pobj1 = addparameter(Kobj1, 'k1', 0.2);
set(Kobj1, 'ParameterVariableNames', 'k1');
```

- 3** Enter the initial amount for the species DNA= 50 and mRNA = 0. Select the species using the function `sbioselect`, which returns an object.

```
Sobj1 = sbioselect(Mobj, 'Type', 'species', 'Name', 'DNA');
set(Sobj1, 'InitialAmount', 50);
```

The value for mRNA defaults to 0.

- 4** Check the initial amounts for the species.

```
Mobj.Species
```

MATLAB displays a summary list.

```
SimBiology Species Array
```

Index:	Compartment:	Name:	InitialAmount:	InitialAmountUnits:
1	contents	DNA	50	
2	contents	mRNA	0	

Adding the Reaction for Translation

A simple model of translation shows only the mRNA and protein product. For more details, see “Translation” on page 2-4.

- 1** Enter the reaction mRNA → mRNA + protein with reaction rate equation $v = k \cdot \text{mRNA}$.

```
Robj2 = addreaction(Mobj, 'mRNA -> mRNA + protein');
Kobj2 = addkineticlaw(Robj2, 'MassAction');
```

- 2** Define the reaction rate constant k2.

```
Pobj2 = addparameter(Kobj2, 'k2', 20.0);
set(Kobj2, 'ParameterVariableNames', 'k2');
```

Adding the Reactions for Gene Regulation

Transcription of DNA to mRNA is regulated by the binding of the protein product from translation to the DNA. As more protein is produced, the DNA is

bound with the protein more often and less time is available for transcription with the unbound DNA. For more details, see “Gene Repression” on page 2-4.

Enter the reversible reaction for DNA + protein \leftrightarrow DNA_protein with a forward reaction rate equation $v = k3 \cdot \text{DNA} \cdot \text{protein}$ and a reverse rate $v = k3r \cdot \text{DNA_protein}$.

```
Robj3 = addreaction(Mobj, 'DNA + protein  $\leftrightarrow$  DNA_protein');  
Kobj3 = addkineticlaw(Robj3, 'MassAction');  
Pobj3 = addparameter(Kobj3, 'k3', 0.2);
```

```
Pobj3r = addparameter(Kobj3, 'k3r', 1.0);  
set(Kobj3, 'ParameterVariableNames', {'k3', 'k3r'});
```

Adding the Reactions for mRNA and Protein Degradation

Protein and mRNA degradation are important reactions for regulating gene expression. The steady-state level of the compounds is maintained by a balance between synthesis and degradation reactions. Proteins are hydrolyzed to amino acids with the help of proteases, while nucleic acids are degraded to nucleotides.

1 Enter the reaction for mRNA degradation to nucleotides.

```
Robj4 = addreaction(Mobj, 'mRNA -> null');  
Kobj4 = addkineticlaw(Robj4, 'MassAction');  
Pobj4 = addparameter(Kobj4, 'k4', 1.5);  
set(Kobj4, 'ParameterVariableNames', 'k4');
```

2 Enter the reaction for protein degradation to amino acids.

```
Robj5 = addreaction(Mobj, 'protein -> null');  
Kobj5 = addkineticlaw(Robj5, 'MassAction');  
Pobj5 = addparameter(Kobj5, 'k5', 1.0);  
set(Kobj5, 'ParameterVariableNames', 'k5');
```

Simulating the Model

After you create the model, enter reactions, and set parameters, you can simulate the dynamic behavior of a model.

- 1 Get a listing of the configuration set attached to the model.

```
cs = getconfigset(Mobj)
```

The configuration set object defines the parameters needed for a simulation.

MATLAB displays a listing of the configuration set property values.

```
Configuration Settings - default (active)
  SolverType:          sundials
  StopTime:           10.000000

  SolverOptions:
  AbsoluteTolerance:  1.000000e-006
  RelativeTolerance:  1.000000e-003
  SensitivityAnalysis: false

  RuntimeOptions:
  StatesToLog:        all

  CompileOptions:
  UnitConversion:     false
  DimensionalAnalysis: true

  SensitivityAnalysisOptions:
  InputFactors:       0
  Outputs:            0
```

To change simulation stop time you can use the following syntax:

```
set(cs, 'StopTime', 8.0);
```

In this example leave the stop time at the default (10.0)

- 2 Run the simulation.

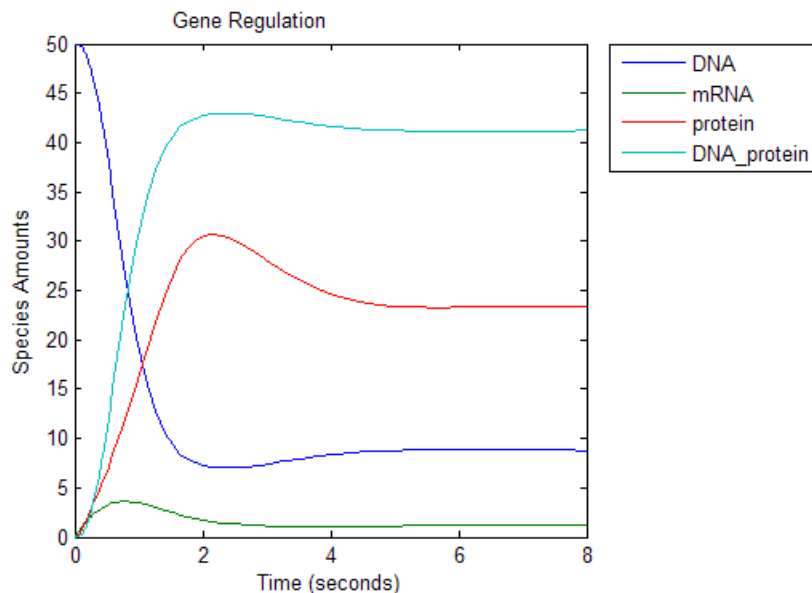
```
[t_ode, x_ode, names] = sbiosimulate(Mobj, cs);
```

- 3 Plot the results.

```
figure;
set(gcf, 'color', 'white');
```

```
plot(t_ode, x_ode(:,1:4));  
legend(names, 'Location', 'NorthEastOutside')  
title('Gene Regulation');  
xlabel('Time (seconds)');  
ylabel('Species Amounts');
```

MATLAB plots a figure with the simulation results.



See Also

- “Performing Simulations”
- “Stiff Deterministic Solvers” — Brief description of when to use stiff deterministic solvers and the types available in the software.

Simulating the Model with a Stochastic Solver

SimBiology software includes three stochastic solvers. The stochastic solvers more accurately calculate the change in species amounts with a small number of molecules.

- 1 Get the active configuration set for a model.

```
cs = getconfigset(Mobj);
```

- 2 Select the stochastic solver and list the configuration set properties.

```
set(cs, 'SolverType', 'ssa');  
cs
```

MATLAB displays properties for the current configuration set. Notice that the SolverOptions for the stochastic solver are different from the ODE options.

```
Configuration Settings - default (active)  
SolverType:          ssa  
StopTime:           10.000000  
  
SolverOptions:  
LogDecimation:      1  
  
RuntimeOptions:  
StatesToLog:        all  
  
CompileOptions:  
UnitConversion:     false  
DimensionalAnalysis: true  
  
SensitivityAnalysisOptions:  
InputFactors:       0  
Outputs:            0
```

- 3 Change the value for the LogDecimation property.

```
cs.SolverOptions.LogDecimation = 10;
```

This lets you record fewer data points.

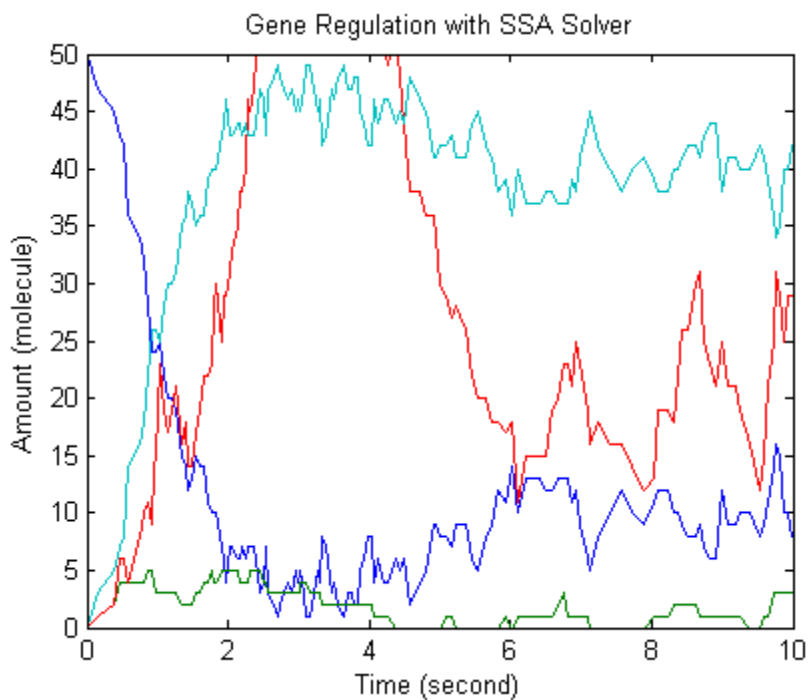
- 4 Run the simulation.

```
[t_ssa, x_ssa] = sbiosimulate(Mobj, cs);
```

- 5 Plot the results.

```
FH1 = figure;  
set(gcf, 'color', 'white');  
plot(t_ssa,x_ssa(:,1:4));  
title('Gene Regulation with SSA Solver');  
xlabel('Time (second)');  
ylabel('Amount (molecule)');  
axis([0, 10, 0, 50]);
```

The resulting plot may resemble the following figure.

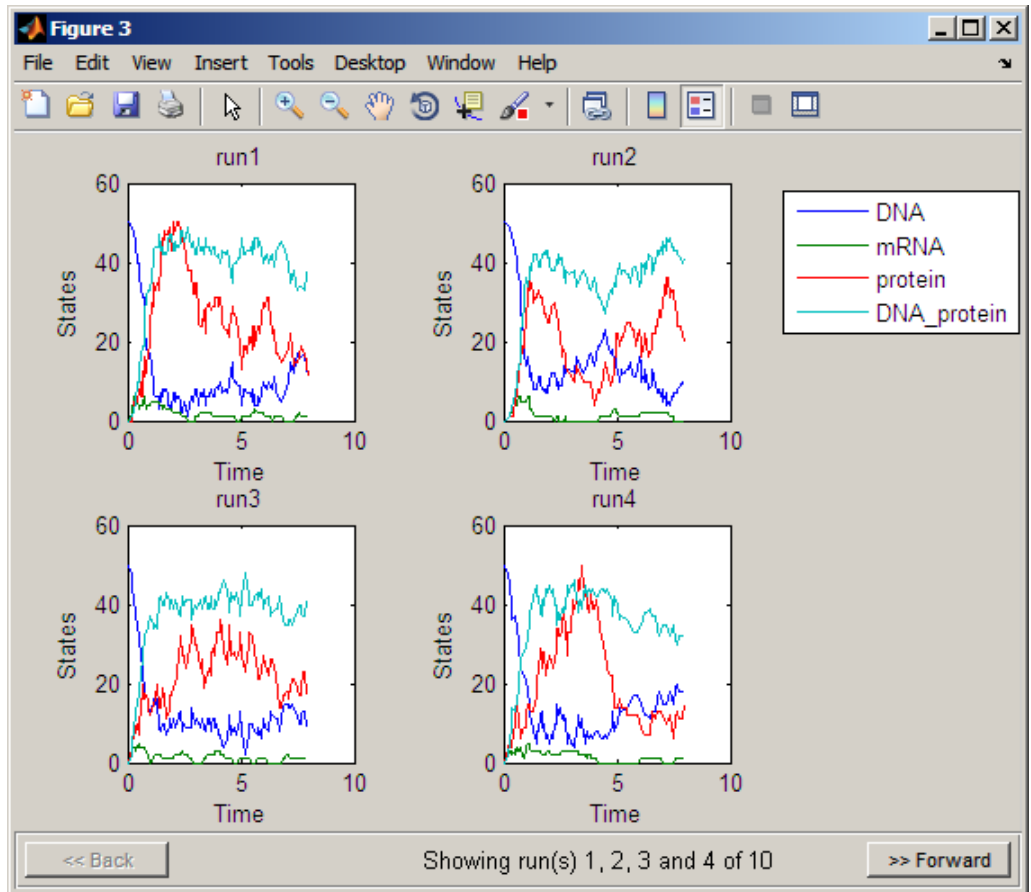


Tip You can also add text labels and arrows to the plot by selecting **Insert > Text Box** and **Insert > Text Arrow**.

- 6 Another method to visualize stochastic simulations is through ensemble runs.

```
simDataObj = sbioensemblerun(Mobj, 10, cs);
sbiosubplot(simDataObj);
```

The resulting plot may resemble the following:



- Click **Back** or **Forward** to navigate through the plots.

Note To remove the model object from the **Workspace** type

```
delete(Mobj);
```

See Also

- “Performing Simulations”
- “Stochastic Solvers” — Brief description of when to use stochastic solvers and the types available in the software.

G

- gene regulation
 - GUI desktop 2-8
 - GUI Diagram 2-16
 - model diagram 2-2
 - reaction list 2-2
 - reactions 2-3
 - tutorial model 2-2

M

- model
 - adding reactions 2-10 2-20 2-42
 - creating 2-8 2-16
 - creating command-line 2-40
 - gene regulation 2-43
 - project file 2-9 2-20
 - protein degradation 2-44
 - simulating 2-15 2-25
 - translation 2-43

R

- reactions
 - degradation 2-44
 - gene regulation 2-43
 - transcription 2-42

- translation 2-43

S

- SimBiology
 - computation with MATLAB 1-2
 - defined 1-2
 - expected user 1-3
 - features and functions 1-16
 - optional software 1-4
 - related software 1-5
 - required software 1-4
 - SBML support in 1-26
 - visualizing data 1-2
- simulation 2-44
 - stochastic solver 2-46
- software
 - optional 1-4
 - required 1-4

T

- tutorial
 - basic 2-1
 - command-line 2-40
- tutorial models
 - gene regulation 2-2