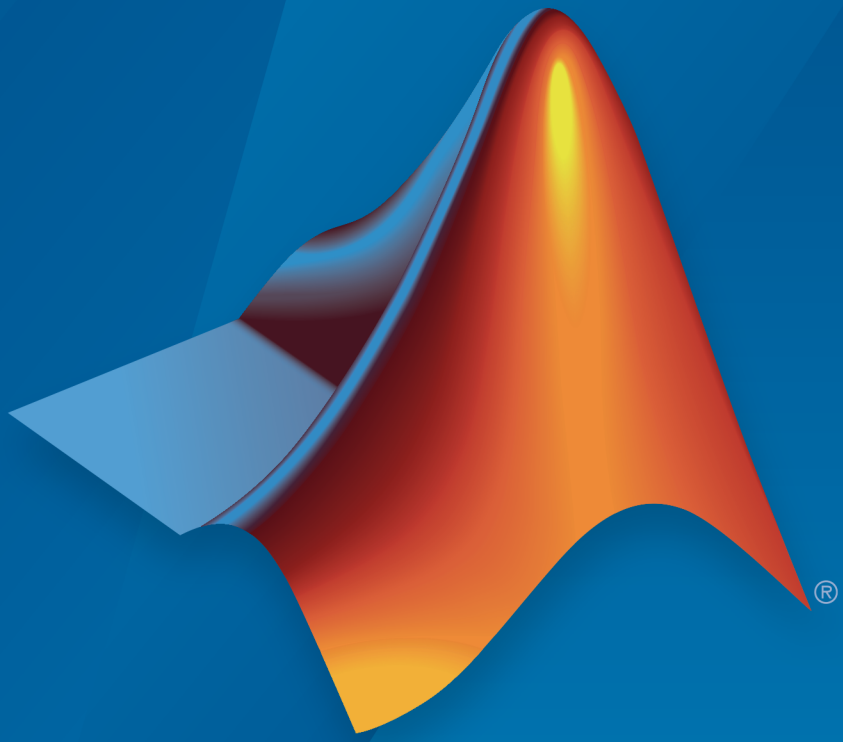
SimBiology®

Getting Started Guide



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SimBiology® Getting Started Guide

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October 2007	Online only	Updated for Version 2.2 (Release 2007b+)
March 2008	Online only	Updated for Version 2.3 (Release 2008a)
October 2008	Online only	Updated for Version 2.4 (Release 2008b)
March 2009	Online only	Updated for Version 3.0 (Release 2009a)
September 2009	Online only	Updated for Version 3.1 (Release 2009b)
March 2010	Online only	Updated for Version 3.2 (Release 2010a)
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September 2012	Online only	Updated for Version 4.2 (Release 2012b)
March 2013	Online only	Updated for Version 4.3 (Release 2013a)
September 2013	Online only	Updated for Version 4.3.1 (Release 2013b)
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October 2014	Online only	Updated for Version 5.1 (Release 2014b)
March 2015	Online only	Updated for Version 5.2 (Release 2015a)
September 2015	Online only	Updated for Version 5.3 (Release 2015b)
March 2016	Online only	Updated for Version 5.4 (Release 2016a)

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3 Getting Started Using the Command Line

1

Introduction

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

SimBiology Product Description

Model, simulate, and analyze biological systems

SimBiology provides an app and programmatic tools to model, simulate, and analyze dynamic systems, focusing on pharmacokinetic/pharmacodynamic (PK/PD) and systems biology applications. It provides a block diagram editor for building models, or you can create models programmatically using the MATLAB® language. SimBiology includes a library of common PK models, which you can customize and integrate with mechanistic systems biology models.

A variety of model exploration techniques let you identify optimal dosing schedules and putative drug targets in cellular pathways. SimBiology uses ordinary differential equations (ODEs) and stochastic solvers to simulate the time course profile of drug exposure, drug efficacy, and enzyme and metabolite levels. You can investigate system dynamics and guide experimentation using parameter sweeps and sensitivity analysis. You can also use single subject or population data to estimate model parameters.

Key Features

- App for PK/PD and mechanistic systems biology modeling
- Ordinary differential equations (ODEs) and stochastic solvers
- Library of PK models
- Parameter estimation techniques for single-subject and population data, including nonlinear mixed-effects models
- Sensitivity analysis and parameter sweeps for investigating parameter effects on system dynamics
- Diagnostic plots for individual and population fits
- Methods for creating and optimizing dosing schedules

Compiler Setup

To prepare SimBiology models for accelerated simulations, install and set up a compiler:

1. Install a C compiler (if one is not already installed on your system). For a current list of supported compilers, see Supported and Compatible Compilers at`www.mathworks.com`.
2. Ensure that any user-defined functions in your model can be used for code generation from MATLAB, so they can convert to compiled C. For more information, see Language, Function, and Object support for C and C++ code generation (this documentation requires MATLAB Coder™ license) or contact MathWorks Technical Support.

Tip On 32-bit Windows® platforms, the LCC compiler is automatically installed. However, for better performance of the acceleration functionality, you may want to install a supported compiler other than LCC, and it will be selected automatically.

On 64-bit Windows platforms, if you have not installed another compiler, SimBiology uses the LCC64 compiler for model accelerations. If you have installed another supported compiler, it will be selected automatically.

More About

- "Simulation"
- "Accelerating Model Simulations and Analyses"

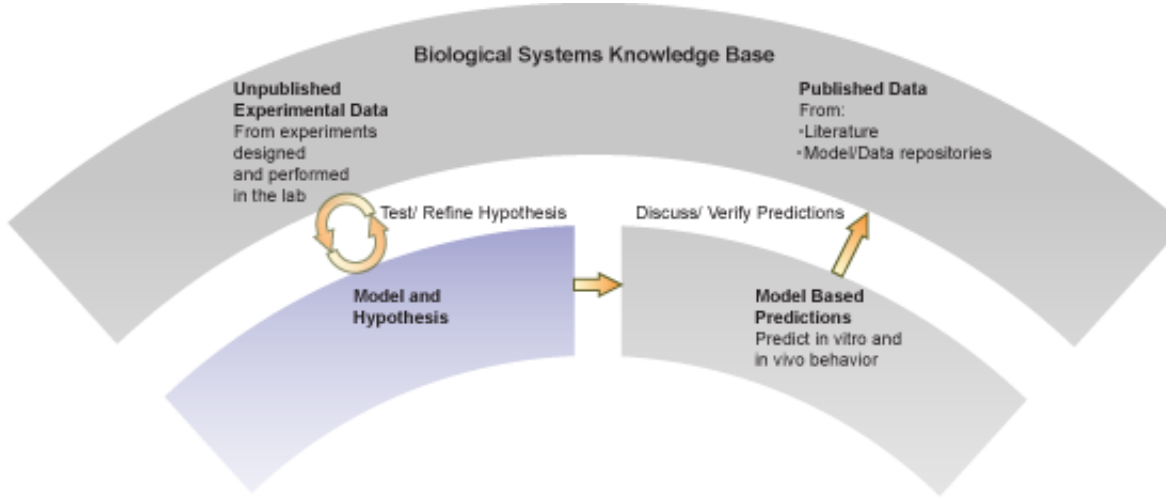
Integrating SimBiology Models into Your Existing Workflow

In this section...

Existing Workflow in Experimental Research

Consider the following typical workflow in experimental research.

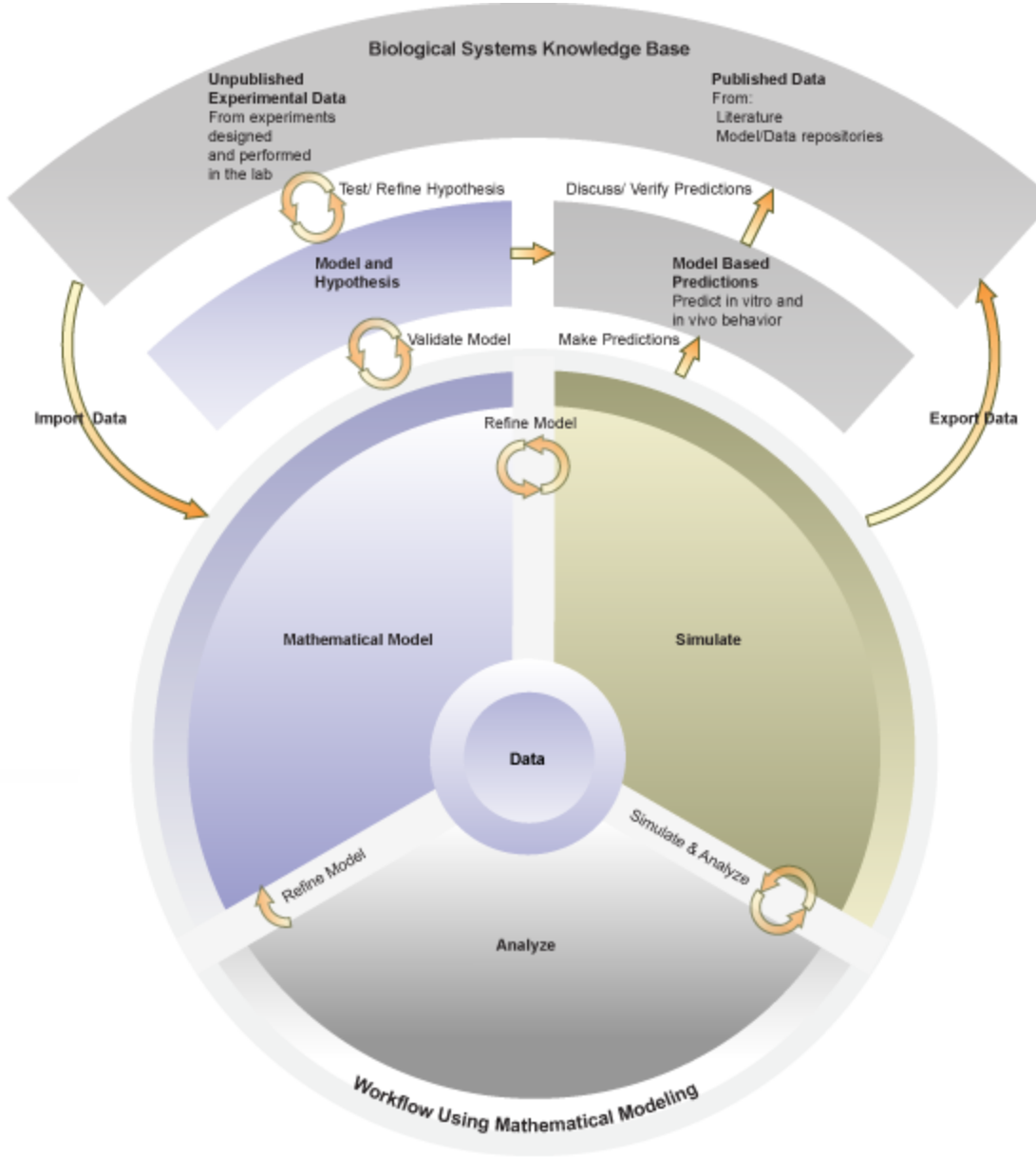
1. Use preliminary results and published data to develop a model and hypothesis in your area of interest.
2. Validate your model by making predictions and designing experiments to test your model and hypothesis.
3. Make further predictions based on your model.
4. Publish results and predictions.
5. Continue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



Workflow Incorporating Mathematical Modeling

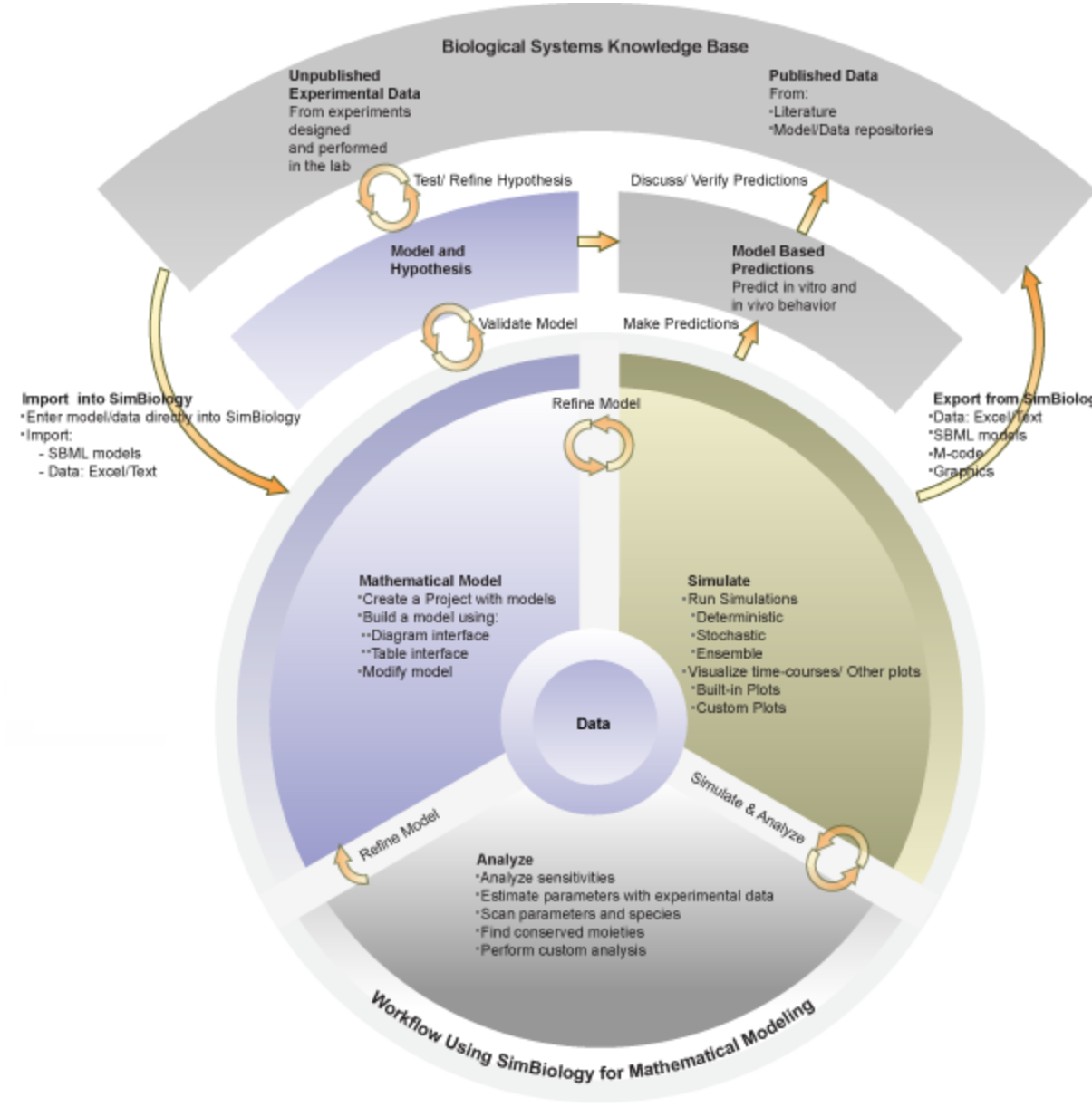
Mathematical modeling integrates into the preceding workflow by providing the means to:

- 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.


Biological Systems Knowledge Base
Unpublished Experimental Data
From experiments designed and performed in the lab
Published Data
From:
Literature
Model/Data repositories
Test/ Refine Hypothesis
Discuss/ Verify Predictions
Model and Hypothesis
Model Based Predictions
Predict in vitro and in vivo behavior
Validate Model
Make Predictions
Import Data
Refine Model
Export Data
Mathematical Model
Simulate
Data
Refine Model
Simulate & Analyze
Analyze
Workflow Using Mathematical Modeling

Workflow Using SimBiology Models for Mathematical Modeling

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


Biological Systems Knowledge Base
Unpublished Experimental Data
From experiments designed and performed in the lab
Published Data
From:
•Literature
•Model/Data repositories
Test/ Refine Hypothesis
Discuss/ Verify Predictions
Model and Hypothesis
Model Based Predictions
Predict in vitro and in vivo behavior
Validate Model
Make Predictions
Import into SimBiology
•Enter model/data directly into SimBiology
•Import:
- SBML models
- Data: Excel/Text
Refine Model
Export from SimBiology
•Data: Excel/Text
•SBML models
•M-code
•Graphics
Mathematical Model
•Create a Project with models
•Build a model using:
••Diagram interface
••Table interface
•Modify model
Simulate
•Run Simulations
•Deterministic
•Stochastic
•Ensemble
•Visualize time-courses/ Other plots
•Built-in Plots
•Custom Plots
Data
Simulate & Analyze
Refine Model
Analyze
•Analyze sensitivities
•Estimate parameters with experimental data
•Scan parameters and species
•Find conserved moieties
•Perform custom analysis
Workflow Using SimBiology for Mathematical Modeling

Using SimBiology Desktop vs. Command Line

There are two ways to use SimBiology:

- **SimBiology desktop** — Use the desktop GUI (graphical user interface) to interactively iterate through the model building and analysis workflow. For more information, see “SimBiology Desktop Overview” on page 2-2.
- **Command line** — Use the MATLAB command line to programmatically write and save scripts for batch processing, and to automate the model building and analysis workflow. For more information, see “Getting Started Using the SimBiology Command Line ” on page 3-2.

SBML Support

In this section...

What Is SBML?

Systems Biology Markup Language (SBML) is a standard format for sharing systems biology models among various modeling and simulation software tools. The current specification is available at `http://sbml.org/documents/`.

Importing from SBML Files

Import an SBML model from a file or URL using `sbmlimport`.

Because SimBiology supports a subset of the SBML level 3 version 1 specification, the following SBML features are not imported into the SimBiology model:

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

Exporting a SimBiology Model to SBML Format

SimBiology Features Supported by SBML

The following SimBiology model information is included in the SBML format file:

- Compartments, species, parameters, reactions, rules, and events that are defined in the model and have their `Active` property set to `true`.
- All unit definitions in SBML-compliant format.
- Model component properties with SBML equivalents, such as notes, and unit values for species and parameters.
- The reaction rate equation, but not the kinetic law definition.

  #### Example

  In SimBiology, the Henri-Michaelis-Menten equation, $V_m*S/(K_m+S)$, is a definition stored in the Kinetic Laws library. Specifically, for a one-substrate enzyme-catalyzed reaction, if you assign $V_m = V_a$, $K_m = K_a$, and $S = A$, then the reaction rate equation is exported to SBML as $V_a*S/(K_a+A)$.

SimBiology Features Not Supported by SBML

The following SimBiology features are not supported by SBML and are not included in the saved SBML format file. You can store this information in a SimBiology project file, which has an `.sbproj` extension.

- **Projects** — Models, analysis tasks, and data.
- **Kinetic law information** — SimBiology models store kinetic law information such as the kinetic law name and a kinetic law definition.
- **Variant information** — Collections of quantities (compartments, species, and/or parameters) that you can use to alter a model's initial or base configuration.
- **Dosing information** — Exogenous increments to the amount (or concentration) of a species in a model.
- **Custom MATLAB function files** — Custom functions that you used in your SimBiology model.
- Features and properties specific to SimBiology software, such as **Name** (of `Rule` objects only), **Tag**, and **Active**.

Tip Because the previous information is not supported by SBML, we recommend saving SimBiology project files to capture this information.

2

Getting Started Using the SimBiology Desktop

SimBiology Desktop Overview

The SimBiology desktop is a graphical user interface containing a set of integrated tools that are designed to facilitate building, simulating and analyzing models of dynamic systems with a focus on Systems Biology and Pharmacokinetics. Tasks are graphical interfaces that configure simulation and analysis settings used to investigate model behavior. One such task is parameter estimation that calibrates a model against imported data. Tasks produce results that can be further analyzed within the desktop. The models, tasks, imported data and task results are saved in a SimBiology project.

SimBiology also provides a set of libraries. These libraries provide built-in elements for defining kinetic laws, graphical blocks, and units that can be used when building a model. A library of plots provides commonly used visualizations for task results. These libraries can be extended with custom elements.

Opening the Desktop

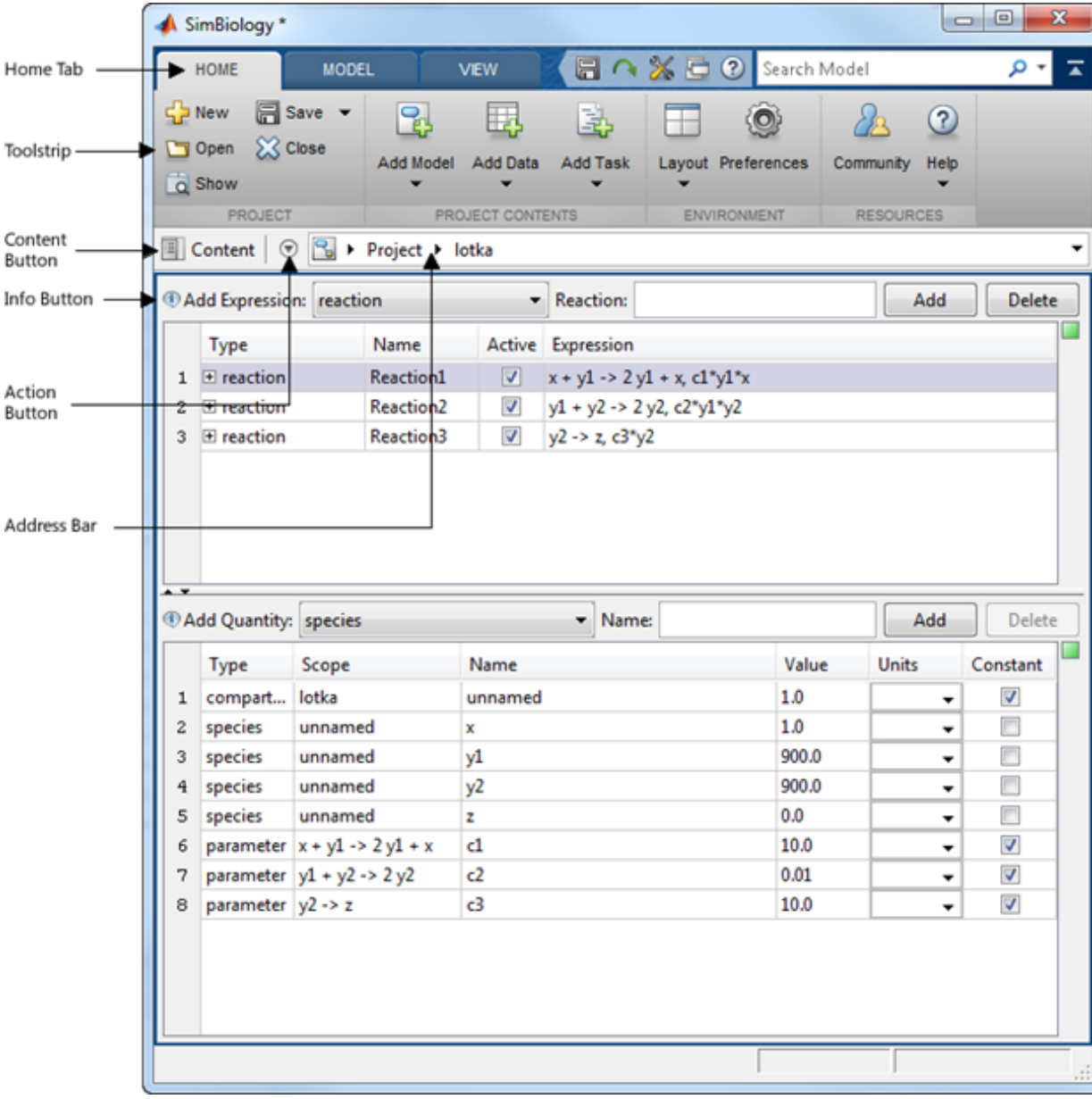
Open the desktop by typing the following at the MATLAB command line.

```
simbiology
```

Alternatively, select **SimBiology** from the **Apps** tab.

Main Desktop Window

The main SimBiology desktop window provides tools for building models, importing and exploring data, visualizing task results, and extending SimBiology libraries. Tasks are defined and executed using the Task Editor.


Home Tab
Toolstrip
Content Button
Info Button
Action Button
Address Bar
SimBiology *
HOME
MODEL
VIEW
Search Model
New
Save
Open
Close
Show
Add Model
Add Data
Add Task
Layout
Preferences
Community
Help
PROJECT
PROJECT CONTENTS
ENVIRONMENT
RESOURCES
Content
Project
lotka
Add Expression:
reaction
Reaction:
Add
Delete
Type
Name
Active
Expression
1 reaction Reaction1 x + y1 -> 2 y1 + x, c1*y1*x
2 reaction Reaction2 y1 + y2 -> 2 y2, c2*y1*y2
3 reaction Reaction3 y2 -> z, c3*y2
Add Quantity:
species
Name:
Add
Delete
Type
Scope
Name
Value
Units
Constant
1 compart... lotka unnamed 1.0
2 species unnamed x 1.0
3 species unnamed y1 900.0
4 species unnamed y2 900.0
5 species unnamed z 0.0
6 parameter x + y1 -> 2 y1 + x c1 10.0
7 parameter y1 + y2 -> 2 y2 c2 0.01
8 parameter y2 -> z c3 10.0

Home Tab	Allows you to open and save projects, add models, tasks, and data to a project.
Toolstrip	Displays the tabs specific to the open panel.
Content button	Allows you to quickly access the project files, built-in libraries, and recent files.
Info Button	Shows you the context sensitive help when you hover over it.
Action Button	Contains additional functionality related to the open panel.
Address Bar	Shows the name of the panel that is open.

Additional Tools

You can access additional tools such as the MATLAB Code Capture Tool by selecting **Home > Layout > MATLAB Code Capture Tool**.

Models

A SimBiology model is composed of species, compartments, parameters, reactions, rules, and events. Species, compartments, and parameters are categorized as model quantities. Reactions, rules, and events are categorized as model expressions. The dynamics of the model are governed by these expressions.

A SimBiology model can also have modifiers associated with it. There are two types of modifiers, variants and doses. Variants allow you to store alternative quantity values that can be applied to a model during analysis. Doses allow you to increase the amount of a species during a simulation.

Adding a Model

Select **Home > Add Model** to add a model to a project. You can create a new model, load a model from a SimBiology project, or import a SBML file. In addition, you can add commonly used PK models from the PK library.

When a model is open in the main desktop window, the toolstrip will add tabs for working with the model. One of those tabs is the **Model** tab. It contains buttons for editing the model in tabular or diagram form, and creating tasks.

Data

Data can be imported for use with tasks such as parameter fitting. Once the data is imported you can visualize and perform preliminary data processing.

Adding Data

To add data, select **Home** > **Add Data**. You can import data from:

- CVS formatted files
- Microsoft® Excel® files
- SimBiology project files
- MATLAB MAT files
- SAS® XPORT formatted files
- The MATLAB workspace

When data is open in the main desktop window, you can classify data columns and assign units. The toolstrip will add tabs for working with the data. One of those tabs is the **Define Plot** tab which is used to create plots. Another tab is the **Explore Data** tab. It allows you to:

- Exclude data rows – You can exclude data rows manually or using MATLAB expressions. Excluded data is ignored when running tasks.
- Add new data columns – You can add new data columns by using MATLAB expressions on other existing data columns. You can use the new columns when running tasks.

Tasks

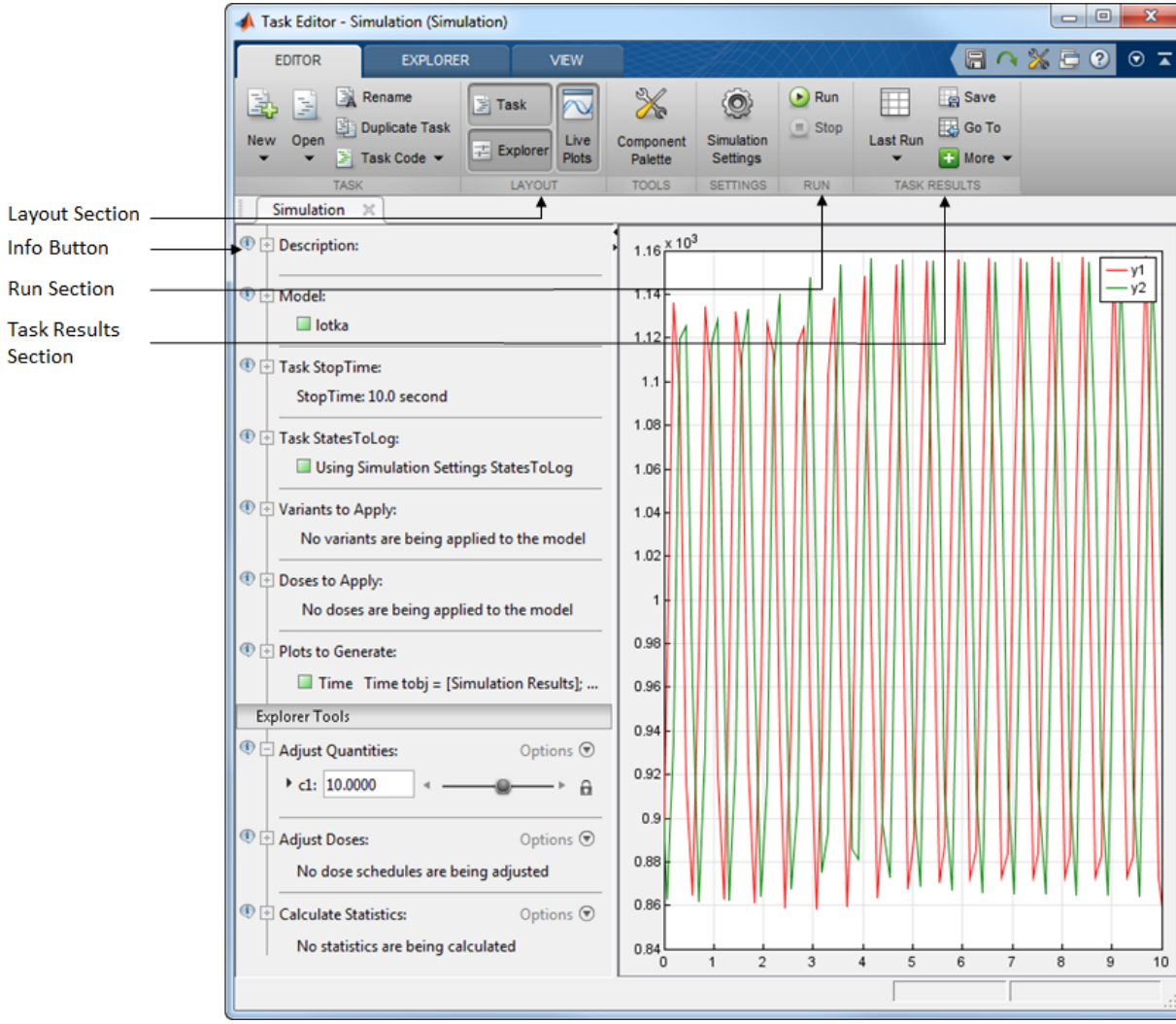
Tasks are analyses that can be performed on a model. There are several built-in tasks such as simulation, estimation, and sensitivity analysis. In addition, custom tasks can be created using the MATLAB language.

Adding a Task

Select **Home** > **Add Task** to add a task to a project. Alternatively, you can select **Model** > **Add Task** when a model is open in the main desktop window.

A task is opened in a separate window called the **Task Editor**. The editor consists of three section: general task setup, interactive task setup, and live visualization of results. The general setup is used to define settings such as simulation stop time, and variants and doses applied during task execution. The interactive task setup provides sliders for exploring model behavior. The sliders and live visualization plots can be configured using the tools on the **Explorer** tab.

For example, a simulation task appears as follows.



Layout Section	Allows you to configure the open sections of the Task Editor.
Info Button	Shows you the context sensitive help when you hover over it.
Run Section	Press the **Run** button to execute the task.

Task Results Section	Allows you to manage results generated from executing the task.

Task Results

Task results generated at the completion of a task run are stored as **Last Run**. These results are overwritten every time the task is executed. To avoid overwriting a particular set of results, use the **Save** button in the **Task Results** section.

A list of all saved results can be accessed from the **Task Results** section. The **Go To** button will open the selected results. When task results are open in the main desktop window, the toolstrip will add tabs for working with the results. One of those tabs is the **Define Plot** tab. There you can visualize results, create additional plots, and export results to the MATLAB workspace.

Related Examples

- "Create and Simulate a Simple Model"
- "Estimate Pharmacokinetic Parameters Using SimBiology Desktop" on page 2-9

Load a Model from an SBML-formatted File

This example shows how to import an SBML model from a file.

You can import an SBML model from a file or URL in SimBiology Desktop. Because SimBiology supports a subset of the SBML Level 2 Version 4 specification, some SBML features are not imported into the SimBiology model.

Open SimBiology desktop by typing `simbiology` in the MATLAB Command Window or clicking **SimBiology** on the **Apps** tab.

On the **Home** tab, select **Add Model > Load Model from File**.

Navigate to the folder `\MATLAB\R2013b\toolbox\simbio\simbiodemos\` and open the sample file named `lotka.xml`.

SimBiology loads the `lotka` model.

More About

- "Importing from SBML Files" on page 1-10

Estimate Pharmacokinetic Parameters Using SimBiology Desktop

Model and Data Description

This example shows how to estimate one-compartment pharmacokinetic (PK) parameters given experimental drug concentration data. Suppose you have measurements of drug plasma concentration from four individuals after bolus doses and want to estimate corresponding PK parameters, namely the volume of the central compartment (*V*) and clearance rate (*Cl*) of each individual. For one-compartment PK models, the drug concentration follows an exponential decline $C_t = C_0 e^{-k_e t}$. C_t is the drug concentration at time *t*. C_0 is the initial concentration. k_e is the elimination rate constant that depends on the clearance and volume of the central compartment $k_e = \frac{Cl}{V}$.

The synthetic data in this example contains measurements of drug plasma concentration of four individuals after they receive the bolus doses. The data contains the variables: `ID`, `Time`, `DrugConc`, and `Dose`. `ID` is the grouping variable which lists the ID of each individual, `Time` is the time at which each measurement was performed, `DrugConc` is the drug plasma concentration, and `Dose` is the dosing information for each individual. This data is saved as `pkProfiles_1Comp.mat` in *`matlabroot`*`\help\toolbox\simbio\examples`. *`matlabroot`* is the folder where you have installed MATLAB.

Estimating PK parameters using a one-, two-, or multi-compartment model in the SimBiology desktop requires the data to have at least three variables (or columns):

- Independent variable (such as time)
- Dependent variable (such as measured drug concentration at each time)
- Dosing variable (such as dose amount at each dose time)

Optionally, you can also have a grouping variable such as group or patient ID and one or more dependent and dosing variables.

Next Step

“Import and Explore Data” on page 2-10

Import and Explore Data

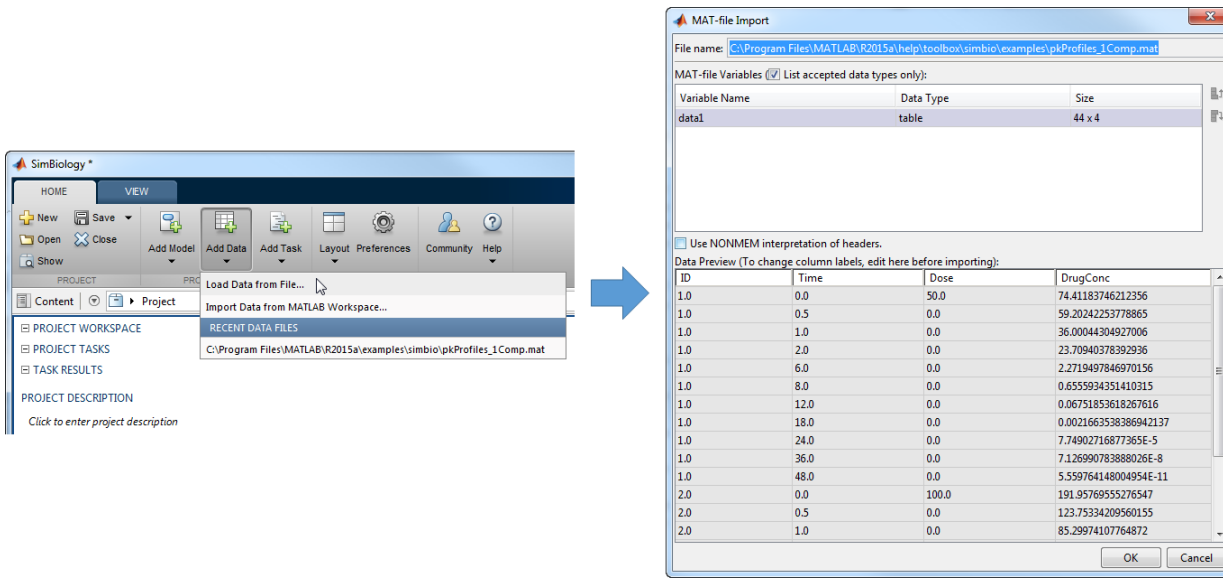
Import Data

Open SimBiology desktop by typing `simbiology` in the MATLAB Command Window.

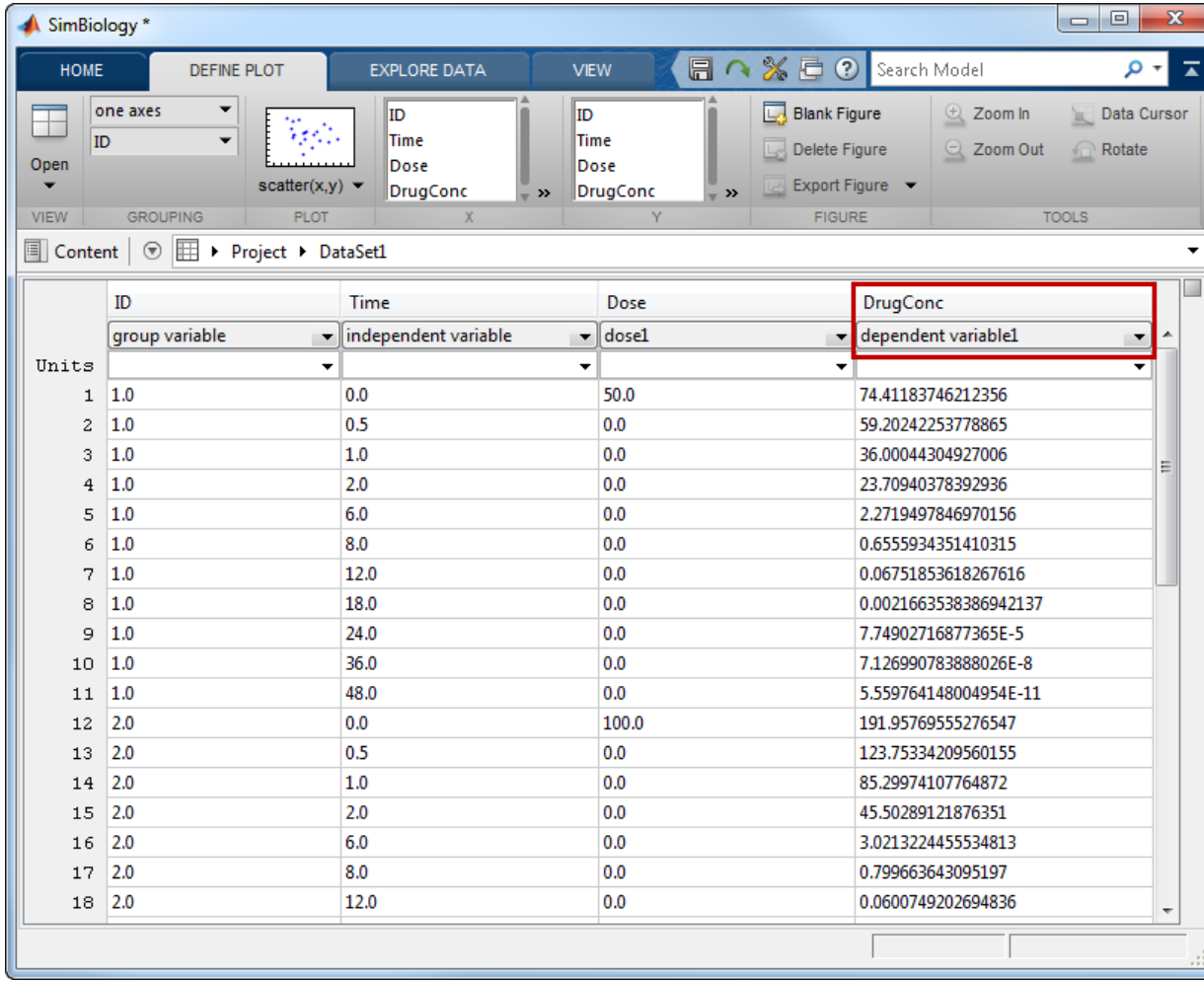
Open SimBiology desktop by typing `simbiology` in the MATLAB Command Window.

On the **Home** tab, select **Add Data** > **Load Data from File**.

Navigate to the folder *`matlabroot`*`\help\toolbox\simbio\examples`. *`matlabroot`* is the folder where you have installed MATLAB. Select the sample file named `pkProfiles_1Comp.mat`. Click OK.



Based on the names of variables (columns), SimBiology categorizes the variables. In this example, SimBiology is able to categorize the data into group variable, independent variable, and dose variable as shown under each data column in the table. However, **DrugConc** is not categorized as a dependent variable. From the drop-down list under **DrugConc**, select `dependent variable1`. Note that for different data sets, you may have to manually categorize one or more data variables as appropriate.

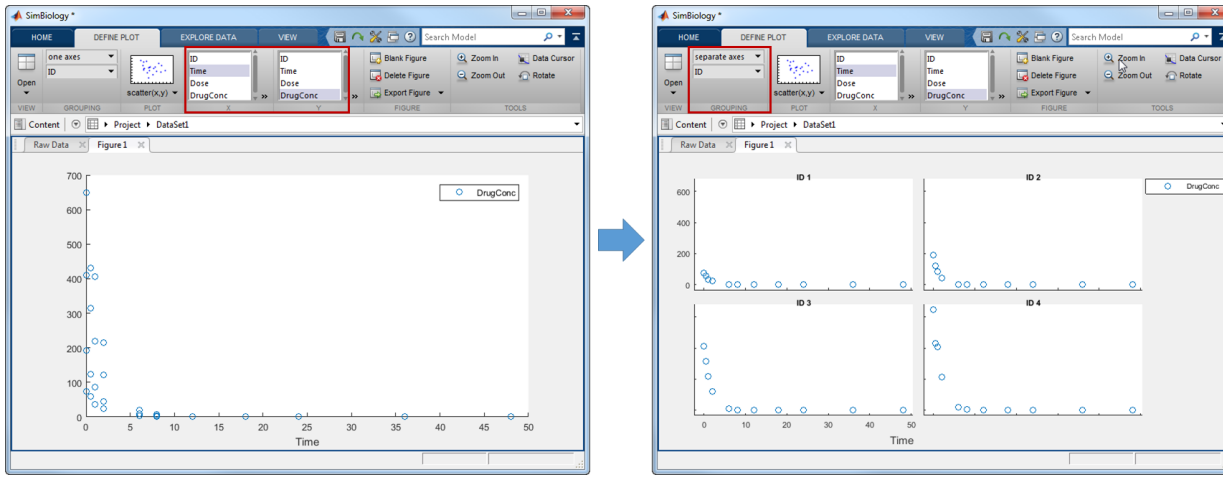


	ID	Time	Dose	DrugConc
	group variable	independent variable	dose1	dependent variable1
Units				
1	1.0	0.0	50.0	74.41183746212356
2	1.0	0.5	0.0	59.20242253778865
3	1.0	1.0	0.0	36.00044304927006
4	1.0	2.0	0.0	23.70940378392936
5	1.0	6.0	0.0	2.2719497846970156
6	1.0	8.0	0.0	0.6555934351410315
7	1.0	12.0	0.0	0.06751853618267616
8	1.0	18.0	0.0	0.0021663538386942137
9	1.0	24.0	0.0	7.74902716877365E-5
10	1.0	36.0	0.0	7.126990783888026E-8
11	1.0	48.0	0.0	5.559764148004954E-11
12	2.0	0.0	100.0	191.95769555276547
13	2.0	0.5	0.0	123.75334209560155
14	2.0	1.0	0.0	85.29974107764872
15	2.0	2.0	0.0	45.50289121876351
16	2.0	6.0	0.0	3.0213224455534813
17	2.0	8.0	0.0	0.799663643095197
18	2.0	12.0	0.0	0.0600749202694836

Explore Data

After you import data, you can explore it by using the plotting tools available directly from SimBiology. From the **Define Plot** tab, select **Time** as the variable for the *X*-axis and **DrugConc** for the *Y*-axis. By default, SimBiology plots data from all individuals using one axes.

To plot each individual data on separate axes, select **separate axes** in the **Grouping** section.



To estimate PK parameters using this data, you must create a PK model.

Previous Step

"Model and Data Description" on page 2-9

Next Step

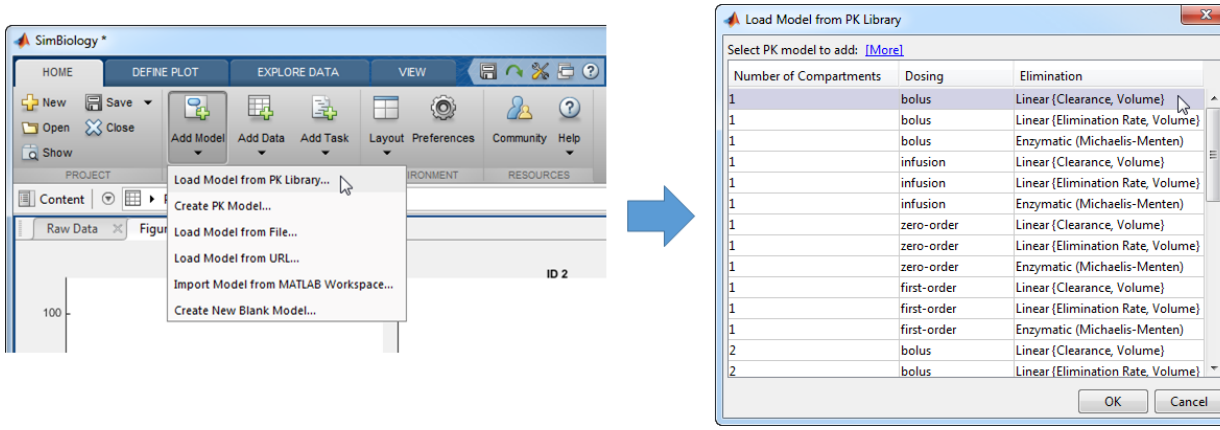
"Create a PK Model" on page 2-13

Create a PK Model

The easiest way to create a one-compartment model is to use the built-in PK library. From the **Home** tab, select **Add Model** > **Load Model from PK Library**. A list of model options is provided that allows you to pick features of compartmental PK models such as the number of compartments, dosing types, and elimination types.

Select the one-compartment model with the **bolus** dosing and **Linear {Clearance, Volume}** elimination option.

Note: This elimination option defines the drug elimination from the body in terms of the clearance rate (`Cl`), `Cl = ke * Central`. k_e is the elimination rate constant, and `Central` is the volume of central compartment. For details, see Elimination Types.



SimBiology builds a one-compartment model. By default, the model is displayed in **Table Overview** mode. To graphically visualize the model, select **Open** > **Diagram** on the **Model** tab.

After you create a model, you can fit the model to the data.

Create a PK Model Using Wizard (Alternative Approach)

The PK wizard option provides you with more flexibility in configuring the model. Select **Add Model** > **Create PK Model**. You can select the number of compartments, dosing

and elimination types, and specify whether a particular compartment has a response variable associated with it. In the context of fitting, if your experimental data has the response data measured for that compartment, select the **Response** check box.

Previous Step

"Import and Explore Data" on page 2-10

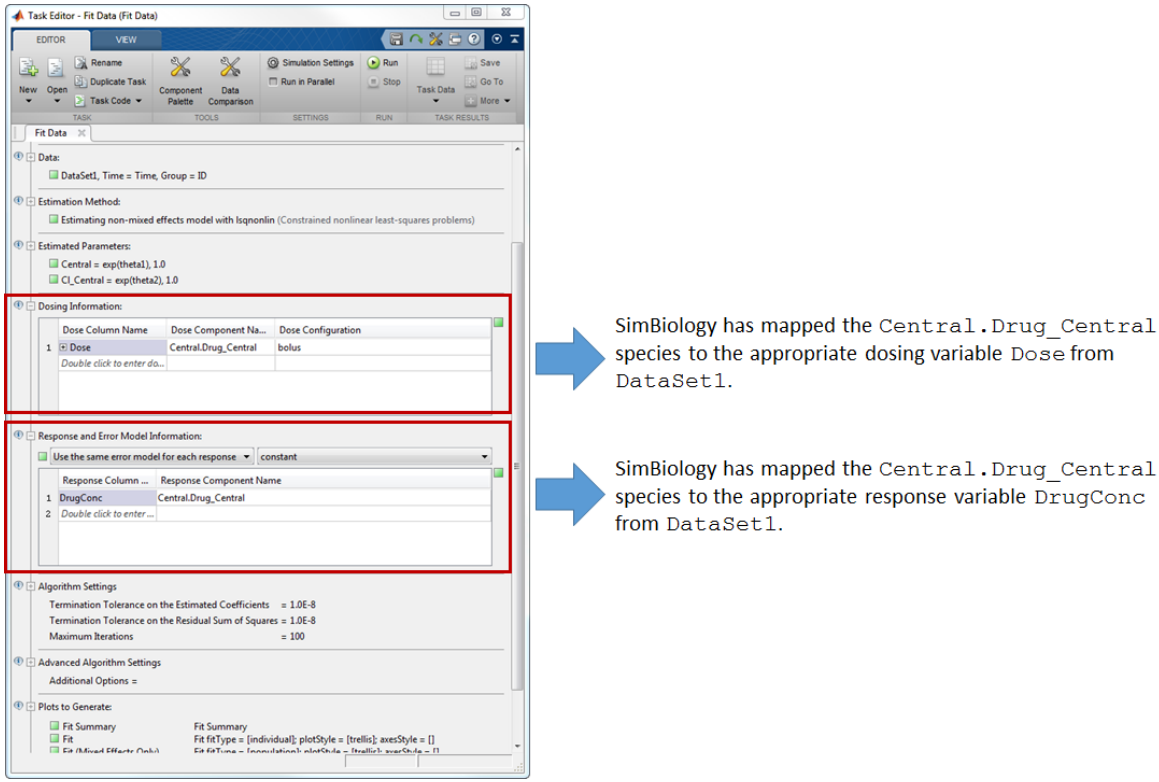
Next Step

"Fit Data" on page 2-15

Fit Data

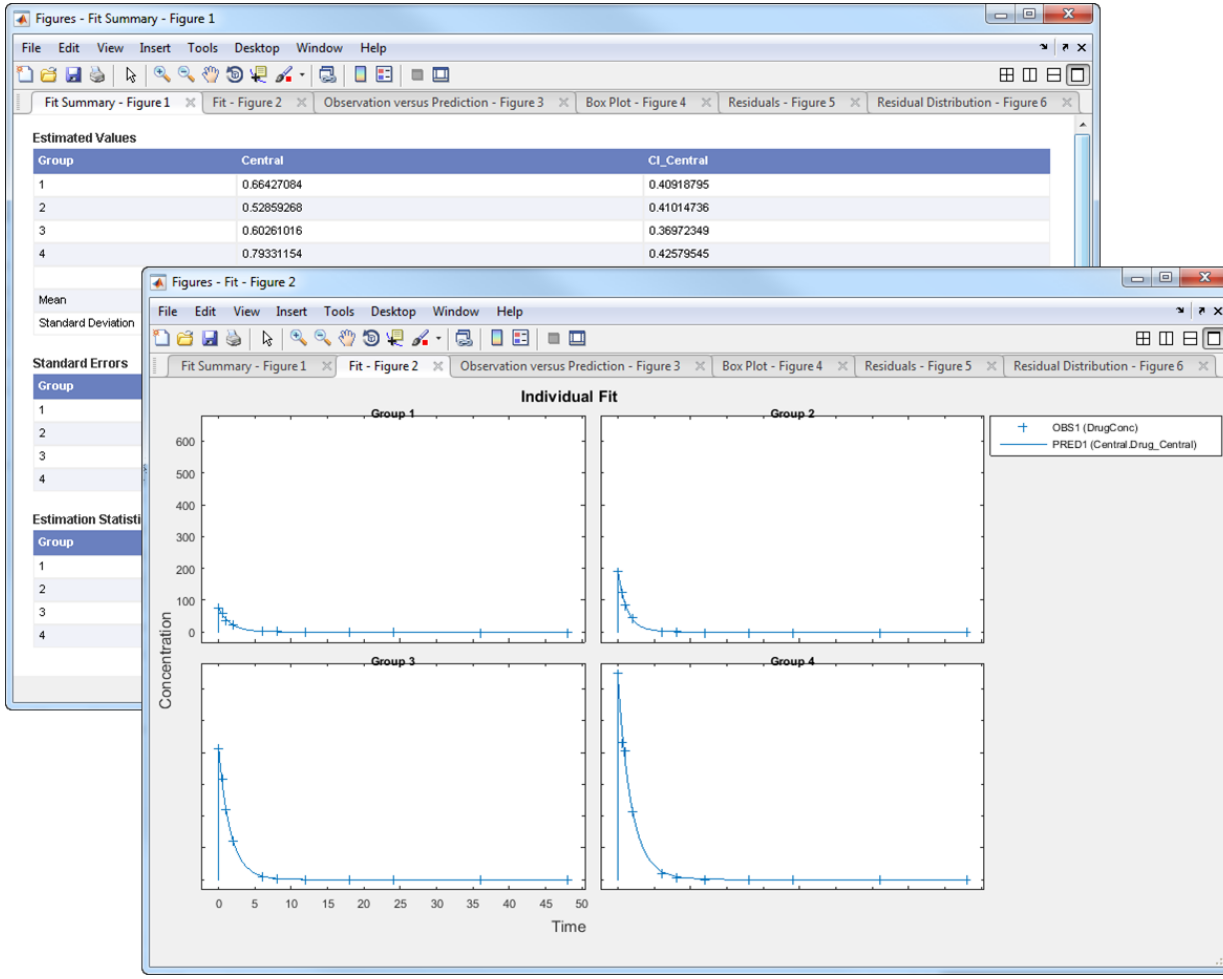
You can estimate parameters of a model using a fit task. From the **Home** tab, select **Add Task** > **Fit data**.

When using a model that you create using the PK library or wizard, you can verify the automatic mapping between the model species and data variables by expanding the **Dosing Information** and **Response and Error Model Information** sections.

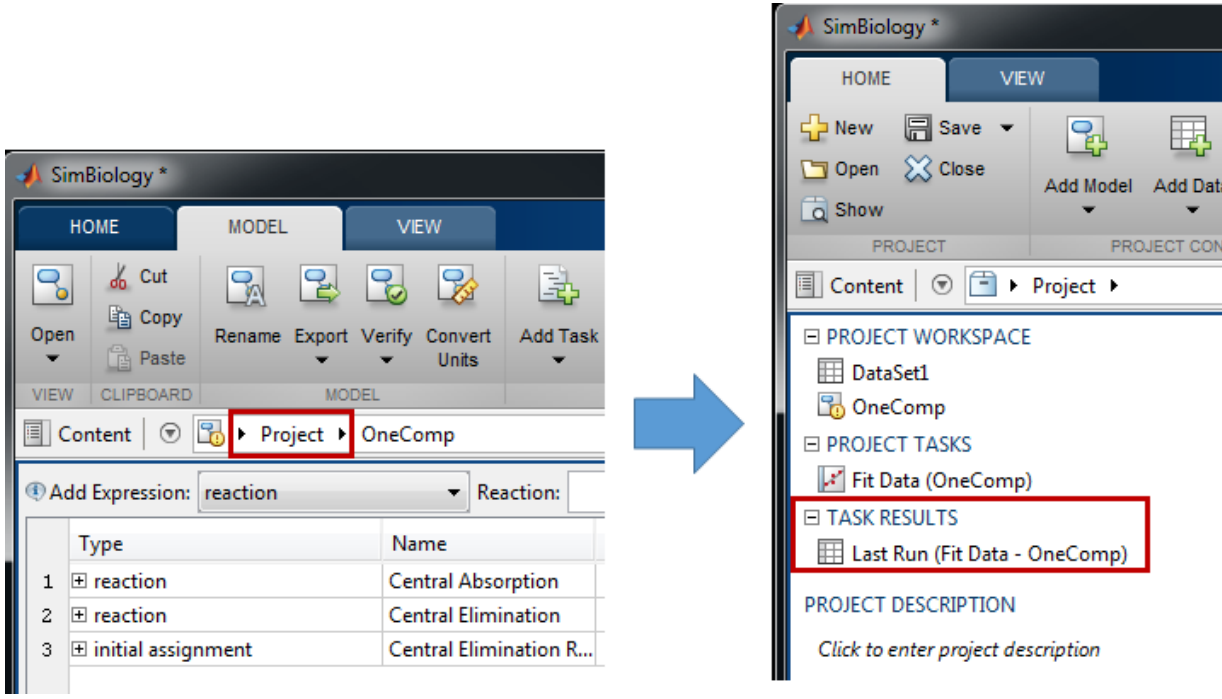


Click **Run** to estimate parameters.

The task generates six figures related to the estimated results by default. If you want different figures, before you run the task, you can specify which plots to generate in the **Plots to Generate** section of the task.



SimBiology stores the results from the fit task in the **Last Run** entry under the **TASK RESULTS** section of the Project. You can navigate to the project area by clicking the **Project** on the navigation bar of the main desktop window.

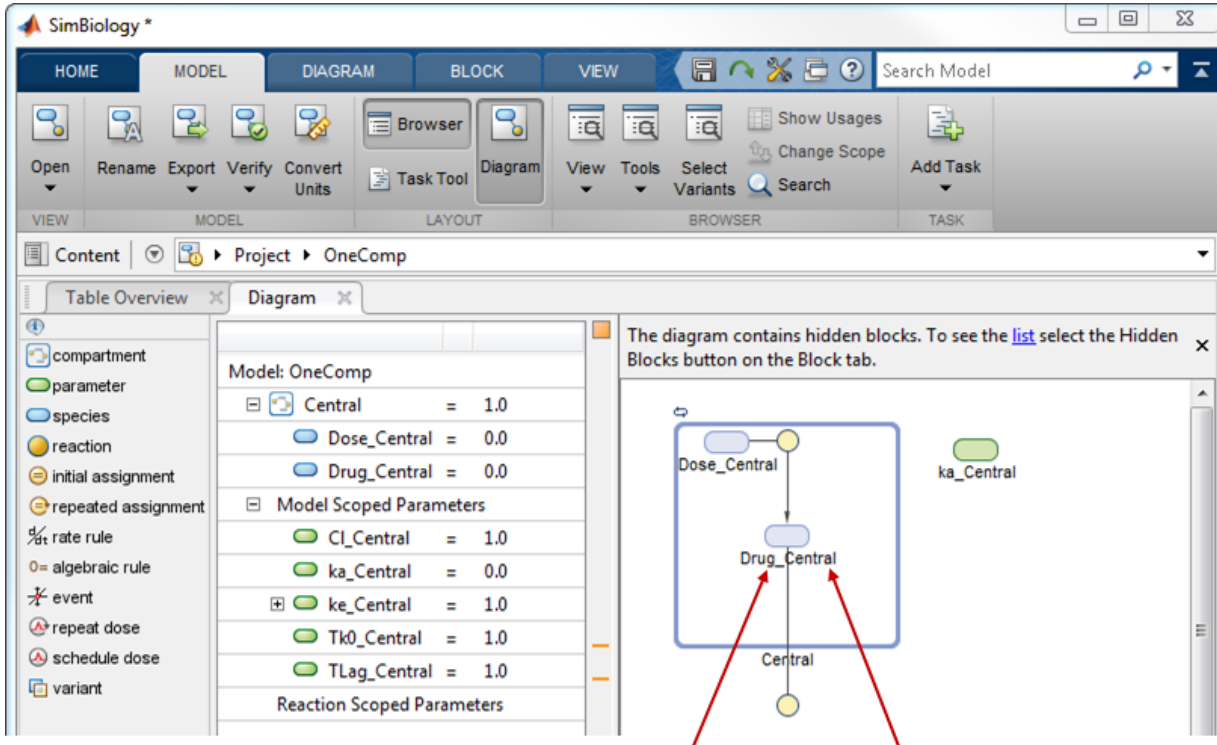


Each time you run the same fit task, this **Last Run** entry is overwritten. If you plan to run the task again and want to keep the results of the last run, save the data. Right-click on the **Last Run** entry and select **Save Data** and specify a name for the data. When you rerun the task, the results are stored in the **Last Run** entry, and your previously saved data is unchanged. Note that each task has its own **Last Run** entry.

Automatic Mapping Between Data and Model

To estimate PK parameters in your model, SimBiology requires you to map your data to the model. If you construct a model using the PK library or wizard, SimBiology recognizes which model species correspond to which variables (columns) in the data set that you have imported.

In this example, since you specify a bolus dosing, the dose target is the `Drug_Central` species, which is also the measured response. Hence SimBiology maps the `Drug_Central` species to both `Dose` and `DrugConc` columns. The following diagram illustrates such mapping.



DataSet1

	ID	Time	Dose	DrugConc
	group variable	independent variable	dose1	dependent variable1
Units				
1	1.0	0.0	50.0	74.41183746212356
2	1.0	0.5	0.0	59.20242253778865
3	1.0	1.0	0.0	36.00044304927006
4	1.0	2.0	0.0	23.70940378392936
5	1.0	6.0	0.0	2.2719497846970156
6	1.0	8.0	0.0	0.6555934351410315
7	1.0	12.0	0.0	0.06751853618267616
8	1.0	18.0	0.0	0.0021663538386942137
9	1.0	24.0	0.0	7.749027168773 65E-5
10	1.0	36.0	0.0	7.126990783888026E-8
11	1.0	48.0	0.0	5.559764148004954E-11
12	2.0	0.0	100.0	191.95769555276547
13	2.0	0.5	0.0	123.75334209560155
14	2.0	1.0	0.0	85.29974107764872
15	2.0	2.0	0.0	45.50289121876351
16	2.0	6.0	0.0	3.0213224455534813
17	2.0	8.0	0.0	0.799663643095197
18	2.0	12.0	0.0	0.0600749202694836

For the first order dose, the dose target is `Dose_Central`, instead of `Drug_Central`. For details, see dosing types.

Manually Mapping Data to a Custom Model

If you are using a custom model you created without using the wizard or PK library, you must manually do the mapping in the **Dosing Information** and **Response and Error Model Information** sections before you run the fit task.

Create a Variant Using Estimated Parameter Values

If you plan to use these estimated parameters later in your modeling workflow, you can optionally create a variant of the model using the mean values of parameter estimates. Open the **Last Run** or any saved result entry by double-clicking it. Go to the **Summary** tab, and scroll down to the **Estimated Values** section. Click **Create Variant from Mean Values**. When prompted, enter a name of the variant. This allows you to save the estimated parameter values without changing the original model, and reuse these values. For instance, you can apply these variant parameter values during simulation by specifying the variant in the **Variants to Apply** section of a simulation task.

Previous Step

"Create a PK Model" on page 2-13

Related Examples

- "Create and Simulate a Simple Model"

More About

- "SimBiology Desktop"
- "Nonlinear Regression"

Create Standalone Applications using SimBiology Desktop

You can create standalone applications for model distribution and simulation from the SimBiology desktop. The application can be an executable that runs outside of MATLAB or a MATLAB app. To deploy a standalone application, you need MATLAB Compiler™.

To build an executable for model simulation, first add a simulation task and open it. Then in the **Task Editor**, on the **Editor** tab, select **Create App > Deploy**. For a MATLAB app, select **Create App > Package as MATLAB App**.

You can include model exploration tools in the application, such as sliders to adjust quantity values and dose schedules, as well as calculated statistics. To test the user interface and see the final deployed application or MATLAB app, select **Create App > Launch**.

To run standalone applications, install the MATLAB Runtime in a target computer. For more information, see “Download and Install the MATLAB Runtime”. Standalone applications run on Windows, Linux®, and Mac.

3

Getting Started Using the Command Line

Getting Started Using the SimBiology Command Line

Use the MATLAB command line to programmatically write and save scripts for batch processing, and to automate the model building and analysis workflow.

See the following tutorials to get started.

Modeling and Simulation

- "Construct a Simple Model" on page 3-3
- " Model a Gene-Regulation Pathway" on page 3-5
- "Simulate the Yeast Heterotrimeric G Protein Cycle"
- "Simulate Biological Variability of the Yeast G Protein Cycle Using the Wild-Type and Mutant Strains"
- "Create and Simulate a Model with a Custom Function"
- "Calculate Sensitivities"

Estimation

- "Fit a One-Compartment Model to an Individual's PK Profile"
- "Fit a Two-Compartment Model to PK Profiles of Multiple Individuals"
- "Estimate Category-Specific PK Parameters for Multiple Individuals"
- "Estimate a Parameter from the Yeast G protein Model"
- "Modeling the Population Pharmacokinetics of Phenobarbital in Neonates"

Deployment

- "Deploy a SimBiology Model"

Construct a Simple Model

This example shows you how to construct a simple model with two species (A and B) and a reaction. The reaction is `A -> B`, which follows the mass action kinetics with the forward rate parameter `k`. Hence the rate of change is $dA/dt = -k * A$.

Create a SimBiology model named `simpleModel`.

```
m1 = sbiomodel('simpleModel');
```

Add a reaction that involves two species `A` and `B`, where `A` is converted to `B`.

```
r1 = addreaction(m1,'A -> B');
```

SimBiology automatically add species `A` and `B` to the model.

```
m1.species
```

```
   SimBiology Species Array

   Index:    Compartment:    Name:    InitialAmount:    InitialAmountUnits:
   1         unnamed         A        0
   2         unnamed         B        0
```

Set the initial amount of the first species (`A`) to 10.

```
m1.species(1).InitialAmount = 10;
```

Define the kinetic law of the reaction to follow the mass action kinetics. You can achieve this by adding a kinetic law object to the reaction `r1`.

```
kineticLaw = addkineticlaw(r1,'MassAction');
```

Add a rate constant parameter to the mass action kinetic law. You must set the `ParameterVariableNames` property of the kinetic law object to the name of the parameter `'k1'` so that the reaction rate can be determined.

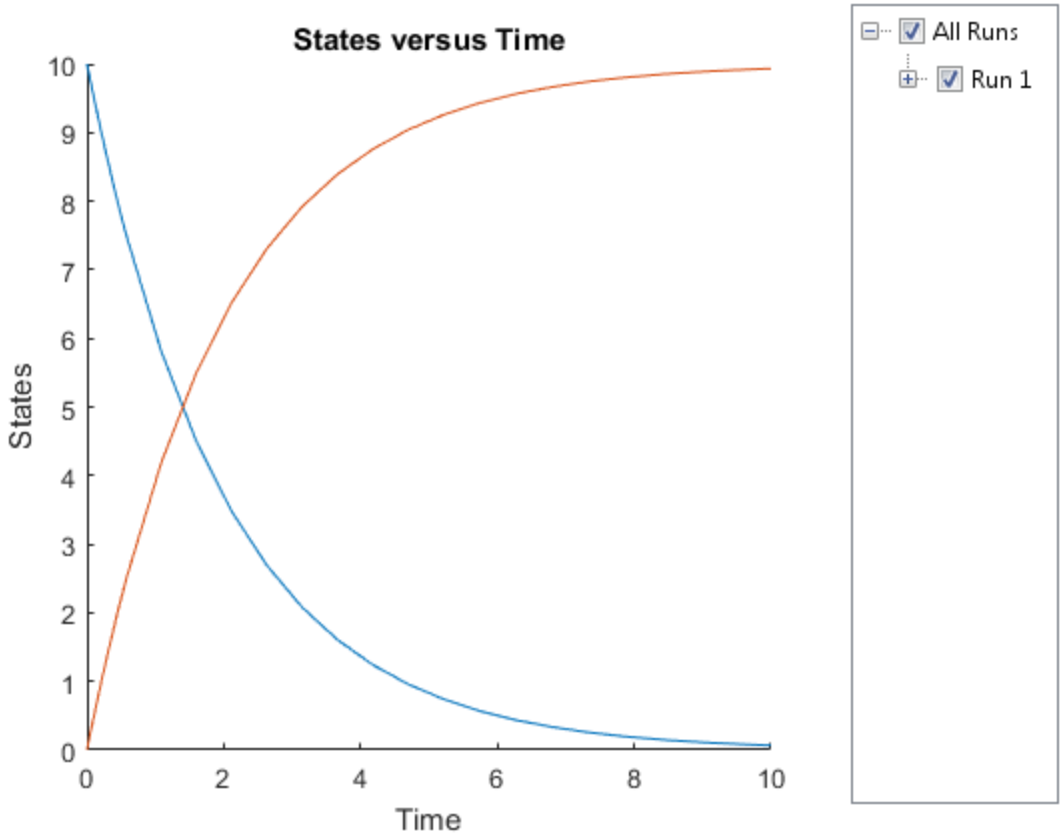
```
p1 = addparameter(kineticLaw,'k',0.5);
kineticLaw.ParameterVariableNames = 'k';
```

Simulate the model.

```
sd = sbiosimulate(m1);
```

Plot the simulation results.

```
sbioplot(sd);
```



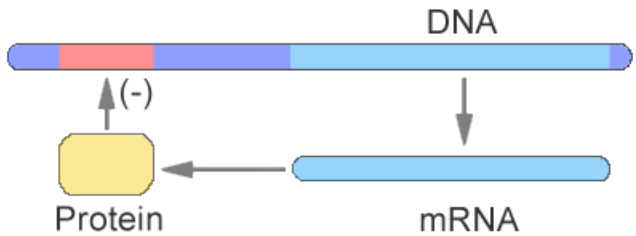
Model a Gene-Regulation Pathway

In this section...

About The Gene Regulation Model

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.

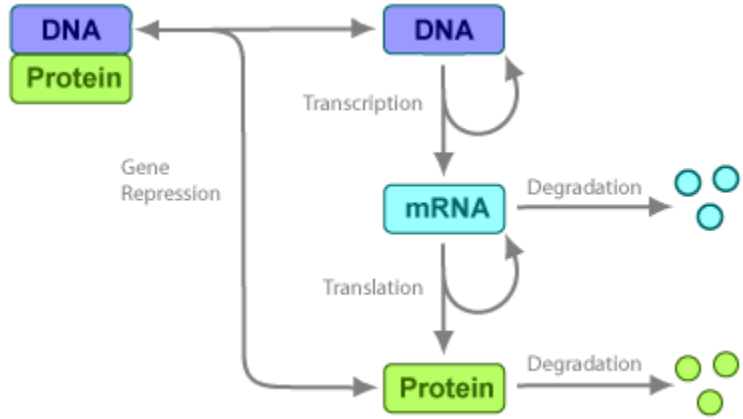


Another way of looking at a systems biology model is to list the reactions in a model with the processes they represent.

```
DNA -> DNA + mRNA              (transcription)
mRNA -> mRNA + protein         (translation)
```

```
DNA + protein -> DNAProteinComplex  (binding)
DNAProteinComplex -> 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.

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` = 0.20 second^{-1}

Translation

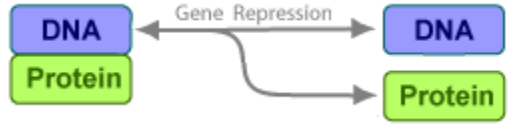
After the mRNA moves from the nucleus to the cytoplasm, it can bind with ribosomes. The ribosomes move along the mRNA and create proteins with the help of tRNAs bound to amino acids. A simple model of translation shows only the mRNA and protein product.

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 second^{-1}

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 -> DNAProteinComplex`
Reaction rate	`v = k3 * DNA * protein` molecule/second
Species	`DNA` = `50` molecule
	`protein` = `0` molecule
Parameters	`k3` = `0.2` 1/(molecule*second)

Reverse Reaction (Unbinding)

Reaction	`DNAProteinComplex -> DNA + protein`
Reaction rate	`v = k3r * DNA_protein` molecule/second
Species	`DNAProteinComplex` = `0` molecule
Parameters	`k3r` = `1` second^{-1}

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

Reaction	`DNA + protein <-> DNA_protein`
Reaction rate	`v = k3 * DNA * protein - k3r * DNA_protein` molecule/second
Species	`DNA` = `50` molecule
	`protein` = `0` molecule
Parameters	`k3` = `0.2` 1/(second*molecule)
	`k3r` = `1` second^{-1}

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 second^{-1}

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 molecule
Parameters	`k5` = 1 second^{-1}

Create a SimBiology Model

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

1 Create a SimBiology model with the name `cell`.

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

```
   SimBiology Model - cell

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

2 Add a compartment named `comp` to the model and set the unit of compartment capacity.

```
compObj = addcompartment(Mobj,'comp');
compObj.CapacityUnits = 'liter';
```

Add the Reaction for Transcription

1 Add the reaction `DNA -> DNA + mRNA` to the model. SimBiology automatically adds the species `DNA` and `mRNA` to the model with the default initial amount of 0.

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

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 Display the added species of the model.

```
Mobj.Species
```

```
SimBiology Species Array

Index:    Compartment:    Name:    InitialAmount:    InitialAmountUnits:
1         comp            DNA      0
2         comp            mRNA     0
```

3 Set the initial amount of `DNA` to `50` as well the amount units for both species.

```
Mobj.Species(1).InitialAmount       = 50;
Mobj.Species(1).InitialAmountUnits  = 'molecule';
Mobj.Species(2).InitialAmountUnits  = 'molecule';
```

4 Specify the kinetics of the reaction to be mass action by creating a mass action kinetic law object, `Kobj1`.

```
Kobj1 = addkineticlaw(Robj1,'MassAction');
```

For a nonreversible reaction, `MassAction` kinetics defines the reaction rate expression as *forward rate constant* * *reactants*.

5 The kinetic law serves as a map between parameters and species needed by the reaction rate expression and parameters and species in the model. To see the parameters and species that must be mapped, retrieve the `ParameterVariables` and `SpeciesVariables` properties of `Kobj1`.

```
Kobj1.ParameterVariables

ans =

    'Forward Rate Parameter'

Kobj1.SpeciesVariables

ans =

    'MassAction Species'
```

6 Since the kinetic law requires a forward rate parameter, create a parameter, `k1`, and set its value to `0.2`. Map the parameter `k1` to the forward rate parameter, by setting the `ParameterVariablesNames` property of `Kobj1` to `k1`.

```
Pobj1               = addparameter(Kobj1,'k1');
Pobj1.Value         = 0.2;
Pobj1.ValueUnits    = '1/second';
Kobj1.ParameterVariableNames = 'k1';
```

7 For mass action kinetics, the `SpeciesVariables` are automatically assigned to the reactant species. Therefore, the `SpeciesVariablesNames` property of `Kobj1` is automatically set to `DNA`. The reaction rate expression is now defined as follows.

```
Robj1.ReactionRate

ans =

k1*DNA
```

Add the Reaction for Translation

A simple model of translation shows only the mRNA and protein product. For more details, see “Translation” on page 3-7.

1 Enter the reaction `mRNA -> mRNA + protein` and set its kinetic law to mass action. Also set the amount unit of the species `protein`.

```
Robj2 = addreaction(Mobj,'mRNA -> mRNA + protein');
Mobj.Species(3).InitialAmountUnits = 'molecule';
Kobj2 = addkineticlaw(Robj2,'MassAction');
```

2 Define the reaction rate constant `k2` for the reaction.

```
Pobj2               = addparameter(Kobj2,'k2');
Pobj2.Value         = 20;
Pobj2.ValueUnits    = '1/second';
Kobj2.ParameterVariableNames = 'k2';
```

3 The reaction rate is now defined as follows.

```
Robj2.ReactionRate


ans =

k2*mRNA
```

Add the Reaction 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 3-7.

1 Enter the reversible reaction for the binding and unbinding of DNA and protein. Add a parameter `k3` as the forward rate constant, and `k3r` as the reverse rate constant.

```
Robj3 = addreaction(Mobj,'DNA + protein <-> DNAProteinComplex');
Mobj.Species(4).InitialAmountUnits = 'molecule';
Kobj3 = addkineticlaw(Robj3,'MassAction');
Pobj3 = addparameter(Kobj3,'k3','Value',0.2,'ValueUnits','1/(molecule*second)');
Pobj3r = addparameter(Kobj3,'k3r','Value',1.0,'ValueUnits','1/second');
Kobj3.ParameterVariableNames = {'k3','k3r'};
```

2 Display the reaction rate.

```
Robj3.ReactionRate


ans =
```

```
k3*DNA*protein - k3r*DNAProteinComplex
```

Add 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. Add a parameter `k4` as the forward rate constant.

```
Robj4 = addreaction(Mobj,'mRNA -> null');
Kobj4 = addkineticlaw(Robj4, 'MassAction');
Pobj4 = addparameter(Kobj4,'k4','Value',1.5,'ValueUnits','1/second');
Kobj4.ParameterVariableNames = 'k4';
```

2. Display the reaction rate of mRNA degration.

```
Robj4.ReactionRate
```

```
ans =

k4*mRNA
```

3. Enter the reaction for protein degradation to amino acids. Add a parameter `k5` as the forward rate constant for the reaction.

```
Robj5 = addreaction(Mobj,'protein -> null');
Kobj5 = addkineticlaw(Robj5,'MassAction');
Pobj5 = addparameter(Kobj5,'k5','Value',1.0,'ValueUnits','1/second');
Kobj5.ParameterVariableNames = 'k5';
```

4. Display the reaction rate of protein degradation.

```
Robj5.ReactionRate
```

```
ans =

k5*protein
```

Simulate the Model

Simulate model to see its dynamic behavior.

1. First turn on the optional unit conversion feature. This feature automatically converts the units of physical quantities into one consistent system. This conversion is in preparation for correct simulation, but species amounts are returned in the unit that you specified (`molecule` in this example).

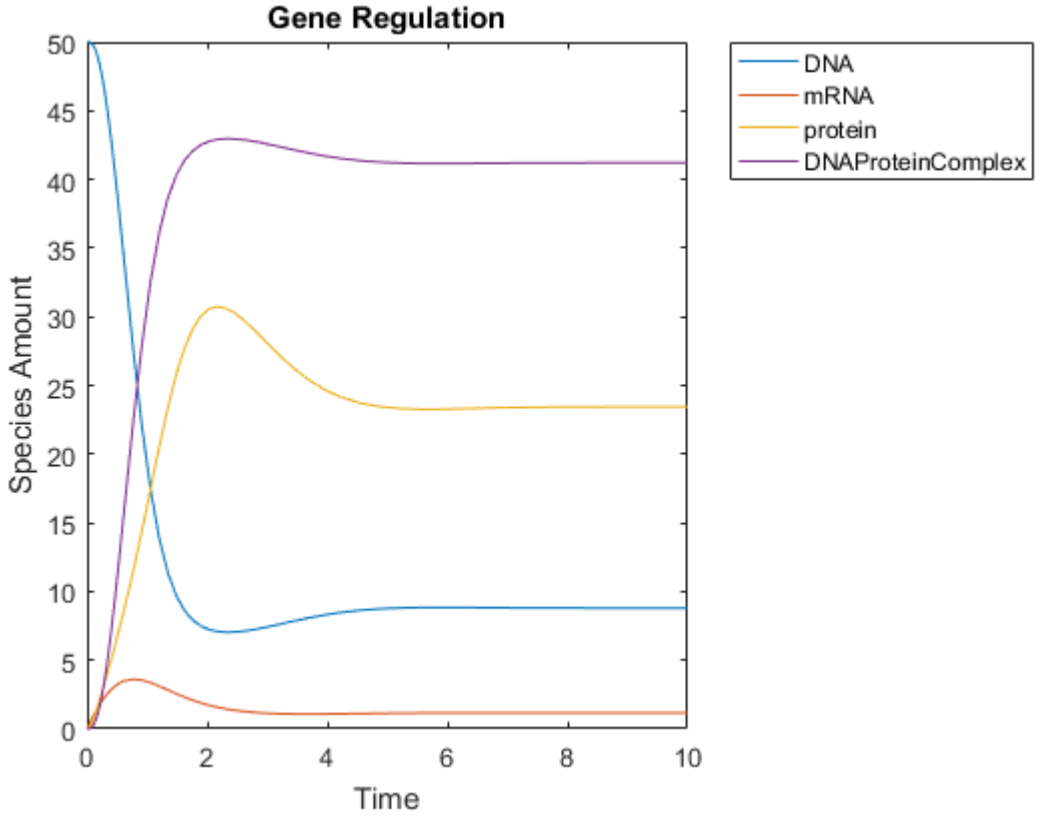
   ```
   configset = getconfigset(Mobj);
   configset.CompileOptions.UnitConversion = true;
   ```

2. Run the simulation.

   ```
   [t, simdata, names] = sbiosimulate(Mobj);
   ```

3. Plot the results.

   ```
   plot(t,simdata)
   legend(names,'Location','NorthEastOutside')
   title('Gene Regulation');
   xlabel('Time');
   ylabel('Species Amount');
   ```


Gene Regulation
Species Amount
Time
0
5
10
15
20
25
30
35
40
45
50
0
2
4
6
8
10
DNA
mRNA
protein
DNAProteinComplex