SimBiology®

User's Guide

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SimBiology® User's Guide

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2 Structural Analysis

Modeling

What is a Model?

In this section...

Model Definition

A SimBiology® *model* is composed of a set of expressions (reactions, differential equations, discrete events), which together describe the dynamics of a biological system. You write expressions in terms of quantities (compartments, species, parameters), which are also enumerated in the model.

Expressions

There are three distinct types of expressions in SimBiology:

- Reactions
- Rules
- Events

Reactions

A *reaction* describes a process such as a transformation, transport, or binding/unbinding process between reactants and products.

Example reactions include:

```
Creatine + ATP <-> ADP + phosphocreatine
cytoplasm.speciesA -> nucleus.speciesA
```

Rules

A *rule* is a class of mathematical expressions that include differential equations, initial assignments, repeated assignments, and algebraic constraints.

For example, you can use a rule to:

- Specify values for model components that are required for comparison with experimental data. For example, specify the active fraction of total protein.
- Assign values to model components based on the values of other components in the model. For example, define a parameter's value as being proportional to a species or another parameter.
- Define mass balance equations.
- For species, use rate rules as an alternative to the differential rate expression generated from reactions.

Events

An *event* describes an instantaneous change in the value of a quantity (compartment, species, parameter). The discrete transition occurs when a user-specified condition becomes true. The condition can be a specific time or a specific time-independent condition.

For example, you can use an event to:

- Activate or deactivate a specific species (activator or inhibitor species)
- Change a parameter value based on external signals
- Change reaction rates in response to addition or removal of a species
- Replicate an experimental condition, such as the addition or removal of an activating agent (such as a drug) to or from a sample

Quantities

SimBiology uses three types of quantities in models:

- Compartments
- Species
- Parameters

Compartments

A *compartment* defines a physically bounded region that contains species. A compartment is characterized by a capacity expressed as volume, area, or length. A compartment can also contain other compartments, which adds hierarchy to a model.

For example, a compartment named `cytoplasm` might contain a compartment named `nucleus`, thereby partitioning species based on their location.

Species

A *species* characterizes the state of the biological system by representing the amount (or concentration) present in the system for that entity. Examples of species are `DNA`, `ATP`, and `creatine`. Species' amounts (or concentrations) vary during a simulation as a result of their participation in reactions, differential equations, and events. Therefore, species represent the dynamical state of a biological system.

Parameters

A *parameter* is a quantity that is referred to by expressions. It typically remains constant during a simulation. For example, parameters are used as rate constants in reactions.

You can configure a parameter to vary during a simulation. This is useful, for example, to model the change in a reaction rate given the concentration of a catalyst or a change in temperature.

Model Hierarchy

Note the following conditions imposed on quantities in the model hierarchy:

- Models must contain at least one compartment.
- A compartment can contain one or more compartments.
- Species are always contained within a compartment.

More About

“Representing a Model and Model Modifiers” on page 1-6

Model Modifiers

In this section...
"Variants" on page 1-5
"Doses" on page 1-5

In addition to expressions and quantities, which are model components, SimBiology provides the following constructs (or objects) that you use to modify or perturb a model from its base configuration.

Variants

A *variants* is a collection of quantities (compartments, species, and/or parameters) that you can use to alter a model's initial or base configuration, which is easier than individually modifying each quantity separately. For example, assuming that a different set of parameter values characterizes differences between wild type and mutant strains, you can use a variant to group parameter values indicative of these strains. You apply variants to a model to evaluate the model behavior under "variant" conditions. Note that the model's original configuration is only temporarily altered, for example during a simulation.

For example, you can use a variant to compare:

- Two different species, such as human versus mouse
- Wild type versus mutant strains
- Different experimental conditions

Doses

A *dose* is used to increment the amount (or concentration) of a species exogenously. For example, you can use a dose to model the instantaneous supply of a drug regimen during the simulation of a model. For details, see "Doses" on page 1-42.

Representing a Model and Model Modifiers

In this section...
"Construct a Simple Model" on page 1-6
"SimBiology Objects" on page 1-6

Construct a Simple Model

The following code shows how to construct a simple model consisting of one compartment, two species, a parameter, and a reaction:

```
% Create a model named example
model = sbiomodel('example');
% Add a compartment named cell to model
compartment = addcompartment(model, 'cell');
% Add two species, A and B, to the cell compartment
species_1 = addspecies(compartment, 'A');
species_2 = addspecies(compartment, 'B');
% Add a parameter, K1, to model with a value of 3
parameter = addparameter(model, 'K1', 3);
% Add the reaction A -> B to the model
reaction = addreaction(model, 'A -> B', 'ReactionRate', 'K1');
```

SimBiology Objects

In SimBiology, models and their components are implemented as objects. For example, in the previous code, `model` is a model object composed of a compartment object, `compartment`, which in turn is composed of species, parameter and reaction objects. These objects have properties and methods associated with them, which you use to access and configure them. Use the `get` method to list the property values of an object. Use the `set` method to change the property values of an object.

SimBiology objects are handle objects, which has implications for how they behave during copy operations. In particular, handle objects do not behave as arrays of doubles do in MATLAB®. To learn how handle objects affect copy operations, see Copying Objects in the MATLAB Programming Fundamentals documentation.

More About

- "Model Object" on page 1-8

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Model Object

A `model object` represents a model and is composed of quantities and expressions. Quantities represent the state variables in the system while expressions depict the relationships between quantities and therefore describe the dynamics of the model.

For information about...	See...
Creating a model	`sbiomodel`
Methods and properties of a model	`model object`
Removing models from MATLAB Workspace	`clear`
Deleting models	`sbioreset`

Objects Representing Quantities

The following objects represent quantities in a model:

- Compartment
- Species
- Parameter

Scoping of Compartments, Species, and Parameters

Scoping refers to which object another object is contained in. Scoping affects compartments, species, parameters, and rules.

- A compartment is scoped to (or contained in) a model or another compartment.
- Although a model can contain multiple compartments, each species is scoped to only one compartment.
- A parameter is scoped to a model or a kinetic law.

Naming of Compartments and Species

Note the following when naming objects within a model:

- Compartment names must be unique within a model.
-

More About

- "Compartment Object" on page 1-10
- "Species Object" on page 1-11
- "Parameter Object" on page 1-15

Compartment Object

A `compartment object` represents a compartment, which is a physically isolated region. It lets you associate pools of species to that physically isolated region. It has a capacity associated with it.

All models must contain at least one compartment. A compartment is scoped to a model or another compartment. A compartment contains one or more species. Each compartment within a model must have a unique name.

You can add a compartment explicitly (using the `addcompartment` method) or add a reaction (using the `addreaction` method) to create a compartment.

For information about...	See...
Creating and adding a compartment to a model	`addcompartment`, `addreaction`
Methods and properties of a compartment	`compartment object`

Species Object

A `species object` represents a species, which is the amount of a chemical or entity that participates in reactions. A species is always scoped to a compartment.

When adding species to a model with multiple compartments, you must specify qualified names, using *`compartmentName.speciesName`*. For example, `nucleus.DNA` denotes the species `DNA` in the compartment `nucleus`.

For information about...	See...
Creating and adding a species to a model	`addspecies`
Methods and properties of a species	`species object`

How Species Amounts Change During Simulations

The amount of a species can remain constant or vary during the simulation of a model. Use the following properties of a `species object` to specify how the amount of a species changes during a simulation:

- `ConstantAmount` property — When set to `true`, the species amount does not change during a simulation. The species can be part of a reaction or rule, but the reaction or rule cannot change its amount. When set to `false`, the species amount is determined by a reaction or a rule, but not both.
- `BoundaryCondition` property — When set to `true`, the species amount is either constant or determined by a rule, but not determined by a chemical reaction. In other words, the simulation does not create a differential rate term from the reactions for this species, even if it is in a reaction, but it can have a differential rate term created from a rule.

Keeping a Species Amount Unchanged

Set `ConstantAmount` to `true` and `BoundaryCondition` to `false` for a constant species, whose amount is not changed by a reaction or rule. In this case, the species acts like a parameter. It cannot be in a reaction, and it cannot be varied by a rule.

ConstantAmount	BoundaryCondition	Reaction	Rule	Changed By
True	False	No	No	Never

Example — Species **E** is not part of the reaction, but it is part of the reaction rate equation. **E** is constant and could be replaced with the constant `Vm = k2*E`.

```
     reaction: S -> P
reaction rate: kcat*E*S/(Km + S)
```

Changing a Species Amount with a Reaction or Rule

Set `ConstantAmount` to `false` and `BoundaryCondition` to `false` for a species whose amount is changed by a reaction or rule, but not both.

ConstantAmount	BoundaryCondition	Reaction	Rule	Changed By
False	False	Yes	No	Reaction
False	False	No	Yes	Rule

Example 1 — Species **A** is part of a reaction, and it is in the reaction rate equation. The species amount or concentration is determined by the reaction. This is the most common category of a species. A differential rate equation for the species is created from the reactions.

```
     reaction: A -> B
reaction rate: k*A
```

Example 2 — Species **E** is not part of the reaction, but it is in the reaction rate equation. **E** varies with another reaction or rule.

```
     reaction: S -> P
reaction rate: kcat*E*S/(Km + S)
```

Example 3 — Species **G** is not part of a reaction, and it is not in a rate equation. **G** varies with an algebraic rule or rate rule.

```
    rate rule: dG/dt = k
```

Changing a Species Amount with a Rule When Species is Part of a Reaction

Set `ConstantAmount` to `false` and `BoundaryCondition` to `true` for a species whose amount is changed by a rule, but the species is also part of a reaction, and a differential rate term from the reaction is not created. The amount of the species changes with the rule, and a differential rate term is created from the rule.

ConstantAmount	BoundaryCondition	Reaction	Rule	Changed By
False	True	Yes	Yes	Rule

Example 1 — Species **A** is not changed by the rate equation, but changes according to a rate rule. However, **A** could be in the rate equation that changes other species in the reaction.

```
     reaction: A -> B
reaction rate: k1 or k1*A
    rate rule: dA/dt = k2*A (solution is  A = k2*t)
               (enter in SimBiology as A = k2*A)
```

Example 2 — Species **A** is not in the rate equation, but changes according to an algebraic rule.

```
      reaction: A -> B + C
 reaction rate: k or k*A
algebraic rule: A = 2*C
                (enter in SimBiology as 2*C - A)
```

Keeping a Species Amount Unchanged When Species is Part of a Reaction that Adds or Removes Mass

Set `ConstantAmount` to `false` and `BoundaryCondition` to `true` for a constant species that is part of a reaction, but a differential rate term is not created from the reaction. The differential rate term is created from a rule.

ConstantAmount	BoundaryCondition	Reaction	Rule	Changed By
True	True	Yes	No	Never

During simulation, a differential rate equation is not created for the species. `dSpecies/dt` does not exist.

Example 1 — **A** is a *`infinite source`* and its amount does not change. B increases with a zero order rate (`k` and `k*A` are both constants). A source refers to a species where mass is added to the system.

```
     reaction: A -> B
```

```
reaction rate: k or k*A
```

Example 2 — B decreases with a first-order rate, but **A** is an *infinite sink* and its amount does not change. A *sink* refers to a species where mass is subtracted from the system.

```
     reaction: B -> A
reaction rate: k*B
```

Example 3 — The **null** species is a reserved species name that can act as a source or a sink.

```
     reaction: null -> B
reaction rate: k

     reaction: B -> null
reaction rate: k*B
```

Example 4 — **ATP** and **ADP** are in the reaction and have constant values, but they are not in the reaction rate equation.

```
     reaction: S + ATP -> P + ADP
reaction rate: Vm*S/(Km + S)
```

Parameter Object

A `parameter object` represents a parameter, which is a value that typically remains constant during a simulation. For example, you use parameters to define reaction rate constants. In some circumstances it is useful to allow parameter values to vary. In these cases you can specify a parameter as nonconstant.

For information about...	See...
Creating and adding a parameter to a model	`addparameter`
Methods and properties of a parameter	`parameter object`

Scope of Parameter Objects

When you create a parameter, you scope it to either a model or a reaction.

Parameters Scoped to a Model

Parameters scoped to a model can be used (or referenced) by any expression (reaction, rule, or event) in the model.

Parameters Scoped to a Reaction

Parameters scoped to a reaction can be used (or referenced) by only the reaction rate expression.

Objects Representing Expressions

The following objects represent expressions in a model:

- Reaction object
- KineticLaw object
- Rule object
- Event object

When Reactions, Rules, and Events Specify Parameters

Reactions, rules and events can specify one or more parameters. A parameter is scoped a model or a kinetic law. Note the following when using a reaction, rule, or event to specify a parameter:

- When a *reaction* specifies a parameter, the parameter can be scoped to the model or the kinetic law that is part of that reaction. If more than one reaction specifies the same parameter, the parameter must be scoped to the model. If two parameters have the same name, one at the model level and the other at the kinetic law level, the software uses the parameter at the kinetic law level for the reaction rate that specifies the parameter.
- When a *rule* specifies a parameter, the parameter must be scoped to the model.
- When an *event* specifies a parameter, the parameter must be scoped to the model.

For more information, see “Scope of Parameter Objects” on page 1-15.

More About

- “Definitions and Evaluations of Reactions” on page 1-17
- “Definitions and Evaluations of Rules” on page 1-23
- “Event Object” on page 1-30
- “Create and Simulate a Model with a Custom Function” on page 1-48

Definitions and Evaluations of Reactions

A reaction is a mathematical expression that describe a transformation, transport, or binding process that changes one or more species. Typically, an amount of a species is changed through a reaction.

In SimBiology, a reaction is represented by a `reaction object`, which has the following properties.

- `Reaction` property — Mathematical expression that describes the reaction
- `ReactionRate` property — Mathematical expression that defines the rate at which the reactants combine to form products. You can provide this information explicitly or use the `KineticLaw` property to populate this information.
- `KineticLaw` property — Object that specifies a rate law that defines the type of reaction rate. Examples include Henri-Michaelis-Menten and Mass Action. The object also specifies `species objects`, or `parameter objects`. This property is optional. It serves as a template for a reaction rate and provides a convenient way of applying a specific rate law to multiple reactions. If you use this property, it automatically populates the `ReactionRate` property.

A reaction is scoped to a model.

For information about...	See...
Creating and adding a reaction to a model	`addreaction`
Methods and properties of a reaction	`reaction object`
Creating and adding a kinetic law to a reaction	`addkineticlaw`
Methods and properties of a kinetic law	`KineticLaw object`

Writing Reaction Expressions

Use standard chemistry reaction notation to create the mathematical expression for a reaction (`Reaction` property of a `reaction object`).

Following are rules for writing reaction expressions:

- Use spaces before and after species names and stoichiometric values.
- Stoichiometry values must be positive.

- If a stoichiometry value is not specified, it is assumed to be `1`.
- In a model with a single compartment, specify species using *`speciesName`*. In a model with multiple compartments, specify species using qualified names: *`compartmentName.speciesName`*. For example, `nucleus.DNA` denotes the species `DNA` in the compartment `nucleus`.
- Enclose names with non-alphanumeric characters (including spaces) in brackets.
- Reactions can be reversible (`<->`) or irreversible (`->`).

Examples of reaction expressions include:

```
Creatine + ATP <-> ADP + phosphocreatine
glucose + 2 ADP + 2 Pi -> 2 lactic acid + 2 ATP + 2 H2O
cytoplasm.A -> nucleus.A
[compartment 1].[species A] -> [compartment 2].[species A]
```

Note: Same species can be used multiple times in the list of reactions or products. The expression `'2 A'` is equivalent to `'A + A'`.

Writing Reaction Rate Expressions Explicitly

Use any valid MATLAB code to create the mathematical expression for a reaction rate (`ReactionRate` property of a `reaction object`). The reaction rate can specify compartments, species, or parameters.

Following are rules for writing reaction rate expressions:

- The expression must be a single MATLAB statement that returns a scalar.
- In a model with a single compartment, specify species using *`speciesName`*. In a model with multiple compartments, specify species using qualified names: *`compartmentName.speciesName`*. For example, `nucleus.DNA` denotes the species `DNA` in the compartment `nucleus`.
- Enclose names with non-alphanumeric characters (including spaces) in brackets.
- Do not end the reaction rate expression with any of the following:
    - Semicolon
    - Comma
    - Comment text preceded by `%`

- Line continuations indicated by `...`

For example, if you have the following reaction expression:

```
Creatine + ATP <-> ADP + phosphocreatine
```

and the reaction follows Mass Action kinetics, then the reaction rate expression would be:

```
K*Creatine*ATP - Krev*ADP*phosphocreatine
```

Tip If your reaction rate expression is not continuous and differentiable, see "Using Events to Address Discontinuities in Rule and Reaction Rate Expressions" on page 1-38 before simulating your model.

Creating Reaction Rate Expressions Using Kinetic Law Objects

A `KineticLaw object` is scoped to a reaction and specifies:

- A rate law that defines the type of reaction rate. Examples include Henri-Michaelis-Menten and Mass Action.
- species and parameters

A `KineticLaw object` serves as a template for a reaction rate and provides a convenient way of applying a specific rate law to multiple reactions. You can use this object to create a reaction rate, which populates the `ReactionRate` property of the `reaction object`.

For example, if you create a `KineticLaw object` that specifies Henri-Michaelis-Menten for the `KineticLawName`, species `S`, and parameters `Vm` and `Km`, the reaction rate law is:

$$V_{\mathrm{m}} * S / (K_m + S)$$

Then if you create a `reaction object` that specifies the previous `KineticLaw object` and species the following reaction expression:

```
A -> B
```

with `Vm` = `Va` and `Km` = `Ka` and `S` = `A`, then the reaction rate equation is:

Va*A/(Ka + A)

Examples of Creating Reaction Rates

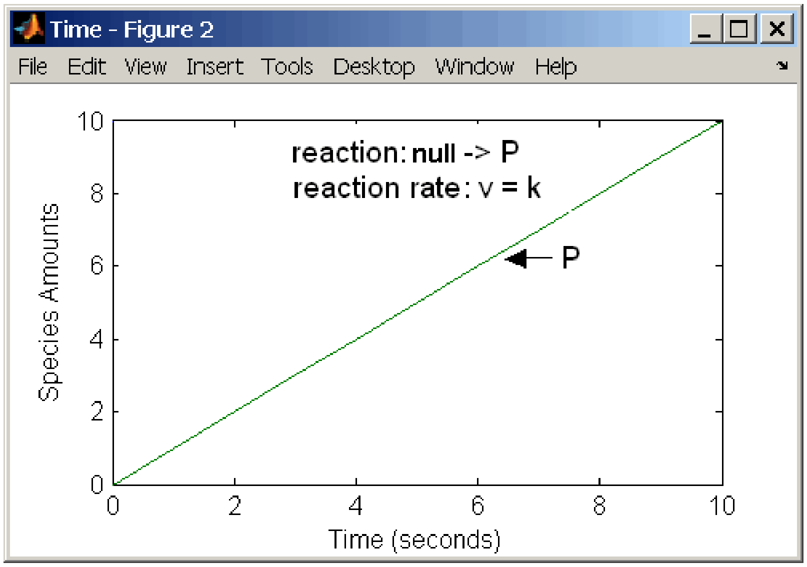
Example of Creating a Zero-Order Reaction

With a zero-order reaction, the reaction rate does not depend on the concentration of reactants. Examples of zero-order reactions are synthesis from a `null` species, and modeling a source species that is added to the system at a specified rate.

```
     reaction: null -> P
reaction rate: k mole/second
      species: P =  0 mole
   parameters: k =  1 mole/second
```

Note: When specifying a `null` species, the reaction rate must be defined in units of amount per unit time not concentration per unit time.

Entering the reaction above into the software and simulating produces the following result:



Zero-Order Mass Action Kinetics

Note: If the amount of a reactant with zero-order kinetics reaches zero before the end of a simulation, then the amount of reactant can go below zero regardless of the solver or tolerances you set.

Examples of Creating Other Reactions

For examples of creating other reaction rates, see "Create Reaction Rates" on page A-2.

How Reaction Rates Are Evaluated

Reaction Rate Dimensions

When calculating species fluxes, SimBiology must determine whether you specified reaction rates in dimensions of amount/time or concentration/time. When all compartments in a model have a capacity of one unit, amount and concentration are numerically equivalent.

For all other models, the numerical results of the simulation depend on which interpretation SimBiology selects. SimBiology determines whether a reaction rate is in dimensions of amount/time or concentration/time via dimensional analysis of `ReactionRate` expressions. This minimum level of dimensional analysis always occurs, even when `DimensionalAnalysis` and `UnitConversion` are off.

The `DefaultSpeciesDimension` property defines the dimensions of species appearing in a reaction rate. SimBiology infers the dimensions of parameters appearing in a reaction rate from their `ValueUnits` property. If any parameters appearing in a reaction rate expression do not have units, SimBiology interprets the reaction rate in dimensions of amount/time. Therefore, the only way to specify that a reaction rate has dimensions of concentration/time is to assign appropriate units to all parameters.

Reactions Spanning Multiple Compartments

Specify reactions that span compartments using the syntax *`compartment1Name`*.*`species1Name`* –> *`compartment2Name`*.*`species2Name`*. The reaction rate dimensions must resolve to amount/time when:

- Species span multiple compartments.
- The reaction is reversible mass action and the products are in multiple compartments.

Examples

Consider a reaction `a + b -> c`. Using mass action kinetics, the reaction rate is `k*a*b`, where `k` is the rate constant of the reaction. If you specify that initial amounts of `a` and `b` are `0.01 molarity` and `0.005 molarity` respectively, then the reaction rate is in concentration/time (and units of `molarity/second`) if the units of `k` are `1/(molarity*second)`. If you specify `k` with another equivalent unit definition, for example, `1/((moles/liter)*second)`, SimBiology checks whether the physical quantities match. If the physical quantities do not match, you see an error and the model is not simulated.

If, in the previous example, you specify that initial amounts of `a` and `b` are `0.01` and `0.005` respectively, without specifying units, SimBiology checks whether `DefaultSpeciesDimension` is `substance` or `concentration`. If `DefaultSpeciesDimension` is `concentration`, and you set units on the rate constant such that the reaction rate dimensions resolve to concentration/time, SimBiology scales the species amounts for compartment capacity, and returns the species values in concentration.

If you specify initial amounts of `a` and `b` as `0.01 molarity` and `0.005 mole` respectively, include the volume scaling for `b` in the reaction rate expression. Include volume scaling in the rate constant, and set the units of the rate constant accordingly (`1/(mole*second)` for concentration/time, or `1/(molarity*second)` for amount/time).

Viewing Equations for Reactions

You can view the system of equations that SimBiology creates when you build a model using reaction expressions. For details, see “View Model Equations” on page 1-56.

More About

“Create and Simulate a Model with a Custom Function” on page 1-48

Definitions and Evaluations of Rules

In this section...

Overview

Rules are mathematical expressions that allow you to define or modify model quantities, namely compartment capacity, species amount, or parameter value.

Rules can take the form of initial assignments, assignments during the course of a simulation (repeated assignments), algebraic relationships, or differential equations (rate rules). Details of each type of rule are described next.

Initial Assignment

An initial assignment rule lets you specify the initial value of a model quantity as a numeric value or as a function of other model quantities. It is evaluated once at the beginning of a simulation.

An initial assignment rule is expressed as `Variable = Expression`, and the rule is specified as the `Expression`. For example, you could write an initial assignment rule to set the initial amount of `species2` to be proportional to `species1` as `species2 = k * species1` where `k` is a constant parameter.

Initial assignments are evaluated in the order in which they occur in the model. Note that their effects can change when you reorder them.

Repeated Assignment

A repeated assignment rule lets you specify the value of a quantity as a numeric value or as a function of other quantities repeatedly during the simulation. It is evaluated at every time step, which are determined by the solver during the simulation process.

A repeated assignment rule is expressed as `Variable = Expression`, and the rule is specified as the `Expression`. For example, to repeatedly assign the value of `50` to species `x` throughout the simulation, define the repeated assignment rule as `x = 100`.

Repeated assignments are reordered automatically and evaluated as a set of simultaneous constraints. Thus it is not possible to create circular sets of assignments such as `a = b + 1` and `b = a + 1`.

Algebraic Rules

An algebraic rule lets you specify mathematical constraints on one or more model quantities that must hold during a simulation. It is evaluated continuously during a simulation.

An algebraic rule takes the form `0 = Expression`, and the rule is specified as the `Expression`. For example, if you have a mass conservation equation such as `species_total = species1 + species2`, write the corresponding algebraic rule as `species1 + species2 - species_total`.

However, repeated assignment rules are mathematically equivalent to algebraic rules, but result in exact solutions instead of approximated solutions. Therefore, it is recommended that you use repeated assignment rules instead of algebraic rules whenever possible. Use algebraic rules only when:

- You cannot analytically solve the equations to get a closed-form solution. For example, there is no closed-form solution for `x^4 + ax^3 + bx^2 + cx + k = 0` whereas the closed-form solution for `kx — c = 0` is `x = c/k`.
- You have multiple equations with multiple unknowns, and they could be inconvenient to solve.

Tip If you use an algebraic or rate rule to vary the value of a parameter or compartment during the simulation, make sure the `ConstantValue` property of the parameter or `ConstantCapacity` of the compartment is set to `false`.

Repeated Assignment vs. Algebraic Rules

Repeated assignment rules are mathematically equivalent to algebraic rules, but result in exact solutions. However, algebraic rules are solved numerically, and the accuracy depends on the error tolerances specified in the simulation settings. In addition, there are several advantages to repeated assignment rules such as better computational performance, more accurate results since no rules have to be solved numerically (hence no approximations), and sensitivity analysis support.

Tip

- If you can analytically solve for a variable, use a repeated assignment rule instead of an algebraic rule.
- In repeated assignment rules, the constrained variable is explicitly defined as the left-hand side, whereas in algebraic rules it is inferred from the degrees of freedom in the system of equations. See also “Considerations When Imposing Constraints” on page 1-26.

Rate Rules

A rate rule represents a differential equation and lets you specify the time derivative of a model quantity. It is evaluated continuously during a simulation.

A rate rule is represented as $\frac{dVariable}{dt} = Expression$, which is expressed in SimBiology as `Variable = Expression`. For example, if you have a differential equation for species x, $\frac{dx}{dt} = k(y + z)$, write the rate rule as: `x = k * (y + z)`.

For examples of rate rules, see “Create Rate Rules” on page B-2.

Writing Rule Expressions

Use MATLAB syntax to write a mathematical expression for a rule. Note that no semicolon or comma is needed at the end of a rule expression. If your algebraic, repeated assignment, or rate rule expression is not continuous or differentiable, see “Using Events to Address Discontinuities in Rule and Reaction Rate Expressions” on page 1-38 before simulating your model.

Considerations When Imposing Constraints

Suppose you have a species `y` whose amount is determined by the equation `y = m * x - c`. In SimBiology, the algebraic rule to describe this constraint is written as `m * x - c - y`. If you want to use this rule to determine the value of `y`, then `m`, `x`, and `c` must be variables or constants whose values are known or determined by other equations. Therefore, you must ensure that the system of equations is not overconstrained or underconstrained. For instance, if you have more equations than unknowns, then the system is overconstrained. Conversely, if you have more unknowns than the equations, then the system is underconstrained.

Tip The behavior of an underconstrained system could be fixed by adding additional rules or by setting the `ConstantValue` or `ConstantCapacity` or `ConstantAmount` property of some of the components in the model.

Conservation of Amounts When Simulation Time = 0 and Time > 0

During a simulation (i.e., at simulation time > 0), if there are any changes to the volume of a compartment where the species reside, SimBiology conserves species amounts rather than concentrations.

At the beginning of a simulation (i.e., at time = 0), SimBiology evaluates the initial assignment rules one after another based on the order they appear in the model rather than as a set of mathematical constraints to be analyzed together. More specifically, at time = 0, SimBiology:

1. Initializes variables for species, compartments, and parameters using the `InitialAmount`, `Capacity`, and `Value` properties.
2. Updates the variables by evaluating initial assignment rules in the order they appear, thus not conserving species amounts if the compartment’s volume changes.
3. Updates the variables by evaluating repeated assignment rules as a set of constraints that conserve species amounts when the compartment’s volume changes.

At time > 0, SimBiology:

- Updates the variables by evaluating repeated assignment rules as a set of constraints that conserve species amounts when the compartment's volume changes.

SimBiology defines a compartment's volume before evaluating repeated assignments, and if you have a repeated assignment rule or an event that changes the volume and depends on time (either explicitly or implicitly), then you will see the effect of conservation of species amount(s) at time > 0.

Illustration of Conservation of Amounts

Consider the following example that illustrates such conservation of amounts. Suppose there is a one-compartment model with a drug that degrades according to the mass action kinetics with the forward reaction rate `k`. In order to distinguish the amount and concentration units, the drug is represented in two different species: one in an amount unit (milligram) and another one in a concentration unit (milligram/liter).

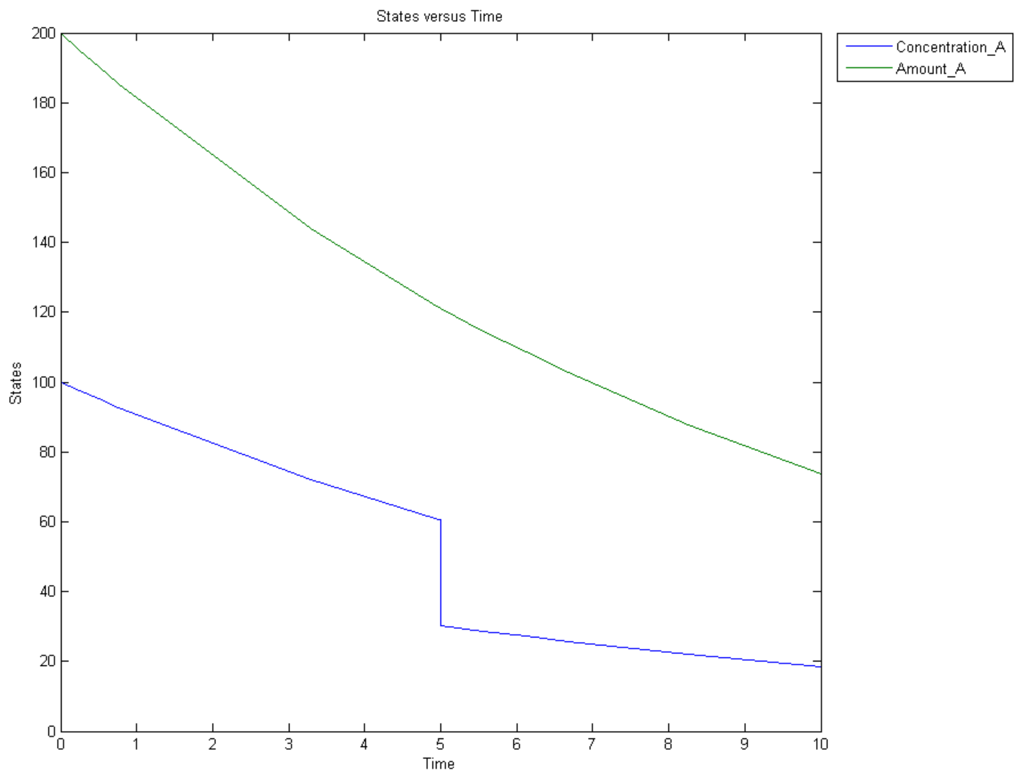
Compartment, Species, and Parameter	**Initial Values**
`cell` (compartment)	1.0 liter
`Amount_A` (drug A in amount units)	0.0 milligram
`Concentration_A` (drug A in concentration units)	100.0 milligram/liter
`k` (forward rate parameter)	0.1 hour^{-1}

Here is an initial assignment, repeated assignment, and event as they appear in the model.

Rules and Event	**Formula**
Initial assignment	`cell = 2.0`
Repeated assignment	`Amount_A = Concentration_A * cell`
Event	**Trigger**: `time >= 5`; **EventFcns**: `cell = 4.0`

The initial compartment volume is doubled at time = 0 by the initial assignment, and doubled again at time >= 5 by the event.

The model is simulated, and the final results are shown in the following States versus Time figure.



At time = 0, the volume of the cell is doubled to 2.0 liters via the initial assignment, and consequently the amount of drug A becomes 200 milligram as defined by the repeated assignment. But the concentration does not change and is still 100 milligram/liter. This illustrates that the amount is not conserved at time = 0. However, at time >= 5, the volume of the `cell` becomes 5.0 liter and causes a drop in the concentration (milligram/liter) to conserve the amount (milligram) of drug A. Thus this example illustrates that at time > 0 the amount (instead of the concentration) of drug A is conserved at all times, but not at time = 0.

Examples

"Create Rate Rules" on page B-2.

"Create and Simulate a Model with a Custom Function" on page 1-48.

Event Object

In this section...

Overview

In SimBiology, an event is a discrete transition in value of a quantity or expression in a model. This discrete transition occurs when a customized condition becomes true. The condition can be a specific time and/or a time-independent condition. Such conditions are defined in an `Event object`.

Event Triggers

An event object has a `Trigger` property that specifies a condition that must be true to trigger the event to execute.

Typical event triggers are:

- A specific simulation time — Specify that the event must change the amounts or values of species or parameters. For example, at time = 5 s, increase the amount of an inhibitor species above the threshold to inhibit a given reaction.
- In response to state or changes in the system — Change amounts/values of certain species/parameters in response to events that are not tied to any specific time. For

example, when species A reaches an amount of 30 molecules, double the value of reaction rate constant k. Or when temperature reaches 42 °C, inhibit a particular reaction by setting its reaction rate to zero.

Note: Currently, events cannot be triggered at time = 0. However, you can get the event to happen just after time = 0 by using `'time > timeSmall'` as the event trigger where `timeSmall` can be a tiny fraction of a second such as 1.0 picosecond.

Event Functions

An event has an `EventFcns` property that specifies what occurs when the event is triggered. Event functions can range from simple to complex. For example, an event function might:

- Change the values of compartments, species, or parameters.
- Double the value of a reaction rate constant.

Specifying Event Triggers

The `Trigger` property of an event specifies a condition that must become true for an event to execute. Typically, the condition uses a combination of relational and logical operators to build a trigger expression.

A trigger can contain the keyword `time` and relational operators to trigger an event that occurs at a specific time during the simulation. For example, `time >= x`. For more information see the `Trigger` property.

Use MATLAB syntax to write expressions for event triggers. Note that the expression must be a single MATLAB statement that returns a logical. No semicolon or comma is needed at the end of an expression. MATLAB uses specific operator precedence to evaluate trigger expressions. Precedence levels determine the order in which MATLAB evaluates an expression. Within each precedence level, operators have equal precedence and are evaluated from left to right. To find more information on how relational and logical operators are evaluated see "Relational Operations" and "Logical Operations" in the MATLAB Programming Fundamentals documentation.

Some examples of triggers are:

Trigger	Explanation
`'(time >= 5) && (speciesA < 1000)'`	Execute the event when the following condition becomes true: Time is greater than or equal to `5`, and `speciesA` is less than 1000. **Tip** Using a `&&` (instead of `&`) evaluates the first part of the expression for whether the statement is true or false, and skips evaluating the second statement if this statement is false.
`'(time >= 5) || (speciesA < 1000)'`	Execute the event when the following condition becomes true: Time is greater than or equal to `5`, or if `speciesA` is less than 1000.
`'(s1 >= 10.0) || (time >= 250) && (s2 < 5.0E17)'`	Execute the event when the following condition becomes true: Species, `s1` is greater than or equal to `10.0` or, time is greater than or equal to `250` and species `s2` is less than `5.0E17`. Because of operator precedence, the expression is treated as if it were `'(s1 >=10.0) || ((time>= 250) && (s2<5.0E17))'`. Thus, it is always a good idea to use parenthesis to explicitly specify the intended precedence of the statements.
`'((s1 >= 10.0) || (time >= 250)) && (s2 < 5.0E17)'`	Execute the event when the following condition becomes true: Species `s1` is greater than or equal to `10` or time is greater than or equal to `250`, and species `s2` is less than `5.0E17`.

Trigger	Explanation
`'((s1 >= 5000.0) && (time >= 250)) || (s2 < 5.0E17)'`	Execute the event when the following condition becomes true: Species `s1` is greater than or equal to `5000` and time is greater than or equal to `250`, or species `s2` is less than `5.0E17`.

Tip If `UnitConversion` is on and your model has any event, follow the recommendation below.

Non-dimensionalize any parameters used in the event `trigger` if they are not already dimensionless. For example, suppose you have a trigger `x > 1`, where *x* is the species concentration in mole/liter. Non-dimensionalize *x* by scaling (dividing) it with a constant such as `x/x0 > 1`, where *x0* is a parameter defined as 1.0 mole/liter. Note that *x* does not have to have the same unit as the constant *x0*, but must be dimensionally consistent with it. For example, the unit of *x* can be picomole/liter instead of mole/liter.

Specifying Event Functions

The `EventFcns` property of an event specifies what occurs when the event is triggered. You can use an event function to change the value of a compartment, species, or parameter, or you can specify complex tasks by calling a custom function or script.

Use MATLAB syntax to define expressions for event functions. The expression must be a single MATLAB assignment statement that includes =, or a cell array of such statements. No semicolon or comma is needed at the end of the expression.

Following are rules for writing expressions for event functions:

EventFcn	Explanation
`'speciesA = speciesB'`	When the event is executed, set the amount of `speciesA` equal to that of `speciesB`.
`'k = k/2'`	When the event is executed, halve the value of the rate constant `k`.
`{'speciesA = speciesB','k = k/2'}`	When the event is executed, set the amount of `speciesA` equal to that of `speciesB`, and halve the value of the rate constant `k`.

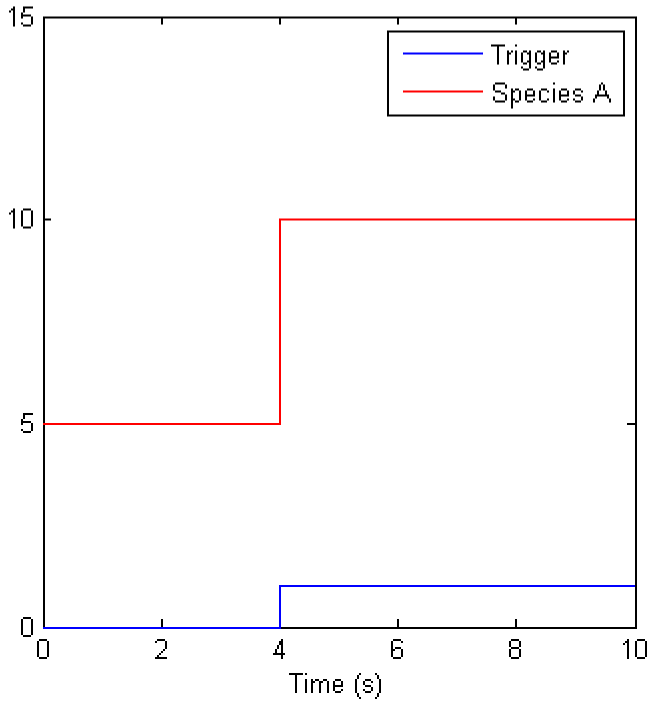
EventFcn	Explanation
`'kC = my_func(A,B,kC)'`	When the event is executed, call the custom function `my_func()`. This function takes three arguments: The first two arguments are the current amounts of two species (`A` and `B`) during simulation and the third argument is the current value of a parameter, `kC`. The function returns the modified value of `kC` as its output.

Simulation Solvers for Models Containing Events

To simulate models containing events, use a deterministic (ODE or SUNDIALS) solver or the stochastic `ssa` solver. Other stochastic solvers do not support events. For more information, see "Choosing a Simulation Solver" on page 3-5.

How Events Are Evaluated

Consider the example of a simple event where you specify that at `4s`, you want to assign a value of `10` to species `A`.



At `time = 4 s` the trigger becomes true and the event executes. In the previous figure assuming that `0` is false and `1` is true, when the trigger becomes true, the amount of species `A` is set to `10`. In theory, with a perfect solver, the event would be executed exactly at `time = 4.00 s`. In practice there is a very minute delay (for example you might notice that the event is executed at `time = 4.00001 s`). Thus, you must specify that the trigger can become true at or after `4s`, which is `time >= 4 s`.

Trigger	EventFcn
`time >= 4`	`A = 10`

The point at which the trigger becomes true is called a *rising edge*. SimBiology events execute the `EventFcn` *only* at rising edges.

The trigger is evaluated at every time step to check whether the condition specified in the trigger transitions from false to true. The solver detects and tracks *falling edges*, which is when the trigger becomes false, so if another rising edge is encountered, the event is reexecuted. If a trigger is already true before a simulation starts, then the event does not execute at the start of the simulation. The event is not executed until the solver encounters a rising edge. Very rarely, the solver might miss a rising edge. An example of this is when a rising edge follows very quickly after a falling edge, and the step size results in the solver skipping the transition point.

If the trigger becomes true exactly at the stop time of the simulation, the event might or might not execute. If you want the event to execute, increase the stop time.

Note: Since the rising edge is instantaneous and changes the system state, there are two values for the state at the same time. The simulation data thus contains the state before and after the event, but both points are at the same time value. This leads to multiple values of the system state at a single instant in time.

Evaluation of Simultaneous Events

When two or more trigger conditions simultaneously become true, the solver executes the events sequentially in the order in which they are listed in the model. You can reorder events using the `reorder` method. For example, consider this case.

Event Number	`Trigger`	`EventFcn`
1	`SpeciesA >= 4`	`SpeciesB = 10`
2	`SpeciesC >= 15`	`SpeciesB = 25`

The solver tries to find the rising edge for these events within a certain level of tolerance. If this results in both events occurring simultaneously, then the value of `SpeciesB` after the time step in which these two events occur, will be `25`. If you reorder the events to reverse the event order, then the value of `SpeciesB` after the time step in which these two events occur, will be `10`.

Consider an example in which you include event functions that change model components in a dependent fashion. For example, the event function in Event 2, stipulates that `SpeciesB` takes the value of `SpeciesC`.

Event Number	`Trigger`	`EventFcn`
1	`SpeciesA >= 4`	`SpeciesC = 10`
2	`time >= 15`	`SpeciesB = SpeciesC`

Event 1 and Event 2 might or might not occur simultaneously.

- If Event 1 and Event 2 do not occur simultaneously, when Event 2 is triggered, `SpeciesB` is assigned the value that `SpeciesC` has at the time of the event trigger.
- If Event 1 and Event 2 occur simultaneously, the solver executes Event 1 first, then executes Event 2. In this example, if `SpeciesC = 15` when the events are triggered, after the events are executed, `SpeciesC = 10` and `SpeciesB = 10`.

Evaluation of Multiple Event Functions

Consider an event function in which you specify that the value of a model component (`SpeciesB`) depends on the value of model component (`SpeciesA`), but `SpeciesA` also is changed by the event function.

Trigger	**EventFcn**
`time >= 4`	`{'SpeciesA = 10, SpeciesB = SpeciesA'}`

The solver stores the value of `SpeciesA` at the rising edge and before any event functions are executed and uses this stored value to assign `SpeciesB` its value. So in this example if `SpeciesA = 15` at the time the event is triggered, after the event is executed, `SpeciesA = 10` and `SpeciesB = 15`.

When One Event Triggers Another Event

In the next example, Event 1 includes an expression in the event function that causes Event 2 to be triggered (assuming that `SpeciesA` has amount less than `5` when Event 1 is executed).

Event Number	**Trigger**	**EventFcn**
1	`time >= 5`	`{'SpeciesA = 10, SpeciesB = 5'}`
2	`SpeciesA >= 5`	`SpeciesC = SpeciesB`

When Event 1 is triggered, the solver evaluates and executes Event 1 with the result that `SpeciesA = 10` and `SpeciesB = 5`. Now, the trigger for Event 2 becomes true and the solver executes the event function for Event 2. Thus, `SpeciesC = 5` at the end of this event execution.

You can thus have event cascades of arbitrary length, for example, Event 1 triggers Event 2, which in turn triggers Event 3, and so on.

Cyclical Events

In some situations, a series of events can trigger a cascade that becomes cyclical. Once you trigger a cyclical set of events, the only way to stop the simulation is by pressing **Ctrl +C**. You lose any data acquired in the current simulation. Here is an example of cyclical events. This example assumes that `Species B <= 4` at the start of the cycle.

Event Number	`Trigger`	`EventFcn`
1	`SpeciesA > 10`	`{SpeciesB = 5, SpeciesC = 1'}`
2	`SpeciesB > 4`	`{SpeciesC = 10, SpeciesA = 1'}`
3	`SpeciesC > 9`	`{SpeciesA = 15, SpeciesB = 1'}`

Using Events to Address Discontinuities in Rule and Reaction Rate Expressions

The solvers provided with SimBiology gives inaccurate results when the following expressions are not continuous and differentiable:

- Repeated assignment rule
- Algebraic rule
- Rate rule
- Reaction rate

Either ensure that the previous expressions are continuous and differentiable or use events to reset the solver at the discontinuity, as described in “Deterministic Simulation of a Model Containing a Discontinuity”.

Objects Representing Model Modifiers

Variant and dose objects can modify or perturb a model from its base configuration.

For an example of creating and using an event in a model, see .

More About

- “Variant Object” on page 1-40
- “Doses” on page 1-42

Variant Object

A `variant object` represents a variant, which is an alternate value for a compartment, species, or parameter in a model. You can apply this alternate value during a simulation, which lets you evaluate model behavior with a different value, without having to search and replace the value, or create an additional model with the new value.

You can use a variant to store an alternate value for any of the following:

- Compartment `Capacity` property
- Species `InitialAmount` property
- Parameter `Value` property

The alternate value applies temporarily, only during a simulation, and does not alter the model's values permanently. If you determine that the values in a variant accurately define your model, you can permanently replace the values in your model with the values stored in the variant object by using the `commit` method.

Creating and Simulating with Variants

1. Create a `variant object` and add it to a model using the `addvariant` method.
2. (Optional) Set the `Active` property of the `variant object` to true if you always want the variant to be applied before simulating the model.
3. Enter the model and variant object as input arguments to `sbiosimulate`. This applies the variant only for the current simulation and supersedes any active variant objects on the model.

   or

   If you followed step 2, simply call `sbiosimulate` on the model object to apply the variant.

For an example of creating and using a variant in a model, see “Simulate Biological Variability of the Yeast G Protein Cycle Using the Wild-Type and Mutant Strains” on page 1-46.

For information about...	See...
Creating and adding a variant to a model	`addvariant`

For information about...	See...
Creating a stand-alone variant	`sbiovariant`
Methods and properties of a variant	`Variant object`
Appending contents to variants	`addcontent`
Replacing model values permanently with values from a variant	`commit`

Simulating with Multiple Variants in a Model

When you use multiple variants during a simulation, and there are duplicate specifications for a property's value, the last occurrence for the property value in the array of variants is used during simulation. You can find out which variant is applied last by looking at the indices of the variant objects stored on the model.

If you specify variants as arguments to `sbiosimulate`, this applies the variants for the current simulation in the order that they are specified, and supersedes any active variant objects on the model.

Similarly, in the variant contents (`Content` property), if there are duplicate specifications for a property's value, the last occurrence for the property in the contents is used during simulation.

Doses

Doses let you increase the amount of a species in a SimBiology model during simulation, either at specific time points or predefined time intervals. For example, you can use a dose object to model an instantaneous supply of a drug regimen during the simulation of a model. The increase in the amount of a species occurs only during simulation and does not alter the species' value permanently (that is, the value in the model is not changed).

Representing Doses

In SimBiology, doses are represented by two types of dose objects.

- `ScheduleDose object` — Applies a dose to a single species at a predefined list of time points
- `RepeatDose object` — Repeatedly applies a dose to a single species at regularly spaced time intervals

SimBiology dose objects support the following common dosing types.

Dosing Strategy	Description
Bolus	Instantaneous increase in the amount of drug in the compartment
Infusion	Increase of the drug at a fixed rate over a period of time, which is calculated from the dose amount
Zero-order	Increase of the drug at a fixed rate calculated from the dose amount and dose duration
First-order	Increase of the drug via the first-order absorption kinetics

Creating Dose Objects

There are two common ways to create dose objects. One way is to create a dose object using the `sbiodose` or `adddose` function. Another is to create dose objects automatically from data containing dosing information. This first approach is useful when you want to explore different dosing strategies through simulation. The second approach is useful if you already have a data set with dosing information and plan to use such dosing information in your simulation or parameter estimation.

Create a Dose Object Using sbiodose or adddose

`sbiodose` creates a standalone dose object that is not attached to any model. You can apply a standalone dose to different models during simulation by specifying it as a dosing argument for `sbiosimulate` or attach it to any model using `adddose`. You can also use it during parameter estimation using `sbiofit` or `sbiofitmixed`.

`adddose` creates a dose object and adds it to a model. Use this function if you want to attach a dose object to a model. You must set its `Active` property to `true` to apply the dose to the model during simulation.

The following examples show how to add a dose object to a one-compartment PK model using `sbiodose` and set up the dose properties manually. Alternatively, you can use the built-in PK models with different dosing types. For details, see “Create Pharmacokinetic Models” on page 4-24.

Dosing Strategy	Example	Dose Object Properties Configuration
Bolus	“Add a Series of Bolus Doses to a One-Compartment Model”	To create a bolus dose, set the `Amount` and `TargetName` properties of a dose object. You might also need to configure other properties such as `RepeatCount`, `Interval` or scheduled dose times (`Time`) if you are applying a series of doses. For details on these properties, see `ScheduleDose object` and `RepeatDose object` .
Infusion	“Add an Infusion Dose to a One-Compartment Model”	Unlike a bolus dose, you also need to specify the infusion rate (`Rate` property) of the dose object.
Zero-order	“Increase Drug Concentration in a One-Compartment Model via Zero-order Dosing”	Unlike a bolus dose, you need to additionally create a zero-order duration parameter and specify the duration parameter name (`DurationParameterName` property) of the dose object.

Dosing Strategy	Example	Dose Object Properties Configuration
First-order	"Increase Drug Concentration in a One-Compartment Model via First-order Dosing"	Unlike bolus, infusion, or zero-order, you need to create an additional reaction for the drug absorption.

Create Dose Objects from Dosing Data

If you already have dosing data for one or more subjects or patients that you would like to use in your parameter estimation, first create a `groupedData object` from your data set. Then use `createDoses` function to automatically generate an array of dose objects that you can specify as an input argument for `sbiofit` or `sbiofitmixed` for fitting. For a complete workflow see "Modeling the Population Pharmacokinetics of Phenobarbital in Neonates".

Simulation Solvers for Models Containing Doses

To simulate models containing doses, use a deterministic (ODE or SUNDIALS) solver. Stochastic solvers do not support doses. For details, see "Choosing a Simulation Solver" on page 3-5.

See Also

`adddose` | `RepeatDose object` | `sbiodose` | `ScheduleDose object`

Scoping

In SimBiology, scoping refers to which object another object is contained in. For example, a compartment is scoped to (or contained in) a model or another compartment, a species is scoped to a compartment, and a parameter is scoped to a model or a kinetic law.

Suppose, you have added a parameter `k1` to a model, then the parameter is scoped to the model. But if you add it to a kinetic law, then it is scoped to the kinectic law only.

Simulate Biological Variability of the Yeast G Protein Cycle Using the Wild-Type and Mutant Strains

This example shows how to create and apply a variant to the G protein model of a wild-type strain. The variant represents a parameter value for the G protein model of a mutant strain. Thus, when you simulate the model without applying the variant, you see results for the wild type strain, and when you simulate the model with the variant, you see results for the mutant strain. This example uses the model described in Model of the Yeast Heterotrimeric G Protein Cycle.

The value of the parameter `kGd` is `0.11` for the wild-type strain and `0.004` for the mutant strain. To represent the mutant strain, you will store an alternate value of `0.004` for the `kGd` parameter in a variant object, and apply this variant when simulating the model.

For information on variants, see "Variant Object" on page 1-40.

Load the `gprotein.sbproj` project, which includes the variable `m1`, a SimBiology model object.

```
sbioloadproject gprotein
```

You can create a variant of the original model by specifying a different parameter value for the `kGd` parameter of the model. First, add a variant to the `m1` model object.

```
v1 = addvariant(m1,'mutant_strain');
```

Next, add a parameter `kGd` with a value of `0.004` to the variant object `v1`.

```
addcontent(v1,{'parameter','kGd','Value',0.004});
```

Simulate the wild type model.

```
[t,x,names] = sbiosimulate(m1);
```

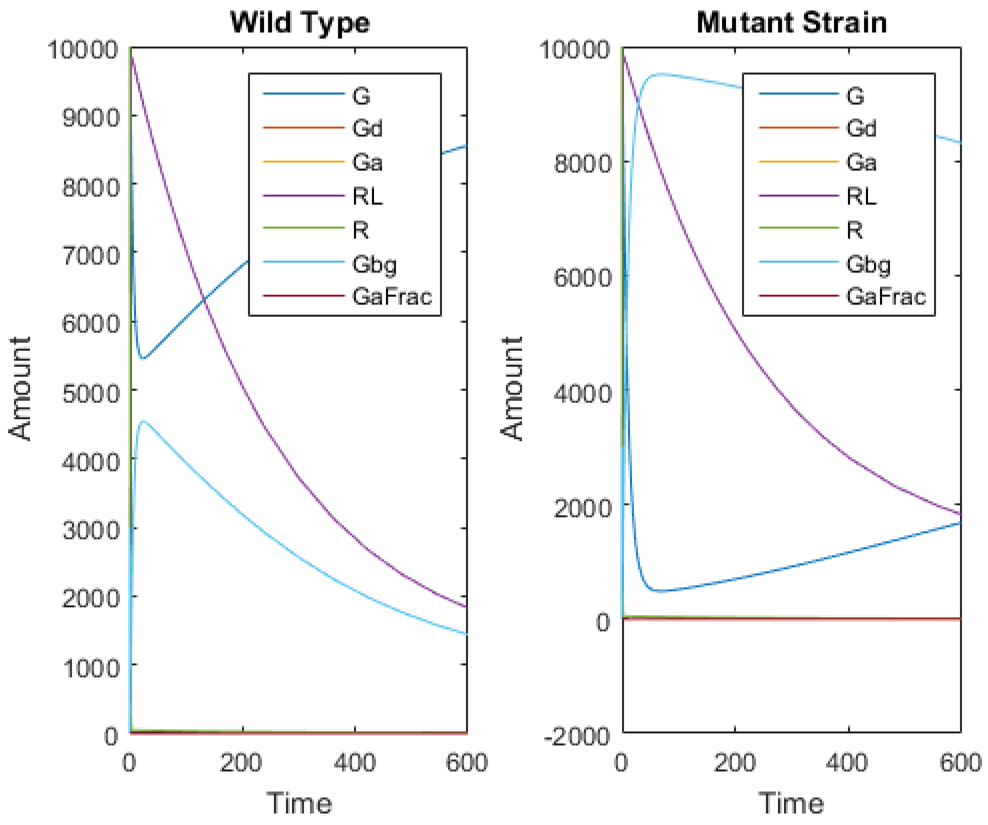
Simulate the mutant strain model by applying the variant.

```
[tV,xV,names] = sbiosimulate(m1,v1);
```

Plot and compare the simulated results.

```
subplot(1,2,1)
plot(t,x);
```

```
legend(names);
xlabel('Time');
ylabel('Amount');
title('Wild Type');

subplot(1,2,2)
plot(tV,xV);
legend(names);
xlabel('Time');
ylabel('Amount');
title('Mutant Strain');
```



Create and Simulate a Model with a Custom Function

In this section...

Overview

Prerequisites for the Example

This example assumes you have a working knowledge of:

- MATLAB desktop
- Creating and saving MATLAB programs

About the Example Model

This example uses the model described in Model of the Yeast Heterotrimeric G Protein Cycle.

This table shows the reactions used to model the G protein cycle and the corresponding rate parameters (rate constants) for each reaction. For reversible reactions, the forward rate parameter is listed first.

No.	Name	Reaction[1]	Rate Parameters
1	Receptor-ligand interaction	`L + R <-> RL`	`kRL`, `kRLm`
2	Heterotrimeric G protein formation	`Gd + Gbg -> G`	`kG1`
3	G protein activation	`RL + G -> Ga + Gbg + RL`	`kGa`

No.	Name	Reaction[1]	Rate Parameters
4	Receptor synthesis and degradation	`R <-> null`	`kRdo`, `kRs`
5	Receptor-ligand degradation	`RL -> null`	`kRD1`
6	G protein inactivation	`Ga -> Gd`	`kGd`
[1] Legend of species: L = ligand (alpha factor), R = alpha-factor receptor, Gd = inactive G-alpha-GDP, Gbg = free levels of G-beta:G-gamma complex, G = inactive Gbg:Gd complex, Ga = active G-alpha-GTP			

Assumptions of the Example

This example assumes that:

- An inhibitor (`Inhib` species) slows the inactivation of the active G protein (reaction 6 above, `Ga –> Gd`).
- The variation in the amount of inhibitor (`Inhib` species) is defined in a custom function, `inhibvalex`.
- The inhibitor (`Inhib` species) affects the reaction by changing the amount of rate parameter `kGd`.

About the Example

This example shows how to create and call a custom function in a SimBiology expression. Specifically, it shows how to use a custom function in a rule expression.

About Using Custom Functions in SimBiology Expressions

You can use custom functions in:

- Reaction rate expressions (`ReactionRate` property)
- Rule expressions (`Rule` property)
- Event expressions (`EventFcns` property or `Trigger` property)

The requirements for using custom functions in SimBiology expressions are:

- Create a custom function. For more information, see `function`.
- Change the current folder to the folder containing your custom MATLAB file. Do this by using the `cd` command or by using the Current Folder field in the MATLAB

desktop toolbar. Alternatively, add the folder containing your file to the search path. Do this by using the `addpath` command or see “Change Folders on the Search Path”.

- Call the custom function in a SimBiology reaction, rule, or event expression.

Tip If your rule or reaction rate expression is not continuous and differentiable, see “Using Events to Address Discontinuities in Rule and Reaction Rate Expressions” on page 1-38 before simulating your model.

Create a Custom Function

The following procedure creates a custom function, `inhibvalex`, which lets you specify how the inhibitor amount changes over time. The inputs are time, the initial amount of inhibitor, and a parameter that governs the amount of inhibitor. The output of the function is the amount of inhibitor.

1 In the MATLAB desktop, select **File > New > Script**, to open the MATLAB Editor.

2 Copy and paste the following function declaration:

```
% inhibvalex.m
function Cp = inhibvalex(t, Cpo, kel)

% This function takes the input arguments t, Cpo, and kel
% and returns the value of the inhibitor Cp.
% You can later specify the input arguments in a
% SimBiology rule expression.
% For example in the rule expression, specify:
% t as time (a keyword recognized as simulation time),
% Cpo as a parameter that represents the initial amount of inhibitor,
% and kel as a parameter that governs the amount of inhibitor.

if  t < 400
    Cp = Cpo*exp(-kel*(t));
else
    Cp = Cpo*exp(-kel*(t-400));
end
```

3 Save the file (name the file `inhibvalex.m`) in a directory that is on the MATLAB search path, or to a directory that you can access.

4 If the location of the file is not on the MATLAB search path, change the working directory to the file location.

Load the Example Model

Load the `gprotein` example project, which includes the variable `m1`, a model object:

```
sbioloadproject gprotein
```

The `m1` model object appears in the MATLAB Workspace.

Add the Custom Function to the Example Model

The following procedure creates a rule expression that calls the custom function, `inhibvalex`, and specifies the three input values to this function.

1 Add a repeated assignment rule to the model that specifies the three input values to the custom function, `inhibvalex`:

  ```
  rule1 = addrule(m1, 'Inhib = inhibvalex(time, Cpo, Kel)',...
                  'repeatedAssignment');
  ```

  The `time` input is a SimBiology keyword recognized as simulation time

2 Create the two parameters used by the `rule1` rule and assign values to them:

  ```
  p1 = addparameter(m1, 'Cpo', 250);
  p2 = addparameter(m1, 'Kel', 0.01);
  ```

3 Create the species used by the `rule1` rule:

  ```
  s1 = addspecies(m1.Compartments, 'Inhib');
  ```

Define a Rule to Change Parameter Value

The value of rate parameter `kGd` is affected by the amount of inhibitor present in the system. Add a rule to the model to describe this action, but first change the `ConstantValue` property of the parameter `kGd` so that it can be varied by a rule.

1 Change the `ConstantValue` property of the `kGd` parameter to `false`.

  ```
  p3 = sbioselect(m1, 'Type', 'parameter', 'Name', 'kGd');
  p3.ConstantValue = false;
  ```

2 Add a repeated assignment rule to the model to define how the `kGd` parameter is affected by the `Inhib` species.

```
rule2 = addrule(m1, 'kGd = 1/Inhib', 'repeatedAssignment');
```

Add an Event to Reset the Solver at a Discontinuity

The custom function, `inhibvalex`, introduces a discontinuity in the model when time = 400. To ensure accurate simulation results, add an event to the model to reset the solver at the time of the discontinuity. Set the event to trigger at the time of the discontinuity (time = 400). The event does not need to modify the model, so create an event function that multiplies a species value by 1.

```
addevent(m1, 'time>=400', 'G=1*G');
```

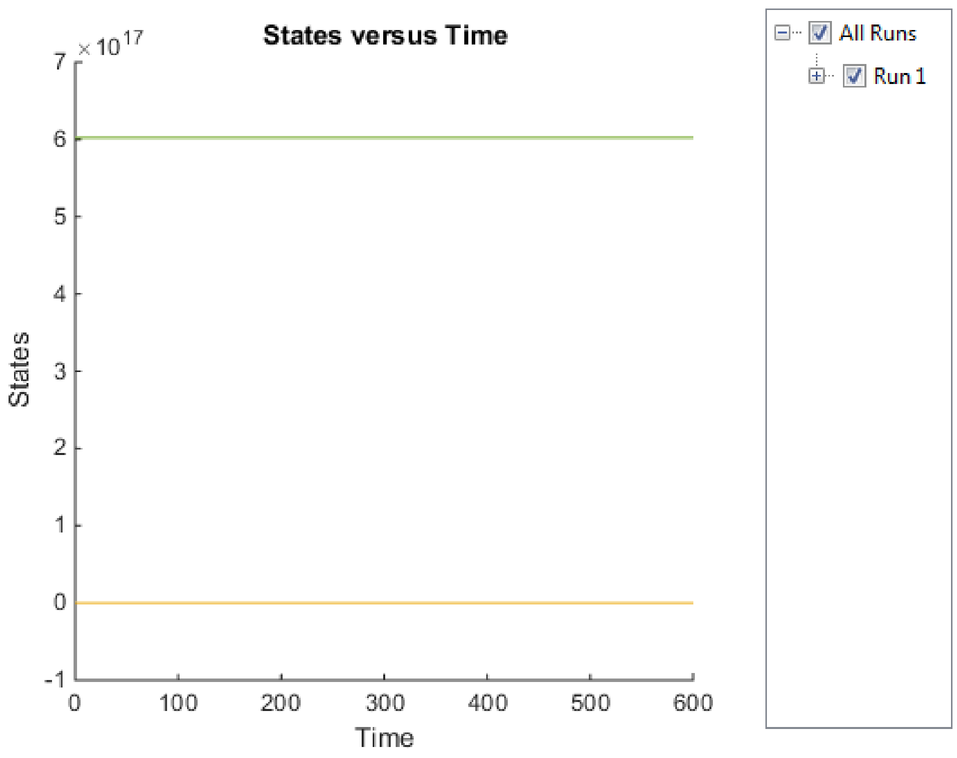
Simulate the Modified Model

1. Configure the simulation settings (`configset object`) for the `m1` model object to log all states during the simulation.

   ```
   cs = getconfigset(m1);
   cs.RuntimeOptions.StatesToLog = 'all';
   ```
2. Simulate the model.

   ```
   simDataObj = sbiosimulate(m1);
   ```
3. Plot the results.

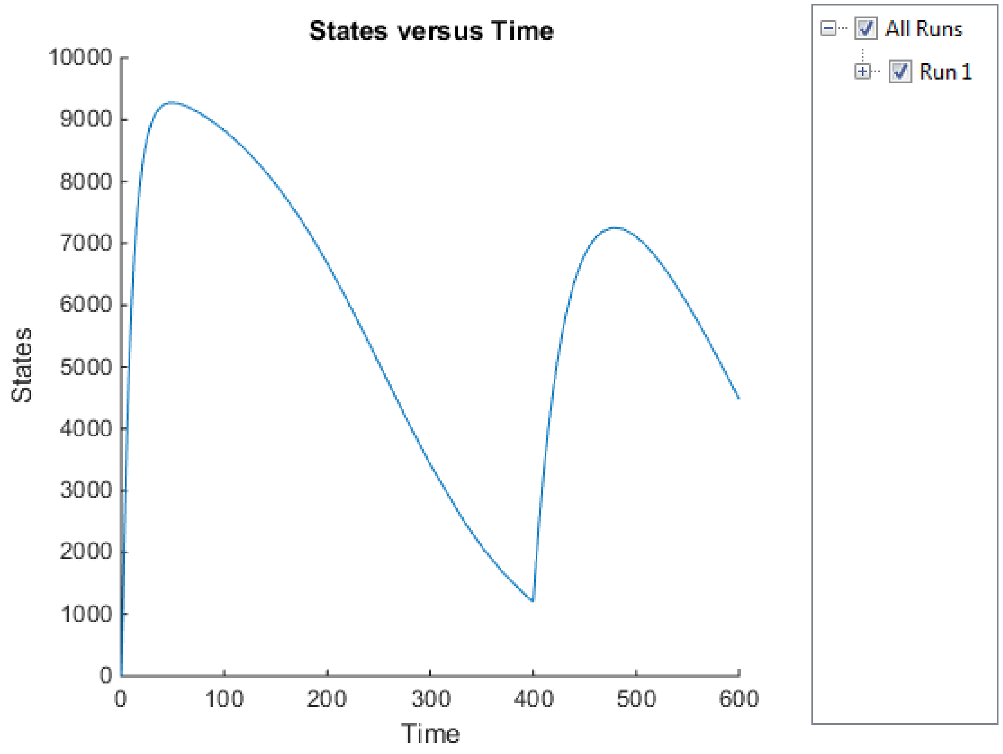
   ```
   sbioplot(simDataObj);
   ```



The plot does not show the species of interest due to the wide range in species amounts/concentrations.

4 Plot only the species of interest. `Ga`.

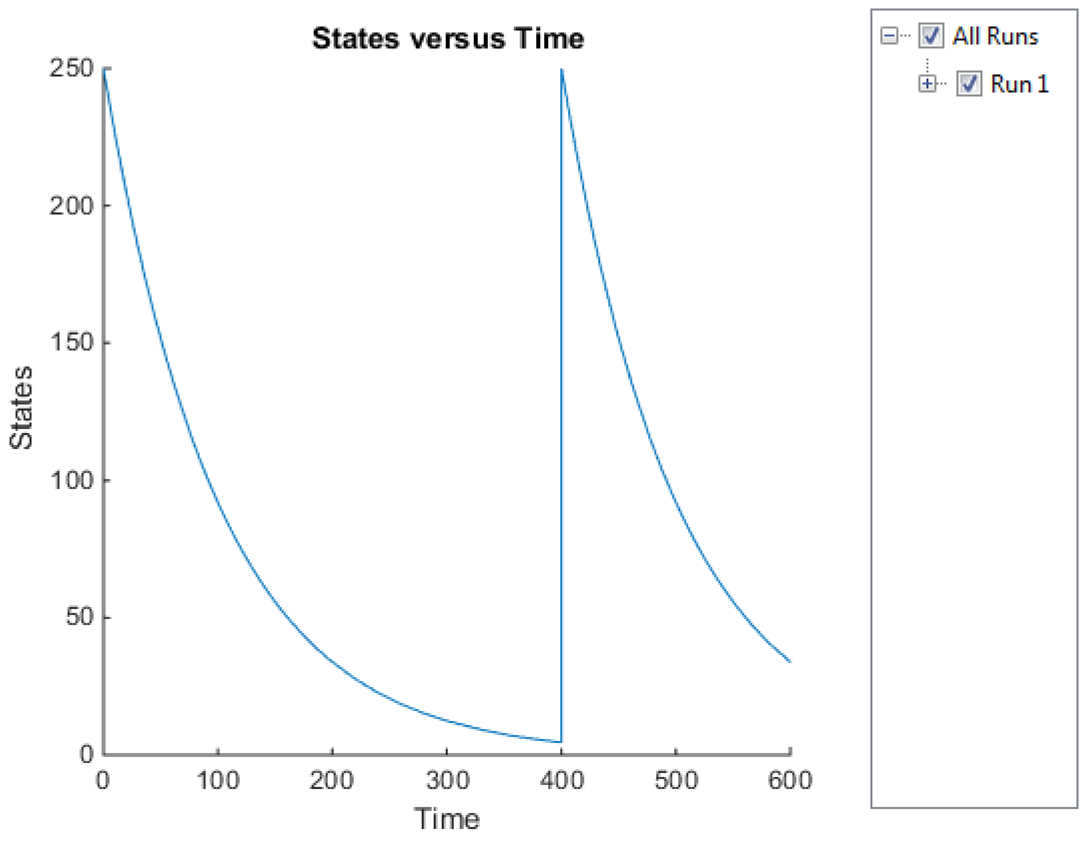
```
GaSimDataObj = selectbyname(simDataObj,'Ga');
sbioplot(GaSimDataObj);
```



Notice the change in the profile of species `Ga` at time = `400` seconds (simulation time). This is the time when the inhibitor amount is changed to reflect the re-addition of inhibitor to the model.

5 Plot only the inhibitor (`Inhib` species).

```
InhibSimDataObj = selectbyname(simDataObj,'Inhib');
sbioplot(InhibSimDataObj)
```



See Also

`addpath` | `cd` | `function`

More About

- "Change Folders on the Search Path"

View Model Equations

You can view the system of equations that SimBiology creates when you build a model using reactions, rules, events, variants, and doses. Viewing model equations is useful for:

- Publishing purposes
- Model debugging

For details, see the getequations method of a `Model` object.

Structural Analysis

Overview of Structural Analysis

Structural analyses let you verify and investigate the structure of your model and its quantities and expressions before actually simulating the model. These static inspections help you to:

- Confirm the model is ready for simulation.
- Better understand the relationships between quantities and expressions in the model.

For more information, see:

- "Model Verification" on page 2-3
- "Conserved Moiety Determination" on page 2-6
- "Determining the Adjacency Matrix for a Model" on page 2-12
- "Determining the Stoichiometry Matrix for a Model" on page 2-14

Model Verification

In this section...

What is Model Verification?

SimBiology has functionality that helps you find and fix warnings that you might need to be aware of, and errors that would prevent you from simulating and analyzing your model.

Model verification checks many aspects of the model including:

- Model structure
- Validity of mathematical expressions
- Dimensional analysis
- Unit conversion issues

When to Verify a Model

You can check your model for warnings and errors at any time when constructing or working with your model. For example:

- Verify your model during construction to ensure that the model is complete.
- Verify the model after changing simulation settings, dimensional analysis settings, or unit conversion settings.

Analyses such as simulation, scanning, and parameter fitting automatically verify a model.

Tip Repeatedly running a task using a different variant or setting a different value for the `InitialAmount` property of a species, the `Capacity` property of a compartment, or the `Value` property of a parameter, generates warnings only the first time you simulate a model. Use the verification functionality described in this section to display warnings again.

Verifying That a Model Has No Warnings or Errors

Use the `verify` method to see a list of warnings and errors in your model.

Use the `sbiolastwarning` and `sbiolasterror` functions to return the last warning and last error encountered during verification.

More About

For an example of verifying a model, see "Verifying a Model" on page 2-5.

Verifying a Model

1 Create a model with a reaction that references K1, an undefined parameter:

```
% Create a model named example
model = sbiomodel('example');
% Add a compartment named cell to model
compartment = addcompartment(model, 'cell');
% Add two species, A and B, to the cell compartment
species_1 = addspecies(compartment, 'A');
species_2 = addspecies(compartment, 'B');
% Add the reaction A -> B to the model
reaction = addreaction(model, 'A -> B', 'ReactionRate', 'K1');
```

2 Verify the model to check for warnings and errors:

```
verify(model)
```

```
??? --> Error reported from Expression Validation:
The name 'K1' in reaction 'A -> B' does not refer to any in-scope species,
parameters, or compartments.
```

3 Address the error by defining the parameter K1:

```
% Add a parameter, K1, to the model with a value of 3
parameter = addparameter(model, 'K1', 3);
```

4 Verify the model again:

```
verify(model)
```

Conserved Moiety Determination

In this section...

Introduction to Moiety Conservation

Conserved moieties represent quantities that are conserved in a system, regardless of the individual reaction rates.

Consider this simple network:

```
reaction 1: A -> B
reaction 2: B -> C
reaction 3: C -> A
```

Regardless of the rates of reactions 1, 2, and 3, the quantity `A + B + C` is conserved throughout the dynamic evolution of the system. This conservation is termed structural because it depends only on the structure of the network, rather than on details such as the kinetics of the reactions involved. In the context of systems biology, such a conserved quantity is sometimes referred to as a conserved moiety. A typical, real-world example of a conserved moiety is adenine in its various forms ATP, ADP, AMP, etc. Finding and analyzing conserved moieties can yield insights into the structure and function of a biological network. In addition, for the quantitative modeler, conserved moieties represent dependencies that can be removed to reduce a system's dimensionality, or number of dynamic variables. In the previous simple network, in principle, it is only necessary to calculate the time courses for `A` and `B`. After this is done, `C` is fixed by the conservation relation.

Algorithms for Conserved Cycle Calculations

The `sbioconsmoiety` function analyzes conservation relationships in a model by calculating a complete set of linear conservation relations for the species in the model object.

`sbioconsmoiety` lets you specify one of three algorithms based on the nature of the model and the required results:

- `'qr'` — `sbioconsmoiety` uses an algorithm based on `QR` factorization. From a numerical standpoint, this is the most efficient and reliable approach.
- `'rreduce'` — `sbioconsmoiety` uses an algorithm based on row reduction, which yields better numbers for smaller models. This is the default.
- `'semipos'` — `sbioconsmoiety` returns conservation relations in which all the coefficients are greater than or equal to zero, permitting a more transparent interpretation in terms of physical quantities.

For larger models, the `QR`-based method is recommended. For smaller models, row reduction or the semipositive algorithm may be preferable. For row reduction and `QR` factorization, the number of conservation relations returned equals the row rank degeneracy of the model object's stoichiometry matrix. The semipositive algorithm can return a different number of relations. Mathematically speaking, this algorithm returns a generating set of vectors for the space of semipositive conservation relations.

In some situations, you may be interested in the dimensional reduction of your model via conservation relations. Recall the simple model, presented in “Introduction to Moiety Conservation” on page 2-6, that contained the conserved cycle `A + B + C`. Given `A` and `B`, `C` is determined by the conservation relation; the system can be thought of as having only two dynamic variables rather than three. The `'link'` algorithm specification caters to this situation. In this case, `sbioconsmoiety` partitions the species in the model into independent and dependent sets and calculates the dependence of the dependent species on the independent species.

Consider a general system with an `n`-by-`m` stoichiometry matrix `N` of rank `k`, and suppose that the rows of `N` are permuted (which is equivalent to permuting the species ordering) so that the first `k` rows are linearly independent. The last `n – k` rows are then necessarily dependent on the first `k` rows.

The matrix `N` can be split into the following independent and dependent parts,

$$\mathrm{N} = \begin{pmatrix} N_R \\ N_D \end{pmatrix}$$

where `R` in the independent submatrix N_R denotes 'reduced'; the (`n – k`)-by-`k` link matrix `LO` is defined so that $N_D = LO * N_R$. In other words, the link matrix gives the dependent rows N_D of the stoichiometry matrix, in terms of the independent rows N_R. Because each row in the stoichiometry matrix corresponds to a species in the model, each row of the link matrix encodes how one dependent species is determined by the `k` independent species.

More About

For examples of determining conserved moieties, see:

- "Determining Conserved Moieties" on page 2-9
- Finding Conserved Quantities in a Pathway Model

Determining Conserved Moieties

1 Load the Goldbeter Mitotic Oscillator project, which includes the variable `m1`, a model object:

```
sbioloadproject Goldbeter_Mitotic_Oscillator_with_reactions
```

The `m1` model object appears in the MATLAB Workspace.

2 Display the species information:

```
m1.Compartments.Species

SimBiology Species Array

Index:  Compartment:  Name:  InitialAmount:  InitialAmountUnits:
 1       unnamed       C        0.01
 2       unnamed       M        0.01
 3       unnamed       Mplus    0.99
 4       unnamed       Mt       1
 5       unnamed       X        0.01
 6       unnamed       Xplus    0.99
 7       unnamed       Xt       1
 8       unnamed       V1       0
 9       unnamed       V3       0
 10      unnamed       AA       0
```

3 Display the reaction information:

```
m1.Reactions

SimBiology Reaction Array

   Index:    Reaction:
   1         AA -> C
   2         C -> AA
   3         C + X -> AA + X
   4         Mplus + C -> M + C
   5         M -> Mplus
   6         Xplus + M -> X + M
   7         X -> Xplus
```

4 Use the simplest form of the `sbioconsmoiety` function and display the results. The default call to `sbioconsmoiety`, in which no algorithm is specified, uses an algorithm based on row reduction.

```
[g sp] = sbioconsmoiety(m1)

g =

     0     1     1     0     0     0
     0     0     0     1     1     0
     0     0     0     0     0     1


sp =

    'C'
    'M'
    'Mplus'
    'X'
    'Xplus'
    'AA'
```

The columns in `g` are labeled by the species `sp`. Thus the first row describes the conserved relationship, `M + Mplus`. Notice that the third row indicates that the species AA is conserved, which is because AA is constant (`ConstantAmount = 1`).

5 Call `sbioconsmoiety` again, this time specifying the semipositive algorithm to explore conservation relations in the model. Also specify to return the conserved moieties in a cell array of strings, instead of a matrix.

```
cons_rel = sbioconsmoiety(m1,'semipos','p')

cons_rel =

    'AA'
    'X + Xplus'
    'M + Mplus'
```

6 Use the `'link'` option to study the dependent and independent species.

```
[SI,SD,L0,NR,ND] = sbioconsmoiety(m1, 'link');
```

7 Show the list of independent species:

```
SI

SI =

    'C'
    'M'
    'X'
```

8 Show the list of dependent species:

```
SD

SD =

    'Mplus'
    'Xplus'
    'AA'
```

9 Show the link matrix relating `SD` and `SI` by converting the `L0` output from a sparse matrix to a full matrix:

```
L0_full = full(L0)

L0_full =

         0   -1.0000         0
         0         0   -1.0000
         0         0         0
```

10 Show the independent stoichiometry matrix, N_R by converting the `NR` output from a sparse matrix to a full matrix:

```
NR_full = full(NR)

NR_full =

     1    -1    -1     0     0     0     0
     0     0     0     1    -1     0     0
     0     0     0     0     0     1    -1
```

11 Show the dependent stoichiometry matrix, N_D by converting the `ND` output from a sparse matrix to a full matrix:

```
ND_full = full(ND)

ND_full =

     0     0     0    -1     1     0     0
     0     0     0     0     0    -1     1
     0     0     0     0     0     0     0
```

Determining the Adjacency Matrix for a Model

In this section...

What Is an Adjacency Matrix?

An *adjacency matrix* lets you easily determine:

- The reactants and products in a specific reaction in a model
- The reactions that a specific species is part of, and whether the species is a reactant or product in that reaction

An adjacency matrix is an *N*-by-*N* matrix, where *N* equals the total number of species and reactions in a model. Each row corresponds to a species or reaction, and each column corresponds to a species or reaction.

The matrix indicates which species and reactions are involved as reactants and products:

- Reactants are represented in the matrix with a `1` at the appropriate location (row of species, column of reaction). Reactants appear above the diagonal.
- Products are represented in the matrix with a `1` at the appropriate location (row of reaction, column of species). Products appear below the diagonal.
- All other locations in the matrix contain a `0`.

For example, if a `model object` contains one reaction equal to `A + B -> C` and the `Name` property of the reaction is `R1`, the adjacency matrix is:

```
        A      B      C      R1
A       0      0      0      1
B       0      0      0      1
C       0      0      0      0
R1      0      0      1      0
```

Retrieving an Adjacency Matrix for a Model

Retrieve an adjacency matrix for a model by passing the `model object` as an input argument to the `getadjacencymatrix` method.

1 Read in `m1`, a model object, using `sbmlimport`:

```
m1 = sbmlimport('lotka.xml');
```

2 Get the adjacency matrix for `m1`:

```
[M, Headings] = getadjacencymatrix(m1)

M =

   (5,1)        1
   (5,2)        1
   (6,3)        1
   (7,4)        1
   (1,5)        1
   (2,5)        1
   (2,6)        1
   (3,6)        1
   (3,7)        1


Headings =

    'x'
    'y1'
    'y2'
    'z'
    'Reaction1'
    'Reaction2'
    'Reaction3'
```

3 Convert the adjacency matrix from a sparse matrix to a full matrix to more easily see the relationships between species and reactions:

```
M_full = full(M)

M_full =

     0     0     0     0     1     0     0
     0     0     0     0     1     1     0
     0     0     0     0     0     1     1
     0     0     0     0     0     0     0
     1     1     0     0     0     0     0
     0     0     1     0     0     0     0
     0     0     0     1     0     0     0
```

Determining the Stoichiometry Matrix for a Model

In this section...
"What Is a Stoichiometry Matrix?" on page 2-14
"Retrieving a Stoichiometry Matrix for a Model" on page 2-15

What Is a Stoichiometry Matrix?

A *stoichiometry matrix* lets you easily determine:

- The reactants and products in a specific reaction in a model, including the stoichiometric value of the reactants and products
- The reactions that a specific species is part of, and whether the species is a reactant or product in that reaction

A stoichiometry matrix is an *M*-by-*R* matrix, where *M* equals the total number of species in a model, and *R* equals the total number of reactions in a model. Each row corresponds to a species, and each column corresponds to a reaction.

The matrix indicates which species and reactions are involved as reactants and products:

- Reactants are represented in the matrix with their stoichiometric value at the appropriate location (row of species, column of reaction). Reactants appear as negative values.
- Products are represented in the matrix with their stoichiometric value at the appropriate location (row of species, column of reaction). Products appear as positive values.
- All other locations in the matrix contain a `0`.

For example, consider a `model object` containing two reactions. One reaction (named `R1`) is equal to `2 A + B -> 3 C`, and the other reaction (named `R2`) is equal to `B + 3 D -> 4 A`. The stoichiometry matrix is:

```
        R1   R2
A       -2    4
B       -1   -1
C        3    0
D        0   -3
```

Retrieving a Stoichiometry Matrix for a Model

Retrieve a stoichiometry matrix for a model by passing the `model object` as an input argument to the `getstoichmatrix` method.

1 Read in `m1`, a model object, using `sbmlimport`:

```
m1 = sbmlimport('lotka.xml');
```

2 Get the stoichiometry matrix for `m1`:

```
[M,objSpecies,objReactions] = getstoichmatrix(m1)

M =

   (2,1)        1
   (2,2)       -1
   (3,2)        1
   (3,3)       -1
   (4,3)        1


objSpecies =

    'x'
    'y1'
    'y2'
    'z'


objReactions =

    'Reaction1'
    'Reaction2'
    'Reaction3'
```

3 Convert the stoichiometry matrix from a sparse matrix to a full matrix to more easily see the relationships between species and reactions:

```
M_full = full(M)

M_full =

     0     0     0
     1    -1     0
     0     1    -1
     0     0     1
```

Selecting Absolute Tolerance and Relative Tolerance for Simulation

In this section...
"Algorithm" on page 2-17
"Absolute Tolerance Scaling" on page 2-18

SimBiology uses `AbsoluteTolerance` and `RelativeTolerance` to control the accuracy of integration during simulation. Specifically, `AbsoluteTolerance` is used to control the largest allowable absolute error at any step during simulation. It controls the error when a solution is small. Intuitively, when the solution approaches 0, `AbsoluteTolerance` is the threshold below which you do not worry about the accuracy of the solution since it is effectively 0. `RelativeTolerance` controls the relative error of a single step of the integrator. Intuitively, it controls the number of significant digits in a solution, except when it is smaller than the absolute tolerance, and $-\log_{10}(RelativeTolerance)$ is the number of correct digits.

Algorithm

At each simulation step `i`, the solver estimates the local error `e` in the state `j` of the simulation. The solver reduces the size of time step `i` until the error of the state satisfies:

$$\left|e(i,j)\right| \le \max\left(RelativeTolerance * \left|y(i,j)\right|, AbsoluteTolerance(i,j)\right)$$

Thus at state values of larger magnitude, the accuracy is determined by `RelativeTolerance`. As the state values approach zero, the accuracy is controlled by `AbsoluteTolerance`.

The correct choice of values for `RelativeTolerance` and `AbsoluteTolerance` varies depending on the problem. The default values may work for first trials of the simulation. As you adjust the tolerances, consider that there are trade-offs between speed and accuracy:

- If the simulation takes too long, you can increase (or loosen) the values of `RelativeTolerance` and `AbsoluteTolerance` at the cost of some accuracy.
- If the results seem inaccurate, you can decrease (or tighten) the relative tolerance values by dividing with 10^N, where N is a real positive number. But this tends to slow down the solver.

- If the magnitude of the state values is high, you can decrease the relative tolerance to get more accurate results.

Absolute Tolerance Scaling

How SimBiology uses `AbsoluteTolerance` to determine the error depends on whether the `AbsoluteToleranceScaling` property is enabled. By default, `AbsoluteToleranceScaling` is enabled which means each state has its own absolute tolerance that may increase over the course of simulation:

$$AbsoluteTolerance(i, j) = CSAbsTol * Scale(i, j)$$

`CSAbsTol` is the `AbsoluteTolerance` property defined in `SolverOptions` of the active configuration set object.

For a state that has a nonzero initial value, the scale is the maximum magnitude over the state, as seen over the simulation thus far:

$$Scale(i, j) = \max\left(\left|y(1 : i, j)\right|\right)$$

For a state that has an initial value of zero, the scale is estimated as the state value after taking a trial step of size `AbsoluteToleranceStepSize` using the Euler method. Let us call this value `ye(j)`. Then:

$$Scale(i, j) = \max\left(\left|\left[ye(j); y(2 : i, j)\right]\right|\right)$$

If an initial state is zero and has no dynamic at time = 0, then:

$$AbsoluteTolerance(i, j) = CSAbsTol$$

Doses, events, and initial assignment rules at simulation time = 0 are not considered when calculating absolute tolerance scaling.

More About

- “Model Simulation” on page 3-3
- “Choosing a Simulation Solver” on page 3-5
- “Ordinary Differential Equations”

Simulation and Analysis

Simulation and Analysis

After creating models in SimBiology, you can simulate and analyze them.

Typical Workflow

To simulate a model, SimBiology:

1. Converts the model expressions and quantities to a system of differential equations.
2. Uses deterministic or stochastic solvers to numerically solve these equations.
3. Determines the changes in species amounts and parameter values over time.

For more information, see “Model Simulation” on page 3-3.

SimBiology also lets you analyze models. These analyses include a basic simulation of the model as well as additional evaluations such as:

- “Sensitivity Calculation” on page 3-21
- “Perform a Parameter Scan” on page 3-34
- Parameter estimation using “Nonlinear Regression” on page 3-48 and “Nonlinear Mixed-Effects Modeling” on page 3-38

Model Simulation

In this section...

Simulating a Model

Simulate a model by providing the `model object` as an input argument to the `sbiosimulate` function.

When you simulate a model, you can return results (time points, state data, and state names) in two forms:

- Three separate arrays
- One `SimData object`

A `SimData object` also includes metadata such as the types and names for the logged states, the configuration set used during simulation, and the date of the simulation. It is a convenient way of keeping time data, state data, and associated metadata together. A `SimData object` has associated properties and methods, which you can use to access and manipulate the data.

For more information on simulating a model, see "Simulate the Yeast Heterotrimeric G Protein Cycle" on page 3-16.

Plotting Simulation Results

If you return time and state data from a simulation in three output arguments, you can use these arguments as inputs to the `plot` function to view your results. For more information, see `sbiosimulate`.

If you return time and state data from a simulation in a `SimData object`, you can use the `SimData object` as an input to the `sbioplot` function to view your results.

For more information on plotting simulation results, see "Simulate the Yeast Heterotrimeric G Protein Cycle" on page 3-16.

Interpreting Simulation Results

After running a simulation, you may see negative amounts or concentrations for species in the results plot or data array. These negative values can be either:

- Slightly negative due to numerical noise introduced by the simulation process. In this case, you can interpret these values as `0`.
- Significantly negative due to the dynamics in your model not being physical, that is, the dynamics in the system are driving a particular species to be negative. In this case, examine your reaction rate expressions to ensure they implement correct dynamics.

Configuring Stop Time and Other Simulation Settings

A model has a configuration set (`Configset object`) associated with it to control the simulation. You can edit the properties of a `Configset object` to control all aspects of the simulation, including:

- Stop time (`StopTime`, `MaximumNumberOfLogs`, and `MaximumWallClock` properties)
- Time units (`TimeUnits` property)
- Solver and error tolerances (`SolverType` and `SolverOptions` properties)
- Maximum time step size (`MaxStep` property)
- Data to record (`RuntimeOptions` property)
- Frequency of data recording (`OutputTimes` and `LogDecimation` properties)
- Sensitivity analysis (`SensitivityAnalysisOptions` and `SolverOptions` properties)

- Dimensional analysis and unit conversion (`CompileOptions` property)

To view the `Configset object`, provide the `model object` as an input argument to the `getconfigset` method.

To edit the properties of a `Configset object`, use the `set` method.

For more information on viewing and editing the stop time and other simulation settings, see "Simulate the Yeast Heterotrimeric G Protein Cycle" on page 3-16.

Choosing a Simulation Solver

To simulate a model, the SimBiology software converts a model to a system of differential equations. It then uses a solver function to compute solutions for these equations at different time intervals, giving the model's states and outputs over a span of time.

Available solvers are:

- **ODE Solvers** — These include Nonstiff Deterministic Solvers and Stiff Deterministic Solvers. The solver functions implement numerical integration methods for solving initial value problems for ordinary differential equations (ODEs). Beginning at the initial time with initial conditions, they step through the time interval, computing a solution at each time step. If the solution for a time step satisfies the solver's error tolerance criteria, it is a successful step. Otherwise, it is a failed attempt; the solver shrinks the step size and tries again. For more information, see "ODE Solvers" in the MATLAB Mathematics documentation.
- **SUNDIALS Solvers** — At a fundamental level the core algorithms for the SUNDIALS solvers are similar to those for some of the solvers in the MATLAB ODE suite and work as described above in ODE Solvers. For more information, see "SUNDIALS Solvers" on page 3-5.
- **Stochastic Solvers** — Use with models containing a small number of molecules. Stochastic solvers include stochastic simulation algorithm, explicit tau-leaping algorithm, and implicit tau-leaping algorithm. For more information, see "Stochastic Solvers" on page 3-6.

SUNDIALS Solvers

SUNDIALS (Suite of Nonlinear and Differential/Algebraic Equation Solvers) are part of a freely available third-party package developed at Lawrence Livermore National

Laboratory. All other ODE solvers used for simulation of SimBiology models, such as `ode45` and `ode15s`, are part of the MATLAB ODE suite.

When you specify `sundials` for the solver, the software chooses one of two SUNDIALS solvers, CVODE or IDA, as appropriate for your model:

- **CVODE** is a solver for systems of ODEs, both nonstiff and stiff. This is used when a model has no algebraic rules.
- **IDA** is a differential-algebraic equation (DAE) solver, used when one or more algebraic rules are present.

For more information on the SUNDIALS solvers, see `http://www.llnl.gov/casc/sundials/description/description.html`.

Stochastic Solvers

When to Use Stochastic Solvers

The stochastic simulation algorithms provide a practical method for simulating reactions that are stochastic in nature. Models with a small number of molecules can realistically be simulated stochastically, that is, allowing the results to contain an element of probability, unlike a deterministic solution.

Model Prerequisites for Simulating with a Stochastic Solver

Model prerequisites include:

- All reactions in the model must have their `KineticLaw` property set to `MassAction`.
- If your model contains events, you can simulate using the stochastic `ssa` solver. Other stochastic solvers do not support events.

- Your model must not contain doses. No stochastic solvers support doses.

Additionally, if you perform an individual or population fitting on a model whose `configset object` specifies a stochastic solver and options, be aware that during the fitting SimBiology temporarily changes:

- `SolverType` property to the default solver of `ode15s`
- `SolverOptions` property to the options last configured for a deterministic solver

What Happens During a Stochastic Simulation?

During a stochastic simulation of a model, the software ignores any rate, assignment, or algebraic rules if present in the model. Depending on the model, stochastic simulations can require more computation time than deterministic simulations.

Tip When simulating a model using a stochastic solver, you can increase the `LogDecimation` property of the `configset object` to record fewer data points and decrease run time.

Stochastic Simulation Algorithm (SSA)

The Chemical Master Equation (CME) describes the dynamics of a chemical system in terms of the time evolution of probability distributions. Directly solving for this distribution is impractical for most realistic problems. The stochastic simulation algorithm (SSA) instead efficiently generates individual simulations that are consistent with the CME, by simulating each reaction using its propensity function. Thus, analyzing multiple stochastic simulations to determine the probability distribution is more efficient than directly solving the CME.

Advantage

- This algorithm is exact.

Disadvantages

- Because this algorithm evaluates one reaction at a time, it might be too slow for models with a large number of reactions.
- If the number of molecules of any reactants is huge, it might take a long time to complete the simulation.

Explicit Tau-Leaping Algorithm

Because the stochastic simulation algorithm might be too slow for many practical problems, this algorithm was designed to speed up the simulation at the cost of some accuracy. The algorithm treats each reaction as being independent of the others. It automatically chooses a time interval such that the relative change in the propensity function for each reaction is less than your error tolerance. After selecting the time interval, the algorithm computes the number of times each reaction occurs during the time interval and makes the appropriate changes to the concentration of various chemical species involved.

Advantages

- This algorithm can be orders of magnitude faster than the SSA.
- You can use this algorithm for large problems (if the problem is not numerically stiff).

Disadvantages

- This algorithm sacrifices some accuracy for speed.
- This algorithm is not good for stiff models.
- You need to specify the error tolerance so that the resulting time steps are of the order of the fastest time scale.

Implicit Tau-Leaping Algorithm

Like the explicit tau-leaping algorithm, the implicit tau-leaping algorithm is also an approximate method of simulation designed to speed up the simulation at the cost of some accuracy. It can handle numerically stiff problems better than the explicit tau-leaping algorithm. For deterministic systems, a problem is said to be numerically stiff if there are “fast” and “slow” time scales present in the system. For such problems, the explicit tau-leaping method performs well only if it continues to take small time steps that are of the order of the fastest time scale. The implicit tau-leaping method can potentially take much larger steps and still be stable. The algorithm treats each reaction as being independent of others. It automatically selects a time interval such that the relative change in the propensity function for each reaction is less than the user-specified error tolerance. After selecting a time interval, the algorithm computes the number of times each reaction occurs during the time interval and makes the appropriate changes to the concentration of various chemical species involved.

Advantages

- This algorithm can be much faster than the SSA. It is also usually faster than the explicit tau-leaping algorithm.
- You can use this algorithm for large problems and also for numerically stiff problems.
- The total number of steps taken is usually less than the explicit-tau-leaping algorithm.

Disadvantages

- This algorithm sacrifices some accuracy for speed.
- There is a higher computational burden for each step as compared to the explicit tau-leaping algorithm. This leads to a larger CPU time per step.
- This method often dampens perturbations of the slow manifold leading to a reduced state variance about the mean.

More About

- “Ensemble Runs of Stochastic Simulations” on page 3-10
- Analysis of Stochastic Ensemble Data in SimBiology example

References

[1] Gibson M.A., Bruck J. (2000), “Exact Stochastic Simulation of Chemical Systems with Many Species and Many Channels,” Journal of Physical Chemistry, 105:1876–1899.

[2] Gillespie D. (1977), “Exact Stochastic Simulation of Coupled Chemical Reactions,” The Journal of Physical Chemistry, 81(25): 2340–2361.

[3] Gillespie D. (2000), “The Chemical Langevin Equation,” Journal of Chemical Physics, 113(1): 297–306.

[4] Gillespie D. (2001), “Approximate Accelerated Stochastic Simulation of Chemically Reacting Systems,” Journal of Chemical Physics,115(4):1716–1733.

[5] Gillespie D., Petzold L. (2004), “Improved Leap-Size Selection for Accelerated Stochastic Simulation,” Journal of Chemical Physics, 119:8229–8234

[6] Rathinam M., Petzold L., Cao Y., Gillespie D. (2003), “Stiffness in Stochastic Chemically Reacting Systems: The Implicit Tau-Leaping Method,” Journal of Chemical Physics, 119(24):12784–12794.

[7] Moler, C. (2003), “Stiff Differential Equations Stiffness is a subtle, difficult, and important concept in the numerical solution of ordinary differential equations,” MATLAB News & Notes.

Ensemble Runs of Stochastic Simulations

Because stochastic simulations rely on an element of probability, sequential runs produce different results. Therefore, multiple stochastic runs are needed to determine the probability distribution of the simulation results.

Ensemble runs perform multiple simulations of a model using a stochastic solver. They let you gather data from multiple stochastic runs of the model so you can compare and analyze fluctuations in the behavior of a model over repeated stochastic simulations.

Running Ensemble Simulations

The following functions let you perform and analyze ensemble runs at the command line:

- `sbioensemblerun` — Perform a stochastic ensemble run of the MATLAB model object.
- `sbioensembleplot` — Show a 2-D distribution plot or a 3-D shaded plot of the time varying distribution of one or more specified species.
- `sbioensemblestats` — Get mean and variance as a function of time for all the species in the model used to generate ensemble data by running `sbioensemblerun`.

See Also

For examples of simulating models, see:

- “Simulate the Yeast Heterotrimeric G Protein Cycle” on page 3-16
- Analysis of Stochastic Ensemble Data in SimBiology example

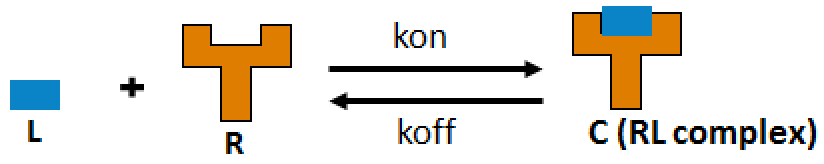
Create and Simulate a Simple Model

This example shows how to create and simulate a simple model of receptor-ligand kinetics using the SimBiology Desktop.

Receptor-Ligand Kinetics

In this model, ligand `L` and receptor `R` species form receptor-ligand complexes through reversible binding reactions. Using the mass action kinetics, the kinetic rate equation for the rate of change in concentration of receptor-ligand complex can be defined as

$\frac{dC}{dt} = k_{on} \cdot L \cdot R - k_{off} \cdot C$, where k_{on} and k_{off} are forward and reverse rate constants, `L`, `R`, and `C` are the concentrations of ligand, receptor, and receptor-ligand complex respectively. The objective of this simulation is to find the concentrations of all three species (`L`, `R`, and `C`) as the reaction progresses given initial amounts of species and rate constants.



Create a Model

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

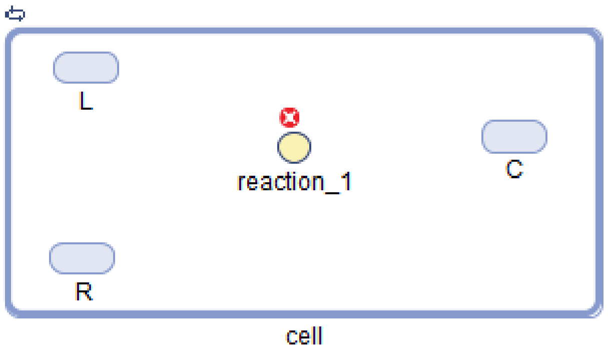
On the **Home** tab, select **Add Model** > **Create New Blank Model**. Name the model as `m1` when prompted.

Select **Open** > **Diagram** to open the diagram view.

Rename the compartment to `cell` by double-clicking the text `unnamed`.

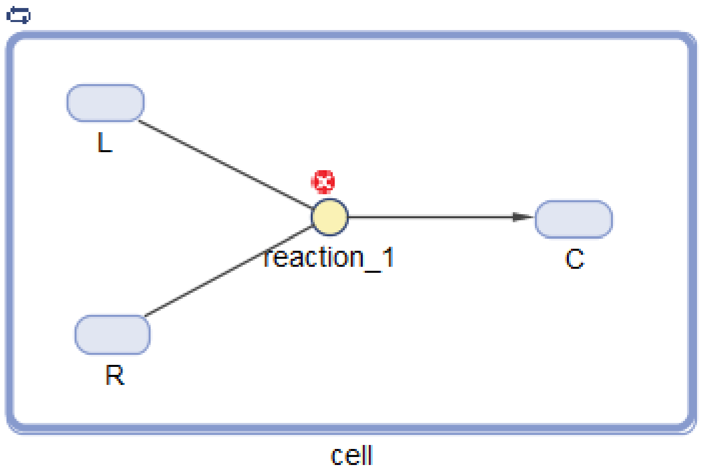
Drag and drop three species blocks species and one reaction block reaction inside the `cell` compartment.

Rename the species to `L` , `R`, and `C` as follows.



Connect the Species and Reaction Blocks

To connect the ligand species block to the reaction block, press and hold the **Ctrl** key (Windows® and Linux®) or the **Option** key (Macintosh®), click the `L` species block, and drag the line to `reaction_1`. Similarly connect `R` to `reaction_1` and `reaction_1` to `C`.



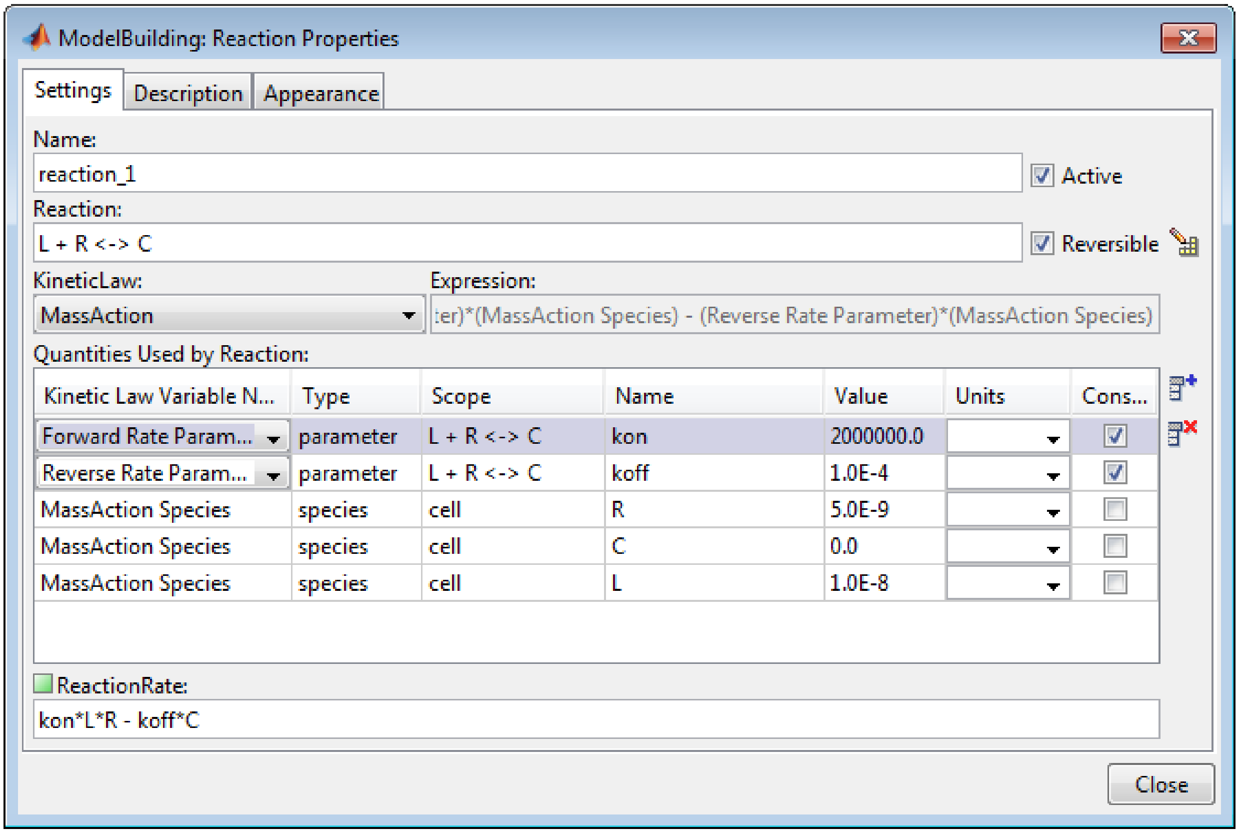
Update the Reaction Properties and Initial Amounts of the Reactant Species

Update the `reaction_1` properties to set the reaction as a reversible reaction, select mass action as kinetic law, and define the forward and reverse rate parameters:

- Double-click the `reaction_1` block to open the Reaction Properties dialog box.
- On the **Settings** tab, select **Reversible**.

- From **KineticLaw** drop-down list, select **MassAction**.
- Under **Quantities Used by Reaction**, enter `kon` as the name and `2.0E6` as the value for **Forward Rate Parameter**, and `koff` and `1E-4` for **Reverse Rate Parameter**.

Update the initial amounts of reactant species by entering `5E-9` and `1E-8` as `R` and `L` species values respectively. Click **Close**.



Name: reaction_1 ✓ Active

Reaction: L + R <-> C ✓ Reversible

KineticLaw: MassAction

Expression: ter)*(MassAction Species) - (Reverse Rate Parameter)*(MassAction Species)

Quantities Used by Reaction:

Kinetic Law Variable N...	Type	Scope	Name	Value	Units	Cons...
Forward Rate Param...	parameter	L + R <-> C	kon	2000000.0		✓
Reverse Rate Param...	parameter	L + R <-> C	koff	1.0E-4		✓
MassAction Species	species	cell	R	5.0E-9		
MassAction Species	species	cell	C	0.0		
MassAction Species	species	cell	L	1.0E-8		

ReactionRate: kon*L*R - koff*C

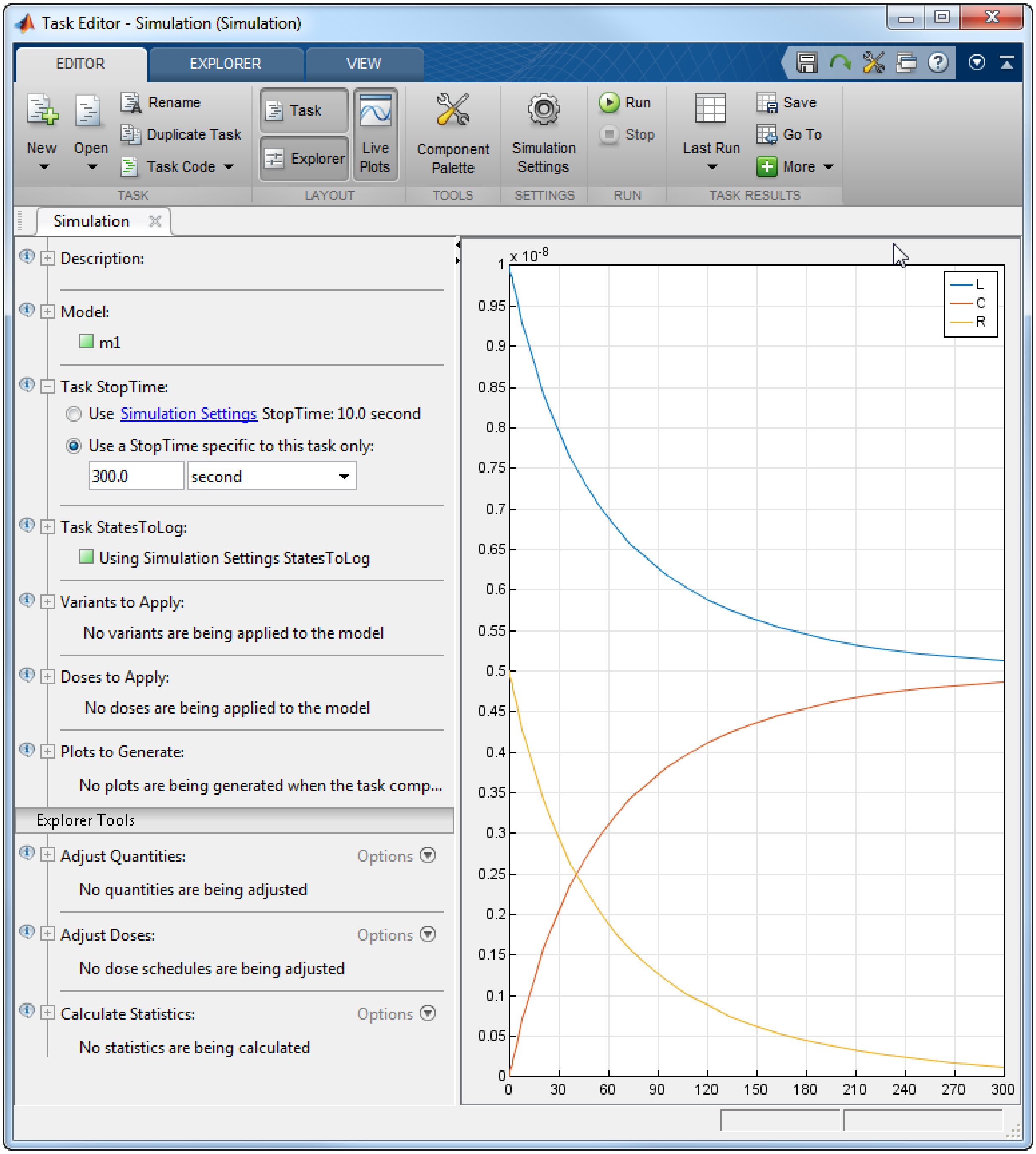
Add a Simulation Task

On the **Model** tab, select **Add Task > Simulate model**. This opens a new window called **Task Editor**, where you can edit and run the task. Given the previous initial amounts and rate parameters, the reaction reaches a saturated state after 300 seconds. Therefore, set the simulation stop time to 300 seconds instead of 10 seconds, which is the default stop time. To do so, expand the **Task Stop Time** section, select **Use a Stop Time specific to this task only**, and enter 300.

Simulate the Model

To simulate the model, click the **Run** button.

Once the simulation is finished, the Live Plots section shows the States versus Time plot for each species.



Description:

Model:

🟩 m1

Task StopTime:

Use Simulation Settings StopTime: 10.0 second

[✓ Use a StopTime specific to this task only:]

300.0 second

Task StatesToLog:

🟩 Using Simulation Settings StatesToLog

Variants to Apply:

No variants are being applied to the model

Doses to Apply:

No doses are being applied to the model

Plots to Generate:

No plots are being generated when the task comp...

Explorer Tools

Adjust Quantities: Options

No quantities are being adjusted

Adjust Doses: Options

No dose schedules are being adjusted

Calculate Statistics: Options

No statistics are being calculated

Simulate the Yeast Heterotrimeric G Protein Cycle

This example shows how to configure simulation settings, add an event to the model to trigger a time-based change, save, and plot the simulation results. This example uses the model described in "Model of the Yeast Heterotrimeric G Protein Cycle" on page C-17 to illustrate model simulation.

Load the `gprotein.sbproj` project, which includes the variable `m1`, a SimBiology model object.

```
sbioloadproject gprotein
```

Set the simulation solver to `ode15s` and set a stop time of `500` by editing the `SolverType` and `StopTime` properties of the `configset object` associated with the `m1` model.

```
csObj = getconfigset(m1);
csObj.SolverType = 'ode15s';
csObj.StopTime   = 500;
```

Specify to log simulation results of all species.

```
csObj.RuntimeOptions.StatesToLog = 'all';
```

Suppose the amount of the ligand species `L` is 0 at the start of the simulation, but it increases to a particular amount at time = 100. Use `sbioselect` to select the species named `L` and set its initial amount to 0. Use `addevent` to set up the desired event.

```
speciesObj = sbioselect(m1,'Type','species','Name','L');
speciesObj.InitialAmount = 0;
evt = addevent(m1,'time >= 100','L = 6.022E17');
```

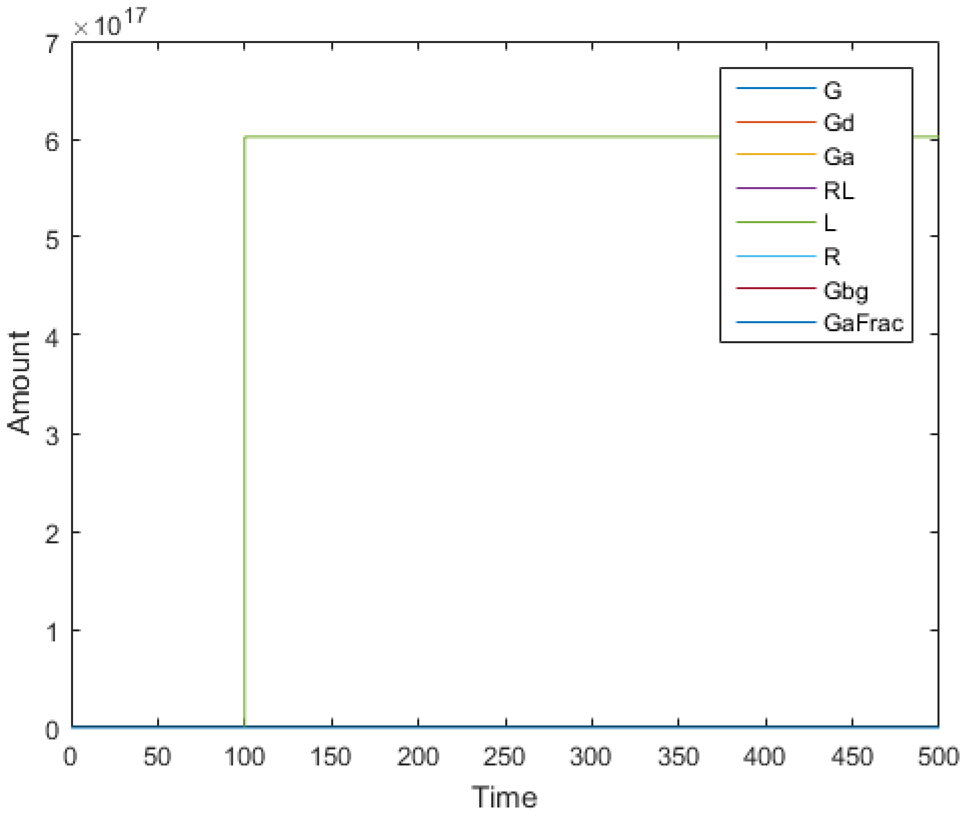
Simulate the model.

```
[t,x,names] = sbiosimulate(m1);
```

Simulate the simulation results. Notice that the species L amount increases when the event is triggered at simulation time 100. Changes in other species do not show up in the plot due to the wide range in species amounts.

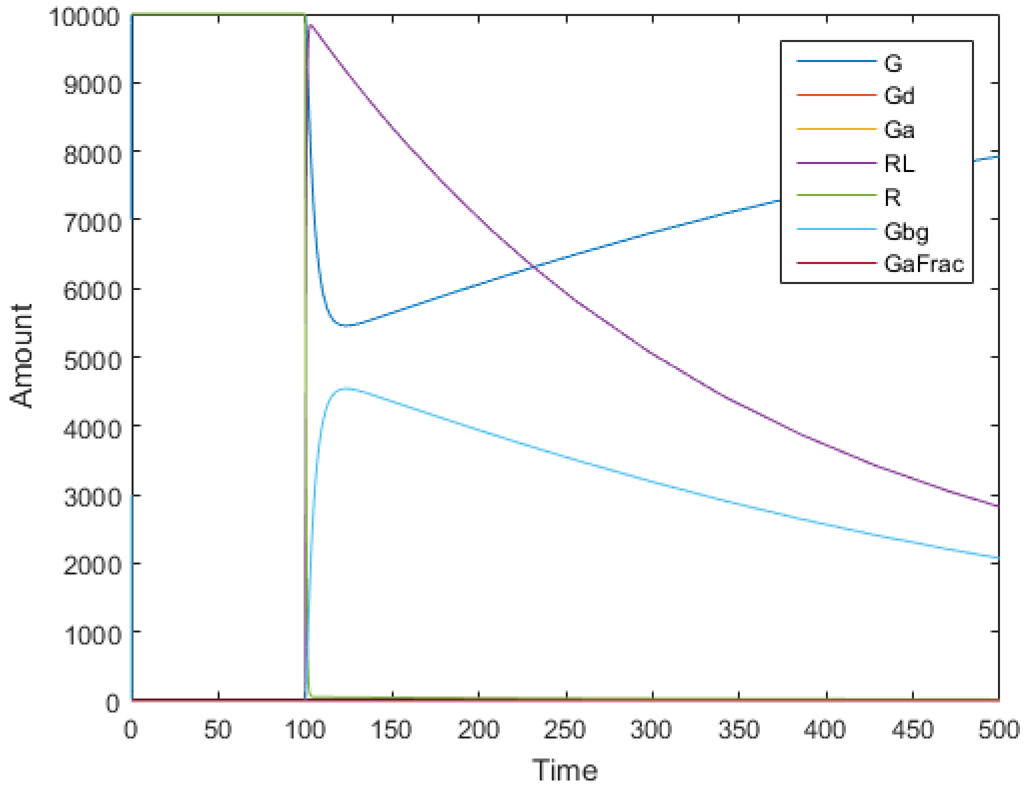
```
plot(t,x);
legend(names)
```

```
xlabel('Time');
ylabel('Amount');
```



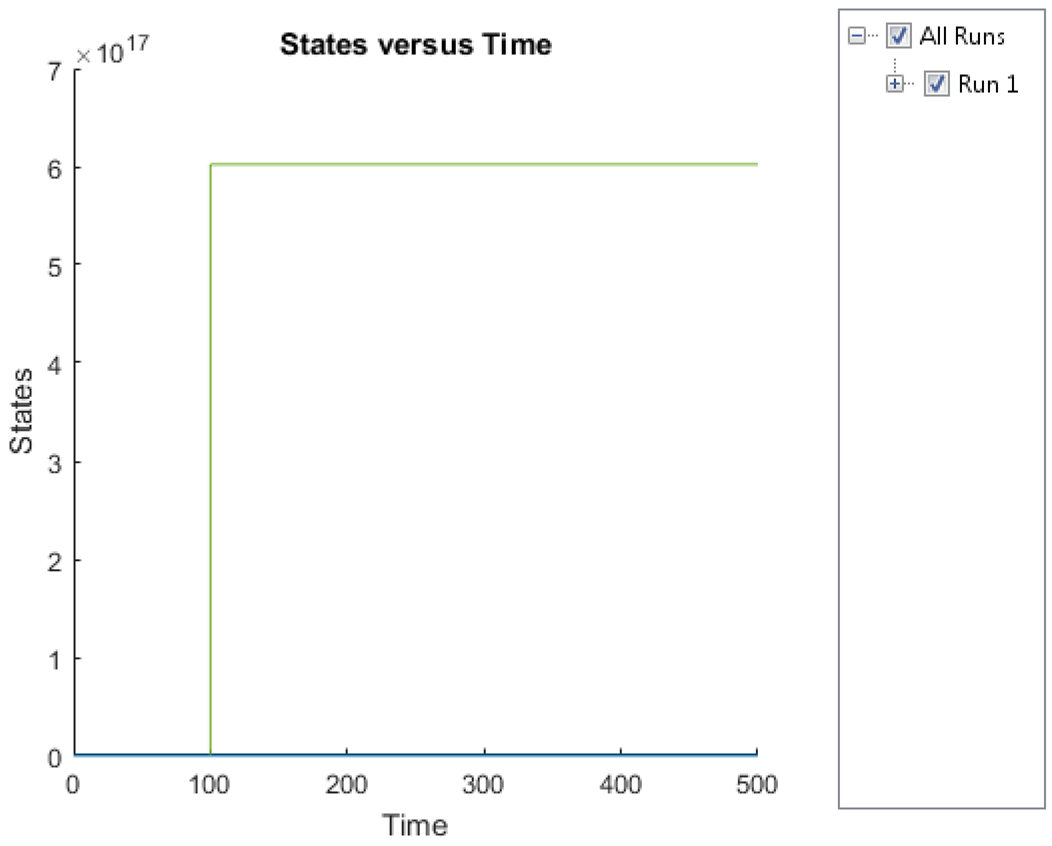
To see the changes of other species, plot without the species L (the 5th species) data.

```
figure
plot(t,x(:,[1:4 6:8]));
legend(names{[1:4 6:8]});
xlabel('Time');
ylabel('Amount');
```



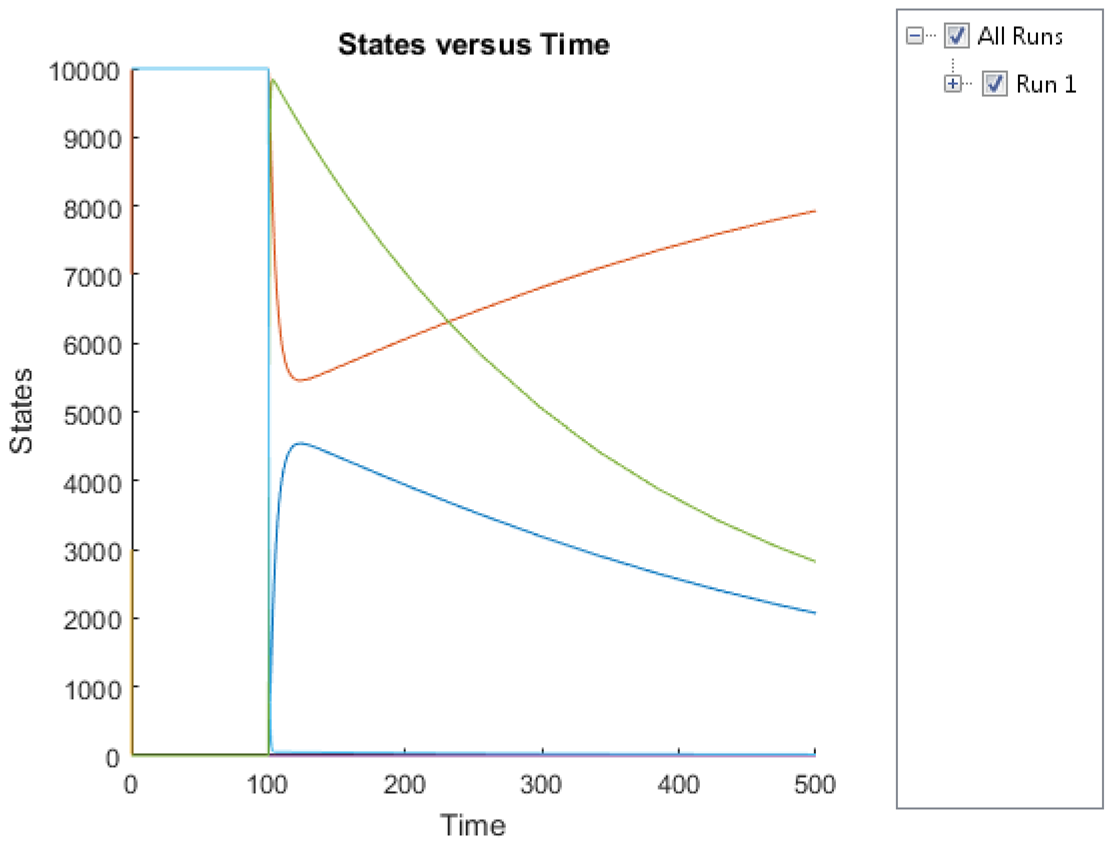
Alternative to storing simulation data in separate outputs, such as `t`, `x`, and `names` as above, you can store them all in a single `SimData object`. You can then use `selectbyname` to extract arrays containing the simulation data of your interest.

```
simdata     = sbiosimulate(m1);
sbioplot(simdata);
```



Expand **Run 1** to see the names of species and parameter that are plotted.

```
simdata_noL = selectbyname(simdata, {'Ga','G','Gd','GaFrac','RL','R'});
sbioplot(simdata_noL);
```


States versus Time
States
Time
0
1000
2000
3000
4000
5000
6000
7000
8000
9000
10000
0
100
200
300
400
500
All Runs
Run 1

Sensitivity Calculation

In this section...

About Calculating Sensitivities

Calculating sensitivities lets you determine which species or parameter in a model is most sensitive to a specific condition (for example, a drug), defined by a species or parameter. Calculating sensitivities calculates the time-dependent sensitivities of all the species states with respect to species initial conditions and parameter values in the model.

Thus, if a model has a species `x`, and two parameters `y` and `z`, the time-dependent sensitivities of `x` with respect to each parameter value are the time-dependent derivatives

$$\frac{\partial x}{\partial y}, \frac{\partial x}{\partial z}$$

where, the numerator is the sensitivity output and the denominators are the sensitivity inputs to sensitivity analysis.

For more information on the calculations performed, see "References" on page 3-24.

Model Requirements for Calculating Sensitivities

Sensitivity analysis is supported only by the ordinary differential equation (ODE) solvers. The software calculates local sensitivities by combining the original ODE system for a model with the auxiliary differential equations for the sensitivities. The additional equations are derivatives of the original equations with respect to parameters. This method is sometimes called “forward sensitivity analysis” or “direct sensitivity analysis”. This larger system of ODEs is solved simultaneously by the solver.

SimBiology sensitivity analysis uses “complex-step approximation” to calculate derivatives of reaction rates. This technique yields accurate results for the vast majority of typical reaction kinetics, which involve only simple mathematical operations and functions. When a reaction rate involves a nonanalytic function, this technique can lead to inaccurate results. In this case, either sensitivity analysis is disabled, or sensitivity analysis warns you that the computed sensitivities may be inaccurate. An example of such a nonanalytic function is the MATLAB function `abs`. If sensitivity analysis gives questionable results on a model whose reaction rates contain unusual functions, you may be running into limitations of the complex-step method. Contact MathWorks Technical Support for additional information.

Note: Models containing the following active components do not support sensitivity analysis:

- Nonconstant compartments
- Algebraic rules
- Events

Note: You can perform sensitivity analysis on a model containing repeated assignment rules, but only if the repeated assignment rules do not determine species or parameters used as inputs or outputs in sensitivity analysis.

Calculate Sensitivities using sbiosimulate or SimFunctionSensitivity Object

You can calculate sensitivities using `sbiosimulate` or the `SimFunctionSensitivity object`.

Calculate using sbiosimulate

Set the following properties of the `SolverOptions` property of your `configset` object, before running the `sbiosimulate` function:

- `SensitivityAnalysis` — Set to `true` to calculate the time-dependent sensitivities of all the species states defined by the `Outputs` property with respect to the initial conditions of the species and the values of the parameters specified in `Inputs`.

- `SensitivityAnalysisOptions` — An object that holds the sensitivity analysis options in the configuration set object. Properties of `SensitivityAnalysisOptions` are:
  - `Outputs` — Specify the species and parameters for which you want to compute the sensitivities. This is the numerator as described in "About Calculating Sensitivities" on page 3-21.
  - `Inputs` — Specify the species and parameters with respect to which you want to compute the sensitivities. Sensitivities are calculated with respect to the `InitialAmount` property of the specified species. This is the denominator, described in "About Calculating Sensitivities" on page 3-21.
  - `Normalization` — Specify the normalization for the calculated sensitivities:
    - `'None'` — No normalization
    - `'Half'` — Normalization relative to the numerator (species output) only
    - `'Full'` — Full dedimensionalization

    For more information about normalization, see `Normalization`.

After setting `SolverOptions` properties, calculate the sensitivities of a model by providing the `model object` as an input argument to the `sbiosimulate` function.

The `sbiosimulate` function returns a `SimData object` containing the following simulation data:

- Time points, state data, state names, and sensitivity data
- Metadata such as the types and names for the logged states, the configuration set used during simulation, and the date of the simulation

A `SimData object` is a convenient way of keeping time data, state data, sensitivity data, and associated metadata together. A `SimData object` has properties and methods associated with it, which you can use to access and manipulate the data.

For illustrated examples, see:

- "Calculate Sensitivities" on page 3-25
- Parameter Scanning, Parameter Estimation, and Sensitivity Analysis in the Yeast Heterotrimeric G Protein Cycle

Calculate using SimFunctionSensitivity object

Create a `SimFunctionSensitivity object` using the `createSimFunction` specifying the `'SensitivityOutputs'` and `'SensitivityInputs'` name-value pair arguments. Then execute the object. For an illustrated example, see “Calculate Sensitivities Using SimFunctionSensitivity Object”.

References

Ingalls, B.P, and Sauro, H.M. (2003). Sensitivity analysis of stoichiometric networks: an extension of metabolic control analysis to non-steady state trajectories. J Theor Biol. *222(1)*, 23–36.

Martins, J.R.R.A., Sturdza, P., and Alanso, J.J. (Jan. 2001). The connection between the complex-step derivative approximation and algorithmic differentiation. AIAA Paper *2001–0921*.

Martins, J.R.R.A., Kroo, I.M., and Alanso, J.J. (Jan. 2000). An automated method for sensitivity analysis using complex variables. AIAA Paper *2000–0689*.

Calculate Sensitivities

In this section...

Overview

About the Example Model

This example uses the model described in "Model of the Yeast Heterotrimeric G Protein Cycle" on page C-17 to illustrate SimBiology sensitivity analysis options.

This table lists the reactions used to model the G protein cycle and the corresponding rate parameters (rate constants) for each mass action reaction. For reversible reactions, the forward rate parameter is listed first.

No.	Name	Reaction[1]	Rate Parameters
1	Receptor-ligand interaction	`L + R <-> RL`	`kRL`, `kRLm`
2	Heterotrimeric G protein formation	`Gd + Gbg -> G`	`kG1`
3	G protein activation	`RL + G -> Ga + Gbg + RL`	`kGa`
4	Receptor synthesis and degradation	`R <-> null`	`kRdo`, `kRs`
5	Receptor-ligand degradation	`RL -> null`	`kRD1`
6	G protein inactivation	`Ga -> Gd`	`kGd`

[1] Legend of species: L = ligand (alpha factor), R = alpha-factor receptor, Gd = inactive G-alpha-GDP, Gbg = free levels of G-beta:G-gamma complex, G = inactive Gbg:Gd complex, Ga = active G-alpha-GTP

About the Example

Assume that you are calculating the sensitivity of species `Ga` with respect to every parameter in the model. Thus, you want to calculate the time-dependent derivatives

$$\frac{\partial(Ga)}{\partial(kRLm)},\frac{\partial(Ga)}{\partial(kRL)},\frac{\partial(Ga)}{\partial(kG1)},\frac{\partial(Ga)}{\partial(kGa)}\dots$$

Load and Configure the Model for Sensitivity Analysis

1. The `gprotein_norules.sbproj` project contains a model that represents the wild-type strain (stored in variable `m1`).

   ```
   sbioloadproject gprotein_norules m1
   ```
2. The options for sensitivity analysis are in the configuration set object. Get the configuration set object from the model.

   ```
   csObj = getconfigset(m1);
   ```
3. Use the `sbioselect` function, which lets you query by type, to retrieve the `Ga` species from the model.

   ```
   Ga = sbioselect(m1,'Type','species','Where','Name','==','Ga');
   ```
4. Set the `Outputs` property of the `SensitivityAnalysisOptions` object to the `Ga` species.

   ```
   csObj.SensitivityAnalysisOptions.Outputs = Ga;
   ```
5. Use the `sbioselect` function, which lets you query by type, to retrieve all the parameters from the model and store the vector in a variable, `pif`.

   ```
   pif = sbioselect(m1,'Type','parameter');
   ```
6. Set the `Inputs` property of the `SensitivityAnalysisOptions` object to the `pif` variable containing the parameters.

   ```
   csObj.SensitivityAnalysisOptions.Inputs =  pif;
   ```
7. Enable sensitivity analysis in the configuration set object (`csObj`) by setting the `SensitivityAnalysis` option to `true`.

   ```
   csObj.SolverOptions.SensitivityAnalysis = true;
   ```
8. Set the `Normalization` property of the `SensitivityAnalysisOptions` object to perform `'Full'` normalization.

   ```
   csObj.SensitivityAnalysisOptions.Normalization = 'Full';
   ```

Perform Sensitivity Analysis

Simulate the model and return the data to a `SimData object`:

```
simDataObj = sbiosimulate(m1);
```

Extract and Plot Sensitivity Data

You can extract sensitivity results using the `getsensmatrix` method of a `SimData object`. In this example, `R` is the sensitivity of the species `Ga` with respect to eight parameters. This example shows how to compare the variation of sensitivity of `Ga` with respect to various parameters, and find the parameters that affect `Ga` the most.

1 Extract sensitivity data in output variables `T` (time), `R` (sensitivity data for species `Ga`), `snames` (names of the states specified for sensitivity analysis), and `ifacs` (names of the input factors used for sensitivity analysis):

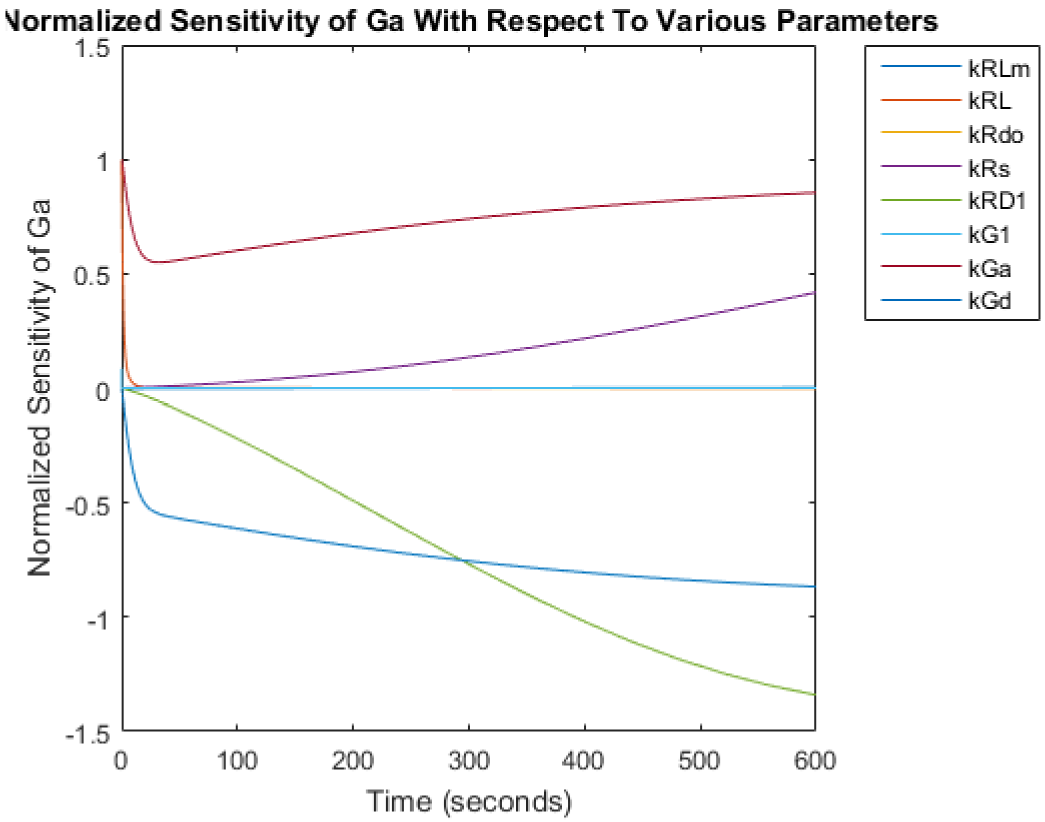
   ```
   [T, R, snames, ifacs] = getsensmatrix(simDataObj);
   ```

2 Because `R` is a 3-D array with dimensions corresponding to times, output factors, and input factors, reshape `R` into columns of input factors to facilitate visualization and plotting:

   ```
   R2 = squeeze(R);
   ```

3 After extracting the data and reshaping the matrix, plot the data:

   ```
   figure;
   plot(T,R2);
   title('Normalized Sensitivity of Ga With Respect To Various Parameters');
   xlabel('Time (seconds)');
   ylabel('Normalized Sensitivity of Ga');
   leg = legend(ifacs, 'Location', 'NorthEastOutside');
   set(leg, 'Interpreter', 'none');
   ```



From the previous plot you can see that `Ga` is most sensitive to parameters `kGd`, `kRs`, `kRD1`, and `kGa`. This suggests that the amounts of active G protein in the cell depends on the rate of:

- Receptor synthesis
- Degradation of the receptor-ligand complex
- G protein activation
- G protein inactivation

Identify Important Network Components from an Apoptosis Model Using Sensitivity Analysis

This example shows how to identify important network components in an apoptosis model using sensitivity analysis in the SimBiology desktop.

Apoptosis

An apoptosis is programmed cell death which is triggered by a wide variety of stimuli or signaling events. When a cell encounters such signals, the level of `Casp3*` (activated caspase3 protease) increases leading to an increased break down of proteins important for cell survival. As a result, the cell dies. Research has shown that the level of `Casp3*` is controlled by XIAP (X-linked inhibitor of apoptosis protein) that binds to `Casp3*` and inactivates it so that `Casp3*` can no longer break down essential proteins of the cell, thus effectively controlling the apoptosis [1], [2].

Sensitivity Analysis

Most biological networks are complex with several interactions and feedback loops, and it might not be obvious to see which model component(s) should be controlled to have a desired outcome such as a decrease in concentration of a particular species.

"Sensitivity Calculation" on page 3-21 lets you determine which species or parameters in a model are most sensitive to a specific condition, such as a drug, thus providing insights on important targets within the model.

Using SimBiology you can calculate time-dependent sensitivities of all the species states with respect to species initial conditions and parameter values in the model. The objective of this simulation is to find important network components in an apoptosis model based on a hypothesis that the apoptosis signal is directly proportional to the level of `Casp3*` in the cell. This example shows how to calculate the sensitivity of species `Casp3*` with respect to every species in the model as follows:

$$\frac{\partial(Casp3^*)}{\partial(Casp3)}, \frac{\partial(Casp3^*)}{\partial(Casp8)}, \frac{\partial(Casp3^*)}{\partial(XIAP)}, \ldots$$

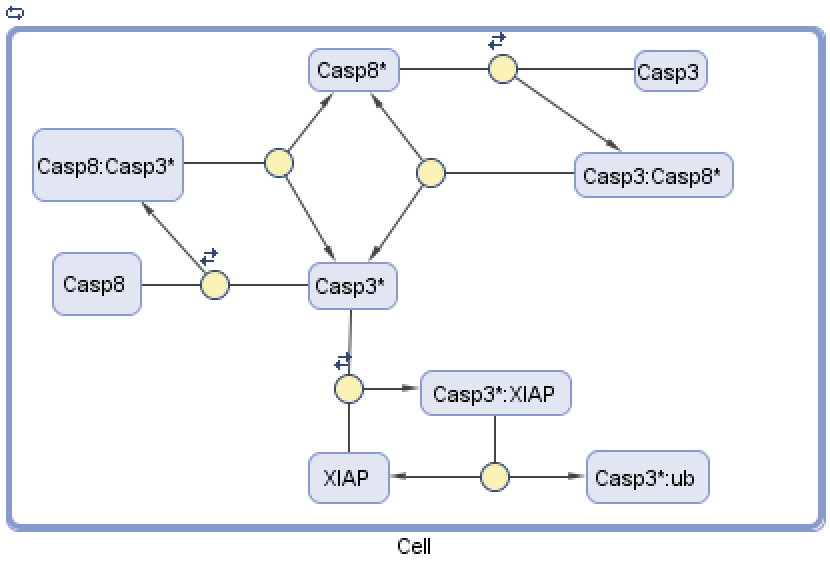
Load the Apoptosis Model

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

On the **Home** tab, click **Open** and navigate to the folder *`matlabroot`*`\help\toolbox\simbio\examples`, where *`matlabroot`* is the folder where MATLAB is installed, and open the SimBiology project file named `apoptosis.sbproj`.

Note: If you are using a Macintosh platform, press **Command+Shift+G** in the File Browser dialog box, and enter the full path to the folder.

By default, SimBiology opens the model in the **Table Overview** mode, where it shows the model's reactions and quantity in a tabular format. The model contains nine species, nine parameters, and six reactions. To view the model graphically, select **Open > Diagram**.



Add a Sensitivity Analysis Task

On the **Model** tab, select **Add Task > Calculate sensitivities**.

Under **Normalization for Computed Sensitivities**, select **Full (full dedimensionalization)**, which specifies the data should be made dimensionless. For more information, see Normalization.

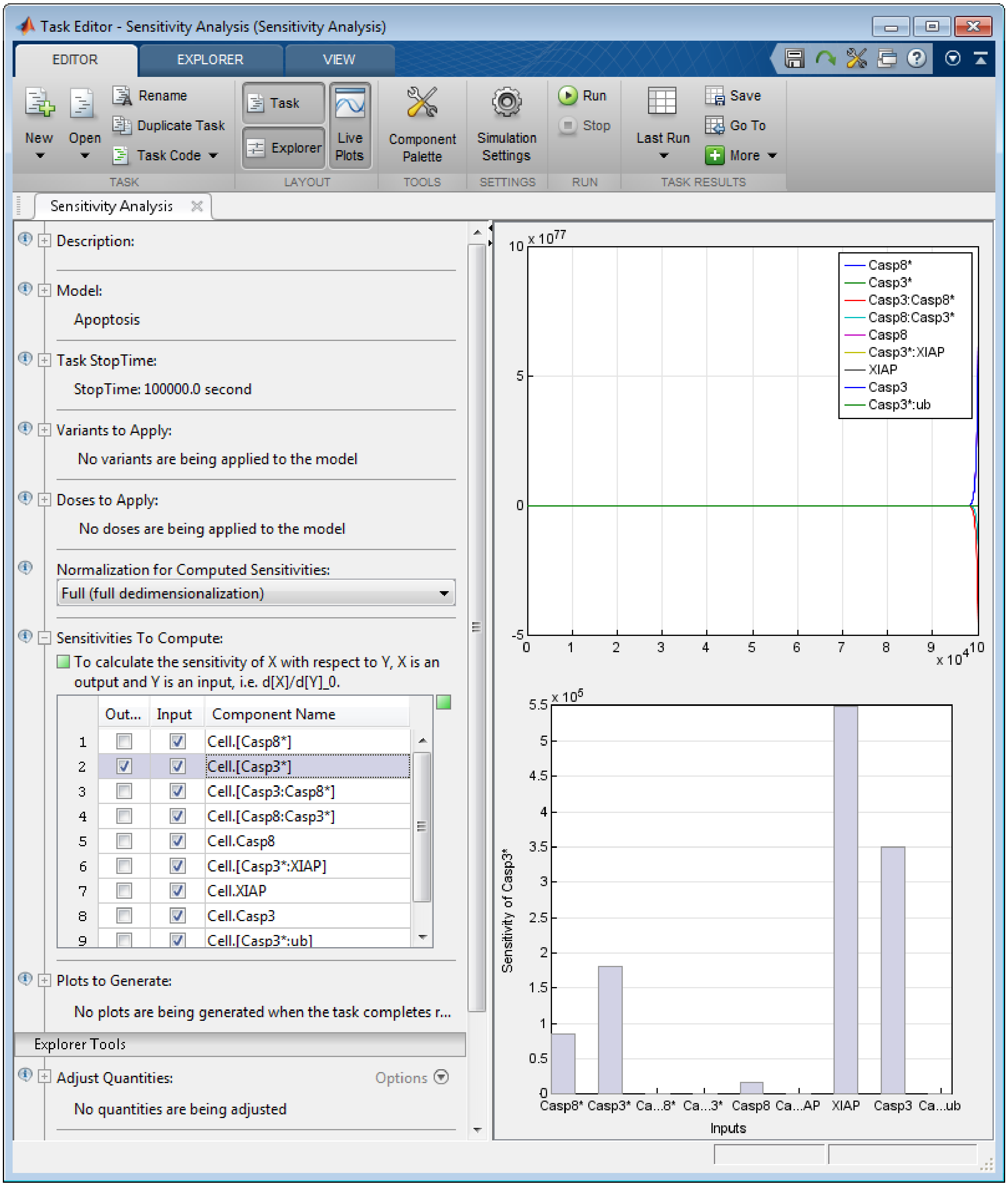
Specify the species for sensitivity calculations by adding all nine species under the **Sensitivities to Compute** section. The fastest way to do this is to use the context menu of the table and select **Add All Species**. Alternatively, you can drag and drop from **Component Palette** or enter each species name manually.

Since the level of `Casp3*` is hypothesized to control apoptosis, select `Cell.[Casp3*]` as the only output. Select the rest of the species as inputs. Multiple sensitivity inputs and outputs can be set or cleared by selecting multiple rows and using the context menu options. If you want to find out how sensitive `Casp3*` is to its initial concentration over the course of simulation, select `Cell.[Casp3*]` as an input as well.

Perform Sensitivity Calculation

Click the **Run** button on the **Task** tab to perform the sensitivity analysis.

After calculation, the Live Plots section shows two figures: States vs Time figure (top) and Sensivitity figure (bottom), which contains sensitivity values of `Casp3*` with respect to all species integrated across time.



Description:

Model:

Apoptosis

Task StopTime:

StopTime: 100000.0 second

Variants to Apply:

No variants are being applied to the model

Doses to Apply:

No doses are being applied to the model

Normalization for Computed Sensitivities:

Full (full dedimensionalization)

Sensitivities To Compute:

🟩 To calculate the sensitivity of X with respect to Y, X is an output and Y is an input, i.e. d[X]/d[Y]_0.

	Out...	Input	Component Name
1	☐	✓	Cell.[Casp8*]
2	✓	✓	Cell.[Casp3*]
3	☐	✓	Cell.[Casp3:Casp8*]
4	☐	✓	Cell.[Casp8:Casp3*]
5	☐	✓	Cell.Casp8
6	☐	✓	Cell.[Casp3*:XIAP]
7	☐	✓	Cell.XIAP
8	☐	✓	Cell.Casp3
9	☐	✓	Cell.[Casp3*:ub]

Plots to Generate:

No plots are being generated when the task completes r...

Adjust Quantities:

No quantities are being adjusted

The plot shows that `Casp3*` is most sensitive to XIAP concentration since XIAP has the highest sensitivity value among all the other species. Therefore, such sensitivity analysis indicates that XIAP could be one of the most important network components or drug targets in this model to control the `Casp3*` level and subsequent apoptosis events.

References

[1] Aldridge, B.B., Haller, G., Sorger, P.K., Lauffenburger, D.A. (2006). Direct Lyapunov exponent analysis enables parametric study of transient signalling governing cell behaviour. Syst Biol (Stevenage) *153*, 425-432.

[2] Wikipedia. (2013). XIAP, http://en.wikipedia.org/wiki/XIAP

Perform a Parameter Scan

This example shows how to perform a parameter scan by simulating a model multiple times, each time varying the value of a parameter.

In the model described in Model of the Yeast Heterotrimeric G Protein Cycle, the rate of G protein inactivation (`kGd`) is much lower in the mutant strain versus the wild-type strain (`kGd = 0.004` versus `kGd = 0.11`), which explains higher levels of activated G protein (`Ga`) in the mutant strain. For a detailed look at how varying the level of `kGd` affects the level of `Ga`, perform a parameter scan over five values of `kGd`.

Load the `gprotein.sbproj` project, which includes the variable `m1`, a model object.

```
sbioloadproject gprotein
```

The `m1` model object appears in the MATLAB Workspace.

View the variants in the `m1` model.

```
m1.Variants
```

```
SimBiology Variant - mutant (inactive)

ContentIndex:     Type:        Name:          Property:       Value:
1                 parameter    kGd            Value           0.004
```

This model contains one variant named `mutant` that holds the content for the `kGd` parameter. This variant is inactive.

Assign the variant to a variable, `variantObj`, so you can use it to perform the scan.

```
variantObj = m1.Variants(1);
```

Create a vector of five evenly spaced values for `kGd` ranging from `0.001` to `0.15`.

```
kGdValues = linspace(1e-3,0.15,5)
```

```
kGdValues =

    0.0010    0.0382    0.0755    0.1127    0.1500
```

Initialize a variable, `scanData`, which you will later use to hold an array of `SimData` objects to store the results of the parameter scan .

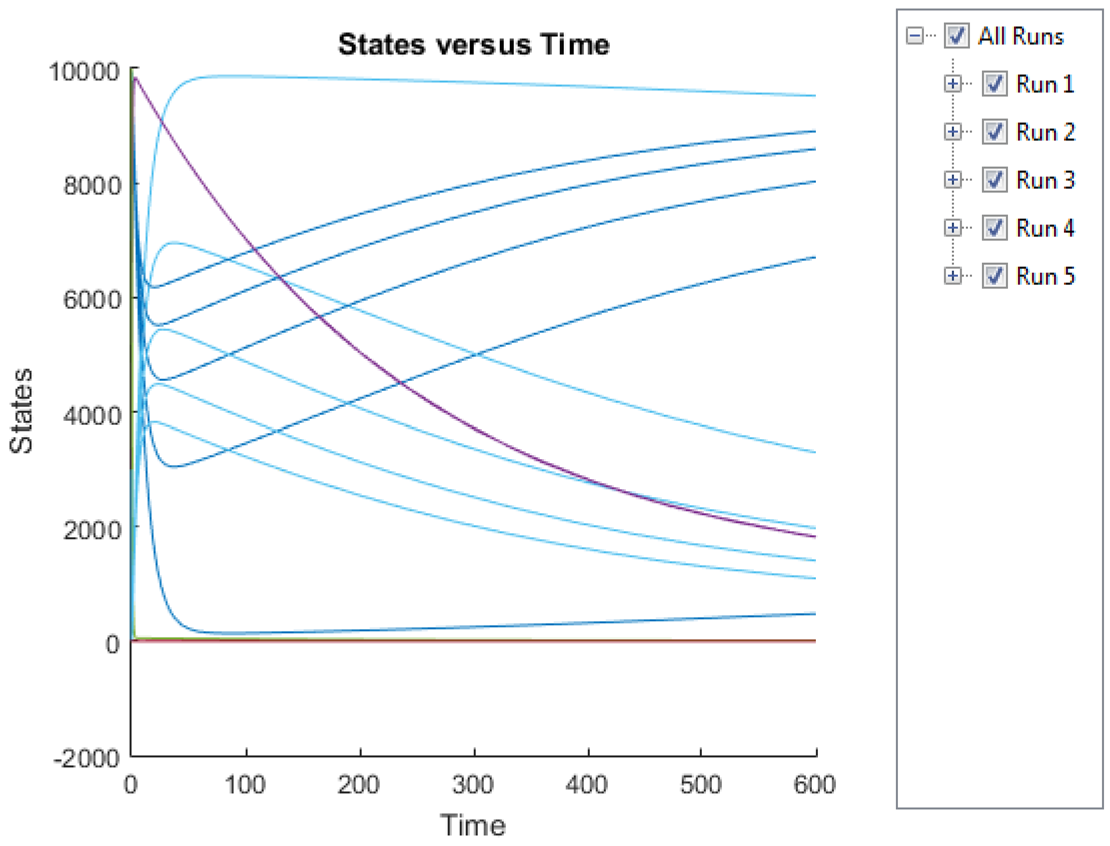
```
scanData = [];
```

Loop over the five `kGd` values. During the loop, assign each value to the mutant variant, and use the variant during each simulation. Store the results of the five simulations in an array of `SimData` objects.

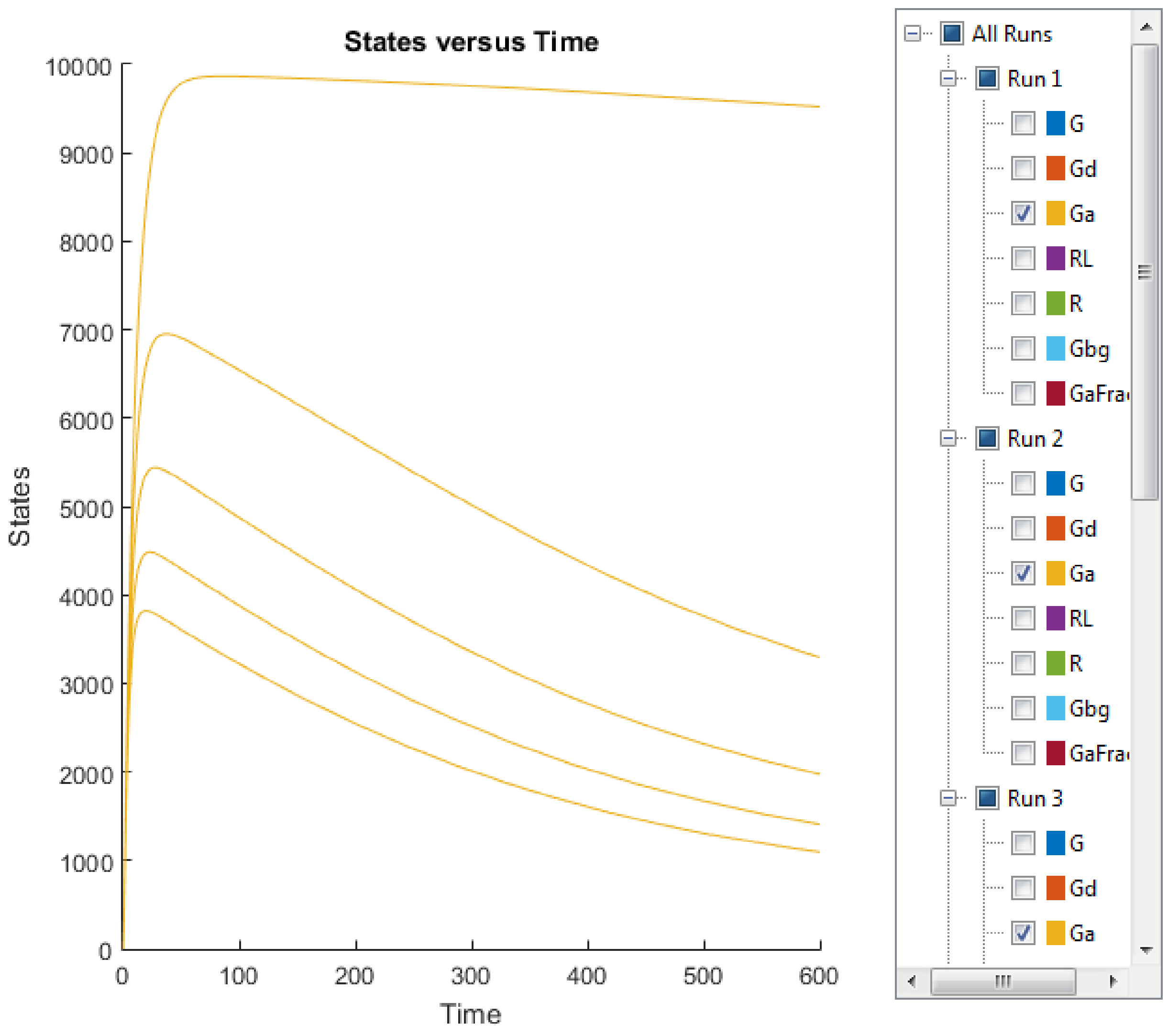
```
for kGd = kGdValues
    % Set the value (4th column) of the kGd variant (1st row)
    variantObj.Content{1}{4} = kGd;
    % Simulate the m1 model using the kGd variant
    simDataObj = sbiosimulate(m1,variantObj);
    % Store the results in an array of SimData objects
    scanData = [scanData;simDataObj];
end
```

The `scanData` array now contains five `SimData` objects, with each object containing the data from one simulation in the parameter scan. Use `sbioplot` to plot the data.

```
sbioplot(scanData);
```



Uncheck **All Runs** , expand each **Run**, and select the `Ga` species to display only its simulation data. This shows how varying the level of `kGd` affects the level of `Ga`.



More About

- "Model of the Yeast Heterotrimeric G Protein Cycle" on page C-17

Nonlinear Mixed-Effects Modeling

In this section...

What Is a Nonlinear Mixed-Effects Model?

A mixed-effects model is a statistical model that incorporates both *fixed effects* and *random effects*. Fixed effects are population parameters assumed to be the same each time data is collected, and random effects are random variables associated with each sample (individual) from a population. Mixed-effects models work with small sample sizes and sparse data sets, and are often used to make inferences on features underlying profiles of repeated measurements from a group of individuals from a population of interest.

As with all regression models, their purpose is to describe a response variable as a function of the predictor (independent) variables. Mixed-effects models, however, recognize correlations within sample subgroups, providing a reasonable compromise between ignoring data groups entirely, thereby losing valuable information, and fitting each group separately, which requires significantly more data points.

For instance, consider population pharmacokinetic data that involve the administration of a drug to several individuals and the subsequent observation of drug concentration for each individual, and the objective is to make a broader inference on population-wide parameters while considering individual variations. The nonlinear function often used for such data is an exponential function since many drugs once distributed in a patient are eliminated in an exponential fashion. Thus the measured drug concentration of an individual can be described as:

$$y_{ij} = \frac{D_i}{V} e^{-k_i t_{ij}} + a\varepsilon_{ij} \ ,$$

where y_{ij} is the jth response of the ith individual, D_i is the dose administered to the ith individual, V is the population mean volume of distribution, a is an error parameter, and $\varepsilon_{ij} \sim N(0,1)$, representing some measurement error. The elimination rate parameter (k_i) depends on the clearance and volume of the central compartment $k_i = \frac{Cl_i}{V}$. Both k_i and Cl_i are for the ith patient, meaning they are patient-specific parameters.

To account for variations between individuals, assume that the clearance is a random variable depending on individuals, varying around the population mean. For the ith individual, $Cl_i = \theta_1 + \eta_i$, where θ_1 is the fixed effect (population parameter for the clearance) and η_i is the random effect, that is, the deviation of the ith individual from the mean clearance of the population $\eta_i \sim \mathrm{N}(0, \sigma_\eta^2)$.

If you have any individual-specific covariates such as weight w that linearly relate to the clearance, you can try explaining some of the between-individual differences. For example, if w_i is the weight of the ith individual, then the model becomes $Cl_i = \theta_1 + \theta_2 * w_i + \eta_i$, where θ_2 is the fixed effect of weight on clearance.

A general nonlinear mixed-effects (NLME) model with constant variance is as follows:

$$y_{ij} = f(x_{ij}, p_i) + \varepsilon_{ij}$$
$$p_i = A_i\theta + B_i\eta_i$$
$$\varepsilon_{ij} \sim N(0, \sigma^2)$$
$$\eta_i \sim N(0, \Psi)$$

y_{ij}	Data vector of individual-specific response values
f	General, real-valued function of p_i and x_{ij}
x_{ij}	Data matrix of individual-specific predictor values
p_i	Vector of individual-specific model parameters
θ	Vector of fixed effects, modeling population parameters
η_j	Vector of multivariate normally distributed individual-specific random effects
A_i	Individual-specific design matrix for combining fixed effects

B_i	Individual-specific design matrix for combining random effects
ε_{ij}	Vector of group-specific errors, assumed to be independent, identically, normally distributed, and independent of η_i
Ψ	Covariance matrix for the random effects
σ^2	Error variance, assumed to be constant across observations

In addition to the constant error model, there are other error models such as proportional, exponential, and combined error models. For details, see “Error Models” on page 3-43.

Nonlinear Mixed-Effects Modeling Workflow

SimBiology lets you estimate fixed effects θs and random effects ηs as well as the covariance matrix of random effects Ψ. However, you cannot alter A and B design matrices since they are automatically determined from the covariate model you specify. Use the `sbiofitmixed` function to estimate nonlinear mixed-effects parameters. These steps show one of the workflows you can use at the command line.

1. Import data.
2. Convert the data to the `groupedData` format.
3. Define dosing data. For details, see “Doses” on page 1-42.
4. Create a structural model (one-, two-, or multicompartment model). For details, see “Create Pharmacokinetic Models” on page 4-24.
5. Create a covariate model to define parameter-covariate relationships if any. For details, see “Specify a Covariate Model” on page 3-41.
6. Map the response variable from data to the model component. For example, if you have the measured drug concentration data for the central compartment, then map it to the drug species in the central compartment (typically the `Drug_Central` species).
7. Specify parameters to estimate using the `estimatedInfo object`. It lets you optionally specify parameter transformations, initial values, and parameter bounds. Supported transforms are `log`, `probit`, `logit`, and `none` (no transform).
8. (Optional) You can also specify an error model. The default model is the constant error model. For instance, you can change it to the proportional error model if you assume the measurement error is proportional to the response data. See “Specify an Error Model” on page 3-43.

9 Estimate parameters using `sbiofitmixed`, which performs “Maximum Likelihood Estimation” on page 3-44.

10 (Optional) If you have a large, complex model, the estimation might take longer. SimBiology lets you check the status of fitting as it progresses. See “Obtain the Fitting Status” on page 3-45.

For a complete workflow example, see “Modeling the Population Pharmacokinetics of Phenobarbital in Neonates”.

Specify a Covariate Model

When specifying a nonlinear mixed-effects model, you define parameter-covariate relationship using a covariate model (`CovariateModel object`). For example, suppose you have PK profile data for multiple individuals and are estimating three parameters (clearance *Cl*, compartment volume *V*, and elimination rate *k*) that have both fixed and random effects. Assume the clearance *Cl* has a correlation with a covariate variable weight (w) of each individual. Each parameter can be described as a linear combination of fixed and random effects.

$$Cl_i = \theta_1 + \theta_2 * w_i + \eta_{1i},$$

$$V_i = \theta_3 + \eta_{2i},$$

$$k_i = \theta_4 + \eta_{3i},$$

where θs represent fixed effects and ηs represent random effects, which are normally distributed $\begin{pmatrix} \eta_{1i} \\ \eta_{2i} \\ \eta_{3i} \end{pmatrix} \sim MVN(0, \Psi)$. By default, the random effects are uncorrelated. So

$$\Psi = \begin{pmatrix} \sigma_1^2 & 0 & 0 \\ 0 & \sigma_2^2 & 0 \\ 0 & 0 & \sigma_3^2 \end{pmatrix}.$$

1 Construct an empty `CovariateModel` object.

```
covModel = CovariateModel;
```

2 Set the `Expression` property to define the relationships between parameters (*Cl*, *V*, and *k*) and covariate (*w*). You must use `theta` as a prefix for all fixed effects and `eta` for random effects.

```
covModel.Expression = {'Cl = theta1 + theta2*w + eta1','V = theta3 + eta2','k = the
```

The `FixedEffectNames` property displays the fixed effects defined in the model.

```
covModel.FixedEffectNames

ans =

    'theta1'
    'theta3'
    'theta4'
    'theta2'
```

The `FixedEffectDescription` property displays which fixed effects correspond to which parameter. For instance, *theta1* is the fixed effect for the *Cl* parameter, and *theta2* is the fixed effect for the weight covariate that has a correlation with *Cl* parameter, denoted as *Cl/w*.

```
covModel.FixedEffectDescription

ans =

    'Cl'
    'V'
    'k'
    'Cl/w'
```

3 Specify initial estimates for the fixed effects. Create a structure containing initial estimates using the `constructDefaultFixedEffectValues` function.

```
initialEstimates = constructDefaultFixedEffectValues(covModel)

initialEstimates =

    theta1: 0
    theta2: 0
    theta3: 0
    theta4: 0

initialEstimates.theta1 = 1.20;
initialEstimates.theta2 = 0.30;
initialEstimates.theta3 = 0.90;
initialEstimates.theta4 = 0.10;
```

4 Set the initial estimates to the `FixedEffectValues` property.

```
covModel.FixedEffectValues = initialEstimates;
```

Specify a Covariance Pattern Among Random Effects

By default, `sbiofitmixed` assumes no covariance among random effects, that is, a diagonal covariance matrix is used. Suppose you have η_1, η_2, and η_3, and there is a covariance σ_{12} between η_1 and η_2. You can indicate this using a pattern matrix where 1 indicates a variance or covariance parameter which is estimated by `sbiofitmixed`. For instance, a pattern matrix $\begin{pmatrix} 1 & 1 & 0 \\ 1 & 1 & 0 \\ 0 & 0 & 1 \end{pmatrix}$ represents $\begin{pmatrix} \sigma_1^2 & \sigma_{12} & 0 \\ \sigma_{21} & \sigma_2^2 & 0 \\ 0 & 0 & \sigma_3^2 \end{pmatrix}$.

Define such a pattern using an `options` struct.

```
options.CovPattern = [1 1 0;1 1 0;0 0 1];
```

Then you can use `options` as an input argument for `sbiofitmixed`. For a complete workflow, see “Nonlinear Mixed-Effects Modeling Workflow” on page 3-40.

Specify an Error Model

During the “Nonlinear Mixed-Effects Modeling Workflow” on page 3-40, you can optionally specify an error model using a structure.

```
options.ErrorModel = 'proportional';
```

Then you can use `options` as one of the input arguments when you run `sbiofitmixed`.

Supported error models are constant (default), proportional, combined, and exponential models. For details, see “Error Models” on page 3-43.

Error Models

SimBiology supports the error models described in the following table. For instance, if you assume every observation has a constant amount of noise, use the constant error model, which is the default. Instead, if you assume the error is proportional to the response data, then the proportional error model might be more appropriate.

Error Model	Mathematical Representation	Standard Deviation of Error Model
constan (default	$y = f + a\varepsilon$	a
proport	$y = f + b\lvert f \rvert \varepsilon$	$b\,\lvert f \rvert$
combin	$y = f + (a + b\lvert f \rvert)\varepsilon$	$a+b\,\lvert f \rvert$
exponential	$y = f * \exp(a\varepsilon)$ or equivalently,	$\sqrt{e^{a^2} - 1} * e^a$
	$\log(y) = \log(f) + a\varepsilon$	a
Here, y is the response, f is the function value, ε is a standard mean-zero and unit-variance (Gaussian) variable, and a and b are error parameters. For instance, if you assume the error is approximately 5% of each observation, use the proportional error model with b = 0.05. In SimBiology, f typically represents the simulation result.		

Maximum Likelihood Estimation

SimBiology estimates the parameters of a nonlinear mixed-effects model by maximizing a likelihood function, which can be described as

$$p(y \mid \theta, \sigma^2, \Psi) = \int p(y \mid \theta, \eta, \sigma^2)\, p(\eta \mid \Psi)\, d\eta\ ,$$

where y is the response data, θ is the vector of fixed effects, σ^2 is the error variance, Ψ is the covariance matrix for random effects, and η is the vector of unobserved random effects. $p(y \mid \theta, \sigma^2, \Psi)$ is the marginal density of y, $p(y \mid \theta, \eta, \sigma^2)$ is the conditional density of y given the random effects η, and the prior distribution of η is $p(\eta \mid \Psi)$.

This integral contains a nonlinear function of the fixed effects and variance parameters that you want to maximize. Typically for nonlinear models, the integral does not have a closed form, and needs to be solved numerically, which involves simulating the function at each time step of an optimization algorithm. Therefore, the estimation can take a long time for complex models, and initial values of parameters might play an important role for successful convergence. SimBiology provides these iterative algorithms to solve the integral and maximize the likelihood if you have Statistics and Machine Learning Toolbox™.

- `LME` — Use the likelihood for the linear mixed-effects model at the current conditional estimates of θ and η. This is the default.
- `RELME` — Use the restricted likelihood for the linear mixed-effects model at the current conditional estimates of θ and η.
- `FO` — First-order (Laplacian) approximation without random effects.
- `FOCE` — First-order (Laplacian) approximation at the conditional estimates of θ.
- stochastic EM — Use the Expectation-Maximization (EM) algorithm in which the E step is replaced by a stochastic procedure.

For a complete workflow, see “Nonlinear Mixed-Effects Modeling Workflow” on page 3-40.

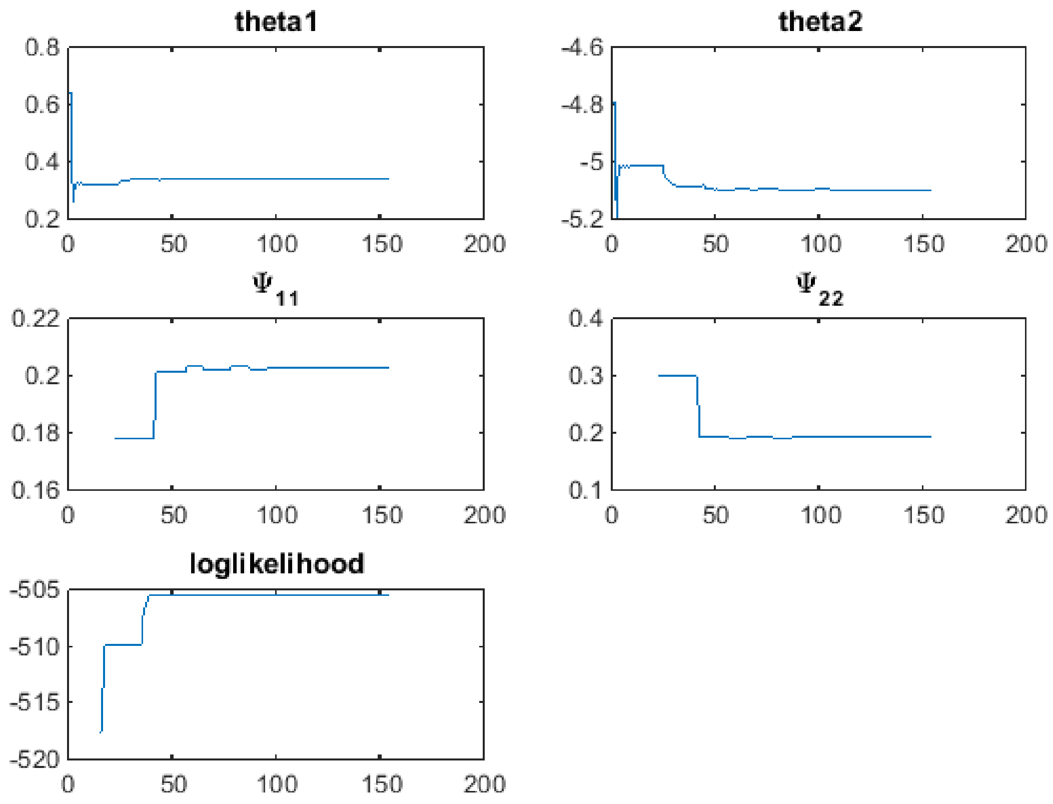
Obtain the Fitting Status

During the estimation of mixed-effects parameters of a large and complex model that may take a longer time, you may want to obtain the status of fitting as it progresses. The `sbiofitstatusplot` function dynamically shows the progress of the fitting by plotting the values of fixed effects parameters (`theta`) and the estimates of the variance parameters, that is, the diagonal elements of the covariance matrix of the random effects (Ψ), and the log-likelihood.

To obtain the status plot, you must set the `OutputFcn` filed of a `statset` option as follows.

```
fitOptions.Options = statset('OutputFcn',@sbiofitstatusplot);
```

You can then specify `fitOptions` as one of input arguments when you run `sbiofitmixed`. The next figure is an example of the fit status plot.



Here are some tips for interpreting the plot.

- The fitting function tries to maximize the log-likelihood. When the plot begins to display a flat line, this might indicate that maximization is complete. Try setting the maximum iterations to a lower number to reduce the number of iterations you need and improve performance.
- Plots for the fixed effects (`theta`s) and the variance parameters (Ψs) should show convergence. If you see oscillations, or jumps without accompanying improvements in the log-likelihood, the model may be overparameterized. Try the following:
  - Reduce the number of fixed effects.

- Reduce the number of random effects.
- Simplify the covariance matrix pattern of random effects (if you have previously changed it from the default diagonal matrix).

For a complete workflow, see “Nonlinear Mixed-Effects Modeling Workflow” on page 3-40.

Nonlinear Regression

In this section...
"What is Nonlinear Regression?" on page 3-48
"Fitting Options in SimBiology" on page 3-49
"Error Models" on page 3-43
"Maximum Likelihood Estimation" on page 3-51
"Fitting Workflow for sbiofit" on page 3-52

What is Nonlinear Regression?

The purpose of regression models is to describe a response variable as a function of independent variables. Multiple linear regression models describe the response as a linear combination of coefficients and functions of independent variables. Nonlinearities can be modeled using nonlinear functions of independent variables. However, the coefficients always enter the model in a linear fashion.

Nonlinear regression models are more mechanistic models of nonlinear relationships between the response and independent variables. The parameters can enter the model as exponential, trigonometric, power, or any other nonlinear function. The unknown parameters in the model are estimated by minimizing a statistical criterion such as the negative log likelihood or the sum of squared deviations between observed and predicted values.

In the case of pharmacokinetic (PK) studies, the response data usually represent some measured drug concentrations, and independent variables are often dose and time. The nonlinear function often used for such data is an exponential function since many drugs once distributed in a patient are eliminated in an exponential fashion. One PK parameter to estimate in this case is the rate at which the drug is eliminated from the body given the concentration-time data.

For instance, consider drug plasma concentration data from a single individual after an intravenous bolus dose measured at different time points with some errors. Assume the measured drug concentration follows a monoexponential decline: $C_t = C_0 e^{-k_e t} + a\varepsilon$.

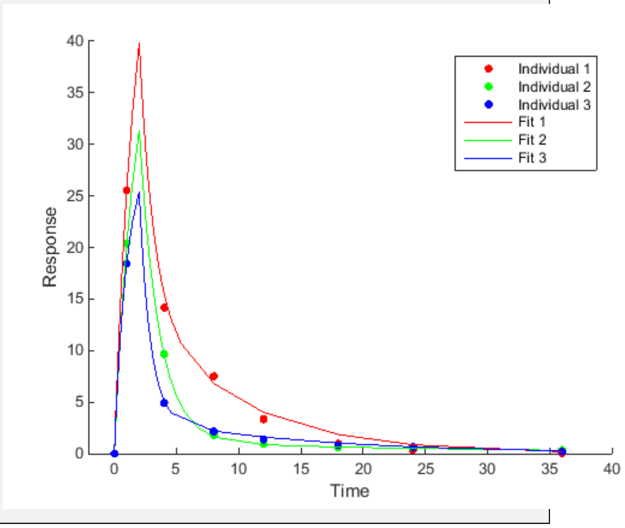
This model describes the time course of drug concentration in the body (C_t), as a function of the drug concentration after an intravenous bolus dose at t = 0 (C_0), time (t), and elimination rate parameter (k_e). ε is the mean-zero and unit-variance variable, that is, $\varepsilon \sim N(0,1)$ representing the measurement error and a is the error model parameter (here, standard deviation).

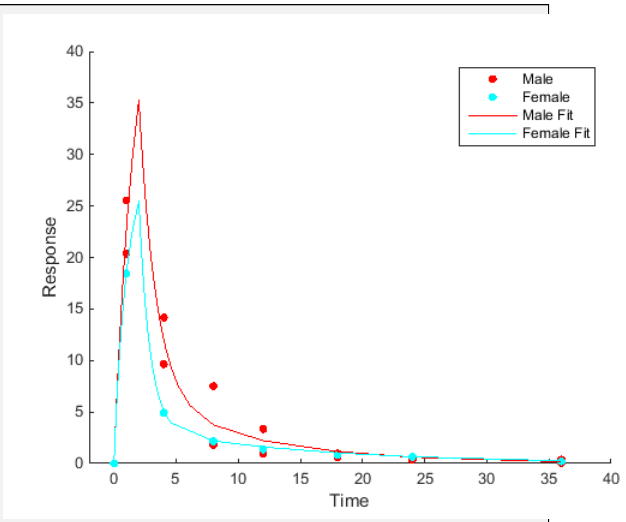
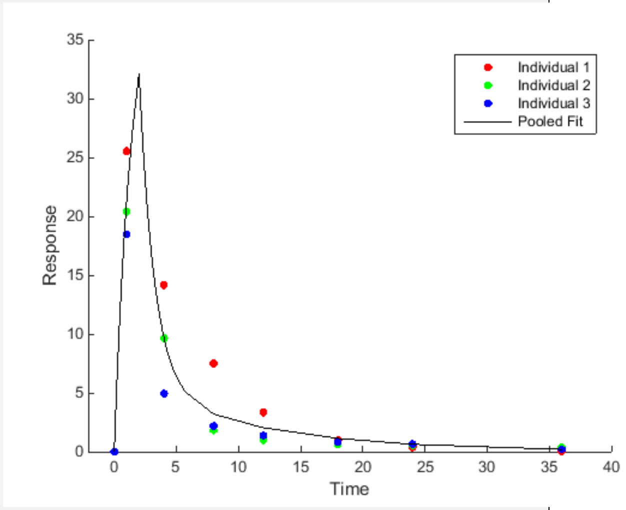
More generically, you can write the model as $y_j = f(x_j; p) + g(\varepsilon_j)$, where y_j is the jth response of interest (such as C_t), f is a function of known quantities x (such as C_0 and time t), model parameters p (such as k_e), and an error model $g(\varepsilon_j)$.

If there are multiple observations on multiple individuals, the model becomes $y_{ij} = f(x_{ij}; p_j) + g(\varepsilon_{ij})$ where y_{ij} is the jth observation of the ith individual. Additionally, you can categorize your data into different groups based on different categories such as sex, age, or height.

Fitting Options in SimBiology

This table summarizes nonlinear regression options available in SimBiology.

Fitting Option	Example
Individual-specific parameter estimation (Unpooled fitting) Fit each individual separately, resulting in one set of parameter estimates for each individual.	

Category- or group-specific parameter estimation Fit each category or group separately, resulting in one set of parameter estimates for each category.	
Population-wide parameter estimation (Pooled fitting) Fit all of the data pooled together, resulting in just one set of parameter estimates.	

Error Models

SimBiology supports the error models described in the following table. For instance, if you assume every observation has a constant amount of noise, use the constant error model, which is the default. Instead, if you assume the error is proportional to the response data, then the proportional error model might be more appropriate.

Error Model	Mathematical Representation	Standard Deviation of Error Model
constan (default	$y = f + a\varepsilon$	a
proport	$y = f + b\lvert f \rvert \varepsilon$	$b \lvert f \rvert$
combin	$y = f + (a + b\lvert f \rvert)\varepsilon$	$a+b \lvert f \rvert$
exponential	$y = f * \exp(a\varepsilon)$ or equivalently,	$\sqrt{e^{a^2} - 1} * e^a$
	$\log(y) = \log(f) + a\varepsilon$	a
Here, y is the response, f is the function value, ε is a standard mean-zero and unit-variance (Gaussian) variable, and a and b are error parameters. For instance, if you assume the error is approximately 5% of each observation, use the proportional error model with b = 0.05. In SimBiology, f typically represents the simulation result.		

Maximum Likelihood Estimation

To fit nonlinear regression models in SimBiology, use `sbiofit`. It minimizes the negative of the logarithm of the likelihood function. For normally distributed errors, the negative log-likelihood is:

$$-\ln \mathrm{L} = \sum_i^N \frac{\left(y_i - f\left(x_i; p\right)\right)^2}{2\sigma_i^2} + \sum_i^N \ln \sqrt{2\pi\sigma_i^2}$$

This formulation uses the following notation.

L	Log likelihood
N	Number of experimental observations
y_i	The ith experimental observation
$f\left(x_i; p\right)$	Predicted value of the ith observation, which is a function of independent variables x_i and estimated parameters p
σ_i	Standard deviation of the ith observation.

The exponential error model is additive and normally distributed on the log scale.

Therefore, the objective function becomes $-\ln \mathrm{L} = \sum_{i}^{N} \frac{\left(\ln y_i - \ln f\left(x_i ; p\right)\right)^2}{2\sigma_i^2} + \sum_{i}^{N} \ln \sqrt{2\pi\sigma_i^2}$

For details about objective functions and estimation methods, see “Objective Functions”.

Fitting Workflow for sbiofit

The following steps show one of the workflows you can use at the command line to fit a PK model.

1. Import data.
2. Convert the data to the `groupedData` format.
3. Define dosing data. For details, see “Doses” on page 1-42.
4. Create a structural model (one-, two-, or a multicompartment model). For details, see “Create Pharmacokinetic Models” on page 4-24.
5. Map the response variable from data to the model component. For example, if you have the measured drug concentration data for the central compartment, then map it to the drug species in the central compartment (typically the `Drug_Central` species).
6. Specify parameters to estimate using an `estimatedInfo object`. Optionally, you can specify parameter transformations, initial values, and parameter bounds.
7. Perform parameter estimation using `sbiofit`.

For illustrated examples, see the following.

- “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 Parameters of a G protein Model

In this section...

Overview

About the Example Model

This example illustrates parameter estimation using time-course data from one experiment, using the `sbioparamestim` function. For information on all available parameter estimation and population fitting techniques, see .

This example uses the model described in "Model of the Yeast Heterotrimeric G Protein Cycle" on page C-17 to illustrate parameter estimation.

This table lists the reactions used to model the G protein cycle and the corresponding rate parameters (rate constants) for each mass action reaction. For reversible reactions, the forward rate parameter is listed first.

No.	Name	Reaction[1]	Rate Parameters
1	Receptor-ligand interaction	`L + R <-> RL`	`kRL`, `kRLm`
2	Heterotrimeric G protein formation	`Gd + Gbg -> G`	`kG1`
3	G protein activation	`RL + G -> Ga + Gbg + RL`	`kGa`
4	Receptor synthesis and degradation	`R <-> null`	`kRdo`, `kRs`
5	Receptor-ligand degradation	`RL -> null`	`kRD1`
6	G protein inactivation	`Ga -> Gd`	`kGd`

No.	Name	Reaction[1]	Rate Parameters
[1] Legend of species: L = ligand (alpha factor), R = alpha-factor receptor, Gd = inactive G-alpha-GDP, Gbg = free levels of G-beta:G-gamma complex, G = inactive Gbg:Gd complex, Ga = active G-alpha-GTP			

About the Example

The study used to build the example model (Yi et al., 2003) reported the estimated value of parameter `kGd` as `0.11` for the wild-type strain. In "Calculate Sensitivities" on page 3-25, the analysis showed that `Ga` is sensitive to parameters `kGd`, `kRs`, `kRD1`, and `kGa`.

This example shows:

- How to estimate the parameter `kGd` and determine its effect on the model
- How to estimate parameters `kGd`, `kRs`, `kRD1`, and `kGa` to obtain a better fit to the experimental data

Loading the Example Model

The `gprotein.sbproj` project contains a model for the wild-type strain (stored in variable `m1`). Load the G protein model for the wild-type strain:

```
sbioloadproject gprotein
```

The `m1` model object appears in the MATLAB Workspace.

Defining Experimental Data

The study used for this example (Yi et al., 2003) reports, in a plot, the experimental data as the fraction of active G protein. Store the time data for the experimental results in a variable, `tExpt`, and store the values for the fraction of active G protein in a variable, `GaFracExpt`:

```
tExpt  = [0 10 30 60 110 210 300 450 600]';
GaFracExpt = [0 0.35 0.4 0.36 0.39 0.33 0.24 0.17 0.2]';
```

Note: For this simple example, you stored the experimental data in a variable in the MATLAB Workspace by typing the data values. However, typically, you import larger data sets into a MATLAB variable. For more information about importing data into variables, see "Methods for Importing Data".

Simulating the G Protein Model

1 Simulate the model and return the results to a `SimData object`:

```
simDataObj = sbiosimulate(m1);
```

2 Retrieve the time and state data for the `GaFrac` parameter:

```
[tOrig, GaFracOrig] = selectbyname(simDataObj,'GaFrac');
```

Calculating R^2 for the G Protein Model

R^2 is the square of the correlation between the response values and the predicted response values. Therefore, R^2 measures how successful the fit is in explaining the variation of the data.

1 Calculate the sum of squares about the mean (SST):

```
sst = norm(GaFracExpt - mean(GaFracExpt))^2;
```

2 Interpolate the data to get time points that match the time points in the experimental data using the `pchip` interpolation method:

```
GaFracResampled = interp1(tOrig, GaFracOrig, tExpt, 'pchip');
```

3 Calculate the sum of squares due to error (SSE):

```
sse = norm(GaFracExpt - GaFracResampled)^2;
```

4 Calculate the R^2 value for the simulation data before parameter estimation:

```
rSquareOrig = 1-sse/sst

rSquareOrig =

    0.8968
```

For more information about the functions used here, see the `norm` and `interp1` reference pages.

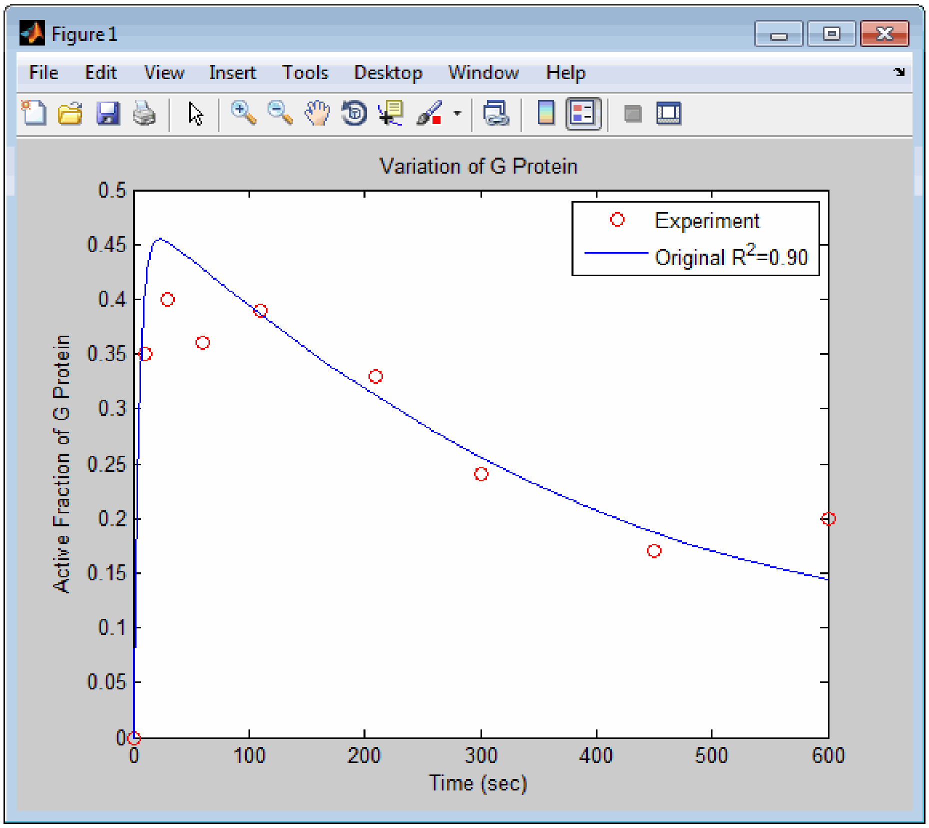
Plotting the Experimental Results and Simulation Data

1 Plot the experimental data for active G protein:

```
plot(tExpt, GaFracExpt, 'ro');
title('Variation of G Protein');
xlabel('Time (sec)');
ylabel('Active Fraction of G Protein');
legend('Experiment');
```

2 Plot the simulation data in the same plot:

```
hold on;
plot(tOrig, GaFracOrig);
legendText = {'Experiment', sprintf('Original R^2=%4.2f',...
               rSquareOrig)};
legend(legendText{:});
```



Note: Leave this figure window open so you can use it to plot and compare results of using the estimated parameters later in this example.

Estimating the kGd Parameter in the G Protein Model

The study used to build the G protein model reported an estimated value of `0.11` for the parameter `kGd` in the wild-type strain (Yi et al., 2003). This example estimates the value of `kGd`.

1. Create a variable for the parameter to estimate. Also create a variable for the parameter corresponding to the experimental data to which you are fitting:

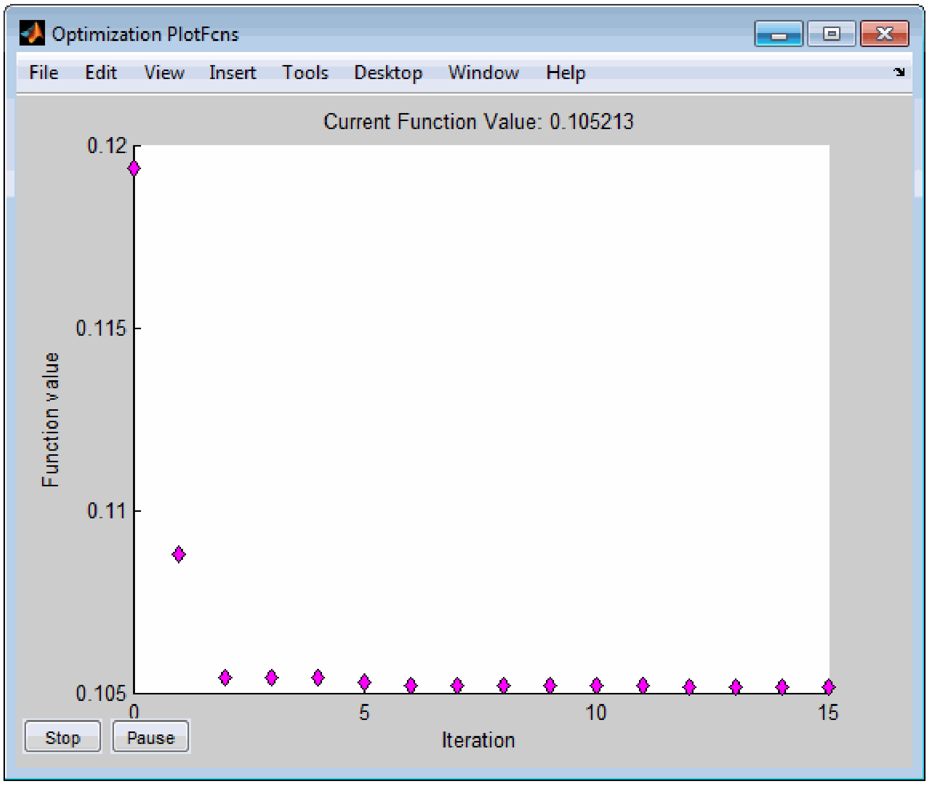
```
paramToEst = sbioselect(m1, 'Name', 'kGd');
GaFrac = sbioselect(m1, 'Name', 'GaFrac');
```

2. Specify plotting of each iteration of the parameter estimation to see how optimization is progressing:

```
opt = optimset('PlotFcns',@optimplotfval,'MaxIter',15);
```

3. Use the current value of the `kGd` parameter in the model as the starting value for optimization:

```
[estValues1, result1] = sbioparamestim(m1, tExpt, GaFracExpt, ...
                        GaFrac, paramToEst, {}, {'fminsearch',opt});
```


Optimization PlotFcns
File Edit View Insert Tools Desktop Window Help
Current Function Value: 0.105213
Function value
0.12
0.115
0.11
0.105
0
5
10
15
Iteration
Stop
Pause

Note: Close this figure before proceeding with the example.

Simulating and Plotting Results Using the Estimated Parameter

Use the estimated value of the `kGd` parameter to see how it affects simulation results.

1 Use a variant to store the estimated value of `kGd`:

```
estvarObj = addvariant (m1, 'Optimized kGd');
addcontent(estvarObj, {'parameter', 'kGd', 'Value', estValues1});
```

2 Apply the value stored in the variant, simulate the model, and return the results:

```
simDataObj1 = sbiosimulate(m1, estvarObj );
```

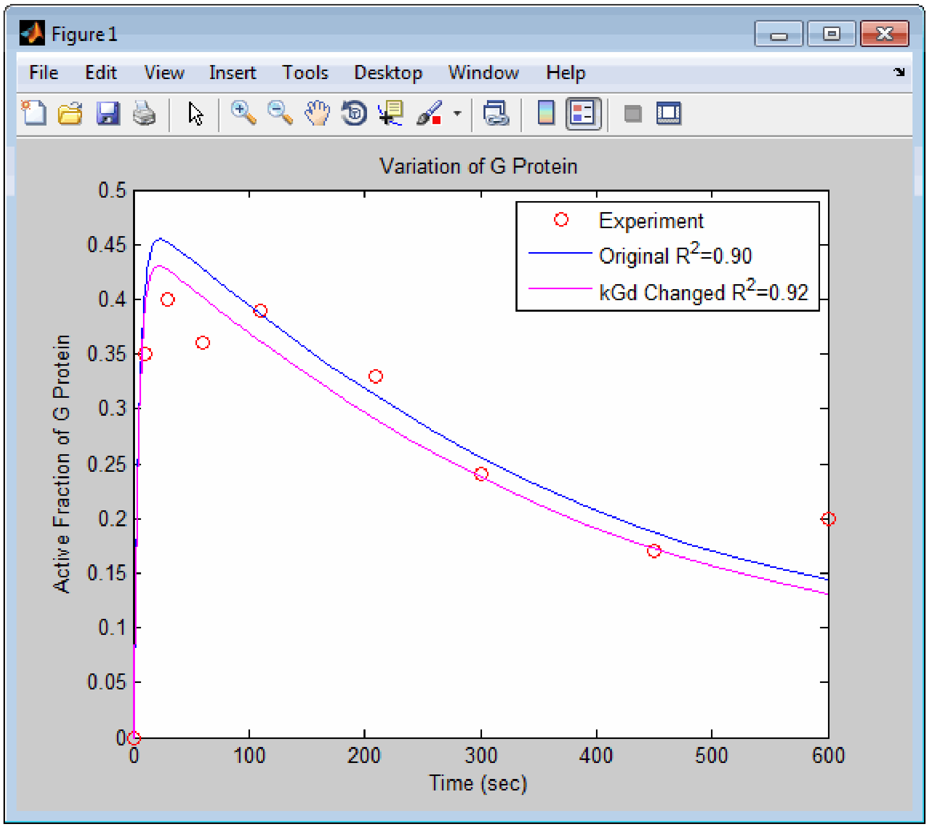
```
[t1, GaFrac1] = selectbyname(simDataObj1,'GaFrac');
```

3 Calculate the R^2 value with the new estimate obtained using `'fminsearch'`:

```
GaFrac1Resampled = interp1(t1, GaFrac1, tExpt, 'pchip');
sse1 = norm(GaFracExpt - GaFrac1Resampled)^2;
rSquare1 = 1 - sse1/sst

rSquare1 =

    0.9199
```

4 Plot the data and compare. If you left the previous figure open, because `hold` is `on`, the new plot appears in the existing figure to facilitate the comparison:

```
plot(t1, GaFrac1, 'm-');
legendText{end + 1} = sprintf('kGd Changed R^2=%4.2f', rSquare1);
legend(legendText{:});
```



The figure shows the best fit achieved by changing the parameter `kGd`.

Note: Leave this figure window open, so that you can use it later in this example.

Estimating Other Parameters in the G Protein Model

The example illustrating sensitivity analysis ("Calculate Sensitivities" on page 3-25) showed that `Ga` is sensitive to parameters `kRs`, `kRD1`, `kGa`, and `kGd`. Based on the results from the sensitivity analysis, this tutorial shows you how to estimate these parameters. The sensitivity data is presented in "Extract and Plot Sensitivity Data" on page 3-27.

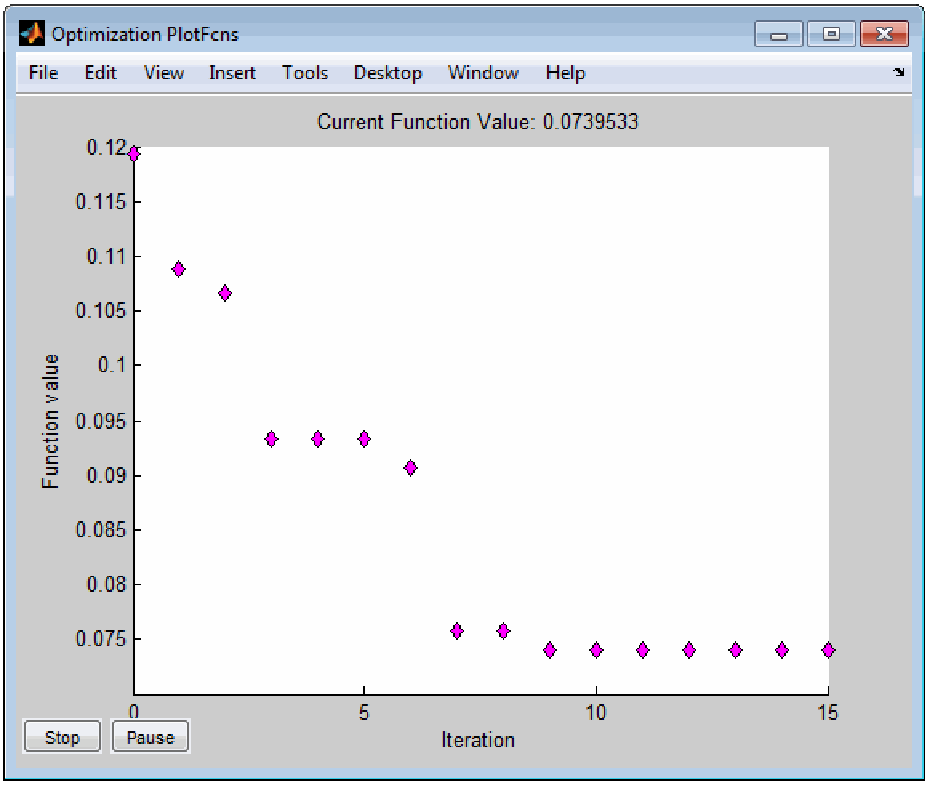
Note: Although this example estimates four parameters to fit the data, there is no published experimental data that verifies these values, and this example is only for illustration.

1 Create a variable containing the parameters to estimate:

```
paramsToEst = [sbioselect(m1, 'Name', 'kRs');...
               sbioselect(m1, 'Name', 'kRD1');...
               sbioselect(m1, 'Name', 'kGa');...
               sbioselect(m1, 'Name', 'kGd')];
```

2 Estimate the parameters. Use the current values of parameters in the model as the starting values for optimization. Use the `opt` variable you created previously to specify plotting of each iteration of the parameter estimation to see how optimization is progressing:

```
[estValues2, result2] = sbioparamestim(m1, tExpt, GaFracExpt,...
                        GaFrac, paramsToEst, {}, {'fminsearch',opt});
```



Note: Close this figure before proceeding with the example.

3 Compare original parameter values and the estimated parameter values obtained with `'fminsearch'`:

```
% Original parameter values
paramsToEst

SimBiology Parameter Array

Index:     Name:     Value:     ValueUnits:
1          kRs       4
2          kRD1      0.004
3          kGa       1e-005
```

```
4         kGd      0.11

% Estimated parameter values
num2str(estValues2)

ans =

      4.549
  0.0031018
9.0068e-006
    0.12381
```

4 Calculate the R^2 value using the new estimates obtained with `'fminsearch'`:

```
estvarObj2 = addvariant(m1, 'Optimized kRs, kRD1, kGa, and kGd');
addcontent(estvarObj2, ...
    {{'parameter', 'kRs', 'Value', estValues2(1)}, ...
    {'parameter', 'kRD1', 'Value', estValues2(2)}, ...
    {'parameter', 'kGa', 'Value', estValues2(3)}, ...
    {'parameter', 'kGd', 'Value', estValues2(4)}});
simDataObj2 = sbiosimulate(m1, estvarObj2);
[t2, GaFrac2] = selectbyname(simDataObj2, 'GaFrac');
GaFrac2Resampled = interp1(t2, GaFrac2, tExpt, 'pchip');
sse2 = norm(GaFracExpt - GaFrac2Resampled)^2;
rSquare2 = 1 - sse2/sst

rSquare2 =

    0.9603
```

5 Plot the data and compare. If you left the previous figure open, because `hold` is `on`, the new plot appears in the existing figure to facilitate the comparison:

```
plot(t2, GaFrac2, 'g-');
legendText{end + 1} = sprintf('4 Constants Changed R^2=%4.2f',...
                      rSquare2);
legend(legendText{:});
```

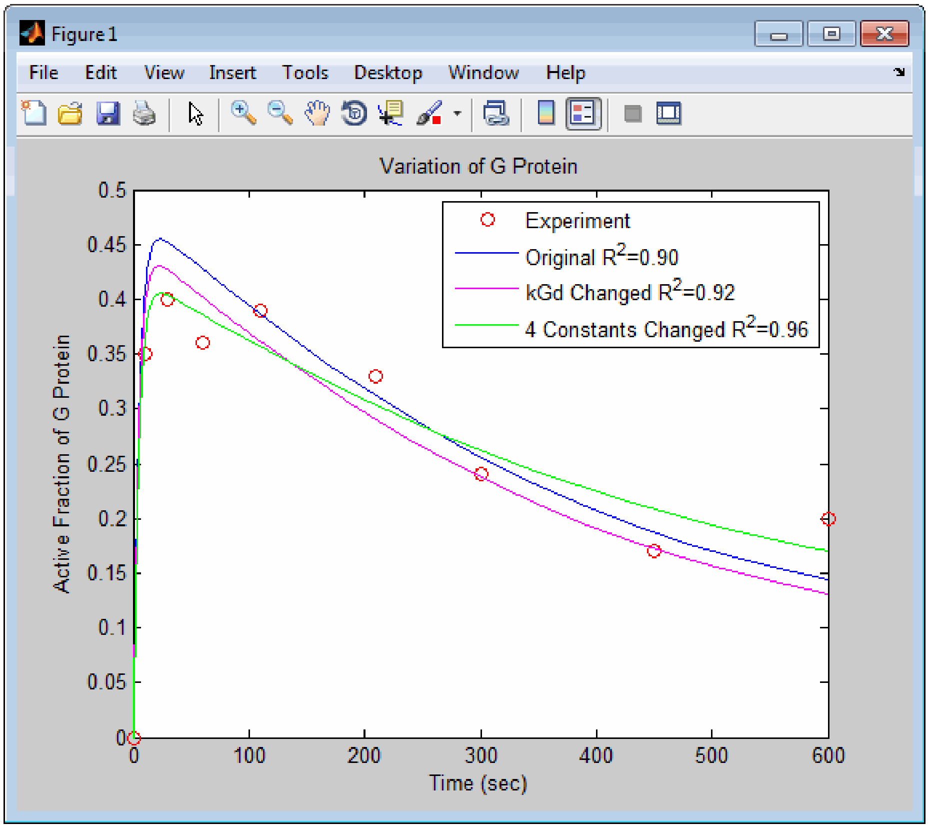


Figure 1
File Edit View Insert Tools Desktop Window Help
Variation of G Protein
Experiment
Original R²=0.90
kGd Changed R²=0.92
4 Constants Changed R²=0.96
Active Fraction of G Protein
0.5
0.45
0.4
0.35
0.3
0.25
0.2
0.15
0.1
0.05
0
0
100
200
300
400
500
600
Time (sec)

Accelerating Model Simulations and Analyses

In this section...

What Is Acceleration?

Normally, when simulating or analyzing a model in SimBiology, you express the model in MATLAB code. You can accelerate the simulation or analysis by converting the model to compiled C code, which executes faster. Because this compilation step has a small time overhead, acceleration is not recommended for individual simulations of small models. However, for large models, or for repeated simulations during analysis, acceleration can provide a significant speed increase that outweighs the small time overhead.

What Simulations and Analyses Can Be Accelerated?

You can accelerate the following:

- Simulating models
- Calculating sensitivities

Note: For parameter estimations (using `sbioparamestim`) and population fittings (using `sbionlinfit`, `sbionlmefit`, or `sbionlmefitsa`), acceleration is automatically enabled, if the prerequisites for accelerating simulations and analyses are met.

When to Accelerate Simulations and Analyses

The functionality to accelerate simulations performs optimally under the following conditions:

- Running many simulations with different initial conditions
- Running very long simulations (for example, simulations that take longer than a minute to run)

Prerequisites for Accelerating Simulations and Analyses

To prepare your 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.

Accelerate a Simulation or Analysis

Accelerating simulations is a two step process:

1. Use the `sbioaccelerate` function to prepare your model for accelerated simulations. Use the same input arguments that you plan to use with `sbiosimulate`. For example:

   ```
   sbioaccelerate(modelObj, configsetObj, doseObj);
   ```

   This step prepares your model for acceleration and may take a minute or longer to complete for very large models.

Note: You need to run `sbioaccelerate` again, before running simulations, if you make any modifications to this model, other than:

- Changes to any variants
- Changes to values for the `InitialAmount` property of species
- Changes to the `Capacity` property of compartments
- Changes to the `Value` property of parameters

2 Use the `sbiosimulate` function with the same input arguments that you used with `sbioaccelerate`. For example:

```
simdataObj = sbiosimulate(modelObj, configsetObj, doseObj);
```

Troubleshooting Accelerated Simulations and Analyses

If you have user-defined functions, do not use persistent variables in these functions. Persistent variables are not compatible with the functionality used for accelerating simulations.

If you specify user-defined functions in SimBiology expressions, you might see the following warning if your code is not compatible with code generation from MATLAB:

```
The SimBiology Expression and any user-defined functions
could not be accelerated. Please check that these expressions
and any user-defined functions are supported for code generation
as described in the Code Generation from MATLAB documentation.
```

where *Expression* is any of the following:

- Reaction rate/rule expression
- Repeated assignment rule expression
- Event trigger expression
- Event function expression

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.

Pharmacokinetic Modeling

Pharmacokinetic Modeling Functionality

In this section...

Overview

SimBiology software extends the MATLAB computing environment for analyzing pharmacokinetic (PK) data using models. The software lets you do the following:

- Create models — Use a model construction wizard. Alternatively, extend any model with pharmacodynamic (PD) model components, or build higher fidelity models. See "Model" on page 4-3 for more information.
- Fit data — Fit nonlinear, mixed-effects models to data, and estimate the fixed and random effects, or fit the data using nonlinear least squares. For more information, see "Analyze Data Using Models" on page 4-4.
- Generate diagnostic plots — For more information, see "Analyze Data Using Models" on page 4-4.

The software lets you work with different model structures, thus letting you try multiple models to see which one produces the best results.

Required and Recommended Software for Pharmacokinetic Modeling

Required Software

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.

Statistics and Machine Learning Toolbox (Version 7.3 (R2010a) or greater)	Provides fitting tools including functions used to analyze nonlinear mixed effects.

Recommended Software

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

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 specify additional methods for likelihood maximization. If you do not have this product, SimBiology uses `fminsearch` provided by MATLAB for likelihood maximization.

How SimBiology Supports Pharmacokinetic Modeling

Import and Work with Data

You can import tabular data into the SimBiology desktop or the MATLAB Workspace. The supported file types are `.xls`, `.csv`, and `.txt`. You can specify that the data is in a NONMEM® formatted file. The import process interprets the columns according to the NONMEM definitions.

From the SimBiology desktop, you can filter the raw data to suppress outliers, visualize data using common plots (such as `plot`, `semilog`, `scatter`, or `stairs`), and perform basic statistical analysis. You also can use functions to process and visualize the data at the command line.

Model

SimBiology provides an extensible modeling environment. You can do any of the following:

- Create a PK model using a model construction wizard to specify the number of compartments, the route of administration, and the type of elimination.
- Extend any model with pharmacodynamic (PD) model components, or build higher fidelity models.
- Build or load your own SimBiology, or SBML model.

For more information on building SimBiology models, see "What is a Model?" on page 1-2.

Analyze Data Using Models

Perform both individual and population fits to grouped longitudinal data:

- Individual fit — Fit data using nonlinear least-squares method, specify parameter transformations, estimate parameters, and calculate residuals and the estimated coefficient covariance matrix.
- Population fit — Fit data, specify parameter transformations, and estimate the fixed effects and the random sources of variation on parameters using nonlinear mixed-effects models.

  You can use the following methods to estimate the fixed effects:

  - `LME` — Linear mixed-effects approximation
  - `RELME` — Restricted LME approximation
  - `FO` — First-order estimate
  - `FOCE` — First-order conditional estimate

  For more information about each of these methods, see `nlmefit` in the Statistics and Machine Learning Toolbox documentation.
- Population fit using a stochastic algorithm — Fit data, specify parameter transformations, and estimate the fixed effects and the random sources of variation on parameters, using the Stochastic Approximation Expectation-Maximization (SAEM) algorithm. SAEM is more robust with respect to starting values. This functionality relaxes assumption of constant error variance.

  For more information, see `nlmefitsa` in the Statistics and Machine Learning Toolbox documentation.

In addition, you can generate diagnostic plots that show:

- The predicted time courses and observations for an individual or the population

- Observed versus predicted values
- Residuals versus time, group, or predictions
- Distribution of the residuals
- A box-plot for random effects or parameter estimates from individual fitting

Using the Command Line Versus the SimBiology Desktop

SimBiology extends MATLAB and lets you access pharmacokinetic modeling functionality at the command line and in 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 lets you encapsulate models, data, tasks, task settings, and diagnostic plots into one convenient package, namely a SimBiology project.

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

Pharmacokinetic Modeling Example

For an example showing pharmacokinetic modeling functionality at the command line, see Modeling the Population Pharmacokinetics of Phenobarbital in Neonates.

Acknowledgements: Tobramycin Data Set

Acknowledgements for data in the `tobramycin.txt` file in the `/matlab/toolbox/simbio/simbiodemos` folder:

References

[1] Original Publication: Aarons L, Vozeh S, Wenk M, Weiss P, and Follath F. "Population pharmacokinetics of tobramycin." *Br J Clin Pharmacol.* 1989 Sep;28(3):305–14.

Data set provided by Dr. Leon Aarons, (`laarons@fs1.pa.man.ac.uk`)

The data in the `tobramycin.txt` file were downloaded from the Web site of the Resource Facility for Population Kinetics `http://depts.washington.edu/rfpk/service/datasets/index.html` (no longer active). Funding source: NIH/NIBIB grant P41-EB01975.

The original data set was modified as follows:

- Header comments were removed.
- The file was converted to a tab-delimited format.
- Missing values in the `HT` column were denoted with `"."` instead of `100000000.000`.

Importing Data — Supported Files and Data Types

In this section...

Supported Files and Data Types

You can import tabular data to the SimBiology desktop or to the MATLAB Workspace. The supported file types are `.xls`, `.csv`, and `.txt`. You can specify that the data is in a NONMEM formatted file. The import process interprets the columns according to the NONMEM definitions. For more information see "Support for Importing NONMEM Formatted Files" on page 4-7.

From the SimBiology desktop, you can filter the raw data to suppress outliers, visualize data using common plots (such as `plot`, `semilog`, `scatter`, or `stairs`), and perform basic statistical analysis. You also can use functions to process and visualize the data at the command line.

Note: If your data set contains dosing information that is infusion data, the data set must contain the rate and not an infusion duration.

Unit Conversion

Regardless of whether unit conversion functionality is on or off, dosing in the data file must be expressed in amounts (or as `amount/time` for infusion rate). By default **Unit Conversion** is off, so you must ensure that units for the data are consistent with each other. If you want to turn on unit conversion, see "Unit Conversion for Imported Data" on page 4-33 .

Support for Importing NONMEM Formatted Files

You can specify that the data is in a NONMEM formatted file. The following table highlights the interpretation of this data in SimBiology software.

Column Header	Interpretation
ID	text (string), numeric, or categorical values that identify the record or group. The import process assumes that contiguous data with the same value contains data from one individual. If the data contains non-contiguous references to the same value, the import process assigns the second ID encountered an indexed valued derived from the group first encountered. For example, if the ID columns contains [1 1 1 2 2 2 1 1 1], the IDs assigned are 1, 2, 1_1.
TIME	Monotonically increasing positive values within each group, indicating time of observation or dose or text (string). The data file can specify clock (2:30 as a string) or decimal values (6.25). The import process assigns a value of 0 to the first TIME value in the data file. The import process assigns subsequent values relative to the first value. The following table is an example of how the import process interprets the clock values as decimal values. Original Clock Values → Imported Values: 10:00 → 0 10:30 → 0.5 11 → 1 12:30 → 2.5 If the data file also contains a DATE column, the import process uses it with the TIME column in calculating the relative TIME values. The column cannot contain Inf.

Original Clock Values	Imported Values
10:00	0
10:30	0.5
11	1
12:30	2.5

Column Header	Interpretation
DATE, DAT1, DAT2, or DAT3	Defines the day of the observation or the dose. The column can contain the month as a number (9) or a string (Sep). Specify date in the following formats: • DATE — The column can specify month/day/year or month-day-year. If you specify two numbers, the import process assumes they are month and day. You can use either / or - as a separator. • DAT1 — The column can specify day/month/year or day-month-year. If you specify two numbers, the import process assumes they are day and month. • DAT2 — The column can specify year/month/day or year-month-day. If you specify two numbers, the import process assumes they are month and day. • DAT3 — The column can specify year/day/month or year-day-month. If you specify two numbers, the import process assumes they are day and month. **Note:** • If you specify only one number, the import process assumes it is the day. • You can omit the year or specify 1, 2, 3, or 4 digits. If you specify two-digit years, it is assumed to be in the 1900s. • If the data has the DAT1, DAT2, or DAT3 column, set the DateLabel property of a NMFileDef object accordingly using sbionmfiledef. Then specify the object as the second input argument when you run sbionmimport.
DV	Numeric value of an observation. Column cannot contain Inf or –Inf.

Column Header	Interpretation
`MDV`	Defines whether a row describes an observation: • Row contains 0 — Observation event • Row contains 1 — Not an observation event
`EVID`	Defines the type of event described for the row in the record: • 0 — Observation event; row contains an observed value. • 1 — Dose event; row describes a dose. • 2 — Other event; row describes some other event such as measurement of a covariate. If a column contains values for dose, but `EVID` is not `1`, the import process ignores the value. You see a warning and the value is ignored. If `EVID` is set to 2, then only those specified row data are imported as covariate data. However, if you have an `EVID` column as well as one or more covariate columns, but do not specify a value of `2` anywhere in the `EVID` column, then SimBiology imports all the row data as covariate values. The import process does not support values `3` and `4`. You see a warning and the value is ignored.

Column Header	Interpretation
CMT	Indicates which compartment is used for observation value or for dose received. The interpretation also depends on EVID: • Observation event (EVID = 0) — CMT column indicates which compartment was used for observation value. • Dose Event (EVID = 1) — CMT column indicates which compartment received the dose. **Note:** SimBiology numbers compartments starting with 1, while NONMEM numbers them starting with 0. For instance, if a NONMEM data file contains doses and measurements for CMT = 0, SimBiology generates data columns named Dose1 and Response1 respectively.
AMT	Positive number indicating dose. 0 or NaN specifies no dose administered. The column cannot contain Inf.
RATE	Positive number indicating rate of infusion. 0 specifies an infinite rate (equivalent to a bolus dose), and NaN specifies no rate. The column cannot contain Inf.
II	Positive number defining the time between doses.
ADDL	When the data specifies a number of identical serial doses at specific intervals (defined by II), ADDL specifies the number of doses in the series excluding the initial dose. If the data specifies II but not ADDL, then SimBiology assumes that the dosing occurs for the duration of that data record.

Unsupported NONMEM Definitions

The import process does not support (and therefore ignores) the rows containing the following values or definitions:

- EVID values 3 and 4
- SS column for specifying steady state doses
- PCMT column to define whether to compute a prediction for the row

- `CALL` column for calling the ERROR or the PK subroutine
- If rate is specified as being less than zero, it is assumed to be zero

Creating a Data File with SimBiology Definitions

If you are creating a file containing population data that you want to later import into SimBiology, create the data file with the following columns:

- Group column — Specify text, numeric, or categorical values. The rows in the file that have the same Group column value are for the same individual.
- Time column — Specify monotonically increasing positive values within each group that define the time of the dose, observation and/or covariate measurements.
- Zero or more dosing columns — Create one dosing column for each compartment being dosed. In each column, specify positive values representing doses in amount that are added to a species. Use `0` or `NaN` to specify that no dose was applied at the specified time. This is useful for times when an observation was recorded but no dose was applied.
- Zero, or more rate columns — Specify positive values. Zero specifies an infinite rate and `NaN` specifies that no rate applies. The rate column is associated with a dosing column and defines the rate at which the dose is administered.
- Zero or more observation columns — Specify numeric values or `NaN`s. You can only specify one observation value at a particular time for each group. `NaN` values define that no observation was recorded at the specified time. This is useful for times when a dose was applied but no observation was recorded.
- Zero or more covariate columns — Specify numeric values or `NaN`s. Each value defines the covariate value at the specified time. `NaN` values define that no covariate observation was recorded at the specified time.

  If you set an `EVID` value of `2` for some rows, then SimBiology imports only those rows as covariate data. If you do not mention an `EVID` value of `2` anywhere and have one or more covariate columns, then SimBiology imports all the row data as covariate data.

Importing Data

In this section...

Import Data from Files

Use the `dataset` function to import tabular data with named columns into an array that you can use in fitting and analysis at the command line. Use this function when you want to import the data without NONMEM interpretation of column headers. The `dataset` function lets you specify parameter/value pair arguments in which you can specify options such as the type of delimiter, and whether the first row contains header names. For more information, see `dataset`.

To prepare the data file for import, remove any comments that are present at the beginning of the file.

Examples:

```
% text files
data = dataset('file', 'tobramycin.txt')
% text files with . in place of missing values
data = dataset('file', 'tobramycin.txt', 'TreatAsEmpty', '.')

% For Excel files
data = dataset('xlsfile', 'tobramycin.xls')
```

You can also construct the `dataset` array from variables in the MATLAB Workspace.

```
% Create a 10x2 array
x = rand(10,2);
% Construct a dataset array containing x
data = dataset({x(:, 1), 'Column1'}, {x(:,2), 'Column2'})
```

If you import the data as separate variables containing doubles, you can construct the `dataset` array by concatenating the variables.

```
% Create 2 10x1 vectors
```

```
x = rand(10,1);
y = rand(10,1);
% Construct a dataset array containing x and y
data = dataset({x, 'Column1'}, {y, 'Column2'})
```

After you finish analyzing your data, you can export any new variables in the MATLAB Workspace to a variety of file formats.

Importing Data from NONMEM-Formatted Files

Use the `sbionmimport` function to import data from NONMEM formatted files. To import the data without NONMEM interpretation of column headers, see “Import Data from Files” on page 4-13.

To prepare the data file for import, remove any comments that are present at the beginning of the file and select one of the following methods to import your data:

- If the data file contains only the column header values shown in “Support for Importing NONMEM Formatted Files” on page 4-7, use the syntax shown in the following example:

  ```
  filename = 'C:\work\datafiles\dose.xls';
  ds = sbionmimport(filename);
  ```
- If the data file has column header labels different from the table shown in “Support for Importing NONMEM Formatted Files” on page 4-7 and you want to apply NONMEM interpretation of headers:

  1. Create a NONMEM file definition object. This object lets you define what the column headers in the data file mean in SimBiology. In the following example, the column containing response values is `CP`, whereas in NONMEM formatted files the column is labelled `DV`.

     To use the tobramycin data set [1], create a NONMEM file definition object and define the following:

     ```
     def = sbionmfiledef;
     def.DoseLabel = 'DOSE';
     def.GroupLabel = 'ID';
     def.TimeLabel = 'TIME';
     def.DependentVariableLabel = 'CP';
     def.MissingDependentVariableLabel = 'MDV';
     def.EventIDLabel = 'EVID';
     def.ContinuousCovariateLabels = {'WT', 'HT', 'AGE', 'SEX', 'CLCR'};
     ```

Your file can contain any name for column headings. See `sbionmfiledef` for the list of properties you can configure in the NONMEM file definition object.

2 Use the `sbionmimport` function to import your data file with the column header definitions as specified in the NONMEM file definition object. For example, browse to *`matlabroot`*`/toolbox/simbio/simbiodemos/` (where *`matlabroot`* is the folder where MATLAB is installed).

```
[data, pkDataObject] = sbionmimport('tobramycin.txt', def, ...
   'TreatAsEmpty', '.');
```

This example shows you how to obtain the PKData object, `PKDataObj`, while importing, since you will use the PKData object in fitting the model later.

The `sbionmimport` function accepts property-name-value pairs accepted by `dataset`. For example, if the data set does not contain column headers, use `'ReadVarNames', false` to specify that `sbionmimport` should read values from the first row of the file.

For information about creating a model to fit the data, see “Create a Pharmacokinetic Model Using the Command Line” on page 4-26.

Other Resources for Importing Data

For detailed information about supported data formats and the functions for importing data into the MATLAB Workspace, see the “Methods for Importing Data”.

You also can import data using the MATLAB Import Wizard (see “Import Images, Audio, and Video Interactively”. Use the Import Wizard, to import data as text files (such as `.txt` and `.dat`), MAT-files, and spreadsheet files, (such as `.xls`).

The MATLAB Import Wizard processes the data source. The wizard recognizes data delimiters, as well as row or column headers, to facilitate the process of data selection and importation into the MATLAB Workspace. You can import the data to the SimBiology desktop from the MATLAB Workspace.

Import Data from a NONMEM-Formatted File Using the SimBiology Desktop

This example shows how to import data from a NONMEM-formatted file. The data can be in any of the following supported file formats: .xlsx, .xls, .csv, and .txt. Note: Before importing any NONMEM formatted data from a file, remove any comments that are present at the beginning of the file.

Load Sample Data

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

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

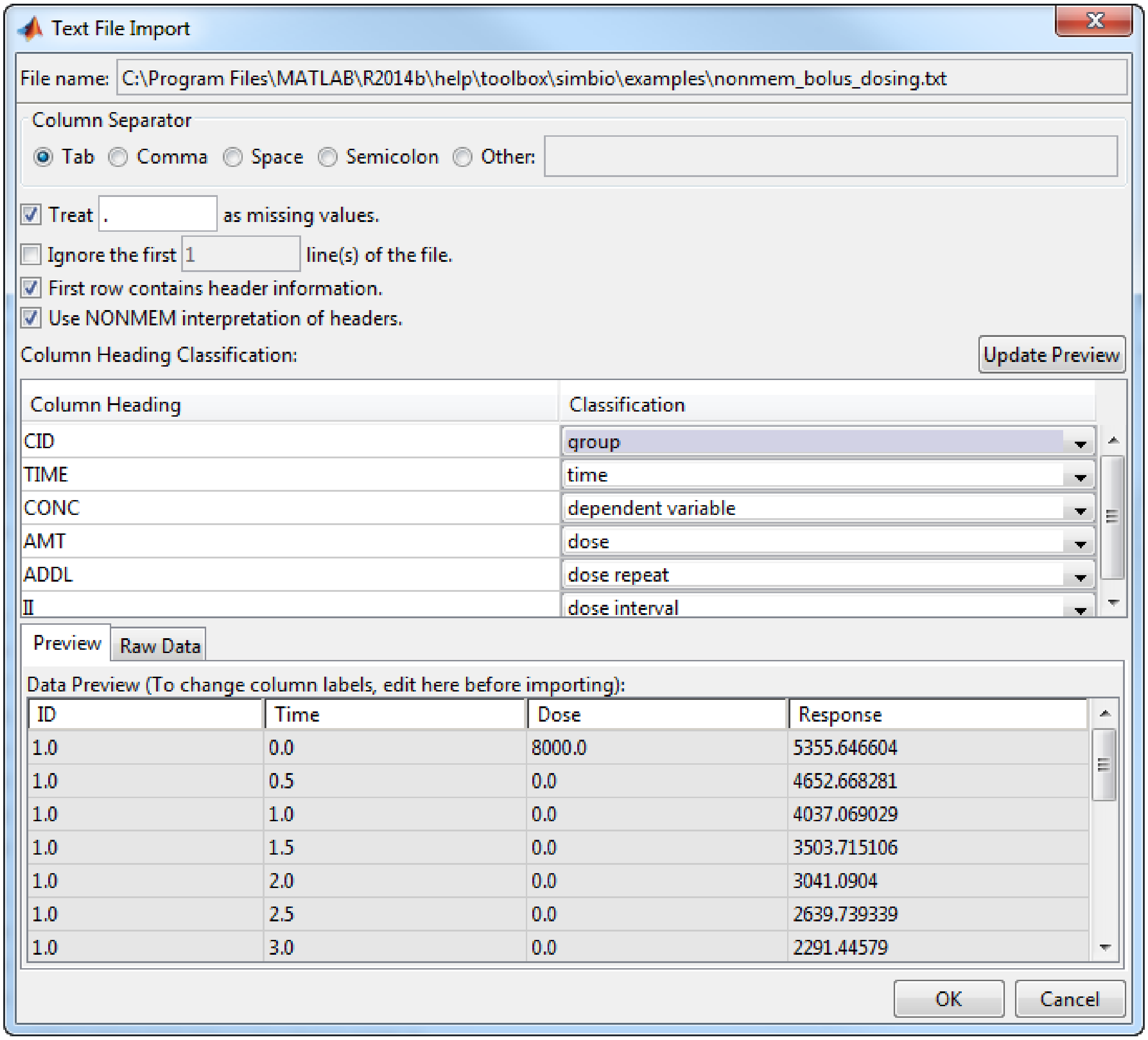
Navigate to the folder *`matlabroot`*`\help\toolbox\simbio\examples`, where *`matlabroot`* is the folder where MATLAB is installed, and open a sample NONMEM-formatted file named `nonmem_bolus_dosing.txt`. This file contains synthetically generated data for 20 individuals who received bolus doses every 8 hours for 5 times, and drug plasma concentrations were recorded every half hour for 60 hours.

Note: If you are using a Macintosh platform, press **Command+Shift+G** in the File Browser dialog box, and enter the full path to the folder.

Configure NONMEM Data Settings

From the **Text File Import** dialog box, select **Tab** as **Column Separator**, and select **Use NONMEM interpretation of headers**.

The **CID** column heading corresponds to groups of patients. Select `group` to identify it as a group column, and click **Update Preview**.



File name: C:\Program Files\MATLAB\R2014b\help\toolbox\simbio\examples\nonmem_bolus_dosing.txt

Column Separator: [✓ Tab] Comma Space Semicolon Other:

[✓] Treat . as missing values.

[ ] Ignore the first 1 line(s) of the file.

[✓] First row contains header information.

[✓] Use NONMEM interpretation of headers.

Column Heading Classification:

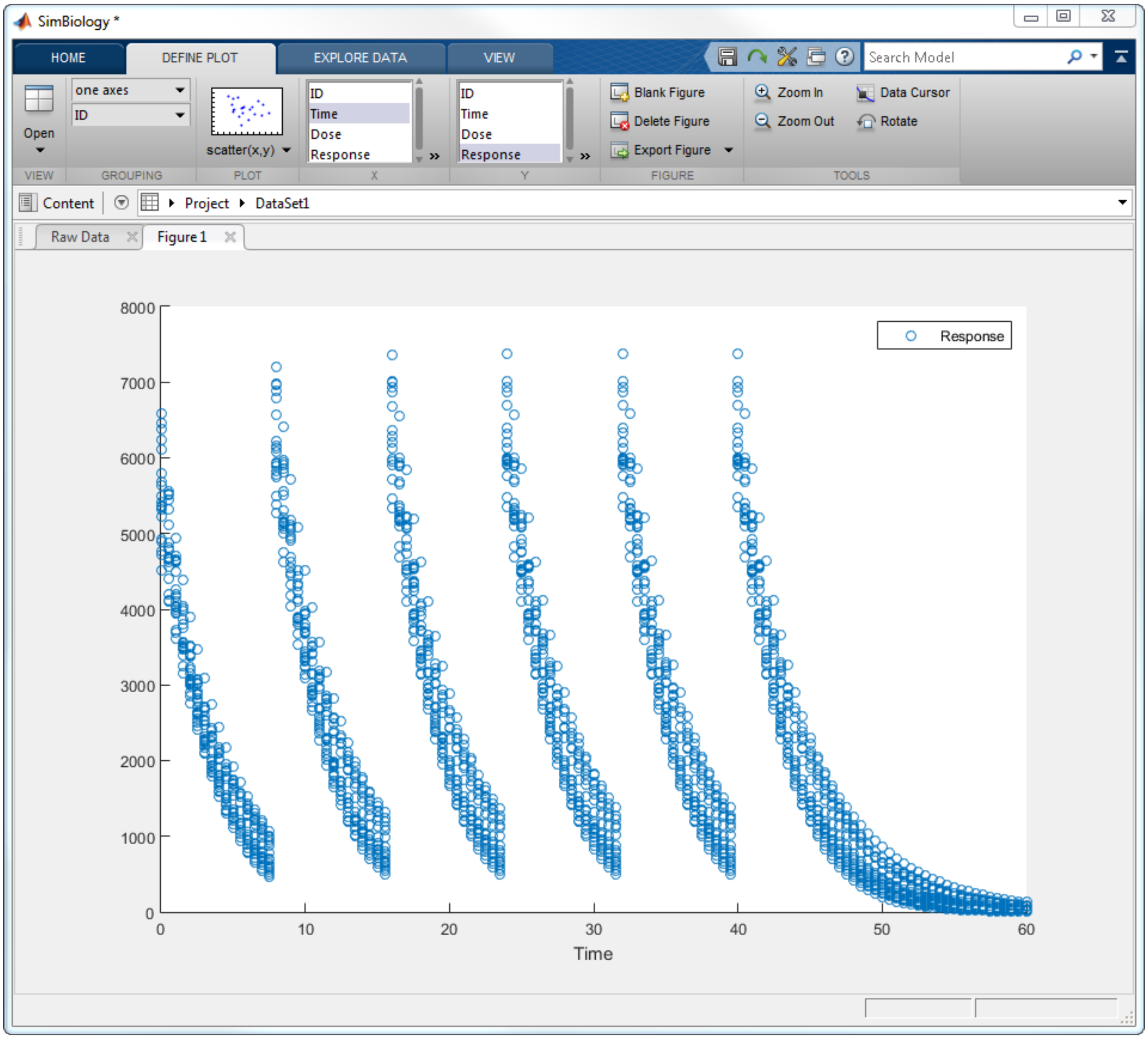
Column Heading	Classification
CID	group
TIME	time
CONC	dependent variable
AMT	dose
ADDL	dose repeat
II	dose interval

Data Preview (To change column labels, edit here before importing):

ID	Time	Dose	Response
1.0	0.0	8000.0	5355.646604
1.0	0.5	0.0	4652.668281
1.0	1.0	0.0	4037.069029
1.0	1.5	0.0	3503.715106
1.0	2.0	0.0	3041.0904
1.0	2.5	0.0	2639.739339
1.0	3.0	0.0	2291.44579

Note: The import dialog maps NONMEM column headings to appropriate data classification categories for SimBiology to interpret the data. If there is any ambiguity, a warning message is shown at the bottom of the window.

Click **OK** to load the data, and SimBiology generates a scatter plot of time versus response for all individuals as shown next.

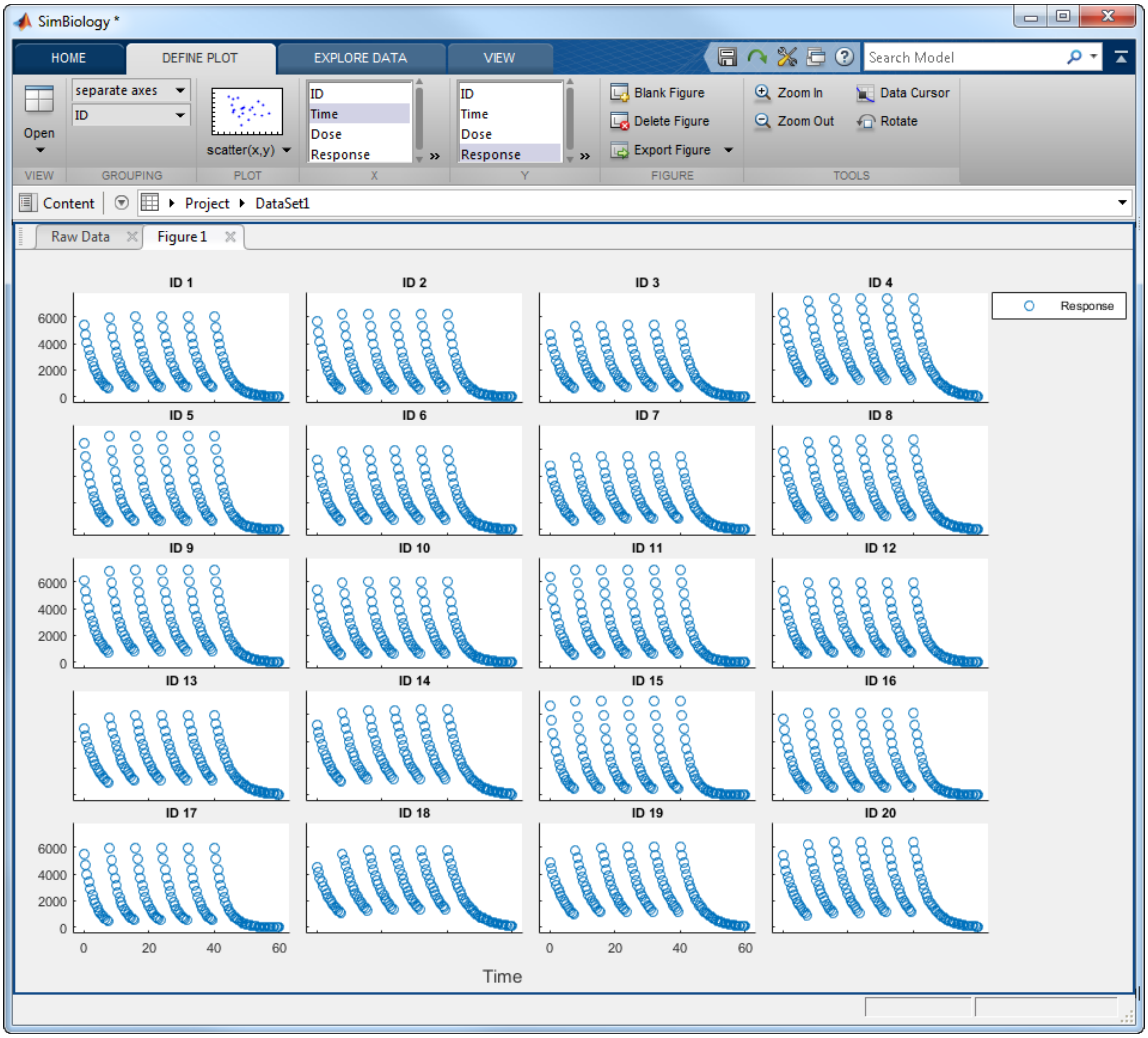


View Raw Data

Click the **Raw Data** tab at the bottom of the plot to see a tabular format of the data. Notice that SimBiology has generated an updated **Dose** column and a **Response** column, which is the CONC column of the original NONMEM data. You can assign appropriate units using the drop-down list under each column.

Define Plot Settings

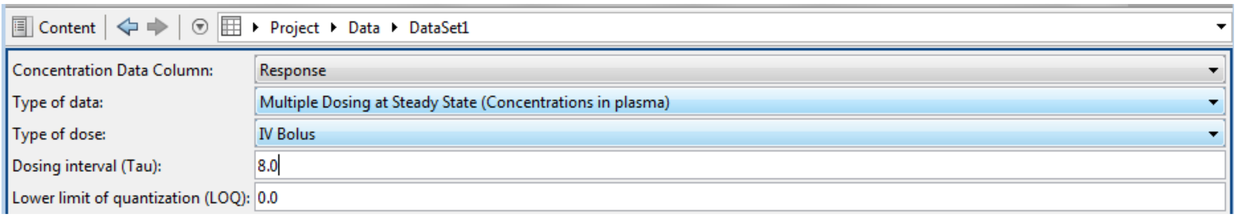
Instead of having shown in one axes for all patients, you can have separate axes for each individual. Go back to the **Figure 1** tab. On the **Define Plot** tab, in the **Grouping** section, select **separate axes** instead of **one axes**. SimBiology then generates separate axes for all individuals.



Noncompartmental Analysis (NCA) Parameters

If the imported data includes columns labeled `independent variable`, `dependent variable`, and `dose`, then SimBiology calculates noncompartmental analysis (NCA) parameters including AUC, MRT, terminal half life, and clearance that can be useful initial estimates for parameter estimation tasks.

To view NCA parameters, select **Open** > **NCA**. Since the imported data contains multiple doses, change the **Type of data** to **Multiple Dosing at Steady State (Concentrations in plasma)**, and enter `8.0` for **Dosing interval (Tau)**.



Concentration Data Column:	Response
Type of data:	Multiple Dosing at Steady State (Concentrations in plasma)
Type of dose:	IV Bolus
Dosing interval (Tau):	8.0
Lower limit of quantization (LOQ):	0.0

The **Table of NCA Parameters** is then updated. In order to see the description of each parameter and select which parameter to include in the calculation, right-click anywhere on the table, and select **NCA Parameters to Calculate**.

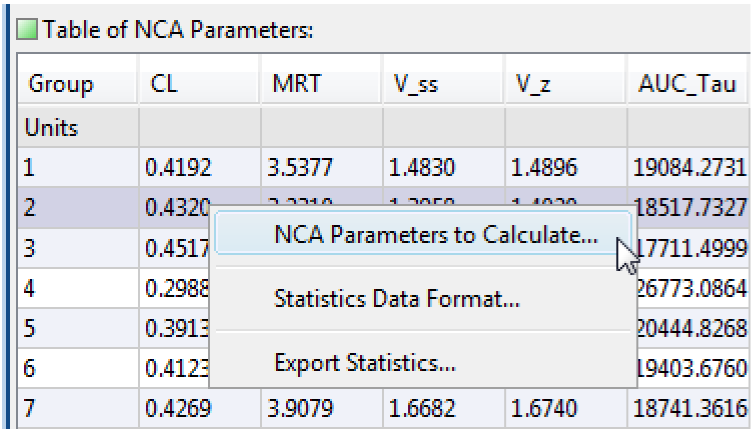


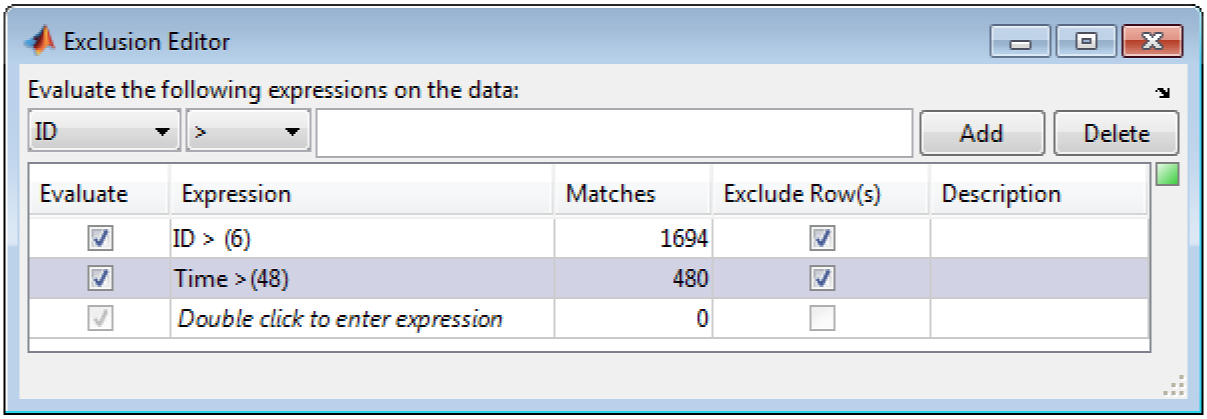
Table of NCA Parameters:

Group	CL	MRT	V_ss	V_z	AUC_Tau
Units					
1	0.4192	3.5377	1.4830	1.4896	19084.2731
2	0.4320	[illegible]	[illegible]	[illegible]	18517.7327
3	0.4517				17711.4999
4	0.2988				26773.0864
5	0.3913				20444.8268
6	0.4123				19403.6760
7	0.4269	3.9079	1.6682	1.6740	18741.3616

You can also export the parameters as a dataset or separate variables to the MATLAB Workspace using the **Export Statistics** option.

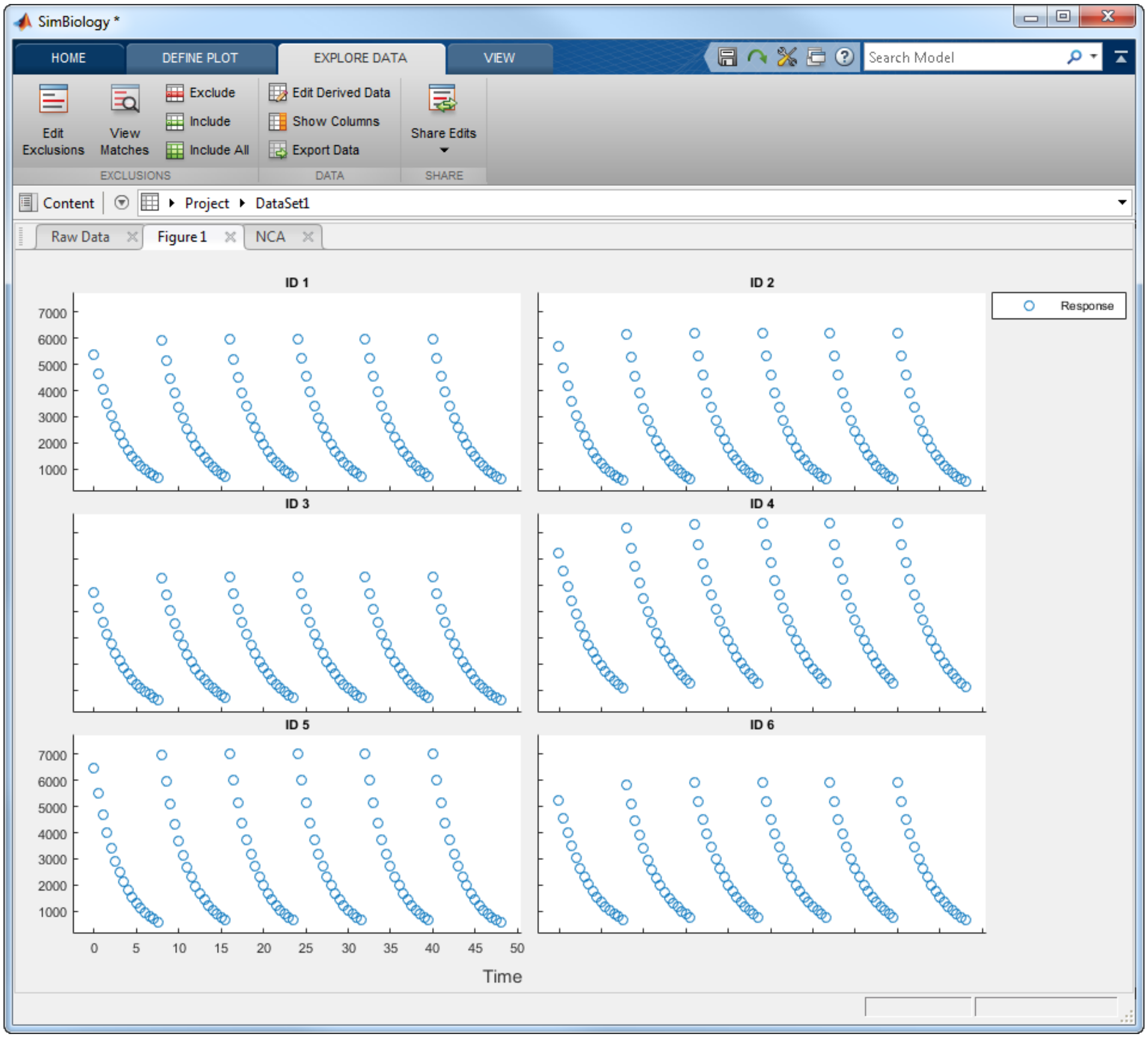
Filter Data

You can filter the data and select which data to plot by defining data exclusion rules. On the **Explore Data** tab, click **Edit Exclusions**. To exclusively view the response data of the first six individuals for day 1 and day 2, add two exclusions: `ID > (6)`, and `Time > (48)`. Select **Exclude Row(s)** for each expression as shown next.



Evaluate	Expression	Matches	Exclude Row(s)	Description
✓	ID > (6)	1694	✓	
✓	Time > (48)	480	✓	
✓	*Double click to enter expression*	0		

Go back to the **Figure 1** tab, and it now shows only the first six individual data for the first two days.



If necessary, you can add additional data exclusion expressions and share them via **Share Edits** icon on the **Explore Data** tab.

More About

- "Support for Importing NONMEM Formatted Files" on page 4-7

Create Pharmacokinetic Models

In this section...

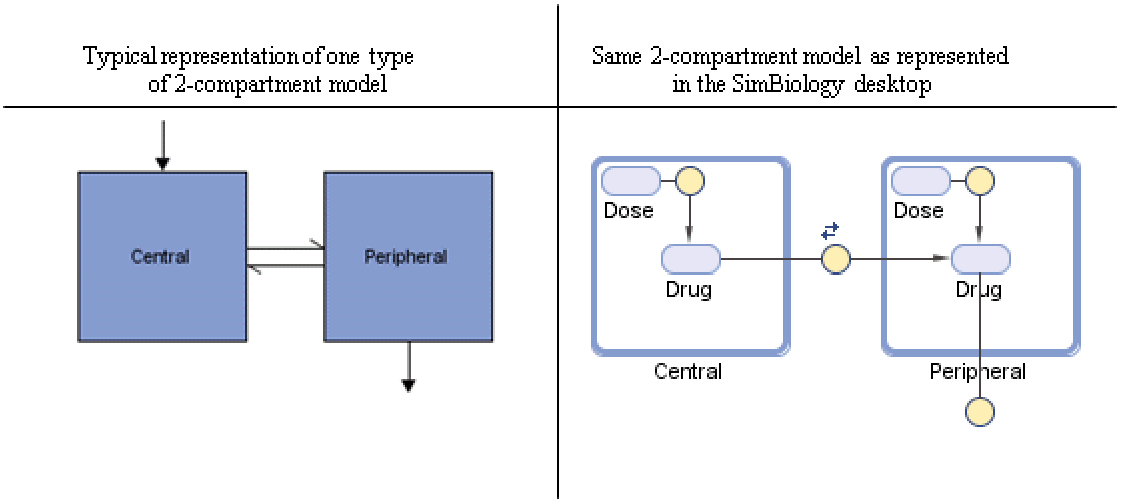
Ways to Create or Import Pharmacokinetic Model

To start modeling, you can:

- Create a PK model using a model construction wizard that lets you specify the number of compartments, the route of administration, and the type of elimination.
- Extend any model to build higher fidelity models.
- Build or load your own model. Load a SimBiology project or SBML model.

How SimBiology Models Represent Pharmacokinetic Models

The following figure compares a model as typically represented in pharmacokinetics with the same model shown in the SimBiology model diagram. For this comparison, assume that you are modeling administration of a drug using a two-compartment model with any dosing input and linear elimination kinetics. (The model structure remains the same with any dosing type.)


Typical representation of one type of 2-compartment model
Same 2-compartment model as represented in the SimBiology desktop
Central
Peripheral
Dose
Drug
Dose
Drug
Central
Peripheral

Comparison of views in PK

Note the following:

- SimBiology represents the concentration or amount of a drug in a given compartment or volume by a species *object* contained within the compartment.
- SimBiology represents the exchange or flow of the drug between compartments and the elimination of the drug by reactions.
- SimBiology represents intercompartmental clearance by a parameter (`Q`) which specifies the clearance between the compartments.
- SimBiology drives the dosing schedule with a combination of species (`Drug` and/or `Dose`) and reactions (`Dose -> Drug`), depending on whether the administration into the compartment follows bolus, zero-order, infusion, or first-order dosing kinetics. For more information on the components added and parameters estimated, see "Dosing Types" on page 4-28.

You can also view this model as a regression function, `y = f(k,u)`, where `y` is the predicted value, given values of an input `u`, and parameter values `k`. In SimBiology the model represents `f`, and the model is used to generate a regression function if `y`, `k`, and `u` are identified in the model.

Create a Pharmacokinetic Model Using the Command Line

To create a PK model with the specified number of compartments, dosing type, and method of elimination:

1 Create a `PKModelDesign` object. The `PKModelDesign` object lets you specify the number of compartments, route of administration, and method of elimination, which SimBiology uses to construct the model object with the necessary compartments, species, reactions, and rules.

```
pkm = PKModelDesign;
```

2 Add a compartment specifying the compartment name, and optionally, the type of dosing, and the method of elimination. Also specify whether the data contains a response variable measured in this compartment and whether the dose(s) have time lags. For example, if using the tobramycin data set [1], specify a compartment named `Central`, with `Bolus` for the `DosingType` property, `linear-clearance` for the `EliminationType` property, and `true` for the `HasResponseVariable` property.

```
pkc1 = addCompartment(pkm, 'Central', 'DosingType', 'Bolus', ...
                      'EliminationType', 'linear-clearance', ...
                      'HasResponseVariable', true);
```

For a description of other `DosingType` and `EliminationType` property values, see "Dosing Types" on page 4-28 and "Elimination Types" on page 4-30.

For a description of the `HasResponseVariable` property, see `HasResponseVariable`. At least one compartment in a model must have a response. Although SimBiology supports multiple responses per compartment, when adding compartments to a `PKModelDesign` object, you are limited to one response per compartment.

Note: To add a compartment that has a time lag associated with any dose that targets it, set the `HasLag` property to `true`:

```
pkc_lag = addCompartment(pkm, 'Central', 'DosingType', 'Bolus', ...
                         'EliminationType', 'linear-clearance', ...
                         'HasResponseVariable', true, 'HasLag', true);
```

Or after adding a compartment, set its `HasLag` property to `true`:

```
pkc1.HasLag = true;
```

---

3 Optionally, add a second compartment named `Peripheral`, with no dosing, no elimination, and no time lag. Set the `HasResponseVariable` property to `true`. If you are using the tobramycin data set [1], skip this step and use only one compartment.

```
pkc2 = addCompartment(pkm, 'Peripheral', 'HasResponseVariable', true);
```

The model construction process adds the necessary parameters, including a parameter representing intercompartmental clearance `Q`. You can add more compartments by repeating this step. The addition of each compartment creates a chain of compartments in the order of compartment addition, with a bidirectional flow of the drug between compartments in the model.

Use the handle to the compartment (`pkc1` or `pkc2`), to change compartment properties.

4 Construct a SimBiology model object.

```
[modelObj, PKModelMapObj] = pkm.construct
```

The `construct` method returns a SimBiology model object (`modelObj`) and a `PKModelMap` object (`PKModelMapObj`) that contains the mapping of the model components to the elements of the regression function. For more information about the `PKModelMap` object, see "Defining Model Components for Observed Response, Dose, Dosing Type, and Estimated Parameters" on page 4-36.

Note: If you change the `PKModelDesign` object, you must create a new model object using the `construct` method. Changes to the `PKModelDesign` do not automatically propagate to a previously constructed model object.

5 Perform parameter fitting as shown in "Perform Data Fitting with PKPD Models" on page 4-40.

The model object and the `PKModelMap` object are input arguments for the `sbionlmefit`, `sbionlmefitsa` and `sbionlinfit` functions used in parameter fitting.

For information on ...	See ...
Dosing types	"Dosing Types" on page 4-28
Elimination types	"Elimination Types" on page 4-30
Parameter fitting	"Perform Data Fitting with PKPD Models" on page 4-40

For information on ...	See ...
Simulating the model and a description of configuration sets	"Model Simulation" on page 3-3

Dosing Types

When creating models, SimBiology creates the following model components for each compartment in the model, regardless of the dosing type:

- Two species (`Drug_CompartmentName` and `Dose_CompartmentName`) for each compartment.
- A reaction (`Dose_CompartmentName -> Drug_CompartmentName`) for each compartment, governed by mass action kinetics.
- A parameter (`ka_CompartmentName`) for each compartment, representing the absorption rate of the drug when absorption follows first-order kinetics. This is the forward rate parameter for the `Dose_CompartmentName -> Drug_CompartmentName` reaction.
- A parameter (`Tk0_CompartmentName`) for each compartment, representing the duration of drug absorption when absorption follows zero-order kinetics.
- A parameter (`TLag_CompartmentName`) for each compartment, representing the time lag for any dose that targets that compartment and also that is specified as having a time lag.

For dosing types that have a fixed infusion or absorption duration (`infusion` and `zero-order`), you can use overlapping doses. The doses are additive.

The following table describes the dosing types, the default parameters to estimate, and lists the model components created and used for dosing.

Dosing Type	Description	SimBiology Model Components Used	Default Parameters to Estimate
`''`(empty string)	No dose	The species (`Drug_CompartmentName`) in each compartment	None
SimBiology desktop — `bolus`	Assumes that the drug amount is increased instantly at the dose time.	The species (`Drug_CompartmentName`) in each compartment	None

Dosing Type	Description	SimBiology Model Components Used	Default Parameters to Estimate
Command line — `Bolus`	In the SimBiology model, the initial concentration of the drug is based on dose amount and volume of the compartment containing the drug.		
SimBiology desktop — `infusion` Command line — `Infusion`	Assumes that the infused drug amount increases at a constant known absorption (or infusion) rate over a known duration. The imported data set must contain the rate and not an infusion duration. SimBiology uses this information to change the species concentration at the constant rate over the duration specified in the data set.	The species (`Drug_CompartmentName`) in each compartment	None
SimBiology desktop — `zero-order` Command line — `ZeroOrder`	Assumes that the drug is added at a constant rate over fixed, but unknown duration.	• The species `Drug_CompartmentName` in each compartment • The parameter (`TkO_CompartmentName`) in each compartment that has zero-order dosing. This parameter represents the duration of drug absorption	`TkO_CompartmentName` (absorption duration)

Dosing Type	Description	SimBiology Model Components Used	Default Parameters to Estimate
SimBiology desktop — `first-order` Command line — `FirstOrder`	Assumes that the rate at which the drug is absorbed is not constant. In the SimBiology model, absorption rate is assumed to be governed by mass-action kinetics.	• A species (`Dose_CompartmentName`) representing the dose amount before it is absorbed • A species (`Drug_CompartmentName`) for each compartment • A parameter (`ka_CompartmentName`) representing the absorption rate of the drug • A `MassAction` `reaction` (`Dose_CompartmentName —> Drug_CompartmentName`) with forward rate parameter (`ka_CompartmentName`)	`ka_CompartmentName` (absorption rate)

If you are using a custom model, or want to simulate a model with the dosing schedule applied, see the following additional sources of information:

For information on ...	See ...
Preparing the model before simulating	"Prerequisites for Using Custom SimBiology Models in Data Fitting" on page 4-36

Elimination Types

Elimination Type	Description	SimBiology Model Components Created	Default Parameters to Estimate
SimBiology desktop — `Linear {Elimination Rate, Volume}`	Assumes simple mass-action kinetics in the elimination of the drug. In the SimBiology model, elimination	• A parameter representing the elimination rate (`ke_CompartmentName` • A `MassAction reaction (drug`	• Compartment volume (`Capacity` property) • Elimination rate constant (`ke_CompartmentName`)

Elimination Type	Description	SimBiology Model Components Created	Default Parameters to Estimate
Command line — `'linear'`	is specified by mass-action kinetics with the elimination rate constant specified by the forward rate parameter (`ke`).	`—> null)` with forward rate parameter (`ke_CompartmentName` specific to the compartement	• Inter-compartmental clearance (`Q`) when there is more than one compartment. See "Intercompartmental Clearance" on page 4-32.
SimBiology desktop — `Linear {Clearance, Volume}` Command line — `'linear-clearance'`	Assumes simple mass-action kinetics in the elimination of the drug. In the SimBiology model, similar to `Linear {Elimination Rate, Volume}`. But, in addition, this option lets you specify the model in terms of clearance (`Cl`) where, `Cl = ke * volume`).	• A parameter representing the clearance (`Cl_CompartmentName` • A parameter representing the elimination rate constant (`ke_CompartmentName` • An `InitialAssignment` rule that initializes `ke_CompartmentName` based on the initial values for `Cl_CompartmentName` and compartment volume • A `MassAction reaction (drug —> null)` with forward rate parameter (`ke_CompartmentName`	• Compartment volume (`Capacity` property) • Clearance (`Cl_CompartmentName`) • Inter-compartmental clearance (`Q`) when there is more than one compartment. See "Intercompartmental Clearance" on page 4-32.

Elimination Type	Description	SimBiology Model Components Created	Default Parameters to Estimate
SimBiology desktop — `Enzymatic (Michaelis-Menten)` Command line — `'enzymatic'`	Assumes that elimination is governed by Michaelis-Menten kinetics.	• Parameter representing the Michaelis constant, (`Km_CompartmentName` • A parameter for maximum velocity (`Vm_CompartmentName` • A reaction with Michaelis-Menten kinetics (`drug -> null`), with kinetic law parameters `Vm_CompartmentName` and `Km_CompartmentName`	• Compartment volume (`Capacity` property) • Parameter (`Km_CompartmentName`) • Parameter (`Vm_CompartmentName`) • Inter-compartmental clearance (`Q`) when there is more than one compartment. See "Intercompartmental Clearance" on page 4-32

Intercompartmental Clearance

The compartments created when you generate a SimBiology model form a chain and each pair of linked compartments are connected by a transport reaction similar to linear elimination. The addition of two compartments, `C1` and `C2`, generates a reversible mass-action reaction `C1.Drug_C1 <-> C2.Drug`. The forward rate parameter is the compartmental clearance, Q_{12}, divided by the volume of `C1`. The reverse rate parameter is Q_{12}, divided by the volume of `C2`.

The process of adding each pair of compartments in the chain C_m and C_n generates the following model components:

- A parameter Q_{mn} representing the compartmental clearance between those two compartments. This parameter is added to the list of parameters to be estimated (`Estimated` property of `PKModelMap` object).
- A parameter (`kmn`) representing the rate of transfer of the drug from `Cm` to `Cn`, where $k_{mn} = Q_{mn}/V_m$.
- A parameter (`knm`) representing the rate of `Cn` to `Cm`, where $k_{nm} = Q_{mn}/V_n$.

- A reversible mass-action reaction between the two compartments, `Cm.Drug_Cm <-> Cn.Drug_Cn`, with forward rate parameter `kmn`, and reverse rate parameter `knm`.
- An initial assignment rule that initializes the value of the parameter `kmn`, based on the initial values for `Cm` and `Qmn`.
- An initial assignment rule that initializes the value of the parameter `knm`, based on the initial values for `Cn` and `Qmn`.

Unit Conversion for Imported Data

Unit conversion converts the matching physical quantities to one consistent unit system in order to resolve them. This conversion is in preparation for correct simulation, but SimBiology returns the physical quantities in the model in units that you specify.

Regardless of whether unit conversion is `on` or `off`, you must express dosing data in amount. By default, **Unit Conversion** is `off`, so you must ensure that units for the data and the model are consistent with one another.

If **Unit Conversion** is `on`, you must specify units. If using the SimBiology desktop, specify units in the **Raw Data** tab, when data is selected in the **Project Explorer**. If using the command line, specify units in the `PKData` object.

Parameters in the model have default units. If unit conversion is `on`, you can change the units as long as the dimensions are consistent. These default units, which you might use to specify the values for the initial guess, are as follows.

Physical Quantity or Model Parameter	Unit
Capacity (compartment volume)	`liter`
First-order elimination rate	`1/second`
`Km` — Michaelis constant	`milligram/liter`
`Vm` — (`Vmax`) Maximum reaction-velocity (Michaelis-Menten kinetics)	`milligram/second`
Clearance	`liter/second`
`Tk0 (absorption duration)`	`second`
`ka` (absorption rate)	`1/second`

Use the configuration settings options to turn unit conversion `on` or `off`. For details, see “Model Simulation” on page 3-3.

For details on dimensional analysis for reaction rates, see “How Reaction Rates Are Evaluated” on page 1-21.

About Data Fitting in PKPD Models

In this section...

Data Fitting Functionality

SimBiology lets you perform individual and population fitting on grouped data. This functionality uses Statistics and Machine Learning Toolbox features (Version 7.3 or later).

- Individual fit — Fit data separately for each individual using the nonlinear least squares method, estimate parameters, and calculate residuals and the estimated coefficient covariance matrix.
- Population fit — Estimate the fixed effects and the random sources of variation on parameters, using nonlinear mixed-effects models.

  You can use the following methods to estimate the fixed effects:

  - `LME` — Linear mixed-effects approximation
  - `RELME` — Restricted LME approximation
  - `FO` — First-order estimate
  - `FOCE` — First-order conditional estimate

The following results are returned for population fitting:

- The maximized log-likelihood for the fitted model
- The estimated error variance for the fitted model
- The Akaike information criterion for the fitted model
- The Bayesian information criterion for the fitted model
- The standard errors for the estimates of the fixed effects
- The error degrees of freedom for the model
- The weighted residuals for the fitted model

In addition, you can generate diagnostic plots that show:

- The predicted time courses and observations for an individual or the population
- Observed versus predicted values
- Weighted residuals versus time, group, or predictions
- Distribution of the weighted residuals
- A box-plot for random effects or parameter estimates from individual fitting

Prerequisites for Data Fitting

Before you fit parameters, the SimBiology desktop or the MATLAB Workspace must contain the following:

- Data to use in the fitting (See “Importing Data — Supported Files and Data Types” on page 4-7 for more information.)
- A model to fit (See “Create Pharmacokinetic Models” on page 4-24 for more information.)

If you plan to use the command line, see the following for more information:
“Perform Data Fitting with PKPD Models” on page 4-40

Prerequisites for Using Custom SimBiology Models in Data Fitting

Overview

If you created a PK model using either the `PKModelDesign` object's `construct` method at the command line or the wizard in the SimBiology desktop, you can skip this section. This section provides information about working with a custom SimBiology model.

When using a custom model, you must provide information about whether dosing is applicable and define which components of the SimBiology model represent the observed response, the dose, and the estimated parameters. Use the `PKModelMap` object to define these settings as shown in “Defining Model Components for Observed Response, Dose, Dosing Type, and Estimated Parameters” on page 4-36.

Defining Model Components for Observed Response, Dose, Dosing Type, and Estimated Parameters

The `PKModelMap` object holds information about the dosing type and defines which components of the SimBiology model represent the observed response, the dose, and the parameters to be estimated.

If you are using a custom SimBiology model that you did not create using either the `PKModelDesign` object's `construct` method or the wizard, you must create a `PKModelMap` object to define these relationships.

Consider the following regression function, `y = f(k,u)`, where `y` is the measured or observed response, given values of an input `u`, and parameter values `k`. In SimBiology, the model represents `f`, which is used to generate the regression function, if `y`, `k`, and `u` are identified in the model. You must, therefore, use the `PKModelMap` object to define which components of the model represent `y`, `k`, and `u`. If applicable, the `PKModelMap` object also needs information on the type of dosing or input being given to the model.

1. Import an SBML model:

   ```
   modelObj = sbmlimport('lotka');
   ```

2. Create a `PKModelMap` object:

   ```
   PKModelMapObj = PKModelMap;
   ```

3. Use the name of the model component to specify the corresponding property in the `PKModelMap` object.

Model Component Represents	PKModelMap Object Property
Object being driven by an input	`Dosed`
Measured response	`Observed`
Parameters to be estimated	`Estimated`

   For example:

   ```
   set(PKModelMapObj, 'Observed', 'unnamed.y1');
   set(PKModelMapObj, 'Estimated', {'Reaction1.c1', 'Reaction2.c2'});
   ```

   Note: When specifying species names, qualify the name with the compartment name in the form `compartmentName.speciesName` (for example, `nucleus.DNA`). For names of parameters scoped at the reaction level, use `reactionName.parameterName`. For parameters scoped at the model level, you do not have to qualify the name.

4. Use the `DosingType` property to specify the type of dosing, if applicable. The allowed types are `''`, `'Bolus'`, `'Infusion'`, `'FirstOrder'`, and `'ZeroOrder'`.

   For example:

```
set(PKModelMapObj, 'DosingType', 'Bolus');
```

Note: When using custom models with `DosingType` set to `zero-order`, you must include a parameter that represents the duration of drug absorption. Set the `ZeroOrderDurationParameter` property of the `PKModelMap` object to the name of the duration parameter. For example, `set(PKModelMapObj, 'ZeroOrderDurationParameter', 'Kdo');`.

The previous example sets the observed response to a species `y1`, contained by a compartment (`unnamed`), and sets the parameters to be estimated to the parameters `c1` and `c2` that are scoped to the reactions, `Reaction1` and `Reaction2`, respectively.

For information on ...	See ...
`PKModelMap` object properties and allowed values	`PKModelMap object` `Dosed`, `DosingType`, `Estimated`, and `Observed`, `ZeroOrderDurationParameter`
Allowed dosing types	"Dosing Types" on page 4-28
Parameter scoping	"When Reactions, Rules, and Events Specify Parameters" on page 1-16
Parameter fitting	"Perform Data Fitting with PKPD Models" on page 4-40

Dosing Multiple Compartments in a Model

1 Use the name of the model component to specify the `Dosed` property in the `PKModelMap` object.

   For example, assume that a model contains two compartments named `Central` and `Peripheral`. Specify the species names in the dosed compartments. For example:

```
set(PKModelMapObj, 'Dosed, {'Central.Drug_Central', ...
   'Peripheral.Drug_Peripheral'});
```

2 Use the `DosingType` property to specify the type of dosing if applicable. The allowed types are `''`, `'Bolus'`, `'Infusion'`, `'FirstOrder'`, and `'ZeroOrder'`. When specifying dosing for multiple compartments, the order in the `Dosed` property is the order in which the dosing type is applied.

For example, if Central takes zero-order dosing and Peripheral takes a first-order dosing enter:

```
set(PKModelMapObj, 'DosingType', {'ZeroOrder', 'FirstOrder'});
```

3. Because the model includes zero-order as a DosingType, you must include a parameter that represents the duration of drug absorption and is used when simulating the model with dosing information or during fitting. Set the ZeroOrderDurationParameter property of the PKModelMap object to the name of the duration parameter. For example,

   ```
   set(PKModelMapObj, 'ZeroOrderDurationParameter', {'Kdo', ''})
   ```

   Specify the parameters in the same order as the species in the Dosed property.

Perform Data Fitting with PKPD Models

In this section...

Data Fitting Workflow

The following steps show one of the workflows you can use at the command line to fit a PK model and estimate parameters:

1. Import data as shown in "Importing Data" on page 4-13.
2. Specify the structural model by creating a PK model as shown in "Create a Pharmacokinetic Model Using the Command Line" on page 4-26. Alternatively, if you have a SimBiology model that you want to use in fitting, see "Prerequisites for Using Custom SimBiology Models in Data Fitting" on page 4-36.
3. Classify the data set to use in fitting. See "Specify and Classify the Data to Fit" on page 4-41.
4. Specify the initial guesses for the parameters to be estimated, as shown in "Set Initial Estimates" on page 4-43.
5. Perform individual or population fits:

   - For individual fits:

    - (Optional) Specify an error model or weights. See "Specify an Error Model" on page 4-49.
    - (Optional) Set tolerances.
    - (Optional) Specify maximum iterations.
    - (Optional) Specify to pool the data, which simultaneously fits data from multiple dose levels using the same model parameters for each dose.
  - For population fits:
    - Specify the statistical model:
      - Specify the covariate model and the covariance matrix. See "Specify a Covariate Model" on page 4-46 and "Specify the Covariance Pattern of Random Effects" on page 4-48.
      - (Optional) Specify the error model. See "Specify an Error Model" on page 4-49.
    - (Optional) Set tolerances.
    - (Optional) Specify maximum iterations.

6. Obtain and visualize results.

Specify and Classify the Data to Fit

In order to use the imported data in fitting, you must identify required columns in the data set that was previously imported as shown in "Importing Data" on page 4-13.

Use the `PKData` object to specify the data set containing the observed data to use in fitting. The properties of the `PKData` object specify what each column in the data represents.

To create the `PKData` object:

1. Create the `PKData` object for the data set `data`.

   ```
   pkDataObject = PKData(data);
   ```
   `PKData` assigns the data set `data` to the read-only `DataSet` property.
2. Use the column headers in the data set to specify the following properties for the column in the data set.

Column in Data Set Represents	PKData Object Property
Group identification labels	`GroupLabel`
Independent variable (For example, time)	`IndependentVarLabel`
Dependent variable (For example, measured response)	`DependentVarLabel`
Amount of dose given	`DoseLabel`
Rate of infusion (when applicable). Data must contain rate (`amount/time`) and not infusion time.	`RateLabel`
Covariates (For example, age, gender, weight)	`CovariateLabels`

For example, for the tobramycin data set [1]:

```
pkDataObject.GroupLabel          = 'ID';
pkDataObject.IndependentVarLabel = 'Time';
pkDataObject.DependentVarLabel   = 'Response';
pkDataObject.DoseLabel           = 'Dose';
pkDataObject.CovariateLabels     = {'WT','HT','AGE', 'SEX', 'CLCR'};
```

Note: For the subset of data belonging to a single group (as defined by the column in your data set that represents group identification labels, which you map to the `GroupLabel` property), the software allows multiple observations made at the same time. If this is true for your data, be aware that:

- These data points are not averaged, but fitted individually.
- Different number of observations at different times cause some time points to be weighted more.

Tip If dosing applies to more than one compartment in the model, specify the `DoseLabel` property as follows:

```
    pkDataObject.DoseLabel =  {'Dose1', 'Dose2'};
```

`Dose1` and `Dose2` are names of columns containing dose information for compartments. A one-to-one relationship must exist between the number and order of elements in the `DoseLabel` property and the `Dosed` property of the corresponding `PKModelMap` object.

Tip If your model measures multiple responses, specify the `DependentVarLabel` property as follows:

```
    pkDataObject.DependentVarLabel =  {'Response1', 'Response2'};
```

`Response1` and `Response2` are names of columns containing response measurements. A one-to-one relationship must exist between the number and order of elements in the `DependentVarLabel` property and the `Observed` property of the corresponding `PKModelMap` object.

When you assign a column containing group identification labels to the `GroupLabel` property, `PKData` sets these read-only properties as follows:

- The `GroupNames` property is set to the unique names found in the group column.
- The `GroupID` property is set to an integer corresponding to the unique names found in the group column.

Specify Solver Type and Options for Fitting

If you specify a stochastic solver and options in the `Configset object` associated with your model, be aware that during fitting SimBiology temporarily changes:

- `SolverType` property to the default solver of `ode15s`
- `SolverOptions` property to the options last configured for a deterministic solver

Set Initial Estimates

Caution If your model includes active variants that specify alternate values for the parameters to estimate, the variants are ignored for those parameters during fitting.

To set the initial estimates (or initial guesses) for the parameters with fixed effects to estimate, first identify the sequence of the parameters in the model by querying the

`PKModelMap` object. Next, construct a vector, `beta0`, containing the initial conditions. For information about `PKModelMap` objects, see step 4 in "Create a Pharmacokinetic Model Using the Command Line" on page 4-26.

1 Query the `Estimated` property of the `PKModelMap` object:

```
PKModelMapObj.Estimated
```

MATLAB returns the sequence of the parameters to be estimated. For example:

```
ans =

    'Central'
    'Cl_Central'
```

2 Set the initial estimates for the parameters. For example:

```
beta0 = [10.0, 1.0];
```

For information on ...	See ...
The parameters added to the model	• "Dosing Types" on page 4-28 • "Elimination Types" on page 4-30
Default units for the above parameters	"Unit Conversion for Imported Data" on page 4-33

Specify a Nonlinear, Mixed-Effects Model

Suppose data for a nonlinear regression model falls into one of m distinct groups $i = 1, ..., m$. (Specifically, suppose that the groups are not nested.) To specify a general, nonlinear, mixed-effects (NLME) model for this data:

1 Define group-specific model parameters φ_i as linear combinations of fixed effects β and random effects b_i.

2 Define response values y_i as a nonlinear function f of the parameters and group-specific covariate variables X_i.

The model is:

$$\varphi_i = A_i\theta + B_i\eta_i, \text{where } \eta_i \sim N(0,\Psi)$$
$$y_i = f(\varphi_i, X_i) + \varepsilon_i$$
$$\text{Alternatively}, \log y_i = \log f(\varphi_i, X_i) + \varepsilon_i$$

This formulation of the nonlinear, mixed-effects model uses the following notation:

φ_i	A vector of group-specific model parameters
θ	A vector of fixed effects, modeling population parameters
η_i	A vector of multivariate, normally distributed, group-specific, random effects
A_i	A group-specific design matrix for combining fixed effects
B_i	A group-specific design matrix for combining random effects
X_i	A data matrix of group-specific covariate values
y_i	A data vector of group-specific response values
f	A general, real-valued function of φ_i and X_i
ε_i	• For `sbionlmefit`, you can specify different error models as shown in "Specify an Error Model" on page 4-49. • For `sbionlmefitsa`, you can specify different error models as shown in "Specify an Error Model" on page 4-49.
Ψ	A covariance matrix for the random effects
σ^2	The error variance, assumed to be constant across observations

For example, consider a one-compartment model with first-order dosing and linear clearance. The group-specific parameters (φ) in the model are clearance (Cl), compartment volume (V), and absorption rate constant (k_a). From the model:

$$\begin{pmatrix} Cl \\ V \\ ka \end{pmatrix} = \begin{pmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{pmatrix} \begin{pmatrix} \theta_{Cl} \\ \theta_V \\ \theta_{ka} \end{pmatrix} + \begin{pmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{pmatrix} \begin{pmatrix} \eta_{Cl} \\ \eta_V \\ \eta_{ka} \end{pmatrix}$$

In SimBiology, B_i is an identity matrix. That is, `sbionlmefit` does not support the specification of a different random-effects design matrix. You can alter the design matrices, as necessary, to introduce weighting of individual effects.

The Statistics and Machine Learning Toolbox function `nlmefit` fits the general, nonlinear, mixed-effects model to data, estimating the fixed and random effects. The function also estimates the covariance matrix Ψ for the random effects. Additional diagnostic outputs allow you to assess trade-offs between the number of model parameters and the goodness of fit. See "Mixed-Effects Models" in the Statistics and Machine Learning Toolbox documentation for more information.

Specify a Covariate Model

Construct a `CovariateModel` object to define the relationship between parameters and covariates. After constructing the object, modify the `FixedEffectValues` property of the object before using the object as an input argument to `sbionlmefit` or `sbionlmefitsa`, to estimate nonlinear mixed effects.

If the "Specify a Nonlinear, Mixed-Effects Model" on page 4-44 assumes a group-dependent covariate such as weight (*w*), the model becomes:

$$\begin{pmatrix} Cl \\ V \\ ka \end{pmatrix} = \begin{pmatrix} 1 & 0 & 0 & w_i \\ 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & 0 \end{pmatrix} \begin{pmatrix} \theta_{Cl} \\ \theta_V \\ \theta_{ka} \\ \theta_{Cl/w} \end{pmatrix} + \begin{pmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{pmatrix} \begin{pmatrix} \eta_{Cl} \\ \eta_V \\ \eta_{ka} \end{pmatrix}$$

Thus, the parameter for clearance (*Cl*) for an individual is $Cl_i = \theta_{Cl} + \theta_{Cl/w} * w_i + \eta_{Cl_i}$.

Use the following procedure to specify a covariate model. If you are using the tobramycin data set, make sure you first complete the following procedures:

- "Importing Data from NONMEM-Formatted Files" on page 4-14
- "Create a Pharmacokinetic Model Using the Command Line" on page 4-26
- "Specify and Classify the Data to Fit" on page 4-41
- "Set Initial Estimates" on page 4-43

1 Use the `CovariateModel` constructor function to construct an empty `CovariateModel` object:

```
covModel = CovariateModel;
```

2 Set the `Expression` property of the object to define the relationship between parameters and covariates in the `CovariateModel` object, where `Cl`, `v`, and `ka` are parameters, `weight` is a covariate, `theta1`, `theta2`, `theta3`, and `theta4` are fixed effects, and `eta1`, `eta2`, and `eta3` are random effects.

```
covModel.Expression = {'Cl = exp(theta1 + theta4*weight + eta1)',...
                       'v = exp(theta2 + eta2)',...
                       'ka = exp(theta3 + eta3)'};
```

3 Display a list of the descriptions of the fixed effects (`theta1` and `theta2`) in the `CovariateModel` object:

```
disp('Fixed Effects Descriptions:');
disp(covModel.FixedEffectDescription)
```

Your output appears as follows, where each string describes the role of a fixed effect in the expression equation:

```
Fixed Effects Descriptions:
    'Cl'
    'v'
    'ka'
    'Cl/weight'
```

4 Use the `constructDefaultFixedEffectValues` method of the `CovariateModel` object to create a structure containing the initial estimates for the fixed effects in the object. The initial estimates in this structure are set to a default of zero:

```
initialEstimates = covModel.constructDefaultFixedEffectValues
```

Your output appears as:

```
initialEstimates =

    theta1: 0
    theta2: 0
    theta3: 0
    theta4: 0
```

5 Edit the `initialEstimates` structure to set the initial estimates of the fixed effects:

```
initialEstimates.theta1 = 1.408;
initialEstimates.theta2 = 0.061;
initialEstimates.theta3 = 0.31;
```

Tip Typically, these initial estimates are values you determine from a previous fit of the data.

6 Use the modified `initialEstimates` structure to update the `FixedEffectValues` property of the `CovariateModel` object:

```
covModel.FixedEffectValues = initialEstimates;
```

Now `covModel`, the `CovariateModel` object, is ready to submit as an input argument to `sbionlmefit` or `sbionlmefitsa`.

Specify the Covariance Pattern of Random Effects

By default, the function you use to perform population fits (`nlmefit` or `nlmefitsa`) assumes a diagonal covariance matrix (no covariance among the random effects). To specify a different covariance pattern of random effects, use the `'CovPattern'` option. In the previous example, assuming that each of the parameters has random effects and that *Cl* and *V* exhibit covariance, the covariance pattern of random effects would be a logical array:

$$\begin{pmatrix} 1 & 1 & 0 \\ 1 & 1 & 0 \\ 0 & 0 & 1 \end{pmatrix}$$

1. Create an options `struct` with the specified covariance pattern:

```
options.CovPattern = [1, 1, 0; 1, 1, 0; 0, 0, 1];
```

2. Specify the arguments for `sbionlmefit` or `sbionlmefitsa`:

```
[results, simdataI, simdataP] = sbionlmefit(modelObj,...
     PKModelMapObj, pkDataObject, beta0, options)
```

If you are using the tobramycin data set [1], do the following:

1. Create an options `struct` with the specified covariance pattern:

```
options.CovPattern = [1, 0; 0, 1];
```

2. Specify the arguments for `sbionlmefit`:

```
[results, simdataI, simdataP] = sbionlmefit(modelObj,...
     PKModelMapObj, pkDataObject, beta0, options)

results =

  NLMEResults handle

  Properties:
                    FixedEffects: [2x3 dataset]
                   RandomEffects: [97x2 dataset]
    IndividualParameterEstimates: [97x2 dataset]
    PopulationParameterEstimates: [97x2 dataset]
    RandomEffectCovarianceMatrix: [2x2 dataset]
         EstimatedParameterNames: {2x1 cell}
```

```
                    CovariateNames: {'WT'  'HT'  'AGE'  'SEX'  'CLCR'}
               FixedEffectsStruct: [1x1 struct]
                            stats: [1x1 struct]

results.FixedEffects

ans =

    Description         Estimate    StandardError
    'Central'           3.0478      0.064369
    'Cl_Central'        1.3054      0.061095
```

For more information, see `nlmefit` or `nlmefitsa` in the Statistics and Machine Learning Toolbox documentation.

Fitting the model and estimating the covariance matrix Ψ often leads to further refinements. A relatively small estimate for the variance of a random effect suggests that it can be removed from the model. Similarly, relatively small estimates for covariances among certain random effects suggest that a full covariance matrix is unnecessary. Since random effects are unobserved, Ψ must be estimated indirectly. Specifying a diagonal or block-diagonal covariance pattern for Ψ can improve convergence and efficiency of the fitting algorithm.

Specify an Error Model

You can specify any of the following error models when using the `sbionlinfit`, `sbionlmefit`, or `sbionlmefitsa` function. Each model defines the error using a standard normal (Gaussian) variable *e*, the function value *f*, and one or two parameters, *a* and *b*. The default error model is `'constant'`.

- `'constant'`: $y = f + a*e$ (default)
- `'proportional'`: $y = f + b*\mathrm{abs}(f)*e$
- `'combined'`: $y = f + (a+b*\mathrm{abs}(f))*e$
- `'exponential'`: $y = f*\exp(a*e)$, or equivalently $\log(y) = \log(f) + a*e$

To define an error model:

1. Create an `optionStruct` input argument and set the `ErrorModel` field to specify one of the above error models. For example:

   ```
   optionStruct.ErrorModel = 'proportional';
   ```

2 Specify the `optionStruct` input argument for `sbionlinfit`, `sbionlmefit`, or `sbionlmefitsa`, as shown in "Perform Individual Fitting" on page 4-55 or "Perform Population Fitting" on page 4-51.

See also or `nlinfit`, `nlmefit`, or `nlmefitsa` in the Statistics and Machine Learning Toolbox documentation.

Specify Parameter Transformations

To specify parameter transformations, use the `ParamTransform` option in `sbionlinfit`, `sbionlmefit` and `sbionlmefitsa`. The `ParamTransform` option lets you specify either no transformation, or the `log`, `probit`, or `logit` transformation.

Note: Do not use the `ParamTransform` option to specify parameter transformations when providing a `CovariateModel` object to a fitting function. The `CovariateModel` object provides the parameter transformation.

The underlying algorithm in `nlmefit` assumes that parameters follow a normal distribution. This assumption may not hold for biological parameters that are constrained to be positive, such as volume and clearance. You may specify a transformation function for the estimated parameters, so that the transformed parameters follow a normal distribution.

By default, the SimBiology fitting functions choose a log transform for all estimated parameters. Parameters that are constrained between the values `0` and `1`, like absorption fraction, can be transformed by the `probit` or `logit` transformations described below.

The `probit` function is the inverse cumulative distribution function (CDF) associated with the standard normal distribution. To apply the `probit` transform to a variable `x` in MATLAB, use the Statistics and Machine Learning Toolbox function `norminv`: `t = norminv(x)`. To untransform a variable `t`, use the function `normcdf`: `x = normcdf(t)`.

The `logit` function is the inverse of the sigmoid function. To apply the `logit` transform to a variable `x` in MATLAB, use the following expression: `t = log(x) - log(1-x)`. To untransform the variable `t`, use `x = 1/(1+exp(-t))`.

1 For the `ParamTransform` option, specify a vector of values equal to the number of parameters to be estimated. The values must be one of the integer codes listed in

`nlmefitsa` or `nlmefit` specifying the transformation for the corresponding value of the parameters to be estimated. For example

```
options.ParamTransform = [0 1 2];
```

See `nlmefit` and `nlmefitsa` for more information.

2 Specify the arguments for `sbionlmefit` or `sbionlmefitsa`, as shown in "Perform Population Fitting" on page 4-51.

For individual fitting, see "Perform Individual Fitting" on page 4-55.

Perform Population Fitting

The `sbionlmefit` and `sbionlmefitsa` functions let you specify a SimBiology model that you want to use in fitting. These functions use the `nlmefit` and `nlmefitsa` functions from the Statistics and Machine Learning Toolbox to fit data with both fixed and random sources of variation using nonlinear mixed-effects and return the estimates. Both `nlmefit`and `nlmefitsa` fit the model by maximizing an approximation to the marginal likelihood with random effects integrated out assuming the following:

- Random effects are multivariate, normally distributed, and independent between groups.
- Observation errors are independent, identically normally distributed, and independent of random effects.

1 (Optional) Set the tolerance or maximum iteration options. Use an options structure that is an input argument for `sbionlmefit` or `sbionlmefitsa`:

```
optionStruct.Options.TolX = 1.0E-4;
optionStruct.Options.TolFun = 1.0E-4;
optionStruct.Options.MaxIter = 200;
```

2 Specify the model object, the `PKModelMap` object, the `PKData` object, the `PKCovariateModel` object, a vector containing the initial estimates for the fixed effects, and the options:

```
[results, simdataI, simdataP] = sbionlmefit(modelObj,...
 PKModelMapObj, pkDataObject, CovariateModelObject, beta0, optionStruct);
```

Note: If your population fit uses multiple doses, make sure each element in the `Dosed` property of the `PKModelMap object` is unique.

Note: In your `PKData object`, for each subset of data belonging to a single group (as defined in the data column specified by the `GroupLabel` property), the software allows multiple observations made at the same time. If this is true for your data, be aware that:

- These data points are not averaged, but fitted individually.
- Different number of observations at different times cause some time points to be weighted more.

`sbionlmefit` and `sbionlmefitsa` return the following:

- *`results`*, an object containing estimated values and other statistics. For more information, see the `sbionlmefit` and `sbionlmefitsa` reference pages.
- *`simdataI`*, a `SimData object` containing the data from simulating the model using the estimated parameter values for individuals, which includes both the fixed and random effects.
- *`simdataP`*, `SimData object` containing the data from simulating the model using the estimated parameter values for the population, which includes only the fixed effects.

3 Plot the data from the data set. For example, in the imported data set used for fitting, `ds`, `ID`, `Time`, and `Response` are the column headers for the columns containing group IDs, time, and the response variable, respectively.

```
p = sbiotrellis(ds, 'ID', 'Time', 'Response')
```

Note: If your data set has multiple responses, with column headers `Response1` and `Response2` containing the response variables, you plot the data as follows:

```
Response = {'Response1', 'Response2'}
p = sbiotrellis(ds, 'ID', 'Time', Response)
```

---

4 Use the `plot` method on the trellis plot object `p`, returned by `sbiotrellis` to overlay data, using default values for the second and third input arguments.

```
p.plot(simdataP, [], '', PKModelMapObj.Observed);
```

For a description of the results, see `sbionlmefit` in the SimBiology documentation.

For more information, see the following topics in the Statistics and Machine Learning Toolbox documentation:

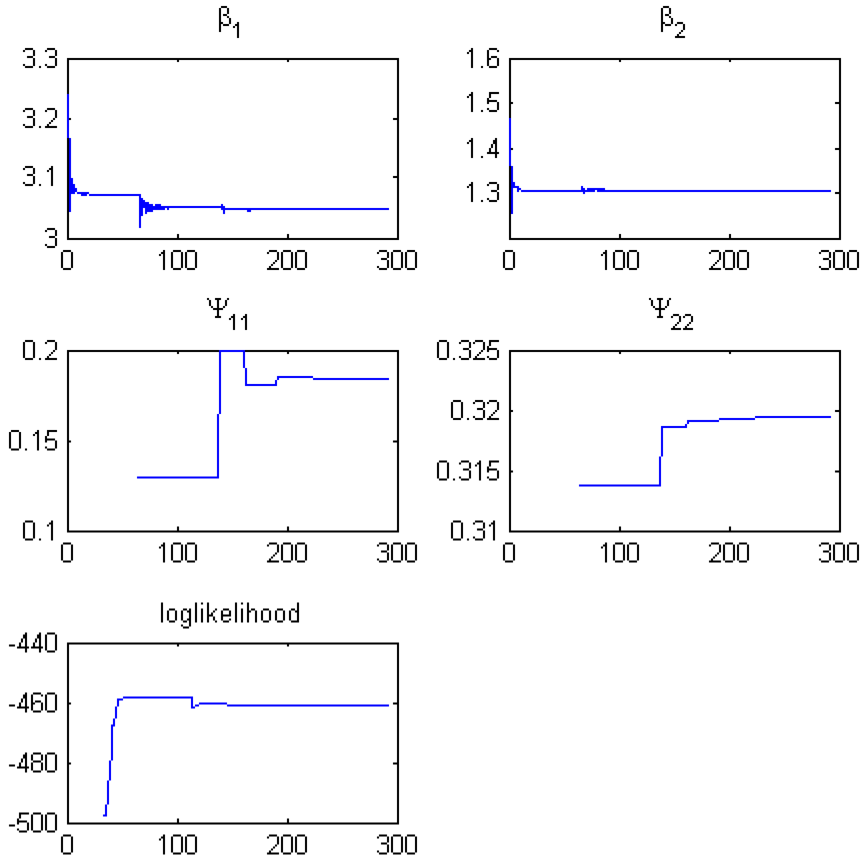
- “Nonlinear Regression”
- “Mixed-Effects Models”
- `nlmefit`

Obtaining the Status of Fitting

The `sbiofitstatusplot` function dynamically plots the progress of the fitting task. During the task, the function plots the fixed effects (β), the estimates for the diagonal elements of the covariance matrix for the random effects (Ψ), and the log-likelihood. This functionality is useful for large and complex models when you expect the time to return the results to be longer than a few minutes. Use the options structure that is an argument for the `sbionlmefit` function:

```
% Create options structure with 'OutputFcn'.
options.Options.OutputFcn = @sbiofitstatusplot;
% Pass options structure with OutputFcn to sbionlmefit function.
results = sbionlmefit(..., options);
```

The following figure shows the type of plots obtained.



Tips for interpreting status plots:

- The fitting function tries to maximize the log-likelihood. When the plot begins to display a flat line, this might indicate that maximization is complete. Try setting the maximum iterations to a lower number to reduce the number of iterations you need and improve performance. For information on how to set iteration options, see "Perform Population Fitting" on page 4-51.
- Plots for the fixed effects (ß) and the estimates for the diagonal elements of the covariance matrix for the random effects (Ψ), should show convergence. If you see oscillations, or jumps without accompanying improvements in the log-likelihood, the model may be over-parameterized. Try the following:

- Reduce the number of fixed effects.
- Reduce the number of random effects.
- Simplify the covariance matrix pattern of random effects.

See also `sbiofitstatusplot` in the SimBiology documentation.

Simultaneously Fitting Data from Multiple Dose Levels

When performing population fitting using nonlinear regression, you can simultaneously fit data from multiple dose levels by either:

- Using `sbionlmefit` with a `CovariateModel` object input argument and omitting the random effect (`eta`) from the expressions in the `CovariateModel` object.
- Using `sbionlmefit` with an `InitEstimates` input argument and setting the `REParamsSelect` field or name-value pair input argument to a 1-by-*n* logical vector, with all entries set to `false`, where *n* equals the number of fixed effects.

Perform Individual Fitting

The `sbionlinfit` function lets you specify a SimBiology model to fit using the `nlinfit` function (individual fit). The `nlinfit` function uses nonlinear least squares and returns parameter estimates, residuals, and the estimated coefficient covariance matrix.

1. (Optional) Specify an error model, set the tolerance, set the maximum iteration, or set the data pooling option, which lets you simultaneously fit data from multiple dose levels using the same model parameters for each dose. Use an options structure that is an input argument for `sbionlinfit`:

   ```
   optionStruct.ErrorModel = 'proportional';
   optionStruct.TolX = 1.0E-8;
   optionStruct.TolFun = 1.0E-8;
   optionStruct.MaxIter = 100;
   optionStruct.Pooled = true;
   ```
2. Specify the model object, the `PKModelMap` object, the `PKData` object, a vector containing the initial estimates for the fixed effects, and the options:

   ```
   [results, simdataI] = sbionlinfit(modelobj,...
    PKModelMapObj, PKDataObj, beta0, optionStruct);
   ```

Note: If your individual fit uses multiple doses, ensure each element in the `Dosed` property of the `PKModelMap object` is unique.

Note: In your `PKData` object, for each subset of data belonging to a single group (as defined in the data column specified by the `GroupLabel` property), the software allows multiple observations made at the same time. If this is true for your data, be aware that:

- These data points are not averaged, but fitted individually.
- Different number of observations at different times cause some time points to be weighted more.

`sbionlinfit` returns the following:

- A *`results`* array of objects, with each object containing the following for one group:
  - `ParameterEstimates` — A `dataset` array containing fitted coefficients and their standard errors.
  - `CovarianceMatrix` — Estimated covariance matrix for the fitted coefficients.
  - `beta` — Vector of scalars specifying the fitted coefficients in transformed space.
  - `R` — Residuals.
  - `J` — Jacobian of `modelObject`.
  - `COVB` — Estimated covariance matrix for the transformed coefficients.
  - `mse` — Scalar specifying the estimate of the error of the variance term.
  - `errorparam` — Estimated parameters of the error model or an empty array if you specified weights using the `'Weights'` name-value pair argument.
- *`simdataI`*, a `SimData` object containing the data from simulating the model using the estimated parameter values, for individuals.

3. Plot the data from the data set. For example, in the imported data set (`ds`), `ID`, `Time` and `Response` are the column headers for the columns containing group IDs, time, and the response variable respectively.

```
p = sbiotrellis(ds, 'ID', 'Time', 'Response')
```

Note: If your data set has multiple responses, with column headers `Response1` and `Response2` containing the response variables, then plot the data as follows:

```
Response = {'Response1', 'Response2'}
p = sbiotrellis(ds, 'ID', 'Time', Response)
```

---

4. Use the plot method on the trellis plot object `p`, returned by `sbiotrellis` to overlay data, using default values for the second and third input arguments.

   ```
   p.plot(simdataI, [], '', PKModelMapObj.Observed);
   ```

For more information, see “Nonlinear Regression” and `nlinfit` in the Statistics and Machine Learning Toolbox documentation.

PK/PD Modeling and Simulation to Guide Dosing Strategy for Antibiotics

This example shows how to perform a Monte Carlo simulation of a pharmacokinetic/pharmacodynamic (PK/PD) model for an antibacterial agent. This example is adapted from Katsube et al. [1] This example also shows how to use the SimBiology exported model to perform parameter scans in parallel.

This example requires Statistics and Machine Learning Toolbox™. The performance can be improved if you have the Parallel Computing Toolbox™ software.

Background

Katsube et al. [1] used a PK/PD modeling and simulation approach to determine the most effective dosage regimens for doripenem, a carbapenem antibiotic. The objectives of their study were:

- Develop a PK/PD model to describe the antibacterial effect of doripenem against several Pseudomonas aeruginosa strains
- Use Monte Carlo simulations to compare the efficacy of four common antibiotic dosage regimes, and to determine the most effective dosing strategy
- Investigate the effect of renal function on the antibacterial efficacy of the treatments

In this example, we will implement the antibacterial PK/PD model developed by Katsube et al. [1] in SimBiology®, and replicate the results of the Monte Carlo simulation described in their work.

References

[1] T. Katsube, Y. Yano, T. Wajima, Y. Yamano and M. Takano. Pharmacokinetic/pharmacodynamic modeling and simulation to determine effective dosage regimens for doripenem. *Journal of Pharmaceutical Sciences* (2010) 99(5), 2483-91.

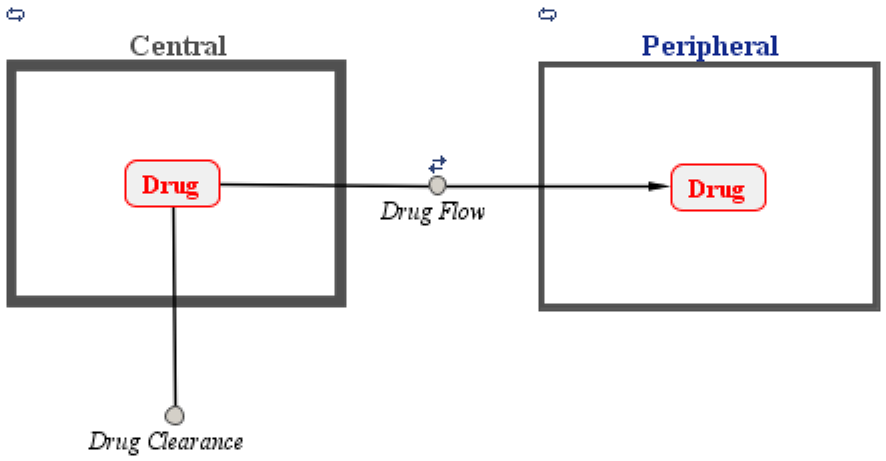
PK/PD Model

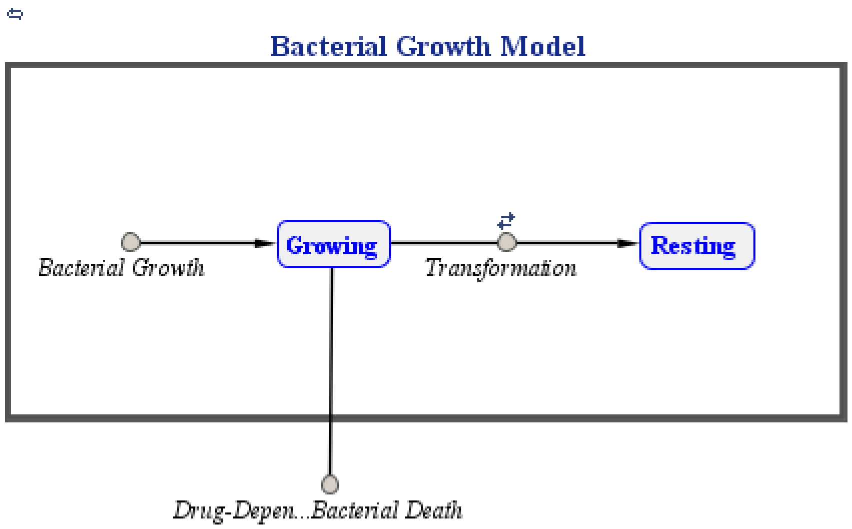
Katsube et al. assumed a two-compartment infusion model with linear elimination from the central compartment to describe the pharmacokinetics of the doripenem. For the bacterial growth model, they assumed that the total bacterial population is comprised of drug-susceptible growing cells and drug-insensitive resting cells. The antibacterial effect of the drug was included in the killing rate of the bacteria via a simple Emax type model:

$$KillingRate = \frac{Kmax * [Drug] * [Growing]}{KC50 + [Drug]}$$

where `[Drug]` is the concentration (ug/ml) of the drug in the central compartment, and `[Growing]` is the count of the growing bacterial population in CFU/ml (CFU = Colony Forming Units). `Kmax` is the maximal killing rate constant (1/hour) and `KC50` is the Michaelis-Menten rate constant (ug/ml).

A graphical view of the SimBiology implementation of the model is shown below.





```
% Load model
sbioloadproject('AntibacterialPKPD.sbproj', 'm1') ;
```

Dosage Regimens

Katsube et al. simulated the model using four common antibiotic dosage strategies.

- 250 mg two times a day (b.i.d.)
- 250 mg three times a day (t.i.d.)
- 500 mg two times a day (b.i.d.)
- 500 mg three times a day (t.i.d.)

Infusion dosing was used in all four dosages regimens, and infusion time was set to 30 minutes. In SimBiology, these dosage regimens have been implemented as dose objects.

```
% Select dose objects in the model
doseNames = {'250 mg bid', '250 mg tid', '500 mg bid', '500 mg tid'};
for iDoseGrp = 1:length(doseNames)
    doseRegimens(iDoseGrp) = sbioselect(m1, 'Name', doseNames{iDoseGrp}) ;
end
```

Description of the Virtual Population

A virtual population of individuals was generated based on the distribution of demographic variables and PK/PD parameters. The type of distribution and the values of the distribution parameters were based on data from earlier clinical trials of doripenem conducted in Japan.

Note: In [1], 5,000 virtual patients were simulated in each dosage group. In this example, we will use 1,000 patients in each group. To simulate a different population size, change the value of `nPatients` below.

```
% Setup
nPatients    = 1000         ; % Number of patients per dosage group
nDoseGrps    = 4            ; % Number of tested dosage regimens
```

Distribution of Demographic Variables:

Weight (`Wt`) and age (`Age`) were sampled from a normal distribution with a mean of 51.6 kg and 71.8 years, respectively, and a standard deviation of 11.8 kg and 11.9 years, respectively. 26% of the population was assumed to be female. Serum creatinine levels (`Scr`) were sampled from a lognormal distribution with a typical value of 0.82 mg/dL, and coefficient of variation (CV) of 32%. The creatinine clearance rates (`CrCL`) were calculated using the Cockcroft-Gault equation.

```
% Note: The inputs to the lognrnd function are the mean (mu) and standard
% deviation (sigma) of the associated normal distribution. Here and
% throughout the example, mu and sigma were calculated from the reported
% typical value and coefficient of the lognormal distriution. See the
% lognstat documentation for more information.

% Patient demographics
Wt   = normrnd(51.6     , 11.8  , nPatients , nDoseGrps )   ; % units: kg
Age  = normrnd(71.8     , 11.9  , nPatients , nDoseGrps )   ; % units: years
Scr  = lognrnd(-0.2485  ,0.3197 , nPatients , nDoseGrps )   ; % units: ml/minute

% Gender ratio
id       = 1:nPatients*nDoseGrps                            ;
idFemale = randsample(id , round(0.26*nDoseGrps*nPatients)) ; % 26% Female

% Creatinine Clearance (using Cockcroft-Gault equation)
CrCL            = (140 - Age).*Wt./(Scr*72)                 ; % units: ml/minute
CrCL(idFemale)  = CrCL(idFemale)*0.85                       ; % multiply by 0.85 for fe
```

Distribution of Pharmacokinetic (PK) parameters:

PK parameters, `Central`, `k12` and `k21`, were sampled from a lognormal distribution with typical values of 7.64 liters, 1.59 1/hour and 2.26 1/hour, respectively, and a 20% coefficient of variation (CV). `Central` is the distribution volume of the central compartment, and `k12` and `k21` are transfer rate constants between the `Central` and the `Peripheral` compartments. The drug clearance rate, `CL`, was assumed to depend linearly on the creatinine clearance rate via the following equation:

$$CL = 1.07 * CrCL + 45.6 + \varepsilon$$

where ε is the additive residual error sampled from a normal distribution with a mean of 0 ml/minute and standard deviation of 22 ml/minute.

```
% PK parameters
Central = lognrnd(2.01   , 0.2 , nPatients, nDoseGrps)         ; % units: liter
k12     = lognrnd(0.4441 , 0.2 , nPatients, nDoseGrps)         ; % units: 1/hour
k21     = lognrnd(0.7958 , 0.2 , nPatients, nDoseGrps)         ; % units: 1/hour
CL      = 1.07*CrCL + 45.6 + normrnd(0,22,nPatients,nDoseGrps) ; % units: ml/minute
```

Distribution of Pharmacodynamic (PD) parameters:

Growing-to-resting transformation rate constants, `k1` and `k2`, were sampled from a lognormal distribution with typical value of 5.59e-5 and 0.0297 1/hour, respectively, each with a CV of 20%. Kmax was sampled from a lognormal distribution with a typical value of 3.5 1/hour and 15.9% CV. Katsube et al. assumed that values k1, k2 and Kmax were independent of the bacterial strain being treated. The value of Beta, the net growth rate constant, was fixed at 1.5 1/hour.

Based on experiments with several strains, the authors concluded that the value of KC50 was linearly dependent on the minimum inhibition concentration (MIC) of bacterial strain via the following equation.

$$ln(KC50) = -1.91 + 0.898 * ln(MIC) + \varepsilon$$

where ε is the additive residual error sampled from a normal distribution with a mean of 0 and standard deviation of 1.06 ug/ml. In the simulation, the MIC values were sampled from a discrete distribution, and the KC50 value was calculated for the selected MIC using the above equation.

```
% Discrete distribution of MIC values based on 71 P. aeruginosa strains
micValue  = [0.0625, 0.125, 0.25, 0.5 , 1 , 2 , 4 , 8 , 16 , 32 ] ;
micFreq   = [   5  ,    8 ,  9   , 14  , 7 , 8 , 9 , 5 , 2  , 4  ] ;

k1   = lognrnd(-9.8116, 0.2  , nPatients, nDoseGrps)        ; % units: 1/hour
k2   = lognrnd(-3.5362, 0.2  , nPatients, nDoseGrps)        ; % units: 1/hour
Kmax = lognrnd( 1.2332, 0.159, nPatients, nDoseGrps)        ; % units: 1/hour

% Sample MIC values from a discrete distribution using randsample
MIC = nan(nPatients, nDoseGrps) ; % preallocate
for iDoseGrp = 1:nDoseGrps
    MIC(:, iDoseGrp) = randsample(micValue , nPatients, true , micFreq);
end

KC50 = exp(-1.91 + 0.898*log(MIC) + 1.06*randn(nPatients , nDoseGrps)) ; % units: micr
```

Simulation Setup & Design

You will convert the model to a SimBiology exported model, which facilitates performing parameter scans in parallel. When you export the model, you choose which species, parameters, or compartments can be varied. In this example, you will vary 8 parameters, Central, k12, k21, CL, k1, k2, Kmax, and KC50.

```
% Select the parameters you want to vary.
paramNames = {'Central', 'k12', 'k21', 'CL', 'k1', 'k2', 'Kmax', 'KC50'};
for iParam = 1:length(paramNames)
```

```
    parameters(iParam) = sbioselect(m1, 'Name', paramNames{iParam});
end

% Created the exported model, using the selected parameters and doses
exportedModel = export(m1, parameters, doseRegimens);

% Accelerate the model
accelerate(exportedModel);
```

For all dosage scenarios, the model was simulated until t = 2 weeks from the time of the first dose. Total bacterial count, CFU, was sampled every 24 hours (once a day) for the entire duration of the dosage regimen.

```
tObs      = 0:24:336       ; % hour
nTPoints  = length(tObs)   ; % Number of sampling points

% Specify that the simulation should report these output times
exportedModel.SimulationOptions.OutputTimes = tObs;
```

Start the Worker Pool

If you have the Parallel Computing Toolbox software, you can use local workers to distribute each simulation to a different worker. If you also have the MATLAB® Distributed Computing Server™, you can run your simulations on a cluster.

You can create a pool of workers using the current cluster profile with this command:

```
parpool
```

Monte Carlo Simulation of Patients with Severe Infection

The antibacterial efficacy of a drug can be measured using different PK/PD indices. Katsube et al. set the criterion for bacterial elimination at `log10(CFU) < 0`, where CFU is the total bacterial count. The efficacy of each dose regimen was measured as the fraction of the population that achieved the success criteria in the dosage group. This efficacy metric, `Pr{log10(CFU) < 0}`, was tracked as a function of time for each dosage group.

In their simulation studies, the authors investigated the efficacy of the dosage regimens on two classes of patients:

- Moderate infection (Initial bacterial count = 1e4 CFU/ml)
- Severe infection (Initial bacterial count = 1e7 CFU/ml)

In this example, we will replicate the results for the severe infection case only. Note that you can easily simulate the other scenario, patients with moderate infection, by changing the initial amount of bacterial count in the model to 1e4 CFU/ml.

```
% Preallocate
log10CFU     = cell(1,nDoseGrps) ;


for iDoseGrp = 1:nDoseGrps

    % Select the exported doess
    currentDose = getdose(exportedModel, doseNames{iDoseGrp});

    cfu = nan(nTPoints , nPatients)    ; % preallocate

    disp(['Simulating group ',  num2str(iDoseGrp), ' ... '])
    parfor iPatient = 1:nPatients

       % Use parameter values for current patient
       % Define the parameters in the same order used when exporting
       parameterValues = [
           Central(iPatient , iDoseGrp)
           k12(iPatient, iDoseGrp)
           k21(iPatient, iDoseGrp)
           CL(iPatient , iDoseGrp)
           k1(iPatient , iDoseGrp)
           k2(iPatient , iDoseGrp)
           Kmax(iPatient, iDoseGrp)
           KC50(iPatient, iDoseGrp)
           ];

        % Simulate
        simData = simulate(exportedModel, parameterValues, currentDose) ;

        % Extract bacterial count data for Growing and Resting population
        [~, bactCount]  = selectbyname(simData, {'Growing', 'Resting'}) ;

        % Sum of growing and resting bacterial
        cfu(:, iPatient) = sum(bactCount, 2) ;

    end

    % Calculate log10(CFU)
    log10CFU{iDoseGrp}  = log10(cfu) ;
```

```
end

% Save results
log10CFU_250bid = log10CFU{1} ;
log10CFU_250tid = log10CFU{2} ;
log10CFU_500bid = log10CFU{3} ;
log10CFU_500tid = log10CFU{4} ;
```

```
Simulating group 1 ...
Simulating group 2 ...
Simulating group 3 ...
Simulating group 4 ...
```

Clean Up the Worker Pool

If you previously called `parpool` to start some workers, be sure to close them using the following command:

```
delete(gcp)
```

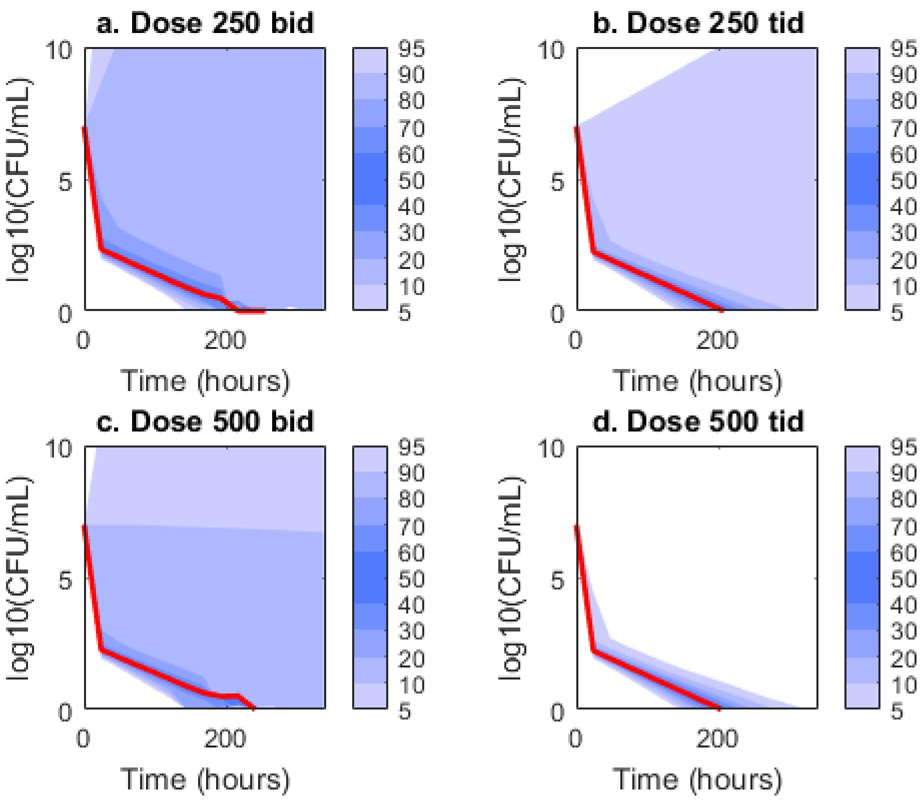
The function `gcp` (get current pool) returns the pool created by `parpool`, and the `delete` command closes the pool.

Time Course Profiles of Bacterial Counts

We plot the median (in red) and percentile (shaded) profiles of the `log10(CFU)` levels for all four dosage regimens. Observe that in all four groups, the median time course profile shows that bacterial eradication is complete before the end of the treatment period (336 hours). However, it is evident from the higher percentile profiles that the treatments are not successful for all patients. The 95th and 90th percentile profiles also indicate that dosing a lower amount with a higher frequency (250 tid) is more effective than less frequent dosing with higher amount (500 bid).

```
hax1(1) = subplot(2,2,1)
plotCFUCount(tObs, log10CFU_250bid, 'a. Dose 250 bid' )
hax1(2) = subplot(2,2,2)
plotCFUCount(tObs, log10CFU_250tid, 'b. Dose 250 tid' )
hax1(3) = subplot(2,2,3)
plotCFUCount(tObs, log10CFU_500bid, 'c. Dose 500 bid' )
hax1(4) = subplot(2,2,4)
plotCFUCount(tObs, log10CFU_500tid, 'd. Dose 500 tid' )
```

```
% Link subplot axes
linkaxes(hax1)


hax1 =

  Axes with properties:

             XLim: [0 1]
             YLim: [0 1]
           XScale: 'linear'
           YScale: 'linear'
    GridLineStyle: '-'
         Position: [0.1300 0.5838 0.3347 0.3412]
            Units: 'normalized'

  Use GET to show all properties


hax1 =

  1x2 Axes array:

    Axes    Axes


hax1 =

  1x3 Axes array:

    Axes    Axes    Axes


hax1 =

  1x4 Axes array:

    Axes    Axes    Axes    Axes
```



Effect of Renal Function on Antibacterial Activity

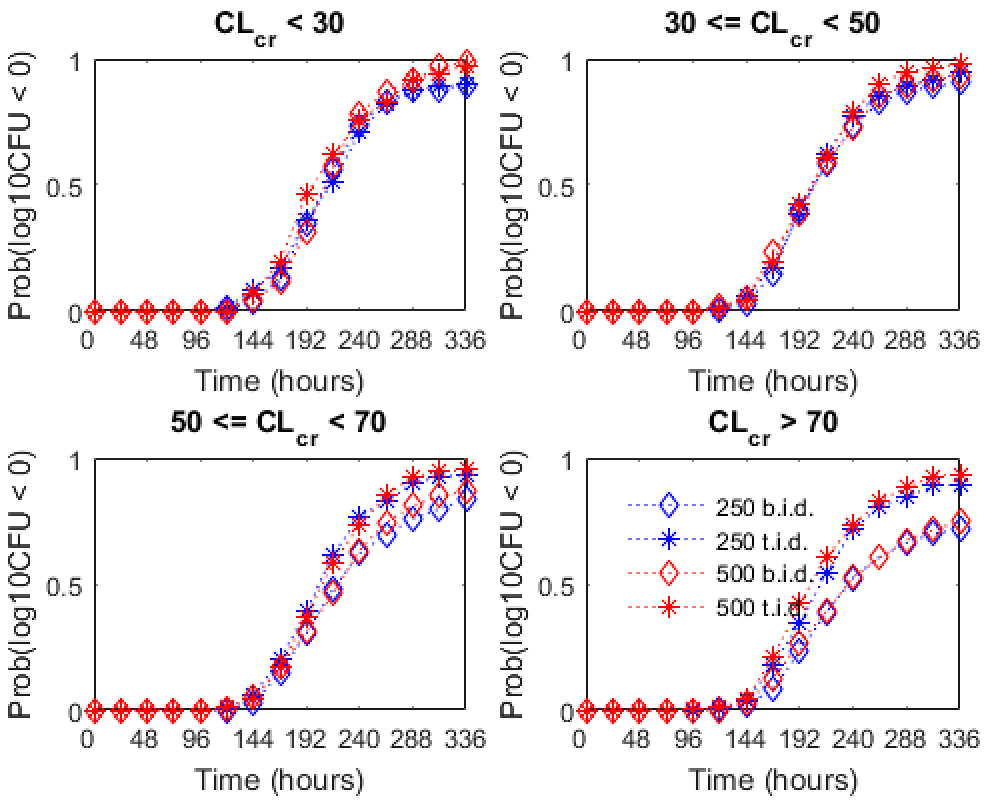
Finally, the authors compared the efficacy profiles of the dosages regimens as a function of the renal function. They classified the patients into four renal function groups based on the creatinine clearance rates (`CrCL`):

- Creatinine Clearance Group 1: `CrCL` < 30
- Creatinine Clearance Group 2: 30 <= `CrCL` < 50
- Creatinine Clearance Group 3: 50 <= `CrCL` < 70
- Creatinine Clearance Group 4: `CrCL` >= 70

The next figure shows the effect of renal function (creatinine clearance rate) on the antibacterial efficacy of the four dosage regimens. Observe that in the normal renal function group (CrCL >= 70), the efficacy profiles of the four treatment strategies are significantly different from each other. In this case, the 500 mg t.i.d. dose is much more effective than the other regimens. In contrast, simulations involving patients with renal dysfunction (CrCL < 30 and 30 <= CrCL < 50), we don't see much difference between the treatment groups. This indicates that for patients with a renal dysfunction, a less intense or less frequent dosing strategy would work almost as well as a dosing strategy with higher frequency or dosing amount.

```
% Preallocate
idCrCLGrp   = false(nPatients, nDoseGrps) ;

% Line Style
ls = {'bd:', 'b*:', 'rd:', 'r*:'} ;

titleStr = {'CL_c_r < 30'           , ...
            '30 <= CL_c_r < 50'     , ...
            '50 <= CL_c_r < 70'     , ...
            'CL_c_r > 70'            };

f = figure;
f.Color = 'w'

for iCrCLGrp = 1:4 % Creatinine Clearance Groups

    hax2(iCrCLGrp) = subplot(2,2, iCrCLGrp) ;
    title( titleStr{iCrCLGrp}    ) ;
    ylabel('Prob(log10CFU < 0)' ) ;
    xlabel('Time (hours)'       ) ;

end

% Set axes properties
set(hax2,   'XTick'         , 0:48:336      , ...
            'XTickLabel'    , 0:48:336      , ...
            'Ylim'          , [0 1]         , ...
            'Xlim'          , [0 336]       , ...
            'NextPlot'      , 'add'         , ...
            'Box'           , 'on'          );

% Plot results by renal function group:
for iDoseGrp = 1:nDoseGrps

    % Extract indices for renal function
    idCrCLGrp(:, 1) = CrCL(:,iDoseGrp) < 30                                     ;
```

```
        idCrCLGrp(:, 2) = CrCL(:,iDoseGrp) >= 30 & CrCL(:,iDoseGrp) < 50           ;
        idCrCLGrp(:, 3) = CrCL(:,iDoseGrp) >= 50 & CrCL(:,iDoseGrp) < 70           ;
        idCrCLGrp(:, 4) = CrCL(:,iDoseGrp) >= 70                                   ;

        for iCrCLGrp = 1:4 % Creatinine Clearance Groups

            % Calculate probability
            Pr = sum( ( log10CFU{iDoseGrp}(:, idCrCLGrp(:, iCrCLGrp)') < 0) , 2 )/sum(idCrC

            % Plot
            plot(hax2(iCrCLGrp), tObs, Pr , ls{iDoseGrp}, 'MarkerSize', 7)
        end

    end

    legend(hax2(4), {'250 b.i.d.', '250 t.i.d.', '500 b.i.d.', '500 t.i.d.'} )
    legend location NorthWest
    legend boxoff

    linkaxes(hax2)


    f =

      Figure (2) with properties:

          Number: 2
            Name: ''
           Color: [1 1 1]
        Position: [360 502 560 420]
           Units: 'pixels'

      Use GET to show all properties
```


CL_{cr} < 30
30 <= CL_{cr} < 50
50 <= CL_{cr} < 70
CL_{cr} > 70
Prob(log10CFU < 0)
Time (hours)
0
48
96
144
192
240
288
336
0
0.5
1
250 b.i.d.
250 t.i.d.
500 b.i.d.
500 t.i.d.

Deploy a SimBiology Model

This example shows how to deploy a graphical application that simulates a SimBiology model. The example model is the Lotka-Volterra reaction system as described by Gillespie [1], which can be interpreted as a simple predator-prey model.

This example requires MATLAB Compiler™

Overview

You can create stand-alone SimBiology applications using the MATLAB Compiler and the SimBiology exported model. To make your application compatible with the MATLAB Compiler, do the following:

- Create an exported model, using the model's `export` method.
- Accelerate the model (optional).
- Save the model to a MAT file.
- Ensure your application loads the model from the MAT file.
- Add the `%#function` pragma to the application's top-level function.
- Call the `mcc` function, explicitly adding the MAT file and the exported model's dependent files to the application.

Load the Model

```
sbioloadproject lotka m1
```

Create the Exported Model

```
exportedModel = export(m1);
```

Accelerate the Model

Acceleration requires a correctly configured MEX compiler (see the documentation for `mex -setup`).

```
accelerate(exportedModel);
```

Save the Exported Model

Uncomment the next line to save the model in exportedLotka.mat

```
% save exportedLotka exportedModel
```

Call `mcc`

The top-level function for the application, `simulateLotkaGUI.m`, has already been updated to use the exported model MAT file. It also contains the following `%#function` pragma, which tells the MATLAB Compiler that the application uses a SimBiology exported model: `%#function SimBiology.export.Model`

Now, determine the list of files to explicitly add to the application. This list includes the MAT file containing the exported model and any files listed in the `DependentFiles` property of the exported model. Note that this MAT file must be loaded into the workspace before `mcc` is called, so that the exported model's files are available for deployment.

```
% To speed up compilation, we use the option |-N -p simbio|, which informs
% |mcc| that the deployed application does not depend on any additional
% toolboxes. For the purposes of this example, we programmatically
% construct the |mcc| command.
mccCommand = ['mcc -m simulateLotkaGUI.m -N -p simbio -a exportedLotka.mat ' ...
    sprintf(' -a %s', exportedModel.DependentFiles{:})];

% Uncomment the following line to execute the |mcc| command. This may take
% several minutes.
%
% eval(mccCommand)
```

References

[1] Gillespie D.T. "Exact Stochatic Simulation of Coupled Chemical Reactions," (1977) *The Journal of Physical Chemistry*, 81(25), 2340-2361.

Estimating the Bioavailability of a Drug

In this example, you will use the parameter estimation capabilities of SimBiology™, to calculate `F`, the bioavailability, of the drug ondansetron. You will calculate `F` by fitting a model of absorption and excretion of the drug to experimental data tracking drug concentration over time.

Background

Most drugs must be absorbed into the bloodstream in order to become active. An intravenous (IV) administration of a drug is one way to achieve this. However, it is impractical or impossible in many cases.

When a drug is not given by IV, it follows some other route into the bloodstream, such as absorption through the mucous membranes of the GI tract or mouth. Drugs administered through a route other than IV administration are generally not completely absorbed. Some portion of the drug is directly eliminated and never reaches the bloodstream.

The percentage of drug absorbed is the bioavailability of the drug. Bioavailability is one of the most important pharmacokinetic properties of a drug. It is useful when calculating safe dosages for non-IV routes of administration. Bioavailability is calculated relative to an IV administration. When administered intravenously, a drug has 100% bioavailability. Other routes of administration tend to reduce the amoutn of drug that reaches the blood stream.

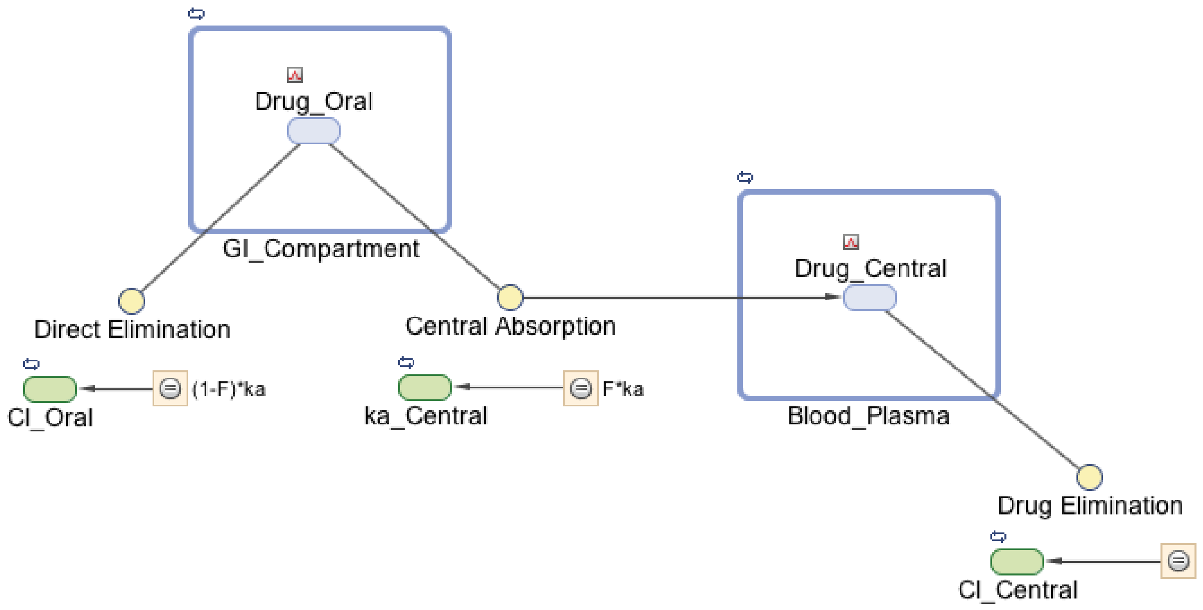
Modeling Bioavailability

Bioavailability can be modeled using one of several approaches. In this example, you use a model with a GI compartment and a blood plasma compartment. Oral administration is modeled by a dose event in the GI compartment. IV adminsitration is modeled by a dose event in the blood plasma compartment.

The example models the drug leaving the GI compartment in two ways. The available fraction of the drug is absorbed into the bloodstream. The remainder is directly eliminated. The total rate of elimination, `ka`, is divided into absorption, `ka_Central`, and direct elimination, `Cl_Oral`. The bioavailability, `F`, connects total elimination with `ka_Central` and `Cl_Oral` via two initial assignment rules.

```
ka_Central = F*ka
Cl_Oral = (1-F)*ka
```

The drug is eliminated from the `Blood_Plasma` compartment through first-order kinetics, at a rate determined by the parameter `Cl_Central`.



Load the project that contains the model `m1`.

```
sbioloadproject('Bioavailability.sbproj','m1')
```

Format of the Data for Estimating Bioavailability

You can estimate bioavailability by comparing intrapatient measurements of drug concentration under different dosing conditions. For instance, a patient receives an IV dose on day 1, then receives an oral dose on day 2. On both days, we can measure the blood plasma concentration of the drug over some period of time.

Such data allow us to estimate the bioavailability, as well as other parameters of the model. Intrapatient time courses were generated for the drug ondansetron, reported in [3] and reproduced in [1].

Load the data, which is a table.

```
load ondansetron_data
```

Convert the data to a `groupedData` object because the fitting function `sbiofit` requires it to be a `groupedData` object.

```
gd = groupedData(ondansetron_data);
```

Display the data.

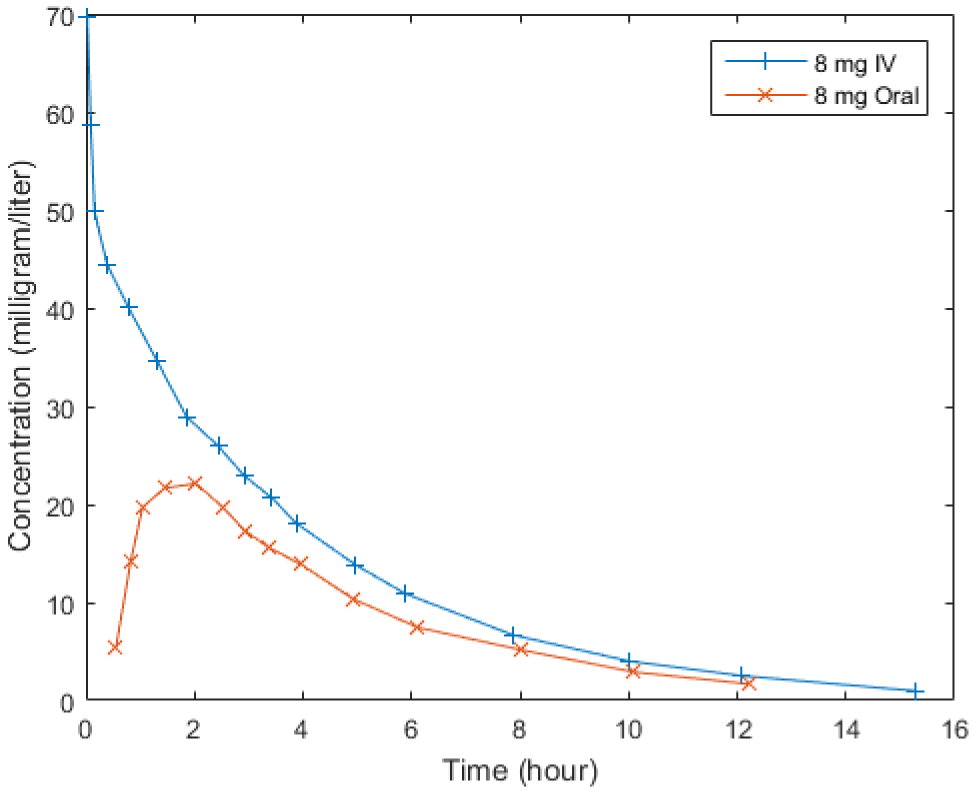
```
gd
```

```
gd = 

      Time        Drug       Group    IV     Oral
    ________    ________    _____    ___    ____

           0         NaN    1          8    NaN  
    0.024358      69.636    1        NaN    NaN  
    0.087639      58.744    1        NaN    NaN  
     0.15834      49.824    1        NaN    NaN  
     0.38895      44.409    1        NaN    NaN  
     0.78392      40.022    1        NaN    NaN  
      1.3182      34.522    1        NaN    NaN  
      1.8518      28.972    1        NaN    NaN  
      2.4335       25.97    1        NaN    NaN  
      2.9215      22.898    1        NaN    NaN  
        3.41       20.75    1        NaN    NaN  
      3.8744      18.095    1        NaN    NaN  
      4.9668      13.839    1        NaN    NaN  
      5.8962      10.876    1        NaN    NaN  
      7.8717      6.6821    1        NaN    NaN  
       10.01      4.0166    1        NaN    NaN  
       12.08      2.5226    1        NaN    NaN  
      15.284     0.97816    1        NaN    NaN  
           0         NaN    2        NaN      8  
     0.54951      5.3091    2        NaN    NaN  
     0.82649      14.262    2        NaN    NaN  
      1.0433       19.72    2        NaN    NaN  
      1.4423      21.654    2        NaN    NaN  
      2.0267      22.144    2        NaN    NaN  
      2.5148      19.739    2        NaN    NaN  
      2.9326      17.308    2        NaN    NaN  
      3.3743      15.599    2        NaN    NaN  
      3.9559      13.906    2        NaN    NaN  
      4.9309      10.346    2        NaN    NaN  
      6.1155      7.4489    2        NaN    NaN  
      8.0002      5.1919    2        NaN    NaN  
      10.091      2.9058    2        NaN    NaN  
      12.228      1.6808    2        NaN    NaN  
```

The data have variables for time, drug concentration, grouping information, IV, and oral dose amounts. Group 1 contains the data for the IV time course. Group 2 contains the data for the oral time course. `NaN` in the Drug column means no measurement was made at that time. `NaN` in one of the dosing columns means no dose was given through that route at that time.

Plot the pharmacokinetic profiles of the oral dose and IV administration.

```
plot(gd.Time(gd.Group==1),gd.Drug(gd.Group==1),'Marker','+')
hold on
plot(gd.Time(gd.Group==2),gd.Drug(gd.Group==2),'Marker','x')
legend({'8 mg IV','8 mg Oral'})
xlabel('Time (hour)')
ylabel('Concentration (milligram/liter)')
```



Notice there is a lag phase in the oral dose of about an hour while the drug is absorbed from the GI tract into the bloodstream.

Fitting the Data

Estimate the following four parameters of the model:

- Total forward rate out of the dose compartment, `ka`
- Clearance from the `Blood_Plasma` compartment, `clearance`
- Volume of the `Blood_Plasma` compartment
- Bioavailability of the orally administered drug, `F`

Set the initial values of these parameters and specify the log transform for all parameters using an `estimatedInfo` object.

```
init = [1 1 2 .8];
estimated_parameters = estimatedInfo({'log(ka)','log(clearance)',...
                      'log(Blood_Plasma)','logit(F)'},'InitialValue',init);
```

Because `ka`, `clearance`, and `Blood_Plasma` are positive physical quantities, log transforming reflects the underlying physical constraint and generally improves fitting. This example uses a logit transform on `F` because it is a quantity constrained between 0 and 1. The logit transform takes the interval of 0 to 1 and transforms it by taking the log-odds of `F` (treating `F` as a probability). For a few drugs, like theophyline, constraining `F` between 0 and 1 is inappropriate because oral bioavailability can be greater than 1 for drugs with unusual absorption or metabolism mechanisms.

Next, map the response data to the corresponding model component. In the model, the plasma drug concentration is represented by `Blood_Plasma.Drug_Central`. The corresponding concentration data is the `Drug` variable of the groupedData object `gd`.

```
responseMap = {'Blood_Plasma.Drug_Central = Drug'};
```

Create the dose objects required by `sbiofit` to handle the dosing information. First, create the IV dose targeting `Drug_Central` and the oral dose targeting `Dose_Central`.

```
iv_dose   = sbiodose('IV','TargetName','Drug_Central');
oral_dose = sbiodose('Oral','TargetName','Drug_Oral');
```

Use these dose objects as template doses to generate an array of dose objects from the dosing data variables `IV` and `Oral`.

```
doses_for_fit = createDoses(gd,{'IV','Oral'},'',[iv_dose, oral_dose]);
```

Estimate parameters using `sbiofit`.

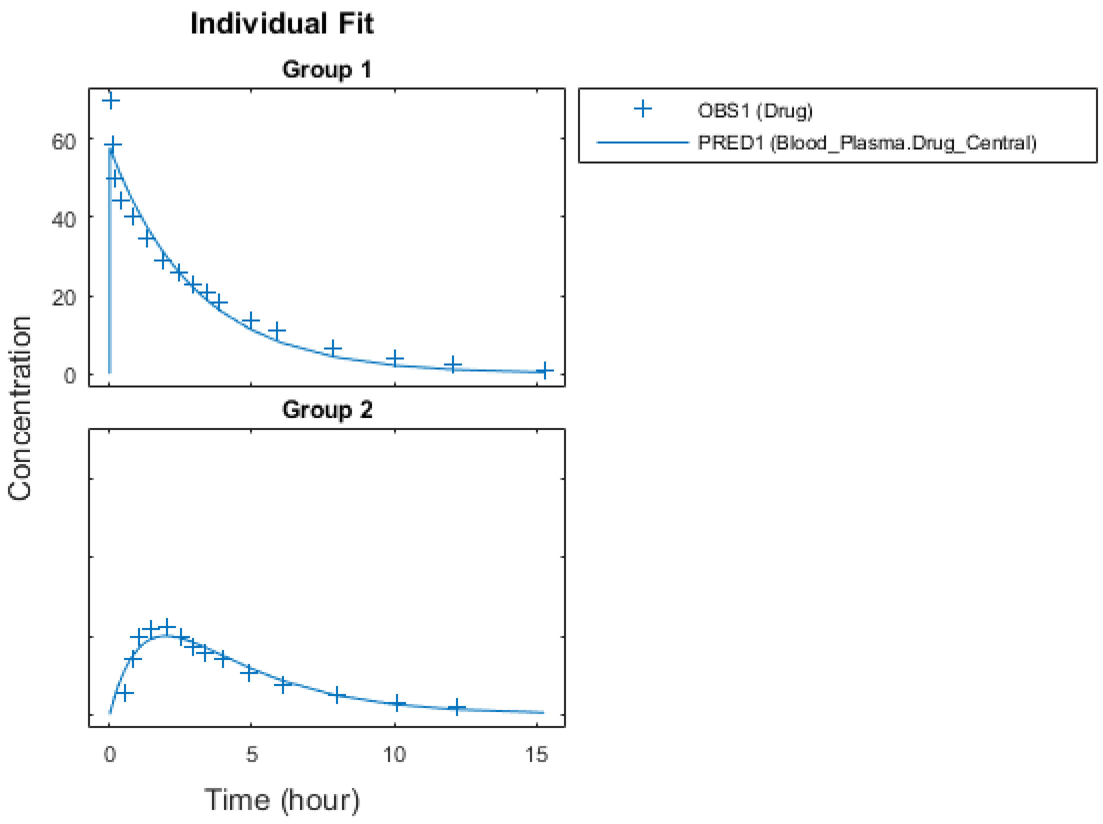
```
opts = optimoptions('lsqnonlin','Display','final');
results = sbiofit(m1, gd,responseMap,estimated_parameters,doses_for_fit,...
                  'lsqnonlin',opts,[],'pooled',true);
```

```
Local minimum possible.

lsqnonlin stopped because the final change in the sum of squares relative to
its initial value is less than the selected value of the function tolerance.
```

Interpreting Results

First, check if the fit is successful.

```
plot(results)
```



Overall, the results seem to be a good fit. However, they do not capture a distribution phase over the first hour. It might be possible to improve the fit by adding another compartment, but more data would be required to justify such an increase in model complexity.

When satisfied with the model fit, you can draw conclusions about the estimated parameters. Display the parameters stored in the results object.

```
results.ParameterEstimates
```

```
ans = 

         Name         Estimate    StandardError
    ______________    ________    _____________

    'ka'              0.74025      0.16777     
    'clearance'        45.442       2.8902     
    'Blood_Plasma'     138.63       4.5328     
    'F'                0.6626     0.068487     
```

The parameter F is the bioavailability. The result indicates that ondansetron has approximately a 66% bioavailability. This estimate in line with the literature reports that oral administration of ondansetron in the 2-24 milligram range has a 60% bioavailability [1,3].

Blood_Plasma is the volume of distribution. This result is reasonably close to the 160 liter Vd reported for ondansetron [1]. The estimated clearance is 45.4 L/hr.

ka does not map directly onto a widely reported pharmacokinetic parameter. Consider it from two perspectives. We can say that 66% of the drug is available, and that the available drug has an absorption parameter of 0.4905/hr. Or, we can say that drug clearance from the GI compartment is 0.7402/hr, and 66% of the drug cleared from the GI tract is absorbed into the bloodstream.

Generalizing This Approach

lsqnonlin, as well as several other optimization algorithms supported by sbiofit, are local algorithms. Local algorithms are subject to the possibility of finding a result that is not the best result over all possible parameter choices. Because local algorithms do not guarantee convergence to the globally best fit, when fitting PK models, restarting the fit with different initial conditions multiple times is a good practice. Alternatively, sbiofit supports several global methods, such as particle swarm, or genetic algorithm optimization. Verifying that a fit is of sufficient quality is an important step before drawing inferences from the values of the parameters.

This example uses data that was the mean time course of several patients. When fitting a model with data from more patients, some parameters might be the same between patients, some not. Such requirements introduce the need for hierarchical modeling. You can perform hierarchical modeling can by configuring the `CategoryVariableName` flag of `EstimatedInfo` object.

References

1. Roila, Fausto, and Albano Del Favero. "Ondansetron clinical pharmacokinetics." Clinical Pharmacokinetics 29.2 (1995): 95-109.
2. Colthup, P. V., and J. L. Palmer. "The determination in plasma and pharmacokinetics of ondansetron." European Journal of Cancer & Clinical Oncology 25 (1988): S71-4.

A

Creating Reaction Rates

Create Reaction Rates

Define Reaction Rates with Mass Action Kinetics

Definition of Mass Action Kinetics

Mass action describes the behavior of reactants and products in an elementary chemical reaction. Mass action kinetics describes this behavior as an equation where the velocity or rate of a chemical reaction is directly proportional to the concentration of the reactants.

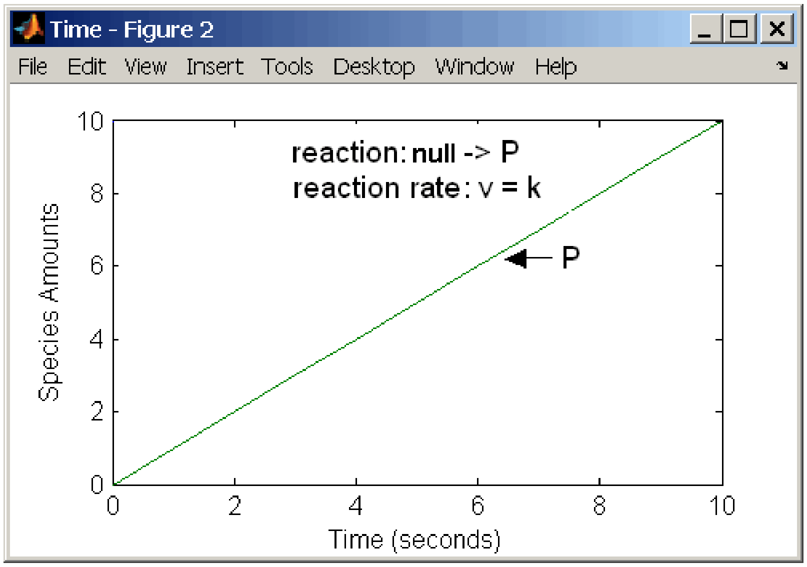
Zero-Order Reactions

With a zero-order reaction, the reaction rate does not depend on the concentration of reactants. Examples of zero-order reactions are synthesis from a `null` species, and modeling a source species that is added to the system at a specified rate.

```
     reaction: null -> P
reaction rate: k mole/second
      species: P =  0 mole
   parameters: k =  1 mole/second
```

Note: When specifying a `null` species, the reaction rate must be defined in units of amount per unit time not concentration per unit time.

Entering the reaction above into the software and simulating produces the following result:



Zero-Order Mass Action Kinetics

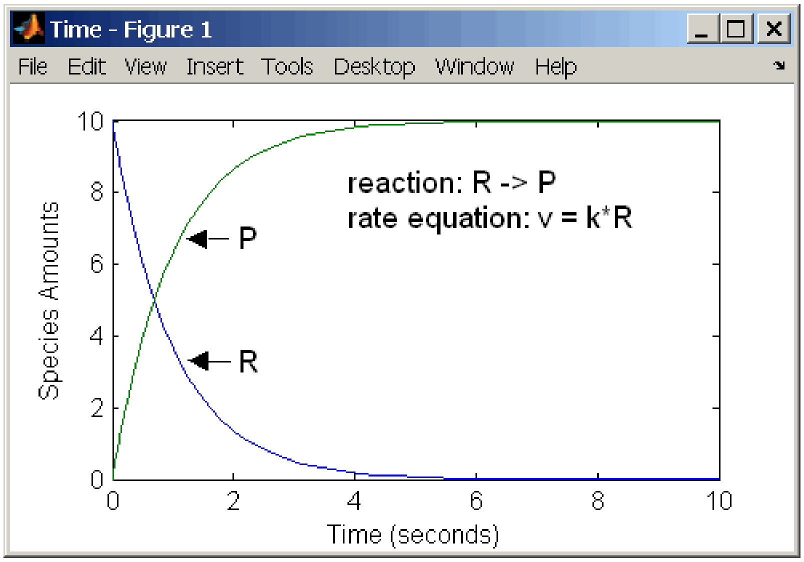
Note: If the amount of a reactant with zero-order kinetics reaches zero before the end of a simulation, then the amount of reactant can go below zero regardless of the solver or tolerances you set.

First-Order Reactions

With a first-order reaction, the reaction rate is proportional to the concentration of a single reactant. An example of a first-order reaction is radioactive decay.

```
     reaction: R -> P
reaction rate: k*R mole/(liter*second)
      species: R = 10 mole/liter
               P =  0 mole/liter
   parameters: k =  1 1/second
```

Entering the reaction above into the software and simulating produces the following results:



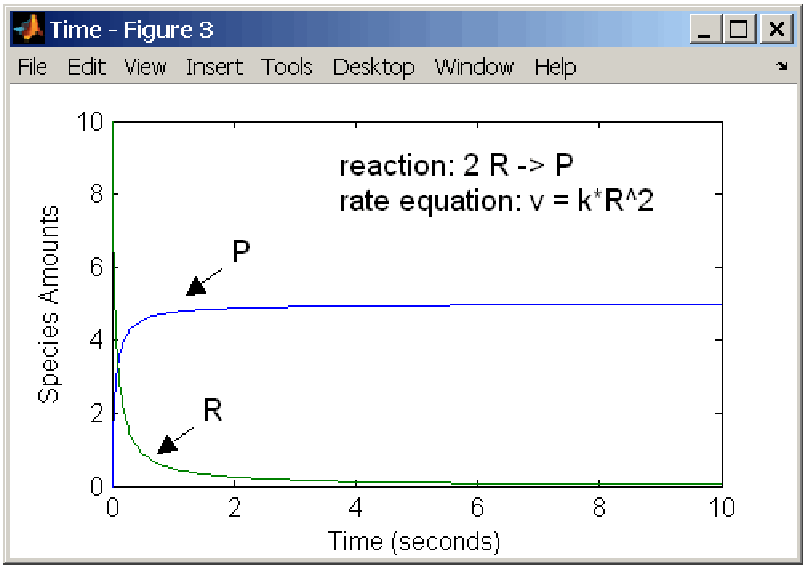
First-Order Mass Action Kinetics

Second-Order Reactions

A second-order reaction has a reaction rate that is proportional to the square or the concentration of a single reactant or proportional to two reactants. Notice the space between the reactant coefficient and the name of the reactant. Without the space, `2R` would be considered the name of a species.

```
     reaction: 2 R -> P
reaction rate: k*R^2 mole/(liter*second)
      species: R = 10 mole/liter
               P =  0 mole/liter
   parameters: k =  1 liter/(mole*second)
```

Entering the reaction above into the software and simulating produces the following results:

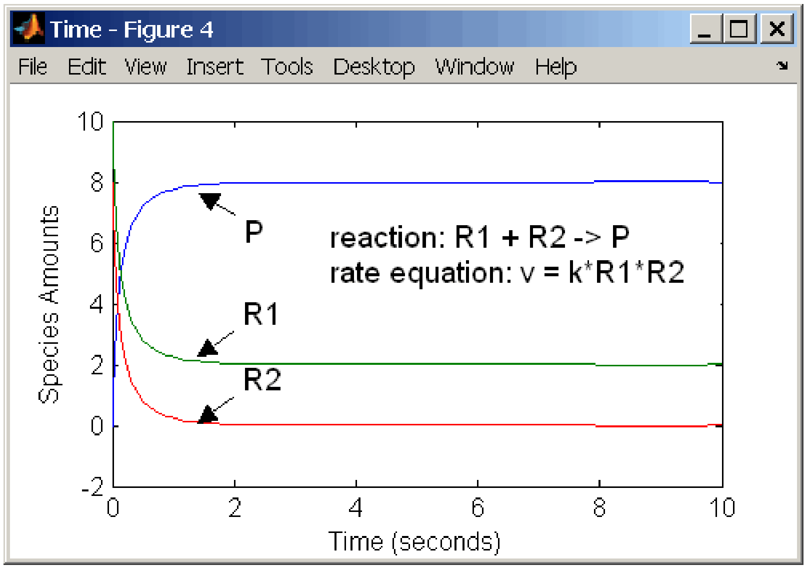


Second-Order Kinetics with Single Reactant

With two reactants, the reaction rate depends on the concentration of two of the reactants.

```
     reaction: R1 + R2 -> P
reaction rate: k*R1*R2 mole/(liter*second)
      species: R1 = 10 mole/liter
               R2 =  8 mole/liter
                P =  0 mole/liter
   parameters:  k =  1 liter/(mole*second)
```

Enter the reaction above into the software and simulating produces the following results. There is a difference in the final values because the initial amount of one of the reactants is lower than the other. After the first reactant is used up, the reaction stops.



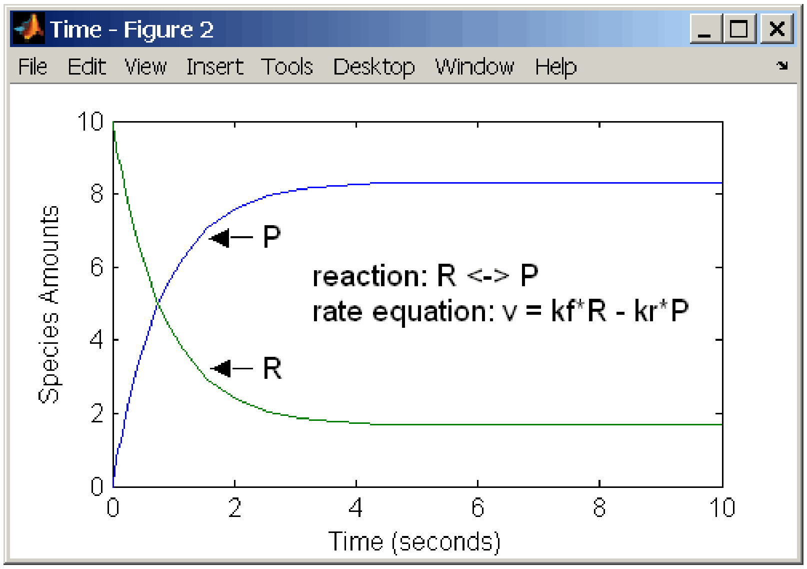
Second-Order Kinetics with Two Reactants

Reversible Mass Action

You can model reversible reactions with two separate reactions or with one reaction. With a single reversible reaction, the reaction rates for the forward and reverse reactions are combined into one expression. Notice the angle brackets before and after the hyphen to represent a reversible reaction.

```
     reaction: R <-> P
reaction rate: kf*R - kr*P mole/(liter*second)
      species: R = 10   mole/liter
               P =  0   mole/liter
   parameters: kf = 1   1/second
               kr = 0.2 1/second
```

Entering the reaction above into the software and simulating produces the following results. At equilibrium when the rate of the forward reaction equals the reverse reaction, `v = kf*R - kr*P = 0` and `P/R = kf/kr`.


Time - Figure 2
File Edit View Insert Tools Desktop Window Help
Species Amounts
Time (seconds)
0
2
4
6
8
10
P
R
reaction: R <-> P
rate equation: v = kf*R - kr*P

Define Reaction Rates with Enzyme Kinetics

Simple Model for Single Substrate Catalyzed Reactions

A simple model for enzyme-catalyzed reactions starts a substrate S reversibly binding with an enzyme E. Some of the substrate in the substrate/enzyme complex is converted to product P with the release of the enzyme.

$$S + E \underset{k1r}{\overset{k1}{\rightleftarrows}} ES \xrightarrow{k2} E + P$$

$$v1 = k1[S][E], \quad v1r = k1r[ES], \quad v2 = k2[ES]$$

This simple model can be defined with

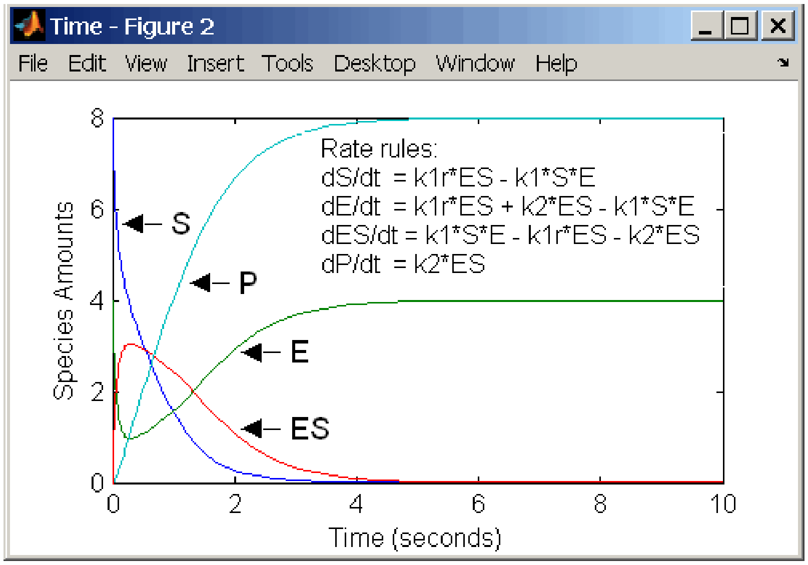
- Differential rate equations. See “Enzyme Reactions with Differential Rate Equations” on page A-9.
- Reactions with mass action kinetics. See “Enzyme Reactions with Mass Action Kinetics” on page A-11.
- Reactions with Henri-Michaelis-Menten kinetics. See “Enzyme Reactions with Irreversible Henri-Michaelis-Menten Kinetics” on page A-12.

Enzyme Reactions with Differential Rate Equations

The reactions for a single-substrate enzyme reaction mechanism (see “Simple Model for Single Substrate Catalyzed Reactions” on page A-9) can be described with differential rate equations. You can enter the differential rate equations into the software as rate rules.

```
     reactions: none
 reaction rate: none
    rate rules: dS/dt  = k1r*ES - k1*S*E
                dE/dt  = k1r*ES + k2*ES - k1*S*E
                dES/dt = k1*S*E - k1r*ES - k2*ES
                dP/dt  = k2*ES
       species: S =  8   mole
                E =  4   mole
               ES =  0   mole
                P =  0   mole
    parameters:  k1 = 2   1/(mole*second)
                k1r = 1   1/second
                 k2 = 1.5 1/second
```

Remember that the rate rule `dS/dt = f(x)` is written in a SimBiology rate rule expression as `S = f(x)`. For more information about rate rules see "Rate Rules" on page 1-25.



Rate rules:
dS/dt = k1r*ES - k1*S*E
dE/dt = k1r*ES + k2*ES - k1*S*E
dES/dt = k1*S*E - k1r*ES - k2*ES
dP/dt = k2*ES

Alternatively, you could remove the rate rule for `ES`, add a new species `Etotal` for the total amount of enzyme, and add an algebraic rule `0 = Etotal - E - ES`, where the initial amounts for `Etotal` and `E` are equal.

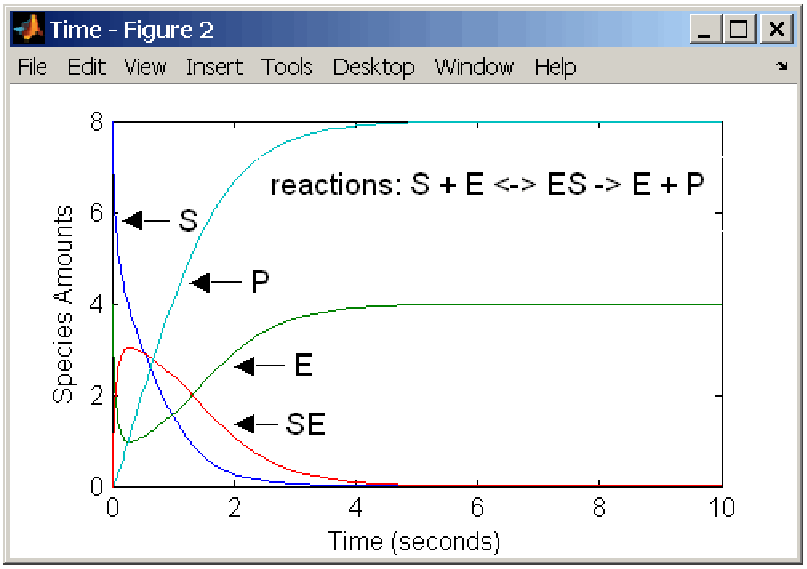
```
      reactions: none
  reaction rate: none
     rate rules: dS/dt = k1r*ES - k1*S*E
                 dE/dt = k1r*ES + k2*ES - k1*S*E
                 dP/dt = k2*ES
 algebraic rule: 0 = Etotal - E - ES
        species: S =  8   mole
                 E =  4   mole
                ES =  0   mole
                 P =  0   mole
            Etotal =  4   mole
     parameters: k1 = 2   1/(mole*second)
                k1r = 1   1/second
                 k2 = 1.5 1/second
```

Enzyme Reactions with Mass Action Kinetics

Determining the differential rate equations for the reactions in a model is a time-consuming process. A better way is to enter the reactions for a single substrate enzyme reaction mechanism directly into the software. The following example using models an enzyme catalyzed reaction with mass action kinetics. For a description of the reaction model, see "Simple Model for Single Substrate Catalyzed Reactions" on page A-9.

```
     reaction: S + E -> ES
reaction rate: k1*S*E (binding)

     reaction: ES -> S + E
reaction rate: k1r*ES (unbinding)

     reaction: ES -> E + P
reaction rate: k2*ES (transformation)
      species: S =  8   mole
               E =  4   mole
              ES =  0   mole
               P =  0   mole
   parameters: k1  = 2   1/(mole*second)
               k1r = 1   1/second
               k2  = 1.5 1/second
```

The results for a simulation using reactions are identical to the results from using differential rate equations.



Enzyme Reactions with Irreversible Henri-Michaelis-Menten Kinetics

Representing an enzyme-catalyzed reaction with mass action kinetics requires you to know the rate constants `k1`, `k1r`, and `k2`. However, these rate constants are rarely reported in the literature. It is more common to give the rate constants for Henri-Michaelis-Menten kinetics with the maximum velocity `Vm=k2*E` and the constant `Km = (k1r + k2)/k1`. The reaction rate for a single substrate enzyme reaction using Henri-Michaelis-Menten kinetics is given below. For information about the model, see "Simple Model for Single Substrate Catalyzed Reactions" on page A-9.

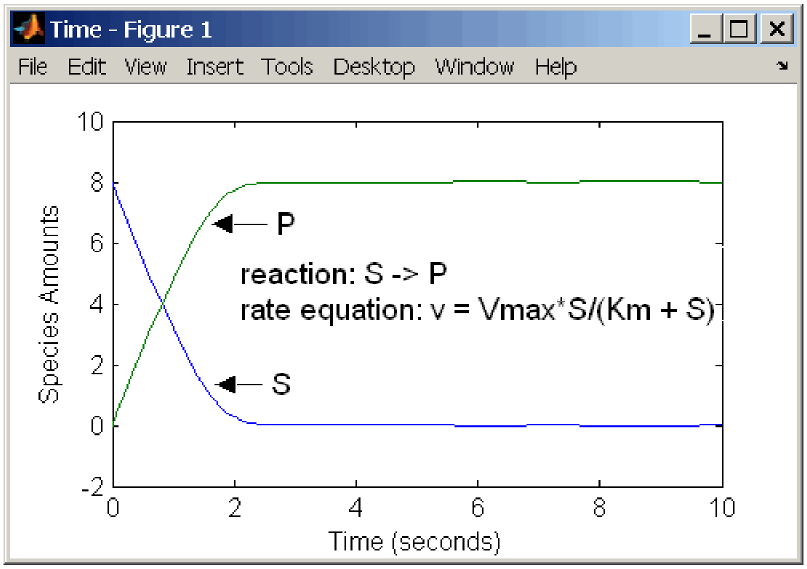
$$v = \frac{Vmax[S]}{Km + [S]}$$

The following example models an enzyme catalyzed reaction using Henri-Michaelis-Menten kinetics with a single reaction and reaction rate equation. Enter the reaction defined below into the software and simulate.

```
     reaction: S -> P
reaction rate: Vmax*S/(Km + S)
      species:    S =  8    mole
```

```
                    P =   0    mole
    parameters: Vmax =   6    mole/second
                   Km =   1.25 mole
```

The results show a plot slightly different from the plot using mass action kinetics. The differences are due to assumptions made when deriving the Michaelis-Menten rate equation.



Create Rate Rules

Create Rate Rules

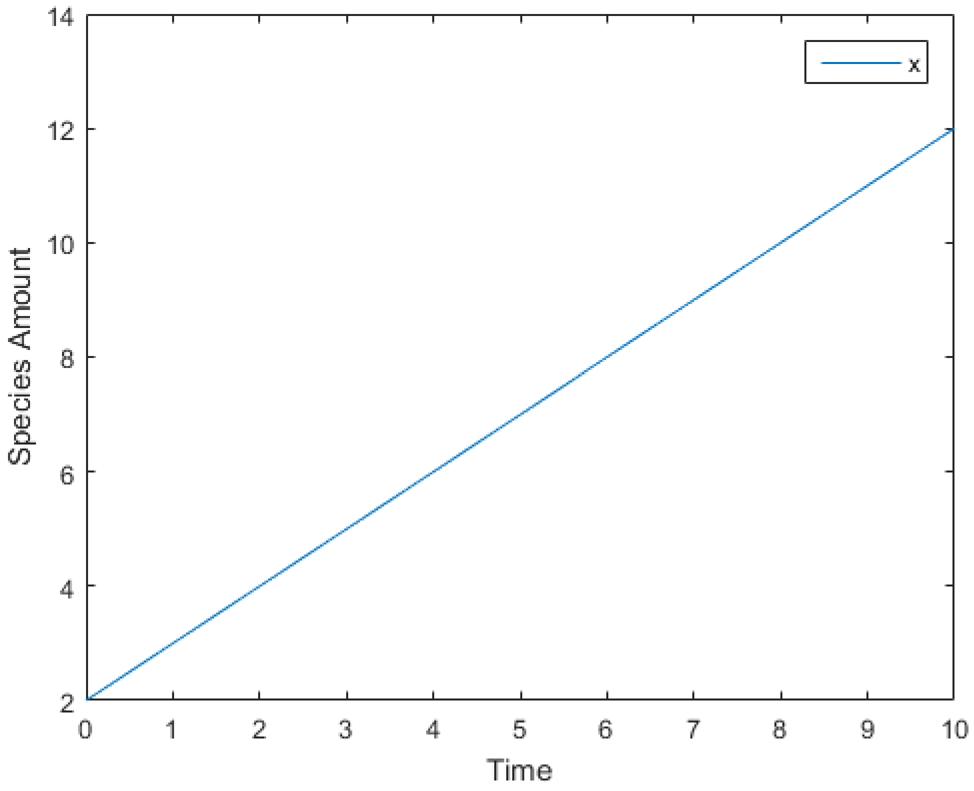
Create a Rate Rule for a Constant Rate of Change

This example shows how to increase the amount or concentration of a species by a constant value using the zero-order rate rule. For example, suppose species x increases by a constant rate k. The rate of change is:

$$dx/dt = k$$

Set the initial amount of species x to 2, and the value of parameter k to 1. Use the following commands to set up a SimBiology model accordingly and simulate it.

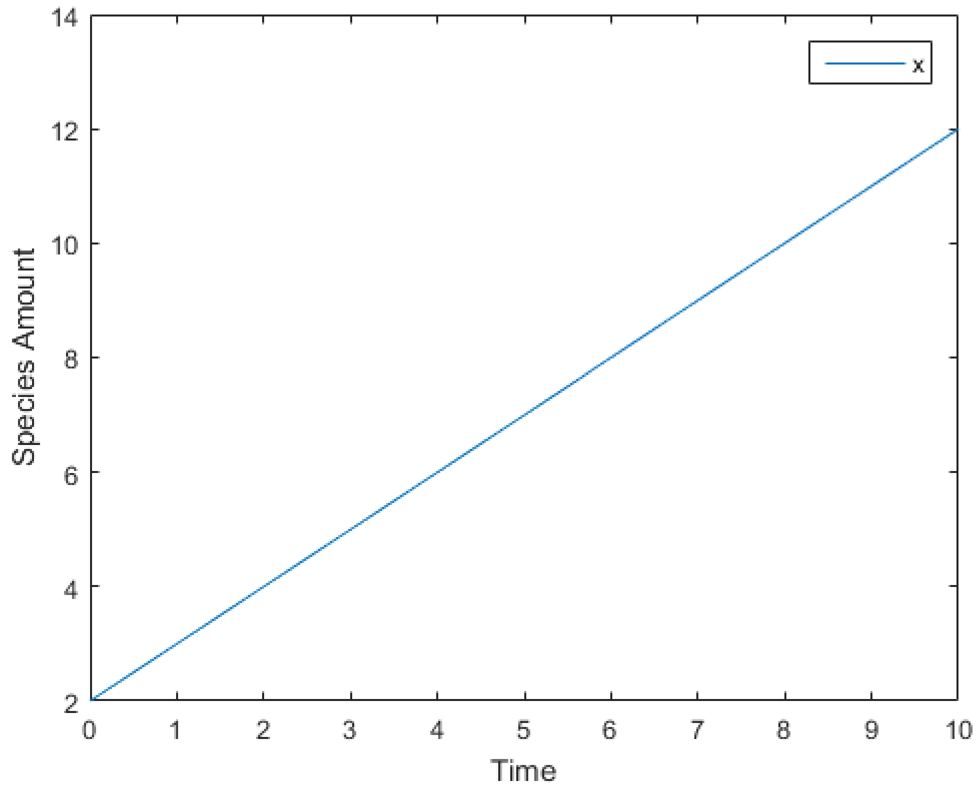
```
m = sbiomodel('m');
c = addcompartment(m,'comp');
s = addspecies(m,'x','InitialAmount',2);
p = addparameter(m,'k','Value',1);
r = addrule(m,'x = k','RuleType','rate');
[t,sd,species] = sbiosimulate(m);
plot(t,sd);
legend(species)
xlabel('Time');
ylabel('Species Amount');
```



Alternatively, you could model a constant increase in a species using the Mass Action reaction `null` -> `x` with the forward rate constant `k`.

```
clear
m = sbiomodel('m');
c = addcompartment(m,'comp');
s = addspecies(m,'x','InitialAmount',2);
r = addreaction(m,'null -> x');
kl = addkineticlaw(r,'MassAction');
p = addparameter(kl,'k','Value',1);
kl.ParameterVariableNames = 'k';
[t,sd,species] = sbiosimulate(m);
plot(t,sd);
legend(species)
```

```
xlabel('Time');
ylabel('Species Amount');
```



Create a Rate Rule for an Exponential Rate of Change

This example shows how to change the amount of a species similar to a first-order reaction using the first-order rate rule. For example, suppose the species x decays exponentially. The rate of change of species x is:

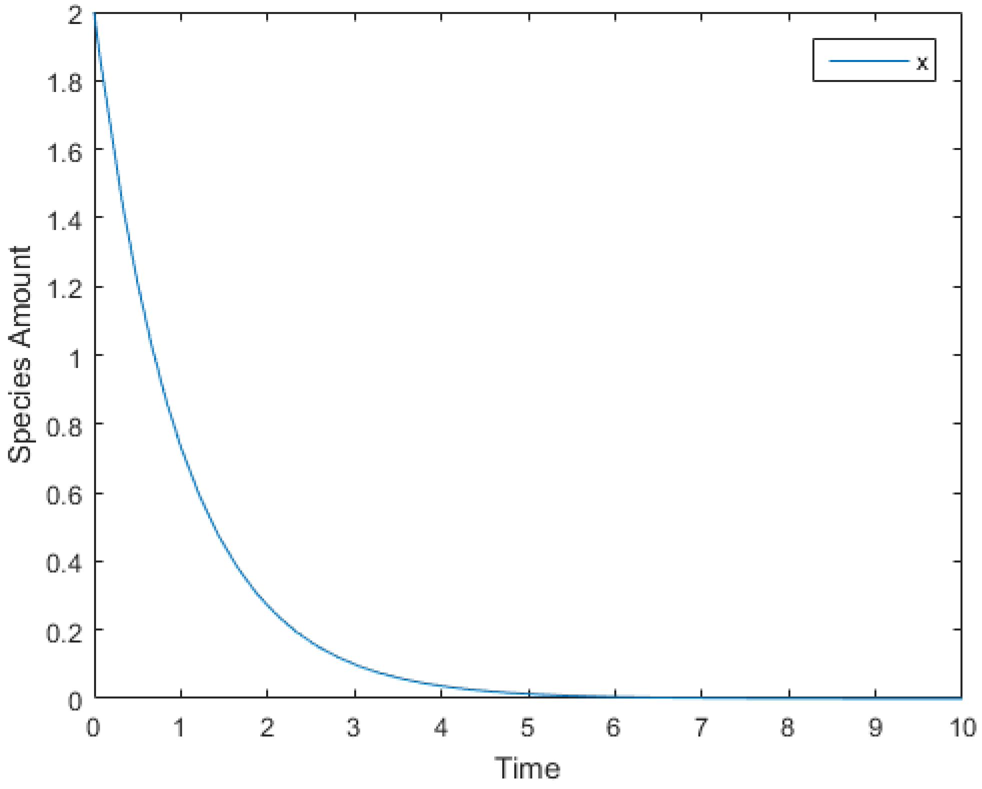
$$dx/dt = -k * x$$

The analytical solution is:

$$C_t = C_0 * e^{-kt}$$

where C_t is the amount of species at time t, and C_0 is the initial amount. Use the following commands to set up a SimBiology model accordingly and simulate it.

```
m = sbiomodel('m');
c = addcompartment(m,'comp');
s = addspecies(m,'x','InitialAmount',2);
p = addparameter(m,'k','Value',1);
r = addrule(m,'x = -k * x','RuleType','rate');
[t,sd,species] = sbiosimulate(m);
plot(t,sd);
legend(species);
xlabel('Time');
ylabel('Species Amount');
```



If the amount of a species `x` is determined by a rate rule and `x` is also in a reaction, `x` must have its BoundaryCondition property set to `true`. For example, with a reaction `a -> x` and a rate rule $\frac{dx}{dt} = k * x$, set the BoundaryCondition property of species `x` to `true` so that a differential rate term is not created from the reaction. The amount of `x` is determined solely by a differential rate term from the rate rule. If the BoundaryCondition property is set to `false`, you will get the following error message such as `Invalid rule variable 'x' in rate rule or reaction`.

Create a Rate Rule to Define a Differential Rate Equation

Many mathematical models in the literature are described with differential rate equations for the species. You could manually convert the equations to reactions, or you could enter the equations as rate rules. For example, you could enter the following differential rate equation for a species `C`:

$$\frac{dC}{dt} = v_i - v_d X \frac{C}{K_c + C} - k_d C$$

as a rate rule in SimBiology: `C = vi - (vd*X*C)/(Kc + C) - kd*C`

Create a Rate Rule for the Rate of Change That Is Determined by Another Species

This example shows how to create a rate rule where a species from one reaction can determine the rate of another reaction if it is in the second reaction rate equation. Similarly, a species from a reaction can determine the rate of another species if it is in the rate rule that defines that other species. Suppose you have a SimBiology model with three species (`a`, `b`, and `c`), one reaction (`a -> b`), and two parameters (`k1` and `k2`). The rate equation is defined as $b = -k_1 * a$, and rate rule is $dc/dt = k_2 * a$. The solution for the species in the reaction are:

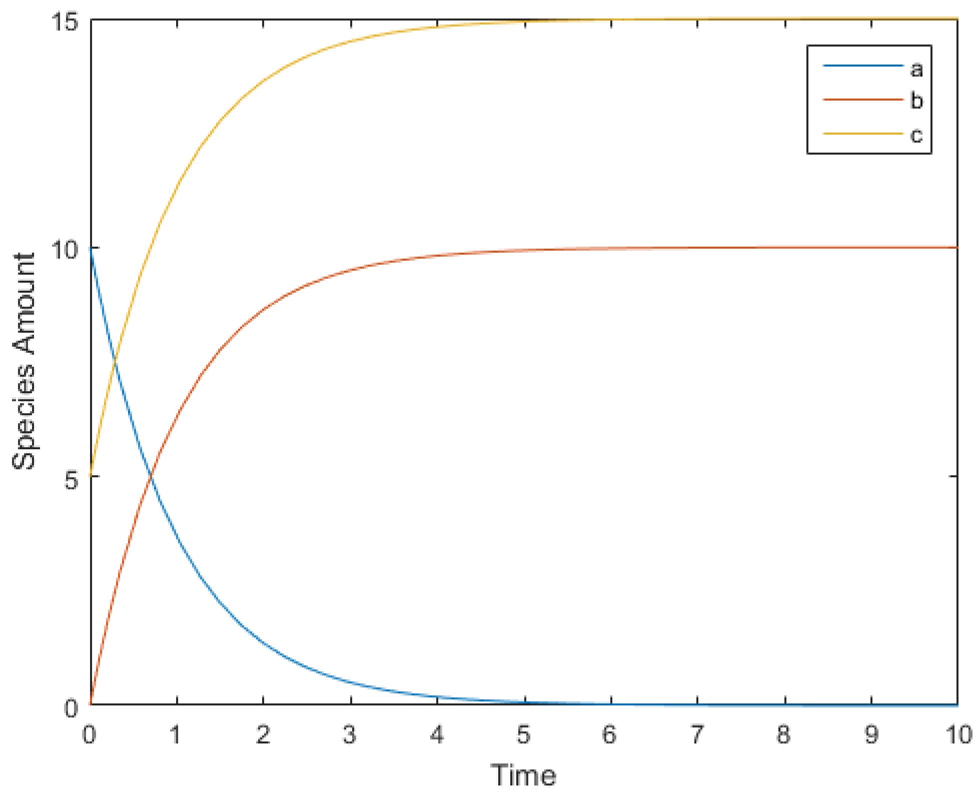
$\mathrm{a} = \mathrm{a_o e^{-k_1 t}}$, $\mathrm{b} = \mathrm{a_o(1-e^{-k_1 t})}$.

Since the rate rule $dc/dt = k_2 * a$ is dependent on the reaction, $dc/dt = k_2(a_o e^{-k_1 t})$. The solution is:

$$c = c_o + k_2 a_o/k_1(1 - e^{-k_1 t})$$

Enter the following commands to set up a SimBiology model accordingly and simulate it.

```
m = sbiomodel('m');
c = addcompartment(m,'comp');
s1 = addspecies(m,'a','InitialAmount',10,'InitialAmountUnits','mole');
s2 = addspecies(m,'b','InitialAmount',0,'InitialAmountUnits','mole');
s3 = addspecies(m,'c','InitialAmount',5,'InitialAmountUnits','mole');
rxn = addreaction(m,'a -> b');
kl = addkineticlaw(rxn,'MassAction');
p1 = addparameter(kl,'k1','Value',1,'ValueUnits','1/second');
rule = addrule(m,'c = k2 * a','RuleType','rate');
kl.ParameterVariableNames = 'k1';
p2 = addparameter(m,'k2','Value',1,'ValueUnits','1/second');
[t,sd,species] = sbiosimulate(m);
plot(t,sd);
legend(species);
xlabel('Time');
ylabel('Species Amount');
```



15
10
5
0
0
1
2
3
4
5
6
7
8
9
10
Time
Species Amount
a
b
c

Models Used in Examples

Minimal Cascade Model for a Mitotic Oscillator

Albert Goldbeter modified a model with enzyme cascades [Goldbeter and Koshland 1981] to fit cell cycle data from studies with embryonic cells [Goldbeter 1991]. He used this model to demonstrate thresholds with enzyme cascades and periodic behavior caused by negative feedback.

There are two SimBiology model variations using Goldbeter's model. The first model uses the differential rate equations directly from Goldbeter's paper. The second model is built with reactions using Henri-Michaelis-Menten kinetics.

In this section...
"Goldbeter Model" on page C-2
"SimBiology Model with Rate Rules" on page C-5
"SimBiology Model with Reactions" on page C-6
"References" on page C-16

Goldbeter Model

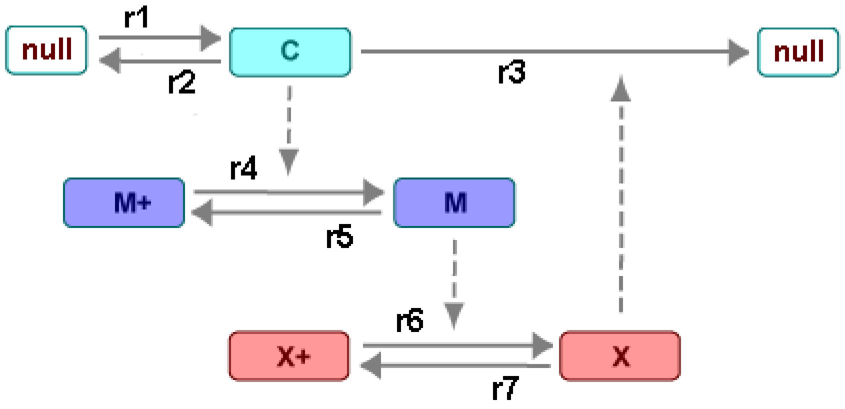
About the Goldbeter Model

Albert Goldbeter created a simple cell division model from studies with embryonic cells [Goldbeter 1991]. This model demonstrates thresholds with enzyme cascades and periodic behavior caused by negative feedback.

There are six species in Goldbeter's minimal mitotic oscillator model [Goldbeter 1991].

- C — Cyclin. The periodic behavior of cyclin activates and deactivates an enzyme cascade.
- M+, M — Inactive (phosphorylated) and active forms of cdc2 kinase. Kinases catalyze the addition of phosphate groups onto amino acid residues.
- X+, X — Inactive and active (phosphorylated) forms of a cyclin protease. Proteases degrade proteins by breaking peptide bonds.

The reactions are labeled `r1` to `r7` on the following diagram.



This model shows:

- How thresholds with cdc2 kinase activation (M+ -> M) and protease activation (X+ -> X) can occur as the result of covalent modification (for example, phosphorylation or dephosphorylation), but without the need for positive feedback.
- How periodic behavior with cdc2 kinase activation can occur with negative feedback and the time delay associated with activation/deactivation enzyme cascades.

Reaction Descriptions and Model Assumptions

The following list describes each of the reactions in Goldbeter's minimal mitotic oscillator with some of the simplifying assumptions. For a more detailed explanation of the model, see [Goldbeter 1991].

- Cyclin (C) is synthesized at a constant rate (r1) and degraded at a constant rate (r2).
- Cyclin (C) does not complex with cdc2 kinase (M).
- Cyclin (C) activates cdc2 kinase (M+ -> M) by increasing the velocity of the phosphatase that activates the kinase. Inactive cdc2 kinase (M+) is activated by removing inhibiting phosphate groups (r4).
- The amount of deactivating kinase (not modeled) for the cdc2 kinase (M) is constant. Active cdc2 kinase (M) is deactivated by adding inhibiting phosphate group (r5).
- The activation of cyclin protease (X+ -> X) by the active cdc2 kinase (M) is direct without other intervening cascades. Cyclin protease (X) is activated by adding phosphate groups (r6).

- The amount of deactivating phosphatase (not modeled) for the cyclin protease (X) is constant. Active cyclin protease (X) is deactivated by removing the activating phosphate groups (r7).
- The three species of interest are cyclin (C), active dephosphorylated cdc2 kinase (M), and active phosphorylated protease (X). The total amounts of (M + M+) and (X + X+) are constant.

Mathematical Model

Goldbeter's minimal mitotic oscillator model is defined with three differential rate equations and two algebraic equations that define changing parameters in the rate equations.

Differential Rate Equation 1, Cyclin (C)

The following differential rate equation is from [Goldbeter 1991] for cyclin (C).

$$\frac{dC}{dt} = v_i - v_d X \frac{C}{K_d + C} - k_d C$$

Differential Rate Equation 2, Kinase (M)

The following differential rate equation is for cdc2 kinase (M). Notice that (1 - M) is the amount of inactive (phosphorylated) cdc2 kinase (M+).

$$\frac{dM}{dt} = V_1 \frac{(1-M)}{K_1 + (1-M)} - V_2 \frac{M}{K_2 + M}$$

$$V_1 = \frac{VM_1[C]}{K_c + [C]}$$

Differential Rate Equation 3, Protease (X)

Differential rate equations for cyclin protease (X). Notice that (1 - X) is the amount of inactive (unphosphorylated) cyclin protease (X+).

$$\frac{dX}{dt} = V_3 \frac{(1-X)}{K_3 + (1-X)} - V_4 \frac{X}{K_4 + X}$$

$$V_3 = VM_3[M]$$

SimBiology Model with Rate Rules

SimBiology Model with Rules

In the literature, many biological models are defined using differential rate and algebraic equations. With SimBiology software, you can enter the equations directly as SBML rules. The example in this section uses Goldbeter's mitotic oscillator to illustrate this point.

Writing differential rate equations in an unambiguous format that a software program can understand is a fairly simple process.

- Use an asterisk to indicate multiplication. For example, `k[a]` is written `k*a`.
- Remove square brackets that indicate concentration from around species. The units associated with the species will indicate concentration (`moles/liter`) or amount (`moles`, `molecules`).

  SimBiology software uses square brackets around species and parameter name to allow names that are not valid MATLAB variable names. For example, you could have a species named `glucose-6-phosphate dehydrogenase` but you need to add brackets around the name in reaction rate and rule equations.
- Use parentheses to clarify the order of evaluation for mathematical operations. For example, do not write a Henri-Michaelis-Menten rate as `Vm*C/Kd + C`, because `Vm*C` is divided by `Kd` before adding `C`, and then `C` is added to the result.

The following equation is the rate rule for “Differential Rate Equation 1, Cyclin (C)” on page C-4:

```
dC/dt = vi - (vd*X*C)/(Kd + C) - kd*C
```

The following equations are the rate and `repeatedAssignment` rules for “Differential Rate Equation 2, Kinase (M)” on page C-4:

```
dM/dt = (V1*Mplus)/(K1 + Mplus) - (V2*M)/(K2 + M)
V1 = (VM1*C)/(Kc + C)
Mplus = Mt - M
```

The following equations are the rate and `repeatedAssignment` rules for “Differential Rate Equation 3, Protease (X)” on page C-4:

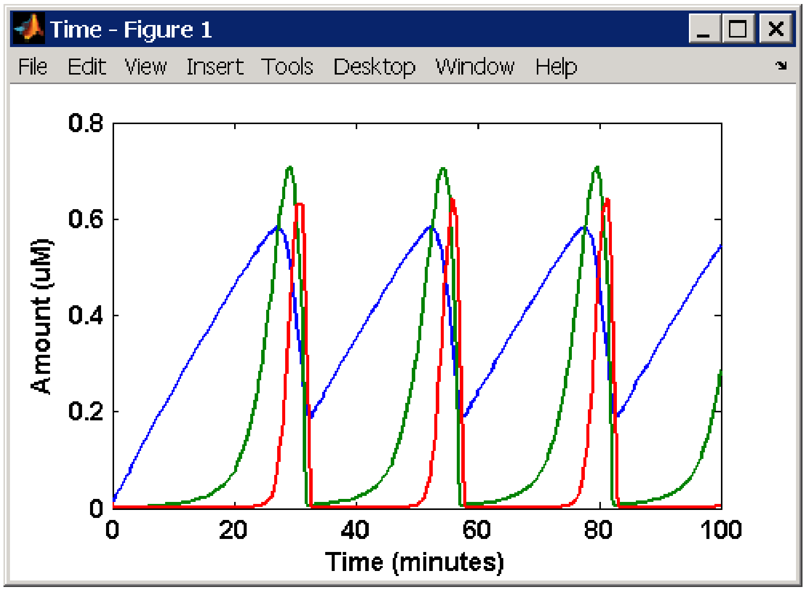
```
dX/dt = (V3*Xplus)/(K3 + Xplus) - (V4*X)/(K4 + X)
V3 = VM3*M
Xplus = Xt - X
```

Rules

The active (M) and inactive (`Mplus`) forms of the kinase are assumed to be part of a conserved cycle with the total concentration (Mt) remaining constant during the simulation. You need only one differential rate equation with a mass balance equation to define the amounts of both species. Similarly, the active (X) and inactive (`Xplus`) forms of the protease are part of a second conserved cycle.

SimBiology Simulation with Rules

This is a simulation of Goldbeter's minimal mitotic oscillator using differential rate and algebraic equations. Simulate with the `sundials` solver and plot species `C`, `M`, and `X`. For a description of the model, see “SimBiology Model with Rules” on page C-5.



SimBiology Model with Reactions

- “Converting Differential Rate Equations to Reactions” on page C-7
- “Calculating Initial Values for Reactions” on page C-9

- "SimBiology Simulation with Reactions" on page C-15

Converting Differential Rate Equations to Reactions

In the literature, many models are defined with differential rate equations. With SimBiology software, creating the differential equations from reactions is unnecessary; you can enter the reactions and let the software calculate the equations.

Some models are defined with differential rate equations, and you might need the reactions to be compatible with your model. Two rules you can use to convert differential rate equations to reactions are:

- **For a positive term** — The species described by the equation is placed on the right as a product, and the species in the term are placed on the left as reactants.
- **For a negative term** — The species described by the equation is placed on the left as a product, and the species in the term are also placed on the left as reactants.

  You need to determine the products using additional information, for example, a reaction diagram, a description of the model, or an understanding of a reaction. If a reaction is catalyzed by a kinase, then you can conclude that the product has one or more additional phosphate groups.

A simple first-order reaction has differential rate equation `dR/dt = +kr[P] - kf[R]`. The negative term implies that the reaction is `R -> ?` with an unknown product. The positive term identifies the product and completes the reaction, `R <-> P`.

Reactions R1 to R3 from Equation E1

The differential rate equation 1 is repeated here for comparison with the reactions. See "Differential Rate Equation 1, Cyclin (C)" on page C-4.

$$\frac{dC}{dt} = v_i - v_d X \frac{C}{K_d + C} - k_d C$$

The reaction and reaction rate equations from the differential rate equation E1 are given below:

```
r1      reaction: null -> C
   reaction rate: vi

r2      reaction: C -> null
   reaction rate: kd*C
```

```
r3      reaction: C -> null
   reaction rate: (vd*X*C)/(Kd + C)
```

Reactions R4 and R5 from Equation E2

The differential rate equation 2 and algebraic equation 2 are repeated here for comparison with the reactions. See “Differential Rate Equation 2, Kinase (M)” on page C-4.

$$\frac{dM}{dt} = V_1 \frac{(1-M)}{K_1 + (1-M)} - V_2 \frac{M}{K_2 + M}$$

$$V_1 = \frac{VM_1[C]}{K_c + [C]}$$

The reaction and reaction rate equations from the differential rate equation E2 are given below:

```
r4              reaction: Mplus -> M
           reaction rate: V1*Mplus/(K1 + Mplus)
 repeatedAssignment rule: V1 = VM1*C/(Kc + C)

r5      reaction: M -> Mplus
   reaction rate: V2*M/(K2 + M)
```

Reactions R6 and R7 from Equation E3

The differential rate equation for equation 3 and algebraic equation 3 is repeated here for comparison with the reactions.

$$\frac{dX}{dt} = V_3 \frac{(1-X)}{K_3 + (1-X)} - V_4 \frac{X}{K_4 + X}$$

```
V3 = VM3*[M]
```

The reaction and reaction rate equations from the differential rate equation E3 are given below:

```
r6               reaction: Xplus -> X
            reaction rate: V3*Xplus]/(K3 + Xplus)
  repeatedAssignment rule: V3 = VM3*M

r7      reaction: X -> Xplus
   reaction rate: V4*X/(K4 + X)
```

Calculating Initial Values for Reactions

After you converted the differential rate equations to the reactions and reaction rate equations, you can start to fill in initial values for the species (reactants and products) and parameters.

The initial values for parameters and amounts for species are listed with four different units in the same dimension:

- A — Original units in the Goldbeter 1991 paper.
- B — Units of concentration with time converted to second. When converting a to b, use `1 minute = 60 second` for parameters.

$$\frac{\text{X uM}}{\text{minute}} \times \frac{\text{1e-6 mole/liter}}{\text{1 uM}} \times \frac{\text{1 minute}}{\text{60 second}} = \frac{\text{Y mole}}{\text{liter*second}}$$

- C — Units of amount as moles. When converting concentration to moles, use a cell volume of `1e-12` liter and assume that volume does not change.

$$\frac{\text{Y mole}}{\text{liter*second}} \times \frac{\text{1e-12 liter}}{} = \frac{\text{Z mole}}{\text{second}}$$

- D — Units of amount as molecules. When converting amount as moles to molecules, use `6.022e23 molecules = 1 mole`.

$$\frac{\text{Z mole}}{\text{second}} \times \frac{\text{6.022e23 molecule}}{\text{1 mole}} = \frac{\text{N molecules}}{\text{second}}$$

With dimensional analysis on and unit conversion off, select all of the units for one letter. For example, select all of the As. If dimensional analysis and unit conversion are on, you can mix and match letters and get the same answer.

Reaction 1 Cyclin Synthesis

R1		Value	Units
reaction	null -> C	----	----
reaction rate	vi	----	A. uM/minute
		----	B. mole/(liter*second)
		----	C. mole/second

R1		Value	Units
		----	D. molecule/second
parameters	vi	0.025	A. uM/minute
		4.167e-10	B. mole/(liter*second)
		4.167e-22	C. mole/second
		205	D. molecule/second
species	C	0.01	A. uM
		1e-8	B. mole/liter
		1.0e-20	C. mole
		6.022e+3	D. molecule

Reaction 2 Cyclin Undifferentiated Degradation

R2		Value	Units
reaction	`C -> null`	----	----
reaction rate	`kd*C`	----	A. uM/minute
		----	B. mole/(liter*second)
		----	C. mole/second
		----	D. molecule/second
parameters	`kd`	0.010	A. 1/minute
		1.6667e-4	B, C, D. 1/second
species	`C`	0.01	A. uM
		1e-8	B. mole/liter
		1.0e-20	C. mole
		6.022e+3	D. molecule

Reaction 3 Cyclin Protease Degradation

R3		Value	Units
reaction	`C -> null`	----	----
reaction rate	`(vd*X*C)/(Kd + C)`	----	A. uM/minute
		----	B. mole/(liter*second)

R3		Value	Units
		----	C. mole/second
		----	D. molecule/second
parameter	vd	0.25	A. 1/minute
		0.0042	B, C, D. 1/second
parameter	Kd	0.02	A. uM
		2.0e-8	B. mole/liter
		2.0e-020	C. mole
		12044	D. molecule
species	C (substrate)	0.01	A. uM
		1e-8	B. mole/liter
		1.0e-20	C. mole
		6.022e+3	D. molecule
species	X (enzyme)	0.01	A. uM
		1e-8	B. mole/liter
		1.0e-20	C. mole
		6.022e+3	D. molecule

Reaction 4 Cdc2 Kinase Activation

R4		Value	Units
reaction	`Mplus -> M`	----	----
reaction rate	`(V1*Mplus)/(K1 + Mplus)`	----	A. uM/minute
		----	B. mole/(liter*second)
		----	C. mole/second
		----	D. molecule/second
`repeatedAssignm` rule	`V1 = (VM1*C)/(Kc + C)`	----	
parameter	V1 (variable by rule)	0.00	A. uM/minute
			B. mole/(liter*second)

R4		Value	Units
			C. mole/second
			D. molecule/second
parameter	VM1	3.0	A. uM/minute
		5.0e-8	B. mole/(liter*second)
		5.0000e-020	C. mole/second
		30110	D. molecule/second
parameter	Kc	0.5	A. uM
		5.0000e-7	B. mole/liter
		5.0e-19	C. mole
		3.011e+5	D. molecule
parameter	K1	0.005	A. uM
		5e-9	B. mole/liter
		5e-21	C. mole
		3.011e+3	D. molecule
species	Mplus (inactive substrate)	0.99	A. uM
		9.9e-7	B. mole/liter
		9.9e-19	C. mole
		5.962e+5	D. molecule
species	M (active product)	0.01	A. uM
		1e-8	B. mole/liter
		1.0e-20	C. mole
		6.022e+3	D. molecule
species	C	0.01	A. uM
		1e-8	B. mole/liter
		1.0e-20	C. mole
		6.022e+3	D. molecule

Reaction 5 Cdc2 Kinase Deactivation

R5		Value	Units
reaction	`M -> M_plus`	----	----
reaction rate	`(V2*M)/(K2 + M)`	----	A. uM/minute
		----	B. (mole/liter-second)
		----	C. mole/second
		----	D. molecule/second
parameter	`V2`	1.5	A. uM/minute
		2.5000e-008	B. mole/liter-second
		2.5000e-020	C. mole/second
		15055	D. molecule/second
parameter	`K2`	0.005	A. uM
		5.0000e-009	B. mole/liter
		5.0000e-021	C. mole
		3011	D. molecule
		1.0e-20	C. mole
species	`Mplus` (inactive)	0.99	A. uM
		9.9e-7	B. mole/liter
		9.9e-19	C. mole
		5.962e+5	D. molecule
species	`M` (active)	0.01	A. uM
		1e-8	B. mole/liter
		1.0e-20	C. mole
		6.022e+3	D. molecule

Reaction 6 Protease Activation

R6		Value	Units
reaction	`Xplus -> X`	----	----
reaction rate	`(V3*Xplus)/(K3 + Xplus)`	----	A. uM/minute
		----	B. mole/(liter*second)

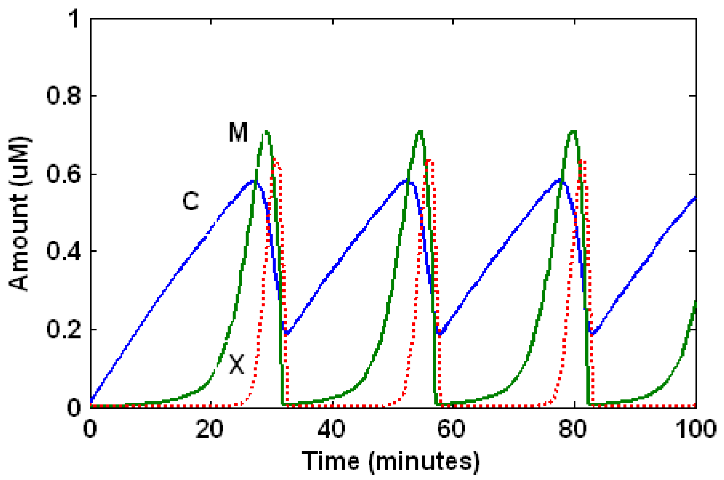
R6		Value	Units
		----	C. mole/second
		----	D. molecule/second
repeatedAssignment rule	V3 = VM3*M	----	
parameter	V3 (variable by rule)		A. uM/minute
			B. mole/liter-second
			C. mole/second
			D. molecule/second
parameter	VM3	1.0	A. 1/minute
		0.0167	B, C, D. 1/second
parameter	K3	0.005	A. uM
		5e-9	B. mole/liter
		5e-21	C. mole
		3.011e+3	D. molecule
species	Xplus (inactive substrate)	0.99	A. uM
		9.9e-7	B. mole/liter
		9.9e-19	C. mole
		5.962e+5	D. molecule
species	X (active product)	0.01	A. uM
		1e-8	B. mole/liter
		1.0e-20	C. mole
		6.022e+3	D. molecule
species	M (enzyme)	0.01	A. uM
		1e-8	B. mole/liter
		1.0e-20	C. mole
		6.022e+3	D. molecule

Reaction 7 Protease Deactivation

R7		Value	Units
reaction	`X -> X_plus`	----	----
reaction rate	`(V4*X)/(K4 + X)`	----	A. uM/minute
		----	B. mole/(liter*second)
		----	C. mole/second
		----	D. molecule/second
parameter	`V4`	0.5	A. uM/minute
		8.3333e-009	B. mole/(liter*second)
		8.3333e-021	C. mole/second
		5.0183e+003	D. molecule/second
parameter	`K4`	0.005	A. uM
		5e-9	B. mole/liter
		5e-21	C. mole
		3011	D. molecule
species	`Xplus` (inactive)	0.99	A. uM
		9.9e-7	B. mole/liter
		9.9e-19	C. mole
		5.962e+5	D. molecule
species	`X` (active)	0.01	A. uM
		1e-8	B. mole/liter
		1.0e-20	C. mole
		6.022e+3	D. molecule

SimBiology Simulation with Reactions

This is a simulation of Goldbeter's minimal mitotic oscillator with rate and algebraic equations. Simulate with the `sundials` solver and plot species `C`, `M`, and `X`. For a description of the model, see “SimBiology Model with Reactions” on page C-6.



References

[1] Goldbeter A. (1991), “A minimal cascade model for the mitotic oscillator involving cyclin and cdc2 kinase,” Proceedings of the National Academy of Sciences USA, 88:9107-9111.

[2] Goldbeter A., Koshland D. (1981), “An amplified sensitivity arising from covalent modification in biological systems,” Proceedings of the National Academy of Sciences USA, 78:6840-6844.

[3] Goldbeter A., Koshland D. (1984), “Ultrasensitivity in biochemical systems controlled by covalent modification,” The Journal of Biological Chemistry, 259:14441-14447.

[4] Goldbeter A., home page on the Web, http://www.ulb.ac.be/sciences/utc/GOLDBETER/agoldbet.html

[5] Murray A.W., Kirschner M.W. (1989), “Cyclin synthesis drives the early embryonic cell cycle,” Nature, 339:275-280.

Model of the Yeast Heterotrimeric G Protein Cycle

In this section...

Background on G Protein Cycles

G Proteins

Cells rely on signal transduction systems to communicate with each other and to regulate cellular processes. G proteins are GTP-binding proteins that are involved in the regulation of many cellular processes. There are two known classes of G proteins: the monomeric G proteins (one GTPase), and the heterotrimeric G proteins (three different monomers). The G proteins usually facilitate a step requiring energy. This energy is supplied by the hydrolysis of GTP by a GTPase activating protein (GAP). The exchange of GDP for GTP is catalyzed by a guanine nucleotide releasing protein (GNRP) [Alberts et al. 1994].

$$Gprotein + GTP \underset{GNRP}{\overset{GAP}{\rightleftarrows}} Gprotein + GDP$$

G protein-coupled receptors (GPCRs) are the targets of many pharmaceutical agents. Some estimates suggest that 40 to 50% of currently marketed drugs target GPCRs and that 40% of current drug discovery focus is on GPCR targets. Some examples include those for reducing stomach acid (ranitidine which targets histamine H2 receptor), migraine (sumatriptan, which targets a serotonin receptor subtype), schizophrenia (olanzapine, which targets serotonin and dopamine receptors), allergies (desloratadine, which targets histamine receptors). One approach in pharmaceutical research is to model signaling pathways to analyze and predict both downstream effects and effects in related pathways. This tutorial examines model building and analysis of the G protein cycle in the yeast pheromone response pathway using the SimBiology desktop.

G Proteins and Pheromone Response

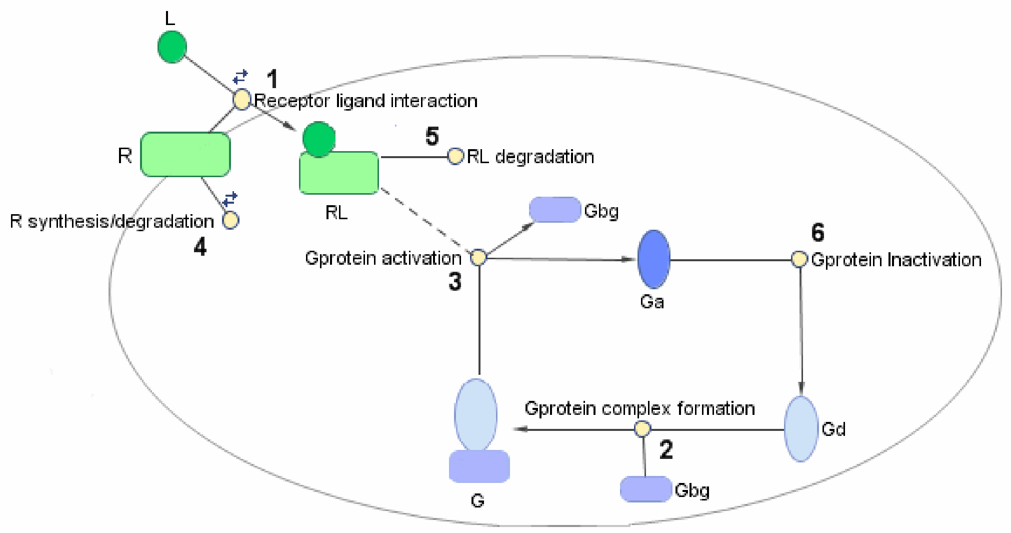
In the yeast *Saccharomyces cerevisiae*, G protein signaling in pheromone response is a well characterized signal transduction pathway. The pheromone secreted by *alpha* cells activates the G protein-coupled α-factor receptor (Ste2p) in *a* cells which results in a variety of cell responses including cell-cycle arrest and synthesis of new proteins. The authors of the study performed a quantitative analysis of this cycle, compared the regulation of G protein activation in wild-type yeast haploid *a* cells with cells containing mutations that confer supersensitivity to α-factor. They analyzed the data in the context of cell-cycle arrest and pheromone-induced transcriptional activation and developed a mathematical model of the G protein cycle that they used to estimate rates of activation and deactivation of active G protein in the cell.

Modeling a G Protein Cycle

Reactions Overview

Systems biologists represent biological pathways and processes as reactions with reaction rates, and treat the components of these pathways as individual species.

The G protein cycle in the yeast pheromone-response pathway can be condensed into a set of biochemical reactions. These reactions are complex formation, transformation, or disassociation reactions that Yi and colleagues [Yi et al. 2003] use to simplify and describe the system. In this example, α-factor, α-factor receptor, and the G protein subunits are all treated as species participating in reactions. The system can be graphically represented as follows.



Graphical Representation of the G protein cycle in yeast pheromone response. The numbers represent reaction numbers referenced in the text. L = Ligand (alpha factor), R = alpha-factor receptor, Gbg = free levels of G-beta:G-gamma complex, Ga = active G-alpha-GTP, Gd = inactive G-alpha-GDP, G = inactive Gbg:Gd complex.

The following table shows you the reactions used to model the G protein cycle and the corresponding rate constants (rate parameters) for each reaction. For reversible reactions, the forward rate parameter is listed first.

No.	Name	Reaction	Rate Parameters
1	Receptor-ligand interaction	`L + R <-> RL`	`kRL`, `kRLm`
2	Heterotrimeric G protein formation	`Gd + Gbg -> G`	`kG1`
3	G protein activation	`RL + G -> Ga + Gbg + RL`	`kGa`
4	Receptor synthesis and degradation	`R <-> null`	`kRdo`, `kRs`
5	Receptor-ligand degradation	`RL -> null`	`kRD1`
6	G protein inactivation	`Ga -> Gd`	`kGd`

Note that in reaction 3 (G protein activation), RL appears on both sides of the reaction. This is because RL is treated as a modifier or catalyst, and the model assumes that there is no synthesis or consumption of RL in this reaction.

The authors use a set of ordinary differential equations (ODEs) to describe the system. In the software, you can represent the biological pathway as a system of biochemical reactions and the software creates the ODEs for you. Alternatively, if you have a set of ODEs that describe your system you can enter these as rate rules. For an example of modeling using rate rules, see "SimBiology Model with Rate Rules" on page C-5.

Assumptions, Experimental Data, and Units in the G Protein Model

The authors have obtained experimental data either through their own measurements or through published literature. As with any other model, the G protein cycle model simplifies the biological process while also trying to reconcile the experimental data. Consider these points:

- Reaction 2 — Binding and formation of the heterotrimeric G protein complex is treated as a single-step reaction.
- Reaction 3 — Activation of G protein is modeled as a single-step. Guanine nucleotide exchange factors (GEFs) are not modeled.
- Reactions 3 and 6 — The parameters for the rate of G protein activation and deactivation (kGa and kGd) have been estimated based on the dose response curves in the reference paper. The SimBiology model being built in this tutorial directly uses those values.
- Reactions 4 and 5 — Receptor synthesis and degradation are handled purely as two simple reaction steps.
- Reaction 6 — Deactivation of G protein by the regulator of G protein signaling (RGS) protein Sst2p is modeled as a single step. Sst2p is not modeled.

  The reaction is modeled with an estimated reaction rate of 0.11 s^{-1}) in the Sst2p containing wild-type strain. The uncatalyzed reaction rate is estimated to be 0.004 s^{-1} in a strain with a deletion of SST2 (*sst2Δ*, mutant strain).
- Free GDP, GTP, and Pi are not included in the model.

This tutorial shows you how to plot the experimental data over the simulation plot of the active G protein fraction. You can estimate the values of the experimental data of interest for this example from the coordinates of the plots found in Figure 5 of the reference paper [Yi et al. 2003]. The following values were obtained by comparing the coordinates of the standards with those of the unknowns in the figure.

Time	Fraction of Active Ga (Experimental)
0	0.00
10	0.35
30	0.40
60	0.36
110	0.39
210	0.33
300	0.24
450	0.17
600	0.20

Note: The SimBiology **Dimensional Analysis** feature is not used in this tutorial. For this tutorial, the values of all species are converted to have the unit `molecule`, and all rate parameters are converted to have either the unit `1/second` or the units `1/(molecule*second)`, depending on whether the reaction is first or second order. You should leave the **InitialAmountUnits** box for species and the **ValueUnits** box for rate parameters empty for the models in this tutorial.

References

[1] Tau-Mu Yi, Hiroaki Kitano, and Melvin I. Simon. A quantitative characterization of the yeast heterotrimeric G protein cycle. PNAS (2003) vol. 100, 10764-10769.

[2] Alberts, B., Bray, D., Lewis, J., Raff, M., Roberts, K., and Watson, J.D. Molecular Biology of the Cell, 3rd edition, Garland Publishing, 1994.

Related Examples

- "Parameter Scanning, Parameter Estimation, and Sensitivity Analysis in the Yeast Heterotrimeric G Protein Cycle"

Model of M-Phase Control in *Xenopus* Oocyte Extracts

John Tyson's Computational Cell Biology Lab created a mathematical model for M-phase control in *Xenopus* oocyte (frog egg) extracts [Marlovits et al. 1998]. The M-phase control model shows principles by which you can apply phosphorylation and regulatory loops in your own models. Publications typically list systems of ordinary differential equations (ODEs) that represent a model system. This example shows you how to interpret these ODEs in the form of reaction pathways that are easier to represent and visualize in SimBiology software.

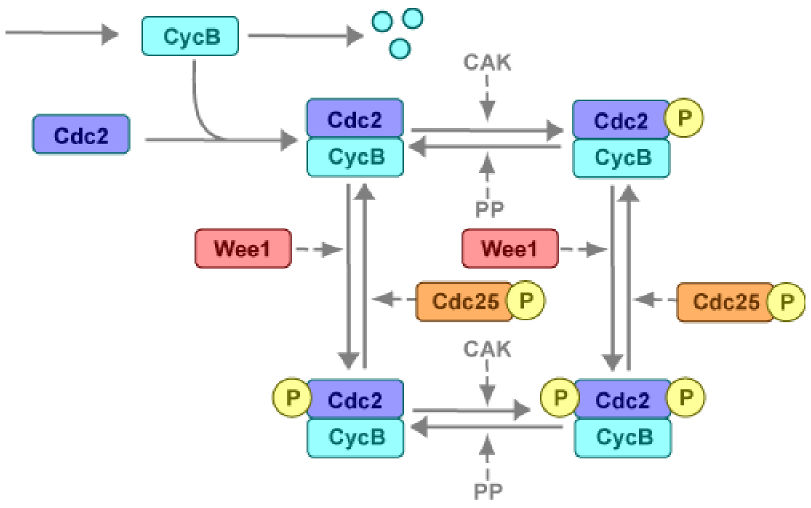
The model is centered around M-phase promoting factor (MPF). There are two positive feedback loops where MPF increases its synthesis and a negative feedback loop where MPF decreases its amount by increasing its degradation.

In this section...

M-Phase Control Model

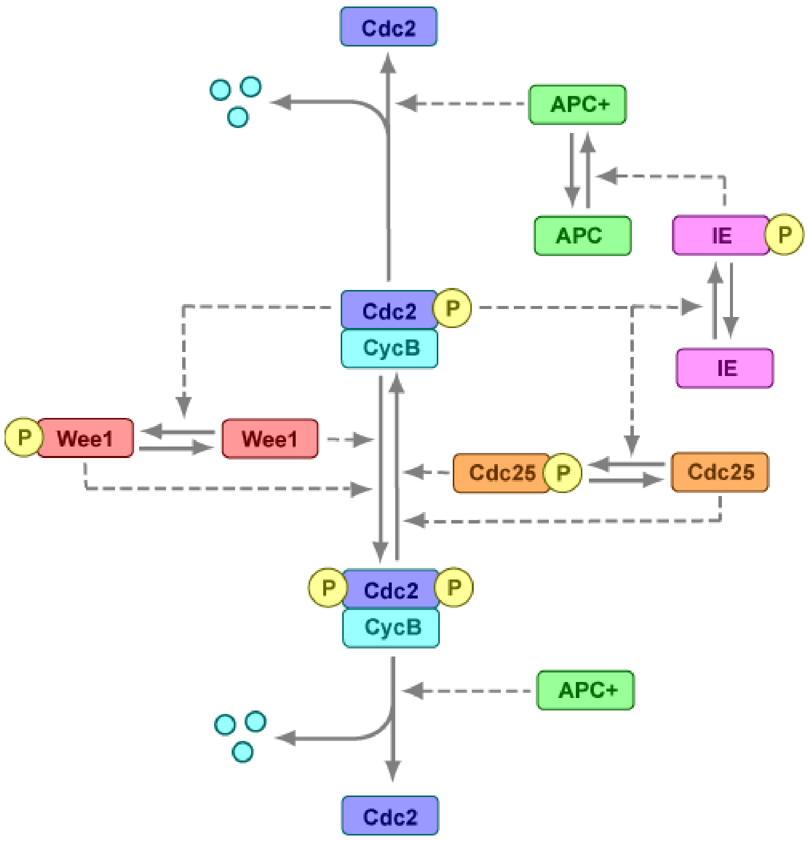
Synthesis Reactions

Cyclin B (CycB) dimerizes with Cdc2 kinase (Cdc2) to form M-phase promoting factor (MPF).



Regulation Reactions with Active MPF

Positive feedback loops with M-phase promoting factor (MPF) activate the Cdc25 phosphatase and deactivate the Wee1 kinase. A negative feedback loop with MPF activates anaphase-promoting complex (APC) that regulates the degradation of the Cyclin B subunit.



M-Phase Control Equations

- "Equation 12, Wee1 Activation/Deactivation" on page C-30
- "Equation 13, Intermediate Enzyme Activation/Deactivation" on page C-30
- "Equation 14, APC Activation/Deactivation" on page C-31
- "Equation 17, Rate Parameter K2" on page C-31
- "Equation 18, Rate Parameter Kcdc25" on page C-31
- "Equation 19, Rate Parameter Kwee1" on page C-32

About the Rate Equations in This Example

Models in systems biology are commonly described in the literature with differential rate equations. However, SimBiology software defines a model using reactions. This section shows you how to convert models published in the literature to a SimBiology format. The equation numbers match the published paper for this model [Marlovits et al. 1998]. Equations that are missing in the sequence involve the Cdk inhibitor (CKI) protein, which is not currently modeled in the SimBiology version.

Converting Differential Equations to Reactions

The rules for writing reaction and reaction rate equations from differential rate equations include not only the equations but also an understanding of the reactions. *`dx/dt`* refers to the species the differential rate equation is defining. *`kinetics`* refers to the species in the reaction rate.

- Positive terms: Rate species are placed on right side of the reactions; reaction rate equation species are placed on the left.

$$kinetics \rightarrow \frac{dx}{dt}$$

- Negative terms: Rate species are placed on the left side of the reaction because the species are being used up in some way; reaction rate equation species are also placed on left. You need to deduce the products from additional information about the model.

$$\text{kinetics or } (\frac{\text{dx}}{\text{dt}}) \rightarrow \text{products?}$$

The following table will help you deduce the products for a reaction. In this example, by convention, phosphate groups on the right side of a species name are activating while phosphate groups on left are inhibiting.

Enzyme	Description	Reaction
`wee1`	Kinase, add inhibiting phosphate group	MPF —> P-MPF
`cdc25`	Phosphatase, remove inhibiting phosphate group	P-MPF —> MPF + P
`kcak`	Kinase, add activating phosphate group	MPF —> MPFp
`kpp`	Phosphatase, remove activating phosphate group	MPF-P —> MPF + P
`MPF`	Kinase, add activating or inhibiting phosphate group	Wee1/Cdc25/IE —> X-P or P-X
`ki`	Add inhibiting Cki	Cki + MPF —> Cki:MPF
`kir`	Remove inhibiting Cki	Cki:MPF —> Cki + MPF

Equation 1, Cyclin B

Differential rate equation for cyclin B [Marlovits et al. 1998].

$$\frac{d[\mathrm{CycB}]}{dt} = +\mathrm{k1}\ -\mathrm{k2}[\mathrm{CycB}]\ -\mathrm{k3}[\mathrm{Cdc2}][\mathrm{CycB}]$$

Rate rule using SimBiology format for the differential rate equation 1. For a model using this rule, see "SimBiology Model with Rate and Algebraic Rules" on page C-32.

```
Rule 1  [CycB] = k1 - K2*[CycB] - k3*[Cdc2]*[CycB]
```

Reaction and reaction rate equations derived from the differential rate equation. For a model using these reactions, see "SimBiology Model with Reactions and Algebraic Rules" on page C-38.

```
Reaction 1   AA -> CycB           v = k1
Reaction 2   CycB -> AA           v = K2*[CycB]
Reaction 3   Cdc2 + CycB -> MPF   v = k3*[Cdc2]*[CycB]
```

Equation 2, M-Phase Promoting Factor

Differential rate equation for M-phase promoting factor (MPF) [Marlovits 1998]. Note that the parameter name `kcakr` [Marlovits et al. 1998] is changed to `kpp` [Borisuk 1998] in the following reaction equations. MPF is a heterodimer of cdc2 kinase and cyclin B.

$$\begin{aligned}\frac{d[\mathrm{MPF}]}{dt} = {} & +\mathrm{k3}[\mathrm{Cdc2}][\mathrm{CycB}]\ \text{-}\mathrm{K2}[\mathrm{MPF}] \\ & +\mathrm{kpp}[\mathrm{MPFp}]\ \text{-}\mathrm{kcak}[\mathrm{MPF}] \\ & +\mathrm{Kcdc25}[\mathrm{pMPF}]\ \text{-}\mathrm{Kwee1}[\mathrm{MPF}] \\ & +\mathrm{kir}[\mathrm{Cki{:}MPF}]\ \text{-}\mathrm{ki}[\mathrm{MPF}][\mathrm{Cki}]\end{aligned}$$

Rate rule using SimBiology format for the differential rate equation 1. For a model using this rule, see “SimBiology Model with Rate and Algebraic Rules” on page C-32.

```
Rule 2 MPF = kpp*MPFp - (Kwee1 + kcak + K2)*MPF + Kcdc25*pMPF + k3*Cdc2*CycB
```

Reaction and reaction rate equations derived from the differential rate equation. For a model using these reactions, see “SimBiology Model with Reactions and Algebraic Rules” on page C-38. A reaction name in parentheses denotes a reaction repeated in another differential rate equation.

```
(Reaction 3) Cdc2 + CycB -> MPF      v = k3*[Cdc2]*[CycB]
Reaction 4   MPF -> Cdc2 + AA        v = K2*[MPF]
Reaction 5   MPFp -> MPF             v = kpp*[MPFp]
Reaction 6   MPF -> MPFp             v = kcak*[MPF]
Reaction 7   pMPF -> MPF             v = Kcdc25*[pMPF]
Reaction 8   MPF -> pMPF             v = Kwee1*[MPF]
```

Equation 3, Inhibited M-Phase Promoting Factor

Differential rate equation for inhibited M-phase promoting factor (pMPF) [Marlovits 1998].

$$\begin{aligned}\frac{d[\mathrm{pMPF}]}{dt} = {} & -\mathrm{K2}[\mathrm{pMPF}] \\ & +\mathrm{kpp}[\mathrm{pMPFp}]\ \text{-}\mathrm{kcak}[\mathrm{pMPF}] \\ & +\mathrm{Kwee1}[\mathrm{MPF}]\ \text{-}\mathrm{Kcdc25}[\mathrm{pMPF}] \\ & +\mathrm{kd}[\mathrm{Cki{:}pMPF}]\end{aligned}$$

Rate rule using SimBiology format for the differential rate equation 3. For a model using this rule, see “SimBiology Model with Rate and Algebraic Rules” on page C-32.

```
Rule 3 pMPF = Kwee1*MPF - (Kcdc25 + kcak + K2)*pMPF + kpp*pMPFp
```

Reaction and reaction rate equations derived from the differential rate equation. For a model using these reactions, see “SimBiology Model with Reactions and Algebraic Rules” on page C-38.

```
Reaction 11  pMPF -> Cdc2 + AA      v = K2*[pMPF]
Reaction 12  pMPFp -> pMPF          v = kpp*[pMPFp]
Reaction 13  pMPF -> pMPFp          v = kcak*[pMPF]
(Reaction 8) MPF -> pMPF            v = Kwee1*[MPF]
(Reaction 7) pMPF -> MPF            v = Kcdc25*[pMPF]
```

Equation 4, Inhibited and Activated M-Phase Promoting Factor

Differential rate equation for inhibited and activated M-phase promoting factor (pMPFp) [Marlovits 1998].

$$\begin{aligned}\frac{d[\mathrm{pMPFp}]}{dt} = &-\mathrm{K2}[\mathrm{pMPFp}]\\ &+\mathrm{kcak}[\mathrm{pMPF}] -\mathrm{kpp}[\mathrm{pMPFp}]\\ &+\mathrm{Kwee1}[\mathrm{MPFp}] -\mathrm{Kcdc25}[\mathrm{pMPFp}]\\ &+\mathrm{kd}[\mathrm{Cki{:}pMPFp}]\end{aligned}$$

Rate rule using SimBiology format for the differential rate equation. For a model using this rule, see “SimBiology Model with Rate and Algebraic Rules” on page C-32.

```
Rule 4 pMPFp = Kwee1*MPFp - (kpp + Kcdc25 + K2)*pMPFp + kcak*pMPF
```

Reaction and reaction rate equations derived from the differential rate equation. For a model using these reactions, see “SimBiology Model with Reactions and Algebraic Rules” on page C-38.

```
Reaction 15   pMPFp -> Cdc2 + AA      v = K2*[pMPFp]
(Reaction 13) pMPF -> pMPFp           v = kcak*[pMPF]
(Reaction 12) pMPFp -> pMPF           v = kpp*[pMPFp]
Reaction 16   MPFp -> pMPFp           v = Kwee1*[MPFp]
Reaction 17   pMPFp -> MPFp           v = Kcdc25*[pMPFp]
```

Equation 5, Activated M-Phase Promoting Factor

Differential rate equation for activated M-phase promoting factor (MPFp) [Marlovits 1998].

$$\frac{d[\text{MPFp}]}{dt} = -\text{K2}[\text{MPFp}] \\ +\text{kcak}[\text{MPF}] - \text{kpp}[\text{MPFp}] \\ +\text{Kcdc25}[\text{pMPFp}] - \text{Kwee1}[\text{MPFp}] \\ +\text{kir}[\text{CKI:MPFp}] - \text{ki}[\text{CKI}][\text{MPFp}]$$

Rate rule using SimBiology format for the differential rate equation 1. For a model using this rule, see “SimBiology Model with Rate and Algebraic Rules” on page C-32.

```
Rule 5  MPFp = kcak*MPF - (kpp + Kwee1 + K2)*MPFp + Kcdc25*pMPFp
```

Reaction and reaction rate equations derived from the differential rate equation. For a model using these reactions, see “SimBiology Model with Reactions and Algebraic Rules” on page C-38.

```
Reaction 19    MPFp -> MPF + AA         v = K2*[MPFp]
(Reaction 6)  MPF -> MPFp              v = kcak*[MPF]
(Reaction 5)  MPFp -> MPF              v = kpp*[MPFp]
(Reaction 17) pMPFp -> MPFp            v = Kcdc25*[pMPFp]
(Reaction 16) MPFp -> pMPFp            v = Kwee1*[MPFp]
```

Equation 11, Cell Division Control 25

Differential rate equation for activating and deactivating Cdc25 [Marlovits 1998].

$$\frac{d[\text{Cdc25p}]}{dt} = +\frac{\text{k25}[\text{MPFp}][\text{Cdc25}]}{\text{Km25}+[\text{Cdc25}]} - \frac{\text{k25r}[\text{Cdc25p}]}{\text{Km25r}+[\text{Cdc25p}]}$$

Rate rule in SimBiology format for the differential rate equation 1. For a model using this rule, see “SimBiology Model with Rate and Algebraic Rules” on page C-32. Note that since there isn't a rate rule for `Cdc25`, its amount is written as `(TotalCdc25 - Cdc25p)`.

```
Rule 11 Cdc25p = (k25*MPFp*(TotalCdc25 - Cdc25p))/(Km25 + (TotalCdc25 - Cdc25p)) - (k25
```

Reaction and reaction rate equations derived from the differential rate equation. For a model using these reactions, see “SimBiology Model with Reactions and Algebraic Rules” on page C-38.

```
Reaction 36 Cdc25 -> Cdc25p,  v = k25*[MPFp]*[Cdc25]/(Km25 + [Cdc25])
Reaction 37 Cdc25p -> Cdc25,  v = k25r*[Cdc25p]/(Km25r + [Cdc25p])
```

Equation 12, Wee1 Activation/Deactivation

Differential rate equation for activating and deactivating Wee1 kinase [Marlovits 1998]. The kinase (MPFp) phosphorylates active Wee1 (Wee1) to its inactive form (Wee1p). The dephosphorylation of inactive Wee1 (Wee1p) is by an unknown phosphatase.

$$\frac{d[Wee1]}{dt} = -\frac{ku[MPFp][Wee1]}{Kmw + [Wee1]} + \frac{kwr[Wee1P]}{Kmwr + [Wee1P]}$$

Rate rule in SimBiology format for the differential rate equation 1. For a model using this rule, see "SimBiology Model with Rate and Algebraic Rules" on page C-32.

```
Rule 12  Wee1p = (kw*MPFp*(TotalWee1 - Wee1p))/(Kmw + (TotalWee1 - Wee1p))
                                   - (kwr*Wee1p)/(Kmwr + Wee1p)
```

Reaction and reaction rate equations derived from the differential rate equation. For a model using these reactions, see "SimBiology Model with Reactions and Algebraic Rules" on page C-38.

```
reaction 38 Wee1 -> Wee1p, v = (kw*[MPFp]*[Wee1])/(Kmw + [Wee1])
reaction 39 Wee1p -> Wee1, v = (kwr*[Wee1p])/(Kmwr + [Wee1p])
```

Equation 13, Intermediate Enzyme Activation/Deactivation

Differential rate equation for activating and deactivating the intermediate enzyme (IE) [Marlovits 1998]. The active kinase (MPFp) phosphorylates the inactive intermediate enzyme (IE) to its active form (IEp).

$$\frac{d[IEp]}{dt} = +\frac{kie[MPFp][IE]}{Kmie + [IE]} - \frac{kier[IEp]}{Kmier + [IEp]}$$

Rate rule in SimBiology format for the differential rate equation 1. For a model using this rule, see "SimBiology Model with Rate and Algebraic Rules" on page C-32.

```
Rule 13 IEp = (kie*MPFp*(TotalIE - IEp))/(Kmie + (TotalIE - IEp))
                - (kier*IEp)/(Kmier + IEp)
```

Reaction and reaction rate equations derived from the differential rate equation. For a model using these reactions, see "SimBiology Model with Reactions and Algebraic Rules" on page C-38.

```
reaction 40 IE -> IEp, v = (kie*[MPFp]*[IE])/(Kmie + [IE])
reaction 41 IEp -> IE, v = (kier*[IEp])/(Kmier + [IEp])
```

Equation 14, APC Activation/Deactivation

Differential rate equation for [Marlovits 1998].

$$\frac{d[APCa]}{dt} = +\frac{kap[IEP][APCi]}{Kmap + [APCi]} - \frac{kapr[APCa]}{Kmapr + [APCa]}$$

Rate rule in SimBiology format for the differential rate equation 1. For a model using this rule, see "SimBiology Model with Rate and Algebraic Rules" on page C-32.

```
Rule 14 APCa = (kap*IEp*(TotalAPC - APCa))/(Kmap + (TotalAPC - APCa))
                 - (kapr*APCa)/(Kmapr + APCa)
```

Reaction and reaction rate equations derived from the differential rate equation. For a model using these reactions, see "SimBiology Model with Reactions and Algebraic Rules" on page C-38.

```
Reaction 42 APCi -> APCa, v = (kap*[IEp]*[APCi])/(Kmap + [APCi])
Reaction 43 APCa -> APCi,  v = (kapr*[APCa])/(Kmapr + [APCa])
```

Equation 17, Rate Parameter K2

Algebraic equation to define the rate parameter K2 [Marlovits 1998]. Inactive APC (APCi) is catalyzed by IE (intermediate enzyme) to active APC (APCa).

$$k2 = V_2'[APC] + V_2''[APC']$$

Algebraic rule in SimBiology format for the algebraic equation 17. For a model using this rule, see "SimBiology Model with Rate and Algebraic Rules" on page C-32.

```
Algebraic Rule 17  V2i*(TotalAPC - APCa) + V2a*APCa - K2
```

Algebraic rule when simulating with reactions. For a model using this rule with reactions, see "SimBiology Model with Reactions and Algebraic Rules" on page C-38. `V2'` is renamed to `V2i` and `V2"`is renamed to `V2a`. APCi (APC) is the inactive form of the enzyme while APCa (APC') is the active form. K2 is the independent variable.

```
Algebraic Rule 1 (V2i*APCi) + (V2a*APCa) - K2
```

Equation 18, Rate Parameter Kcdc25

Algebraic equation to define the rate parameter `Kcdc25` [Marlovits 1998]. Inactive Cdc25 (`Cdc25`) is phosphorylated by MPF to active Cdc25 (Cdc25p).

$$kcdc25 = V_{25}'[Cdc25] + V_{25}''[Cdc25p]$$

Algebraic rule in SimBiology format for the algebraic equation 18. For a model using this rule, see "SimBiology Model with Rate and Algebraic Rules" on page C-32.

```
Algebraic Rule 18  V25i*(TotalCdc25 - Cdc25p) + V25a*Cdc25p - Kcdc25
```

Algebraic rule when simulating with reactions. `Kcdc25` is the independent variable. For a model using this rule with reactions, see "SimBiology Model with Reactions and Algebraic Rules" on page C-38.

```
Algebraic Rule 2 (V25i*Cdc25) + (V25a*Cdc25p) - Kcdc25
```

Equation 19, Rate Parameter Kwee1

Algebraic equation to define the rate parameter [Marlovits 1998]. Active Wee1 (`Wee1`) is phosphorylated by MPF to inactive Wee1 (`Wee1p`).

$$k_{wee1} = V_{wee1}'[Wee1p] + V_{wee1}''[Wee1]$$

Algebraic rule in SimBiology format for rate parameter equation 19. For a model using this rule, see "SimBiology Model with Rate and Algebraic Rules" on page C-32.

```
Algebraic Rule 19  Vwee1i*Wee1p + Vwee1a*(TotalWee1 - Wee1p) - Kwee1
```

Algebraic rule when simulating with reactions. `Kwee1` is the independent variable. For a model using this rule with reactions, see "SimBiology Model with Reactions and Algebraic Rules" on page C-38.

```
Algebraic Rule 3 (Vwee1i*Wee1p) + (Vwee1a*Wee1) - Kwee1
```

SimBiology Model with Rate and Algebraic Rules

- “Rate Rule 2, M-Phase Promoting Factor (MPF)” on page C-36
- “Rate Rule 3, Inhibited M-Phase Promoting Factor (pMPF)” on page C-36
- “Rate Rule 4, Activated but Inhibited M-Phase Promoting Factor (pMPFp)” on page C-36
- “Rate Rule 5, Activated M-Phase Promoting Factor (MPFp)” on page C-36
- “Rate Rule 11, Activated Cdc25 (Cdc25p)” on page C-37
- “Rate Rule 12, Inhibited Wee1 (Wee1p)” on page C-37
- “Rate Rule 13, Activated Intermediate Enzyme (IEp)” on page C-37
- “Rate Rule 14, Activated APC (APCa)” on page C-37
- “Algebraic Rule 17, Rate Parameter K2” on page C-37
- “Algebraic Rule 18, Rate Parameter Kcdc25” on page C-38
- “Algebraic Rule 19, Rate Parameter Kwee1” on page C-38

Overview

There is one rate rule for each equation defining a species and one algebraic rule for each variable parameter in the M-phase control model [Marlovits 1998]. For a list and description of the equations, see “M-Phase Control Equations” on page C-24.

A basic model includes rate rules 1 to 5 and 11 to 14 with algebraic rules 17, 18, and 19.

Writing Differential Rate Equations as Rate Rules

Writing differential rate equations in an unambiguous format that a software program can understand is a simple process when you follow the syntax rules for programming languages.

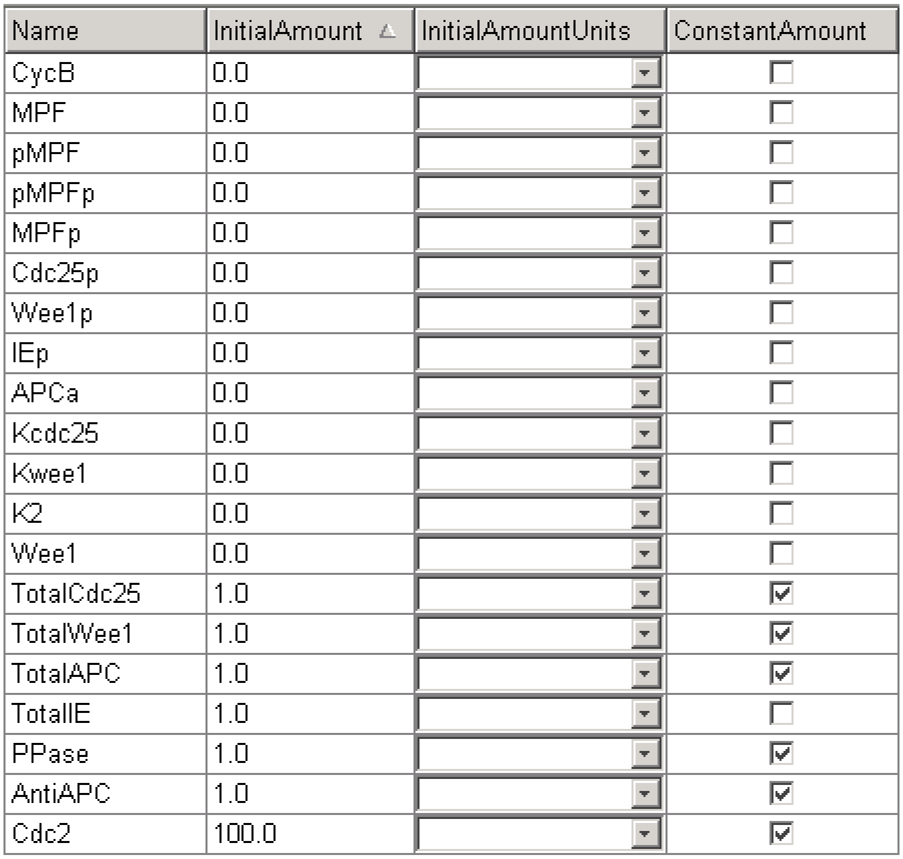
- Use an asterisk to indicate multiplication. For example, `k[A]` is written `k*A` or `k*[A]`. The brackets around the species `A` do not indicate concentration.
- SimBiology uses square brackets around species and parameter name to allow names that are not valid MATLAB variable names. For example, you could have a species named `glucose-6-phosphate dehydrogenase` but you need to add brackets around the name in reaction rate and rule equations.

  ```
  [glucose-6-phosphate dehydrogenase]
  ```
- Use parentheses to clarify the order of evaluation for mathematical operations. For example, do not write Henri-Michaelis-Menten reaction rates as `Vm*C/Kd +`

C, because Vm*C is divided by Kd before adding C to the result. Instead, write this reaction rate as (Vm*C)/(Kd + C).

Species

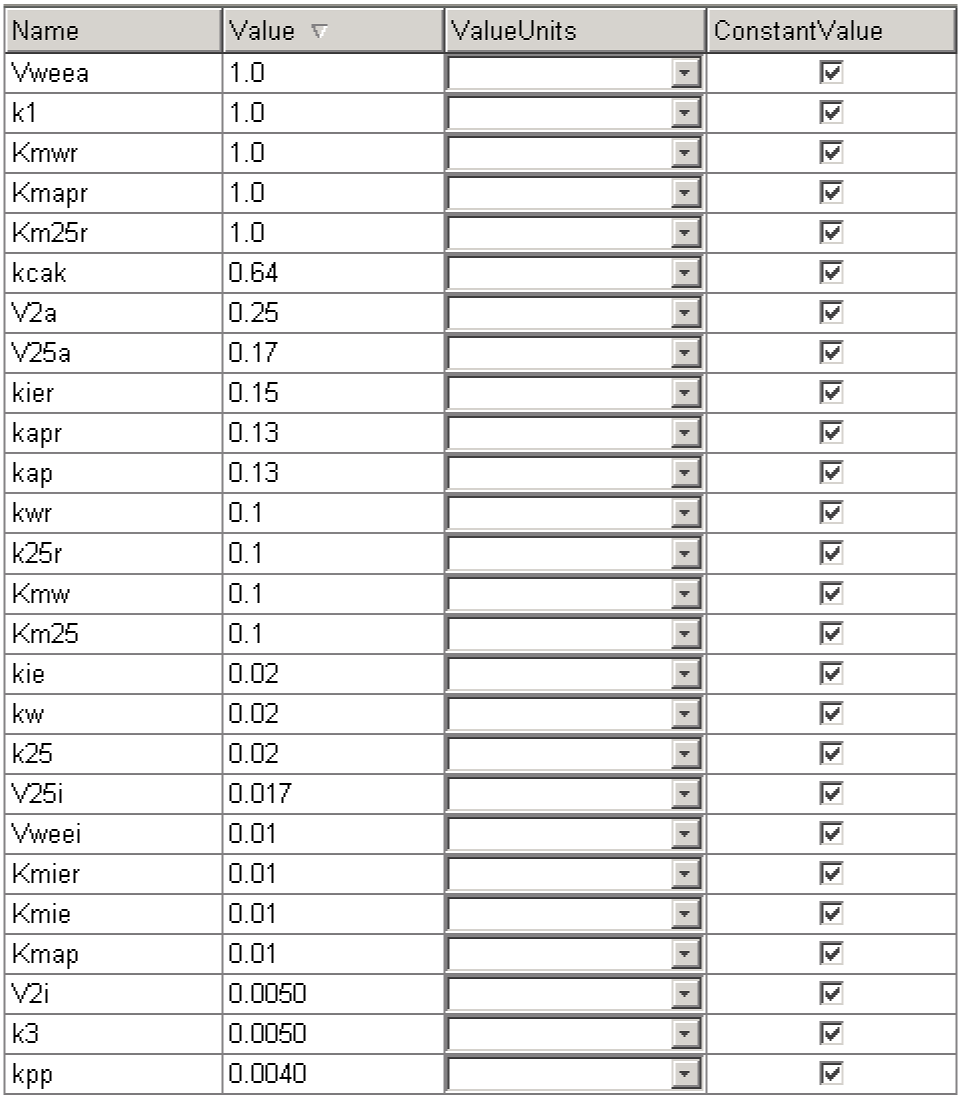
The following table lists species in the model with their initial amounts. There are three variable parameters modeled as species (K2, Kcdc25, and KWee1). You could also model the variable parameters as parameters with the property **ConstantAmount** cleared.



Name	InitialAmount △	InitialAmountUnits	ConstantAmount
CycB	0.0		☐
MPF	0.0		☐
pMPF	0.0		☐
pMPFp	0.0		☐
MPFp	0.0		☐
Cdc25p	0.0		☐
Wee1p	0.0		☐
IEp	0.0		☐
APCa	0.0		☐
Kcdc25	0.0		☐
Kwee1	0.0		☐
K2	0.0		☐
Wee1	0.0		☐
TotalCdc25	1.0		☑
TotalWee1	1.0		☑
TotalAPC	1.0		☑
TotalIE	1.0		☐
PPase	1.0		☑
AntiAPC	1.0		☑
Cdc2	100.0		☑

Parameters

The following table lists parameters in the model with their initial values. The property **ConstantValue** is selected for all of the parameters.



Name	Value ▽	ValueUnits	ConstantValue
Vweea	1.0		✓
k1	1.0		✓
Kmwr	1.0		✓
Kmapr	1.0		✓
Km25r	1.0		✓
kcak	0.64		✓
V2a	0.25		✓
V25a	0.17		✓
kier	0.15		✓
kapr	0.13		✓
kap	0.13		✓
kwr	0.1		✓
k25r	0.1		✓
Kmw	0.1		✓
Km25	0.1		✓
kie	0.02		✓
kw	0.02		✓
k25	0.02		✓
V25i	0.017		✓
Vweei	0.01		✓
Kmier	0.01		✓
Kmie	0.01		✓
Kmap	0.01		✓
V2i	0.0050		✓
k3	0.0050		✓
kpp	0.0040		✓

Rate Rule 1, Cyclin B (CycB)

The rate rule is from "Equation 1, Cyclin B" on page C-26.

```
rate rule: CycB = k1 - K2*CycB - k3*Cdc2*CycB
  species: CycB = 0 nM
```

```
            Cdc2 = 100 nM, [x]constant
parameters: k1 = 1 nM/minute
            K2 = 0 1/minute, []constant
            k3 = 0.005 1/(nM*minute)
```

K2 is a variable rate parameter whose value is defined by an algebraic rule. See "Algebraic Rule 17, Rate Parameter K2" on page C-37. Its value varies from 0.005 to 0.25 1/minute.

Rate Rule 2, M-Phase Promoting Factor (MPF)

The rate rule is from "Equation 2, M-Phase Promoting Factor" on page C-26.

```
 rate rule: MPF = kpp*MPFp - (Kwee1 + kcak + K2)*MPF + Kcdc25*pMPF
                  + k3*Cdc2*CycB
   species: MPF = 0 nM
            MPFp = 0 nM
            pMPF = 0 nM
parameters: kpp = 0.004 1/minute
            kcak = 0.64 1/minute
            k3 = 0.005 1/(nM*minute)
            K2 = 0 1/minute
            Kcdc25 = 0 1/minute
            Kwee1 = 0 1/minute
```

K2, Kcdc25, and Kwee1 are variable rate parameters whose values are defined by algebraic rules. See "Algebraic Rule 17, Rate Parameter K2" on page C-37, "Algebraic Rule 18, Rate Parameter Kcdc25" on page C-38, and "Algebraic Rule 19, Rate Parameter Kwee1" on page C-38.

Rate Rule 3, Inhibited M-Phase Promoting Factor (pMPF)

The rate rule is from "Equation 3, Inhibited M-Phase Promoting Factor" on page C-27.

```
rate rule: pMPF = Kwee1*MPF - (Kcdc25 + kcak + K2)*pMPF + kpp*pMPFp
```

Rate Rule 4, Activated but Inhibited M-Phase Promoting Factor (pMPFp)

The rate rule is from "Equation 4, Inhibited and Activated M-Phase Promoting Factor" on page C-28.

```
rate rule: pMPFp = Kwee1*MPFp - (kpp + Kcdc25 + K2)*pMPFp + kcak*pMPF
```

Rate Rule 5, Activated M-Phase Promoting Factor (MPFp)

The rate rule is from "Equation 5, Activated M-Phase Promoting Factor" on page C-28.

```
rate rule: MPFp = kcak*MPF - (kpp + Kwee1 + K2)*MPFp + Kcdc25*pMPFp
```

Rate Rule 11, Activated Cdc25 (Cdc25p)

The rate rule is from "Equation 11, Cell Division Control 25" on page C-29.

```
rate rule: Cdc25p = (k25*MPFp*(TotalCdc25 - Cdc25p))/(Km25 + (TotalCdc25 - Cdc25p))
                      - (k25r*PPase*Cdc25p)/(Km25r + Cdc25p)
```

Rate Rule 12, Inhibited Wee1 (Wee1p)

The rate rule is from "Equation 12, Wee1 Activation/Deactivation" on page C-30.

```
rate rule: Wee1p = (kw*MPFp*(TotalWee1 - Wee1p))/(Kmw + (TotalWee1 - Wee1p))
                     - (kwr*PPase*Wee1p)/(Kmwr + Wee1p)
```

Rate Rule 13, Activated Intermediate Enzyme (IEp)

The rate rule is from "Equation 13, Intermediate Enzyme Activation/Deactivation" on page C-30.

```
rate rule: IEp = (kie*MPFp*(TotalIE - IEp))/(Kmie + (TotalIE - IEp))
                        - (kier*PPase*IEp)/(Kmier + IEp)
```

Rate Rule 14, Activated APC (APCa)

The rate rule is from "Equation 14, APC Activation/Deactivation" on page C-31.

```
rate rule: APCa = (kap*IEp*(TotalAPC - APCa))/(Kmap + (TotalAPC - APCa))
                     - (kapr*AntiAPC*APCa)/(Kmapr + APCa)
```

Algebraic Rule 17, Rate Parameter K2

K2 is a variable rate parameter whose value is determined by the amount of active and inactive APC. The algebraic rule is from "Equation 17, Rate Parameter K2" on page C-31.

```
algebraic rule: V2i*(TotalAPC - APCa) + V2a*APCa - K2
       species: APCi = 1 nM
                APCa = 0 nM
                TotalAPC = 1 nM [x]constant
    parameters: K2  = 0 or 0.25 1/minute, []constant
                V2i = 0.005 1/(nM*minute)
                V2a = 0.25  1/(nM*minute)
```

Algebraic Rule 18, Rate Parameter Kcdc25

`Kcdc25` is a variable rate parameter whose value is determined by the amount of active and inactive `Cdc25`. The algebraic rule is from "Algebraic Rule 18, Rate Parameter Kcdc25" on page C-38.

```
algebraic rule: V25i*(TotalCdc25 - Cdc25p) + V25a*Cdc25p - Kcdc25
```

Algebraic Rule 19, Rate Parameter Kwee1

`Kwee1` is a variable rate parameter whose value is determined by the amount of active and inactive `Wee1`. The algebraic rule is from "Equation 19, Rate Parameter Kwee1" on page C-32.

```
algebraic rule: Vweei*Wee1p + Vweea*(TotalWee1 - Wee1p) - Kwee1
```

SimBiology Model with Reactions and Algebraic Rules

Overview

There can be one or more reactions for an equation defining a species and one algebraic rule for each variable parameter in the M-phase control model [Marlovits 1998]. For a list and description of the equations, see “M-Phase Control Equations” on page C-24.

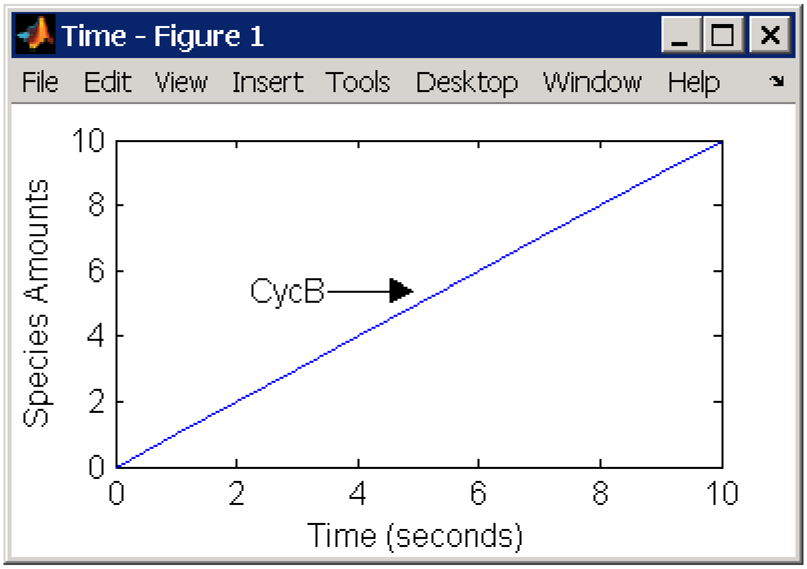
A basic model includes reactions 1 to 8, 11 to 13, 15 to 17, 19, and 36 to 43 with algebraic rules from equations 17, 18, and 19.

Reaction 1, Synthesis of Cyclin B

Cyclin B is synthesized at a constant rate.

```
     reaction: AA -> CycB
reaction rate: k1 nM/minute
    parameter: k1 = 1 nM/minute
      species: CycB = 0 nM
               AA = 100 nM [x]constant [x]boundary
```

Simulate reaction 1 with the `sundials` solver.



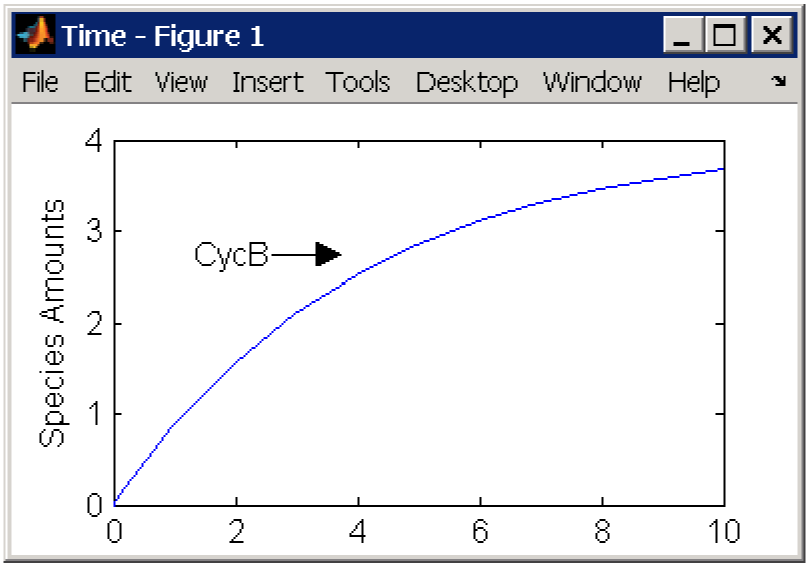
Reaction 2, Degradation of Cyclin B

Cyclin B is degraded at the end of the M-phase.

```
      reaction: CycB -> AA
 reaction rate: K2*CycB nM/minute
    parameters: K2  = 0 1/minute, []constant, variable by rule
                V2i = 0.005 1/nM*minute
                V2a = 0.25  1/nM*minute
       species: CycB = 0 nM
                APCi = 1 nM
                APCa = 0 nM
                AA = 100 nM [x]constant [x]boundary
algebraic rule: (V2i*APCi) + (V2a*APCa) - K2
```

Initially, Cyclin B degradation is low. This implies the amount of active APC (APCa) = 0 and inactive APC (APCi) = APCtotal = 1 nM.

Test the algebraic rule by simulating reactions 1 and 2 with `APCi = 0` and `APCa = 1`.

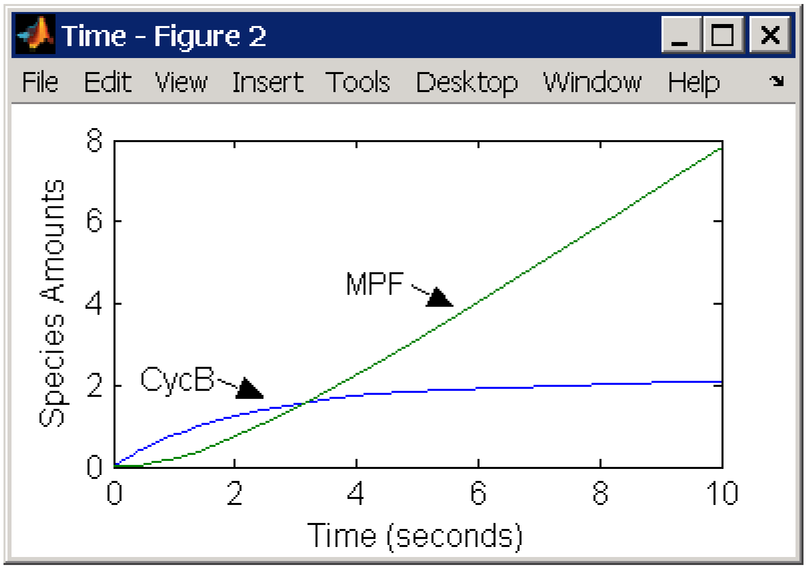


Reaction 3, Dimerization of Cyclin B with Cdc2 Kinase

Cyclin B dimerizes with Cdc2 kinase to form M-phase promoting factor (MPF).

```
     reaction: Cdc2 + CycB -> MPF
reaction rate: k3*Cdc2*CycB nM/minute
   parameters: k3 =   0.005 1/(nM*minute)
      species: Cdc2 = 100     nM
               CycB =   0     nM
               MPF  =   0     nM
```

Test the model by simulating with `K2 = 0.25`.

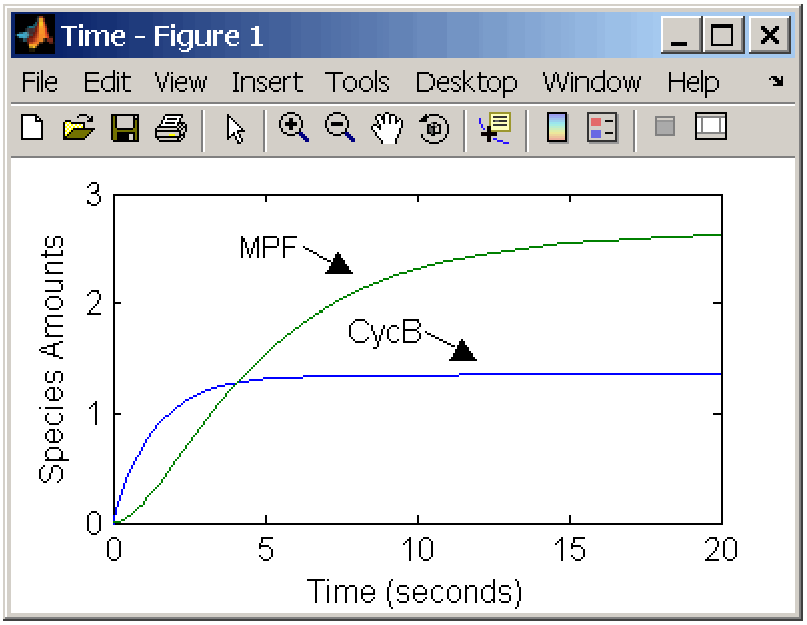


Reaction 4, Degradation of Cyclin B on MPF

Cyclin B is tagged with ubiquitin groups and degrades while bound to Cdc2.

```
      reaction: MPF -> Cdc2 + AA
 reaction rate: K2*[MPF]
    parameters: K2 = 0 or 0.25 1/minute, variable by rule
                v2i = 0.005 1/(nM*minute)
                v2a = 0.25 1/(nM*minute)
       species: MPF = 0 nM
                APCi = 1 nM
                APCa = 0 nM
                AA = 100 nM [x]constant [x]boundary
algebraic rule: (v2i*APCi) + (v2a*APCa) - K2
```

Test the simulation with `APCa = 1 and APCi = 0`. Because the amount of APCa (active) is high, K2 increases and the degradation starts to balance the synthesis of MPF.



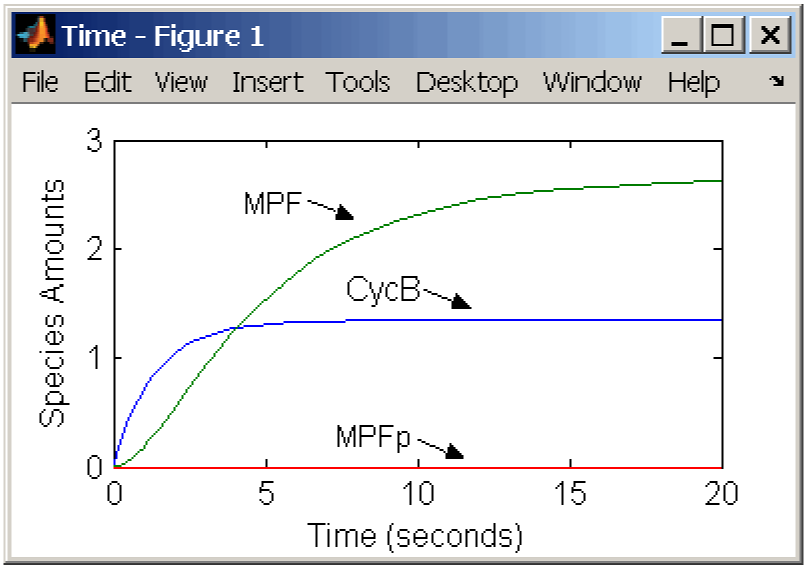
Reaction 5, Deactivation of Active MPF

Active MPF (MPFp) is dephosphorylated on Thr-161 by an unknown phosphatase (PP) to inactive MPF (MPF).

```
     reaction: MPFp -> MPF
reaction rate: kpp*[MPFp]
   parameters: kpp = 0.004 1/minute
      species: MPFp = 0 nM
               MPF = 0 nM
```

`kcakr = 0.004` 1/minute [Marlovits 1998, p. 175], but is renamed to `kpp` [Borisuk 1998].

Test simulation with APCa = 1 and APCi = 0. MPF increases without reaching steady state.



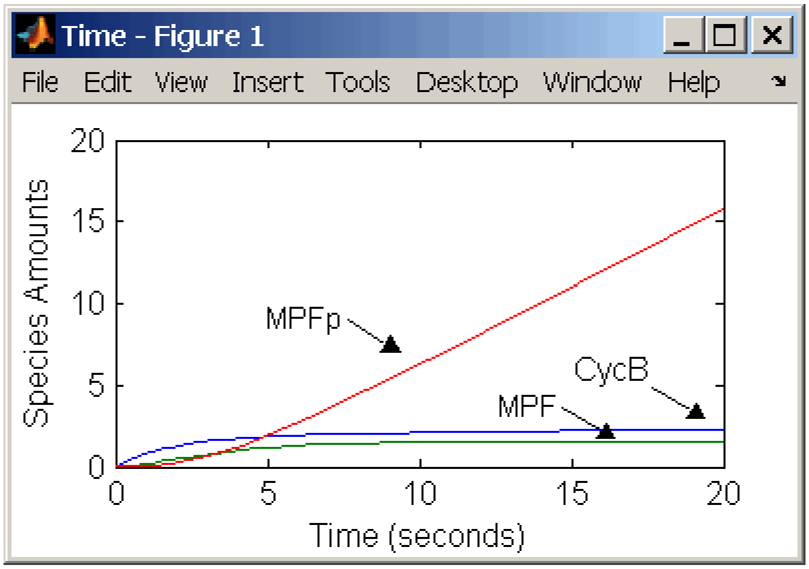
Reaction 6, Activation of MPF

Inactive MPF (MPF) is phosphorylated on Thr-161 by an unknown cyclin activating kinase (CAK).

```
     reaction: MPF -> MPFp
reaction rate: kcak*[MPF]
   parameters: kcak = 0.64 1/minute
      species: MPF = 0 nM
               MPFp = 0 nM
```

The kinase reaction that phosphorylates MPF to the active form is 160 times faster than the phosphatase reaction that dephosphorylates active MPF.

Simulate the model with reactions 1 to 6. Notice that after adding reaction 6, most of the product goes to active MPF (MPFp).



Reaction 7, Remove Inhibiting Phosphate from Inhibited MPF

Cdc25 phosphatase removes the inhibiting phosphate groups at the threonine 14 and tyrosine 15 residues on Cdc2 kinase.

```
     reaction: pMPF -> MPF
reaction rate: Kcdc25*[pMPF]
   parameters: Kcdc25 = 0.0 1/minute or 0.017 1/minute, variable by
                                                   algebraic rule
               V25i = 0.017 1/(mM*minute)
               V25a = 0.17 1/mM*minute
      species: pMPF = 0 nM
               MPF = 0 nM
               Cdc25 = 1 nM (inactive)
               Cdc25p = 0 nM (active)
algebraic rule: (V25i*Cdc25) + (V25a*Cdc25p) - Kcdc25
```

Initially, all of the Cdc25 phosphatase is in the inactive form (Cdc25).

Enter the initial value for Kcdc25 as 0.0 and let the first time step calculate the value from the rule, or enter an initial value using the rule.

Initially, set **ConstantAmount** for Cdc25 and Cdc25p to test reactions 1 through 7. Then after you can add the reactions to regulate the Cdc25 phosphatase by clearing the **ConstantAmount** property.

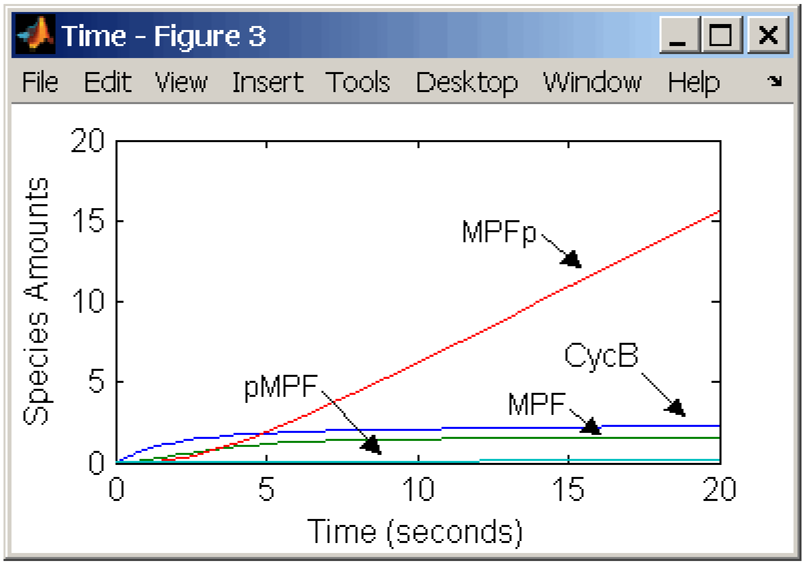
Reaction 8, Inhibition of MPF by Phosphorylation

Addition of inhibiting phosphate groups by Wee1 kinase to inhibit active M-phase promoting factor (MPF). Myt1 kinase is also involved with the phosphorylation, but its contribution is grouped with Wee1.

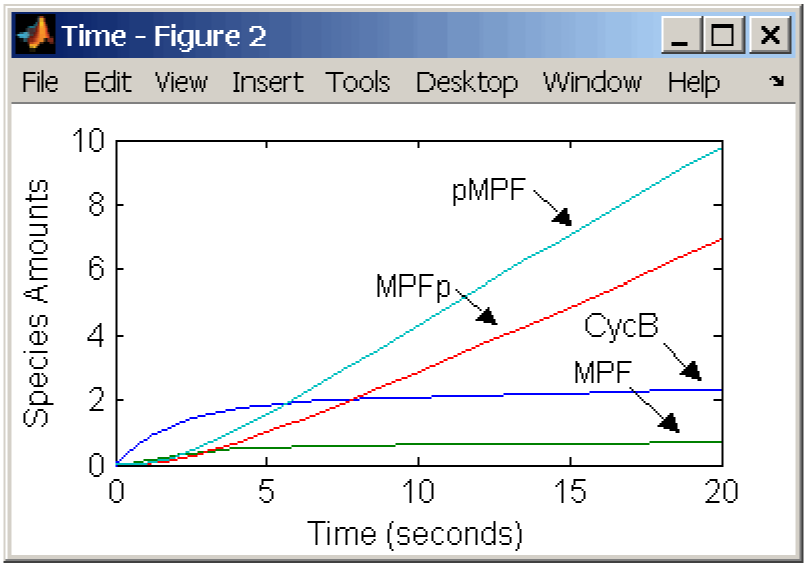
```
     reaction: MPF -> pMPF
reaction rate: Kwee1*[MPF]
   parameters: Kwee1 = 0.0 1/minute or 0.01 1/minute, variable by
                                                algebraic rule
               Vwee1i = 0.01 1/(nM*minute)
               Vwee1a = 1.0 1/(nM*minute)
      species: MPF = 0 nM
               pMPF = 0 nM
               Wee1p = 1 nM (inactive)
               Wee1 = 0 nM  (active)
algebraic rule: (Vwee1i*Wee1p) + (Vwee1a*Wee1) - Kwee1
```

The initial capitalization for the parameter Kwee1 is a convention to indicate that this value changes during the simulation.

Test the simulation for reactions 1 through 8 with `Wee1p` (inactive) `= 1` and `Wee1` (active) `= 0`.



Test the simulation with `Wee1p` (inactive) = `0` and `Wee1` (active) = `1`.



Reaction 11, Degradation of Cyclin B on Inhibited MPF

Degradation of cyclin B (`CycB`) on inhibited MPF (`pMPF`). Cyclin B is tagged with ubiquitin groups and degrades while bound to Cdc2.

```
      reaction: pMPF -> Cdc2 + AA
 reaction rate: K2*[pMPF] nM/minute
    parameters: K2 = 0 or 0.25 1/minute, variable by rule
                V2i = 0.005 1/nM*minute
                V2a = 0.25 1/nM*minute
       species: MPF = 0 nM
                APCi = 1 nM
                APCa = 0 nM
                AA = 100 nM [x]constant [x]boundary
                Cdc2 = 100 nm
algebraic rule: (V2i*APCi) + (V2a*APCa) - K2
```

Test the simulation with Wee1 active (`Wee1 = 1`) and APC active (`APCi = 1`).

Reaction 12, Deactivation of MPF to Inhibited MPF

Inhibited/active MPF (pMPFp) is dephosphorylated on Thr-161 by an unknown phosphatase (PP) to inhibited MPF (pMPF). Compare reaction 12 with reaction 5.

```
     reaction: pMPFp -> pMPF
reaction rate: kpp*[pMPFp]
   parameters: kpp = 0.004 1/minute
      species: pMPFp = 0 nM
               pMPF  = 0 nM
```

Reaction 13, Activation of Inhibited MPF

Inhibited MPF (pMPF) is phosphorylated on Thr-161 by an unknown cyclin-activating kinase (CAK). Compare reaction 13 with reaction 6.

```
     reaction: pMPF -> pMPFp
reaction rate: kcak*[pMPF] nM/minute
   parameters: kcak = 0.64 1/minute
      species: pMPF = 0 nM
               pMPFp = 0 nM
```

Test the simulation with Wee1p = 1 (inactive)/ Wee1 = 0 and then test with Wee1p = 0 (inactive)/ Wee1 = 1.

Reaction 15, Degradation of Cyclin B on Active but Inhibited MPF

Degradation of cyclin B (`CycB`) on inhibited MPF (`pMPF`). Cyclin B is tagged with ubiquitin groups and degrades while bound to cdc2 kinase.

```
      reaction: pMPFp -> Cdc2 + AA
 reaction rate: K2*[pMPFp] nM/minute
    parameters: K2 = 0 or 0.25 1/minute, variable by rule
                v2i = 0.005 1/nM*minute
                v2a = 0.25 1/nM*minute
       species: MPF = 0 nM
                APCi = 1 nM
                APCa = 0 nM
                AA = 100 nM [x]constant [x]boundary
                Cdc2 = 100 nm
algebraic rule: (V2i*APCi) + (V2a*APCa) - K2
```

Reaction 16, Inhibit MPF by Phosphorylation

Addition of inhibiting phosphate groups by Wee1 kinase to inhibit active M-phase promoting factor (MPF). Myt1 kinase is also involved with the phosphorylation, but its contribution is grouped with Wee1.

```
      reaction: MPFp -> pMPFp
 reaction rate: Kwee1*[MPFp] nM/minute
    parameters: Kwee1 = 1/minute []constant, variable by rule
                Vweei = 0.01 1/nM*minute
                Vweea = 1 1/nM*minute
       species: MPFp = 0 nM
                pMPFp = 0 nM
                Wee1p = 1 nM (inactive)
                Wee1 = 0 nM (active)
algebraic rule: (Vwee1i*Wee1p) + (Vwee1a*Wee1) - Kwee1
```

Reaction 17, Remove Inhibiting Phosphate from Activated MPF

Remove the inhibiting phosphate group from pMPFp with cdc25 phosphatase.

```
     reaction: pMPFp -> MPFp
reaction rate: Kcdc25*[pMPFp]
   parameters: Kcdc25 = 0 1/minue, []constant, variable by rule
               V25i = 0.017 1/nM*minute
               V25a = 0.17 1/nM*minute
      species: pMPFp = 0 nM
```

```
               MPFp = 0 nM
algebraic rule: (V25i*Cdc25) + (V25a*Cdc25p) - Kcdc25
```

Reaction 19, Degradation of Cyclin B on Activated MPF

Degradation of cyclin B (CycB) on inhibited MPF (pMPF). Cyclin B is tagged with ubiquitin groups and degrades while bound to cdc2 kinase.

```
      reaction: MPFp -> MPF + AA
 reaction rate: K2*[MPFp] nM/minute
    parameters: K2 = 0 or 0.25 1/minute, variable by rule
                V2i = 0.005 1/nM*minute
                V2a = 0.25 1/nM*minute
       species: MPF = 0 nM
                MPFp = 0 nM
                APCi = 1 nM
                APCa = 0 nM
                AA = 100 nM [x]constant [x]boundary
                Cdc2 = 100 nm
algebraic rule: (V2i*APCi) + (V2a*APCa) - K2
```

Reaction 36, Activation of Cdc25 by Activated MPF

Activation of cdc25 phosphatase by phosphorylation with active M-phase promoting factor (MPFp).

```
     reaction: Cdc25 + (MPFp) -> Cdc25p + (MPFp)
reaction rate: (k25*[MPFp]*[Cdc25])/(Km25 + [Cdc25])
   parameters: k25 = 0.02 1/minute
               Km25 = 0.1 nM
      species: Cdc25 = 1 nM (inactive)
               Cdc25p = 0 nM (active)
```

Initially MPF is inhibited (MPF* reacts to pMPF*).

Reaction 37, Deactivation of Cdc25

Deactivation of cdc25 phosphatase by dephosphorylation with an unknown phosphatase.

```
     reaction: Cdc25p -> Cdc25
reaction rate: (k25r*[Cdc25p])/(Km25r + [Cdc25p])
   parameters: k25r = 0.1 nM/minute
               Km25r = 1 nM
```

```
      species: Cdc25 = 1 nM (inactive)
               Cdc25p = 0 nM (active)
```

Reaction 38, Deactivation of Wee1 by Active MPF

Deactivation of Wee1 kinase by phosphorylation with active M-phase promoting factor (MPFp).

```
     reaction: Wee1 + (MPFp) -> Wee1p + (MPFp)
reaction rate: (kw*[MPFp]*[Wee1])/(Kmw + [Wee1]) nM/minute
   parameters: kw = 0.02 1/minute
               Kmw = 0.1 nM
      species: Wee1p = 1 nM (inactive)
               Wee1 = 0 nM (active)
```

Initially MPF is inhibited (MPF* reacts to pMPF*).

Reaction 39, Activation of Wee1

Activation of Wee1 kinase by dephosphorylation with an unknown kinase.

```
     reaction: Wee1p -> Wee1
reaction rate: (kwr*[Wee1p])/(Kmwr + [Wee1p]) nM/minute
   parameters: kwr = 0.1 nM/minute
               Kmwr = 1 nM
      species: Wee1p = 1 nM (inactive)
               Wee1 = 0 nM (active)
```

Reaction 40, Activation of Intermediate Enzyme by Active MPF

The inactive intermediate enzyme (IE) is activated by phosphorylation with active M-phase promoting factor (MPFp).

```
     reaction: IE + (MPFp) -> IEp + (MPFp)
reaction rate: (kie*[MPFp]*[IE])/(Kmie + [IE])
   parameters: kie = 0.02 1/minute
               Kmie = 0.01nM
      species: IE = 1 nM (inactive)
               IEp = 0 nM (active)
```

Reaction 41, Deactivation of IE

The active intermediate enzyme (IE) is deactivated by dephosphorylation.

```
     reaction: IEp -> IE
reaction rate: (kier*[IEp])/(Kmier + [IEp])
   parameters: kier = 0.15 nM/minute
               Kmier = 0.01 nM
      species: IE = 1 nM (inactive)
               IEp = 0 nM (active)
```

Reaction 42, APC Activation by IEp

Anaphase-promoting complex (APC) is activated by an active intermediate enzyme (`IEp`).

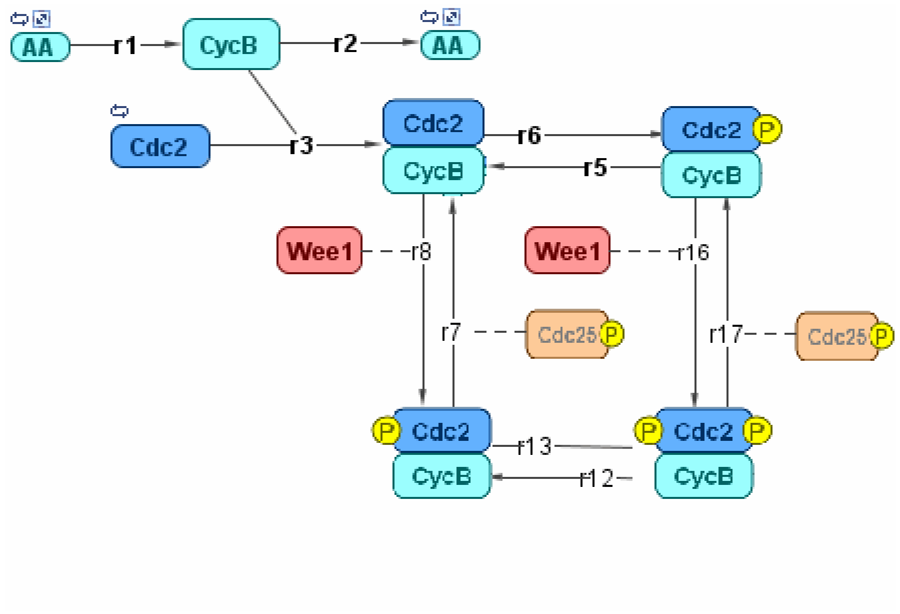
```
     reaction: APCi + IEp -> APCa + IEp
reaction rate: (kap*[IEp]*[APCi])/(Kmap + [APCi])
   parameters: kap = 0.13 1/minute
               Kmap = 0.01 nM
     species : APCi = 1 nM
               APCa = 0 nM
```

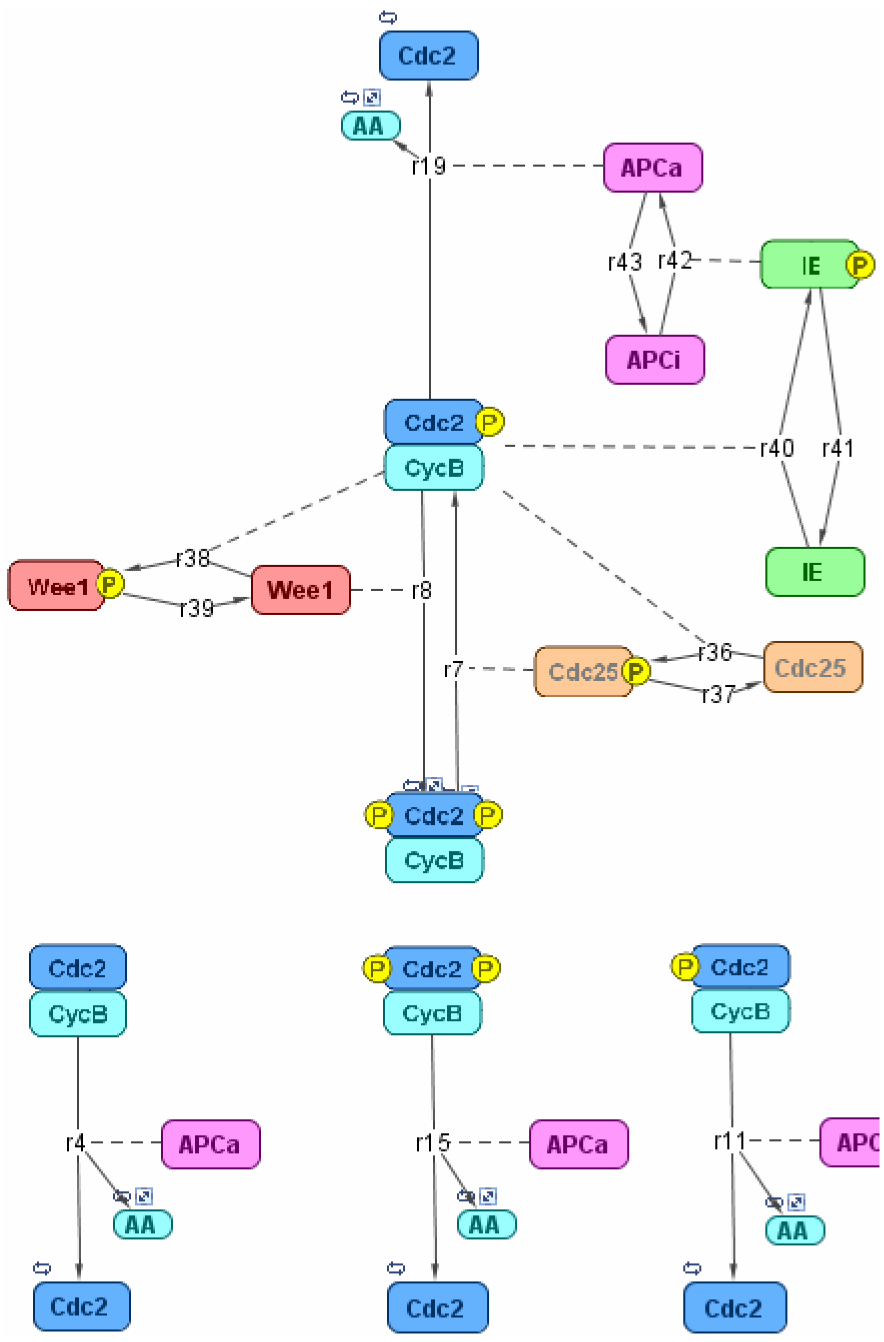
Reaction 43, APC Deactivation

Anaphase-promoting complex (APC) is deactivated.

```
     reaction: APCa -> APCi
reaction rate: (kapr*[APCa])/(Kmapr + [APCa])
   parameters: kapr = 0.13 nM/minute
               Kmapr = 1 nM
     species : APCi = 1 nM
               APCa = 0 nM
```

Block Diagram of the M-Phase Control Model with Reactions


AA
r1
CycB
r2
AA
Cdc2
r3
Cdc2
CycB
r6
r5
Cdc2 P
CycB
Wee1
r8
Wee1
r16
r7
Cdc25 P
r17
Cdc25 P
P Cdc2
CycB
r13
r12
P Cdc2 P
CycB


Cdc2
AA
r19
APCa
r43
r42
IE P
APCi
Cdc2 P
CycB
r40
r41
IE
Wee1 P
r38
r39
Wee1
r8
r36
Cdc25 P
r37
Cdc25
r7
P Cdc2 P
CycB
Cdc2
CycB
r4
APCa
AA
Cdc2
P Cdc2 P
CycB
r15
APCa
AA
Cdc2
P Cdc2
CycB
r11
APC
AA
Cdc2

References

[1] Borisuk M, Tyson J (1998), “Bifurcation analysis of a model of mitotic control in frog eggs,” Journal of Theoretical Biology, 195(1):69–85, PubMed 9802951.

[2] Marlovits G, Tyson C, Novak B, Tyson J (1998), “Modeling M-phase control in Xenopus oocyte extracts: the surveillance mechanism for unreplicated DNA,” Biophysical Chemistry, 72(1-2):169–184, PubMed 9652093.

[3] Novák B, Tyson J (1993), “Numerical analysis of a comprehensive model of M-phase control in Xenopus oocyte extracts and intact embryos,” Journal of Cell Science, 106(4):1153–1168, PubMed 8126097.