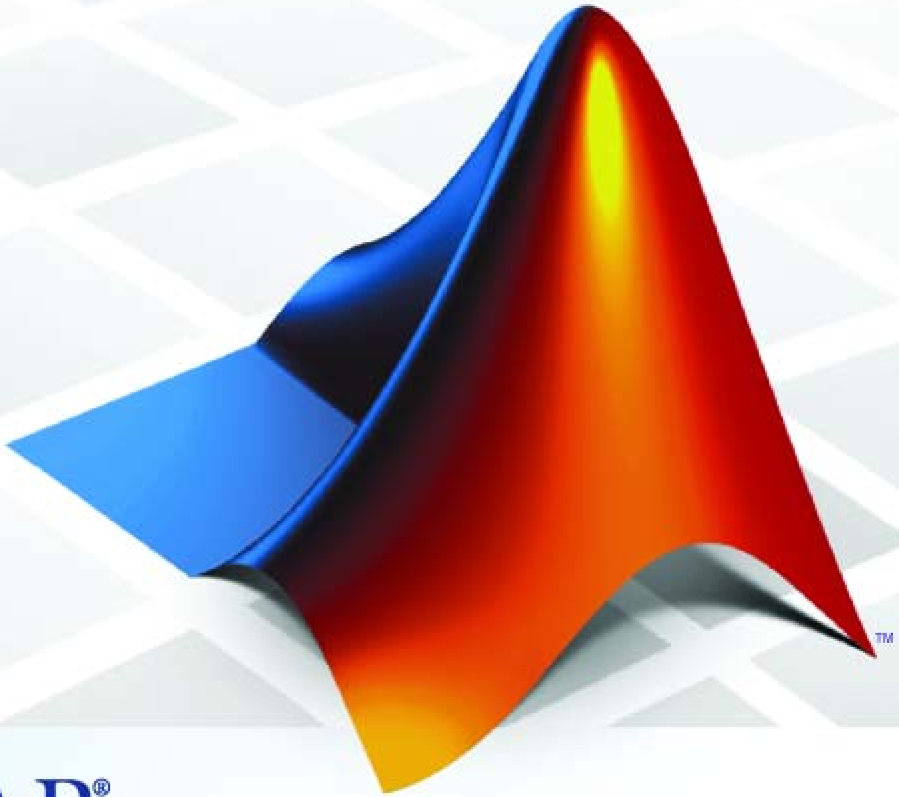
SimBiology® 2
User's Guide



MATLAB®

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SimBiology® User's Guide

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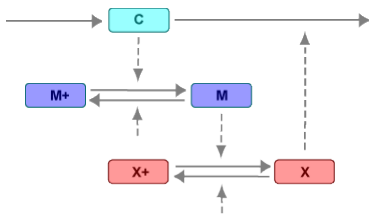
Modeling

This chapter is a collection of topics relevant to modeling in general, but is presented in the context of using SimBiology® software to model biological processes. It begins with the familiar concepts of mass action and enzyme kinetics.



Mass Action Kinetics

In this section...

Definition of Mass Action Kinetics

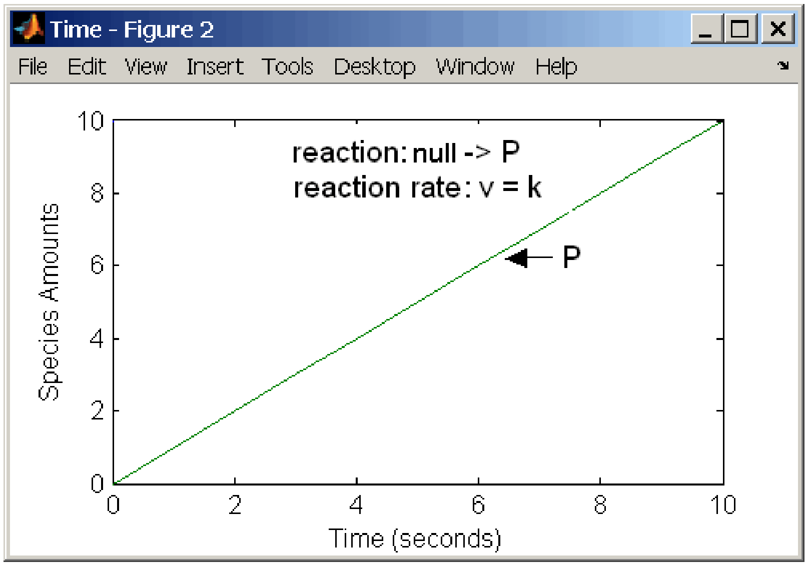
Mass action describes the behavior of reactants and products in an elementary chemical reaction. Mass action kinetics describes this behavior as an equation where the velocity or rate of a chemical reaction is directly proportional to the concentration of the reactants.

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/(liter*second)
       species: P =  0 mole
    parameters: k =  1 mole/(liter*second)
```

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



Zero-Order Mass Action Kinetics

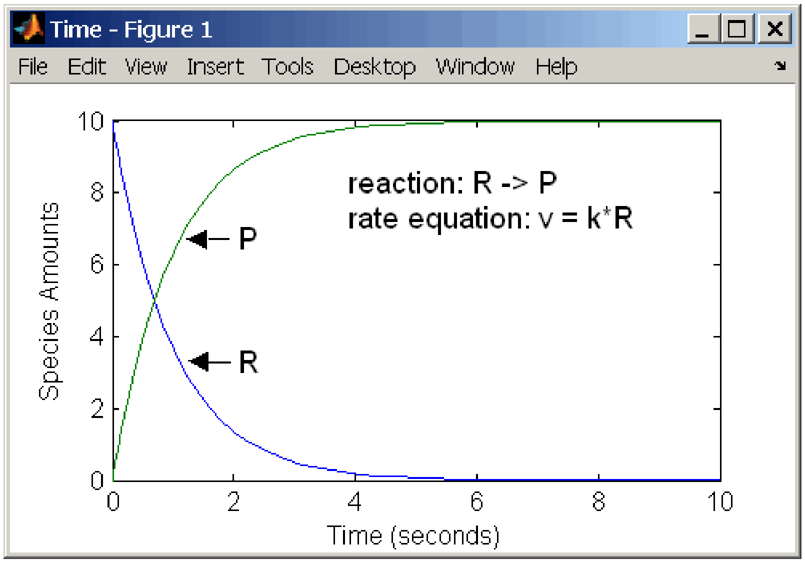
Note If the amount of a reactant with zero-order kinetics reaches zero before the end of a simulation, then the amount of reactant can go below zero regardless of the solver or tolerances you set.

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:



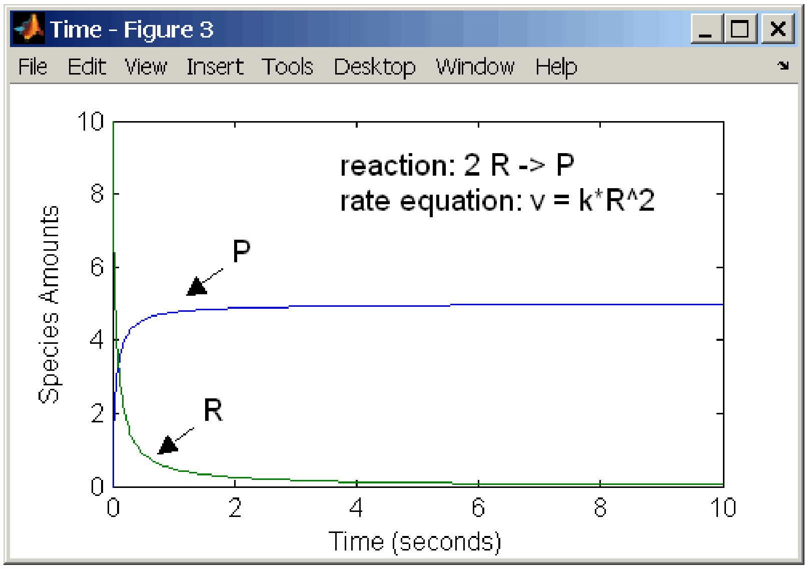
First-Order Mass Action Kinetics

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:



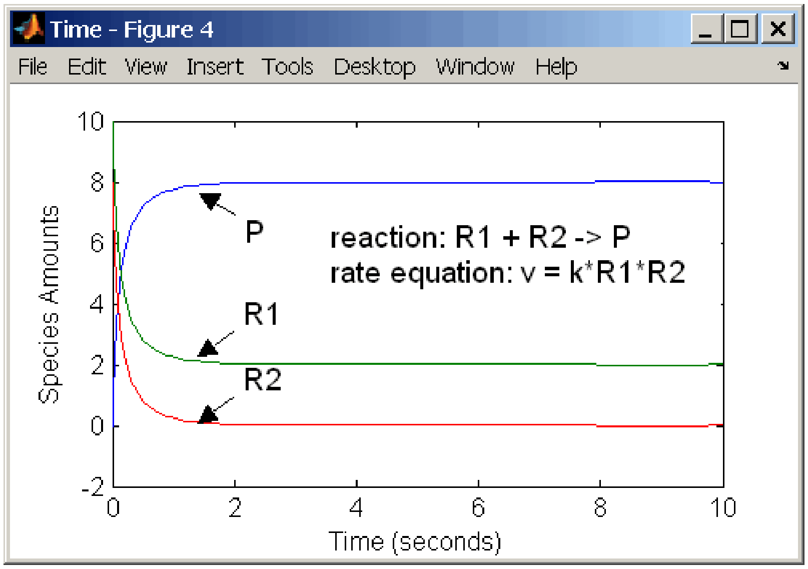
Second-Order Kinetics with Single Reactant

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.



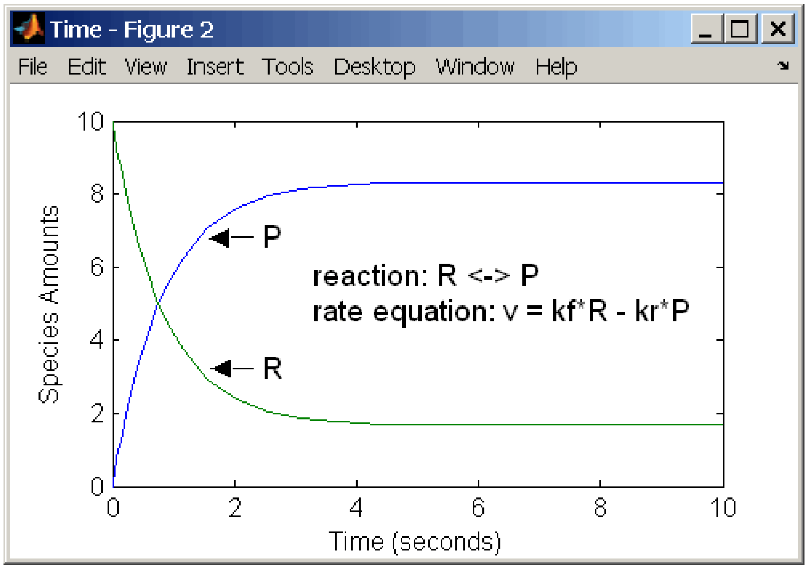
Second-Order Kinetics with Two Reactants

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`.



Enzyme Kinetics

In this section...

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.

$$S + E \underset{k1r}{\overset{k1}{\rightleftarrows}} ES \xrightarrow{k2} E + P$$

$$v_1 = k_1[S][E], \quad v_{1r} = k_{1r}[ES], \quad v_2 = k_2[ES]$$

This simple model can be defined with

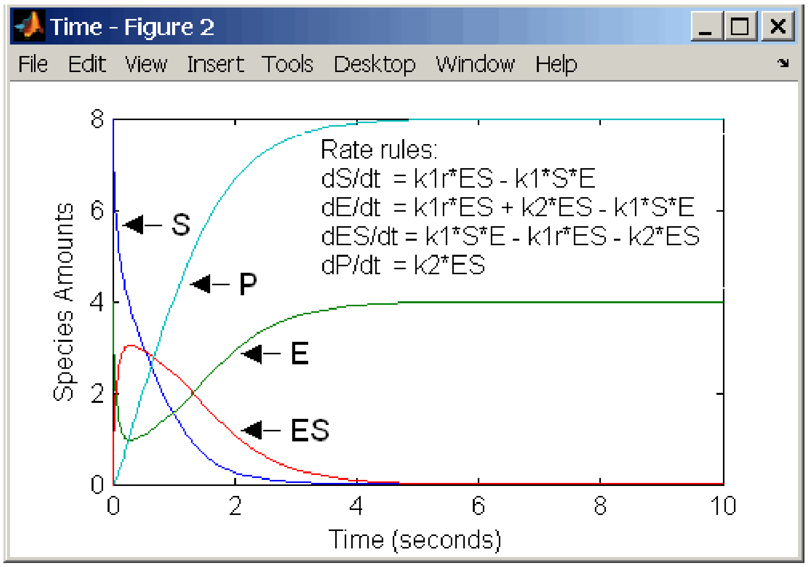
- Differential rate equations. See "Enzyme Reactions with Differential Rate Equations" on page 1-10.
- Reactions with mass action kinetics. See "Enzyme Reactions with Mass Action Kinetics" on page 1-12.
- Reactions with Henri-Michaelis-Menten kinetics. See "Enzyme Reactions with Irreversible Henri-Michaelis-Menten Kinetics" on page 1-13.

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 1-10) 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 to enter rate rules using the form `dS/dt = f(x)` as `S = f(x)`.



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

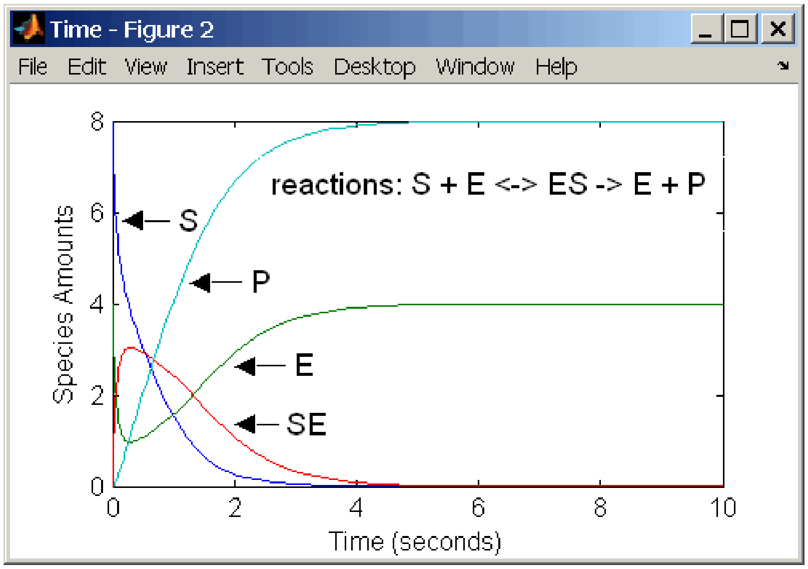
Determining the differential rate equations for the reactions in a model is a time-consuming process. A better way is to enter the reactions for a single substrate enzyme reaction mechanism directly into the software. The following example using models an enzyme catalyzed reaction with mass action kinetics. For a description of the reaction model, see "Simple Model for Single Substrate Catalyzed Reactions" on page 1-10.

```
     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 1-10.

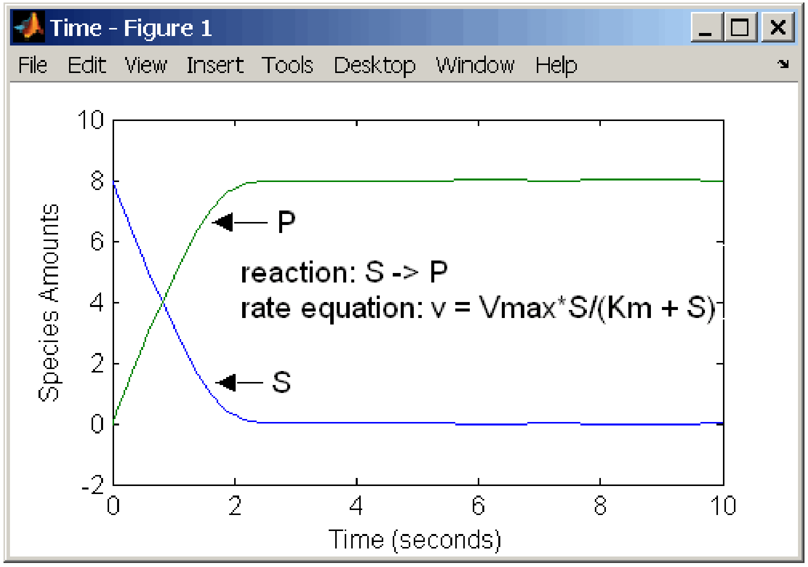
$$v = \frac{\mathrm{Vmax}[S]}{\mathrm{Km} + [S]}$$

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.



Use of Constant Amount and Boundary Condition for Species

In this section...

Definition of Constant and Boundary Properties

There are two properties (constant amount, boundary condition) to specify how the amount of a species changes or does not change during a simulation. Based on the conditions of your model you can decide how to use these properties.

The SBML specification (Level 2, Version 1) added the property `BoundaryCondition` to the model definition.

Species with BoundaryCondition = Yes — The species amount is either constant or determined by a rule, but in either case the amount is 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.

Species with ConstantAmount = No — The species amount is determined by a reaction or a rule, but not both.

Species with ConstantAmount = Yes — The species amount does not change during a simulation. The species can be in a reaction or rule, but it cannot have a rule that changes its amount.

Constant = NO, Boundary = NO

The value of a species can change, and it can change with either a reaction or rule, but not both

Constant	Boundary	Reaction	Rule	Changed By
NO	NO	YES	NO	Reaction
NO	NO	NO	YES	Rule

Example 1 — Species **A** is in 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 in 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 in a reaction, and it is not in a rate equation. **G** varies with an algebraic rule or rate rule.

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

Constant = YES, Boundary = NO

The value of a species cannot change. When a species has its `ConstantValue` selected and `BoundaryCondition` not selected, it acts like a parameter. It cannot be in a reaction and it cannot be varied by a rule.

Constant	Boundary	Reaction	Rule	Changed By
YES	NO	NO	NO	Never

Example — Species **E** is not in the reaction, but it is in 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)
```

Constant = NO, Boundary = YES

The value of a species can change, and it is in a reaction, but a differential rate term from the reaction is not created. The value of the species change with a rule and a differential rate term is created from the rule.

Constant	Boundary	Reaction	Rule	Changed By
NO	YES	YES	YES	Rule

From the SBML specification (Level 2, Version 1), "By default, when a species is a product or reactant of one or more reactions, its concentration is determined by those reactions. In SBML, it is possible to indicate that a given species' concentration is not determined by the set of reactions even when that species occurs as a product or reactant; i.e., the species is on the boundary of the reaction system but is a component of the rest of the model."

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)
```

Constant = YES, Boundary = YES

The value of the species can change. It is in a reaction, but a differential rate term is not created from the reaction. The differential rate term is created from a rule.

Constant	Boundary	Reaction	Rule	Changed By
YES	YES	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)
```

Model Edges

As you build complex models from simpler pathways, there are edges in the model that you need to define before simulating the model. Knowing where the model edges are located is important because a species that is initially constant or unregulated can later vary as you add details to your model. The concept of a model edge overlaps with SBML boundaries, but not always.

Model edge — Species with constant amounts that might or might not be modeled in the reaction and reaction rate equations. Examples are cofactors, NAD^+, ATP, and DNA.

Model edge — Enzymes with constant amounts that are not regulated. For example, a Michaelis-Menten rate equation with `Vmax` specified as a parameter assumes that the amount of enzyme catalyzing the reaction remains constant.

$$v = \frac{V_{max}*[\text{Substrate}]}{K_m + [\text{Substrate}]}$$

You may want to temporarily model a regulated enzyme in a rate equation. If the amount of enzyme is constant, then this species is a model edge. After adding the reaction(s) that change the amount of the enzyme,

$$v = \frac{k*[\mathbf{Enzyme}]*[\text{Substrate}]}{K_m + [\text{Substrate}]}$$

Model edge — Null or source species that synthesizes another species at a constant rate (zero order reaction). Mass is added to the system.

Model edge — Degradation of a species to a null or sink species (first-order reaction). Mass is taken away from the system.

Parameter and Scope

In this section...

Definition of Parameter Scope

A *parameter* is a quantity that can change or can be constant. SimBiology® parameters are generally used to define rate constants.

A SimBiology parameter is defined either globally at the model level or locally at the kinetic law level. *Scope* refers to this definition of the parameter at the model or kinetic law level.

- If the scope of the parameter is global in the model, it can be used by any event or rule, or by any reaction rate expression in the model.
- If the scope of the parameter is at the kinetic law level, it can be used only by the reaction rate expression for which it was defined.

If you create a new parameter in the **Project Settings-Parameters** pane, the scope is set by default to the `model`. When you create a new parameter to define a reaction rate equation in the **Project Settings-Reactions** pane's **Kinetic Law** tab, you can choose whether to assign the parameter locally to the kinetic law or globally to the model.

SimBiology parameters are resolved hierarchically:

- For reaction rate, the software hierarchically uses the value of the parameter at the kinetic law level first. If no such parameter is at the kinetic law level, the software looks for the parameter at the model level.
- If two parameters have the same name, one at the model level and the other at the kinetic law level, the software uses the value of the parameter at the kinetic law level for the reaction rate. the software uses the value of the parameter at the model level for any rules or events that reference the parameter.

Therefore, if you want to vary a parameter that is being referenced in a reaction rate equation, that parameter must have a unique name, and have scope at the model level.

Using a Parameter in Events and Rules

When you want to refer to a parameter in an event or rule expression, or in more than one reaction rate equation, the parameter scope must be at the model level.

If you want to vary a parameter that is being referenced in a reaction rate equation, that parameter must have a unique name, and have scope at the model level. See "Definition of Parameter Scope" on page 1-20 for more information.

To change the scope from kinetic law level to model level,

Note To vary a parameter with a rule or an event, clear the **ConstantValue** check box in the **Project Settings-Parameters** pane, **Settings** tab.

Changing the Scope of a Parameter

When you want to refer to a parameter in an expression for a rule, or in more than one reaction rate equation, the parameter scope must be at the model level. The software hierarchically uses the value of the parameter at the kinetic law level first. If no such parameter is at the kinetic law level, the software searches for the parameter at the model level.

If you have already configured a reaction to use a parameter that is at the kinetic law level, change the scope to the model level by doing the following:

1. In the **Project Explorer**, double-click **Parameters**, to open the **Parameters** pane.

2. In the **Parameters** table, right-click a parameter row select **Change Parameter Scope** to change the scope of the selected parameter from kinetic law to model, or the reverse.

Rules

In this section...

What is a Rule?

A rule is an model component that defines the value for a parameter or the amount of a species.

There are three types of rules in SimBiology®, Assignment, Algebraic, and Rate rules. Rules are evaluated at each time step during a simulation.

- Use assignment rules to specify the initial value of a parameter or initial amount of a species using an expression.
- Use algebraic rules for equations that are not rates of change.
- Use rate rules for equations that determine the rate of change for a parameter value, species amount or compartment capacity.

For species, use rate rules as an alternative to the differential rate expression generated from reactions.

What Is an Algebraic Rule?

An algebraic rule is a model component that defines the value for a non-constant parameter or the amount of a species that is determined through a algebraic equation instead of a differential relationship.

An algebraic rule is an equation that defines the value of a variable that you may not be able to define with a reaction. Use algebraic rules for defining equity constraints that are not rates of change.

There are three types of rules that are evaluated at each time step during a simulation. The first is a rate rule, the second is an algebraic rule, and the third is a repeatedAssignment rule. An algebraic rule is defined by the equation

```
0 = f(W) - x
```

The variable `x` can be a species amount or parameter value. The function `f(W)` is an expression that can include other species and parameters. Enter an algebraic rule using the form

```
f(W) - x
```

Mass Balance Equations

There are some models in the literature that are defined with differential rate equations and algebraic mass balance equations.

A mass balance equation can define the amount of a species and reduce the number of differential rate equations that need to be solved. For example, a common signal transduction pathway can include a reaction `Ei -> Ea` where an enzyme transforms from an active form to an inactive form and back. The amount of inactive enzyme `Ei` is defined by the differential rate equation `dEi/dt = Vm*Ei/Km + Ei`. If the total amount of the enzyme is known or remains constant, the total amount of enzyme `Ea` can be defined with the algebraic equation `Ea = Et - Ei` instead of a differential equation.

SimBiology models are defined by reactions, and the corresponding differential rate equations are calculated for all species. Adding a mass balance equation as an algebraic rule, and setting `Et` to be constant, would overdefine the model and cause a simulation error (the number of equations cannot be greater then the number of independent variables). If want to use a mass balance equation, you have to let `Et` vary, then `Et` is an independent variable that is not defined by a reaction and the simulation works.

What is a Rate Rule?

A rate rule is defined by the equation

```
dx/dt = f(W)
```

The variable x can be a species amount, parameter value, or compartment dimension (volume or area). The function f(W) is an expression that can include other species and parameters. Enter a rate rule using the form

```
x = f(W)
```

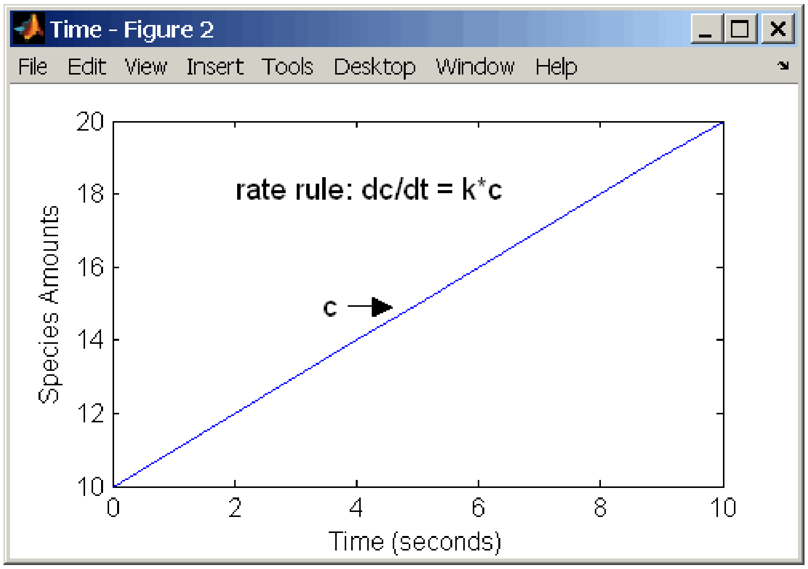
Use Case: When the Rate of Change Is Constant

You can increase or decrease the amount or concentration of a species by a constant value using a zero order rule. For example, the species c increases by a constant rate k. You could also include species and parameters that have their ConstantAmount or ConstantValue properties selected.

```
      reaction: none
 rate equation: none
     rate rule: dc/dt = k
       species: c = 0 mole
    parameters: k = 1 mole/second
```

The solution is $c = kt + c_0$, where c_0 is the initial amount or concentration of the species c.

Enter the rule described above as c = k. From the **RuleType** list, select rate, enter the values for c and k, and then simulate.



Alternatively, you could model a constant increase in a species with the reaction `null -> C`.

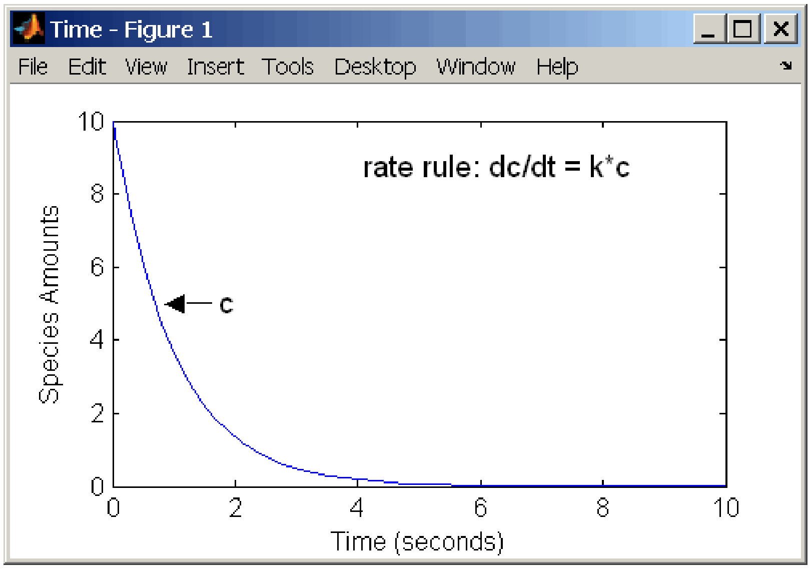
Use Case: When Rate of Change Is Exponential

You can change the amount of a species similar to a first-order reaction using a first-order rate rule. For example, the species `c` decays exponentially. You could also include a parameter with its `ConstantValue` property cleared or set to `false`.

```
       reaction: none
  rate equation: none
      rate rule: dc/dt = -k*c
        species: c = 10 mole
     parameters: k =  1 1/second
```

The solution for the rate rule `dc/dt = -k*c` is $c = c_0 e^{-kt}$.

Enter the rate rule described above and simulate with an ODE solver.



Notice that if the amount of a species `c` is determined by a rate rule and `c` is also in a reaction, `c` must have its property for `BoundaryCondition` selected. For example, with a reaction `a -> c` and a rate rule `dc/dt = k*c`, select the `BoundaryCondtion` for `c` so that a differential rate term is not created from the reaction. The amount of `c` is determined solely by a differential rate term from the rate rule.

If the boundary condition is not selected, you will get the following error message:

```
Invalid rule variable 'in a reaction or another rule'.
```

Use Case: When Rate of Change Is Determined by Another Species

A species from one reaction can determine the rate of another reaction if it is in the second reaction rate equation. In a similar way, a species from a reaction can determine the rate of another species if it is in the rate rule that defines that other species.

```
     reaction: a -> b
rate equation: v = -k1*a
rate rule: dc/dt = k2*a
   species: a = 10 mole
            b =  0 mole
            c =  5 mole
parameters: k1 = 1 1/second
            k2 = 1 1/second
```

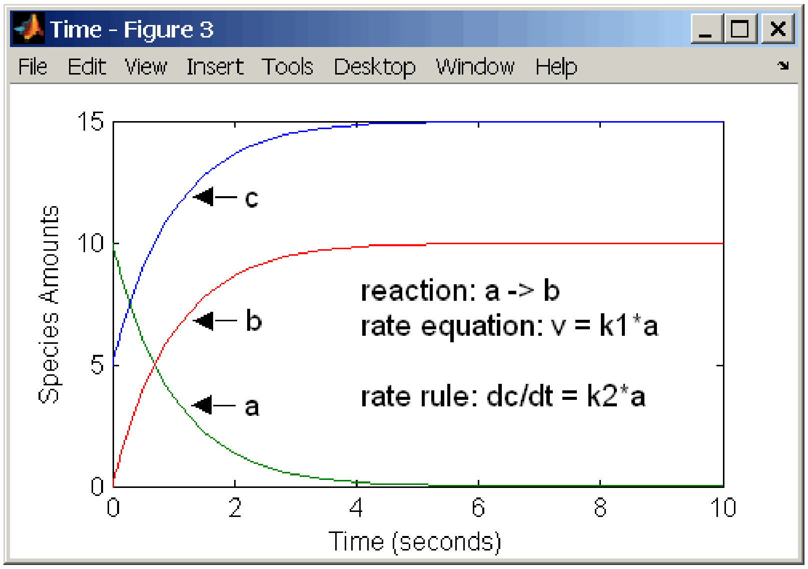
The solution for the species in the reaction are

$$a=a_0e^{-k1t} \text{ and } b=a_0(1-e^{-k1t})$$

With the rate rule `dc/dt = `k_2`*a` dependent on the reaction, `dc/dt = `$k_2(a_oe^{-k1t})$, and the solution is

$$c = c_o + k_2a_o/k_1(1 - e^{-k_1t})$$

Enter the reaction and rule described above and simulate.



Use Case: Expressing Differential Rate Equations as Rules

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
```

What is an initialAssignment Rule?

`initialAssignment` rules are evaluated once at the beginning of a simulation. `initialAssignment` rules are expressed as `Variable = Expression`. For example you could write an `initialAssignment` rule to set the amount of `species1` to be proportional to `species2`.

```
species1 = k/species2
```

What is a repeatedAssignment Rule?

`repeatedAssignment` rules are evaluated at every time-step during a simulation. `repeatedAssignment` rules are expressed as `Variable = Expression`. For example, you could use the rule to specify the amount of `species1` to always be proportional to `species2`.

```
species1 = k/species2
```

Events

In this section...

What is an Event?

Events are used to describe sudden changes in model behavior. An event lets you specify discrete transitions in model component values that occur when a user-specified condition becomes true. You can specify that the event occurs at a particular time, or specify a time-independent condition.

For example, you can use events to activate or deactivate certain species (activator or inhibitor species), change parameter values based on external signals, or change reaction rates in response to addition or removal of species. You can also use an event in a model when you want to replicate an experimental condition, for example, to replicate the addition or removal of an activating agent (such as a drug) to a sample.

Use SimBiology® events to define events that occur when a condition becomes true. When you specify a condition in the `Trigger` you are specifying that the event should be executed when the condition becomes true. Typical triggers are:

- Cause an event to occur at a specific time during simulation — 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.
- Cause an event to occur 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.

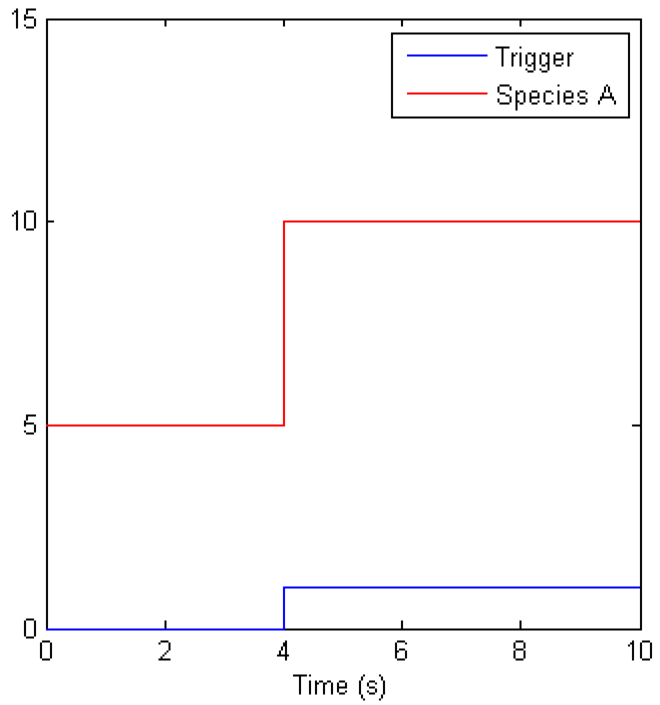
The event that is executed when the `Trigger` becomes true is called an event function (`EventFcn`). Event functions could range from simple to complex, for example, an event function might:

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

To simulate SimBiology models containing events, use the deterministic `sundials` solver or the stochastic `ssa` solver; other solvers do not support events. See “Sundials Solvers” on page 2-15 and “Stochastic Solvers” on page 2-10 for more information.

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` the trigger becomes true and the event is executed. In the figure above 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`. 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`.

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 executed again. If a trigger is already true before a simulation starts, then the event does not execute the 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; one example of this is when a rising edge follows very quickly after a falling edge, and the step size results in the solver skipping over the transition point.

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

Specifying Event Triggers

A `Trigger` is a condition that must become true for an event to be executed. Typically, the condition uses a combination of relational and logical operators to build a trigger 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 “Operators” 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 `&`) tells the software to evaluate the first part of the expression for whether the statement is true or false, and skip evaluating the second statement if this statement is false.

Trigger	Explanation
`'(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 when the time 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`.
`'((s1 >=5000.0) && (time>= 250)) || (s2<5.0E17)'`	Execute the when the time 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`.

For more information on triggers see `Trigger` in the SimBiology Reference Guide.

Specifying Event Functions

The event that is executed when a `Trigger` condition has a rising edge is called an event function (`EventFcn`). You can use an event function to change the value of a species or a parameter, or you can specify complex tasks by calling an M-file containing a user-defined function or script.

An event function is either a single valid MATLAB expression (without ';' in the expression) or a cell-array of single valid MATLAB expressions. For more information see also `EventFcns` in the SimBiology Reference Guide. Some examples of event functions include:

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`.
`'kC = my_func(A, B, kC)'`	When the event is executed call the user-defined function `my_func()`. This function takes 3 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.

Evaluation of Simultaneous Events

When two or more trigger conditions simultaneously become true, the solver executes the events in the order in which they are on the model. You can reorder events using the `reorder` method at the command-line. Alternatively, in the SimBiology desktop, arrange the rows of events in the order you desire, then right-click and select **Reorder Events as Shown in Table**. For example, consider a case where:

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 the two 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 below, 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 may or may 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 stores the value of `SpeciesC` at the rising edge, before any event functions are executed and uses this stored value to assign `SpeciesB` its value. In the above example if `SpeciesC = 15` when the events are triggered, after the events are executed `SpeciesB = 15`, and `SpeciesC = 10`.

Evaluation of Multiple Event Functions

Consider an event function in which you specify that the value of a model component (`SpeciesB`) is dependent 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 the above 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 example below, 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 (assuming that `SpeciesA` is below `5`) 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. An example of cyclical events is shown below. 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'}`

Example — Using an Event to Change Species Amounts

In this section...

Prerequisites

To work through the example, these sections assume you have a working knowledge of the following:

- MATLAB® desktop
- SimBiology® desktop

Overview

This example shows you how to add an event to a model to trigger a time-based change using the model in "Modeling a G Protein Cycle" in *SimBiology Model Reference*.

This table lists 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	Rate Parameters
1	Receptor-Ligand interaction	`L + R <-> RL`	`kRLm`, `kRL`
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`

No.	Name	Reaction	Rate Parameters
5	Receptor-Ligand degradation	`RL -> null`	`kRD1`
6	G protein inactivation	`Ga -> Gd`	`kGd`

This example shows you how to add an event that modifies amount of ligand (L), thus modeling a delay in the addition of α-factor to the cell culture.

Creating an Event to Model Delayed Species Addition

- "Opening and Saving the Example Model" on page 1-39
- "Preparing to Modify the Example Model" on page 1-40
- "Adding an Event to the Example Model" on page 1-40
- "Simulating the Modified Model" on page 1-41

Opening and Saving the Example Model

1 Open the desktop from the MATLAB command line, by typing

```
sbiodesktop
```

The SimBiology desktop opens.

2 **File > Open Project**. . The Open SimBiology Project dialog box opens.

3 Browse to the directory where the product is installed and select the file `matlab/toolbox/simbio/simbiodemos/gprotein.sbproj`, and then click **Open**. The project opens in the SimBiology desktop.

4 Select **File > Save Project As**. The Save SimBiology Project dialog box opens.

5 Specify a name (for example, `gprotein_event_ex`) and location for your project and click **Save**.

Preparing to Modify the Example Model

Copy a model in the project and use the copy to work on this example.

1 In the **Project Explorer**, right-click **Model Session-Heterotrimeric_G_Protein_wt** and select **Copy Model and Add to Project**. The desktop adds the copied model to the **Project Explorer**.

2 Rename the copied model.

  a In the **Project Explorer**, right-click **Model Session** for the copied model and select **Rename Model**. The Rename Model dialog box opens

  b Modify the name, for example, `G_Protein_wt_event`.

  c Click **Save**.

Adding an Event to the Example Model

1 In the **Project Explorer** expand **Table View** for the `G_Protein_wt_event` model and double-click **Events** to open the **Events** pane.

2 In the **Enter Trigger** box, type the following expression and press **Enter**:

```
time >= 100
```

3 In the **EventFcns** box, type the following expression and press **Enter**:

```
L = 6.022E17
```

In the **Settings** tab, note that the species `L` is available.

4 In the row containing the species `L`, double-click the `InitialAmount` column, type `0`, and then press **Enter**.

The **InitialAmount** of `L` is set to be `0.0` when the simulation starts.

5 Save the project by selecting **File > Save Project**.

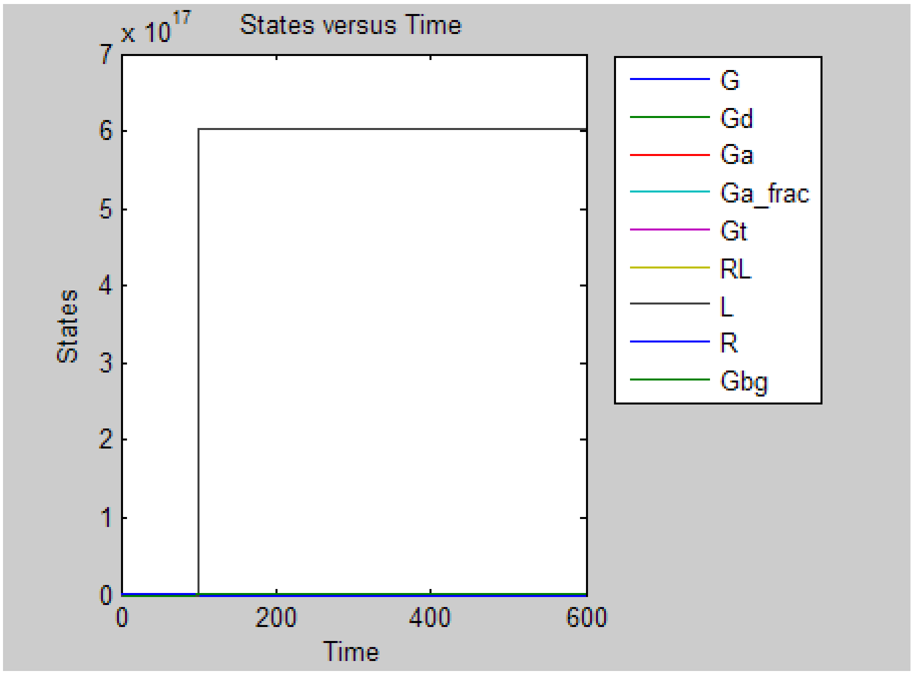
Simulating the Modified Model

1. In the **Project Explorer**, for the `G_Protein_wt_event` model, expand **Model Variable Settings** and double-click **Configuration Settings** to open the pane that contains solver settings.

2. In the **Settings** tab, from the **SolverType** list, select `sundials`. This solver lets you simulate models with events.

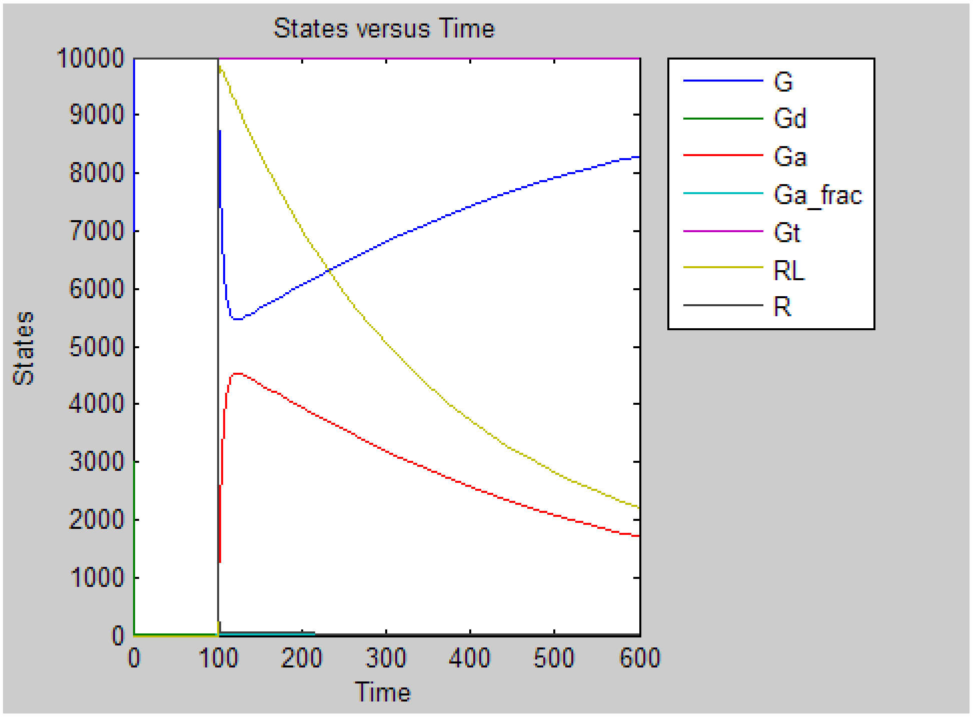
3. In the **Project Explorer**, right-click the `G_Protein_wt_event` model and select **Run Simulation**.

   The simulation runs to completion and plots the result in a figure. Notice that the plot shows that the ligand amount increases when the event is executed.



   The plot does not show the species of interest due to a wide range in species amounts. Follow the next steps to view the species of interest.

4. In the **Project Explorer**, for the `G_Protein_wt_event` model, right-click **Data** and select **Save Data**. The Save Data dialog box opens.
5. Specify a name for the saved data, for example, `event_ex`, and click **Save**. The **Project Explorer** shows a new item with the saved data name under **Simulation**.
6. In the **Project Explorer**, for the `G_Protein_wt_event` model, double-click the saved data, for example, `event_ex`, to open the **Data** pane for the saved data.
7. In the **Plot Type** box, select `Time` and click **Add**.
8. For the new plot, double-click the **Y Arguments** column. The Select Y Arguments dialog box opens.
9. Click **Select All** and then clear the check boxes for the species `L` and `Gbg`
10. Click **OK**.
11. (Optional) Clear the **Create Plot** check box for the first plot.
12. Click **Plot**. Your plot should resemble the one below. Notice the increase in activation of G protein (species `Ga`, shown in red) after ligand (L) is added at `time = 100` (simulation time).


States versus Time
States
Time
0
1000
2000
3000
4000
5000
6000
7000
8000
9000
10000
0
100
200
300
400
500
600
G
Gd
Ga
Ga_frac
Gt
RL
R

Example — Using User-Defined Functions in Expressions

In this section...

Prerequisites

To work through the example, these sections assume you have a working knowledge of the following:

- MATLAB® desktop
- Creating and saving M-files
- SimBiology® desktop

Overview

You can use custom defined functions in reaction rate, rule, and event expressions. When you call the function from within a SimBiology expression, the solver evaluates the expression as written in the M-file, during simulation.

Requirements For Specifying User-Defined Functions

- Create an M-file function. To find out more about M-file functions, see `function` in *MATLAB Function Reference*. To see an example of a function declaration for a SimBiology model, see “Creating an M-File Function” on page 1-46 in this topic.
- Change the working directory to the directory containing your M-file using the `cd` command or using the Desktop as shown in “Current Directory Field” in *MATLAB Desktop Tools and Development Environment*. Alternatively, add the path to the directory containing your M-file using

`addpath` or using the GUI as shown in “Viewing and Setting the Search Path”in *MATLAB Desktop Tools and Development Environment*.

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

While the requirements do not have to be defined in any specific order, you might find it more convenient to start with the first two items before calling the function from within the SimBiology expression because colored cues for model verification in the SimBiology desktop will show an expression as invalid if the function has not yet been defined, or is not on the path or it in the working directory.

Model Used in This Example

This example uses the model in “Modeling a G Protein Cycle” in *SimBiology Model Reference* to illustrate how to create and call user-defined functions in SimBiology expressions. More specifically, the example shows you how to use a user-defined function in a rule expression. You can use user-defined functions similarly in event expressions (`EventFcn` property), event triggers (`Trigger` property) and in reaction rate expressions (`ReactionRate` property).

This table shows you 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	Rate Parameters
1	Receptor-Ligand interaction	`L + R <-> RL`	`kRLm`, `kRL`
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`

For the purpose of this example, assume that:

- An inhibitor (`Inhib`) slows the inactivation of the active G protein (reaction 6 above, Ga –> Gd).
- The variation in the amount of `Inhib` is defined in a function.
- The effect on the reaction is through a change in the rate parameter `kGd`.

Creating an M-File Function

1 In the MATLAB desktop, select **File > New > M-File**, to open a new M-file in 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.
% You can define the input arguments in a
% SimBiology rule expression.
% For example in the rule, define:
% t as time (a keyword recognized as simulation time),
% Cpo as initial amount of inhibitor (species) 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 M-file (name the file `inhibvalex.m`) in a directory that you can access, or that is on the path.

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

Calling the Function in a Rule Expression

Opening and Saving the Example Model

1. Open the desktop from the MATLAB command line, by typing

   ```
   sbiodesktop
   ```

   The SimBiology desktop opens.

2. **File > Open Project**. . The Open SimBiology Project dialog box opens.

3. Browse to the directory in which the product is installed and select the file `matlab/toolbox/simbio/simbiodemos/gprotein.sbproj`, and then click **Open**. The project opens in the SimBiology desktop.

4. Select **File > Save Project As**. The Save SimBiology Project dialog box opens.

5. Specify a name (for example, `gprotein_userfcn_ex`) and location for your project and click **Save**.

Preparing to Modify the Example Model

Copy a model in the project and use the copy to work on this example.

1. In the **Project Explorer**, right-click **Model Session-Heterotrimeric_G_Protein_wt** and select **Copy Model and Add to Project**. The desktop adds the copied model to the **Project Explorer**.

2. Rename the copied model.

a In the **Project Explorer**, right-click **Model Session** for the copied model and select **Rename Model**. The **Rename Model** dialog box opens

b Modify the name to `G_Protein_wt_userfcn`.

c Click **Save**.

Adding User-Defined Functions to the Example Model

The previously defined function `inhibvalex` in "Creating an M-File Function" on page 1-46 lets you specify how the inhibitor amount changes over time. This section shows you how to specify the input values for the function in a rule expression. As defined in the function, the output value is the amount of inhibitor.

Define a new rule to assign the inhibitor value.

1 In the **Project Explorer**, expand **Table View** for the `G_Protein_wt_userfcn` and double-click **Rules** to open the **Rules** pane.

2 In the **Enter Rule** box, type the following expression and press **Enter**:

```
Inhib = inhibvalex(time, Cpo,  Kel)
```

The Rule Variables dialog box opens for you to define the rule variables.

3 From the **Type** list, select `species` for `Cpo` and `Inhib`, and `parameter` for `Kel`. The SimBiology desktop creates the two species and the parameter.

Note If `inhibvalex` is on the list of undefined variables in the Rule Variables dialog box, this means that you have not yet put the M-file on the path or changed the working directory to the location of the M-file.

Leave `inhibvalex` undefined in the Rule Variables dialog box and click **OK**. In the MATLAB desktop, change the **Current Directory** field to the location of the M-file and you can now safely ignore the error indicator for the rule in the SimBiology desktop.

---

4 Click **OK**.

5 In the **Rules** pane from the **RuleType** list, select `repeatedAssignment`.

6 In the **Settings** tab, in **Parameters being used by Rule**, find the row containing the parameter `Kel`. Double-click the **Value** column, type `0.2`, and press **Enter**.

7 In the **Settings** tab, in **Species Being Used by Rule**, find the row containing the species `Cpo`. Double-click in the **InitialAmount** column, type `50` and press **Enter**.

Note You do not have to set a value for the species `Inhib` because it is being specified by a `repeatedAssignment` **Rule**.

8 Save the project by selecting **File > Save Project**.

Defining a Rule to Affect Parameter Value

As described in "Model Used in This Example" on page 1-45 , the parameter `kGd` should be affected by the amount of inhibitor present in the system. Add a rule to describe this action, but first change the `Scope` and `ConstantValue` properties of the parameter `kGd` so that it can be varied by a rule.

Note Although the model has a previously defined parameter called `kGd`, this parameter's scope is currently at the kinetic law level. The parameter must be scoped to the model for it to be varied by a rule or an event.

1 In the **Project Explorer**, expand **Table View** for the `G_Protein_wt_userfcn` model and double-click **Parameters** to open the **Parameters** pane.

2 Select the row containing the parameter `kGd`.

3 Right-click and select **Change Parameter Scope**. Notice that the **Scope** column now shows the model name for this parameter.

4 In the **Settings** tab, clear the **ConstantValue** check box for `kGd`, as this parameter is being varied by a rule.

5 In the **Project Explorer**, double-click **Rules** for the `G_Protein_wt_userfcn` model to open the **Rules** pane.

6 In the **Enter Rule** box, type the following expression and press **Enter**:

```
kGd = 1/Inhib
```

In the **Settings** tab you should see a green square indicating that the rule variables have been previously defined, and that there are no other warnings or errors associated with this rule.

7 For the new rule, in the **Rules** pane from the **RuleType** list, select `repeatedAssignment`.

8 Save the project by selecting **File > Save**.

Simulating the Modified Model

1 In the **Project Explorer**, right-click the `G_Protein_wt_userfcn` model and select **Run Simulation**.

The simulation runs to completion and plots the result in a figure. The plot does not show the species of interest due to a wide range in species. Follow the next steps to view the species of interest.

2 In the **Project Explorer**, for the `G_Protein_wt_userfcn` model, double-click **Data** to open the **Data** pane for the most recent simulation run.

3 Double-click the **Y Arguments** column to open the Select Y Arguments dialog box.

4 Clear the check box for the following species:

```
RL
L
R
Gbg
```

Note Species names are prefixed with the name of the compartment to which the species belongs. The default compartment is 'unnamed'.

---

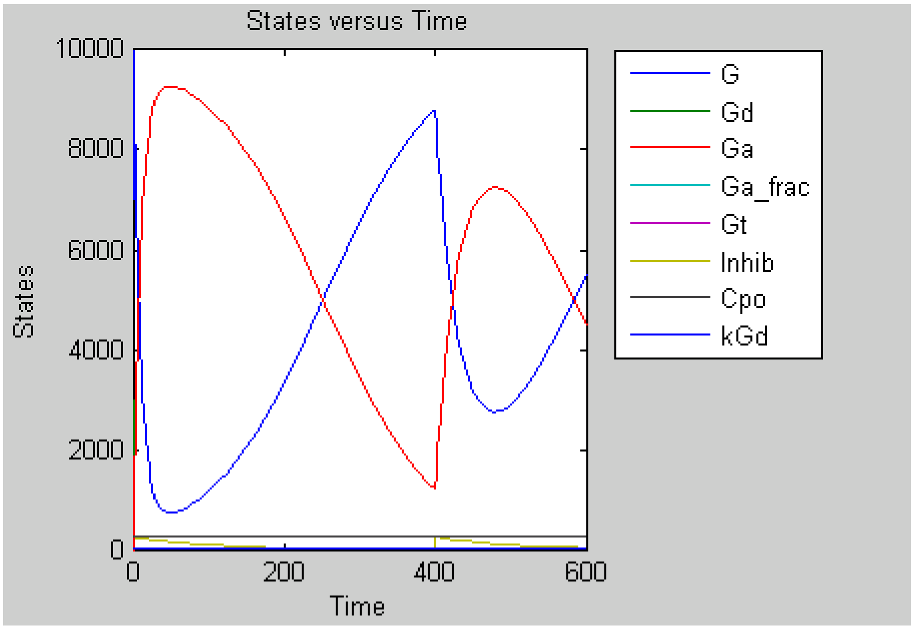
5 In the **Plot Type** box, select `Time` and click **Add**.

6 For the new plot, double-click the **Y Arguments** column to open the Select Y Arguments dialog box.

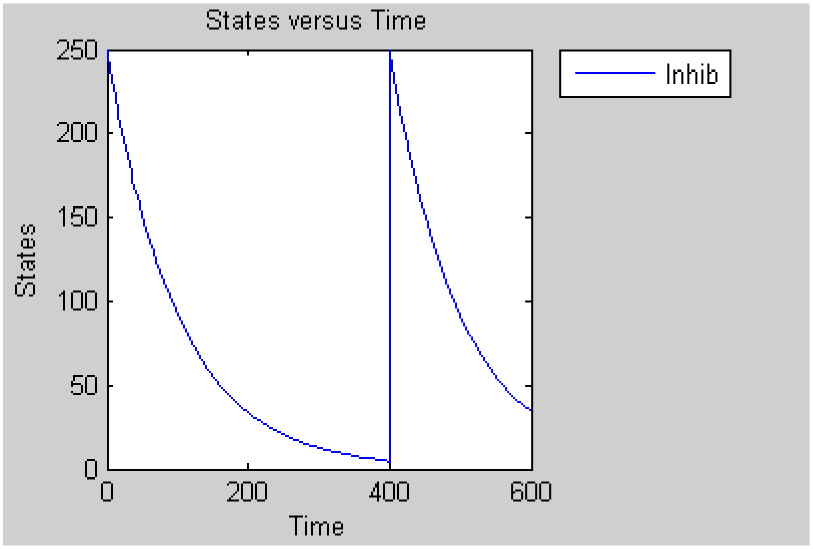
7 Select the check box for the species `Inhib`.

8 Click **OK**.

9 Click **Plot**. Your plots should resemble the following:



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



See Also

To learn about ...	Refer to...
The SimBiology desktop	"Getting Started in the SimBiology Desktop" in the *SimBiology Getting Started Guide*.
M-file functions	`function` in the *MATLAB Function Reference*
Changing the working directory to the directory containing your M-file	`cd` command in the *MATLAB Function Reference* or the "Current Directory Field" in *MATLAB Desktop Tools and Development Environment*.
Adding the directory containing your M-files to the MATLAB search path	`addpath` in the *MATLAB Function Reference* or "Viewing and Setting the Search Path"in *MATLAB Desktop Tools and Development Environment*

Simulation

Simulation Overview

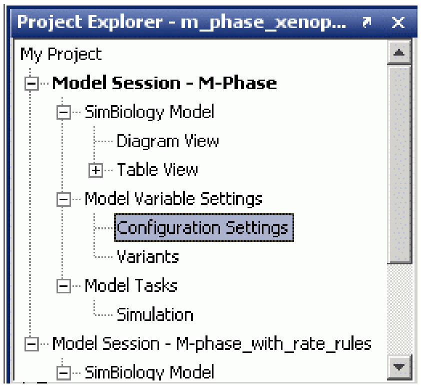
In this section...

Simulation and Configuration Settings

The SimBiology® integrated desktop environment provides convenient access to the configuration sets for simulations.

To access your configuration settings,

- On a **Simulation** task pane, on the **Simulation Settings** tab, next to **Configuration Settings**, click **View** .
- Alternatively, in the **Project Explorer**, under the **Model Variable Settings** node, select the **Configuration Settings** node.



The **Configuration Settings** pane appears, where you can set, change, and save simulation parameters, configure data logging, and compile options.

Where to Find Configuration Settings Controls

Use the following controls on the **Configuration Settings** pane:

- Use the **Settings** tab to set the simulation solver options and timing parameters for the currently selected model, and compile options for unit checking.

  The common simulation properties (solver and timing) are also accessible in the simulation toolbar *only* for simulating from the **Diagram** or **Analysis** menu.

- Use the **Data Logging** tab to choose which species to log and how often.

Where to Find Simulation Controls

To set up and run your simulation, use the following controls on the **Simulation** task pane:

- Use the **Simulation Settings** tab to select your Configuration Settings, or use the default. After you set up custom configuration sets, you can select them by name in the Configuration Settings list.

  Note Use the **Run** button at the top of the **Simulation** task pane to run the simulation with your currently selected Configuration Settings.

  If you are using **Variants** you can view them and commit them to tasks on the **Simulation Settings** tab.

- Use the **Export Results** tab to export simulation data to the MATLAB® Workspace and/or to file every time you run a simulation.

- Use the **Plot Results** tab to configure what plots to generate when you run a simulation.

How Solvers Work

In order to simulate a model, the model is converted to a set of differential equations. The solver functions are used to compute solutions for those equations at different time intervals, giving the model's states and outputs over a span of time. You can then plot these outputs from your simulation.

The MATLAB ODE solvers are designed to handle *ordinary differential equations*. An ordinary differential equation contains one or more derivatives of a dependent variable *y* with respect to a single independent variable *t*, usually referred to as time.

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.

Stiff Versus Nonstiff Models

An ordinary differential equation problem is stiff if the solution being sought is varying slowly, but there are nearby solutions that vary rapidly, so the numerical method must take small steps to obtain satisfactory results. The ODE solvers in MATLAB whose name ends in "s" are for "stiff" problems. Many biological models are numerically stiff because they include species amounts that are changing quickly and others that change slowly.

Stiffness is an efficiency issue. If you don't care how much time a computation takes, you need not be concerned about stiffness. Nonstiff methods can solve stiff problems; they just take a long time to do it.

As an illustration, imagine trying to find the quickest descent through a canyon. An explicit algorithm, which is normally used for nonstiff models, would sample the local gradient to find the descent direction. But following the gradient on either side of the trail will send you bouncing back and forth from wall to wall — the descent will be found but it will take a long time. An implicit algorithm used for stiff models can anticipate where each step is taking you, keep you on the trail with fewer steps, and so save time. Using a stiff solver for a stiff problem can save thousands of solver steps and function evaluations compared to a nonstiff solver.

Methods intended to solve stiff problems efficiently do more work per step, but can take much bigger steps. Stiff methods are implicit. At each step they use MATLAB matrix operations to solve a system of simultaneous linear equations that helps predict the evolution of the solution.

Not all difficult problems are stiff, but all stiff problems are difficult for solvers not specifically designed for them. Solvers for stiff problems can be used exactly like the other solvers.

For an illustrative code example you can run to plot the effects of numerical stiffness on different solvers, see MATLAB News & Notes - May 2003 Cleve's Corner: Stiff Differential Equations.

Selecting a Solver

Choice of solver depends on the problem and time available for computation. There are trade-offs to be made between speed and accuracy. In general, ode45 is the best function to apply as a "first try" for most problems, or ode15s if you suspect that a problem is stiff. As you find out more about the problem you can try other solvers. Experimentation is generally required to determine the best solver for a particular model. As a general guide:

1. Models with either all fast or all slow changing variables are nonstiff problems:

   Use "Nonstiff Deterministic Solvers" on page 2-7.

   - ode45 — Best first guess.
   - Sundials — Alternative best first guess. May be faster.
   - ode23 — May be more efficient than ode45 with crude tolerances and mild stiffness.
   - ode113 — May be more efficient than ode45 with stringent tolerances.

2. Models with both fast and slow changing variables are stiff problems:

   Use "Stiff Deterministic Solvers" on page 2-8.

   - ode15s — Try first if you suspect that a problem is stiff, or if ode45 failed or was very inefficient.
   - Sundials — Alternative best first guess. May be faster.
   - ode23s — May be more efficient than ode15s at crude tolerances, and can solve some stiff problems that ode15s cannot.

- ode23t — Use this solver if the problem is only moderately stiff and you need a solution without numerical damping.
- ode23tb — Like ode23s, this solver may be more efficient than ode15s at crude tolerances.

3 Models with a small number of molecules:

   Use "Stochastic Solvers" on page 2-10.

   - Stochastic — Most accurate, may be too slow if the initial number of molecules for a reactant species is large.
   - Explicit Tau — Speeds up the simulation at the cost of some accuracy; can be orders of magnitude faster than Stochastic. Can be used for large problems (provided the problem is not numerically stiff).
   - Implicit Tau — May be the fastest, at the cost of some accuracy. Can be used for large problems and also for numerically stiff problems. For nonstiff systems may not be a good choice because it adds computational overhead.

   If you use a stochastic solver to simulate a model, the software ignores any rate, assignment, or algebraic rules if present in the model.

Nonstiff Deterministic Solvers

In this section...

When to Use Nonstiff Deterministic Solvers

If you have models with either all fast or all slow changing variables, these may not be numerically stiff; nonstiff deterministic solvers are appropriate to try.

ode45 (Dormand-Prince)

Based on an explicit Runge-Kutta (4,5) formula: the Dormand-Prince pair, ode45 is a one-step solver in computing $y(t_n)$. It needs only the solution at the immediately preceding time point $y(t_{n-1})$. In general, ode45 is the best function to apply as a "first try" for most problems.

ode23 (Bogacki-Shampine)

Based on an explicit Runge-Kutta (2,3) pair of Bogacki and Shampine, ode23 may be more efficient than ode45 at crude tolerances and in the presence of mild stiffness. Like ode45, ode23 is a one-step solver.

ode113 (Adams)

A variable order Adams-Bashforth-Moulton PECE solver, ode113 may be more efficient than ode45 at stringent tolerances and when the ODE function is particularly expensive to evaluate. ode113 is a multistep solver; it normally needs the solutions at several preceding time points to compute the current solution.

Stiff Deterministic Solvers

In this section...

When to Use Stiff Deterministic Solvers

If you have models with a mixture of fast and slow changing variables, such models are numerically stiff. Stiff deterministic solvers are the best choice.

ode15s (stiff/NDF)

A variable order solver based on the numerical differentiation formulas (NDFs), ode15s optionally uses the backward differentiation formulas, BDFs (also known as Gear's method). Like ode113, ode15s is a multistep solver. If you suspect that a problem is stiff or if ode45 failed or was very inefficient, try ode15s.

ode23s (stiff/Mod. Rosenbrock)

The ode23s solver is based on a modified Rosenbrock formula of order 2. Because it is a one-step solver, it may be more efficient than ode15s at crude tolerances. It can solve some kinds of stiff problems for which ode15s is not effective.

ode23t (Mode. stiff/Trapezoidal)

The ode23t solver is an implementation of the trapezoidal rule using a "free" interpolant. Use this solver if the problem is only moderately stiff and you need a solution without numerical damping.

ode23tb (stiff/TR-BDF2)

The ode23tb is an implementation of TR-BDF2, an implicit Runge-Kutta formula with a first stage that is a trapezoidal rule step and a second stage that is a backward differentiation formula of order 2. Like ode23s, this solver may be more efficient than ode15s at crude tolerances.

Stochastic Solvers

In this section...

When to Use Stochastic Solvers

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. The stochastic simulation algorithms provide a practical method for simulating reactions which are stochastic in nature. Depending on the model, stochastic simulations may take more computation time than deterministic simulations.

If you use a stochastic solver to simulate a model, the software ignores any rate, assignment, or algebraic rules if present in the model.

Stochastic Simulation Algorithm (SSA)

Using the stochastic simulation algorithm for a system is equivalent to solving the Chemical Master Equation for the system. The Chemical Master Equation is otherwise impossible to solve for most practical problems. Thus, the stochastic simulation algorithm provides a practical method for simulating stochastic systems. The algorithm simulates one reaction at a time based on the propensity function for each reaction.

Advantage:

- This algorithm is exact.

Disadvantages:

- Since it evaluates one reaction at a time, it may be too slow for large problems.
- If the number of molecules of any of the reactants is huge, it may take a long time to complete the simulation.

Explicit Tau-Leaping Algorithm

Since the stochastic simulation algorithm may be too slow for a lot of practical problems, this algorithm has been designed to speed up the simulation at the cost of some accuracy. The algorithm treats each reaction channel 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 the user-specified error tolerance. After selecting the time interval, the algorithm computes the number of times each reaction channel fires 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.
- This algorithm can be used for large problems (provided the problem is not numerically stiff).

Disadvantages

- Some accuracy is sacrificed for speed.
- Not good for stiff models.
- The error tolerance needs to be specified in such a manner 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 and the “fast modes” are stable. 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 channel as being independent of others. It automatically chooses 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, the algorithm computes the number of times each reaction channel fires 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.
- It can be used 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

- Some accuracy is sacrificed 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 damps out the perturbations off the slow manifold leading to a reduced state variance about the mean.

Ensemble Runs of Stochastic Simulations

Ensemble runs are ensemble simulations that you can use in conjunction with the stochastic solvers to gather data from multiple stochastic runs of the model. Ensemble runs let you investigate fluctuations in the behavior of a stochastic model over repeated simulations.

In contrast, scans are multiple simulations of the model performed with varying values of parameters or initial amounts of species. You can specify the range for the parameter or the species, and each simulation is performed with a different value of the parameter or species amount within the specified range. Scans let you see changes in the model's behavior with respect to changes in species amounts, or parameter values.

You can perform ensemble simulations using the stochastic solvers to gather data from multiple stochastic runs of the model.

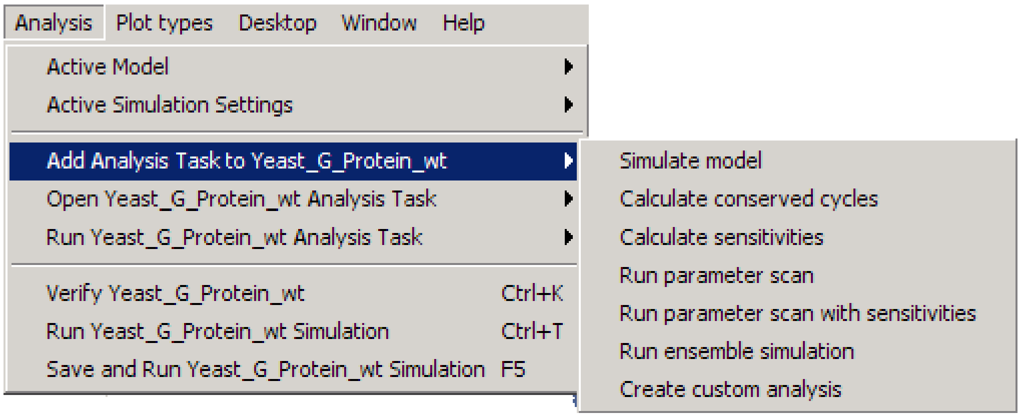
Running Ensemble Simulations at the Command Line

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

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

Running Ensemble Simulations in the Desktop

1 In the MATLAB desktop, from the **Analysis** menu select **Add Analysis Task to *`model_name`* > Run ensemble simulation**.


Analysis
Plot types
Desktop
Window
Help
Active Model
Active Simulation Settings
Add Analysis Task to Yeast_G_Protein_wt
Open Yeast_G_Protein_wt Analysis Task
Run Yeast_G_Protein_wt Analysis Task
Verify Yeast_G_Protein_wt Ctrl+K
Run Yeast_G_Protein_wt Simulation Ctrl+T
Save and Run Yeast_G_Protein_wt Simulation F5
Simulate model
Calculate conserved cycles
Calculate sensitivities
Run parameter scan
Run parameter scan with sensitivities
Run ensemble simulation
Create custom analysis

The desktop adds **Ensemble Run** in the **Project Explorer** and opens the **Ensemble Run** pane.

2 See the context-sensitive

SimBiology Desktop Help for more information on how to set up ensemble runs. To access **SimBiology Desktop Help**, select **Help > SimBiology Desktop Help**.

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.

Sundials Solvers

The Sundials solvers are part of a freely available third-party package developed at Lawrence Livermore National Laboratory. All the other ODE solvers used for simulation of SimBiology® models, such as `ode45`, and `ode15s`, are part of the MATLAB® ODE suite. 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 in the same way, as described in "How Solvers Work" on page 2-3

When you select the **SolverType** `Sundials`, the software automatically chooses one of two Sundials solvers as appropriate for your model: CVODE or IDA. 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.

If your model has events and you want to simulate with a deterministic solver, you must select `Sundials`. The other ODE solvers do not support events.

For more information on the Sundials solvers, see the web site http://www.llnl.gov/casc/sundials/description/description.html.

Analysis

You can perform sensitivity analysis on your model, look for conserved moieties, estimate parameters, and gather data with ensemble stochastic runs.

Sensitivity Analysis

In this section...

About Sensitivity Analysis

Sensitivity analysis lets you calculate the time-dependent sensitivities of all the species states with respect to species initial conditions and parameter values in the model. 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 the "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 non-analytic 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 non-analytic 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 the MathWorks Technical Support group for additional information.

Note Models containing rules and events do not support sensitivity analysis.

For more information on the calculations performed, see "Reference" on page 3-10

Performing Sensitivity Analysis Using the Command Line

You can perform sensitivity analysis at the command line by setting the following properties:

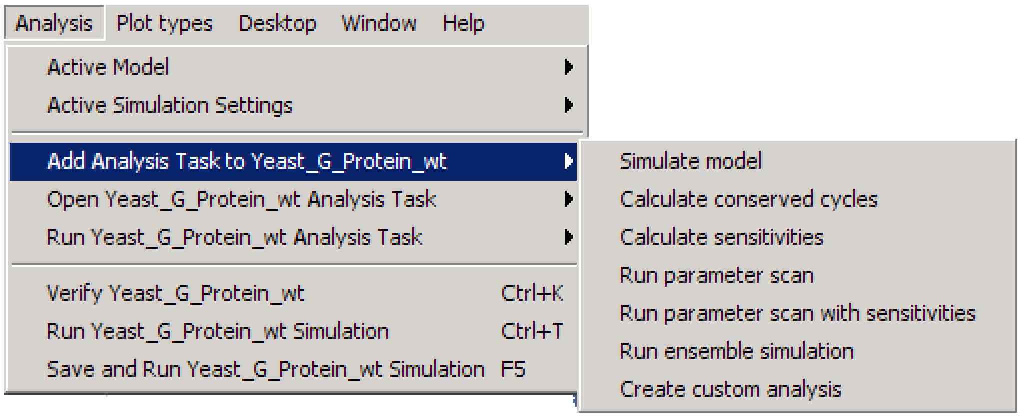
- `SensitivityAnalysis` – Lets you calculate the time-dependent sensitivities of all the species states defined by the `SpeciesOutputs` property with respect to the initial conditions of the species specified in `SpeciesInputFactors` and the values of the parameters specified in `ParameterInputFactors`.
- `SensitivityAnalysisOptions` – An object that holds the sensitivity analysis options in the configuration set object. Properties of `SensitivityAnalysisOptions` are summarized below:
  - `SpeciesOutputs` – Specify the species for which you want to compute the sensitivities. Sensitivities are calculated with respect to the initial conditions of the specified species.
  - `SpeciesInputFactors` – Specify the species with respect to which you want to compute the sensitivities of the species outputs in your model. Sensitivities are calculated with respect to the initial conditions of the specified species.
  - `ParameterInputFactors` – Specify the parameters with respect to which you want to compute the sensitivities of the species outputs in your model. Sensitivities are calculated with respect to the values of the specified parameters.

- `Normalization` – Specify the normalization for the calculated sensitivities.
  - `'None'` specifies no normalization.
  - `'Half'` specifies normalization relative to the numerator (species output) only.
  - `'Full'` specifies full dedimensionalization.

Performing Sensitivity Analysis Using the Desktop

You must have a model open in the desktop for this feature to be enabled. After opening a model, to get started with calculating sensitivities, do the following:

1 In the SimBiology desktop, from the **Analysis** menu select **Add Analysis Task to *`model_name`* > Calculate sensitivities**.


Analysis
Plot types
Desktop
Window
Help
Active Model
Active Simulation Settings
Add Analysis Task to Yeast_G_Protein_wt
Open Yeast_G_Protein_wt Analysis Task
Run Yeast_G_Protein_wt Analysis Task
Verify Yeast_G_Protein_wt Ctrl+K
Run Yeast_G_Protein_wt Simulation Ctrl+T
Save and Run Yeast_G_Protein_wt Simulation F5
Simulate model
Calculate conserved cycles
Calculate sensitivities
Run parameter scan
Run parameter scan with sensitivities
Run ensemble simulation
Create custom analysis

The desktop adds **Sensitivity Analysis** in the **Project Explorer** and opens the **Sensitivity Analysis** pane.

2 See the context-sensitive **SimBiology Desktop Help** for more information on how to set up sensitivity analysis. To access **SimBiology Desktop Help**, select **Help > SimBiology Desktop Help**.

Example of Sensitivity Analysis Using Command Line

This example uses a G protein model built shown in the "Model of the Yeast Heterotrimeric G Protein Cycle " example to illustrate SimBiology sensitivity analysis options.

You can also the following demo that shows you sensitivity analysis of this model by typing the following at the command line:

```
gprotein
```

Loading and Exploring the Model

1 The project `gprotein_norules.sbproj` contains two models, one for the wild-type strain (stored in variable `m1`), and one for the mutant strain (stored in variable `m2`). Load the G Protein model for the wild-type strain.

```
sbioloadproject gprotein_norules m1
```

2 Type the object name.

```
m1
```

MATLAB returns model information, for example:

```
SimBiology Model - Yeast_G_Protein_wt

   Model Components:
     Compartments:      1
     Events:            0
     Parameters:        8
     Reactions:         6
     Rules:             0
     Species:           7
```

3 Display reaction information.

```
m1.Reactions

SimBiology Reaction Array

   Index:    Reaction:
```

```
1          L + R <-> RL
2          R <-> null
3          RL -> null
4          Gd + freeGbg -> G
5          RL + G -> Ga + freeGbg + RL
6          Ga -> Gd
```

4 By convention the G protein example uses the object name `wtmodelObj` to refer to the model object for the wild-type strain. To use this convention, type the following:

```
wtModelObj = m1;
```

Note `m1` and `wtModelObj` are equivalent; they point to the same object. If you change one, the other is changed.

Setting the Configuration Set Object for Sensitivity Analysis

The configuration set object holds the options for simulations. In the configuration set object, you can specify the following:

- The type of solver to use for the simulation
- Stop time of the simulation
- The solver options
- States whose data is logged for you during the simulation
- Whether to perform unit conversion and dimensional analysis
- The input factors for sensitivity analysis, and the type of normalization for the sensitivity data

This example shows you how to calculate and visualize the sensitivity data for one species in the model, active G protein (`Ga`):

1 Retrieve the configuration set object from the model, and change the `StopTime` for the simulation.

```
  csObj = getconfigset(wtModelObj);
  set(csObj, 'StopTime', 600);

csObj

   Configuration Settings - default (active)
     SolverType:                    ode15s
     StopTime:                      600.000000

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

   RuntimeOptions:
     StatesToLog:                   6

   CompileOptions:
     UnitConversion:                false
     DimensionalAnalysis:           false

   SensitivityAnalysisOptions:
     InputFactors:                  0
     Outputs:                       0
```

2 Set the `SpeciesOutputs` property to calculate the sensitivities for the species `Ga` in `wtModelObj`.

```
set(csObj.SensitivityAnalysisOptions,'SpeciesOutputs', sbioselect...
      (wtModelObj, 'Type', 'species', 'Where', 'Name', '==', 'Ga'));
```

Enabling and Setting Sensitivity Analysis Options

To calculate the sensitivity of a species, first enable sensitivity analysis in the configuration set object (`csObj`) by setting the `SensitivityAnalysis` option to `true`.

```
set(csObj.SolverOptions, 'SensitivityAnalysis', true);
```

In this example, there is only one configuration set object (`csObj`) . You can, however, have multiple configuration set objects in a model, but only one configuration set can be active at a time. You could have more than one configuration set object, each of which holds a different configuration for simulation; for example, different solver options, different options for sensitivity, and so on.

Setting Sensitivity Analysis Options

The `SensitivityAnalysisOptions` property holds the input factors that you want to specify, and the type of normalization in use for sensitivity calculations. This example uses all the parameters in the G protein model as input factors for sensitivity analysis. Further, the data is fully normalized and therefore made dimensionless to facilitate the comparison.

1 Retrieve all the parameters in the model and store the vector in a variable.

```
pif = sbioselect(m1,'Type','parameter');
```

2 Set the `ParameterInputFactors` property of the `SensitivityAnalysisOptions` object.

```
set(csObj.SensitivityAnalysisOptions,'ParameterInputFactors', pif);
```

3 Set the `Normalization` property of the `SensitivityAnalysisOptions` object to perform `'Full'` normalization. Often sensitivity numbers are so wide ranging that it is hard to compare the data. Full normalization enables more meaningful comparisons.

```
set(csObj.SensitivityAnalysisOptions,'Normalization', 'Full');
```

Simulating with Sensitivity Analysis Enabled

1 Simulate the model and return the data to a SimData object (`tsObj`).

```
simDataObj = sbiosimulate(wtModelObj);
```

Extracting and Plotting Sensitivity Data

You can extract sensitivity results using `sbiogetsensmatrix`. In this example, `R` is the sensitivity of the species `Ga` with respect to eight parameters. This example shows you 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 Reshape `R` to facilitate visualization and plotting.

a Note the size of `R`.

```
size(R)

342     1     8
```

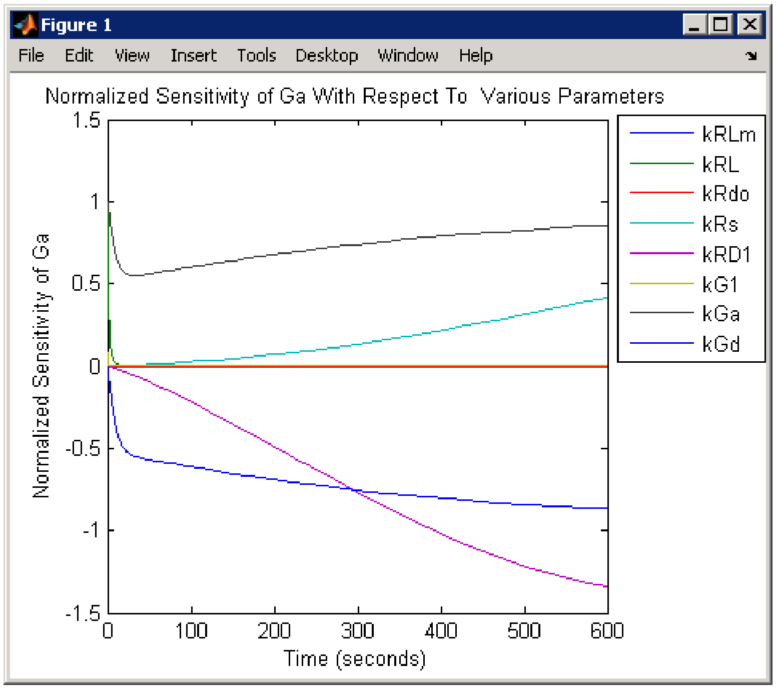
MATLAB indicates that `R` is a `342X1X8` matrix, where the time data = `size(R,1) = 342`, the `StatesToLog = size (R,2) = 1`, and the number of input factors is `size(R,3) = 8`.

b Reshape the matrix such that the data is organized into 8 columns (for the 8 parameter input factors).

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

3 After extracting the data and reshaping the matrix, you can now plot the data.

```
% Open a new figure
figure;
% Plot time (T) against the
% reshaped data R2
plot(T,R2);
title('Normalized Sensitivity of Ga With Respect To Various Parameters');
xlabel('Time (seconds)');
ylabel('Normalized Sensitivity of Ga');
% Use the ifacs variable containing the
% names of the input factors for the legend
legend(ifacs);
```



From the previous plot you can see that `Ga` is sensitive to parameters `kGd`, `kRs`, `kRD1`, and `kGa`. The example for parameter estimation uses this data to illustrate how you can estimate parameters in your model.

Reference

Ingalls, B. P. , and H. M. Sauro. "Sensitivity analysis of stoichiometric networks: an extension of metabolic control analysis to non-steady state trajectories." *Journal of Theoretical Biology* Vol. 222, 2003, pp. 23–36.

Parameter Estimation

In this section...

About Parameter Estimation

Parameter estimation lets you estimate the values of unknown parameters in a model. This is especially useful when some parameters cannot be measured experimentally .

SimBiology® Parameter Estimation

You can estimate a single parameter or all parameters in your model using the `sbioparamestim`. Parameter estimation uses the optimization functions in MATLAB®,Optimization Toolbox™, and Genetic Algorithm and Direct Search Toolbox™ to enable estimation.

Optimization Toolbox, and Genetic Algorithm and Direct Search Toolbox are not required for you to use `sbioparamestim`. If you have these products installed, you can specify optimization methods from these toolboxes as arguments for the `sbioparamestim` function. If you do not have these products installed, `sbioparamestim` uses the MATLAB function `fminsearch` by default. See `sbioparamestim` in the SimBiology® Reference for more information.

Parameter Estimation Example Using a G Protein Model

This example uses a G protein model built in the “Model of the Yeast Heterotrimeric G Protein Cycle ” tutorial to illustrate parameter estimation. The study used to build this model (Yi et al., 2003) reported the estimated value of parameter `kGd` as `0.11` for the wild-type strain.

In “Example of Sensitivity Analysis Using Command Line” on page 3-5, the analysis showed that `Ga` is sensitive to parameters `kGd`, `kRs`, `kRD1`, and `kGa`.

This example first shows you the estimation of the parameter `kGd` and how it affects the model. Next the same example shows how you can estimate parameters `kGd`, `kRs`, `kRD1`, and `kGa` to obtain a better fit to the experimental data.

You can also access a demo that shows you parameter estimation in this model by typing the following at the command line:

```
gprotein
```

Loading and Exploring the Model

1 The project `gprotein_norules.sbproj` contains two models, one for the wild-type strain (stored in variable `m1`), and one for the mutant strain (stored in variable `m2`). Load the G Protein model for the wild-type strain.

   ```
   sbioloadproject gprotein_norules m1
   ```

2 Type the object name that you see in the workspace.

   ```
   m1
   ```

   MATLAB returns model information, for example:

   ```
   SimBiology Model - Yeast_G_Protein_wt

      Model Components:
        Compartments:      1
   ```

```
          Events:           0
          Parameters:       8
          Reactions:        6
          Rules:            0
          Species:          7
```

3 Display reaction information.

```
m1.Reactions

SimBiology Reaction Array

   Index:    Reaction:
   1         L + R <-> RL
   2         R <-> null
   3         RL -> null
   4         Gd + freeGbg -> G
   5         RL + G -> Ga + freeGbg + RL
   6         Ga -> Gd
```

4 By convention the G protein example uses the object name `wtmodelObj` to refer to the model object for the wild-type strain. To use this convention, type the following:

```
wtModelObj = m1;
```

Note `m1` and `wtModelObj` are equivalent; they point to the same object. If you change one, the other is changed.

Importing Target Experimental Data

For this example, you will store the experimental data in a variable in the MATLAB workspace. If you need to import data into MATLAB see "Introduction", in the MATLAB documentation for more information.

The study used for this example (Yi et al., 2003) reports the experimental data in a plot as the fraction of active G (`Ga`). Calculate and store the amount of `Ga` in a variable.

1 The initial amount of total G protein is 1000 molecules. The values for the fraction of active G are stored in Ga_frac. Ga_target contains the values of Ga over time.

```
Gt = 10000;
Ga_frac = [0 0.35 0.4 0.36 0.39 0.33 0.24 0.17 0.2]';
Ga_target = Ga_frac * Gt;
```

2 The time data for the experimental results is stored in t_span.

```
t_span  = [0 10 30 60 110 210 300 450 600]';
```

Simulating the G Protein Model

Display the configuration set that is loaded with the G protein cycle model and simulate the model.

1 Display the configuration set options in the model.

```
wtModelObj.configset

Configuration Settings - default (active)
     SolverType:                   ode15s
     StopTime:                     600.000000

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

   RuntimeOptions:
     StatesToLog:                  6

   CompileOptions:
     UnitConversion:               false
     DimensionalAnalysis:          false

   SensitivityAnalysisOptions:
     InputFactors:                 0
     Outputs:                      0
```

The model configuration set has StopTime set to 600 seconds.

2 Simulate the model and return the results to a time series object.

```
simDataObj = sbiosimulate(wtModelObj);
```

3 Retrieve the time and state data.

```
[t_orig, Ga_orig] = selectbyname(simDataObj,'Ga');
```

Calculating R-Square for the G Protein Model

R-square measures how successful the fit is in explaining the variation of the data. In other words, R-square is the square of the correlation between the response values and the predicted response values.

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

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

2 Interpolate the data to get time points that match the time points in the experimental data with the `cubic` interpolation method.

```
Ga_resampled = interp1(t_orig, Ga_orig, t_span, 'cubic');
```

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

```
sse = norm(Ga_target - Ga_resampled)^2;
```

4 Calculate R-square for the simulation data before parameter estimation.

```
  rsquare_orig = 1-sse/sst


rsquare_orig =

    0.8967
```

For more information about R-square, see “Goodness-of-Fit Statistics” in the Curve Fitting Toolbox documentation. For more information about the functions used here, see `interp1`, `norm`.

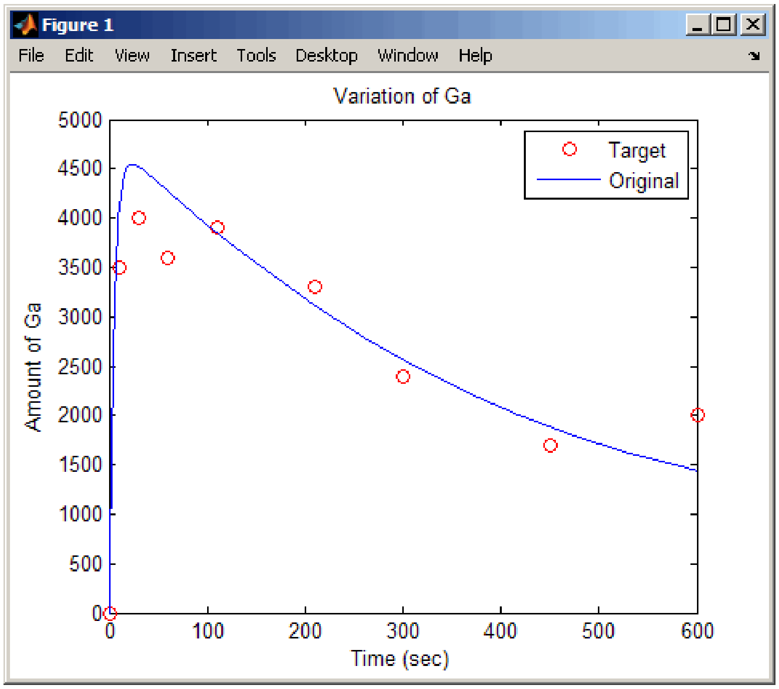
Plotting the Experimental Results and Simulation Data

1 Plot the experimental data for Ga.

```
plot(t_span, Ga_target, 'ro');
title('Variation of Ga');
xlabel('Time (sec)');
ylabel('Amount of Ga');
legend('Target');
```

2 Plot the simulation data in the same plot.

```
hold on;
plot(t_orig, Ga_orig);
legend('Target', 'Original');
```



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

Estimating a Parameter (kGd) 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 `kGd` and calculates the R-square value with the new estimate.

1 Set up the parameter to estimate and the state to match.

```
param_to_tune = sbioselect(wtModelObj,'Type',...
   'parameter','Name','kGd');
Ga = sbioselect(m1,'Type','species','Name','Ga');
```

2 Switch on information about iterations in the display to see how optimization is progressing.

```
opt1 = optimset('Display','iter');
```

3 Use the current values of parameters in the model as the starting values for optimization. Use the default optimization method (`'lsqcurvefit'` if you have Optimization Toolbox installed.

```
[k_new1, result1] = sbioparamestim(wtModelObj, t_span, ...
   Ga_target, Ga, param_to_tune, {}, {'lsqcurvefit',opt1});
```

```
Iteration  Func-count     f(x)         step          optimality   CG-iterations
     0          2     1.4264e+006                    2.84e+007
     1          4    1.11306e+006     0.0105776      8.23e+006            1
     2          6    1.11306e+006     0.0045504      8.23e+006            1
     3          8    1.11306e+006     0.0011376      8.23e+006            0
     4         10    1.11183e+006     0.0002844      6.93e+005            0
     5         12    1.11183e+006     0.0002844      6.93e+005            1
     6         14    1.11183e+006   7.10999e-005     6.93e+005            0
     7         16    1.11183e+006    1.7775e-005     6.93e+005            0
     8         18    1.11183e+006   4.44375e-006     6.93e+005            0
     9         20    1.11183e+006   1.11094e-006     6.93e+005            0
    10         22    1.11183e+006   2.77734e-007     6.93e+005            0
Optimization terminated: norm of the current step is less
 than OPTIONS.TolX.
```

Alternatively, if you do not have Optimization Toolbox, the following command lets you use `'fminsearch'` in MATLAB.

```
[k_new1, result1] = sbioparamestim(wtModelObj, ...
   t_span, Ga_target, Ga, param_to_tune, {}, {'fminsearch',opt1});

 Iteration   Func-count     min f(x)         Procedure
     0            1         1194.32
     1            2         1091.86         initial simplex
     2            4          1054.2         reflect
     3            6          1054.2         contract outside
     4            8          1054.2         contract inside
     5           11          1054.2         shrink
     6           13          1054.2         contract outside
     7           15         1053.95         contract outside
     8           17         1053.95         contract inside
     9           19         1053.86         reflect
    10           21         1053.86         contract inside
    11           23         1053.86         contract inside
    12           25         1053.84         reflect
    13           27         1053.84         contract inside
    14           29         1053.82         reflect
    15           31         1053.82         contract inside
    16           33         1053.34         reflect
    17           36         1053.34         shrink
    18           38         1053.32         reflect
    19           40         1053.32         contract inside
    20           42         1053.32         contract inside
    21           44         1053.32         contract inside
    22           46         1053.32         contract outside
    23           48         1053.32         contract inside
    24           51         1053.32         shrink
    25           53         1053.32         contract outside

Optimization terminated:
 the current x satisfies the termination criteria using OPTIONS.TolX of 1.000000e-004
 and F(X) satisfies the convergence criteria using OPTIONS.TolFun of 1.000000e-004
```

4 Calculate the R-Square value with the new estimate obtained with `'lsqcurvefit'`. The `fval` field in `result1` contains the value of SSE.

```
sse = result1.fval;
rsquare1 = 1-sse/sst
```

```
rsquare1 =

    0.9195
```

Simulating and Plotting Results Using the Estimated Parameter

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

1 Before changing the value, save the old value in case you need it later.

```
kGd0 = get(param_to_tune, 'Value');
set(param_to_tune, 'Value', k_new1);
```

2 Set the parameter to the new value. The `param_to_tune` variable was previously defined as the parameter `kGd` in this exercise.

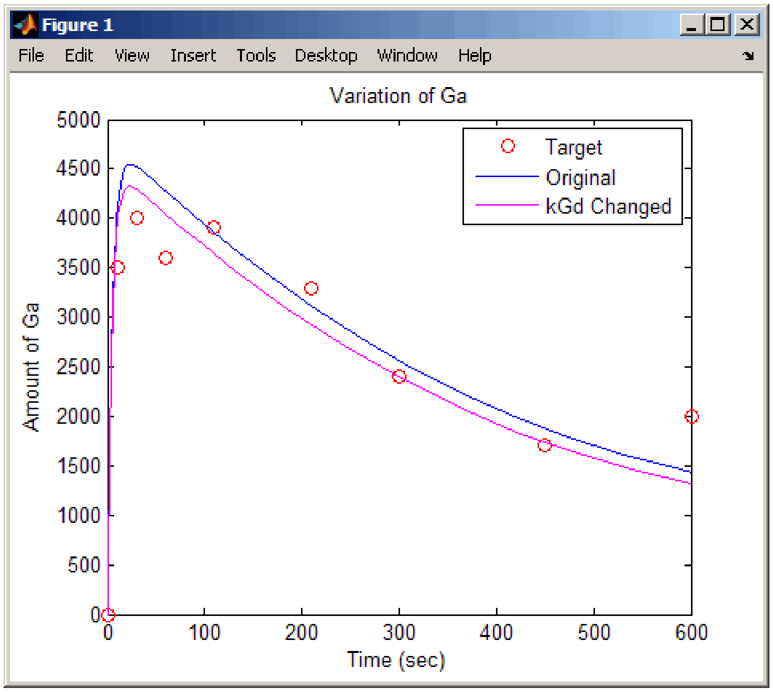
```
set(param_to_tune, 'Value', k_new1);
```

3 Simulate the model and get the results.

```
simDataObj1 = sbiosimulate(m1);
[t1, Ga1] = selectbyname(simDataObj1,'Ga');
```

4 Plot the data and compare. If you have left the previous figure open, since `hold` is on, this plot will appear in that figure to facilitate the comparison.

```
plot(t1, Ga1, 'm-');
legend('Target', 'Original', 'kGd Changed');
```



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

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

Estimating Other Parameters in the G Protein Model

The example illustrating sensitivity analysis ("Example of Sensitivity Analysis Using Command Line" on page 3-5) showed that `Ga` is sensitive to parameters `kGd`, `kRs`, `kRD1`, and `kGa`. Based on this data, this tutorial shows you how to estimate these parameters. The sensitivity data is presented in "Extracting and Plotting Sensitivity Data" on page 3-8.

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 Reset the value of the parameter `kGd` to the original value.

```
set(param_to_tune, 'Value', kGd0);
```

2 Find the indices for each of the parameters to estimate.

```
params = sbioselect(m1, 'Type', 'parameter')

  SimBiology Parameter Array

   Index:    Name:    Value:       ValueUnits:
   1         kRLm     0.01
   2         kRL      3.32e-018
   3         kRdo     0.0004
   4         kRs      4
   5         kRD1     0.004
   6         kG1      1
   7         kGa      1e-005
   8         kGd      0.11
```

Note that the required parameter indices are `4`, `5`, `7`, and `8`.

3 Set the parameter array for estimation.

```
param_to_tune = params([4 5 7 8]);
```

4 Switch on information about iterations in the display to see how optimization is progressing.

```
opt2 = optimset('Display','iter');
```

Note `fminsearch` performs many more iterations and therefore takes more time in the next step.

5 Estimate the parameters. Use the current values of parameters in the model as the starting values for optimization. Use the default optimization method (`'lsqcurvefit'`) if you have Optimization Toolbox installed. Note that the `param_to_tune` argument now contains the array of parameters to be estimated.

```
[k_new2, result2] = sbioparamestim(wtModelObj, t_span,...
    Ga_target, Ga, param_to_tune, {}, {'lsqcurvefit',opt2});
```

```
                                              Norm of      First-order
 Iteration  Func-count     f(x)          step          optimality   CG-iterations
     0          5     1.4264e+006                     2.84e+007
     1         10          611055        3.63737      2.58e+006            1
     2         15          576458          1.188      6.76e+005            1
     3         20          576458      0.0540078      6.76e+005            1
     4         25          576458      0.0135019      6.76e+005            0
     5         30          576458     0.00337549      6.76e+005            0
     6         35          576458    0.000843872      6.76e+005            0
     7         40          576458    0.000210968      6.76e+005            0
     8         45          576458    5.2742e-005      6.76e+005            0
     9         50          576458   1.31855e-005      6.76e+005            0
    10         55          576458   3.29637e-006      6.76e+005            0
    11         60          576458   8.24093e-007      6.76e+005            0
Optimization terminated: norm of the current step is less
 than OPTIONS.TolX.
```

Alternatively, if you do not have Optimization Toolbox the following command lets you use `'fminsearch'` in MATLAB:

```
[k_new2, result2] = sbioparamestim(wtModelObj, t_span, ...
   Ga_target, Ga, param_to_tune, {}, {'fminsearch',opt2});
```

6 Compare original parameter values and the estimated parameter values obtained with `'lsqcurvefit'`.

```
% Original parameter values.
param_to_tune

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.
```

```
k_new2 =

    8.8253
    0.0041
    0.0000
    0.1229
```

7 Calculate the R-Square value with the new estimates obtained with `'lsqcurvefit'`.

```
sse = result2.fval;
rsquare2 = 1-sse/sst


rsquare2 =

    0.9583
```

Moiety Conservation

In this section...

Introduction to Moiety Conservation

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

Consider the 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 and real-world example of a conserved moiety is adenine in its various forms ATP, ADP, AMP, etc. Finding and analyzing conserved moieties may yield insights into the structure and function of a biological network. In addition, for the quantitative modeler, conserved moieties represent dependencies which can be removed to reduce a system's dimensionality, or number of dynamic variables. In the simple network above, for example, in principle, it is only necessary to calculate, the time courses for `A` and `B`; once this is done, `C` is fixed by the conservation relation.

Algorithms for Conserved Cycle Calculations

The `sbioconsmoiety` function lets you calculate a complete set of linear conservation relations for the species in a SimBiology® model object.

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

- When you specify `'qr'`, `sbioconsmoiety` uses an algorithm based on `QR` factorization. From a numerical standpoint, this is the most efficient and reliable approach.
- When you specify `'rreduce'`, `sbioconsmoiety` uses an algorithm based on row reduction, which yields better numbers for smaller models. This is the default.
- When you specify `'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 may 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 the "Introduction to Moiety Conservation" on page 3-24 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`.

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

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

where `R` in the independent submatrix N_R denotes 'reduced', the `(n-k)-by-k` link matrix `L0` is defined so that $N_D = L0 * N_R$. 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.

Examples of Determining Conserved Moieties

G Protein Example (p. 3-26)	Example using the G protein cycle model
Mitotic Oscillator Example (p. 3-30)	Example using the Mitotic Oscillator model

G Protein Example

1 Load the project `gprotein_norules.sbproj`

```
sbioloadproject gprotein_norules
```

MATLAB® populates the workspace with the model objects from the project and lists the objects as `m1` and `m2`.

The project contains two models, one for the wild-type strain (stored in variable `m1`), and one for the mutant strain (stored in variable `m2`). Load the project.

2 Type an object name that you see in the workspace.

```
m1
```

MATLAB returns model information, for example:

```
SimBiology Model - Yeast_G_Protein_wt
```

```
     Model Components:
       Compartments:      1
       Events:            0
       Parameters:        8
       Reactions:         6
       Rules:             0
       Species:           7
```

3 Display the species information.

```
m1.Compartments.Species

SimBiology Species Array

Index:  Compartment:  Name:   InitialAmount: InitialAmountUnits:
 1         unnamed     L       6.022e+017
 2         unnamed     R       10000
 3         unnamed     G       7000
 4         unnamed     Gd      3000
 5         unnamed     freeGbg 3000
 6         unnamed     Ga      0
 7         unnamed     RL      0
```

4 Display reaction information.

```
m1.Reactions

SimBiology Reaction Array

   Index:    Reaction:
   1         L + R <-> RL
   2         R <-> null
   3         RL -> null
   4         Gd + freeGbg -> G
   5         RL + G -> Ga + freeGbg + RL
   6         Ga -> Gd
```

5 By convention, the G protein example uses the object name `wtmodelObj` to refer to the model object for the wild-type strain. To use this convention, type the following:

```
wtModelObj = m1;
```

Note `m1` and `wtModelObj` are equivalent; they point to the same object. If you change one, the other is changed.

6 Use the simplest form of the `sbioconsmoiety` function and display the results.

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

g =

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


sp =

    'L'
    'R'
    'G'
    'Gd'
    'freeGbg'
    'Ga'
    'RL'
```

7 Use the semipositive algorithm to explore conservation relations in the model. The `'p'` specifies that the output should be in the form of a printed cell array.

```
 sbioconsmoiety(wtModelObj,'semipos','p')

ans =

    'G + freeGbg'
    'G + Gd + Ga'
```

As expected, the function predicts the conservation relationship for the different forms of the G protein complex.

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

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

9 Show the list of independent species.

```
SI

SI =

    'R'
    'G'
    'RL'
    'Gd'
    'L'
```

10 Show the list of dependent species.

```
SD

SD =

    'freeGbg'
    'Ga'
```

11 Show the link matrix relating `SD` and `SI`.

```
L0


L0 =
(1,2)       -1
(2,2)       -1
(2,4)       -1
```

12 Show the independent stoichiometry matrix, N_R.

```
NR


NR =
 (1,1)        -1
 (3,1)         1
 (5,1)        -1
 (1,2)        -1
 (3,3)        -1
 (2,4)         1
 (4,4)        -1
 (2,5)        -1
 (4,6)         1
```

13 Show the dependent stoichiometry matrix, N_D.

```
ND

ND =

(1,4)        -1
(1,5)         1
(2,5)         1
(2,6)        -1
```

Mitotic Oscillator Example

1 Load the Goldbeter Mitotic Oscillator model.

```
sbioloadproject Goldbeter_Mitotic_Oscillator_with_reactions
```

MATLAB populates the workspace with the model object from the project and lists the object as `m1`.

2 Explore the model.

```
m1
```

MATLAB returns model information, for example:

```
SimBiology Model - Goldbeter Mitotic Oscillator with reactions

   Model Components:
     Compartments:      1
     Events:            0
     Parameters:        13
     Reactions:         7
     Rules:             4
     Species:           10
```

3 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
```

4 Display 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
```

5 Use the simplest form of the `sbioconsmoiety` function and display the results.

```
[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'
```

6 Use the semipositive algorithm to explore conservation relations in the model.

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

cons_rel =

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

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

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

8 Show the list of independent species.

```
SI

SI =

    'C'
    'M'
```

```
     'X'
```

9 Show the list of dependent species.

```
SD

SD =

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

10 Show the link matrix relating `SD` and `SI`.

```
L0

L0 =

   (1,2)       -1
   (2,3)       -1
```

11 Show the independent stoichiometry matrix, N_R.

```
NR

 NR =

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

12 Show the dependent stoichiometry matrix, N_D.

```
ND

ND =

   (1,4)       -1
   (1,5)        1
   (2,6)       -1
   (2,7)        1
```

Importing and Exporting Model Component Data

In this section...

Importing Model Component Data

You can import lists of species, reactions, parameters, and rules to and from the SimBiology® desktop.

You can import the data from an Excel spreadsheet, or from a comma-separated or tab-separated text file using the **Load Data from File** menu item. The Excel option is only supported on the Windows platform.

1 From the **File** menu, select point to **Load Data from File** and select the component type, for example, **Species**. The Load Species from File dialog box opens.

2 From the **File Type** list, select `Excel`, `comma-separated text file`, or `tab-separated text file`.

3 In the **File Name** box, enter a file path and name or browse to select a file name.

4 If the first row in the file contains header information, select the **First row contains header information** check box.

5 If your model and the file have some identical names, clear the **Overwrite current property values** check box to preserve the values in the model.

6 Select the properties to import. There are required properties based on the component type. For example, the **Name** of the species is a required property. Specify column order using the ⬆ and ⬇ arrows. The first property selected corresponds to the first column in the Excel spreadsheet or text file.

7 Click **OK**. The data from your file is entered into the model.

Note

- If you have preexisting species in the model, the software appends nonidentical species names.
- If you want a species to remain constant throughout a simulation, you can specify this using the Boolean operator TRUE in the Excel or text file. While importing the data, the software will select the **ConstantAmount** check box for that species. The default is `unchecked`.

Exporting Model Component Data

You can export lists of species, reactions, parameters, and rules to and from the SimBiology desktop.

You can export data to an Excel spreadsheet, or to a comma-separated or tab-separated text file using the **Export Data to File** menu item. The Excel option is only supported on the Windows platform.

1. From the **File** menu, point to **Export Data to File** and select the component type, for example, **Species**. The Export Species to File dialog box opens.
2. From the **File Type** list, select `Excel`, `comma-separated text file`, or `tab-separated text file`.
3. In the **File Name** box, enter a file path and name or browse to select a file name.
4. If the first row in the generated file should contain the property names, select the **Write property names to first row in file** check box.
5. Select the properties to export. There are required properties based on the component type. For example, the **Name** of the species is a required property. Specify column order using the ⭱ and ⭳ arrows.

The first property selected corresponds to the first column in the Excel spreadsheet or text file.

6 Click **OK**. The data from your model is entered into the file.

Performing Custom Analysis in the Desktop

In this section…

About Custom Analysis

You can perform custom analysis by setting up **Custom Tasks**, which are user-defined elements that let you script tasks in combination with each other and with other data processing functions. You can use functions from any of the products in your license. Custom tasks let you work within the context of the SimBiology® desktop and use features like plotting, and exporting data within the desktop, while being able to specify custom processing and analysis of the model data.

Open the Example Project

This example shows you how to set up parameter estimation in the desktop for the G protein model shown in the following section:

"Model of the Yeast Heterotrimeric G Protein Cycle ".

1 To open the desktop, at the MATLAB® command line, type

```
sbiodesktop
```

   The **SimBiology Desktop** opens. Use the **Project Explorer** in the left pane to navigate.

2 From the **File** menu, select **Open Project**. The Open SimBiology Project dialog box opens.

3 Browse to the directory in which the product is installed and select the file `gprotein.sbproj` and then click **Open**. The project opens in the SimBiology desktop.

Setting Up a Custom Task

1 From the **Analysis** menu select **Add Analysis Task to Heterotrimeric_G_Protein_wt > Create custom analysis**. The SimBiology desktop adds the custom task to the **Project Explorer**, and opens the task pane.

2 In the **Custom Settings** tab you can define your own script that you can run in the desktop.

   The next section shows an example of how to add the script for custom parameter analysis.

Parameter Estimation Using Custom Task

1 In the **Custom Settings** tab, replace the default function declaration statement with the following:

```
function data = custom(modelobj)
%Parameter Estimation of a G Protein Model

%Target Data

%Preprocess the experimental data

% The estimated amount of total G protein (Gt) is 10000
Gt = 10000;
t_span  = [0 10 30 60 110 210 300 450 600]';
Ga_frac = [0 0.35 0.4 0.36 0.39 0.33 0.24 0.17 0.2]';
Ga_target = Ga_frac * Gt;

fh = figure;
plot(t_span, Ga_target, 'ro');
grid on;
title('Variation of Ga');
xlabel('Time (sec)');
ylabel('Amount of Ga');
lgnd0 = 'Target';
legend(lgnd0);
```

```
% Simulate the model as is to see how Ga in the model varies with
% time. Also calculate the original R-square value
simdata_orig = sbiosimulate(modelobj);
[t_orig, Ga_orig] = selectbyname(simdata_orig,'Ga');
sst = norm(Ga_target - mean(Ga_target))^2;
Ga_resampled = interp1(t_orig, Ga_orig, t_span, 'cubic');
sse = norm(Ga_target - Ga_resampled)^2;
rsquare_orig = 1-sse/sst;

% Plot the original species data
figure(fh);
hold on;
plot(t_orig, Ga_orig);
str_orig = sprintf('R^2 = %6.4f', rsquare_orig);
grid on;
lgnd0 = 'Target';
lgnd_orig = ['Wild-Type model, ', str_orig];
legend(lgnd0, lgnd_orig);

% Parameter to Estimate
param_to_tune = sbioselect(modelobj,'Type','parameter','Name','kGd');

% Match experimental (target) species data to model species data
Ga = sbioselect(modelobj,'Type','species','Name','Ga');

% Estimate the parameter
[k_new1, result1] = sbioparamestim(modelobj, t_span, Ga_target, Ga, par

% Simulation Results of Using the Estimated Parameter Value
%
% Use the estimated value of kGd and see how it affects simulation
% results. Before changing the value, save it to reset it later. We
% will also compute the new R-square value.
%
kGd0 = get(param_to_tune, 'Value');
set(param_to_tune, 'Value', k_new1);
simdata1 = sbiosimulate(modelobj);
[t1, Ga1] = selectbyname(simdata1,'Ga');
sse = result1.fval;
rsquare1 = 1-sse/sst;
```

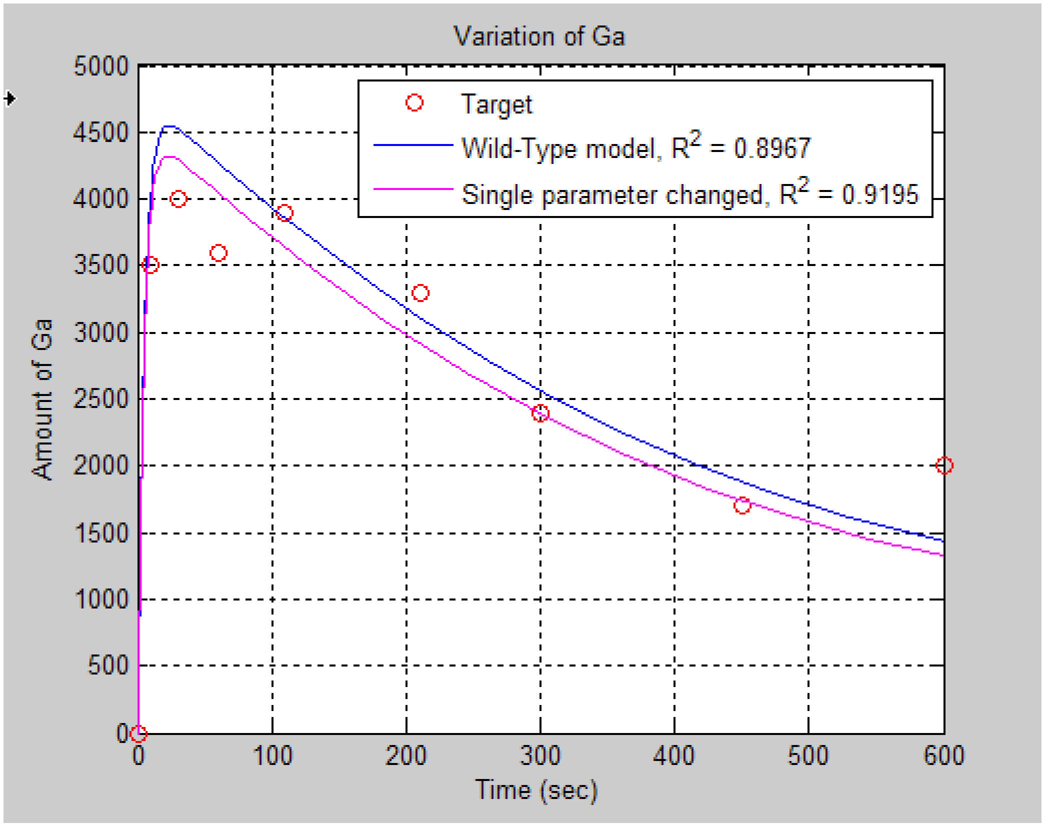
```
% Plot the data and compare
figure(fh);
plot(t1, Ga1, 'm-');
str1 = sprintf('R^2 = %6.4f', rsquare1);
lgnd_kGd = ['Single parameter changed, ', str1];
legend(lgnd0, lgnd_orig, lgnd_kGd);

%Reset the value of the parameter
set(param_to_tune, 'Value', kGd0);

% Reference
%
% Tau-Mu Yi, Hiroaki Kitano, and Melvin I. Simon. PNAS (2003) vol.
% 100, 10764-10769.
```

2 In the **Plot Results** tab, add plots to visualize the results, alternatively you can add plot code to the task script.

3 Click Run to run the task. The plot should look similar to this:


Variation of Ga
Target
Wild-Type model, R^2 = 0.8967
Single parameter changed, R^2 = 0.9195
Amount of Ga
Time (sec)
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
0
100
200
300
400
500
600

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