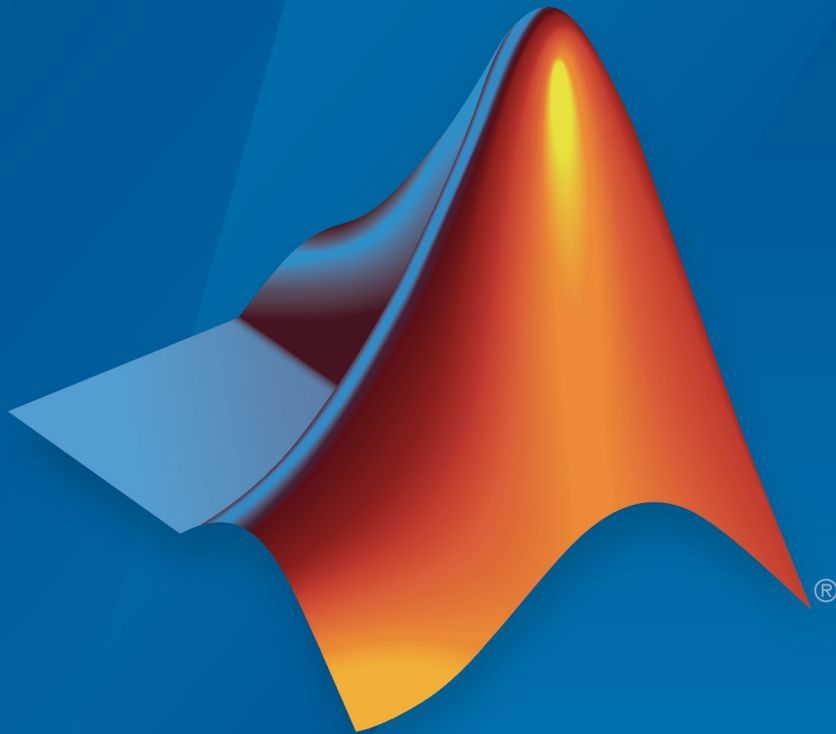


SimBiology[®]

Getting Started Guide



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R2019b

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SimBiology[®] *Getting Started Guide*

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Introduction

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

- “SimBiology Product Description” on page 1-2
- “Compiler Setup” on page 1-3
- “SBML Support” on page 1-4

SimBiology Product Description

Model, simulate, and analyze biological systems

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

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

Key Features

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

Compiler Setup

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

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

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

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

See Also

More About

- [“Simulation”](#)
- [“Accelerating Model Simulations and Analyses”](#)

SBML Support

In this section...
“What Is SBML?” on page 1-4
“Importing from SBML Files” on page 1-4
“Exporting a SimBiology Model to SBML Format” on page 1-5

What Is SBML?

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

Importing from SBML Files

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

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

- Piecewise kinetics — Models with piecewise kinetics are loaded, but the definitions for piecewise kinetics are ignored.
- MATLAB incompatible variable names in `UnitDefinition` — Models that have variable names incompatible with MATLAB in `UnitDefinition` are not loaded and an error message is displayed.
- The `hasOnlySubstanceUnits` attribute does not have a corresponding property in the SimBiology species object. Instead, if the species has no units, SimBiology uses the `DefaultSpeciesDimension` property to determine whether to interpret species names in expressions as substance amounts or concentrations. When you set `DefaultSpeciesDimension` to `substance` and do not specify units, SimBiology interprets species names as substance amounts and does not scale by any compartment capacity (volume). When the property is set to `concentration`, species names are interpreted as concentrations and are scaled by the appropriate compartment capacity. SimBiology does not let you set the initial value of a species as concentration or substance amount independently of how you refer to it in expressions. To provide better compatibility with SBML models having this attribute, SimBiology adds an initial assignment rule or appropriate units during the import process. For details, see the “Compatibility” section of `sbmlimport`.

- Models containing other models as submodels are loaded but submodels are ignored.
- The `fast` attribute of any reaction object is ignored.
- The `delay`, `priority`, `initialValue`, and `persistent` attributes of event objects are ignored.
- XOR, OR, and AND logical operators having three or more arguments are not supported. They are supported for binary operations only.

Read-Only Support for Function Definitions

You can import SBML models with function definitions. SimBiology replaces the function definitions with the corresponding mathematical expressions.

Support for Reaction IDs

You can also load SBML models that use reaction IDs to reference reaction rates in mathematical expressions. SimBiology replaces the references with the corresponding reaction rates.

Exporting a SimBiology Model to SBML Format

SimBiology Features Supported by SBML

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

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

Example

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

SimBiology Features Not Supported by SBML

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

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

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

Getting Started Using the SimBiology Apps

SimBiology Apps Overview

SimBiology provides a set of integrated apps that are designed to facilitate building, simulating, and analyzing models of dynamic systems such as pharmacokinetic/pharmacodynamic (PK/PD) and mechanistic systems biology models.

- The **SimBiology** app lets you build dynamic models interactively using various modeling elements. For instance, you can model a variety of biological systems such as signaling pathways, metabolic networks, and PK/PD models. It also lets you model biological variability and different dosing regimens to investigate various experimental conditions and dosing strategies.
- The **SimBiology Model Analyzer** app lets you perform analyses on models of dynamic systems. You can simulate the dynamic behavior of a model using various solvers and estimate model parameters. To investigate system dynamics and guide experimentation, you can perform sensitivity analysis and parameter sweeps.

For details, visit “SimBiology Apps”.

Getting Started Using the Command Line

- “Getting Started Using the SimBiology Command Line” on page 3-2
- “Construct a Simple Model” on page 3-3
- “Model a Gene-Regulation Pathway” on page 3-5

Getting Started Using the SimBiology Command Line

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

See the following tutorials to get started.

Modeling and Simulation

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

Estimation

- “Fit a One-Compartment Model to an Individual's PK Profile”
- “Fit a Two-Compartment Model to PK Profiles of Multiple Individuals”
- “Estimate Category-Specific PK Parameters for Multiple Individuals”
- “Estimate a Parameter from the Yeast G Protein Model”
- “PK/PD Modeling and Simulation to Guide Dosing Strategy for Antibiotics”
- “Modeling the Population Pharmacokinetics of Phenobarbital in Neonates”

Deployment

- “Deploy a SimBiology Model”

Construct a Simple Model

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

Create a SimBiology model named `simpleModel`.

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

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

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

SimBiology automatically add species A and B to the model.

```
m1.species
```

```
ans =
  SimBiology Species Array

  Index:   Compartment:   Name:   Value:   Units:
  1        unnamed      A       0
  2        unnamed      B       0
```

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

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

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

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

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

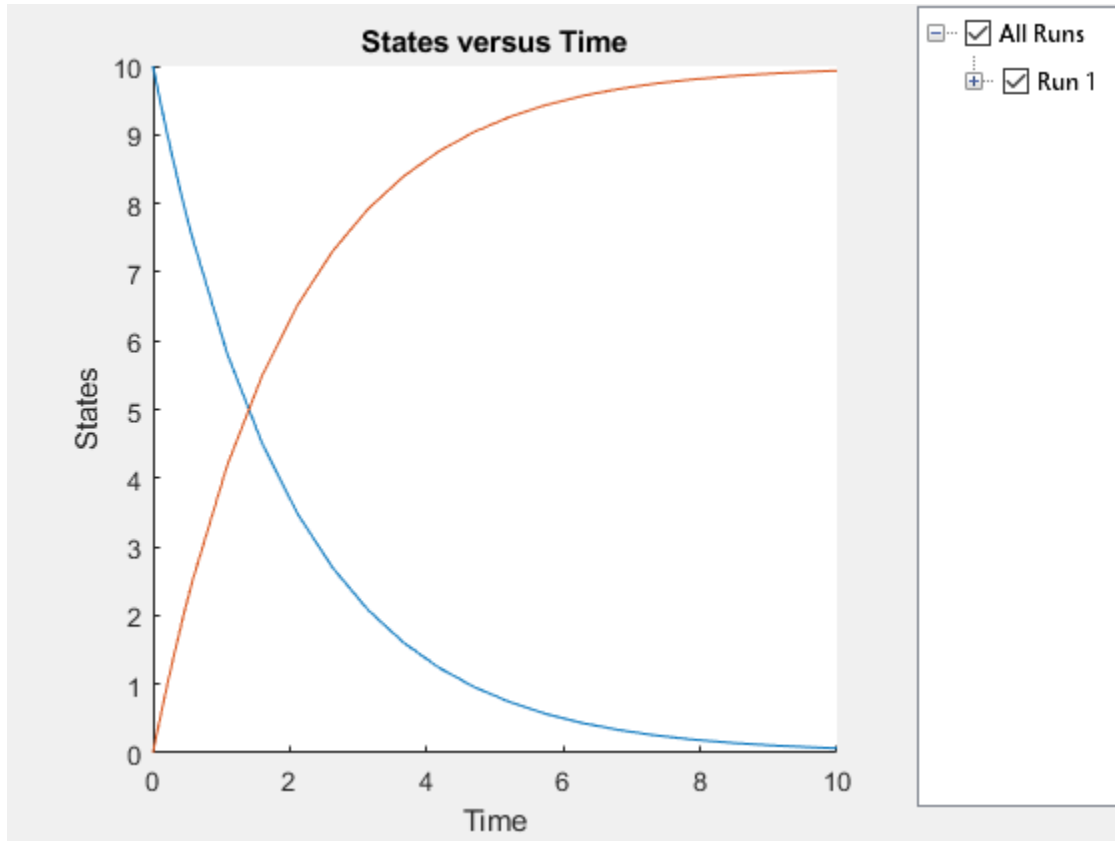
```
p1 = addparameter(kineticLaw, 'k', 0.5);
kineticLaw.ParameterVariableNames = 'k';
```

Simulate the model.

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

Plot the simulation results.

```
sbioplot(sd);
```



Model a Gene-Regulation Pathway

In this section...

“About The Gene Regulation Model” on page 3-5

“Create a SimBiology Model” on page 3-9

“Add the Reaction for Transcription” on page 3-10

“Add the Reaction for Translation” on page 3-11

“Add the Reaction for Gene Regulation” on page 3-12

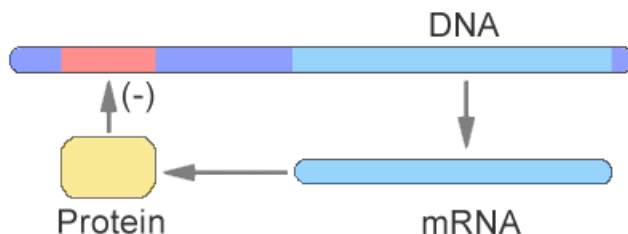
“Add the Reactions for mRNA and Protein Degradation” on page 3-12

“Simulate the Model” on page 3-13

About The Gene Regulation Model

Model Diagram

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

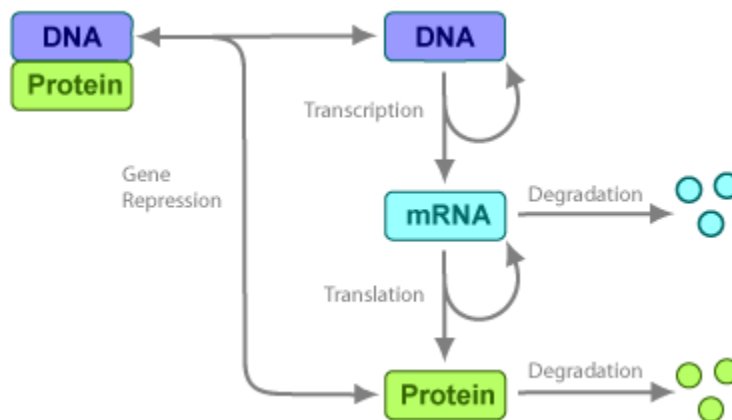


Another way of looking at a systems biology model is to list the reactions in a model with the processes they represent.



```
DNA + protein -> DNAProteinComplex    (binding)
DNAProteinComplex -> DNA + protein    (unbinding)
mRNA -> null                          (degradation)
protein -> null                        (degradation)
```

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



Model Reactions

Reaction equations define a systems biology model at the level of detail needed for a software program to simulate the dynamic behavior of the model. The following reactions for transcription, translation, binding, and degradation describe a simple gene-regulating mechanism.

Transcription

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



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

Reaction DNA \rightarrow DNA + mRNA
 Reaction rate $v = k_1 * \text{DNA molecule/second}$
 Species DNA = 50 molecule
 mRNA = 0 molecule
 Parameters $k_1 = 0.20 \text{ second}^{-1}$

Translation

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



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

Reaction mRNA \rightarrow mRNA + protein
 Reaction rate $v = k_2 * \text{mRNA molecule/second}$
 Species mRNA = 0 molecule
 protein = 0 molecule
 Parameters $k_2 = 20 \text{ second}^{-1}$

Gene Repression

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



Forward Reaction (Binding)

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

Reverse Reaction (Unbinding)

Reaction DNAProteinComplex -> DNA + protein
Reaction rate $v = k3r * DNA_protein$ molecule/second
Species DNAProteinComplex = 0 molecule
Parameters $k3r = 1$ second⁻¹

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

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

Degradation

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



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

Reaction mRNA -> null
 Reaction rate $v = k4 * \text{mRNA molecule/second}$
 Species mRNA = 0 molecule
 Parameters $k4 = 1.5 \text{ second}^{-1}$

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



Reaction protein -> null
 Reaction rate $v = k5 * \text{protein molecule/second}$
 Species protein = 0 molecule
 Parameters $k5 = 1 \text{ second}^{-1}$

Create a SimBiology Model

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

- 1 Create a SimBiology model with the name cell.

```

clear all
Mobj = sbiomodel('cell')

Mobj =
  SimBiology Model - cell

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

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

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

Add the Reaction for Transcription

- 1 Add the reaction $\text{DNA} \rightarrow \text{DNA} + \text{mRNA}$ to the model. SimBiology automatically adds the species DNA and mRNA to the model with the default initial amount of 0.

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

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

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

nucleus and cytoplasm are the names of the compartments.

- 2 Display the added species of the model.

```
Mobj.Species
```

```
ans =
```

```
SimBiology Species Array
```

Index:	Compartment:	Name:	Value:	Units:
1	comp	DNA	0	
2	comp	mRNA	0	

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

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

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

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

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

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


```
Kobj1.ParameterVariables
ans = 1x1 cell array
    {'Forward Rate Parameter'}
```

```
Kobj1.SpeciesVariables
ans = 1x1 cell array
    {'MassAction Species'}
```

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

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

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

```
Robj1.ReactionRate
ans =
    'k1*DNA'
```

Add the Reaction for Translation

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

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

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

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

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

- 3 The reaction rate is now defined as follows.

```
Robj2.ReactionRate
```

```
ans =  
'k2*mRNA'
```

Add the Reaction for Gene Regulation

Transcription of DNA to mRNA is regulated by the binding of the protein product from translation to the DNA. As more protein is produced, the DNA is bound with the protein more often and less time is available for transcription with the unbound DNA. For more details, see “Gene Repression” on page 3-7.

- 1 Enter the reversible reaction for the binding and unbinding of DNA and protein. Add a parameter k_3 as the forward rate constant, and k_{3r} as the reverse rate constant.

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

- 2 Display the reaction rate.

```
Robj3.ReactionRate
```

```
ans =  
'k3*DNA*protein - k3r*DNAProteinComplex'
```

Add the Reactions for mRNA and Protein Degradation

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

- 1 Enter the reaction for mRNA degradation to nucleotides. Add a parameter k_4 as the forward rate constant.

```
Robj4 = addreaction(Mobj, 'mRNA -> null');  
Kobj4 = addkineticlaw(Robj4, 'MassAction');
```

```
Pobj4 = addparameter(Kobj4, 'k4', 'Value', 1.5, 'ValueUnits', '1/second');
Kobj4.ParameterVariableNames = 'k4';
```

- 2 Display the reaction rate of mRNA degradation.

```
Robj4.ReactionRate
```

```
ans =
'k4*mRNA'
```

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

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

- 4 Display the reaction rate of protein degradation.

```
Robj5.ReactionRate
```

```
ans =
'k5*protein'
```

Simulate the Model

Simulate model to see its dynamic behavior.

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

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

- 2 Run the simulation.

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

- 3 Plot the results.

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

