

BioMME Basic Tutorial

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Note to Readers

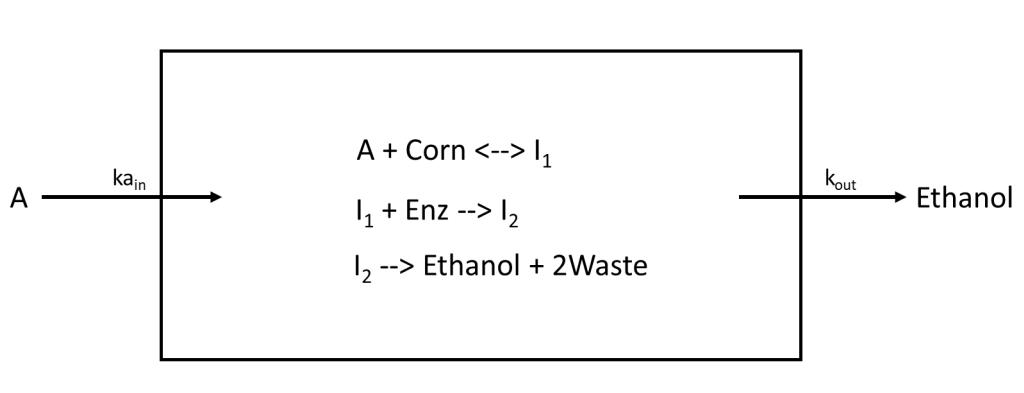
This is a tutorial is a made up example of a chemical reactor process, showcasing some basic features of the BioMME application.

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1 Tutorial

This is a tutorial covering a basic reaction system to show how to create a model in this program. For this tutorial, we present a chemical reactor that has an initial amount of corn in it. A reactant "A" is inputted into the tank at a constant rate and reacts with the corn to make an intermediate species, I_1 . This species undergoes an enzymatic conversion to I_2 , which decomposes to ethanol and a waste product. Ethanol is removed from the process, but waste builds up in the reaction. This reaction scheme is depicted below:



In the following sections of this tutorial, we will design the above system and look at how BioMME can be used to visualize and interpret the data. This tutorial will walk through the following:

1. Entering model variables
2. Build equations of model
3. Enter the input and outputs of the system
4. Enter numerical values for parameters and initial conditions
5. Solve and plot the differential model
6. Explore the different plotting modes
7. Export the model in a variety of ways

1.1 Inputting Variables

To use the online version of this application, visit https://jwomack7512.shinyapps.io/Model_Builder/. Note this app is stored on an Rshiny server that close unused applications after five minutes of inactivity. Your current model can be downloaded in the "Export" tab as an .RDS file and can be loaded in by opening the right sidebar of the application. The application can also be directly downloaded at *insert Github link* and ran in R.

Navigate to the "Create Model —> Define Variables" tab. We start by adding all the variables that are used in the model that we want differential equations for. There is an information button in the top right corner that will give tips, rules, and naming conventions for this page. Variables are entered into the textbox that says "Enter Model Variable". These variables can be entered one at a time or multiple variables can be entered with spaces in between. This model has the following variables:

1. A
2. Corn
3. I_1
4. Enz
5. I_2
6. Ethanol
7. Waste

Below, the first image shows entering the variables in one line using a comma separator. The second image shows the process of editing a description of the variable into the information table. This process is the same for all tables in this application. A square in the datatable can be double clicked to open up edit mode on that column. Any values in that column can be edited. Press "Ctrl + Enter" to save the descriptions. Do not open multiple columns at once.

Variable.Name	Description
	No data available in table

The screenshot shows the BioMME software interface. On the left is a dark sidebar with white text and icons, listing various model components: Home, Create Model (selected), Define Variables, Build Equations, Add Input/Output, Parameter Values, Initial Conditions, Differential Equations, Execute Model, Visualization, Export, Summary, and Documentation. The main area has a light blue header bar with the title 'Add Variables'. Below it is a form with two input fields: 'Enter Model Variable' and 'Variable to Delete', each with a dropdown menu and a 'Delete Variable' button. A large table below lists variables with their names and descriptions. The table has columns for 'Variable.Name' and 'Description'. The first row shows 'A' as a reactant with corn. The second row shows 'Corn' as a tasty treat. The third row, which is highlighted with a blue background, shows 'I_1' with an empty description field. Other rows include 'Enz', 'I_2', 'Ethanol', and 'Waste'.

Variable.Name	Description
1 A	Reactant with Corn
2 Corn	A tasty treat
3 I_1	
4 Enz	
5 I_2	
6 Ethanol	
7 Waste	

1.2 Create Equations

Navigate to "Create Model —> Build Equations". In this section, we will build the model by detailing the sets of reactions that make up the network. The first equation is the reversible chemical reaction:



Here we have a chemical reaction with two reactants, one product, and moves in both directions. Chemical reactions follow the law of mass action. This reaction input can be seen in the below figure. Note that below the "Equation Builder" there is a text version of the chemical reaction being built. When the "Add Equation" button is pressed, the added equations can be seen in the bottom box of this page.

Equation Type	Number of Reactants	Number of Products	<input type="checkbox"/> Options
Chemical Reaction	2	1	

Equation Builder				
#	Reactant 1	Reaction Direction	#	Product 1
1	A	↔ Reversible	1	I ₁
#	Reactant 2	Forward Rate Constant		
1	Corn	k _{f1}		
Reverse Rate Constant				
k _{r1}				

A + Corn (k_{r1})<-->(k_{f1}) I₁

Add Equation

Next, we enter the second equation, the conversion of I_1 to I_2 by the enzyme "Enz". Change the equation type to "Enzyme-Catalyzed Rxn". These reactions follow Michealis-Menten kinetics.



Here, we use the enzyme concentration catalytic rate constant in the MM equation. This can be switched to the Vmax for by selecting the equation options. Below is how this equation should be entered:

The screenshot shows the BioMME software interface. On the left is a sidebar with various tabs: Home, Create Model (selected), Define Variables, Build Equations (selected), Add Input/Output, Parameter Values, Initial Conditions, Differential Equations, Execute Model, Visualization, Export, Summary, and Documentation. The main area has a header with New, Edit, Delete, View, and Options. Below this is a section titled "Equation Type" with a dropdown set to "Enzyme-Catalyzed Rxn". The "Equation Builder" section contains fields for Substrate (I_1), kcat (kcat_2), Product (I_2), Enzyme (Enz), and Km (Km_2). A text input field shows the equation "I_1 + Enz (kcat_2)-->(Km_2) I_2". A blue "Add Equation" button is at the bottom right. At the bottom, there are tabs for Equations, Additional Equations, and Equation Descriptions, with the first tab selected.

The final reaction of this tutorial is:



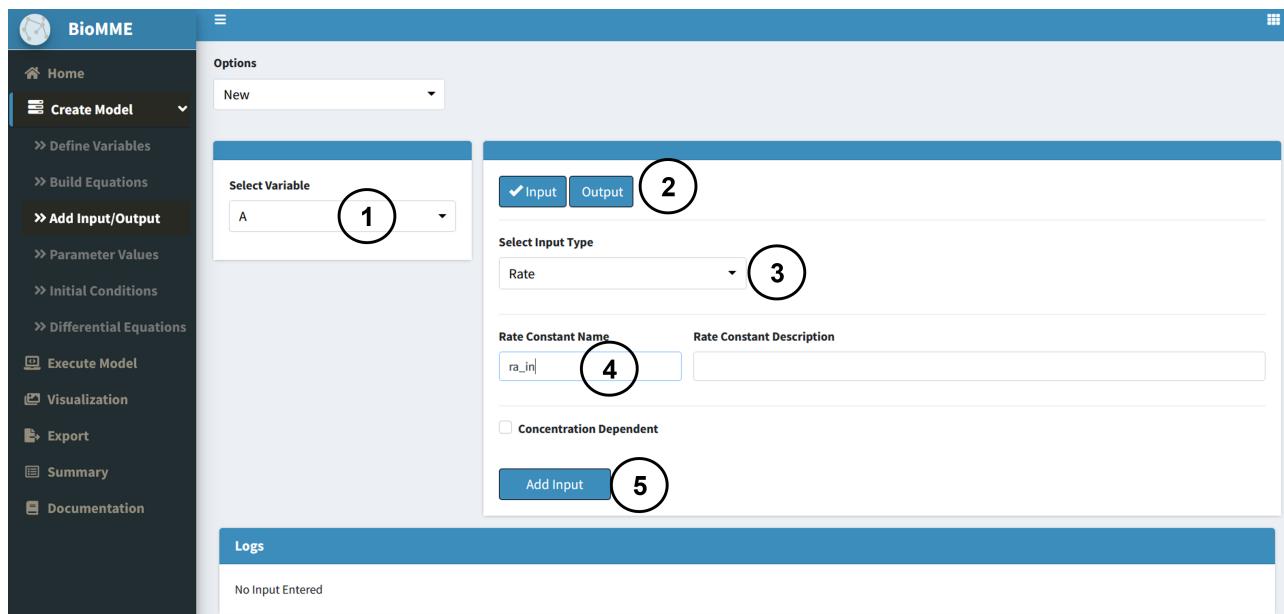
This reaction is similar to the first (chemical reaction) but has two products and one of them has a stoichiometric coefficient of two. Enter this equation and move on to the "Add Input/Output" tab.

The screenshot shows the BioMME software interface with the "Create Model" tab selected in the sidebar. The main area has a header with New, Edit, Delete, View, and Options. Below this is a section for "Equation Type" with a dropdown set to "Chemical Reaction", and fields for "Number of Reactants" (1) and "Number of Products" (2). The "Equation Builder" section contains a table for reactants and products. It shows "Reactant 1" (I_2) with "Reaction Direction" set to "Forward" and "Product 1" (Ethanol). It also shows "Forward Rate Constant" (k_f2) and "Product 2" (Waste). A text input field shows the equation "I_2 -->(k_f2) Ethanol + 2*Waste". A blue "Add Equation" button is at the bottom right. At the bottom, there are tabs for Equations, Additional Equations, and Equation Descriptions, with the first tab selected.

1.3 Input & Outputs

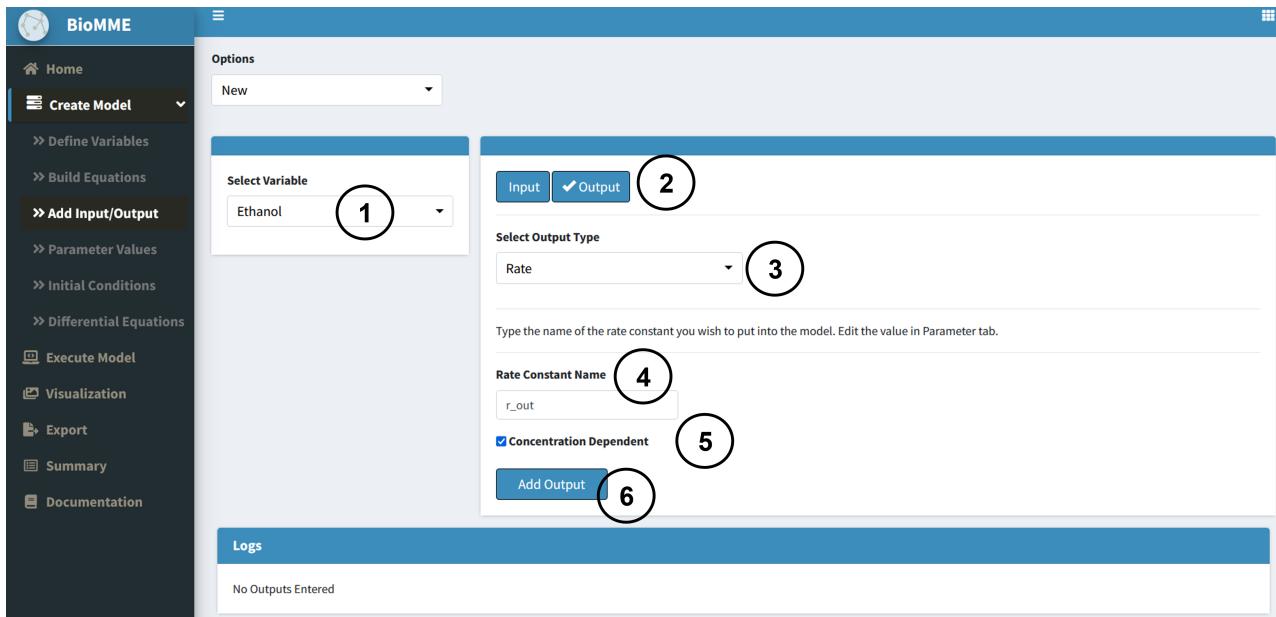
In this section we cover adding input and outputs (IO) of species into the system. Navigate to the "Create Model —> Add Input/Output" tab. In this model we cover an inflow and outflow. The inflow of species "A" is a constant rate and has the following steps:

1. In the left-hand box, select species "A"
2. In the right-hand box, make sure "Input" is selected.
3. Then make sure "Rate" is the selected input type.
4. Give rate constant the name "r2.a.in".
5. Press the Add input button.



This model outputs Ethanol at a concentration dependent rate. The steps are similiar to above and are listed as:

1. In the left-hand box, select species "Ethanol"
2. In the right-hand box, make sure "Output" is selected.
3. Then make sure "Rate" is the selected output type.
4. Give rate constant the name "r_out".
5. Check the box for "Concentration Dependent".
6. Press the "Add Output" button.



You can notice that after each input/output is added, there is a corresponding log recorded in the "Logs" box at the bottom of the page.

1.4 Parameters

Navigate to the next tab: "Create Model —> Parameter Values". This page contains a top filter bar which filters by type of parameter. The is an editable parameter table below with a search bar included. Here you can give your parameters values, change their names, and provide them with descriptions. The parameter values are as follows:

$$\begin{aligned} k_f1 &= 2.5 \\ k_r1 &= 0.5 \\ Km_2 &= 1 \\ kcat_2 &= 1.5 \\ k_f3 &= 0.6 \\ ra_in &= 0.1 \\ r_out &= 0.5 \end{aligned}$$

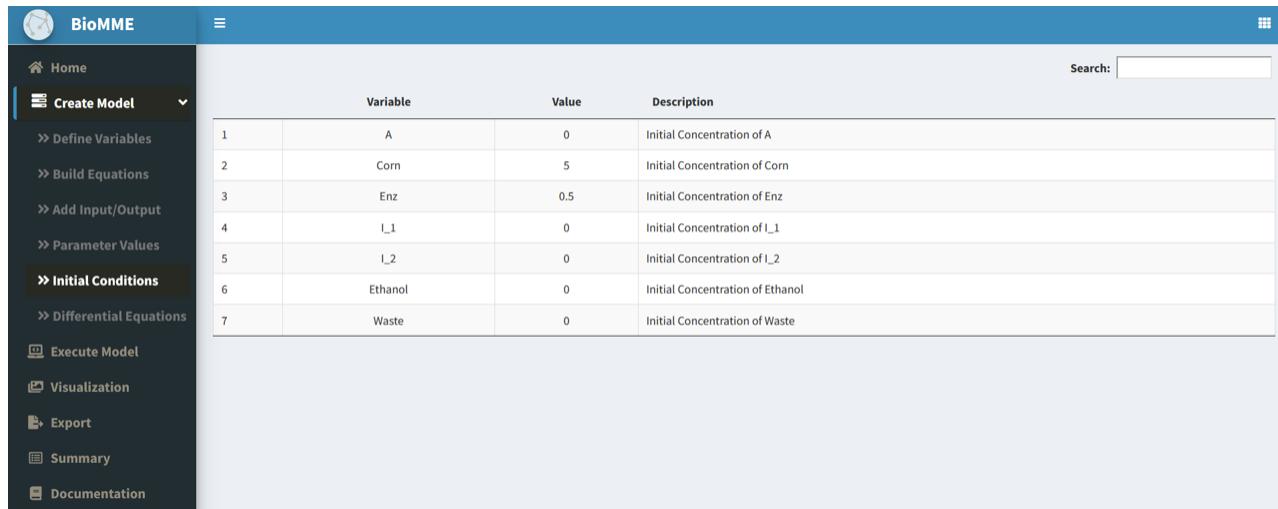
Double click the "Value" column and edit the values to match the above. Press "Ctrl+Enter" to save these values and move on to the "Initial Conditions" tab.

	Parameter	Value	Description
1	k_{f1}	2.5	
2	k_{r1}	0.5	
3	Km_2	1	
4	$kcat_2$	1.5	
5	k_f3	0.6	
6	ra_{in}	0.1	
7	r_{out}	0.5	

1.5 Initial Conditions

Switch to the "Create Model —> Initial Conditions" tab. Notice that this tab is much like the parameter tabs and functions in the same way. In this model, we start with 10 units of corn and 0.5 units of Enz. Enter the values below and move to the next tab.

$$\begin{aligned}A &= 0 \\Corn &= 5 \\Enz &= 0.5 \\I_1 &= 0 \\I_2 &= 0 \\Ethanol &= 0 \\Waste &= 0\end{aligned}$$



The screenshot shows the BioMME software interface. The left sidebar has a dark theme with white text and icons. The 'Create Model' section is expanded, showing options: 'Define Variables', 'Build Equations', 'Add Input/Output', 'Parameter Values', 'Initial Conditions' (which is selected and highlighted in dark grey), and 'Differential Equations'. Below these are 'Execute Model', 'Visualization', 'Export', 'Summary', and 'Documentation'. The main area is titled 'Initial Conditions' and contains a table with the following data:

	Variable	Value	Description
1	A	0	Initial Concentration of A
2	Corn	5	Initial Concentration of Corn
3	Enz	0.5	Initial Concentration of Enz
4	I_1	0	Initial Concentration of I_1
5	I_2	0	Initial Concentration of I_2
6	Ethanol	0	Initial Concentration of Ethanol
7	Waste	0	Initial Concentration of Waste

1.6 Differential Equations

Navigate to "Create Model —> Differential Equations" tab. This tab is simple and displays the current version of the differential equations of this model in a text output. The right sidebar of the "System of Differential Equations" box has an option to "pretty" the equations using a built in algorithm. This does not change the mathematical functions, just makes the equations look nicer (in most cases). Note, these differential equations are calculated each time a new equation is added or when an input/output is added.

System of Differential Equations

(1) $d(A)/dt = -k_f1 * A * Corn + k_r1 * I_1 + ra_in$
(2) $d(Corn)/dt = -k_f1 * A * Corn + k_r1 * I_1$
(3) $d(Enz)/dt = 0$
(4) $d(I_1)/dt = k_f1 * A * Corn - k_r1 * I_1 - kcat_2 * Enz * I_1 / (Km_2 + I_1)$
(5) $d(I_2)/dt = kcat_2 * Enz * I_1 / (Km_2 + I_1) + k_f3 * I_2$
(6) $d(Ethanol)/dt = k_f3 * I_2 - r_out * Ethanol$
(7) $d(Waste)/dt = 2 * k_f3 * I_2$

Generate

*Note if you generate equations and then add more variables, the new variables will show up here with a repeating list of eqns. This is a visual bug that will need to be fixed. Simply click the button to regenerate the equations to fix it.

Right Sidebar

1.7 Execute Model

Navigate to the "Execute Model" tab. This tab solves our model and provides us with the options to customize the solver. For this model, we will just solve using the standard options:

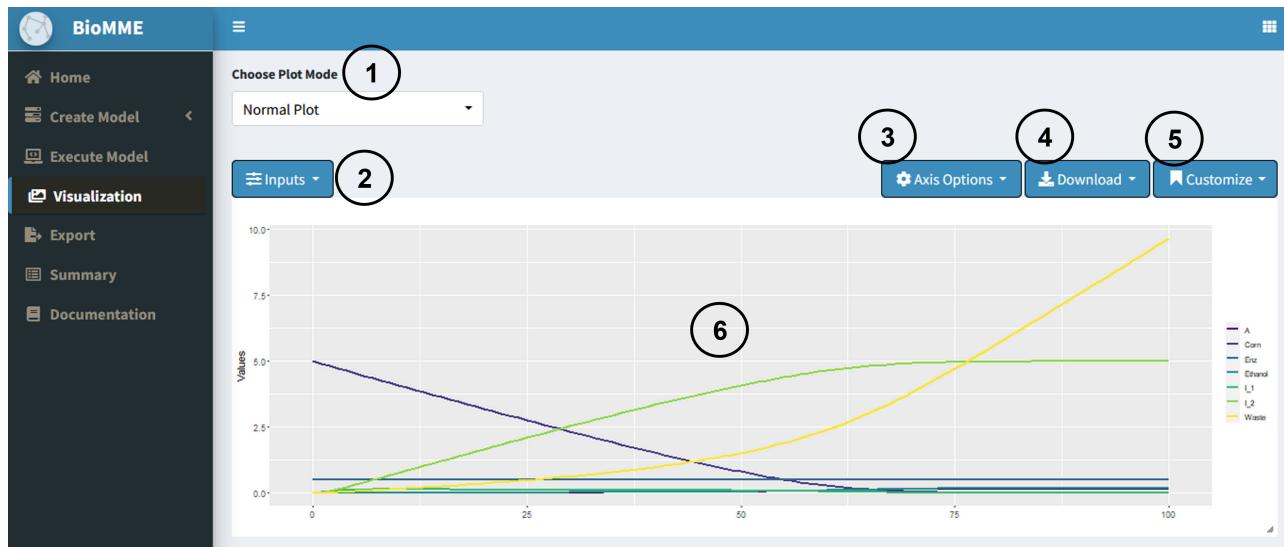
1. Enter the following times: Starting = 0, End = 100, Step = 1.
2. Press the "Run Solver" button.
3. An output table should be generated with the concentration of each species along each time step of the solved model.

time	A	Corn	Enz	I_1	I_2	Ethanol	Waste
0	0	5	0.5	0	0	0	0
1	0.011	4.911	0.5	0.065	0.02	0.004	0.008
2	0.013	4.813	0.5	0.104	0.057	0.021	0.054
3	0.014	4.714	0.5	0.125	0.09	0.048	0.143
4	0.015	4.615	0.5	0.137	0.115	0.079	0.267
5	0.015	4.515	0.5	0.144	0.133	0.107	0.416
6	0.016	4.416	0.5	0.148	0.145	0.131	0.583
7	0.016	4.316	0.5	0.15	0.153	0.15	0.762
8	0.017	4.217	0.5	0.151	0.158	0.164	0.949
9	0.017	4.117	0.5	0.152	0.161	0.175	1.14

1.8 Plotting Model

Navigate to the "Visualization" tab. The plotting tab has four modes, we will cover two of them. In this section we will cover "Normal Plot" which is the default when you enter the tab. The tab auto loads the plot when the model is solved, plotting all species of the model. These are the main features of the plot:

1. Plot mode - Changes the plotting types and features
2. Inputs - Changes what species are plotting in the model
3. Axis Options - Contains axis elements including labels, sizing, and spacing.
4. Download - Button to download plot in different formats.
5. Customize - Options to change line/plot colors, size, and overall appearance.
6. Plot - Plot area with adjustable sizing on bottom right corner.



Thats it! We have made it to the end result. Now there are options to play with to get your graph the way you like it. Check documentation for all options but we can add x,y labels, plot title, change the size and colors of the plot lines, the background of the plot, and much more.

2 Version Control

This section will contain all the version info of relevant R packages used to create this program. This is useful to have for our records as well as for users to have if they are directly downloading the code from github as packages under different versions can cause clashes. For example "RshinydashboardPlus" just did a whole revamp of their package. If the newest version of their package is installed instead of version 0.7, then the app will fail to load.