

# Introduction to Systems Biology using *Cell Illustrator*

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Understanding the level of biological complexity is the focus of the emerging field of systems biology. Many biologists are beginning to turn to systems biology to organize large data sets in a functional way that allows the user to make quantitative predictions. Because the use of programs that organize these data is becoming more prevalent in all areas of biology, it has become essential that students be trained in their use. The primary objective of this lab is to provide students resources that introduce students to *Cell Illustrator*, a simple systems biology program that illustrates and analyzes interacting molecular pathways.

**Keywords:** modeling, systems, predicative, pathways

## Introduction

The chemical changes that occur within a cell involve a large number of interacting species that vary in concentration over time. The mathematics needed to model them is complex, requiring the use of numerical methods for all but the simplest cases. Computer algebra programs, such as Maple, MathCad and Mathematica, include the required numerical methods and can be used to model complex biological systems. However, setting up these calculations still requires some mathematical knowledge and is cumbersome. Furthermore, the format used does not allow the user to easily grasp the connections among the species of the system.

*Cell Illustrator* can perform the same numerical analyses as computer algebra programs but with a visual interface that allows the user to clearly identify all species in the model and how they are related (Nagasaki, 2004). The process for adjusting parameters is also much more intuitive, allowing the user to focus on the changes in the biological system being explored rather than on software syntax. The downside of such a visual program is that it distances the user from the mathematics. It is the purpose of this activity to expose the students to the underlying

mathematics of some simple systems and to teach them how to build and explore them using *Cell Illustrator*. This will enable them to build more complex systems and to have some understanding of the mathematics that underpins their analysis.

In the 2011 document, *Vision and Change in Undergraduate Biology Education: A Call to Action*, released by The American Association for the Advancement of Science, educators are urged to design curriculum in a way that provides a more realistic experience of the scientific process. This includes emphasizing the relationship between biology and other disciplines, particularly by incorporating mathematical, computational, and systems biology approaches into the laboratory setting. In order to increase students' awareness for and comfort with mathematical modeling of biological processes, the following lab was developed for use in 200-level, majors Biology course. Specifically, this lab will introduce students to *Cell Illustrator* and systems biology, first by modeling simple chemical kinetics commonly discussed in introductory chemistry classes, then gradually working up to more complex molecular systems.

## Student Outline

### Analysis of Simple Kinetic Systems with *Cell Illustrator*

#### Introduction

The chemical changes that occur within a cell involve a large number of interacting species that vary in concentration over time. The mathematics needed to model them is complex, requiring the use of numerical methods for all but the simplest cases. Computer algebra programs, such as Maple, MathCad and Mathematica, include the required numerical methods and can be used to model complex biological systems. However, setting up these calculations still requires some mathematical knowledge and is cumbersome. Furthermore, the format used does not allow the user to easily grasp the connections among the species of the system.

*Cell Illustrator* can perform the same numerical analyses as computer algebra programs but with a visual interface that allows the user to clearly identify all species in the model and how they are related. The process for adjusting parameters is also much more intuitive, allowing the user to focus on the changes in the biological system being explored rather than on software syntax. The downside of such a visual program is that it distances the user from the mathematics. It is the purpose of this activity to expose you to the underlying mathematics of some simple systems and to teach you how to build and explore them using *Cell Illustrator*. This will enable you to build more complex systems and to have some understanding of the mathematics that underpins their analysis.

#### A Chemical Kinetics Primer

Chemical kinetics examines the rate of chemical reactions and the factors that affect them. The General Chemistry II course that you have taken provided an introduction to the field.

Let's begin with the simplest system in which  $A \rightarrow B$ . An important question is how the concentration of A and B change over time. The change may be constant or may depend on some function of the concentration. Let's explore two cases in detail.

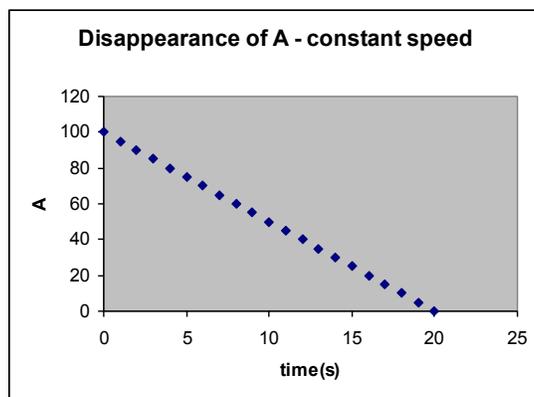
If the change in concentration of A,  $dA/dt$ , is constant, then this can be expressed mathematically as:

$$\frac{dA}{dt} = -k \quad (1)$$

where  $k$  is a constant specific to the reaction called a *rate constant*. Note that the minus sign is necessary because we are focusing on changes in the reactant, A, which must be decreasing. This equation, also referred to as a **rate law**, is not the most useful form because one generally desires to know how the concentration changes over time,  $A(t)$ . The rate law can be converted to an equation for  $A(t)$  using the operation of integration in calculus. For this case, the result is

$$A(t) = A_0 - kt \quad (2)$$

A plot of this function is seen in Fig. 1:



**Figure 1.** The rate of disappearance of reactant “A” is constant for a zeroth order reaction.

Do not be concerned if you are not well-acquainted with the operation of integration. Note that the slope of the graph is constant and negative so one can rationalize that this function of concentration over time follows from equation (1) above even if all of the steps of the derivation are not clear.

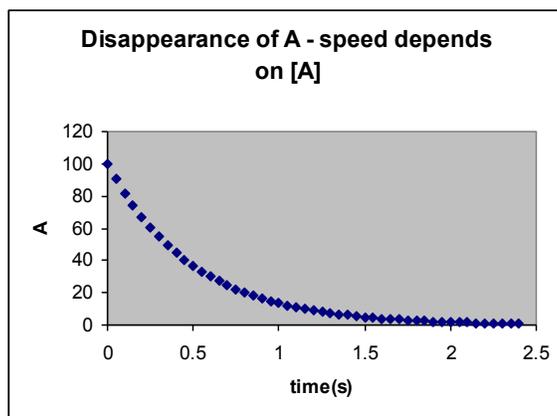
Let's consider the slightly more complex case in which  $dA/dt$  depends on the concentration of A, a situation which frequently occurs in chemical systems. In this case the rate law is:

$$\frac{dA}{dt} = -kA \quad (3)$$

...which gives the following equation for A(t) upon integration:

$$A(t) = A_0 e^{-kt} \quad (4)$$

A plot of this function is seen in Fig.2 :



**Figure 2.** The rate of disappearance of reactant “A” decreases as  $[A]$  decreases for a first order reaction.

Note how this function differs from the one in the previous figure. It is once again possible to rationalize that it is the solution of equation (3). Note that the slope is changing and becomes smaller in magnitude. Equation (3) predicts that the slope will change as the concentration of A changes and that the slope will become smaller in magnitude because the concentration of A, a reactant, must decrease.

### Using Cell Illustrator to Solve Simple Kinetic Systems

Let us now learn how to instruct the program Cell Illustrator to solve the system  $A \rightarrow B$ .

*Cell Illustrator* uses what are called **entities** to represent distinct chemical species. These can either be continuous (can change by any amount) or discrete (can only change in unit increments). In this exercise, we will focus on continuous entities only, the symbol for which is two concentric circles:  $\odot$ .

A **process** is a chemical event that occurs to an entity. These can also be discrete or continuous. We will only consider a continuous process, which is symbolized by a white rectangle:  $\square$ .

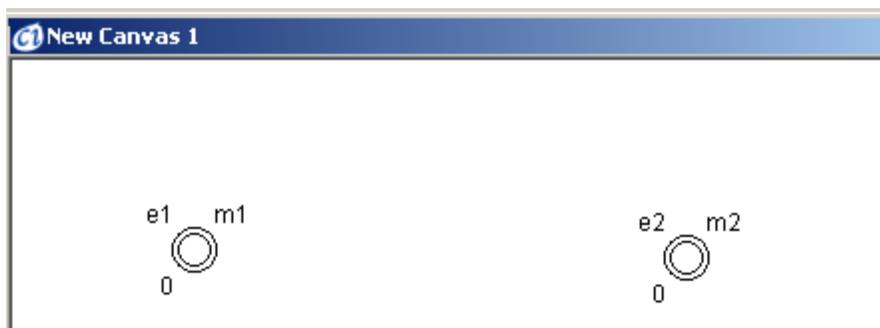
Finally, one must use a **connector** to connect entities to processes. The most general of these is the process connector, symbolized by a simple arrow,  $\rightarrow$ . While this is the only one used in this exercise, you will encounter inhibitory and association connectors in future activities.

Now let's enter the system  $A \rightarrow B$  into *Cell Illustrator*. After you start the program, you will notice a largely blank space with small icons along the top and side borders. To build a model, you will need to create a new canvas upon which to do so.

This is accomplished by clicking on the blue icon in the upper left corner with a + sign in its lower right corner . A blank white window will now appear in the screen. All of the parts of your model must be entered in that white window.

Because there are two chemical species (A and B), you will need to add two entities to the canvas. To do this, click on the double circle icon located in the top left and then click in two well-separated locations on the canvas. Click on the

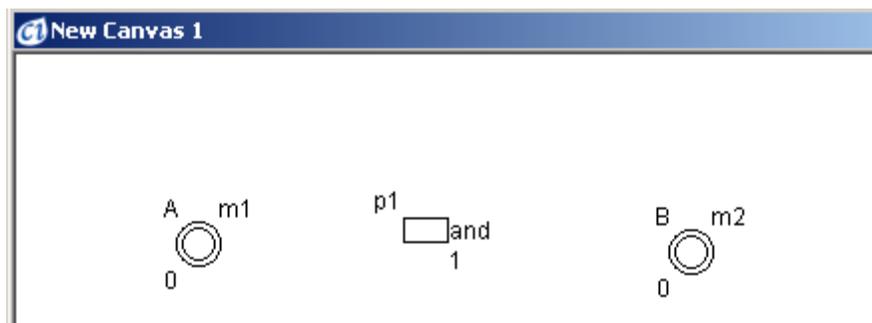
selection mode icon (slanted arrow) in the upper right  to prevent further clicks from adding more entities. The orange undo arrow on the left is helpful for correcting errors. The canvas should appear as the image of Fig. 3:



**Figure 3.** The placement of two continuous entities, e1 and e2, in Cell Illustrator.

Notice that each entity symbol is surrounded by placeholders for three parameters. The number in the lower left is the initial concentration of the species, which is set to zero by default. The e1 and e2 placeholders are the name of the species. You should double-click on “e1” and change it to “A” and then click enter to save the change. Likewise change “e2” to “B”. (Make sure that you have already clicked on the selection mode icon – the slanted arrow – in order to edit the placeholders.) The placeholder in the upper right is the variable name for the concentration of the species. You can leave those as is for now.

Now click on the white rectangle from the top palette and click on the space between the two entities as shown in Fig. 4 to enter the process.

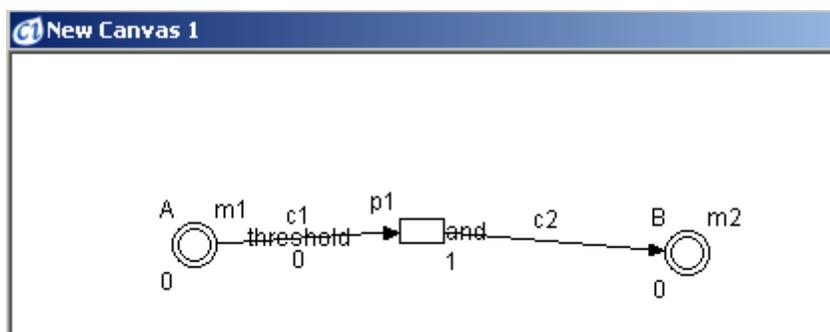


**Figure 4.** The placement of process p1 in *Cell Illustrator*.

Note that the process connector also has three parameters. The one in the upper left is the process name and the number in the lower right is the speed. The speed includes the value of the rate constant and possibly the variable name for the concentration if the speed depends on it. In other words, the speed is what is on the right hand side of equations (1) and (3) without the minus sign.

You must now connect the entities to the process. Click on the downward arrow in the upper palette under the dialog window. Now click on the entity symbol for A and on the process symbol. This will add an arrow between the two. Likewise click on the process connector and then on the entity symbol for B. The arrow will always point toward the last item clicked, so be sure to do these operations in the proper order to achieve the desired result. You will then have to make a change to the process that will allow you to edit the speed later. Ensuring that the process is selected, click the element settings button

along the far right side:  and change the *Kinetic Style* from *Mass* to *Custom*. You should then be able to edit the speed by clicking the lower right hand parameter. Make sure this is set to 1 before moving on. From this point, the canvas should appear as shown in Fig. 5.



**Figure 5.** Connector arrows connect entity A to process p1, and p1 to entity B to set up the reaction  $A \rightarrow B$ .

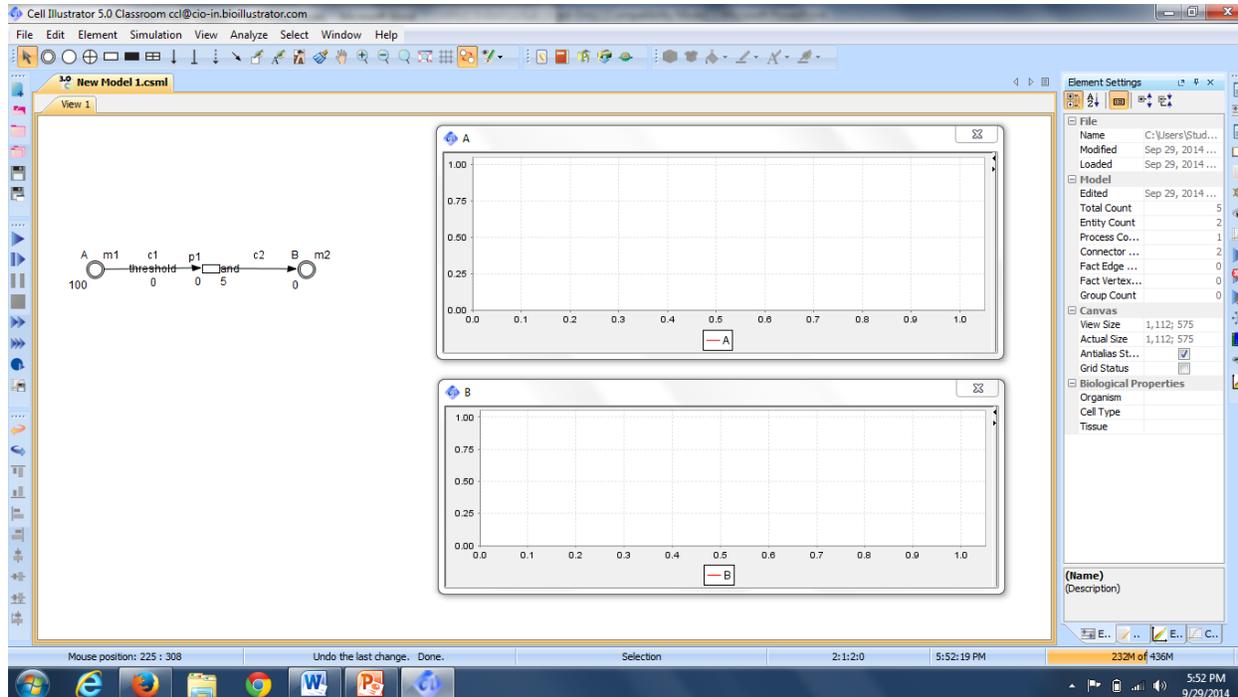
There are name and parameter placeholders for the connector as well, but let's not worry about those at this point. Click on the selection mode icon  before proceeding.

Before running the simulation, you must save the canvas. To do this click on the icon on the left that looks like this:



This will bring up a save window. Substitute an appropriate filename for “new” leaving the “.cml” file type intact. At this point, you will notice that the icons on the right are now active. These are the ones used to initiate a simulation.

The model will require more editing and set up before performing a simulation. Initial values will need to be adjusted for the species concentrations and the appropriate speed needs to be entered. Also, you will need to set up charts to most conveniently view the results. Click on the appropriate placeholders to change the initial concentration of A to 100 and the speed to 5. Now right click on the entity symbol for A and select *Create Chart* from the menu. A window with a chart for A will appear. Move this off to the right. Repeat the process for entity B, moving the resulting chart below the one for A. The canvas should now appear in Fig. 6.



**Figure 6.** Setting up simulation charts for reactant A and product B on the *Cell Illustrator* canvas.

What you have done is set up the program to solve the equation (1) with  $k=5$  assuming an initial A concentration of 100 and an initial B concentration of 0. Save the canvas again.

Running a simulation essentially means instructing the program to solve the equation(s) (in this case equation (1)) and plot out the concentrations of the chemical species over time. To initiate a simulation, press the play simulation icon in the

lower left that looks like this . The simulation will go on for a while. You can stop it after about 20 s on the time axis are completed. To stop, press the icon with the large blue rectangle that is three icons below the play simulation icon.

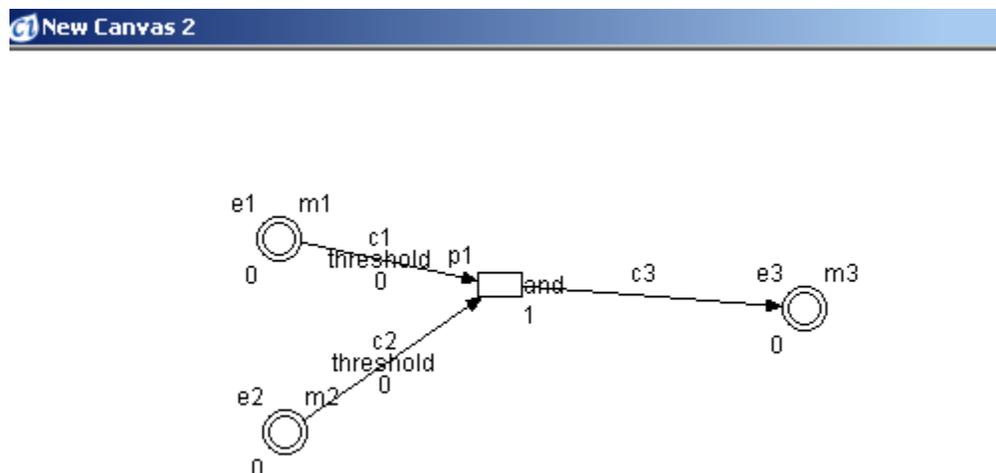
Now let us instruct the program to solve equation (3). To do this, you will only need to change the speed to  $5 \cdot m1$ . Note that this is the right-hand side of equation (3) with  $k=5$  and  $m1=A$ . Be sure to save the canvas first. Now run the simulation. Stop the calculation when the curves near the baseline, which will only be after a second or so.

The curves drawn will appear choppy, which indicates that you should adjust some of the simulation settings. To do this, click on the simulation settings icon on the right about halfway down that looks like this . A window of options will appear. The three parameters of greatest interest are **sampling interval**, **chart update interval** and **simulation time**. The sampling interval refers to how frequently the points are computed whereas the chart update interval refers to how frequently they are displayed. The simulation time is the total time the simulation will run if not stopped. These three parameters need to be reduced in tandem beginning with the simulation time. Its default value of 1000 s must be reduced first to permit reductions in the sampling and chart update intervals. Change its value to 100 and then change the sampling interval and chart update interval to 0.01 and 0.1, respectively. These choices should yield smoother curves. [Note: If further reductions are needed, simulation time of 10 s will permit further reduction in the sampling interval and chart update interval to 0.001 and 0.01, respectively.] Be sure to save the canvas after making any adjustments in simulation settings and before initiating another simulation.

Chemical reactions can also have more than one reactant, so let's consider how to enter the reaction  $A + B \rightarrow C$ . The rate law can take a variety of forms, most commonly the one given below.

$$\frac{dA}{dt} = -kAB \quad (5)$$

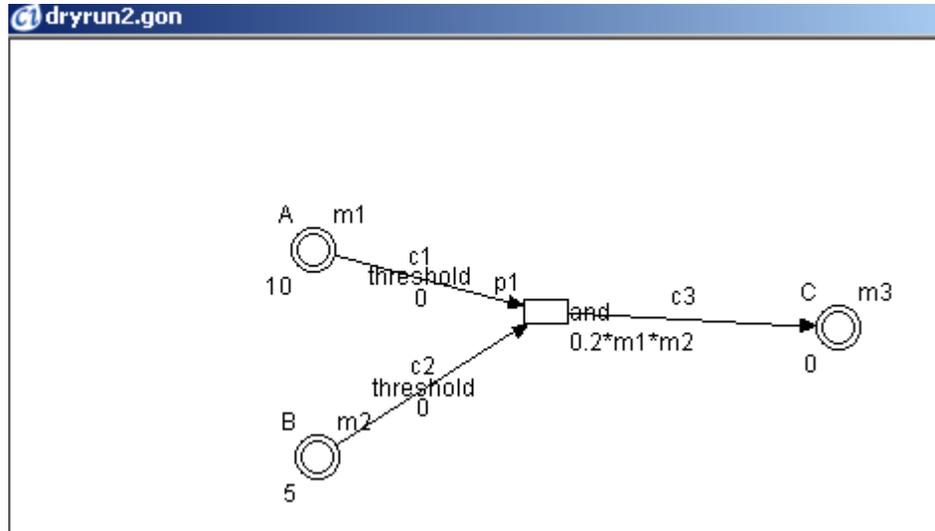
To indicate this reaction, you will need to save and close the existing canvas (use the closed pink folder icon on the left to close the canvas). Now open a new canvas with the blue  icon. You will need to enter three entities for A, B and C, respectively. A and B need to be connected to the same process rectangle. Complete the canvas as shown in Fig. 7. Be sure to change your process kinetic style to custom under the element settings menu as discussed above.



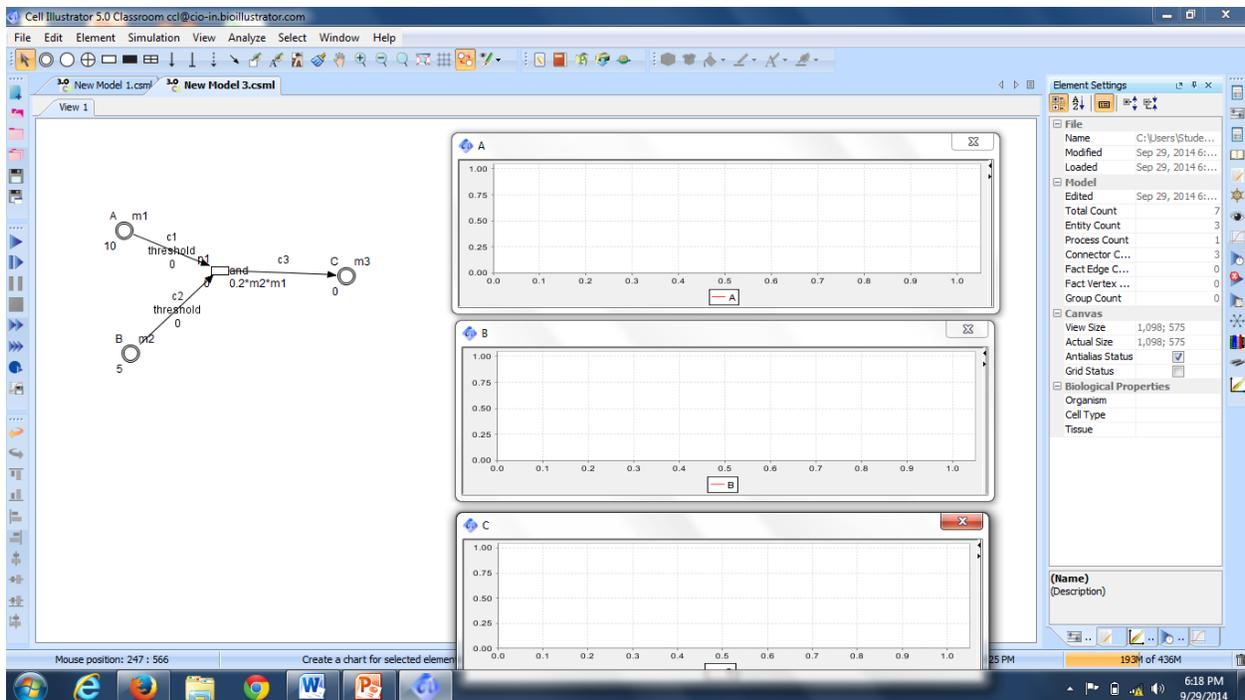
**Figure 7.** Modeling the reaction  $A + B \rightarrow C$  using entities e1 and e2 for reactants, and entity e3 as the product. The entities are connected to process p1 using connector arrows.

Now modify the parameters of the entities and process connector as follows.

This will set up the program to solve equation (5) for the concentration of A over time as well as related equations that give the concentration of B and C over time. The speed is  $0.2 \cdot m_1 \cdot m_2$ , which indicates that the change in concentration depends on both the A and B concentrations with a rate constant of 0.2. The initial concentrations are 10 for A, 5 for B and 0 for C. Also, add charts for the three species. The canvas and screen should appear as indicated in Figs. 8 and 9.



**Figure 8.** Modeling the reaction  $A + B \rightarrow C$  using entities e1 and e2 for reactants A and B, and entity e3 as product C.



**Figure 9.** Setting up simulation charts for reactants A and B, and product C on the Cell Illustrator canvas.

It is prudent to change the simulation settings to simulation time=10, sample interval=0.001 and chart update interval=0.01. Save your canvas and then run the simulation.

### Exercises to Explore in *Cell Illustrator*

1. Return to the example for  $A \rightarrow B$  that you saved. For the case with speed=5, initial A=100 and initial B=0, determine the time required for the concentration of A to drop to half of its initial value. Now change the initial concentration of A to 50 and determine the time required for the concentration of A to drop to half of its value. Do these values differ? If so, by what factor?

2. Continue with the example for  $A \rightarrow B$ . This time, change the speed to  $5 \cdot m1$  with initial A=100 and initial B=0. Also change the simulation settings to simulation time=10, sample interval=0.001 and chart update interval=0.01. Determine the time required for the concentration of A to drop to half of its initial value. Now change the initial concentration of A to 50 and determine the time required for the concentration of A to drop to half of its value. Do these values differ? If so, by what factor? Compare with the results of exercise 1.

3. Set up a template to explore the consecutive reaction  $A \rightarrow B \rightarrow C$ . This is a common reaction sequence in which a reactant is first converted to an intermediate B and then to a final product C. Set the initial concentration of A to 10 and those for B and C to 0. There are two processes as there are two steps in the reaction sequence. Set the speed for the first one ( $A \rightarrow B$ ) to  $0.1 \cdot m1$  and the speed for the second one ( $B \rightarrow C$ ) to  $m2$ . You are essentially having the program solve the following set of equations.

$$\frac{dA}{dt} = -0.1A \quad \frac{dB}{dt} = 0.1A - B \quad \frac{dC}{dt} = B \quad (6)$$

Compare the curves for A, B and C over time. You will note that B goes through a maximum. At what time does this occur and how large is the B concentration at this point?

Now change the speeds to  $m1$  for the first process and  $0.1 \cdot m2$  for the second process. Once again note the time where the concentration of B is a maximum as well as its value at this point. Compare with results for other set of speeds you investigated.

4. Open the template for  $A + B \rightarrow C$  that you saved. Run the simulation again to address the following questions.
- Why does the concentration of A never reach zero? What value does it reach? What amount of C is ultimately produced?
  - What value does the concentration of A reach if you change the initial value to 15? Did this change the results at all? Explain.
  - Obtain results for an initial value of A of 5. How is this different from the preceding results? Explain.

## Materials

### Supplies & Equipment (for Each Lab Group):

- Classroom licenses for Cell Illustrator 5.0 (students work in groups of two or of three): 10 - 15
- Student computers: 10 - 15
- Instructor computer: 1

## Notes for the Instructor

### Acquiring the Program

The *Cell Illustrator* 5.0 program can be obtained through the website:

<http://www.cellillustrator.com/home>

This program can be used in a variety of ways, and so it can be obtained as a free demonstration version, as *Cell Illustrator Player*, as a classroom version, or as a full version.

**Table 1.** Comparison of *Cell Illustrator* models.

	Trial	Player	Classroom	Standard/ Professional
<b>Access duration</b>	Two week s	Indefinite	One year	One year
<b>Price</b>	Free	Free	\$1300 for 10	By quote
<b>Plays models</b>	✓	✓	✓	✓
<b>Build models</b>	✓	No	✓	✓
<b>Unlimited functions</b>	✓	No	No	✓

### *Trial Version*

The free demonstration version comes with two week access, so if the activities are performed within this time span, then students can make their own accounts to have full access to the program.

### *Cell Illustrator Player*

This version is free, but can only be used to play previously made models, not to build new ones. This one is appropriate if the instructor intends only to obtain published models and run simulations.

### *Classroom Version*

If the desired activities are more long term, classroom versions can be acquired. This version has some limitations, but is intended for educational purposes.

### *Standard/Professional Versions*

This has some additional features, such as the ability to support more entities and processes in the model.

It should also be noted that this program requires an updated version of Java.

A sample data set and answer key for the student outline is presented in the appendix.

## Literature Cited

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Nagasaki, M., Doi, A., Matsuno, H., Miyano, S. 2004. Genomic Object Net.I. A platform for modeling and simulating biopathways. *Applied Bioinformatics* 2: 181-184.

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## About the Authors

Rebecca L. Murphy earned her B.S. degree in biology from Centenary College of Louisiana in 2006, and her Ph.D. in biochemistry at Texas A&M University in 2012. She is currently an Assistant Professor of Biology at Centenary College of Louisiana. Her research interests include the improvement of agriculturally important crop species.

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Juan R.G. Rodriguez earned a B.S. degree in physics from Centenary College of Louisiana and his Ph.D. in physics from the University of Arkansas in Fayetteville. He also received postdoctoral training in chemistry and biophysics from Washington University in St. Louis. He is currently an Associate Professor of Physics at the St. Louis College of Pharmacy.

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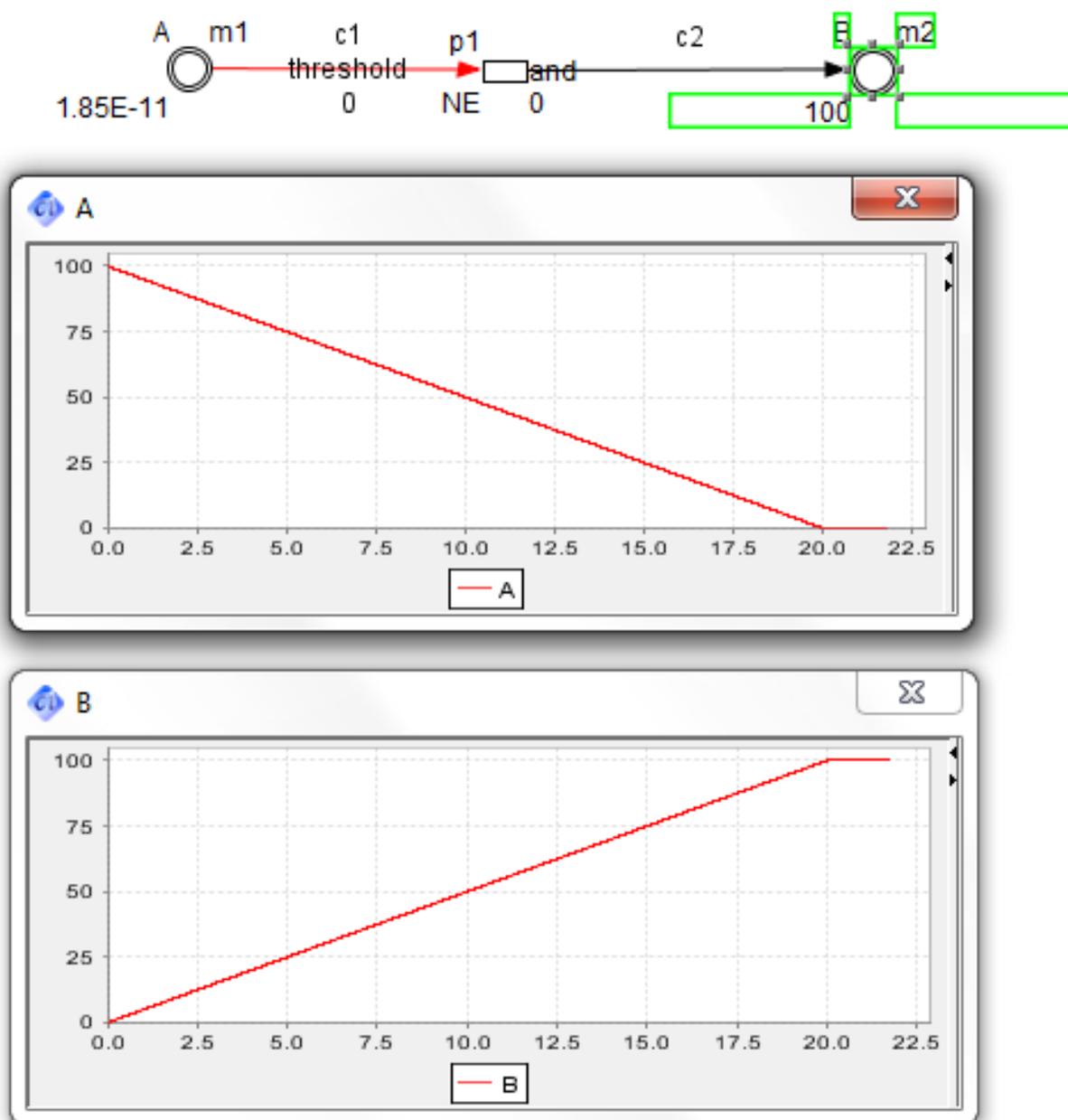
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## Appendix

### Sample Data and Answers to Exercises

This file contains solutions to student exercises in the analysis of kinetic systems.

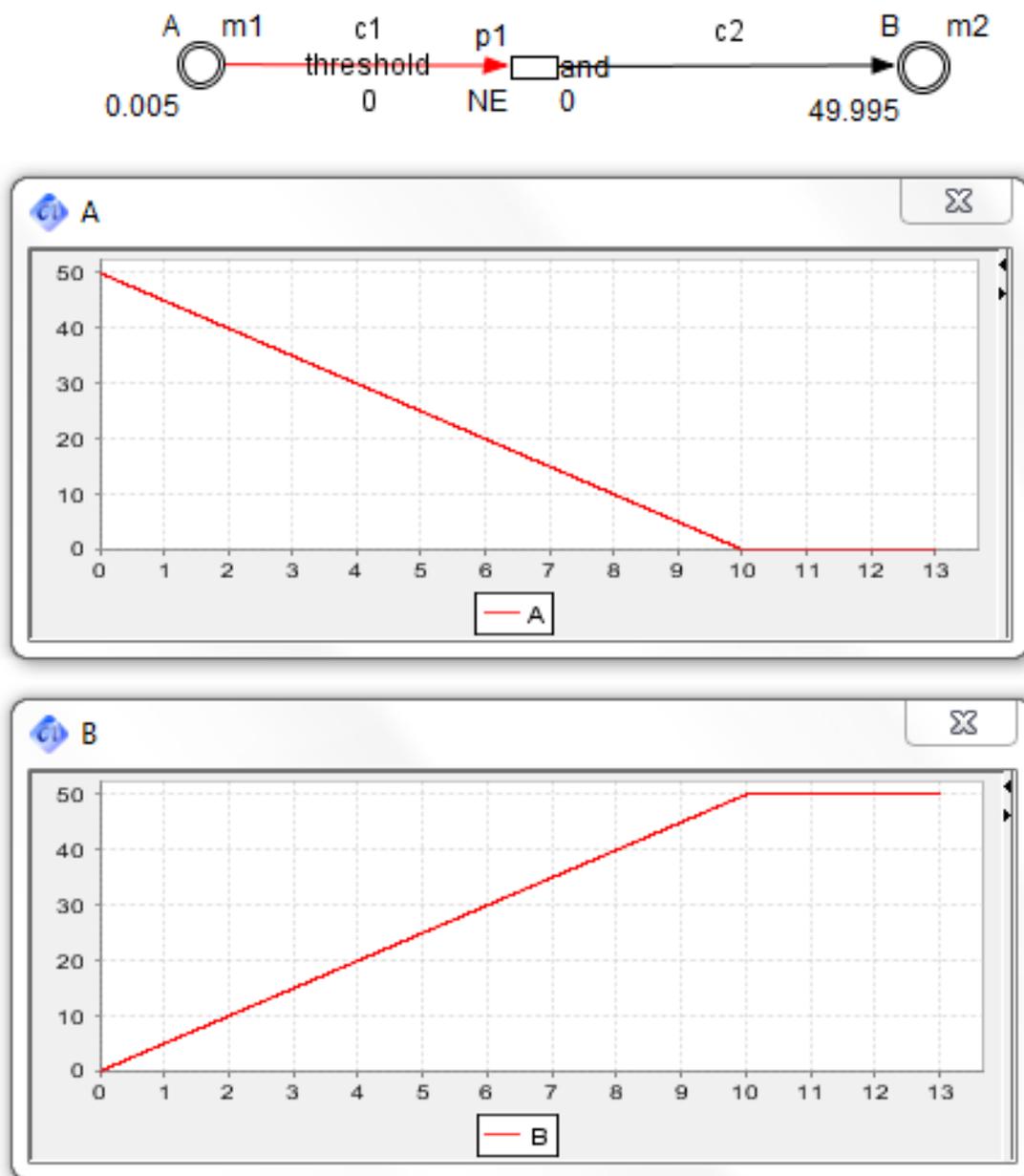
1. Using the reaction  $A \rightarrow B$  that you saved, we began with the case with speed=5, initial A=100 and initial B=0. The graphs below represent the results of this simulation:



**Figure 10.** Reactant and product plots for the zeroth order reaction  $A \rightarrow B$ . The reactant A decreases at a constant rate while the product B increases at that rate.

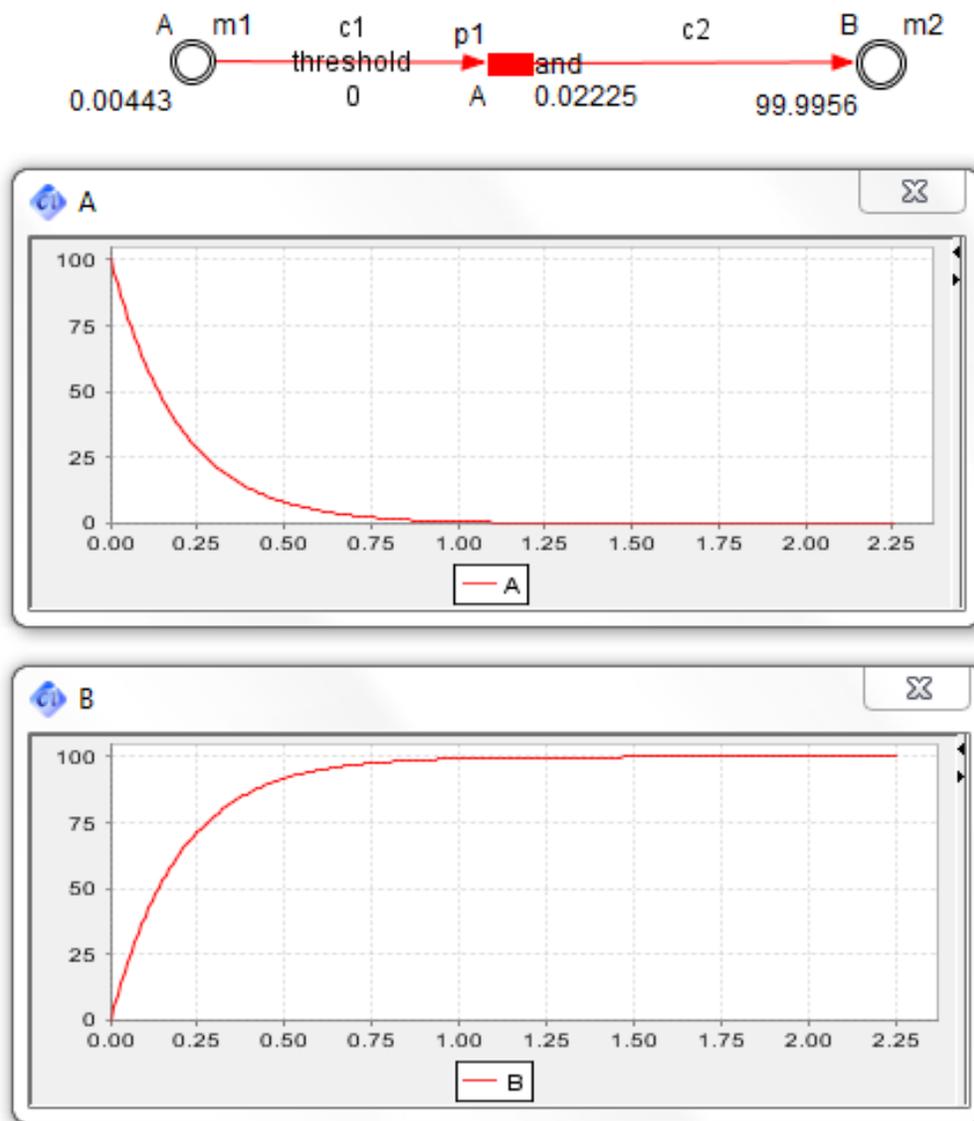
The students are asked to determine the time required for the concentration of A to drop to half of its initial value. From this graph, they should see that  $A=50$  at 10s.

They are then asked to change the initial concentration of A to 50 and determine the time required for the concentration of A to drop to half of its value. The students should see that A goes to half its value (25) in half the time (5s).



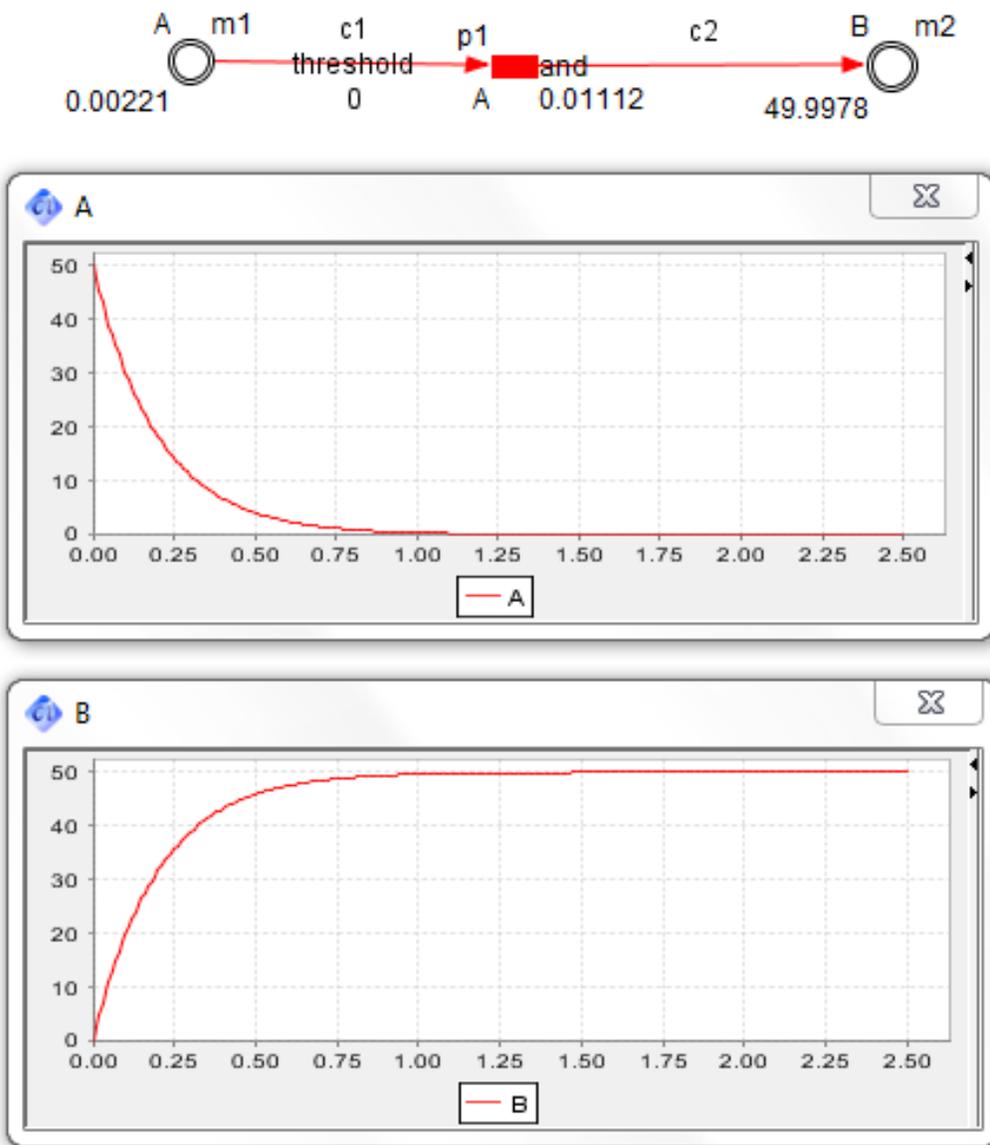
**Figure 11.** Reactant and product plots for the zeroth order reaction  $A \rightarrow B$  with half the initial starting concentration of A. A and B decrease at a constant rate as observed in Figure 10, but do so in half the time.

2. Continuing with the example for  $A \rightarrow B$ , students are asked to change the speed to  $5 \cdot m1$  with initial  $A=100$  and initial  $B=0$ , and determine the time required for the concentration of  $A$  to drop to half of its initial value. In this instance, they should see that it takes approximately 0.14 seconds to reach  $A=50$



**Figure 12.** Reactant and product plots for the first order reaction  $A \rightarrow B$ . The rate of formation of  $B$  decreases as  $A$  is consumed.

They are then asked to change the initial concentration of A to 50 and determine the time required for the concentration of A to drop to half of its value.



**Figure 13.** Reactant and product plots for the first order reaction  $A \rightarrow B$  at half of the starting concentration of A shown in Fig. 12. For a first order reaction the concentration of A decreases by half in the same amount of time for each of the starting values.

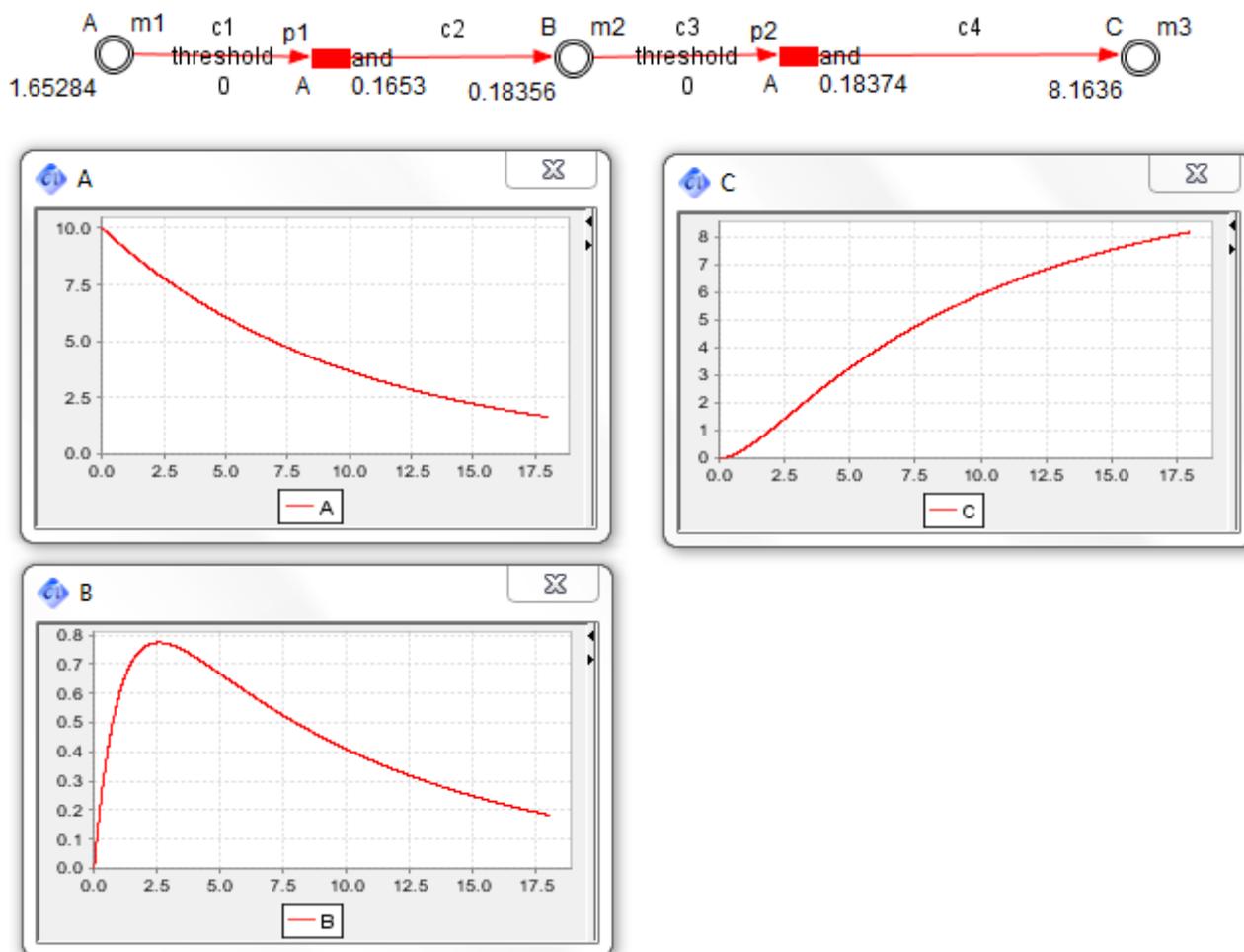
Here they should see that even if the initial concentration is half, it still takes the same amount of time, 0.15s, for  $A=25$ .

In comparing this to question one, it takes the same amount of time to reach half the value because in this case the rate of the reaction is dependent on the concentration of A, whereas in the first example, the rate is constant regardless of the starting concentration.

3. Here, students set up a new template to explore the consecutive reaction  $A \rightarrow B \rightarrow C$ . The initial concentration of A is 10 and those for B and C are 0. The speed for the first stage of the reaction ( $A \rightarrow B$ ) is set to  $0.1 \cdot m1$  and the speed for the second one ( $B \rightarrow C$ ) to  $m2$ .

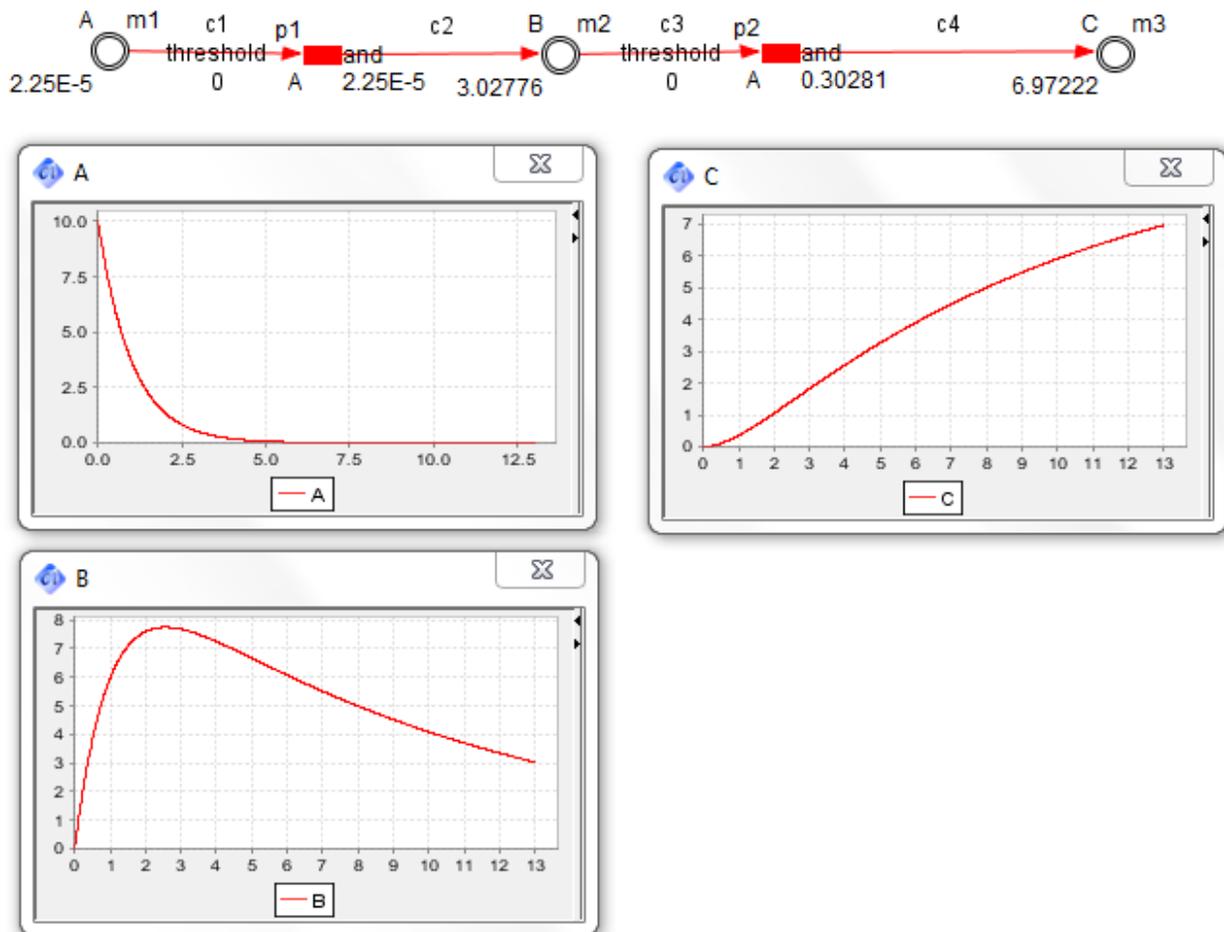
Students are asked at what time does this occur and how large is the B concentration at this point?

For this initial set up, the maximum concentration of B occurs at approximately 2.5 seconds, and is 0.8



**Figure 14.** Reactant and product plots for the reaction  $A \rightarrow B \rightarrow C$ . The maximum value of B is 0.8 and occurs in 2.5 seconds.

In the second part, students change the speeds to  $m_1$  for the first process and  $0.1 \cdot m_2$  for the second process. Now, the maximum concentration of B occurs again at 2.5 seconds, but in this case is 8.

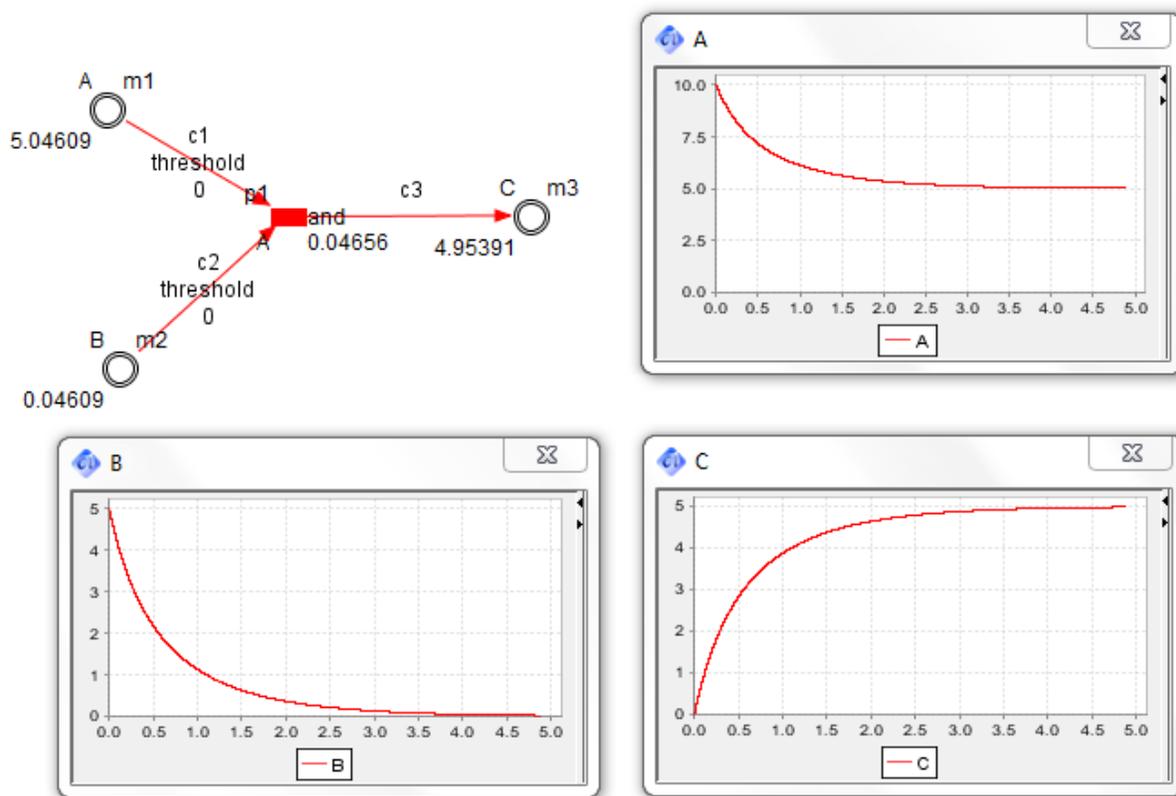


**Figure 15.** Reactant and product plots for the reaction  $A \rightarrow B \rightarrow C$ . The maximum value of B is 8 (tenfold higher) and also occurs in 2.5 seconds when compared to Fig. 14.

The concentration is 10-fold higher at its maximum because in the first example, A is converted to B 10-fold more slowly than B is converted to C. In the second case, A is converted to B ten times more quickly than B to C, and the maximum can accumulate to 10 times the amount.

4. Open the template for  $A + B \rightarrow C$  that you saved. Students run the simulation again to address the following questions:

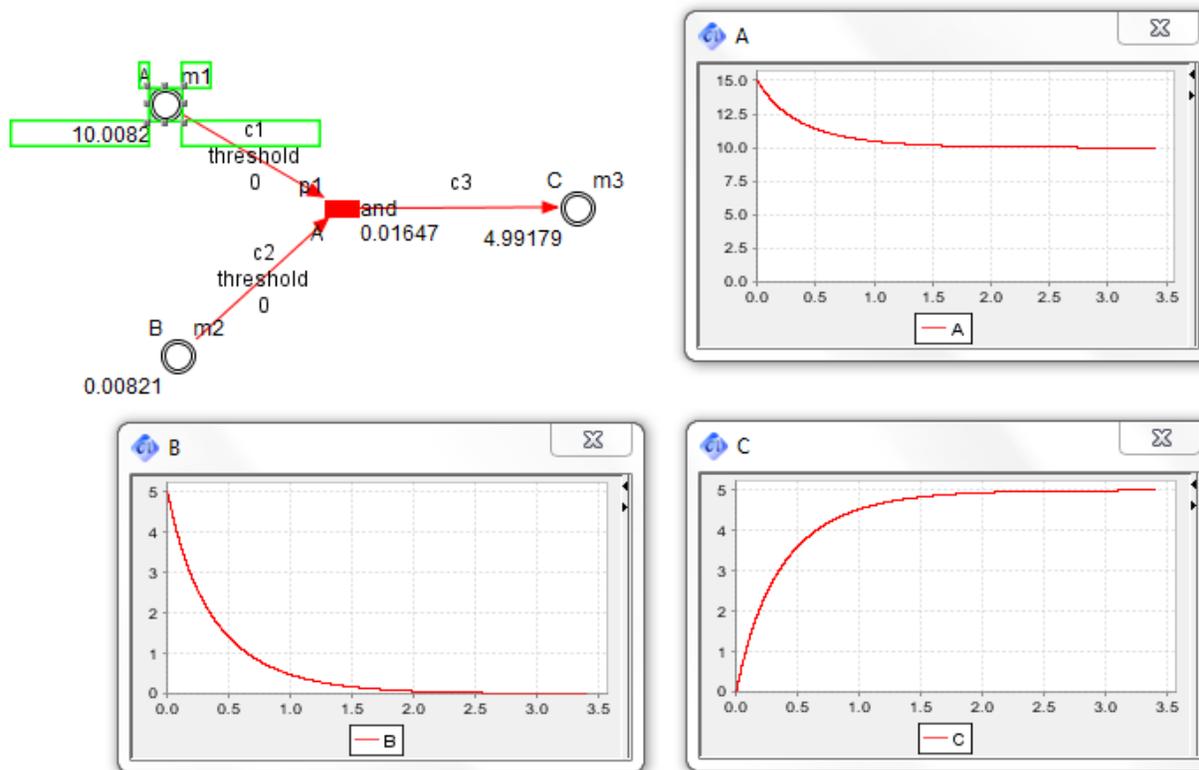
(a) Why does the concentration of A never reach zero? What value does it reach? What amount of C is ultimately produced?



**Figure 16.** Reactant and product plots for the reaction  $A + B \rightarrow C$ . In this case the starting values of A and B are 10 and 5, respectively. Only 5 units of C can be made.

In this example, A goes to 5. This is because B is the rate limiting reactant, and its starting concentration is 5. So as soon as it runs out, the reaction will not consume any more A.

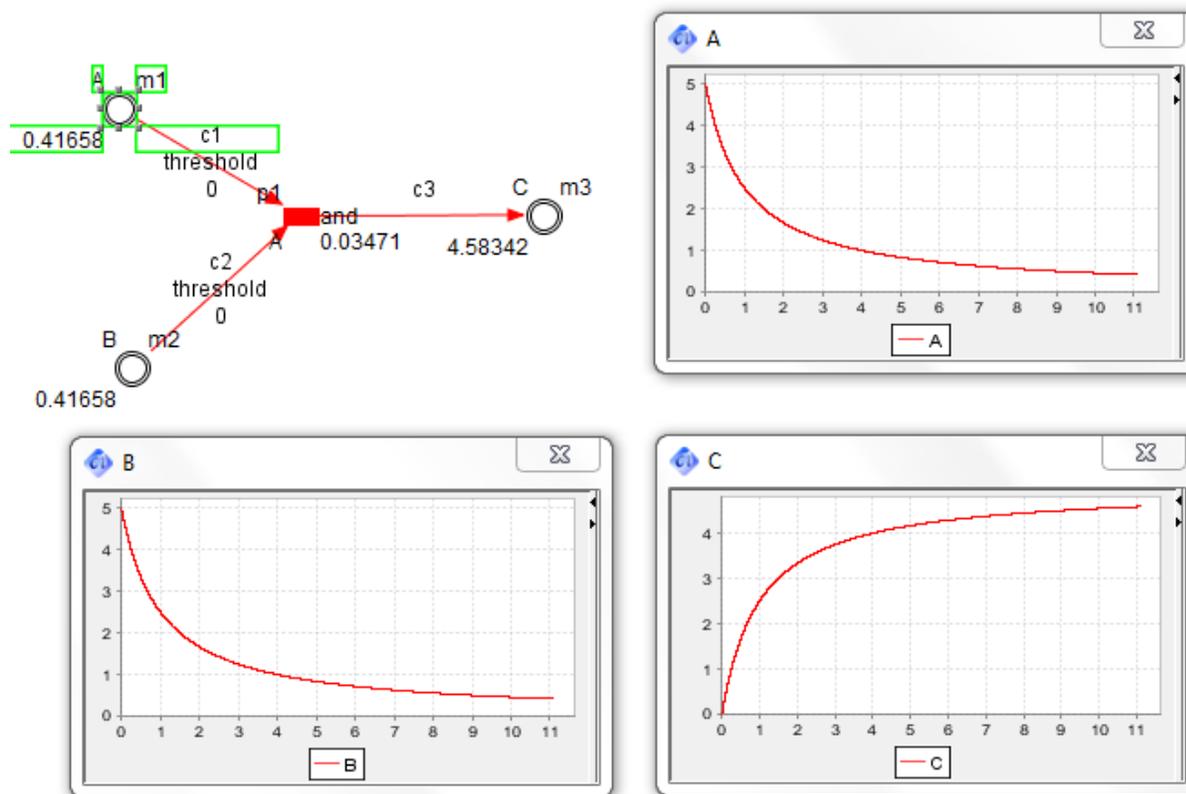
(b) What value does the concentration of A reach if you change the initial value to 15? Did this change the results at all? Explain.



**Figure 17.** Reactant and product plots for the reaction  $A + B \rightarrow C$ . In this case the starting values of A and B are 15 and 5, respectively. Again, only 5 units of C can be made.

Here, the concentration of A goes to 10 when the initial concentration is 15. Again, once all of the 5 units of B are consumed, the reaction will not proceed further in the forward direction.

(c) Obtain results for an initial value of A of 5. How is this different from the preceding results? Explain.



**Figure 18.** Reactant and product plots for the reaction  $A + B \rightarrow C$ . In this case the starting values of A and B are 5 and 5, respectively. Again, only 5 units of C can be made, but both A and B are completely consumed.

In this final example, the asymptote approaches zero because the starting value of A and B are the same, so neither is rate-limiting.