PK Simulation
Tutorials & Beginner's Guide

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System Requirements: MATLAB R2012b (older versions of MATLAB might not work with this program), OSX *(Mac)* or Windows 7 *(PC)*.

Program Description: *PK Simulation is a tool designed to assist researchers in designing PET experiments. PK Simulation allows users to select specific radiotracers, arterial input functions, and compartmental models in order to generate brain-tissue time activity curves. The simulator also includes options to simulate radiotracer "challenges" with endogenous neurotransmitter and/or psychoactive drugs.*

June, 2015 – Hooker Research Group
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Getting Started:

System Requirements:

Be sure your system adheres to the following requirements:

1. Windows 7 (PC) or OSX (Mac).
2. MATLAB version R2012b or newer.

Before continuing, please ensure you are in the "Default View" of MATLAB. (Select "Layout" > "Default" from the Toolbar.)

Add Scripts to MATLAB's Current Path:

Option 1: Add Scripts to the MATLAB Root

1. Download the PK_Simulation.zip folder to the location of your MATLAB root.
    a. To locate your MATLAB root, open MATLAB and type: `matlabroot` into the command prompt.
2. Be sure to unzip all files before trying to use the PK Simulation tool.

Option 2: Add Scripts to a Custom Location

1. Download the PK_Simulation.zip folder to your custom location (i.e. C:\Documents\MyCodes)
2. Open MATLAB
3. Add your custom location to the current path.
    a. Browse for the folder where you downloaded the scripts in the left panel labeled "Current Folder"
    b. Right click on the folder and select "Add to Current Path" > "Selected Folders and Subfolders"

Add Data Files to MATLAB's Current Path:

1. Browse for the data files you wish to analyze in the left panel labeled "Current Folder".
2. Add the data files to the current path.
    a. Right click on the folder containing the data files and select "Add to Current Path" > "Selected Folders and Subfolders"

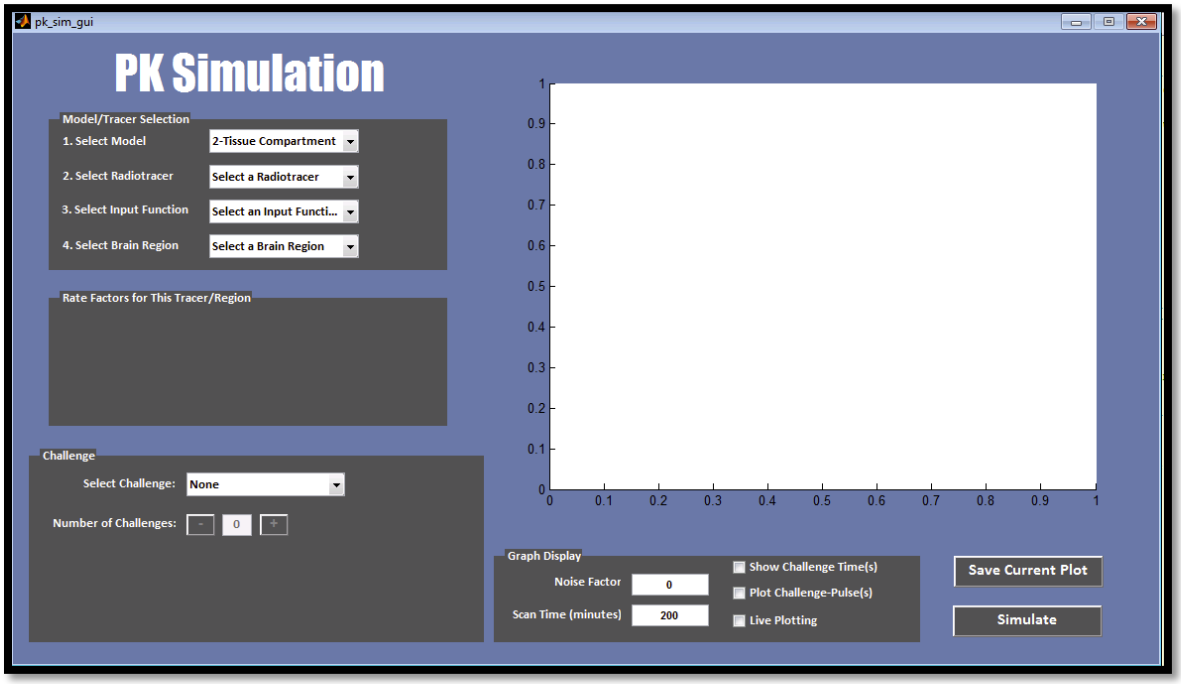
Navigate into the PK Simulation Main Directory

1. Double click on the folder you added to the path. In the left panel labeled "Current Folder" you should see many files and folders, including one file called `pk_sim_main.m`

Open PK Simulation

Type `pk_sim_gui` into the command window. **Figure 1** below shows the window that should appear:

Figure 1:



Congratulations! You have successfully opened PK Simulation on your computer and are ready to start simulating data.

If the window did not appear or MATLAB displayed an error, be sure you have added the PK Simulation scripts to your current path. Try searching your computer for "pk_sim_gui.m" or "pk_sim_gui.fig" and ensure that the location of these files has been added to the current path.

Tutorials

This section of the User Guide contains several tutorials designed to get you comfortable using the PK Simulation Tool.

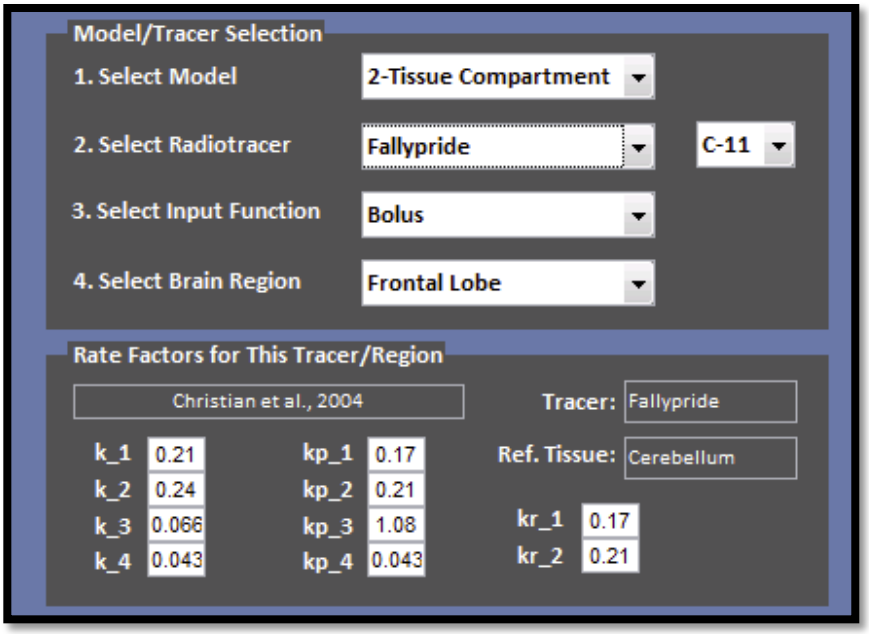
Your First Simulation:

If you have not already done so, type `pk_sim_gui` into the command prompt and hit enter. The PK Simulation tool should open.

1. First **select a compartment model** to work with (for now, stick with the **Two-Tissue Compartment** model). The default model is the Two-Tissue Compartment Model. Deciding which model to use usually depends on the kinetics of the radiotracer that will be used during the scan.

2. Next, **select a radiotracer** from the drop-down list. For this tutorial, we'll have you pick **Fallypride**. After choosing a radiotracer, several pieces of information should pop up in the section of the GUI labeled "Rate Factors for This Tracer/Region." (See **Figure 2** below for an example of what your screen might look like.) Additionally, choosing a radiotracer allows you to select the radioactive isotope that is attached to the ligand. For this tutorial, make sure C-11 is selected from the dropdown menu that appears.

Figure 2:

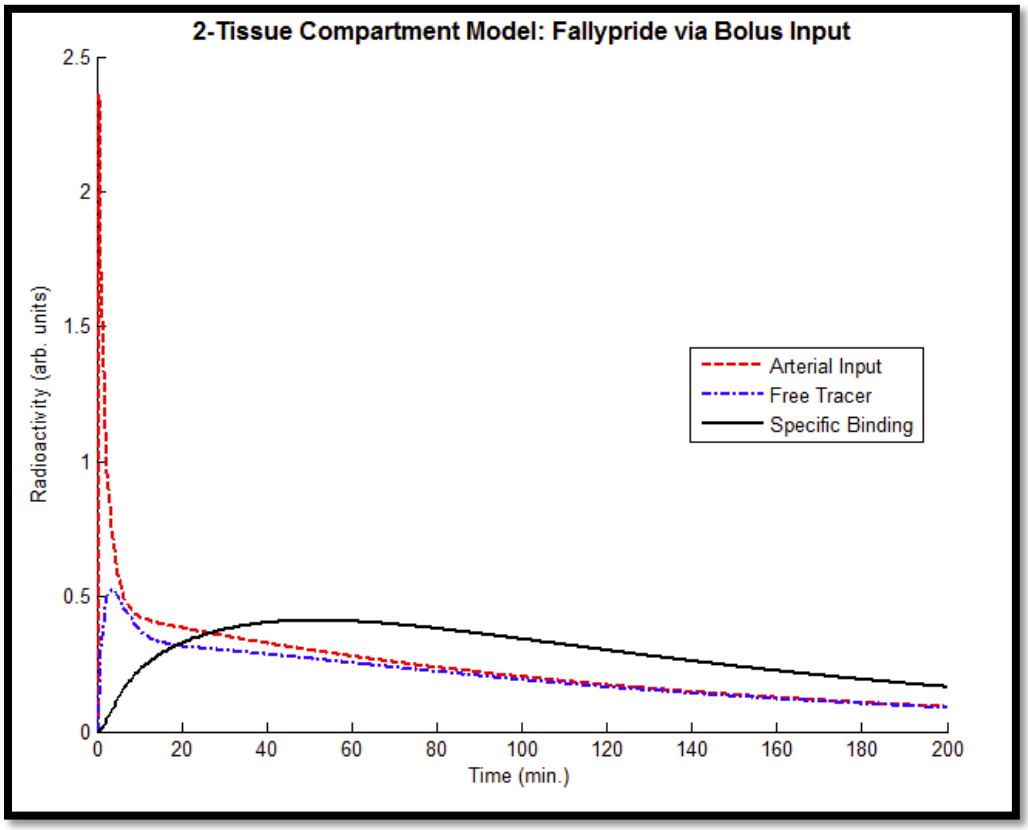


3. **Choose an input function** from the third drop-down list. For this tutorial, choose **Bolus**. There are several built-in functions available and the option to create your own custom input function.

4. **Select a brain region** from the final drop-down list. For this tutorial, select **Frontal Lobe**. The list of brain regions will automatically populate depending on the radiotracer and compartmental model you have chosen.

5. **Click Simulate** in the bottom right corner of the GUI window. A graph should appear in the plot-window, summarizing the results of the simulation. (See **Figure 3** for an example.)

Figure 3:



Using a Custom Input Function:

By default, PK Simulation includes several built-in arterial input functions that can be used in a simulation. These include bolus input, infusion input, and bolus plus continuous infusion. A custom input function enables users to use statistical data collected from blood-plasma during experiments, or to use custom mathematical functions as input. Follow the instructions below to

1. **Be sure your text file is formatted correctly.** The simulation tool expects to read in a text file consisting of two columns of data (columns should be separated by a tab character). If the text file contains headers, that should not affect the way the data is gathered. Take note of the location of your text file.

2. Select **Custom** from the input menu on the main GUI screen. A button should appear that says **Customize**.

Figure 4:

3. Click **Customize**. The Custom Input Function window should appear. From here, you have two options:

Option 1: Use Data From a Text File:

4. Select **Load .txt File** from the drop-down menu at the top.

5. Click **Browse** and select your text file. *(If your text file is written in a format other than .txt (e.g. .bld), click the drop down menu that says "(*.txt)" on the bottom right corner of the Open File dialogue box and click "All Files").*

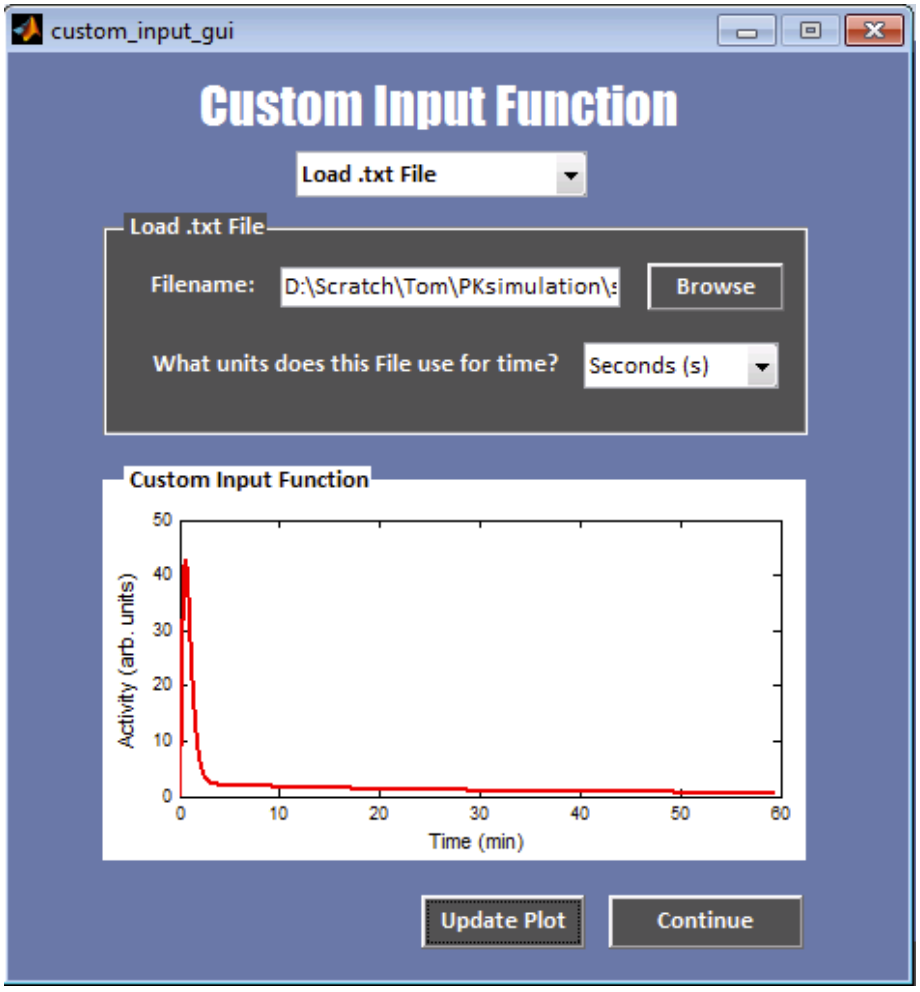
6. In the drop-down menu below the browse button, **select the units of time that your text file is written in**. *For example, if the time column of your text file contains measurements ranging from 0 seconds to 3600 seconds, select "Seconds (s)" from the drop-down menu.* The units of time need to be selected so that the computer can convert everything into minutes. (See **Figure 5** for an example of what you might see up to this point.)

   NOTE: This simulation tool only plots one point every 30 seconds for the duration of the specified scan time.

7. Click **Update Plot** to view your custom input function.

8. Click **Continue** to apply your custom input function to the current simulation.

Figure 5:



Option 2: Use a Custom Equation:

4. Select **Use Custom Equation** from the drop-down menu at the top.

5. Type your desired equation into the **Equation** text box. When typing in an equation, be sure to use **t (time)** as your x-variable. For this tutorial, use the following equation:

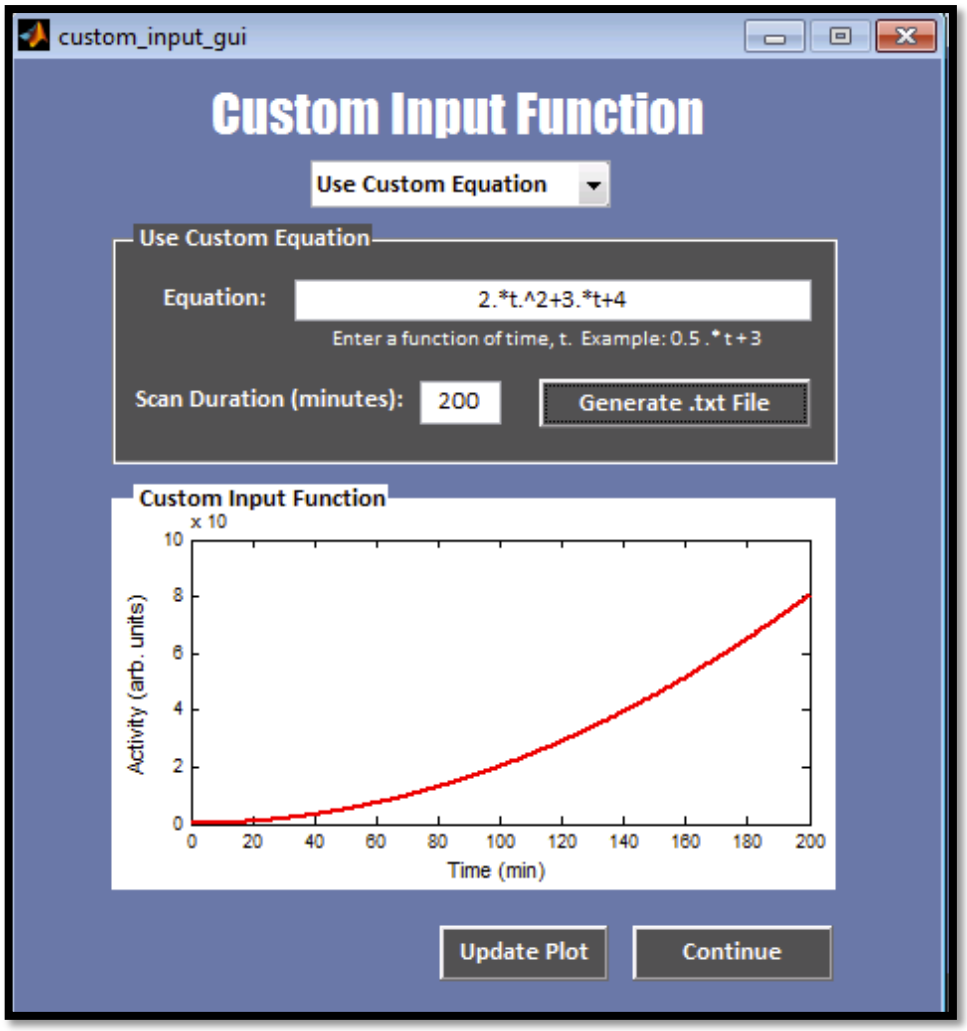
   2.*t.^2+3.*t+4

   (This is equivalent to : $2t^2 + 3t + 4$)

6. Type in the desired scan duration (default = 200 minutes) and click **Generate .txt File** and select a name and location for the custom input. *When you create an equation, a text file is created so that you can re-use the same custom input later by simply loading a txt file.* See **Figure 6** for an updated visual of what everything should look like up to this point.

7. Click **Continue** to apply your custom input to the current simulation.

Figure 6:



Simulating Competitive Binding:

The PK Simulation tool contains a feature that allows users to test how different pharmacological challenges might affect the time activity curve output. Two types of challenges are possible with PK Simulation: **Challenge by Endogenous Neurotransmitter** and **Challenge by Altering Rate Constants**.

Before you begin this tutorial, run a simulation using a Two-Tissue Compartmnet model, Raclopride as your radiotracer, and Infusion as your input function. Also be sure to change the **scan time** to **300 minutes** in the **Graph Display Panel** below the graphs.

Challenge by Endogenous Neurotransmitter:

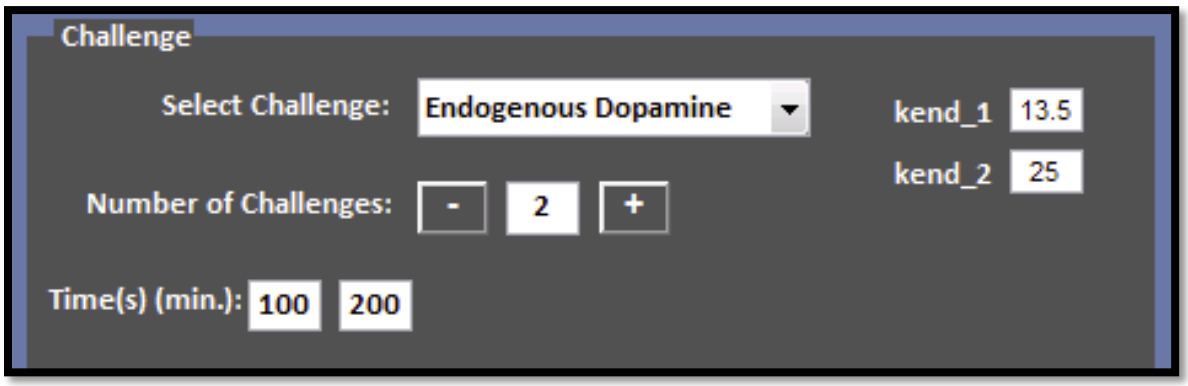
1. To begin a challenge by endogenous neurotransmitter, select **Endogenous Dopamine** from the "Select Challenge" drop-down menu.

2. Increase the **Number of Challenges** to 2 by clicking the **+** button.

3. To alter the amplitude of the endogenous pulse, change the rate constants kend_1 and/or kend_2. For this tutorial, we will leave them as their defaults.

4. Make the first challenge occur at 100 minutes and the second challenge occur at 200 minutes by changing the values in the boxes next to "Time(s) (min):" See **Figure 7** for a view of what the Challenge Panel should look like up to this point:

Figure 7:



5. Be sure the scan time is set to 300 minutes. Click **Simulate** to run the simulation. A graph like the one in **Figure 8** should appear. Toggle the check box next to **Show Challenge Time(s)** to display green vertical lines that mark the times at which challenges occur. Toggle the box next to **Plot Challenge-Pulse(s)** to show a subplot of the endogenous pulses. Checking both boxes would result in a plot like the one in **Figure 9**.

Figure 8:

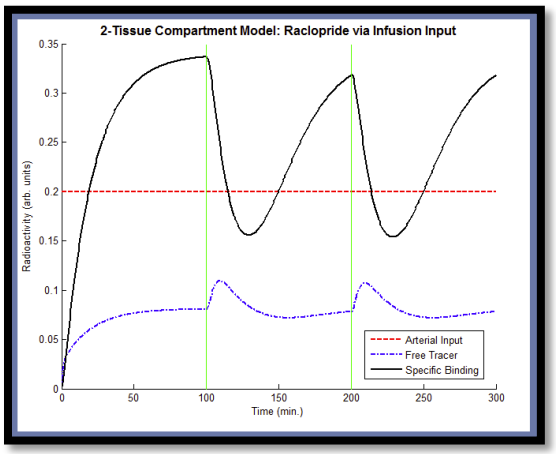
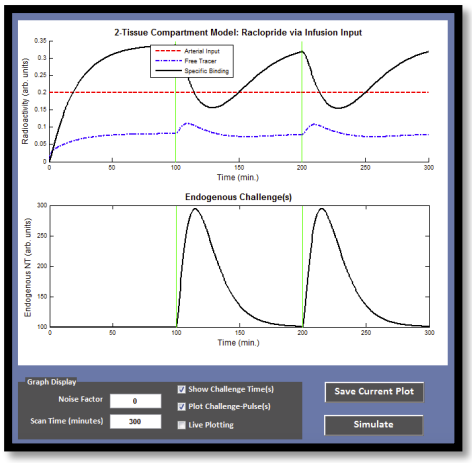


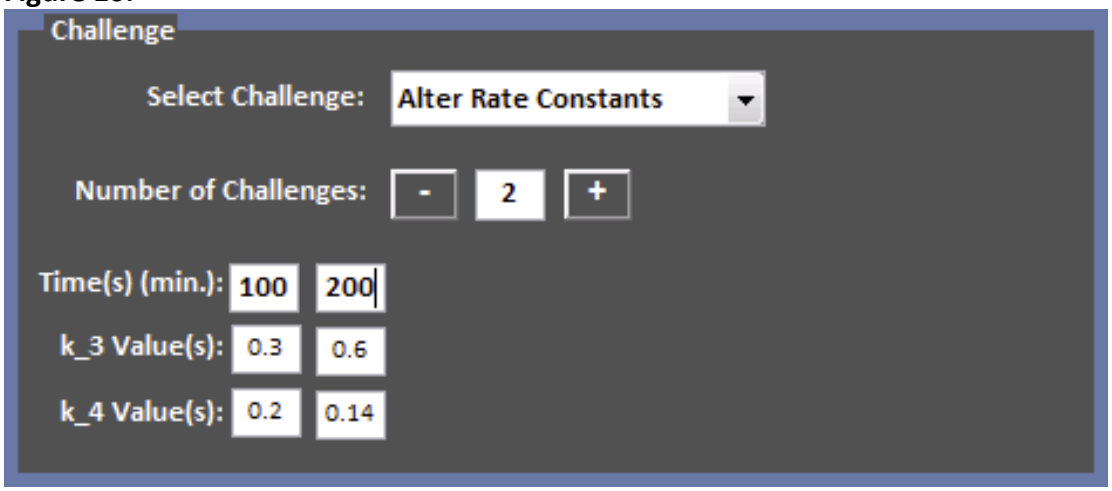
Figure 9:



Challenge by Altering Rate Constants

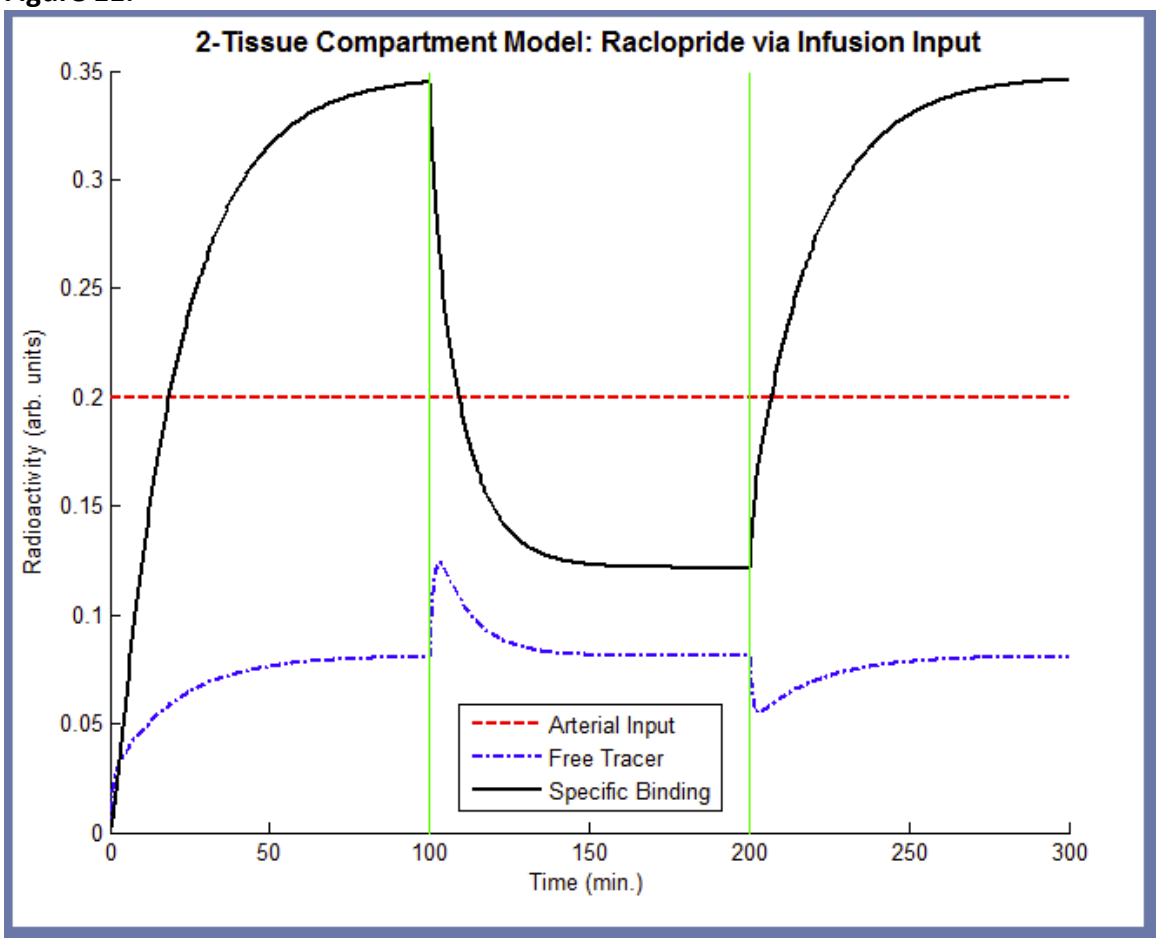
1. Select **Alter Rate Constants** from the drop-down menu in the **Challenge** panel of the GUI.
2. Increase the **Number of Challenges** to 2 by clicking the **+** button.
3. For this tutorial, change the boxes that appear to match the values shown in **Figure 10**. This will make it so that at time = 100 minutes, k3 will decrease to 0.3 and k4 will increase to 0.2 and at time = 200 minutes, both rate constants will return to their original value.

Figure 10:



4. Be sure the scan time is se to 300 minutes. Click **Simulate**. A graph similar to that in **Figure 11** should appear. The vertical green lines mark the times at which rate constants change. To toggle the appearance of these green lines, click the check box next to **Show Challenge Times** in the **Graph Display Panel**.

Figure 11:



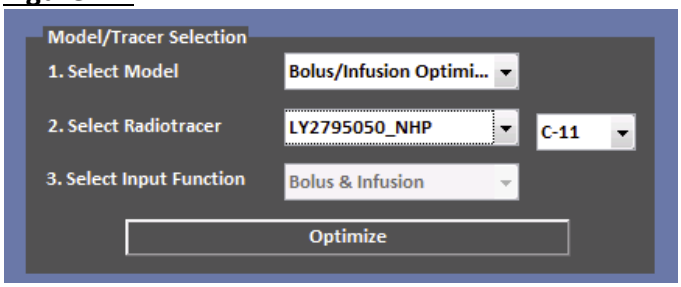
Simulating Bolus + Continuous Infusion Input:

The PK Simulation Tool contains several existing input functions that users can apply to compartment models. One unique input function is the **Bolus & Infusion** input ,which can be selected from the **Input Function drop-down menu** (#3 on the main GUI). The Bolus + Continuous Infusion method is unique because it allows researchers to model tissue uptake without using a compartment model. You will see that when you select **Bolus & Infusion**, the model and brain region menus become disabled and an **Options** button will appear (See **Figure 12**). For a quick tutorial on Bolus & Infusion input, follow the instructions below:

1. Select **Bolus/Infusion Optimization** from the model dropdown menu on the main GUI.

2. Select **LY2795050_NHP** from the Radiotracer dropdown menu on the main GUI.

Figure 12:



3. Click the **Optimize** button. The Bolus + Infusion Options GUI will appear. The name of the radiotracer you selected should be shown in the top right corner.

4. Click the check-box next to **Using Simulated Data**. The label should change to **Using Real Data**. This allows us to use real study data from a .tac file to generate the bolus-infusion curves. *(You can also click "Browse" to substitute another .tac file, or you can uncheck the box and use simulated data.)*

5. Select **merged_Thalamus** from the **Brain Region** dropdown menu.

6. Click the **+** button to get 4 K_{bol} Values to test. Fill in the four boxes with the K_{bol} values of 30, 60, 90, and 120. See **Figure 13** for an image of what you should currently be seeing.

7. Click **Continue** to run the simulation. A graph similar to the one in **Figure 14** should appear. Like any other graph, you can adjust the noise and scan time parameters in the **Graph Display** panel.

Figure 13:

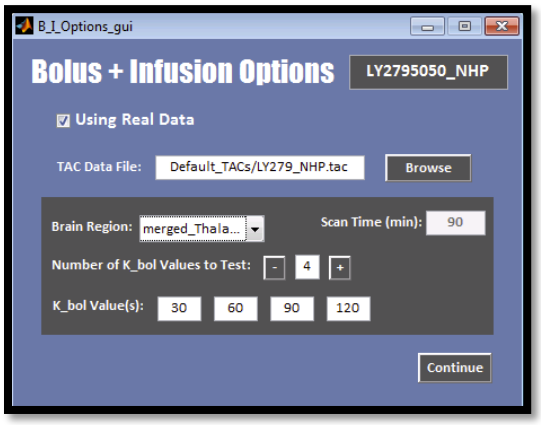
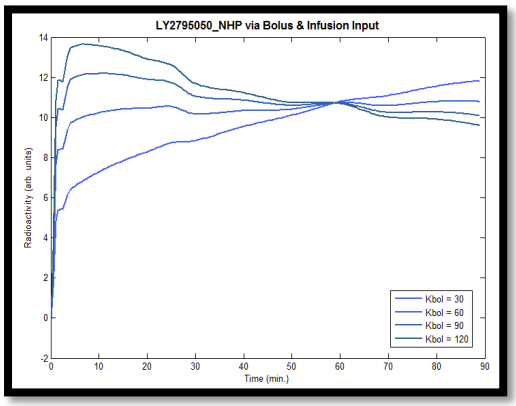


Figure 14:



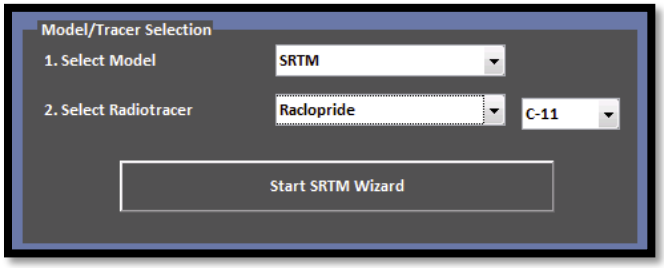
Using a Reference Tissue Model

In addition to the 1-Tissue, 2-Tissue, and 2-Tissue Irreversible Compartment Models, the PK Simulation Tool has a built in Simplified Reference Tissue Model (SRTM). A reference tissue model avoids the need for blood-data by comparing a region of interest to a reference region. For a quick tutorial on how the SRTM feature works, follow the instructions below:

1. Select **SRTM** from the **Model** dropdown menu.

2. Select **Raclopride** from the **Radiotracer** dropdown menu. Your screen should look similar to **Figure 15** below.

Figure 15:



3. Click the button labeled **Start SRTM Wizard**. A large window will appear.

4. Select **Bolus & Infusion** from the **Input Method** dropdown menu.

5. Change the **Kbol** value to **120**.

6. Click **Update Plot** in the R.O.I. panel. A blue line should appear on the graph to the right.

7. Click **Update Plot** in the Reference Region panel. A red line should appear on the graph to the right. Your screen should look similar to **Figure 16** on the next page.

8. Click **Continue**. The main plot should automatically populate. You will see a line representing the concentration of radiotracer in the region of interest, a line representing the concentration of radiotracer in the reference region, and a line representing the Dynamic Binding Potential. The concentrations are plotted on the right-hand y-axis and the dynamic binding potential is plotted on the left-hand y-axis. The graph should look similar to the one in **Figure 17**.

9. To add competition to the SRTM, adjust the settings on the **Challenge** panel the same way you would for any other kinetic model, and click **Simulate**. (See pages 9-12 of this manual for more information about competition.)

Figure 16:

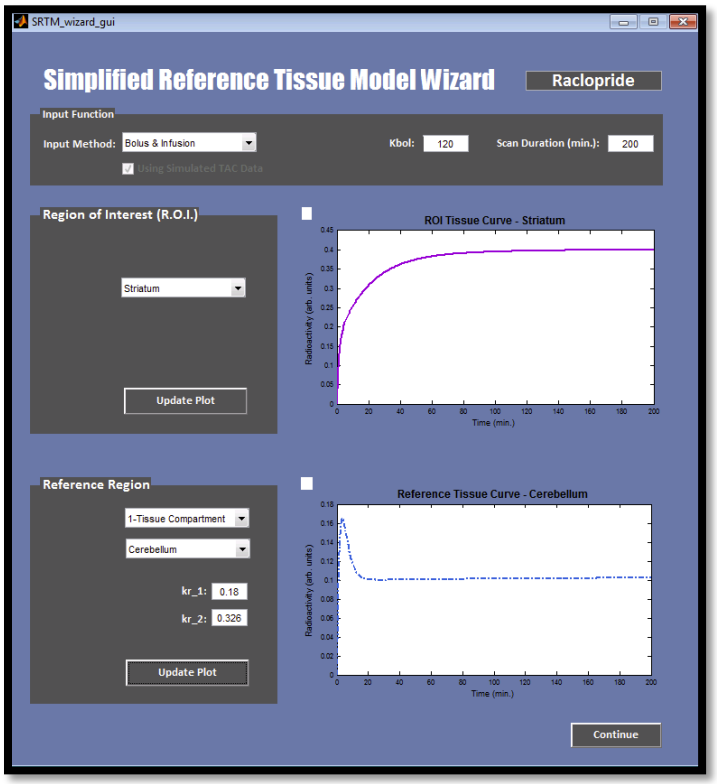
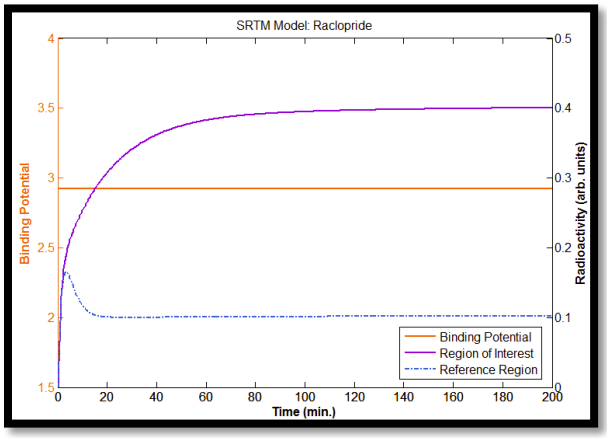


Figure 17:



Add/Edit Radiotracer Properties

While the PK Simulation tool comes with 9 built-in radiotracers, users may wish to add other radiotracers to the tool.

Each of the built-in radiotracers for the PK Simulation Tool is stored as a .txt file. Each time the program is opened, it reads in these text files and converts them into a structure array. The easiest way to add an additional built-in radiotracer is to create a new radiotracer text file. While this is not necessarily difficult to do, careful attention must be paid to the formatting of the text file. Deviations from acceptable formatting will cause the program to crash at startup.

Currently, a small GUI is being developed that should make the addition and deletion of radiotracers more user-friendly in the future.

The formatting of a radiotracer text file is as follows:

```
Radiotracer Name
Reference to literature
Brain Reference Region
Radioactive Ligand (if multiple, put on separate lines)
*
List of all brain areas for which kinetics are available
(if multiple, put on separate lines)
*
*****1-Tissue Compartment*****
Brain Area 1
2 Rate Constants separated by tabs
Brain Area 2
2 Rate Constants separated by tabs
*****2-Tissue Compartment*****
Brain Area 1
4 Rate Constants separated by tabs
Brain Area 2
4 Rate Constants separated by tabs
Brain Area 3
4 Rate Constants separated by tabs
*****Other K-Values*****
kp
4 kp Rate Constants separated by tabs
kr
2 Rate Constants separated by tabs (these are Reference Region rates)
k_da
2 Rate Constants separated by tabs (these are kon & koff for NTs)
Directory of file with TAC data (if N/A, write “Not Available”).
```

If any rate constants or other numbers are unavailable, use the number **0** or **NaN**.

Below, we have included the text file for Diprenorphine:

```
Diprenorphine
Jones, 1994, J. Neurosci Methods
Occipital Cortex
C-11
F-18
*
General
Thalamus
Striatum
Anterior Cortex
Posterior Cortex
Hippocampus
Medulla
Spinal Cord
*
*****1-Tissue Compartment*****
general
0   0
*****2-Tissue Compartment*****
general
0.4 0.15    0.4 0.07
thalamus
1.25    0.247   0.0155  0.112
striatum
1.13    0.228   0.0153  0.124
ant_cx
1.27    0.313   0.0173  0.111
post_cx
1.3 0.308   0.0226  0.119
hippocampus
0.93    0.198   0.0275  0.154
medulla
1.15    0.247   0.0203  0.12
spinal_cord
0.8 0.209   0.0184  0.09
*****Other K-Values*****
kp
0.36    0.19    0.48    0.08
kr
0.4 0.15
k_da
NaN
Not Available
```

All of the radiotracer text files are stored in the directory **PKsimulation → Radiotracers**.

Troubleshooting:

1. The PK Simulation GUI does not appear when I type `pk_sim_gui.`

Enusre that the PK Simulation scripts have been added to the current MATLAB path.
See page 3 for details.