VANTAGE RA QSP MODEL v1.0

User guide

MARCH 2020

Contents

1. Introduction

This document is a step-by-step guide to help the user with installation, setup and usage of the Vantage RA QSP model ("RA Model") and some pre-existing features (like pre-defined variants and doses) in the SimBiology app of MATLAB. However, further analysis of the model, evaluating specific pathways, adding biology into effect diagram, etc. can be done by using other SimBiology features (for more details click here), MATLAB scripts and data analysis tools using R or Microsoft Excel.

2. Installation of the RA Model

The model requires MATLAB with SimBiology. To be able to follow this user guide, please install MATLAB 2019b with SimBiology version 5.9. Note that the model is tested and supported in older versions of MATLAB (earliest version 2017b), with SimBiology (earliest version 5.7) but, some functionality has been changed or removed in SimBiology version 5.9. This includes the replacement of the *Task Editor* of the SimBiology app with the *SimBiology Model Analyzer* app. For more details, please refer to the SimBiology Release Notes.
You will also need to install the Parallel Computing Toolbox to run the simulations in parallel.

To report any issues, please email the Vantage RA team here.

3. Exploring the model

3.1. Opening the project file

1. Ensure that the project file "Vantage RA QSP Model v1.0.sbproj" and the "MM.m" MATLAB script are saved in the same folder.
2. Set the working directory in MATLAB to the folder containing the project file by typing the following command in the *Command Window* in MATLAB (Figure 1),
   cd ("full path of the folder containing the project file").
   For example, if the project file is stored on the C drive in a folder called *Vantage RA Model*, type cd ("C:/Vantage RA Model").
3. Open SimBiology from the *Apps* tab in MATLAB (Figure 1).

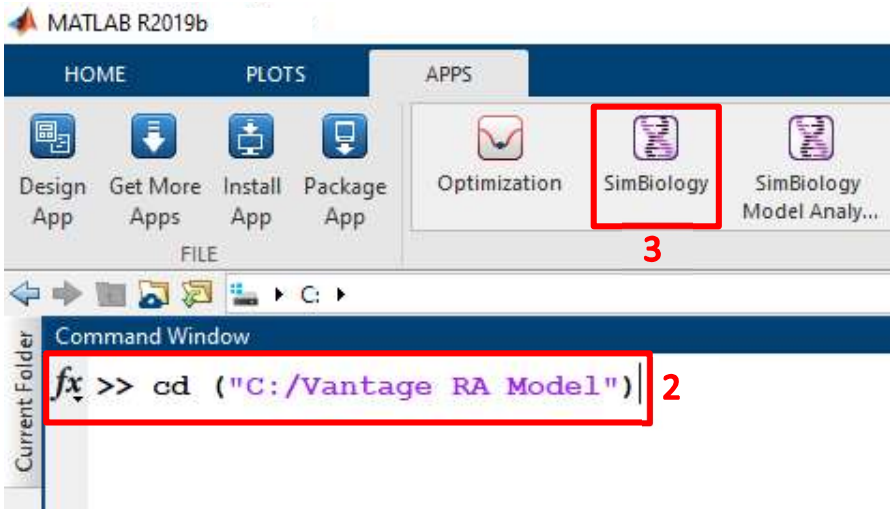


Figure 1

4. If the project file has not been opened recently, click Open, navigate to the location of the project file and select "Vantage RA QSP Model v1.0.sbproj" (Figure 2, box 4a), else the project file will appear in the list of recently opened files. Simply select "Vantage RA QSP Model v1.0.sbproj" from the list. (Figure 2, box 4b).

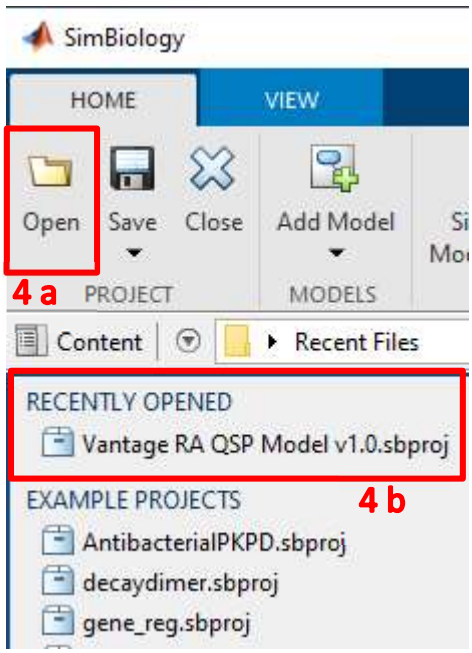


Figure 2

Note that on opening the project file, MATLAB creates a new backup file (.bak) of the version prior to the saved version of the project in the working directory of the project. The files will remain in the working directory unless deleted by the user. Backups are useful when restoring a previous version of the model but can take up a lot of space. Users can delete the backups if they are no longer required.

3.2. Model diagram

Upon opening a new project file, with no previous simulations, the model diagram will be displayed in the SimBiology window. However, if the project has stored simulation results, a window with the following items will be displayed (Figure 3),

Project Workspace, Project Programs, Program Results and Project Description.

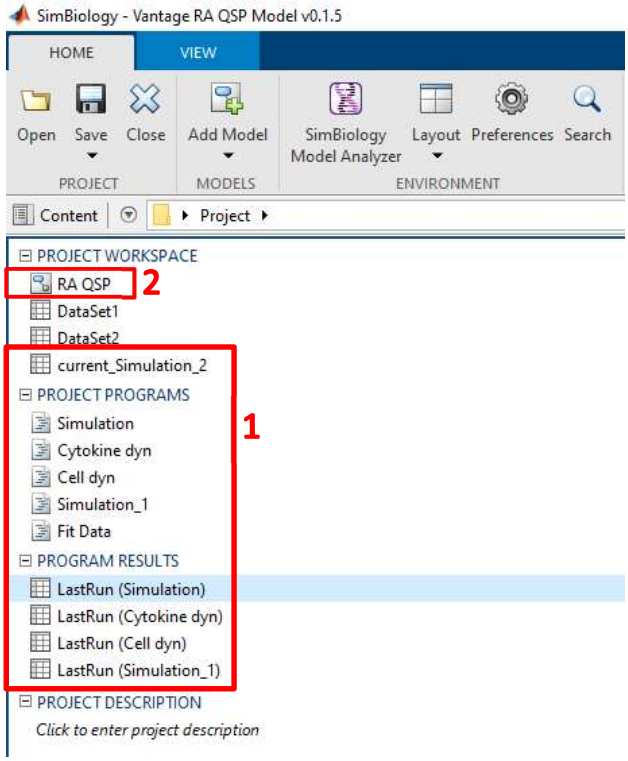


Figure 3

1. To view and analyze any previously run simulations, click on the simulation of interest. This will open the *SimBiology Model Analyzer* app (Figure 3).
2. To view the model diagram and other model components, select ***RA QSP*** from *Project Workspace* (Figure 3). The model diagram will be displayed. Clicking on the different blocks in the diagram will open the *Block Property Editor* that provides the details of the block. To view all the model reactions, parameters, existing variants, doses, events etc. in a tabular form or to view the model in an equation-based format, select the appropriate options from *Open* under the *Model* tab. (Figure 4).

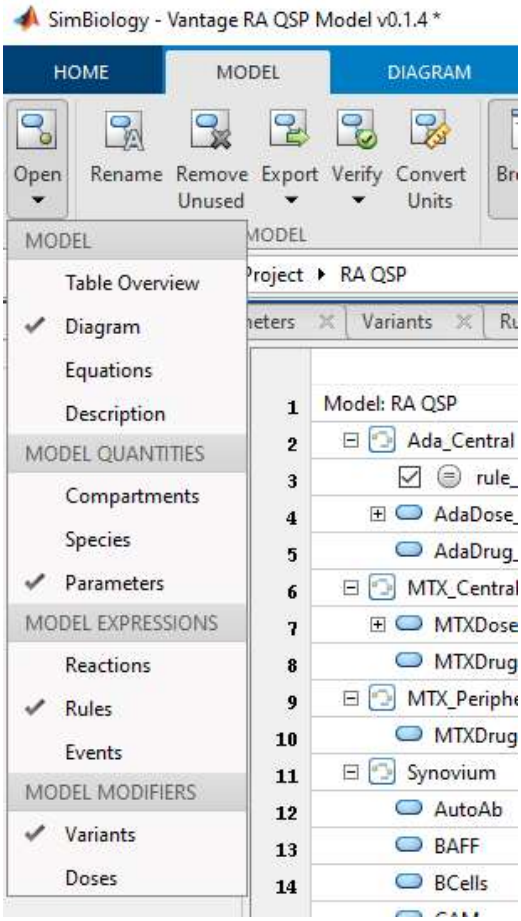


Figure 4

4. Using SimBiology Model Analyzer

Figure 5

1. Open the *SimBiology Model Analyzer* from the *Model* tab (Figure 5). *SimBiology Model Analyzer* will open as a separate window. If the project file has no previously stored

simulations, a blank window will be displayed (Figure 6) else, a panel with the last simulation in the *Workspace* will be opened by default (Figure 7).

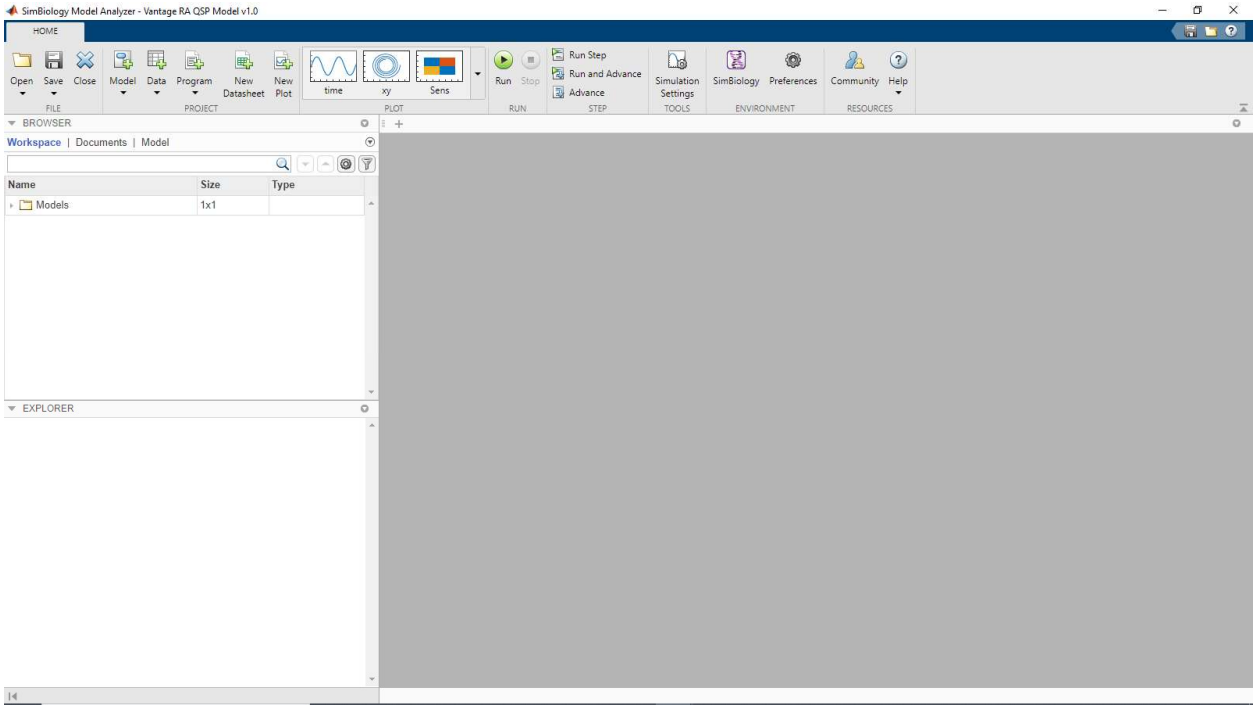


Figure 6

2. Click on *Run* to re-run this simulation (Figure 7). Note that doing this will replace the previously stored results for this simulation.
3. When simulating large models or running repeated multiple simulations, select the checkbox next to the *Prepare the model for accelerated simulation*. This option converts the model to compiled C code to enable faster execution.
4. Additionally, if program can be run in parallel, the *Parallel* option will be enabled in the simulation panel Click on it to enable parallel computing (Figure 7). Note that this requires MATLAB's *Parallel Computing Toolbox*. This option is particularly helpful when running a large set of simulations since it runs them in parallel thus saving computation time.

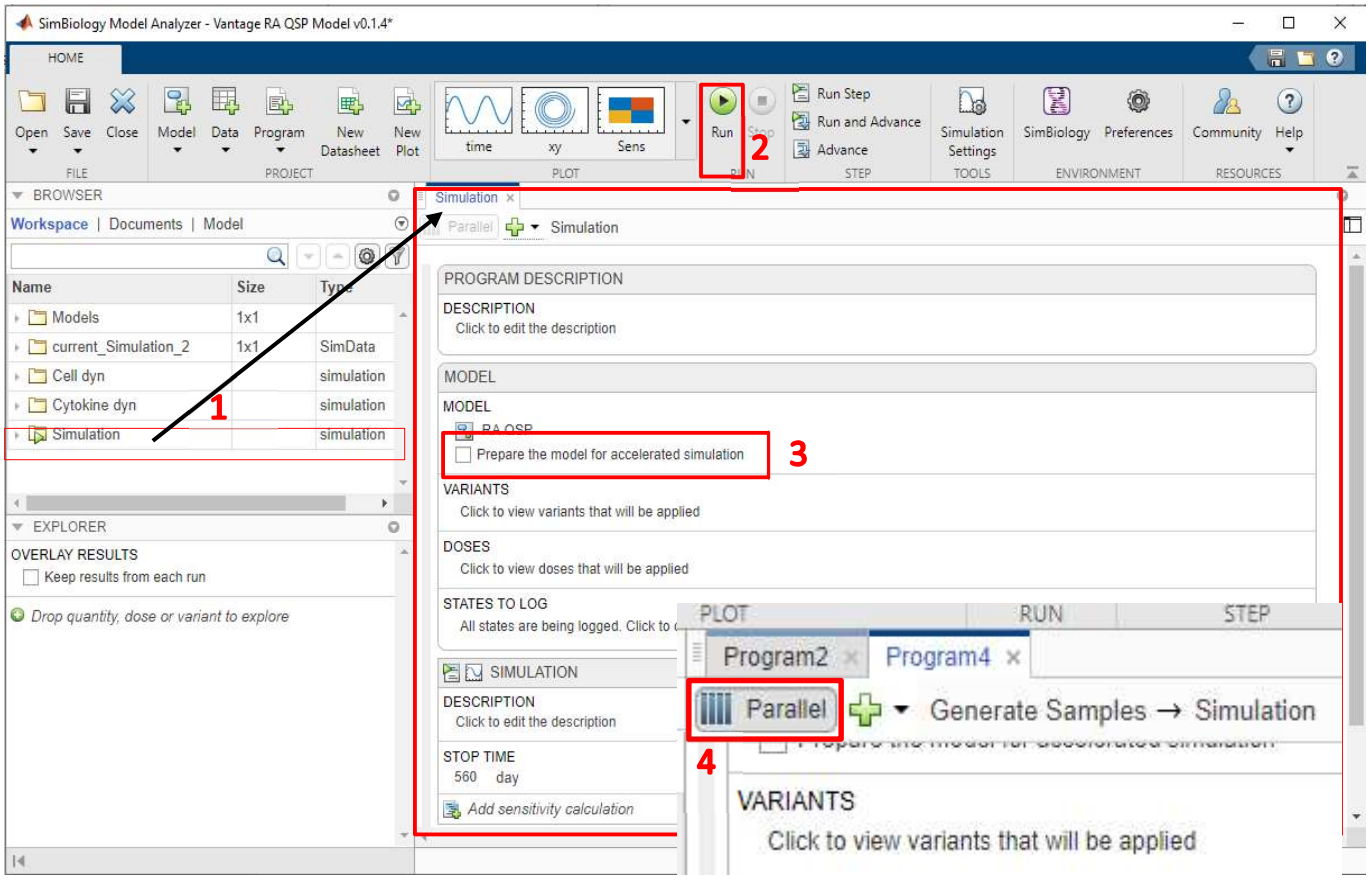


Figure 7

4.1. Running a new simulation

1. Select *Simulate Model* from the *Program* menu (Figure 8). A new program panel (say *Program1*) will be opened (Figure 9).
2. Click on *Run* to simulate the model with the baseline parameter values and initial conditions. (Figure 7, box 2).

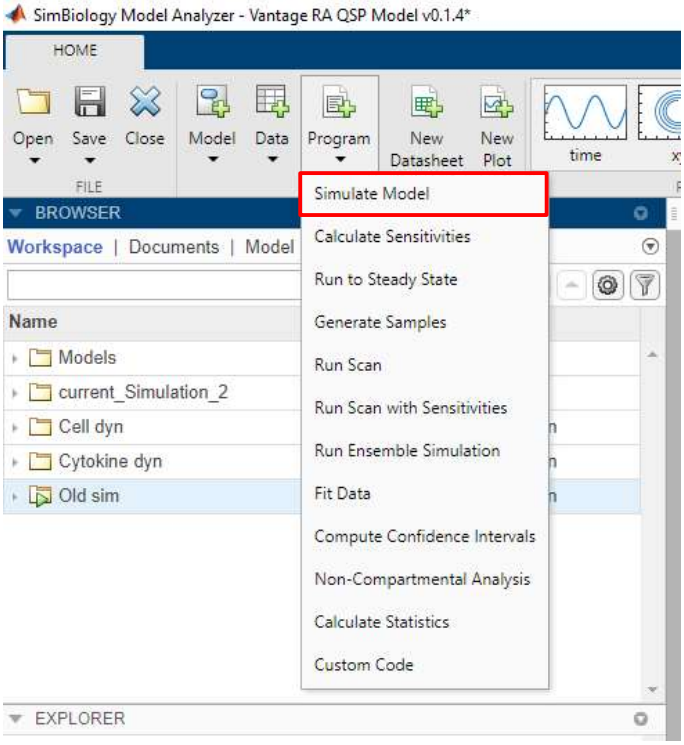


Figure 8

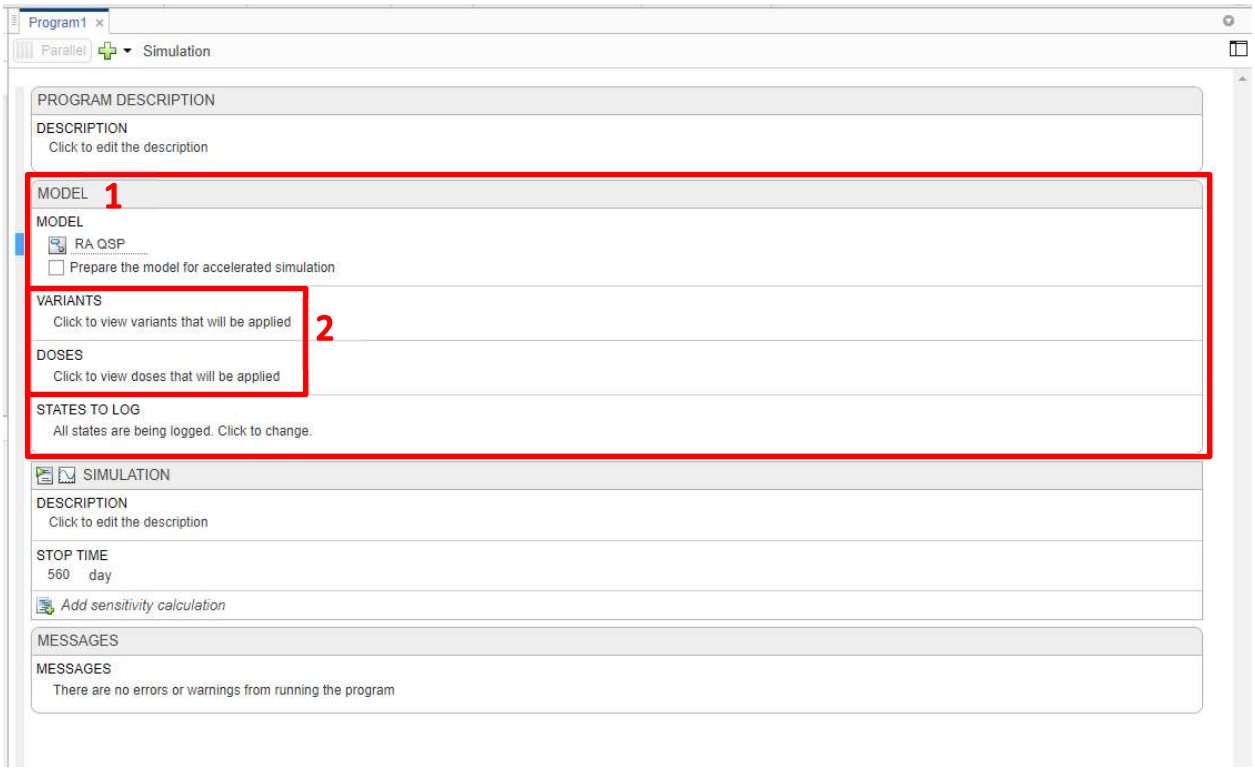


Figure 9

4.2. Viewing and plotting stored results

A new folder is created in the *Workspace* tab under the *Browser* panel for each new program selected from the *Program* menu. Simulation results are stored in the *Last Run* subfolder inside the simulation folder (Figure 10).

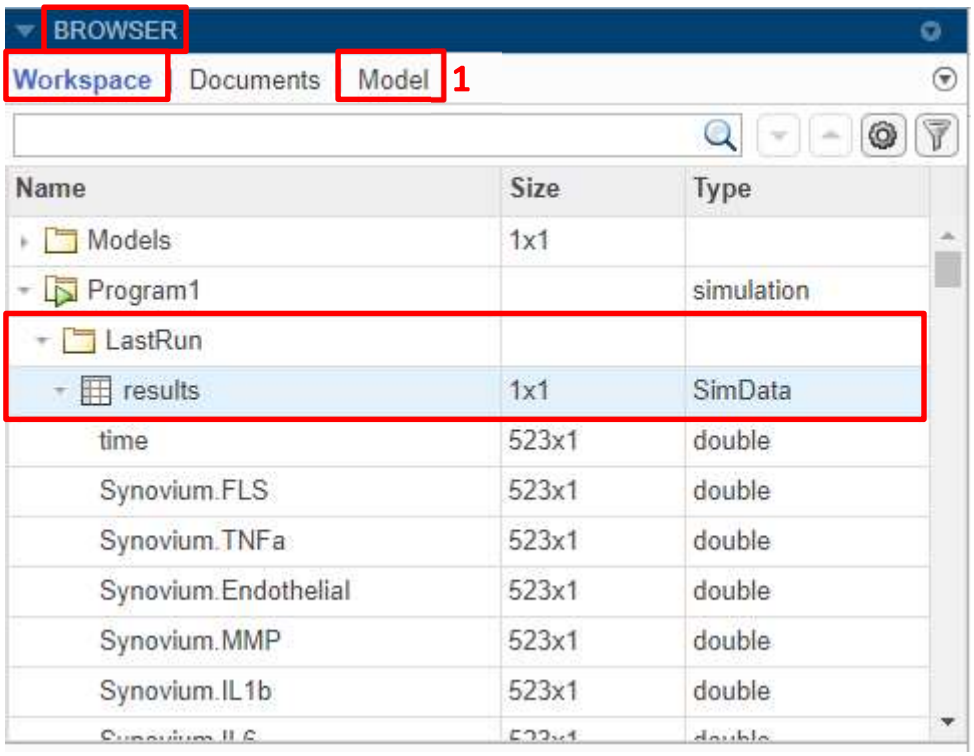


Figure 10

To store the results,

1. Open the *States To Log* tab in the Model subpanel under *Program1* panel (Figure 9, box 1).
2. Check all the items for which the results should be stored (Figure 11).

Figure 11

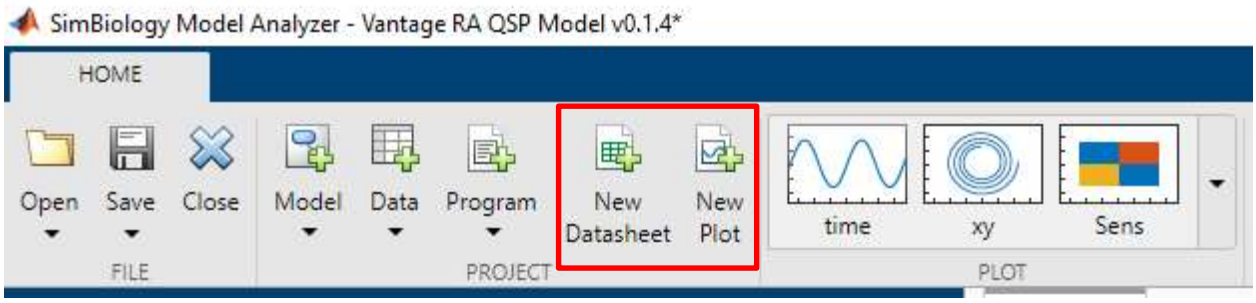
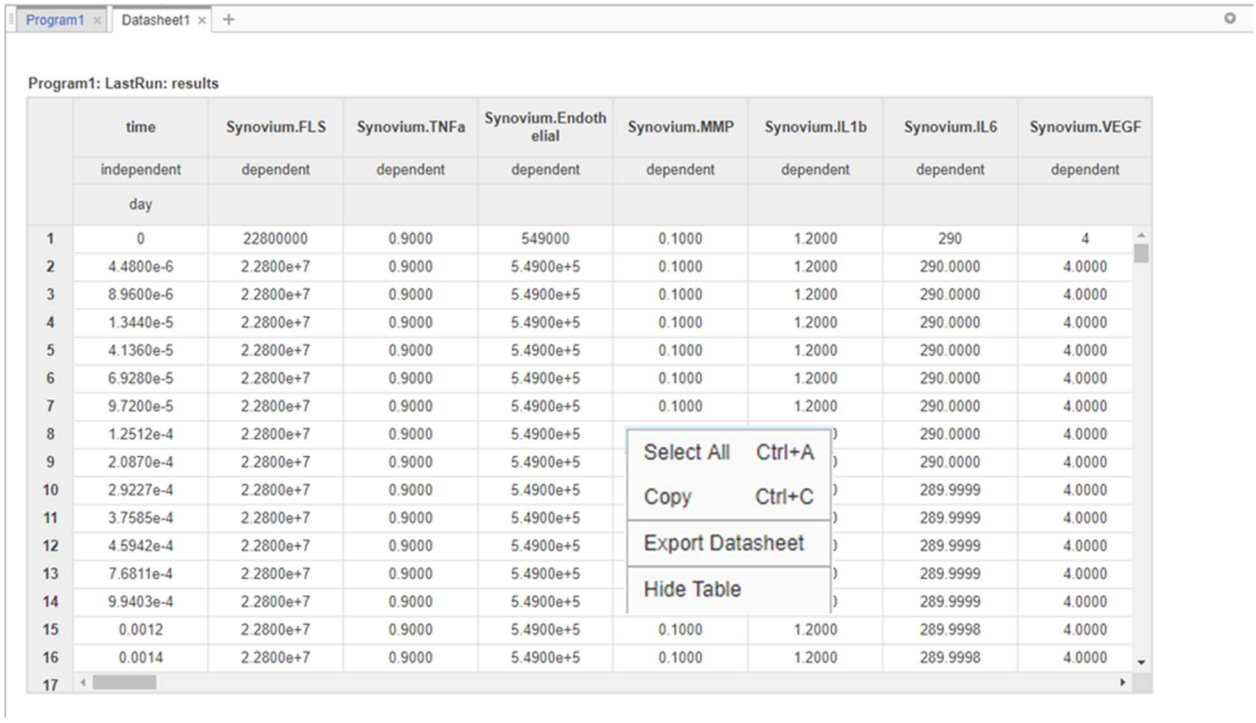


Figure 12

To view the results as a datasheet,

1. Click on the *New Datasheet* menu to open a blank datasheet (Figure 12).
2. Drag and drop the results matrix (Figure 10) into the datasheet. The datasheet will be populated as shown in Figure 13.
3. To view the data for only some species, select the species (hold on the **Shift** key for multiple selection) and drag and drop them into the datasheet.
4. If species are dropped in an existing datasheet, new columns for each species will be added to the existing table. If species from a different simulation are dropped, a new table will be created in the same datasheet.
5. Right click on the table and select *Export Datasheet* to save the datasheet as an Excel file.



	time	Synovium.FLS	Synovium.TNFa	Synovium.Endothelial	Synovium.MMP	Synovium.IL1b	Synovium.IL6	Synovium.VEGF
	independent	dependent	dependent	dependent	dependent	dependent	dependent	dependent
	day							
1	0	22800000	0.9000	549000	0.1000	1.2000	290	4
2	4.4800e-6	2.2800e+7	0.9000	5.4900e+5	0.1000	1.2000	290.0000	4.0000
3	8.9600e-6	2.2800e+7	0.9000	5.4900e+5	0.1000	1.2000	290.0000	4.0000
4	1.3440e-5	2.2800e+7	0.9000	5.4900e+5	0.1000	1.2000	290.0000	4.0000
5	4.1360e-5	2.2800e+7	0.9000	5.4900e+5	0.1000	1.2000	290.0000	4.0000
6	6.9280e-5	2.2800e+7	0.9000	5.4900e+5	0.1000	1.2000	290.0000	4.0000
7	9.7200e-5	2.2800e+7	0.9000	5.4900e+5	0.1000	1.2000	290.0000	4.0000
8	1.2512e-4	2.2800e+7	0.9000	5.4900e+5			290.0000	4.0000
9	2.0870e-4	2.2800e+7	0.9000	5.4900e+5			290.0000	4.0000
10	2.9227e-4	2.2800e+7	0.9000	5.4900e+5			289.9999	4.0000
11	3.7585e-4	2.2800e+7	0.9000	5.4900e+5			289.9999	4.0000
12	4.5942e-4	2.2800e+7	0.9000	5.4900e+5			289.9999	4.0000
13	7.6811e-4	2.2800e+7	0.9000	5.4900e+5			289.9999	4.0000
14	9.9403e-4	2.2800e+7	0.9000	5.4900e+5			289.9999	4.0000
15	0.0012	2.2800e+7	0.9000	5.4900e+5	0.1000	1.2000	289.9998	4.0000
16	0.0014	2.2800e+7	0.9000	5.4900e+5	0.1000	1.2000	289.9998	4.0000
17								

Figure 13

To plot the results,

1. Click on the *New Plot* menu to open a blank plotting window (Figure 12).

2. Drag and drop the results matrix (Figure 10) into the plotting window to plot all the logged species (Figure 14).
3. To plot only some species, select the species (hold on the **Shift** key for multiple selection) and drag and drop them in the plotting window.
4. If species are dropped into an existing plot, a new line representing the new species will be added to the plot.
5. Right click on the plot to export, save, print, close or delete the plot

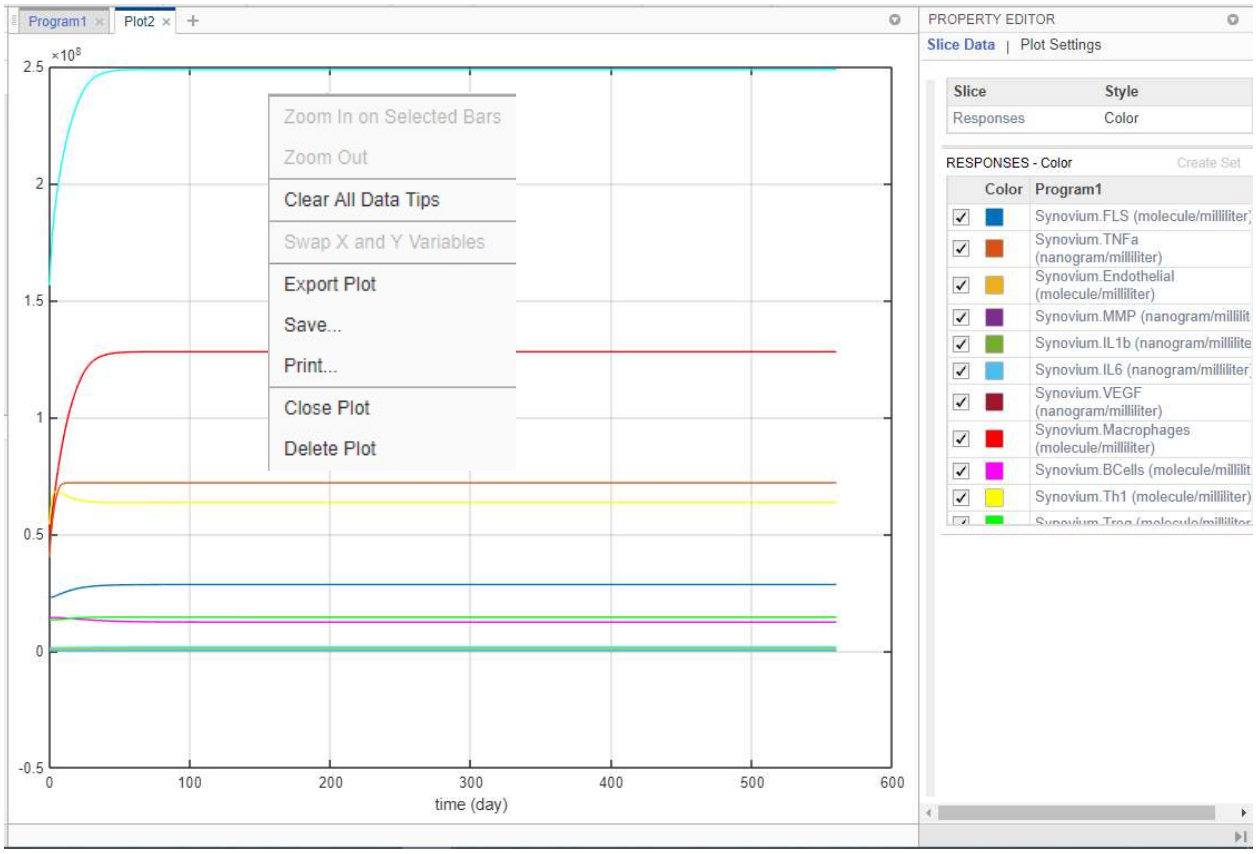


Figure 14

4.3. Adding variants and doses to the simulation

Variants and doses can be added to the simulation, from the *Model* subpanel within the *Program1* panel (Figure 9, box 1).

1. Click on the *Variants* or *Doses* tab to open a list of already existing variants or doses (Figure 9, box 2).
2. Check the items in the list to add them to the simulation.
3. Right click on the list (Figure 15) for additional options as follows
    - Check all – To check all the unchecked items in the list.
    - Uncheck all – To uncheck all the checked items in the list.

- Add new Dose/Add new Variant – This will redirect the user to the SimBiology interface where the user can add new doses or variants. To update the list of doses/variants in the Program panel in SimBiology Model Analyzer, right click and select Add All Doses/Add All Variants.
- Add All Doses/ Add All Variants – This option will update the list of doses/variants with any new doses/variants that were added to the project file.
- Show in Table View – Selecting this option will redirect the user to the SimBiology interface where a table of all doses/variants in the model will be displayed.

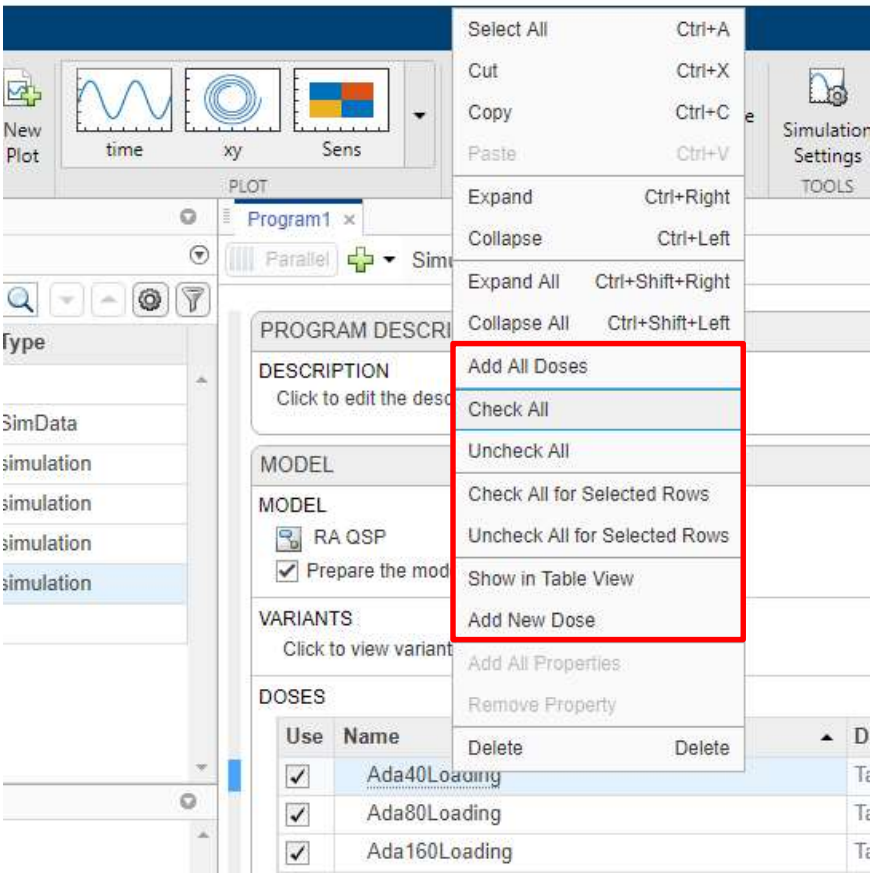


Figure 15

4.4. Generate samples for multiple model parameters

This feature is useful when generating multiple virtual patients by varying user specified parameters or to analyze the influence of parameters on the model species.

1. Select *Generate Samples* from the *Program* panel (Figure 8). A new panel like the one shown in Figure 9, with an additional *Generate Samples* subpanel, (Figure 16) will open.
2. In the *Generate Samples* subpanel, click on the plot button to disable plotting (Figure 16). This reduces simulation time. You can plot the results later as required.

3. In the *Parameter Set* section, set *Type* to either *user defined values* or *values from a distribution*.
    a. For *user defined values* set the parameter combination to either *elementwise* or *cartesian.* This will be used when multiple parameters are varied to generate the samples.
    For *elementwise* sampling, the nth element of the first parameter will be combined with the nth element of all the other parameters. For *cartesian* sampling, each element of the first parameter will be combined with each element of all the other parameters, as is done in a cartesian product.
4. Select the empty cell in the *Component Name* column and type the name of the parameter you wish to vary.
    a. You can use the *Model Browser* to scan through the list of parameters defined in the model (Figure 10, box 1)
    b. More parameters can be added by typing the names in the empty cell in the *Component Name* column.
5. For each parameter, set the type, spacing, range and number of steps or type of distribution and the related parameters based on the *Type* selected in step 3 above.
6. Set the *Sampling* type based on your preference.
7. Click on *Add parameter set to scan* to add another set of parameters.
    a. For multiple parameter sets, set the type of parameter set combination to either *cartesian* or *elementwise.*
8. Click *Run* to generate a sample of the parameters (Figure 7, box 2)

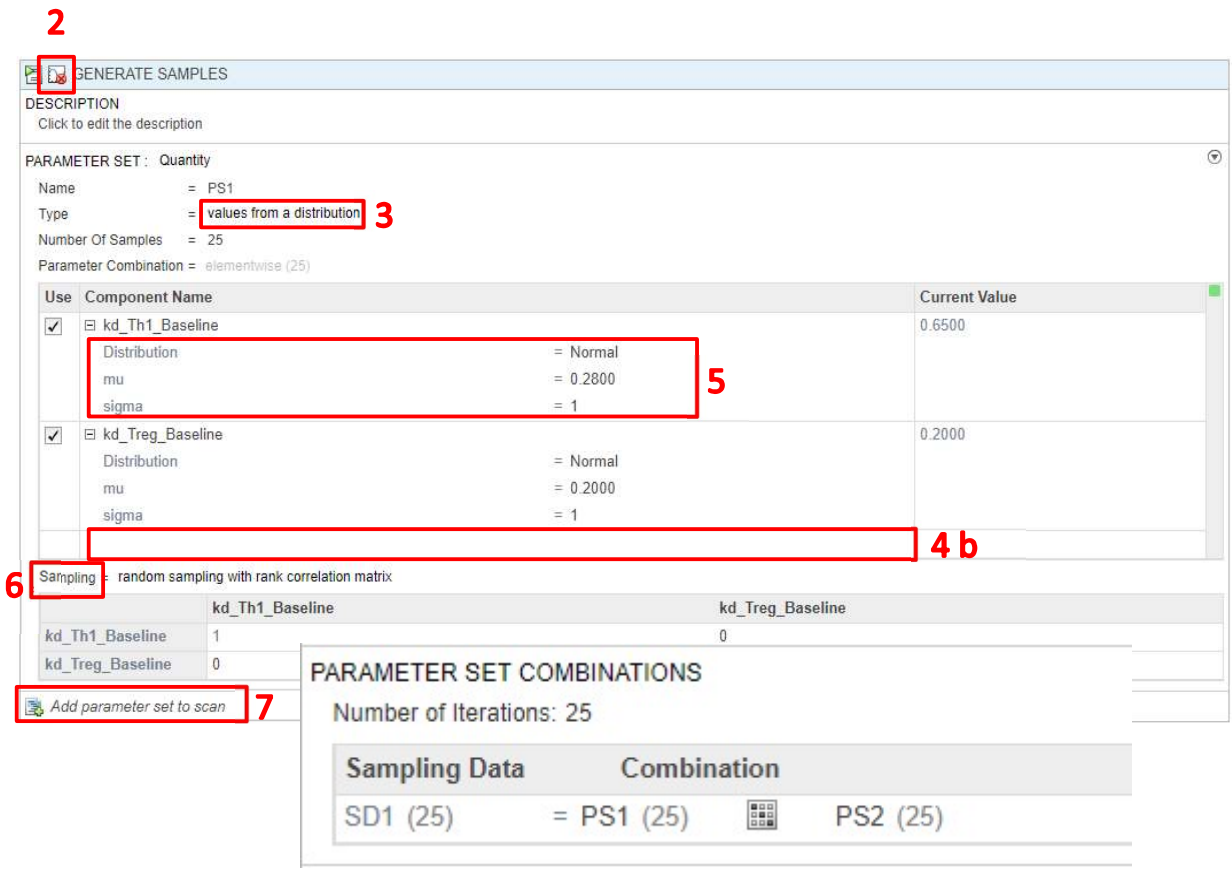


Figure 16

9. The sample will be stored in the *Workspace* in the simulation folder. *Program2* in this example. (Figure 17).

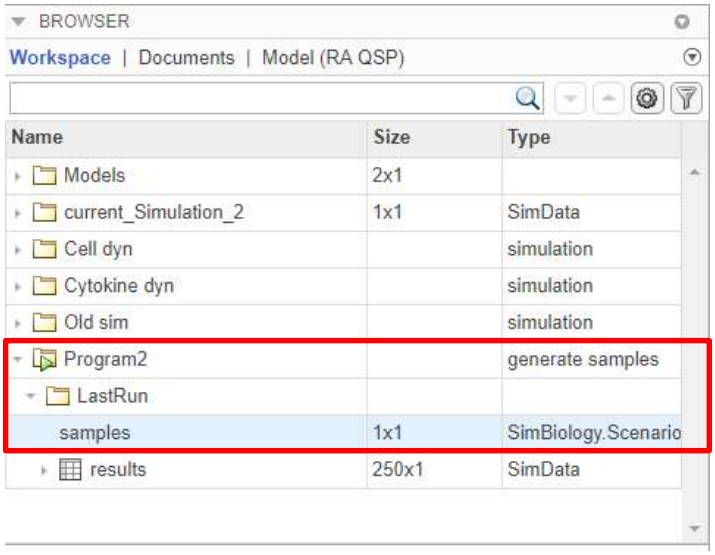


Figure 17

10. View the samples by dragging them into a datasheet as described in Section 4.2.

11. Export the datasheet as an Excel file and use it to add variants to the model file using the *addvariant* function through MATLAB's command line interface.

4.5. Generate multiple virtual patients by sampling the parameter space

This feature is an extension of *Generate Samples*, since it generates samples and runs simulations over the sampled data.

1. Select *Run Scan* from the *Program* panel (Figure 8). A new panel like the one shown in Figure 9, with an additional *Generate Samples* subpanel, will open.
2. Add doses and variants as per your preference following the instructions in Section 3.3.2.
3. Follow the steps described in Section 3.3.3.
4. Click *Run* to simulate the model over the sampled data (Figure 7, box 2).
5. Results will be stored in the *Last Run* folder in the workspace. The results matrix will be a nx1 matrix where n is the number of samples generated.

4.6. Exploring a virtual patient population stored as model variants

A virtual population, of 300 virtual patients, calibrated to respond to MTX, ADA and TCZ in accordance with the clinical data is stored in the model file as 300 model variants. The *Run Scan* program described in Section 4.5 can be used to simulate and explore the virtual patient population.

1. Select *Run Scan* from the *Program* panel (Figure 8). A new panel with a *Generate Samples* subpanel will open (Figure 18).
2. Enable *Parallel*, check the *Prepare the model for accelerated simulation* option (Figure 7, box 3 and 4) and disable plotting in the *Generate Samples* and *Simulation* subpanels (Figure 16, box 2) for faster execution.
3. Select *Variant* from the dropdown list in the *Parameter Set* (Figure 18).

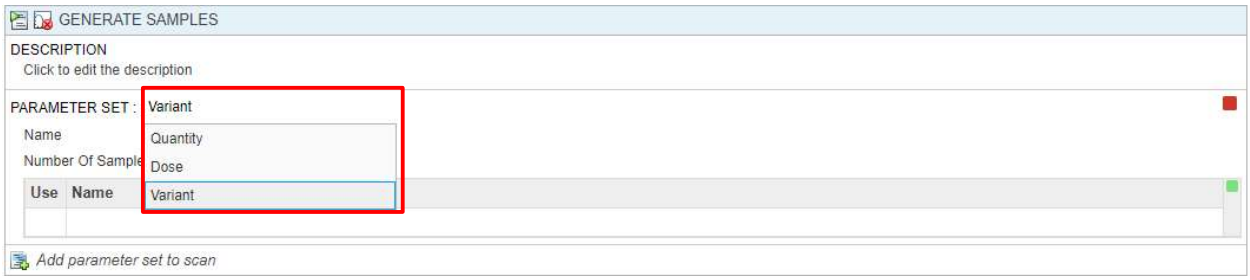


Figure 18

4. Type the name of the saved variants that you wish to simulate in column *Name*. Alternatively, you can select, drag and drop all the variants of your choice from the list displayed in the *Model* tab (Figure 19).

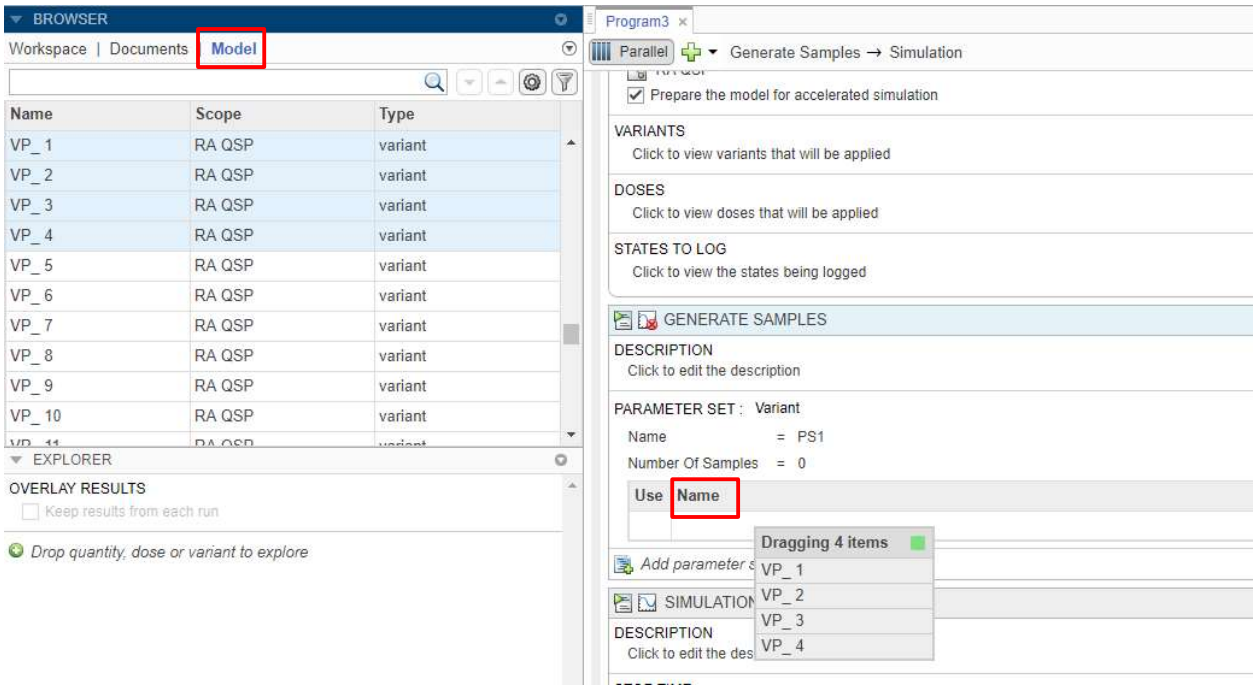


Figure 19

5. Click *Run* to simulate the model for the selected variants.
6. Results will be stored in the *Last Run* folder in the workspace. The results matrix will be a nx1 matrix where n is the number of variants selected.