

Instruction Manual Table of Contents

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Setup the File Directory

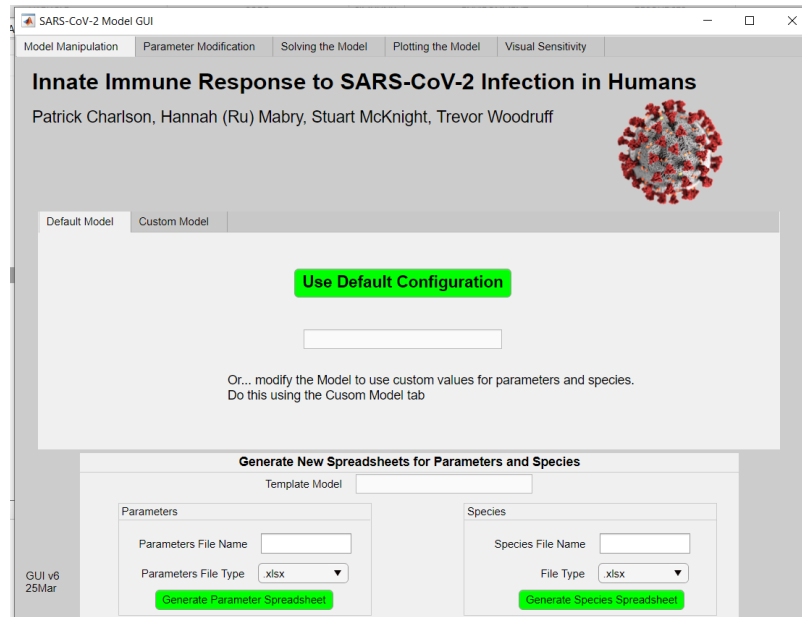
1. Download and extract the files
 - a. There should be 46 function files (.m), a Default Model file (.sbproj), a Default Parameters file (.xlsx), a Default Species file (.xlsx), a graphic (.png), and a GUI file (.mlapp).
 - i. The leveled directory should look like this:
 1. GUI_src
 - a. Default Model
 - i. BuildDefaultModel.m
 - ii. ParameterModification_Default.m
 - iii. SpeciesModification_Default.m
 - b. Model Solving
 - i. AdvancedSolverSetup.m
 - ii. ConfirmExposureTab.m
 - iii. ConfirmsSolverTab.m
 - iv. DefaultSolverSetup.m
 - v. ExportResultsAsCSV.m
 - vi. RemoveViralDose.m
 - vii. RunModelSimulation.m
 - viii. SARS_CoV_2Plot.m
 - ix. ViralExposure.m
 - c. ParameterAndSpeciesTab
 - i. GenerateReactionIndexs_Name_Value_ParameterIndex.m

- ii. GenerateSpeciesIndex_Name_Value.m
 - iii. ParameterModification_FromTable.m
 - iv. ParameterTableIndexAndValueToUpdate.m
 - v. PopulateParameterTable.m
 - vi. PopulateSpeciesTable.m
 - vii. SpeciesModification_FromTable.m
 - viii. SpeciesTableIndexAndValueToUpdate.m
- d. Parameter Modification
 - i. Display_and_Update_Model_Names.m
 - ii. Display_and_Update_Spreadsheet_Names.m
 - iii. FileTypeDetermination.m
 - iv. ImportParamFile_csv.m
 - v. ImportParamFile_xls.m
 - vi. ImportParamFile_xlsx.m
 - vii. ImportSpeciesFile_csv.m
 - viii. ImportSpeciesFile_xls.m
 - ix. ImportSpeciesFile_xlsx.m
 - x. NewParameterSheet.m
 - xi. NewSpeciesSheet.m
 - xii. ParameterModification_v2.m
 - xiii. SpeciesModification_v2.m
- e. Plotting
 - i. ExportMasterPlot.m
 - ii. MasterPlotCustom.m
 - iii. MasterPlotDefault.m
 - iv. SaveMasterPlot.m
- f. Startup
 - i. Coronavirus-covid-19.png
- g. Visual Sensitivity
 - i. AddRowToSensParameterTable.m
 - ii. ExportSensPlot.m
 - iii. ParameterNames.m
 - iv. PopulateSensParameterTable.m
 - v. RemoveRowOfSensParameterTable.m
 - vi. SaveSensPlot.m
 - vii. SensPlotting.m
 - viii. SensSolvesimulations.m
 - ix. SensSpeciesToPlot.m
- 2. Model Generated Data
- 3. Model Generated Plots
- 4. Models
 - a. Default_Model.sbproj
- 5. SpeciesParameterConventions
 - a. Default Values

- i. Default_PARAMS.xlsx
 - ii. default_SPECIES.xlsx
6. SARS_CoV_2.mlapp
- b. Ensure all files are present then place the folders in a folder of your choosing that will be easily accessible to you.

Run the Default Simulation

1. Open and run the GUI (Graphic User Interface)
 - a. The GUI is the SARS_CoV_2.mlapp file
 - b. Running the GUI can be done directly by Typing “RunGUI” into the MATLAB Command line after setting the MATLAB path to include the directory you created. It can also be done by opening the file then pressing run in the app designer.
 - c. The screen you see should look like this:



2. Load the Default Configuration
 - a. Press the “Use Default Configuration” button.
 - b. This will use the default parameter values, default model, and default settings to run the simulation.
 - c. A pop up message titled “Success: Default Imported” will appear when the default settings are applied.
 - d. If you want to view the selected model in the Simbiology Model Builder, press the “Model Builder” button under the Custom Model Tab.
 - e. If you are familiar with Simbiology and want to perform functions that this application does not provide, press the “Model Analyzer” button to open the model in the Simbiology Model Analyzer. **DO NOT MODIFY, ERASE, OR DUPLICATE THE DEFAULT MODEL FILE AND DO NOT PLACE NEW FILES IN**

THE DEFAULT MODEL FOLDER. Modifications made to the default model file may result in major changes to the model results. Instead, save the model under a different file name and a different folder from the default before making any modifications.

Note: if you wish to change the default or make any adjustments to the model, including using the tab titled “Parameter Modification” or the box titled “Generate New Spreadsheets for Parameters and Species”, see the Advanced Simulation section of these instructions.

3. Solve the Model
 - a. Click on the “Solving the Model tab in the upper left corner of the window.
 - i. The new window should look like this:

Note: The tab titled “Advanced Solver Setup” is only for use in running non-default simulations. Please refer to the Advanced Simulation Section of the instructions before making any changes here.

- b. Under “Specify and Use Default Settings”, set a stop time for the simulation in hours.
 - c. Press the “Set Default Solver” button
 - i. You will see a tab titled “Solver” populate with solver type, stop time, and wall clock populate under the heading “Configuration” in the lower right corner.

- ii. The “solver” tab also displays the current settings for absolute tolerance, absolute tolerance scaling, relative tolerance, and sensitivity analysis under the heading “Solver Options” below the Configuration section.
- d. In the box titled “Specify Initial Viral Exposure”, enter your desired values for the initial virus in the body, the viral dose amount, and the time of the viral exposure.
- e. Click the “Add Viral Dose” button.
 - i. You will see a tab titled “exposure” in the lower right corner populate with the information you just entered.
 - ii. If you wish to remove all viral doses, click the “Remove Viral Dose” button and all viral doses will be removed.
- f. Once all of the above information is entered, press the “Run Model Simulation” button.
 - i. The tab titled “Plotting” in the lower right corner should populate with the two default curves for extracellular and intracellular viral concentrations.



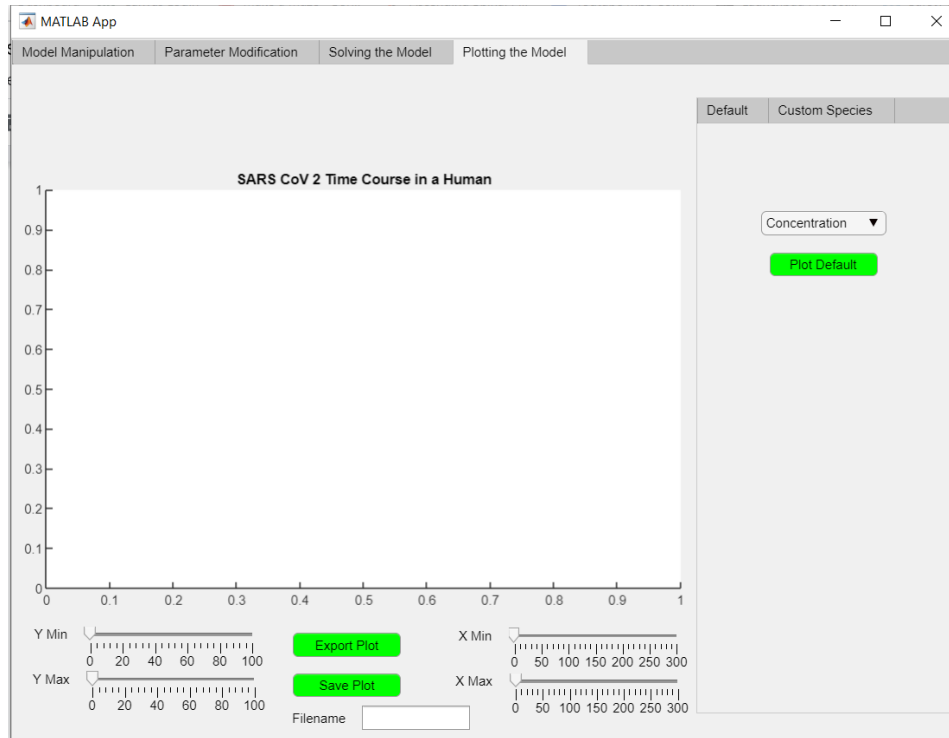
- g. You can adjust the x-axis limits by using the sliders located below the plot.
- h. If you want to export the data from the simulation, enter a file name in the “Results File Name” field and press the “Export as CSV” button.
 - i. This will export the time course data for all species in the simulation to a .csv file located in the same file directory as the files you downloaded earlier. The file can be found in the folder titled “Model Generated Data”.

Note: If you wish to see a larger version of the plot, you can press the “See Larger Plot” button or follow the instructions below for viewing simulation results.

Viewing Simulation Results

1. Click on the “Plotting the Model” tab in the upper left of the window.

- a. The screen you see should look like this:



2. Use the drop down menu under the “Default” tab of the box on the right side to select if you want the results displayed in concentration or in molecule count.
3. Press the “Plot Default” button to plot:
 - a. Extracellular viral concentrations
 - b. Intracellular viral concentrations
4. Ctrl + click on species names in the “Custom Species” box to toggle the plot of each species.
5. The x and y axis limits can be adjusted using the sliders located below the plot.
6. Press the “Export Plot” button to open a pop-out figure of the plot that can be saved as one of multiple file formats.
7. Enter a filename in the box titled “Filename” and press the “Save Plot” button to save the plot as a .jpg file in the “Model Generated Plots” folder in the directory.

Advanced Simulation

This section will cover the advanced features of the simulation. ***These features should be used with caution as changing any of them will possibly cause the model to diverge from the version that we have validated and is known to produce accurate results.***

1. Update Model

*This tool will be used if you want to use a different model file from the default model file. You will need to create a new model file and save it to the file directory using a new file name. This new model file must be placed inside the folder titled “Models”. **DO NOT OVERWRITE THE DEFAULT MODEL FILE, or place new files in the “Default Model” folder.***

The screenshot shows the 'SARS-CoV-2 Model GUI' window. The 'Model Manipulation' tab is active. The title is 'Innate Immune Response to SARS-CoV-2 Infection in Humans' by Patrick Charlson, Hannah (Ru) Mabry, Stuart McKnight, and Trevor Woodruff. A coronavirus icon is on the right. Below the title, there are two tabs: 'Default Model' and 'Custom Model'. The 'Custom Model' tab is selected. A red warning message says: 'You will no longer be using the values which we determined best!'. Below this, 'Step 1: Update Model' is shown with a 'Model Name' dropdown set to 'Mar18_Rescue.sbproj' and an 'Update Model Name' button. To the right are 'Model Builder' and 'Model Analyzer' buttons. 'Step 2: Import Parameter Rate Constants' has a 'Parameter Spreadsheet Name' dropdown set to '12Feb_PARAMS.xlsx', an 'Update Parameter Units' checkbox, and a 'Perform Parameter Modification' button. 'Step 3: Import Species Initial Condition' has a 'Species Spreadsheet Name' dropdown set to '12Feb_PARAMS.xlsx', an 'Update Species Units' checkbox, and a 'Perform Species Modification' button. At the bottom, 'Generate New Spreadsheets for Parameters and Species' is shown with 'Template Model' set to 'Parameters'. It has fields for 'Parameters File Name', 'Parameters File Type' (set to 'xlsx'), and a 'Generate Parameter Spreadsheet' button. There are also fields for 'Species File Name', 'File Type' (set to 'xlsx'), and a 'Generate Species Spreadsheet' button. The bottom left corner says 'GUI v6 25Mar'.

- Click the “Custom Model” tab on the model manipulation page.
 - Use the drop down menu to select the model file that you wish to use to run the simulation.
 - Press the “Update Model Name” Button.
 - The model file and name should now be updated and the default model will no longer be used.
 - The parameters will be based on the new model that you imported, **NOT** on the default model parameters.
- ## 2. Import Parameters Rate Constants

*This tool will be used if you want to import a different set of parameter values than the ones given in the default model file or the default parameter spreadsheet. **DO NOT OVERWRITE THE DEFAULT PARAMETER FILE or place new files in the “Default Values” folder.** You can change the numerical values of each parameter as well as their units, but you cannot change the order or names of the parameters in the spreadsheet.*

- Under the “Custom Model” tab on the model manipulation page, use the drop down menu to select the parameter spreadsheet you wish to use to run the simulation.
- Press the button labeled “Perform Parameter Modification”.

- c. The modified parameters will now be used to run the simulation.
3. Import Species Initial Conditions

*This tool will be used if you want to import a different set of species initial condition values than the ones given in the default model file or the default species spreadsheet. Again, **DO NOT OVERWRITE THE DEFAULT PARAMETER FILE** or place new files in the **“Default Values” folder**.*

 - a. Under the “Custom Model” tab on the model manipulation page, use the drop down menu to select the parameter spreadsheet you wish to use to run the simulation.
 - b. Press the button labeled “Perform Species Modification”.
 - c. The modified initial conditions will now be used to run the simulation.
4. Generate New Spreadsheets for Parameters and Species

If you have made a new model, or modifications to an existing model, this tool will allow you to generate a new set of spreadsheets from the model. This tool is provided as a way to integrate Excel and the functions it offers, as well as to expedite sharing parameter spreadsheets. We recommend making parameter and species modifications using the “Parameter Modification” tab (see section 5 of Advanced Simulation).

 - a. First, update the model name to the model you want to generate a spreadsheet from, the same way you would change the model you are simulating.
 - b. Locate the box at the bottom of the “Custom Model” tab on the model manipulation page titled “Generate New Spreadsheets for Parameters and Species”.
 - c. Provide a file name and select a file type for the new parameter spreadsheet, then press the “Generate Parameter Spreadsheet” button.
 - d. Provide a file name and select a file type for the new species spreadsheet, then press the “Generate Species Spreadsheet” button.
 - e. The new spreadsheets are saved to the “Model Generated Data” folder in the directory.

Note: This tool can also be used to generate a new spreadsheet that reflects any changes made in the “Parameter Modification” tab. Simply make the changes in the parameter modification tab then generate the new spreadsheet.
5. Parameter Modification Tab

This tab is the primary method to modify the parameters and species initial conditions.

 - a. The “Parameter Modification” tab allows you to manipulate parameters and initial conditions directly in the interface without the need of an external spreadsheet.
 - b. There are two tables displayed, the one on the left shows information for each parameter, and the one on the right shows information for initial conditions of each species.

SARS-CoV-2 Model GUI

Model Manipulation | Parameter Modification | Solving the Model | Plotting the Model | Visual Sensitivity

Parameters

#	Reaction	Rate Constant Name	Value	Unit
1	reinfection_transport	kf	1	1/sec
2	exocytosis	kf	1	1/sec
3	BU_mda5	kf	0.0005	1/(mo
3	BU_mda5	kr	0.00025	1/sec
4	delayed virion creation	kf	0.278	1/(mo
5	trans_ISG	kf	1	1/sec
5	trans_ISG	k_nsp16	1	1/mol
5	trans_ISG	k_nsp1	1	1/mol
6	TL_ISG_RNA	kf	3.64	1/sec
7	transcription_ISG	kf	1	1/sec
8	transcription_ISG_early	kf	1	1/sec
9	TL_ISGF3	kf	3000	1/sec
10	BU3	kf	1	1/(mo
10	BU3	kr	1	1/sec
11	late IFN response	kf	1	1/sec
11	late IFN response	kf2	1	1/mol
12	trans_IFN_early	kf	1	1/sec
12	trans_IFN_early	k_nsp16	1	1/mol
12	trans_IFN_early	k_nsp1	1	1/mol
13	TL_early_RNA	kf	1	1/sec
14	TL_IRF37	kf	1	1/sec
15	IFN_sense	kf	1	1/sec
16	transnsp8	k_inhib	1	1/mol
16	transnsp8	kf_1	0.042083	1/sec
17	RI I2	interf2	1	1/mol

Update Parameters

Species

#	Name	Value	Units
1	Covid	1e-09	molarity
2	ACE2	5e-08	molarity
3	ACE2.Covid	0	molarity
4	SARS_CoV_2	0	molarity
5	Covid_transcribed	0	molarity
6	ribosome	1e-06	molarity
7	Ribosome.Covid	0	molarity
8	nsp1	0	molarity
9	S	0	molarity
10	MDA5	1e-07	molarity
11	d_IRF37_p	0	molarity
12	early_RNA	0	molarity
13	IFN_1	0	molarity
14	early_ISG_product	0	molarity
15	d_STAT12_p	0	molarity
16	IRF9	1e-09	molarity
17	ISGF3	0	molarity
18	ISG_RNA	0	molarity
19	ISG_product	0	molarity
20	MDA5.dsRNA	0	molarity
21	SARS_CoV_2	0	molarity
22	OAS_1_mRNA	1e-09	molarity
23	pppa(2'p5'A)n	0	molarity
24	RNaseL_act	0	molarity
25	RNaseL_inact	0	molarity

Update Species

- You can change the value and units for each parameter and species initial condition, but cannot change the reaction number, reaction name, or rate constant name.
 - To make a modification, double click on the box that you wish to modify and enter the new value.
 - Once all parameter modifications have been made, press the "Update Parameters" button.
 - Once all species modifications have been made, press the "Update Species" button.
 - Changes made on this tab will be reflected in the results of the simulation, as well as in any spreadsheets generated after the changes are made.
Note: The new spreadsheet must be generated after the parameters and species initial conditions have been modified and the correct buttons pressed.
- Specify Advanced Solver Parameters
These tools will be used to modify and fine tune the method that the simulation uses to solve the system of differential equations.

The screenshot shows the SARS-CoV-2 Model GUI with the 'Solving the Model' tab selected. The interface is divided into several sections:

- Specify Advanced Solver Parameters:**
 - Stop Time: 300
 - Solver Type: ode15s
 - Wall Clock (sec.): 120
 - Solver Options:
 - Absolute Tolerance: 1e-06
 - Absolute Tolerance Scaling: Off
 - Relative Tolerance: 0.001
 - Sensitivity Analysis: Off
 - Set Advanced Settings button.
- Specify Initial Viral Exposure:**
 - Virus In Body (Before Exposure): 0 molar
 - Viral Dose Exposure: 1e+04 virus cells
 - Time of Viral Exposure: 150 hours
 - Add Viral Dose and Remove Viral Dose buttons.
- Run Model Simulation:**
 - Run Model Simulation button.
 - Results File Name: (empty)
 - Export as CSV button.
- Solver Options (Summary):**
 - Solver Type: (empty)
 - Stop Time: (empty)
 - Wall Clock: (empty)
 - Solver Options:
 - Absolute Tolerance: (empty)
 - Absolute Tolerance Scaling: (empty)
 - Relative Tolerance: (empty)
 - Sensitivity Analysis: (empty)

- a. Stop time
 - i. The end time that the simulation will stop at in hours.
- b. Solver type

To simulate a model, the SimBiology® software converts a model to a system of differential equations. It then uses a solver function to compute solutions for these equations at different time intervals, giving the model's states and outputs over a span of time.

Available solvers are:

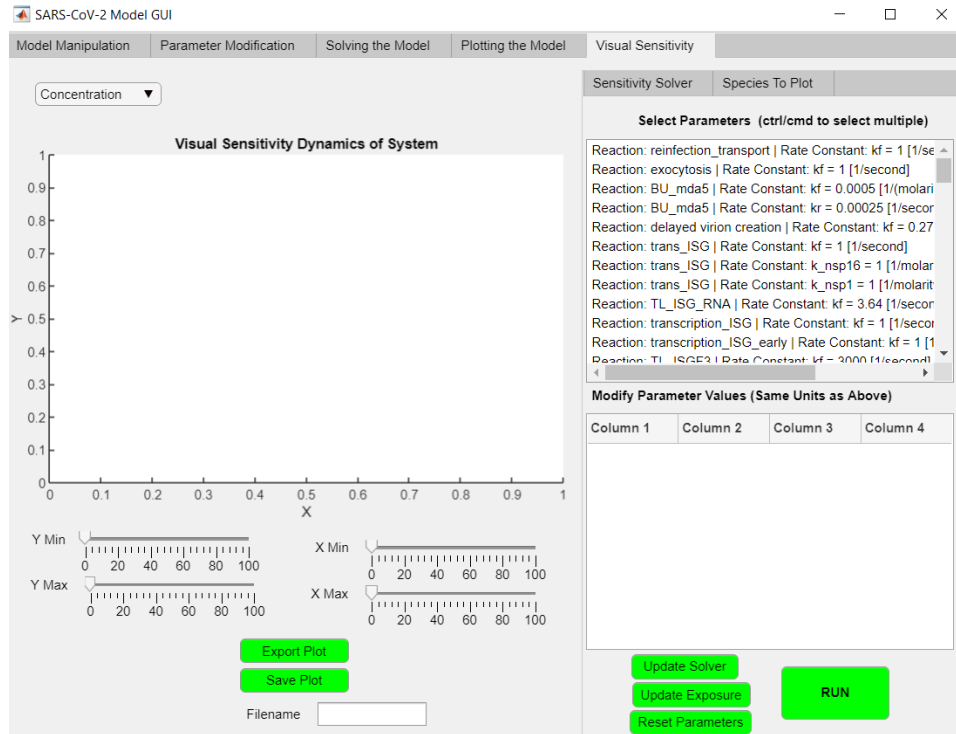
ODE Solvers — These include Nonstiff Deterministic Solvers and Stiff Deterministic Solvers. The solver functions implement numerical integration methods for solving initial value problems for ordinary differential equations (ODEs). Beginning at the initial time with initial conditions, they step through the time interval, computing a solution at each time step. If the solution for a time step satisfies the solver's error tolerance criteria, it is a successful step. Otherwise, it is a failed attempt; the solver shrinks the step size and tries again. For more information, see ODE Solvers.

SUNDIALS Solvers — At a fundamental level the core algorithms for the SUNDIALS solvers are similar to those for some of the solvers in the MATLAB® ODE suite and work as described above in ODE Solvers. SimBiology always uses the SUNDIALS solver to perform sensitivity analysis on a model, regardless of what you have selected as the SolverType. For more information, see SUNDIALS Solvers.

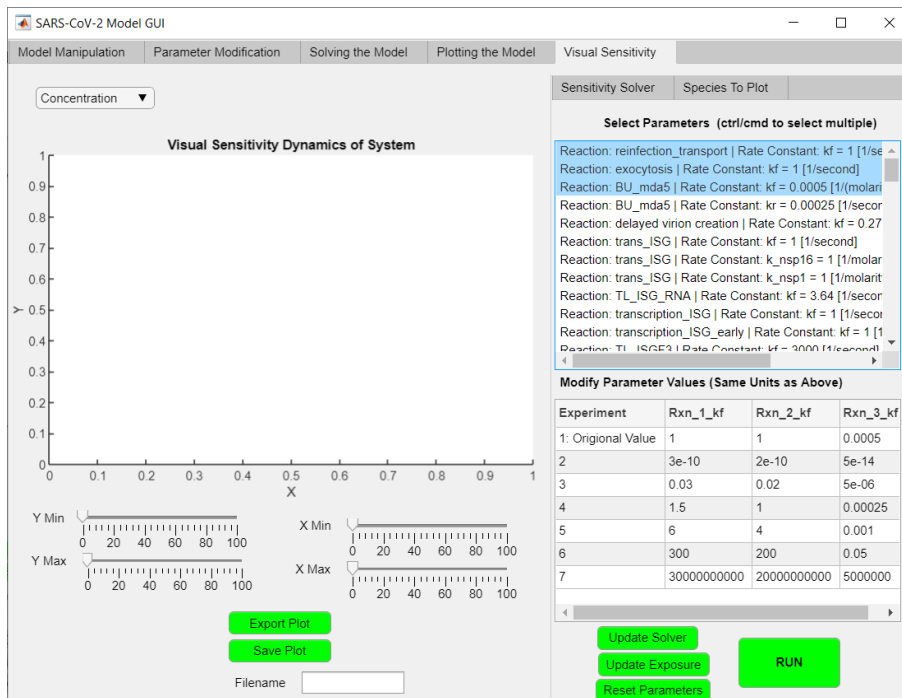
Stochastic Solvers — Use with models containing a small number of molecules. Stochastic solvers include stochastic simulation algorithm, explicit tau-leaping algorithm, and implicit tau-leaping algorithm. For more information, see Stochastic Solvers. NOTE: This solver requires that all of the governing rate equations are formatted as Law of Mass Action, and therefore, to solve this system stochastically, the model equations must be modified and made Law of Mass Action.

Source: <https://www.mathworks.com/help/simbio/ug/choosing-a-simulation-solver.html>

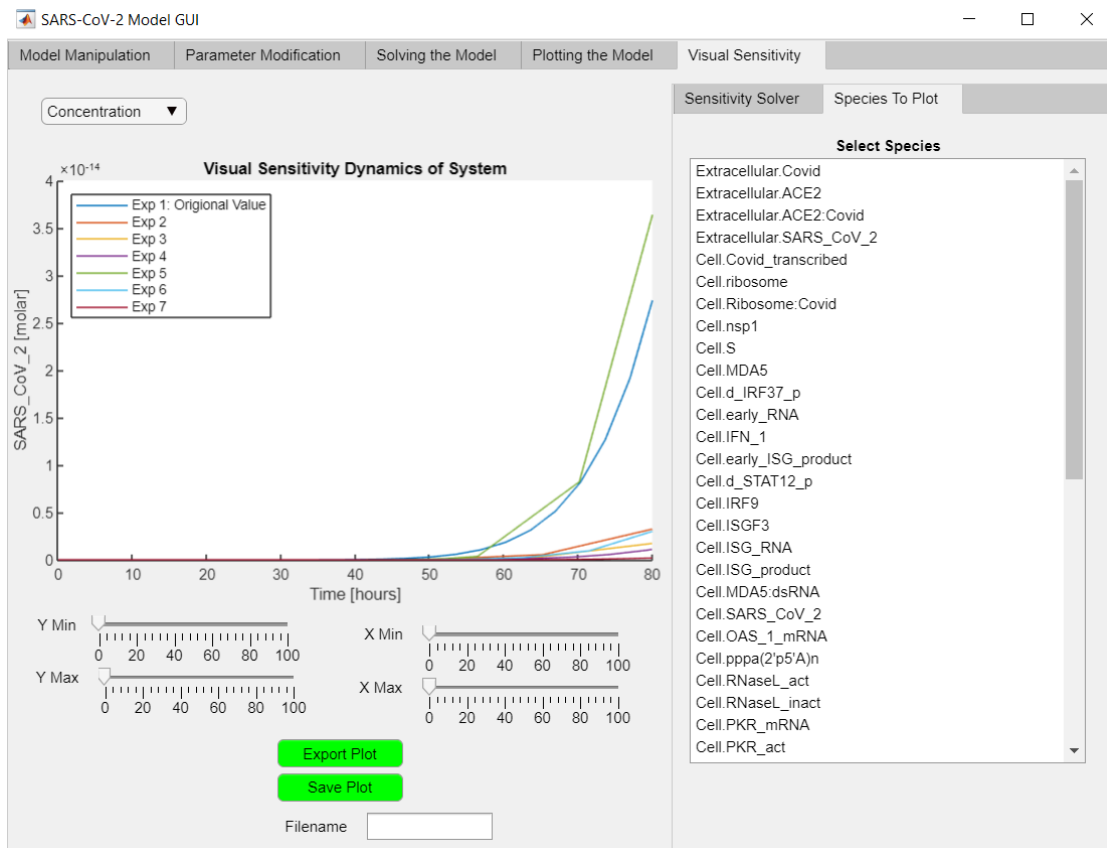
- c. Wall clock
 - i. The real world time, in seconds, that the simulation will run for.
 - d. Absolute Tolerance
 - i. Set the maximum allowable absolute error at any step in the simulation.
 - e. Absolute Tolerance Scaling
 - i. Determines if the software is allowed to scale the absolute tolerance during each step of the simulation.
 - f. Relative Tolerance
 - i. Set the allowable error relative to a state value or vector during each step of the simulation.
 - g. Sensitivity Analysis
 - i. Enabling this option will perform either a local or global sensitivity analysis to identify parameters and equations that the model is most sensitive to changes in.
 - ii. We recommend leaving this option turned off in order to expedite the simulation. If you wish to perform sensitivity analysis it is better to do it in the simbiology model analyzer.
 - h. Log Decimation
 - i. This option determines the frequency at which data from a stochastic simulation will be recorded. This option will only apply if you choose SSA as your solver option.
7. Sensitivity / Batch Experimentation
- This tool will be useful if you wish to perform experiments to obtain a visual representation of how changing one parameter, or a small batch of parameters, affects the model outcome. This can be done even if Sensitivity analysis was set to “off” in the simulation.*
- a. Click on the tab titled “Visual Sensitivity”
 - i. The screen you see should look like this:



- Use the menu titled “Select Parameters” to choose one parameter, or a small batch of parameters, that you would like to change.
- Once the parameters are selected the table titled “Modify Parameter Values” will populate. The table should look like this:



- d. Each row in the table corresponds to an experiment. Each experiment will simulate the model with the values you provide for each parameter in that row. For example, Experiment 1 will use the values in the first row, Experiment 2 will use the values in the second row and so on.
- e. To change the value of a selected parameter in an experiment, double click the cell in the table you wish to change and enter the new value.
Note: The units for the new values will be the same as what is provided in the model. You cannot change the units of the values in this table. You also cannot change the values in the first row. This is done so that the original model solution will always be represented in the output.
- f. If you want to change the solver options for the simulation, click the “Update solver” button and you will be taken back to the appropriate tab.
- g. If you want to change the viral exposure, click the “Update Exposure” button and you will be taken back to the appropriate tab.
- h. Once all the changes have been made, use the drop down menu in the upper left corner to select if the units of the output will be in concentration or in molecule count then press the “RUN” button.
- i. The empty plot will populate with curves showing the concentration/count of intracellular and extracellular SARS-CoV-2 for each experiment. The screen will look like this:



- j. The x and y axis limits can be changed using the sliders provided and the plot can be exported by providing a file name and pressing the export plot button. This will open a MATLAB figure that can be saved as one of many file formats. The plot can also be directly saved into the Model Generated Plots folder by providing a file name and pressing the Save Plot button.
- k. The new tab on the right titled “Species to plot” allows you to select different species to plot, but only one species can be displayed at a time.
- l. Click back to the tab titled “Sensitivity Solver” and press the “Reset Parameters” button to restore the default values for all parameters. This will reset all parameter values, including any changes you made in the “Parameter Modification” tab.