Bifurcation Discovery Tool: User's Guide & Tutorials

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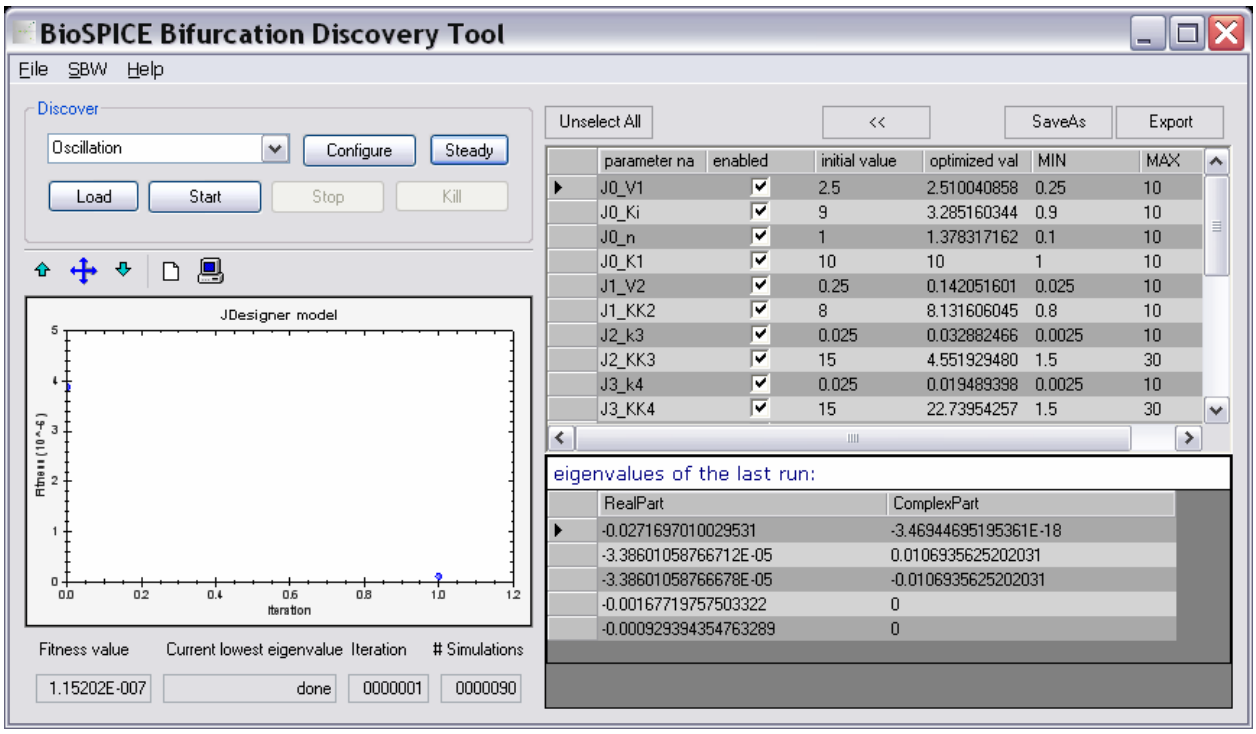
Table of Contents

1 Bifurcation Discovery Tool User's Guide

This user's guide gives an overview of the Bifurcation Discovery Tool interface.



1.1 Discover Panel

Optimization Type – Select to optimize for oscillation or turning point

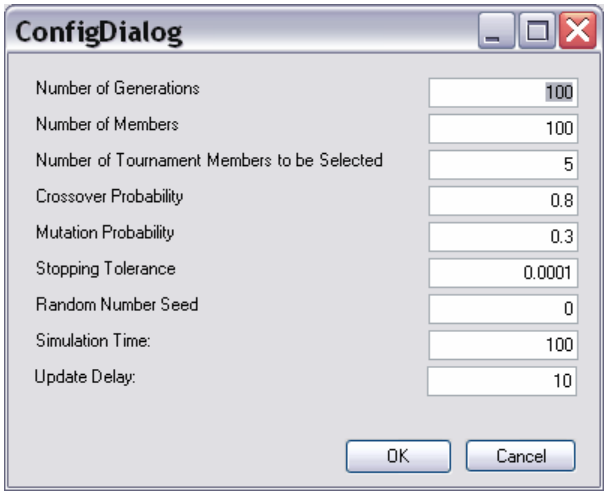
Steady – Compute the steady state for the model and update the values

Start – Starts the optimization

Stop – Stops the optimization and shows updated parameter values

Kill – Cancels the simulation without updating the parameter values

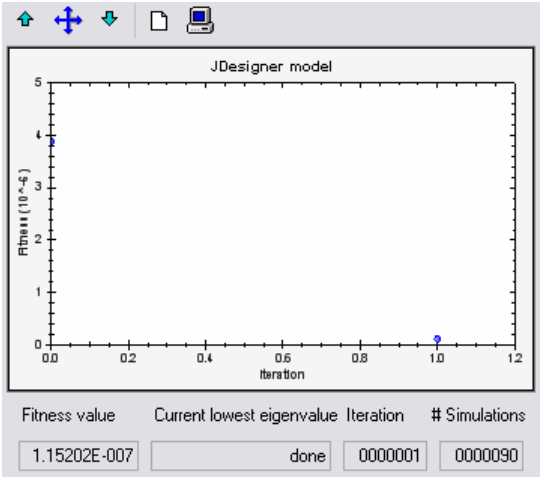
Configure – Opens configuration panel for the Genetic Algorithm:



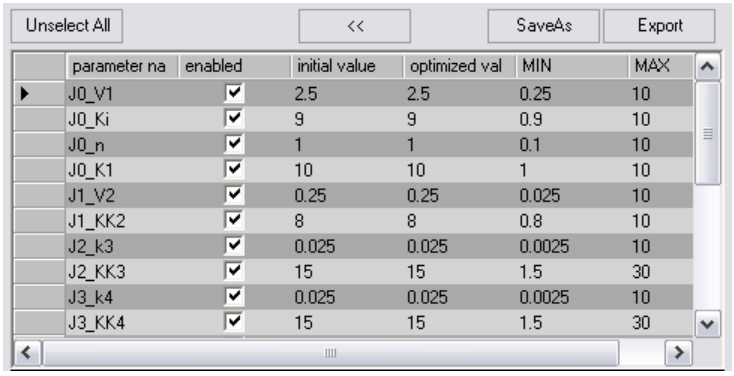
Note: The default values in the dialog box works for most models, for some models you need to tweak these parameter values to optimize the model.

1.2 Plotter Panel

The plotter panel shows the progress of the optimization after each iteration.



1.3 Parameters Panel



	parameter na	enabled	initial value	optimized val	MIN	MAX
▶	J0_V1	☑	2.5	2.5	0.25	10
	J0_Ki	☑	9	9	0.9	10
	J0_n	☑	1	1	0.1	10
	J0_K1	☑	10	10	1	10
	J1_V2	☑	0.25	0.25	0.025	10
	J1_KK2	☑	8	8	0.8	10
	J2_k3	☑	0.025	0.025	0.0025	10
	J2_KK3	☑	15	15	1.5	30
	J3_k4	☑	0.025	0.025	0.0025	10
	J3_KK4	☑	15	15	1.5	30

Parameter Name – shows the name of the parameter

Enabled – check to optimize parameter, uncheck to not optimize parameter

Initial Value – original value of the parameter, click on it to modify value

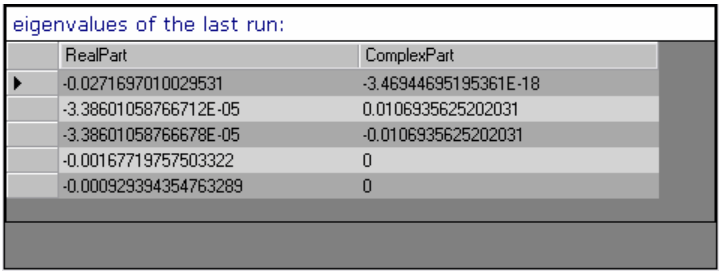
Optimized Value - value returned by the program

Min – the minimum value of the parameter, click on it to modify value

Max – the minimum value of the parameter, click on it to modify value

1.4 Eigenvalue Panel

The Eigenvalue panel shows the eigenvalues after each iteration.



	RealPart	ComplexPart
▶	-0.0271697010029531	-3.46944695195361E-18
	-3.38601058766712E-05	0.0106935625202031
	-3.38601058766678E-05	-0.0106935625202031
	-0.00167719757503322	0
	-0.000929394354763289	0

2 Bifurcation Discovery Tool Tutorials

Please download the Models.zip file from the Bifurcation Discovery Tool Software site; it contains all the sbml models that are used in this tutorial.

2.1 Optimizing parameter values of a model to obtain oscillations

1. Load the SBML model whose parameter values you want to optimize into JDesigner. The picture below shows the Kholodenko's MAP kinase model (BorisEJB.xml) loaded into JDesigner.

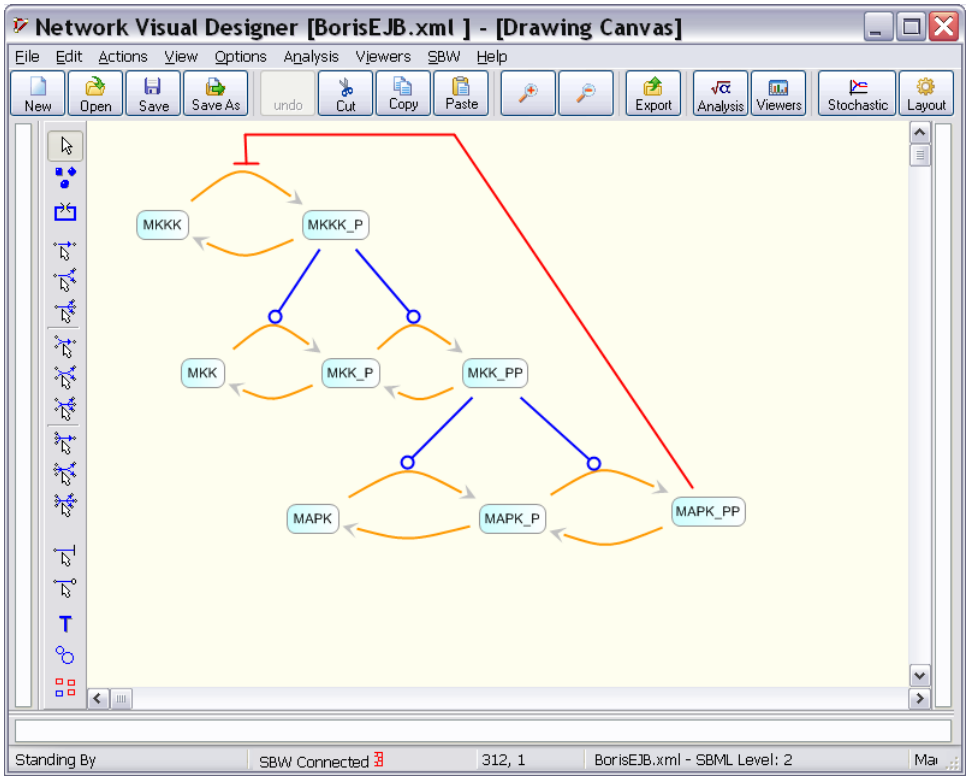


Figure 1: JDesigner with BorisEJB.xml from Kholodenko, EJB, 267, 1583-1588, 2000.

2. Now, click on Bifurcation Discovery Tool in the SBW Menu.

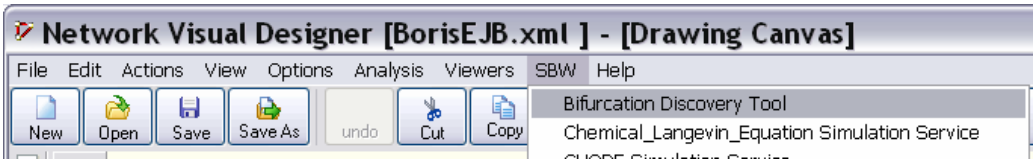


Figure 2: Selecting Bifurcation Discovery Tool in SBW drop down menu

3. Your desktop taskbar will now contain a new window: Biospice Bifurcation Discovery Tool.

Figure 3: Bifurcation Discovery Tool window minimized in the Desktop taskbar

4. Click on the window to maximize it.

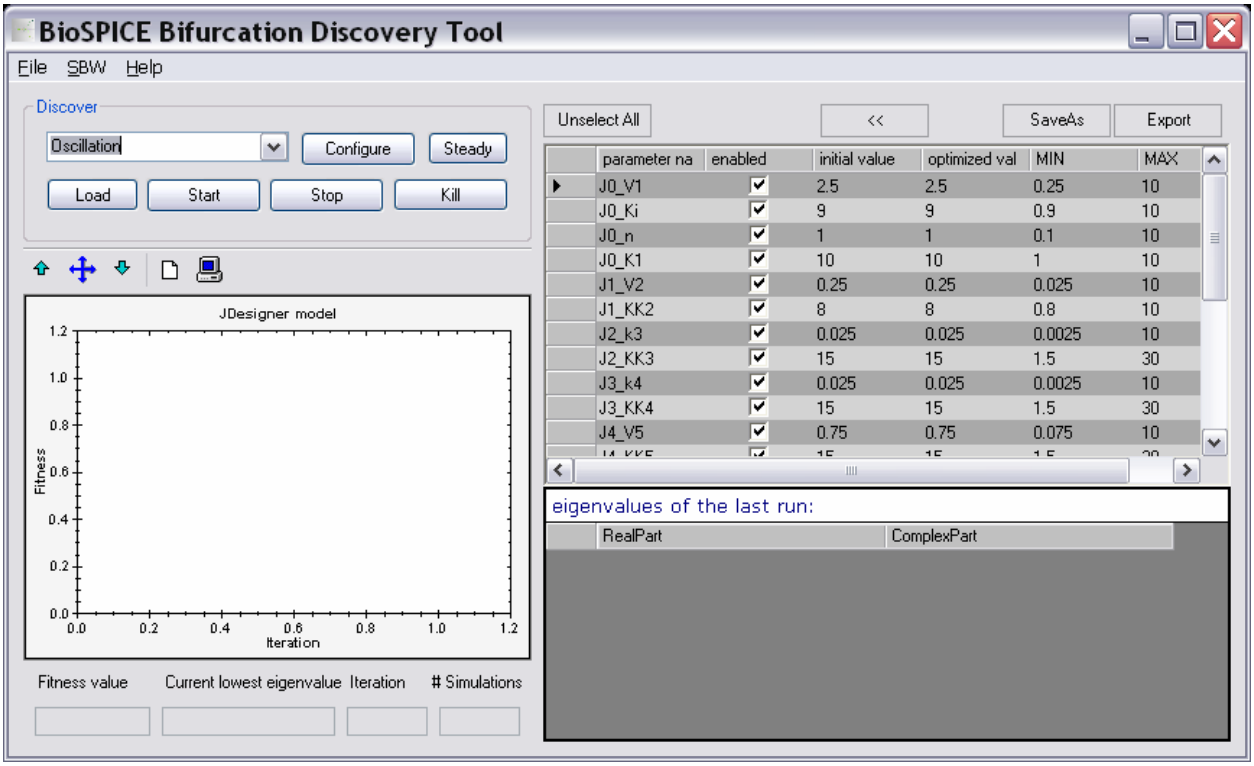


Figure 4: Bifurcation Discovery Tool Graphical User Interface

5. Click on the 

button. That will bring up a dialog box where you can set values for different parameters of the Genetic Algorithm (Note the distinction, these are not model parameters, rather they are program parameters).

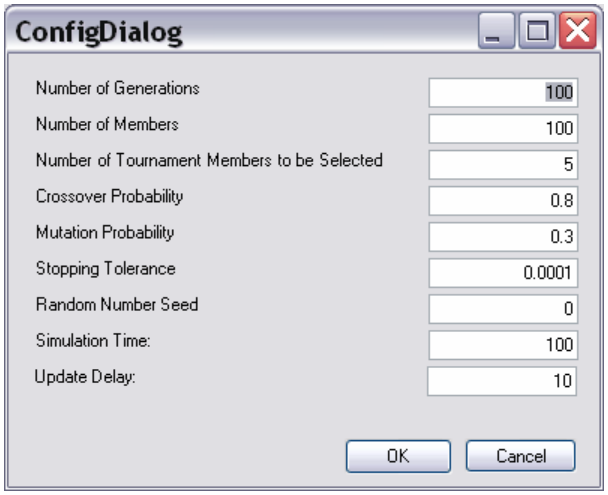


Figure 5: Configuration Dialog box

6. Use the check boxes in the enabled column to select/deselect the parameters you want to optimize. By default all the parameters of the model will be selected, you can deselect the parameters you do not want to fit by clicking twice on the check box.

7. Click on the 

button to start the optimization process.

8. The plotter on the left hand side is updated after each iteration of Genetic Algorithm.

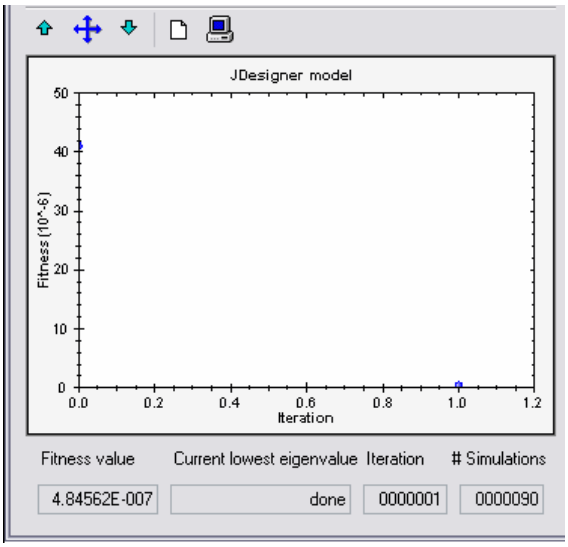


Figure 6: Fitness value of the objective function vs. Iteration

The plotter also contains a label for **Real** (Eigen value with lowest real part).

9. The eigenvalues after each iteration are displayed in the lower right hand corner of the window. The user needs to monitor these eigenvalues constantly. If you notice an eigenvalue with the absolute value of real part less than 10^{-3} and the difference between the real part and imaginary part is of three orders of magnitude (i.e., Img(eigenVal) > 10^{+3} x Re(eigenVal)) then you might be in the oscillatory region.

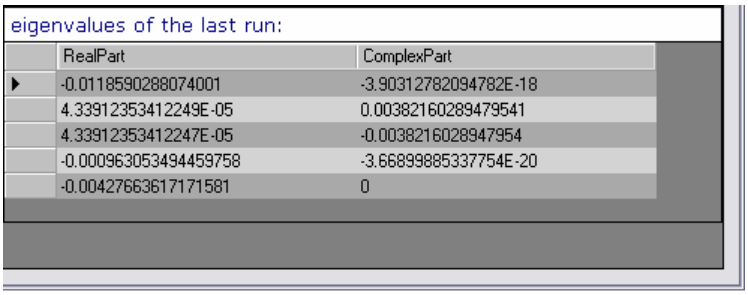


Figure 7: Eigen values after one complete iteration

10. The optimization process will stop automatically when the tolerance/maximum number of generations is reached. Alternatively, the optimization process can be stopped any time by clicking on the 

button.

11. The optimized values can be seen in the Parameters panel:

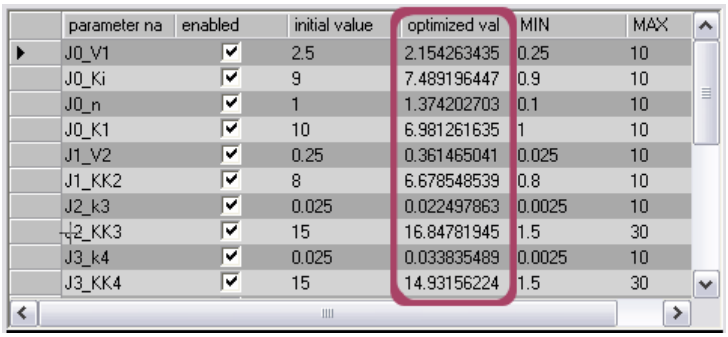


Figure 8: the optimized values for oscillation shown in the Parameters panel.

12. The model with its optimized parameters can be sent to another program, such as JDesigner, to verify the oscillatory behavior.

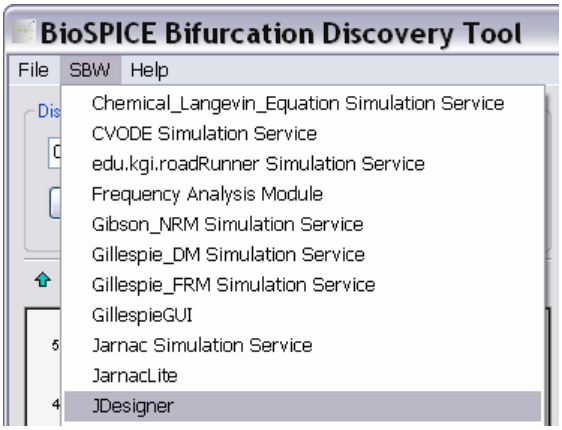


Figure 9: Send optimized parameters back to JDesigner.

2.2 Optimizing parameter values of a model to find a turning point

1. Load the SBML model whose parameter values you want to optimize into JDesigner. The picture below shows the mutual inhibition model of John Tyson[†] (Fig1f.xml).

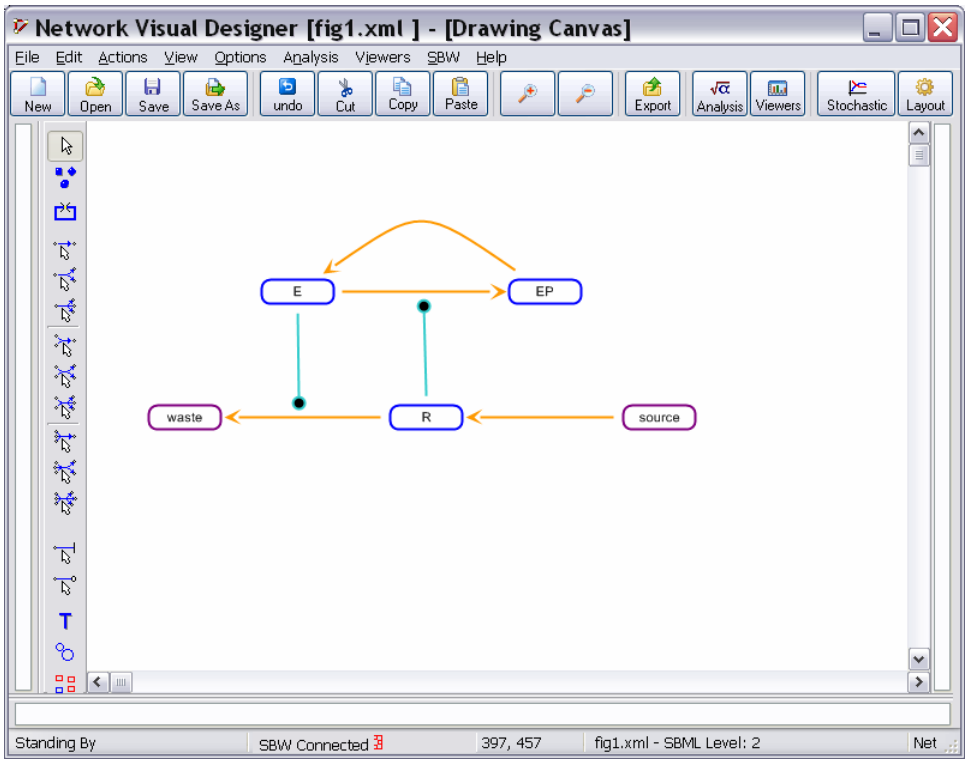


Figure 10: JDesigner with Mutual Inhibition model from Tyson et.al, Curr Opin Cell Biol. 15, 221-231, Figure 1f, 2003.

2. Now, click on Bifurcation Discovery Tool in the SBW Menu.

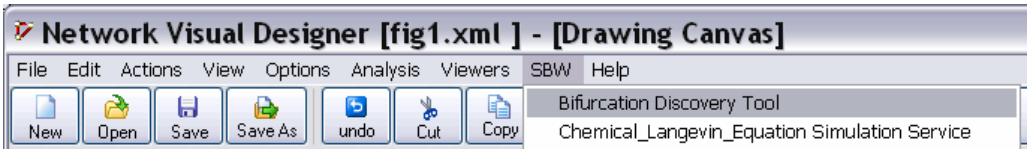


Figure 11: Selecting Bifurcation Discovery Tool in SBW drop down menu

3. Your desktop taskbar will now contain a new window: Biospice Bifurcation Discovery Tool.

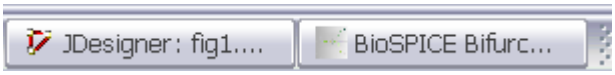


Figure 12: Bifurcation Discovery Tool window minimized in the Desktop taskbar

4. Click on the window to maximize it. Now select Turning point from the drop down list box on the top left hand corner.

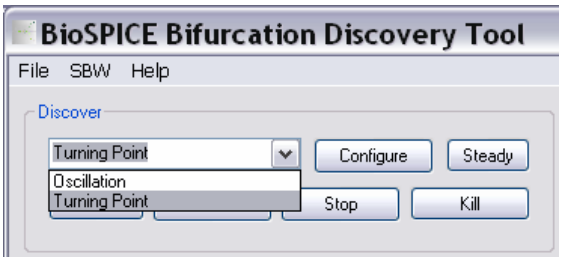


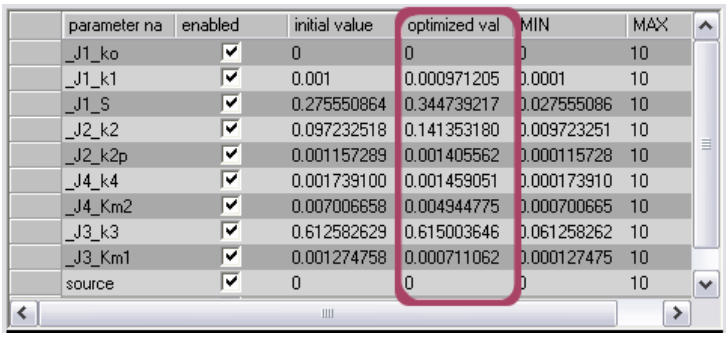
Figure 13: Selecting Turning Point from the list box

5-8. Follow steps 5-8 listed in finding the oscillator.

9. The eigenvalues after each iteration are displayed in the lower right hand corner of the window. The user needs to monitor these eigenvalues constantly. If you notice an eigenvalue with the absolute value less than 10^{-3} and the difference between the lowest eigenvalue and the remaining eigenvalues is 3 orders of magnitude (i.e., min(eigenValues) > 10^{+3} x {eigenVal/minEigenVal}) then you are close to a Turning point.

10. The optimization process will stop automatically when the tolerance/maximum number of generations is reached. Alternatively, the optimization process can be stopped any time by clicking on the  button.

11. The optimized values can be seen in the Parameters panel:



	parameter na	enabled	initial value	optimized val	MIN	MAX
	_J1_ko	☑	0	0	0	10
	_J1_k1	☑	0.001	0.000971205	0.0001	10
	_J1_S	☑	0.275550864	0.344739217	0.027555086	10
	_J2_k2	☑	0.097232518	0.141353180	0.009723251	10
	_J2_k2p	☑	0.001157289	0.001405562	0.000115728	10
	_J4_k4	☑	0.001739100	0.001459051	0.000173910	10
	_J4_Km2	☑	0.007006658	0.004944775	0.000700665	10
	_J3_k3	☑	0.612582629	0.615003646	0.061258262	10
	_J3_Km1	☑	0.001274758	0.000711062	0.000127475	10
	source	☑	0	0	0	10

Figure 14: The optimized values for a turning point in the Parameters panel.

12. The model with its optimized parameters can be sent to another program, using the SBW menu, to verify the oscillatory behavior.