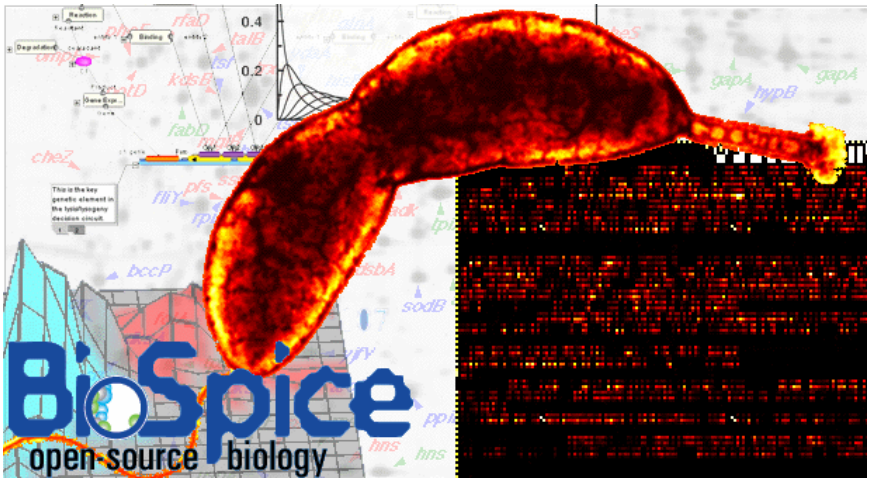
Getting Started with Bio-SPICE: A Tutorial for New Users

Version 1.0



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http://biospice.org

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Chapter 1 Introduction to Bio-SPICE

With the enormous growth of life science research it is clear that tools are needed to store and analyze the large amount of experimental data, to build, simulate and analyze mathematical models, and to visualize data and system dynamics.
This chapter presents the software project Bio-SPICE (Biological Simulation Program for Intra- and Inter-Cell Evaluation) and a short description of system biology.

Introduction to systems biology

Systems biology is the study of the mechanisms underlying complex biological processes as integrated systems of many, diverse, interacting components. Systems biology involves (1) collection of large sets of experimental data (by high-throughput technologies and/or by mining the literature of reductionist molecular biology and biochemistry), (2) proposal of mathematical models that might account for at least some significant aspects of this data set, (3) accurate computer solution of the mathematical equations to obtain numerical predictions, and (4) assessment of the quality of the model by comparing numerical simulations with the experimental data. (http://jigcell.biol.vt.edu/glossary.html)

Modeling biochemical and gene networks

There are several methods of modeling system biology, in particular cellular processes and biochemical interactions. Two very different approaches are Boolean networks and ordinary differential equations (ODEs). For qualitative modeling of large systems, Boolean networks may be more appropriate than an ODE-based model where details of reaction rates are required.

Boolean methods

Qualitative modeling of large systems can most effectively be carried out using a Boolean method. There are several variants of Boolean methods, e.g., PetriNets and Cellular Automata. A Boolean network contains nodes that can have the value 1 (on) or 0 (off). For a specific node, the change from one state to the next is a function of the nodes that are connected to the specified node.

Differential equation-based models

Quantitative modeling is usually carried out with ordinary differential equations, which represent system variables that change as nonlinear

functions of other variables and/or parameters. To describe mass action of biochemical reactions, equations may be written in stochiometric form. There are two general types of solvers for quantitative models, stochastic and deterministic. When small populations of molecules are considered, stochastic modeling is more appropriate since molecular fluctuations may alter the dynamics. With large population sizes, deterministic modeling will be computationally faster as stochastic modeling of large populations is computationally time intensive and should produce results similar to an ODE model.

Stochastic

Stochastic solvers use the Gillespie algorithm or a variant of it. Basically, all possible reactions are examined and the reaction with the shortest time interval is "scheduled". The executed reaction will affect the population of molecules and thereby other reactions. Therefore certain reaction times must be recalculated, and again, the shortest time interval reaction is scheduled. This algorithm was shown to describe the time evolution of a chemical system.

Deterministic

Deterministic solvers use a variety of algorithms to compute the value of the variables in a model. At each time step, all variables are calculated based on either only previous values (explicit methods) or incorporating estimates of the next value (implicit methods). Some of the more known algorithms are forward and backward Euler method (explicit and implicit respectively), Runge Kutta, Gear, CVODE, Crank-Nicolson. The algorithms differ in terms of ease of use (e.g., explicit methods requiring only initial conditions, implicit methods require estimations of variable values), speed of computation (how many function calls per time step) and accuracy especially important in cases of stiff systems.

The Bio-SPICE project

The Bio-SPICE project was started as part of the Bio-Computation program, funded by the Defense Advanced Research Projects Agency (DARPA). The goal was to develop a computational framework that enables the construction of sophisticated models of intracellular processes that can be used to predict and control the behavior of living cells. In addition, Bio-SPICE is also being examined to generate new computational paradigms and engineering applications that utilize biomolecules as an information processing, sensing, or structural components (http://www.darpa.mil/ipto/programs/biocomp/index.htm). In order to understand cellular behavior, we need to understand how the underlying genetic code is executed and to characterize the dynamics of cellular events (see editorial at http://www.liebertonline.com/toc/omi/7/3).

The Bio-SPICE project chose the System Biology Markup Language (SBML) as a language of exchange between the different tools. SBML is a computer-readable format for representing **models of biochemical reaction networks**. For example, SBML is applicable to metabolic networks, cell-signaling pathways and regulatory networks. For further details see the web site http://sbml.org/index.psp.

The Bio-SPICE web site and SourceForge.net

The Bio-SPICE web site https://biospice.org/index.php provides information and software downloads to the Bio-SPICE community.

Figure 1.1 Bio-SPICE web site.

In order to download software from the web site, you must join and become a Bio-SPICE member. Chapter 2, Getting Started describes how to go about joining.

A second source now exists for the Bio-SPICE project is on SourceForge.net, http://sourceforge.net/projects/biospice. The latest version of the Dashboard can be downloaded from SourceForge.net without the need to register as a Bio-SPICE user as on the official Bio-SPICE web site. This reflects the transition from a DARPA funded program to a truly open source environment to fulfill the desire to see Bio-SPICE continue to mature and evolve long after the DARPA funding has ended.

The Bio-SPICE tool kit

The Bio-SPICE tool kit is comprised of the Dashboard and a range of tools.

- Dashboard: GUI application to create and run workflows.
- Data analysis tools: Tools to mine the data

- Database tools: The large amount of data that experiments produce needs to be stored and mined.
- Model analysis tools: A model can provide information through various means of analysis, e.g., bifurcation, parameter sensitivity.
- Model composition & visualization tools: In order to construct a model, tools are provided for model composition, as well as visualization.
- Simulator tools: Models need to be solved using various types of simulators, continuous ODE simulators or stochastic simulators.

Outline

The manual is organized as follows:

- Introduction – This chapter provides a general overview of System Biology and the Bio-SPICE software.
- Getting Started – Chapter 2 describes how to download the Bio-SPICE package and launch the application.
- Model Editor – Chapter 3 presents an simple use case and describes how to edit a model.
- Using the Dashboard – Chapter 4 shows how to use the Dashboard to simulate the model described in Chapter 3.
- Using Bio-SPICE Tools – Chapter 5 provides a brief summary of all the Bio-SPICE tools available.

Chapter 2 Getting Started

This chapter presents the Dashboard application, and shows how to download and install the Dashboard.

The Dashboard

The Bio-SPICE Dashboard is an environment for integrating varied data and tools useful to biologists. The main categories of tools this environment was designed for are model building, model analysis, experimental data analysis, and visualization. However, conceivably any tool that analyzes, transforms, produces, or helps to interpret data could be integrated into the Dashboard. The Dashboard functions in a manner loosely analogous to UNIX shells (especially with respect to UNIX pipe facilities).

The Dashboard is based on the NetBeans application platform, a Java-based tool kit. Tools may be written in any language, however, as the core Dashboard libraries provide support for accessing non-Java tools that are either network enabled, command-line tools, or OAA agents.

Currently, facilities for Java and OAA tools are available, as well as support for TCP/IP, web, and command-line tools via an XML wrapping API.

Users or tool developers interested in integrating their tools into the Dashboard environment can find additional guidance in the Developer's Manual.

System Requirements

Java SDK version 1.4.5. Download from http://java.sun.com.
Linux users: It may be necessary to have super-user permission (i.e., root) before you install the software. Check with your local system administrator.

Bio-SPICE on SourceForge.net

The Bio-SPICE software may be downloaded from the SourceForge.net site at http://sourceforge.net/projects/biospice/.

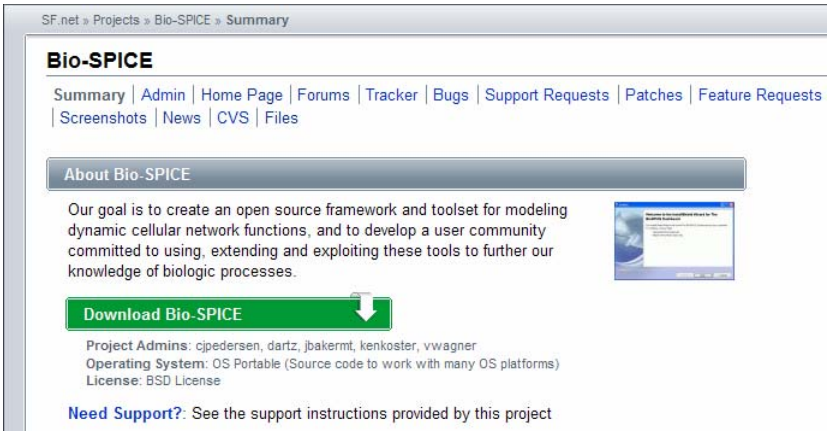


Figure 2.1 SourceForge Dashboard page

Click on the green button `Download Bio-SPICE`, see Fig. 2.1, and you will be directed to the download page. There are three versions of the software for the operating systems: Windows (32bit), Linux (32bit) and Mac (PPC), shown in Fig. 2.2.

File Releases

Below is a list of all files released by this project. Before downloading, you may want to read Release Notes. The current release for each package is shown.

Package	Release (date)	Filename	Size (bytes)	Downloads	Architecture	Type
Dashboard						
Latest	Dashboard 7.0 [Notes] (2005-11-07 16:52)					
		Dashboard-mac-7.0.zip	13402477	6	PPC	.zip
		Dashboard-SetupLinux-7.0.bin	79920321	6	i386	Other Binary Package
		Dashboard-SetupWindows-7.0.exe	70822043	31	i386	.exe (32-bit Windows)
	Dashboard 6.0 [Notes] (2005-02-15 16:53)					
Totals:	2	6	325126102	43		

Figure 2.2 SourceForge Dashboard download page

Installing the Dashboard from SourceForge

There are three versions of the dashboard, for Windows, Linux and Macintosh operating systems. Select the version you need. Then save either the Windows file `Dashboard-SetupWindows-7.0.exe` or the Linux file `Dashboard-SetupLinux-7.0.bin` or the Machintosh file `Dashboard-mac-7.0.zip` on your computer.

The installer will have an icon which looks like this,  for MS Windows, double-click on the icon to launch the installer, see Fig. 2.3.

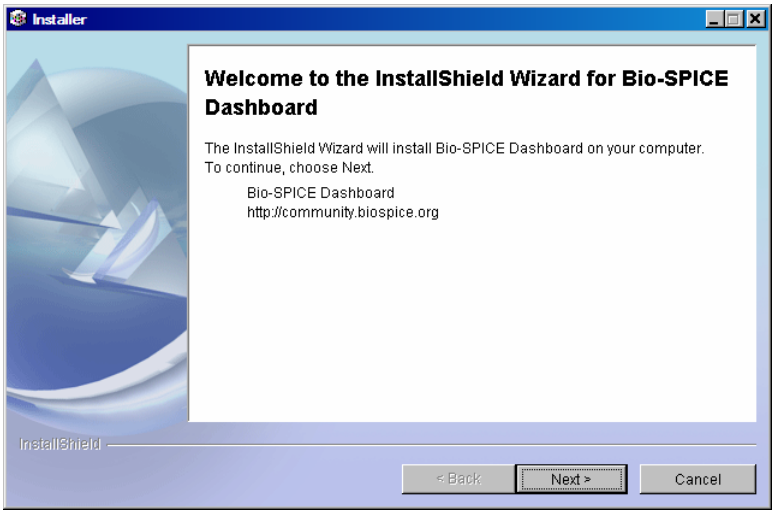


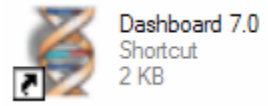
Figure 2.3 Dashboard InstallShield Wizard.

Note: In order for the Dashboard to function you must have a Java VM installed, of a version 1.4 or later. If you do not have Java installed or, have an older version, visit the Java site http://java.sun.com in order to download the appropriate Java VM.

The installer will provide a default folder/directory for installations, but you may change the destination folder/directory. Click the button Browse to open a dialog box displaying the file structure for your system. Traverse the structure to the folder in which you want to install Bio-SPICE. Select the folder name and click the button `open` and then `next`. The installer will then display the installation files. Leave the two check marks for installation of both the Dashboard and OAA for a complete install. Click the button `next` twice to start the installation. After installation click the buttons `next` and then `finish`.

The installation will place four folders, `_jvm`, `_uninstall`, `Dashboard`, and `OAA` in the designated folder, and place three shortcuts, to the Dashboard, to uninstall the Dashboard, and to the OAA Facilitator, on the Desktop.

To launch the Dashboard, double-click on the Dashboard shortcut.



In the next chapter we will show how to use the Dashboard to construct a biochemical model.

The Bio-SPICE documentation, shown in Fig. 2.4, has been integrated into the Dashboard. Click on the menu item `Help>Help Contents` in order to open the documentation window.

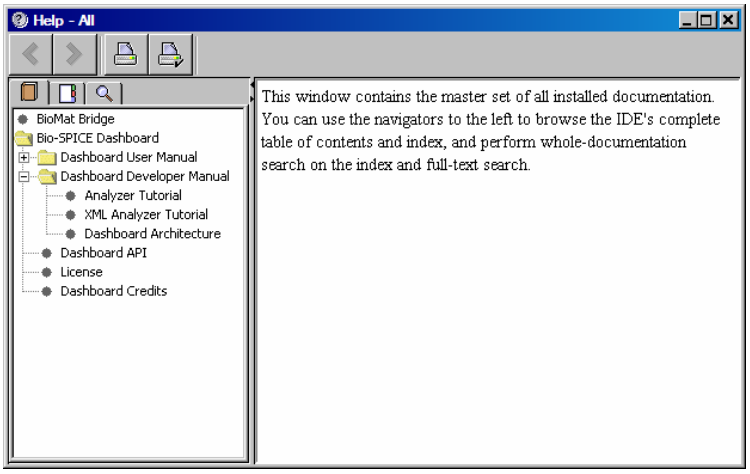


Figure 2.4 Access the Dashboard manual from Bio-SPICE web site.

Chapter 3 Model Editor

This chapter presents how to implement a model with Bio-SPICE. We will use the model editor *BioSpreadsheet* to construct a biochemical model.

Choosing an editor

There are several model editors available in Bio-SPICE. Each simulator provides an accompanying editor, which is best suited for use with the specific simulator. On the other hand, each editor provides an export function that allows you to save the model in SBML format. SBML is the language of exchange for models and each simulator provides you with an import function to read SBML models.

Note: At present there is not full interoperability between all editors and simulators. The import function of one tool may not read correctly the entire SBML model from another tool. See Appendix 2 for a table of interoperability of Bio-SPICE tools.

Simulator contributions to earlier versions of Bio-SPICE all included editors for model construction, due to the fact that no standard data format was established. As the need for interoperability expanded, SBML was chosen as a language of exchange for the various tools. All editors provide an SBML import/export function. One of the original contributors to Bio-SPICE was a team from the University of Tennessee at Knoxville (UTK) and Oak Ridge National Lab (ORNL) which provided the editor BioSpreadsheet with the accompanying stochastic solver ESS.

Downloading an editor

With the move of Bio-SPICE to SourceForge.net, it is best to download Bio-SPICE tools from the web site of the contributing group, if such a site exists. A few of the contributing teams have been found to do a better job making recent tools releases and fixes available to others on their own web site than on the Bio-SPICE web site. Some tools though are only provided on the Bio-SPICE web site https://biospice.org/ . Appendix I provides the list of tools from the various organizations and the web site most convenient to access them.

The tools from the University of Tennessee at Knoxville (UTK) and Oak Ridge National Lab (ORNL) can be found at: http://biocomp.ece.utk.edu/, see Fig. 3.1.

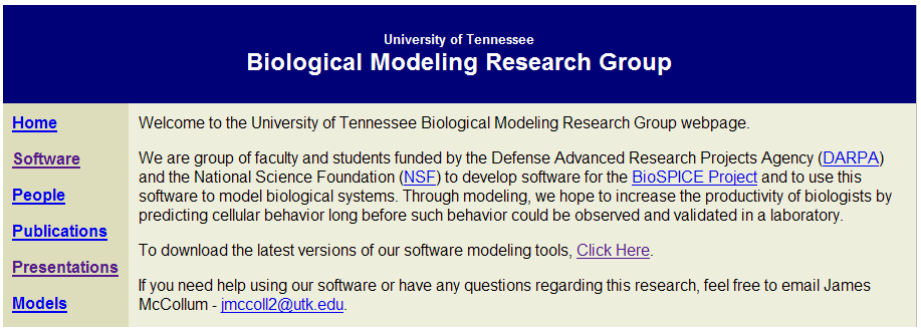


Figure 3.1 University of Tennessee Biological Modeling Research Group webpage.

The editor BioSpreadsheet is a simple-to-use editor for developing models of mass action equations. It was developed in conjunction to the stochastic solver ESS (Exact Stochastic Simulator) as part of the software contribution of UTK/ORNL.

Click the `Software` link to open the download page http://biocomp.ece.utk.edu/tools.html. Click the link `Download Now` and save the file `utkornltools.zip` to disk.
Unzip the file `utkornltools.zip` to install the folder `utkornltools`, which contains the following structure:

The unzipped `utkornltools` folder will look something like this:

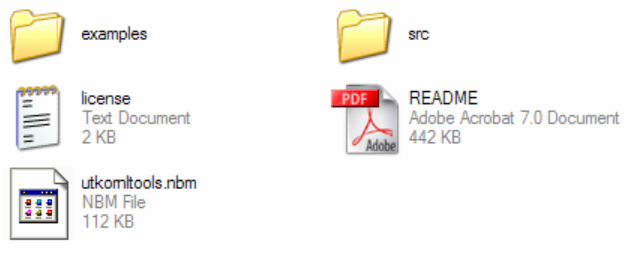


Figure 3.2 Folder `utkornltools`.

The PDF file `README`, on page 3, describes how to install the UTK-ORNL tools in the Bio-SPICE Dashboard. Briefly, the file `utkornltools.nbm` must be installed by using `Install Manually Downloaded Modules` from the menu `Tools>Update Center`. Manual install is used when the tool file resides on your hard drive. Automatic install is used to download the tool file from the

update center. Relaunch the Dashboard to have access to the UTK-ORNL tools. The Dashboard should look as in Fig. 3.3.

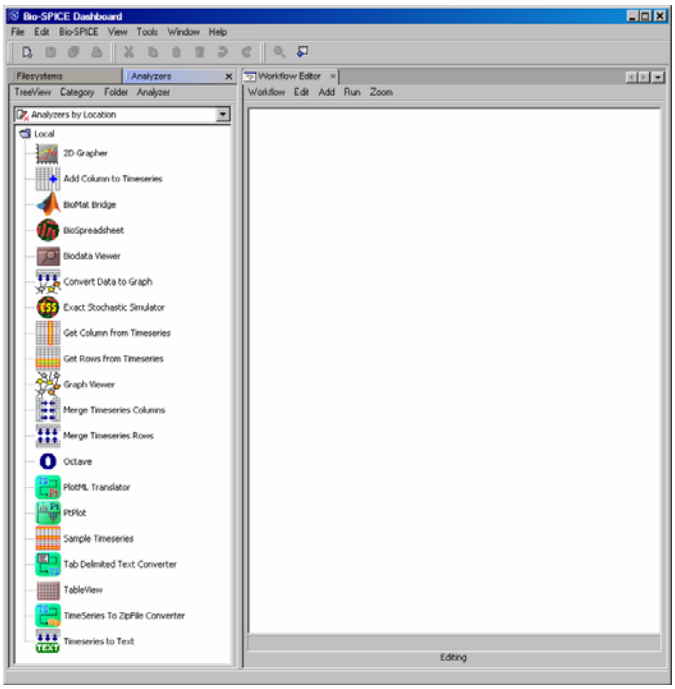


Figure 3.3 Dashboard with UTK-ORNL tools installed.

To launch the BioSpreadsheet editor, you must first place the BioSpreadsheet analyzer on a workflow. Double-click the BioSpreadsheet analyzer on the left pane of the Dashboard and drag the cursor, while holding the left mouse button, to the workflow area on the right pane of the Dashboard.

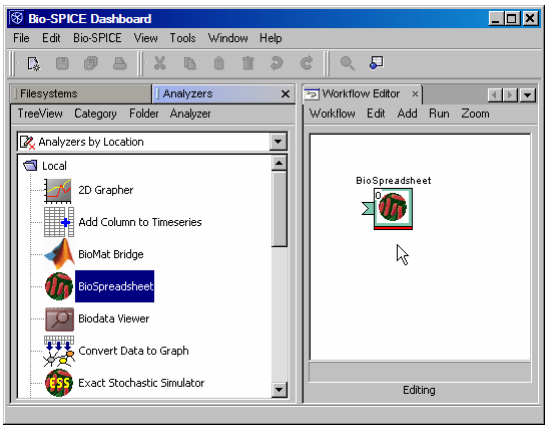


Figure 3.4 BioSpreadsheet analyzer in workflow editor.

Click the menu `Run>Start` in order to start BioSpreadsheet which should open a window as in Fig. 3.5.

Using an editor

The BioSpreadsheet editor has four panes, each associated with a tab Information, Reactions, Species and Parameters, and its corresponding panel.

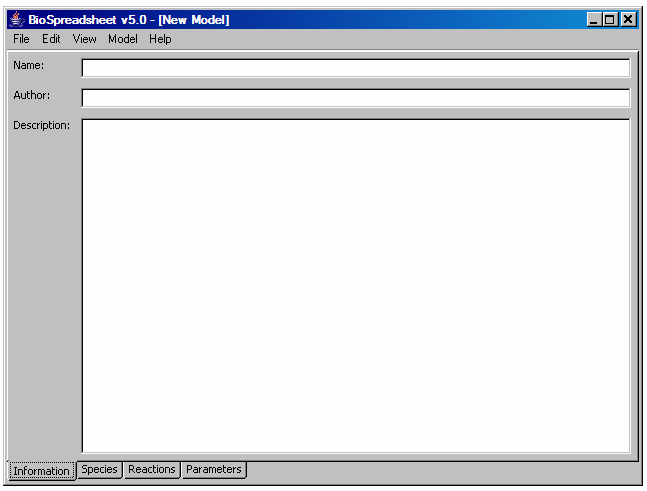


Figure 3.5 BioSpreadsheet application window.

A model in BioSpreadsheet is composed of the model name, the species or variables, the list of reactions and possible parameters. By selecting the desired tag, the appropriate pane will be displayed.

Implementation of a model

In order to demonstrate the BioSpreadsheet editor, a circadian rhythm model will be implemented. This model corresponds to the oscillations in the levels of core gene expression due to negative feedback. The model uses a transcription factor (TF) which undergoes multiple phosphorylation steps. Over the space of a day, TF proteins becomes fully phosphorylated and relieve TF repression so that another "burst" of TF transcription can occur, see Fig. 3.6.

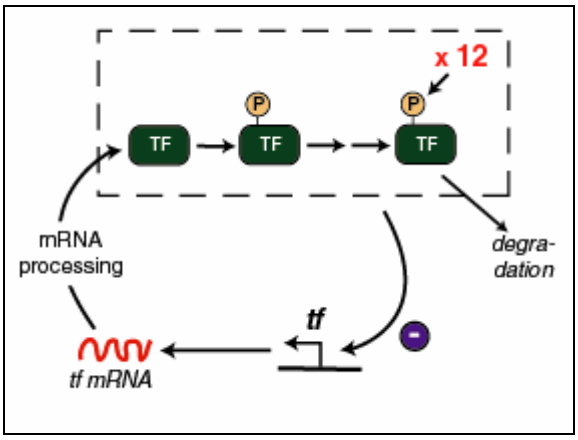


Figure 3.6 Diagram of Circadian model.

$$\frac{d[mRNA]}{dt} = v_R * \frac{K_R}{K_R + [TF_{12}]} - k_d[mRNA]$$

$$\frac{d[TF_0]}{dt} = k_p[mRNA] - k_{ph}[TF_0]$$

$$\frac{d[TF_i]}{dt} = k_{ph}[TF_{i-1}] - k_{ph}[TF_i] \quad \text{for } i = 1...11$$

$$\frac{d[TF_{12}]}{dt} = k_{ph}[TF_{11}] - \frac{v_p[TF_{12}]}{K_P + [TF_{12}]}$$

Figure 3.7 Circadian ODE model. Parameters: Vr=7.0, Kr=0.0005, kd=0.2, kp=0.2,kph=2.0,Vp=3.0,Kp=0.0001.

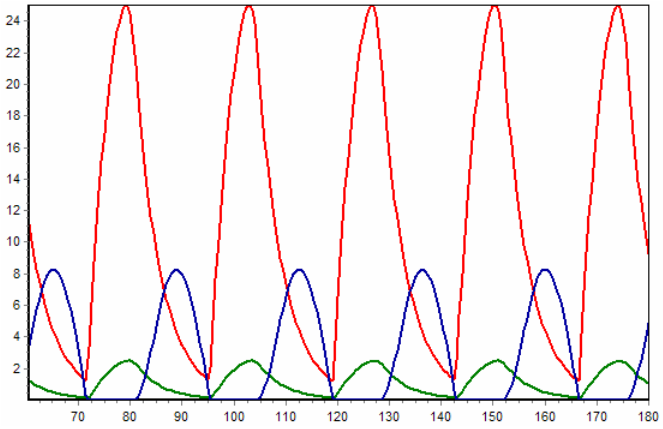


Figure 3.8 Circadian model oscillations of mRNA (red), P0 (green) and P12 (blue).

Since the BioSpreadsheet editor only accepts models in the form of mass action equations, the ODE model of Fig. 3.7 must be converted to mass action form.

Converting a linear ODE is simple since every term represents a mass action reaction. For example, the equation above

$$\frac{d[TF_0]}{dt} = k_p[mRNA] - k_{ph}[TF_0]$$

represents a linear production term and a linear degradation term. Two mass action equations are needed, one for each term. Of course for mass balance, the degradation term for P_0 is equivalent to the production term for P_1.

$$TF_0 \xrightarrow{k_{ph}} TF_1$$

The nonlinear terms, such as those using the Michaelis-Menten formalism are more difficult to convert into mass action form. Since the Michaelis-Menten formalism takes advantage of the quasi-steady-state approximation, this assumption which reduces the complexity of the model is not valid for a system of mass action equations, and must be expanded to its original form.

In order to unpack the equations, new variables are needed. There are two ODEs of the circadian model with Michaelis-Menten terms, the equations for mRNA and TF12. In the case of the ODE for mRNA, the Michaelis-Menten term contributes to the production of mRNA. While in the ODE for TF12, the Michaelis-Menten term is part of the removal of TF12. It is not our intent in this manual to deal with the subject of converting nonlinear ODEs to mass action equations. Figure 3.9 provides the equations for the model of Fig. 3.7 in mass action format. Figure 3.10 illustrates the response of the mass action equation model which is similar to the time course of the original model, shown in Fig. 3.8.

$$TF_{12} + promoter \Rightarrow nlpromoter$$

$$nlpromoter \Rightarrow TF_{12} + promoter$$

$$promoter \Rightarrow mRNA + promoter$$

$$mRNA \Rightarrow WmRNA$$

$$mRNA \Rightarrow mRNA + TF_0$$

$$TF_i \Rightarrow TF_{i+1} \quad (\text{for } i = 0 \text{ to } 11)$$

$$TF_{12} + x \Rightarrow TF_{12}D$$

$$TF_{12}D \Rightarrow TF_{12} + x$$

$$TF_{12}D \Rightarrow x$$

Figure 3.9 Circadian model in mass action form. Rate values are: 18.2, 65.0, 130.0, 0.26, 0.26, 2.6 (i=0 to 11), 3.9, 39.0, 3.9.

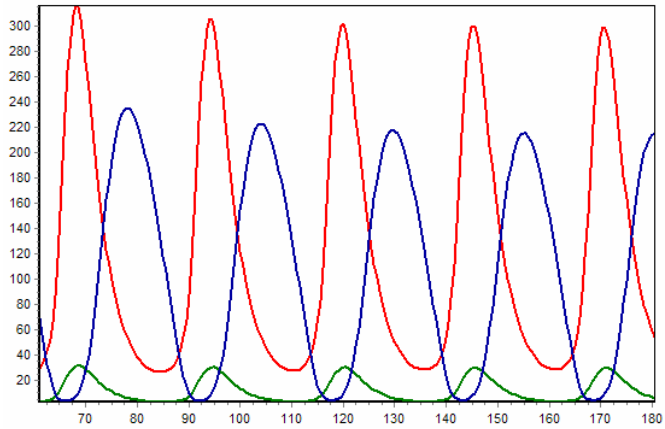


Figure 3.10 Circadian oscillations of mass action model.

Entering Model in BioSpreadsheet

The BioSpreadsheet editor provides a Species panel for declaring the model species and a Reactions panel that is used for entering model equations. Click the `Species` tab to open the Species panel. Click the button `Add`, to insert a blank line, as shown in Figure 3.11.

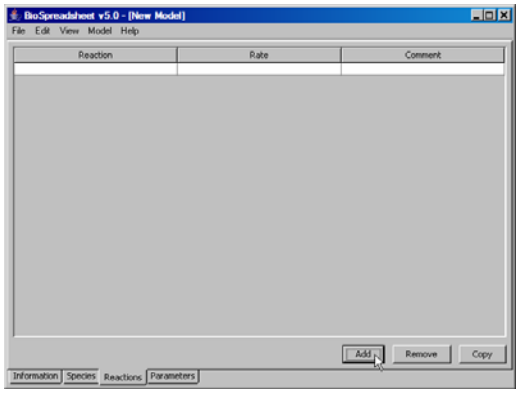


Figure 3.11 BioSpreadsheet Reaction panel.

Each term of the mass action equations is a species that needs to be defined in the BioSpreadsheet Species panel. Only three species have initial values different from zero. The initial value of mRNA is 3, promoter is 2, and x is 10. Figure 3.12 presents the complete species panel for the circadian model.

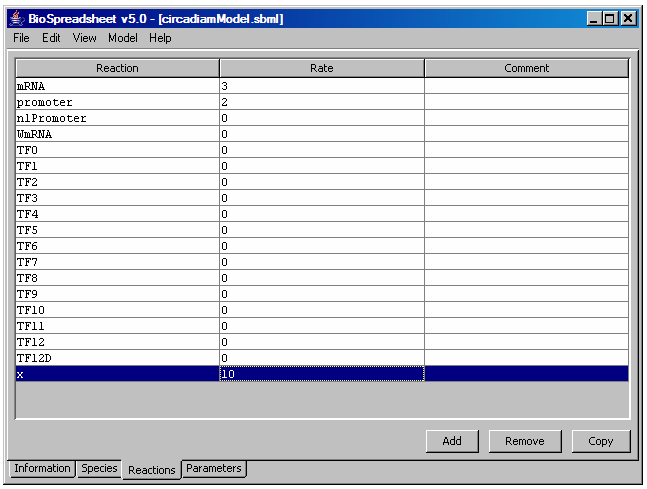


Figure 3.12 Species panel of BioSpreadsheet editor.

The next step is to define the reactions of the model. Select the Reactions tab in the BioSpreadsheet editor. Use the button Add to insert a blank line in the panel. Select the column you want to write in. There are 20 mass action equations in the Circadian model. The final model should look like Figure 3.12.

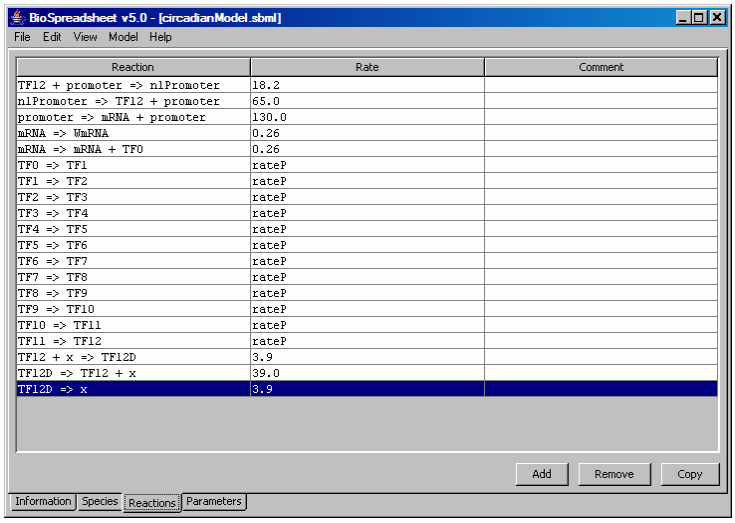


Figure 3.13 Mass action equations for the circadian model.

The last panel we need to modify is the panel Parameters. Since all the phosphorylation steps use the same rate constant, we can define the value as a parameter. Open the Parameter panel by selecting the Parameter tab. Click the button `Add` to insert a new blank line. Click the column with the mouse and enter the parameter `rateP`, click the Tab key and enter the value 2.6.

In order to use the model file within the Dashboard, it must be saved in SBML format. BioSpreadsheet provides an export function, in the File menu, in order to save the model in SBML format. Click `File>Export SBML` to open a Save dialog box. For our example, we have chosen the filename `circadianModel.sbml`.

To edit a SBML file, use the input SBML command to open the file in BioSpreadsheet. Click `File>Import SBML` to open a dialog box to select the desired SBML file.

Chapter 4 Using the Dashboard

This chapter presents the Dashboard application, which is the environment for invoking Bio-SPICE tools. The tools provided by the Dashboard are referred to as analyzers, and any tool that is installed is represented by an icon in the analyzer pane. You will learn how to construct a workflow and run a simulation, as well as how to visualize the results.

Dashboard description

The Bio-SPICE Dashboard is an environment for integrating varied data and tools useful to biologists. The main categories of tools this environment was designed for are model building, model analysis, experimental data analysis, and visualization. However, conceivably any tool that analyzes, transforms, produces, or helps to interpret data could be integrated into the Dashboard. The Dashboard functions in a manner loosely analogous to UNIX shells (especially with respect to UNIX pipe facilities).

The Dashboard is based on the NetBeans application platform, a Java-based tool kit. Tools may be written in any language, however, as the core Dashboard libraries provide support for accessing non-Java tools that are network enabled, command-line tools, or OAA agents.

Currently, facilities for Java and OAA tools are available, as well as support for TCP/IP, web, and command-line tools via an XML wrapping API.

The Dashboard consists of two panes, a left pane for viewing analyzers and the file system, and a right pane for the workflow editor and output visualization. The Dashboard provides a library of tools that you can connect and configure for your needs. By default, the Dashboard contains several basic analyzers, e.g., a table viewer and a data plotter.

Dashboard workflow

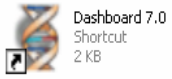
The Dashboard provides an environment where you can connect data files and the various tools of Bio-SPICE. In order to connect the varied data and tools, the Dashboard provides a workflow editor. The workflow editor allows you to define source documents e.g., a SBML model file, and direct the document to a tool, e.g., an editor or a simulator. The tools can produce output data which you can visualize with a graphing tool.

A workflow is an acyclic graph representing a high-level task that a user wishes to run. The individual parts of this task are all the nodes in a workflow,

and consist of all the modules that will be run and the data they will be analyzing or producing. A workflow may contain source documents, destination documents, and analyzers. A source document represents data read from a file. Similarly, a destination document represents data being written to a file. Analyzers may have any number of inputs and/or outputs. For a workflow to be valid, all required inputs and outputs from all nodes (documents and analyzers) must be satisfied. In addition, all source and destination documents must have a file associated with them. Analyzer inputs and outputs may be satisfied by connecting links to other documents and analyzers of matching type. In addition, some analyzer inputs (for example, text) may be satisified by manually editing the input parameters.

In order to run the model we have developed with BioSpreadsheet, the stochastic solver ESS needs to be downloaded.

Running the Dashboard

Windows users should find shortcut links on their desktop to the Dashboard, the OAA factilitator, and the Dashboard Uninstaller. Double-click on the Dashboard shortcut icon 

to launch the application.
To launch the application directly, locate the Dashboard's bin directory.

- On Windows, this is most likely: `C:\Program Files\Bio-SPICE\Dashboard[Version #]\Dashboard\bin`
- On Linux, this is most likely: `/opt/Bio-SPICE/Dashboard2.0.0/Dashboard/bin`

The executable to run the Dashboard is named "runide"

- Windows users: double-click on `runidew.exe`. There is also `runide.exe`, which starts a console window in addition to the Dashboard. Debugging and/or information messages are sometimes printed to this console window.
- Linux users: run `./runide.sh`

By default the Dashboard opens the workflow editor on the right pane, as seen in Figure 4.1. If you find the editor window has closed, you may open the workflow editor by clicking `Bio-SPICE>Open Workflow Editor`. You may open several workflow windows and use the workflow editor tab to select the desired workflow.

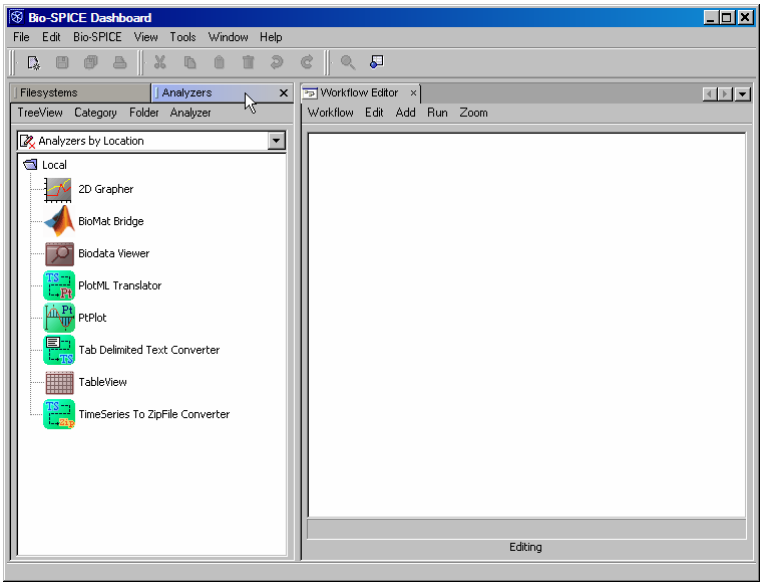
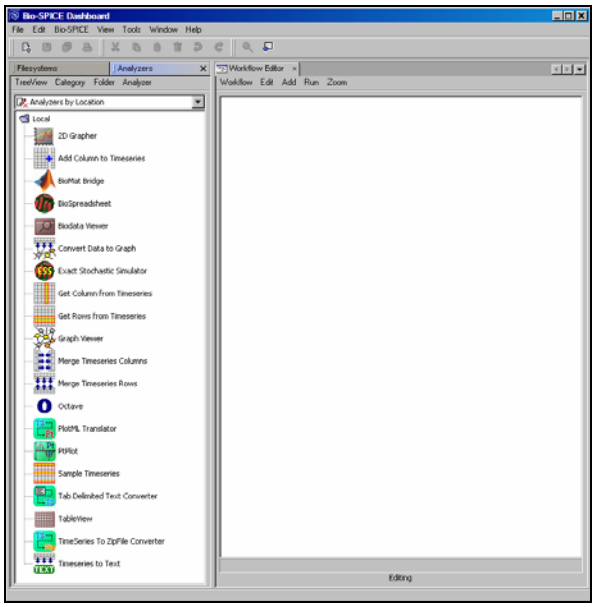


Figure 4.1 Default Dashboard with basic set of Analyzers.

Installing UTK-ORNL tools

In the previous chapter we briefly described how to install the tools from UTK-ORNL in the Bio-SPICE Dashboard. The UTK-ORNL documentation describes the procedure on page 3 of the README document.
Briefly, the file `utkornltools.nbm` must be installed by using `Install Manually Downloaded Modules` from the menu `Tools>Update Center`. After relaunching the Dashboard, the UTK-ORNL tools will appear in the analyzer pane on the left.



4.2 Dashboard with UTK-ORNL tools installed.

Opening a source file

The first step in creating a simulation workflow is to provide input data for the simulation. This is called a source document. Click the menu `Add>Document>Source` as shown in Figure 4.3.

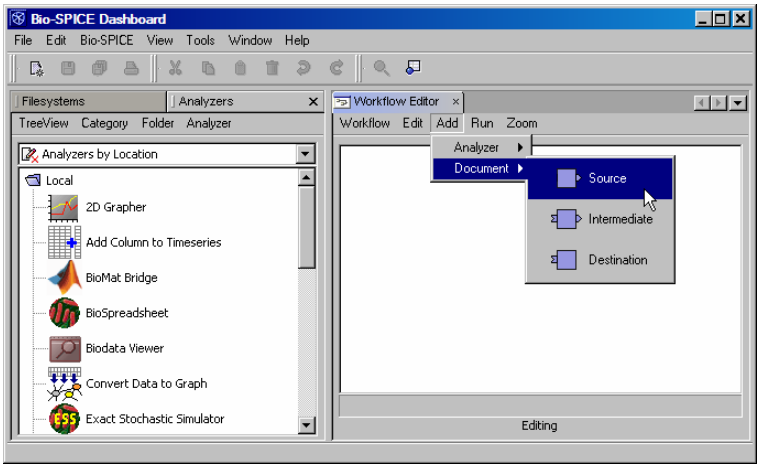


Figure 4.3 Add a source document to the Workflow editor.

The source document icon will appear in the workflow editor pane (see Fig. 4.4). Click the document icon and right-click to open the pull-down menu. Click the item `edit`, as shown in Fig. 4.4. A dialog box will open which allows you to locate the file to load as the source document.

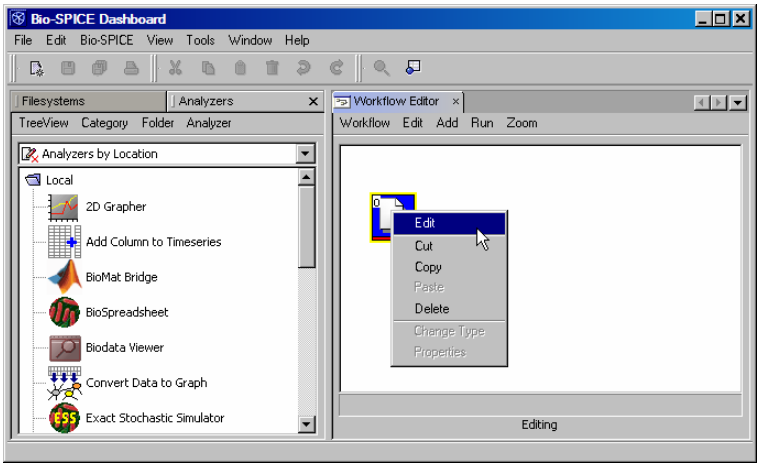


Figure 4.4 Edit the source document to select the input file.

Select the source file `circadianModel.sbml` and the file name will appear above the source document icon, as shown in Fig. 4.5.

Building a workflow

Constructing a workflow entails connecting the building blocks from an initial source document to a final output document or plot. There are two ways to add a component box to the workflow. Using the button Add, you may incorporate a source document or an analyzer. As well, the analyzers presented in the component pane can be selected and dragged onto the workflow pane. In order to connect two components, select the right side of the leading component and extend the black line to the left side of the second component. The Dashboard will allow you to connect two components that are designed to be joined in a workflow, otherwise, attempting to connect two components that are not designed to be connected will fail.

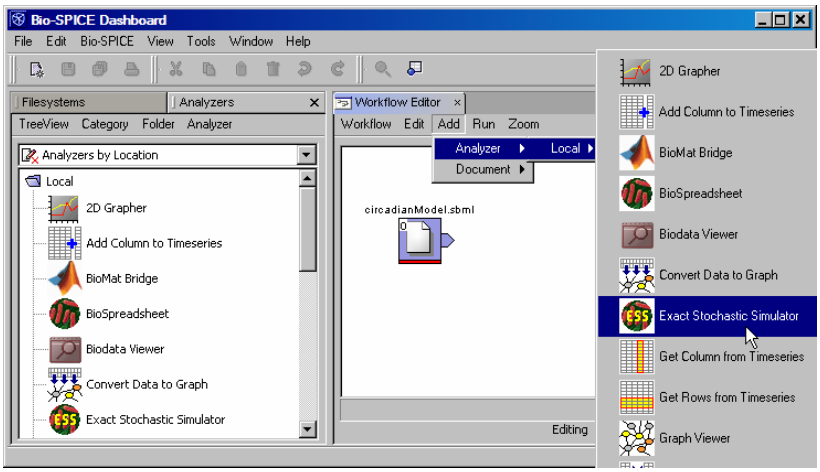


Figure 4.5 Insert a BioSpreadsheet analyzer in the workflow.

The source document is attached to the analyzer by connecting the output socket (rightward protruding arrow head) to the input socket (leftward protruding arrow tail) of the analyzer. Right-click the arrow heard and hold the button as you draw a line to the arrow tail, as seen in Figure 4.6. Once the connection is established the line will remain when you release the button. Double-click the analyzer to open the analyzer parameter box to confirm the input source document format. When this is done, the red line on the bottom of the source document icon will turn to green, meaning the connection is established and verified, as seen in Fig. 4.7.

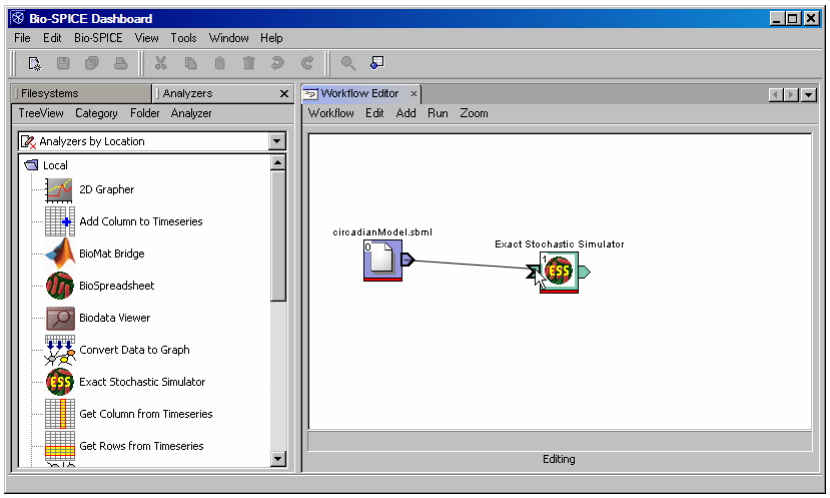


Figure 4.6 Connect source document to analyzer in workflow.

The output from the ESS analyzer may be directed into the 2D Grapher analyzer which is provided with the Dashboard.

There are several ways of adding analyzers to the workflow. You may also select an analyzer from the analyzer pane. Click the analyzer `2D Grapher` and right-click to open a menu, select `Add To Workflow`, as seen in Fig. 4.7.

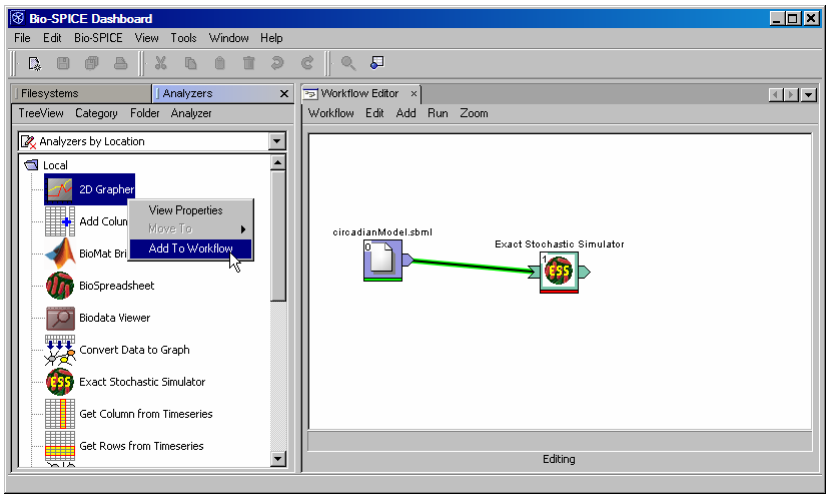


Figure 4.7 Add ESS analyzer from analyzer pane.

Figure 4.8 shows the complete workflow. Click the ESS analyzer to open a dialog window to set simulation parameters. Figure 4.9 shows the three parameters that you must provide, the print interval, end time and seed number, the values 1, 100 and 1 were used respectively, within quotes (“ ”) due to the required string format.

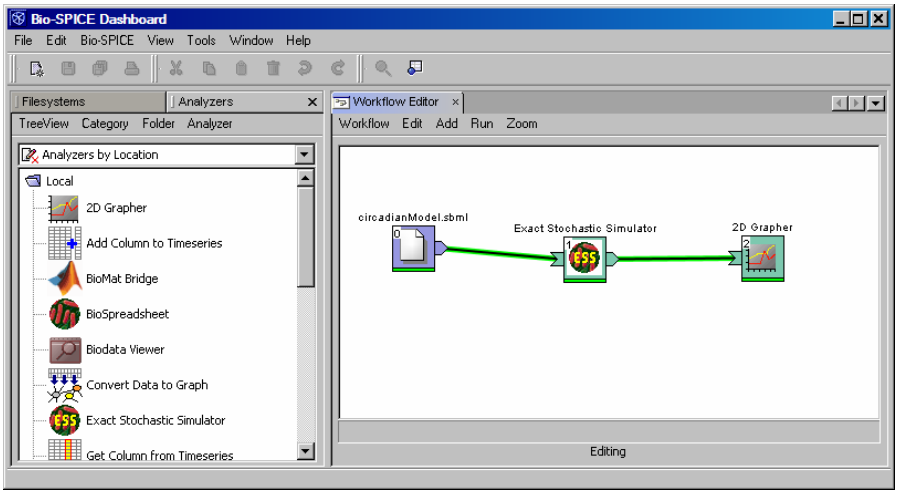


Figure 4.8 Connect ESS analyzer to 2D Grapher analyzer in workflow.

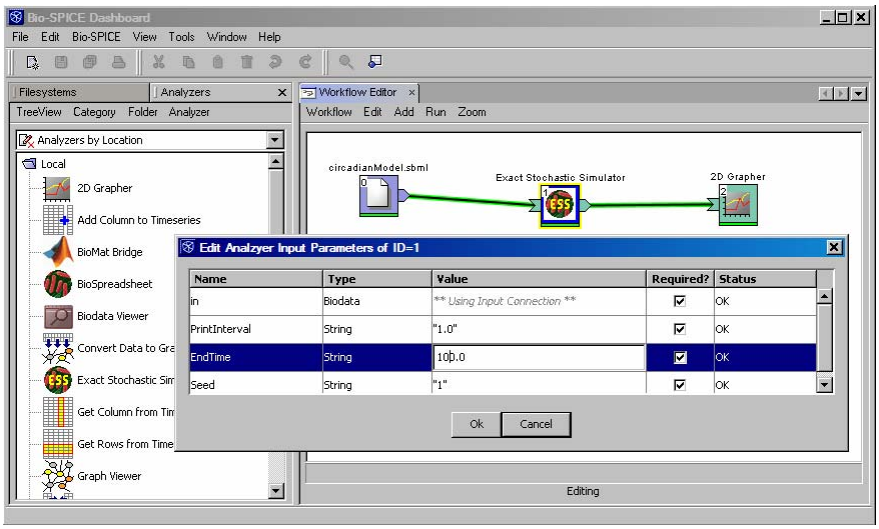


Figure 4.9 ESS analyzer requires three parameters for simulation.

Save the workflow by clicking the menu `Workflow>Save` and typing the filename in the desired folder. For this tutorial, we have chosen `Tutorial_CircModelSim.wf` in folder `tutorialExamples`.

Running a simulation

With a complete workflow, it is possible to run a simulation and examine the time course of the model variables.

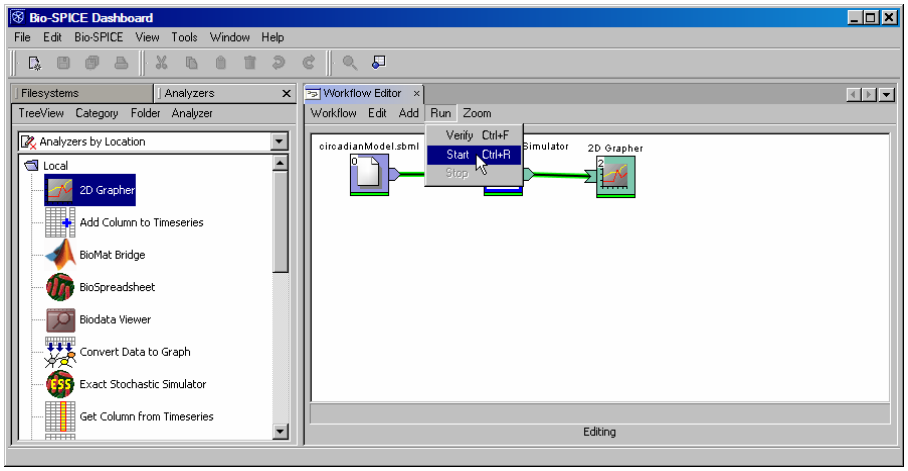


Figure 4.10 Launching a simulation.

To launch a simulation click the menu `Run>Start`. The Dashboard displays the progression of the simulation by highlighting the analyzer of the workflow that is active with a green square.

When the simulation ends, 2D Grapher will display the time course of the model variables, as seen in Fig. 4.11.

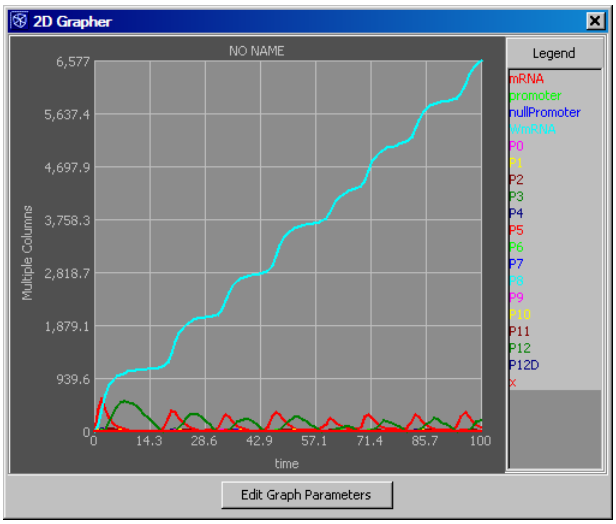


Figure 4.11 Plot of circadian model time course.

The results displayed with 2D Grapher show the time course of all the variable of our model. Normally we want to limit the display to certain specified variables.

The 2D Grapher analyzer allows you to edit the variables to be displayed. To select the variable you wish to display click the button `Edit Graph Parameters`. A window will open, as seen in Figure 4.12. Click the variables you wish to display, using the Shift key to select blocks of variables and the Control (Ctrl) key to select multiple individual variables.

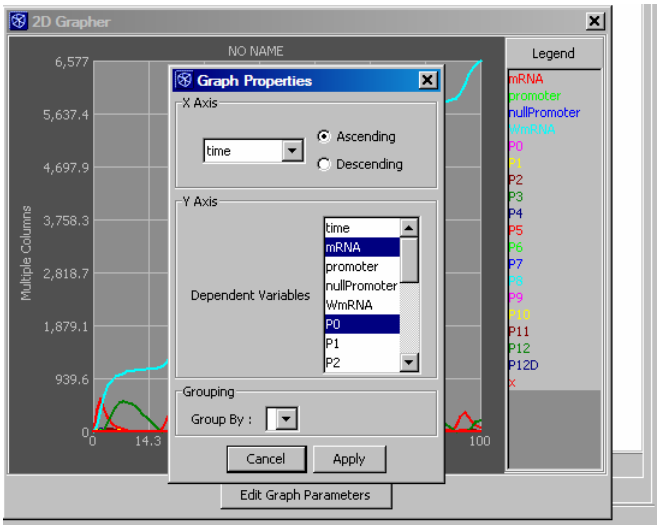


Figure 4.12 Using the 2D Grapher property option you may select specific variable to display.

Click the button Apply in the Graph Properties dialog box in order to update the display, as seen in Fig. 4.13.

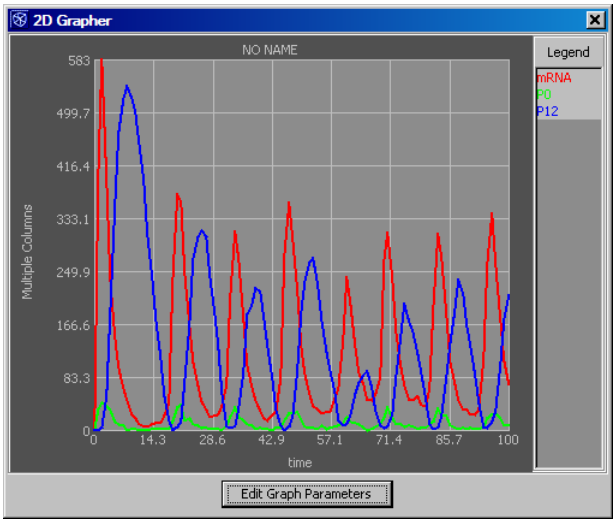


Figure 4.13 Workflow with 2D Grapher analyzer.

Updating a file

So far we have seen how to run a simulation using the Dashboard. After running a simulation we would like to examine the behavior of the model using different parameter values. In order to modify the parameter values we

need to create a workflow consisting of a source document connected to the BioSpreadsheet analyzer. Click the edit menu of the source document, as shown in Fig. 4.4, to load the file you wish to edit. Figure 4.14 presents such a workflow with the source document `circadianModel.sbml` that was described in chapter 3. Click the menu item `Run>Start` to execute the workflow and open the BioSpreadsheet editor with the desired file. Change the parameter value and save the file by clicking `File>Export SBML`. In our case, export the model using the same filename as before. Run the workflow with the updated parameters to view the change in system behavior. If you provide a new filename, the new filename will have to be provided as the source document, which you may change my right-clicking the icon and clicking the item `edit`.

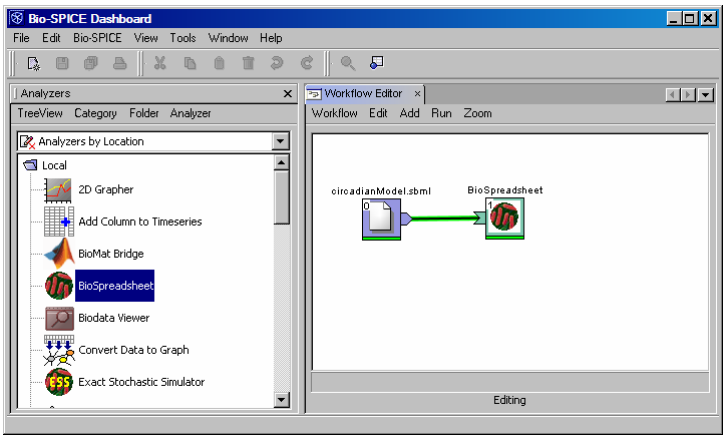


Figure 4.14 A workflow to open BioSpreadsheet editor to update file.

Installing Additional Tools in the Dashboard

In the previous section, we saw how to construct a workflow and run a simulation.

There are several ways of installing tools in the Dashboard. The Dashboard provides a way to connect to an update center from which you may select and download tools.

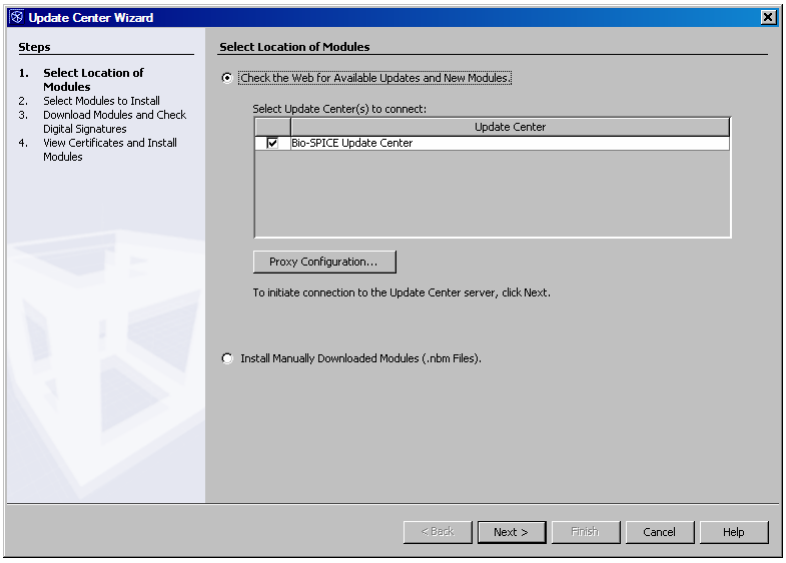


Figure 4.15 The Bio-SPICE update center wizard.

Click the menu item `Tools>Update Center` to open the Update Center wizard, seen in Figure 4.15. Click the button `Next` to view the possible updates available. The wizard will connect to the Bio-SPICE web site and download the list of available components.

Scroll down the list of possible downloads and click the tool you need. Click the right arrow to move the module to the right pane titled `include in install`, as seen in Figure 4.16.

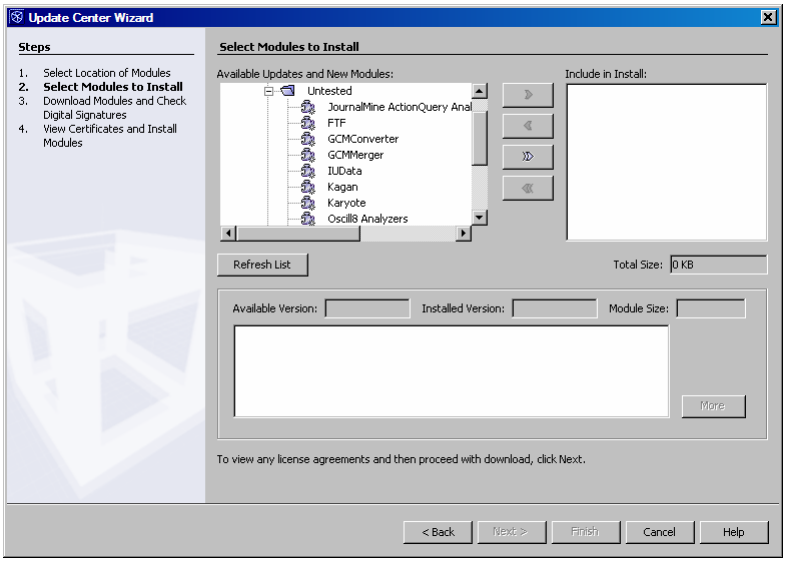


Figure 4.16 Update center wizard with list of available downloads.

Click the button `Next` to download the program, you will be asked to accept the License Agreement. Click the button Finish in order to install the tool.

If the tool is properly installed, you will see the icon in the analyzer pane, after restarting the Dashboard.

Importing an Analyzer

Tool analyzers may be defined by an xml file which can be installed in the Dashboard by using the import Analyzer command. Click the pull-down menu item `Bio-SPICE>import Analyzer` to open a dialog box which displays the file hierarchy. Traverse the file structure in order to reach the folder/directory of interest. Click the file `toolName.xml` and click the button open. After importing the analyzer, the Dashboard needs to be restarted to show the analyzer icon.

Chapter 5 Using Bio-SPICE Tools

The Bio-SPICE toolkit consists of the Dashboard application and numerous types of tools. Users are provided with model editor tools, simulators, database tools as well as visualization tools.

The Bio-SPICE web site, https://biospice.org/index.php provides the tools that may be incorporated into the Dashboard. The listing of the tools may be viewed in several ways, by alphabetical order, by order of organization that developed the tool, or by order of functional category.

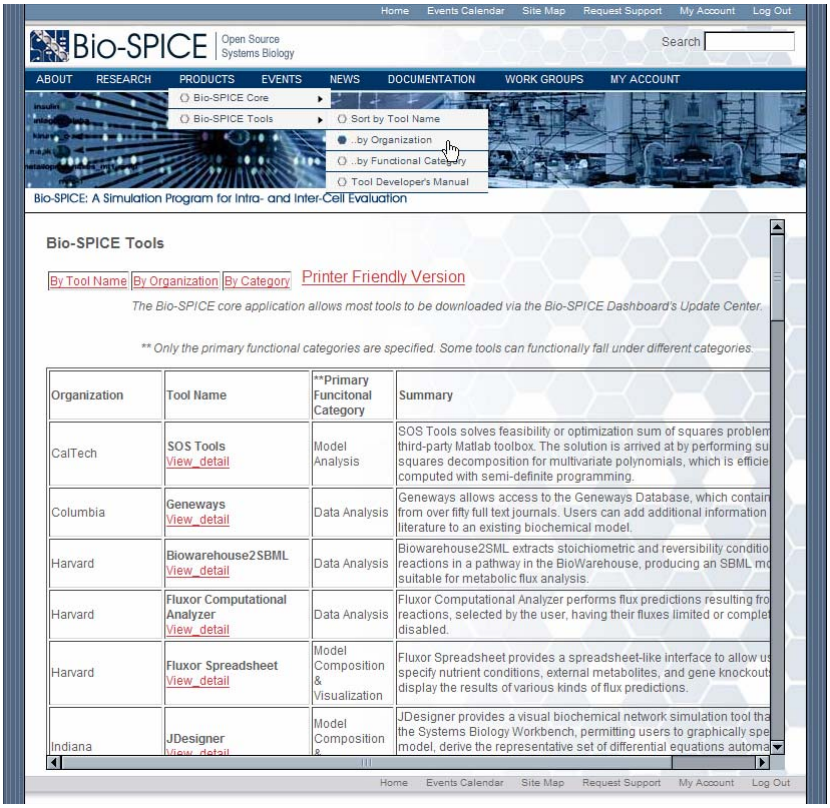


Figure 5.1 Bio-SPICE tools listings by organization.

The tool page provides a description for each tool which can be accessed by clicking the link in red `View_detail` after each tool name.

Appendix 1: Bio-SPICE Components List

Organization	Tools	Web Site
CalTech – California Institute of Technology	SOSTools	https://biospice.org
Columbia	GeneWays	http://geneways.genome center.columbia.edu/
Harvard	BioWarehouse2SBML, Fluxor	http://arep.med.harvard. edu/moma/
KGI – Keck Graduate Institute	JDesigner, Jarnac, MetaTool, Optimizer, SBWMatlab	http://sys-bio.org
LBL – Laurence Berkeley Lab	HomologFinder, SensitivityAnalyzer, Pathway Builder	http://biospice.lbl.gov/P athwayBuilder/
NYU – New York University	NYUMAD, MYUSIM, Simpathica	http://bioinformatics.nyu .edu/Projects/Simpathica
MolSci – The molecular science institute	MONOD	http://monod.molsci.org/
SRI – Stanford Research Institute	BioWarehouse, BioMatBridge, SAL, Hybrid Automata, Symbolic Reachability Tool	http://bioinformatics.ai.s ri.com/
TJU – Thomas Jefferson University	CloneUpdater, MetaCluster, PAINT	http://www.dbi.tju.edu/d bi/tools/paint/
Indiana University	CellX, Karyote Cell Analyzer, Karyote Genome Analyzer	https://systemsbiology.in diana.edu/cellx/
UCLA – University of California at Los Angeles	GeneScreen, IcDNA, MIAME Spice, NCA	http://www.ee.ucla.edu/ ~riccardo/
UCSB – University of California at Santa Barbara	BioSens	http://www.chemengr.uc sb.edu/~ceweb/faculty/d oyle/biosens/
UNC – University of North Carolina	BioNets	http://x.amath.unc.edu:1 6080/BioNetS/
UPENN – University of Pennsylvania	Charon	http://www.cis.upenn.ed u/mobies/charon
UTK-ORNL University of Tennessee and Oak Ridge National Labs	BioGrid, BioSmokey, BioSpreadsheet, ESS, OctaveBridge	http://biocomp.ece.utk.e du/
VaTech – Virginia Institute of Technology	BioPak, JigCell	http://jigcell.biol.vt.edu/
WRAIR – Walter Reed Army Institute of Research	GeneCite, Pathway Screen	

Appendix 2: Bio-SPICE Usability Testing

Five models were used to test several Bio-SPICE tools, editors and simulators, in order to evaluate tool usability. The five models used were:

- **Circadian rhythm**, mRNA transcription and protein phosphorylation (Smolen P et al, *J Neurosci*, 21:6644-6656, 2001)
  14 ODEs; 20 mass action reactions.

- **Circadian rhythm II**, mRNA transcription and protein phosphorylation (same as Circadian rhythm scaled to 95 ODEs; 100 mass action reactions.)

- **Cell division cycle**, cdc2 and cyclin interactions
  (Tyson J, *PNAS*, 88:7328-7332, 1991)
  6 ODEs; 14 reaction equations.

- **Allosteric model for glycolytic oscillations**
  (Goldbeter A & Lefever R, *Biophys J*, 12:1302-1315, 1972)
  2 ODEs (minimal model)

- **Memory induction**
  (Pettigrew D et al, *J Comp Neurosci*, 18:163-181, 2005)
  16 ODEs; 39 reaction equations.

The simulators/editors were evaluated (when possible) with both a code specific implementation of the model using the editor tool and a SBML version which is suppose to be interoperable between simulators/editors. The table below indicates which models were tested with the various simulators/editors. These models can be found at the web site: http://nba.uth.tmc.edu/darpa/
click menu `MODEL CODE` to find a copy of the table with links to the various models. Also, PDF documents of posters presented at DARPA Bio-SPICE conferences can be found in the Document page (click menu `DOCUMENTS`) as well as the Getting Started manual and Jarnac Use Case document.

	Circadian Rhythm I		Circadian Rhythm II		Cell Division Cycle		Allosteric Glycolytic Oscillations		Memory Induction	
	code specific	SBML	code specific	SBML	code specific	SBML	code specific	SBML	code specific	SBML
BioSpreadSheet/ ESS	CR	CR	CR100		CDC					
BioSketchPad/ Charon	CR				CDC					
Jarnac/ JDesigner	CR	CR	CR100		CDC	CDC	AGO		MI	
JigCell	CR	CR	CR100		CDC	CDC	AGO		MI	MI
Simpathica	CR	CR	CR100	CR100	CDC	CDC				
BioNets	CR		CR100		CDC					
PathwayBuilder	CR	CR			CDC	CDC				