

Instruction for CADLIVE Simulator

Example: Drosophila Circadian clock system

TPP_RAPID CONVERSION

Contents

1. Constructing biological networks by CADLIVE Editor	2
2. Login to CADLIVE Simulator	3
3. Startup simulator	3
4. Upload of data for regulator-reaction equations	4
5. Selection of conversion methods	4
6. Editing Mathematical Model (DAEs)	5
7. Selecting analysis types	6
8 Input for control data	6
9. Input of parameters	7
10. Result indication	9
11. Graph visualization	10

NOTICE

If there is anything wrong with calculation and you want to kill your job, access the site of <http://kurata01.bse.kyutech.ac.jp/TEST/Life/kill>, and push the kill simulator button.

1. Constructing biological networks by CADLIVE Editor

CADLIVE Editor is a system for constructing large-scale biological networks (Fig. 1-1) (metabolic and gene regulatory networks) using GUI (Graphic User Interface) and saving them as regulator reaction equations (Fig. 1-2) in a database in the XML format(**Drosophila-Circadian.xml**) compatible to a CADLIVE Simulator.

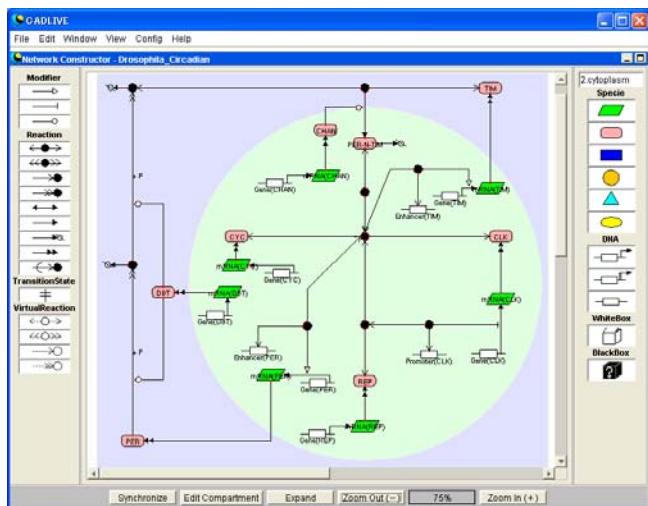


Fig. 1-1 Biochemical map for Drosophila Circadian clock system

The screenshot shows the CADLIVE Data Editor interface. It displays two tables: 'ListOfSpecies' and 'ListOfReactions'. The 'ListOfSpecies' table lists various species and their properties, while the 'ListOfReactions' table lists the reaction equations and their parameters.

SpeciesName	SpeciesClass	BindingSite	Compartment	MassBalance	TotalAmount	Decomposition
PER	protein		cytoplasm	on	variable	on
PER-P	modified		cytoplasm	on	variable	on
PER-P-P	modified		cytoplasm	on	variable	on
TIM	protein		cytoplasm	on	variable	on
DBT	protein		cytoplasm	on	variable	on
PER-P-DBT	modifier_complex		cytoplasm	on	variable	on
PER-P-DBT	modifier_complex		cytoplasm	on	variable	on
CHAN	protein		nucleoplasm	on	variable	on
CLK	protein		nucleoplasm	on	variable	on
CYC	protein		nucleoplasm	on	variable	on
CLK-CYC	complex		nucleoplasm	off	variable	on
CLK-CYC-PER-N-TIM	complex		nucleoplasm	off	variable	on
REP	protein		nucleoplasm	on	variable	on

ReactionName	ModifierReactionEquation	Layer	ReactionType	isConvertible	isTotal
#18	CLK-CYC-REF-CLK-CYC-REF-CLK-CYC-REF-CLK-C	gene	transcription	true	true
#21	CLK-CYC-CLK-CYC-CLK-CYC-CLK-CYC-CLK-CYC-C	gene	transcription	true	true
#26	CLK-CYC-CLK-CYC-CLK-CYC-CLK-CYC-CLK-CYC-C	gene	transcription	true	true
#5	DBT-O-PER-P-P-PER-P	protein	home_association_or...	true	true
#4	DBT-O-PER-P-P-PER-P	protein	home_association_or...	true	true
#9	CHAN-O-PER-P-TIM-PER-N-TIM	protein	invertible_conversion	true	true
#17	mRNA(CLK) -> CLK	gene	transcription	true	
#22	mRNA(PER) -> PER	gene	transcription	true	
#28	mRNA(TIM) -> TIM	gene	transcription	true	
#25	Gene(DBT) -> mRNA(DBT)	gene	transcription	true	
#30	mRNA(DBT) -> DBT	gene	transcription	true	
#31	Gene(CHAN) -> mRNA(CHAN)	gene	transcription	true	

Fig. 1-2 Regulator reaction equations for Drosophila Circadian clock system

2. Login to CADLIVE Simulator

Following the installation of the CADLIVE Simulator, open <http://kurata01.bse.kyutech.ac.jp/TEST/Life/index.html> on a PC browser to display the screen(Fig. 2-1). Input the user name, subsequently his/her password to start up simulation.

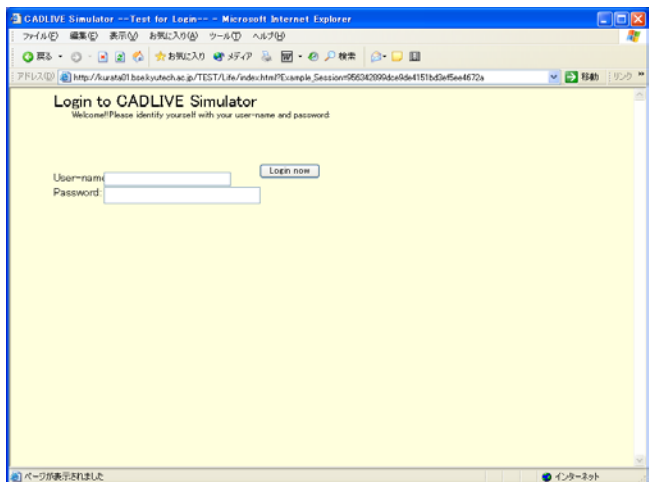


Fig. 2-1 Login screen

3. Startup simulator

Clicking the "Simulator" button on the left hand side (Fig. 3-1) changes the upper region of the screen, as shown in Fig.3-2

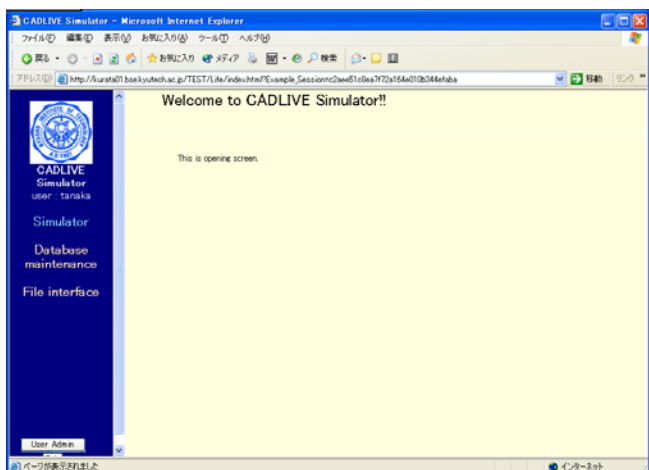


Fig. 3-1 Startup menu

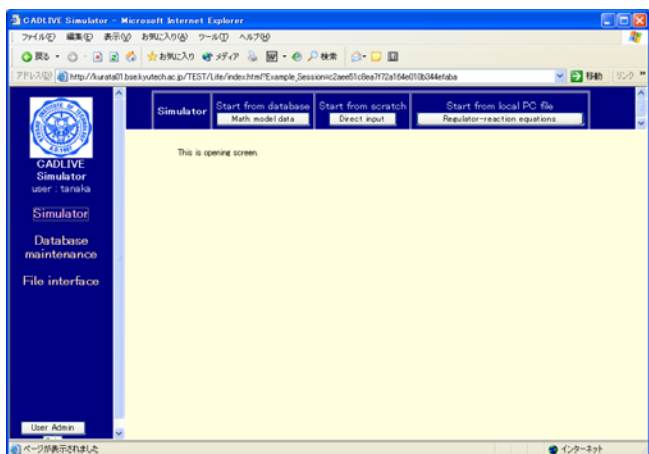


Fig. 3-2 Startup simulation

6. Editing Mathematical Model (DAEs)

Clicking the [Submit] button on the confirmation screen (Fig. 5-2) parses the regulator-reaction equations, converting them into the mathematical model according to the selected conversion method. The resultant mathematical model is displayed as shown in Fig. 6-1.

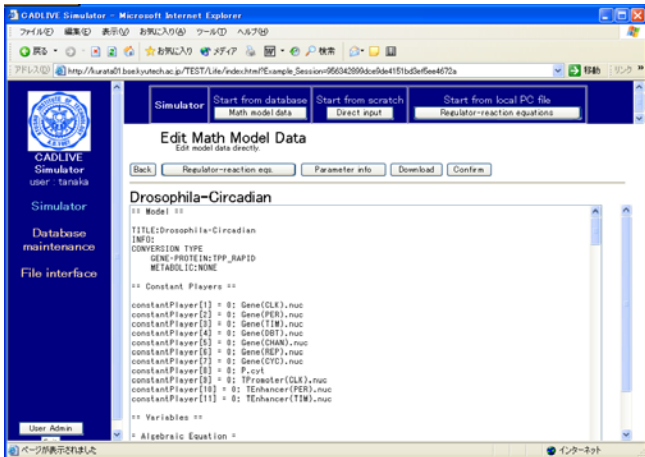


Fig. 6-1 Mathematical model that is obtained from regulator-reaction equations

This screen mainly has seven parts: the header, the definition of constant players, the definition of variables, the definition of the employed parameter labels, the definition of kinetic parameters, the definition of intermediate mathematical expressions, the definition of algebraic equations, and the definition of differential equations.

Clicking the [Regulator-reaction eqs.] button displays another window that shows regulator-reaction equations. Clicking the [Parameter info.] button shows the parameter information. The [Download] button enables users to download various data files to their local PC.

Clicking the [Confirm] button displays the confirmation screen (Fig. 6-2) that is similar to Fig. 6-1. If there is no problem, click the [Submit] button.

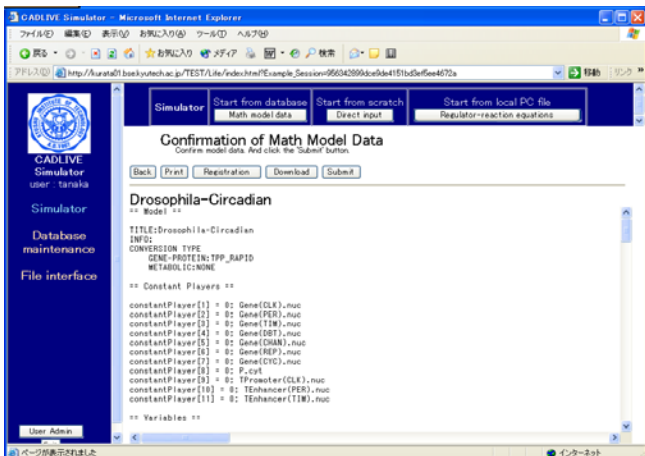


Fig. 6-2 Confirmation screen for a mathematical model

7. Selecting analysis types

Clicking the [Submit] button on the confirmation screen displays the screen (Fig. 7-1), where users select the method for numerical simulation. Select “Dynamic” as analysis type.

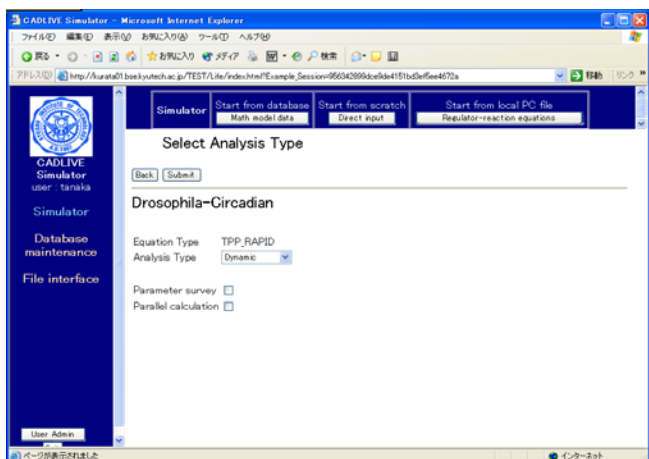


Fig. 7-1 Selection of analysis type

As "Analysis type", users can choose either “Dynamic” or “Steady-state”. “Dynamic” simulates the time evolution of the concentrations by calculating DAEs, and “Steady-state” calculates the concentrations at steady state by solving algebraic equations. The checkbox of "Parameter survey" determines if the simulator surveys the parameter space. Checking the checkbox of "Parallel calculation" carries out parallel calculation that employs the Message Passing Interface (MPI). Notice that the checkbox of "Parallel calculation" cannot be selected prior to checking the parameter survey.

8 Input for control data

Clicking the [Submit] button on the screen for selecting analytical type displays the screen for input of the control data (Fig. 8-1). Here, input the data, as provided by the following table

Table Control parameters

Solver Type (tolerance)	
Runge-Kutta (Adaptive step-size)	relative: 1e-12
Set time span and time step-size.	
Start time	0
End time	400
(Initial)time step-size	0.01
Monitoring interval	2
Set values for Newton-Raphson Method.	
Maximum trial times	20
Tolerance for convergence of functions	1e-12
Tolerance for convergence of variables	1e-12
Ratio of changing parameters	1.1
Other	
G-value	1
Y default value	0.01

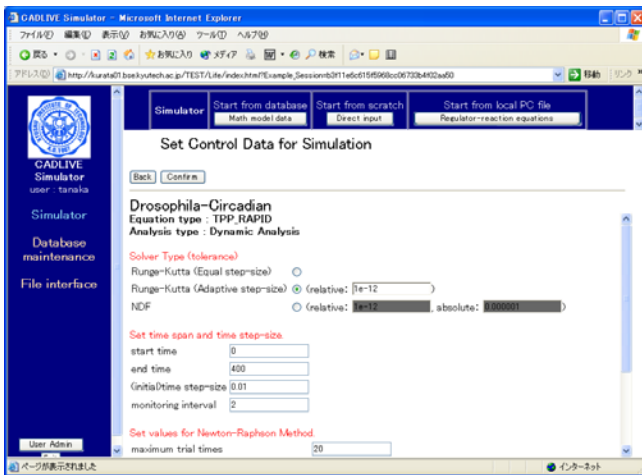


Fig. 8-1 Set control data for simulation

Following data input, clicking the [Confirm] button shows the confirmation screen (Fig. 8-2).

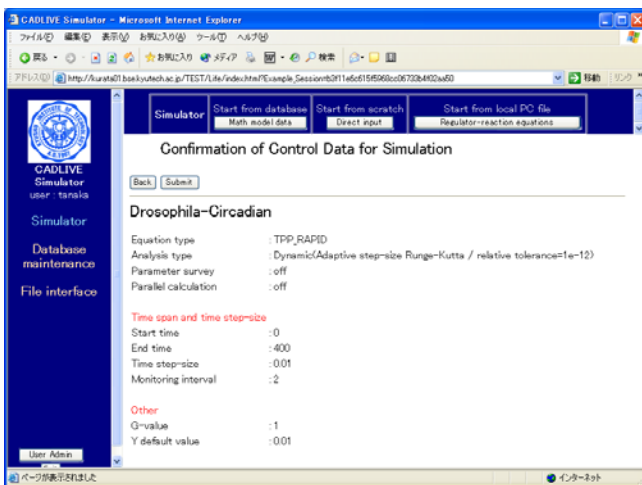


Fig. 8-2 Confirmation screen

9. Input of parameters

Following confirming the control data for simulation, clicking the [Submit] button on the screen (Fig. 8-2) displays the new screen (Fig. 9-1), where users input the kinetic parameters and initial values.

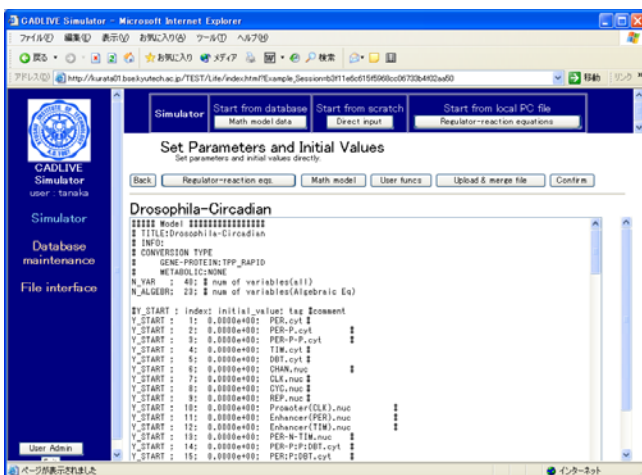


Fig. 9-1 Setting parameters and initial values

In this example, we presented the parameters and initial values that well simulated the circadian clock. Click the [Upload & merge File] button to display the screen (Fig. 9-2).

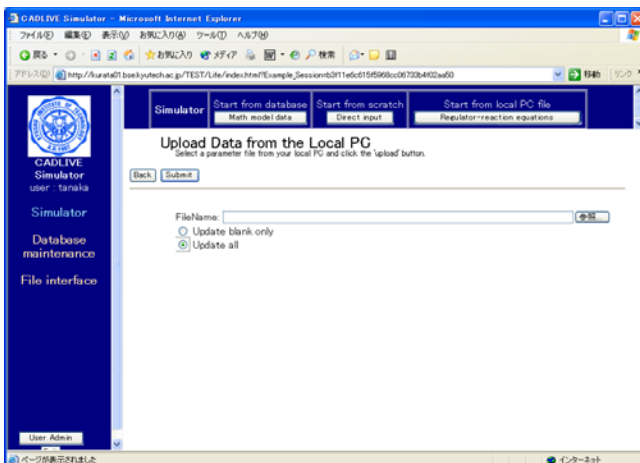


Fig. 9-2 Uploading a parameter file from the local PC

The parameter file that has been made (**TPP_Param_CC.txt**) should be input in the box of "FileName". Check the box of "**Update all**" and click the [Submit] button. The parameters and initial values are automatically input into the mathematical model, as shown in Fig. 9-3

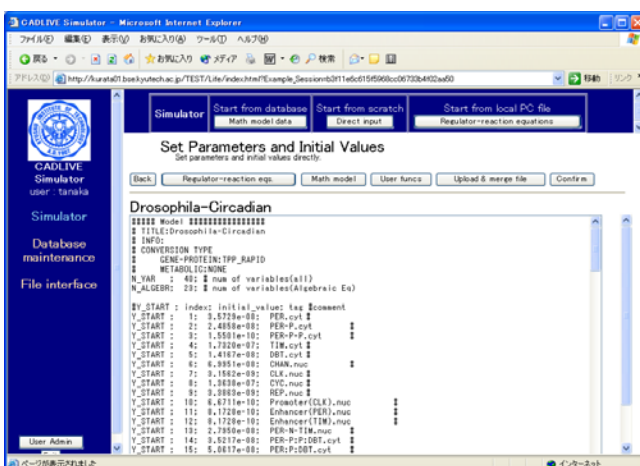


Fig. 9-3 Uploaded parameters and initial values

Users are allowed to edit the mathematical model on the screen (Fig. 9-3) directly.

Following clicking the [Confirm] button, clicking the [Submit] button (Fig. 9-4) starts calculation.

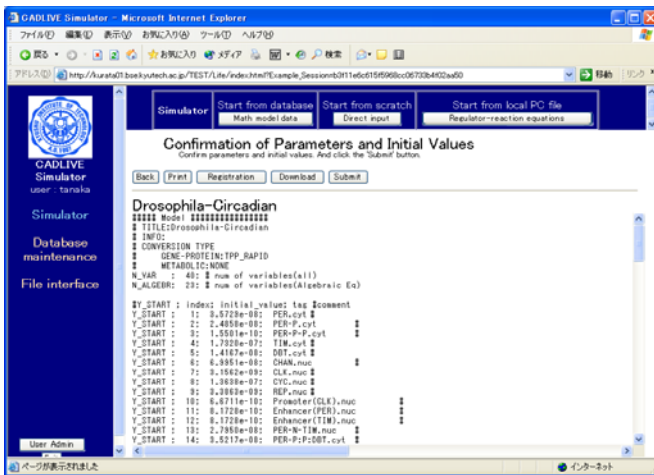


Fig. 9-4 Startup calculation

10. Result indication

The resultant time course data are displayed (Fig. 10-1), which contain the log regarding the calculation time. When simulation fails, the log is shown first, subsequently displaying the input file.

The button of [Save for input] stores the resultant data as the initial values for the subsequent simulation (Fig. 10-1), which is obtained by the [Initial val.] button. The concentrations at the final time and the steady state concentrations can be saved for the subsequent analysis of the time-evolution dynamics and the steady state, respectively. This [Initial val.] button will be not displayed when parameter survey has been carried out.

Clicking the [Graph] button, which is displayed when the time-evolution (Dynamic) is successfully simulated, opens the window for visualizing the results.

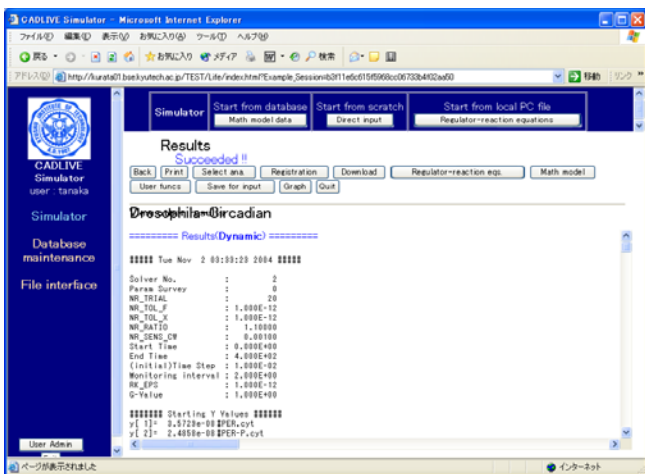


Fig. 10-1 Results

The screens for indicating the results (Fig. 10-1) have the [Registration] button. Clicking the [Registration] button shows the “Registration to the DB” screen (Fig. 10-2) that has also the button of [Registration]. Clicking it saves a series of simulation data as a mathematical model in the database.

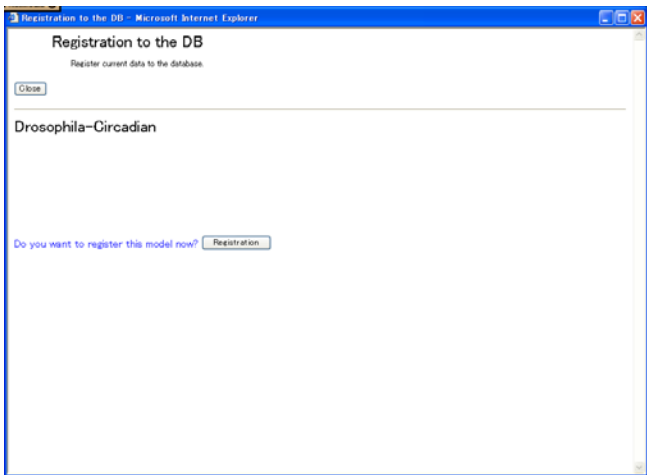


Fig. 10-2 Registration of Data in Database

The screen for results (Fig. 10-2) has the [Download] button. Clicking it displays the download screen (Fig. 10-3). The clicked files are downloaded to a local PC.



Fig. 10-3 Download

11. Graph visualization

In the screen (Fig. 10-1), clicking the [Graph] button displays the window of "Set Graph Data" (Fig. 11-1).

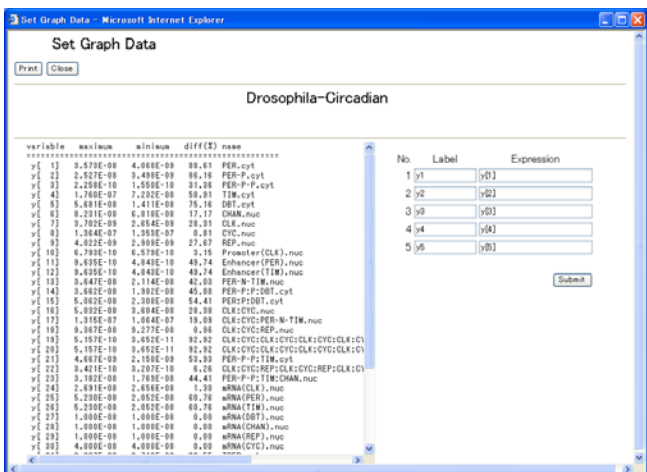


Fig. 11-1. Setting graph data

The right hand side of the screen defines the definition of data that will be plotted on a graph, and can indicate five series of labels and expressions. As default, $y_1 - y_5$ and $y[1] - y[5]$ are set as labels and expressions, respectively. Empty labels and expressions are not allowed. The variables $y[i]$, calculation symbols $+$, $-$, X , $/$, parentheses $(,)$, and time T are allowed to be used for describing the mathematical expression. Here, set $y[1]$, $y[2]$, $y[3]$, $y[4]$, and $y[5]$. After setting them, clicking the [Submit] button displays the screen (Fig. 11-2), where the scaling factor and the regions of X-axis and Y-axis are automatically calculated based on the expression and the minimum/maximum values to visualize the five time-evolution well.

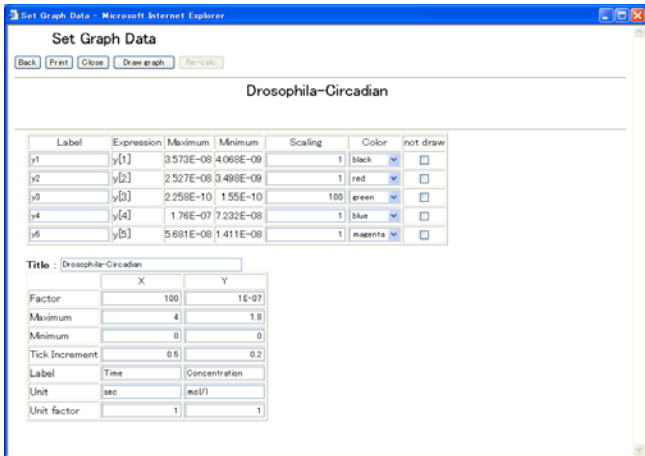


Fig. 11-2 Setting graph data

Users are able to change the labels, the scaling factors, and the color of the lines. Checking the checkbox of “not draw” omits its time evolution from the graph. The button [Re-calc] recalculates the scaling factors and the regions for the X/Y-axes. The table on the lower screen is set for the X/Y-axes. X indicates time, and Y the concentrations of variables. Clicking the [Draw graph] button (Fig. 11-2) displays the results of time-evolution data, as shown in Fig. 11-3.

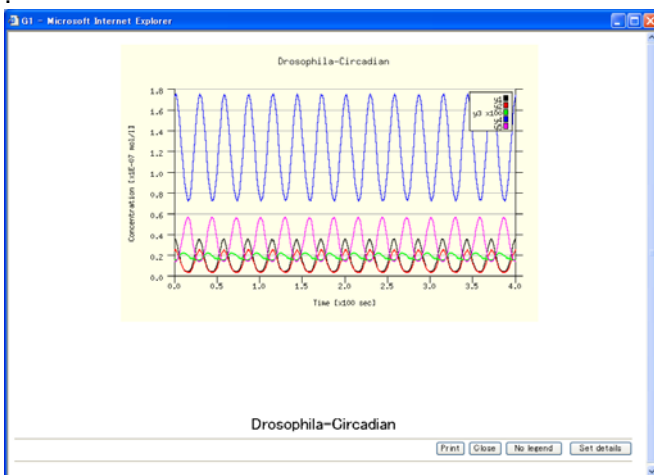


Fig. 11-3 Graph display

The [No legend] button omits the legends. The [Set details] button is able to change the color of the graph and other graph expressions. Clicking the [Set details] button displays the window (Fig.11-4). Users can change the style of the graph by inputting the value in the boxes. The values of the graph size and the location of the legends are determined by using pixel units. The location of the legend is determined by the coordinate of the left and upper legend.

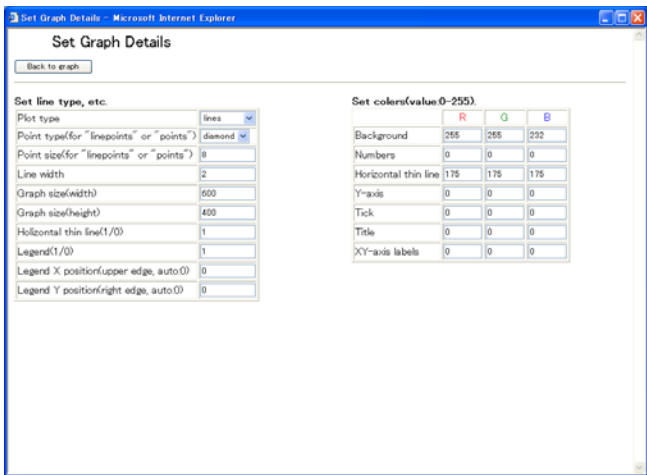


Fig. 11-4 Detailed setting for a graph