

Instruction for CADLIVE Simulator

Example: *E. coli* Ammonia assimilation system

TPP steady-state analysis CONVERSION

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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. Login

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. 1-1). Input the user name, subsequently his/her password to start up simulation.

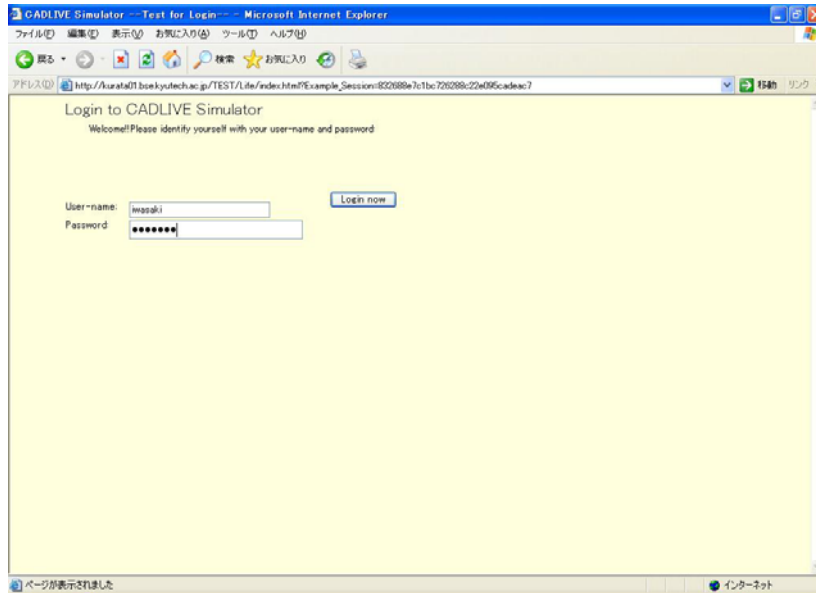


Fig. 1-1 Login screen

2. Startup simulator

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

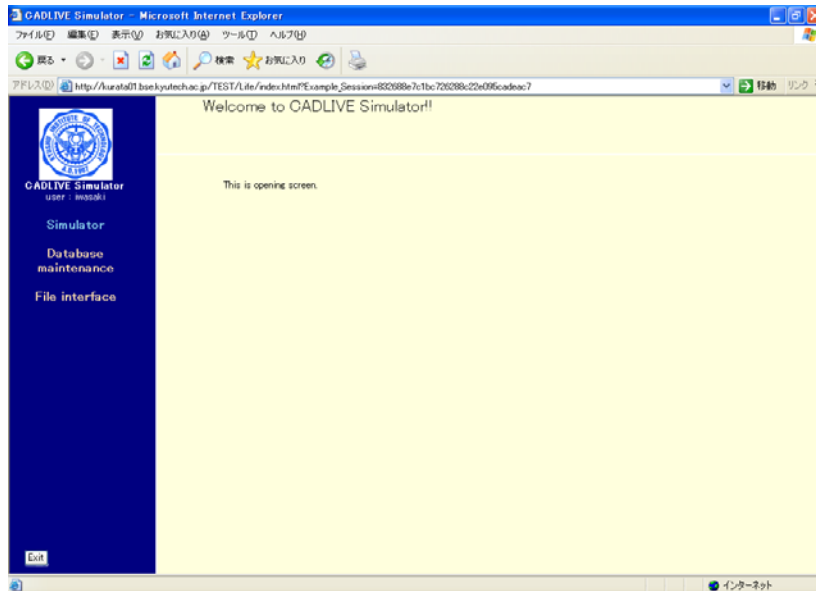


Fig. 2-1Startup menu

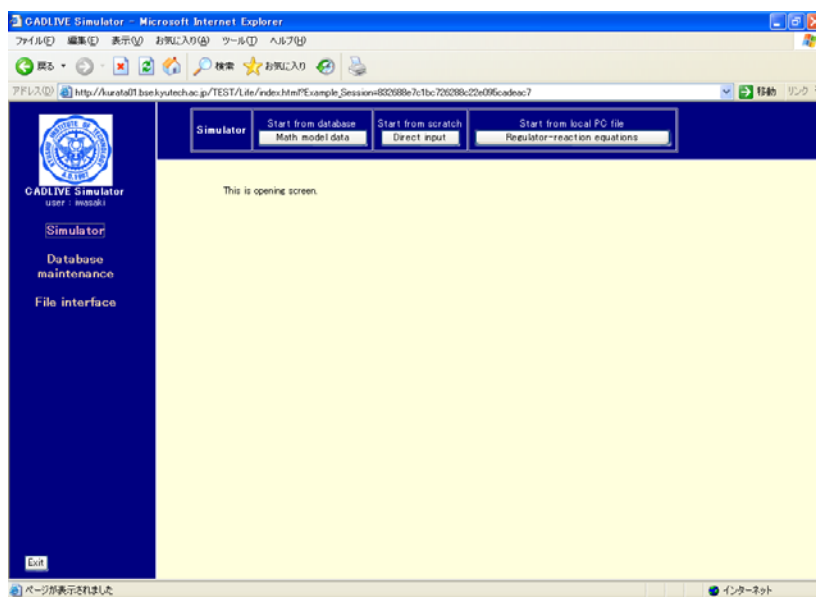


Fig. 2-2 Startup simulation

3. Upload of data for regulator-reaction equations

Clicking the [Regulator-reaction equations] button (Fig. 2-2) displays the new screen. Select the XML data file for the regulator-reaction equations (**NFS_demo.xml**) from users' PC (Fig. 3-1). The data file should be described by using the CADLIVE Editors. Users are required to click the buttons within the screen of CADLIVE, not to carelessly click those of the browser.

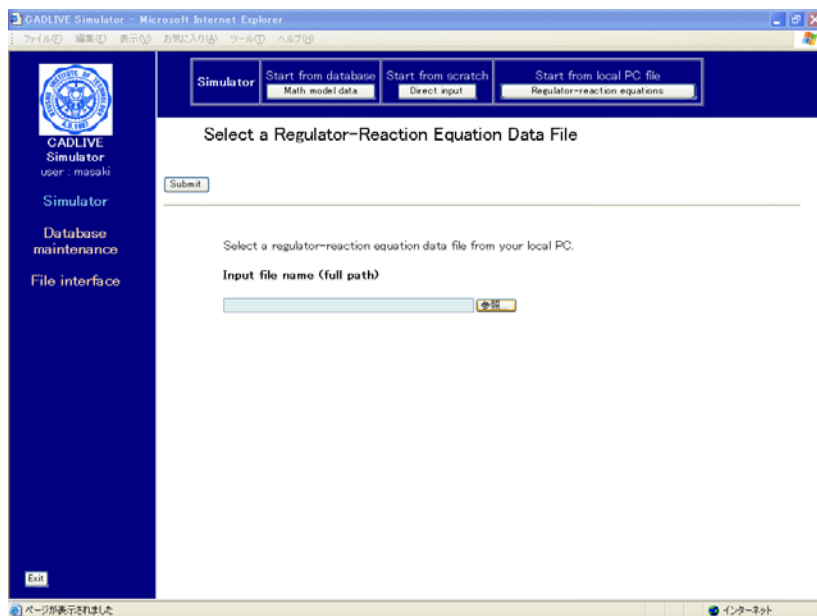


Fig. 3-1 Upload of a regulator-reaction equation file from a PC

4. Selection of conversion methods

The table that indicates the selected regulator-reaction equations appears on the screen (Fig. 4-1). Users choose the conversion method with respect to gene-protein layer and metabolic layer. Select **TPP_RAPID** and **MM**, respectively.

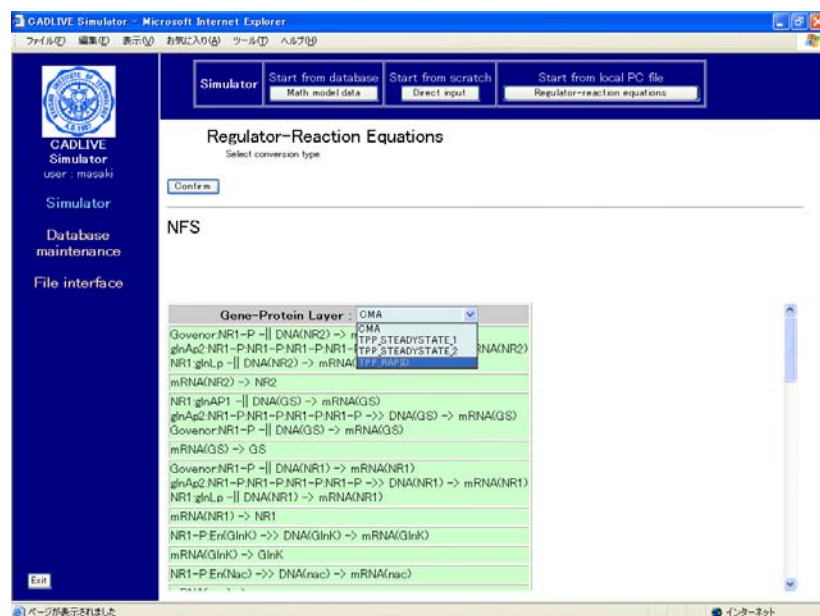


Fig. 4-1 Selection of conversion methods

Following the selection of the conversion method, clicking the [Confirm] button displays the confirmation screen (Fig. 4-2) that is similar to Fig. 4-1.

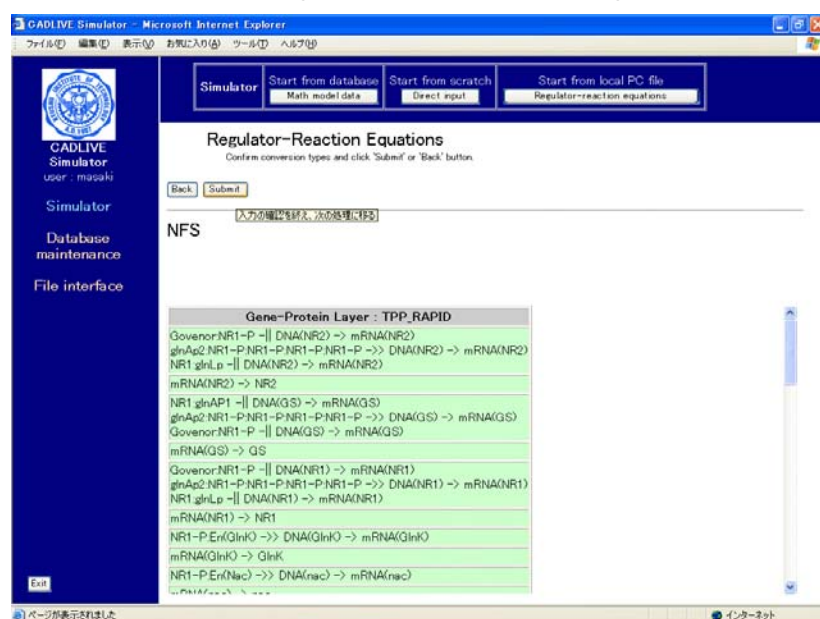


Fig. 4-2 Confirmation screen for the regulator-reaction equations

5. Editing Mathematical Model (DAEs)

Clicking the [Submit] button on the confirmation screen (Fig. 4-2) 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. 5-1.

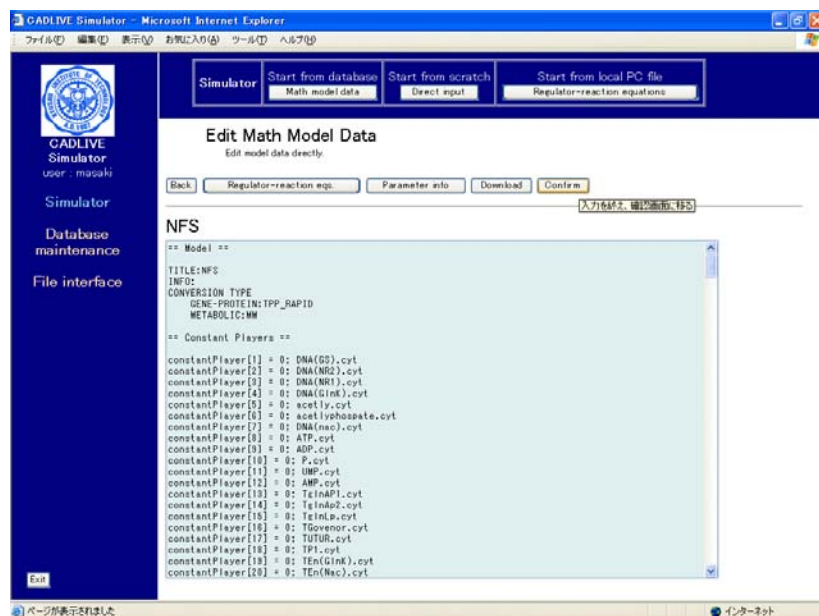


Fig. 5-1 Mathematical model that is obtained from regulator-reaction equations

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. 5-2) that is similar to Fig. 5-1. If there is no problem, click the [Submit] button.

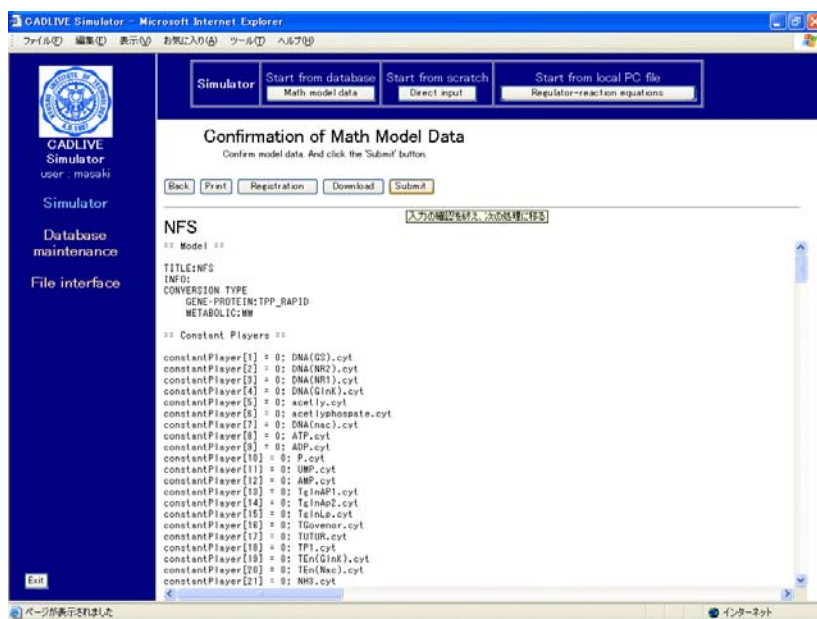


Fig. 5-2 Confirmation screen for a mathematical model

6. Selecting analysis types

Clicking the [Submit] button on the confirmation screen displays the screen (Fig. 6-1), where users select the method for numerical simulation. Select “**Steady-state**” as analysis type.

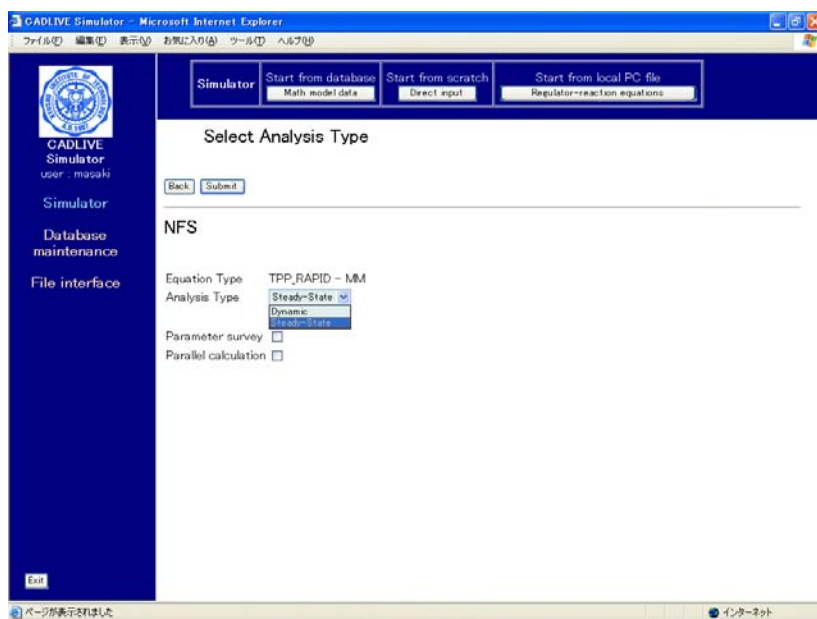


Fig. 6-1 Selection of analysis type

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.

7 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. 7-1). Here, input the data, as provided by the following table.

Table Control parameters

| | |
|--|-------|
| Set values for Newton-Raphson Method. | |
| Maximum trial times | 20 |
| Tolerance for convergence of functions | 1e-16 |
| Tolerance for convergence of variables | 1e-16 |
| Ratio of changing parameters | 1.1 |
| Change width for calc. sensitivity (STD) | 0.001 |
| Other | |
| G-value | 1.0 |
| Y default value | 0.01 |

Change width for calc. sensitivity (STD) means the ratio of the change in the kinetic parameters to their values, which is used to calculate the sensitivity of the dependent variables (concentrations) to the change in the kinetic parameters.

The screenshot shows the CADLIVE Simulator web interface. The title bar indicates it's running in Microsoft Internet Explorer. The sidebar on the left contains links for 'Simulator', 'Database maintenance', and 'File interface'. The main content area is titled 'Set Control Data for Simulation'. At the top, there are buttons for 'Simulator', 'Start from database', 'Start from scratch', and 'Start from local PC file'. Below these, there are input fields for 'Math model data', 'Direct input', and 'Regulator-reaction equations'. The 'Set Control Data for Simulation' section includes a 'Back' button and a 'Confirm' button. The 'NFS' section shows 'Equation type : TPP-RAPID' and 'Analysis type : Steady-State Analysis'. The 'Set values for Newton-Raphson Method' section has input fields for 'Maximum trial times' (20), 'Tolerance for convergence of functions' (1e-12), 'Tolerance for convergence of variables' (1e-12), 'Ratio of changing parameters' (1.1), and 'Change width for calc. sensitivity(STD)' (0.001). The 'Other' section has input fields for 'G-value' (1) and 'Y default value' (0.01). The status bar at the bottom shows 'ページが表示されました' and 'インターネット'.

Fig. 7-1 Set control data for simulation

Following data input, clicking the [Confirm] button shows the confirmation screen (Fig. 7-2).

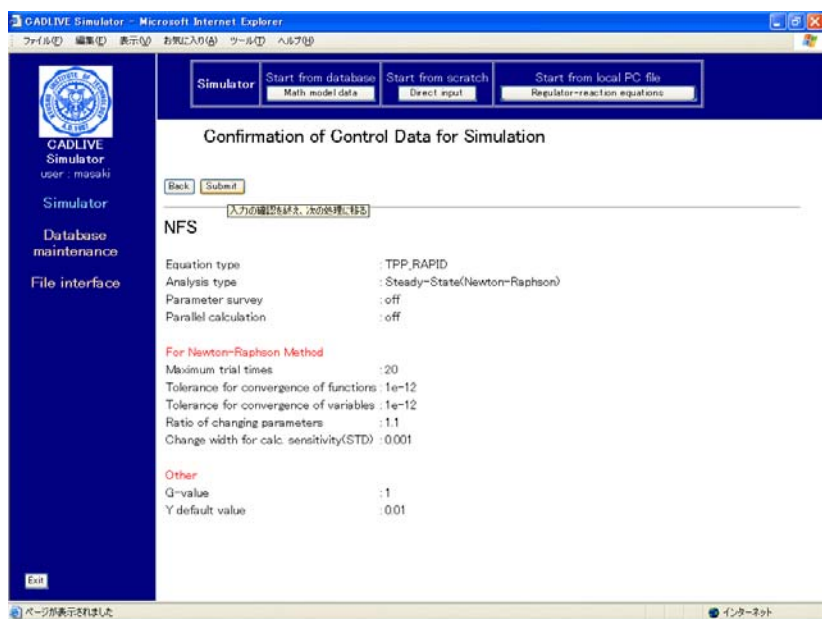


Fig. 7-2 Confirmation screen

8. Input of parameters

Following confirming the control data for simulation, clicking the [Submit] button on the screen (Fig. 7-2) displays the new screen (Fig. 8-1), where users input the kinetic parameters and initial values.

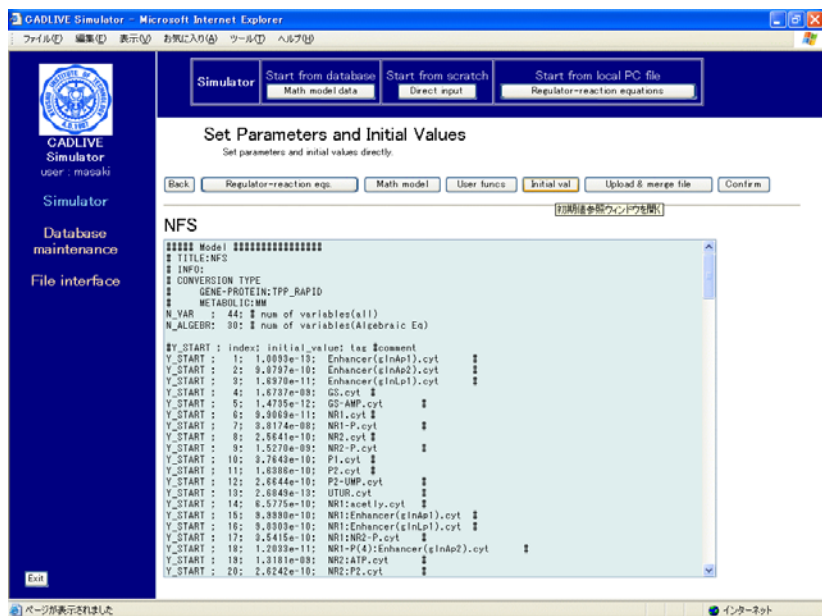


Fig. 8-1 Setting parameters and initial values

In this example, we presented the parameters and initial values that well simulated the ammonia assimilation system. Click the [Upload & merge File] button to display the screen (Fig. 8-2).

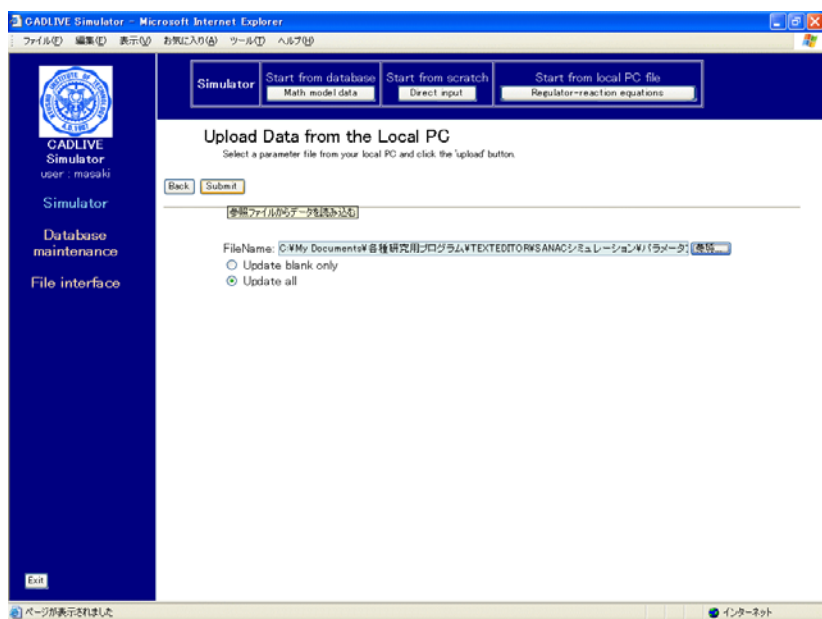


Fig. 8-2 Uploading a parameter file from the local PC

The parameter file that has been made (**TPP_Param_NFS.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. 8-3

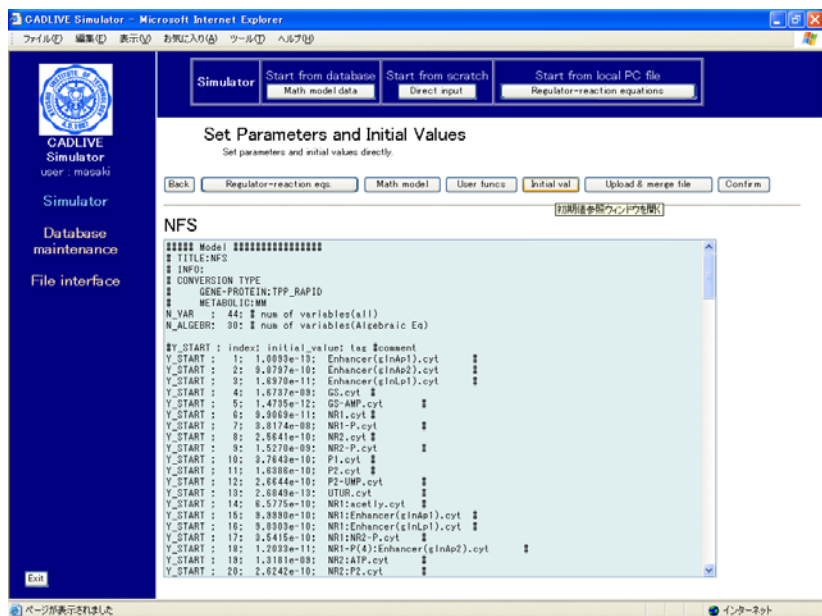


Fig. 8-3 Uploaded parameters and initial values

Following clicking the [Confirm] button, clicking the [Submit] button (Fig. 8-4) starts calculation.

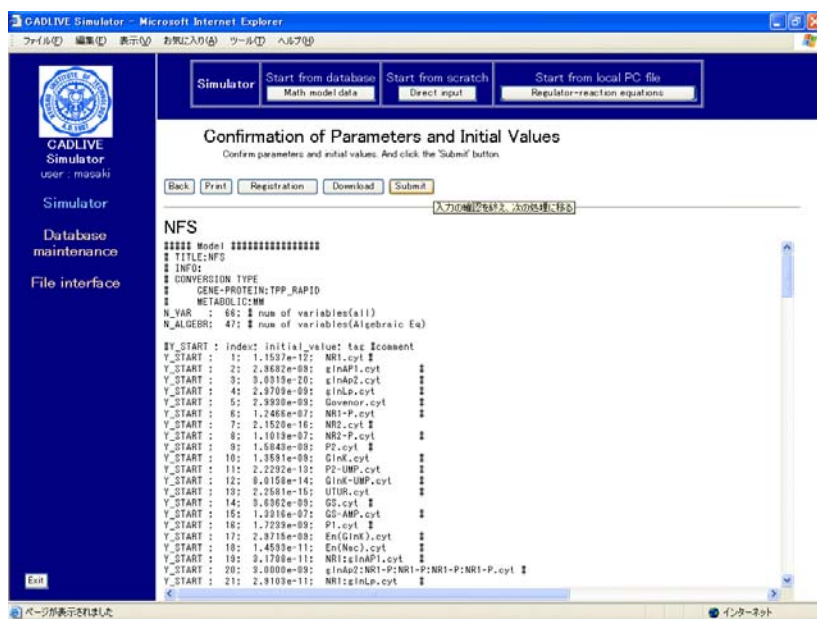


Fig. 8-4 Startup calculation

9. Result indication

The results of the steady state concentrations and the sensitivity are shown in Fig. 9-1. The button of [Save for input] stores the resultant data as the initial values for the subsequent simulation (Fig. 9-1), which will be obtained by the [Initial val.] button. The steady state concentrations can be saved for the subsequent analysis (S-system analysis, simulation of DAEs). This [Initial val.] button will be not displayed when parameter survey has been carried out.

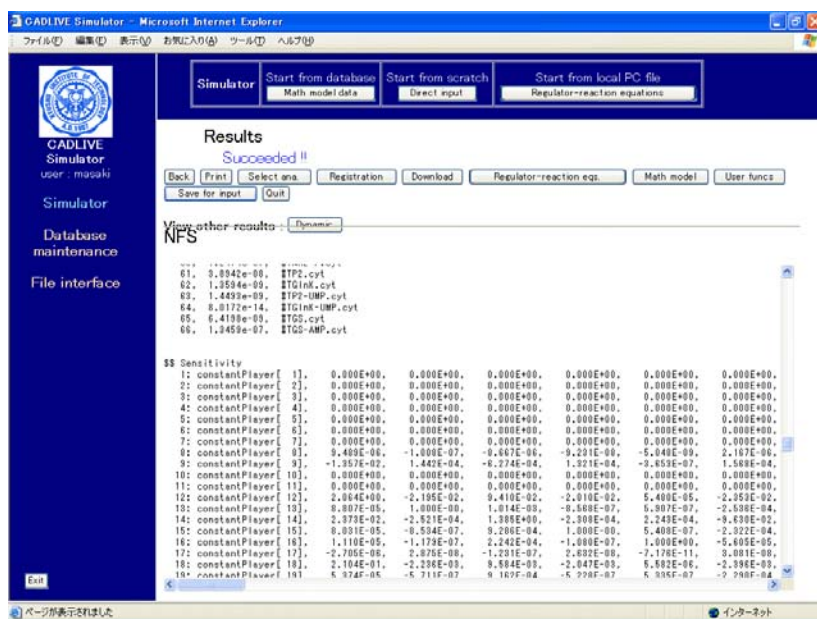


Fig. 9-1 Results

The screens for indicating the results (Fig. 9-1) have the [Registration] button. Clicking the [Registration] button shows the “Registration to the DB” screen (Fig. 9-2) that has also the button of [Registration]. Clicking it saves the steady state concentrations, and a series of sensitivity as a mathematical model in the database.

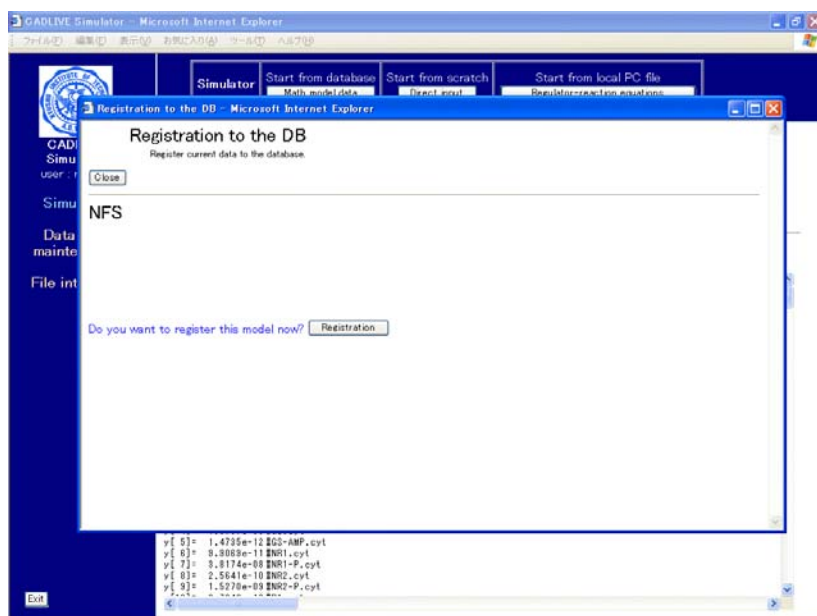


Fig. 9-2 Registration of Data in Database

The screen for results (Fig. 9-2) has the [Download] button. Clicking it displays the download screen (Fig. 9-3). The clicked files are downloaded to a local PC.

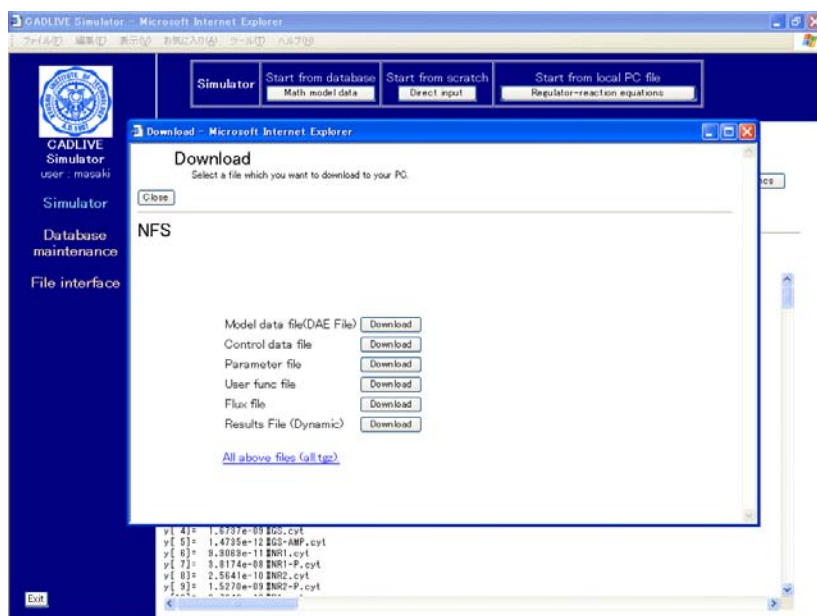


Fig. 9-3 Download