Protein Dose Curves Generation module

version v0.6.1

USER GUIDE

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Contents

1 Copyright

2 License of the code

The module's .py code is distribution under the following license:

3 System Requirements

3.1 Operating system

Packages should work correctly on all systems that support other programs that are mentioned below. All the actions are tested on Windows 8 and Linux Mint 17. So it can be expected good performance on Windows XP/Vista/7 and Linux Debian, Ubuntu, Kubuntu, etc.

3.2 Software

To run the packages the following programs/packages should be installed on your Computer:

- QtiPlot [3] with Python [6] scripting
- Python 2.7.*
  - On commonly used Linux distributions this program is installed by default, but consumer should install python-dev (developer) from Software Manager or by copying following command in the terminal *sudo apt-get install python-dev*
- Python packages:

- NumPy [2]
  - Download instructions for use are here
- SciPy [5]
  - Download instructions for use are here
- LmFit [1]
  - Download instructions for use are here
- PyQt4 [4]
  - Download instructions for use are here

4 Installation

All section's **System Requirements** requirements should be accomplished. To install module must perform following steps:

1. Extract **doseCgen.tar.gz** containing files to QtiPlot's **Python Configuration Files** path. Merge files if needed.
2. Attach scripting action named **PmLtGen.py** from extracted folder **dialogs** (look at section 4.1) to QtiPlot's button. Instructions shown in section 4.3.
3. Copy qti template named **dose_curves_analysis_template.qti** from extracted folder **templates** (look at section 4.1) to your working directory.

4.1 doseCgen.tar.gz

This compressed file contains these files:

- *dialogs* folder which contains scripting action and version file
- *manual* folder which contains user guide pdf
- *modules* folder which contains py files
- *templates* folder which contains Qtiplot's templates
- *psaFit.py* py file

4.2 Python Configuration Files

Python Configuration Files path can be found in the QtiPlot's preferences after these actions (shown in figure 1):

1. Left click on menu bar Edit → Preferences...
2. On the opened settings window click *General* → *File Locations*.
3. Path is in the field *Python Configuration Files*. In the example path is /usr/share/qtiplot.

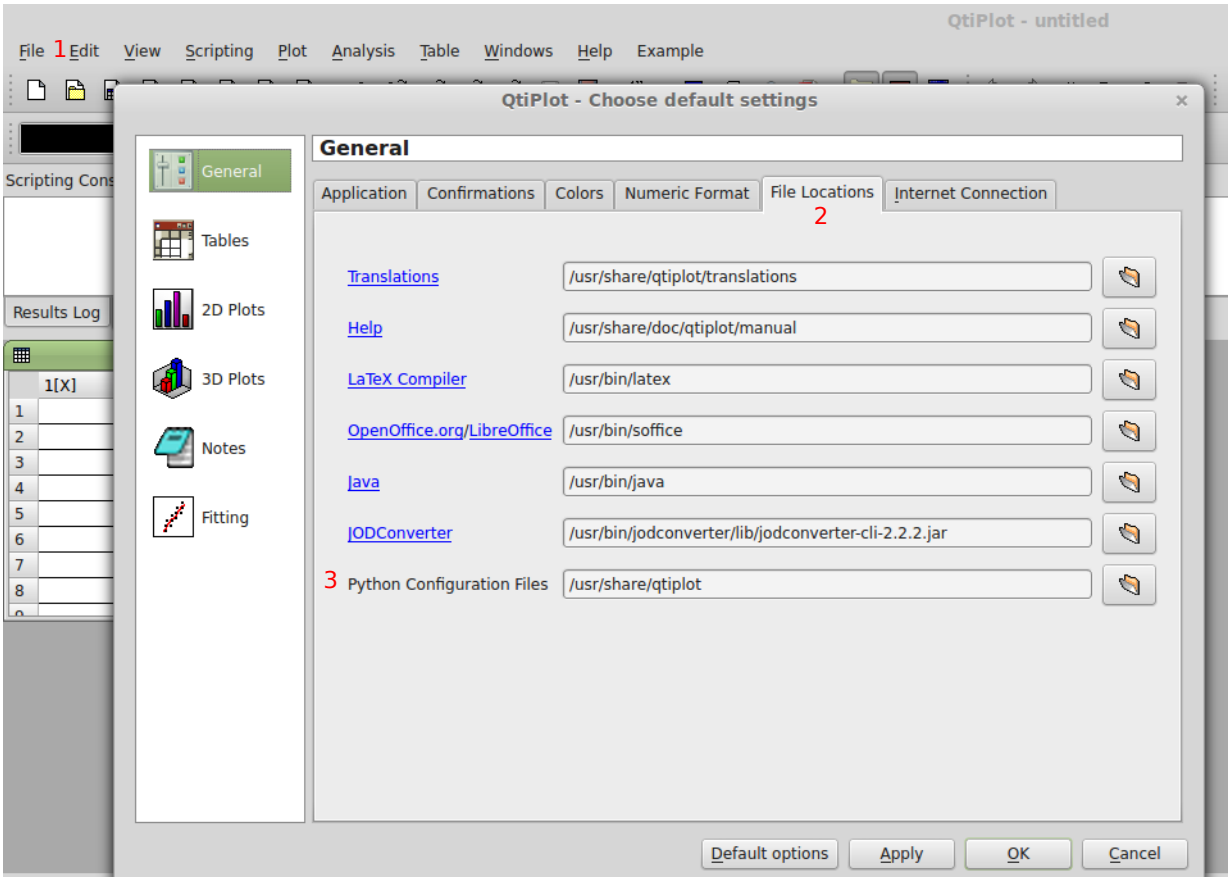


Figure 1 – *Finding path of the Python Configuration Files.*

4.3 Buttons attachment

There is possibility in QtiPlot to create buttons and attach them to the custom scripts/actions instead of creating note objects on the QtiPlot's Project Explorer. This can be done in the following steps (shown in figure 2):

1. Open QtiPlot.
2. Left click on the menu bar *Scripting* → *Add Custom Script Action...*
3. Left click on the button *Choose Folder* in the pop-up window *Add Custom Action* and select the location where the created buttons and menu objects files should be saved. It is recommended to create new folder for this task.
4. Left click on the button *Choose Script* and select the script (*i.e. someAction.py file*).
5. Left click on the button *Choose Icon* and select the image for currently selected script action.
6. Fill the *Text* field. That text will be a name of the created button.
7. Fill the *Tool Tip Text* field. That field data will be a text of the pop-up tool tip. Only works then button is in the *Tool Bar*, not in the *Menu*.
8. Fill the *Shortcut* field. It is recommended but not required option. The command must e unique.

9. Choose the place it the QtiPlot's environmet where the button should be placed. Possible options:

   (a) Already existing *Menu*.

   (b) *Tool Bar*.

   (c) *New Menu*. First create menu then choose it from already existing ones.

10. *Add* new button or *Save* corrected one.

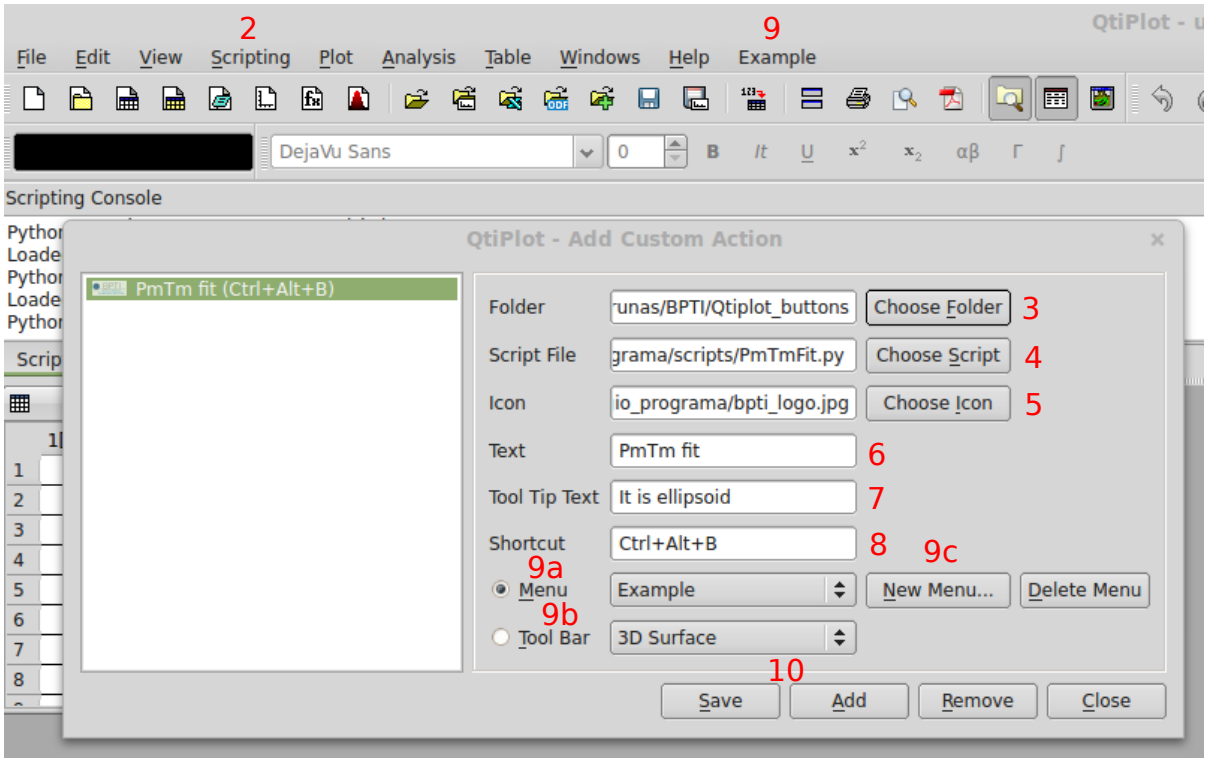


Figure 2 – *Steps of* QtiPlot's *buttons attachement.*

4.4 QtiPlot's template

Modules which perform curves **generation** will work with these tables (shown in figure 3):

1. Table of the initial parameters called **initParams**. This table contains these columns:

   (a) **Param** – each individual model parameters names are written in this column cells. It is possible to add more parameters in the table. If parameter in this table has name(first column cell) and value(second column cell) then it will be initiated in local(currently used) Python's environment as variable during the process.

   (b) **Value** – each individual model parameters values are written in this column cells.

   (c) **UNIT** – if parameter has a unit it is specified here. **Attention** – this cell data does not have any affect in the modules output data. *i.e. cell(UNIT, 11) previous value J/mol was changed to cal/mol – all UNIT column cells become misleading.*

   (d) **note** – place for a note about the parameter.

2. Table of the simulation parameters called **SimParam**. The name of table column is the simulated parameter name. Generation will be done with all values of the chosen parameter in it's (column name match the chosen parameter name) SimParam table column. This means that the number of the generated curves equals to the number of the filled cells in the chosen SimParam table column.

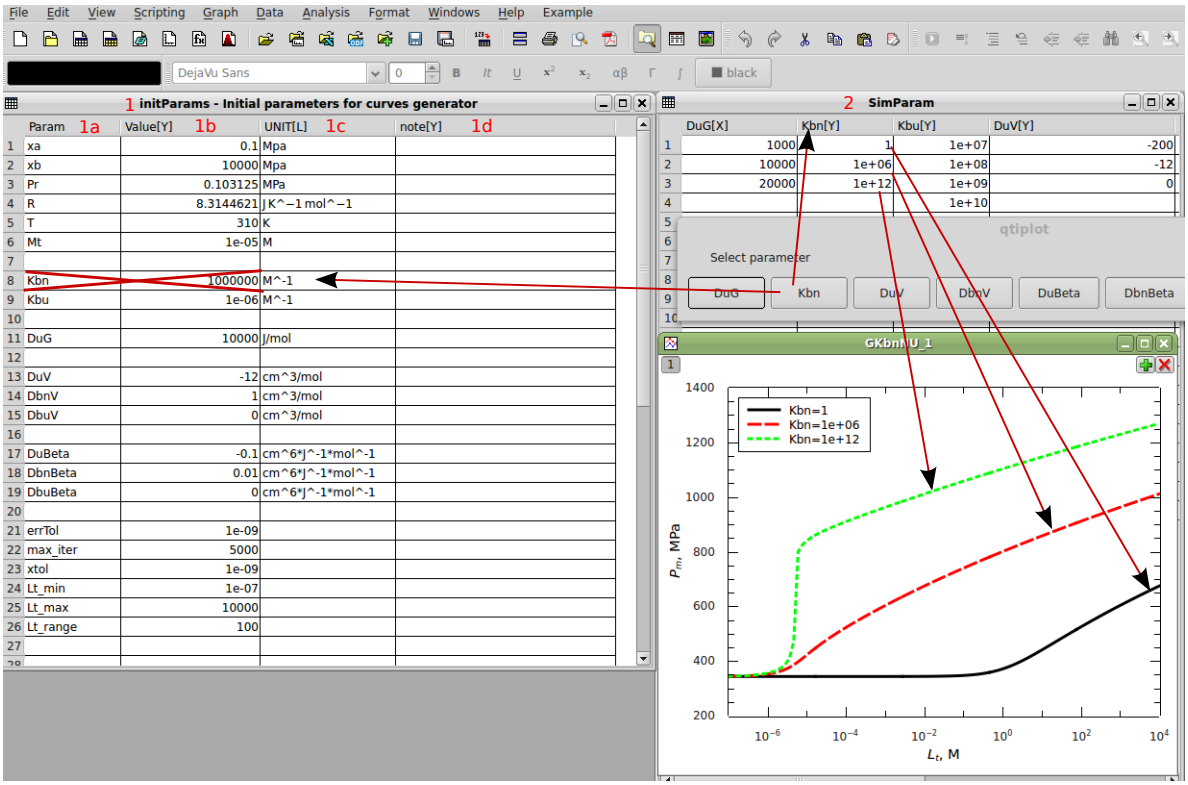


Figure 3 – *Curves generation tables.*

5 Working with Dose Curves Analysis package

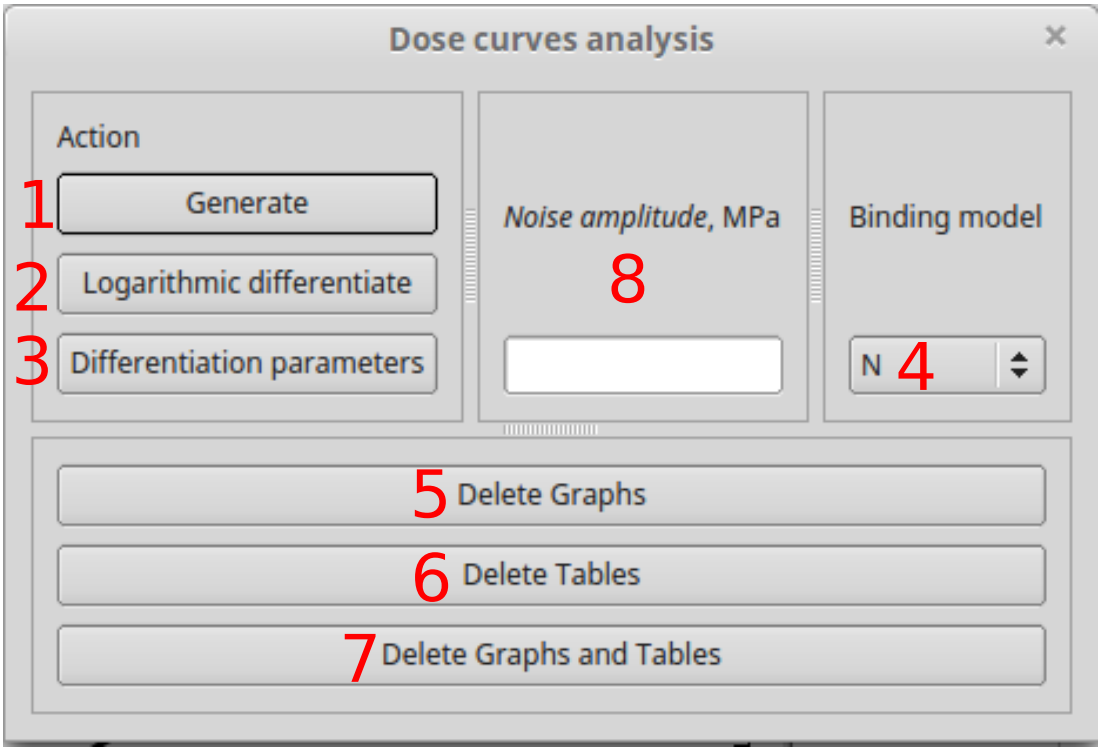


Figure 4 – *Dose Curves Analysis module.*

While running *Dose Curves Analysis* module there is seven possible actions (shown in figure 4):

1. **Generate** (1 in figure 4) – this button generates protein dose curves ($P_m(L_t)$ curves, P_m – melting pressure, L_t – ligand molar concentration). Eq. 8 is used for ligand – [N]ative protein binding model (N model), eq. 9 is used for ligand – [N]ative and [U]nfolded protein binding model (NU model). Numerical Brent's method is used to change transcendental $L_t(P_m)$ equations to $P_m(L_t)$.
   Definition of the parameters that are used in N (eq. 8) and NU (eq. 9) models: P_r – reference pressure, T – temperature, R – gas constant, M_t – protein molar concentration, $\Delta_U G_{P_r}$ – protein [U]nfolding Gibbs free energy change (extrapolated to P_r), $\Delta_U V_{P_r}$ – protein [U]nfolding volume change (extrapolated to P_r), $\Delta_U \beta$ – protein [U]nfolding isothermal compressibility change, $\Delta_{bN} G_{P_r}$ – [N]ative protein binding to ligand Gibbs free energy change (extrapolated to P_r), $\Delta_{bN} V_{P_r}$ – [N]ative protein binding to ligand volume change (extrapolated to P_r), $\Delta_{bN} \beta$ – [N]ative protein binding to ligand isothermal compressibility change.
   Definition of the parameters that are used only in NU model: $\Delta_{bU} G_{P_r}$ – [U]nfolded protein binding to ligand Gibbs free energy change (extrapolated to P_r), $\Delta_{bU} V_{P_r}$ – [U]nfolded protein binding to ligand volume change (extrapolated to P_r), $\Delta_{bU} \beta$ – [U]nfolded protein binding to ligand isothermal compressibility change.
   More information about parameters names are shown in table 1. Sometimes the change of Gibbs energy $\Delta_* G$ is replaced with a binding constant K_* (dependence of these two parameter are shown in 1, 2 equations).

$$K_U = \mathrm{e}^{-\frac{\Delta_U G}{RT}} \tag{1}$$

Table 1 – *Explanation of parameters names and naming which are used in literature and program code.*

Lit. mark	Code mark	Meaning	Example lit. ≡ code
$*_U$	*u	protein [U]nfolding *	$K_U \equiv$ Ku
$D_{bN}*$	Dbn*	ligand – [N]ative protein binding *	$D_{bN}\beta \equiv$ DbnBeta
$D_{bU}*$	Dbu*	lig. – [U]nfolded prot. binding * change	$D_{bU}V \equiv$ DbuV
$K*$	K*	* binding constant	$K_{bU} \equiv$ Kbu
$*_\star G$	*⋆G	⋆ Gibbs free energy *	$D_U G \equiv$ DuG
$*_\star V$	*⋆V	⋆ volume *	$D_{bN}V \equiv$ DbnV
$*_\star \beta$	*⋆Beta	⋆ isothermal compressibility *	$D_{bU}\beta \equiv$ DbuBeta
P_r	Pr	reference pressure	$P_r \equiv$ Pr
$*_{P_r}$	–	* (extrapolated to P_r)	only in literature
R	R	gas constant	$R \equiv$ R
T	T	temperature	$T \equiv$ T
M_t	Mt	protein molar concentration	$R \equiv$ R
–	xa	minimum Pm value	only in code
–	xb	maximum Pm value	only in code
–	errTol	tolerance of y in Brent's method	only in code
–	xtol	tolerance of x in Brent's method	only in code
–	Lt_min	minimum value of Lt	only in code
–	Lt_max	maximum value of Lt	only in code
–	Lt_range	number of Lt samples	only in code

$$\Delta G = -RT \ln K \tag{2}$$

$$K_U = \mathrm{e}^{-\frac{\Delta_U G}{RT}} = \mathrm{e}^{-\left(\Delta_U G_{P_r} + \Delta_U V_{P_r}\,(P_m - P_r) + \frac{\Delta_U \beta}{2}(P_m - P_r)^2\right)/RT} \tag{3}$$

$$K_{bN} = \mathrm{e}^{-\frac{\Delta_{bN} G}{RT}} = \mathrm{e}^{-\left(\Delta_{bN} G_{P_r} + \Delta_{bN} V_{P_r}\,(P_m - P_r) + \frac{\Delta_{bN} \beta}{2}(P_m - P_r)^2\right)/RT} \tag{4}$$

$$K_{bU} = \mathrm{e}^{-\frac{\Delta_{bU} G}{RT}} = \mathrm{e}^{-\left(\Delta_{bU} G_{P_r} + \Delta_{bU} V_{P_r}\,(P_m - P_r) + \frac{\Delta_{bU} \beta}{2}(P_m - P_r)^2\right)/RT} \tag{5}$$

$$K_U = \mathrm{e}^{-\frac{\Delta_U G}{RT}} = \mathrm{e}^{-\left(\Delta_U G_{P_r} + \Delta_U V_{P_r}\,(P_m - P_r) + \frac{\Delta_U \beta}{2}(P_m - P_r)^2\right)/RT} \tag{6}$$

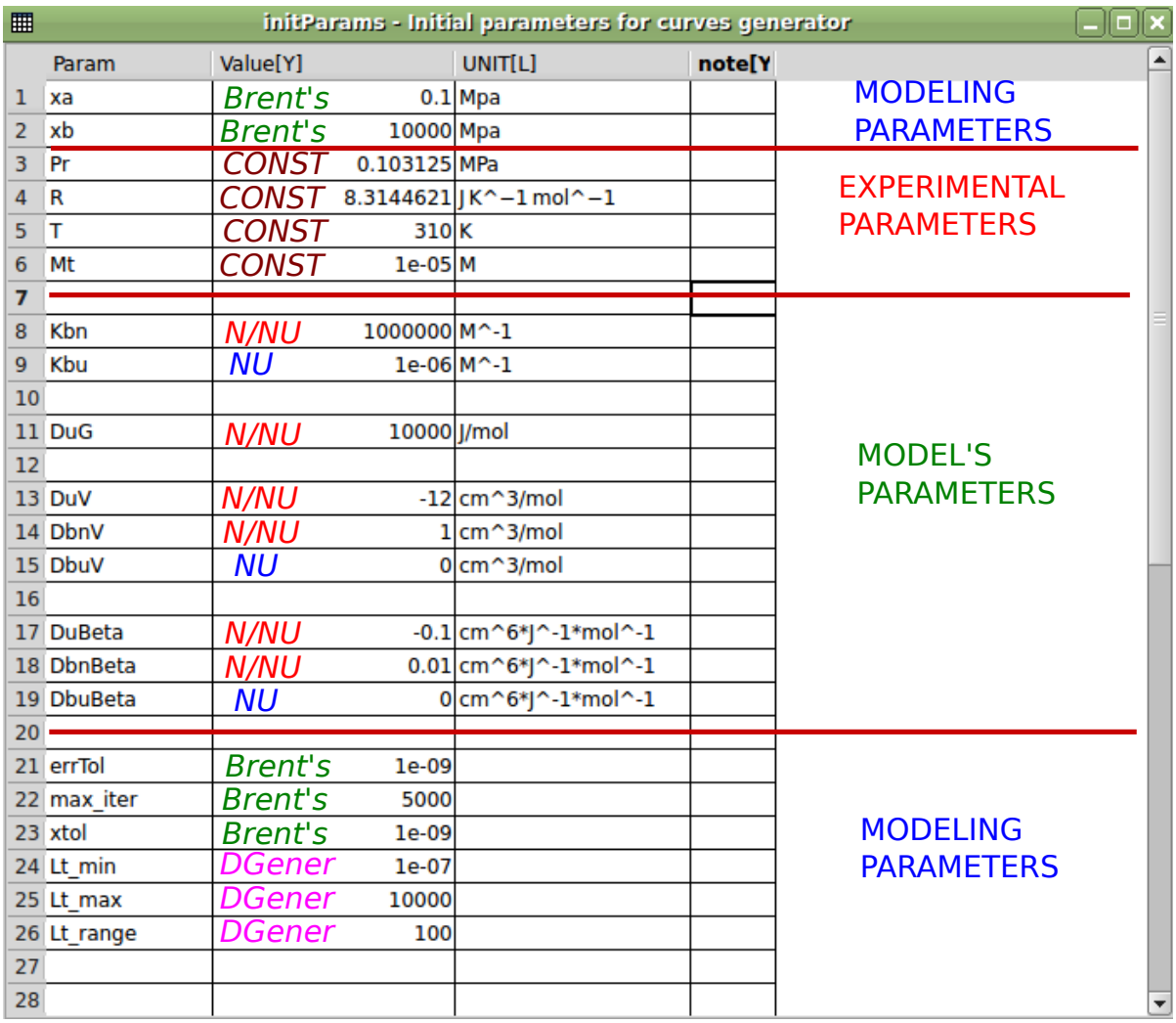
$$K_b = \mathrm{e}^{-\frac{\Delta_b G}{RT}} = \mathrm{e}^{-\left(\Delta_b G_{P_r} + \Delta_b V_{P_r}\,(P_m - P_r) + \frac{\Delta_b \beta}{2}(P_m - P_r)^2\right)/RT} \tag{7}$$

$$L_t(P_m) = (K_U - 1)\left(\frac{M_t}{2K_U} + \frac{1}{K_b}\right) \tag{8}$$

$$L_t(P_m) = (1 - K_U)\left(\frac{M_t}{2} \cdot \frac{K_{bN} + K_{bU}K_U}{K_U(K_{bU} - K_{bN})} + \frac{1}{K_U K_{bU} - K_{bN}}\right) \tag{9}$$

Perform following steps for protein dose curves generation:

(a) Check and edit parameters values in *initParams* (1a,1b in figure 3) and *SimParam* (2 in figure 3) tables. *Brent's, CONST, N/NU, NU(if NU model selected), DGENER* parameters that are shown in figure 5 must be included in *initParams* table.



	Param	Value[Y]		UNIT[L]	note[Y
1	xa	Brent's	0.1	Mpa	
2	xb	Brent's	10000	Mpa	
3	Pr	CONST	0.103125	MPa	
4	R	CONST	8.3144621	J K^−1 mol^−1	
5	T	CONST	310	K	
6	Mt	CONST	1e-05	M	
7					
8	Kbn	N/NU	1000000	M^-1	
9	Kbu	NU	1e-06	M^-1	
10					
11	DuG	N/NU	10000	J/mol	
12					
13	DuV	N/NU	-12	cm^3/mol	
14	DbnV	N/NU	1	cm^3/mol	
15	DbuV	NU	0	cm^3/mol	
16					
17	DuBeta	N/NU	-0.1	cm^6*J^-1*mol^-1	
18	DbnBeta	N/NU	0.01	cm^6*J^-1*mol^-1	
19	DbuBeta	NU	0	cm^6*J^-1*mol^-1	
20					
21	errTol	Brent's	1e-09		
22	max_iter	Brent's	5000		
23	xtol	Brent's	1e-09		
24	Lt_min	DGener	1e-07		
25	Lt_max	DGener	10000		
26	Lt_range	DGener	100		
27					
28					

Figure 5 – *Marked initParams table parameters.*

(b) Select model (4 in figure 4).

(c) Push **Generate** button (1 in figure 4).

(d) Select parameter which to simulate. Selections are created from *SimParam* table. Also the *ALL* buttons means to simulate all selections at once. It is open to add new parameters in *SimParam* table but all *NU* (named **bu**) parameters will be excluded from *N* selection (look at the figure 6).

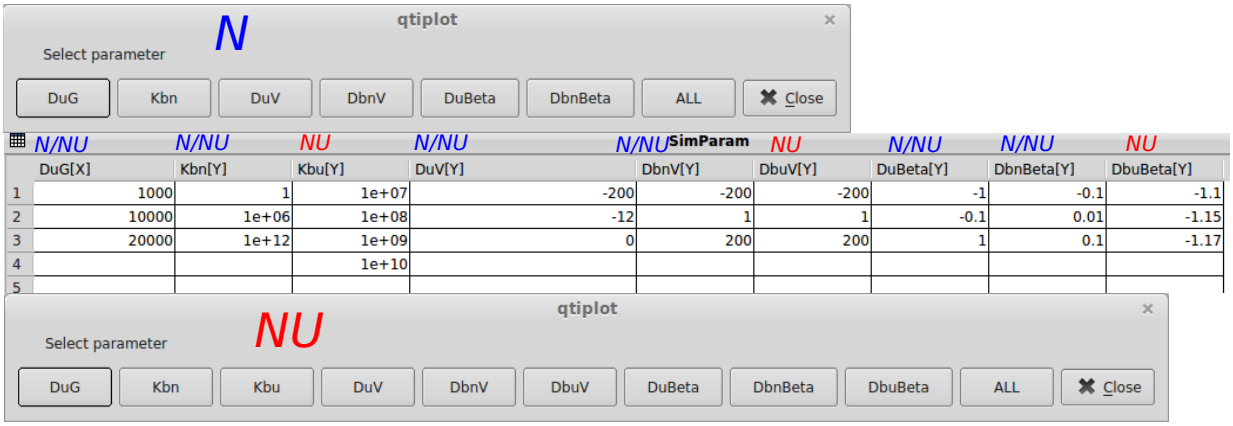


Figure 6 – *Parameters selection example.*

(e) Look at the output (shown in figure 7):

i. Graph named *GParamMODEL_** – this object contains plotted data curves of one parameters simulation. Peening of the name: *G* – graph, *Param* – simulated parameter name, *MODEL* – used mathematical model (*N* or *NU*), * number for name's uniqueness. i.e. *GKbnN_3*.

ii. Table named *TParamMODEL_** – this object contains data curves of one parameters simulation on the left side and initial parameters on the right side. Peening of the name: *T* – table, *Param* – simulated parameter name, *MODEL* – used mathematical model (*N* or *NU*), * number for name's uniqueness. i.e. *TDbuVNU_4*.

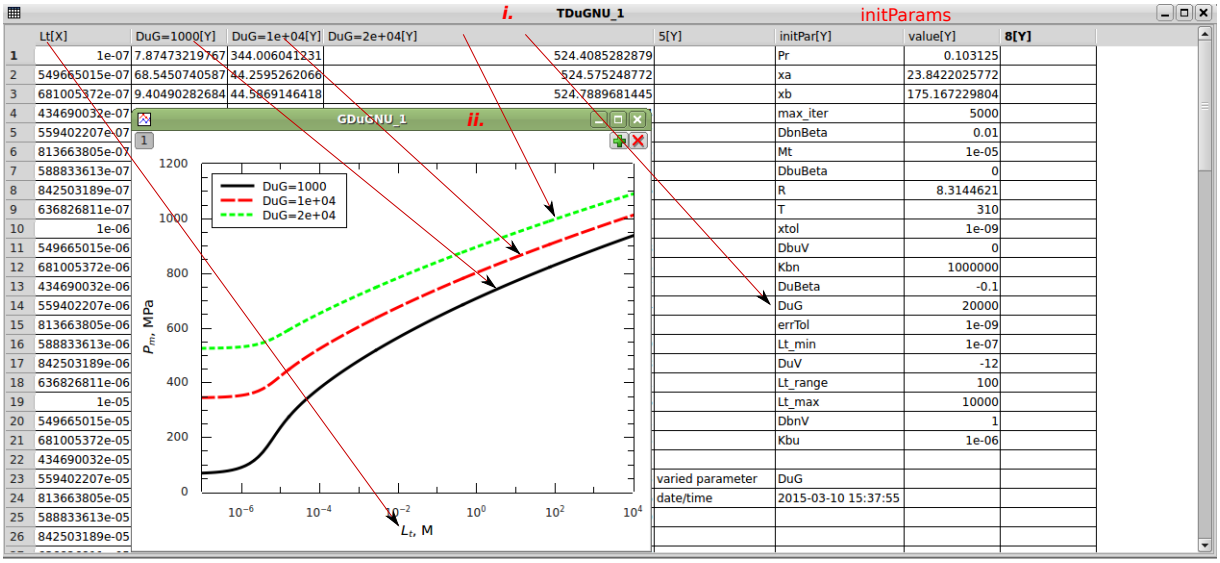


Figure 7 – *Protein dose curves generation output.*

2. **Logarithmic differentiate** (2 in figure 4) – this button calculates logarithmic derivative for selected data (eq. 10).

$$y^{log'} = \frac{\Delta y}{\Delta \log_{10} x} \tag{10}$$

Perform following steps for calculating logarithmic derivative:

(a) Select x and y columns in the table. There is no limit for y columns number.

(b) Push **Logarithmic differentiate** button (2 in figure 4).

(c) Look at the output (shown in figure 8):

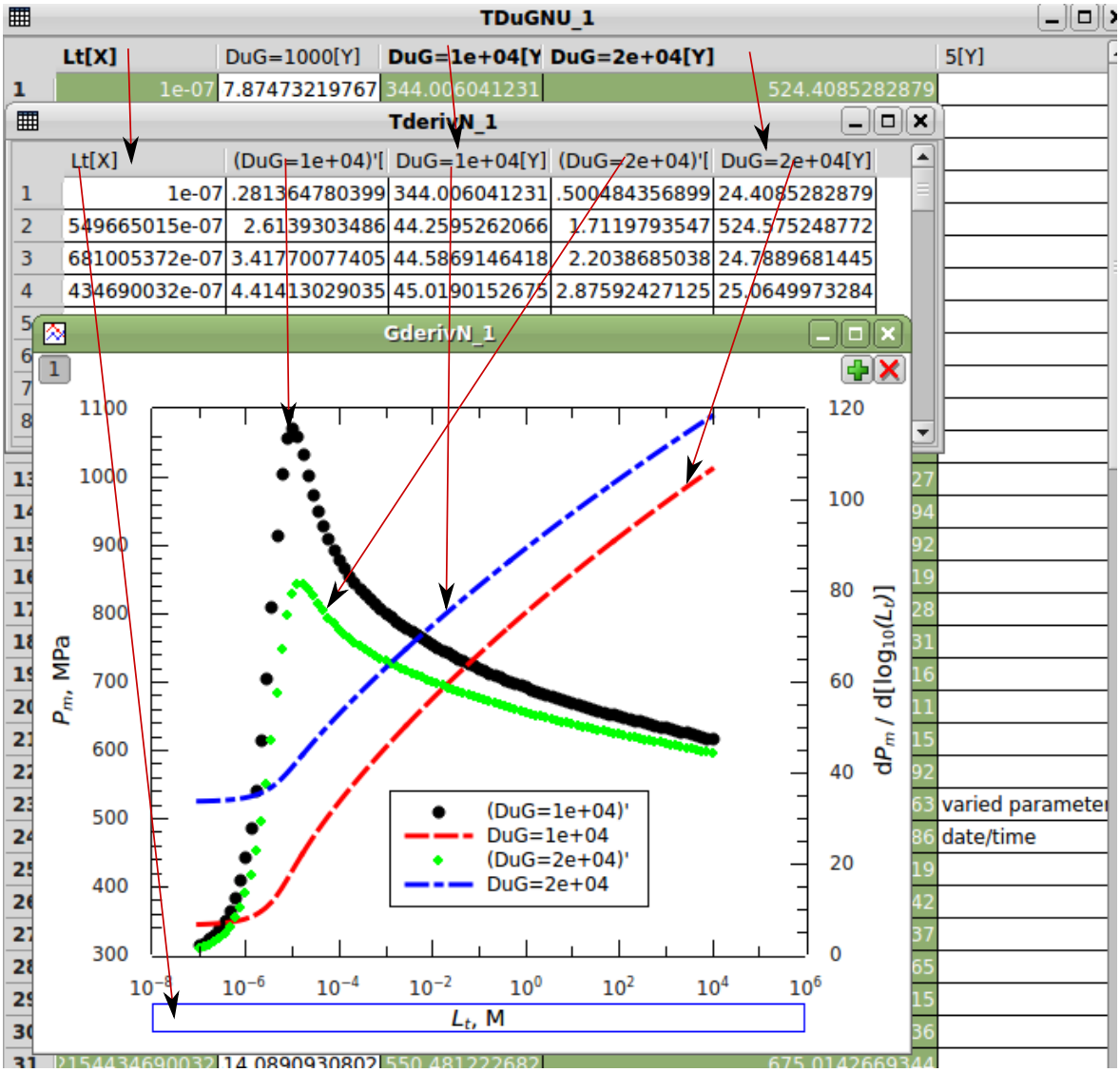


Figure 8 – ***Logarithmic differentiate*** *output.*

i. Graph named *GderivMODEL_** – this object contains plotted data curves (left axis) with log derivative curves (right axis). Peening of the name: *G* – graph, *deriv* – derivative, *MODEL* – used mathematical model (*N* or *NU*), * number for name's uniqueness. i.e. *GderivN_3*.

ii. Table named *TderivMODEL_** – this object contains data curves (3,5,7.. columns) with log derivative curves (2,4,6... columns). Peening of the name: *T* – table, *deriv* – derivative, *MODEL* – used mathematical model (*N* or *NU*), * number for name's uniqueness. i.e. *TderivNU_4*.

3. **Differentiation parameters** (3 in figure 4) – this button calculates these parameters of logarithmic derivative (shown in figure 9):

- h_{Max} – maximum derivative value
- x_{Hmax} – x at maximum derivative value
- s_{Half} – half width at half maximum

- h_{End} – derivative value at the end of the curve

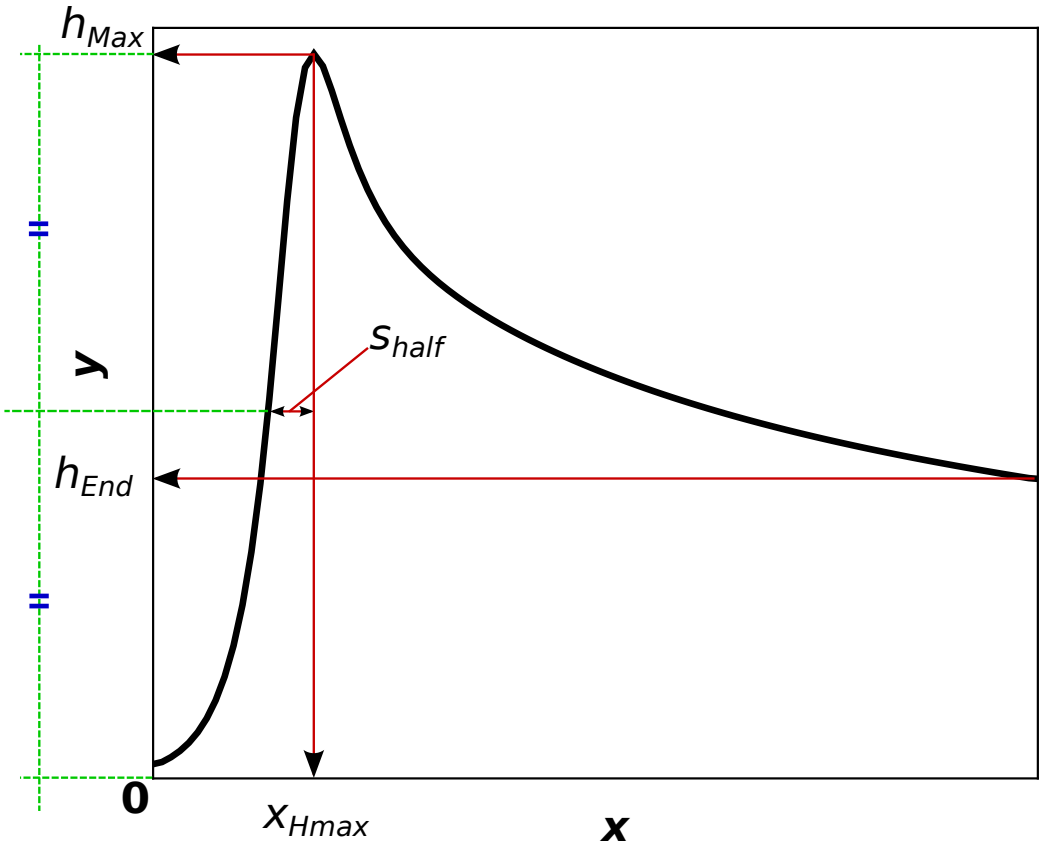


Figure 9 – *Derivative parameters.*

Perform following steps for protein dose curves generation:

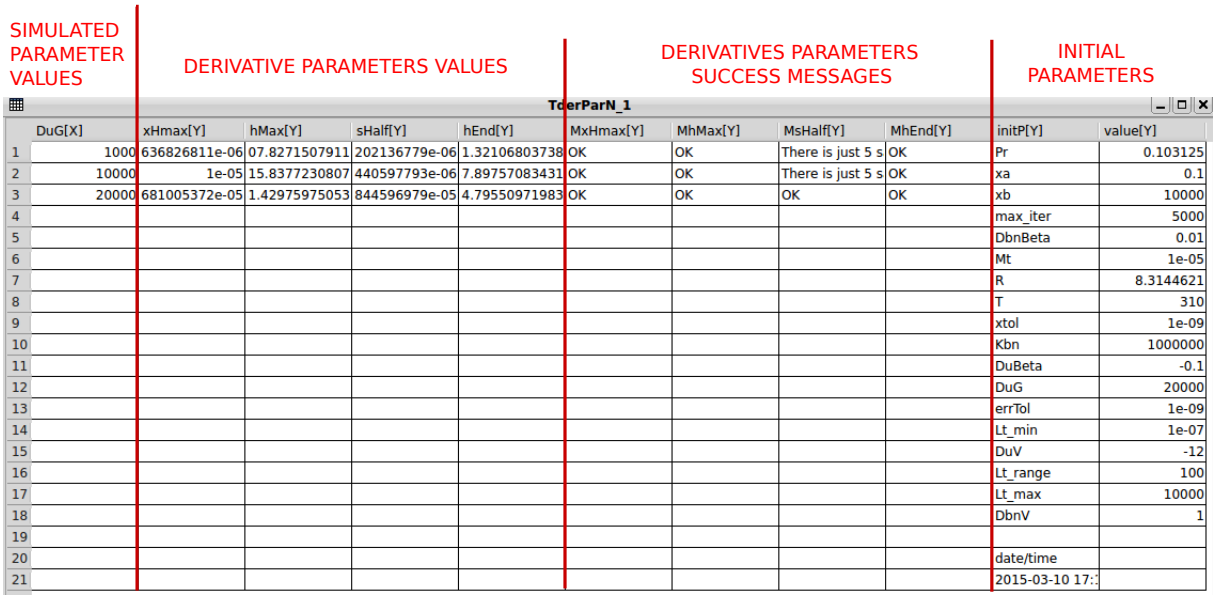
(a) Check and edit parameters values in *initParams* (1a,1b in figure 3) and *SimParam* (2 in figure 3) tables. *Brent's, CONST, N/NU, NU(if NU model selected), DGENER* parameters that are shown in figure 5 must be included in *initParams* table.

(b) Select model (4 in figure 4).

(c) Push **Generate** button (1 in figure 4).

(d) Select parameter which to simulate. Selections are created from *SimParam* table. Also the *ALL* buttons miens to simulate all selections at once. It is open to add new parameters in *SimParam* table but all *NU* (named **bu**) parameters will be excluded from *N* selection (look at the figure 6).

(e) Look at the output (shown in figure 10):



	DuG[X]	xHmax[Y]	hMax[Y]	sHalf[Y]	hEnd[Y]	MxHmax[Y]	MhMax[Y]	MsHalf[Y]	MhEnd[Y]	initP[Y]	value[Y]
1	1000	636826811e-06	07.8271507911	202136779e-06	1.32106803738	OK	OK	There is just 5 s	OK	Pr	0.103125
2	10000	1e-05	15.8377230807	440597793e-06	7.89757083431	OK	OK	There is just 5 s	OK	xa	0.1
3	20000	681005372e-05	1.42975975053	844596979e-05	4.79550971983	OK	OK	OK	OK	xb	10000
4										max_iter	5000
5										DbnBeta	0.01
6										Mt	1e-05
7										R	8.3144621
8										T	310
9										xtol	1e-09
10										Kbn	1000000
11										DuBeta	-0.1
12										DuG	20000
13										errTol	1e-09
14										Lt_min	1e-07
15										DuV	-12
16										Lt_range	100
17										Lt_max	10000
18										DbnV	1
19											
20										date/time	
21										2015-03-10 17::	

Figure 10 – ***Differentiation parameters*** *output.*

i. Table named *TderParMODEL_** – this object contains values of derivative parameters (shown in figure 9) on the left side, messages about these parameters calculations success in the middle and *initParams* table data on the right side. Meaning of the name: *T* – table, *derPar* – derivative parameters, *MODEL* – used mathematical model (*N* or *NU*), * number for name's uniqueness. i.e. *TderParNU_4*.

4. Binding model selection section **N/NU** (4 in figure 4). This action is a switch between models. eq. 8 for N model and eq. 9 for NU model are in use.

5. **Delete Graphs** (5 in figure 4) – this button deletes all graphs.

6. **Delete tables** (6 in figure 4) – this button deletes all table except *fitWizard, initParams* and *SimParam*.

7. **Delete Graphs and Tables** (7 in figure 4) – this button runs 5 and 6 buttons actions at once.

8. **Noise amplitude** (8 in figure 4) – field for random noise (uniform) value. Default value 0. For ex. 5.5 written in the field means that amplitude of y axis noise is 5.5MPa.

6 Results log

Results log is useful Qtiplot's tool. Purpose of this tool in all psaFit modules is to log main information about every experiment:

- Date and time
- Input/Output graphs and tables
- Model and statistical parameters of experiment

Example results log is shown in figure 11.

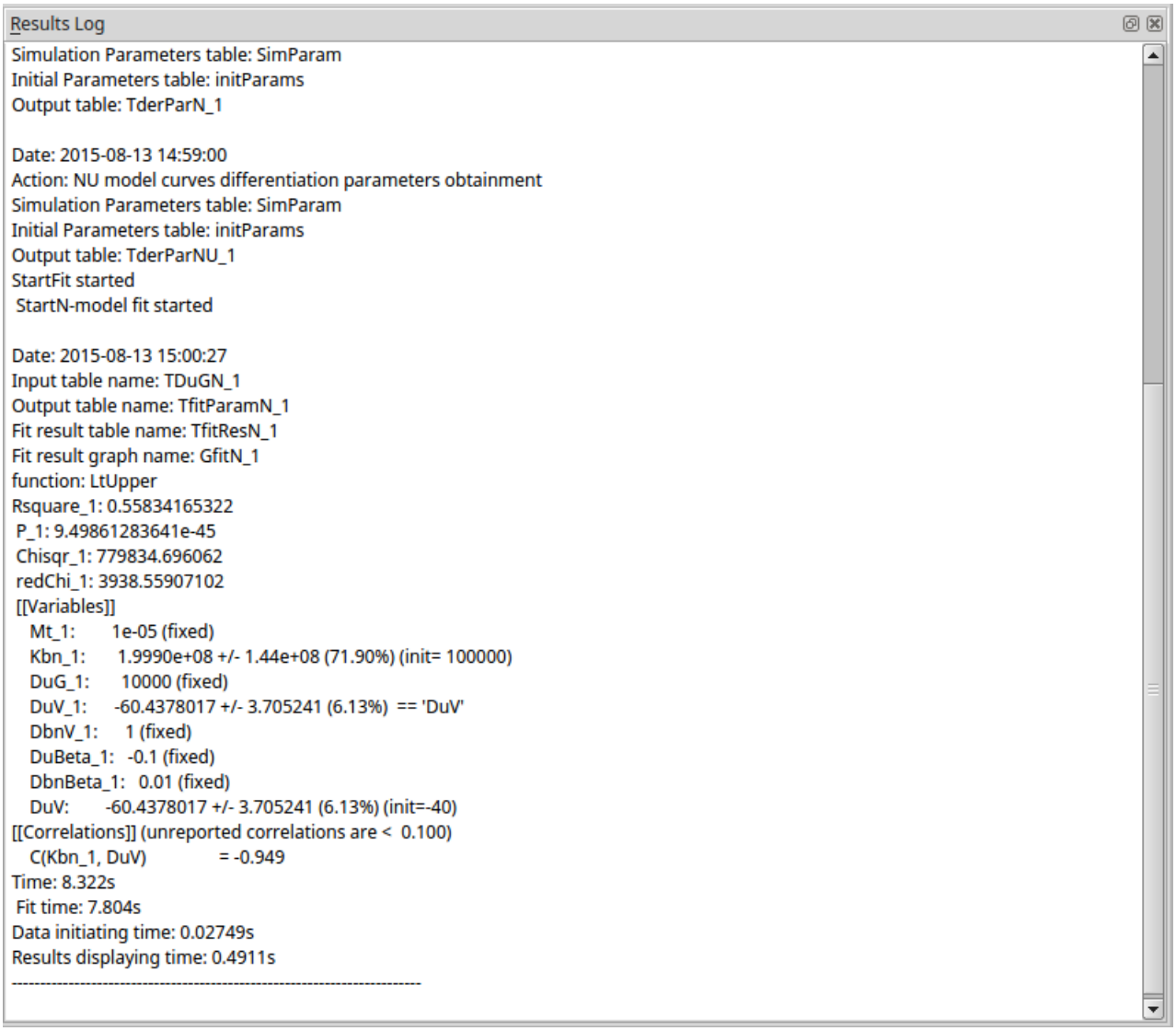


Figure 11 – *Example Qtiplot's results log.*

Reference

[1] Non-Linear Least-Square Minimization and Curve-Fitting for Python — Non-Linear Least-Squares Minimization and Curve-Fitting for Python. (n.d.). Retrieved December 10, 2014, from http://lmfit.github.io/lmfit-py/.

[2] NumPy — Numpy. (n.d.). Retrieved March 04, 2015, from http://www.numpy.org/.

[3] QtiPlot. (n.d.). Retrieved December 11, 2014, from http://www.qtiplot.com/.

[4] Riverbank | Software | PyQt | What is PyQt? (n.d.). Retrieved March 04, 2015, from http://www.riverbankcomputing.com/software/pyqt/intro.

[5] SciPy library — SciPy.org. (n.d.). Retrieved March 04, 2015, from http://www.scipy.org/scipylib/index.html.

[6] Welcome to Python.org. (n.d.). Retrieved December 11, 2014, from https://www.python.org/.

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