Protein Dose Curves Fit module

version v0.6.1

USER GUIDE

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August 19, 2015

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 **doseCfit.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 doseCfit.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.

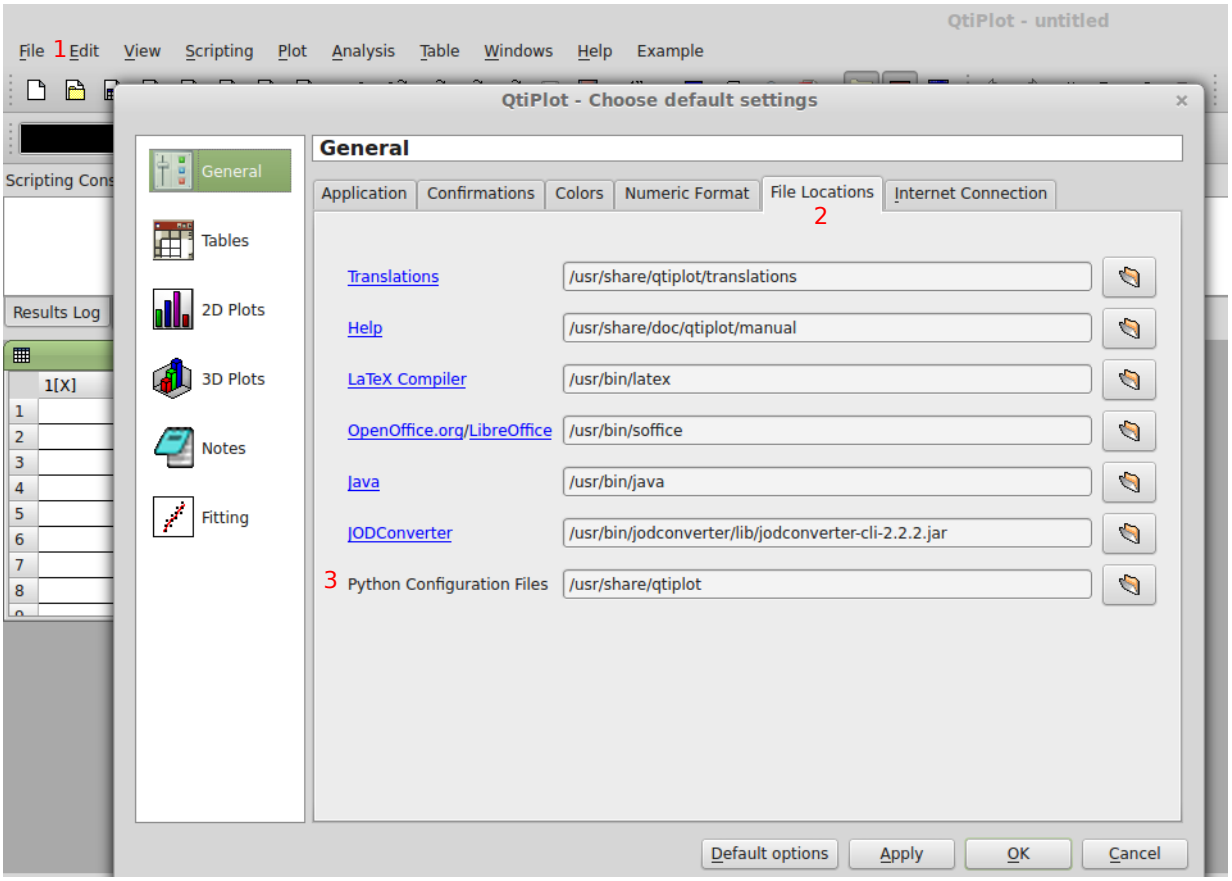


Figure 1 – *Finding path of the Python Configuration Files.*

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.

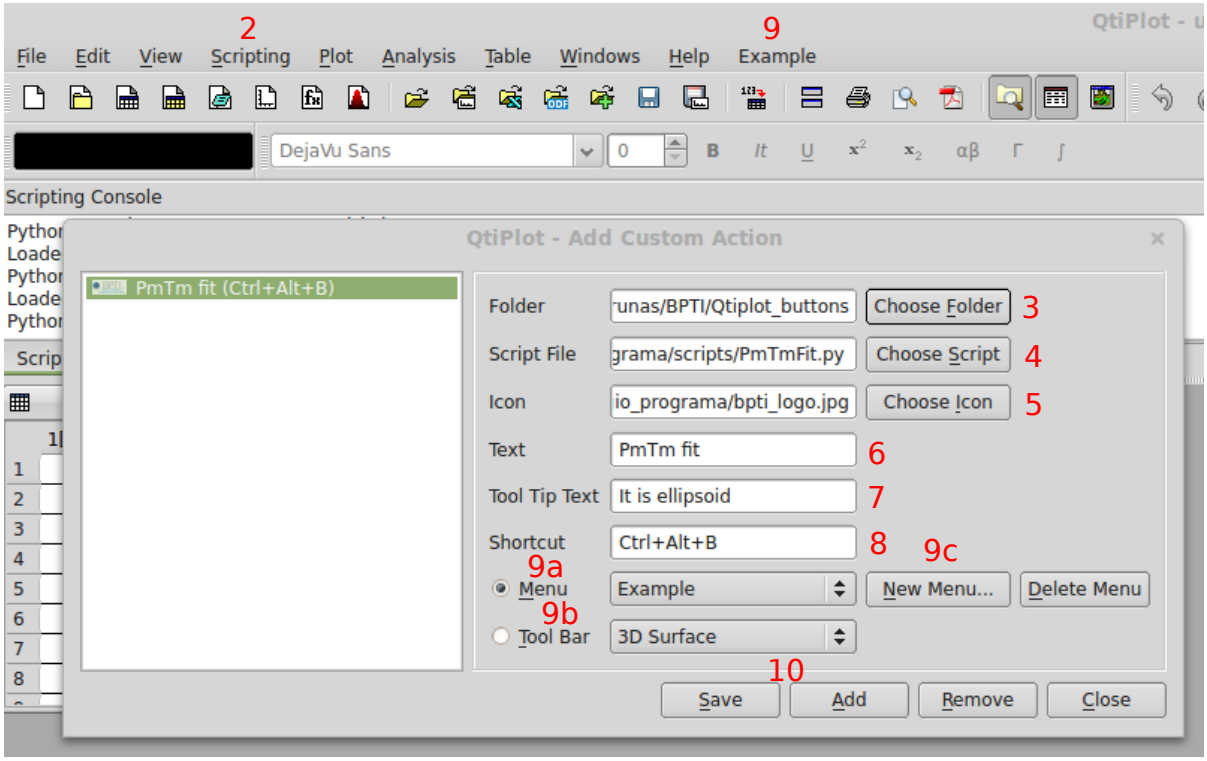


Figure 2 – *Steps of* QtiPlot's *buttons attachement.*

4.4 QtiPlot's template's

Modules which perform curves **fitting** will work with this table (shown in figure 3):

1. Table to manage fit process called **fitWizard**. This table contains these columns:
   (a) **parameter** – name of the parameter.
   (b) **value** – value of the parameter. Default value is 0.0 (zero point zero).
   (c) **vary** – parameter to allow fitting program to vary parameter value from initiadet one (value column or default 0.0). Default value is 1 (means TRUE → vary). If 0 (FALSE) is set on the parameter will not be varied.
   (d) **min** – minimum value that can be reached during fitting process. Default value is $-\infty$ (negative infinity).
   (e) **max** – maximum value that can be reached during fitting process. Default value is $+\infty$ (positive infinity).
   (f) **global** – parameter to set global parameter. This option if more then one curve are fitted – choosed parameter is the same in all curves. Default value is 0 (means FALSE → not global). Not all modules have this option.

fitWizard

	parameter 1a	value 1b	vary 1c	min 1d	max 1e	global 1f
1	xa	1				
2	xb	10000				
3	errTol	1e-09				
4	max_iter	500				
5	xtol	1e-09				
6	Pr	0.103125				
7	R	8.3144621				
8	T	310				
9	Mt	1e-05				
10						
11						
12	Kbn	100000	1	1	1e+13	
13	Kbu	0.0001				
14	DuG	10000				
15	DuV	-40	1			1
16	DbnV	1				
17	DbuV	0				
18	DuBeta	-0.1				
19	DbnBeta	0.01				
20	DbuBeta	0				
21						
22						

Figure 3 – *fitWizard table.*

5 Working with Dose Curves Fit package

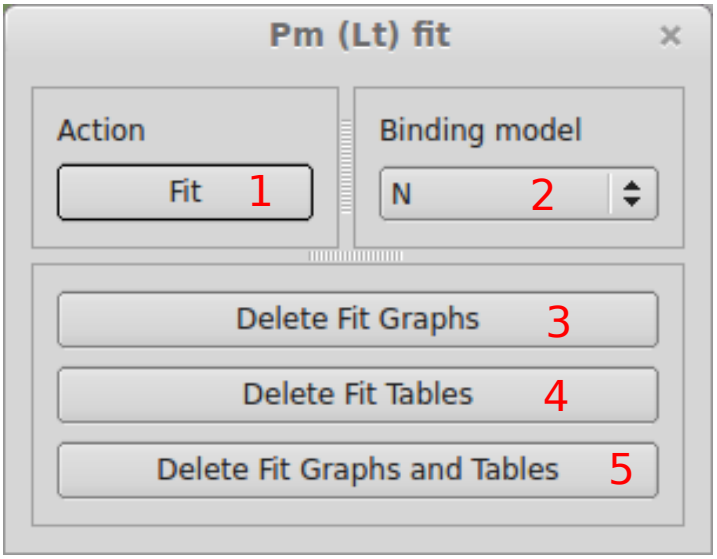


Figure 4 – *Dose Curves Fit module.*

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

1. **Fit** – this button fit experimental data to 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), $\Delta_U V_{P_r}$

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

– protein [U]nfolding volume change (extrapolated to P_r), $\Delta_U\beta$ – protein [U]nfolding isothermal compressibility change, $\Delta_{bN}G_{P_r}$ – ligand binding to [N]ative protein Gibbs free energy change (extrapolated to P_r), $\Delta_{bN}V_{P_r}$ – ligand binding to [N]ative protein volume change (extrapolated to P_r), $\Delta_{bN}\beta$ – ligand binding to [N]ative protein isothermal compressibility change.
Definition of the parameters that are used only in NU model: $\Delta_{bU}G_{P_r}$ – ligand binding to [U]nfolded protein Gibbs free energy change (extrapolated to P_r), $\Delta_{bU}V_{P_r}$ – ligand binding to [U]nfolded protein volume change (extrapolated to P_r), $\Delta_{bU}\beta$ – ligand binding to [U]nfolded protein 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).

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

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

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

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

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

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

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

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

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

Perform following steps for protein dose curves fitting:

(a) Check and edit fitting parameters (look at the System Requirements) – value, vary, min, max, global (1 b-f in figure 3) in *fitWizard* table. **EXPERIMENTAL PARAMETERS** (shown in figure 5) and **MODELING PARAMETERS** should remain as in template, **MODEL'S PARAMETERS** cells must be edited in order to get better fit results.

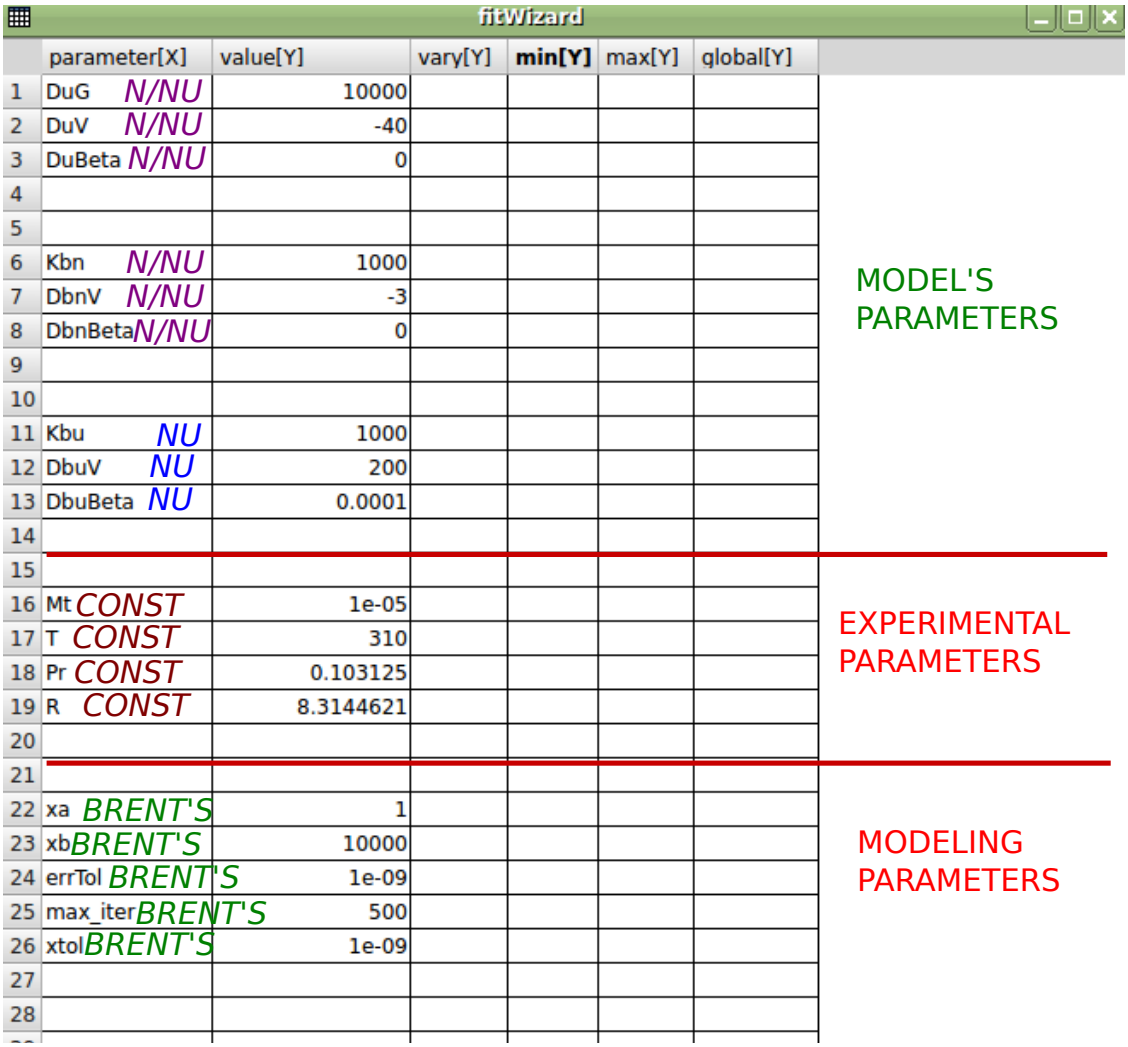


Figure 5 – *Marked fitWizard table parameters.*

(b) Select model (2 in figure 4).

(c) Select x and y columns. There is no limit for y columns number.

(d) Push **Fit** button (1 in figure 4).

(e) Look at the output:

i. Graph (shown in figure 6) named *GfitMODEL_** – this object contains plotted experimental and fit data curves. Meaning of the name: *G* – graph, *fit* – fit, *MODEL* – used mathematical model (*N* or *NU*), * number for name's uniqueness. i.e. *GfitN_3*.

ii. Table (shown in figure 6) named *TfitResMODEL_** – this object contains experimental and fit curves. Meaning of the name: *T* – table, *fit* – fit, *Res* – results, *MODEL* – used mathematical model (*N* or *NU*), * number for name's uniqueness. i.e. *TfitResNU_4*. Graph is plotted from this table.

iii. Table (shown in figure 7) named *TfitParamMODEL_** – this object contains initial and fitted parameters on the left side, messages about fit operations in the middle and *fitWizard* table data on the left. Meaning of the name: *T* – table, *fit* – fit, *Param* – parameters, *MODEL* – used mathematical model (*N* or *NU*), * number for name's uniqueness. i.e. *TfitParamNU_4*.

iv. All information about every fit action is printed to the QtiPlot's Results Log (shown in figure 8).

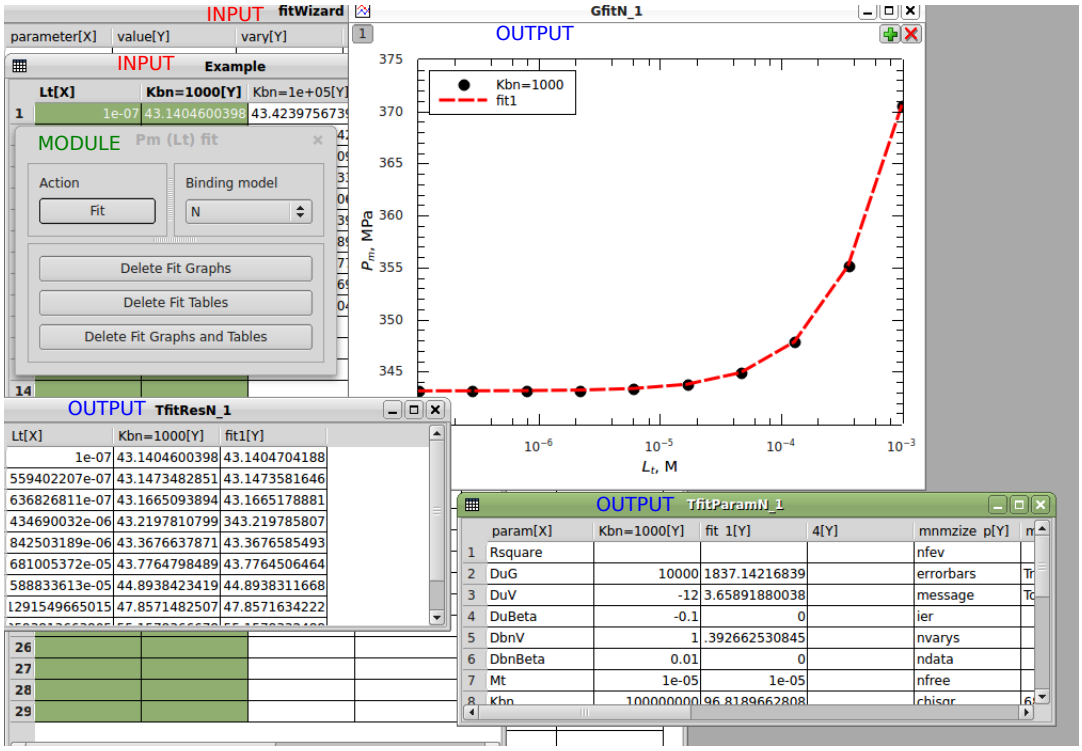
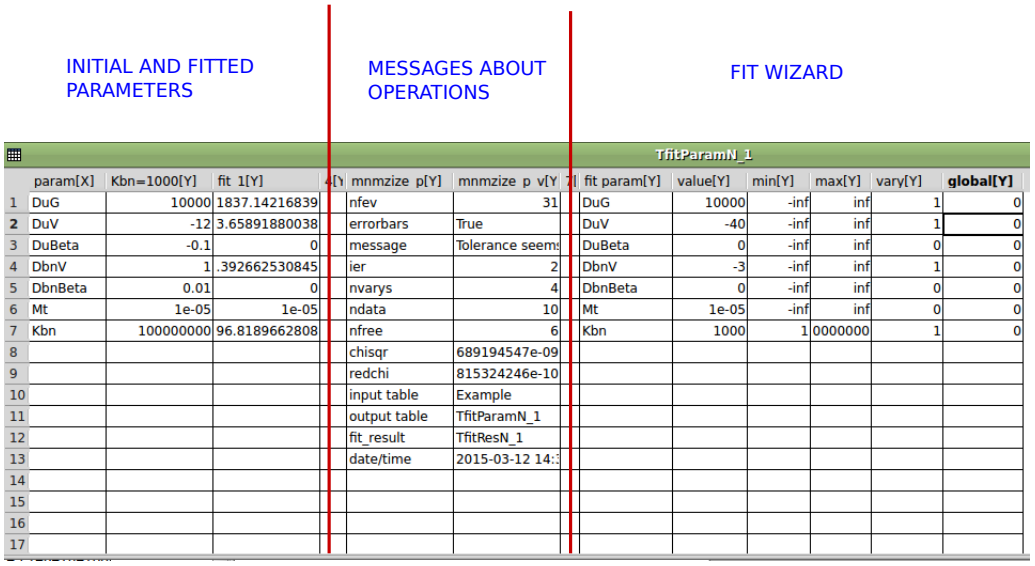


Figure 6 – *Protein dose curves fit output.*



	param[X]	Kbn=1000[Y]	fit 1[Y]	mnmzize p[Y]	mnmzize p v[Y]	fit param[Y]	value[Y]	min[Y]	max[Y]	vary[Y]	global[Y]
1	DuG	10000	1837.14216839	nfev	31	DuG	10000	-inf	inf	1	0
2	DuV	-12	3.65891880038	errorbars	True	DuV	-40	-inf	inf	1	0
3	DuBeta	-0.1	0	message	Tolerance seems	DuBeta	0	-inf	inf	0	0
4	DbnV	1	.392662530845	ier	2	DbnV	-3	-inf	inf	1	0
5	DbnBeta	0.01	0	nvarys	4	DbnBeta	0	-inf	inf	0	0
6	Mt	1e-05	1e-05	ndata	10	Mt	1e-05	-inf	inf	0	0
7	Kbn	100000000	96.8189662808	nfree	6	Kbn	1000	1	0000000	1	0
8				chisqr	689194547e-09						
9				redchi	815324246e-10						
10				input table	Example						
11				output table	TfitParamN_1						
12				fit_result	TfitResN_1						
13				date/time	2015-03-12 14:3						
14											
15											
16											
17											

Figure 7 – *Protein dose curves fit parameters result table.*

2. Binding model selection section **N/NU** (2 in figure 4). This action is a switch between models. eq. 8 for N model and eq. 9 for NU model are in use.

3. **Delete Fit Graphs** (3 in figure 4) – this button deletes graphs that are created by **Fit** button (1 in figure 4).

4. **Delete tables** (4 in figure 4) – this button deletes tables that are created by **Fit** button (1 in figure 4).

5. **Delete Graphs and Tables** – this button runs 3 and 4 buttons actions at once.

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 8.

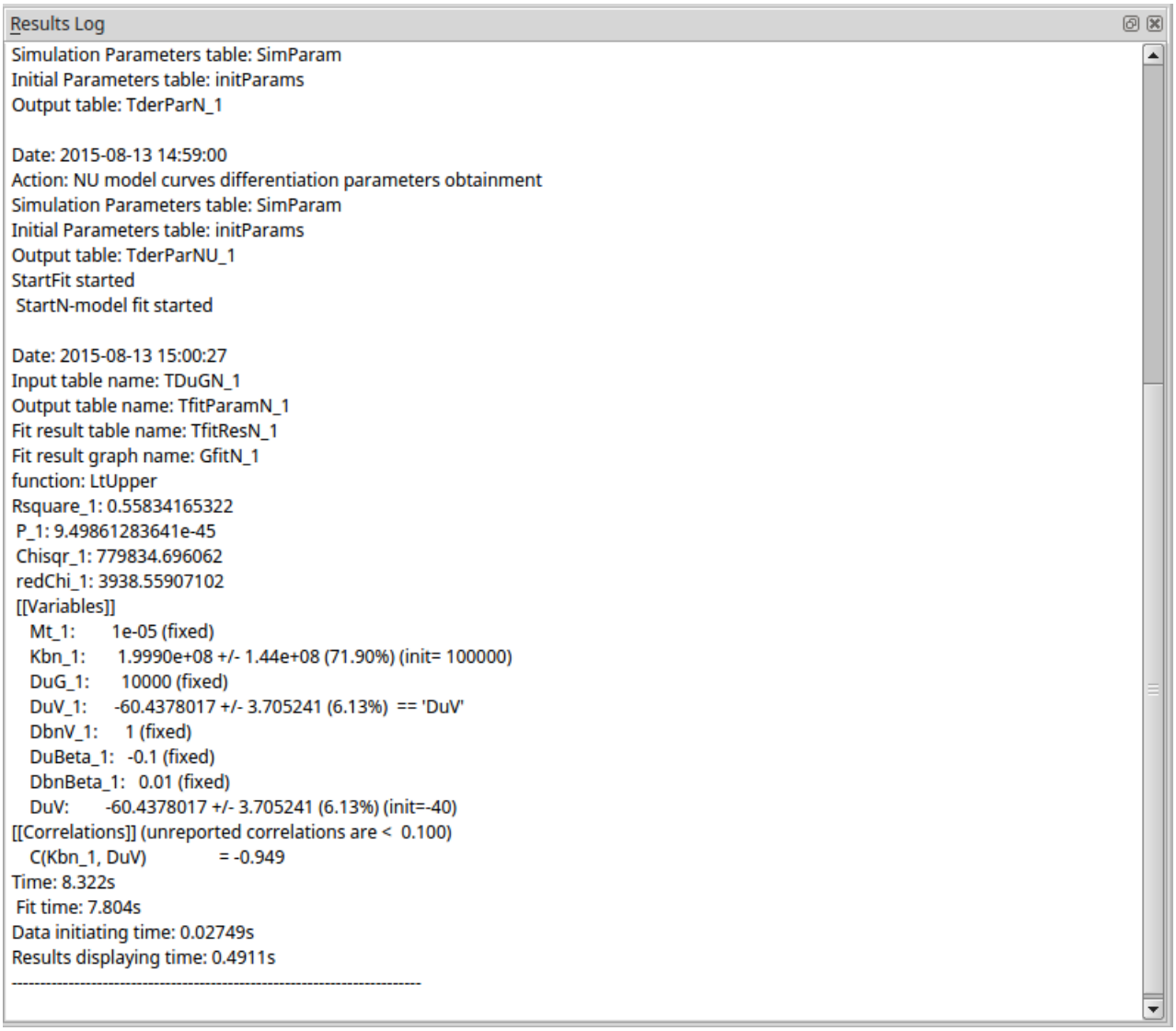


Figure 8 – *Example Qtiplot's results log.*

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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