USER MANUAL

RKinetDS v. 1.2

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1. Introduction

RKinetDS is a software for modeling drug dissolution profiles. It describes a drug dissolution curve by fitting provided data from dissolution tests to a particular model or set of models. Models were chosen from the most popular models used in drug dissolution testing. Their detailed list can be found in the section "Implemented models" of this document. List of possible optimization methods can be found in the section "Optimization methods and parameters" of this document.

The software was written in R language. Graphical user interface (GUI) was developed using Shiny R package.

2. Software requirements

There are no special requirements for the operating system. Software runs on Linux and Windows based systems. The application works in a web browser as well as on a computer. In order to run the software, the R environment is required. It can be downloaded at the following Internet address: https://www.r-project.org/. Installation of additional packages is necessary, that is:

- stringr (https://cran.r-project.org/package=stringr)
- nloptr (https://cran.r-project.org/package=nloptr)
- GenSA (https://cran.r-project.org/package=GenSA)
- rgenoud (https://cran.r-project.org/package=rgenoud)
- config (https://cran.r-project.org/package=config)
- yaml (https://cran.r-project.org/package=yaml)
- shiny (https://cran.r-project.org/package=shiny)
- shinyjs (https://cran.r-project.org/package=shinyjs)
- shinyFiles (https://cran.r-project.org/package=shinyFiles)
- shinythemes (https://cran.r-project.org/package=shinythemes)
- shinycssloaders (https://cran.r-project.org/package=shinycssloaders)
- shinyWidgets (https://cran.r-project.org/package=shinyWidgets)
- plotly (https://cran.r-project.org/package=plotly)
- DT (https://cran.r-project.org/package=DT)

The efficiency of the application depends on the speed of the computer, especially the speed of the processor and the available RAM. It should be noted that when performing complex calculations (e.g. using all built-in models and large number of iterations), the calculation may take a long time.

3. Implemented models

The list of models included in the software is provided below. The software consists of 18 different models, additionally a lag time was added for each of them (excluding one of them).

Explanation of used symbols:

- Q – amount of dissolved substance [%],
- Q_0 – initial amount of substance [%],
- t – time,
- t_{lag} – lag time,
- k, a, b, n – equation' constants.

1. Zero order model

$$Q = k \times t$$

2. Zero order with Q0

$$Q = k \times t + Q_0$$

3. First order model

$$Q = 100 \times (1 - e^{-k \times t})$$

4. First order model with lag time

$$Q = 100 \times (1 - e^{-k \times (t - t_{lag})})$$

5. Second order model

$$Q = 100 \times 1 - \frac{Q_0}{1 + Q_0 \times k \times t}$$

6. Second order model with lag time

$$\mathrm{Q} = 100 \times 1 - \frac{Q_0}{1 + Q_0 \times k \times (\mathrm{t} - \mathrm{t_{lag}})}$$

7. Third order model:

$$\mathrm{Q} = 100 \times (1 - \left(\sqrt{\frac{1}{k \times t} + \frac{1}{Q_0^2}}\right))$$

8. Third order model with lag time:

$$\mathrm{Q} = 100 \times (1 - \left(\sqrt{\frac{1}{k \times (\mathrm{t} - \mathrm{t_{lag}})} + \frac{1}{Q_0^2}}\right))$$

9. Michaelis-Menten model:

$$\mathrm{Q} = \frac{100 \times \mathrm{t}}{k + t}$$

10. Michaelis-Menten model with lag time:

$$\mathrm{Q} = \frac{100 \times (\mathrm{t} - \mathrm{t_{lag}})}{k + (\mathrm{t} - \mathrm{t_{lag}})}$$

11. Weibull model:

$$\mathrm{Q} = 100 \times (1 - \mathrm{e}^{\frac{-\mathrm{t}^n}{a}})$$

12. Weibull model with lag time:

$$\mathrm{Q} = 100 \times (1 - \mathrm{e}^{\frac{-(\mathrm{t} - \mathrm{t_{lag}})^{\mathrm{n}}}{a}})$$

13. Double Weibull model:

$$\mathrm{Q} = 100 \times (\mathrm{A} \times \left(1 - e^{-\frac{t^M}{c}}\right) + B \times \left(1 - e^{-\frac{N}{d}}\right))$$

14. Double Weibull model with lag time:

$$\mathrm{Q} = 100 \times (\mathrm{A} \times \left(1 - e^{-\frac{(t - \mathrm{t_{lag}})^M}{c}}\right) + B \times \left(1 - e^{-\frac{N}{d}}\right))$$

15. Higuchi model:

$$Q = k \times \sqrt{t}$$

16. Higuchi model with lag time:

$$Q = k \times \sqrt{(t - t_{lag})}$$

17. Hixson-Crowell model:

$$Q = 100 \times (1 - (1 - k \times t)^3)$$

18. Hixson-Crowell model with lag time:

$$Q = 100 \times (1 - (1 - k \times (t - t_{lag}))^3)$$

19. Korsmeyer-Peppas model:

$$Q = a \times t^n$$

20. Korsmeyer-Peppas model with lag time:

$$Q = k \times (t - t_{lag})^n$$

21. Hill model:

$$Q = \frac{100 \times t^n}{t_{50}^{\,n} + t^n}$$

22. Hill model with lag time:

$$Q = \frac{100 \times (t - t_{lag})^n}{t_{50}^{\,n} + (t - t_{lag})^n}$$

23. Hopfenberg model:

$$Q = 100 \times (1 - (1 - k \times t)^n)$$

24. Hopfenberg model with lag time:

$$Q = 100 \times \left(1 - \left(1 - k \times (t - t_{lag})\right)^n\right)$$

25. Peppas-Sahlin model:

$$Q = a \times t^n + b \times t^{2 \times n}$$

26. Peppas-Sahlin model with lag time:

$$Q = a \times (t - t_{lag})^{n} + b \times (t - t_{lag})^{2n}$$

27. Quadratic model:

$$Q = 100 \times (a \times t^{2} + b \times t)$$

28. Quadratic model with lag time:

$$Q = 100 \cdot [a \cdot (t - t_{lag})^{2} + b \cdot (t - t_{lag})]$$

29. Logistic model:

$$Q = \frac{A}{1 + e^{-k(t-y)}}$$

30. Logistic model with lag time:

$$Q = \frac{A}{1 + e^{-k((t-t_{lag})-y)}}$$

31. Gompertz model:

$$Q = 100 \times e^{-a \times e^{b \times \log(t)}}$$

32. Gompertz model with lag time:

$$Q = 100 \times e^{-a \times e^{b \times \log(t - t_{lag})}}$$

33. Makoid-Banakar model:

$$Q = k \times t^{a \times e^{-m \times t}}$$

34. Makoid-Banakar model with lag time:

$$Q = k \times (t - t_{lag})^{a \times e^{-m \times (t - t_{lag})}}$$

35. Baker-Lonsdale

$$Q = 100 \times \left(\frac{3}{2} \times \left(1 - \left(1 - \frac{Q}{100}\right)^{\frac{2}{3}}\right) - k \times t\right)$$

36. Baker-Lonsdale with lag time

$$Q = 100 \times \left(\frac{3}{2} \times \left(1 - \left(1 - \frac{Q}{100} \right)^{\frac{2}{3}} \right) - k \times (t - t_{lag}) \right)$$

Additionally, if the user has the appropriate skills in R, it is possible to add or edit model equations used in the program. The procedure was described in the Config files section of this document.

4. Optimization methods and parameters

The software has implemented five optimization methods:

1) SANN

2) nloptr

3) Nelder Mead

4) genSA

5) rgenoud

For each optimization method, the maximum number of iterations can be specified by the user. Moreover, maximum number of iterations in Broyden–Fletcher–Goldfarb–Shanno (BFGS) method can be specified. BFGS is the basis for performing calculations for each of the five optimization methods.

The user can specify the value of stop criterion for optimizing the likelihood function. It is also possible to choose whether to trace optimization function evaluations, or not. If yes, it improves the efficiency of function evaluations.

5. Best model criterion

Software uses various criteria for assessing the goodness-of-fit of a model.

Explanation of used symbols:

- y_i is the observed value,
- $\hat{y}_i$ is the predicted value,
- n is a number of data points,
- SS_{res} is residual sum of squares,
- SS_{tot} is total sum of squares,

- $\bar{y}$ is the mean of the observed values,
- p is number of parameters in the model,
- WSS is the weighted sum of squares.

1. Root-mean-square error (RMSE):

$$RMSE = \sqrt{\frac{\sum_{i=1}^{n}(y_i - y\hat{}_i)^2}{n}}$$

2. Coefficient of determination (R^2):

$$R^2 = 1 - \frac{SS_{res}}{SS_{tot}} = 1 - \frac{\sum_{i=1}^{n}(y_i - y\hat{}_i)^2}{\sum_{i=1}^{n}(y_i - \bar{y})^2}$$

3. Adjusted coefficient of determination (R^2_{adjusted}):

$$R^2_{adjusted} = 1 - (\frac{n-1}{n-p-1}) \times (1 - R^2)$$

4. Akaike information criterion (AIC):

$$AIC = 2k + n \times \ln(WSS) = 2k + n \times \ln\left(\sum_{i=1}^{n} w_i \times (y_i - y\hat{}_i)^2\right)$$

6. Input file

The input file is a tab delimited text file format (*.txt). The first column contains time-points and can be expressed in selected by the user format (minutes, hours etc.). The second column is for dissolved amount of drug substance, and it is expressed in percentages. Users can choose in a software if the provided data file contains headers, or not. Default settings include headers.

Time	Dissolved amount
0	0
1	2.44

Figure 1 Example input data

7. Config files

The software has two config files (.yml) by default. The first one is called factory_config and stores the application's factory settings. The second one is called user_config and saves the current app settings specified by the user. Both files should not be edited by the user without appropriate R knowledge, otherwise the application error may occur.

Config files store information about:

- models' equations,
- selected models,
- optimization methods,
- optimization parameters,
- input data format.

With the appropriate skills in R, the user can add further equation models or update existing ones. To do this, update the configuration file named "factory_config.yml" and add another line in the section “models”.

Figure 2 Configuration “factory_config” file content

You should enter the model name and after the colon enter the model equation. The equations should be entered in a strictly defined way, taking into account that C[i] - parameters for optimization where i is the parameter number, t - time. After updating the configuration file "factory_config.yml", you should also do the same for the file "user_config.yml".

8. GUI elements

Graphical User Interface (GUI) consists of four different tabs: “Main panel”, “Settings”, “Results”, and “More”. Detailed description of each section is described in the next sections.

8.1. Main panel

After opening the application, the “Main panel” displays automatically. The “Main panel” allows the user to:

1) Upload a data file and display the name of a file. The data file can be loaded by clicking on the button called “CHOOSE” on the left side of the app.

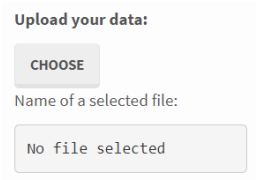

Figure 3 Button for loading a data file

2) Display a graph. A graph is displayed on the right side of the app.

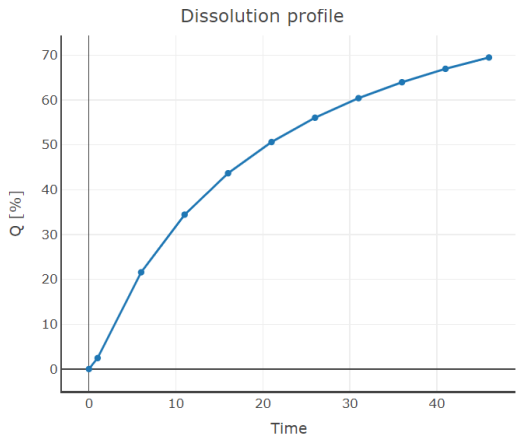

Figure 4 Section displaying a graph

3) Save settings of the application. The selected settings are saved by clicking on the button called “SAVE SETTINGS” on the left side of the app.

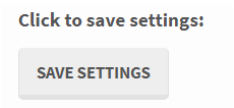

Figure 5 Button for saving settings within “Main panel” window

4) Run the application. The application is started by clicking on the button called “RUN APP”.

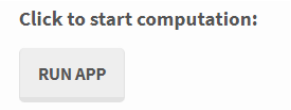

Figure 6 Button for running the application

8.2. Settings

After clicking tabs “Settings”, the settings window will be shown. The user can do this by navigating within “Settings” window and clicking on tabs called: “Models”, “Optimization methods”, and “Data format”.

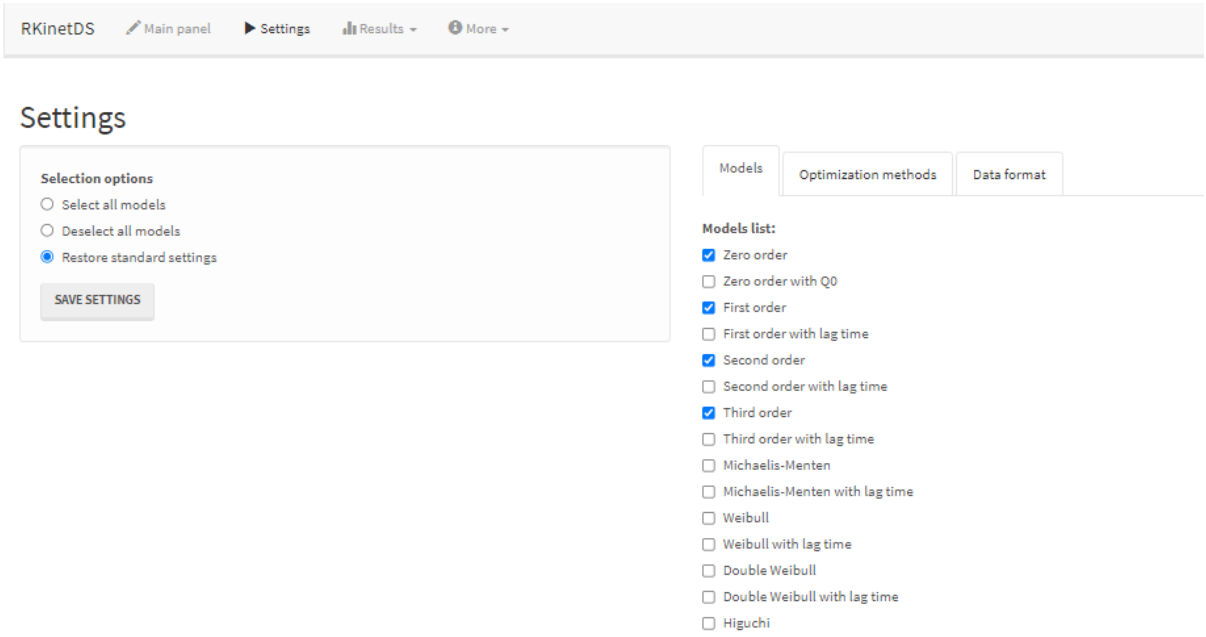

Figure 7 “Settings” window

The “Settings” window allows the user to:

1) Choose models used for computation

The selection of models is done within the tab named “Models” by manually clicking on the appropriate checkbox (right side of the app). It is also a possibility to select or deselect all models at once by clicking bullet buttons (left side of the app).

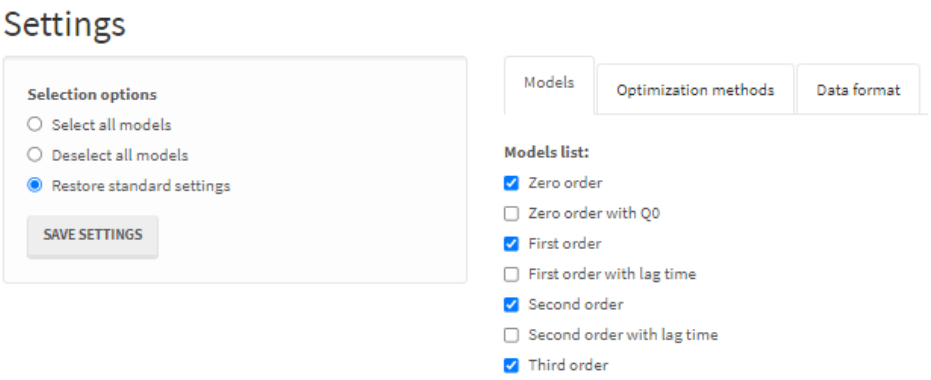

Figure 8 “Models” tab within “Settings” window

2) Choose optimization methods used for computation

The selection of optimization methods is done within the tab named “Optimization methods” by manually clicking on the appropriate checkbox on the right side of the app.

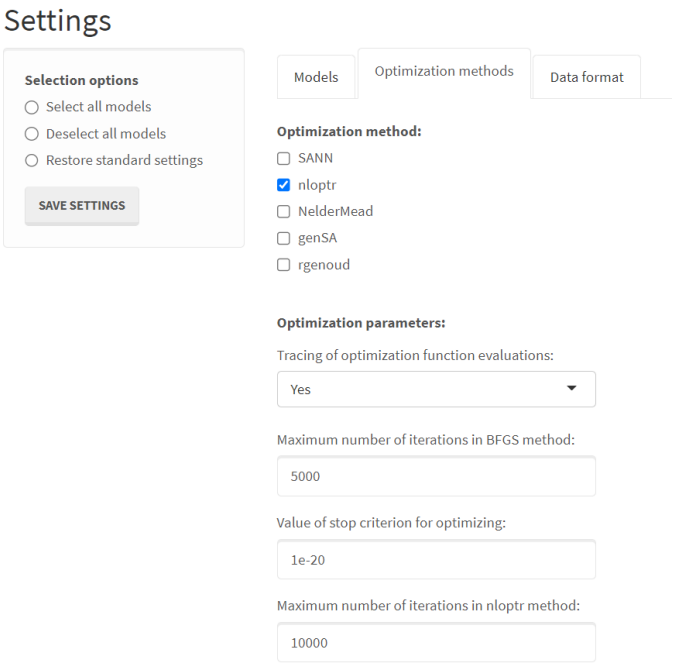

Figure 9 "Optimization methods" tab within "Settings" window

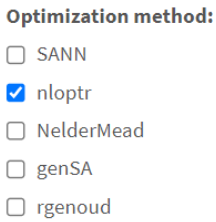

Figure 10 Checkbox for selecting optimization methods

Below the list of optimization methods, there is section that allows to specify the optimization parameters. Options called "Tracing of optimization function evaluations", "Maximum number of iterations in BFGS method", and "Value of stop criterion for optimizing" always should be seen. The selection is made by entering the appropriate value or selecting from the drop-down list.

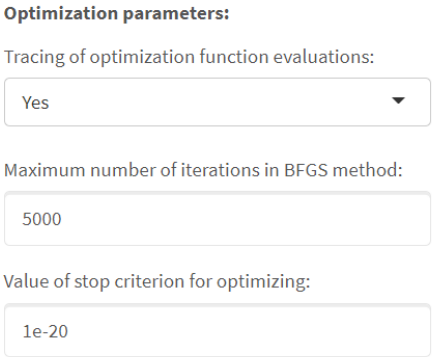

Figure 11 Overall “Optimization parameters” section

In addition, after clicking on a selected model, options related to the given model are displayed, e.g., if “nloptr” method is selected, box named “Maximum number of iterations in nloptr method” should appear.

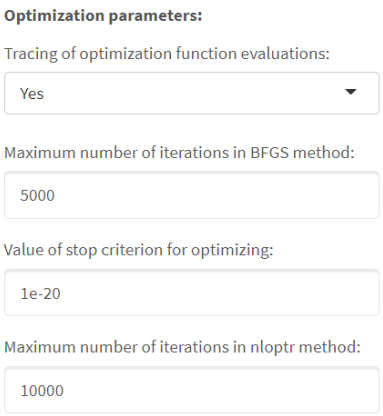

Figure 12 Overall and specific “Optimization parameters” section

3) Modify data format used for computation

The selection of optimization methods is done within the tab named “Data format” from the drop-down list on the right side of the app. It allows to choose whether uploaded data contains headers, or not.

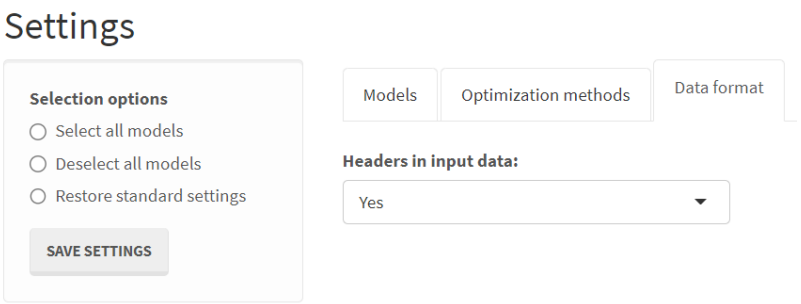

Figure 13 “Data format” tab within “Settings” window

4) Restore standard settings

The possibility of restoring the initial settings is in the section called “Selection options” (left side of the app). It can be done by selecting an appropriate bullet button called “Restore standard settings”.

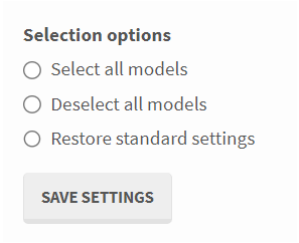

Figure 14 Bullet buttons for selecting “Restore standard settings”

5) Save settings. The selected settings are saved by clicking on the button called “SAVE SETTINGS” on the left side of the app.

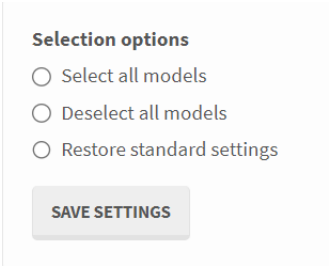

Figure 15 Button for saving settings within “Settings” windows

8.3. Results

After clicking tab named “Results”, a drop-down list is shown. It consists of tabs named: “Used settings”, “Overall results”, “Model results”, and “Error ranking”.

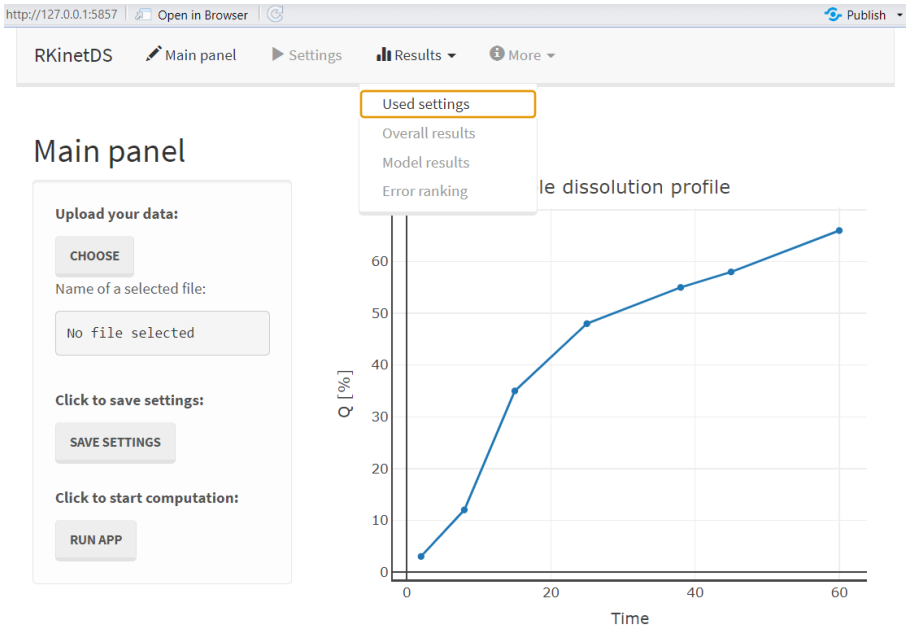

Figure 16 “Results” drop-down list

1) Used settings

After clicking “Used settings” a current, saved configuration settings are displayed. Used settings tab contains information about:

- used models – only selected models' equations are displayed,
- used optimization methods – all possible optimization methods with corresponding “TRUE” (meaning this optimization is used) or “FALSE” (meaning this optimization is not used) value are displayed,
- used optimization parameters – all possible optimization parameters with corresponding values are displayed, even if one or more values are not used during computation,
- used data format – it displays info whether uploaded data file contained headers, or not.

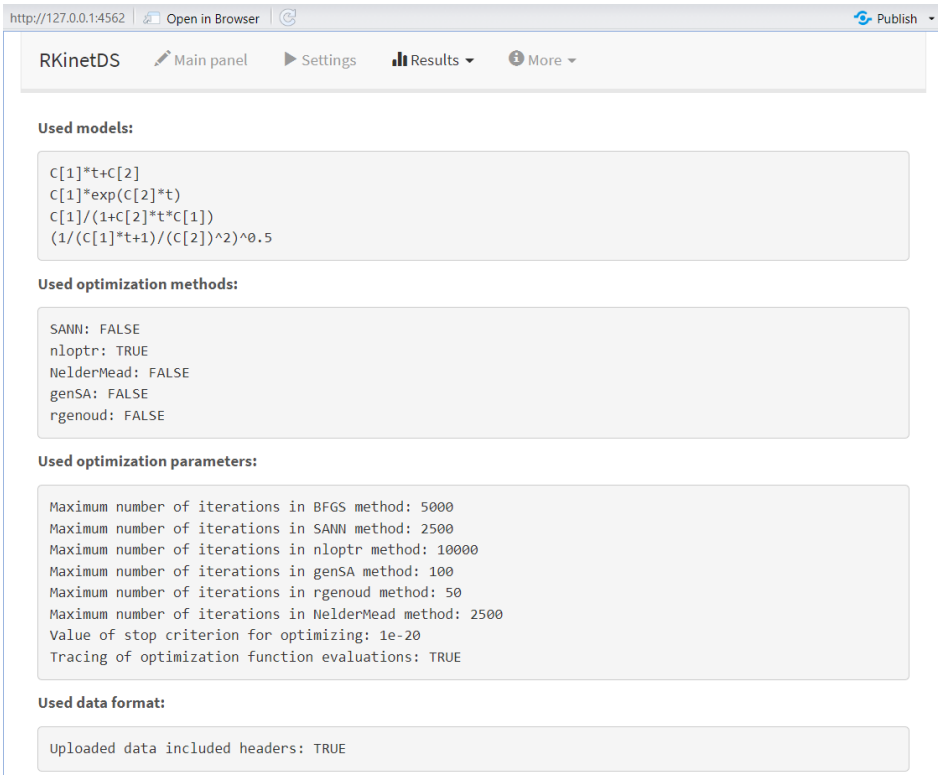

Figure 17 “Used settings” window

2) Overall results

When the application has not yet been started, this tab should display information “Results not found”.

After the running of the app, it should display overall results. They contain information about:

- date of report,
- used optimization methods,
- used optimization parameters,
- detailed results for each model (model name, model equation, parameters for equation after optimization, algebraic form of equation, error),
- information about computer system,
- installed by the user packages and their versions.

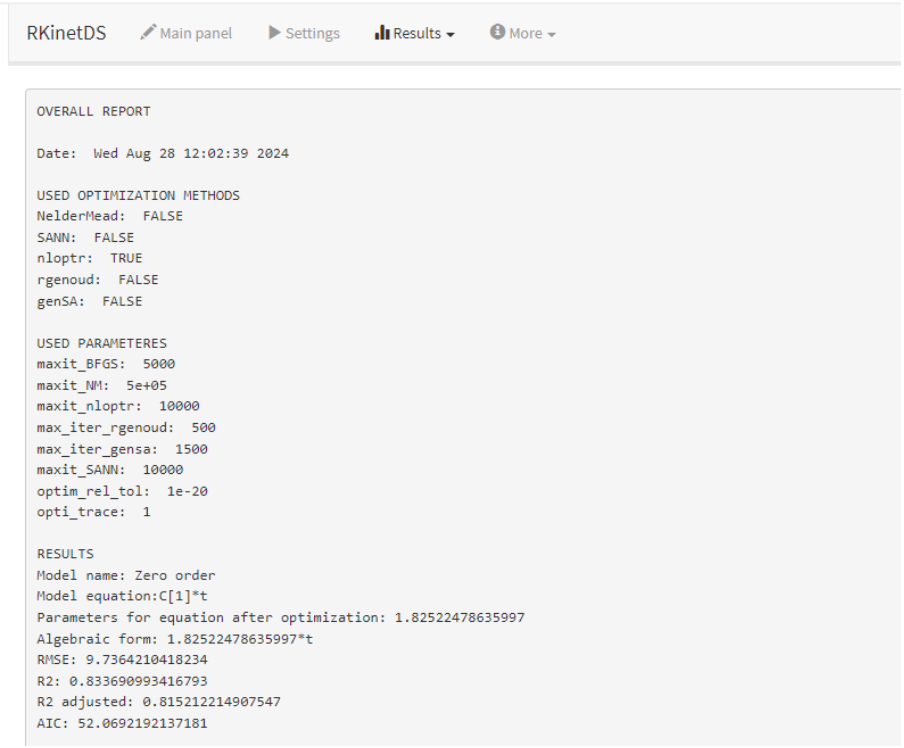

Figure 18 Fragment of a window of tab called “Overall results” within “Results” panel

3) Model results

When the application has not yet been started, this tab should be empty.

After the running of the app, it should display detailed results for each model. All model results are presented in a separate tab, where the tab name is the model's name. Each tab contains:

- graph with results for this model (predicted and observed data is shown)
- model name,

- model equation.
- parameters for equation after optimization,
- algebraic form of equation, which is equation with included calculated parameters,
- RMSE, R^2, $R^2_{adjusted}$ and AIC value,
- file data path when the user can find the results.

The graph is displayed at the top and the results for the model below it.

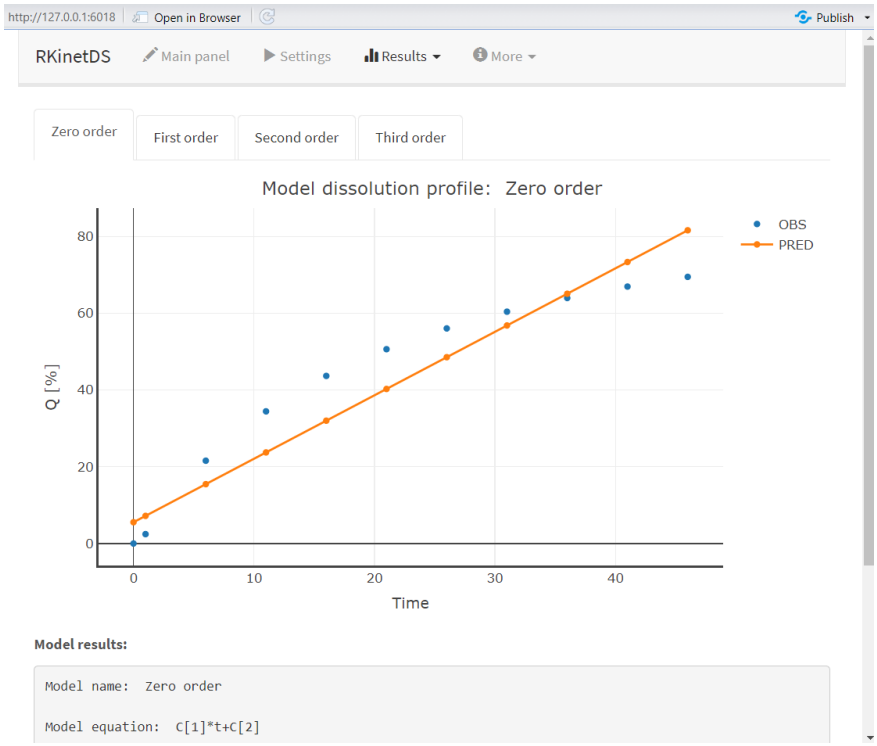

Figure 19 Zero order model graph after calculations

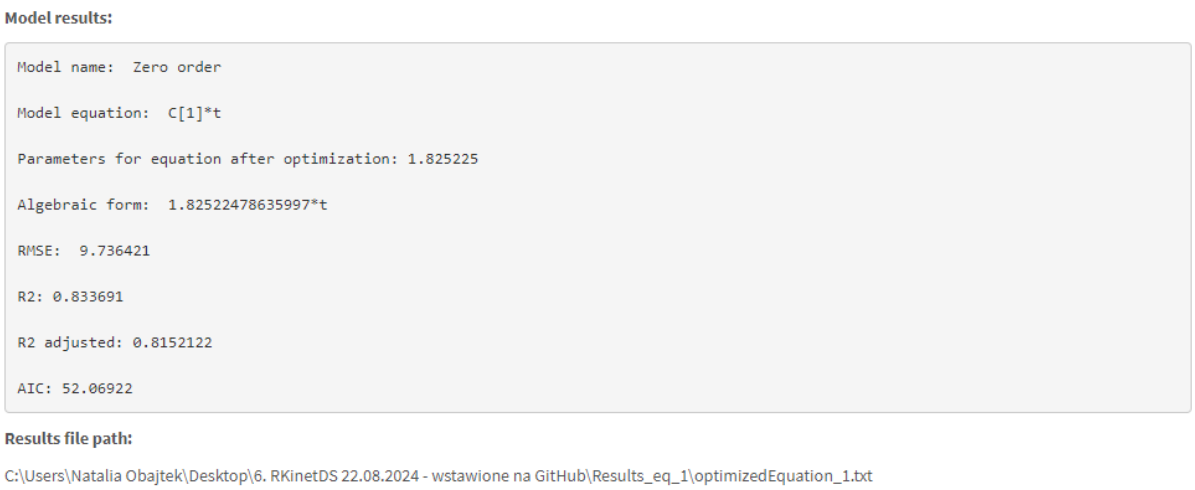

Figure 20 Zero order model results and results file path after calculations

4) Error ranking

When the application has not yet been started, this tab should be empty.

After the running of the app, it should display error ranking. The ranking is in the form of a 4 tables, individually for RMSE, R^2, $R^2_{adjusted}$, and AIC. Every table has 3 columns called "Number", "Equation" and type of error name (e.g. “RMSE”) and rows which number depends on the number of selected models. Models can be sorted by increasing or decreasing error value.

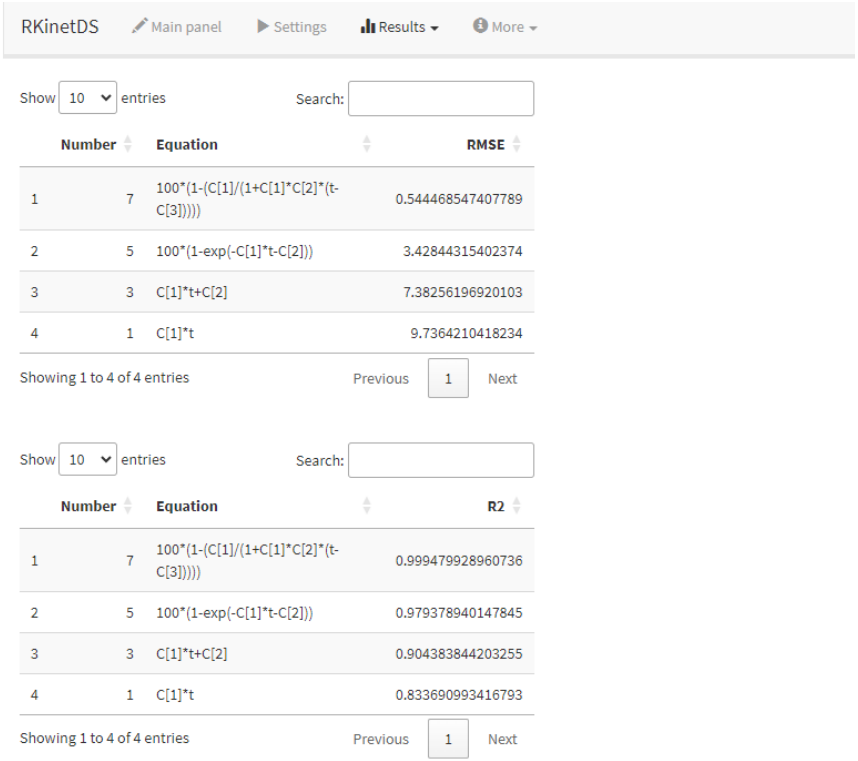

Figure 21 Error ranking displayed after running the app

8.4. More

After clicking tab named “More”, a drop-down list is shown. It consists of tabs named: “Manual”, and “License”.

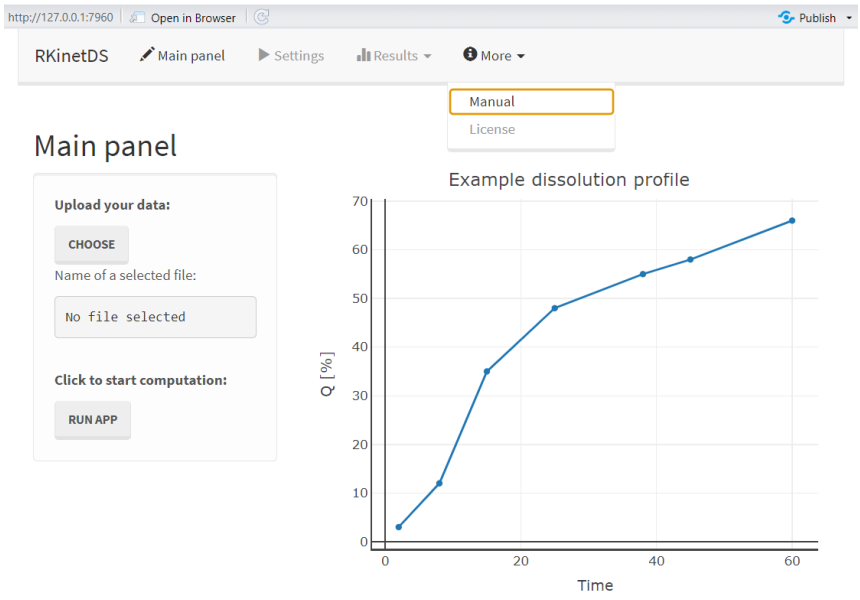

Figure 22 “More” drop-down list

After clicking “Manual” a short version of documentation is displayed.

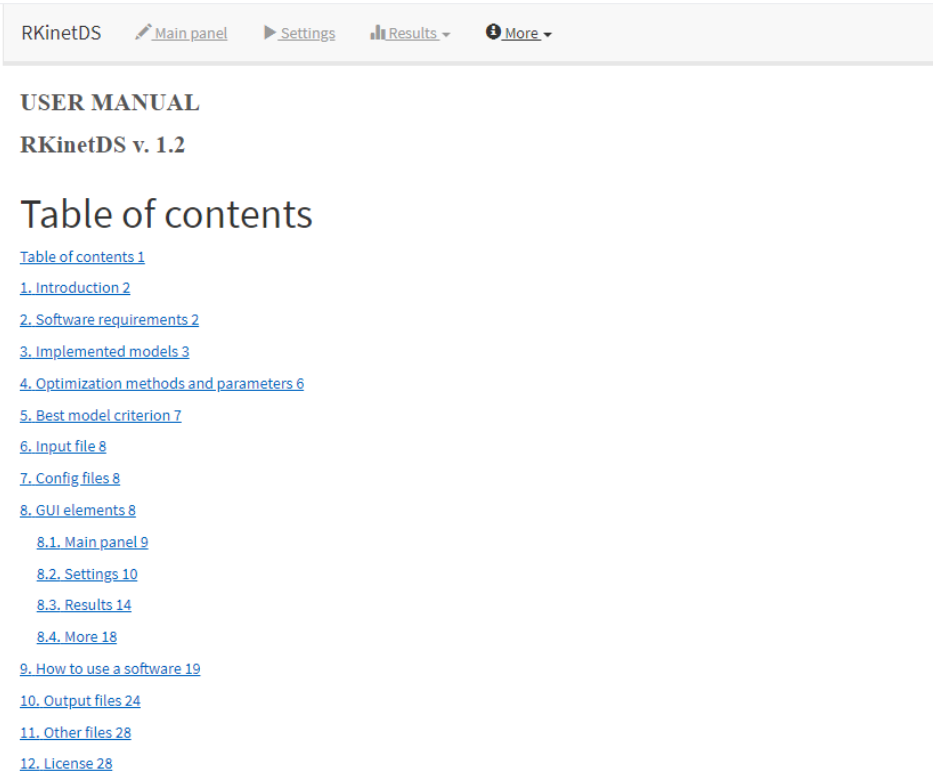

Figure 23 “Manual” window

After clicking “License” a license text is displayed.

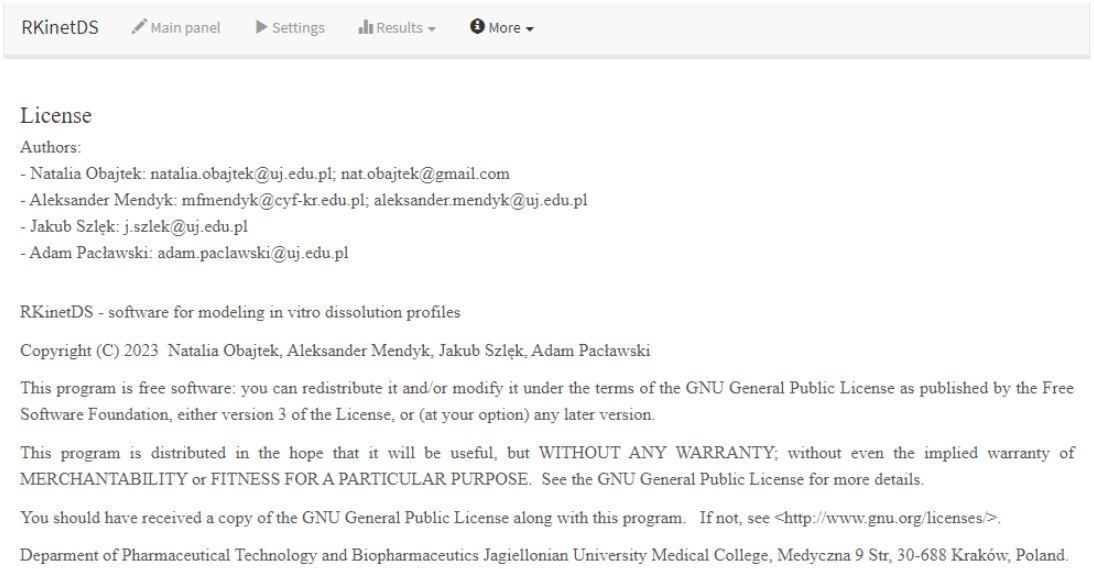

Figure 24 “License” window

9. How to use a software

After opening the application, the “Main panel” displays automatically.

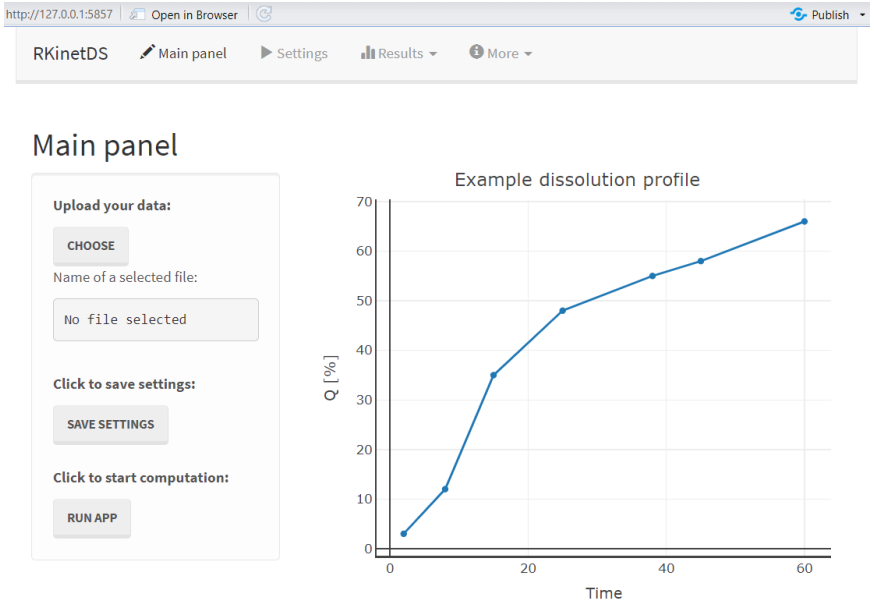

Figure 25 “Main panel” window

The data file can be uploaded to the application by clicking the "CHOOSE" button. It is not possible to upload more than one file at a time. After clicking the button, a new window should appear to browse files.

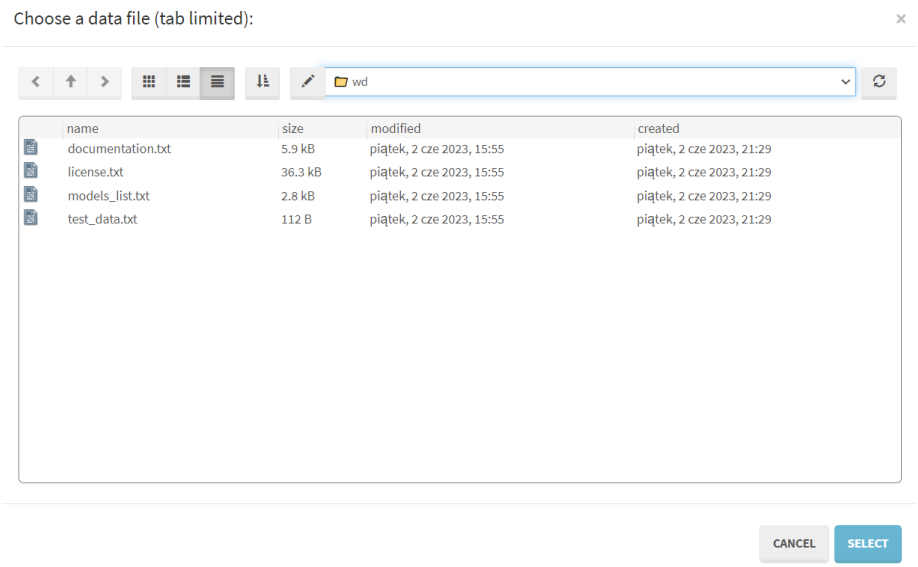

Figure 26 Window that appears after clicking "Choose" button

Select the desired file and click "Select". The windows should close, and you should see the main panel with two main changes: chosen file name in the section “Name of a selected file” and a graph representing the loaded data. Uploading data is a necessary step in order to run the app.

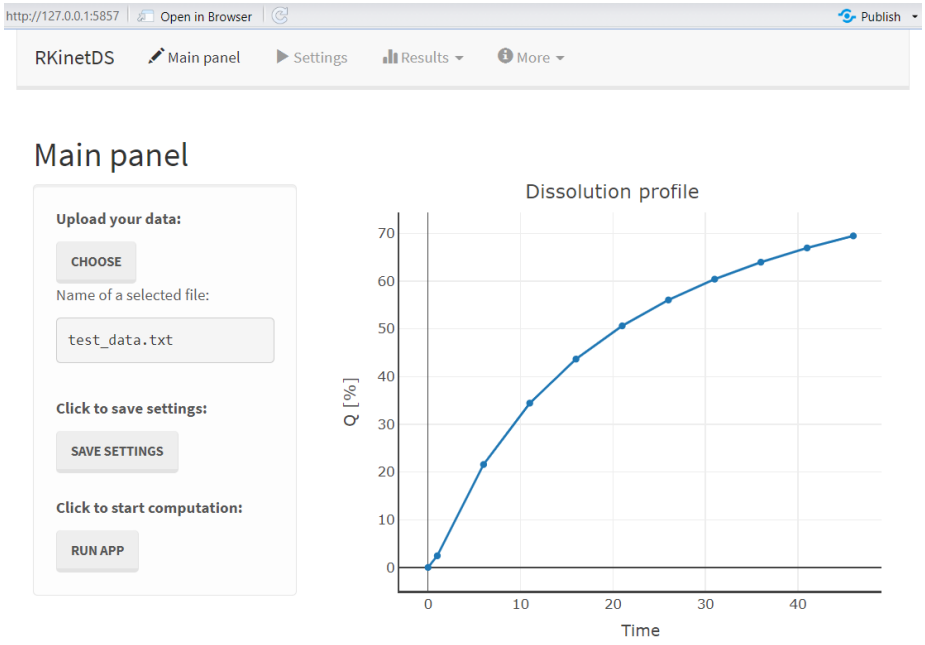

Figure 27 Window that appears after uploading a data file

In the next step, the "Settings" panel should be selected when the user can choose desired models and specify optimization parameters and information about the input file. One or more

models can be used at the same time, as well as one or more optimization methods. Specific value for the maximum iterations and value of stop criterion for optimizing must be provided, otherwise the computation will not complete, and no results will be produced.

If the user's data does not contain headers, it is necessary to select it in the settings. Otherwise, the application will stop working. Default settings include headers.

By default, when opening the application, the factory configuration or the last saved configuration is displayed in the “Settings” panel.

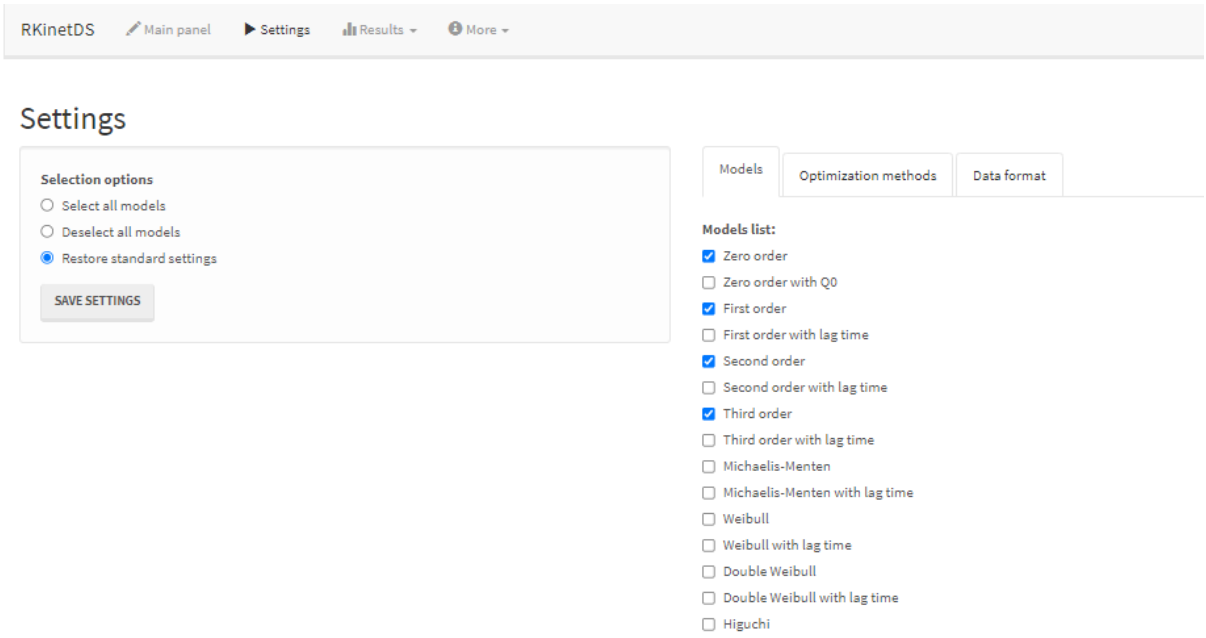

Figure 28 Window that allows user to select desired settings

Clicking button "SAVE SETTINGS" before “RUN APP” is not necessary in order to run app. Settings are automatically captured as the user starts computation by clicking “RUN APP” and they are saved to a config file “user_config.yml”. However, if the user only wants to save data to a user_config file and not run the calculations, the button “SAVE SETTINGS” should be clicked. In this case, when the app is open again, the last saved settings will be displayed. When done correctly, after saving options a message “Settings saved” appears. The user can close this message.

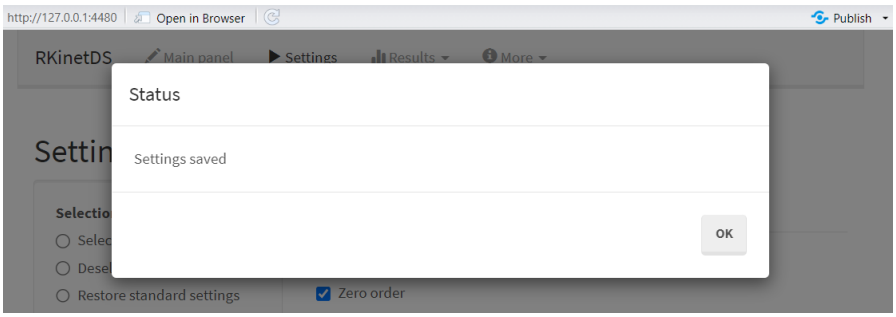

Figure 29 The message shown after saving the settings

After selecting the desired options, the user can go back to “Main panel” and start app by clicking button called “RUN APP”. The message “Wait, model computation in progress” should appear.

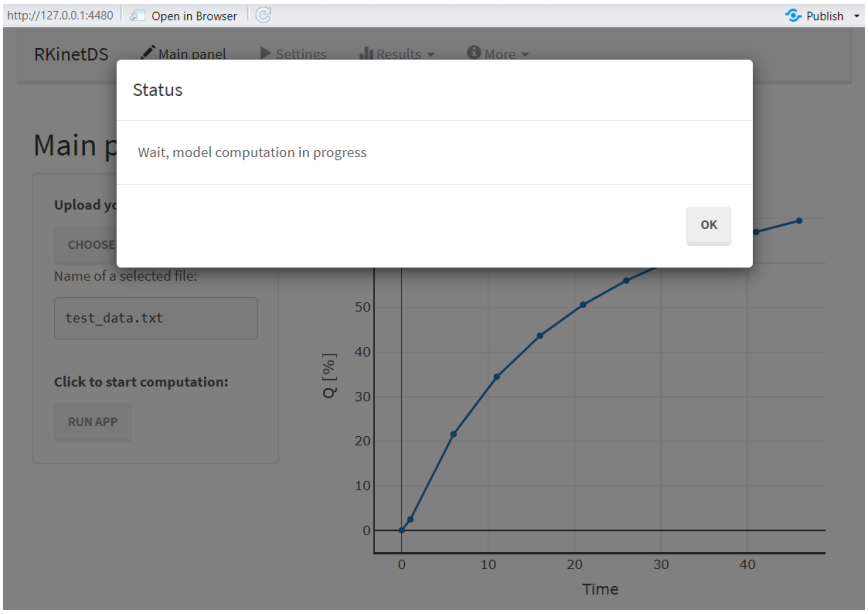

Figure 30 The message shown after running the app

The user can close this message, but it doesn’t mean calculations ended. During calculations the user cannot select any options in the application, and this is a sign that the application is still working. Nevertheless, it is possible to navigate through the tabs without clicking any options. The user also has the calculation progress displayed in the lower right corner of the application, showing how many models have been already calculated.

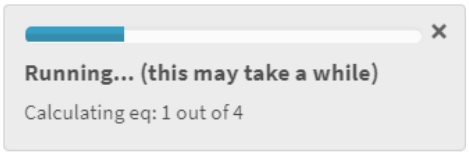

Figure 31 Progress bar

When the calculation is complete, a message “Model computation finished” appears. The user can close this message.

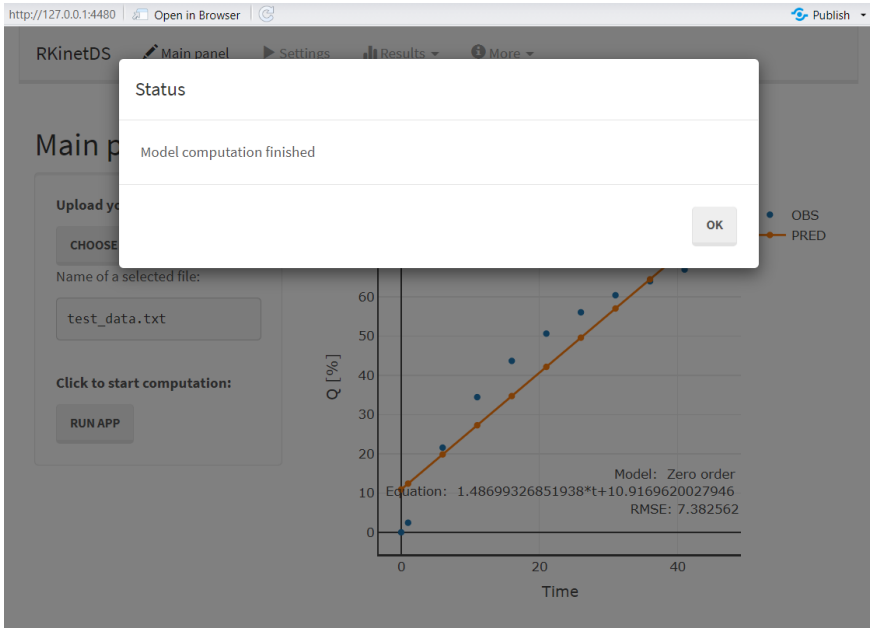

Figure 32 The message shown after the end of calculations

After performing the calculations, the graph, model name, equation and RMSE of the best model is displayed in the “Main panel” on the right side of the app. “PRED” plot shows predicted data and “OBS” plots shows observed data.

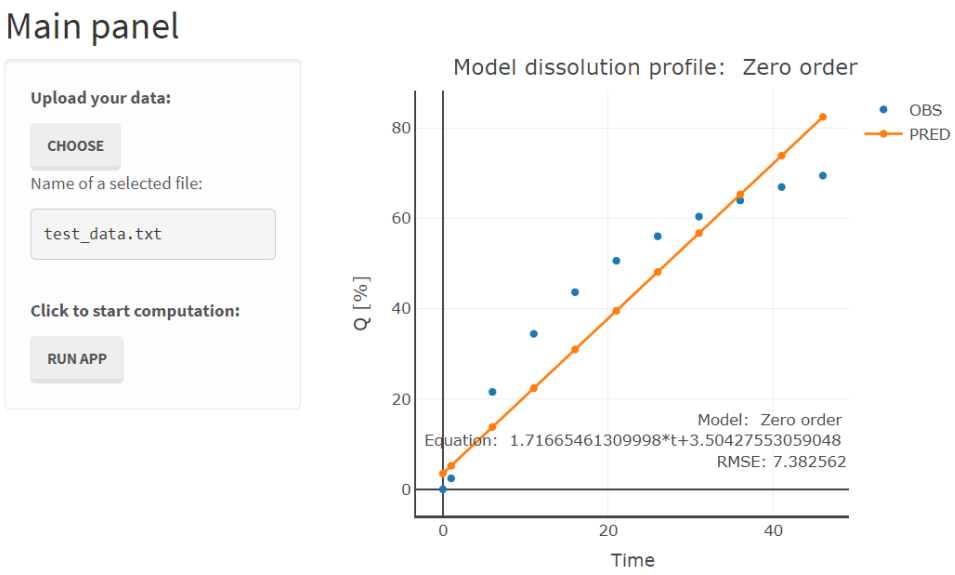

Figure 33 “Main panel” displaying information about the best model

Detailed results for every model can be found in the panel called “Results”. The user can see what settings were used, an overall report for all selected models, detailed results for each model with a graph, and the ranking of the models ranked by the value of the error.

After the calculations are completed and the results are seen by the user, the application can be closed. The computer holds all the results as files. Until the user restarts the application from the same path, the results remain saved. Note that, if the user restarts the apps with the same path, the old files are deleted and replaced with new ones after clicking "RUN APP".

10. Output files

The results are stored in the form of text files. After the calculation is completed, for every used model a separate folder is created called “Results_eq_no” (e.g., 3 selected models mean 3 created folders). Their number (no) corresponds to the model number that can be found in the file called “models_list” (.txt). For example, a folder called “Results_eq_3” stores results for the first order model.

In every folder there are two text files called “optimizedEquation_no” (.txt) and “results_no” (.txt).

Model name: First order with lag time

Model equation: 100*(1-exp(-C[1]*t-C[2]))

Parameters for equation after optimization: 0.02906453 0.03524314

Algebraic form: 100*(1-exp(-0.0290645263309059*t-0.0352431352581918))

RMSE: 3.428443

R2: 0.9793789

R2 adjusted: 0.9742237

AIC: 31.10634

Figure 34 Example "optimizedEquation_no" file results

"Time""Observed" "Predicted"

0 0 3.46293279261763

1	2.44	6.2283544188822
6	21.57	18.9116020154063
11	34.43	29.8793548203243
16	43.66	39.3636450759805
21	50.62	47.5651210987806
26	56.04	54.6572921668741
31	60.4	60.790199258143
36	63.96	66.0935892961171
41	66.94	70.6796600577182
46	69.47	74.6454338137148

Figure 35 Example " results_no" file results

Outside of these folders there also more output files: “overall_report” (.txt) and files with error ranking: RMSE_error_ranking , “R2_error_ranking”, “R2_adjusted_error_ranking”, and “AIC_error_ranking” (.txt).

OVERALL REPORT

Date: Wed Aug 28 12:22:29 2024

USED OPTIMIZATION METHODS

NelderMead: FALSE

SANN: FALSE

nloptr: TRUE

rgenoud: FALSE

genSA: FALSE

USED PARAMETERES

maxit_BFGS: 5000

maxit_NM: 2500

maxit_nloptr: 10000

max_iter_rgenoud: 50

max_iter_gensa: 100

maxit_SANN: 2500

optim_rel_tol: 1e-20

opti_trace: 1

RESULTS

Model name: Zero order

Model equation: C[1]*t

Parameters for equation after optimization: 1.82522478578204

Algebraic form: 1.82522478578204*t

RMSE: 9.7364210418234

R2: 0.833690993416793

R2 adjusted: 0.815212214907547

AIC: 52.0692192137181

Model name: Zero order with Q0

Model equation: C[1]*t+C[2]

Parameters for equation after optimization: 1.4329561842043612.6610950896768

Algebraic form: 1.43295618420436*t+12.6610950896768

RMSE: 7.38256196920104

R2: 0.904383844203255

R2 adjusted: 0.880479805254069

AIC: 47.9806560306938

Model name: First order with lag time

Model equation: 100*(1-exp(-C[1]*t-C[2]))

Parameters for equation after optimization: 0.02906452633090590.0352431352581918

Algebraic form: 100*(1-exp(-0.0290645263309059*t-0.0352431352581918))

RMSE: 3.42844315402374

R2: 0.979378940147845

R2 adjusted: 0.974223675184806

AIC: 31.1063378780258

Model name: Second order with lag time

Model equation: 100*(1-(C[1]/(1+C[1]*C[2]*(t-C[3]))))

Parameters for equation after optimization: 2.423345766322580.0492996015307299-11.6584825100118

Algebraic form: 100*(1-(2.42334576632258/(1+2.42334576632258*0.0492996015307299*(t--11.6584825100118))))

RMSE: 0.544468547407792

R2: 0.999479928960736

R2 adjusted: 0.99925704137248

AIC: -7.37479225391218

INSTALLED PACKAGES AND THEIR VERSIONS

crayon 1.5.2

digest 0.6.31

GenSA1.1.8

ggplot2 3.4.2

nloptr 2.0.3

pkgconfig 2.0.3

pkgload 1.3.2

plotly 4.10.1

rappdirs 0.3.3

RColorBrewer1.1-3

Rcpp 1.0.10

rematch2 2.1.2

rgenoud 5.9-0.3

shiny 1.7.4

shinycssloaders 1.0.0

shinydashboard 0.7.2

shinyFiles 0.9.3

shinyjs 2.1.0

shinythemes 1.2.0

shinyWidgets 0.7.6

Figure 36 Example "overall_report" file results

Number	Equation	R2
7	100*(1-(C[1]/(1+C[1]*C[2]*(t-C[3]))))	0.999479928960736
5	100*(1-exp(-C[1]*t-C[2]))	0.979378940147845
3	C[1]*t+C[2]	0.904383844203255
1	C[1]*t	0.833690993416793

Figure 37 Example "R2_error_ranking" file results

11. Other files

Integral parts of the application are files called “RKinetDS_computational_core” (.R), "Documentation_RKinetDS" (.html) and "license" (.html), which should not be deleted.

RKinetDS_computational_core contains the computational part of the application. It can be used independently of the app by users with appropriate knowledge and skills to run it in an R environment. Documentation file stores information displayed in “Manual” section in the app, and license file stores information displayed in “License” section in the app.

The file named "test_data" (.txt) contains sample data that can be used to test the app. In the file named “models_list” (.txt), the list with models' names and their equation is saved. Every model has assigned its own number that app uses.

12. License

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Version 3, 29 June 2007

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