Outline

1. Introduction

KinetDS is a simple software for curve fitting particularly for description of a cumulative dissolution curve by simple equation. The equations were chosen from the most popular mechanistic and empirical models applied to the drug dissolution curve description. Models parameters are established by linear and non-linear regression (simplex method). The software is Open Source. It was developed in Lazarus environment, therefore source code is available in Object Pascal.

2. How to start?

Simply open the data file (File-Open [Ctrl-O]) or set of files (File-Open loop [Ctrl-L]) and start computations by using menu (Compute-Compute current [Ctrl-G]). The best fit results will be displayed on the Graph tab and the output on the tab Results. The output of the fitting will be saved in the file named *res_orders_{input_file_name}*. If there were several files uploaded, there will be collective report file named after the first data file chosen: *report_{input_file_name}* – you can open it in whatever spreadsheet you'd like to with Tab-delimited filter. And that's all! Enjoy!

3. Main GUI elements

3.1. Menus

File:

- Open file – opens text input data file
- Open loop – opens set of text input data files
- Save – saves current data file to another
- Close – terminates the application

Edit:

- Copy to clipboard – copies current graph to clipboard
- Save as bitmap – saves current graph to a BMP file

Compute:

- Compute current – starts the fitting procedures

Help:

- About – displays “about” window with current version, credits and license

3.2. GUI description

Graph section:

This is the main section of the software, which displays graphically the input data and the fitting output. The best fitted model is presented at first – the rest of the models is presented by pushing the Left/Right buttons on the bottom panel (Fig.1).

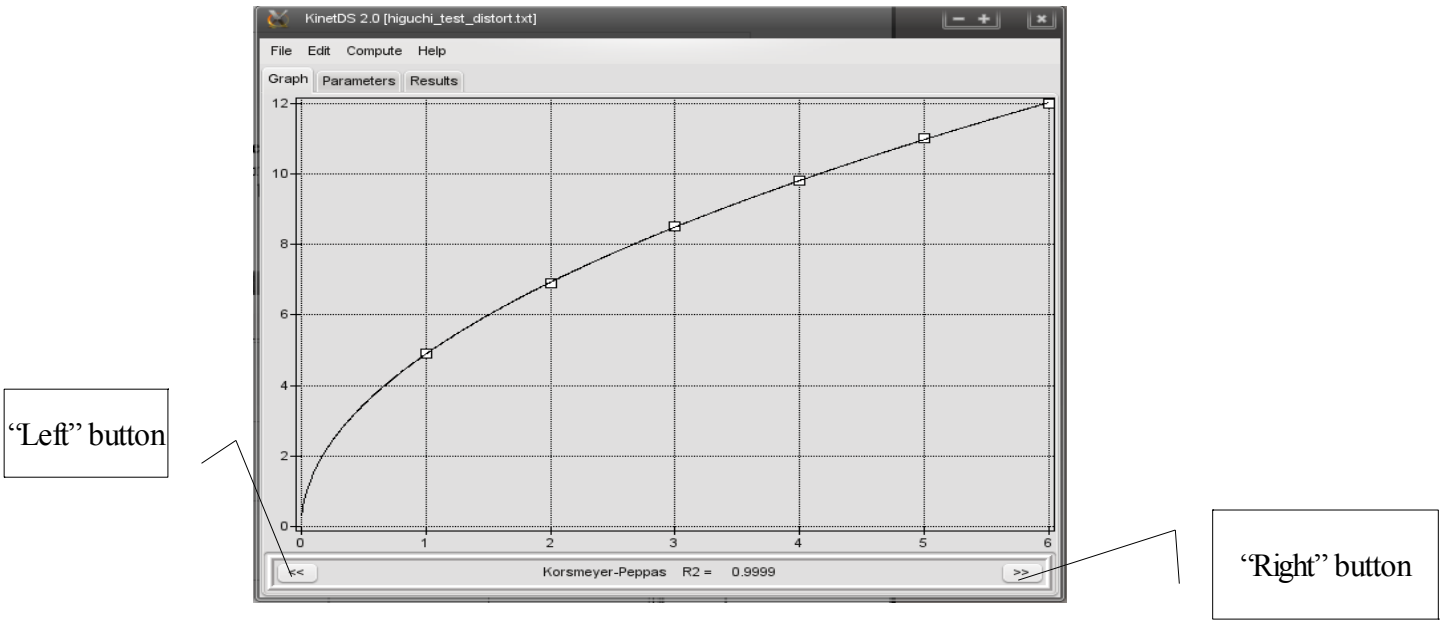

Fig.1. Graph section of KinetDS.

Parameters section

This section describes all the parameters taken under consideration when computations are performed. The default settings are considered as the safest ones.

Models list
This subsection contains the set of models used for empirical search for the best fitting model. You can uncheck any particular model if you did not want it in your computations.

Approximation accuracy
This parameter is used for piecewise work mode – it describes the portion of R^2 value, which is a borderline for a model switch in the next step of data approximation. Its value should be placed between 0 to 1. Generally, the higher is the value of this parameter, the more accurate piecewise regression is with more models employed.

Smooth graph
This tells the program to display graph with more accuracy, which is achieved by computing the function values in between the original data points. Number of these intermediate computations is controlled by corresponding parameter: *Graph accuracy*

Graph accuracy
The number of points between minimum and maximum X axis values taken for smoothing graph when *Smooth graph* is enabled.

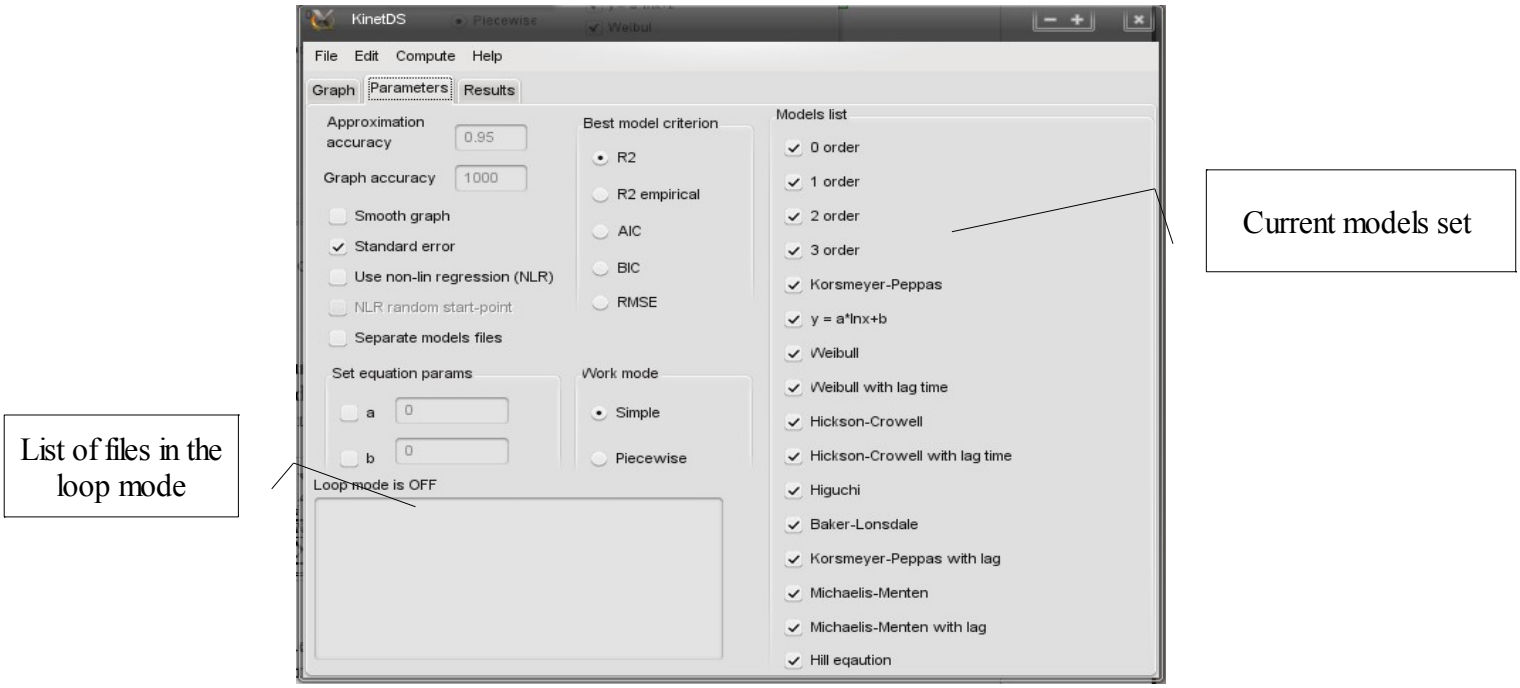

Fig. 2. Parameters section of KinetDS

Best model criterion

R2
Coefficient of determination is expressed as squared Pearson's correlation coefficient

$$R^2 = \frac{\left[N \cdot \sum_{i=1}^{N}(x_i \cdot y_i) - \sum_{i=1}^{N} x_i \cdot \sum_{i=1}^{N} y_i\right]^2}{\left[N \cdot \sum_{i=1}^{N} x_i^2 - \left(\sum_{i=1}^{N} x_i\right)^2\right] \cdot \left[N \cdot \sum_{i=1}^{N} y_i^2 - \left(\sum_{i=1}^{N} y_i\right)^2\right]}$$

where:
y_i – *observed value*
i – data point
N – number of data points

R2 empirical
An empirical coefficient of determination is useful when non-linear model or model with enforced coefficient values is analyzed. By default it is used for Higuchi model (even when R2 is selected as the model ranking measure). It is recommended when *Set equation params* is used.

$$R^2_{emp} = 1 - \frac{\sum_{i=1}^{N} (y_i - \hat{y}_i)^2}{\sum_{i=1}^{N} (y_i - y_{AV})^2}$$

where:
y_i – observed value
$\hat{y}_i$ – model predicted value
y_{AV} – average output value

AIC
Akaike information criterion

$$AIC = 2k + N \cdot \left[\ln \left(\sum_{i=1}^{N} (y_i - \hat{y}_i)^2 \right) \right]$$

BIC
Bayesian information criterion or Schwarz criterion

$$BIC = N \cdot \ln \left(\sum_{i=1}^{N} (y_i - \hat{y}_i)^2 \right) + k \cdot \ln(N)$$

RMSE
Root mean squared error

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

Standard error
Forces KinetDS to compute standard errors of "a" and "b" coefficients from linear regression

Set equation params
Allows to set "a" or "b" parameters values to be set manually if needed.

Use non-lin regression (NLR)
Applies non-linear regression by simplex method. Each model is solved twice: once by linear and second time by non-linear regression. The linear regression coefficients are start-points for simplex method. Adds "NLR results" section to the report file.

NLR random start-point
Adds two iterations with random equations parameters estimates for simplex method. Chooses best solution obtained along with standard NLR procedure and presents it in NLR results section for each equation report

Separate models files

This option allows to get separate files representing each model enumeration over specified independent variable range and with established accuracy. Optionally, the original data range might be in focus with separate accuracy of model enumeration established. A dialog is started, where the user is able to set all the parameters (Fig .3).

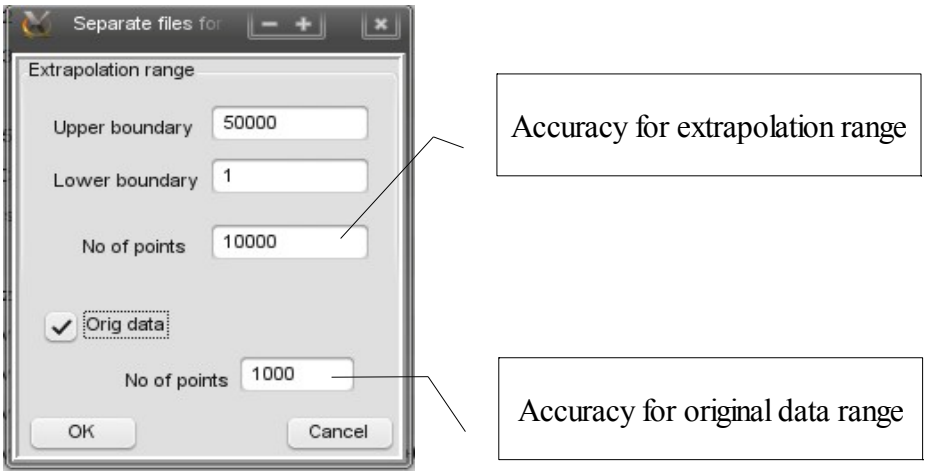

Fig.3. Models enumeration dialog

The resulting files have 2 columns each (X and Y axis) and are named after the original dataset file and the model used for data enumeration.

Work mode

There are two modes of KinetDS work: simple and piecewise. In the simple mode the whole dataset is described by one of the models available from models list. The models are ranked by selected in "*Best model criterion*" parameter value and best fit is displayed as the first graph in the *Graph* area. In the piecewise mode the dataset is processed gradually, point-by-point and the final curve is described as a set of equations. Minimum number of data points to be described by individual equation is 3. The *Approximation accuracy* parameter governs the number of equations assigned to the single curve. This mode is especially useful when the studies are carried out to identify timepoints of dissolution mechanism switch.

Results section

This section displays the results of the computations stored in the *res_orders_{...}* file. You can also open the file manually pushing the button on the bottom panel (Open file...).

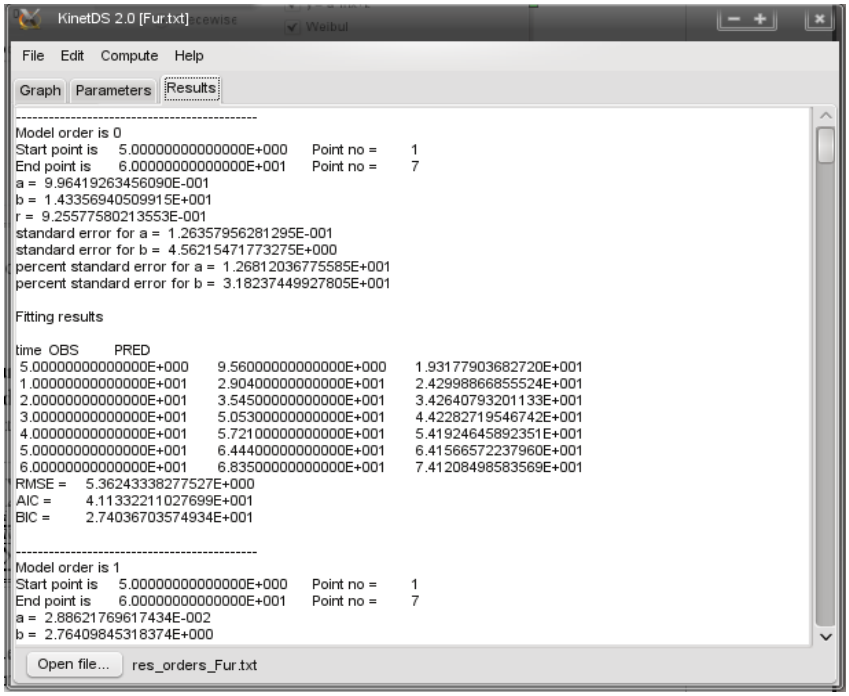

Fig.4. Results section of KinetDS

4. Implemented models

a) kinetic models

- 0 order: $Q = k \cdot t + Q_0$
- 1 order: $Q = Q_0 e^{k \cdot t}$
- 2 order: $\frac{1}{Q} = k \cdot t + \frac{1}{Q_0}$
- 3 order: $\frac{1}{Q^2} = k \cdot t + \frac{1}{Q_0^2}$

where:
Q – amount (%) of drug substance released at the time t
Q_0 – start value of Q
t – time
k – rate constant

b) Higuchi model,

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

c) Korsmeyer-Peppas model,

$$Q = k \cdot t^n$$

where:
n – release exponent

d) Weibull model

$$m = 1 - \exp\left[\frac{-(t)^b}{a}\right]$$

where:

m – amount of drug released *; $Q = 100\% * m$*

a – time constant

b – shape parameter

e) Weibull model with lag time

$$m = 1 - \exp\left[\frac{-\left(t - T_{LAG}\right)^{b}}{a}\right]$$

where:

T_{LAG} – lag time

f) Hixson-Crowell model.

$$Q^{\frac{1}{3}} = k \cdot t + Q_0^{\frac{1}{3}}$$

g) Hixson-Crowell model with lag time

$$Q^{\frac{1}{3}} = k \cdot (t - T_{LAG}) + Q_0^{\frac{1}{3}}$$

h) Baker–Lonsdale model

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

Model-independent parameters

1) DE (dissolution efficiency)

$$DE = \frac{\int_0^t Q\,dt}{Q_{100} \times t} \times 100$$

where:

Q_{100} – maximum amount of drug released (= 100%)

2) MDT (Mean Dissolution Time)

$$MDT = \frac{\sum_{j=1}^{n} t_j^{AV} \times \Delta Q_j}{\sum_{j=1}^{n} \Delta Q_j}$$

where:

$\Delta Q = Q_{(t)} - Q_{(t-1)}$

$t_j^{AV} = (t_i + t_{i-1})/2$

n – amount of timepoints

5. Input and output files formats

The input and output are simple tab-delimited text (TXT) files. A typical input file looks like this:

```
1	0.1
2	1
...
```

The first column is the time-point and the second column is the amount of drug substance released or dissolved. The latter is usually expressed in percentages. It is mandatory that the data is sorted according to the increasing value of the time axis and the amount of drug released is also increasing alongside. This is the major assumption of cumulative dissolution time-curve, which has to be met by the data. It is also impossible to use "0" value. If you want to force your model to respect value "0" use instead something like "0.0001" or even smaller. In the summary: the input data is non-negative, non-zero sorted ascending in both columns. If the input value of time axis (X) is below or equal 0 then system will replace it to 0.00001. If the dissolution amount value (Y) is equal or over 100, then it is transformed into 99.9999999.

The output file comprises of description of all the models selected for fitting in the program run. The description includes models parameters together with linear regression and, if applied, non-linear regression parameters. The data prediction is also included.

```
-----------------------------------------------
Model order is 0
Start point is   5.00000000000000E+000   Point no =      1
End point is    7.40000000000000E+002   Point no =      24
a =  7.68559837945485E-002
b =  5.16025298019910E+001
r =  6.61732275060021E-001
standard error for a =  1.17153554091919E-002
standard error for b =  5.14163478958791E+000
percent standard error for a =  1.52432573636809E+001
percent standard error for b =  9.96392000414972E+000

Fitting results
time            OBS             PRED
 5.00000000000000E+000   1.29232464200000E+001   1.28882587003323E+001
 1.00000000000000E+001   2.31920308500000E+001   2.40012007363899E+001
                ...
 7.30000000000000E+002   9.99200000000000E+001   9.79344624687376E+001
 7.40000000000000E+002   9.99300000000000E+001   9.79879544881798E+001
RMSE =          1.68530062642486E+000

Model independent description
DE =            8.71295807734460E+001
MDT =           9.47894548949265E+001
No of timepoints =              24
-----------------------------------------------
End of file
```

Fig. 5. Typical output file for simple work mode.

In case of piecewise work mode the displayed parameters are the same, however the models included in the output file are the partial models, of which the whole curve is combined. The time axis domains for each models are displayed in the fields "start point" and "end point". It

is noticeable that RMSE value in this case is over 10 times smaller than for the simple work mode - both examples are based on the same dataset.

```
Approximation accuracy =  9.99900000000000E-001
---------------------------------------------
Korsmeyer-Peppas with lag
Model is ln(y) = a*ln(x-lag)+b
Which is equal to  y=K*(x-lag)^A
K =  3.9986209347767852E+0000
A =  7.87370788045575E-001
lag = 5.70000000000000E-001
Start point is   5.00000000000000E+000   Point no =      1
End point is    2.00000000000000E+001   Point no =      4
a =  7.87370788045575E-001
b =  1.38594953536852E+000
r =  9.99476488526092E-001
standard error for a =  1.80200548808809E-002
standard error for b =  4.33771076655962E-002
percent standard error for a =  2.28863645368538E+000
percent standard error for b =  3.12977540369551E+000

-------------------------------------------------
Model order is 0
Start point is   4.00000000000000E+002   Point no =      14
End point is    7.00000000000000E+002   Point no =      20
a =  2.00000000000000E-002
b =  8.40000000000000E+001
r =  1.00000000000000E+000
standard error for a =  0.00000000000000E+000
standard error for b =  0.00000000000000E+000
percent standard error for a =  0.00000000000000E+000
percent standard error for b =  0.00000000000000E+000

Model independent description
DE =            8.71295807734460E+001
MDT =           9.47894548949265E+001

Fitting results

time            OBS             PRED
 5.00000000000000E+000   1.29232464200000E+001    1.29083177292253E+001
 1.00000000000000E+001   2.31920308500000E+001    2.33998069721584E+001
                ...
 7.30000000000000E+002   9.99200000000000E+001    9.99200000000000E+001
 7.40000000000000E+002   9.99300000000000E+001    9.99300000000000E+001
RMSE =          1.44536445490903E-001
No of timepoints =              24
-------------------------------------------------
End of file
```

Fig. 6. The output of the piecewise work mode.

The last type of the output is a collective report produced when loop mode has been employed. The report is produced apart from *res_orders_{...}* files, therefore each data file is always accompanied by its *res_orders_{...}* file no matter if the loop mode was or was not employed. The report file is named after first data file: *report_{name of the first data file}*. The report file was designed to make easier comparisons of models' parameters among predefined set of data. This is especially valid for simple workmode when each model has the same position within the file structure. For piecewise workmode the function of report is only to present the data collectively and is not recommended, however is fully supported. It is advisable to import this file to the spreadsheet and to transform the cells from scientific to the general numbers notification – use tab as the separator and do not merge separators. This

would help in its apprehension. The file is tab-delimited and contains models parameters in columns and datasets in rows (Fig. 7).

File	Model`s order is 0					
res_orders_hicks_crow_lag.txt	a =	10.8617	b =	-25.3406	r =	0.8769
res_orders_higuchi_test.txt	a =	1.4030	b =	3.9715	r =	0.9847
res_orders_higuchi_test_distort.txt	a =	1.4029	b =	3.9400	r =	0.9847
res_orders_testowe_dane3.txt	a =	0.0769	b =	51.6025	r =	0.6617

Fig. 7. Fragment of the *report_{...}* file. Following columns would contain other models parameters.

6. Acknowledgments

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This software is powered by Lazarus RAD environment www.lazarus.freepascal.org

Simplex method based on the code by Dr. Jean Debord from his excellent Pascal library **tpmath**

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7. Citation

If you publish with this software please cite following paper:

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8. Changelog

- added choice of model performance criterion
- added model performance criteria: Akaike, Schwarz, RMSE
- added prediction display for every model in the *res_orders_{...}.txt* report file
- added non-linear regression based on simplex method
- added enumeration of models over specified data range with separate files creation
- added Hill model
- fixed bug with graph in the smooth mode

9. License

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