

Interactive Dose-Response Analysis

(Using Shiny in RStudio)

Yingjia Chen

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This application is developed for conducting dose-response analysis using simple interactive user interface facilitated by Shiny in RStudio. RStudio is a powerful user interface for **R**, which is a free software environment for statistical computing and graphics. R can be downloaded here:

For Windows: <http://cran.r-project.org/bin/windows/base/>

For MAC: <http://cran.r-project.org/bin/macosx/>

To use the application, simply click on the link provided below:

<https://yingjiachen.shinyapps.io/DoseResponseAnalysisApp/>

The user-interface for dose-response analysis is displayed here in Figure 1.

Dose-response Analysis

Data input

Choose File no file selected

Total number of animals

Number of animals responded

Gender

Treatment

Dosage

Choose a model:

Probit model

Constrain the slope?

Yes

Gender subgroup analysis?

Yes

Choose a plot:

Overall

Dose-response Curve

ED50

NULL

Common slope

NULL

Selectivity Index (Relative Potency)

The selectivity is the ratio between effective dosages from different curves

NULL

Model Comparison Statistics

Akaike information criterion (AIC): the smaller, the better.

NULL

Figure 1: Dose-response analysis user interface.

On the left hand side, you will see the **data input** fields that can be tailored to your specific dose-response analysis.



The image shows a web interface titled "Data input". At the top, there is a "Choose File" button and the text "no file selected". Below this are six input fields, each with a label above it: "Total number of animals", "Number of animals responded", "Gender", "Treatment", and "Dosage". Each field is represented by a simple rectangular text box.

Figure 2: Data input fields.

Data input:

The data fields required for dose-response analysis can be inputted flexibly in two ways: upload the data in a comma separated format (csv) file or directly input your data using the user-interface (Figure 2).

1. First, save your data in the .csv format, and then upload it directly into the application (Select "Choose File" or "Browse" and find your saved file, then select "Open"). In your .csv file, the names of the variables have to be exactly specified as following:
treatment: indicating the treatment group to which the animals belong.
dose: indicating the level of dosage the animals received.
sex: sex of animals in the group.
total: number of animals in the group.
response: number of animals that responded to the drug/treatment.

An example of the dataset is displayed here in Figure 3.

	A	B	C	D	E
1	treat	dose	total	response	sex
2	a	10	8	2	0
3	a	11	8	3	1
4	a	12	8	4	1
5	a	13	8	5	0
6	a	14	8	5	0
7	b	10	8	3	1
8	b	11	8	5	0
9	b	12	8	3	1
10	b	13	8	2	0
11	b	14	8	6	1
12					

Figure 3: An example of the .csv file.

2. You can also input the data from the webpage by typing in the values for each of the variables, separated by a comma. For example, suppose you have four groups of animals, with 10 animals per group, then for “Total number of animals”, you just type in “10,10,10,10” in the blank box.

Choose a model:

Probit model

Probit model

2-parameter log-logistic model

Yes

Figure 4: Choose a dose-response model.

Choose a model:

Currently two models are available to choose from: a probit regression model and a two-parameter log-logistic regression model. (Other models may be added; please contact me if there is any other model that you want to fit.)

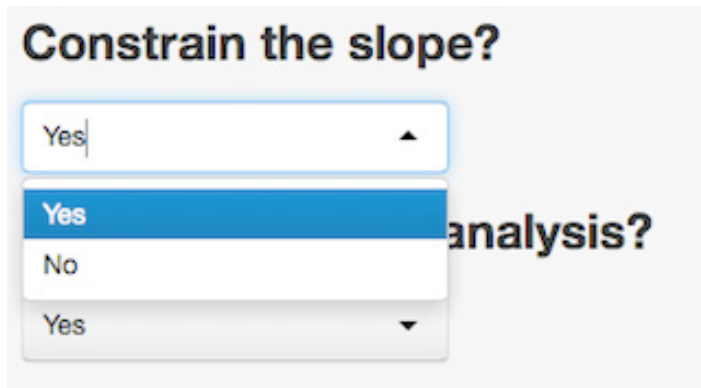


Figure 5: Constraining the slope of the dose-response model.

Constrain the slope:

There is a flexible option to constrain the slope of dose-response model/curve. If you want to constrain the slope of the dose-response curve to be the same across all the comparison groups at the value of ED50, select “yes”.

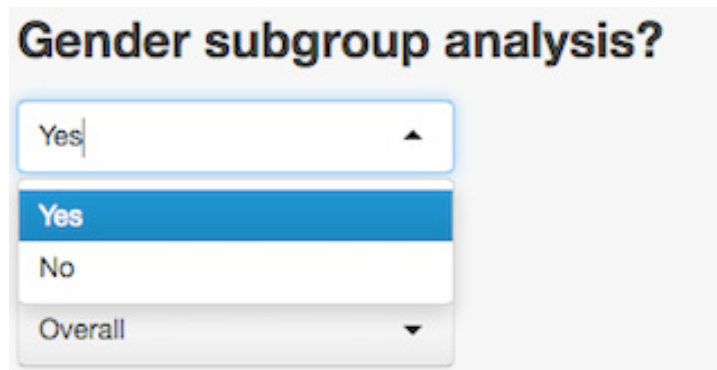


Figure 6: Subgroup analysis option.

Gender subgroup analysis:

This gives you an option to perform a stratified dose-response analysis by gender. Simply choose “No” to perform the overall analysis.



Figure 7: Plot options.

Choose a plot:

The application will generate the dose-response plots for you. You can choose to

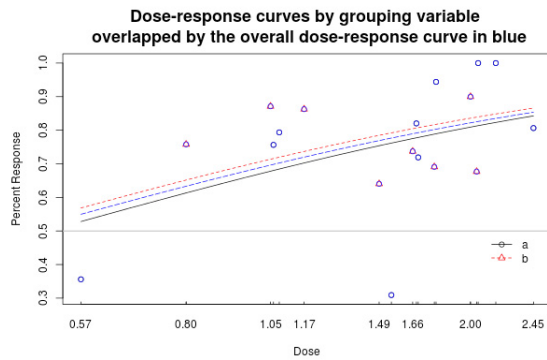
see the overall plot, stratified plots by different groups, or the overlapped plot with both the overall curve and the stratified ones based on your needs.

Once the data is inputted successfully, the dose-response analysis will be performed according to the conditions you pre-specified in the control panel, and the results will be shown automatically on the right hand side. Please note the data used for generating the results shown below were completely arbitrary.

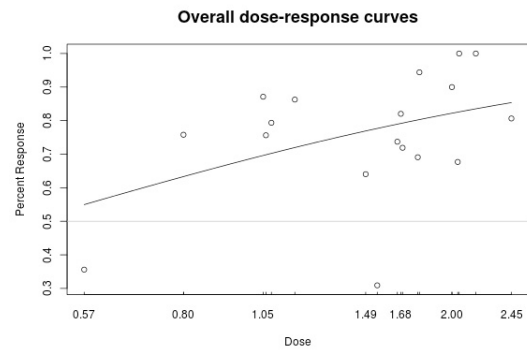
Dose-response Curve: Here, the program displays the dose-response plots.

Example: (with restrained slope)

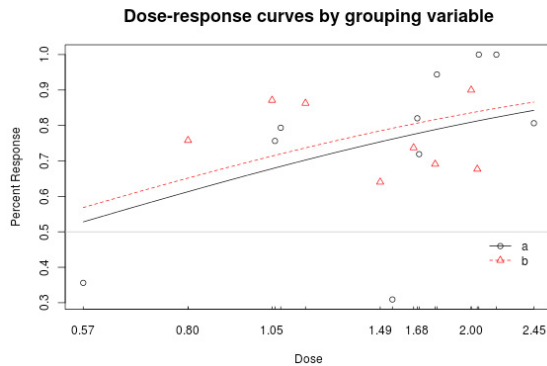
Dose-response Curve



Dose-response Curve



Dose-response Curve



ED50: Here, the program provides the estimated ED50 along with the standard error and the confidence intervals for the estimates.

Example:

ED50

For Male (sex = 0):

Estimated effective doses
(Delta method-based confidence interval(s))

	Estimate	Std. Error	Lower	Upper
a:50	0.576231	0.077400	0.424530	0.7279
b:50	0.966187	0.088798	0.792145	1.1402

For Female (sex = 1):

Estimated effective doses
(Delta method-based confidence interval(s))

	Estimate	Std. Error	Lower	Upper
a:50	2.76743	1.03037	0.74794	4.7869
b:50	115.79249	67.87245	-17.23507	248.8200

Common Slope: Here, the program provides the estimated common slope along with the standard error and the hypothesis testing results, if you choose to restrain the slope in the control panel.

Example:

Common slope

	Estimate	Std. Error	t-value	p-value
Male (sex = 0)	1.2095	0.1606	7.5326	0
Female (sex = 1)	-0.1557	0.0219	-7.1195	0

Selectivity Index (Relative Potency): The selectivity is the ratio between effective dosages from different curves. The statistical method for the selectivity index is the student t test for comparison between two groups, and ANOVA for multiple groups.

Example:

Selectivity Index (Relative Potency)

The selectivity is the ratio between effective dosages from different curves

```
For Male (sex = 0):

Estimated ratios of effect doses

      Estimate Std. Error  t-value p-value
a/b:50/50  0.596398   0.048559 -8.311665    0
For Female (sex = 1):

Estimated ratios of effect doses

      Estimate Std. Error  t-value p-value
a/b:50/50  0.023900   0.014301 -68.254960    0
```

Model Comparison Statistics: The Akaike information criterion (AIC) is used here to perform the model comparison statistically. The smaller the AIC value, the better the model fit.

Example:

Model Comparison Statistics

Akaike information criterion (AIC): the smaller, the better.

```
For Male (sex = 0):

                                     AIC
Probit model                          206.2947
Probit model with common slope        172.4260
Two-parameter Log-logistic model      159.7497
Two-parameter Log-logistic model with common slope 168.1818
For Female (sex = 1):

                                     AIC
Probit model                          153.5950
Probit model with common slope        201.0698
Two-parameter Log-logistic model      153.3706
Two-parameter Log-logistic model with common slope 201.3873
```

Further reference:

Two R packages were used in this application, “drc” and “Shiny”.

- “drc” is an R package for bioassay analysis. The official manual of “drc” can be found at:

<http://cran.r-project.org/web/packages/drc/drc.pdf>.

- “Shiny” is a web application framework for **R**, which turns the dose-response analyses into an interactive web application. It is simple to use, and includes easy and intuitive user inputs. The official website of Shiny can be found at:
<http://shiny.rstudio.com>