

DoseRider: User Guide

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1 Overview of DoseRider and its Purpose

DoseRider is a web-based and R package tool designed to facilitate researchers in analyzing multi-omics dose-response data at the pathway level. The platform provides a robust and flexible framework for modeling both linear and non-linear dose-response relationships using generalized linear mixed models (GLMM) with cubic splines. The goal is to capture complex biological responses to various doses of compounds or chemicals, allowing users to compute critical metrics like Trend Change Doses (TCD) and Benchmark Doses (BMD) for entire pathways.

In toxicogenomics, dose-response modeling typically focuses on individual genes; however, **DoseRider** extends this analysis to the pathway level, providing a more holistic and mechanistic understanding of how specific gene sets respond to different concentrations of exposure compounds. By integrating custom and pre-annotated gene sets, **DoseRider** uncovers essential molecular patterns, enabling researchers to make informed decisions in the context of toxicological risk assessment and regulatory guidelines.

The purpose of **DoseRider** is to offer researchers an intuitive and comprehensive platform that streamlines the analysis of dose-response data across various omics layers, such as transcriptomics, proteomics, and metabolomics. With automated model selection, pathway-specific BMD calculations, and advanced visualizations, the tool enhances the depth and accuracy of dose-response studies, thereby improving the evaluation of chemical safety.

DoseRider supports data for a variety of species, including *Homo sapiens*, *Mus musculus*, *Rattus norvegicus*, *Danio rerio*, *Drosophila melanogaster*, and *Caenorhabditis elegans*. The web application can be accessed at <http://doserider.icbi.at>, while the R package is available at <https://github.com/icbi-lab/doserider>.

2 DoseRider's Workflow

2.1 Workflow overview

DoseRider workflow consists of four key stages, as shown in Figure 1:

1. **Data Preprocessing:** The user uploads dose-response datasets, including raw counts from RNA-seq experiments or intensity values from microarray or metabolite experiments. Dose information and metadata, such as doses administered and sample identifiers, must also be provided. The data is then log-transformed if required for wide dose ranges.
2. **Pathway Modeling:** DoseRider utilizes generalized linear mixed models (GLMMs) to model the dose-response relationships for entire pathways. Each pathway is evaluated using various models, including null models, linear models, and non-linear models with cubic splines. The tool applies random effects at the gene level to account for inter-gene variability.
3. **Model Selection and Validation:** For each pathway, **DoseRider** selects the best-fitting model based on Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC), and significance testing (p -value ≤ 0.05). The selected models are used to predict dose-response curves and identify key metrics, including TCD and BMD.
4. **Visualization and Reporting:** The results are compiled into pathway results tables, and users can visualize dose-response relationships through heatmaps, dose-response curves, and random effects plots. All results can be downloaded in various formats for further analysis.

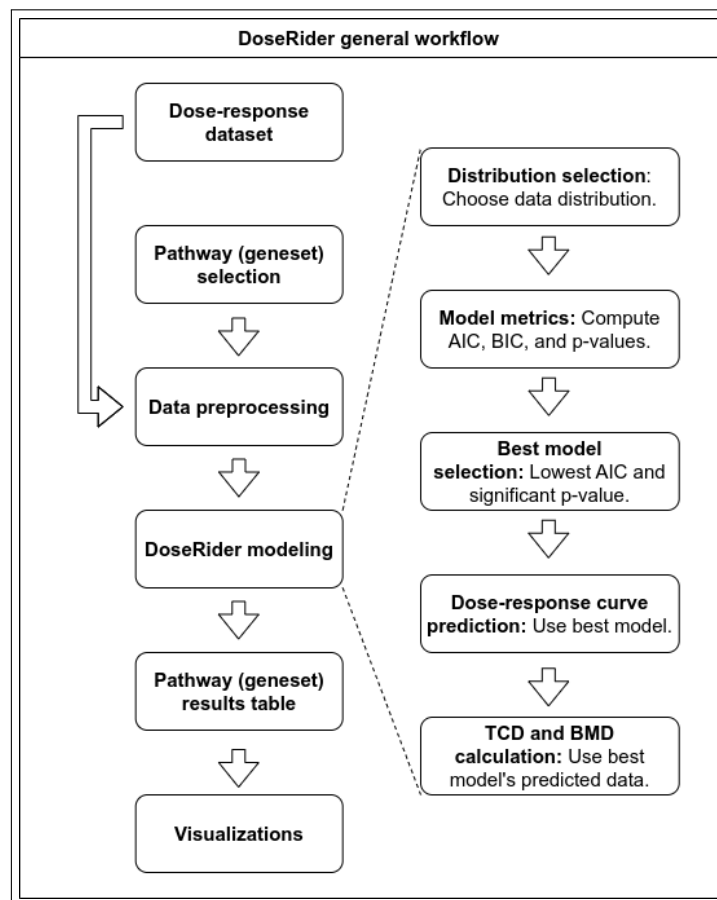


Figure 1: **DoseRider** workflow.

2.2 Data Preprocessing

Data preprocessing is a crucial initial step in the DoseRider workflow, as it ensures that the input data is formatted correctly and is ready for dose-response analysis. DoseRider accepts a variety of multi-omics data types, such as RNA-seq, microarray, proteomics, and metabolomics data, which must be processed and normalized prior to model fitting. The preprocessing phase involves the following steps:

2.2.1 Input Data Requirements

DoseRider expects two primary input files:

- **Expression Data:** This file contains raw or normalized counts for gene expression (in the case of RNA-seq) or intensity values (for microarray, proteomics, or metabolomics experiments). Each row corresponds to a gene or feature, and each column represents a sample or replicate. The data must be in tabular format, typically as a CSV or TSV file.
- **Metadata:** This file includes information about the experimental conditions, such as dose levels, sample identifiers, and additional experimental metadata (e.g., exposure time). The metadata is linked to the expression data through sample identifiers, ensuring that each sample has corresponding dose information.

If survival data is included, DoseRider can also calculate half-maximal inhibitory concentration (IC50) values. This requires additional columns in the metadata file specifying survival rates or other phenotypic measures.

2.2.2 Log Transformation and Normalization

In dose-response experiments, doses are often distributed across several orders of magnitude. For such datasets, DoseRider recommends applying log transformation to the dose values to stabilize variance and improve the interpretability of the model. The user can choose to log-transform doses directly within the web interface.

For expression data that spans a wide range of intensities (e.g., microarray or metabolomics data), DoseRider provides an option to log-transform intensity values as well. This is particularly important when the data contains extreme values, as it helps mitigate the influence of outliers and ensures a more robust model fit.

2.2.3 Gene Set and Feature Filtering

DoseRider includes a gene set filtering step to ensure that only relevant features are included in the dose-response modeling process. This step can be customized to the user's needs:

- **Minimum and Maximum Gene Set Size:** Users can set thresholds for the minimum and maximum size of gene sets to be included in the analysis. By default, gene sets with 20 to 200 genes are considered, though this can be adjusted based on the complexity of the dataset.

Here's the revised version of the **Target Selection**, **Primer Design**, **Specificity Checks**, and **Primer Filtering** sections, adapted for the **DoseRider** context:

2.3 Pathway Selection

DoseRider employs a robust algorithm to determine the most responsive pathways for dose-response analysis. For each gene set, the tool curates a collection of pathways based on the user-specified dataset and the available annotations in the Molecular Signatures Database (MSigDB), Immune-Related Gene Signatures (MIO), or any custom GMT file uploaded by the user. The pathways are initially selected based on size, with the default range set between 20 and 200 genes. This ensures that gene sets are sufficiently representative while minimizing computational load.

The tool further refines pathway selection using Principal Component Analysis (PCA). Pathways where the first principal component (PC1) explains over 70% of the variance are prioritized. Additionally, pathways with an antagonist score below a specified threshold are excluded from analysis, as these exhibit significant opposing gene expression patterns.

Here is a refined version of the **Modeling Dose-Response Relationships** section, rewritten to align with the content and technical details found in the provided **DoseRider** documents:

2.4 Modeling Dose-Response Relationships

DoseRider employs a sophisticated framework of generalized linear mixed models (GLMMs) to capture dose-response relationships at the pathway level. This approach allows researchers to explore both linear and non-linear dose-response behaviors across various omics datasets, such as transcriptomics, proteomics, and metabolomics, while accommodating the inherent variability between individual genes within a pathway.

The modeling process in **DoseRider** involves several stages:

2.4.1 Model Selection

For each gene set or pathway, **DoseRider** evaluates several models to describe the relationship between dose and gene expression. These models include:

- **Null Model:** Assumes no relationship between dose and gene expression, serving as a baseline.
- **Linear Model:** Assumes a direct, linear relationship between dose and gene expression, with dose as the fixed effect.
- **Non-Linear Fixed Model:** Utilizes cubic splines to model dose-response relationships, allowing for non-linear trends. This model is essential when the biological response is not simply proportional to the dose.
- **Non-Linear Mixed Model:** Extends the non-linear model by incorporating random effects, specifically accounting for variability across genes within the same pathway. Random effects in this model allow for gene-specific dose-response curves, enhancing the model's flexibility and accuracy.

DoseRider dynamically selects the best model for each pathway based on the lowest corrected Akaike Information Criterion (AIC) and statistical significance (p-value <0.05) when compared to the null model. The use of AIC ensures a balance between model complexity and goodness-of-fit, avoiding overfitting while capturing critical dose-response patterns.

2.4.2 Smoothing Dose-Response Curves

Once the best model is selected, **DoseRider** generates smoothed dose-response curves using the Best Linear Unbiased Predictor (BLUP). These smoothed curves provide a more intuitive representation of gene expression changes across varying doses, helping to visualize complex non-linear relationships that are typical in toxicogenomics.

2.4.3 Benchmark Dose (BMD) Calculation

A critical feature of **DoseRider** is the calculation of the **Benchmark Dose (BMD)** for each pathway, a key metric used in toxicological risk assessment. The BMD represents the dose at which a significant change in gene expression occurs, relative to a control dose. **DoseRider** computes BMD values based on the smoothed dose-response curves using the BMD-zSD approach. This method estimates the dose where gene expression deviates by a defined number of standard deviations from the baseline expression level, offering a robust and reliable measure for setting regulatory thresholds.

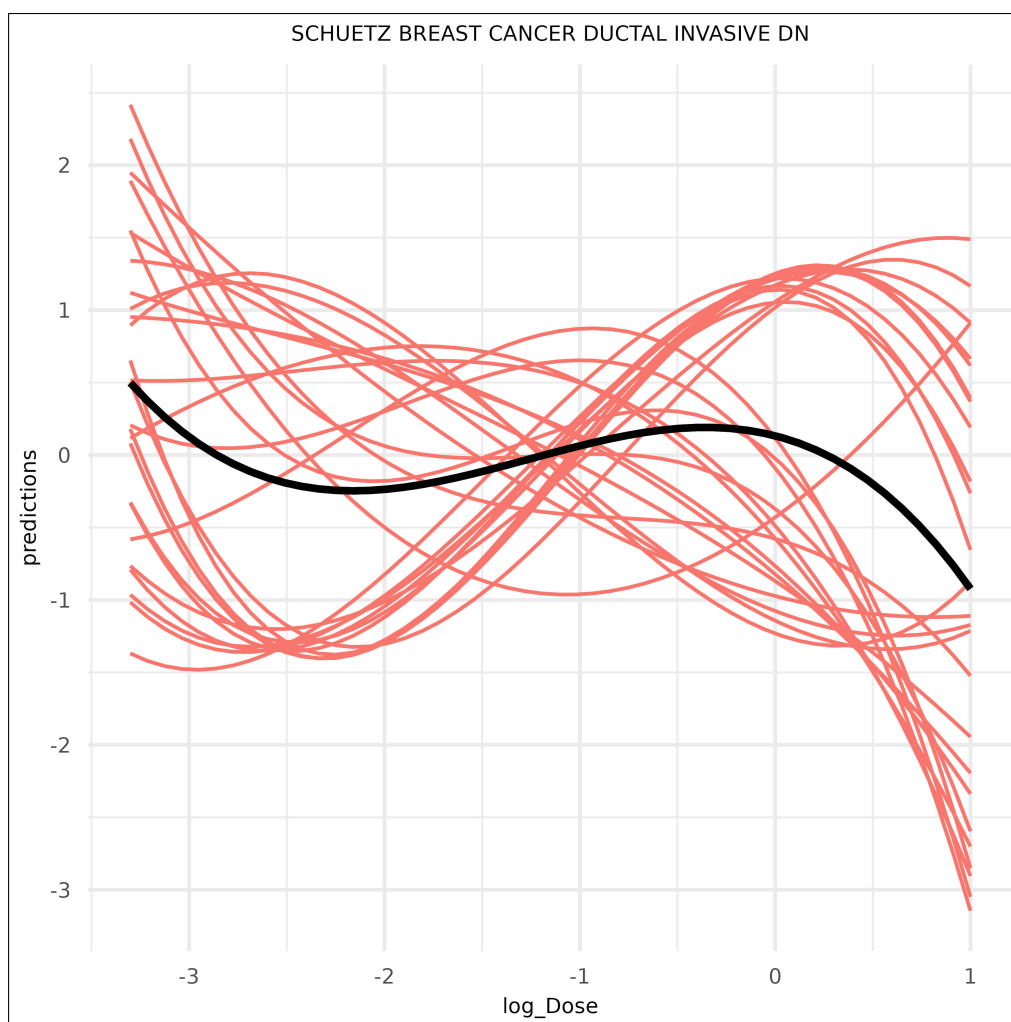


Figure 2: **Dose-Response Modeling in DoseRider.** Non-linear dose-response models using cubic splines with gene-specific random effects allow for accurate representation of gene expression changes across dose levels.

For pathways with biphasic dose-response behaviors, where gene expression increases at low doses and decreases at higher doses (or vice versa), **DoseRider** calculates the BMD at the lowest dose where the benchmark response is observed. This allows for the identification of early responses to toxicants, which are critical for assessing low-dose exposures.

2.4.4 Random Effects and Variability Modeling

To account for the natural variability in gene responses within a pathway, **DoseRider** incorporates gene-specific random effects into the model. This allows for greater flexibility and accuracy in modeling pathways with heterogeneous gene expression patterns. Random effects are particularly useful in toxicogenomics, where different genes within a pathway may respond to doses at different rates or intensities.

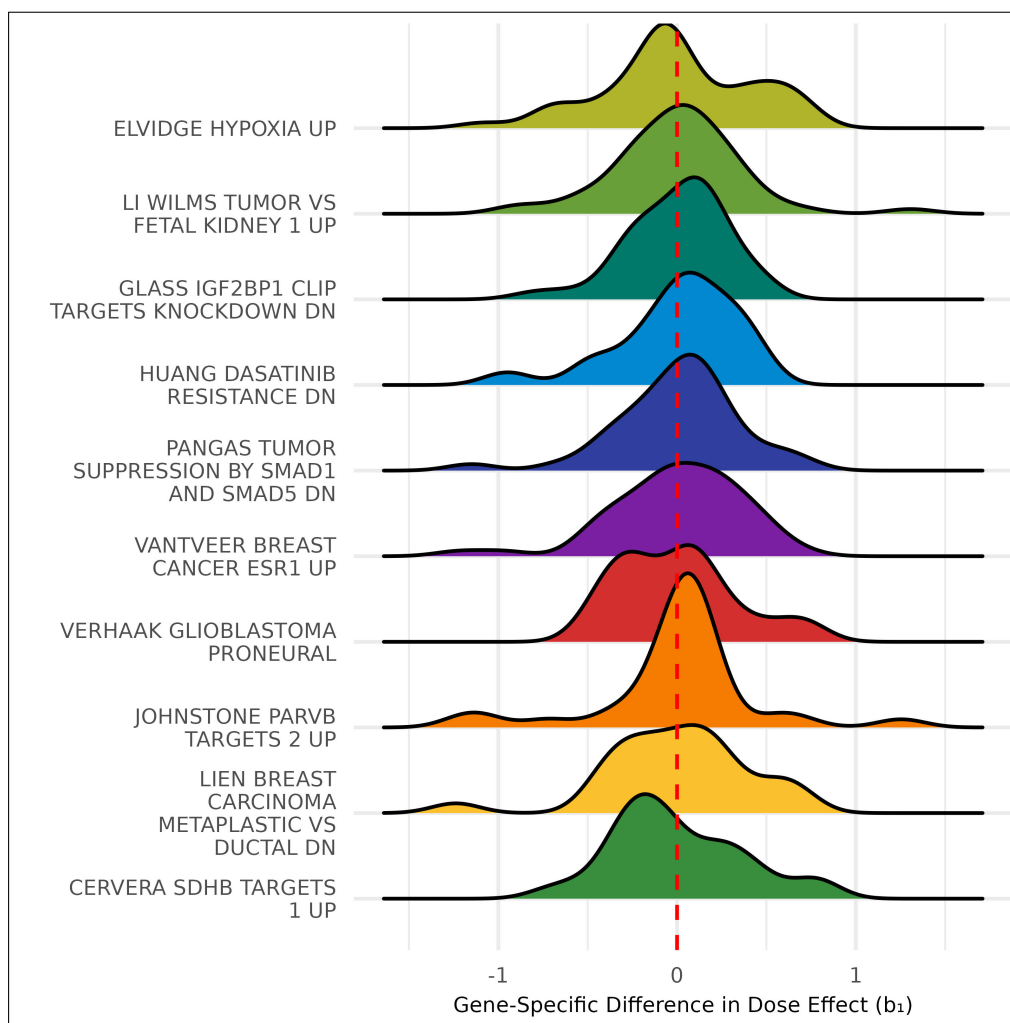


Figure 3: **Random Effect Distribution.** The distribution of gene random effects for each pathway can be visualized to assess dose-response, with wider distributions indicating greater variability in gene responses, and narrower distributions indicating more consistent gene trends within the pathways.

The distribution of random effects is visualized to help researchers assess the variability within each pathway (Fig. 3). Wider distributions indicate greater variability, while narrower distributions suggest more consistent gene responses across doses. This feature helps to identify pathways where a subset of genes shows distinct responses to chemical exposure, providing deeper insights into the biological processes affected by the dose.

2.4.5 Model Validation

After the models are fitted, **DoseRider** compares each model's performance to the null model using statistical metrics, including AICc and p-values. Only models that demonstrate both a significantly lower AICc and a meaningful p-value are retained for further analysis. This rigorous validation ensures that the dose-response relationships detected are both statistically significant and biologically meaningful.

To further enhance the accuracy of the BMD calculations, **DoseRider** employs bootstrapping methods, generating confidence intervals for BMD values by re-fitting the model to sub-sampled data. This process allows for robust estimation of both the upper and lower bounds of BMD values, offering researchers greater confidence in their results.

3 User Interface

The **DoseRider** interface is designed to be user-friendly and intuitive, guiding users through the entire process of setting up, analyzing, and visualizing dose-response relationships for multi-omics data. Below are the key sections and features of the interface, along with their functions.

3.1 Main Dashboard

The main dashboard is the starting point for users to access different features of **DoseRider**. It includes options to:

- **Explore pre-analyzed datasets**
- **Upload your own dataset**
- **View ongoing analyses**

3.1.1 Navigation Bar

The navigation bar provides quick access to various pages within **DoseRider**:


- **Home:** Returns the user to the dashboard.
- **Manual:** Links to the user manual, where detailed instructions can be found.
- **FAQ:** Access to frequently asked questions.
- **Datasets:** Directs users to the pre-analyzed datasets section.

3.2 Upload Your Own Data

The *Upload Your Own Data* page enables users to input their own experimental data for dose-response analysis. This page includes fields for:

- **Chemical name, time point, and omics type**
- **Annotation and metadata files** (required for analysis)
- **Dose/Concentration values** and units

Once the required fields are filled, the user can submit their dataset for analysis.

DoseRider

Home

ManualFAQDatasets

Explore and analyze dose-response data

Upload your data to analyze dose-response relationships across features like proteins, genes, and metabolites. DoseRider applies GLMMs and cubic splines to detect both linear and nonlinear trends at the pathway level. Fill out the form below to start your analysis.

Check the required format for analysis in the [FAQ section](#) or [download](#) our test dataset.

DoseRider requires two files: an expression dataset (genes, proteins, metabolites, etc.) and a metadata file with sample information, including a "dose" column for dose-response modeling, supporting formats like CSV and Excel.

Chemical name*

Time point

Omics type*

Annotation*

Expression data file*

Browse

Metadata file*

Browse

Species*

Dose/Concentration column*

Dose/Concentration units


Submit

Figure 4: Upload your own data: Submit datasets, metadata files, and relevant dose information for analysis.

3.3 Explore Pre-Analyzed Multi-Omics Datasets

Alternatively, the user can use the already pre-analyzed datasets. The *Explore Pre-Analyzed Multi-Omics Datasets* page provides access to pre-analyzed dose-response data for various omics types, species, and time points. Features include:

- Search and filter options to explore datasets by species, omics type, and dose range.
- Option to run new analyses or view results for previously analyzed datasets.

 **DoseRider** Home

Manual FAQ Datasets

Explore pre-analyzed multi-omics datasets

Explore and visualize dose-response relationships using DoseRider with pre-analyzed public datasets. DoseRider leverages Generalized Linear Mixed Models (GLMMs) to examine pathway responses, offering insights into significant pathways and variability across features such as proteins, genes, and metabolites.

Click "View Results" to visualize the outcomes from existing studies, or click "Run Analysis" to perform your own analysis using custom parameters.

For more information on the analysis, visit the [FAQ section](#).

Dose	Time Point	Species	Omic Type	Annotation	Results	New Analysis
1e-04, 1.00e-03, 1.00e-02, 1.00e-01, 5.00e-01, 1.00e+00, 5.00e+00, 1.00e+01 μ M		Homo sapiens	RNA-seq	symbols	View Results	Run Analysis
1e-04, 1.00e-03, 1.00e-02, 1.00e-01, 5.00e-01, 1.00e+00, 5.00e+00, 1.00e+01, 1.00e+02 μ M		Homo sapiens	RNA-seq	symbols	Not analyzed	Run Analysis
1e-04, 1.00e-03, 1.00e-02, 1.00e-01, 5.00e-01, 1.00e+00, 5.00e+00, 1.00e+01 μ M		Homo sapiens	RNA-seq	symbols	Not analyzed	Run Analysis
1e-04, 1.00e-03, 1.00e-02, 1.00e-01, 5.00e-01, 1.00e+00, 5.00e+00, 1.00e+01 μ M		Homo sapiens	RNA-seq	symbols	Not analyzed	Run Analysis
0.500e-04, 1.00e-01, 5.00e-01, 1.00e+00, 5.00e+00, 1.00e+01 μ M		Homo sapiens	RNA-seq	symbols	Not analyzed	Run Analysis
1e-04, 1.00e-03, 1.00e-02, 1.00e-01, 5.00e-01, 1.00e+00, 5.00e+00, 1.00e+01 μ M		Homo sapiens	RNA-seq	symbols	Not analyzed	Run Analysis
1e-04, 1.00e-03, 1.00e-02, 1.00e-01, 5.00e-01, 1.00e+00, 5.00e+00 μ M		Homo sapiens	RNA-seq	symbols	Not analyzed	Run Analysis
1e-04, 1.00e-03, 1.00e-02, 1.00e-01, 5.00e-01, 1.00e+00, 5.00e+00, 1.00e+01 μ M		Homo sapiens	RNA-seq	symbols	Not analyzed	Run Analysis
1e-04, 1.00e-03, 1.00e-02, 1.00e-01, 5.00e-01, 1.00e+00, 5.00e+00, 1.00e+01, 1.00e+02 μ M		Homo sapiens	RNA-seq	symbols	Not analyzed	Run Analysis
1e-04, 1.00e-03, 1.00e-02, 1.00e-01, 5.00e-01, 1.00e+00, 5.00e+00, 1.00e+01 μ M		Homo sapiens	RNA-seq	symbols	Not analyzed	Run Analysis

[Previous](#) [Next](#)

Figure 5: Pre-analyzed datasets page: Explore and visualize datasets based on various species, omics types, and experimental conditions.

3.4 Configure Your Dose-Response Analysis

The *Configure Your Dose-Response Analysis* page allows users to customize their analysis by adjusting feature sets, size filters, and transformation options. This section includes:

- **Dataset summary:** Information about the uploaded dataset, including gene set database and size filters.
- **Feature sets fields:** Allow to choose the database set, such as, MSigDB, Mlo, ConsensuPathDB, etc. And the set size.
- **Data Preprocessing:** Options to log-transform dose/concentration and intensity values, and apply feature filtering.
- **Model Fitting:** Select between *Linear*, *Non-linear (Fixed)*, or *Non-linear (Mixed)* models.
- **Viability Analysis:** Enable or disable viability analysis.

The screenshot shows a web interface for configuring a dose-response analysis. At the top is a blue navigation bar with the 'DoseRider' logo, a 'Home' link, and links for 'Manual', 'FAQ', and 'Datasets'. The main heading is 'Configure your dose-response analysis', followed by a brief instruction: 'Adjust the settings below to custom your analysis of dose-response analysis. Set parameters like feature sets, size filters, and transformation options to refine your results. Once configured, click "Submit" to begin.' The form is divided into four sections, each with a light blue header: 1. 'Dataset summary' (empty). 2. 'Feature sets field' containing: a 'Custom gmt file' checkbox; a 'Feature set database' dropdown menu; 'Minimum set size' and 'Maximum set size' input fields (with values 20 and 200 respectively); and an 'Avoid feature sets (proteins, genes, metabolites) with antagonistic effects by applying the First Principal Component (PC1)' checkbox. 3. 'Data preprocessing' containing: two checkboxes for 'Log-transform dose/concentration values' and 'Log-transform intensity values'; and a 'Models fitting' section with radio buttons for 'Linear', 'Non-linear (Fixed)', and 'Non-linear (Mixed)'. 4. 'Viability analysis' containing a 'Viability analysis' checkbox. A red 'Submit' button is at the bottom of the form. Below the form, footer text reads: '© Monfort-Lanzas, P. Biochemical Immunotoxicology Group, Medical University of Innsbruck 2024' and links for 'Privacy', 'Imprint', and 'References'.

Figure 6: Configure your dose-response analysis: Users can adjust feature set sizes, data preprocessing options, and model fitting parameters.

3.5 Job Status Information

Once a job has been submitted for analysis, users can view the progress on the *Job Status Information* page. This page shows:

- Session URL for checking results later
- Job ID, status, description, and time elapsed

Job Status Information

Session Information

Session URL [Copy URL](#) to check results later

Job Information

ID	4
Status	queued
Description	
Time (s)	

Refresh Page

Cancel

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Figure 7: Job status information: Displays the current status of an analysis job, including job ID, elapsed time, and session link.

3.6 Geneset Dose-Response Model Results

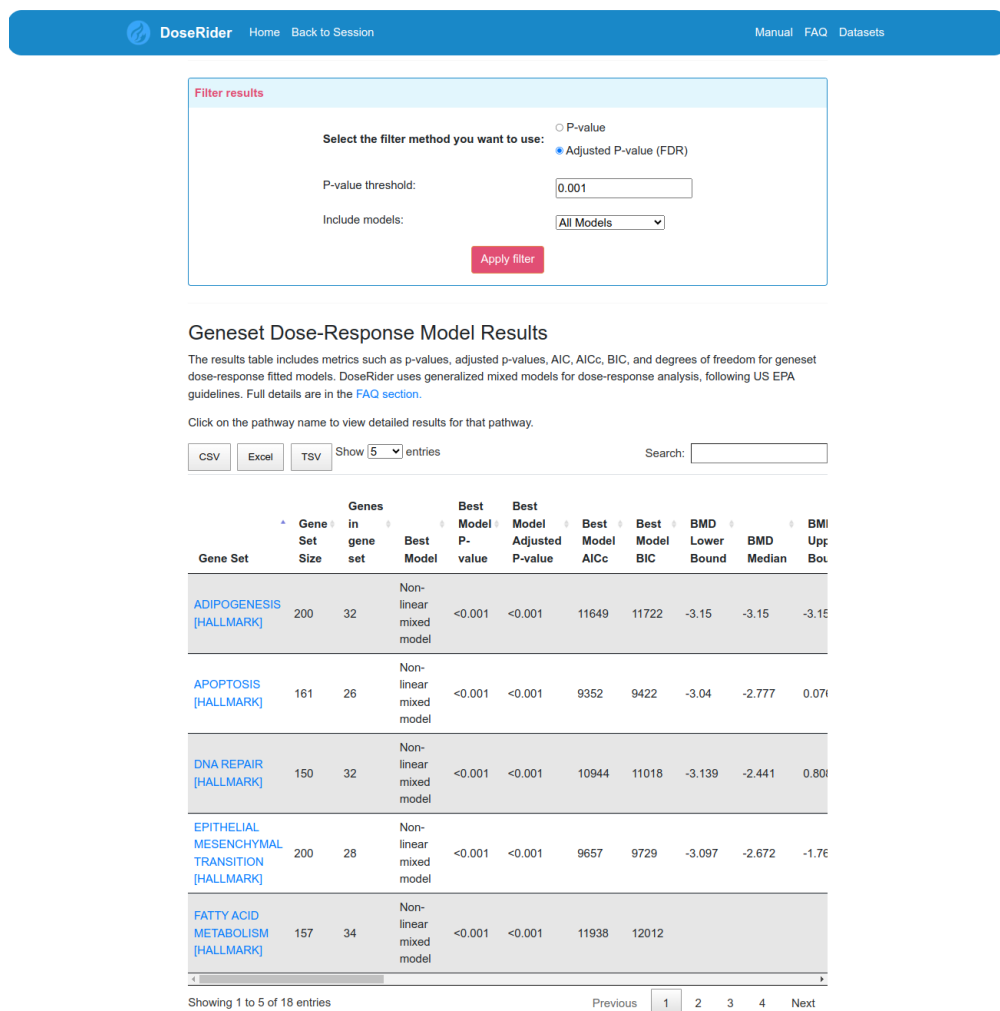
The *Geneset Dose-Response Model Results* page presents detailed results of the dose-response models applied to the selected gene sets or pathways. This section allows users to evaluate the fit and performance of the different models (e.g., linear, non-linear fixed, non-linear mixed), along with important metrics like the Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC), and Benchmark Dose (BMD) values.

The results table on this page includes the following fields, providing a comprehensive overview of each gene set's dose-response model:

1. **Gene Set:** Name of the gene set or pathway analyzed (e.g., APOPTOSIS [HALLMARK]).
2. **Gene Set Size:** The total number of genes in the gene set.
3. **Genes in Gene Set:** The number of genes within the set that were included in the analysis.
4. **Best Model:** The model that best fits the data, selected from linear, non-linear fixed, or non-linear mixed models.
5. **Best Model P-value:** The p-value associated with the best-fitting model, indicating the statistical significance of the model.
6. **Best Model Adjusted P-value:** The adjusted p-value (e.g., using FDR) for the best model, correcting for multiple comparisons.
7. **Best Model AICc:** The corrected Akaike Information Criterion for the best model, balancing model fit with complexity.
8. **Best Model BIC:** The Bayesian Information Criterion for the best model, providing a second criterion for evaluating model fit.
9. **BMD Lower Bound:** The lower confidence interval for the Benchmark Dose, which represents the lowest dose with a significant response.
10. **BMD Median:** The median Benchmark Dose, indicating the dose where a benchmark level of response occurs.
11. **BMD Upper Bound:** The upper confidence interval for the Benchmark Dose, providing the upper range of significant response.
12. **BMD Mean:** The mean Benchmark Dose, offering an average estimate across the data.
13. **Null AIC:** The Akaike Information Criterion for the null model (no dose-response relationship).
14. **Null AICc:** The corrected Akaike Information Criterion for the null model.
15. **Null BIC:** The Bayesian Information Criterion for the null model.
16. **Null df:** The degrees of freedom for the null model.
17. **Linear AIC:** The Akaike Information Criterion for the linear model.
18. **Linear AICc:** The corrected Akaike Information Criterion for the linear model.
19. **Linear BIC:** The Bayesian Information Criterion for the linear model.
20. **Linear df:** The degrees of freedom for the linear model.
21. **Linear ICC:** The intraclass correlation coefficient for the linear model, assessing the consistency of gene responses within the pathway.
22. **Non-linear Fixed AIC:** The Akaike Information Criterion for the non-linear fixed effects model.
23. **Non-linear Fixed AICc:** The corrected Akaike Information Criterion for the non-linear fixed effects model.

24. **Non-linear Fixed BIC:** The Bayesian Information Criterion for the non-linear fixed effects model.
25. **Non-linear Fixed df:** The degrees of freedom for the non-linear fixed effects model.
26. **Non-linear Fixed ICC:** The intraclass correlation coefficient for the non-linear fixed effects model.
27. **Non-linear Mixed AIC:** The Akaike Information Criterion for the non-linear mixed effects model.
28. **Non-linear Mixed AICc:** The corrected Akaike Information Criterion for the non-linear mixed effects model.
29. **Non-linear Mixed BIC:** The Bayesian Information Criterion for the non-linear mixed effects model.
30. **Non-linear Mixed df:** The degrees of freedom for the non-linear mixed effects model.
31. **Non-linear Mixed ICC:** The intraclass correlation coefficient for the non-linear mixed effects model.
32. **P-value (Linear):** The p-value for the linear model, indicating the significance of the dose-response relationship.
33. **P-value (Non-linear Fixed):** The p-value for the non-linear fixed effects model.
34. **P-value (Non-linear Mixed):** The p-value for the non-linear mixed effects model.
35. **Adjusted P-value (Linear):** The adjusted p-value for the linear model, correcting for multiple hypothesis testing.
36. **Adjusted P-value (Non-linear Fixed):** The adjusted p-value for the non-linear fixed effects model.
37. **Adjusted P-value (Non-linear Mixed):** The adjusted p-value for the non-linear mixed effects model.
38. **Optimal Clusters:** The number of optimal gene clusters determined for the pathway, based on the dose-response behavior of the genes.

Users can filter results based on adjusted p-values or model types to focus on significant dose-response relationships. The results table can be exported in various formats, including CSV, Excel, and TSV, for further analysis.



3.7 Top Significant Pathways/Geneset Visualizations

This page provides an overview of the most significant pathways and gene sets identified in the dose-response analysis. The pathways are ranked by their statistical significance (e.g., adjusted p-values), and a variety of visualizations are available to help users explore dose-response relationships, variability within gene sets, and key dose metrics like the Benchmark Dose (BMD) and Trend Change Dose (TCD).

The following plots are available for users to explore the top pathways:

1. **Dotplot of Top Pathways:** This plot shows the top pathways ranked by $-\log(\text{adjusted p-value})$. Larger dots correspond to pathways with more significant dose-response effects. It helps identify the most responsive pathways based on statistical metrics.
2. **Dose Response Heatmap:** This heatmap displays the average gene expression across doses for each pathway. The color intensity represents the magnitude of gene expression changes, allowing users to visualize how the pathway responds to varying doses.
3. **Gene Set Random Effects:** This plot illustrates the distribution of random effects within the top pathways. It provides insights into the variability of individual genes within a pathway in response to doses, highlighting which genes deviate significantly from the expected behavior.
4. **Top Pathway Responses:** This plot visualizes the dose-response relationship for the top pathways, showing predicted expression changes across different doses. It helps to understand the overall dose-response trend for each pathway.
5. **BMD Confidence Intervals:** This plot provides the confidence intervals for the Benchmark Dose (BMD), which represents the dose at which a significant response is observed. The intervals indicate the uncertainty around the BMD estimation.
6. **BMD Density and Peaks:** This plot shows the density distribution of BMD values across the pathways, with peaks representing the doses where significant responses are concentrated. It helps in identifying the most sensitive dose ranges for the pathways.
7. **TCD Density and Peaks:** This plot visualizes the density distribution of Trend Change Dose (TCD) values. TCD represents the dose where a significant trend change occurs in the pathway response. Peaks in this plot highlight dose ranges that trigger notable shifts in pathway behavior.

Users can switch between these plots using the tabs in the interface, allowing for a detailed exploration of the top pathways identified in the analysis.

Showing 1 to 6 of 34 entries
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DoseRider
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Manual
FAQ
Datasets

Plot customization

Top results to plot: 6

Plot width: 8

Plot height: 8

Cluster results: ☐

Apply plot customization

Top Significant Pathways/Geneset Visualizations

Representation of the top significant pathway genesets from the analysis with DoseRider. The pathways are sorted by the $-\log(p\text{-value})$ from those that passed the previous filter. The available plots include: dotplot of top pathways, dose-response heatmap, gene set random effects, top pathway responses, BMD confidence intervals, BMD density and peaks, TCD density and peaks.

Click on the tabs to view the different plots.

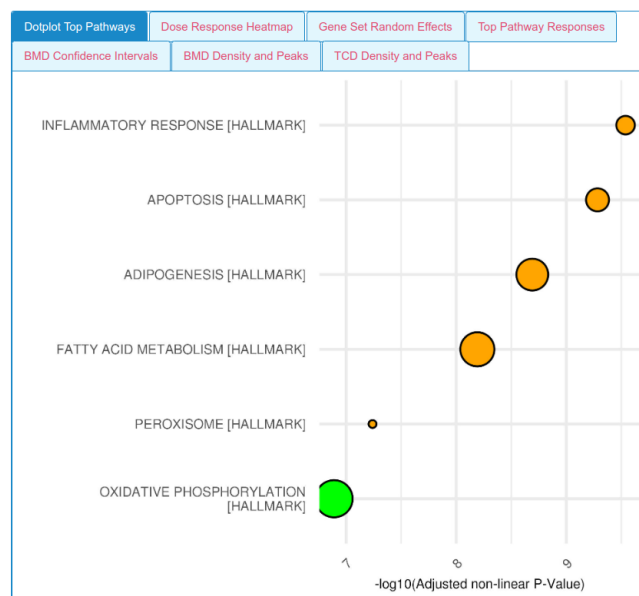


Figure 9: Dotplot of top pathways: Pathways ranked by adjusted p-values, providing an overview of significant dose-response results.

3.8 Pathway/Geneset Detailed Visualizations

This section offers visual representations of dose-response models and pathway responses. It includes:

- **Gene Random Effect Relationships:** Displays variability in gene responses within each pathway.
- **Gene Heatmaps:** Visualize expression changes across doses.
- **Pathway Responses:** Show dose-response predictions and smoothed curves for pathways.

Users can customize plot settings (e.g., plot width, height, and clustering) to refine the visualizations.

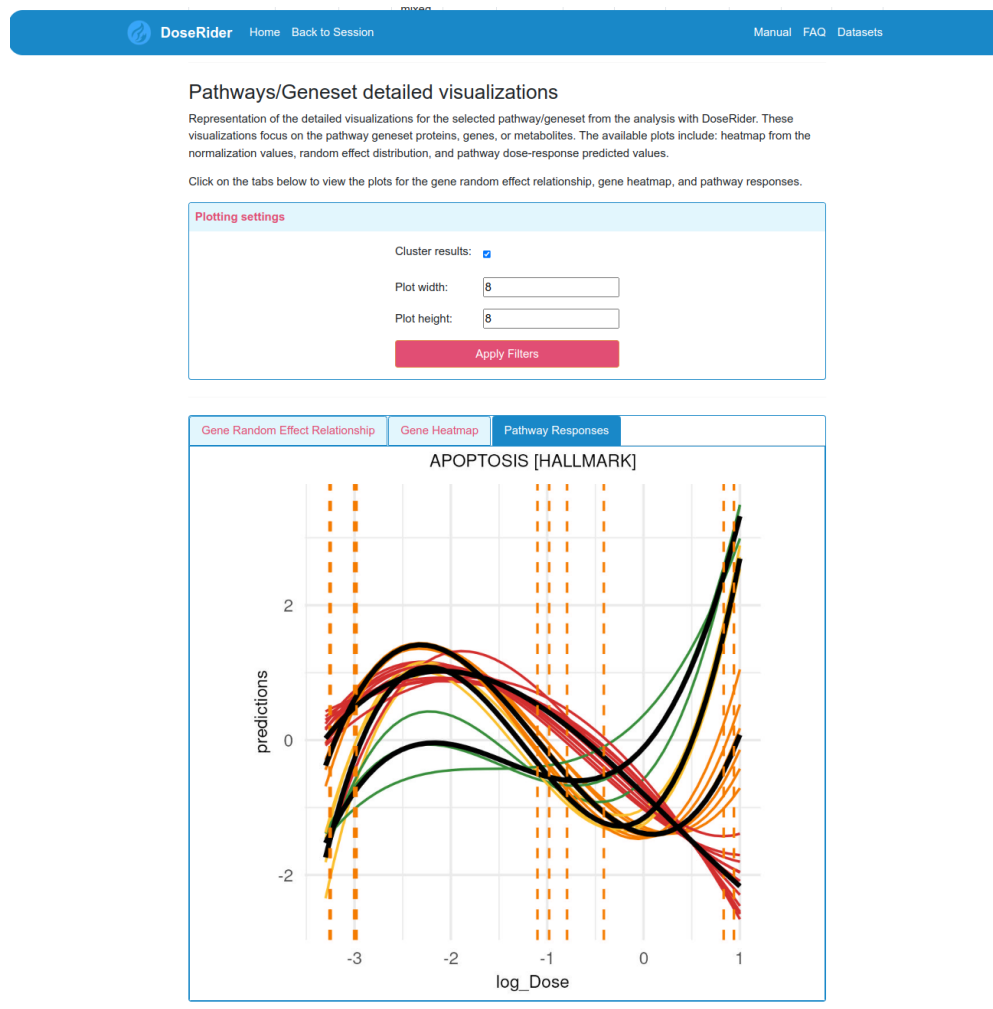


Figure 10: Detailed visualizations of dose-response models: This includes gene random effect relationships, heatmaps, and pathway responses.

4 Troubleshooting

The DoseRider platform is designed to be intuitive and user-friendly. However, issues may occasionally arise during data upload, analysis, or visualization. Below are some common troubleshooting tips for resolving such issues.

4.1 Common Issues and Solutions

- **Problem: Dataset upload fails.**
 - **Solution:** Ensure that your dataset is in the correct format (CSV, TSV, or Excel). Check that the columns are properly labeled, and the dose information is provided in a separate column. If using metadata, ensure that it corresponds accurately with the sample identifiers in the expression data.
- **Problem: Analysis job is stuck in the "queued" status.**
 - **Solution:** This may occur if the server is experiencing high demand. Refresh the page after a few minutes. If the issue persists, cancel the job and resubmit the analysis. Ensure your internet connection is stable during submission.
- **Problem: No results are returned after running the analysis.**
 - **Solution:** Verify that the correct columns for dose and sample identifiers are properly labeled in the metadata file. Double-check the gene set size thresholds and ensure that the dataset contains sufficient variability across doses.
- **Problem: Visualizations do not display or are incomplete.**
 - **Solution:** Ensure that JavaScript is enabled in your browser, and try clearing the browser cache. If the problem persists, try running the analysis in a different browser or updating your current browser to the latest version.
- **Problem: Benchmark Dose (BMD) or Trend Change Dose (TCD) values appear inconsistent or incorrect.**
 - **Solution:** Check the dose units in your metadata file (e.g., μM or mg/L) and ensure they match across all samples. Make sure the data has been preprocessed correctly (e.g., log-transformation of doses if applicable) to avoid skewed results.
- **Problem: Unable to download results in CSV/Excel/TSV format.**
 - **Solution:** Ensure pop-ups are not blocked in your browser settings, as some browsers may prevent automatic downloads. If the problem persists, try exporting the results using a different format.
- **Problem: Unexpected error messages during analysis.**
 - **Solution:** These could be caused by incompatible file formats or errors in the dataset. Double-check the formatting of the uploaded data and ensure the metadata aligns with the expression data. Refer to the file format guidelines in the user manual. Contact technical support if the issue persists.

4.2 Contact Support

If these troubleshooting steps do not resolve your issue, you can reach out to the ****DoseRider**** technical support team at pablo.monfort@i-med.ac.at. Please include details about the issue, such as the dataset format, error messages received, and the steps leading up to the issue.

5 Acronyms

Akaike Information Criterion

Corrected Akaike Information Criterion

Bayesian Information Criterion

Benchmark Dose

Comma-Separated Values

False Discovery Rate

Generalized Linear Mixed Models

Intraclass Correlation Coefficient

JavaScript Object Notation

Principal Component 1

RNA Sequencing

Summarized Experiment Matrix

Single Nucleotide Polymorphism

Tab-Separated Values

Trend Change Dose