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RESEARCH ARTICLE

Gango + BioFunctional: A Computational tool for efficient functional gene analysis

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Abstract

Functional gene analysis is crucial for understanding gene roles in biological processes. However, analyzing data with multiple experimental groups presents significant challenges due to the complexity of data processing and the limitations of existing tools. GANGO + BioFuncional, an R-based Shiny application designed for end-users, addresses these challenges by providing a streamlined and comprehensive workflow for functional gene analysis. This interactive and freely available tool requires no installation, thus significantly enhancing its accessibility. The application is composed of two primary modules: GANGO, which efficiently processes input data and performs functional annotation to Gene Ontology (GO) terms and KEGG pathways; and BioFuncional, dedicated to in-depth analysis and interpretation. Key advantages include a highly user-friendly interface that eliminates the need for programming expertise, robust multi-group analytical capabilities, comprehensive visualization tools (interactive networks and significance-driven bar plots), and seamless compatibility with AI-driven interpretation tools like CURIE. Hosted on a server, GANGO + BioFuncional enhances the efficiency and accessibility of functional gene analysis, making it a valuable asset for both specialists and AI applications, ultimately facilitating deeper biological insights.

Keywords: AI Integration, Computational Tool, Functional Gene Analysis, Gene Ontology, KEGG Pathways, Shiny Application.

Introduction

Functional gene analysis (Figure 1, workflow) is a vital process in biology, enabling researchers to elucidate the roles of genes in various biological processes. The typical workflow involves several key steps:**List of Genes of Interest:** The analysis begins with a set of genes relevant to a particular study, such as differentially expressed genes, mutated genes associated with a disease, or genes in a specific biological pathway.

- **Gene Annotation:** Genes are annotated with functional information from databases like Gene Ontology (GO) and KEGG. These databases provide details on molecular functions, biological processes, and cellular localization.
- **Enrichment Analysis:** Statistical enrichment analysis identifies over-represented biological functions or pathways within the gene list, highlighting the most relevant biological functions.
- **Visualization and Interpretation:** Results are visualized using tools like bar graphs and network diagrams, aiding in the interpretation of key biological themes within the research question, often with reference to existing literature.

Functional gene analysis yields insights into biological mechanisms and aids in generating hypotheses for further research (Thomas, 2000).

From data to understanding: Addressing the challenges of functional gene analysis

While functional gene analysis provides critical insights, analyzing studies with more than two experimental groups significantly increases complexity. Consider a study on a disease and its progression, with the following groups:

Group 1: Healthy individual

Group 2: Patients with early-stage diseGroup 4: Patients with late-stage disease

Identifying genes consistently dysregulated across all stages or specific to a particular stage requires advanced statistical methods. Researchers often rely on multiple software tools and custom scripts (e.g., in R) to manage gene lists, organize data, perform functional analysis, and interpret results. This process is time-consuming, requires programming expertise, and can hinder reproducibility. The lack of user-friendly tools to handle and visualize the complexity of multi-group results therefore necessitates more sophisticated approaches (Gene Ontology Consortium, 2015).

To address these challenges, a specialized computational tool is needed to:

- Enable easy processing of data from multiple experimental groups without requiring programming expertise.
- Provide a user-friendly interface.
- Efficiently handle multiple groups.
- Identify relevant ontologies or KEGG pathways.
- Prepare results for interpretation by specialists and artificial intelligence.

Such a tool would reduce analysis time and effort, improve result accuracy and reliability, and broaden the accessibility of functional gene analysis. GANGO + BioFuncional was developed to provide such a solution.

Benchmarking with existing tools

In response to the need to contextualize the utility of GANGO + BioFuncional, a comparison was conducted with widely used functional enrichment analysis tools such as DAVID, GSEA, and Enrichr. Table 1 provides a benchmark of the main features of these tools compared to GANGO + BioFuncional. Unlike DAVID (Huang et al., 2009) and Enrichr (Chen et al., 2013), GANGO + BioFuncional is specifically designed to simplify the analysis of data with multiple experimental groups, offering an intuitive user interface that minimizes the need for programming knowledge.

Table 1. Benchmark comparison of GANGO + BioFuncional with other widely used functional enrichment analysis tools: DAVID, GSEA, and Enrichr.

Feature / Tool	**GANGO + BioFuncional**	**DAVID**	**GSEA**	**Enrichr**
Multi-group Analysis	Yes (Simplified)	Limited	Yes (Specific)	Limited
User-Friendly Interface	Yes (Shiny, no code)	Moderate (Web)	Moderate (Software)	High (Web)
AI Integration	Yes (CURIE)	No	No	No
Advanced Visualization	Interactive Networks, Z-score Bar Plots	Basic (Graphs)	Advanced (Plots)	Basic (Bar charts)
Installation Required	No (Server)	No (Web)	Yes	No

It highlights GANGO + BioFuncional's unique features, particularly its simplified multi-group analysis capabilities and an intuitive user interface designed to minimize the need for programming knowledge. Unlike DAVID (Huang et al., 2009) and Enrichr (Chen et al., 2013), GANGO + BioFuncional streamlines the analysis of data from multiple experimental groups. Furthermore, it stands out with its integration of AI through CURIE and offers advanced visualization options such as interactive networks and Z-score bar plots, surpassing the basic visualization features of some other tools. The table also indicates whether each tool requires local installation or is accessible via a server or web interface, with GANGO + BioFuncional, DAVID, and Enrichr being server/web-based, while GSEA requires installation

While GSEA (Subramanian et al., 2005) also addresses gene set analysis, GANGO + BioFuncional distinguishes itself by its ability to integrate hierarchical ontology information and generate advanced visualizations such as interactive networks and Z-score bar plots, which enhance the interpretability of results. Furthermore, a notable feature of GANGO + BioFuncional is its integration with artificial intelligence technologies (such as CURIE), facilitating a deeper interpretation of GO terms, an aspect that existing tools do not typically offer. This comparison underscores the unique contributions of GANGO + BioFuncional for functional gene analysis in highly complex scenarios.

Materials and methods

GANGO + BioFunctional is a comprehensive R application, built using the Shiny framework (Chang et al., 2025) (DOWNLOAD AND INSTALL IN https://alexub.shinyapps.io/BioFunctional/). It facilitates the interpretation and visualization of functional analysis related to KEGG pathways and gene ontologies (GO) (Alterovitz et al., 2007; Ashburner et al., 2000; Gene Ontology Consortium, 2015; Kanehisa & Goto, 2000). The application provides researchers with detailed functional information, specifically about biological pathways and gene functions. Utilizing libraries such as Shiny, httr, dplyr, tibble, and rvest in R. GANGO + BioFuncional offers a user-friendly interface for data assessment and analysis. The GANGO + BioFuncional tools have been integrated into this Shiny-based R application.

The development of GANGO stems from prior research detailed in article Monleon-Getino et al. (2020), establishing its foundational components. BioFunctional, on the other hand, represents the significant improvements and enhancements that emerged from subsequent work, specifically those described in article Rodriguez and Monleon-Getino (2024).

The application enables the exploration of KEGG pathways and Gene Ontologies (Gene Ontology Consortium, 2015; Kanehisa & Goto, 2000), facilitating the analysis of complex biological processes. Functions within the application integrate data manipulation and web scraping to extract information from the Kyoto Encyclopedia of Genes and Genomes (KEGG) and QuickGo databases. Parallel processing enhances the efficiency of database queries, enabling rapid results from large datasets.

A key feature is the ability to obtain ancestral information for KEGG pathways and gene ontologies, which simplifies the understanding of their hierarchy and the classification of samples within a dataset. Users can study datasets at different levels of taxonomy directly from raw data. The application also generates interactive networks to visualize relationships between experimental groups and ontologies, preserving classification information. These networks are crucial for understanding the relationships within the displayed system.

These features make the software a valuable tool for analysts studying biological pathways, providing an intuitive interface with advanced data processing techniques. It allows researchers to elucidate the complexity of biological functions and gain insights into gene and molecular component relationships.

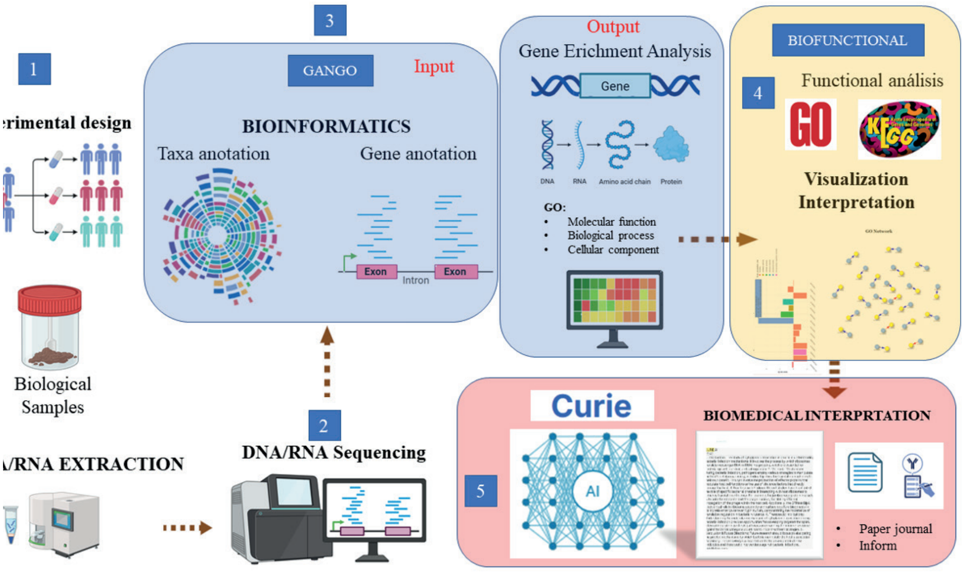

Figure 1. GANGO + BioFunctional Workflow. This diagram illustrates the complete process from biological sample collection to the functional interpretation of genetic results obtained using the GANGO+ BioFunctional ap-

plication. The workflow comprises the following key stages: 1) Experimental design and biological sample collection, followed by DNA/RNA extraction. 2) DNA/RNA sequencing. 3) GANGO: Bioinformatics procedures, outputting gene enrichment analysis. 4) BioFunctional: Visualization and quantification of the functional analysis (Gene Ontologies and KEGG). 5) Biomedical interpretation: Facilitating biomedical interpretation of the functional analysis through Artificial Intelligence. (Biomedical icons in this diagram were extracted using https://www.biorender.com/).

What is GANGO?

GANGO is an algorithm (Figure 1,3) that performs enrichment analysis to map genes, taxa, and groups to ontologies. It processes data from text files and generates an information-rich file for the BioFunctional algorithm. This algorithm represents KEGG pathways and ontologies, facilitating functional analysis and interpretation.

What are ontologies?

In bioinformatics, ontologies are structured vocabularies that standardize the description and classification of biological entities (e.g., genes) and their relationships. They aid in organizing and interpreting complex biological data (Gene Ontology Consortium, 2015).

What is KEGG?

KEGG (Kyoto Encyclopedia of Genes and Genomes) is a database of biological pathways, which are a series of molecular actions within a cell that lead to a specific product or change (Kanehisa & Goto, 2000).

What is enrichment analysis?

Enrichment analysis is a statistical method used to determine if a set of genes is over-represented in a particular category (e.g., a biological pathway or gene ontology term) compared to what would be expected by chance (Subramanian et al., 2005)

What is gene functional analysis?

Gene functional analysis is the process of determining the biological roles of genes, including the study of gene expression, protein interactions, and the effects of gene mutations (Reinitz & Hammer, 2004).

What is BioFunctional?

BioFunctional (Figure 1,4) is a software that extends Gene Ontology (GO) and KEGG pathway (metabolism) enrichment analysis. It generates network and bar plot visualizations and enhances previous gene ontology analysis by incorporating hierarchical information. This enables users to filter relevant GO ontologies or KEGG pathways through statistical analysis and facilitates functional interpretation using curated literature or the Biost3 research group's artificial intelligence tool, CURIE. CURIE[1] is currently under development by our research group and is pending publication (Figure 1,

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[1] CURIE is not directly integrated with GANGO + BioFunctional. Instead, it is an independent computational application currently undergoing testing on the research group's computational server. While GANGO + BioFunctional results are formatted to be readily interpretable by AI tools like CURIE, CURIE itself is presently only available within the University of Barcelona's facilities.

5). The appendix describes its functionality.

For a detailed understanding of BioFunctional, please refer to “BioFunctional: A Comprehensive App for Interpreting and Visualizing Functional Analysis of KEGG Pathways and Gene Ontologies” (Rodriguez & Monleon-Getino, 2024).

Description of the BioFuncional + GANGO application

The BioFuncional + GANGO application provides a workflow for functional analysis, specifically for elucidating Gene Ontology (GO) terms and KEGG pathway enrichment. This methodology allows researchers to derive biological meaning from gene lists or taxonomic classifications from experiments like transcriptomics or metagenomics. The application comprises two primary modules: GANGO and BioFuncional.

GANGO: Gene ontology and KEGG assignment

The GANGO module processes input data. It accepts a list of genes or taxa, is organized into user-defined groups, and performs the following operations:

- Data Input: Accepts a list of genes by taxa and their grouping.
- Functional Annotation: Maps input identifiers to Gene Ontology (GO) terms and KEGG pathways, associating each gene by taxon with its known biological functions, molecular activities, and involvement in specific biological pathways.
- Output Generation: Produces a dataset linking genes/taxa to GO terms and KEGG pathways, serving as input for subsequent analysis.

BioFuncional: Functional analysis and interpretation

The BioFuncional module processes the output from GANGO to interpret functional enrichment. It performs the following steps:

- Data Preprocessing:
- Column Selection: Pre-selects essential data columns. Users can also designate additional columns for filtering in later steps.
- File Export: Allows users to download preprocessed data files.
- Hierarchical Analysis:
- GO Hierarchy Integration: Incorporates GO hierarchical structure, retrieving ancestral relationships between GO terms to provide a framework for understanding the specificity and relationships among enriched functions.
- Hierarchical Data Augmentation: Integrates hierarchical information into the dataset, enabling analysis of functional enrichment at different levels of biological specificity.
- Network Analysis:
- Interactive Network Generation: Constructs interactive networks representing relationships between experimental groups and enriched GO terms.
- Customization: Allows users to customize network visualization by selecting GO categories and applying filters based on GO term hierarchy.

- Bar Plot Visualization (See Figure 2):
- Ontology Ranking: Generates bar plots that rank GO terms based on their enrichment within specified experimental groups.
- Significance Determination: Bar plots help identify pertinent GO terms for further investigation using a Z-score transformation, allowing users to visually assess the significance of functional enrichment.
- The bar plot then visualizes these Z-scores, making it easy to identify the most over-represented (or under-represented) GO terms in the comparison between the healthy and bacterial infection groups.
- Interpretation Guidance:
- Selection of Relevant Terms: Bar plots facilitate the selection of relevant GO terms for further interpretation, potentially involving tools or literature review.
- Emphasis on Group-Specific Terms: The application emphasizes focusing on GO terms most pertinent to the experimental groups of interest (e.g., treatment groups).

Results and discussion

In Appendix 1 of the article's supplementary materials, a detailed, step-by-step graphical tutorial of the GANGO + BioFunctional application's workflow can be found. This tutorial presents a real-world case study to demonstrate the tool's comprehensive functionality, specifically focusing on the functional analysis between a group of healthy individuals and a group with bacterial infection. RNA-Seq data from the study "Dysregulated transcriptional responses to SARS-CoV-2 in the periphery" (McClain et al., 2021) were utilized for this purpose, encompassing samples from subjects affected by bacterial infection versus healthy controls.

The overall workflow detailed in Appendix 1 for the GANGO + BioFunctional + CURIE application involves several key stages: it begins with experimental design and biological sample collection, followed by DNA/RNA extraction and subsequent sequencing. Next, the GANGO module performs bioinformatics procedures to output gene enrichment analysis. This is followed by the BioFunctional module, which handles the visualization and quantification of functional analysis (Gene Ontologies (GO)). Finally, the workflow culminates in biomedical interpretation, which is facilitated through Artificial Intelligence, such as the CURIE.

Implications and novelties

GANGO + BioFuncional offers several key advantages:

- **Streamlined Workflow:** It integrates GANGO and BioFuncional into a single application, simplifying the functional gene analysis process.
- **User-Friendly Interface:** The Shiny-based R application provides an intuitive interface, reducing the need for programming expertise.
- **Multi-Group Analysis:** The tool is designed to handle complex datasets with multiple experimental groups.

- **Comprehensive Analysis:** It combines enrichment analysis, hierarchical analysis, network visualization, and bar plot visualization.
- **Enhanced Interpretation:** It facilitates the selection of relevant GO terms and emphasizes group-specific results.
- **AI Integration**: Results are formatted to be readily interpretable by Artificial Intelligence tools like CURIE, developed by the Biost3 research group.

Specifically, to highlight the most relevant GO terms, the Enrichment Analysis (EA) values for each GO term are used. These EA values are then transformed into Z-scores.

Z-score transformation

Essentially, BioFuncional's bar plots (Figure 2) concisely represent the most relevant GO terms, categorized by GO type. Specifically, the Enrichment Analysis (EA) values for each GO term are transformed into Z-scores to highlight significance. This standardization allows for easy comparison of the relative importance of different GO terms.

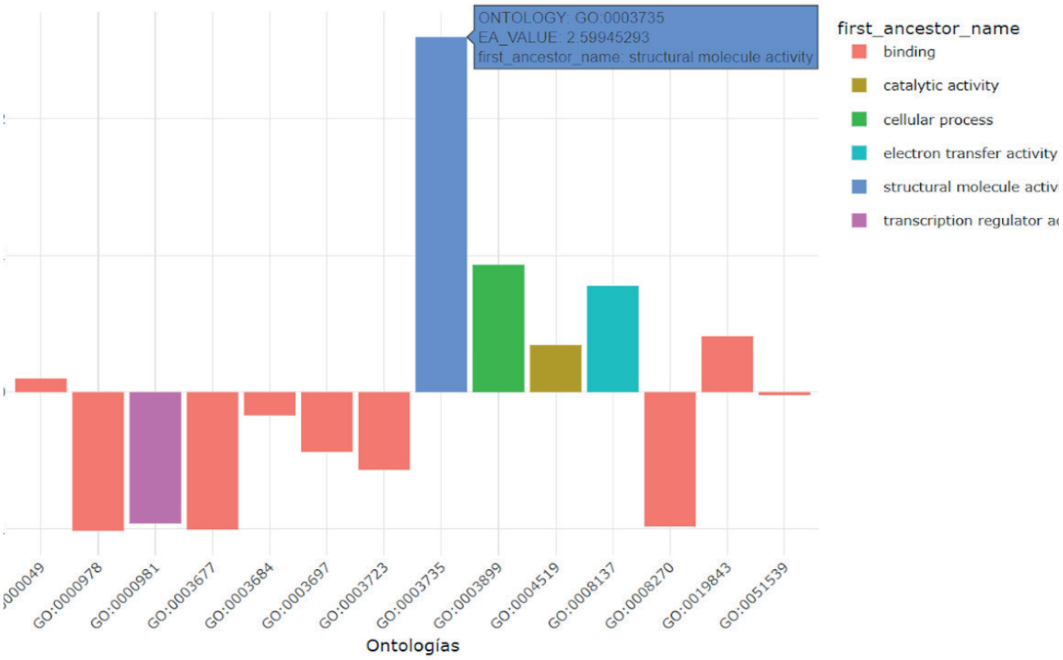

Figure 2. Bar Plot of Enriched Gene Ontologies from BioFuncional Analysis. This bar plot visualizes the Gene Ontology (GO) terms, ranked based on their enrichment within specified experimental groups, as determined by the BioFuncional application. The X-axis displays the enriched Gene Ontologies, representing specific biological functions or processes. The Y-axis represents the Z-score transformation, which allows users to visually assess the significance of functional enrichment. Z-scores make it easy to identify the most over-represented (positive Z-scores) or under-represented (negative Z-scores) GO terms in the comparison, specifically between the healthy and bacterial infection groups in this example.

A Z-score measures how far a data point is from the mean (average) of the dataset. It's calculated in units of standard deviations.

- A Z-score of 0 means the data point is exactly at the mean.
- A positive Z-score means the data point is above the mean.
- A negative Z-score means the data point is below the mean.

In this context, transforming the EA values to Z-scores allows us to:

- **Standardize:** Put all the EA values on a common scale, making it easier to compare the relative importance of different GO terms, even if their original EA values had very different ranges.
- **Highlight Significance:** GO terms with higher absolute Z-scores (farther from zero) are considered significantly more enriched. A large positive Z-score indicates a GO term is more enriched than average, while a large negative Z-score indicates it is less enriched.

These features make GANGO + BioFuncional a valuable tool for researchers in biology, genetics, and related fields.

Beyond transcriptomics: Expanding applicability to other omics data

GANGO + BioFuncional has been developed with a primary focus on functional gene analysis, particularly for data derived from transcriptomics. While GANGO is not directly designed to process raw data from other omics types such as proteomics or metabolomics, its modular architecture allows for broader applicability.

Users working with proteomics or metabolomics data would first need to translate their findings into relevant Gene Ontologies (GO) or KEGG pathways and then use BioFuncional to present ontologies, conveniently select them, and interpret them using CURIE. This can be achieved through established bioinformatics workflows in R, for instance, by using database searches (e.g., with Bioconductor packages like org.Hs.eg.db for gene IDs or clusterProfiler for enrichment analysis) to map protein identifiers or metabolites to their corresponding genes, and then performing enrichment analysis to obtain GO terms or KEGG pathways. Subsequently, these pre-processed GO or KEGG terms, when formatted appropriately, can be seamlessly integrated into BioFuncional for advanced visualization, hierarchical analysis, and AI-driven interpretation, thereby leveraging the full capabilities of our tool for a wider range of biological insights.

Accuracy and reliability

The accuracy and reliability of GANGO + BioFuncional's results are ensured through several key design principles and integrated features, including its robust statistical foundation (with Z-score transformation), its ability to integrate complex hierarchical and multi-group data, and a user-friendly design that minimizes errors and facilitates comprehensive data visualization and expert validation:

- Statistical Foundation: The tool's core relies on statistical enrichment analysis, a method used to identify biological functions or pathways that are significantly over-represented in a given gene list compared to what would be expected by chance. This statistical rigor forms the basis of the reliability of the identified enrichments.
- Z-score Transformation for Significance: To enhance the assessment of significance and enable robust comparisons, GANGO + BioFuncional transforms Enrichment Analysis (EA) values into

Z-scores. This standardization places all values on a common scale, making it easier to compare the relative importance of different Gene Ontology (GO) terms and highlight those that are most significantly enriched (further from zero).

- Hierarchical Information Integration: The tool incorporates the hierarchical structure of GO terms and KEGG pathways, providing a framework to understand the specificity and relationships among enriched functions. This integration of hierarchical data allows for analysis at different levels of biological specificity, contributing to more precise and reliable interpretations.
- Robust Multi-Group Analytical Capabilities: GANGO + BioFuncional is specifically designed to handle complex datasets involving multiple experimental groups. This capability ensures that the tool can robustly process and analyze diverse and complex biological scenarios, which is crucial for the reliability of comparative studies.
- Comprehensive Visualization Tools: The application provides comprehensive visualization tools, including interactive networks and significance-driven bar plots. These visualizations aid in the interpretation of key biological themes, making complex data more digestible and allowing users to visually assess the significance of functional enrichment, thereby increasing confidence in the results.
- User-Friendly and Streamlined Workflow: By integrating various analysis steps into a single, intuitive R-based Shiny application, GANGO + BioFuncional reduces the need for programming expertise and streamlines the analysis process. A simplified workflow can minimize user errors, indirectly contributing to the reliability of the outputs. The explicit goal of the tool's development was to "improve result accuracy and reliability".
- Facilitating Cross-Referencing and Validation: While the tool provides robust analytical outputs, the manuscript also emphasizes the importance of manual interpretation by experts. It suggests cross-referencing GO analysis results with other relevant data (e.g., other enrichment analyses, gene expression data, protein-protein interaction networks, phenotype data) to validate findings and look for consistency and convergence of evidence from multiple sources. This highlights that the tool provides the necessary data for users to perform their own validation steps.
- AI Integration (with transparency): GANGO + BioFuncional is compatible with AI-driven interpretation tools like CURIE. While CURIE is noted to be in an experimental phase and potentially subject to inconsistencies, this integration points towards future enhancements in interpretation and the potential for increased reliability as the AI technology matures.

Conclusions

In summary, GANGO + BioFuncional provides a significant advancement in functional analysis for high-throughput biological data. By integrating efficient data processing with robust analytical and visualization capabilities, this application empowers researchers to streamline complex analyses, enhance the interpretability of their findings, and ultimately derive more meaningful biological insights. Its user-friendly design, capacity to handle multi-group studies, and compatibility with AI-driven interpretation tools make it a valuable asset for a wide range of biological research, facilitating a deeper understanding of gene function and its implications.

Appendix A. Supplementary material

Supplementary material associated with this article can be found on https://doi.org/10.62063/ecb-63. To access the supplementary material, please visit the article landing page.

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Conflict of interest

The authors declare no conflict of interest.

Data availability statement

All necessary files for the analysis are provided in the correct format and can be download in https://github.com/amonleong/Biofunctional

Ethics committee approval

Ethics committee approval is not required for this study.

Authors' contribution statement

The authors acknowledge their contributions to this paper as follows: **Study conception and design**: AR, TM; **Data collection**: AR, XT; **Analysis and interpretation of results**: XT, GC, JM; **Manuscript draft preparation**: TM, AR, GC. All authors reviewed the results and approved the final version of the manuscript.

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