A Comprehensive Review of Applying Enrichr in Recent Biomedical Research Articles

Abstract

Enrichr is a widely used web-based tool for gene set enrichment analysis. This article synthesizes mentions of Enrichr in recent research papers to provide a comprehensive overview of how Enrichr is utilized across various biomedical studies. We examine the diverse applications of Enrichr, including its role in identifying pathways associated with diseases, predicting drug targets, interpreting omics data, and inferring cell population changes. The article highlights the importance of careful parameter selection, validation of results, and integration of Enrichr with other bioinformatics tools for robust and meaningful biological insights. The analysis underscores the power of Enrichr as a versatile tool for hypothesis generation and functional interpretation in biomedical research, while also emphasizing the need for methodological transparency and awareness of potential limitations.

1. Introduction

Functional enrichment analysis is a cornerstone of modern biomedical research, enabling researchers to interpret high-throughput omics data and generate novel hypotheses about underlying biological mechanisms. Among the many available tools for this purpose, Enrichr stands out due to its user-friendly interface, comprehensive database of gene sets, and ease of integration with various bioinformatics workflows. This review aims to provide a synthesized overview of how Enrichr has been used in recent research, drawing from a collection of research paper summaries that highlight its diverse applications and potential limitations. By examining these studies, we seek to illustrate the strengths and weaknesses of Enrichr, while also providing guidance on best practices for its utilization.

Enrichr's utility stems from its ability to identify statistically significant overrepresentation of a user-provided gene list within a vast collection of pre-defined gene sets [2, 3, 6, 7, 9]. These gene sets are derived from various sources, including Gene Ontology (GO), Kyoto Encyclopedia of Genes and Genomes (KEGG), Reactome, WikiPathways, and many other curated databases [2, 3, 6, 7, 9]. By comparing the input gene list to these gene sets, Enrichr can reveal the biological processes, molecular functions, cellular components, and pathways that are most significantly associated with the genes of interest [2, 3, 6, 7, 9]. This information can then be used to generate hypotheses about the functional roles of the genes and their involvement in specific biological processes or diseases [2, 3, 6, 7, 9].

Despite its widespread use, Enrichr is not without limitations. The accuracy and reliability of its results depend on several factors, including the quality of the input data, the choice of appropriate gene set libraries, the statistical methods used for enrichment analysis, and the interpretation of the results within the appropriate biological context [2, 3, 6, 7, 9]. It is crucial to carefully consider these factors when using Enrichr and to validate its findings using independent experimental approaches.

This review will explore these issues by examining how Enrichr has been applied in a variety of biomedical research areas. We will focus on studies that have used Enrichr to identify pathways associated with diseases [2, 3, 6, 7, 9], predict drug targets [4, 11, 12, 19], interpret omics data [3, 6, 7, 9], and infer cell population changes [13]. By analyzing these examples, we hope to provide a comprehensive guide to using Enrichr effectively and responsibly.

2. Methods

This review is based on a synthesis of summaries from recent research papers that mention the use of Enrichr. These summaries provide a concise overview of the study's objectives, methods, and key findings, with a particular focus on how Enrichr was utilized. The summaries were analyzed to extract information about the following aspects of Enrichr usage:

- **Input data:** What type of data was used as input for Enrichr (e.g., gene lists, protein lists, differentially expressed genes)? How was the input data generated?
- **Enrichr parameters:** Which gene set libraries were used for enrichment analysis (e.g., GO, KEGG, Reactome)? What statistical methods were used to assess the significance of enrichment? What significance thresholds were applied?
- **Output and interpretation:** How were the results from Enrichr interpreted in the context of the study's objectives? What conclusions were drawn based on the Enrichr analysis?
- **Validation:** Were the Enrichr findings validated using independent experimental approaches or other bioinformatics tools?
- **Limitations:** What limitations of Enrichr usage were acknowledged by the authors?

The information extracted from the summaries was then synthesized to identify common themes, best practices, and potential pitfalls in the use of Enrichr. The analysis also considered the limitations of relying on summaries, which may not provide a complete picture of the study's methodology or results.

3. Applications of Enrichr in Biomedical Research

3.1. Identifying Pathways Associated with Diseases

One of the most common applications of Enrichr is to identify biological pathways and processes associated with specific diseases [2, 3, 6, 7, 9, 15, 16, 19, 22, 27, 37, 38, 45]. By analyzing gene lists derived from disease-related studies, researchers can use Enrichr to gain insights into the underlying mechanisms of disease and identify potential therapeutic targets [2, 3, 6, 7, 9, 15, 16, 19, 22, 27, 37, 38, 45].

For example, one study used Enrichr to perform enrichment analysis on ACTB-associated genes, revealing associated Biological Processes (BP), Molecular Functions (MF), and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways [2]. While the abstract lacked specific details, it is likely that the researchers uploaded a gene list representing genes significantly correlated with ACTB expression and used Enrichr's library of gene sets to identify statistically significant overrepresentation of the input gene list within pre-defined gene sets from GO and KEGG [2].

Another study used Enrichr to functionally characterize differentially expressed genes (DEGs) identified in a meta-analysis of colorectal cancer (CRC) RNA-Seq datasets [29]. The researchers performed GO and KEGG pathway enrichment analysis on upregulated and downregulated DEG lists, revealing enrichment in pathways related to RNA transport and cell cycle (upregulated) and mineral absorption (downregulated) [29]. This information provided insights into the biological processes and pathways potentially disrupted in CRC based on the observed gene expression changes [29].

In a study on *Lentinula edodes*, Enrichr KG was used to connect a set of genes (identified through a multi-step process involving other bioinformatic tools) with their associated diseases, based on the pre-existing curated knowledge in DisGeNET [38]. This allowed for the systematic identification of potential disease targets of *L. edodes* extracts and provided a biological rationale for further in-vitro experiments to confirm the hypothesis [38]. This demonstrates how Enrichr can be integrated within a more complex systems biology approach.

3.2. Predicting Drug Targets

Enrichr can also be used to predict potential drug targets by identifying compounds associated with the expression of genes of interest [4, 11, 12, 19]. By leveraging Enrichr's comprehensive library of compound databases, researchers can identify potential perturbagens that may alter gene expression profiles in a desired manner [4, 11, 12, 19].

For instance, one study leveraged Enrichr to identify potential drug candidates targeting the identified biomarkers of UVB radiation-related senescent fibroblasts, Apoe and Gdf15 [11]. The researchers used Enrichr to access the Drug Signatures database (DSigDB) and identified drugs with expression signatures significantly enriched for the input genes [11]. The output from Enrichr listed drug candidates ranked by their p-value and adjusted p-value, suggesting potential drugs that might effectively modulate the expression or activity of the identified senescence biomarkers [11].

Another study utilized Enrichr to identify potential pharmacological targets for mitigating T-2 toxin-induced articular cartilage damage [12]. The researchers leveraged Enrichr's database to connect their identified hub genes with known drug targets. From the Enrichr output, etoposide and diatrizoic acid were selected as the key drug candidates based on their low p-values, suggesting strong statistical evidence linking these drugs to the biological processes and pathways involving the input hub genes [12].

A study on COVID-19 also used Enrichr to identify potential drug targets for both cancer and COVID-19 based on the identified biomarkers and common genes [19]. The authors leveraged Enrichr's capabilities to perform drug–gene interaction analysis, specifically using databases such as DSigDB within the Enrichr platform to identify drugs that show interactions with the input gene lists [19].

3.3. Interpreting Omics Data

Enrichr is a valuable tool for interpreting various types of omics data, including transcriptomics, proteomics, and genomics [3, 6, 7, 9]. By analyzing gene or protein lists derived from these datasets, researchers can use Enrichr to identify the biological processes and pathways that are most significantly affected by the experimental conditions [3, 6, 7, 9].

For example, one study utilized Enrichr for functional enrichment analysis of differentially expressed genes (DEGs) identified through RNA sequencing of SARS-CoV-2 infected versus uninfected Calu-3 cells [7]. The authors leveraged Enrichr's capabilities to analyze the DEGs against three different functional annotation databases: Gene Ontology (GO), Kyoto Encyclopedia of Genes and Genomes (KEGG) Pathways, and WikiPathways [7]. The enriched terms represented biological functions and pathways that were over-represented among the DEGs compared to what would be expected by chance alone, providing insights into the impact of the virus on cellular processes [7].

In another study, researchers leveraged Enrichr to perform GO and KEGG pathway enrichment analyses on DEGs from a meta-analysis of wound healing microarray datasets [6]. This allowed them to identify pathways and functions significantly enriched in the DEGs and

co-expression modules, helping to interpret the biological relevance of these enriched pathways and functions within the context of wound healing [6].

A study using proteomics also utilized Enrichr for functional interpretation of proteomic data obtained from comparing established bronchopulmonary dysplasia (eBPD) lungs to control lungs [13]. While the researchers did not use Enrichr for gene set enrichment analysis of differentially expressed genes, they used their in-house Protein-MiniOn package for that purpose and leveraged Enrichr to infer changes in cell populations based on the differential abundance of proteins identified via mass spectrometry [13].

A study on glioblastoma also employed Enrichr in a standard manner for GSEA, leveraging KEGG pathways to identify biological processes enriched in a set of upregulated genes from GBM samples [18]. The findings informed the interpretation of the DEG results and suggested potential mechanistic insights into GBM pathogenesis [18].

3.4. Inferring Cell Population Changes

In addition to its more common applications, Enrichr can also be used to infer changes in cell populations within a tissue based on the relative abundance of proteins associated with those cell types [13]. By comparing the protein profile of a tissue to gene sets representing specific cell types, researchers can use Enrichr to identify cell types that are over- or under-represented in the tissue [13].

For example, one study strategically used Enrichr not for typical pathway or gene ontology analysis, but rather for a less common application: inferring changes in cell populations within a tissue based on the relative abundance of proteins associated with those cell types [13]. The researchers used the HubMAP "Anatomical Structures, Cell Types, plus Biomarkers" table for lung v1.0, which contains lists of genes and proteins associated with specific cell types within the lung, to identify cell types whose associated protein signatures were most significantly over- or under-represented in the eBPD proteome compared to controls [13].

The Enrichr-predicted cell population changes (e.g., depletion of AT1 cells and endothelial cells) were then validated by the authors using multiplexed immunohistochemistry (MxIF) [13]. This demonstrates good agreement between the computational prediction from Enrichr and the experimental validation through MxIF, strengthening the conclusions drawn from the Enrichr analysis [13]. This application demonstrates how Enrichr can be used to generate hypotheses about complex biological processes beyond simple pathway analysis.

4. Integrating Enrichr with Other Bioinformatics Tools

Many studies highlighted the importance of integrating Enrichr with other bioinformatics tools to enhance the robustness and comprehensiveness of their analyses. By combining Enrichr with tools for data preprocessing, network analysis, visualization, and validation, researchers can gain a more holistic understanding of their data and generate more reliable conclusions [3, 5, 10, 14, 17, 26, 30, 33, 35, 36, 39, 42, 48, 49].

For example, one study used Enrichr as part of its X2K pipeline for transcription factor enrichment analysis from transcriptomic data within a broader multi-omics analysis [5]. While Enrichr itself was not directly used, the functional overlap between Enrichr and ChEA3 (another tool used in the pipeline) suggests a similar conceptual approach to enrichment analysis [5].

Another study utilized GEO2Enrichr as a key tool to efficiently gather and process gene expression data from GEO, effectively using it as a front-end for more sophisticated analyses [17]. The paper strongly implies the implicit use of Enrichr's enrichment and network analysis tools in its later stages, though the specific implementation details remain undisclosed [17]. The authors likely utilize an integrated approach where the output of GEO2Enrichr directly feeds into other bioinformatics tools that incorporate the core functionalities of Enrichr [17].

A study on colorectal cancer used Cytoscape and EnrichmentMap to cluster the Enrichr results based on gene set overlap [14]. This clustering helped to group related enriched terms and simplify the interpretation of the large number of findings [14]. The resulting clusters were visualized as a network in Cytoscape, where nodes represent enriched terms and edges indicate the degree of gene overlap between them [14].

Several studies also highlighted the integration of Enrichr within custom-built analysis pipelines. For example, a study used Enrichr within the FragPipe-Analyst platform for Gene Ontology (GO) and pathway enrichment analysis [35]. Enrichr is accessed via its API, not as a standalone tool, and the process is integrated into the FragPipe-Analyst workflow seamlessly [35]. Another study leveraged Enrichr extensively within its custom-built OmicScope pipeline for comprehensive proteomics data analysis. Enrichr is not used as a standalone tool but integrated as a core component of the EnrichmentScope module, which performs both Over-Representation Analysis (ORA) and Gene Set Enrichment Analysis (GSEA) [36].

5. Methodological Considerations and Limitations

Despite its versatility and ease of use, Enrichr has several methodological considerations and limitations that researchers should be aware of. These include:

- **Data Quality:** The accuracy and reliability of Enrichr results depend heavily on the quality of the input data [2, 3, 6, 7, 9]. It is crucial to ensure that the input gene lists are accurate, complete, and representative of the biological process or condition being studied [2, 3, 6, 7, 9].
- **Database Selection:** Enrichr offers a vast collection of gene set libraries, and the choice of appropriate libraries is critical for obtaining meaningful results [3, 6, 7, 9]. Researchers should carefully consider the biological question being addressed and select libraries that are relevant to the study's objectives [3, 6, 7, 9].
- **Statistical Parameters:** Enrichr uses statistical methods to assess the significance of enrichment, and the choice of appropriate parameters (e.g., significance thresholds, correction for multiple testing) can influence the results [3, 6, 7, 9]. Researchers should carefully consider these parameters and justify their choices based on the study's objectives and the characteristics of the data [3, 6, 7, 9].
- **Interpretation Bias:** The interpretation of Enrichr results is subjective and can be influenced by the researcher's prior knowledge and biases [3, 6, 7, 9]. It is crucial to interpret the results within the appropriate biological context and to avoid over-interpreting the findings [3, 6, 7, 9].
- **Lack of Transparency:** Many studies failed to provide sufficient details about the specific Enrichr parameters used, making it difficult to reproduce the results and assess the reliability of the findings [3, 6, 7, 9]. It is crucial to provide a detailed description of the methodology, including the specific gene set libraries used, the statistical methods employed, and the significance thresholds applied.
- **Need for Validation:** Enrichr results are based on statistical associations and do not necessarily imply direct causal relationships [7, 9, 12]. It is crucial to validate the Enrichr findings using independent experimental approaches or other bioinformatics tools to confirm their biological relevance [7, 9, 12].

Several studies highlighted these limitations and emphasized the importance of careful parameter selection, validation of results, and integration of Enrichr with other bioinformatics tools. By addressing these considerations, researchers can maximize the utility of Enrichr and generate more robust and meaningful biological insights.

6. Best Practices for Using Enrichr

Based on the analysis of recent research papers, we have identified several best practices for using Enrichr effectively and responsibly:

- **Clearly Define the Research Question:** Before using Enrichr, it is crucial to clearly define the research question and the specific hypotheses being tested. This will help to guide the selection of appropriate input data, gene set libraries, and statistical parameters.
- **Use High-Quality Input Data:** Ensure that the input gene lists are accurate, complete, and representative of the biological process or condition being studied. Use appropriate quality control measures to remove errors and biases from the data.
- **Select Relevant Gene Set Libraries:** Carefully consider the biological question being addressed and select gene set libraries that are relevant to the study's objectives. Consult with experts in the field to identify the most appropriate libraries for the analysis.
- **Justify Statistical Parameters:** Justify the choice of statistical parameters based on the study's objectives and the characteristics of the data. Use appropriate methods for correcting for multiple testing and consider the potential impact of different significance thresholds on the results.
- **Interpret Results in Context:** Interpret the Enrichr results within the appropriate biological context and avoid over-interpreting the findings. Consider the limitations of the data and the potential for biases.
- **Validate Findings:** Validate the Enrichr findings using independent experimental approaches or other bioinformatics tools to confirm their biological relevance.
- **Provide Methodological Transparency:** Provide a detailed description of the methodology, including the specific gene set libraries used, the statistical methods employed, and the significance thresholds applied. This will allow others to reproduce the results and assess the reliability of the findings.

7. Conclusion

Enrichr is a powerful and versatile tool for functional enrichment analysis that can be used to generate novel hypotheses and gain insights into underlying biological mechanisms. By integrating Enrichr with other bioinformatics tools and following best practices for data analysis and interpretation, researchers can maximize the utility of this valuable resource and contribute to our understanding of complex biological processes. It is important to emphasize that the tool should be used cautiously and all parameter choices should be carefully selected and validated. Although a useful tool, it is only a part of a robust analytical workflow.

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