Mapping Omics datasets on KEGG Metabolic Pathways

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Abstract. 150–250 words.

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1 Introduction

1.1 Importance of Metagenomic Approaches

Metagenomic approaches are increasingly recognized as a basis for understanding the ecology and evolution of microbial ecosystems, as well as for studying and understanding the evolution of certain diseases. Microbial communities are made up of bacteria, archaea, fungi, yeasts, eukaryotes, and viruses, which often live together in the same habitat. With the size and complexity of microbial communities, the omics data that results from their analysis this data is a difficult task [23], and a different approach is needed for the treatment of this data, as the total diversity of the biosphere cannot be studied if it is not framed in an appropriate meta-context. Until recently, there were no tools to systematically study global community function and the environment at a molecular level, because complex microbial communities are generally not amenable to laboratory study. Metagenomic approaches have provided the first large-scale insights into the function of complex microbial communities and are increasingly recognized as a basis for understanding the ecology and evolution of microbial ecosystems as genetic and metabolic networks.

1.2 Development of Bioinformatics Tools

Over the last decade, pathway analysis has emerged as a valuable aid to understanding the data generated by various "omics" technologies. As a result, several robust software tools have been developed to support pathway analysis for genomic and proteomic studies [25]. These tools combine powerful statistical analysis with visualization capabilities to help researchers identify significant

pathways involved in the conditions under study. The first pathway analysis tools were usually designed to obtain a list of differentially expressed genes [2] and compare the number of differentially expressed genes detected in each pathway of interest with the number of genes expected to be found in the pathway in question just by chance - a procedure known as over-representation analysis [16].

1.3 Current Challenges in Omics Data Analysis

The key to linking these large-scale data sets to practical values lies in bioinformatics technologies, not only in terms of computational methods but also in terms of knowledge bases. Thus, the new panorama we are facing requires the development of new software tools [3] to characterize, reconstruct, and model biochemical and regulatory pathways, as a result of the integration of functions in microbial community interactions. Metabolic networks provide an intuitive and powerful framework for understanding cellular systems. To date, virtually all pathway analysis tools have been designed and developed for the analysis of genomic or proteomic data, but not metabolomic data [25]. Although several bioinformatics resources are available for meta-omics analysis, many of them require significant computational expertise. Web interfaces are easier to use, but in most cases, they have difficulty dealing with large data files, such as those obtained in metagenomics, metatranscriptomics, or metaproteomics experiments [23]. The biological interpretation of these large datasets benefits from easy-to-use tools that automatically convert raw data into complete information, ideally with little input from users and a reduced analysis time. Bioinformatics tools for mapping pathways in meta-omics analyses are essential tools that seek to decode the complex networks of genes and proteins involved in metabolism, creating maps that elucidate the pathways within a cell, providing clarity on how genes and proteins interact and function in various biological processes, such as metabolism, signaling, and regulation. The advantages of using these tools are quite significant, as they can process and analyze voluminous data sets, which were once a cornerstone in understanding complex biological mechanisms. In addition, they help identify potential targets for therapeutic intervention and biomarkers for disease states. On the other hand, there are also disadvantages associated with these tools, as they often require a great deal of computing power and can be complex, which poses a challenge for users, who may have to overcome a steep learning curve. The development of these tools often involves programming languages suitable for data analysis and computational science, such as Python, R, or Java, and they usually incorporate specialized bioinformatics packages or libraries such as Bioconductor for R and Biopython for Python. In terms of the type of identifiers these tools use, they are based on established biological identifiers, such as Ensembl IDs, Gene Ontology IDs, or KEGG Orthology IDs. Many pathway mapping tools come with an interactive identification feature, which allows users to interact with specific elements of a pathway for further exploration or to obtain additional data on specific genes or proteins. Similarly, some tools represent several samples simultaneously. This makes it possible to carry out comparative analyses, such as contrasting diseased states with healthy

states, thus revealing differential expressions within pathways. This feature is essential for researchers who want to understand the biological implications of their experimental data in more detail. The integration of taxonomy into these tools is also of great importance, as it allows researchers to identify evolutionary relationships and distinctions between species, providing a deeper understanding of genetic and metabolic diversity in different organisms. These tools also allow for the analysis of differential expression, providing information on which genes or proteins are positively or negatively regulated under specific conditions, such as environmental stress, disease states, or stages of development.

1.4 Discussion on methodologies and tools

With the availability of manually curated metabolic network pathway diagrams and the ever-increasing volume of omics data to visualize, several tools have been developed to facilitate the interpretation of functional annotation results and represent the genes or proteins identified in metabolic pathways. For example, KEGG Mapper is a collection of pathway mapping tools, BRITE, and MODULES, supporting the integration and interpretation of large genomic and molecular datasets. It provides a comprehensive database that integrates systemic functional information with genomic and chemical data, allowing the visualization and analysis of molecular interaction networks [12]. Despite requiring an understanding of biological systems and KEGG's organizational structure for effective use, KEGG Mapper offers interactive functionalities, enabling users to explore detailed information on molecular interactions and functions. Covering a wide range of organisms, from prokaryotes to eukaryotes, the tool adapts to the specificity of each organism's pathway maps and genomic information. Its tools, such as "Search&Color Pathway", make it possible to map gene expression data, indicating positive or negative regulation [12]. It accepts lists of gene, protein, and small molecule identifiers, with formats depending on the specific tool used within KEGG Mapper, and offers visual outputs and graphics for pathways and functional hierarchies in a variety of image formats for presentations and publications [11].

KEGGCharter, reCOGnizer, and UPIMAPI are computational tools that complement each other in the analysis and interpretation of omics data [23]. KEGGCharter focuses on the representation of omics results in KEGG metabolic pathways, highlighting differential gene expression and the taxonomic classification of enzymes, which is particularly useful in metagenomic studies. ReCOGnizer offers homology-based annotation of protein domains, integrating multiple functional databases and providing data on domain names and EC numbers. UPIMAPI performs sequence homology-based annotation, collecting data from UniProtKB and other external databases [23]. These tools require specific data entry formats and detailed knowledge of the databases used, but are useful for comprehensive functional characterization and taxonomic classification based on enzyme or domain assignments, allowing for a rich and integrative analysis of complex biological datasets.

MetPA is a metabolic pathway analysis tool designed for the visualization of metabolomic data [25]. It uses R and Java languages and packages such as KEGGgraph, Graphviz, and ImageMagick to render detailed metabolic networks, available in a web interface that supports zooming without loss of quality and dynamic manipulation. The tool is designed to handle large-scale metabolomics data, covering 11 common model organisms, including humans and Escherichia coli. It offers statistical analyses such as t-test, ANOVA, and linear regression to investigate concentration differences of individual metabolites about phenotypes represented in a compound concentration table. The information is visualized as a network in a web interface, providing a robust and user-friendly metabolic pathway analysis environment [25].

DAVID is web-accessible software that integrates genomic functional annotations with intuitive graphical summaries, simplifying the annotation and rapid summarization of data according to shared categories [4], such as Gene Ontology and protein domains. Although its performance may be limited by internet connectivity and the current state of integrated databases, DAVID offers an interactive interface that facilitates navigation, detailed exploration of pathways, and visualization of genomic data. With programming languages such as Perl, Java, and Visual Basic for automation, and supporting various types of gene or protein identifiers, DAVID aids in the interpretation of differentially expressed data, easing the transition from data collection to biological significance [4]. Results are provided in HTML tables for easy review and further analysis, including links to original annotation sources for in-depth exploration.

Another tool, CellDesigner 3.5, is a modeling tool for biochemical and gene-regulatory networks, using standardized graphical notation and SBML (Systems Biology Markup Language) to facilitate the exchange of models. It offers comprehensive graphical representation and SBML interoperability, integrates with simulation and analysis software, and has an intuitive interface. It requires knowledge of SBML and its graphical notation for effective use and, as it is computer software, it may have collaborative limitations compared to web-based tools. It is programmed in Java and integrates with Systems Biology Workbench (SBW) enabled packages for analysis and simulation [7]. CellDesigner supports various biological identifiers and is not directly applicable to the representation of experimental data samples. It can include differential gene expressions in its models. It exports models in SBML format and graphic formats such as PNG and SVG for inclusion in publications [7].

GenMAPP version 2 is a tool that allows users to visualize and analyze genome-scale data, such as microarray data, in biological pathways [22]. Implemented in Visual Basic 6.0, it supports multiple gene and species annotations and allows for the customized creation of databases for a potentially unlimited number of species. This tool integrates ETL processes for extracting data from public resources such as Ensembl, Entrez Gene, and Affymetrix, supporting a wide range of identifiers such as Ensembl gene IDs, UniProt IDs, Entrez Gene IDs, and Affymetrix probe set IDs. A unique feature is the dynamic coloring of genes in pathways based on user-defined criteria, providing access to gene

annotations and external database links via HTML back pages [22]. The tool is designed to handle genome-scale datasets and interpret pathway-level changes in a wide range of organisms, including but not limited to humans, mice, yeast, worms, and others, and allows visualization of differential gene expression data and other types of biological data (e.g. SNPs, splicing variations) in the context of pathways. It uses the Microsoft Jet format for experimental datasets (.gex), gene databases (.gdb), and pathways (.mapp), and allows export to HTML, and to graphic export formats for visualization, such as PNG and SVG.

KGML-ED allows dynamic visualization, interactive navigation, and editing of KEGG pathway diagrams. This tool supports the interactive and dynamic exploration of roads, allowing the editing and creation of new roads, and facilitating the integration of user-specific data [17]. Although it requires familiarity with the KGML format and the underlying structure of KEGG pathways, KGML-ED offers semi-static and dynamic visualization techniques for enhanced, user-specific pathway analysis. Implemented in Java and using the Gravisto graph visualization toolkit, KGML-ED supports KGML identifiers for genes, allowing detailed mapping and annotation within the KEGG framework. It has interactive capabilities for browsing and modifying pathway diagrams, with user-driven customization options. The focus of KGML-ED is the manipulation and visualization of pathway diagrams rather than the representation of experimental data samples, and it allows users to color pathway components based on external analysis results [17].

MetaCore™ is a web-based computational platform for systems biology that analyzes high-throughput molecular data and integrates it for visualization and statistical analysis in the context of biological networks, pathways, and processes. With paid access and complexity for new users, it requires high-quality data and uses Perl, HTML/JavaScript, and Flash Player Plug-in [5]. It accepts identifiers such as LocusLink, SwissProt, RefSeq, and Unigene. Interactivity is possible and depends on the specific data set used by the user, focusing on *Homo sapiens* and mammals. It supports differential gene expression analysis and accepts various data input and output formats, including XML, JSON, CSV, TSV, PDF, PNG, JPEG, HTML, XLS, and XLSX [5]. Similarly, MetaDrug™ is designed to predict the main xenobiotic metabolites in humans, along with their enzymatic interactions and ADME/Tox properties. It uses algorithms to prioritize metabolites integrates quantitative structure-activity relationship (QSAR) models and provides visualization of predicted data and gene signature networks. However, it requires integration with Pipeline Pilot for future developments [5]. MetaDrug™ supports various molecular and biochemical identifiers and offers interactive capabilities. Both tools support integration with other databases and computational tools, which facilitates complex analysis of biological systems and allows users to create networks and pathways that are relevant to their experimental data and research goals [5].

Pathway Tools is bioinformatics software designed to simulate and visualize integrated collections of genomic, metabolic, and regulatory pathway data. It supports a wide range of bioinformatics data types and enables metabolic recon-

structions and predictions, as well as visualization of regulatory interactions and omics data analysis [14]. Throughout its releases, Pathway Tools has improved its capabilities and expanded its database from 800 genome/pathway databases (PGDBs) [13] to over 20,000 [15], and covering a diverse taxonomy including *E. coli*, *B. subtilis* and *P. difficile*. While learning the tool can be steep for new users and some functionalities are restricted to software or web modes, the tool maintains interactivity and compatibility with different data input and output formats, such as GenBank, SBML, and BioPAX, facilitated in recent versions by the SmartTables feature. The integration of machine-inferred and manually curated data offers a reliable and rich representation of the data for users [14].

The iPath tool is a web tool for visualizing and analyzing cellular pathways that provides interactive maps for central metabolism, secondary metabolite biosynthesis, and regulatory pathways [26]. It offers an interactive and user-friendly interface for exploring a wide range of metabolic pathway data, with the ability to map a variety of identifiers, such as KEGG, and customize maps with data such as differential expression. Throughout updates, iPath has expanded its dataset and functionalities, including new modules for KEGG pathways, reactions, and species [1]. Despite the improved interface and user experience, the tool is still dependent on internet access, which can limit accessibility for users with limited bandwidth. The latest version supports interactive analysis with details on nodes and edges, reflecting advances in the display engine and data management [1]. Export options have been improved, allowing customized maps to be included in publications or other documents.

Similarly, PathVisio is a software tool for visualizing, editing, and analyzing biological pathways, with integration into biological databases to enrich pathway information [19]. It is cross-platform due to its Java implementation and integrates with GenMAPP and MAPPFinder for statistical analysis, using GPML, an XML format for storing pathways that is extensible and backward compatible. Although it requires manual data entry, which can be time-consuming, PathVisio is enhanced by its ability to interact with other scientific tools, such as Cytoscape and Eu. Gene, increasing its applicability in bioinformatics workflows. It supports a wide range of biological entity identifiers and enables high-throughput visual data analysis [19]. The tool offers export to various graphical formats, making it useful in many areas of biological research.

Pathview is a set of tools for integrating and visualizing data based on metabolic pathways, mapping user data onto graphs of relevant pathways to facilitate analysis and interpretation. As part of the Bioconductor project, it integrates with several R packages for comprehensive data analysis and supports a wide range of identifiers for genes/proteins and compounds/metabolites [18]. Although it relies on external databases, such as KEGG, for pathway information and requires knowledge of R to use effectively, Pathview compensates with complete functionality, accessibility, and ease of automation. It is interactive, dealing with datasets of different scales and complexity, and compatible with over 2000 species. It supports the visualization of differential gene expression and other types of quantitative data, accepts data in matrix or vector formats, and gen-

erates pathway visualizations in the native KEGG and Graphviz visualizations, with customization options for nodes and edge attributes.

Pathway Tools is a Java-based application [21] and offers a visual representation of an organism's biochemical network, automatically generated from a Pathway/Genome Database (PGDB). The layout is automated, supporting large-scale data analysis and facilitating biological interpretation of omics data [20]. The tool is designed to work with whole organism datasets, integrating with Omics Viewer to overlay gene expression data and other quantitative data. However, it requires a learning curve to take full advantage of its capabilities and depends on the completeness of the underlying PGDB. Enhancements over the years include interactive web and desktop views, semantic zoom support, poster generation, and colorful, animated views for time series data [20]. It accepts tab-delimited files provided by the user, increasing its interactivity and applicability in cellular network visualization and high-throughput data analysis.

Reactome Knowledgebase is an online database that details cellular processes such as signal transduction and DNA replication in an ordered network of molecular transformations. It is a tool both for archiving biological processes and for discovering functional relationships in datasets [6]. It offers comprehensive coverage of human biological processes, with Enhanced High-Level Diagrams for enhanced visualization and in-memory data analysis tools for improved accessibility. It requires a learning curve due to the complexity of the data and focus on human biological processes. Reactome is a manually curated database that provides an intuitive web interface for pathway knowledge and a suite of data analysis tools. It allows interactive visualization of omics data on pathway diagrams and offers the export of pathway diagrams for further analysis and customization by the user [8]. Both versions support a variety of identifiers and are capable of handling large data sets.

Table 1. The available analytical tools and web servers designed for mapping pathway data, including their functions, advantages, disadvantages, supported languages, packages, types of identifiers, interac-tivity, sample representation, taxonomy considerations, differential expression analysis capabili-ties, and input/output formats.

Article Output format	Publishing date	Website	Tools	What tools do
Kanehisa M. et al.	10 November 2011	Oxford Academic	KEGG Mapper	KEGG Mapper is a collection of tools for pat

1.5 Context and importance/relevance of the project

At the forefront of bioinformatics, the project under analysis is part of the emerging field of metagenomic approaches, an area recognized for its potential in deciphering the complexity and dynamics of microbial ecosystems, as well as its relevance in the study of disease evolution. In this context, the ability to map

omics datasets into metabolic pathways represents an indispensable tool in interpreting complex interactions in genetic and metabolic networks. Metagenomics opens the door to a more comprehensive understanding of microbial ecology, enabling significant advances in science and medicine, particularly in the identification of new biomarkers and therapeutic targets.

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