SOFTWARE TOOL ARTICLE

REVISED MetaboMAPS: Pathway sharing and multi-omics data visualization in metabolic context [version 2; peer review: 2 approved]

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Abstract

Metabolic pathways are an important part of systems biology research since they illustrate complex interactions between metabolites, enzymes, and regulators. Pathway maps are drawn to elucidate metabolism or to set data in a metabolic context. We present MetaboMAPS, a web-based platform to visualize numerical data on individual metabolic pathway maps. Metabolic maps can be stored, distributed and downloaded in SVG-format. MetaboMAPS was designed for users without computational background and supports pathway sharing without strict conventions. In addition to existing applications that established standards for well-studied pathways, MetaboMAPS offers a niche for individual, customized pathways beyond common knowledge, supporting ongoing research by creating publication-ready visualizations of experimental data.

Keywords

Systems Biology, Metabolic Maps, Pathways, SVG, Metabolism, Data Visualization, Omics Data

Open Peer Review

Reviewer Status ✓ ✓

	Invited Reviewers	
	1	**2**
version 2 (revision) 17 Jul 2020		✓ report
version 1 24 Apr 2020	✓ report	? report

1 **Rachel Cavill**, Maastricht University, Maastricht, The Netherlands

2 **Bianca H. Habermann**, Aix-Marseille University, CNRS, IBDM UMR 7288, Marseille, France

Any reports and responses or comments on the article can be found at the end of the article.

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Author roles: Koblitz J: Conceptualization, Software, Visualization, Writing – Original Draft Preparation; **Schomburg D**: Funding Acquisition, Supervision, Writing – Review & Editing; **Neumann-Schaal M**: Project Administration, Validation, Writing – Review & Editing

Competing interests: No competing interests were disclosed.

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First published: 24 Apr 2020, **9**:288 https://doi.org/10.12688/f1000research.23427.1

REVISED **Amendments from Version 1**

In response to reviewer comments, we have included a more detailed review of comparable resources to emphasize the characteristics of MetaboMAPS and help users to select the best tool for their use case. Furthermore, we improved the formulations in the introduction as suggested.

Any further responses from the reviewers can be found at the end of the article

Introduction

The field of systems biology is based on the integration of data from different biological fields, e.g. transcriptomics, proteomics, metabolomics, modelling, to gain a detailed understanding of an organism. However, the data integration is still challenging to date. In particular, correlating transcriptome or proteome data to metabolome data requires careful revision based on expert knowledge of metabolic pathways and intensive manual work (Cavill *et al.,* 2016). Therefore, easily accessible tools are needed to help during analysis and interpretation of multi-omics data. When one tries to understand metabolic changes, pathway maps are often used for guidance (Cavill *et al.,* 2016). However, the number of pathway maps in scientific publications is large, as is the diversity. Solely the TCA cycle was drawn hundreds of times, being one of the most conserved pathways among all domains of life. However, even such conserved pathways exhibit differences among species: the gut pathogen *Clostridioides difficile* uses an incomplete TCA cycle (Dannheim *et al.,* 2017) and some Cyanobacteria use a TCA cycle with an additional GABA shunt and a variety of anaplerotic reactions (Will *et al.,* 2019). Conclusively, there are pathway maps that can be used for a broad range of different organisms while others are exclusive for a few species. For this reason, the overall display of pathway maps, as provided by e.g. KEGG and BRENDA, have their limitations: while pathways are widely available and immense useful for model organisms, the maps cannot provide organism- or group-specific modifications for pathways that are exclusive for small groups of organisms or are currently incompletely understood. For visualization of multi-omics data, a specific map is required both, regarding the organism and the underlying scientific question. Here we present MetaboMAPS (Koblitz, 2020), a novel web-based tool that on one hand, serves as a platform to share metabolic pathway maps in an organism-dependent manner. On the other hand, MetaboMAPS assists during interpretation of metabolism-associated data by visualizing experimental data sets on pathway maps.

Methods

Implementation

PHP is used to access an internal SQL database and to handle file and user management. In addition, a user-friendly web interface is integrated to handle pathway exploration and user interactions. The pathways can be uploaded, stored and downloaded in SVG format. SVG manipulation, including zoom, editing, and plotting of data, is done with the JavaScript Library D3. Hosting, infrastructure maintenance, and issue tracking is provided by the enzyme database BRENDA.

Operation

MetaboMAPS (Koblitz, 2020) can be accessed with every modern browser. Log-in is required for upload, editing, and sharing of pathways, but not for exploring pathways, data visualization and downloads.

Results

Sharing metabolic pathways

MetaboMAPS (Koblitz, 2020) is a platform where users can upload individual metabolic pathways and release them for the scientific community. In this process, the pathway gets a unique accession number for reference in publications. Furthermore, the user can link pathways to publications. If the pathway map includes unpublished information, it can be uploaded in confidential mode. In this way, the pathway can be shared with specified colleagues and used for data visualization, but is not available for the general public. Pathways can be found by searching category, name, assigned identifier (e.g. EC number, locus tag), or accession. A unique feature of MetaboMAPS is that uploaded maps must not follow strict conventions as other tools require. The style, detail level and content of the maps is according to the scientist's needs, and since the maps can be downloaded and modified, they can also be adjusted by other users. Pathway rating and the possibility to add comments increase the quality of uploaded pathways via community contributions. In this way, MetaboMAPS does not compete with but complements curated, comprehensive maps that are already well established. It offers a niche for tentative, novel or incomplete pathways to support ongoing research beyond common knowledge. Since MetaboMAPS creates reproducible, customizable visualizations of high quality, it is suitable to generate publication-ready figures with little effort.

Each pathway is associated with one or more organisms. In fact, it is possible to add the same pathway to hundreds of different organisms. An organism overview shows all pathway maps that are associated to a selected organism. On the other hand, the pathway overview page displays all background information, such as a list of authors, the pathway description, links to publications, and all organisms that are associated to this pathway. The pathways and information are also easily accessible on mobile devices.

Users can upload their own metabolic pathways in SVG format. We chose this particular format because it can be displayed in every modern browser, can be easily manipulated, is completely scalable, and of small file size. Additionally, SVG-files can be exported from every program that users eventually use to draw a metabolic pathway (e.g. Inkscape, Adobe Illustrator, Microsoft Powerpoint, LibreOffice Impress) and users can continue to work with their preferred software.

Multi-omics data visualization

A unique and highly useful feature of MetaboMAPS is the possibility to visualize experimental data on metabolic pathways. Suitable data sets include but are not limited to transcriptomic, proteomic, metabolomic studies, flux distributions, 13C-flux measurements and others. The process for sharing pathway maps and using them for visualization is shown in Figure 1. The first step is the upload of an existing metabolic pathway in

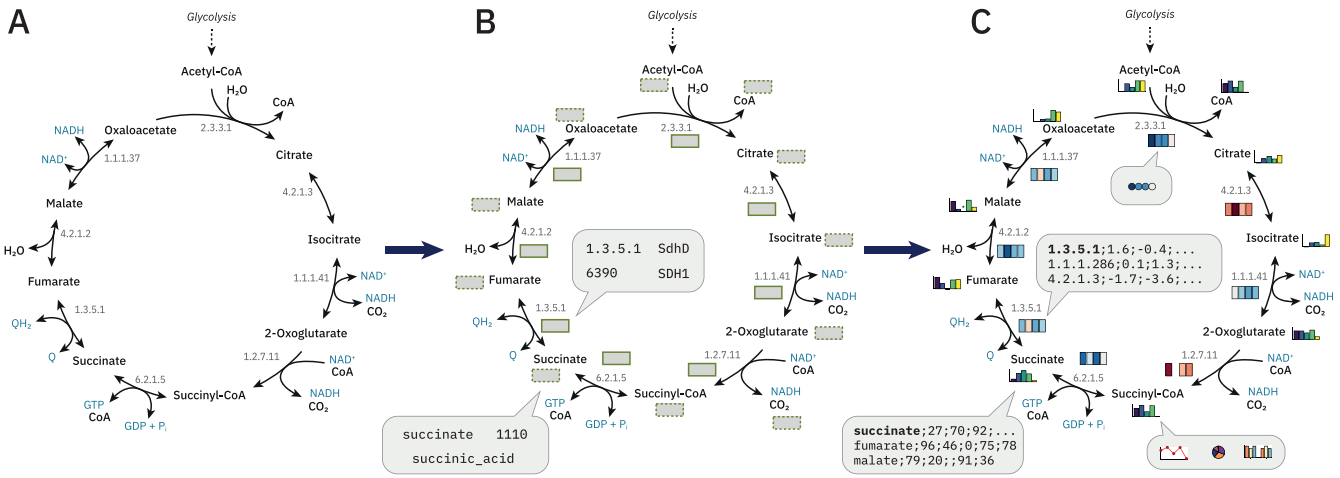

Figure 1. The process of data visualization on MetaboMAPS. (**A**) Upload the metabolic pathway in SVG format. Alternatively, you can use an existing pathway. (**B**) Draw plot boxes for metabolite (dashed border) and reaction (solid border) associated data. Assign identifiers to each plot box (e.g. EC numbers, locus tags, GI, metabolite synonyms, database IDs). (**C**) Load your own data set (as CSV file) and visualize reaction and metabolite dependent data simultaneously.

SVG format (Figure 1A). Afterwards, the user can add further information and assign the pathway to a pathway category. In the second step, an intuitive online editor is used to draw plot boxes (Figure 1B), which define the positions where the experimental data should be visualized. Each plot box can be assigned to one or more identifiers, either organism-specific (e.g. locus tags, GIs) or general (e.g. EC numbers, metabolite names). Data from the BKMS (Lang *et al.*, 2011) and BRENDA (Jeske *et al.*, 2019) databases are used to provide auto-completion of metabolites and enzymes, synonym matching, and cross-linking identifiers to other databases, e.g. BRENDA, KEGG, and MetaCyc. The identifier connects a row in the uploaded data set to a specific plot box. In the third step, any type of numerical data can be loaded in the browser and is visualized in the respective plot box (Figure 1C). Data must be in CSV-format, containing the identifiers that connect the data to plot boxes in the first row. Different types of visualization, like colour scales, a number of plot types (e.g. bar charts, line charts, heat maps), and other visual settings offer a high degree of customization. In the end, the pathway including the data visualization as well as legends can be downloaded in SVG or PNG-format.

Discussion

Among the resources for biological pathway maps, the KEGG pathways (> 500 pathways; Kanehisa *et al.*, 2019), MetaCyc (> 3800 pathways; Caspi *et al.*, 2018), and WikiPathways (>2800 pathways; Slenter *et al.*, 2018) are most considerable, having thousands of users per month and offering a large number of pathway maps. These tools differ in their application and are appropriate for different use cases. KEGG offers revised maps of high quality that can be used for visualization purposes mainly by R packages (Luo *et al.*, 2017). MetaCyc has a large number of organism-specific pathways that are popular among biochemists, but are barely used for data integration. In contrast to the other tools, WikiPathways is a community-driven approach, that requires a little effort from the users by relying on PathVisio for pathway creation. PathVisio ensures that pathways are created in compliance with established standards and can also be used to integrate experimental data.

At this moment, MetaboMAPS is a relatively small resource, but it is intended to grow with the community. The main difference to other approaches is the freedom in pathway creation and the data visualization without relying on specific external software, particular data formats or steep learning curves. MetaboMAPS allows specific, indivualized or yet incompletely understood pathways and link them to the demands on data visualization. This complements the major pathway resources available. Linking the pathways to publications will also allow re-use of the pathway. MetaboMAPS addresses biologists with nominal bioinformatical knowledge and researchers that want to share published pathway maps without much effort.

Conclusion

In summary, MetaboMAPS (Koblitz, 2020) is a platform for sharing metabolic pathway maps and visualizing data in a metabolic context. It encourages scientists to share individual pathway maps without strict conventions and offers customizable and reproducible visualizations of experimental data. It will grow in collaboration with the community and by further development by the BRENDA team.

Data availability

All data underlying the results are available as part of the article and no additional source data are required.

Software availability

Software available from: https://metabomaps.brenda-enzymes.org.

Source code available from: https://github.com/JuliaHelmecke/MetaboMAPS.

Archived source code at time of publication: https://doi.org/10.5281/zenodo.3742817 (Koblitz, 2020).

Acknowledgements

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PubMed Abstract | Publisher Full Text | Free Full Text

Open Peer Review

Current Peer Review Status: ✔ ✔

Version 2

Reviewer Report 24 July 2020

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✔ **Bianca H. Habermann**
Aix-Marseille University, CNRS, IBDM UMR 7288, Marseille, France

The authors have addressed my concerns adequately.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Computational Biology, Systems Biology, Data Integration, Evolutionary Biology, Mitochondria

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 10 June 2020

https://doi.org/10.5256/f1000research.25857.r63432

? **Bianca H. Habermann**
Aix-Marseille University, CNRS, IBDM UMR 7288, Marseille, France

MetaboMAPS is an interesting small application for making available and displaying numerical data on non-standard pathways. It can be seen as complementing the well-known and standard pathway resources, such as KEGG and others. The advancement of MetaboMAPS is the possibility to store and present incomplete or so far not described pathways. Moreover, it has a nice visualization toolbox to

display numerical data on the pathways.

There are some points that should be addressed:

1. The way the introduction is formulated currently indicates that well-established pathway resources are ignorant concerning species-specific differences of pathways. This is not true. KEGG for instance offers a rich selection of organisms and indicates that genes are missing/added to the classical pathway. It is true however when it comes to the overall display of the pathway map, which is – I think – what the authors want to express here. They should reformulate this to reflect what they mean to say properly.

2. I do not fully understand, why it is necessary to point out the disadvantages of printed pathway maps (in a book, citation Michal & Schomburg) – which by default cannot be used for any form of computerized work?

3. Sparse information is given – also on the website – of how to upload user-provided pathways. For instance, it seems necessary to add an organism, before adding a pathway. This is very un-intuitively presented at the website and should be improved.

4. The SVG format offers many advantages. However, it is not so easy to e.g. build on an existing pathway from other resources, as they often do not offer download in SVG format. Do the authors have any thoughts on how the interoperability with existing pathway resources could be improved, e.g. by allowing more and different formats for upload?

5. Should the resource become more widely used for pathways that are incomplete, it will become a problem that users don't stick to the same nomenclature. How do the authors think about consolidating novel pathways coming from multiple users that illustrate the same biological pathway, yet under a different name?

6. Whether or not it is an advantage to offer such great flexibility with respect to the pathway map is questionable. Often, users don't sick to official gene symbols, but use synonyms or other, officially not recognized gene names. The authors should comment on how they could address this issue of unconventional gene names or rarely used synonyms.

Is the rationale for developing the new software tool clearly explained?
Yes

Is the description of the software tool technically sound?
Yes

Are sufficient details of the code, methods and analysis (if applicable) provided to allow replication of the software development and its use by others?
Yes

Is sufficient information provided to allow interpretation of the expected output datasets and any results generated using the tool?
Yes

Are the conclusions about the tool and its performance adequately supported by the findings presented in the article?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Computational Biology, Systems Biology, Data Integration

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 23 Jun 2020

Julia Koblitz, Braunschweig University of Technology, Braunschweig, Germany

We highly appreciate your feedback regarding MetaboMAPS and the quality of our paper. We uploaded a new version of the latter to address your concerns.

Point 1 and 2: We changed to the manuscript accordingly.

Point 3: Thank you for your helpful feedback regarding the upload of pathway maps. We reimplemented the upload procedure to be more intuitive and user friendly. Basically, the user can now define which organisms are associated after uploading a pathway. Furthermore, we added a submenu to the navigation bar.

Point 4: Interoperability is an important topic. The SVG format was our favourite choice because it can be exported from nearly every tool that users eventually use to draw their pathways. Additionally, there exists a number of conversion tools to convert nearly every vector-based format to SVG (we provide How-Tos on the website). Also existing platforms often provide export to SVG, e.g. we tried to add pathways exported from WikiPathways and BRENDA and it worked perfectly fine. However, we are open to include other data formats (e.g. KGML) in the future. Therefore, we would like to rely on user surveys once the tool has a larger community.

Point 5: Regarding concerns about pathway nomenclature, we agree that this will be an issue in the future. At this point, we group pathways roughly using 19 pathway categories. Pathways can furthermore be found using identifiers such as EC numbers or metabolites using the search function. However, with increasing numbers of pathways, we will consider implementing a system based on pathway ontologies (e.g. https://www.ebi.ac.uk/ols/ontologies/pw) at a later time point.

Point 6: We agree that flexibility is associated with high variability. For this reason, we implemented a system underlying the identifiers that gives the most possible consistency and connectivity, but maintains the flexibility: among inofficial gene names and locus tags, EC numbers are used for reactions and linked to the BRENDA enzyme database. Furthermore, a synonym database is used to match all known metabolite synonyms and connect them to other databases, i.e. BRENDA, KEGG, MetaCyc, and Sabio-RK.

Competing Interests: No competing interests were disclosed.

Reviewer Report 28 May 2020

https://doi.org/10.5256/f1000research.25857.r63026

Rachel Cavill
Department of Data Science and Knowledge Engineering, Maastricht University, Maastricht, The Netherlands

The authors, through this short descriptive paper, present MetaboMaps, a new tool for uploading pathways and overlaying data from multiple omics. The pathways are visualised clearly with multiple options for the type of overlays available.

The program is open source and publicly available, making it easy for others to access and examine as needed.

This paper would be strengthened by including a better review of other platforms/tools which do similar or related tasks. In particular, the authors should look at wikipathways, and the combination of wikipathways with pathvisio or cytoscape, and explore how their approach differs from what is currently available through these tools. By highlighting the differences and similarities between approaches it will make it easier for potential users to evaluate the platform and select the best tool for their datasets.

Is the rationale for developing the new software tool clearly explained?
Partly

Is the description of the software tool technically sound?
Yes

Are sufficient details of the code, methods and analysis (if applicable) provided to allow replication of the software development and its use by others?
Yes

Is sufficient information provided to allow interpretation of the expected output datasets and any results generated using the tool?
Yes

Are the conclusions about the tool and its performance adequately supported by the findings presented in the article?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: multi-omics integration, pathway analysis, omics data visualisation.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 23 Jun 2020

Julia Koblitz, Braunschweig University of Technology, Braunschweig, Germany

Thank you for your feedback regarding our manuscript. We uploaded a new version of our paper and included a review on other resources as suggested.

Competing Interests: No competing interests were disclosed.