SOFTWARE TOOL ARTICLE

UPDATE Interactive exploratory data analysis of Integrative Human Microbiome Project data using Metaviz [version 2; peer review: 3 approved]

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Abstract

The rich data produced by the second phase of the Human Microbiome Project (iHMP) offers a unique opportunity to test hypotheses that interactions between microbial communities and a human host might impact an individual's health or disease status. In this work we describe infrastructure that integrates Metaviz, an interactive microbiome data analysis and visualization tool, with the iHMP Data Coordination Center web portal and the *HMP2Data* R/Bioconductor package. We describe integrative statistical and visual analyses of two datasets from iHMP using Metaviz along with the *metagenomeSeq* R/Bioconductor package for statistical analysis of differential abundance analysis. These use cases demonstrate the utility of a combined approach to access and analyze data from this resource.

Keywords

metagenomics, visualization, R/Bioconductor, Integrative Human Microbiome Project

This article is included in the **Bioinformatics** gateway.

Open Peer Review

Approval Status

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2. **Edoardo Pasolli** , University of Naples Federico II, Naples, Italy
3. **Levi Waldron** , City University of New York, New York, USA

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

This article is included in the **Bioconductor** gateway.

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UPDATE Updates from Version 1

In this version, we prioritized improving the usability and accessibility of using Metaviz for interactive visual exploration of the Human Microbiome Project data resources including adding tutorials and updating documentation for use cases such as generating diversity plots. The documentation updates also include creating a vignette in the *metavizR* R/Bioconductor package for visualizing variables from protected resources in a local R session. We also provide default workspaces for the HMP datasets available in Metaviz and they are linked from metaviz.org. We include information on how we expect to update the data served through Metaviz based on changes to the *HMP2Data* R/Bioconductor package. Also, we have updated Figures with higher resolution images. Finally, we provided more explanation of the taxonomic features that we found as differentially abundant and detailed the provenance of the taxonomic assignments. We have updated the references section to reflect citation changes due to these updates.

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

Introduction

Metagenomics allows researchers to perform a microbial community census and investigate associations between host phenotype and community status. Metagenomics has been used successfully to track pathogen spread¹ and identify intervention strategies in childhood malnutrition². Integrative analysis of samples using multiple sequencing technologies allows for comparison at various levels of granularity. The second phase of the Human Microbiome Project (iHMP) offers a unique opportunity to test hypotheses of interactions between the microbial community and the human host. To examine the iHMP data resource, we use Metaviz³, an interactive microbiome exploratory data analysis and visualization tool, and *metagenomeSeq*⁴, an R/Bioconductor package for statistical analysis of differential abundance analysis, for combined visual and statistical analysis.

Human Microbiome Project Phase II

The second phase of the HMP, also called the Integrative Human Microbiome Project (iHMP), consisted of focused studies of three diseases – Inflammatory Bowel Disease (IBD), Type II Diabetes (T2D), and Multi-Omic Microbiome Study: Pregnancy Initiative (MOMS-PI)⁵. The overall goal of the project was to identify associations between human microbiome community census data and the three diseases. Each of the studies were structured for the specific disease and consisted of separate cohorts.

Metaviz

Metaviz⁶ is a web-based interactive visualization tool for microbiome data analysis. The architecture consists of a JavaScript front-end suite of charts (based on D3.js and Canvas) and a navigation component that lets users select portions of taxonomic hierarchies to visualize and analyze. Metaviz supports two backend data stores – a graph database and the *metavizR* R/Bioconductor package. Metaviz is tightly integrated with the *metagenomeSeq* statistical testing package so differential abundance testing results can be viewed

directly in a Metaviz session. We host an instance of Metaviz that we call the UMD Metagenome Browser (<http://metaviz.cbcb.umd.edu>).

Related work

Visualization tools for large-scale sequencing consortium projects provide a mechanism to explore and interact with data from multiple studies. These applications help users analyze individual datasets and examine trends across the entire project. MAGI is a web-application that enables a user to examine data from TCGA data⁷. The Earth Microbiome Project provides an interactive visualization web-application to analyze its data⁸. EMPeror offers interactive 3D visualizations of PCA plots to show distances between microbiome samples⁹. QIIME packages a number of tools for static plotting of Principal Coordinate Analysis and stacked bar plots¹⁰. MetaPhlAn2 uses a visualization package called GraphPhlan to produce phylogenetic trees and other plots¹¹. The *HMP2Data* R/Bioconductor provides processed 16S sequencing data from the iHMP project in Bioconductor data structures¹². We implemented Metaviz using design patterns from Epiviz¹³, an interactive epigenetics visualization tool, that visualizes data from a variety of epigenetic sequencing projects. We show how we leverage the microbiome measurement-based design of Metaviz to implement interactive exploration and hypothesis-testing of the iHMP resource.

Implementation

Metaviz integration with HMP infrastructure

The HMP Data Access and Coordination Center maintains a data repository and web portal (<https://www.ihmpdcc.org>). From this web portal, users can browse metadata for datasets, raw sequencing files, and processed files including taxonomic community profile abundance matrices. We implemented several mechanisms to interact with the HMP data resources through Metaviz⁶.

Data loaded into UMD Metagenome Browser

We loaded the 16S community profile abundance matrices for the samples from the IBD, T2D, and MOMS-PI studies as provided by the *HMP2Data* Bioconductor package¹² into the **UMD Metagenome Browser**. A user can select each dataset from the application start screen. **Figure 1** details the number of samples, with metadata to the extent available as of May 2020 from the *HMP2Data* package, from each project currently available in the UMD Metagenome Browser.

HMP Data Portal linking to Metaviz

When browsing the samples available from the HMP Data Portal, a user can view an individual abundance matrix in Metaviz using the Metaviz tool link from the file description page. When the user clicks the link, a redirect occurs to the UMD Metagenome Browser with a new workspace containing a FacetZoom navigation utility and a heatmap for that sample. **Figure 1A** shows the direct link functionality for samples in the IBD dataset and resulting workspace in Metaviz (**Figure 1B**).

Metaviz import of Data Portal Manifest

In the HMP data portal, a user can select files with a shopping cart utility and download the selections as a manifest file. In the UMD Metagenome Browser, the user can upload the manifest

Figure 1. Metaviz and iHMP data infrastructure integration. Top: iHMP data accessible through the UMD Metagenome Browser. Middle (A, B): Single sample link from data portal to UMD Metagenome Browser. Bottom (C, D): Multiple samples manifest file upload and selection to UMD Metagenome Browser. We provide several mechanisms to access the HMP dataset from Metaviz. First, we loaded the three datasets (IBD, T2D, and MOMS-PI) into the hosted instance of Metaviz directly. A user can choose any of these datasets from the data selections screen then samples can be chosen within each dataset. We also link to the HMP Data Portal for single samples as shown in the Middle panel (A, B). Finally, the HMP Data Portal provides a “cart” functionality where a user can select multiple samples and download a manifest listing those files (C). A user can upload a manifest file containing selections from the 16S community abundance profiles from the same dataset (IBD, T2D, or MOMS-PI) to the UMD Metagenome Browser and a new Metaviz workspace is created with those files (D).

file to create a Metaviz workspace on the fly for those samples. Currently, only files from the same project can be viewed in one workspace. Resolving taxonomic hierarchies across datasets in Metaviz is future work that could use a utility such as the *metagenomeFeatures* R/Bioconductor package¹⁴. Figure 1C shows the manifest file workflow for samples from the IBD dataset and resulting workspace in Metaviz (Figure 1D).

Metaviz usage

For ease of use, we provide tutorials at <https://epiviz.github.io/tutorials/metaviz/>. As a community resource, we plan to update the Metaviz database within a month of Bioconductor releases of *HMP2Data*. We maintain links to the HMP Data Portal through the update of *HMP2Data* package URLs and provide

default workspaces for the HMP2 datasets as well as those in *HMP16SData* R/Bioconductor package (<https://epiviz.github.io/metaviz-workspaces/>). For generating data summaries, we recommend using the *HMP2Data* package with appropriate R libraries to summarize sample information and the interactive HMP Data Portal for data summaries over different samples or study attributes. We provide instructions in the *metavizr* vignette to handle visualizing data that would be added to an analysis session like protected variables from dbGAP.

Operation

The HMP Data Portal and Metaviz are web applications that can run in any modern browser. We recommend using Firefox (version 65 or later) or Chrome (version 65 or later) for best

performance. *Metavizr* is a Bioconductor package and general guidelines from Bioconductor for requirements and installation should be followed (<https://bioconductor.org/install/>).

Use cases

metavizr analysis of WGS vs 16S data from same samples

In the IBD cohort of the iHMP dataset, investigators sequenced a subset of samples using whole metagenome and 16S sequencing. We developed functions in *metavizr* to compare 16S and whole metagenome data for individual samples. Using the taxonomic profiles of the IBD samples, we matched the taxonomic features discovered with both sequencing methods. With this subset of features, we generated a single taxonomic hierarchy then loaded the 16S and whole metagenome abundance measurements into a *metavizr* object. **Figure 2** shows an example analysis with stacked plots and scatter plots that link to a single FacetZoom to compare the degree of consistency of the data across sequencing methods.

IBD dataset

The IBD study consisted of two phases: a pilot, which we refer to in this work as the IBD Stool Pilot, and a larger phase that we call IBD iHMP. We use the taxonomic profiles for each

phase available from the *HMP2Data* package and use the same taxonomic classification identifiers in the package. To upload project data on to the UMD Metagenome Browser, we extracted 16S count table and taxonomic annotation using the *otu_table()* and *tax_table()* methods of *HMP2Data* package. We then use *metagenomeSeq* and *metavizr* to import the count data along with taxonomy and sample metadata into a neo4j graph database¹⁵ using the *metavizr* neo4j import functionality. We used *Metaviz*⁶ for exploratory analysis and *metagenomeSeq* for confirmatory statistical testing. We examined the IBD Stool Pilot and IBD iHMP dataset separately.

IBD Stool Pilot dataset

The IBD Stool Pilot dataset contains 16S and whole metagenome sequencing results of stool samples from 41 Crohn's disease (CD) subjects and 10 ulcerative colitis (UC) subjects. We focused our analysis on 16S sequencing and used *Metaviz* to visually identify taxa that showed a difference in abundance between CD and UC subjects. **Figure 3** shows a typical visualization.

We also used *metagenomeSeq* to test the differential abundance of features aggregated to each level of the taxonomy using the *fitFeatureModel* method that is based on a zero-inflated

Figure 2. Comparison between 16S and WGS taxonomic profiling using *metavizr*. We identified taxa present in the taxonomic hierarchy for each method and created a merged dataset. A FacetZoom (bottom) shows the common taxonomic features, two Stacked Plots (middle) show the proportion of all features aggregated to the Order level, and a set of scatter plots (top) for samples with WGS abundance on the X-axis and 16S abundance on the Y-axis. For WGS, the relative proportion output from MetaPhlan for taxa at the order level were transformed to counts per 1000 reads. The scatter plots show the variability in taxonomic community census estimates between sequencing methods. A static similar stacked plot visualization is shown in the main HMP consortium manuscript at the genus and species level across samples for comparison¹⁶. *Metavizr* allows users to make specific selections of the FacetZoom to compare taxa at various levels. The scatter plot also allows comparison at single sample resolution. Code to create this *Metavizr* session is available at the following gist: <https://gist.github.com/jkanche/9216d465d18ab106be7a43f5340eb38a>.

log-normal linear model. As shown in [Table 1](#), two species had an absolute log fold-change greater than 1 and adjusted (Benjamini-Hochberg) p-value less than 0.1. Visually inspecting the IBD Stool Pilot data by aggregating counts to each level of the taxonomy we found the following features appearing differentially abundant: “c__Betaproteobacteria”, “o__Burkholderiales”, “f__Ruminococcaceae”, “g__Lachnospira”, “g__[Ruminococcus]”, “g__Faecalibacterium”, “s__589277”, “s__333166”, “s__564806”, “s__369227”, “s__358104”, “s__369486”, “s__gnavus:360015”, “s__prausnitzii:851865”. These taxonomic features describe paths in the taxonomy of the Kingdom Bacteria that was derived from the SILVA¹⁷ database. The documentation

(<https://ibdmdb.org/tunnel/public/HMP2/16S/1806/products>) for the abundance profiles used in this analysis denotes that this taxonomic string was generated with the sequence of an OTU derived with the UPARSE algorithm¹⁸ that was mapped to the SILVA database. Among these features, “c__Betaproteobacteria” refers to Class Betaproteobacteria, “o__Burkholderiales” to Order Burkholderiales, while values towards the leaves of the taxonomy refer to entries in the SILVA database that have an identifier and a sequence but have not been provided formal names in the binomial nomenclature system. Comparing the visual analysis results and the *metagenomeSeq* differential abundance testing results in **Table 1** shows that the taxonomic feature s_369227

Figure 3. Metaviz Analysis of IBD Stool 16S Pilot Dataset. A Metaviz workspace with a FacetZoom taxonomic hierarchy, heatmap, and boxplot for the specific feature in this instance s__369227. This identifier was from the community abundance profiles available from the HMP2Data package. We identified taxonomic features at each level of the hierarchy using this integrated view and the results for features with a potential differential abundance are listed in Supplementary Table 1. The workspace is available at: <http://metaviz.cbcb.umd.edu/?ws=oLq2Fr9AwVc>.

Table 1. metagenomeSeq analysis of IBD Stool 16S Pilot dataset.

	Log fold change	se	p-value	Adjusted p-value
s_ :369227	1.864583442	0.431193725	1.53061E-05	0.000734694
s_ :363232	1.193035074	0.275415013	1.47914E-05	0.000734694

We used the fitFeatureModel of *metagenomeSeq* and aggregated counts to each level of the taxonomic hierarchy. Our analysis identified s_369227 under family *Lachnospiraceae* and s_363232 under genus *Dorea* as differentially abundant between samples from subjects diagnosed with Ulcerative Colitis and Crohn's Disease.

(member of the Lachnospiraceae family which are strictly anaerobic¹⁹) was identified using both methods. Members of Lachnospiraceae are abundant in human intestinal tracts and have been linked specifically to production of butyric acid¹⁹. Also, colonization with a specific strain of Lachnospiraceae in obese mice has been linked to development of hyperglycemia²⁰. The second taxon, s__363232, is a member of the genus *Dorea* which has recently been shown to be associated with diarrhea predominant irritable bowel syndrome²¹.

IBD iHMP

The IBD iHMP dataset consists of samples from subjects with CD, UC, and those without IBD (nonIBD). For these samples, we analyzed the 16S sequencing data of an ileum biopsy from the first visit for each subject, which yielded 72 samples with 32 from CD, 18 from CD, and 22 from nonIBD. We used *metagenomeSeq* to compute an F-statistic to determine if any taxonomic feature is associated with at least one group using the *fitZig* method (based on a zero-inflated Normal linear model on log-transformed counts appropriate for multi-category experiment designs). **Figure 4** shows an example using Metaviz to visualize abundance profiles for phylum Fusobacteria, which was found to be differentially abundant across the three

groups. Differential abundance of members of this phylum has previously been reported in studies of IBD²². Analysis code and results are available as *Extended data*²³.

Conclusion

In this work we presented software infrastructure linking Metaviz to the iHMP data resources⁶. We detailed the 16S taxonomic community profile data from iHMP available in the UMD Metagenome Browser. We then described linking the UMD Metagenome Browser to the iHMP Data Portal for single files and the manifest file utility for multiple file selections. We also performed visual exploratory and confirmatory differential abundance analysis of data from the IBD study. We first visualize 16S and whole metagenome sequencing abundance measurements for the same samples in *metavizr*. Then we use Metaviz and *metagenomeSeq* to analyze two datasets, IBD Stool Pilot and iHMP IBD, to examine taxonomic feature abundances in samples from UC, CD, and those without IBD. These illustrative analyses demonstrate the utility of Metaviz for integrative analysis with the HMP data resources. Visual inspection of taxonomic features coupled with statistical testing provides an effective mechanism to explore and test associations between bacterial communities and their human hosts.

Figure 4. IBD Biopsy iHMP Multiple Groups Analysis. Using statistical analysis we identified taxonomic features that showed a difference in abundance between the three subject diagnosis categories: UC, CD, or nonIBD in the Fusobacteria phylum. This Metaviz workspace is available at: <http://metaviz.cbcb.umd.edu/?ws=wHsHT56U8Ru>.

Data availability

Source data

The 16S abundance matrices for IBD, T2D and the MOMS-PI studies were downloaded from the *HMP2Data* Bioconductor package. These datasets are then loaded into the neo4j graph database using import methods available in the *metaviz*²⁴ Bioconductor package. These import scripts are available at <https://gist.github.com/jkanche/c57d8220a33b41e21c4f6769a7aef7e4>.

Extended data

Figshare: Differential Abundance Analysis - IBD (Figure 4). <https://doi.org/10.6084/m9.figshare.12404222.v2>²³.

This file contains differential abundance analysis code and results.

Extended data are available under the terms of the [Creative Commons Attribution 4.0 International license](#) (CC-BY 4.0).

Software availability

Metaviz is available at: <http://metaviz.cbcb.umd.edu>.

Source code available from: <https://github.com/epiviz/Metaviz>.

Archived source code at time of publication: <http://doi.org/10.5281/zenodo.3871869>⁶.

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References

- Miller RR, Montoya V, Gardy JL, et al.: **Metagenomics for pathogen detection in public health**. *Genome Med*. 2013; **5**(9): 81.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Blanton LV, Charbonneau MR, Salih T, et al.: **Gut bacteria that prevent growth impairments transmitted by microbiota from malnourished children**. *Science*. 2016; **351**(6275).
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Wagner J, Chelaru F, Kancherla J, et al.: **Metaviz: interactive statistical and visual analysis of metagenomic data**. *Nucleic Acids Res*. 2018; **46**(6): 2777–2787.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Paulson JN, Stine OC, Bravo HC, et al.: **Differential abundance analysis for microbial marker-gene surveys**. *Nat Methods*. 2013; **10**(12): 1200–1202.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Integrative HMP (iHMP) Research Network Consortium: **The integrative human microbiome project: Dynamic analysis of microbiome-host omics profiles during periods of human health and disease**. corresponding author. *Cell Host Microbe*. 2014; **16**(3): 276–289.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Kancherla J, Chelaru F, Hcorrada J, et al.: **epiviz/Metaviz: release for submission (Version 0.1.1)**. *Zenodo*. 2020.
<http://www.doi.org/10.5281/zenodo.3871869>
- Leiserson MDM, Gramazio CC, Hu J, et al.: **MAGI: Visualization and collaborative annotation of genomic aberrations**. *Nat Methods*. 2015; **12**(6): 483–484.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Thompson LR, Sanders JG, McDonald D, et al.: **A communal catalogue reveals Earth's multiscale microbial diversity**. *Nature*. 2017; **551**(7681): 457–463.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Vázquez-Baeza Y, Pirrung M, Gonzalez A, et al.: **EMPeror: a tool for visualizing high-throughput microbial community data**. *Gigascience*. 2013; **2**(1): 16.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Caporaso JG, Kuczynski J, Stombaugh J, et al.: **QIIME allows analysis of high-throughput community sequencing data**. *Nat Methods*. 2010; **7**(5): 335–336.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Truong DT, Franzosa EA, Tickle TL, et al.: **MetaPhlAn2 for enhanced metagenomic taxonomic profiling**. *Nat Methods*. 2015; **12**(10): 902–903.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Stansfield J, Smirnova E, Zhao N, et al.: **HMP2Data: 16s rRNA sequencing data from the Human Microbiome Project 2**. 2019.
[Publisher Full Text](#)
- Chelaru F, Smith L, Goldstein N, et al.: **Epiviz: Interactive visual analytics for functional genomics data**. *Nat Methods*. 2014; **11**(9): 938–40.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Olson ND, Shah N, Kancherla J, et al.: **metagenomeFeatures: An R package for working with 16S rRNA reference databases and marker-gene survey feature data**. *bioRxiv*. 2018.
[Publisher Full Text](#)
- The Neo4j Graph Database**.
[Reference Source](#)
- Human Microbiome Project Consortium: **Structure, function and diversity of the healthy human microbiome**. *Nature*. 2012; **486**(7402): 207–14.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Yilmaz P, Parfrey LW, Yarza P, et al.: **The SILVA and “all-species Living Tree Project (LTP)” taxonomic frameworks**. *Nucleic Acids Res*. 2014; **42**(Database issue): D643–D648.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Edgar, RC: **UPARSE: Highly accurate OTU sequences from microbial amplicon reads**. *Nat Methods*. 2013; **10**(10): 996–998.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Meehan CJ, Beiko RG: **A phylogenomic view of ecological specialization in the lachnospiraceae, a family of digestive tract-associated bacteria**. *Genome Biol Evol*. 2014; **6**(3): 703–713.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Kameyama K, Itoh K: **Intestinal Colonization by a Lachnospiraceae Bacterium Contributes to the Development of Diabetes in Obese Mice**. *Microbes Environ*. 2014; **29**(4): 427–430.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Maharshak N, Ringel Y, Katibian D, et al.: **Fecal and Mucosa-Associated Intestinal Microbiota in Patients with Diarrhea-Predominant Irritable Bowel Syndrome**. *Dig Dis Sci*. 2018; **63**(7): 1890–1899.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Strauss J, Kaplan GG, Beck PL, et al.: **Invasive potential of gut mucosa-derived fusobacterium nucleatum positively correlates with IBD status of the host**. *Inflamm Bowel Dis*. 2011; **17**(9): 1971–1978.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Bravo HC: **Differential Abundance Analysis - IBD (Figure 4)**. *figshare*. Online resource. 2020.
<http://www.doi.org/10.6084/m9.figshare.12404222.v2>
- Bravo HC, Chelaru F, Wagner J, et al.: **metaviz: R Interface to the metaviz web app for interactive metagenomics data analysis and visualization**. 2020.
[Publisher Full Text](#)

Open Peer Review

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Ekaterina Smirnova

Department of Biostatistics, Virginia Commonwealth University, Richmond, USA

No further comments to make.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Biostatistics (working on Human Microbiome Project data)

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 20 July 2020

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The authors present a web tool for exploratory analysis of iHMP data, based on their existing

metaviz software. The figures from the manuscript were easy to reproduce using the links and code provided. It seems like a useful new way to view, explore, and download iHMP data. I have only a couple minor comments:

1. The figures are low-resolution and text is a bit blurry. The lightest yellow text in Figure 2 isn't readable.
2. From <http://metaviz.cbcb.umd.edu/> it's not immediately obvious how to find the iHMP (HMP2) data. IBD and T2D do appear a ways down a list of available datasets, but this list takes a very long time to load for me ("loading datasets and sample annotations..."). I didn't find MOMS-PI but I may not have waited long enough. It would be worth providing direct links in the manuscript to workspaces for each dataset, like is already done for Figure 3.
3. Perhaps explain the feature variables like c__Betaproteobacteria, o__Burkholderiales, f__Ruminococcaceae, g__Lachnospira, g__[Ruminococcus], g__Faecalibacterium, s__:589277, s__:333166, s__:564806, s__:369227, s__:358104, s__:369486, s__gnavus:360015, s__prausnitzii:851865 for readers who are familiar with scientific taxonomy names but not this format.

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: bioinformatics, bioinformatics, metagenomics, human microbiome analysis.

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 21 Apr 2021

Hector Corrada Bravo

Reviewer Comment: The figures are low-resolution and text is a bit blurry. The lightest yellow text in Figure 2 isn't readable.

Author Response: We updated the color scheme for Figure 2. We also updated figures with a higher resolution.

Reviewer Comment: From <http://metaviz.cbcb.umd.edu/> it's not immediately obvious how to find the iHMP (HMP2) data. IBD and T2D do appear a ways down a list of available datasets, but this list takes a very long time to load for me ("loading datasets and sample annotations..."). I didn't find MOMS-PI but I may not have waited long enough. It would be worth providing direct links in the manuscript to workspaces for each dataset, like is already done for Figure 3.

Author Response: We developed default workspaces for IBD, T2D, and MOMS-PI as well as put them at <https://epiviz.github.io/metaviz-workspaces/>

Reviewer Comment: Perhaps explain the feature variables like c__Betaproteobacteria, o__Burkholderiales, f__Ruminococcaceae, g__Lachnospira, g__[Ruminococcus], g__Faecalibacterium, s__:589277, s__:333166, s__:564806, s__:369227, s__:358104, s__:369486, s__gnavus:360015, s__prausnitzii:851865 for readers who are familiar with scientific taxonomy names but not this format.

Author Response: We added the following text to the manuscript: "These taxonomic features describe paths in the taxonomy of the Kingdom Bacteria that was derived from the SILVA¹⁶ database. The documentation (<https://ibdmdb.org/tunnel/public/HMP2/16S/1806/products>) for the abundance profiles used in this analysis denotes that this taxonomic string was generated using the sequence of an OTU derived with the UPARSE algorithm¹⁷ that was mapped to the SILVA database. Among these features, "c__Betaproteobacteria" refers to Class Betaproteobacteria, "o__Burkholderiales" to Order Burkholderiales, while values towards the leaves of the taxonomy refer to entries in the SILVA database that have an identifier and a sequence but have not been provided formal names in the binomial nomenclature system"

Competing Interests: No competing interests were disclosed.

Reviewer Report 16 July 2020

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The manuscript by Justin Wagner *et al.* presents an infrastructure that integrates Metaviz, an interactive microbiome data analysis and visualization tool that was previously published by the same authors, with the iHMP Data Coordination Center web portal and the HMP2Data R/Bioconductor package. The authors give an overall overview of the infrastructure in addition to a couple of use cases.

This is a nice and timely contribution that helps in using the large and complex set of available HMP data. The manuscript is already well structured, I have just few comments:

1. Please check all the links reported in the text. For example, the link to the data repository and web portal (<https://ihmpdcc.org>) doesn't seem to work.
2. How will the proposed infrastructure deal with likely updates (in terms of new data) of the HMP web portal?
3. Which are the options available to save/export the results generated in the proposed infrastructure? Please comment more about this in the text.

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?

Partly

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: Microbiome and bioinformatics

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 21 Apr 2021

Hector Corrada Bravo

Reviewer Comment: Please check all the links reported in the text. For example, the link to the data repository and web portal (<https://ihmpdcc.org>) doesn't seem to work.

Author Response: We have updated the link to <http://www.ihmpdcc.org> and checked that it resolves.

Reviewer Comment: How will the proposed infrastructure deal with likely updates (in terms of new data) of the HMP web portal?

Author Response: We updated the manuscript with the following: "As a community resource, we plan to update the Metaviz database within a month of Bioconductor releases of HMP2Data. We maintain links to the HMP Data Portal through the update of HMP2Data package URLs and provide default workspaces for the HMP2 datasets as well as those in HMP16SData R/Bioconductor package (<https://epiviz.github.io/metaviz-workspaces/>)"

Reviewer Comment: Which are the options available to save/export the results generated in the proposed infrastructure? Please comment more about this in the text.

Author Response: We added the following tutorial to https://epiviz.github.io/tutorials/metaviz/save_plots/

Competing Interests: No competing interests were disclosed.

Reviewer Report 06 July 2020

<https://doi.org/10.5256/f1000research.26859.r64704>

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Manuscript "Interactive exploratory data analysis of Integrative Human Microbiome Project data using Metaviz" by Wagner *et al.* provides a novel interactive tool for visualization of interactive Human Microbiome Project (iHMP) Data. This tool encompasses both the HMP Data coordination center (DAC) portal as well as the Bioconductor HMP2Data package. Given the size and complexity of HMP data, this visualization tool allows users to explore major data summaries and patterns. As such, this work is very timely and is highly recommended for publication.

Major comments:

1. How does the tool handle HMP DAC and HMP2Data package data updates? There is discussion that user can upload additional data manifest from HMP DAC portal, but what if the data already available through Metaviz tool is updated on the DAC or Bioconductor?
2. Is there an option to download data summaries? Such as demographics table, number of samples by body site, etc.
3. MOMS-PI and T2D studies have protected meta data available through dbGap. If users apply for dbGap and get access, is there an option to merge meta data by sample ids and visualize using this tool?
4. It would be helpful to provide instructions how to create diversity boxplots by disease status (as in Figure 3). I tried creating these but could not produce them on the same plot.
5. I recommend making alpha diversity plots by disease status a default plot when the data is selected using visualization tool.

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?

Partly

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: Biostatistics (working on Human Microbiome Project data)

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 21 Apr 2021

Hector Corrada Bravo

Reviewer Comment: How does the tool handle HMP DAC and HMP2Data package data

updates? There is discussion that user can upload additional data manifest from HMP DAC portal, but what if the data already available thought Metaviz tool is updated on the DAC or Bioconductor?

Author Response: We updated the manuscript with the following: “As a community resource, we plan to update the Metaviz database within a month of Bioconductor releases of HMP2Data. We maintain links to the HMP Data Portal through the update of HMP2Data package URLs and provide default workspaces for the HMP2 datasets as well as those in HMP16SData R/Bioconductor package (<https://epiviz.github.io/metaviz-workspaces/>)”

Reviewer Comment: Is there an option to download data summaries? Such as demographics table, number of samples by body site, etc.

Author Response: We updated the manuscript with the following: “For generating data summaries, we recommend using the HMP2Data package with appropriate R libraries to summarize sample information and the interactive HMP Data Portal for data summaries over different samples or study attributes. We provide instructions in the metavizr vignette to handle visualizing data that would be added to an analysis session like protected variables from dbGAP”

Reviewer Comment: MOMS-PI and T2D studies have protected meta data available through dbGap. If users apply for dbGap and get access, id there an option to merge meta data by sample ids and visualize using this tool?

Author Response: We added a vignette to the metavizr Bioconductor package (<https://github.com/epiviz/metavizr/pull/2/commits/756cc049a2c9264355e15df42cfa64d71ee141ae#diff-46f4a8e59ff35c66f1220d9cdc6abf687d92771b424f4a6dfed1434c998cd500>) for added a protected variable and then generate new plots with it.

Reviewer Comment: It would be helpful to provide instructions how to create diversity boxplots by disease status (as in Figure 3). I tried creating these but could not produce them on the same plot.

Author Response: We added a tutorial at metaviz.org for including a diversity plot (https://epiviz.github.io/tutorials/metaviz/diversity_plot/).

Reviewer Comment: I recommend making alpha diversity plots by disease status a default plot when the data is selected using visualization tool.

Author Response: We created default workspaces at <https://epiviz.github.io/metaviz-workspaces/> with alpha diversity plots on either the disease or an interesting attribute.

Competing Interests: No competing interests were disclosed.

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