ReconMap: An interactive visualisation of human metabolism

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Abstract

A genome-scale reconstruction of human metabolism, Recon 2, is available but no interface exists to interactively visualise its content integrated with omics data and simulation results. We manually drew a comprehensive map, ReconMap 2.0, that is consistent with the content of Recon 2. We present it within a web interface that allows content query, visualization of custom datasets and submission of feedback to manual curators. ReconMap can be accessed via \url{http://vmh.uni.lu}, with network export in a Systems Biology Graphical Notation compliant format. A Constraint-Based Reconstruction and Analysis (COBRA) Toolbox extension to interact with ReconMap is available via \url{https://github.com/opencobra/cobratoolbox}.

1 INTRODUCTION

A genome-scale metabolic reconstruction represents the full portfolio of metabolic and transport reactions that can occur in a given organism. From such reconstruction, a mathematical model can be derived, allowing one to simulate of an organism’s phenotypic behaviour under a particular condition [Palsson, 2006]. Recon 2 [Thiele it et al., 2013] is a very comprehensive knowledge-base of human metabolism and has been applied for numerous biomedical studies, including the mapping and analysis of omics data sets [Aurich and Thiele, 2016].

However, despite numerous visualization efforts using automated layouts [Jensen and Papin, 2014], there is no genome-scale yet biochemically intuitive human metabolic map available for visualization of omic data in its network context. Here, we release ReconMap, a comprehensive, manually curated map of human metabolism presented utilising the Google Maps Application Programming Interface (API) for highly responsive interactive navigation within a platform that facilitates queries and custom data visualization.

2 FEATURES

ReconMap content was derived from Recon 2.04, obtained from the Virtual Metabolic Human database (VMH, \url{http://vmh.uni.lu}). Reactions (hyperedges) were manually laid out using the biochemical network editor CellDesigner [Funahashi it et al., 2008]. Each metabolite (node) was designated by its abbreviation and a letter corresponding to the compartment, in which the reaction occurs (e.g., `[c]` for cytosol). Metabolites present in a high number of reactions (e.g., common cofactors, water) were replicated across the map to avoid excessive hyperedge crossover.

ReconMap is presented using the Molecular Interaction NEtwoRks VisuAlization (MINERVA, [Gawron it et al., 2016], platform built on the Google Maps API, that together permit content query, low latency web display and interactive navigation of generic and context-specific genome-scale molecular networks. Each metabolite and

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reaction in ReconMap links to the corresponding curated content provided by the VMH database. Moreover, we also used MINERVA functions to connect to standard external databases, such as the CHEMBL database [Bento et al., 2013].

### 2.1 Overlay of simulation results and multi-omics datasets

Recon-derived simulation results can be visualized on ReconMap using a new extension to the COBRA Toolbox [Schellenberger et al., 2011]. The user can perform a simulation, e.g., Flux Balance Analysis, using the COBRA toolbox function `optimizeCBmodel`, then call the function `buildFluxDistLayout` to write the input file for a ReconMap Overlay. This permits the user to translate each flux value into a custom thickness and color within a simple tab-delimited highlight certain ReconMap reactions. Similarly, registered users can display omic data on ReconMap via the "Overlay" menu, which utilises the MINERVA framework to generate a new ReconMap overlay that can assign a different color and thickness to each node and reaction.

### 2.2 Community-driven refinement of ReconMap & Recon2

All users may post suggestions for refinement and expansion that are linked to a specific metabolite or reaction. Each suggestion is forwarded to ReconMap and Recon2 curators for consideration when planning further curation effort. As such, ReconMap enables the community-driven refinement of human metabolic reconstruction and visualization.

### 2.3 Connecting ReconMap and PDMap

The Parkinson’s disease map (PDMap, [Fujita et al., 2014]) displays molecular interactions known to be involved in the pathogenesis of Parkinson’s disease. A total of 168 metabolites interlink ReconMap and PDMap via standard identifiers. This feature is particularly interesting when mapping omics datasets on both maps, thereby allowing the simultaneous investigation of metabolic and non-metabolic pathways relevant for Parkinson’s and other neurodegenerative diseases.
3 IMPLEMENTATION

ReconMap was drawn using CellDesigner, is displayed using the MINERVA platform, built on the Google Map API, using reconstruction content from the VMH database http://vmh.uni.lu. Scripts for visualisation of COBRA Toolbox simulation results using ReconMap are available here: https://opencobra.github.io/. To get started, see the tutorial here: https://github.com/opencobra/cobratoolbox/tree/master/maps/ReconMap.

4 DISCUSSION

ReconMap allows for efficient visualization of human metabolic reactions and metabolites, connections with numerous online resources and the VMH database, which hosts Recon 2 along with manually curated information. ReconMap is a generic visualization of human metabolism and serves as a template from which cell-, tissue-, and organ-specific maps may be generated. Moreover, omics data can be directly mapped onto the map as well as flux distributions resulting from simulations via an extension to The COBRA Toolbox. ReconMap can be readily connected to disease-specific maps, such as the Parkinson’s disease map, thereby enabling investigations beyond metabolic pathways. Future directions include subsystem maps, conserved moiety tracing, drug target search, and increased synergy with simulation tools.

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