Visualizing metabolite fluxes on WikiPathways pathways using a PathVisio plugin

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Biological pathways provide intuitive frameworks to integrate and co-analyze different kinds of biological data, such as system-wide transcriptomic, proteomic, and metabolomic measurements. While insightful, pathway analysis is generally limited to qualitative conclusions, and the analyses can only be as powerful as the curated annotations can enable. Using our open-source pathway analysis platform, PathVisio, we will bridge pathway analysis to the wealth of quantitative approaches already in development for metabolic network modeling, such as flux balance analysis and dynamic simulation. Our focus will be on the visualization of the modeling results, which will be critical for understanding how simulated models correlate with experimental measurements.

The same biological processes that are visualized in pathways are also described by quantitative models. For example, the arrows that connect entities within metabolic pathways actually represent metabolite fluxes. The integration of large scale data analysis with modeled or measured fluxomics data, will help to gain more insights into the mechanism of the biological process.

PathVisio [1] is a tool for displaying and editing biological pathways. It enables the user to draw pathways as diagrams like in PowerPoint or Photoshop, but PathVisio is also aware of the biological context of a pathway, because biological entities (such as genes, proteins, metabolites) are linked to online resources using database identifiers. This also allows experimental data (e.g. microarray data) to be mapped and visualized on the pathway diagram. Currently it is not possible to define identifiers for the reactions in PathVisio. To enable the visualization of flux data as well, we need to add reaction identifiers to the interactions. Therefore it is necessary to incorporate reaction identifiers into the GPML pathway format used by PathVisio and WikiPathways, and editors will then be able to define identifiers for reactions like it is now possible for biological entities.

PathVisio uses BridgeDb [2], an identifier mapping framework for biological applications, to allow the translation of identifiers between different systems. There are different reaction databases available, like KEGG, BiGG or Reactome. We will create a new BridgeDb reaction database using the BridgeDbCreator (http://bridgedb.org/wiki/BridgeDbCreator) tool to be able to map between these databases. This will allow the user to define reactions using any of these identifier systems.

In order to visualize quantitative models in pathways, we will architect a flexible, standards-based visualization approach by using Molecular Interaction Maps (MIM) [3] or Systems Biology Graphical Notation (SBGN) [4]. This will enable visualization of any conforming model, including visualization of the model output (e.g. flux changes). The Molecular Interaction Map (MIM) notation is a graphical notation for depicting diagrams of biochemical and cellular processes designed to alleviate ambiguity that exists in many diagrams currently found in publications. MIM diagrams are similar to road maps or electronic circuit diagrams, and are used to define entities and their interactions in biological systems. There are a number of existing plugins in PathVisio such as PathVisio-MIM [5] and PathVisio-Validator [6] which help biologists draw diagrams in accordance with graphical standardized notations. Currently, the PathVisio validator plugin supports the MIM notation through the MIM Schematron rule-set.
Finally, we will create a PathVisio plugin for visualizing flux data on biological pathways and for performing flux balance analysis. The approach will be applicable to all pathways in WikiPathways [7], an open platform for curating, sharing and publishing biological pathways.

Visualization of cutting-edge models, including their outputs, have traditionally lagged behind development of the models themselves. As such, the proposed integrated visualization will have several important impacts on the field:

- makes modeling results immediately more accessible and interpretable to biologists who wish to learn from them
- enables researchers who develop flux modeling approaches to better improve and distribute their models
- facilitates new ways to explore effects on mechanism, such as genetic effects. In our group, we are planning to use pathways to link copy number variations and polymorphisms in genes to their biological consequences. These changes will often affect model kinetics, so by integrating flux modeling with pathways, we can use models to evaluate which of the observed genetic changes will significantly alter metabolism.

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References: