iPath3.0: interactive pathways explorer v3

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ABSTRACT

iPath3.0 (http://pathways.embl.de) is a web-application for the visualization and analysis of cellular pathways. It is freely available and open to everyone. Currently it is based on four KEGG global maps, which summarize up to 158 traditional KEGG pathway maps, 192 KEGG modules and other metabolic elements into one connected and manually curated metabolic network. Users can fully customize these networks and interactively explore them through its redesigned, fast and lightweight interface, which highlights general metabolic trends in multi-omics data. It also offers navigation at various levels of details to help users further investigate those trends and ultimately uncover novel biological insights. Support for multiple experimental conditions and time-series datasets, tools for generation of customization data, programmatic access, and a free user accounts system were introduced in this version to further streamline its workflow.

INTRODUCTION

Metabolic networks provide an intuitive and powerful framework for understanding cellular systems. With the availability of manually curated pathway diagrams of metabolic networks and the ever increasing volume of omics data to visualize, several tools (1–4) were developed to help scientists explore and visually integrate these data onto pathway diagrams. iPath (1,2), one of the first tools to popularize this concept online, proved useful in various contexts. For instance, it has been used to map differentially expressed functional transcripts between early and late plant development (5), and metabolic pathways that differentiate Crohn’s disease form healthy phenotypes in human gut metaproteogenomic samples (6).

Here we present iPath3.0, the latest version of iPath, which greatly improves the user experience by speeding up the rendering of the maps and user interactions, by adding two new global maps and by enriching its biological knowledge base with 62 novel KEGG pathway modules (7), 1700 new reactions, 1500 new KEGG Orthology entries (KO) and close to 3000 new species.

USER INTERFACE AND PATHWAY CUSTOMIZATION

iPath3.0’s pathway explorer provides zooming and panning controls that allow the user to easily navigate the complex pathway maps. Clicking on nodes and edges in the map displays popup windows with detailed information about the associated data, such as enzymes, reactions, pathway maps and compounds involved, each hyper-linked to the original annotations source. With several built-in data mapping tools and extensive customization options, users can upload various types of data associated with enzymes or compounds to customize any overview or species-specific pathways map.

IMPROVEMENTS AND NEW FEATURES

A major advance in iPath3.0 is its new display engine. Implemented in Javascript and SVG, it greatly speeds up the rendering of the maps, brings faster and lighter user interactions, and therefore streamlines the whole user experience compared to the previous Flash-based engine. The performance of the search engine was greatly improved as well, and the results extended to display the number of map elements matched by each entry, and are emphasized upon selection.

Mapping conflicts, which occur when multiple IDs with different customization match the same element in the map,
Customized maps can also be exported for further editing and publication. Available export formats are Scalable Vector Graphics (svg), Portable Network Graphics (png), Encapsulated Postscript (eps) and Portable Document Format (pdf).

**ILLUSTRATIVE EXAMPLE**

To illustrate new features of iPath3.0 we compared the metabolic repertoire of *Escherichia coli* O157:H7 Xuzhou21 (ELX) and *E. coli* K-12 MDS42 (ECOK). We used the new feature ‘Element selection based on ID overlap’ from the tools section to customize the ‘Global metabolism’ map based on their KOs. Reactions highlighted in blue (Figure 1) show that most enzymatic functions of these strains overlap, while those highlighted in brown are specific to ECOK and in green specific to ELX. By displaying detailed information about the ECOK-specific reaction highlighted in the Pentose phosphate pathway (Figure 1), we found that both strains have the Ribose 5-phosphate isomerase (*Rip*) required for this reaction however ECOK has both *RipA* and *RipB* while ELX has only *RipA*. Using the conflict resolution tool (Figure 1) users could chose to color this match in blue if the finding is not of interest to their research question or keep it in brown to emphasize it. Resolving more conflicts is made easy by the ‘Selection match statistics’ panel which lists all conflicts and highlights them upon selection. Other hits were truly strain-specific as shown for K00480.

This example illustrates how iPath3.0 simplifies the navigation and the comparison of metabolic pathways profiles, but several other examples and video tutorials are also available in the online help section.

**COMPARISON WITH OTHER TOOLS**

KEGG Atlas (4) and Pathway projector (3) are web tools for pathway exploration. Both offer map navigation through zooming and panning, taxonomic filtering as well as limited map customizations. On top of these functionalities iPath3.0 offers a wide array of additional features covered in the previous section ‘Improvement and new features’, which sets it apart from these tools as not only a pathway explorer, but also an advanced visual analysis tool for metabolic data.

**DISCUSSION**

The new built-in color generation tools and the modernization of the web interface of iPath3.0 greatly improve and streamline the user experience. The addition of time-series visualization and programmatic access opens novel exploration perspectives. With all these improvements we hope that iPath3.0 will help scientists to comprehensively explore more cellular pathways with less effort and in a shorter time span. Meanwhile we will continue improving iPath by providing users with additional live editing features, an integrated viewer for traditional KEGG maps, and the possibility to upload user defined global maps.
Figure 1. Overlap and differences between the metabolic enzymes of *Escherichia coli* O157:H7 Xuzhou21 (green) and *E. coli* K-12 MDS42 (brown). The panel on the left shows detailed information about the element matched by K00480. The panel in the middle displays customization match statistics in a sortable and searchable table. Clicking the conflict number highlights (in pink) the elements associated with the conflict. The right panel shows details about the Ribose 5-phosphate isomerase and gives an example of conflict resolution, where clicking on the select button will change the color of the highlighted element to blue.

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