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Databases and ontologies

Bringing data from curated pathway resources to Cytoscape with OmniPath

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Abstract

Summary: Multiple databases provide valuable information about curated pathways and other resources that can be used to build and analyze networks. OmniPath combines 61 (and continuously growing) network resources into a comprehensive collection, with over 120 000 interactions. We present here the OmniPath App, a Cytoscape plugin to flexibly import data from OmniPath via a simple and intuitive interface. Thus, it makes possible to directly access the large body of high-quality knowledge provided by OmniPath within Cytoscape for inspection and further use with other tools.

Availability and implementation: The OmniPath App has been developed for Cytoscape 3 in the Java programing language. The latest source code and the plugin can be found at: https://github.com/saezlab/Omnipath_Cytoscape and http://apps.cytoscape.org/apps/omnipath, respectively.

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Supplementary information: Supplementary data are available at *Bioinformatics* online.

1 Introduction

Analysis of signaling pathways is essential for understanding complex mechanisms behind biological processes. As a result, a variety of databases containing pathway signaling information have been developed over the recent years. Despite the abundance of resources, the fragmentation of the available databases and their differences in focus and granularity severely hamper the creation of a reasonably comprehensive signaling pathway database (Miryala *et al.*, 2018). To bypass this major obstacle, OmniPath (Türei *et al.*, 2016) provides integrated access to 61 resources encompassing 99 255 interactions between 12 189 proteins and complexes, along with 18 722 transcriptional and 3068 post-transcriptional regulatory relationships, available through requests by the HTTP protocol. OmniPath provides its data in a completely integrated and uniform format by a web service at http://omnipathdb.org/ and via a python (pypath, https://github.com/saezlab/pypath) and R-package (OmnipathR, https://github.com/saezlab/OmnipathR). However, it would be desirable to provide access via a graphical user interface that also allows users to connect OmniPath with analysis tools.

Cytoscape (Shannon *et al.*, 2003; Smoot *et al.*, 2011) is a *de facto* standard software for biological network analysis and visualization. A number of external apps for importing pathway data in Cytoscape 3 already exists: WikiPathways (Kutmon *et al.*, 2014),

ReactomeFIViz (Wu *et al.*, 2014), KEGGscape (Nishida *et al.*, 2014) and CyPath2 (Cerami *et al.*, 2011). Apart from small overlap in content with OmniPath, these apps use primarily data converted from a process description representation (Le Novere, 2015). In contrast, OmniPath is based mainly on activity flow resources and describes networks as signed-directed graphs that are more suitable for multiple modeling and analytical approaches.

We here present the OmniPath App for Cytoscape, which makes possible a customized import of pathway data by directly querying the OmniPath web server, hence relieving users from dealing with URL queries and allows direct connection to other Apps for further analysis. More information about the curation status and the quality of the resources can be found at www.omnipathdb.org

2 Application features

The OmniPath App allows loading pathway data while fine-tuning the custom network by selecting any combination of 61 network resources and filtering the interactions by direction or sign. OmniPath includes for human: (i) signaling pathways [extending the original OmniPath as described in Türei *et al.* (2016)], (ii) kinase–substrate interactions, (iii) transcription factor–target interactions [regulons, as described in Garcia-Alonso *et al.* (2019)] and (iv)
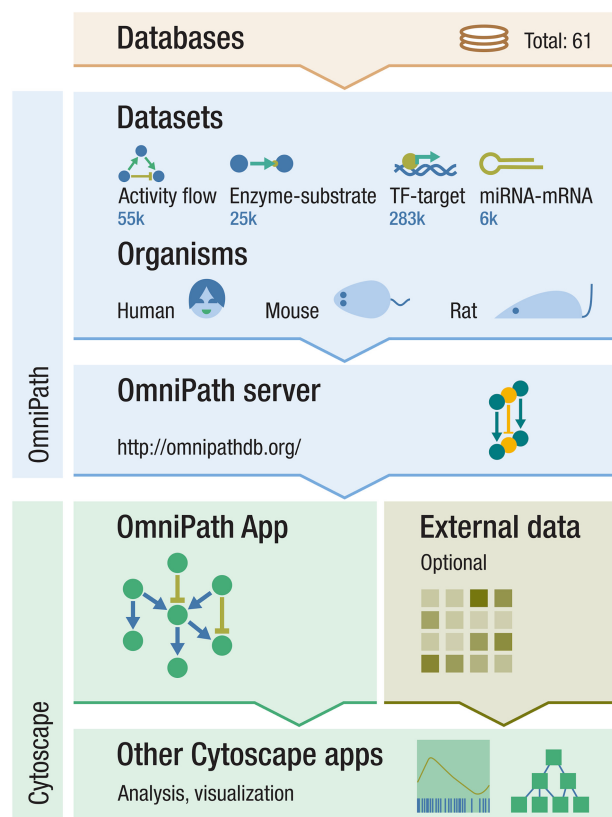
Fig. 1. OmniPath App basic workflow. The user selects organism, dataset and databases from the pre-defined options. The OmniPath App constructs the query based on the inputs and requests access to the OmniPath server. The server returns the interactions and the network is visualized in Cytoscape. Once the network is imported, other apps can be used to optionally import data into Cytoscape and perform network analysis

miRNA–mRNA interactions. In addition, OmniPath provides the networks and regulons translated to mouse or rat by gene homology. A more comprehensive list of signaling pathways resources can be found at http://omnipathdb.org/info.

Once the network has been loaded it is possible to map a large variety of annotation features to the proteins. To achieve this, the OmniPath App queries the annotations database of OmniPath. Currently, 14 467 features are available from the App which belong to 57 annotation categories and come from 32 original databases. For example, the user might select the feature 'Notch pathway' from the category 'SignaLink pathways'. The result will be a new node attribute in the network with 'True' values for the 69 proteins belonging to this pathway and 'False' for all the others.

The goal of the OmniPath App is to combine the feature-rich analyses allowed by the large collection of apps in Cytoscape with the comprehensive collection of resources available in the OmniPath web server. By importing these pathways into Cytoscape, it is possible to make full use of Cytoscape built-in functionalities and external apps to perform computational analyses of these networks.

3 Operation

We developed the OmniPath App for Cytoscape 3 in Java language. The app is designed to load signaling pathways by querying the OmniPath web server (http://omnipathdb.org/). The web server implements a simple REST style API that can be accessed by HTTP requests.

The OmniPath App provides an easy and user-friendly way to construct such queries and imports the resulting networks into Cytoscape. The user interface consists of a main control panel

completely incorporated in the Cytoscape control panel. The control panel gathers the user input needed to formulate a query for the OmniPath web server. The users are able to specify the organism, the dataset and any combination of the available databases (Fig. 1). Once the query has been constructed and the user submits the request to the OmniPath web server, the server returns the interactions in a tabular format and the network is visualized in the typical Cytoscape environment.

The imported network is a graph, in most cases directed, with effect signs (stimulatory vs. inhibitory). Nodes are annotated by gene names and UniProt IDs to provide easy mapping to other Cytoscape tools. The edges are annotated by several labels, such as (i) *is_directed*—shows if the edge is directed and (ii) *is_stimulation* and *is_inhibition*—indicate the sign of the interaction, conflicting signs among databases are possible. The *source* field indicates the databases reporting the interaction and the references field reports the PubMed IDs of the papers mentioning the interaction. The latest version of our app also allows to select an interaction from the graph and directly retrieves links to the PubMed records which support that interaction.

We provide two case studies in the Supplementary Material to demonstrate how the OmniPath app can be easily coupled with other plugins, allowing researchers to perform extended computational analyses. The first case study shows how OmniPath data can be easily imported to Cytoscape to perform enrichment analysis for a regulon (STAT3) of interest. The second case study illustrates a pipeline to build dynamic models of signal transduction pathways by combining prior knowledge with perturbation data.

4 Conclusion

In this article, we presented the OmniPath app for Cytoscape, a plugin to download custom networks from the OmniPath web service. The OmniPath app gives access to 61 network resources, many of which have not been available before in Cytoscape. Researchers can conveniently load and visualize pathway data and integrate it into their workflows in Cytoscape. As OmniPath increases the resources it includes, so will their availability for Cytoscape.

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