SOFTWARE TOOL ARTICLE

BridgeDb app: unifying identifier mapping services for Cytoscape [version 1; peer review: 2 approved]

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Abstract
The BridgeDb app for Cytoscape allows users to map and annotate identifiers of genes, proteins and metabolites in the context of biological networks. The app greatly simplifies the identifier mapping process in Cytoscape by providing a unified interface to different mapping resources and services. The app also provides a programming interface via Cytoscape Commands that can be utilized for identifier mapping by other Cytoscape apps. In this article we provide a technical guide to the BridgeDb app for mapping identifiers in Cytoscape.

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**Introduction**

Cytoscape\(^1\) is a powerful network visualization tool and platform for data integration and analysis. However, identifier mapping remains a challenge when working with biological data from different sources. We developed the BridgeDb app for Cytoscape to provide utilities for mapping and annotating identifiers in the network context. Built on the BridgeDb open-source framework for identifier mapping\(^2\), the BridgeDb app provides a graphical user interface (GUI) for users and a command interface for other Cytoscape apps to perform identifier mapping in Cytoscape networks. As a result, BridgeDb enables or simplifies the processes of identifier translation, biological entity unification, and functional annotation.

**Implementation**

The BridgeDb identifier mapping framework (http://bridgedb.org/\(^3\)) was designed to provide standardized access to gene, protein and metabolite identifier mapping services such as Ensembl BioMart\(^4\), Synergizer\(^5\) and BridgeDb web services and BridgeDb database files. By creating a Java-based abstract layer, BridgeDb enables bioinformatics applications to connect to different mapping resources through the same interface, which greatly alleviates the burden of exploring, maintaining and switching between resources.

Built upon BridgeDb framework and API, the BridgeDb app for Cytoscape can be used to connect to different mapping resources and map identifiers in Cytoscape networks. The BridgeDb app was implemented based on the Cytoscape 3 API. Its predecessor was the CyThesarus plugin for Cytoscape 2. To take advantage of the new OSGi based architecture in Cytoscape 3 and its clearly defined and simplified API, we have rewritten the CyThesarus plugin into an OSGi bundle app. Figure 1 illustrates the implementation details. The identifier mapping API of BridgeDb framework was wrapped by Cytoscape Task and TaskFactory API, which provide identifier mapping utilities to users through graphical user interfaces for managing mapping resources and performing identifier mapping. The BridgeDb app Tasks were also registered to Cytoscape as command services allowing other apps, such as Mosaic\(^6\) and NOA\(^7\) apps, and the Merge Network tool, to take advantage of BridgeDb app’s identifier mapping capacities.

**Results**

**BridgeDb app user interface**

The BridgeDb app provides an intuitive GUI to perform identifier mapping in Cytoscape networks, consisting of two interactive dialogs for resource management and identifier mapping, respectively, which can be opened via the menu item Apps/BridgeDb.

The resource management dialog allows user to add, remove, and select or deselect mapping resources. Once the resources are configured, they will be saved in a global property file and therefore shared among different Cytoscape sessions. Currently BridgeDb app supports local and remote delimited text files, BridgeDb database files, BridgeDb web service, BioMart web service, and Synergizer web service. Web services are easy to access and up to date and therefore are preferable for annotating small to medium-size networks (less than 1,000 nodes). It is highly recommended to download and use the BridgeDb database files for mapping identifiers in large networks in order to save time. Local delimited text files are useful when mapping between non-standard or customized identifiers. To avoid ambiguity, it is recommended to select only one resource unless multiple resources are believed to be complementary to each other. Particularly, resources for different species should not be selected at the same time. Database or text files are also preferable when reproducibility is essential. We will update the app to support more mapping resources as BridgeDb API keeps being developed.

The identifier mapping dialog is the main interface for mapping identifiers stored in the node table in the selected Cytoscape network. The user needs to choose the source identifier types, columns in the node table that contain the source identifiers, target identifier types, and columns to save the target identifiers. When mapping, all specified source identifier types in all selected resources will be queried for matching identifiers. If one source identifier can be mapped onto multiple target identifiers, all target identifiers can be saved as a list in the node table. If a target column exists in the node table, all values in the column will be overwritten with the target identifiers; otherwise, a new column will be created and filled with the target identifiers. Besides a set of supported identifier types (e.g., Entrez Gene ID and UniProt accession), a mapping resource such as BridgeDb database may also have a set of supported attributes (e.g., gene symbol and description).
BridgeDb app command interface

The BridgeDb app also provides a set of Cytoscape commands, which can be used by scripting or by other Cytoscape apps (client apps) to take advantage of the identifier mapping capacities provided by BridgeDb app. Table 1 provides a selected list of commands supported by BridgeDb. Every command has an optional argument appName in order to allow every client app to have its own set of identifier mapping resources. Morris et al. (sets.App, published together in the Cytoscape App collection) provided an example of how to use commands in client apps.

Example use cases

Use cases of BridgeDb app include identifier translation, biological entity unification, and functional annotation in Cytoscape networks. Box 1 provides an example of how to use BridgeDb app to facilitate annotation and integration of networks from public databases. In particular, this example shows the steps to generate a TP53 interaction network by merging networks from different sources using BridgeDb app and Merge Network tool. Figure 2 illustrates the process of the Cytoscape app NOA annotating Cytoscape networks with Gene Ontology by utilizing BridgeDb app's command services.

Table 1. Selected BridgeDb app commands. Arguments with asterisks (*) are required.

| Command               | Arguments                                                      | Description                                                                 |
|-----------------------|-----------------------------------------------------------------|-----------------------------------------------------------------------------|
| bridgedb resource add | classPath=IDMapper class path* connString=BridgeDb connection string* displayName=display name appName=name of client Cytoscape app | Add a mapping resource. appName is the name of the client Cytoscape app that is using this command. |
| bridgedb resource remove | connString=BridgeDb connection string* appName=name of Cytoscape app | Remove a mapping resource.                                                 |
| bridgedb resource select | connString=BridgeDb connection string* select=true or false appName=name of client Cytoscape app | Select or deselect an mapping resource.                                    |
| bridgedb id mapping | network=Cytoscape network name* sourceColumn=source column in node table* targetColumn=target column in node table* sourceldType=target ID type* targetldType=target ID type* appName=name of client Cytoscape app | Map identifiers from a column in node table to another in a Cytoscape network. |
| bridgedb resource config dialog | appName=name of client Cytoscape app | Open the resource management/configuration dialog. |
| bridgedb main dialog | appName=name of client Cytoscape app | Open the main BridgeDb app dialog.                                         |

Box 1. Example: Using BridgeDb app for merging TP53 interaction networks from different sources

1. Install and start Cytoscape 3.1.0 or above
2. Select File > Import > Network > Public Databases... 
3. Enter search condition TP53 AND human, press Search, select database IntAct, and click Import
4. After importing, click No when asking about whether to manually merge networks, and close the import dialog
5. If needed, install BridgeDb from Apps > App Manager
6. Select File > Import > Network > URL... > Example: Human Protein-Protein: Rual et al. ... Nature 2005
7. Use default when asking about setting of the new network
8. Select Apps > BridgeDb > Manager ID Mapping Resources
9. Click Databases. Select database type .bridge
10. Click Download, download Hs_Derby_[date].zip, and unzip the file
11. In Cytoscape, select the unzipped .bridge file
12. Review supported identifier types and click Close
13. Select network rual.sif in Network panel
14. Select Apps > BridgeDb > Map Identifiers
15. Select name as the Source Column in Node Table
16. Select Entrez Gene as Source ID Type(s)
17. Select Uniprot/TrEMBL as Target ID Type
18. Click Insert in the destination ID types table
19. Select Attribute: Symbol as the second Target ID Type
20. Click OK, wait, then click No to close
21. Search for TP53 in the Cytoscape search box
22. Select Select > Nodes > First Neighbors of Selected Nodes > Undirected
23. Select File > New > Network > From selected nodes, all edges
24. Select Tool > Merge > Networks... 
25. Select the network from IntAct and rual.sif(1)
26. Click Advanced Network Merge
27. Select Matching columns: uniprotkb_accession for IntAct, and Uniprot/TrEMBL for rual.sif(1)
28. Click Merge to get a TP53 interaction network merged from the two sources
Figure 2. NOA app utilizing BridgeDb app services for gene ontology annotation.

Conclusions
In this paper, we presented the BridgeDb app for Cytoscape. By providing a unified interface to various mapping resources, BridgeDb app enables identifier mapping in the network context and therefore greatly eases the process of data integration in Cytoscape.

Software availability
Software available from: http://apps.cytoscape.org/apps/bridgedb
Latest source code: https://github.com/jjgao/bridgedb.cytoscape
Source code as at the time of publication: https://github.com/F100Research/bridgedb.cytoscape

Archived source code as at the time of publication: http://www.dx.doi.org/10.5281/zenodo.10465
License: Lesser GNU Public License 2.1: https://www.gnu.org/licenses/old-licenses/lgpl-2.1.html

Author contributions
JG, CZ, MI and ARP participated in the design of the described software. JG and MI participated in the development of BridgeDb framework. JG, CZ and LZ implemented the BridgeDb app. JG, CZ, MI, DX, NS and ARP contributed to the development and writing of this article.
Competing interests
No competing interests were disclosed.

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The paper by Gao et. al. describes a Cytoscape app/plugin for cross-database mapping of gene, protein and metabolite identifiers in biological networks. For example, the app can map EntrezGene identifiers to UniProt identifiers for all genes or selected genes in a Cytoscape network. This is an important and useful application that among other application enables the merging of networks obtained from different sources (as shown in demonstration). The app is reasonably user-friendly and intuitive. Most importantly, it does not require any programming knowledge and is accessible via a GUI. I appreciate that it either uses local downloaded files for mapping (for heavy usage) or BridgeDb web services (for smaller networks). The demo in the paper worked flawlessly on my MacBook Air.

Potential future improvements may include ortholog mapping e.g. from mouse to human to enable cross-species network analyses.

Competing Interests: No competing interests were disclosed.

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.

Reviewer Report 10 July 2014

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BridgeDB app provides Cytoscape users and app developers with powerful functionality to address the ID mapping problem in integrative data analysis. App user and command interfaces are well-documented; the workflow is functional and recommended for anyone wishing to learn how to use the app.

As a minor suggestion, it would be reassuring to new users if they were able to validate the result of the workflow example in some way.

This is a very useful extension of Cytoscape functionality with broad appeal.

Competing Interests: Our team is co-developer of Cytoscape.

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.