**Systems biology**

**PaxtoolsR: pathway analysis in R using Pathway Commons**

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Associate Editor: Igor Jurisica

Received on 23 June 2015; revised on 16 November 2015; accepted on 9 December 2015

**Abstract**

**Purpose:** PaxtoolsR package enables access to pathway data represented in the BioPAX format and made available through the Pathway Commons webservice for users of the R language to aid in advanced pathway analyses. Features include the extraction, merging and validation of pathway data represented in the BioPAX format. This package also provides novel pathway datasets and advanced querying features for R users through the Pathway Commons webservice allowing users to query, extract and retrieve data and integrate these data with local BioPAX datasets.

**Availability and implementation:** The PaxtoolsR package is compatible with versions of R 3.1.1 (and higher) on Windows, Mac OS X and Linux using Bioconductor 3.0 and is available through the Bioconductor R package repository along with source code and a tutorial vignette describing common tasks, such as data visualization and gene set enrichment analysis. Source code and documentation are at http://www.bioconductor.org/packages/paxtoolsr. This plugin is free, open-source and licensed under the LGPL-3.

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**1 Introduction**

The amount of biological pathway data in machine-readable databases and formats continues to increase. Pathway analysis allows researchers to gain new understanding of the functions of biological systems. A common task has been to aggregate pathway data across databases. This task has been simplified through the creation of standardized data representations, such as the Biological Pathway Exchange (BioPAX) format (Demir et al., 2010). Pathway Commons is an ongoing effort to aggregate pathway data over a number of databases supporting the BioPAX notation and webservices to access these data (Cerami et al., 2011). The core component that facilitates the development of projects using data in the BioPAX format, such as Pathway Commons, has been Paxtools, a BioPAX application programming interface (API) written in Java (Demir et al., 2013).

Although the R programming language is widely used in areas of computational biology, there is a deficiency in the availability of pathway data provided through R packages. A recent review by Kramer et al. (2013, 2014) describes 12 R packages for working with pathway data. The majority of these packages—including KEGGgraph, PathView and ReactomePA—utilizes and provides data from KEGG and Reactome. A number of the packages are generic parsers for a variety of formats, including the Systems Biology Markup Language (SBML), KEGG Markup Language (KGML) and BioPAX.

Through the PaxtoolsR package, we extend the literature-curated pathway data available to R users, we provide a number of Paxtools API functions, and provide an interface to the Pathway Commons webservice. Through this interface, PaxtoolsR provides native support for the aggregated Pathway Commons database, including data imported from the NCI Pathway Interaction Database (PID), PantherDB, HumanCyc, Reactome, PhoshoSitePlus and HPRD.

**2 Implementation and functionality**

PaxtoolsR is implemented using the rJava R package (http://www.rforge.net/rJava/) which allows R code to call Java methods.
Although R users could use rJava to directly call methods in the Paxtools library, these tend not to follow typical R language conventions, and therefore, PaxtoolsR simplifies the usage of Paxtools in R. PaxtoolsR implements two main sets of features: (i) functions available through the Paxtools console application and (ii) functions available provided through the Pathway Commons webservice. Below, we first describe the main data formats used by the PaxtoolsR package and then describe the functions provided by PaxtoolsR. Additionally, the PaxtoolsR provides a vignette (found on the project website) to guide users in using the provided functionality, such as the visualization of networks directly in R using existing R graph libraries, such as igraph (Csardi and Nepusz, 2006) and RCytoscape (Shannon et al., 2013), and combining the analysis of gene expression microarrays with pathway data using gene set enrichment analysis (GSEA) (Subramanian et al., 2005).

2.1 Data formats
There are several primary data formats used by the PaxtoolsR package: BioPAX, simple interaction format (SIF) and extensible markup language (XML); here we describe the role of each of these formats in the PaxtoolsR package.

2.1.1 BioPAX format
The BioPAX format is an RDF/OWL-based language described previously and used as the main input format for the functions provided via the Paxtools Java library (Demir et al., 2010, 2013). BioPAX representations for databases aggregated by Pathway Commons can be downloaded from the project website (http://www.pathwaycommons.org). The currently aggregated databases, include HPRD, HumanCyc, NCI PID, Panther, PhosphoSitePlus and Reactome, among others.

2.1.2 Simple Interaction Format (SIF)
The SIF format is a tab-delimited, plain-text network edge list that describes how two molecules are related in a binary fashion, and is generated from BioPAX datasets by searching certain graphical patterns (Babar et al., 2014). The SIF format composed of three columns: PARTICIPANT A, INTERACTION TYPE and PARTICIPANT B. There are a number of interaction types, which are described in the package vignette. The conversion from BioPAX to SIF is lossy, but remains useful for applications that require binary interactions, which includes many existing network analysis software tools.

2.1.3 Extensible markup language
BioPAX file validation and search results of Pathway Commons results are returned as R XML (http://www.omegahat.org/RSXML/) objects where further data can be extracted using XPath expressions in R.

2.2 Convert, merge and validate local BioPAX files
A number of BioPAX-related functions are available in PaxtoolsR. These functions can both operate on local BioPAX files and those retrieved from Pathway Commons. PaxtoolsR provides a programming interface for the BioPAX format and for the functions provided through the Paxtools console application. These functions allow importing data into R through the SIF format and conversion of BioPAX files into a variety of formats, including the GSEA gene set format. Functions are also provided to extract subnetworks from BioPAX files and the merging of multiple BioPAX files through a previously described method that merges equivalent elements.

Fig. 1. Pathway Commons graph query of interactions between AKT1 and MTOR using PaxtoolsR and visualized using igraph. Data for the figure were retrieved with the command: graphPc(source=c("AKT1","IRS1","MTOR","IGF1R"), kind="PATHSBETWEEN", format="BINARY_SIF") (Demir, 2013; Demir et al., 2013). Additionally, PaxtoolsR provides methods to summarize the usage of BioPAX classes and validate BioPAX datasets (Rodchenkov et al., 2013).

2.3 Query and traverse data from pathway commons
PaxtoolsR provides a number of functions for interacting with the Pathway Commons webservice. PaxtoolsR allows users to query Pathway Commons data via two functions. The first involves searching for specific molecular species or pathways of interest, using the searchPc() function. The second is the graphPc() function, which allows users to query subnetworks of interest. Figure 1 shows the usage of the graphPc() command to extract a small subnetwork involving the kinases AKT1 and MTOR. This subnetwork is then converted to a binary SIF network and visualized using igraph in R; this showcases how Pathway Commons data can be easily visualized using existing R packages. The traverse() function allows the extraction of specific entries from BioPAX records, such as the phosphorylation site information from proteins described in a BioPAX dataset.

3 Conclusion
The PaxtoolsR package extends the available biological pathway data available to researchers working primarily in an R environment. This package makes many of the features available from the BioPAX Paxtools API and the Pathway Commons webservice. The data and functionality provided here can be used for a wide range of biological pathway analysis studies and can be easily integrated with the rich ecosystem of existing R packages. Future development of this R package is expected as additions are made to the underlying Paxtools Java library and Pathway Commons webservice. Furthermore, we invite developers of network analysis R packages interested in the Pathway Commons data to work with us to help make the data we provide available to their methodologies.
Acknowledgement

We thank Alex Root and Eric M. Liu for helpful discussions.

Funding

This research was supported by the US National Institutes of Health grant (U41 HG006623-02), the Ruth L. Kirschstein National Research Service Award (F32 CA192901), and through funding for the National Resource for Network Biology (NRNB) from the National Institute of General Medical Sciences (NIGMS) grant (P41 GM103504).

Conflict of Interest: none declared.

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