Systems biology

IntAct App: a Cytoscape application for molecular interaction network visualization and analysis

Eliot Ragueneau1, Anjali Shrivastava1, John H. Morris2, Noemi del-Toro1, Henning Hermjakob1,* and Pablo Porras1,*

1European Bioinformatics Institute (EMBL-EBI), European Molecular Biology Laboratory, Wellcome Genome Campus, Hinxton, Cambridgeshire CB10 1SD, UK and 2Resource for Biocomputing, Visualization, and Informatics, Department of Pharmaceutical Chemistry, University of California, San Francisco, CA 94158 2517, USA

*To whom correspondence should be addressed.

Associate Editor: Lenore Cowen

Received on January 28, 2021; revised on April 8, 2021; editorial decision on April 24, 2021; accepted on April 27, 2021

Abstract

Summary: IntAct App is a Cytoscape 3 application that grants in-depth access to IntAct’s molecular interaction data. It builds networks where nodes are interacting molecules (mainly proteins, but also genes, RNA, chemicals...) and edges represent evidence of interaction. Users can query a network by providing its molecules, identified by different fields and optionally include all their interacting partners in the resulting network. The app offers three visualizations: one only displaying interactions, another representing every evidence and the last one emphasizing evidence where mutated versions of proteins were used. Users can also filter networks and click on nodes and edges to access all their related details. Finally, the application supports automation of its main features via Cytoscape commands.

Availability and implementation: Implementation available at https://apps.cytoscape.org/apps/intactapp, while the source code is available at https://github.com/EBI-IntAct/IntactApp.

Contact: hhe@ebi.ac.uk or pporras@ebi.ac.uk

1 Introduction

IntAct is an open-source molecular interaction database which captures experimental evidence from the literature in high detail (Orchard et al., 2014), following the deep curation model developed in the IMEx Consortium (Porras et al., 2020). One of the challenges faced by IntAct is to provide efficient ways to access and display the rich detail of its data. Cytoscape is an answer to this issue, as it grants biologists unparalleled flexibility to visualize, manipulate and analyse networks, especially through the many tools available as Cytoscape apps (Shannon et al., 2003).

Different tools, such as PSICQUIC (del-Toro et al., 2013) or the BioGateway App (Holmås et al., 2020) already provide access to IntAct’s molecular interactions. However, they do not represent the full depth of detail in IntAct data as they are meant to integrate other databases as well, and therefore use a shallow model of the available data.

IntAct App aims to provide full access to the different layers of IntAct, ensuring their readability by offering different predefined styles, nested navigation and filtering capabilities on multiple levels.

2 Features

Users can build IntAct networks by querying for a set of molecule names, identifiers or descriptors. These will define the network participants, visualizing interactions between them and, optionally, all interacting partners. Ambiguous symbols or identifiers, matching more than one molecule in IntAct, can be dealt with thanks to a preview panel displaying all matches found per search term. IntAct App provides two query modes that are distinct in the way this ambiguity is dealt with:

- ‘Exact query’, to minimize the possibility of ambiguity. It should be used when the user has precise, unambiguous identifiers. It requires complete identifiers or gene names.
- ‘Fuzzy search’, a broader search to collect everything associated with the given terms. It also allows partial matches of names and descriptions for the target molecules.

IntAct App provides three styling options, or ‘views’, of its networks. The ‘Evidence’ view represents every evidence (one interaction observed by one technology in one publication) as a distinct edge. The ‘Summary’ view collapses all interaction evidence between each pair of molecules into a single edge. Finally, the ‘Mutation’ view also separates each evidence but highlights edges in which one of the participants is mutated.

To highlight cross-species interactions, molecules are styled according to the species they belong to with a palette based on their taxonomy.
IntAct App allows style customization via the interactive legend, so that users can reassign node color according to their preference.

Selection of IntAct network elements triggers the display of all information relative to them in the application panel. Available data are fully described in the user guide (https://ebi-intact.github.io/IntActApp/).

The drop-down information menus on this panel can also be used to filter the data according to different criteria, such as the confidence score associated with the interactions (Villaveces et al., 2015), interaction types, detection methods or molecule species.

IntAct App also supports the creation of sub-networks, Cytoscape session saves and its core features are available via command line, thus allowing automation and scripting access (https://ebi-intact.github.io/IntActApp/automation_support).

3 Use case

Angiotensin-converting enzyme 2 (ACE2) is a crucial protein in the COVID-19 pandemic as it has been identified as the entrance receptor for the surface spike glycoprotein (S) of SARS-CoV-2 (Hoffmann et al., 2020). In IntAct App, a fuzzy search with the term ‘ACE2’ builds a network with eight orthologs of ACE2, including the human processed form. Two yeast hits, which map to a completely different protein sharing the same symbol, can be easily discarded through the preview panel.

The human ACE2 (Q9BYF1) shows evidence of interaction with 7 Spike proteins coming from different viruses, including human SARS-CoV (MI Score: 0.98) and SARS-CoV-2 (MI Score: 0.99). Shifting to ‘Evidence’ view allows to see the full extent of evidence behind these well-characterized interactions. The ‘Mutation’ view (Fig. 1) tells that mutations on both Spike and ACE2 might have an impact on their binding. Several of these mutations were found to increase the interaction strength, among which N501T, a mutation of the Spike protein on the same position as N501Y, which is found on the highly transmissible VOC 202012/01 strain (Leung et al., 2021) and other emerging strains. The information recorded in IntAct highlights the importance of the N501 residue in Spike-ACE2 binding and could help refine current hypothesis about the increased transmissibility of some of these strains.

4 Conclusion

IntAct App allows for the representation of molecular interaction networks derived from the IntAct database, providing unprecedented access to the full level of experimental detail featured in IntAct records. For the first time, users can easily navigate and filter details about interaction detection methods, experimental hosts, binding regions or mutations affecting interaction outcome, using customizable and flexible styling options to focus on different aspects of the data. The app is also meant to complement IntAct’s website, providing support for representation of large networks.

Planned development will focus on providing advanced query types, for example allowing the construction of full interactomes, and exploring integration capabilities with other apps and functionalities of Cytoscape.

Acknowledgements

The authors would like to acknowledge the colleagues that provided feedback during the development of this application: Brigit Meldal, Kalpana Panneerselvam and Livia Perfetto. They would also like to acknowledge our testers: Alistair MacDougall, Andrés Basela Fraga, Carola Gómez-Rodríguez, John Salamon, Miguel Andrade, Ruth Isserlin, Sandra Orchard and Théo Gauvrit.

Funding

The IntAct team at EMBL-EBI received funding from EMBL core funding, Open Targets (grant agreements OTAR-044 and OTAR02-048) and the Wellcome Trust (Biomedical Resources grant INVAR #3367). J.H.M.’s work is funded by NIGMS P41 GM103504. The work of E.R. was supported by the Higher Education, Research and Innovation Department of the French Embassy to the United Kingdom.

Conflict of Interest: none declared.

References

del-Toro, N. et al. (2013) A new reference implementation of the PSICQUIC web service. Nucleic Acids Res., 41, W601–W606.
Hoffmann, M. et al. (2020) SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell, 181, 271–280.e8.
Holmás, S. et al. (2020) The cytoscape BioGateway app: explorative network building from an RDF store. Bioinformatics, 36, 1966–1967.
Leung, K. et al. (2021) Early transmissibility assessment of the N501Y mutant strains of SARS-CoV-2 in the United Kingdom, October to November 2020. Eurosurveill, 26, 2002106.
Orchard, S. et al. (2014) The MIntAct project–IntAct as a common curation platform for 11 molecular interaction databases. Nucleic Acids Res., 42, D358–D363.
Porras, P. et al. (2020) Toward a unified open access dataset of molecular interactions. Nat. Commun., 11, 1–12.
Shannon, P. et al. (2003) Cytoscape: a software Environment for integrated models of biomolecular interaction networks. Genome Res., 13, 2498–2504.
Villaveces, J. M. et al. (2015) Merging and scoring molecular interactions utilising existing community standards: tools, use-cases and a case study. Database, 2015, bat131.