Bioinformatics, 34(21), 2018, 3764–3765
doi: 10.1093/bioinformatics/bty393
Advance Access Publication Date: 14 May 2018
Applications Note

OXFORD

Systems biology

TimeXNet Web: identifying cellular response networks from diverse omics time-course data

Phit Ling Tan[1], Yosvany López[2], Kenta Nakai[1] and Ashwini Patil[1,*]

[1]Human Genome Center, The Institute of Medical Science, The University of Tokyo, Tokyo 108-8639, Japan and [2]Department of Medical Science Mathematics, Medical Research Institute, Tokyo Medical and Dental University, Tokyo 113-8510, Japan

*To whom correspondence should be addressed.
Associate Editor: Bonnie Berger

Received on January 31, 2018; revised on April 19, 2018; editorial decision on May 7, 2018; accepted on May 9, 2018

Abstract

Summary: Condition-specific time-course omics profiles are frequently used to study cellular response to stimuli and identify associated signaling pathways. However, few online tools allow users to analyze multiple types of high-throughput time-course data. TimeXNet Web is a web server that extracts a time-dependent gene/protein response network from time-course transcriptomic, proteomic or phospho-proteomic data, and an input interaction network. It classifies the given genes/proteins into time-dependent groups based on the time of their highest activity and identifies the most probable paths connecting genes/proteins in consecutive groups. The response sub-network is enriched in activated genes/proteins and contains novel regulators that do not show any observable change in the input data. Users can view the resultant response network and analyze it for functional enrichment. TimeXNet Web supports the analysis of high-throughput data from multiple species by providing high quality, weighted protein-protein interaction networks for 12 model organisms.

Availability and implementation: http://txnet.hgc.jp/

Contact: ashwini@hgc.jp

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

1 Introduction

Studying the cellular response to stimulus requires monitoring the change in cell state in the form of changes in gene expression patterns, protein levels and epigenetic or post-translational modifications over time. Analyzing these high-throughput datasets in combination with large molecular interaction networks provides a powerful approach to understanding cellular response. Several computational methods help solve this problem (Basha *et al.*, 2013; Gitter *et al.*, 2013; Jain *et al.*, 2016; Tuncbag *et al.*, 2012). However, they either do not work with time-course data or work exclusively with gene expression profiles, and few tools provide a web interface with support for multiple species.

TimeXNet Web is a web server that identifies cellular response networks from time-course omics data and a molecular interaction network in multiple species. It allows users to view the predicted response networks and analyze them for functional enrichment. TimeXNet Web implements the TimeXNet algorithm, which identifies the response sub-network by finding the most probable paths connecting genes/proteins activated at successive time points within a given interaction network (Patil *et al.*, 2013). This is done by first classifying the genes/proteins measured at three or more time points into three time-dependent groups—early, intermediate and late—and using minimum cost flow optimization to find the paths connecting the early genes/proteins to the late ones through the intermediate group of genes/proteins. The resultant sub-network is time-sensitive and enriched in genes/proteins undergoing large change on exposure to stimulus. TimeXNet also identifies novel regulators that do not themselves show an observable change in state, but connect genes/proteins with high fold changes. TimeXNet has been evaluated in several species and has been shown to be faster and more accurate than other similar algorithms (Patil and Nakai, 2014).

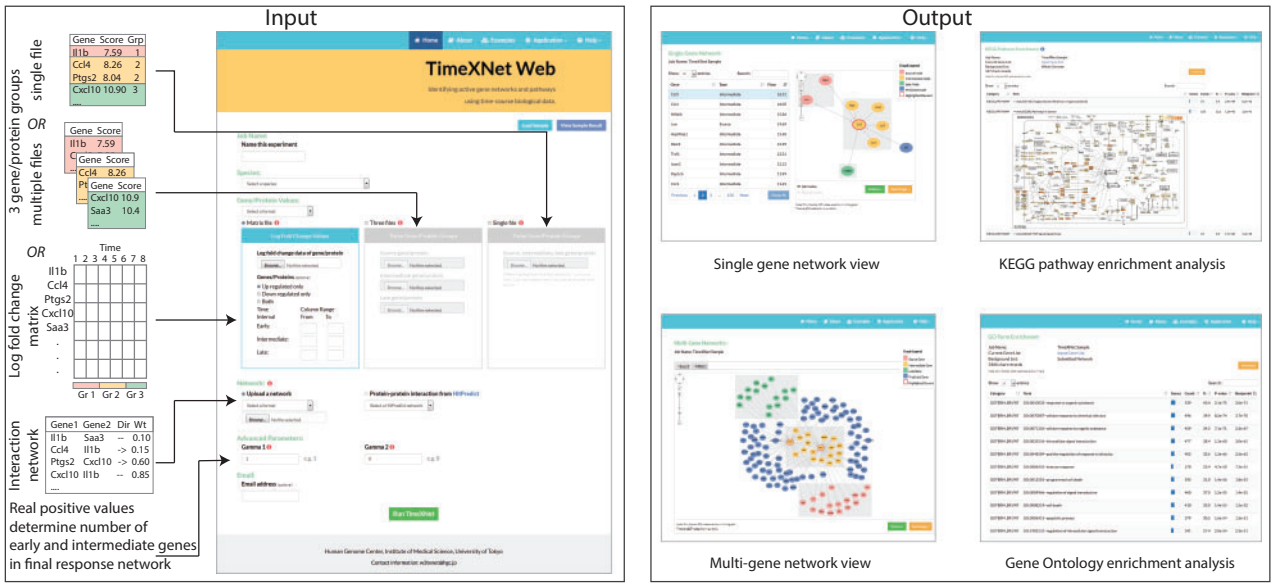

Fig. 1. TimeXNet Web input and output interfaces. Nodes in response networks are colored by their time of highest observed fold change

2 TimeXNet Web input

TimeXNet Web requires two types of input data (Fig. 1). First, it requires a set of genes/proteins with their observed change over time and their time of maximum change. This can be given as a matrix of log fold changes in gene expression, protein content or phosphorylation levels at multiple time points. The user can specify if genes/proteins with >2-fold up or down-regulation are to be considered. TimeXNet Web automatically classifies the input genes/proteins into three groups (early, intermediate and late) based on their time of maximum change, or as specified by the user. Alternatively, the user can give pre-calculated groups of genes/proteins with scores either in a single file or in three separate files. In principle, any type of high-throughput data that can be expressed in log fold change values over three or more time points can be used as input for TimeXNet Web (details in Supplementary Material).

Second, TimeXNet Web requires a molecular interaction network with weighted edges from which the condition-specific subnetwork will be extracted. TimeXNet Web provides high quality, scored protein–protein interaction networks for 12 model organisms from the HitPredict database (Lopez *et al.*, 2015), updated annually. The user can also provide a custom interaction network with edge scores and directions. TimeXNet Web supports several gene/protein identifiers, such as, name, UniProt, Entrez, Ensembl, RefSeq or user-defined identifiers, allowing users to submit gene/protein lists and interaction network in different formats. Other input values include real positive values—gamma1 and gamma2, which determine the number of genes/proteins from the early and intermediate groups to be included in the response network, respectively.

3 TimeXNet Web output

The output of TimeXNet Web is a cellular response network that maximally connects genes/proteins activated at consecutive time points. The network interactions and genes/proteins are assigned flows, or scores, indicating their connectivity and functional importance. The predicted response network can be downloaded in tab-delimited files, or in a format that can be imported into Cytoscape (Shannon *et al.*, 2003). TimeXNet Web provides an interface to view the sub-networks for selected genes/proteins (Fig. 1). Combined networks of multiple genes/proteins to identify connecting network paths can also be viewed. The genes/proteins in the network views are colored according to their time of change. Gene ontology term enrichment and KEGG (Kanehisa *et al.*, 2017) pathway enrichment can be performed using the DAVID web service (Jiao *et al.*, 2012). The response network can be mapped onto KEGG pathways using Pathview (Luo and Brouwer, 2013).

TimeXNet Web was used to identify the human ER stress response network from time-course proteomics data, the mouse innate immune response network from time-course phospho-proteomic data, and the response network of human myeloma cells to chemotherapy from time-course transcriptomic data (details in Supplementary Material).

Conflict of Interest: none declared.

References

Basha,O. *et al.* (2013) ResponseNet2.0: revealing signaling and regulatory pathways connecting your proteins and genes—now with human data. *Nucleic Acids Res.*, **41**, W198–W203.

Gitter,A. *et al.* (2013) Linking the signaling cascades and dynamic regulatory networks controlling stress responses. *Genome Res.*, **23**, 365–376.

Jain,S. *et al.* (2016) Reconstructing the temporal progression of HIV-1 immune response pathways. *Bioinformatics*, **32**, i253–i261.

Jiao,X. *et al.* (2012) DAVID-WS: a stateful web service to facilitate gene/protein list analysis. *Bioinformatics*, **28**, 1805–1806.

Kanehisa,M. *et al.* (2017) KEGG: new perspectives on genomes, pathways, diseases and drugs. *Nucleic Acids Res.*, **45**, D353–D361.

Lopez,Y. *et al.* (2015) HitPredict version 4: comprehensive reliability scoring of physical protein-protein interactions from more than 100 species. *Database (Oxford)*, **2015**, bav117.

Luo,W. and Brouwer,C. (2013) Pathview: an R/Bioconductor package for pathway-based data integration and visualization. *Bioinformatics*, **29**, 1830–1831.

Patil,A. *et al.* (2013) Linking transcriptional changes over time in stimulated dendritic cells to identify gene networks activated during the innate immune response. *PLoS Comput. Biol.*, **9**, e1003323.

Patil,A. and Nakai,K. (2014) TimeXNet: identifying active gene sub-networks using time-course gene expression profiles. *BMC Syst. Biol.*, **8(Suppl. 4)**, S2.

Shannon,P. (2003) Cytoscape: a software environment for integrated models of biomolecular interaction networks. *Genome Res.*, **13**, 2498–2504.

Tuncbag,N. *et al.* (2012) SteinerNet: a web server for integrating 'omic' data to discover hidden components of response pathways. *Nucleic Acids Res.*, **40**, W505–W509.