KDDN: an open-source Cytoscape app for constructing differential dependency networks with significant rewiring

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ABSTRACT

Summary: We have developed an integrated molecular network learning method, within a well-grounded mathematical framework, to construct differential dependency networks with significant rewiring. This knowledge-fused differential dependency networks (KDDN) method, implemented as a Java Cytoscape app, can be used to optimally integrate prior biological knowledge with measured data to simultaneously construct both common and differential networks, to quantitatively assign model parameters and statistically detect rewiring p-values and to provide user-friendly graphical results. The KDDN algorithm is computationally efficient and provides users with parallel computing capability using ubiquitous multi-core machines. We demonstrate the performance of KDDN on various simulations and real gene expression datasets, and further compare the results with those obtained by the most relevant peer methods. The acquired biologically plausible results provide new insights into network rewiring as a mechanistic principle and illustrate KDDN’s ability to detect them efficiently and correctly. Although the principal application here involves microarray gene expressions, our methodology can be readily applied to other types of quantitative molecular profiling data.

Availability: Source code and compiled package are freely available for download at http://apps.cytoscape.org/apps/kddn

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Supplementary information: Supplementary data are available at Bioinformatics online.

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1 INTRODUCTION

Modeling biological networks is an important tool in systems biology to study the orchestrated activities of gene products in cells (Mitra et al., 2013). Significant rewiring of these networks provides a unique perspective on phenotypic transitions that can occur in biological systems. Thus, instead of asking ‘which genes are differentially expressed’, a more interesting question is ‘which genes are differentially connected?’ (Hudson et al., 2012; Mitra et al., 2013). To systematically characterize selectively activated or deactivated regulatory components and mechanisms, the modeling tools must effectively distinguish significant rewiring from random background fluctuations. Although specific biological networks cannot be constructed by the existing knowledge alone, novel incorporation of prior knowledge into data-driven approaches can improve the robustness and biological relevance of network inference.

Differential dependency network (Zhang et al., 2009; Zhang and Wang, 2010) and its knowledge-fused extension (Tian et al., 2011, 2014) KDDN have been developed to infer biological networks with significant rewiring by integrating experimental data and biological knowledge. The unique and attractive features of the KDDN software tool are as follows: (i) it is easy to use with a user-friendly graphic user interface (GUI) and cutting-edge performance; (ii) both conserved and differential biological networks can be inferred via efficient closed-form numerical solutions; (iii) model parameters are determined statistically aligned with the expected performance; (iv) prior knowledge (condition specific or non-specific) is incorporated for inferring dependency networks under different conditions; and (v) statistical significance on the differential connections and the type I error rate are rigorously assessed.

The KDDN Cytoscape 3.x app adapts and extends recent KDDN algorithms in the literature (Tian, et al., 2011, 2014; Zhang et al., 2009; Zhang and Wang, 2010) (Fig. 1). Via a user-friendly GUI, users can easily install KDDN software and perform network analysis by just a few clicks. KDDN software has been tested thoroughly on both synthetic and real gene expression data, and has been successfully applied to a wide range of research projects, including yeast oxidative stress response, breast cancer recurrence, muscular dystrophy and estrogen exposures. Helpful tips for users to use the software in an efficient manner yet with fully informed limitations are provided in Supplementary Information.

2 DESCRIPTION

2.1 Methods and software

KDDN algorithm jointly learns the conserved biological network and statistically significant rewiring across different conditions. Condition-specific data and prior knowledge are
quantitatively fused via an extended Lasso model with $\ell_1$ reg-
ularized convex optimization formulation (Tian et al., 2014).
Based on the unique nature of the problem, we derive an efficient
closed-form solution for the embedded subproblem solved by the
block-wise coordinate descent algorithm. We conduct the
computational complexity analysis on the KDDN algorithm
(Supplementary Information). As existing knowledge is often
non-specific or imperfect, KDDN uses a ‘minimax’ strategy to
maximize the benefit of prior knowledge while confining its nega-
tive impact under the worst-case scenario. Furthermore, KDDN
matches the values of model parameters to the expected false-
positive rates on network edges at a specified significance level,
and assesses edge-specific $P$-values on each of the differential
connections (Tian et al., 2014).

KDDN is implemented as an open-source cross-platform
Cytoscape 3.x app with parallel computing capability in Java.
The control panel will guide users to navigate through the
experiment settings that allow flexible configuration of the ana-
lytic tasks. KDDN software takes the quantitative expression
values of relevant genes/proteins as input, and incorporates the
prior knowledge applicable to either or both conditions (e.g.
KGML files downloaded from KEGG pathway Web site can
be directly imported as prior knowledge). In addition to inferring
common and/or significant rewiring with edge-specific $P$-values,
conventional differential analysis is simultaneously performed
allowing users to compare expression fold changes and network
rewiring side by side. The constructed networks are visualized
seamlessly in Cytoscape, and detailed numerical results together
with model parameters are presented in dedicated panels (Fig. 2).
All experimental settings and results can be conveniently
exported for further analysis.

2.2 Case study
We applied KDDN to analyze the network rewiring in budding
yeast *Saccharomyces cerevisiae* in response to oxidative stress,
focused on cell cycle-related genes. Integrating the prior biolo-
gical knowledge in the KEGG yeast pathway and gene expres-
sion data (GSE7645), the significant differential networks
constructed by KDDN are given in Figure 2, where red edges
indicate the connections existing under control and green edges
indicate the connections created under stress, exclusively.

Oxidative stress is a harmful condition in cell, due to the fail-
ure of the antioxidant defense system to effectively remove reac-
tive oxygen molecules and other oxidants (Lee et al., 2011). The
result shows that *Yap1*, *Rho1* and *Msn4* are among differential
hubs and at the center of the network response to oxidative
stress; they are activated under oxidative stress and many con-
nections surrounding them are created (green edges). *Yap1* is a
major transcription factor that responds to oxidative stress;
*Msn4* is considered as a key responder to environmental stresses,
including oxidative stress; *Rho1* is known to resist oxidative
damage and facilitate cell survival; *Ctt1* acts as an antioxidant,
and it coordinates with *Yap1* to protect cells from oxidative
stress. The stress-induced interaction between *Hog1* and
*Fus1*, detected by KDDN, is also observed in an earlier study. The
biologically plausible results suggest not only the network rewir-
ing as a mechanistic principle in determining phenotypes but also
KDDN’s ability to detect them efficiently and correctly.

Detailed descriptions of method, software and more case stu-
dies are included in the Supplementary Information.

3 DISCUSSION
The KDDN Cytoscape app presents an integrated software tool
to construct biological networks and detect significant rewiring
across different conditions. Supported by a well-grounded math-
ematical framework, KDDN integrates the abundant biological
knowledge and condition-specific experimental data to depict the
overall dependency networks and their dynamics. Tested on both
simulations and real gene expression data, KDDN outperforms
peer methods (Supplementary Information) and demonstrates
its effectiveness in revealing significant topological changes.
We expect KDDN to be a useful tool for performing
differential network analysis in many biological contexts (Mitra
et al., 2013).

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REFERENCES


