Drug Resistance Updates 17 (2014) 64–76

Contents lists available at ScienceDirect

Drug Resistance Updates

journal homepage: www.elsevier.com/locate/drup

Prediction of dynamical drug sensitivity and resistance by module network rewiring-analysis based on transcriptional profiling

Tao Zeng [a], Diane Catherine Wang [b], Xiangdong Wang [c,*], Feng Xu [d,*], Luonan Chen [a,e,*]

[a] Key Laboratory of Systems Biology, Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences, Shanghai, China
[b] Department of Medicine, Royal Berkshire Hospital, Reading, UK
[c] Fudan University Center for Clinical Bioinformatics, Zhongshan Hospital, Fudan University Shanghai School of Medicine, China
[d] Department of Infectious Diseases, Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China
[e] Institute of Industrial Science, University of Tokyo, Tokyo 153-8505, Japan

ARTICLE INFO

Keywords:
Drug sensitivity
Resistance
Systems biology
Network
Bioinformatics

ABSTRACT

Revealing functional reorganization or module rewiring between modules at network levels during drug treatment is important to systematically understand therapies and drug responses. The present article proposed a novel model of module network rewiring to characterize functional reorganization of a complex biological system, and described a new framework named as module network rewiring-analysis (MNR) for systematically studying dynamical drug sensitivity and resistance during drug treatment. MNR was used to investigate functional reorganization or rewiring on the module network, rather than molecular network or individual molecules. Our experiments on expression data of patients with Hepatitis C virus infection receiving Interferon therapy demonstrated that consistent module genes derived by MNR could be directly used to reveal new genotypes relevant to drug sensitivity, unlike the other differential analyses of gene expressions. Our results showed that functional connections and reconnections among consistent modules bridged by biological paths were necessary for achieving effective responses of a drug. The hierarchical structures of the temporal module network can be considered as spatio-temporal biomarkers to monitor the efficacy, efficiency, toxicity, and resistance of the therapy. Our study indicates that MNR is a useful tool to identify module biomarkers and further predict dynamical drug sensitivity and resistance, characterize complex dynamic processes for therapy response, and provide biologically systematic clues for pharmacogenomic applications.

1. Introduction

The investigation of responses to artificial signals such as drugs or drug resistance in therapy at molecular levels is challenging, but important for the understanding of complex mechanisms during drug treatment, although there are cellular responses to distinguish external and internal challenges (Welch, 1992). The on- or off-status of drug responses is determinate and manipulatable, and used for comparative studies on drug sensitivity and resistance as a control or case condition. Therapy-responsive genes have been intensively investigated recently (Wang et al., 2012; Ottaviani et al., 2012; Kariko et al., 2011; Tatebe et al., 2010). It has been recognized that biological functions are generally facilitated not only by individual genes or proteins, but also by interactions between networks or modules, which are responsible for dynamical behaviors and diverse functions of living organisms. The study on dynamical drug sensitivity and efficacy to therapy can elucidate the principle of drug responses at the network level (Alsford et al., 2012; Barretina et al., 2012), based on a molecular network or structures, e.g., network motifs and modules, which can benefit the identification of efficient biomarkers in pharmacogenomic applications (Sim and Ingelman-Sundberg, 2011; Hoppe et al., 2011; Torkamani and Schork, 2012; Lussier and Li, 2012).

Recent attention has been diverted from the single gene to particular functions or pathways like DNA-damage response in cancer therapy (Powell and Bindra, 2009; Lord and Ashworth, 2012). This is different from conventional studies on drug sensitivity that have mainly focused on responsive genes (Duffy et al., 2011; Yuasa et al., 2011; Chan et al., 2011; Chen et al., 2009; Cohen et al., 2011).

* Corresponding authors at: Key Laboratory of Systems Biology, Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences, Shanghai, China (L. Chen); Fudan University Center for Clinical Bioinformatics, Zhongshan Hospital, Fudan University Shanghai School of Medicine, China (X. Wang); Department of Infectious Diseases, Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China (F. Xu).
E-mail addresses: xiangdong.wang@clintransmed.org (X. Wang), xufeng99@yahoo.com (F. Xu), lnchen@sibs.ac.cn (L. Chen).

http://dx.doi.org/10.1016/j.drup.2014.08.002
1368-7646/

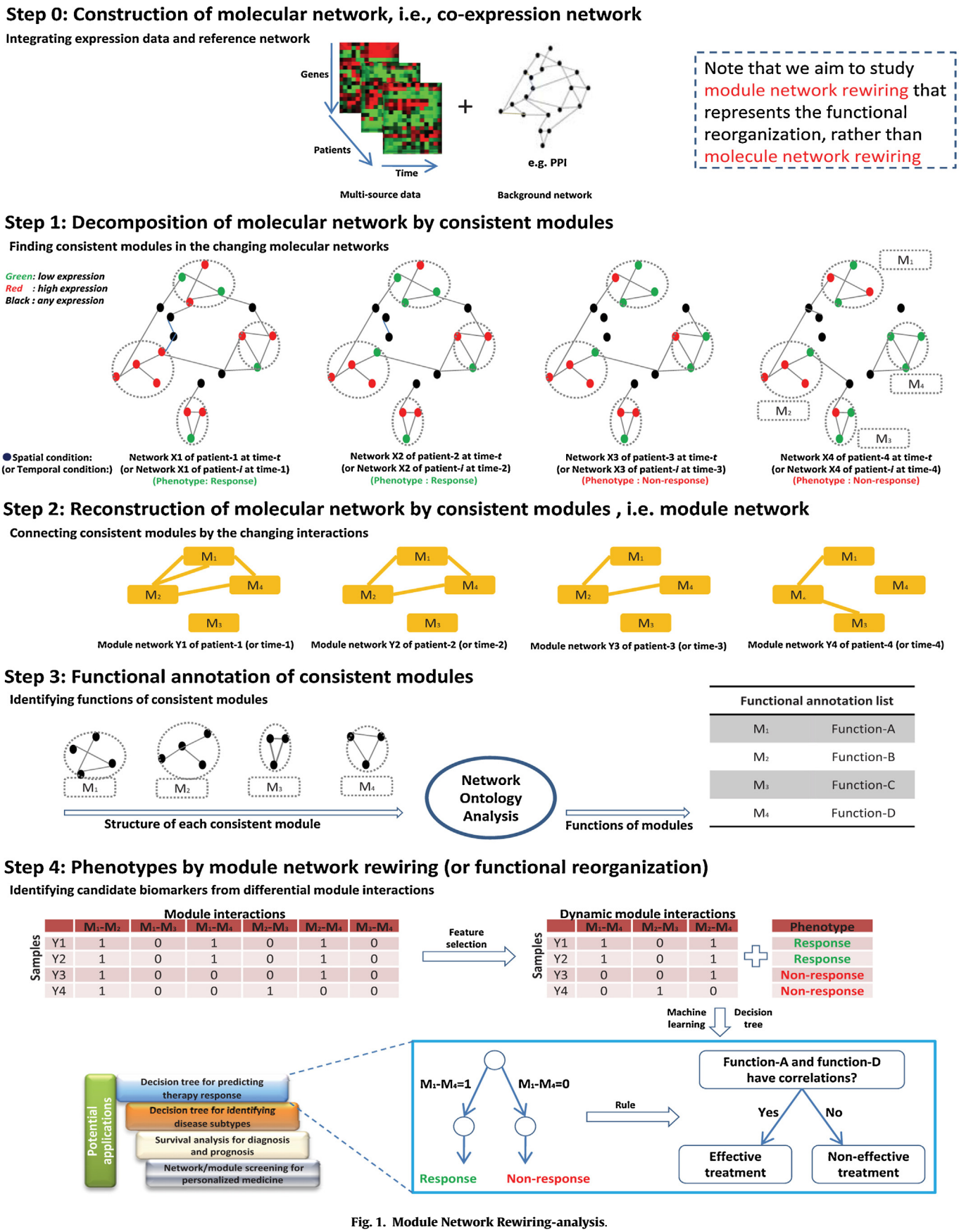

Fig. 1. Module Network Rewiring-analysis.