HL105

# Identifying active gene sub-networks from time-course gene expression profiles using TimeXNet

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**Abstract**

Time-course gene expression profiles are frequently used to study cellular response to stimulus and to infer molecular pathways involved in cellular response. We introduce a method, TimeXNet, which identifies active gene sub-networks with temporal paths using time-course gene expression profiles in the context of a weighted gene regulatory and protein-protein interaction network. TimeXNet uses a specialized form of the network flow optimization approach to identify the most probable paths connecting the genes with significant changes in expression at consecutive time intervals.

TimeXNet was used to study the innate immune response using time course gene expression profiles of activated immune cells. The innate immune response is the first level of protection in organisms against invading pathogens. It is primarily mediated by the Toll-like receptors functioning through the Myd88-dependent and TRIF-dependent pathways. We classified the immune response into three consecutive time-dependent stages – early, intermediate and late - and used TimeXNet to identify the most probable paths in the molecular network between genes expressed in the early and the late phases of the immune response, while taking into account those expressed in the intervening time. The resultant network contained several new and known regulators of the innate immune response, as well as those transiently expressed between sampled time points. The predicted temporal network suggested a role for the protein phosphatase 2a catalytic subunit α in the regulation of the immunoproteasome during the late phase of the response. An analysis of time course gene expression profiles from Myd88-knockout and TRIF-knockout dendritic cells helped clarify the differences between the Myd88-dependent and TRIF-dependent pathways in the innate immune response. Compared to other similar methods, TimeXNet identified up to 40% more novel regulators from independent experimental datasets. It also predicted paths within a greater number of associated KEGG pathways with longer overlaps (up to 7 consecutive edges) within these pathways. TimeXNet was also shown to be robust to the presence of noisy interactions in the molecular interaction network1.

TimeXNet was further evaluated using the yeast osmotic stress response1. TimeXNet was able to predict a significant part of the HOG MAPK pathway which forms the primary response to yeast hyperosmotic stress. Compared to other methods, it was able to predict twice as many known regulators acting in the yeast response pathways.

Thus, TimeXNet is a reliable tool that can be used to study cellular response to stimuli through the identification of time-dependent active gene sub-networks in diverse biological systems. TimeXNet is available as a stand-alone Java application that can be run via a user interface as well as on command line. It accepts three groups of genes as input and displays the predicted response network in Cytoscape. It is available for free to non-commercial users at http://timexnet.hgc.jp/.