

Network information improves cancer outcome prediction

Janine Roy, Christof Winter, Zerrin Isik and Michael Schroeder

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Abstract

Disease progression in cancer can vary substantially between patients. Yet, patients often receive the same treatment. Recently, there has been much work on predicting disease progression and patient outcome variables from gene expression in order to personalize treatment options. Despite first diagnostic kits in the market, there are open problems such as the choice of random gene signatures or noisy expression data. One approach to deal with these two problems employs protein–protein interaction networks and ranks genes using the random surfer model of Google's PageRank algorithm. In this work, we created a benchmark dataset collection comprising 25 cancer outcome prediction datasets from literature and systematically evaluated the use of networks and a PageRank derivative, NetRank, for signature identification. We show that the NetRank performs significantly better than classical methods such as fold change or t-test. Despite an order of magnitude difference in network size, a regulatory and protein–protein interaction network perform equally well. Experimental evaluation on cancer outcome prediction in all of the 25 underlying datasets suggests that the network-based methodology identifies highly overlapping signatures over all cancer types, in contrast to classical methods that fail to identify highly common gene sets across the same cancer types. Integration of network information into gene expression analysis allows the identification of more reliable and accurate biomarkers and provides a deeper understanding of processes occurring in cancer development and progression.

Keywords: network-based; outcome prediction; gene expression; PageRank; cancer biomarker

INTRODUCTION

Cancer outcome prediction aims to address the problem of learning how to forecast disease progression from gene expression and thus allowing refined treatment options. A recent success in the area is the diagnostic kit MammaPrint[®], which predicts metastasis formation in breast cancer from the expression of 70 genes. It has been in the market since 2007 and has been tested on over 3000 patients in the meantime. The original paper underlying MammaPrint[®] argued that up to 80% of patients receive unnecessary

chemotherapy [1] and showed a prediction accuracy of 83%, which was later corrected to 69% [2]. Despite its success, the approach has been criticized. Ein-Dor *et al.* [3] compared the 70 genes signature published by van't Veer *et al.* [1] and a different signature of 76 genes by Wang *et al.* [4]. Ein-Dor *et al.* concluded that 'the overlap between these gene sets is almost zero' and 'many equally predictive lists could have been produced'. Recently, Venet *et al.* [5] continued along these lines and showed in a systematic analysis that 60% of the analyzed signatures

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Christof Winter obtained his PhD in Bioinformatics at Technische Universität Dresden in the group of Michael Schroeder where he was working on structural protein interactions and regulatory networks in pancreatic cancer. Currently, he works as a postdoctoral fellow in the group of Leo Sael at Lund University, Sweden, on breast cancer genomics.

Zerrin Isik obtained her PhD on pathway enrichment systems to assess biological activity of cell processes at Middle East Technical University, Ankara, in 2011. Now she is working in the Bioinformatics group of Michael Schroeder.

Michael Schroeder is the head of the Bioinformatics Department at Technische Universität Dresden. His research interests lie in protein interactions, functional annotation based on text-mining and drug repositioning.

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