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System biology modeling : the insights for computational drug discovery

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Abstract:

Traditional treatment strategy development for diseases involves the identification of target proteins related to disease states, and the interference of these proteins with drug molecules. Computational drug discovery and virtual screening from thousands of chemical compounds have accelerated this process. The thesis presents a comprehensive framework of computational drug discovery using system biology approaches. The thesis mainly consists of two parts: disease biomarker identification and disease treatment discoveries. The first part of the thesis focuses on the research in biomarker identification for human diseases in the post-genomic era with an emphasis in system biology approaches such as using the protein interaction networks. There are two major types of biomarkers: Diagnostic Biomarker is expected to detect a given type of disease in an individual with both high sensitivity and specificity; Predictive Biomarker serves to predict drug response before treatment is started. Both are essential before we even start seeking any treatment for the patients. In this part, we first studied how the coverage of the disease genes, the protein interaction quality, and gene ranking strategies can affect the identification of disease genes. Second, we addressed the challenge of constructing a central database to collect the system level data such as protein interaction, pathway, etc. Finally, we built case studies for biomarker identification for using dabetes as a case study. The second part of the thesis mainly addresses how to find treatments after disease identification. It specifically focuses on computational drug repositioning due to its low lost, few translational issues and other benefits. First, we described how to implement literature mining approaches to build the disease-protein-drug connectivity map and demonstrated its superior performances compared to other existing applications. Second, we presented a valuable drug-protein directionality database which filled the research gap of lacking alternatives for the experimental CMAP in computational drug discovery field. We also extended the correlation based ranking algorithms by including the underlying topology among proteins. Finally, we demonstrated how to study drug repositioning beyond genomic level and from one dimension to two dimensions with clinical side effect as prediction features.

Description:

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