Preface

Drug design is a complex and resource-demanding process, hinged on the inherent complexity of diseases, which arise from deregulated interactions between multiple genes. The reductionist approach, which has served the pharma industry for decades, has been producing declining R&D returns in recent years, leading not only to ever-increasing costs, but also to reduced efficacy, thus affecting the quality of healthcare. More than a decade ago, developing a new drug was associated with a cost of $890 million. In 2016, the estimate is a staggering $2870 million. These costs are driving the emergence of new technologies and methodologies which will eventually shape a phenomenal paradigm shift in the research and development of drugs.

Most disease-associated genes have a small influence by themselves. However, in the context of a molecular interaction network of cellular processes, these individual influences are combined in such a way that the resulting influence severely deregulates the network. In that regard, both the disease and the corresponding treatment introduce perturbations within the biological network, which should be assessed by means of a systems-level approach.

Pathway analysis is a thriving research area in systems biology, attempting to unravel the systemic effects of disease and drug-induced perturbations. Pathway analysis relies on the wealth of complex biological data produced by omics technologies. These technologies typically produce a list of differentially expressed genes between a control and a disease state. The data, however, have been removed from the biological context from which they were extracted. Pathway analysis methods attempt to rectify this by using prior biological knowledge pertaining to the structure and operation of biological pathways along with statistical, mathematical, and computational methods.

Towards the direction of understanding what pathway analysis can offer to both the experimentalist and the modeler, the reader is introduced in the first chapter to a general methodology which outlines common workflows shared by several methods, such as preprocessing of the omics data, choosing a null hypothesis, as well as gene- and pathway-level statistics. Furthermore, the evolution of pathway analysis methods is documented, beginning from simple overrepresentation analysis and leading to complex pathway-level, or even sub-pathway-level approaches. We continue in the second chapter with a comprehensive review covering pathway and sub-pathway based approaches involved in various aspects of drug design and discovery, an emerging area known as systems pharmacology. This chapter provides insights into how pathway analysis methods can be employed to elucidate drug mechanism of action, identify novel drug targets, increase treatment efficacy by identifying drugs or drug combinations, which modulate multiple targets, infer novel therapeutic indications for existing drugs, and predict drug side effects.

Subsequently, in the third chapter, we present an overview of pathway analysis methods developed to model the temporal aspects of drug- or disease-induced perturbations and extract relevant dynamic themes. In the fourth and final chapter, several state-of-the-art methods in pathway analysis are outlined, which address the important problem of identifying differentially expressed pathways and sub-pathways. We cover various aspects of the methodological arsenal of this area, as well as the evolution of tools developed for differential expression analysis.

In conclusion, the present work offers the reader a guided walkthrough to one of the most promising research areas in modern life sciences, enabling a deeper understanding of involved concepts and methodologies via an interdisciplinary view, focusing from well-established approaches to cutting-edge research.

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