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Systems Biology

Volume 6
Series Editors:
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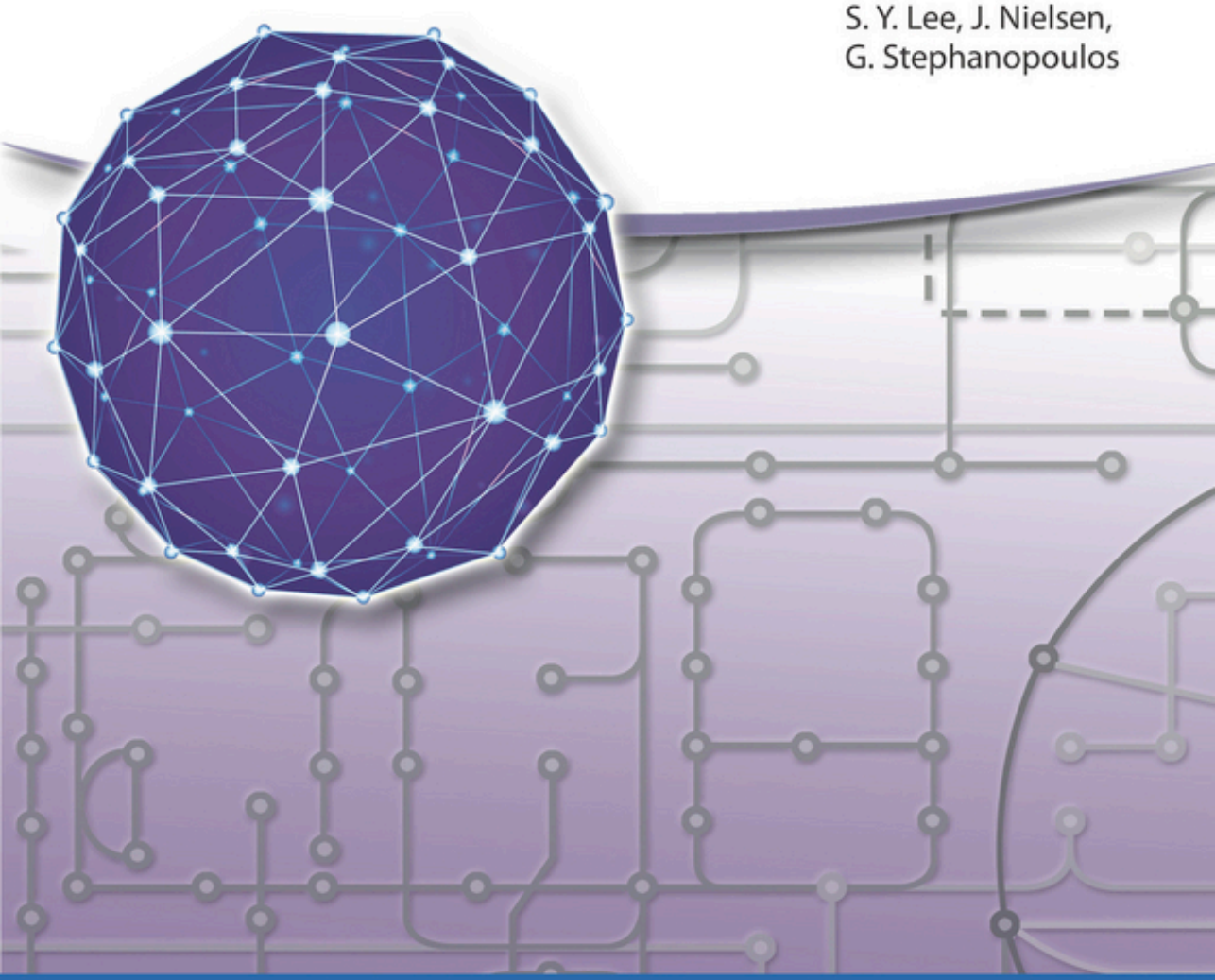

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WILEY-VCH
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Cover
Sphere – fotolia_©ket4up

Library of Congress Card No.: applied for

British Library Cataloguing-in-Publication Data
A catalogue record for this book is available from the British Library.

Bibliographic information published by the Deutsche Nationalbibliothek
The Deutsche Nationalbibliothek lists this publication in the Deutsche Nationalbibliografie; detailed bibliographic data are available on the Internet at <http://dnb.d-nb.de>.

Print ISBN: 978-3-527-33558-9
ePDF ISBN: 978-3-527-69616-1
ePub ISBN: 978-3-527-69617-8
Mobi ISBN: 978-3-527-69615-4
oBook ISBN: 978-3-527-69613-0

Cover Design Adam Design
Typesetting SPi Global, Chennai, India
Printing and Binding

Printed on acid-free paper

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1
Integrative Analysis of Omics Data

Tobias Österlund, Marija Cvijovic, and Erik Kristiansson

Summary

Data generation and analysis are essential parts of systems biology. Today, large amounts of omics data can be generated fast and cost-efficiently thanks to the development of modern high-throughput measurement techniques. Their interpretation is, however, challenging because of the high dimensionality and the often substantial levels of noise. Integrative analysis provides a framework for analysis of the omics data from a biological perspective, starting from the raw data, via preprocessing and statistical analysis, to the interpretation of the results. By integrating the data into structures created from biological information available in resources, databases, or genome-scale models, the focus moves from the individual transcripts or proteins to the entire pathways and other relevant biochemical functions present in the cell. The result provides a context-based interpretation of the omics data, which can be used to form a holistic and unbiased view of biological systems at a molecular level. The concept of integrative analysis can be used for many forms of omics data, including genome sequencing, transcriptomics, and proteomics, and can be applied to a wide range of fields within the life sciences.

1.1
Introduction

Systems biology is an interdisciplinary approach to biology and medicine that employs both experimentation and mathematical modeling to achieve a better understanding of biological systems by describing their shape, state, behavior, and evolutionary history. An important aim of systems biology is to deliver predictive and informative models that highlight the fundamental and presumably conserved relationships of biomolecular systems and thereby provide an improved insight into the many cellular processes [1]. Systems biology research methodology is a cyclical process fueled by quantitative experiments in combination with mathematical modeling (Figure 1.1) [2, 3]. In its most basic form, the cycle starts with the formulation of a set of hypotheses, which is followed by knowledge generation

Systems Biology, First Edition. Edited by Jens Nielsen and Stefan Hohmann.

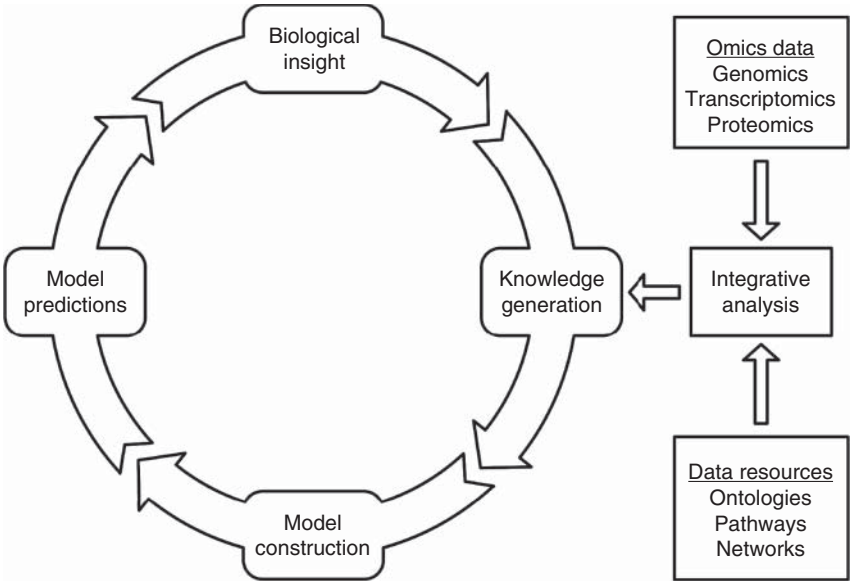

Figure 1.1 Systems biology research methodology. In the systems biology cycle, novel hypotheses are first formulated, which is followed by knowledge generation, model construction, and model predictions, which, in turn, leads to new biological insights. The development of high-throughput techniques have enabled rapid and cost-efficient generation of omics data from, for example, genome sequencing, transcriptomics, and proteomics. Integrative analysis provides a framework where omics data is systematically analyzed in a biological context, by data integration into known biological networks or other data resources, which enables improved interpretation and easier integration into quantitative models.

and model construction where an abstract description of the biological system (a model) is formulated and its parameters are estimated from data taken from the literature. The final step is defined by model predictions, where the constructed model is used to address the original hypotheses by providing a quantitative analysis of the system, which, in turn, generates new biological insight.

The development of high-throughput measurement techniques in the recent years has resulted in an unprecedented ability to rapidly and cost efficiently generate molecular data. Bioassays are today established for large-scale characterization of genes and their expression at the different layers defined by the central dogma: the genome, the transcriptome, and the proteome. The resulting data, which in this chapter will be referred to as *omics data*, is however complex because of its high dimensionality and is therefore hard to interpret and directly integrate into quantitative models. The concept of *integrative analysis* is a framework to systematically analyze the different components of omics data in relation to their corresponding biological functions and properties. The resulting biological interpretation can be used to form a holistic and unbiased view of biological systems at a molecular level. Thanks to the comprehensiveness of the

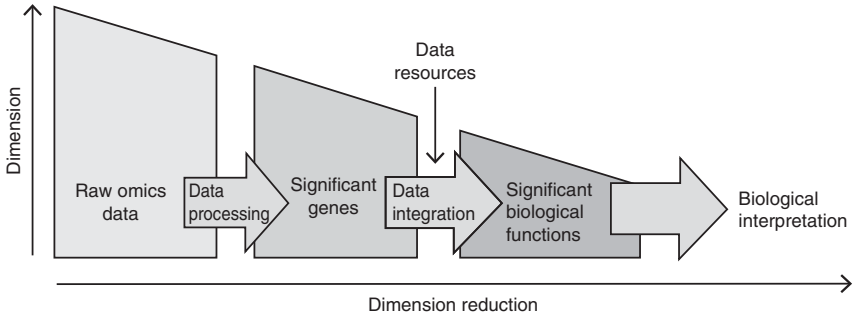

Figure 1.2 Description of the concept of integrative analysis as a tool for reduction of the dimension of omics data. Integrative analysis starts with raw omics data, which is typically affected by high levels of noise and errors. Computational and statistical approaches are first used to process the data to produce a ranked list of genes that are found to be of significant importance in the experiment. The gene list is used as input to the data integration, where known biological information is used as a basis for the interpretation of the data. During integrative analysis, the dimension of the data is significantly reduced, from potentially millions of data points to a limited number of significant biological functions and pathways, which considerably facilitates the interpretation.

omics data, all components (i.e., genes, transcripts, or proteins) can be measured simultaneously, which opens up opportunities for testing of existing hypotheses as well as generation of completely new hypotheses of the studied biological system.

The process of integrative analysis can be divided into two main steps: data processing and data integration (Figure 1.2). Integrative analysis starts from raw omics data and ends with the biological interpretation, and during this process the dimensionality of the data is reduced. The first step, the data processing, takes the high-dimensional omics data, and by applying computational and statistical tools, removes noise and errors while identifying genes and other components that contain information significant for the experiment. The next step, the data integration, uses the list of identified genes to pinpoint relevant functions and pathways by integrating the data on top of a "scaffold" built using established biological information collected from various resources and databases. The result, which is based on the combined analysis of the genes with similar functional properties, has a substantially reduced dimension, which considerably facilitates its interpretation.

Many studies in the life sciences aim to understand biological systems, often in relation to a perturbation caused by, for example, disease, genetic variability, changes in environmental parameters, or other factors introduced through laboratory experiments. A commonly used measurement technique is transcriptomics, where the transcriptional response is analyzed and the genes that are differentially expressed between investigated conditions are identified. In this setting, the data integration shifts the focus from what *genes* are differentially expressed to providing a *biological context* where activated and repressed pathways, functions, or subnetworks can be identified. This provides a more relevant view of the data, which paves the way toward more sound and detailed biological conclusions.

In this chapter, we provide a broad overview of integrative analysis of omics data. We will describe the general concept of integrative analysis and provide an outline of the many associated computational steps. It should, however, be pointed out that this topic has been extensively researched during the recent years and – due to the scope of the topic at hand – we will not be able to cover all aspects and details in a single chapter. We have therefore provided a comprehensive set of references throughout the text, which are the recommended starting points for further reading. Also, our main focus throughput this chapter will be on data generated by techniques from genomics, transcriptomics, and proteomics. This means that other types of data, which are commonly encountered in systems biology, such as metabolomics and lipidomics, will receive little attention, and here we instead refer the reader to the recent reviews by Robinson *et al*. [4] and Kim *et al*. [5].

The chapter is organized as follows. Section 1.2 contains an overview of some the types of omics data that are commonly used in integrative analysis. This is followed by Section 1.3, where we focus on the data processing, starting from the quality assessment of the raw data to statistical analysis. Section 1.4 explains the concepts of data integration and describes the different approaches and data resources that can be used. We end the chapter with an outlook discussing future challenges related to the continuous growth of biological information.

1.2 Omics Data and Their Measurement Platforms

In this section three commonly used types of omics data will be described, namely genome sequencing, transcriptomics (RNA sequencing and microarrays), and mass spectrometry (MS)-based proteomics.

1.2.1 Omics Data Types

Genome sequencing is used for determining the order of the complete set of nucleotides present in an organism. The comparative analysis of the genome of a strain or a multicellular organism in relation to a reference genome is referred to as "resequencing," which enables identification of the complete genotype and its variation between individuals. This includes both small mutations, such as single nucleotide polymorphisms (SNPs) and short insertions/deletions (indels), and larger structural variations such as genome rearrangements and copy number alterations [6]. The resulting information, containing a list of all identified genetic variants, is often subjected to integrative analysis in order to provide a biological context where the genotype can be linked to a phenotype [7]. Whole-genome and exome resequencing are important techniques for the study of human disease [8], and in, for example, cancer, the set of germline and somatic mutations are