

Summaries

Summary

Michael P. Stumpf, Brian D. Robertson, Ken Duncan and Douglas B. Young
Systems biology and its impact on anti-infective drug development

Systems biology offers the potential for more effective selection of novel targets for anti-infective drugs. In contrast to conventional reductionist biology, a systems approach allows targets to be viewed in a wider context of the entire physiology of the cell, with the potential to identify key susceptible nodes and to predict synergistic effects of blocking multiple pathways. In addition to the holistic perspective provided by systems biology, the emphasis on quantitative analysis is likely to add further rigour to the process of target selection. Systems biology also offers the potential to incorporate different levels of information into the selection process. Consideration of data from microbial population biology may be important in the context of predicting future drug-resistance profiles associated with targeting a particular pathway, for example. This chapter provides an overview of major themes in the developing field of systems biology, summarising the core technologies and the strategies used to translate datasets into useful quantitative models capable of predicting complex biological behaviour.

Keywords: imaging, integrative systems biology, mathematical models, metabolomics, metabonomics, networks, proteomics, targets, transcriptomics

Summary

Hans Peter Fischer and Christoph Freiberg
Applications of transcriptional profiling in antibiotics discovery and development

This chapter will review specific applications of microarray technology and related data analysis strategies in anti-bacterial research and development. We present examples of microarray applications spanning the entire antibiotics research and development pipeline, from target discovery, assay development, pharmacological evaluation, to compound safety studies. This review emphasizes the utility of microarrays for a systematic evaluation of novel chemistry as antibiotics agents. Transcriptional profiling has revolutionized the process of target elucidation and has the potential to offer substantial guidance in the identification of new targets. Microarrays will continue to be a workhorse of anti-infectives discovery programs ranging from efficacy assessments of antibiotics (“forward pharmacology”) to drug safety evaluations (“toxicogenomics”).

Summary

Helena I. Boshoff and Cynthia S. Dowd
Chemical Genetics: an evolving toolbox for target identification and lead optimization

Chemical genetics combines chemistry with biology as a means of exploring the function of unknown proteins or identifying the proteins responsible for a particular phenotype. Chemical genetics is thus a valuable tool in the identification of novel drug targets. This chapter describes the application of chemical genetics in traditional and systems-based approaches to drug target discovery and the tools/approaches that appear most promising for guiding future pharmaceutical development.

Summary

Julia E. Bandow and Michael Hecker

Proteomic profiling of cellular stresses in *Bacillus subtilis* reveals cellular networks and assists in elucidating antibiotic mechanisms of action

Proteomic profiling provides a global view of the protein composition of the cell. In contrast to the static nature of the genome sequence, which provides the blueprint for all protein-based cellular building blocks, the proteome is highly dynamic. The protein composition is constantly adjusting to facilitate survival, growth, and reproduction in an ever-changing environment. In a quest to understand the regulation of cellular networks and the role of individual proteins in the adaptation process, the proteomic response to stress and starvation was analyzed in wild-type and mutant strains. The knowledge derived from these proteomic studies was applied to investigating the bacterial response to antibiotics. It was found that proteomics presents a powerful tool for hypothesis generation regarding antibiotic mechanism of action.

Summary

Jesper Højer-Pedersen, Jørn Smedsgaard and Jens Nielsen

Elucidating the mode-of-action of compounds from metabolite profiling studies

Metabolite profiling has been carried out for decades and is as such not a new research area. However, the field has attracted increasing attention in the last couple of years, and the term metabolome is now often used to describe the complete pool of metabolites associated with an organism at any given time. Mass spectrometry (MS) and nuclear magnetic resonance (NMR) spectroscopy are the best candidates for comprehensive analysis of the metabolome and the application of these technologies is presented in this chapter. In this relation, the importance of efficient metabolite screening for discovery of novel drugs is discussed. Related to metabolite profiling, the principals underlying the application of labeled substrates to quantify *in vivo* metabolic fluxes are introduced, and the chapter is concluded by discussing the perspectives of metabolite measurements in systems biology.

Keywords: drug discovery, metabolite profiling, fingerprinting, MS, CE-MS GC-MS, LC-MS, flux analysis, systems biology, metabolite analysis

Summary

Andrei L. Osterman and Tadhg P. Begley

A Subsystems-based approach to the identification of drug targets in bacterial pathogens

This chapter describes a three-stage approach to target identification based upon subsystem analysis. Subsystems analysis focuses on related metabolic pathways as a unit and is a biochemically-informed approach to target selection. The process involves three stages of analysis; the first stage, selection of the target subsystem, is guided by information about its essentiality and on the predicted vulnerability of the targeted pathway or enzyme to inhibition. The second stage involves analysis of the target subsystem by means of comparative genomics, including genome context analysis and metabolic reconstruction. The third stage evaluates the selection of the specific target genes within the subsystem by target

prioritization and validation. The whole process allows for a careful consideration of spectrum, druggability, biological rationale and the metabolic role of the specific target within the context of an integrated circuit within a specific metabolic pathway.

Summary

Jorrit J. Hornberg, Frank J., Bruggeman, Barbara M. Bakker and Hans V. Westerhoff
Metabolic control analysis to identify optimal drug targets

This chapter describes the basic principles of metabolic control analysis (MCA) which is a quantitative methodology to evaluate the importance and relative contribution of individual metabolic steps in the overall functioning of a particular system. The flux in a metabolic pathway or subsystem is determined by the control coefficients of the individual enzymes or components which reflects the extent to which the component is rate-limiting. The perturbation of an individual step is measured by its elasticity coefficient. The effect of perturbation of a single step on the entire pathway or subsystem is, in turn, measured by the response coefficient. Differential control analysis can be used to compare flux through a single metabolic pathway in a pathogen with the same pathway in its host to identify uniquely vulnerable steps with the greatest potential for specifically inhibiting flux through the pathogen metabolic pathway. The utility of this methodology is illustrated with the glycolytic cycle of Trypanosomes.

Summary

Michael Strong and David Eisenberg
The protein network as a tool for finding novel drug targets

Proteins are often referred to as the molecular workhorses of the cell since they are responsible for the majority of functions within a living cell. From the generation of energy, to the replication of DNA, proteins play a central role in most cellular functions. Because of their importance to cellular viability, proteins are commonly the target of therapeutic drugs, ranging from antimicrobial to anticancer drugs. With the rise of drug resistant and multi-drug resistant forms of many diseases, it has become increasingly important to develop new strategies to identify alternative drug targets. One such strategy arises from the analysis of protein networks. Protein networks help define individual proteins within the context of all other cellular proteins. In this chapter we discuss methods for the identification and analysis of genome-wide protein networks, and discuss how protein networks can be used to aid the identification of novel drug targets.

Keywords: protein network, protein interactions, protein linkages, drug targets

Summary

François Pognan
Toxicogenomics applied to predictive and exploratory toxicology for the safety assessment of new chemical entities: a long road with deep potholes

Toxicology is the perturbation of metabolism by external factors such as xenobiotics, environmental factors or drugs. As such toxicology covers a broad range of fields from studies of the whole organism responses to minute biochemical events. Mechanistic toxicogenomics is an attempt to harness genomic tools to understand the physiological basis

for a toxic event based on an analysis of transcriptional, translational or metabolomic profiles. These studies are complicated by non-toxic adaptive responses in transcript, protein or metabolite expression levels that have to be distinguished from those that are proximally related to the toxic event. Substantial progress has been made on the identification of biomarkers and the establishment of screens derived from such toxicogenomics studies. The ultimate goal, of course, is Predictive toxicogenomics, which is an attempt to infer the likelihood of occurrence of a toxic event with exposure to a new agent based upon comparative responses with large databases of gene, protein or metabolite expression data. Gene expression databases are currently limited by the fact that measurable toxic phenotypes generally precede or at best coincide with the earliest observable changes in transcriptional profiles. Unfortunately, predictive protein databases have been limited by technical difficulties. Metabonomics-based databases, which would probably have the highest predictive value, are limited in turn by the inability to perform high dose studies in humans. This chapter will conclude by reviewing those elements of toxicogenomics that apply specifically to the development of anti-infectives and the potential for accurately modelling the toxicity of future drugs.

Summary

Hiroaki Kitano

The application of the theory of biological robustness to complex host-pathogen systems

Infectious diseases are still the number one killer of human beings. Even in developed countries, infectious diseases continue to be a major health threat. This article explores a conceptual framework for understanding infectious diseases in the context of the complex dynamics between microbe and host, and explores theoretical strategies for anti-infectives. The central pillar of this conceptual framework is that biological robustness is a fundamental property of systems that is closely interlinked with the evolution of symbiotic host-pathogen systems. This theory argues that there are specific architectural features of such robust yet evolvable systems and interpretable trade-offs between robustness, fragility, resource demands, and performance. This concept applies equally to both microbes and host. Pathogens have evolved to exploit the host using various strategies as well as effective escape mechanisms. Modular pathogenicity islands (PAI) derived from horizontal gene transfer, highly variable surface molecules, and a range of other countermeasures enhance the robustness of a pathogen against attacks from the host immune system. The host has likewise evolved complex defensive mechanisms to protect itself against pathogenic threats, but the host immune system includes several trade-offs that can be exploited by pathogens and induces undesirable inflammatory reactions. Due to the complexity of the dynamics emerging from the interactions of multiple microbes and a host, effective counter-measures require an in-depth understanding of system dynamics as well as detailed molecular mechanisms of the processes that are involved.

Summary

Andrew R. Joyce and Bernhard Ø. Palsson

Toward whole cell modeling and simulation: comprehensive functional genomics through the constraint-based approach

The increasing availability of various system-level, or so-called ‘omics’, data sets, in concert with existing data from the primary research literature, is facilitating the development of genome-scale metabolic models for many organisms. By incorporating the metabolic reaction

stoichiometry as well as other physico-chemical properties into systemic network reconstructions, these models account for the constraints that restrict an organism's phenotypic behavior. Accordingly, unlike many contemporary modeling strategies, this constraint-based modeling approach does not attempt to predict network behavior exactly; rather, it seeks to clearly distinguish those network states that a system can achieve from those that it cannot. A variety of analytical tools have been designed and developed to probe these models, thus enabling studies that investigate the metabolic capabilities of a number of organisms, that generate and test experimental hypotheses, and that predict accurately metabolic phenotypes and evolutionary outcomes. This chapter introduces the concepts that underlie the constraint-based modeling approach, and describes several of its applications with an emphasis on those potentially relevant to the drug development field. In addition, while this chapter focuses on the primary application of the constraint-based approach to date, namely in modeling metabolic networks, the latter sections of the chapter discuss its relatively recent application to modeling other cellular systems. Finally, the chapter concludes with an assessment of future directions focusing on the efforts that will be required to utilize the constraint-based approach in generating a holistic model of a viable organism.

Keywords: systems biology; flux balance analysis (FBA); computational modeling; constraints-based reconstruction and analysis; extreme pathways.

Summary

Dirk Schnappinger

Genomics of the host-pathogen interaction

The complete sequences of hundreds of microbial genomes have provided drug discovery pipelines with thousands of new potential drug targets. Their availability has also stimulated the development of a variety of innovative approaches that allow functional studies to be performed on the entire genome of an organism. This chapter describes how these approaches have been applied to the analysis of host-pathogen interactions and discusses how such studies might facilitate the development of new antibiotics.

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