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Current Opinion in Biotechnology

Biomedical applications of genome-scale metabolic network reconstructions of human pathogens

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The growing global threat of antibiotic resistant human pathogens has coincided with improved methods for developing and using genome-scale metabolic network reconstructions. Consequently, there has been an increase in the number of high-quality reconstructions of relevant human and zoonotic pathogens. Novel biomedical applications of pathogen reconstructions focus on three key aspects of pathogen behavior: the evolution of antibiotic resistance, virulence factor production, and host–pathogen interactions. New methods using these reconstructions aim to improve understanding of microbe pathogenicity and guide the development of new therapeutic strategies. This review summarizes the latest ways that genome-scale metabolic network reconstructions have been used to study human pathogens and suggests future applications with the potential to mitigate infectious disease.

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Current Opinion in Biotechnology 2018, **51**:70–79

This review comes from a themed issue on **Systems biology**

Edited by **Nathan Price** and **Eran Segal**

https://doi.org/10.1016/j.copbio.2017.11.014

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Introduction

Despite advancements in medicine, hygiene, and infrastructure, microbes that can survive and cause disease within a human host remain a global health concern [1]. Successful chronic infection of a human host is dependent on multiple pathogen behaviors including the development of antibiotic resistance [2,3], the production of virulence factors [4], and the exploitation of host and microbiota resources [5,6] (Figure 1). Aspects of these behaviors have been linked to pathogen metabolism [7•,8], opening up exciting opportunities for the development of novel therapeutic strategies with emerging technologies [9•,10]. However, identifying potential therapies, given the wide range of possible genetic mutations, host environments, and metabolic targets, remains a significant challenge [11,12]. One approach to overcome this problem has been the use of systems-level computational models, specifically genome-scale metabolic network reconstructions (GENREs).

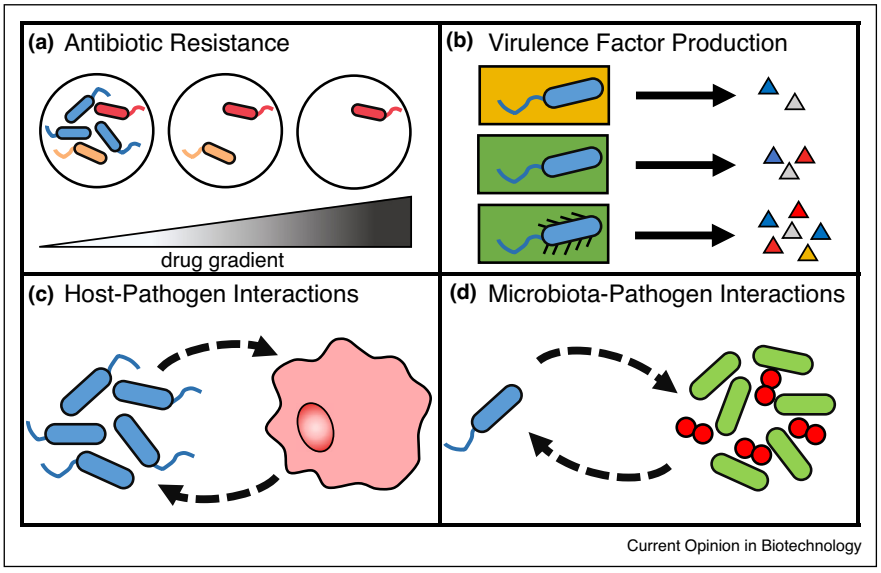
A GENRE is a mathematical framework of all known metabolic reactions inside an organism [13] (Box 1). The reactions and associated metabolites are formatted into what is known as a stoichiometric matrix. Functional relationships between genes and reactions can also be characterized with the model as gene–protein-reaction (GPR) rules allowing for the systematic simulation of gene knockouts [14,15]. GENREs are often evaluated with an approach called flux balance analysis (FBA) in which the network is optimized to maximize or minimize flux through an objective function such as biomass production [16]. Overall, GENREs are useful tools for probing various aspects of microbial metabolism [17,18].

In recent years, GENREs have become increasingly prevalent in the study of human pathogens. GENREs are ideal for predicting cellular phenotypes [17] (e.g. growth and virulence factor production) across a wide range of environments (e.g. media or host conditions). Of particular value, such predictions can be informed by available systems-level omics data, which can be integrated into a GENRE to generate condition-specific models [18]. The increase in available annotated genomes [19] and improved methods for drafting network reconstructions [20,21] have made it easier than ever to model pathogens of interest. Recent genome-scale metabolic network reconstructions of pathogenic bacteria [22••,23–27], fungi [28], and parasites [29•,30–32] have elucidated genes and pathways essential to the survival and growth of human and zoonotic pathogens. Here, we summarize the current applications of genome-scale metabolic network reconstructions toward studying three key behaviors of human pathogens: evolution of antibiotic resistance, production of virulence factors, and host–pathogen interactions. Looking forward, we speculate how such approaches can be applied to mitigate infectious disease.

Human pathogen models and antibiotic resistance

Pathogen metabolism plays an important but poorly understood role in the development of antibiotic resistance [7•,33,34]. Several approaches integrating systems-

Figure 1



Key behaviors of human pathogens during infection. Over the course of infection, pathogens can develop resistance to antibiotic treatments **(a)**, express different virulence factors (triangles) in response to their environment **(b)**, and interact with host tissues **(c)** and resident microbiota **(d)**. Metabolic network models of human pathogens can offer insight into each of these processes.

level experimental data with genome-scale metabolic network reconstructions have recently been applied to elucidate metabolic dependencies of resistance as well as potential drug targets (Table 1).

Understanding metabolic dependencies on the evolution of antibiotic resistance

One such approach has been the pairing of genome-scale metabolic models with omics data collected from adaptive laboratory evolution (ALE) experiments (Figure 2a). Adaptive laboratory evolution is an experimental method used to study molecular changes and genetic mutations that arise as a population of bacteria adapts to a selective environmental pressure (e.g. nutrient or oxygen limitation, antibiotic pressure) [35,36]. Data from ALE experiments in the absence of antibiotics have been compared to genome-scale models to evaluate the relationship between phenotypic growth, omics data, and model-predicted optimal growth [37]. ALE experiments have also been used to examine multiple aspects of resistance including the role of antibiotic tolerance in facilitating resistance, the impact of selection regime (e.g. dose) on resistance mechanisms and mutations, and the influence of past treatment history on collateral sensitivity [33,38,39•].

Two groups have recently developed methods to incorporate adaptive evolutions of resistance with genome-scale metabolic models. Zampieri *et al.* evolved *Escherichia coli* to three different antibiotics on two different carbon sources to evaluate the impact of metabolism on the development of antibiotic resistance [40••]. Metabolomics data were collected throughout the evolution experiments. In parallel to ALE experiments, the authors systematically constrained reactions in a metabolic network reconstruction of *E. coli* to calculate shadow prices for every metabolite in the model, where 'shadow prices' refer to the sensitivity of biomass production to a change in a given metabolite availability. Metabolites with negative shadow prices are predicted to be limiting for biomass production, and thus reactions with a large number of limiting metabolites are considered to be important for pathogen growth. The authors predicted that a reaction was important for the development of resistance if a large number of the metabolites in it had negative shadow prices and metabolite levels were altered in ALE metabolomics data.

In a second study, Banerjee *et al.* developed a pipeline to identify metabolites with the potential to restore susceptibility in antibiotic resistant populations of the zoonotic pathogen *Chromobacterium violaceum* [41•]. Phenotypic and metabolomics data from ALE experiments of *C. violaceum* to two separate antibiotics were incorporated into a genome-scale metabolic network reconstruction to generate wild-type and resistant models. Scaled shadow prices were calculated following flux balance analysis and antibiotic treatment was predicted to result in redox imbalance. The alteration of intracellular NAD/NADH ratios was proposed as a potential intervention to restore antibiotic susceptibility in resistant populations.

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