Metabolic flux balance analysis and the in silico analysis of Escherichia coli K-12 gene deletions

ABSTRACT

Supplementary information:

INTRODUCTION

Introduction The knowledge of a complete genome sequence holds the potential to reveal the 'blueprints' for cellular life. The genome sequence contains the information to propagate the living system, and this information exists as open reading frames (ORFs) and regulatory information. Computational approaches have been developed (and are continuously being improved) to decipher the information encoded in the DNA. However, it is becoming evident that cellular functions are intricate and the integrated function of biological systems involves many complex interactions among the molecular components within the cell. To understand the complexity inherent in cellular networks, approaches that focus on the systemic properties of the network are also required. The complexity of integrated cellular systems leads to an important point, namely that the properties of complex biological processes cannot be analyzed or predicted based solely on a description of the individual components, and integrated systems based approaches must be applied. The focus of such research represents a departure from the classical reductionist approach in the biological sciences, and moves toward the integrated approach to understanding the interrelatedness of gene function and the role of each gene in the context of multi genetic cellular functions or genetic circuits. The engineering approach to analysis and design of complex systems is to have a mathematical or computer model; e.g. a dynamic simulator of a cellular process that is based on fundamental physicochemical laws and principles. Herein, we will analyze the integrated function of the metabolic pathways, and there has been a long history of mathematical modeling of metabolic networks in cellular systems, which dates back to the 1960s. While the ultimate goal is the development of dynamic models for the complete simulation of cellular metabolism, the success of such approaches has been severely hampered by the lack of kinetic information on the dynamics and regulation of metabolism. However, in the absence of kinetic information it is still possible to assess the theoretical capabilities and operative modes of metabolism using flux balance analysis (FBA). We have developed an in silico representation of Escherichia coli (E. coli in silico) to describe the bacterium's metabolic capabilities. E. coli in silico was derived based on the annotated genetic sequence, biochemical literature, and the online bioinformatic databases. The properties of E. coli in silico were analyzed and compared to the in vivo properties of E. coli, and it was shown that E. coli in silico can be used to interpret the metabolic phenotype of many E. coli mutants. However, the utilization of the metabolic genes is dependent on the carbon source and the substrate availability. Thus, the mutant phenotype is also dependent on specific environmental parameters. Therefore, herein we have utilized E. coli in silico to computationally examine the condition dependent optimal metabolic pathway utilization, and we will show that the FBA can be used to analyze and interpret the metabolic behavior of wildtype and mutant E. coli strains.

CONCLUSION

Conclusions Herein, we have utilized an in silico representation of E. coli

to study the condition dependent phenotype of E. coli and central metabolism gene deletion strains. We have shown that a computational analysis of the metabolic behavior can provide valuable insight into cellular metabolism. The present in silico study builds on the ability to define metabolic genotypes in bacteria and mathematical methods to analyze the possible and optimal phenotypes that they can express. These capabilities open the possibility to perform in silico deletion studies to help sort out the complexities of E. coli mutant phenotypes.