Chapter XXVII
Applications of Metabolic Flux Balancing in Medicine

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ABSTRACT

This chapter summarizes the fundamentals of metabolic flux balancing as a computational tool of metabolic engineering and systems biology. It also presents examples from the literature for its applications in medicine. These examples involve mainly liver metabolism and antibiotic production. Metabolic flux balancing is a computational method for the determination of metabolic pathway fluxes through a stoichiometric model of the cellular pathways, using mass balances for intracellular metabolites. It is a powerful tool to study metabolism under normal and abnormal conditions with a view to engineer the metabolism. Its extended potential in medicine is emphasized in the future trends.

INTRODUCTION

Systems biology studies simultaneously the complex interaction of the many cell components using many levels and forms of biological information and data in order to understand how they work together or not. After the single cell, the natural challenge for the systems biology is to understand the integrated functioning of the tissues, organs and the whole organism such as the human body.

In systems biology, metabolism is the final manifestation of the integrated functioning, regulation and control of genes, transcription, translation and enzyme action. The effects of some genetic alterations cannot always be observed in the phenotype but the genetic effects can be observed in the physiology or metabolome. Metabolism is the fundamental determinant of cell physiology and the chemical engine that drives the living process. Metabolic engineering is the study of metabolism using scientific and engineering tools in order to understand it better under normal and abnormal conditions such as disease, injury, stress or mutation. Metabolic engineering is therefore an important component of systems biology and metabolic flux balancing is a powerful tool of metabolic engineering (Stephanopoulos et al, 1998; Palsson, 2006).

The objectives of this chapter are to introduce the fundamentals of metabolic flux balancing and show its potential as a tool of systems biology through its applications in medicine.

FUNDAMENTALS OF METABOLIC FLUX BALANCING

Metabolism converts substrates into metabolic energy, redox potential and metabolic end products that are essential for cellular function. Several independent reactions that govern the synthesis and organisation of the macromolecules into a functioning cell can be classified as fueling reactions, biosynthetic reactions, polymerisation reactions and assembly reactions.

Characteristics of metabolic pathways can be summarized as follows:

- Almost all metabolic reactions are reversible.
- Metabolic pathways however, are irreversible.
- Every metabolic pathway has a first committed step.
- All metabolic pathways are regulated.
- Metabolic pathways in eukaryotic cells occur in specific cellular locations.
- Different metabolic pathways are connected by metabolites that participate in more than one pathway by pathway branching. These metabolites, therefore, connect one reaction sequence with another.
- Co-factors like ATP, NADH and NADPH also take part in pathway integration because of their central roles in biosynthetic reactions. Biosynthetic reactions continuously form and utilise these co-factors and hence connect individual reactions both within the same pathway and between different pathways.

While cell composition may vary with cell-type and physiological and environmental conditions, a typical cell can be assumed to contain: protein, RNA, DNA, lipids, lipopolysaccharides, peptidoglycan, glycogen and free amino acids. The 12 precursor metabolites formed in the biosynthetic pathways are used to synthesize about 75-100 building blocks, coenzymes and prosthetic groups needed for cellular synthesis. The major biosynthetic pathways involved in cell growth include the biosynthesis of amino acids, nucleotides, sugars, amino sugars and lipids. The building blocks produced in biosynthetic reactions are sequentially linked into long branched or unbranched polymeric chains during polymerisation reactions. These long polymeric chains are called the macromolecules of cellular biomass and can be grouped into ribonucleic acid (RNA), deoxyribonucleic acid (DNA), proteins, carbohydrates, free amino acids and lipids.