PREFACE

Metabolism represents a complex system characterized by a high variability in metabolites' structures, concentrations and regulation ratios. Such variability is observed at different metabolic scales going from metabolites to metabolic profiles via chemical reactions and metabolic pathways, and under static or dynamic aspects. These components vary quantitatively and qualitatively by different processes including apparition-disappearence, increase-decrease in concentration and regulation levels, variation of local enzymatic activity or global pathway expression, etc. These different processes lead to different structural, functional and evolutive states of the metabolic system. Analysis of the different metabolic states and their control processes (generating or governing) require the use of different mathematical tools which provide appropriate solutions to different questions on the system:

Complex topologies of metabolic systems can be mathematically structured by using appropriate matrices giving separated information on the different components of system. These matrices give invariant or variant characteristics of the system: Stoichiometric matrix characterizes *a priori* the system by all its chemical reactions (invariant characteristics), and is used as a basis to predict the states of adjustable (variant) parameters (e.g. metabolic flux distributions) in the system. On the other hand, concentration matrix characterizes *a posteriori* a metabolic system by variant parameters consisting of different metabolites analysed in different individuals (subjects). From such a matrix, a correlation analysis can be applied to highlight different relationships between metabolites' levels. This helps to understand the organization and relative behaviors of metabolites in the system.

Beyond relationships between metabolites, metabolic systems can be analysed under the polymorphism concept consisting in identifying different metabolic poles or trends representing output products or responses of system. Such identification can be achieved by correspondence analysis which extracts the extreme metabolic profiles showing the highest regulations for some metabolites. By reference to these metabolic trends, all the metabolic profiles of the population can be classified into homogeneous groups by means of cluster analysis. At population level, the metabolic profiles represent polymorphic units of the metabolic system.

Beyond correlations between metabolites and associations of metabolic profiles to metabolic trends, a third variability can be analysed consisting of atypical profiles in the population due to atypical values for some metabolites. Identification of such atypical cases can be achieved by means of different outlier diagnostics. Outlier extraction leads to homogenize the studied population on the hand, and can bring interesting information on eventual new populations on the other hand.

A part from static analysis, metabolic systems can be analysed under kinetic or dynamic aspects by considering the variations of parameters (e.g. concentrations) in time. Time-dependent variation analysis includes deterministic compartment models, stochastic fitting and dynamic stability analysis.

These different computational approaches to variability analysis of metabolic systems are presented in this book and illustrated by different numerical applications and figures.