

A Primer on Metabolic Pathway Analysis

Eberhard O. Voit

Brief description of the instructor indicating the relevant qualifications and teaching experience

Eberhard Voit is Professor of Biometry and Epidemiology and of Biochemistry and Molecular Biology at the Medical University of South Carolina. He is an active researcher and one of the leading experts in Biochemical Systems Theory (BST) and Canonical Modeling with S-systems. Voit has taught at all levels of graduate education, from introductory biostatistics courses for non-majors, to advanced courses like *Modeling and Simulation* and *Systems Analysis II* and *III*. He has graduated seven Ph.D. students and seventeen Master's students and has served on about 50 graduate student advisory committees. Voit has taught several modeling workshops in the U.S. (including at ISMB 2000), Portugal, and Japan for graduate students and faculty in biology and engineering. In addition to over 100 scientific papers and book chapters and two reference books on *Canonical Nonlinear Modeling* (Van Nostrand/Reinhold, 1991) and *Metabolic Engineering* (Cambridge University Press, 2002), Voit has co-authored a 150-page self-learner tutorial to a software package for systems analysis (*The User's Guide to ESSYNS*, Medical University of South Carolina Press, 1989) and published a single-author 540-page undergraduate/graduate-level textbook on the *Computational Analysis of Biochemical Systems* (Cambridge University Press, 2000), which familiarizes biologists with the fascinating world of complex systems modeling.

Title and expected goals, objectives and motivation of the tutorial

A Primer on Metabolic Pathway Analysis

Recent advances in genomics and metabolic profiling have begun to produce unprecedented amounts of data that await analysis and interpretation. The clustering of genes that are up or down regulated in response to a stimulus is an excellent strategy for identifying known and unknown genes involved in the response. However, it is not sufficient a tool for understanding the well-orchestrated overall response with which an organism reacts to perturbations. True explanations of why some processes are turned on or off require effective mathematical modeling approaches that provide a bridge between genomic, biochemical, and physiological levels. These approaches must be sophisticated enough to capture with some validity the complexity observed in metabolic pathways, gene networks, and physiological responses, but simple enough to be tractable when applied to phenomena of relevant magnitude.

The proposed tutorial exposes the attendee to a biomathematical framework, called *Canonical Modeling*, that has proven very effective in the analysis of metabolic pathways and regulatory gene circuits. The tutorial will consist of five modules. The first discusses the need for mathematical models beyond simple kinetic rate laws and

introduces the concept of power-law representations for biochemical processes. The second module discusses simple, yet effective rules for translating the diagram of a pathway or network into canonical model equations. The third module provides methods of parameter estimation. In addition to traditional methods, new ideas about parameter estimation from metabolic profiles will be discussed. The final module solidifies the material from the first four modules in a detailed case study that deals with some aspects of the heat shock response in yeast.

Intended audience

The tutorial presents an introduction for *biologists* who do not necessarily have a strong computational background but would like to experience what can be learned about metabolic pathways with modeling methods. Even though differential equations are involved, high school mathematics is sufficient, if it is accompanied by openness toward new concepts and a willingness to venture into unfamiliar territory. No experience in statistics, programming or algorithm development is necessary.

Length: half day

Detailed outline of the presentation

Module 1: Need for Models

- ?? Approaches to representing and analyzing biochemical and genetic systems.
- ?? Desirable features of “good” models; exact representations *vs.* approximations.
- ?? Combination and complementation of algebraic analyses and computer simulations.
- ?? Concepts of change and of differential equations; general system equations.

Module 2: Maps and Equations

- ?? Essential components of systems models.
- ?? Basic terminology and notation; dependent variables, independent variables, parameters; flow of material *versus* flow of information.
- ?? Guidelines for translating biochemical and genetic systems into convenient graphical representations (*maps*); correct maps, faulty maps; didactic and actual examples.
- ?? Power-law representation and canonical S-system models. Meaning of parameters.
- ?? Guidelines for designing basic models.

Module 3: A Typical Analysis

- ?? Concept of a steady state.
- ?? Stability.
- ?? Sensitivities, gains, robustness.
- ?? Dynamics.
- ?? Bolus experiments.
- ?? Persistent changes in system components.
- ?? Introduction to the freeware *PLAS*.

Module 4: Parameter Estimation

- ?? Survey of methods for estimating parameter values.
- ?? Data needs for the various approaches. Advantages and limitations of these approaches.
- ?? Estimation of kinetic orders from steady-state data.
- ?? Estimation of kinetic orders and rate constants from traditional rate laws.
- ?? Estimation of parameters from dynamic data.
- ?? Representative didactic and actual examples.

Module 6: Detailed Case Study: Heat Shock Response in Yeast

- ?? Available data.
- ?? Model design and implementation; basic analysis.
- ?? Typical computer experiments: bolus experiments, changes in dependent or independent variables, changes in parameter values.
- ?? Exploration of the rationale for complex regulatory structure.
- ?? Interpretation

General Discussion

- ?? Philosophical and technical questions from the audience.
- ?? Strengths and limitations of canonical modeling.
- ?? What's the future?