Current knowledge of biological systems is composed of a vast set of data that accumulate with an increasing rate. Advances in analytical methods and development of sophisticated techniques and instrumentation have provided the tools that allow us to know more than we can understand. However, it is well understood that living organisms are characterized by high complexity. This complexity increases from unicellular organisms to isolated tissue cells and multicellular structures, such as tissues and organs. The development of tools and frameworks that will organize the available biological knowledge and will help in the analysis, understanding, and redesign of biological systems is of immediate importance. A hierarchy of mathematical structures and computational approaches for utilizing experimental information to derive insights into cell function and for design of improved function will be presented. These approaches can be quantitative or qualitative and they can provide with predictive power or constructive guidance. The pros and cons of the different approaches will be set forth for discussion.
QUANTITATIVE & QUALITATIVE SYSTEMS BIOTECHNOLOGY: ANALYSIS NEEDS AND SYNTHESIS APPROACHES

Vassily Hatzimanikatis
Northwestern University

THE ENGINEERING VIEW OF A LIVING CELL

ENVIRONMENT

Signal transduction

REGULATION

Transcriptional regulation

Translational regulation

Enzyme regulation

TRANSCRIPTION

Translation

Biotransformation

DNA
Metabolites
Polymers

STOICHIOMETRY
Biochemical Engineering:

Retrofitting ancient (bio)chemical plants

Key to retrofitting:

Qualitative and Quantitative understanding of the processes involved
- Transcription
- Translation
- Biotransformation
and their interactions

\[
\begin{align*}
\text{C}_6\text{H}_{12}\text{O}_6 & \rightarrow \text{C}_3\text{H}_4\text{O}_3 \\
\text{ATP} & \text{NADH}
\end{align*}
\]
DESCRIPTION AND PREDICTION

WHAT IS THE MEANING (AND VALUE) OF “PREDICTIVE METHODS” CONSIDERING:

• PARTIAL INFORMATION
• UNCERTAINTY
• UNKNOWN INTERACTIONS
• DIMENSIONS
  (COMPONENTS/PARAMETERS/TIME)
• TIME SCALES
• BIOCHEMICAL vs INTEGRATIVE

CRITICAL ISSUES

EVERY MATHEMATICAL DESCRIPTION OF INTEGRATED BIOLOGICAL SYSTEMS IS AN APPROXIMATION

BUILDING MATHEMATICAL DESCRIPTIONS OF CELLULAR SYSTEMS AND FRAMEWORKS FOR THEIR STUDY IS AN ART (B. Palsson)

EVERY MATHEMATICAL DESCRIPTION AND FRAMEWORK SHOULD BE EVALUATED WITH RESPECT TO THEIR CAPABILITY IN RESOLVING THE CRITICAL ISSUES
"very long" because we want to assume that there are no "end effects"; that is, we ignore the fact that at the tube entrance and exit the flow will not necessarily be parallel everywhere to the tube surface.

**BSL**

**DESCRIPTION AND PREDICTION**

- O. Levenspiel and Reaction Engineering
- M. Savageau and BST

**BST is not about models:**

**It is about understanding biological principles using models**
S-SYSTEMS FRAMEWORK IS
AN APPROXIMATION, BUT A GOOD ONE

- SUITABLE FOR INCORPORATING PARTIAL INFORMATION
- CONSIDERATION OF UNCERTAINTY
  (Petkov & Maranas)
- FLEXIBLE IN DESCRIBING INTERACTIONS
  (Hatzimanikatis, Floudas, Bailey)
- MINIMUM SET OF PARAMETERS
- DESCRIPTION OF DYNAMICS
  \{ COMPUTATIONALLY EASY \}
- “EXPANDABLE” FOR INTEGRATED PROCESSES

THE CORNELL SINGLE-CELL MODEL

A CLASSIC SUCCESSFUL EXAMPLE OF
QUANTITATIVE MODELING OF
INTEGRATED CELLULAR PROCESSES

IT GREATLY ENRICHED OUR UNDERSTANDING
OF COMPLEX (SPECIFIC) PROBLEMS

IT HAS NOT BEEN USED TO ITS ULTIMATE
POTENTIAL AS A DISCOVERY TOOL
CHALLENGES

• GIVEN A DESCRIPTION OF A CELLULAR PROCESS, WHAT ARE THE SYSTEMS ENGINEERING (AND COMPUTATIONAL) FRAMEWORKS FOR ANALYSIS, UNDERSTANDING, (USEFULLY) INTEGRATING EXPERIMENTAL INFORMATION?

• GIVEN A SET OF DATA OF A CERTAIN KIND, WHAT ARE THE “MODELING” FRAMEWORKS AND ASSOCIATED SYSTEMS ENGINEERING METHODS FOR “MAKING SENSE” AND GETTING GUIDANCE?

QUANTITATIVE vs QUALITATIVE
PREDICTION vs UNDERSTANDING
PARAMETER FITTING vs PARAMETER EXPLORATION

SOME EXAMPLES

• BIFURCATION ANALYSIS OF GLYCOLYSIS
  (Selkov; Heinrich)

• TIME-SCALE ANALYSIS OF BIOCHEMICAL REACTIONS
  (Heineken, Aris; Palsson, Liao, Lightfoot)

• SCALING PROPERTIES OF BOOLEAN NETWORKS VIEWED AS GENETIC NETWORKS
  (Kauffman)

• OPTIMIZATION METHODS FOR BIOCHEMICAL RXN NETWORKS
  (Palsson; Domach; Voit; Hatzimanikatis, Floudas, Bailey)

• MODEL REDUCTION OF COMPLEX PATHWAYS
  (Savageau; Palsson; Mavrovtoumiotis)

• ROBUSTNESS ANALYSIS OF BIOCHEMICAL SYSTEMS
  (Leibler; Doyle; Hatzimanikatis, Bailey)

• “SMALL” SYSTEM SIMULATION STUDIES
  (Arkin, McAdams, Ross)
HIERARCHY OF MATHEMATICAL STRUCTURES FOR UTILIZING EXPERIMENTAL INFORMATION: METABOLISM

EXTERNAL METABOLITE MEASUREMENTS

- ISOTOPIC TRACER EXPERIMENTS
- FLUXES IN/OUT OF CELLS
- METABOLIC STOICHIOMETRY

METABOLITE MEASUREMENTS

- FLUXES WITHIN CELL

(LOG)LINEAR KINETIC MODELS

- METABOLIC CONTROL ANALYSIS
- OPTIMIZATION
- DYNAMICS (STABILITY, ROBUSTNESS)

EXTENSIVE MEASUREMENTS

- NONLINEAR KINETIC MODELS OF CELLULAR PROCESSES

PARAMETRIC STUDIES & OPTIMIZATION, GLOBAL STABILITY ANALYSIS

Adapted from J.E. Bailey, Biotechnol. Prog., 14(1), 8-20 (1998)

HIERARCHY OF MATHEMATICAL STRUCTURES FOR UTILIZING EXPERIMENTAL INFORMATION: TRANSCRIPTION & TRANSLATION

GENE/PROTEIN EXPRESSION PATTERNS

- PROTEIN-DNA PROTEIN-PROTEIN INTERACTIONS
- CLUSTERING
- GENOMIC INFORMATION

BOOLEAN NET MODELS

- “STATES”
- WIRING IDENTIFICATION
- KNOCK OUTS
- TARGET IDENTIFICATION

THERMODYNAMICS & KINETIC DATA

- PROTEIN EXPRESSION
- NONLINEAR KINETIC MODELS OF GENE & PROTEIN EXPRESSION

GLOBAL STABILITY ANALYSIS, WIRING ANALYSIS AND DESIGN, TARGET DESIGN, MUTATION ANALYSIS, PARAMETRIC STUDIES & OPTIMIZATION
HIERARCHY OF MATHEMATICAL STRUCTURES FOR UTILIZING EXPERIMENTAL INFORMATION: SIGNAL TRANSDUCTION

STIMULUS RESPONSE

ISOTOPIC TRACER EXPERIMENTS

PATHWAY SENSITIVITY

GENOMIC INFORMATION

PROTEIN-PROTEIN INTERACTIONS

PATHWAY IDENTIFICATION

BOOLEAN NET MODELS, PETRI NET MODELS, QUALITATIVE KINETIC MODELS

TARGET IDENTIFICATION

EXPERIMENTAL DESIGN

DYNAMICS

EXTENSIVE MEASUREMENTS

EXPERIMENTAL DESIGN

KINETIC PARAMETERS

NONLINEAR KINETIC MODELS OF SIGNAL TRANSDUCTION PATHWAYS

PARAMETRIC STUDIES & OPTIMIZATION, GLOBAL STABILITY ANALYSIS