Quantitative and Qualitative Systems Biotechnology: Analysis Needs and Synthesis Approaches

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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

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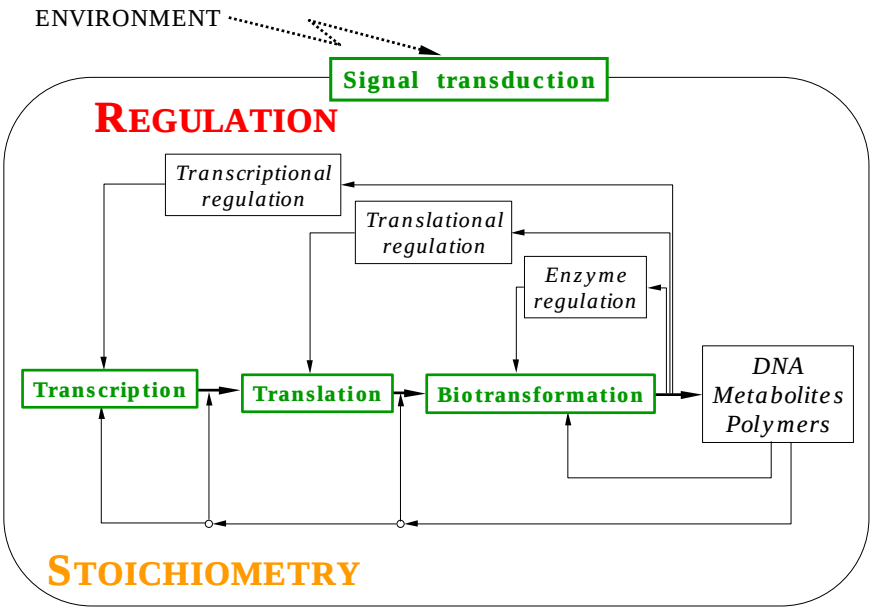
THE ENGINEERING VIEW OF A LIVING CELL



Biochemical Engineering :

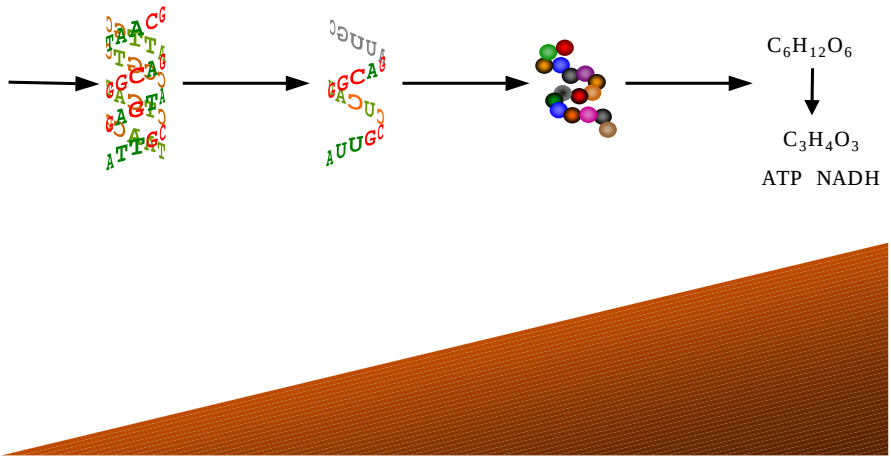
Retrofitting ancient (bio)chemical plants

Key to retrofitting:

Qualitative and Quantitative understanding of the processes involved

- Transcription
- Translation
- Biotransformation

and their interactions



TECHNOLOGY
LIMITATIONS

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***

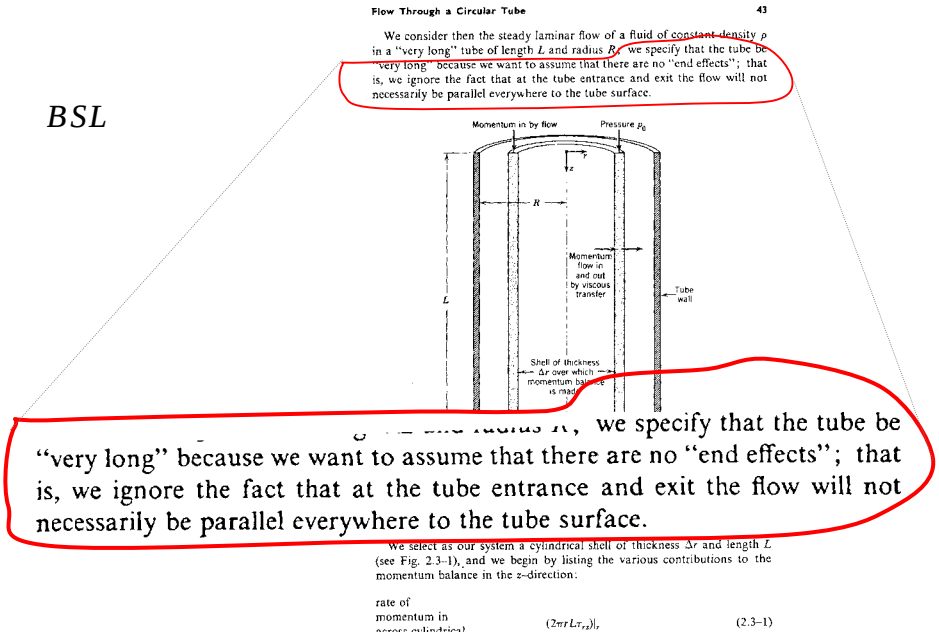
EVERY MATHEMATICAL DESCRIPTION OF
INTEGRATED BIOLOGICAL SYSTEMS
IS AN APPROXIMATION

BUILDING MATHEMATICAL DESCRIPTIONS OF
CELLULAR SYSTEMS AND FRAMEWROKS
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

DESCRIPTION AND PREDICTION

BSL



Flow Through a Circular Tube 43

We consider then the steady laminar flow of a fluid of constant density ρ in a "very long" tube of length L and radius R; we specify that the tube be "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.

Momentum in by flow

Pressure p_0

z

R

L

Momentum flow in and out by viscous transfer

Tube wall

Shell of thickness Δr over which momentum balance is made

"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.

We select as our system a cylindrical shell of thickness Δr and length L (see Fig. 2.3–1), and we begin by listing the various contributions to the momentum balance in the z-direction:

rate of momentum in across cylindrical $(2\pi rL\tau_{rz})|_{r}$, (2.3–1)

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 INCORPORTATING 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

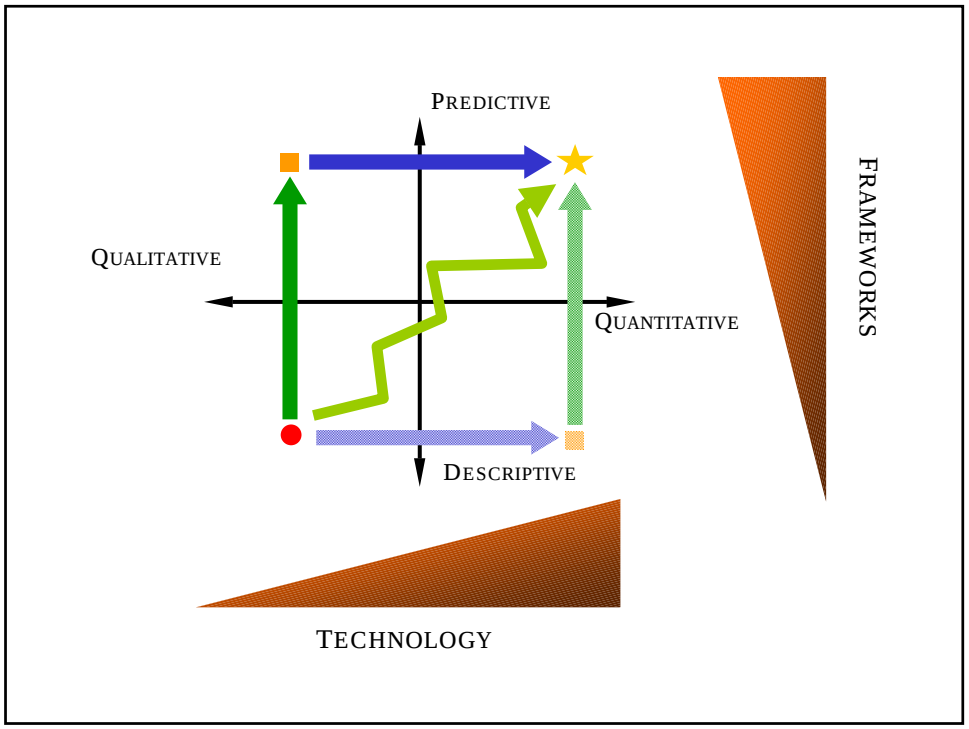
CHALLENGES

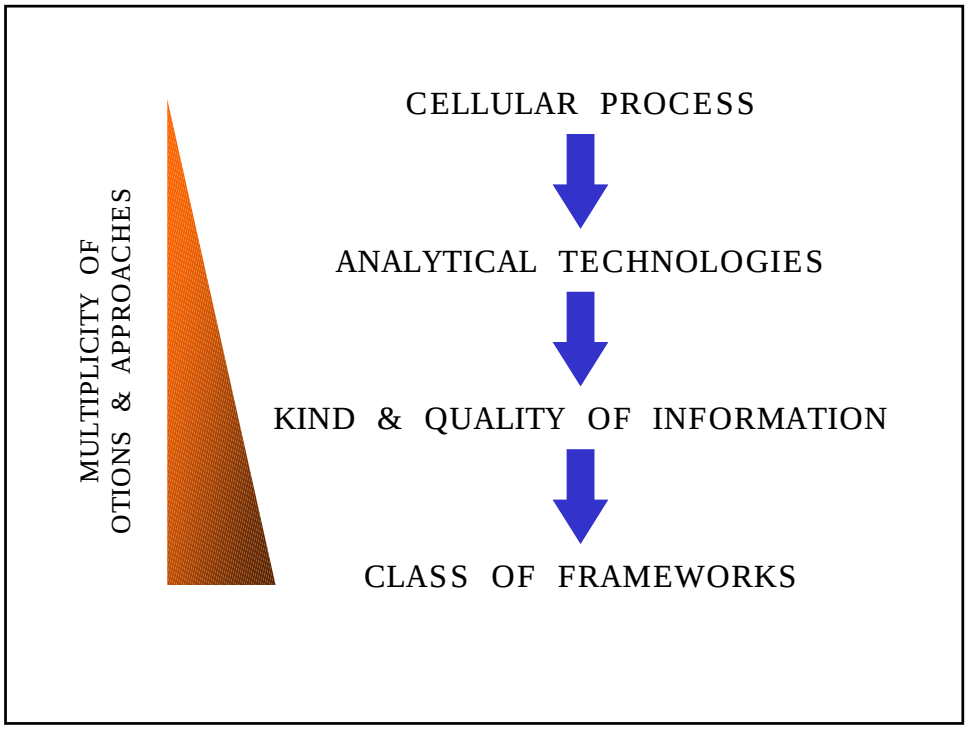
- GIVEN A DESCRIPTION OF A CELLULAR PROCESS, WHAT ARE THE SYSTEMS ENGINEERING (AND COMPUTATIONAL) FRAMEWROKS FOR ANALYSIS, UNDERSTANDING, (USEFULLY) INTEGRATING EXPERIMENTAL INFORMATION ?
- GIVEN A SET OF DATA OF A CERTAIN KIND, WHAT ARE THE "MODELING" FRAMEWORKS AND ASSOCIATED SYSTEMS ENGINERING METHODS FOR "MAKING SENSE" AND GETTING GUIDANCE ?

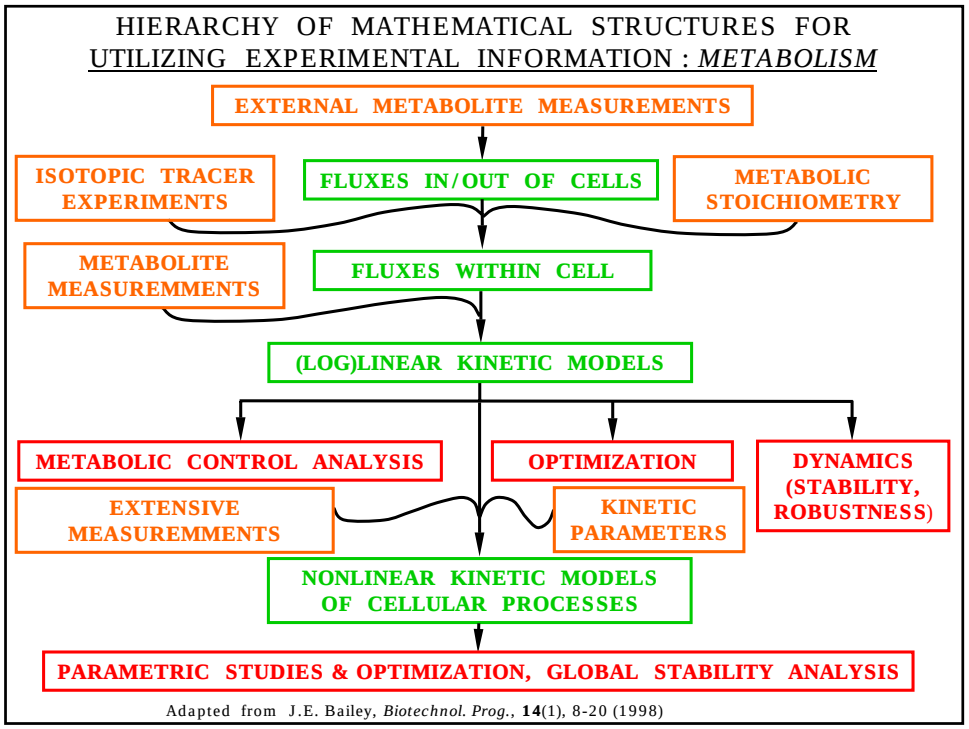
QUANTITATIVE vs QUALITATIVE
PREDICTION vs UNDERSTANDING
PARAMETER FITTING vs PARAMETER EXPLORATION

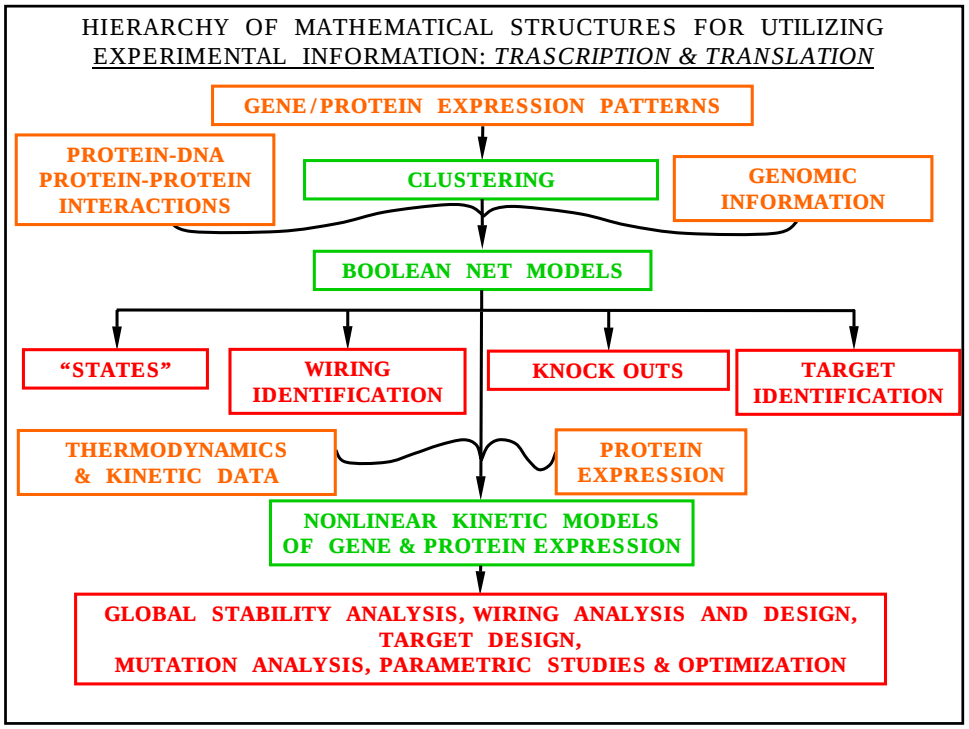
SOME EXAMPLES

- BIFURCATION ANALYSIS OF GLYCOLYSIS
  (Selkov; Heinrich)
- TIME-SCALE ANALYSIS OF BIOCHEMICAL REACTIONS
  (Heineken, Aris; Palsson, Liao, Lightfoot)
- SCALLING 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; Mavrovouniotis)
- ROBUSTNESS ANALYSIS OF BIOCHEMICAL SYSTEMS
  (Leibler; Doyle; Hatzimanikatis, Bailey)
- "SMALL" SYSTEM SIMULATION STUDIES
  (Arkin, McAdams, Ross)


PREDICTIVE
QUALITATIVE
QUANTITATIVE
DESCRIPTIVE
FRAMEWORKS
TECHNOLOGY


MULTIPLICITY OF
OTIONS & APPROACHES
CELLULAR PROCESS
ANALYTICAL TECHNOLOGIES
KIND & QUALITY OF INFORMATION
CLASS OF FRAMEWORKS


HIERARCHY OF MATHEMATICAL STRUCTURES FOR
UTILIZING EXPERIMENTAL INFORMATION : METABOLISM
EXTERNAL METABOLITE MEASUREMENTS
ISOTOPIC TRACER EXPERIMENTS
FLUXES IN/OUT OF CELLS
METABOLIC STOICHIOMETRY
METABOLITE MEASUREMMENTS
FLUXES WITHIN CELL
(LOG)LINEAR KINETIC MODELS
METABOLIC CONTROL ANALYSIS
OPTIMIZATION
DYNAMICS (STABILITY, ROBUSTNESS)
EXTENSIVE MEASUREMMENTS
KINETIC PARAMETERS
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: TRASCRIPTION & 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*