Modelling and control of biochemical systems

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Trouble with complex systems

Things we understand easily

- Separate entities
- Small numbers
- Direct effects
- Causal chains

... but living systems are

- Continuous
- Complex
- Dynamic
- Adaptive
- Stochastic
- Evolved
Modelling the metabolic network
Modelling the metabolic network
Anatomy of a metabolic system
Threonine pathway in E. Coli

Aspartate → Aspartyl-P → Asp semi-alde → Homoserine → P-Homoserine → Threonine
Anatomy of a metabolic system
Threonine pathway in E. Coli

1. Aspartate
2. Aspartyl-P
3. Asp semiald
4. Homoserine
5. P-Homoserine
6. Threonine
Anatomy of a metabolic system
Threonine pathway in E. Coli

1. Aspartate
   - 2. Aspartyl-P
     - 3. Asp semiald
       - 4. Homoserine
         - 5. P-Homoserine
           - 6. Threonine
             - 2.7.2.4
             - 1.2.1.11
             - 1.1.1.3
             - 2.7.1.39
             - 4.2.3.1
             - Lysine
Anatomy of a metabolic system

Threonine pathway in E. Coli

Aspartate → Aspartyl-P → Asp semiald → Homoserine → P-Homoserine → Threonine

Lysine

Enzyme IDs:
- 2.7.2.4
- 1.2.1.11
- 1.1.1.3
- 2.7.1.39
- 4.2.3.1

Genes:
- asd
- thrA
- thrB
- thrC
Anatomy of a metabolic system
Threonine pathway in E. Coli

Aspartate → Aspartyl-P → Asp semi-aldehyde → Homoserine → P-Homoserine → Threonine

Transcription factors: asd, thrA, thrB, thrC
Dynamic laws for metabolic networks
derived from balance of concentrations

A → B → C

Homoserine → O-phospho-homoserine → Threonine
Dynamic laws for metabolic networks
derived from balance of concentrations

Reaction velocities

\[ v_1 = v_1(a, b) \]
\[ v_2 = v_2(b, c) \]

Balance equations

\[ \frac{da}{dt} = -v_1 \]
\[ \frac{db}{dt} = v_1 - v_2 \]
\[ \frac{dc}{dt} = v_2 \]
Dynamic laws for metabolic networks

derived from balance of concentrations

\[
\frac{dx_i}{dt} = \sum_k n_{ik} v_k (\vec{x}, \vec{p})
\]

Reaction velocities

\[ v_1 = v_1(a, b) \]
\[ v_2 = v_2(b, c) \]

Balance equations

\[ \frac{da}{dt} = -v_1 \]
\[ \frac{db}{dt} = v_1 - v_2 \]
\[ \frac{dc}{dt} = v_2 \]
Levels of modelling in systems biology

1. Pathway analysis
   Flux balance, substance transformation, ...

2. Kinetic modelling
   Parameter fitting, model selection, ...

3. Control and bifurcation analysis
   Sensitivities, qualitative behaviour, ...

4. Optimality / Shaping by evolution
   Robust design, cost-benefit calculation, ...

5. Model integration
   Modularisation, experimental standards, ...
Essential views on complex systems

- Modularity
- Control analysis
- Global modes
Modularity
Modularity

Basic assumption in natural sciences

Many biological systems look modular (and many don't)

The whole is more .. is more than the sum of its parts

Modular modelling calls for experimental standards
SBMLmerge
for computer-assisted model integration

Threonine pathway

KEGG chart “Glycine, serine and threonine metabolism”

http://sysbio.molgen.mpg.de/SBMLmerge/

www.genome.ad.jp/kegg/
SBMLmerge
for computer-assisted model integration

Merged model

http://sysbio.molgen.mpg.de/SBMLmerge/
Turn modules into simple black boxes
Model reduction by balanced truncation

Liebermeister W., Baur U., Klipp E. (2005), FEBS Journal, 272 (16), 4034 - 4043
Sensitivity analysis
Metabolic control theory
Overall effects of local perturbations

- Enzyme overexpressed !!
- Change in concentration ??
- Change in flux ??
Metabolic response coefficients
Summarising the infinite causal chains

Parameter change
One enzyme overexpressed...

Metabolic change
Altered concentrations?
Redirected fluxes?

Δp_m

Response coefficients

First-order approximation
Δs_i \approx R_{p_m}^{s_i} \Delta p_m
Spectral response coefficients
Systemic response to forced oscillations

Spectral response coefficients
Resonance in noise spectra: a systemic property

Feedback system below Hopf bifurcation

Intrinsic noise due to small particle numbers

Modes of collective behaviour
Global modes in complex systems
Effective variables to describe collective motion

Vibration mode of an elastic plate
Global modes in complex systems
Effective variables to describe collective motion

Vibration mode of an elastic plate

\[ S(t) = a_1(t)S_1 + a_2(t)S_2 + a_3(t)S_3 + \ldots \]

- Oscillatory coefficients
- Overall shape
- Basic modes
Elementary flux modes
A quantitative definition for metabolic pathways

\[ \vec{v} = a_1 \vec{k}_1 + a_2 \vec{k}_2 + \ldots \]

Model reduction is based on collective modes
Balanced truncation preserves only the dominant global behaviour

Liebermeister W., Baur U., Klipp E. (2005), FEBS Journal, 272 (16), 4034 - 4043
Global modes in microarray data

Gene expression during the cell cycle

Data from:
Global modes in microarray data
Independent component analysis

Gene profile

\[ x_i(t) = m_1(t)a_{i1} + m_2(t)a_{i2} + \ldots \]

Components

W. Liebermeister (2002), Bioinformatics 18, 51-60
Network component analysis
Global modes reflect the activity of transcription factors

Transcription rates of amino acid biosynthesis genes
Zaslaver et al (2004), Nat Genet 36, 486-491
Network component analysis
Global modes reflect the activity of transcription factors

Transcription factors

Genes

TF activities
inferred from NCA

Transcription network
from RegulonDB

Promoter activities
Zaslaver et al (2004), Nat Genet 36, 486-491
Inferring new regulatory interactions
Use putative connections and good fit of NCA model

Initial network:
Known and putative arrows

Selecting of arrows
Supported by expression data
Trouble with complex systems

Things we understand easily

Separate entities
Small numbers
Causal chains
Direct effects

... but living systems are

Continuous
Complex
Dynamic
Adaptive
Stochastic
Evolved
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www.enfin.org

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Metabolic response coefficients

**Reaction elasticities**
Local response (system clamped)

\[ \varepsilon_i^k = \frac{dv_k(x,p)}{dx_i} \]
Change in substrate

\[ \pi^k_m = \frac{dv_k(x,p)}{dp_m} \]
Change in enzyme

**Response coefficients**
Global systemic response

\[ R_{s_i}^{p_m} = \frac{ds_i(p)}{dp_m} \]
Steady state concentrations / fluxes

\[ R_{j_k}^{p_m} = \frac{dj_k(p)}{dp_m} \]

\[ R^s = (N \varepsilon)^{-1} N \pi \]
Control coefficients matrix \( C^s \)
SBMLmerge helps to couple kinetic models

Annotate the model elements
String search in data bases
Automatic recommendations

Check the model for problems
Syntax (low-level validity of SBML code)
Semantics (annotations and their ontology)
Mathematics (order of computation,...)
Physics (thermodynamics, conservation laws, ...)
Biology (parameter ranges, properties of organism,...)

Model merging, accounting for
Redundant model elements
Conflicting information
Logical cycles

http://sysbio.molgen.mpg.de/SBMLmerge/
ICA is a matrix decomposition
... based on the assumption of statistical independence

\[ X = S A + \text{noise} \]
NCA is also based on a matrix decomposition
... and accounts for the transcriptional network

Transcription rates
experimental

Gene input weights
connections constrained by network

Transcription factor activities
Gene input functions
Example: Lac operon in E. Coli

Alberts et al, Molecular biology of the cell

Fuzzy metabolic networks
What if parameters are uncertain?

Parameters for reaction E1 are uncertain (statistical distribution)

Fuzzy metabolic networks
What if parameters are uncertain?

Probabilities of forward flux

Distribution of reaction velocities

Fuzzy metabolic networks
Studying the effects of parameter variability

Log-normal, correlated parameter distributions