SUMMARY AND KEYWORDS

Introduction

Why Modelling? Biology is a quantitative natural science. Mathematics is the basis of all quantitative natural sciences. What constitutes a good model? Large-scale models versus minimal models.

Some notable quotes

- "With four parameters I can fit an elephant, and with five I can make him wiggle his trunk." (John von Neumann)
- "Everything should be made as simple as possible, but no simpler." (Albert Einstein)
- "All exact science is dominated by the idea of approximation." (Betrand Russell)

Nonlinear Dynamics and Dynamical Systems

Important terms

phase-space, state-space (Zustandsraum), cellular automata, Boolean networks, discrete-time systems, continuous time-systems, iterated maps, the logistic map $x_{n+1} = rx_n(1-x_n)$, fixpoints and their stability.

Ordinary Differential Equations (ODEs)

- **1-dim ODEs:** linear ODE $\dot{x} = a \cdot x(t)$, exponential growth and decay, graphical solution of the ODE $\dot{x} = f(x)$, fixpoints, stability, multi-stability, derivative (slope) at the fixpoint.
- **2-dim ODEs:** Nullclines, Jacobian matrix, linear stability analysis, Taylor expansion, Lotka-Volterra Equation, predator-prey systems, chaos.
- **Further Reading:** D. Kaplan and L. Glass. Understanding Nonlinear Dynamics. Springer 1995.

Modelling Cellular Metabolism

Important terms: Stoichiometry, rate equation, Michaelis-Menten equation, rapid-equilibrium approximation, quasi-steady state approximation.

The general form of a metabolic system (homogeneous environment, well-stirred),

$$\frac{dx}{dt} = N \cdot \nu(x, k) \tag{1}$$

with x denoting a vector of the concentrations of metabolites, N denoting the $m \times r$ stoichiometric matrix, μ denotes a set of (usually nonlinear) rate equations and k a set of parameters. The

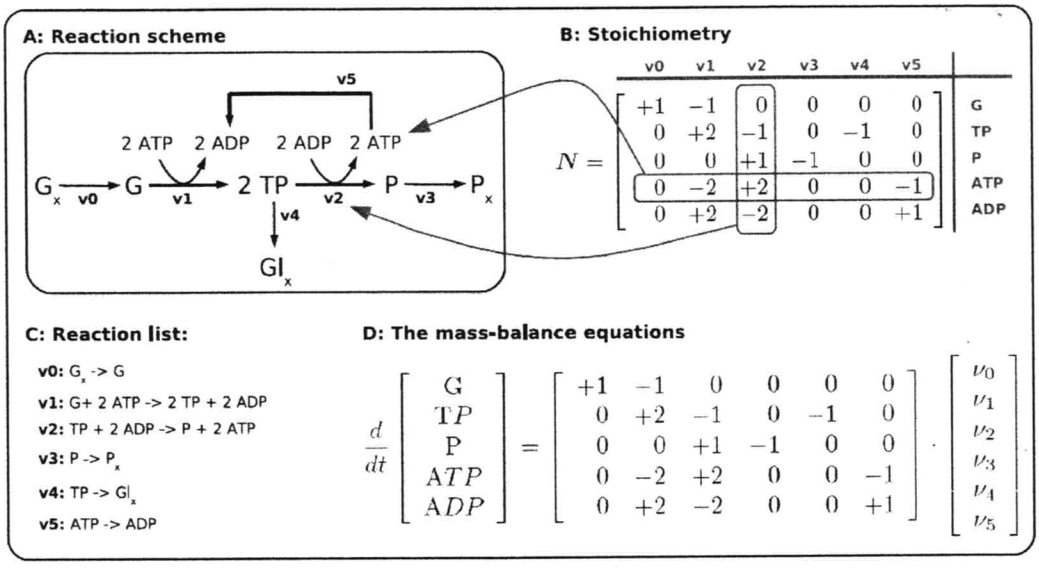


Figure 1: Example of a metabolic network. (A) Reaction scheme. Note that visual representations are often ambiguous. (B) The stoichiometric matrix. (C) A list of reactions. (D) Mass-balance equations. The figure is taken from: R. Steuer and B. H. Junker (2009) Computational Models of Metabolism: Stability and Regulation in Metabolic Networks. Advances in Chemical Physics, Volume 142. Rice, Stuart A. (editor), ISBN-10: 0-470-46499-2 ISBN-13: 978-0-470-46499-1 - John Wiley & Sons (2009)

columns of N correspond to r reactions, the rows of N correspond to m metabolites. Typically, $r \geq m$.

Moiety conservation

In biochemical reaction networks subgroups of chemical species are often conserved. That is, transferred from one molecule to another but the total amount does not change (= moiety conservation). A typical example is adenosine diphosphate (ADP) that is phosphorylated to adenosine triphosphate (ATP) and dephosphorylated back to ADP (the moiety may also include AMP). See Figure 1.

Conserved moieties correspond to linearly dependent row in the matrix N. In this case $rank(N) < m$ and $E \cdot N = 0$ where E denotes a matrix whose columns form a basis of the left nullspace of N (E has $m - rank(N)$ rows). The matrix N can be split into independent (N^0) and dependent rows (N_D),

$$N = \begin{bmatrix} N^0 \\ N_\mathrm{D} \end{bmatrix} \quad , \tag{2}$$

such that $N = L \cdot N^0$ where L denotes a Link-matrix.

Network Analysis

Simplest method of analysis, based on reaction databases. Interpretation of metabolism as a 'graph' (i.e., a substrate graph: two metabolites are 'connected' if they are substrate and product in a common reaction; reaction graph: two reactions are 'connected' if a substrate of

one is a product of the other; directed and undirected variants are possible; often co-factors and highly connected metabolites are not considered). Analysis using graph-theoretic measures: diameters, distribution of connectivity, shortest pathlengths, clustering, centrality. Note that metabolism itself is a bipartite graph (two types of nodes, reactions and metabolites).

Constraint-based analysis

Before looking at details of the rate equation, we can look at the constraint imposed by the steady state assumption,

$$0 = N \cdot \nu^0 \quad . \tag{3}$$

Here ν^0 is a vector of reaction rates. The vector is an element of the right nullspace (or kernel) of the stoichiometric matrix. The vector ν^0 is typically underdetermined (fewer constraints than unknown fluxes, the number of unknown fluxes is $r - rank(N)$).

- **Elementary Flux Modes (EFMs)** Enumeration of possible pathways. A flux mode is a set of reactions that can give rise to a steady state flux vector ν^0. An elementary flux mode is a flux mode where no reaction can be removed (= zero flux) and the resulting reactions can still be a flux mode. The set of EFMs is unique for a given stoichiometry. The number of EFMs is typically (much) higher than the dimension of the nullspace.
- **Flux-balance analysis (FBA):** Unknown fluxes are estimated using optimality principles. That is, the flux vector ν^0 is assumed to be such that a give objective function is maximized (such as ATP production of biomass formation). The optimal solution is typically not unique. The most common objective is the biomass objective function (BOF), i.e., growth.

$$\begin{aligned} &\max_{\nu^0} \nu_{\text{bio}} \\ &s.t.\ N \cdot \nu^0 = 0\ , \\ &\quad \alpha_i \leq \nu_i^0 \leq \beta_i, \end{aligned} \tag{4}$$

Chemical Reaction Kinetics

mass-action, rate constants, reversibility, thermodynamics, chemical equilibrium, detailed balance.

Enzyme Kinetics

Enzymes are catalysts that accelerate reactions. A simple model for basic enzyme function was established by Michaelis and Menten. The enzyme binds substrate to form an enzyme-substrate complex. The complex undergoes a transformation and the product is released.

$$E + S \Longleftrightarrow ES \longrightarrow E + P \tag{5}$$

An overall rate equation can be derived using either a quasi-steady state or a rapid-equilibrium assumption. The resulting rate equation is

$$\nu = \frac{k_{\text{cat}}[E][S]}{K_M + [S]} = \frac{V_M[S]}{K_M + [S]} \quad , \tag{6}$$

where $[E]$ denotes the total concentration of enzyme, $[S]$ the concentration of substrate, k_{cat} the catalytic activity of the enzyme (turnover number), and K_M denotes the half-saturation (or Michaelis-Menten) constant. The maximal reaction rate is $V_{\text{M}} = k_{\text{cat}}[E]$.

Lineweaver-Burke, Inhibition and Activation

Several models exist for inhibition and activation of enzymes. Most well known: competitive inhibition, uncompetitive inhibition, mixed (noncompetitive) inhibition.

A useful way to look at rate equations is a Lineweaver-Burke plot. In a double-reciprokal plot, the Michaelis-Menten equations corresponds to a straight line of the form $y = a \cdot x + b$,

$$\frac{1}{\nu} = \frac{K_M}{V_M}\frac{1}{[S]} + \frac{1}{V_M} \quad . \tag{7}$$

However, nonlinear regression (fitting) using numerical software is superior to estimate enzyme-kinetic parameters.

Reversible rate equations

The reversible form of the Michaelis-Menten equation is

$$\nu = \frac{V_f \frac{[S]}{K_S} - V_b \frac{[P]}{K_P}}{1 + \frac{[S]}{K_S} + \frac{[P]}{K_P}} \quad . \tag{8}$$

The equation can be rewritten as

$$\nu = \nu_f - \nu_b = \nu_f \left(1 - \frac{\nu_b}{\nu_f}\right) \tag{9}$$

with

$$\frac{\nu_b}{\nu_f} = \frac{V_b}{V_f}\frac{K_S}{K_P}\frac{[P]}{[S]} \tag{10}$$

At equilibrium ($\nu = 0$), we obtain

$$\frac{[P]^0}{[S]^0} = K_{\text{eq}} \Longleftrightarrow K_{\text{eq}} = \frac{V_f}{V_b}\frac{K_P}{K_S} \tag{11}$$

The latter is known as *Haldane relationship*. The rate equation can then be written as

$$\nu = \frac{V_f \frac{[S]}{K_S}}{1 + \frac{[S]}{K_S} + \frac{[P]}{K_P}} \cdot \left(1 - \frac{[P]}{[S]}\frac{1}{K_{\text{eq}}}\right) \quad . \tag{12}$$

The rate equations is separated into two parts: a kinetic contribution that depends on Michaelis-Menten constants, and a thermodynamic contribution that only depends on concentrations and (chemical) equilibrium values. Note that the K_{eq} are also not independent.

Other rate equations

Other rate equations can be derived, dependent on the mechanism of the enzyme (random binding, sequential binding, ping-pong, etc ...). It is sometimes possible to approximate rate equations with a generic function. For example for a reaction

$$S_1 + S_2 + \cdots \Longleftrightarrow P_1 + P_2 + \ldots \quad , \tag{13}$$

we can write

$$\nu = \frac{V_M \prod \frac{[S_i]}{K_{S,i}}}{D} \cdot \left(1 - \frac{\Gamma}{K_{\text{eq}}}\right) \quad . \tag{14}$$

where Γ denotes the mass-action ratio

$$\Gamma = \frac{\prod_{i=1}^{n_s}[S_i]}{\prod_{j=1}^{n_p}[P_j]} \quad , \tag{15}$$

and D denotes a polynomial of the form

$$D = \prod_{i=1}^{n_s}\left(1 + \frac{[S_i]}{K_{S,i}}\right) + \prod_{j=1}^{n_p}\left(1 + \frac{[P_j]}{K_{P,j}}\right) - 1 \quad . \tag{16}$$

Note the structural similarity with the form above: a kinetic term multiplied with a thermodynamic term. Note also that generic rate equation are *approximations*. For example they do not account for competition between specific pairs of substrates and products.

- **Further Reading:** Herbert M. Sauro (2014) Enzyme Kinetic for Systems Biology. Ambrosius Publishing (ISBN 978-0-9824773-3-5).
- **Further Reading:** Liebermeister W, Uhlendorf J, Klipp E. (2010) Modular rate laws for enzymatic reactions: thermodynamics, elasticities and implementation. Bioinformatics. 26(12):1528-34. doi: 10.1093/bioinformatics/btq141.

The 'recipe' for kinetic metabolic models

1. Assemble list of reactions. Best from appropriate database to ensure consistent stoichiometry. Define system boundaries (external metabolites).
2. Brief stoichiometric analysis: check for conserved moieties, check that flux solutions are possible (the right nullspace needs to allow for at least one nonzero flux vector). Check overall consistency of the stoichiometry.
3. Assign rate equations (generic equations if needed).
4. Assign kinetic parameters. Parameters can also be defined within a range. Note that some parameters are interdependent (for example equilibrium constants). Different parameter sets can represent different states (e.g. a wildtype versus a mutant). A typical rate equation has one K_M value for each substrate and product, one maximal velocity $V_{\max}$, and an equlibrium constant K_{eq}.
5. Explore model using techniques from Nonlinear Dynamics and Metabolic Control Analysis: steady-state, stability, sensitivities, control coefficients.

Some further resources

- https://www.genome.jp/kegg/
- https://www.brenda-enzymes.org/
- equilibrator.weizmann.ac.il/
- https://reactome.org/
- https://kbase.us/
- http://modelseed.org/
- https://www.ebi.ac.uk/biomodels-main/

The (logarithmic) sensitivity

One of the most important concepts is the sensitivity of a function to a parameters. The sensitivity of a value $y = f(p)$ with respect to a parameter p is defined as the derivative

$$\lim_{\Delta p \to 0} \frac{\Delta f(p)}{\Delta p} = \frac{df(p)}{dp} \quad . \tag{17}$$

However, the value depends on the absolute values of parameters. It is more useful to look at relative sensitivities

$$\frac{d\left(\frac{f(p)}{f(p^0)}\right)}{d\left(\frac{p}{p^0}\right)} = \frac{p^0}{f(p^0)} \frac{df(p)}{dp} = \frac{d\ln f(p)}{d\ln p} \quad . \tag{18}$$

Example:

$$\nu(x) = \frac{V_M \cdot x}{K_M + x} \quad \Rightarrow \quad \frac{d\ln \nu(x)}{d\ln x} = \underbrace{\frac{1}{1 + \frac{x}{K_M}}}_{\in(0,1]} \quad . \tag{19}$$

The logarithmic sensitivities have an intuitive interpretation as the kinetic order. For a Michaelis-Menten function, the logarithmic sensitivity with respect to the substrates ranges from 1 (linear regime, substrate concentration small compared to K_M) to 0 (saturation, substrate concentration large compared to K_M).

Exercise

What are the logarithmic sensitivities of the following functions with respect to the variable x?

$$\nu(x) = k \cdot x \tag{20}$$

$$\nu(x) = k \cdot x^\gamma \tag{21}$$

$$\nu(x) = \frac{V_M \cdot x^n}{K_M^n + x^n} \tag{22}$$

$$\nu(x) = \frac{V_M}{1 + \frac{x^n}{K_I^n}} \tag{23}$$

Metabolic Control Analysis

Metabolic Control Analysis (MCA) considers how a perturbation propgates through a metabolic network. Typically: how a change in enzyme concentration (or other parameter) affects the steady with respect to metabolite concentrations and flux values. There is an extensive literature on MCA, see for example:
`https://en.wikipedia.org/wiki/Metabolic_control_analysis`
MCA is also conceptually similar to classic sensitivity or control theory (from engineering). There are (slightly) different formulations. Similar to other sensitivities, the formulation can be in absolute terms or scaled (i.e. logarithmic sensitivities). In the terminology of MCA, the partial derivatives of a reaction rate with respect to its substrates are called *elasticities* ϵ_x^ν,

$$\epsilon_x^\nu = \frac{\partial \nu(x)}{\partial x}, \tag{24}$$

the scaled elasticities are

$$\hat{\epsilon}_x^{\nu} = \frac{\partial \ln \nu(x)}{\partial \ln x} \quad . \tag{25}$$

A set of reactions and a set of metabolites, results in an elasticity matrix ϵ. Note that the Jacobian matrix is $J = N \cdot \epsilon$ at a steady state (assuming no mass-conservation).

The (unscaled) concentration control coefficient specify how the concentrations change after the perturbation of a parameter (typically an enzyme concentration) that affects (one or more fluxes). In terms of derivatives,

$$C^X = \frac{dx}{dp} / \frac{\partial \nu}{\partial p} = \frac{dx}{d\nu} \quad . \tag{26}$$

However, in general no explicit function for the concentrations of the form $x = f(p)$ are known. Therefore, we consider

$$N \cdot \nu(x,p) = 0 \quad \Rightarrow \quad N \left[\frac{\partial \nu}{\partial x} \frac{dx}{dp} + \frac{\partial \nu}{\partial p} \right] = 0 \quad , \tag{27}$$

and obtain

$$\frac{dx}{dp} = \underbrace{- \left[N \cdot \frac{\partial \nu}{\partial x} \right]^{-1} \cdot N}_{:= C^X} \cdot \frac{\partial \nu}{\partial p} \tag{28}$$

using the definition

$$C^X = - \left[N \cdot \frac{\partial \nu}{\partial x} \right]^{-1} \cdot N = -J^{-1} \cdot N \quad . \tag{29}$$

The definition gets slightly more complicted if the Jacobian matrix is not invertible (for example due to conserved moieties). In this case, a link matrix L has to be introduced, see *further reading*. For a set of concentrations and a set of reactions (or enzymes), the concentration control coefficients are a matrix. Multiplication of the concentration control coefficient with (any) vector of the nullspace of N results in the summation theorem,

$$C^X \cdot K = 0 \quad . \tag{30}$$

Likewise, multiplication of the concentration control coefficient with the elasticity matrix results in the connectivity theorem,

$$C^X \cdot \epsilon = -1 \quad . \tag{31}$$

Similar to C^X, the flux control coefficient denotes the changes in flux upon pertubations,

$$\frac{d\nu}{dp} = \frac{\partial \nu}{\partial p} + \frac{\partial \nu}{\partial x} \frac{dx}{dp} = \left[1 + \frac{\partial \nu}{\partial x} \cdot C^X \right] \frac{\partial \nu}{\partial p} \quad , \tag{32}$$

and

$$C^{\nu} := 1 + \frac{\partial \nu}{\partial x} \cdot C^X \quad . \tag{33}$$

The corresponding summation theorem (for unscaled coefficient) is

$$C^{\nu} \cdot K = K \quad . \tag{34}$$

Scaled Control Coefficients

Similar to partial derivatives, it is often useful to consider scaled control coefficients. These provide a measure of the relative changes of concentrations and fluxes upon relative changes in parameters (that is, a scaled control coefficient of $\hat{C}^{\nu}$ implies that if the corresponding enzyme is changed by 1% the respective flux changes by 1%). We define scaled elasticities,

$$\hat{\epsilon} = D_{\nu^0}^{-1} \cdot \epsilon \cdot D_{x^0} \quad , \tag{35}$$

scaled concentration control coefficients $\hat{C}^X$,

$$\hat{C}^X = D_{x^0}^{-1} \cdot C^X \cdot D_{\nu^0} \quad , \tag{36}$$

and scaled flux control coefficients $\hat{C}^{\nu}$,

$$\hat{C}^{\nu} = D_{\nu^0}^{-1} \cdot C^{\nu} \cdot D_{\nu^0} \quad , \quad \Longleftrightarrow \quad \hat{C}^{\nu} = 1 + \hat{\epsilon} \cdot \hat{C}^X \quad , \tag{37}$$

where D_{x^0} and D_{ν^0} denote diagonal matrices with elements x^0 and ν^0 on the diagonal, respectively.

Further reading

- Heinrich R. and Schuster S. (1996) The Regulation of Cellular Systems, Chapman and Hall.
- R. Steuer and B. H. Junker (2009) Computational Models of Metabolism: Stability and Regulation in Metabolic Networks. Advances in Chemical Physics, Volume 142. Rice, Stuart A. (editor), ISBN-10: 0-470-46499-2 ISBN-13: 978-0-470-46499-1 - John Wiley & Sons

Protein phosphorylation and cellular signaling

One of the most important signaling motives are protein phosphorylation cycles, i.e., a post-translational modification of a protein in which an amino acid residue is phosphorylated by a protein kinase, and dephosphorylated by a protein phosphatase. Phosphorylation changes the structural conformation of the protein, the phosphorylated protein has a modified function (e.g. phosphorylation may activate or deactivate a protein). See Figure2. Important examples are two-component signaling systems and mitogen-activated protein kinase (MAPK or MAP kinase) systems (as well as many others, e.g., phosphorylation of enzymes).

Simple models follow mass-action kinetics. For a simple phosphorylation cycle, we obtain

$$\frac{d[R_p]}{dt} = \underbrace{k_1 \cdot S \cdot [R]}_{=\nu_1} - \underbrace{k_2 \cdot [R_p]}_{=\nu_2} \tag{38}$$

where the kinase activity represents the signal S, and the activity of the phosphatase is assumed to be constant (and included in the rate constant k_2). The systems exhibits mass conservation $[R_p] + [R] = R^T$, where R_T denotes the amount of total protein. The steady state can be solved straightforwardly ($\rightarrow$ Exercise),

$$[R_p]^0 = \frac{k_1 \cdot S \cdot R^T}{k_2 + k_1 \cdot S} \quad . \tag{39}$$

Note that the dependence on the kinase activity (signal) is hyperbolic, whereas the dependence on the total protein is linear.

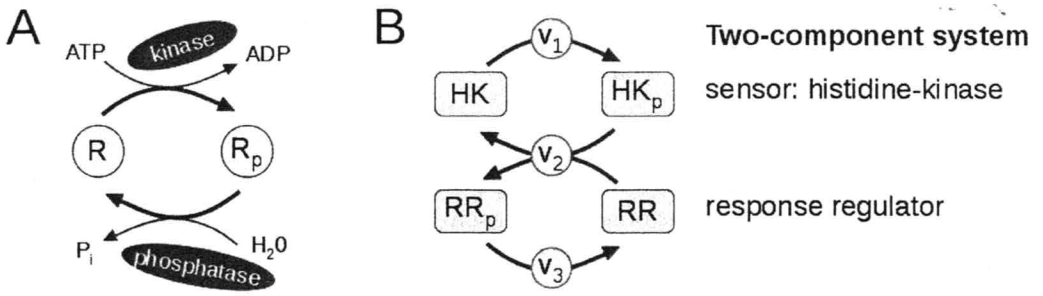


Figure 2: Protein phosphorylation cycle. (A) A protein phosphorylation cycle. A kinase phosphorylates an (amino acid residue of a) protein. The phosphorylated protein has a modified function (active or inactive). Dephosphorylation can be catalyzed by a phosphatase or be spontanous. (B) A two-component system. Two-component signaling system typically consist of a (membrane-bound) histidine kinase protein that autophosphorylates in the presence of a signal and phosphorylates a partner response regulator protein. An important example is the EnvZ/OmpR two-component system.

Robustness of two-component systems

The cellular environment fluctuates and protein expression is stochastic. Cells evolved mechanisms to cope with such fluctuations. A well known example is the robustness of (some) two-component systems with respect to fluctuations in the total amounts of proteins.

To model a two-component system (using mass-action kinetics), we consider the dynamics of the histidine kinase [H] and the response regulator [R]. Both exist in the phosphorylated an unphosphorylated form. The ODEs are

$$\frac{d[H_p]}{dt} = \underbrace{k_1 \cdot S \cdot [H]}_{=\nu_1} - \underbrace{k_2 \cdot [R] \cdot [H_p]}_{=\nu_2} \quad \text{and} \quad \frac{d[R_p]}{dt} = \underbrace{k_2 \cdot [R] \cdot [H_p]}_{=\nu_2} - \underbrace{k_3 \cdot [R_p]}_{=\nu_3} \quad , \tag{40}$$

with $[H_p] + [H] = H^T$ and $[R_p] + [R] = R^T$. The solution is lengthy (a quadratic equation).

In many two-component systems, the (unphosphorylated) sensor kinase also acts as a phosphatase for the response regulator $\rightarrow$ redundancy the phosphorylated form 'activates' the response regulator, the unphosphorylated form 'deactivates' the response regulator. A possible reason was to prevent residual (auto- or unspecific) activation of the response regulator. The equations, however, show that the effect is more profound. At steady-state, we know that $\nu_1 = \nu_3$. Hence, if the dephosphorylation reaction is $\nu_3 = k_3 \cdot [R_p] \cdot [H]$, the steady state solution for the active response regulator is

$$[R_p]^0 = \frac{k_1}{k_3} \cdot S \quad \text{for} \quad [R_p]^0 \leq R^T \quad . \tag{41}$$

The resulting equation is independent of the expression of the proteins ($\rightarrow$ perfect adaptation, integral feedback).

Further reading

- Batchelor E, Goulian M. (2003) Robustness and the cycle of phosphorylation and dephosphorylation in a two-component regulatory system. Proc Natl Acad Sci U S A. 100(2):691-6. DOI: 10.1073/pnas.0234782100

- Steuer R, Waldherr S, Sourjik V, Kollmann M.(2011) Robust signal processing in living cells. PLoS Comput Biol. 7(11):e1002218. doi: 10.1371/journal.pcbi.1002218.

Ultrasensitivity

An *ultrasensitive* response describes a response that is more sensitive to changes in input than the hyperbolic Michaelis-Menten response. Ultrasensitivity was first (heuristically) described by A. Hill in 1910 to describe the sigmoidal O2 binding curve of haemoglobin. The Hill equation is

$$O = \frac{k_p \cdot [L]^n}{K_A^n + [L]^n} \tag{42}$$

where O denotes some output (such as the fractional binding), $[L]$ the concentration of a ligand, k_p a proportionality constant, K_A the half-stauration constant, and n the *Hill coefficient.*

- **Exercise:** What is the logarithmic sensitivity of the output with respect to the ligang concentration?

A *mechanistic* model for ultrasensitivity was proposed by Goldbeter and Koshland, the Goldbeter-Koshland switch. The switch arises if the reactions in a protein phosphorylation cycle are close to saturation. Similar to Equation (43),

$$\frac{d[R_p]}{dt} = \underbrace{\frac{k_1 \cdot S \cdot [R]}{K_{m1} + [R]}}_{=\nu_1} - \underbrace{\frac{k_2 \cdot [R_p]}{K_{m2} + [R_p]}}_{=\nu_2} \tag{43}$$

The solution provides the 'Goldbeter-Koshland' function, a sigmoidal response curve.

- **Exercise:** To calculate the steady-state solution $[R_p]^0 = f(S)$ is straightforward but lengthy. It is much simpler to calculate the inverse function $S = g([R_p]^0)$ and plot this function.

There are now several other known mechanisms that result in ultrasensitivity. See articles by Ferrell and Ha.

Further reading

- Goldbeter A, Koshland DE (1981). An amplified sensitivity arising from covalent modification in biological systems. Proc. Natl. Acad. Sci. U.S.A. 78 (11): 68404. doi:10.1073/pnas.78.11.6840
- `https://en.wikipedia.org/wiki/Goldbeter-Koshland_kinetics`
- Ferrell JE Jr, Ha SH. (2014) Ultrasensitivity part I: Michaelian responses and zero-order ultrasensitivity. Trends Biochem Sci. 39(10):496-503. doi: 10.1016/j.tibs.2014.08.003.
- Ferrell JE Jr, Ha SH. (2014) Ultrasensitivity part II: multisite phosphorylation, stoichiometric inhibitors, and positive feedback. Trends Biochem Sci. 39(11):556-69. doi: 10.1016/j.tibs.2014.09.003.
- Ferrell JE Jr, Ha SH. (2014) Ultrasensitivity part III: cascades, bistable switches, and oscillators. Trends Biochem Sci. 39(12):612-8. doi: 10.1016/j.tibs.2014.10.002.

The dynamics of cellular signaling

Protein networks form complex dynamic systems. Models are constructed using general rules for chemical kinetics (mass-action, binding, unbinding, etc ...). Protein modifications play an important role.

- **Recommended reading:** Tyson JJ, Chen KC, Novak B. (2003) Sniffers, buzzers, toggles and blinkers: dynamics of regulatory and signaling pathways in the cell. Curr Opin Cell Biol. 15(2):221-31.

It is recommended to consider some of the examples described by Tyson et al. (2003). Note, however, that these are just examples of network motifs that exhibit a certain dynamics. Other examples are possible.

In particular, Tyson et al (2003) consider the following systems:

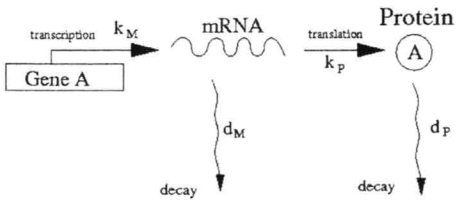
- **(1b) Phosphorylation cycle with mass-action kinetics:** same as the example above. The response is a hyperbolic Michaelis-Menten function.
- **(1c) Phosphorylation cycle with Michaelis-Menten kinetics:** ultrasensitive response. Goldbeter-Koshland function.
- **(1d) Perfect adaptation:** similar to the case of concentration robustness considered above. A protein is activated and deactivated by a signal. Deactivation, however, takes place after a time lag (via an intermediate variable). Therefore the steady-state concentration does not change, but the system exhibits a transient activation $\rightarrow$ detection of changes in the input signal (also circuits that implement fold change detection rely on perfect adaptation).
- **(1e) Mutual activiation:** two proteins mutually activate each other. The result is a bistable system in which a transient input activates the output, and the activation persists even when the input is removed.
- **(1f) Mutual inhibition:** two proteins mutually inhibit each other. The result is a tug-of-war situation. Depending on initial conditions (and signal strength) one protein 'wins' $\rightarrow$ bistable switch.
- **(1g) Negative feedback and homeostasis:** negative feedback is one of the most important control techniques. The output is fed back into the system such that deviations from the desired state are reduced. Similar to, e.g., thermostats.

Negative feedback is prone to instability. With increasing feedback strength, the following dynamics occur: first the response time is reduced, up to the point at which critical damping occurs. At this point, the feedback is as strong as it can get, without overshooting. For stronger feedback, damped oscillations occur. For even stronger feedback, the system (can) go into sustained oscillations ($\rightarrow$ Hopf-bifurcation). Negative feedbacks are prone to instability and are underlie cellular oscillations. An early model of cellular oscillations is the Goodwin oscillator.

Modelling gene expression as a stochastic system

Proteins and mRNA molecules are often present in low copy numbers. In this case, a description by continuous deterministic differential equations is not appropriate and the system must be described as a stochastic birth-and-death process that considers synthesis and decay of individual molecules.

A simple example is the transcription of an mRNA M and its translation into a protein A.



The differential equations for the continuous concentrations $[R]$ of mRNA and of the protein $[A]$ are

$$\frac{d[R]}{dt} = \nu_{\text{transcription}} - \nu_{\text{decay}} \qquad \frac{d[A]}{dt} = \nu_{\text{translation}} - \nu_{\text{decay}} \quad . \tag{44}$$

For low copy numbers, we describe the system by a state $\mathbf{x}(t) = (R, A)$ at time t where R and M are positive integers and denote the respective number of molecules.

The time evolution is given by transitions between different states $\mathbf{x} \to \mathbf{x}'$. In our case, there are 4 possibilities (we always assume that only one event occurs, the probability that two events occur exactly at the same time is vanishingly low).

$$\begin{array}{ll} (R, A) \to (R+1, A) & \text{transcription of one mRNA} \\ (R, A) \to (R-1, A) & \text{decay of one mRNA} \\ (R, A) \to (R, A+1) & \text{translation of one protein} \\ (R, A) \to (R, A-1) & \text{decay of one protein} \end{array}$$

These transitions are stochastic, i.e., they occur with a certain probability that depends on the current state of the system. Instead of a deterministic trajectory, the time evolution of the system is therefor given as the probability distribution $p(\mathbf{x}, t)$ to be in state $\mathbf{x}$ at time t.

The Master Equation

The time evolution of the probability distribution $p(\mathbf{x}, t)$ is described by the *master equation*,

$$\frac{\mathrm{d}p(\mathbf{x}, t)}{\mathrm{d}t} = \sum_{\mathbf{x}'} \left[w(\mathbf{x}' \to \mathbf{x})\, p(\mathbf{x}', t) - w(\mathbf{x} \to \mathbf{x}')\, p(\mathbf{x}, t) \right] \quad . \tag{45}$$

Here, $w(\mathbf{x}' \to \mathbf{x})$ denotes the probability for a transition $\mathbf{x}' \to \mathbf{x}$. The master equation can also be written in matrix form.

Gillespie Algorithm

Unfortunately, the master equation is difficult to solve, either numerically or analytically. In most cases, therefore, instead of solving the time of evolution of the probability distribution, individual trajectories are simulated. These trajectories are *realizations* of the stochastic system, i.e., they are possible solutions that are consistent with the transition probabilities of the master equation. statistically correct trajectory (possible solution) of a stochastic equation. A well known algorithm to simulate a stochastic trajectory was proposed by Dan Gillespie (→ *Gillespie algorithm*):

1: The system is in $\mathbf{x}$ at time t.

2: Estimate the transition probabilities w_i for all feasible transitions from this state to another state $\mathbf{x} \to \mathbf{x}'$.

3: Estimate the time intervals Δt after which a (any) transition happens (the waiting time is exponentially distributed),

$$\Delta t = -\frac{1}{u_0}\log(\xi_1) \qquad \text{with} \qquad u_0 = \sum w_i$$

Here, ξ_1 is a (uniform) random number in $(0, 1]$.

4: Estimate *which* transition happens. The probability for an individual transition is proportional to w_i, therefore the following equation holds for the transition w_α that actually happens,

$$\sum_{i=1}^{\alpha-1} w_i \leq \xi_2 u_0 < \sum_{i=1}^{\alpha} w_i \quad ,$$

with $\xi_2 \in [0, 1]$ being another (uniform) random number in $(0, 1]$.

5: Update the state $\mathbf{x}$ and time t ($t \to t + \Delta t$) and continue with step **1** until the final time is reached.

Topics not talked about

- Specific models, such as: circadian clocks, chemotaxis, the cell cycle
- Spatial models, reaction-diffusion systems, pattern formation and partial differential equations.
- Neural dynamics, models of ion channels, excitability, action potentials, oscillations and bursting, Hodgkin-Huxley model, integrate-and-fire models.
- Models of evolution, population dynamics, hypercycles (→ Manfred Eigen, 1971)
- Models of ecosystems, ecological modelling