Lecture Notes :

Dynamical Systems in Biology

From Mathematical Biology to Systems Biology

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Contents

1 Introduction

Organisational stuff:

- Which faculty ? Master or bachelor ?
- Computer exercises. Matlab. Who does not know to program ?
- Communication via ILIAS
- Lecture notes ready midnight before the lecture
- If something is unclear: Ask !

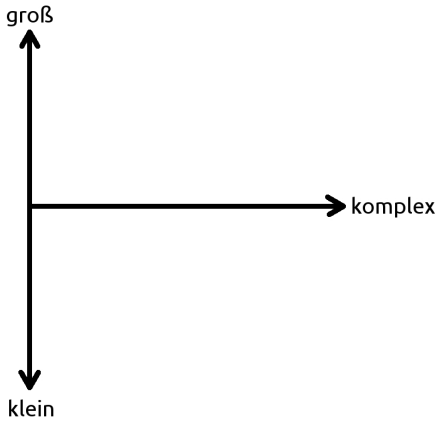

Figure 1.1: The three directions of physics

- The direct and the inverse problem
  - Direct problem
    - Look at biology
    - Write down equations
    - Investigate equations and their solutions
  - Inverse problem
    - Start from data
    - Estimate parameters in models
    - Essentially statistical

Relationship Mathematical Biology to Systems Biology
Mathematical Biology :

- Only few players, small systems
- Long tradition, oldest paper here from 1798
- Often not close to biology
- Data were often not available

Systems Biology :

- Investigates intracellular networks, "systems"
- Applies systems theory of engineering for the analysis
- First ideas around 1950
  - N. Wiener, 1948: Cybernetics, or Control and Communication in the Animal and the Machine [117]
  - L. von Bertalanffy, 1948: Zu einer allgemeinen Systemlehre, Biologia Generalis [114]
- Real birthday: 2001
- Disappointment about Human Genome Project
- Close to data

Relation between physics and biology
Biology:

- static
- qualitative
- descriptive

Physics:

- dynamic

- quantitative
- predictive

Physics:

- Believing in fundamental laws was very productive
- Use mathematics to formulate laws

Biology:

- Principles instead of hard fundamental laws
- But, due to evolution, "function" makes sense in biology
- Use mathematics to understand function and principles

Evolution is cool, needs just two ingredients :

- Variability
- Restricted resources

Benefits and goals of mathematical models in biology:

- Make assumptions explicit
- Understand essential properties, failing models
- Condense information, handle complexity
- Understand the role of dynamical processes, e.g. feed-back
- Impossible experiments become possible
- Prediction and control
- Understand what is known
- Discover general principles
- "You don't understand it until you can model it"

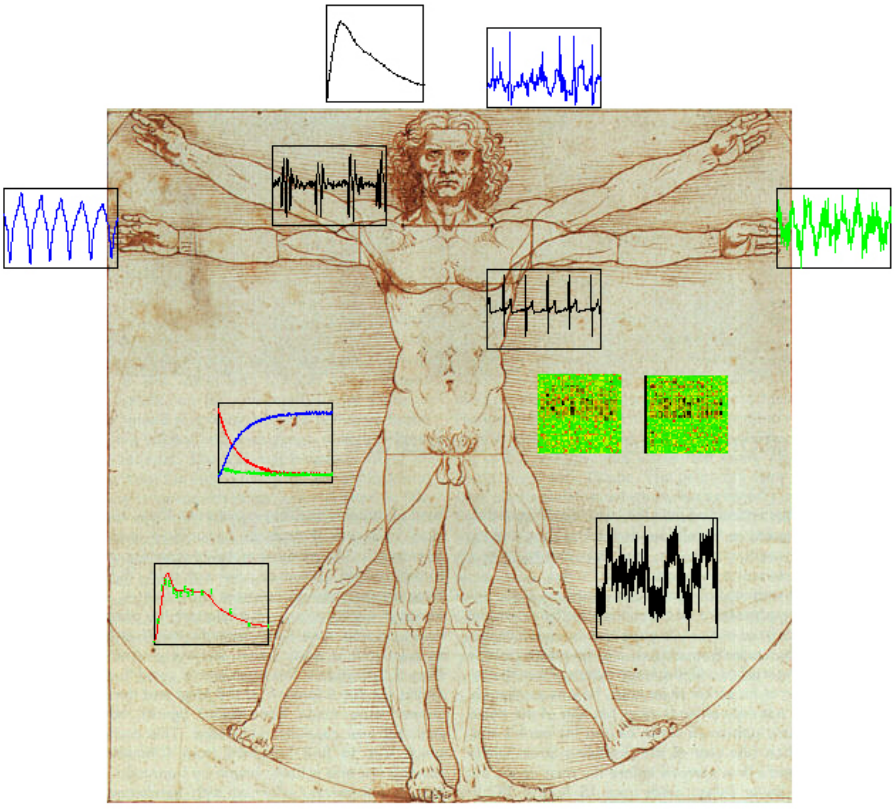

Figure 1.2: We are a dynamical system on all time and length scales

Literature: FOLIE

- J.D. Murray: Mathematical Biology [76]. The Bible
- F. Brauer, C. Castillo-Chávez: Mathematical Models in Population Biology and Epidemiology [12]
- J. Keener, J. Sneyd: Mathematical Physiology [51]. From biochemistry to muscle and ear. My favorite
- C.P. Fall, E.S. Marland, J.M. Wagner, J.J. Tyson: Computational Cell Biology [20]. All about cells

- F.C. Hoppenstaedt, C.S. Peskin: Modeling and Simulation in Medicine and Biology [41]. Direction biomedical engineering
- M. Farkos: Dynamical Models in Biology. [21]. Pretty mathematical, population dynamics
- D.S. Jones, B.D. Sleeman: Differential Equations and Mathematical Biology [48], mathematical
- Bulletin of Mathematical Biology: Special Issue "Classics of Theoretical Biology" Volume 52 & 53, Reprints of classical papers with discussion
- Biochemistry:
  - L. Stryer: Biochemistry [6]. The hard tour
  - H. Rehm, F. Hammar: Biochemie light [88]. The gentle tour

2 Integration of differential equations

Remark on the dealing with numerics

- Never try to reinvent the wheel !
- Some issues one really has to understand, e.g. stiff differential equations
- Many algorithms one can just apply, e.g. random number generators
- THE book: "Numerical Recipes" [81]

All models in the following will be differential equations

Task: Given

- Dynamical system:

$$\dot{\vec{x}} = \vec{f}(\vec{x}) \quad ,$$

- Initial values $\vec{x}(t_0)$

- Find a trajectory $\vec{x}(t_i)$, $t_i > t_0$, which coincides with the true trajectory up to a controllable error.

  Nomenclature, skip all vectors:

$$\frac{d}{dt} = \dot{}, \quad \frac{d}{dx} = ', \text{ Note: } \ddot{x} = \dot{f}(x) = f'(x)\dot{x} = f'(x)f(x) \tag{1}$$

Principal idea:

- Integration stepsize : h
- Taylor expansion :

$$x_{t+h} = x_t + \dot{x}_t h + \frac{1}{2}\ddot{x}_t h^2 + \frac{1}{6}x_t^{(3)} h^3 + \mathcal{O}(h^4) \tag{2}$$

  $\dot{x_t}$ given by $f(x_t)$, but one does not want to calculate $x^{(n)}$

- Truncation after first order : Euler method:

$$x_{t+h} = x_t + f(x_t)h + \mathcal{O}(h^2)$$

  "First order method" WS 1

- Idea: Higher order procedure by clever function evaluations
  - Consider:

$$\begin{aligned} k_1 &= f(x_t)h \\ \text{Define:} & \\ x_{t+h} &:= x_t + f\left(x_t + \frac{1}{2}k_1\right)h \\ x_{t+h} &= x_t + f\left(x_t + \frac{1}{2}f(x_t)h\right)h \\ x_{t+h} &= x_t + \left[f(x_t) + f'(x_t)\frac{1}{2}f(x_t)h\right]h \\ x_{t+h} &= x_t + f(x_t)h + \frac{1}{2}f'(x_t)f(x_t)h^2 \end{aligned}$$

  - By eq. (1) the 2. order term in eq. (2) cancels, resulting in 2. order method called (midpoint method).

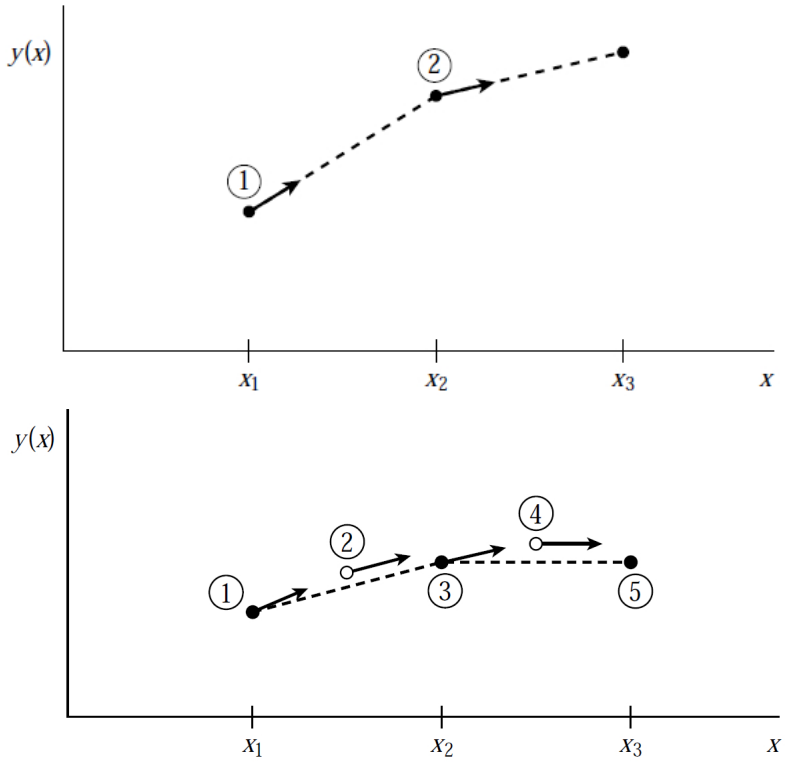

Figure 2.1: Euler and midpoint method

This can be iterated

- In general:

$$\begin{aligned} k_1 &= f(x_t)\, h \\ k_j &= f\left(x_t + \sum_l \Gamma_{jl} k_l\right) h \\ x_{t+h} &= x_t + \sum_{j=1}^{p} \gamma_j k_j \end{aligned}$$

Especially:

$$\begin{aligned} k_1 &= f(x_t)\, h \\ k_2 &= f(x_t + k_1/2)\, h \\ k_3 &= f(x_t + k_2/2)\, h \\ k_4 &= f(x_t + k_3)\, h \\ x_{t+h} &= x_t + \frac{k_1}{6} + \frac{k_2}{3} + \frac{k_3}{3} + \frac{k_4}{6} + \mathcal{O}(h^5) \end{aligned}$$

is called 4. order Runge-Kutta method (1895)

- In general:

  One 4. order Runge-Kutta step with stepsize h is more accurate than 2 midpoint steps with $h/2$, is more accurate than 4 Euler steps with $h/4$

Step size control

- Procedure to control the error
- Internal assessment of the error and adjustment of step size h
- Example: Runge-Kutta 4/5:
  - Integrate with Runge-Kutta 4. order
  - Integrate with Runge-Kutta 5. order with small addidional effort
  - Derive upper bound for error from the difference
  - If error too large, reduce step size h
  - Relative and/or absolute error ...

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Implicit methods for stiff systems

- Stiff systems: Systems with very different time scales.
- Consider

$$\begin{aligned} \dot{x}_1 &= 998\, x_1 + 1998\, x_2 \\ \dot{x}_2 &= -999\, x_1 - 1999\, x_2 \end{aligned}$$

with $x_1(0) = 1$, $x_2(0) = 0$

- Solution :

$$\begin{aligned} x_1(t) &= 2e^{-t} - e^{-1000\,t} \\ x_2(t) &= -e^{-t} + e^{-1000\,t} \end{aligned}$$

  Very different time scales: 1 and 1/1000

- Runge-Kutta must take care of the fast time scale, although it is irrelevant
- Reason: Consider

$$\dot{x} = -c\,x, \quad c > 0, \quad \text{Solution: } x(t) = x(0)\,e^{-ct}$$

  Consider Euler method, arguments also holds for higher order methods

$$x_{t+h} = x_t + \dot{x}_t h = (1 - ch)x_t$$

  Method is called explicit, because x_{t+h} is explicitly given as function of x_t.

- Instable, if $|1 - ch| > 1$, i.e. $h > 2/c$
- Consequence: If c is large, process is fast, h must be small
- Note: Euler method corresponds to

$$\dot{x}_t \approx \frac{x_{t+h} - x_t}{h}, \qquad \text{forward difference}$$

Solution:

- Implicit method:

$$x_t = x_{t+h} - \dot{x}_{t+h} h \underbrace{=}_{here} x_{t+h} + c x_{t+h} h = x_{t+h}(1 + ch)$$

  Result:

$$x_{t+h} = \frac{x_t}{1 + ch}$$

  Stable for all h !

- Note: Implicit Euler method corresponds to

$$\dot{x}_{t+h} \approx \frac{x_{t+h} - x_t}{h}, \qquad \text{backward difference}$$

- For non-linear differential equations $\dot{x} = f(x)$ it follows

$$x_{t+h} = x_t + f(x_{t+h})h, \qquad \text{"implicit"}$$

  Has to be solved numerically

  - Linearise $f(x_{t+h})$, yields Jacobian J
  - Solution needs the inverse of J. Effort $\propto (\dim\, x)^3$
  - Trade-off between many Runge-Kutta steps with small step size and inversion of a matrix with "normal" step size

Lessons learned:

- Numerical integration of differential equations by clever function evaluations
- Runge-Kutta 4. order typically the method of choice
- Stiff systems need implicit methods

Part I
From Mathematical Biology ...

3 Population dynamics

Mathematical biology (also Physics :-) is essentially populations dynamics:
Populations of:

- Molecules
- Viruses
- Animals
- Occupation number formalism in quantum mechanics (a und $a^\dagger$)
- Mails

3.1 One Species

T.R. Malthus, 1798: An Essay on the Principle of Population [65]
Dark clouds above mankind !

$$\dot{N} = \text{ births } - \text{ deaths } + \text{ migration}$$

- 1798 not too much migration
- Births: $\propto N$
- Deaths $\propto N$

$$\dot{N} = aN - bN = (a-b)N$$

$$N(t) = N(0)e^{(a-b)t}$$

- $a - b < 0$: Extinction
- $a - b > 0$: Growth without limits

- Case $a = b$ not relevant: Conditions that have to be fine-tuned can not be realized in biology

That can not be, model is intuitive, but wrong

Definition: Per capita growth rate: $\frac{\dot{N}}{N} = a - b$

Verhulst, 1838 [111] & Pearl, Reed 1920 [79]:
Logistic differential equation[1] ($x = N$):

$$\dot{x} = ax - bx^2$$

or:

$$\dot{x} = (a - bx)x$$

with state-dependent per capita growth rate $\dot{x}/x$: $(a - bx)$, comprising:

- limited resources
- wars
- Appreciation of predictions of exponential models (Club of Rome)

Analogy to mails WS 2

Transformation: $r = a$, $K = a/b$:

$$\dot{x} = rx\left(1 - \frac{x}{K}\right), \quad r, K > 0$$

Solution by visual inspection:

- x small: $\dot{x} = rx \Longrightarrow x(t) \propto e^{rt}$
- x large: $\dot{x} = -\frac{r}{K}x^2 \Longrightarrow x(t) \propto \frac{K}{r}\frac{1}{t}$
- $x = K$: $\dot{x} = 0$

Solution by separation of variables:

$$\int \frac{dx}{x(K - x)} = \frac{r}{K}\int dt$$

[1] Not to be confused with the logistic difference equation

With partial fraction decomposition:

$$\frac{1}{x(K-x)} = \frac{1}{K}\left(\frac{1}{x} + \frac{1}{K-x}\right)$$

follows:

$$\begin{aligned}\frac{r}{K}\,t + c &= \frac{1}{K}\left(\int \frac{1}{x}\,dx + \int \frac{1}{K-x}\,dx\right) \\ &= \frac{1}{K}\left(\log x - \log(K-x)\right)\end{aligned}$$

With $x(t=0) = x_0 < K$ determine integration constant c

$$c = \frac{1}{K}\left(\log x_0 - \log(K-x_0)\right)$$

Solution for $x(t)$, sort terms, exponentiate

$$x(t) = \frac{Kx_0}{x_0 + (K-x_0)e^{-rt}}$$

Also holds for $x_0 \geq K$

Consider 2. derivative

$$\ddot{x} = r^2 x\left(1 - \frac{2x}{K}\right)\left(1 - \frac{x}{K}\right)$$

Change of sign at $x = K/2$, inflection point
This a testable prediction of the model

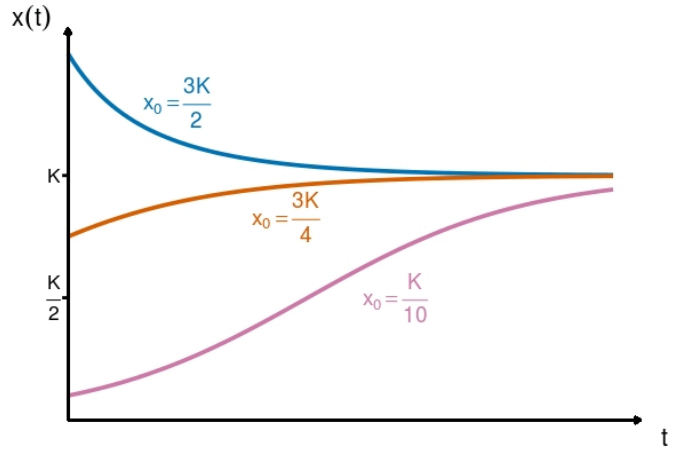

Figure 3.1: Solution of logistic differential equation

Interpretation:

- $K = a/b$: Capacity of biotope
- r: Velocity of convergence

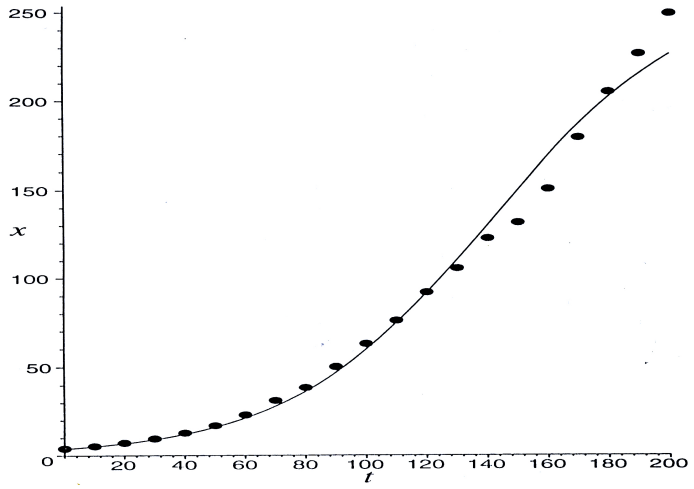

Figure 3.2: Inhabitants of the USA 1790-1990

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3.2 Lotka-Volterra System

Describes oscillatory predator-prey systems

Example: Fur statistics of the Hudson Bay Company

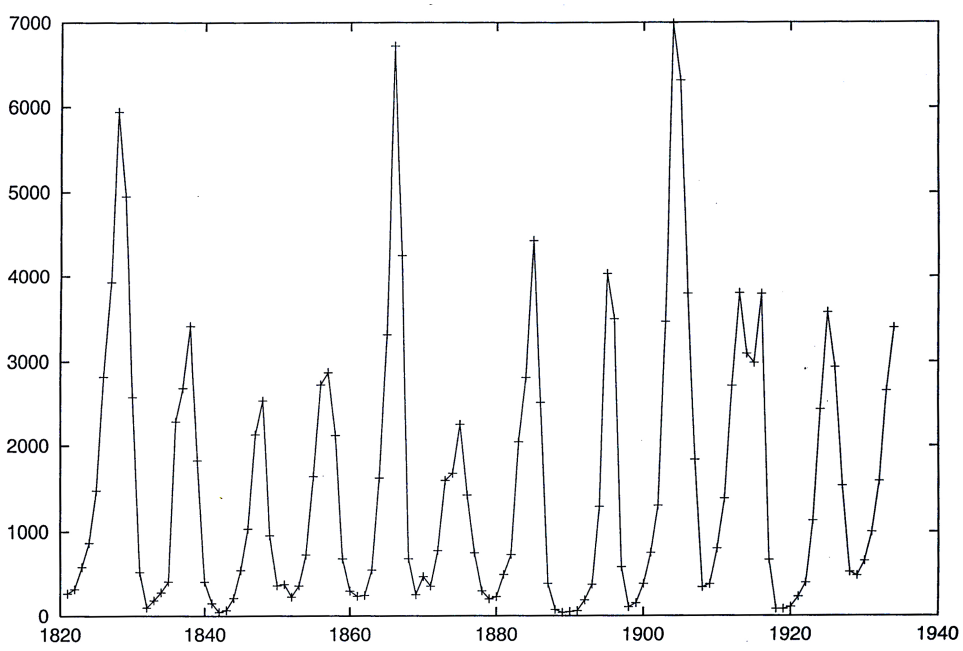


Figure 3.3: Canadian lynx data 1820-1936

Original literature from 1925 & 1926: [63, 113]
Lotka was about chemical reaktions

- Predator-prey model, motivated by oscillations in fish populations in the adria
- Prey: $x(t)$
- Predator: $y(t)$

Assumptions:

- Without predator the prey accumulates proportional to its number with $a\,x$.

- Prey is diminished by being eaten proportional to the number of both : $-b\,xy$

  b: Chasing efficiency

- Predator accumulates through eating prey proportional to the number of both: $c\,xy$

  c: Eating-to-offspring efficiency

- Predators die proportional to their number : $-d\,y$

- Well mixed populations. Ordinary differential equation instead of partial differential equations

Results in:

$$\begin{aligned} \dot{x} &= ax - bxy \\ \dot{y} &= cyx - dy \end{aligned}$$

Can be read as change in growth/death-rate

$$\begin{aligned} \dot{x} &= (a - by)\,x \\ \dot{y} &= (cx - d)\,y \end{aligned}$$

The following analysis will show that this model can physically/biologically impossibly be correct for three fundamental reasons

For analysis: Transformation to dimensionless quantities

- No unique procedure
- But always helpful

$$u(\tau) = \frac{cx(t)}{d}, \quad v(\tau) = \frac{by(t)}{a}, \quad \tau = at, \quad \alpha = \frac{d}{a}$$

yields:

$$\begin{aligned} \frac{du}{d\tau} &= u(1 - v) \\ \frac{dv}{d\tau} &= \alpha v(u - 1) \end{aligned}$$

Note: There is only one real free parameter: α

Fixed points: $LHS = 0$

- $u = v = 0$ not interesting
- $u = v = 1$ interesting

In (u, v)-phase space:

$$\frac{dv}{du} = \alpha \frac{v(u-1)}{u(1-v)}$$

with singular points at $u = v = 0$ and $u = v = 1$

Solution by separation of variables:

$$\int \frac{1-v}{v} dv = \alpha \int \frac{u-1}{u} du$$

yields :

$$\log v - v + C = \alpha(-\log u + u)$$

or:

$$-\log vu^{\alpha} + v + \alpha u = C$$

- $C(u, v)$ is a conserved quantity of the dynamics: "First Integral"
- Theorem:
  - Given a D-dimensional dynamical system with $\frac{D}{2}$ conserved quanities
  - Then, the system is integrable
  - It can be transfered to a torus, superposition of circular movements
  - Discussion sun-planet system, difference to harmonic oscillator, frequency amplitude dependency 2/19
- Lotka-Volterra-system is a conservative system
  - But C is not a Hamilton function
  - Equations of motion do not follow from Hamilton equations with $H = C$

$$\begin{aligned} \frac{\partial C}{\partial v} &= -\frac{1}{v} + 1 \neq (\pm)\dot{u} \\ \frac{\partial C}{\partial u} &= -\alpha \frac{1}{vu} + \alpha \neq (\mp)\dot{v} \end{aligned}$$

WS 3

– Therefore introduce clever transformation [53, 54, 55]:
– General Lokta-Volterra system

$$\dot{n}_i = \epsilon_i n_i + \frac{1}{\beta_i}\alpha_{ij}\, n_i n_j, \quad \alpha_{ij} = -\alpha_{ji}, \alpha_{kk} = 0 \tag{3}$$

Einstein's sum convention
– Non-trivial fixed point n_j^* from $\dot{n}_i = 0$

$$\epsilon_i \beta_i + \alpha_{ij} n_j^* = 0, \quad n_j^* = -\alpha_{ij}^{-1} \epsilon_i \beta_i \tag{4}$$

– Transformation of variables

$$z_i = \log(n_i/n_i^*)$$

– Solved for n_i:

$$n_i = n_i^* e^{z_i}$$

This is not a canonical transformation !
– With (index i suppressed)

$$\dot{z} = \frac{\partial}{\partial t} \log \frac{n}{n^*} = \frac{n^*}{n}\frac{\dot{n}}{n^*} = \frac{\dot{n}}{n}, \quad \dot{n} = \dot{z}\, n = \dot{z}\, n^* e^z$$

inserted in eq. (3), using eq. (4)

$$\dot{z}_i = \gamma_{ij}\tau_j \left(e^{z_j} - 1\right) = \gamma_{ij}\frac{\partial G}{\partial z_j}$$

with

$$\gamma_{ij} = \frac{\alpha_{ij}}{\beta_i \beta_j}, \quad \tau_j = n_j^* \beta_j, \quad G = \tau_j (e^{z_j} - z_j)$$

– Now:

$$Q = z_1, \quad P = z_2$$

Define Hamilton function

$$H = \gamma\tau_1(e^Q - Q) + \gamma\tau_2(e^P - P), \quad \text{with } \gamma = \gamma_{12} = -\gamma_{21}$$

and obtain Hamilton equations

$$\dot{Q} = \frac{\partial H}{\partial P}, \quad \dot{P} = -\frac{\partial H}{\partial Q} \tag{5}$$

- Conservative/Hamiltonian systems & biology
  - In biology, there are always random pertubations ϵ of the dynamics:

$$\dot{\vec{x}} = \vec{f}(\vec{x}) + \vec{\epsilon}$$

  - Hamiltonian systems are not stable under random perturbations.
  - Solutions diverge

    "Proof"
    * Hamilton-Jacobi formalism
    * Easist to solve Hamiltonian: $H = 0$
    * Find canonical transformation to $H = 0$, Münchhausen-transformation
    * Hamilton's equation of motion for $x = (q, p)$

$$\dot{x} = 0$$

      Euler method

$$x_{t+h} = x_t$$

      Noise ϵ is also somehow transformed: η

$$x_{t+h} = x_t + \eta_t$$

      Brownian motion

$$< x^2(t) > \propto t$$

      Variance diverge
  - 1st reason, Lotka-Volterra can not be realised biologically.
  - Remark: Eq. (5) can not be integrated by Runge-Kutta. Needs symplectic integrators [27, 15] to ensure "energy conservation"

Characterisation of the dynamics

- Minimum of $C(u, v)$ given by:

$$\frac{\partial C(u,v)}{\partial u} = 0$$
$$C(u, v) = -\log v u^{\alpha} + v + \alpha u$$

$$-\alpha\frac{1}{uv}v + 0 + \alpha = 0$$

$$\Longrightarrow u_{min} = 1$$

Correspondingly:

$$\frac{\partial C(u,v)}{\partial v} = 0 \Longrightarrow v_{min} = 1$$

Remember $u = v = 1$ was non-trivial fixed point

- In original variables: $x_{min} = d/c$, $y_{min} = a/b$
- It holds

$$C_{min} = 1 + \alpha$$

- Expansion around $C_{min}, u_{min} = v_{min} = 1$:

$$\begin{aligned} u &= u_{min} + x = 1 + x \\ v &= v_{min} + y = 1 + y \end{aligned}$$

$$C = -\log(1+y) - \alpha\log(1+x) + (1+y) + \alpha(1+x)$$

With $\log(1+z) \approx z - z^2/2$, it follows

$$C = -y + y^2/2 - \alpha(x - x^2/2) + 1 + y + \alpha(1+x)$$

and

$$y^2/2 + \alpha x^2/2 = C - (1+\alpha) > 0$$

an ellipse-equation.

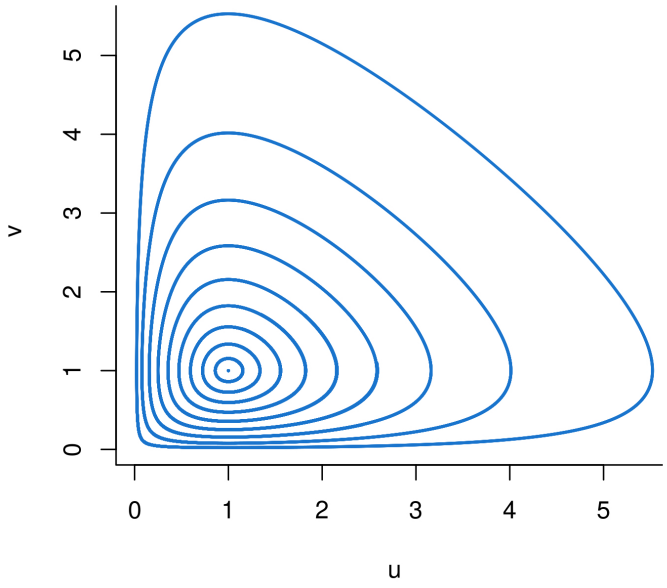


Figure 3.4: (u, v)-diagram

No characteristic scale: 2nd reason the biologically not plausible/possible 1F/20

- Or:

$$\begin{aligned} \frac{du}{d\tau} &= u(1-v) \\ \frac{dv}{d\tau} &= \alpha v(u-1) \end{aligned}$$

with

$$\begin{aligned} u &= u_{min} + x = 1 + x \\ v &= v_{min} + y = 1 + y \end{aligned}$$

yields:

$$\begin{aligned} \frac{dx}{d\tau} &= -(1+x)\, y \\ \frac{dy}{d\tau} &= \alpha(1+y)\, x \end{aligned}$$

- Since x, y are small, neglect xy

$$\begin{aligned} \frac{dx}{d\tau} &= -y \\ \frac{dy}{d\tau} &= \alpha x \end{aligned}$$

or:

$$\ddot{x} = -\alpha x$$

To remember: Lotka-Volterra is an oscillatory conservative/Hamiltonian system

For small amplitudes: Harmonic oscillator

Digression: Linear (local) stability analysis of fixed points
Consider:

$$\begin{aligned} \dot{x}_1 &= f_1(x_1, x_2) \\ \dot{x}_2 &= f_2(x_1, x_2) \end{aligned}$$

with fixed points x_1^* und x_2^*

$$\begin{aligned} 0 &= f_1(x_1^*, x_2^*) \\ 0 &= f_2(x_1^*, x_2^*) \end{aligned}$$

- Stability of fixed point: Linearise dynamics at fixed point

  With

$$x_1 = x_1^* + \tilde{x}_1, \quad x_2 = x_2^* + \tilde{x}_2$$

$$\dot{x}_1 = \dot{x}_1^* + \dot{\tilde{x}}_1 = f_1(x_1^* + \tilde{x}_1, x_2^* + \tilde{x}_2) \approx f_1(x_1^*, x_2^*) + \frac{\partial f_1(x_1^*, x_2^*)}{\partial x_1}\tilde{x}_1 + \frac{\partial f_1(x_1^*, x_2^*)}{\partial x_2}\tilde{x}_2 + \mathcal{O}(\tilde{x}^2)$$

$$\dot{x}_2 = \dot{x}_2^* + \dot{\tilde{x}}_2 = f_2(x_1^* + \tilde{x}_1, x_2^* + \tilde{x}_2) \approx f_2(x_1^*, x_2^*) + \frac{\partial f_2(x_1^*, x_2^*)}{\partial x_1}\tilde{x}_1 + \frac{\partial f_2(x_1^*, x_2^*)}{\partial x_2}\tilde{x}_2 + \mathcal{O}(\tilde{x}^2)$$

  Yields with $\vec{\tilde{x}} = \begin{pmatrix} \tilde{x}_1 \\ \tilde{x}_2 \end{pmatrix}$

$$\dot{\vec{\tilde{x}}} = \left(\begin{array}{cc} \frac{\partial f_1}{\partial x_1} & \frac{\partial f_1}{\partial x_2} \\ \frac{\partial f_2}{\partial x_1} & \frac{\partial f_2}{\partial x_2} \end{array} \right) \Bigg|_{x^*} \dot{\vec{\tilde{x}}} = A\vec{\tilde{x}} \qquad \text{the linearised system}$$

- Solution:

$$\vec{\tilde{x}}(t) = \vec{\tilde{x}}(0)e^{At}$$

e^{At} defined by power series[2]:

$$e^{At} = 1 + At + \frac{1}{2}A^2t^2 + \ldots$$

Diagonalise A

$$A = VDV^T = V \left(\begin{array}{cc} a+ic & 0 \\ 0 & b+ic \end{array} \right) V^T, \quad V \text{ orthogonal matrix}$$

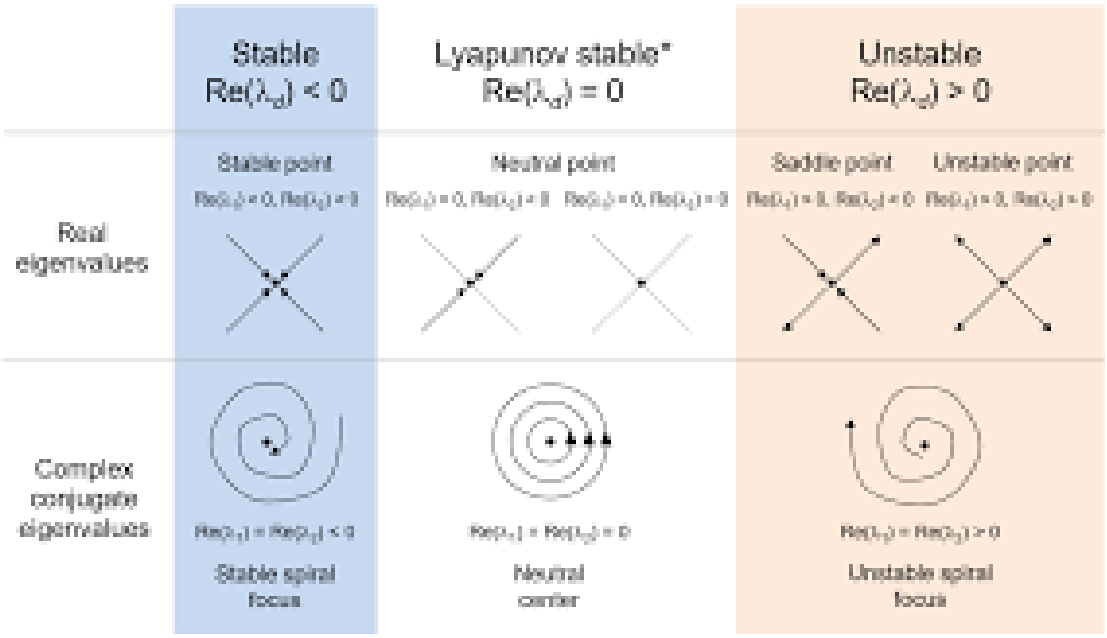
$$\vec{\tilde{x}}(t) = \vec{\tilde{x}}(0) \exp\left(V \left(\begin{array}{cc} a+ic & 0 \\ 0 & b+ic \end{array} \right) V^T t \right)$$

Eigen-values $\lambda_{1,2}$ of A determine the qualitative behavior:

$$\tilde{x}_1(t) = a_1 e^{Re(\lambda_1)t} \cos(Im(\lambda_1)t + \phi_1) + a_2 e^{Re(\lambda_2)t} \cos(Im(\lambda_2)t + \phi_2)$$

- In general: If ...
  - both real parts negative: stable fixed point
  - eigen-values real: purely exponential
  - eigen-values complex: spiral
  - eigen-values purely imaginary: whirl

[2]Cool papers on this topic: [71, 72]



Real part	Imaginary part	Denotation
-, -	0	stable knot
+, +	0	unstable knot
+, -	0	sattle point
-, -	$\neq 0$	stable vortex
+, +	$\neq 0$	unstable vortex
0, 0	$\neq 0$	whirl

Eigen-values of A:

$$\det(A-\lambda I) = \det\begin{pmatrix} a-\lambda & b \\ c & d-\lambda \end{pmatrix} = (a-\lambda)(d-\lambda)-bc = \lambda^2-(a+d)\lambda+(ad-bc) = 0$$

$$\lambda_{1,2} = \frac{tr\,A}{2} \pm \sqrt{\left(\frac{tr\,A}{2}\right)^2 - \det A}$$

Thus:
Both eigen-values have negative real part, i.e. fixed point is stable, if:

- $tr\,A(x^*, y^*) < 0$

- $\det A(x^*, y^*) > 0$

Typically, in general population dynamics

$$\begin{aligned} \dot{x} &= xF(x,y) \\ \dot{y} &= yG(x,y) \end{aligned}$$

with $F(x,y)$, $G(x,y)$ per capita growth rate

Thus

$$\left(\begin{array}{cc} \frac{\partial f}{\partial x} & \frac{\partial f}{\partial y} \\ \frac{\partial g}{\partial x} & \frac{\partial g}{\partial y} \end{array} \right) \Bigg|_{(x^*,y^*)} = \left(\begin{array}{cc} x^*F_x(x^*,y^*) + F(x^*,y^*) & x^*F_y(x^*,y^*) \\ y^*G_x(x^*,y^*) & y^*G_y(x^*,y^*) + G(x^*,y^*) \end{array} \right)$$

Four possibilities for fixed points

- $(0,0)$

$$A = \left(\begin{array}{cc} F(0,0) & 0 \\ 0 & G(0,0) \end{array} \right)$$

- $(K,0)$ with $F(K,0) = 0$

$$A = \left(\begin{array}{cc} KF_x(K,0) & KF_y(K,0) \\ 0 & G(K,0) \end{array} \right)$$

- $(0,M)$ with $G(0,M) = 0$

$$A = \left(\begin{array}{cc} F(0,M) & 0 \\ MG_x(0,M) & MG_y(0,M) \end{array} \right)$$

- The most general case
  $(K,M) \neq (0,0)$, $F(K,M) = 0$, $G(K,M) = 0$

$$A = \left(\begin{array}{cc} KF_x(K,M) & KF_y(K,M) \\ MG_x(K,M) & MG_y(K,M) \end{array} \right)$$

It always simplifies

End of Digression

Back to Lotka-Volterra

- Consider dimensionless version

$$\begin{aligned} \frac{du}{d\tau} &= u(1-v) \\ \frac{dv}{d\tau} &= \alpha v(u-1) \end{aligned}$$

- Linearising around fixed point

$$\dot{\vec{x}} = \begin{pmatrix} 0 & 1 \\ -\alpha & 0 \end{pmatrix} \vec{x} = A\vec{x}$$

  Note: symplectic structure

  Eigen-values from

$$\lambda^2 + \alpha = 0$$

- Yields purely imaginary eigen-values

$$\lambda_{1,2} = \pm i\sqrt{\alpha} \quad \Longrightarrow \text{ whirl}$$

- Disturb structure of the dynamics slightly

$$\begin{array}{rclcrcl} \dot{u} & = & u(1-v) & = & u - uv & \text{to} & (1+\epsilon_1)u - (1+\epsilon_2)uv + \epsilon_3 v + \epsilon_4 u^2 v + ... \\ \dot{v} & = & \alpha v(u-1) & = & -\alpha v + \alpha v u & \text{to} & -(\alpha + \epsilon_5)v + \ldots \end{array}$$

  apart from set of measure zero of disturbances $\Longrightarrow$ A_{11}, $A_{22} \neq 0$ and thus:

$$Re(\lambda_{1,2}) \neq 0$$

- Ergo: 3rd reason: The (integrable Hamiltonian) whirl solution ist not stable against even the smallest disturbances of the model structure.

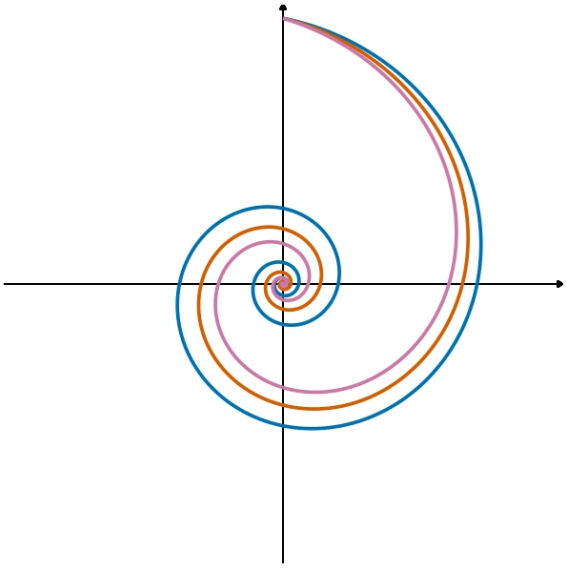


Figure 3.5: Deformation of stable vortex

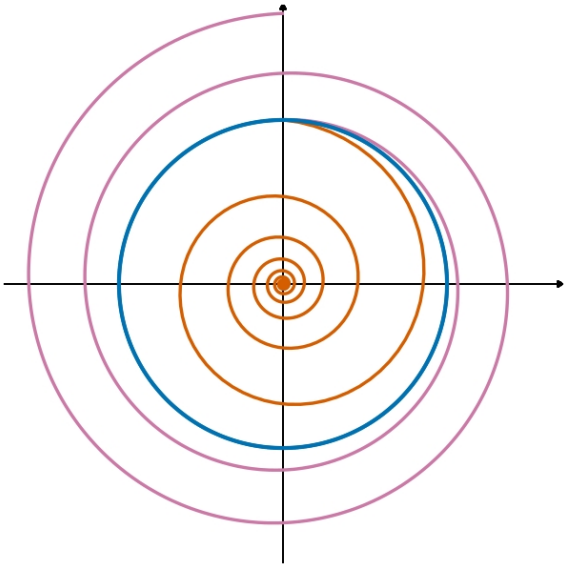


Figure 3.6: Deformation of whirl

Summary:

- Lotka-Volterra shows that a simple predator-prey model can oscillate

- Lotka-Volterra is unbiological since conservative
  - Unstable trajectories under random disturbances of the dynamics
  - No scale fixed
  - Unstable qualitative dynamics under disturbance of model structure

WS 4

Extensions of the Lotka-Volterra system
Goal must be a limit cycle.
Limit cycle:

- Repelling fixed point ...
- ... but attractive periodic long-term solution
- Unique long-term solution independent of initial values
- Fixed scale, remember size of the island
- Non-conservative(non-Hamiltonian): dissipative
- Stable under the two kind of pertubations

Classical example: van der Pol Oszillator, 1922 [110]
Remark:

- Developed for oscillator circuit based on a triode
- Later generalised for modelling neural activity [10]

$$\ddot{x} = \mu\,(1 - x^2)\,\dot{x} - \omega_0^2 x, \quad \mu > 0$$

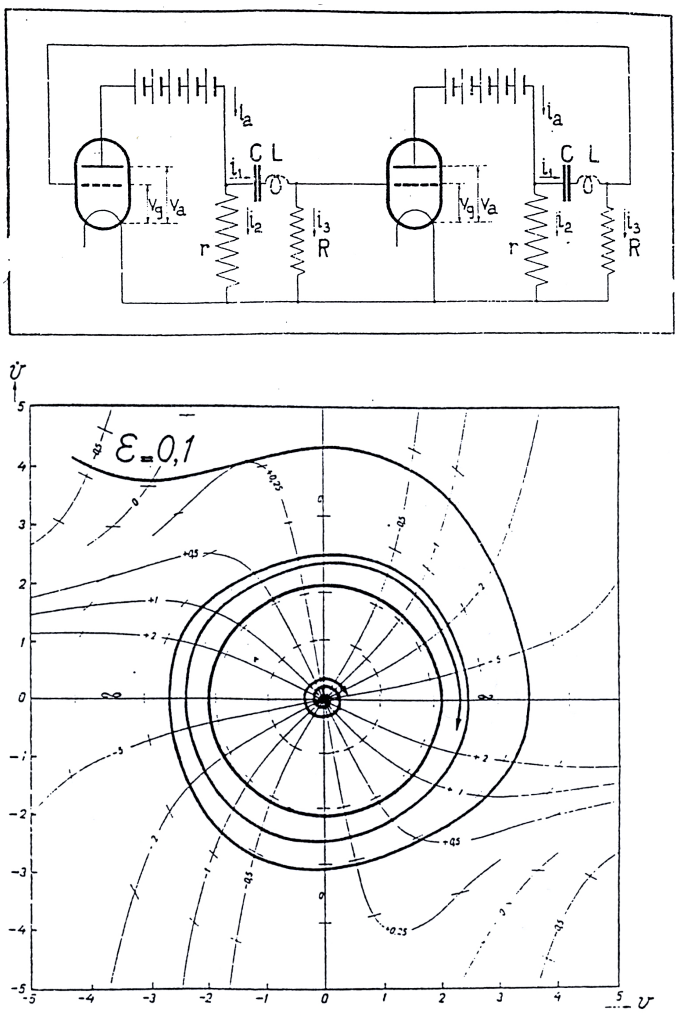


Figure 3.7: Van-der-Pol oscillator

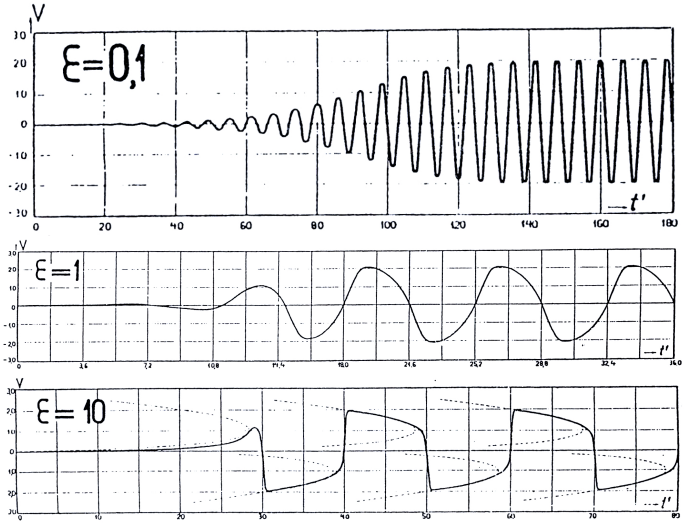


Figure 3.8: Van-der-Pol oscillator

The effect:
x^2-term:

- If $x^2 < 1$: negative damping: System take up energy (battery)
- If $x^2 > 1$: damping: Systems dissipates energy (resistor)
- Consequence: An attractor, in this case a limit cycle:

  Independent from initial values, each trajectory approaches a one-dimensional invariant set. Potential interpretation.

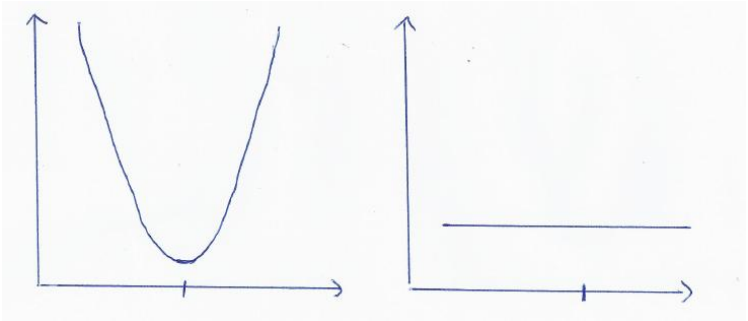


Figure 3.8: Aristotelian potential perpendicular to the trajectory. Left limit cycle, right Hamiltonian system

- Liouville theorem does not hold. Phase space volume is destroyed.

  From two to one dimension

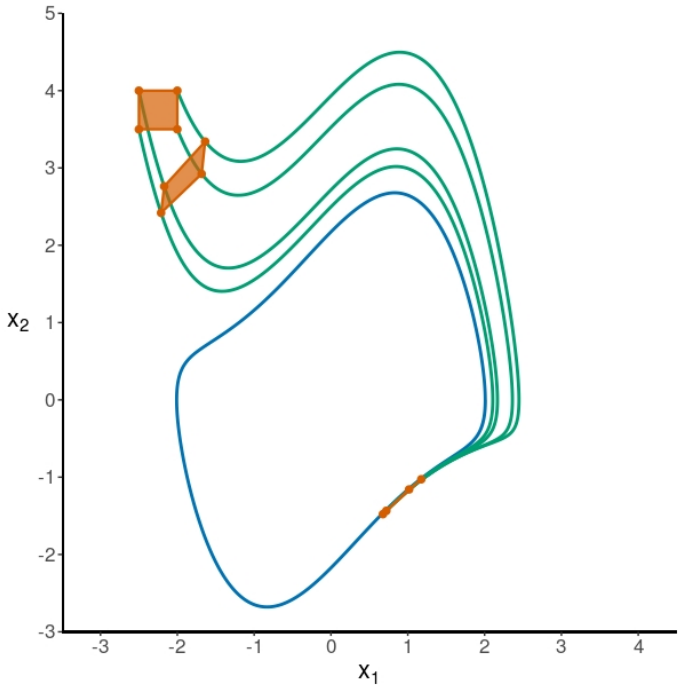


Figure 3.9: Phase space volume not conserved

- Due to attractiveness, limit cycles can reliably be integrated by Runge-Kutta methods

Physics point of view: An open system, not in equilibrium with surrounding

- Small amplitude: low-entropic energy is taken up
- Large amplitude: energy is dissipated high-entropically
- In general: Entropy difference feeds structure formation

2M/20

Linear stability analysis:

$$\begin{aligned} \dot{x}_1 &= x_2 \\ \dot{x}_2 &= \mu\,(1 - x_1^2)\,x_2 - \omega_0^2 x_1 \end{aligned}$$

Fixed point:

$$\begin{aligned} 0 &= x_2 \\ 0 &= \mu\,(1 - x_1^2)\,x_2 - \omega_0^2 x_1 \end{aligned}$$

at (0,0).

Linearising at (0,0):

$$A = \left.\frac{\partial \vec{f}}{\partial \vec{x}}\right|_{x^*} = \begin{pmatrix} 0 & 1 \\ -\omega_0^2 & \mu \end{pmatrix}$$

$$\det \begin{pmatrix} -\lambda & 1 \\ -\omega_0^2 & \mu - \lambda \end{pmatrix} = \lambda^2 - \lambda\mu + \omega_0^2$$

$$\lambda_{1,2} = \frac{\mu}{2} \pm \sqrt{\mu^2/4 - \omega_0^2}$$

Eigen-values:

- Positive real parts $\Longrightarrow$ Fixed point $(0, 0)$ is repelling
- Structurally stable: Positive real part stays positive if structure of the system is slightly pertubated
- $\mu < 2\omega_0$ unstable vortex
- $\mu \geq 2\omega_0$ unstable knot

Digression: Global analysis:
Poincaré-Bendixson Theorem: Asymptotic solutions in time continuous two-dimensional systems:

- Stable fixed points
- Limit cycles
- (exploding solutions)
- Hamiltonian systems, essentially harmonic oszillator

Proof:
Uniqueness of the solution. Trajectories can not cross each other

This changes essentially in three dimensions: Chaos

End of digression

Remember: There are always stochasitc disturbances of the dynamics
Stochastic van der Pol oscillator:

$$\ddot{x} = \mu\left(1 - x^2\right)\dot{x} - x + \epsilon,$$

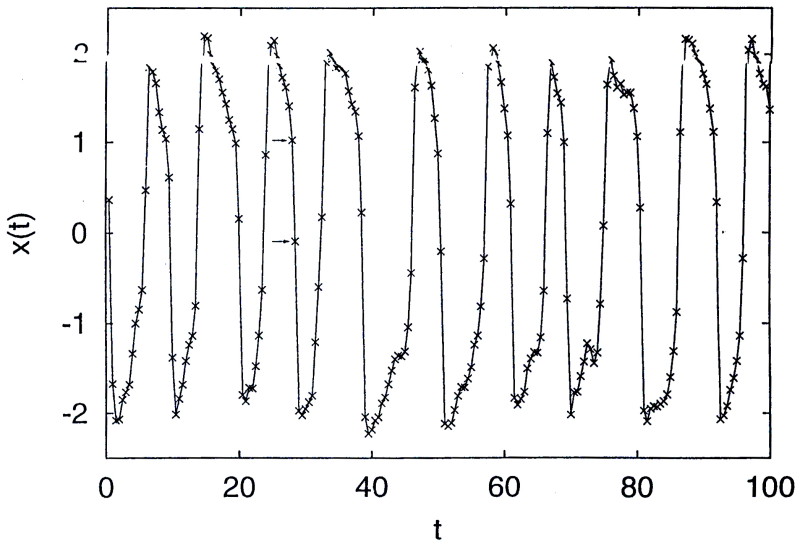


Figure 3.10: Stochastic van-der-Pol oscillator

Back to Lotka-Volterra:

$$\begin{aligned} \dot{x} &= ax - bxy \\ \dot{y} &= cyx - dy \end{aligned}$$

- Try Verhulst-dynamics for prey

$$\begin{aligned} \dot{x} &= ax\left(1 - \frac{x}{K_x}\right) - bxy \\ \dot{y} &= cyx - dy \end{aligned}$$

  In general not sufficient, can show stable fixed point behavior

- Other interaction terms

  Example: Saturation. Predators can only eat a finite number of prey per day

$$\begin{aligned} \dot{x} &= ax - b\,\frac{x}{S+x}\,y \\ \dot{y} &= cy\,\frac{x}{S+x} - dy \end{aligned}$$

  This works out

  Remark:

  Terms of the type $\frac{x}{S+x}$, we will see again in Chap. 6 Enzyme Dynamics.

- Many extentions, e.g. competition of two predators y, z about the same prey x

$$\begin{aligned} \dot{x} &= ax - b_1xy - b_2xz \\ \dot{y} &= cyx - dy \\ \dot{z} &= ezx - fz \end{aligned}$$

  One can show: One of the predators will die off. Principle of competive exclusion

- Stochastic versions, see [14] 2/17

WS 5

3.3 Infection Models

First paper: Kermack & McKendrick, 1927 [52], nice review [3]
Questions to be answered:

- How will an infection develop ?
- Will it become an epidemic ?

- How to vaccinate ?
- How does an epidemic spread spatially ?

SIR-models
Denotations:

- S: Susceptible
- I: Infectious
- R: Removed (immune, isolated, dead)

Sequence:

$$S \to I \to R$$

3.3.1 Well mixed

Assumptions

- Effects fast compared to infection-free life expectancy
- Infection by two-point interaction: rSI
- Removal proportional to I: $-aI$
- Well mixed population

Result SIR model:

$$\dot{S} = -rSI \tag{6}$$
$$\dot{I} = rSI - aI \tag{7}$$
$$\dot{R} = aI \tag{8}$$

Consistency check:

$$\dot{S} + \dot{I} + \dot{R} = 0 \Longrightarrow S(t) + I(t) + R(t) = N$$

particle conservation o.k.

Note: Three dimensional system, one conserved quantity $\Longrightarrow$ not an integrable system

Fixed points:

$$\begin{aligned} 0 &= -rSI \\ 0 &= rSI - aI \\ 0 &= aI \end{aligned}$$

- $(S^*, I^*, R^*) = (\tilde{S}, 0, \tilde{R})$ with

$$\begin{aligned} \tilde{S} &= \tilde{S}(S(0), I(0), R(0)) \\ \tilde{R} &= \tilde{R}(S(0), I(0), R(0)) \end{aligned}$$

  Note: in contrast to van der Pol oscillator: Fixed point depends on initial values

- Good news: $I^* = 0$, but does this put our minds to ease ?
- Under which condition an infection grows ?

  Eq. (7):

$$\dot{I} = (rS - a)I$$

  - Decreasing for $S < \frac{a}{r} =: \rho$
  - Increasing for $S > \frac{a}{r} =: \rho$
  - ρ: Relative removal rate

Initial conditions

$$S(0) > 0,\ \dot{S}(0) < 0, \quad I(0) > 0, \quad R(0) = 0$$

Most relevant question:

- Given $S(0)$, $I(0)$, r, a: Will the infection spread to become an epidemic
- Or: $\dot{I}(0) > 0$ or $\dot{I}(0) < 0$

$$\dot{I}(0) = (rS(0) - a)\, I(0)$$

$$\begin{aligned} \dot{I}(0) < 0 \qquad & \text{if } S(0) < \frac{a}{r} = \rho \\ \dot{I}(0) > 0 \qquad & \text{if } S(0) > \frac{a}{r} = \rho \end{aligned}$$

Distinction of cases:
Case 1:

- Since $\dot{S}(t) \leq 0$ and thus $S(t) \leq S(0)$ follows for $S(0) < \frac{a}{r}$:

$$\dot{I} = (rS - a)I \leq 0, \quad \forall t \geq 0$$

  Infection dies off

Case 2:

- The other way round: If $S(0) > \frac{a}{r}$ an epidemic follows, i.e. $I(t) > I(0)$ for a certain time $t > 0$.
- This is a threshold phenomenon

Instead of relative removal rate $\rho = \frac{a}{r}$ or contact rate $1/\rho = \frac{r}{a}$, often reproduction rate:

$$R_0 = \frac{r\,S(0)}{a}, \qquad \text{critical value} = 1$$

Number of secondary infected by one primary infected in complete susceptible population

Consider (S, I) phase space:

$$\frac{dI}{dS} = -\frac{(rS - a)I}{rSI} = -1 + \frac{\rho}{S}$$

Separation of variables:

$$\int dI = \int dS \, \left(-1 + \frac{\rho}{S}\right)$$

yields:

$$I + S - \rho \log S = C = I(0) + S(0) - \rho \log S(0) \tag{9}$$

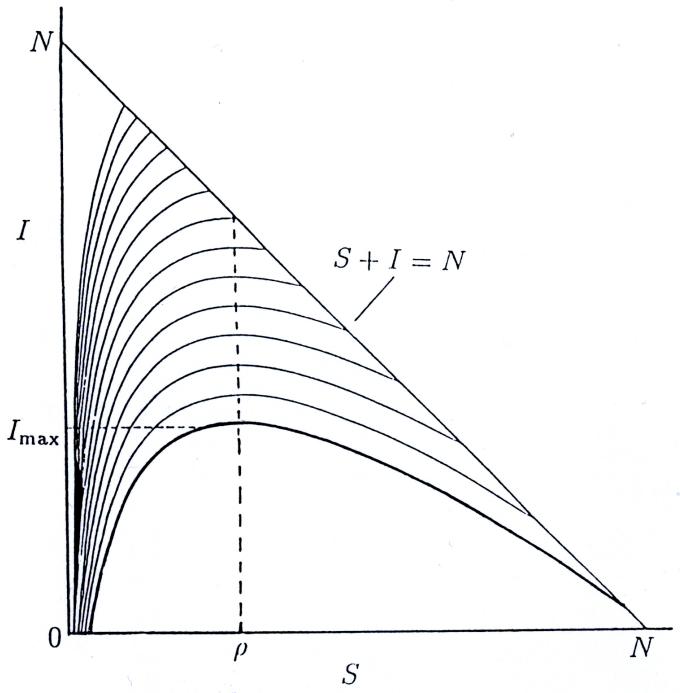


Figure 3.11: Initial values: I(0)+S(0)=N

How severe will the epidemic be ?

- Condition for the maximum number of infected

$$\dot{I} = rSI - aI = I(rS - a) = 0$$

  Consequence :
  Maximum at $S = \frac{a}{r} = \rho$

- Eq. (9) results in

$$\begin{aligned} I_{max} &= \rho \log \rho - \rho + I(0) + S(0) - \rho \log S(0) \\ &= N - \rho + \rho \log \rho / S(0) \end{aligned}$$

  Good news: After maximum is reached, $I = 0$ is stable fixed point.

Naive expectation: Whole population will be infected, at the end $R(\infty) = N$

But
Important consequence/prediction of SIR model:

From eqs. (6, 8) follows:

$$\frac{dS}{dR} = -\frac{S}{\rho}$$

Yields:

$$S(t) = S(0)e^{-R(t)/\rho} \geq S(0)e^{-N/\rho}, \quad \text{since } N \geq R(t)$$

and

$$S(0)e^{-N/\rho} > 0, \quad \text{since } S(0) > 0$$

Thus, it follows

$$S(t) > 0 \quad \forall t$$

especially

$$0 < S(\infty) = N - R(\infty)$$

since $I(\infty) = 0$

$$S(\infty) = S(0)\ \exp\left[-\frac{R(\infty)}{\rho}\right] = S(0)\ \exp\left[-\frac{N - S(\infty)}{\rho}\right]$$

Transcendent equation, solution numerically/graphically
Total number of infected

$$I_{total} = I(0) + S(0) - S(\infty)$$

Consequence, model prediction:
The epidemics ends because of lack of infectious not because of lack of susceptibles !

- The more deadly an infection is, the smaller is the probability that it results in an epidemic
- Example: Ebola. Discuss last epidemic, $S(0)$ large
- Problem of epidemic is not dieing but infection
- Worst case: Highly infectious, slowly killing. Example: HIV

Comparison to empirical data

- Weak epidemics
  - I, R small
  - r small
  - a large,
  - ρ large
  - Ergo: R/ρ small

  Often $R(t)$, resp. dR/dt removed per time interval, in worth case deads/day are reported.

$$\frac{dR}{dt} = aI = a(N - R - S) = a\left(N - R - S(0)\exp\left[-\frac{R}{\rho}\right]\right)$$

  $\frac{R}{\rho} \ll 1$

  Approximate:

$$\frac{dR}{dt} = a\left(N - R - S(0) + \frac{S(0)R}{\rho} - \frac{S(0)R^2}{2\rho^2}\right)$$

  Solution:

$$R(t) = \frac{\rho^2}{S(0)}\left[\left(\frac{S(0)}{\rho} - 1\right) + \alpha\tanh\left(\frac{\alpha a t}{2} - \phi\right)\right]$$

  with

$$\alpha = \alpha(S(0), \rho, N) = \left[\left(\frac{S(0)}{\rho} - 1\right)^2 + \frac{2S(0)(N - S(0))}{\rho^2}\right]^{1/2}$$

$$\phi = \phi(S(0), \rho, \alpha) = \frac{\tanh^{-1}\left(\frac{S(0)}{\rho} - 1\right)}{\alpha}$$

  Removal Rate:

$$\frac{dR}{dt} = \frac{\alpha^2 a \rho^2}{2S(0)} \frac{1}{\cos^2\left(\frac{\alpha a t}{2} - \phi\right)}$$

  With effectivly 3 free parameters

  Example: Bombay plague epidemic 1905-06

Removed = dead, $dR(t)/dt$ = deads/week

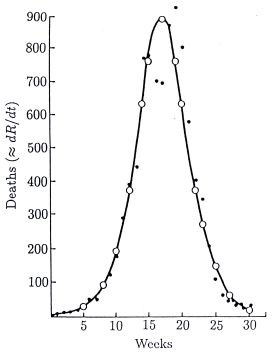


Figure 3.12: Bombay pest epidemic 1905-1906

- Severe Epidemic I: Influenca at an english school

  Reported: I(t)

  Fit of the complete system

  $N = 763$, $S(0) = 762$, $I(0) = 1$, $\rho = 202$ (from fit)

  Condition for epidemic $S(0) > \rho$ clearly fulfilled

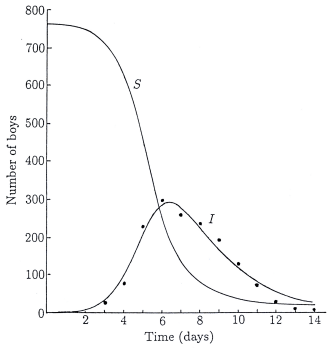


Figure 3.13: Influenca epidemic at an english school

- Severe epidemic II, Eyam (closed to Sheffield)
  Plague 1666, trigger of the plague in London

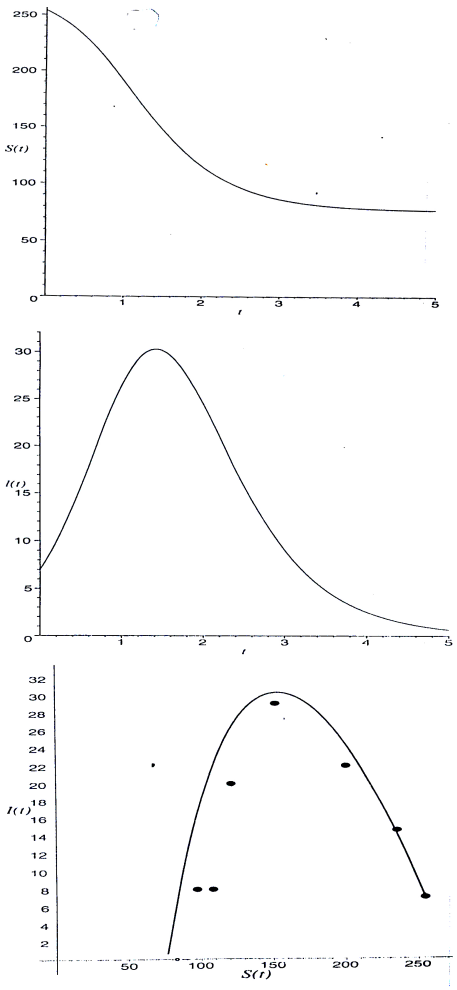


Figure 3.14: Plague epidemic in Eyam

Applications of the model:

- What are optimal vaccination strategies ?
  How many % of the people in which intervals ? [100]

Goal of vaccination: Reduction of reproduction rate R_0

$$R_0 = \frac{rS(0)}{a}, \quad p : \text{immunised fraction} \quad R_{eff} = \frac{r(1-p)S(0)}{a} = R_0(1-p)$$

Target: Get R_0 to $R_0 < 1$

- Herd immunity

  Let people get infected to become immune

  Fraction p of immune people to obtain $R_{eff} < 1$

  $$R_0(1-p) < 1 \quad \Longrightarrow \quad p > \frac{R_0 - 1}{R_0}$$

  Example, close to Covid-19 in Germany

  - Assume $N = 10^8$
  - Let R_0 be 2
  - Gives $p = 0.5$
  - Assume mortality of 1 %
  - Gives 500.000 deaths
  - No chance

Examples for Extensions:

- HIV

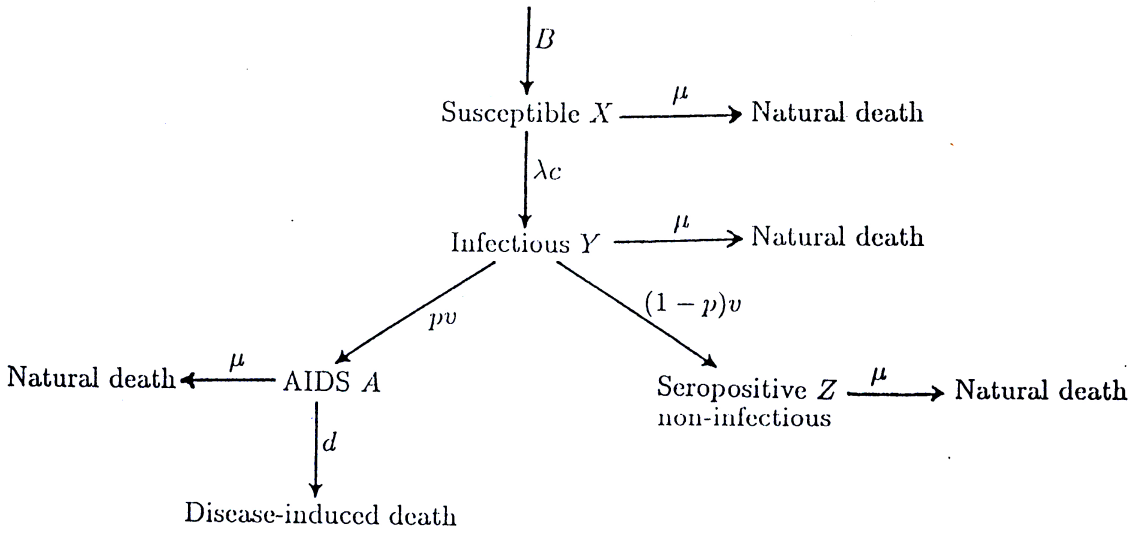


Figure 3.15: AIDS

- Additional state E: Exposed
  - infected
  - not yet infectious
  - $SEIR$ model
- Malaria:
  - Survivers are immune for a while and then susceptible again
  - Add: $R \longrightarrow Im \longrightarrow S$
  - The circle closes

WS 6
2F/20

3.3.2 Spatial Effects

- In the following without R, it is anyway only attached
- Central questions: Do epidemic waves exist ?

- Model spatial effects by diffusion, i.e. heat equation

$$\dot{u} = D\nabla^2 u$$

  Solution:

$$u(x,t) = \frac{1}{\sqrt{4\pi Dt}} \exp\left(-\frac{x^2}{4Dt}\right)$$

  Gaussian with variance increasing linearly in time.

  Probability density of Brownian motion.

Yields:

$$\dot{S} = -rSI + D\nabla^2 S \tag{10}$$
$$\dot{I} = rSI - aI + D\nabla^2 I \tag{11}$$

a reaction-diffusion-equation

Epidemic wave:

- $I(x,t) = I(z)$
- $S(x,t) = S(z)$
- with $z = x - vt$ and $0 \leq I(z)$, $S(z) < const$

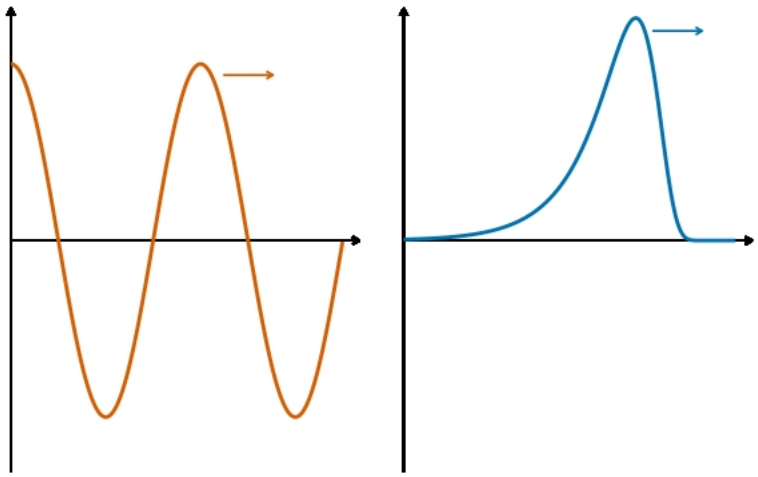


Figure 3.16: Wave as usual, wave in general

3/19

- Note:
$$\frac{\partial I}{\partial t} = \frac{\partial I}{\partial z}\frac{\partial z}{\partial t} = -v\frac{\partial I}{\partial z} \qquad \text{and} \qquad \frac{\partial I}{\partial x} = \frac{\partial I}{\partial z}$$
For S accordingly

- Yields 2. order ordinary differential equation in z

Strategy :

- Choose wave as ansatz
- Check whether it works out, remember separation ansatz in QM

Failing Example: heat equation

$$-v\frac{du}{dz} = D\frac{d^2u}{dz^2} \Longrightarrow u(z) = A + Be^{-vz/D}$$

Unbounded solution: heat equation does not produce waves

Back to eqs. (10,11)
Dimensionless quantities, $S_0 = S(0)$

$$\tilde{I} = \frac{I}{S_0},\ \tilde{S} = \frac{S}{S_0},\ \tilde{x} = \left(\frac{rS_0}{D}\right)x,\ \tilde{t} = rS_0t,\ \lambda = \frac{a}{rS_0}$$

yields, tildes suppressed

$$S'' + cS' + \lambda IS = 0 \tag{12}$$
$$I'' + cI' + I(S - \lambda) = 0 \tag{13}$$

c: velocity of propagation

Non-negative I with $I(\infty) = I(-\infty) = 0$

Linearise eq. (13) at leading edge of the wave: $S \to 1$

$$I'' + cI' + I(1 - \lambda) \approx 0$$

Solution:

$$I(z) \propto \exp\left[(-c \pm \{c^2 - 4(1-\lambda)\}^{1/2})z\right]$$

- Since for $z \to \infty$, $I(z) \to 0$ with $I(z) \geq 0$, it must not oscillate
- There are waves if

$$c \geq 2\sqrt{1-\lambda} \quad \text{and} \quad \lambda = \frac{a}{rS_0} < 1$$

- Remember reproduction rate

$$R_0 = \frac{rS_0}{a} = \frac{1}{\lambda} > 1$$

  was the condition for an epidemic to occur
- In dimensional units: $v = \sqrt{rS_0D(1 - a/rS_0)}$
- Accordingly linearise eq. (12)

  The full beauty:

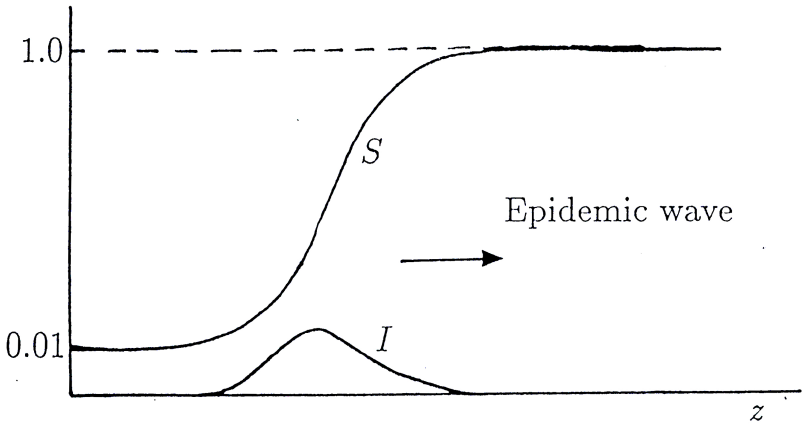


Figure 3.17: Epidemic wave

- The wave can only move in one direction, because $R_0 < 1$ "in the back" of the wave

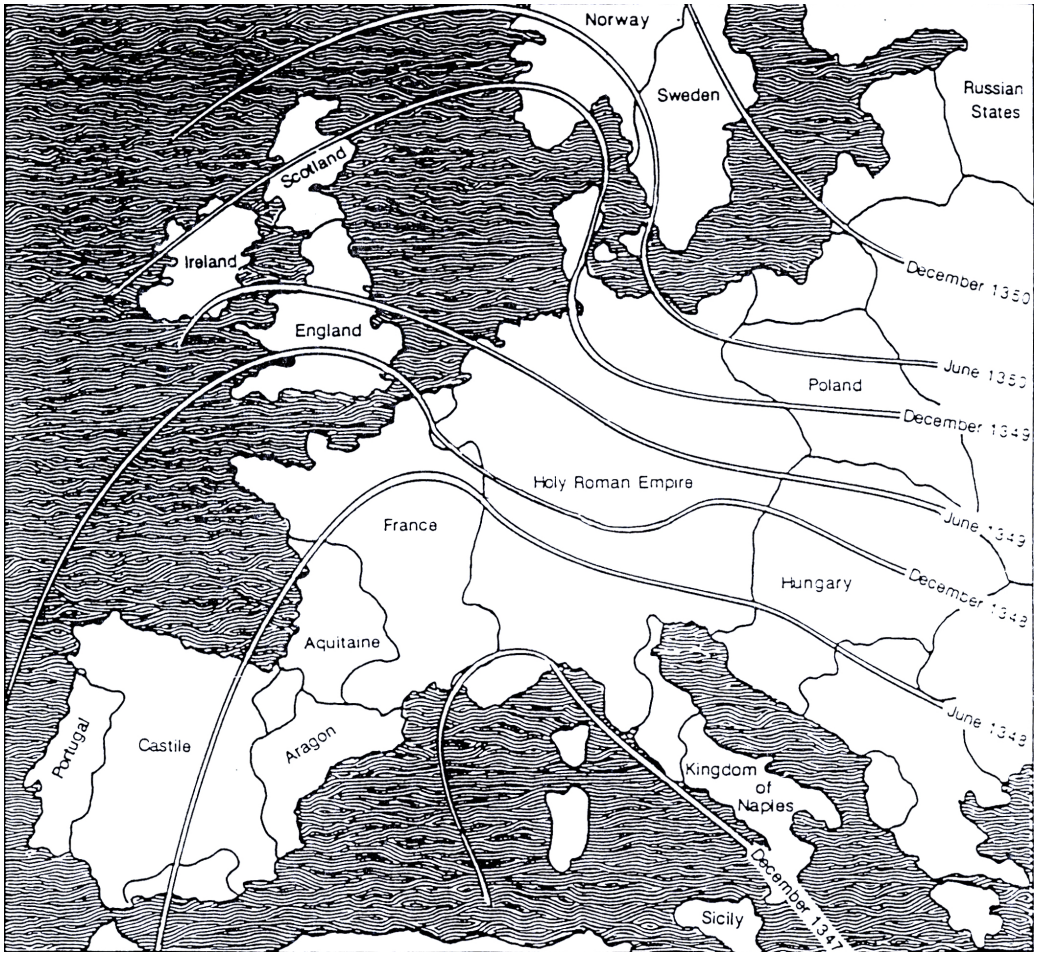


Figure 3.18: Spread of plague in Europe

- Note: The plague from 1348 set the building of our cathedral on hold for nearly 100 years

Reaction-diffusion equations are a large field

- Lotka-Volterra with diffusion
- The most famous: Belousov-Zhabotinski-Reaction
- See also Sec. 5 Pattern Formation by Turing mechanism

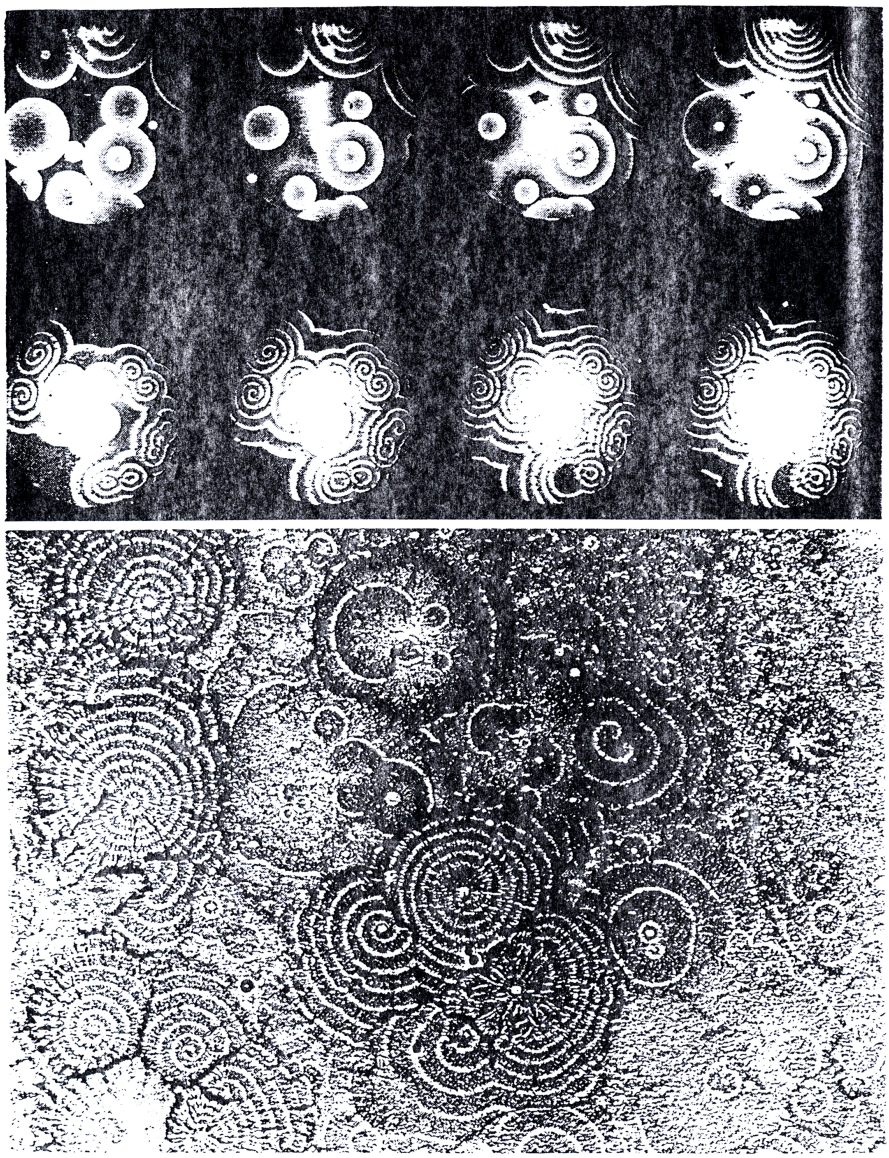


Figure 3.19: Reaction-diffusion equation

Figure 3.20: Reaction-diffusion equation

From the middle ages to the modern world means loss of notion of variance :-)

- Middle ages
  - Spatial effects were modeled by diffusion
  - This is realistic for the middle ages, traveling by carriages
  - Take snapshots at fixed time intervals $\Delta t = 1$
  - Random displacements over short distances

    $$x(t+1) = x(t) + \epsilon(t)$$

    Probabilty distribution of $\epsilon(t)$ must decay rapidly with $x \to \pm\infty$.

- With Gaussian $\epsilon(t)$ Brownian motion, i.e. diffusion, results

- Today
  - Most of us still travel slow and for short distances
  - Some travel very fast on long distances, airplanes
  - Snapshots: Random displacement over short distances and some very large jumps
  - Can not be captured by a Gaussian
  - Need "fat tailed" distributions

    Most famous example: Cauchy-distribution

$$p_{Cauchy}(x, a, \gamma) = \frac{1}{\pi} \frac{\gamma^2}{(x-a)^2 + \gamma^2}$$

  - Consider variance, 2. moment for a centralised distribution, $a = 0$

$$\sigma^2 = \int_{-\infty}^{\infty} dx\, x^2 p(x) = \frac{1}{\pi}\gamma^2 \int_{-\infty}^{\infty} dx\, \frac{x^2}{x^2 + \gamma^2} = \infty$$

    Notion of 2. moment, variance, is lost. Also no higher moments.

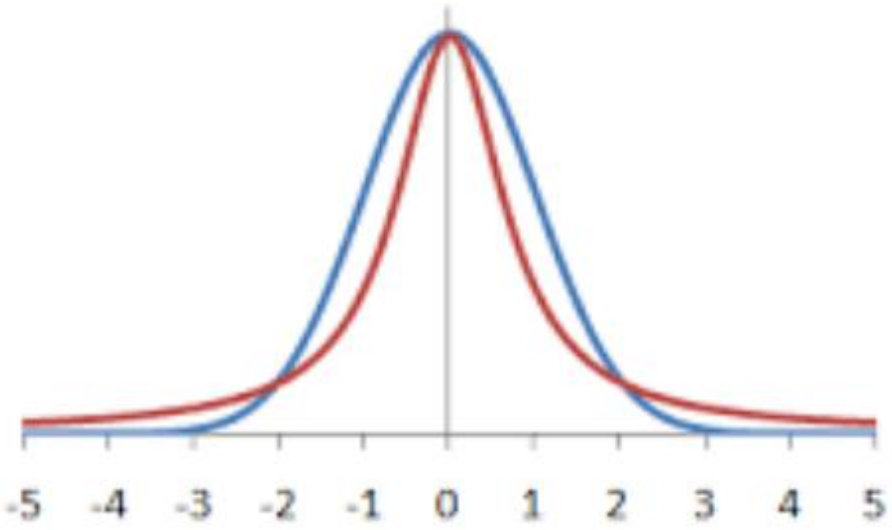
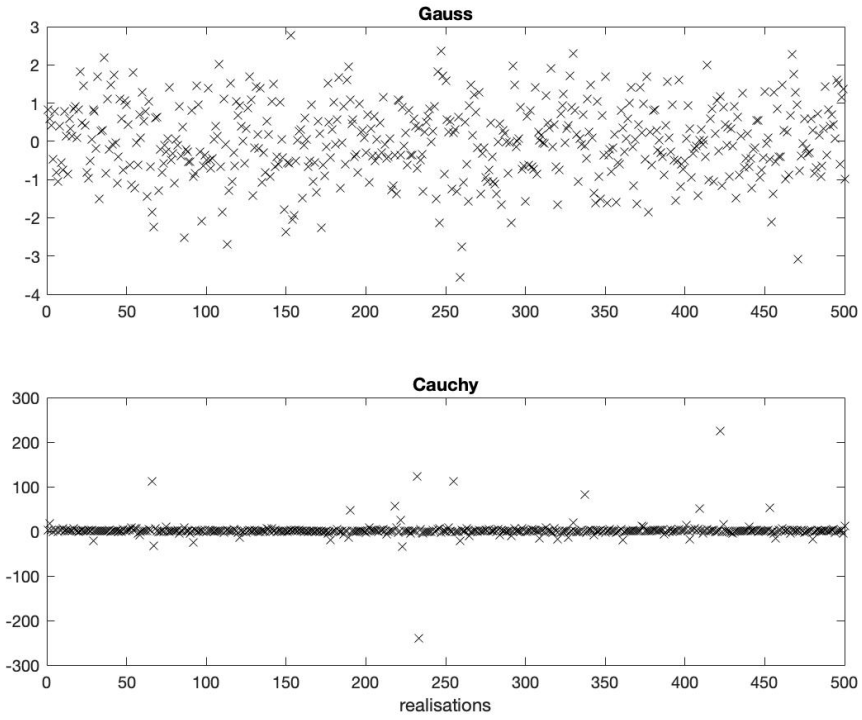
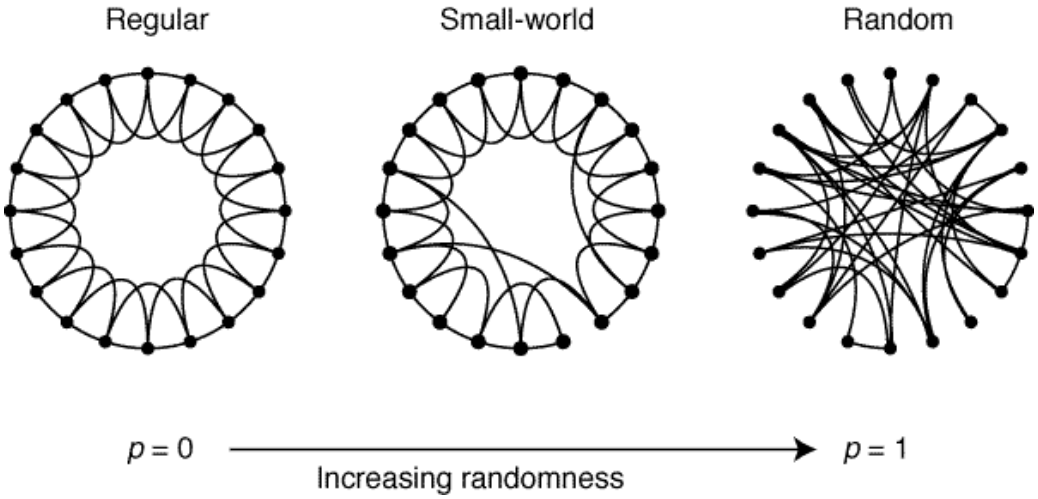


Figure 3.21: Blue: Gauss, red: Cauchy



- Current research: Infection models for small world networks



  Six degrees of separation

  – Actors

  - Letters in the US
  - Erdos numbery
  - Lewinsky number

Lessons learned:

- Logistic differential equation predicts sigmoidal dynamics for small $x(0)$
- Simple predator-prey models show oscillatory behavior
- Lotka-Volterra is conservative/Hamiltonian
  - Diverging trajectories under random pertubation
  - Scale not fixed
  - Model structure not robust
  - Saturation gives desired limit cycle
- Infections show threshold behavior for epidemics
- Epidemics end because of lack of infectious
- Considering diffusion gives infection waves

3M/20
3/17
WS 7

4 Excitable Systems

$\exists$ two types of cells

- Non-ecxitable cells: stimulus leads to monotone relaxation back to equilibrium
  Example: skin cells
- Excitable cells: (sufficient) stimulus leads to action potential
  Example: neurons

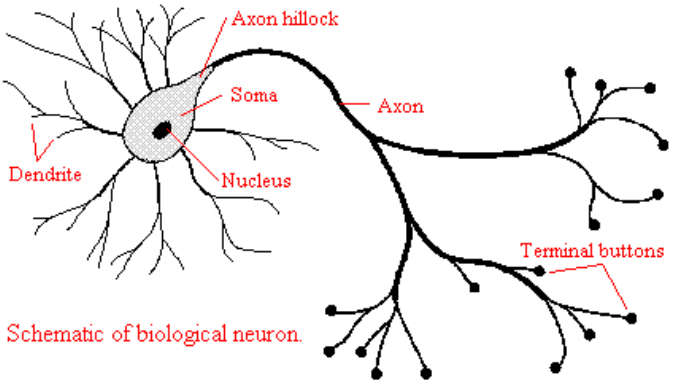


Figure 4.1: Neuron

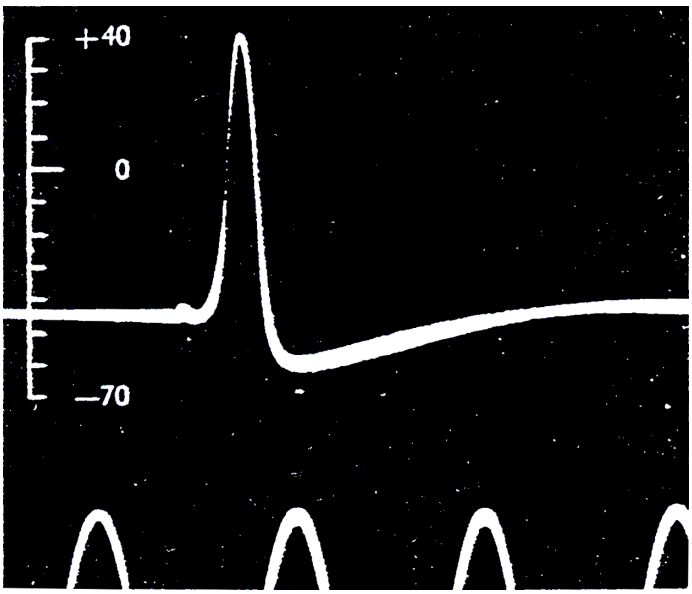


Figure 4.2: Action potential

Vivid example:
Match:

- Gently rub: Nothing happens
- Hard rub: It burns

or toilette flush :-)

Important quantity: **Nernst potential**
Effect of specifically permeable membranes:
Two Forces:

- electric, driven by energy
- osmotic, driven by entropy

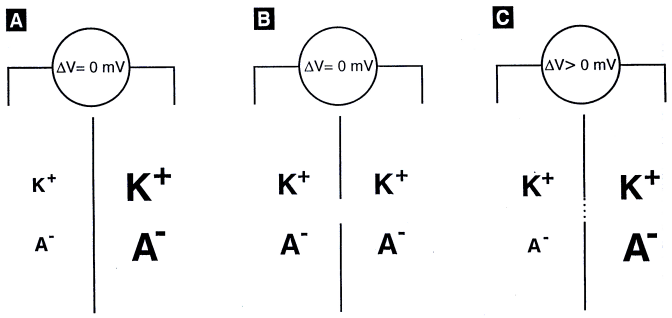


Figure 4.3: Nernst potential

Consider change of Gibb's free energy while crossing the membrane :

$$\Delta G = -kT \log \frac{[Ion]_{out}}{[Ion]_{in}} + ze\Delta V$$

In equilibrium:

$$\Delta V = V_{Nernst} = \frac{kT}{ze} \log \frac{[Ion]_{out}}{[Ion]_{in}}$$

In the case of more types of ions it becomes more complicate

Squid axon:

	Na^+	K^+
Intra cellular	50 mM	397 mM
Extra cellular	437 mM	20 mM
Nernst potential	+56 mV	-77 mV

Consequence: Currents in different directions in the range between -77 mV und $+56\,mV$

Resting potential: $-65\,mV$

4.1 Hodgkin-Huxley Model

Read the paper, please.

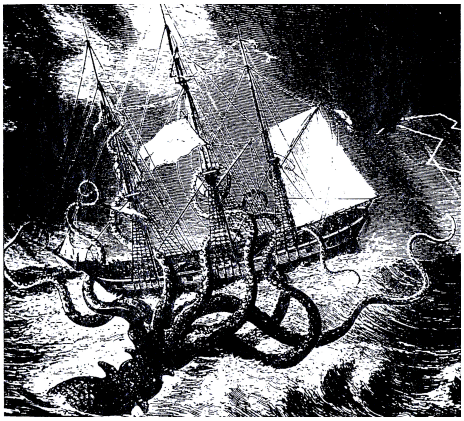


Figure 4.4: The infamous giant squid, having nothing to do with the work of Hodgkin and Huxley on the squid qiant axon

- Model very close to experimental data [39, 40]
- Data from squid axons

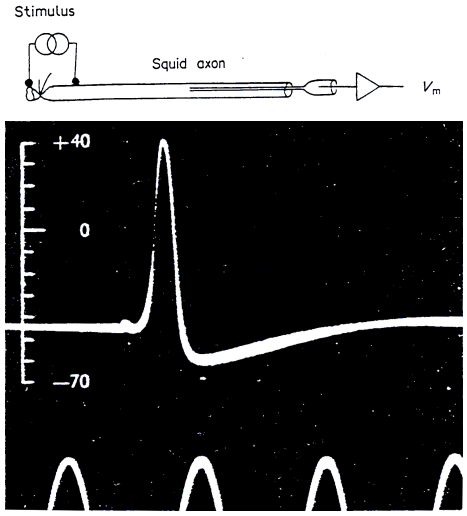


Figure 4.5: Squid axon und actions potential

- Derived without understanding of the molecular mechanism, but ingenious speculation about
- Very successful: "Most important model in all of the physiological literature"
- Nobel prize 1963

Nice summary: [89]

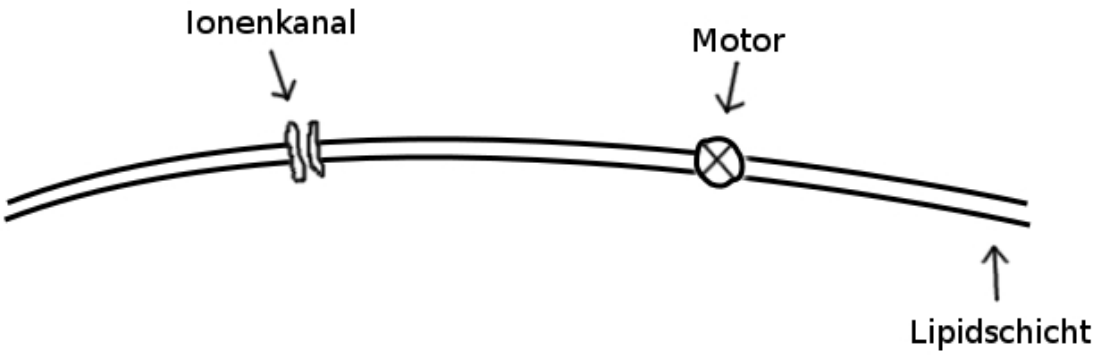


Figure 4.6: Membrane with pumps and ion channels

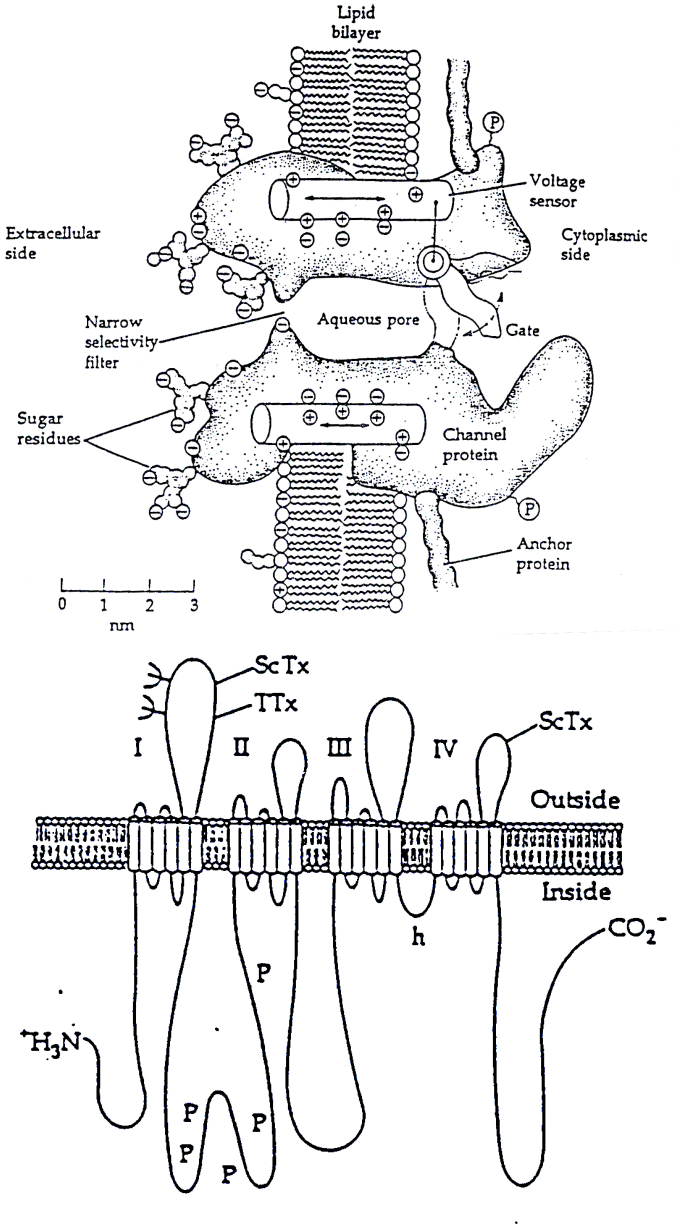


Figure 4.7: Ion channel

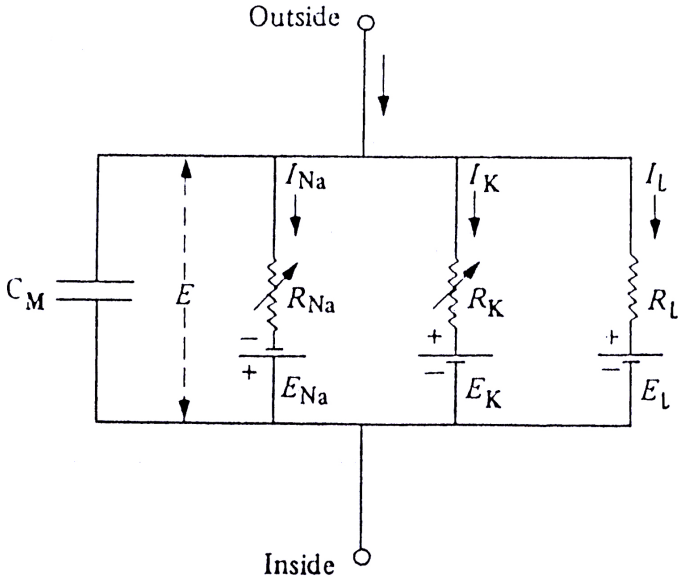


Figure 4.8: Equivalent circuit diagram

Starting point

$$C_m\dot{V} + I_{ion}(V) = 0$$

Relevant ions in squid axon:

- Na^+
- K^+
- Rest (mainly Cl^-) taken together as leackage current

Assumption $I \propto V$ yields:

$$C_m\dot{V} = -g_{Na}(V - V_{Na}) - g_K(V - V_K) - g_L(V - V_L) + I_{app}$$

with conductivities g_{Na}, g_K, g_L, und I_{app}: externally applied current

In short:

$$C_m\dot{V} = -g_{eff}(V - V_{eq}) + I_{app}$$

with

- $g_{eff} = g_{Na} + g_K + g_L$
- $V_{eq} = (g_{Na}V_{Na} + g_K V_K + g_L V_L)/g_{eff}$
- $R_m = 1/g_{eff}$ is $\approx 1000\Omega cm^2$
- Time constant: $\tau_m = C_m R_m \approx 1$ msec

Consequence:

- With constant external current I_{app}, membrane potential quickly converges to:

$$V = V_{eq} + R_m I_{app}$$

- Experimental fact: This holds for small currents I_{app} but not for sufficiently large ones.
- Ergo:
  - $I \propto V$ can not be true
  - Conductivities g must be dynamic.
  - Ingenious assumption: They dependent on V

Strategy:
Divide and conquer

- Isolate the parts, completely non-physiological
- Model them, based on completely non-physiological experiments
- Put everything together again
- Correctly describes the physiological situation

Experimental techniques

- Space-clamp

- Separate analysis of Na^+ und K^+ channels by blocking with tetrodotoxin, TTX, (Na^+) und tetrathylammonium, TEA, (K^+)
- Voltage clamp

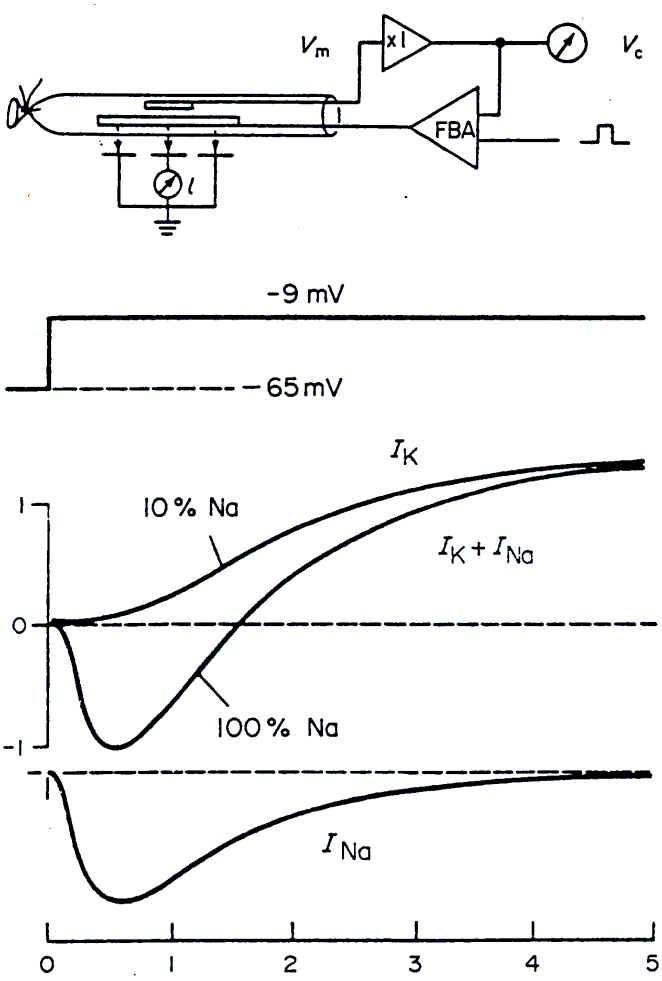


Figure 4.9: Space and voltage clamp technique

  - Control $I_{app}(t)$, such that $V = \text{const}$
  - Voltage jumps
  - $\dot{V} = 0 \Longrightarrow g_i(t)(V - V_{eq_i}) = I_{app}(t) = \text{current through membrane}$

$$g_i(t) = \frac{I_{app}(t)}{V - V_{eq_i}}$$

- Yields time dependent measurement of conductivity
- Note: Not possible *in vivo* since V varies, completely non-physiological

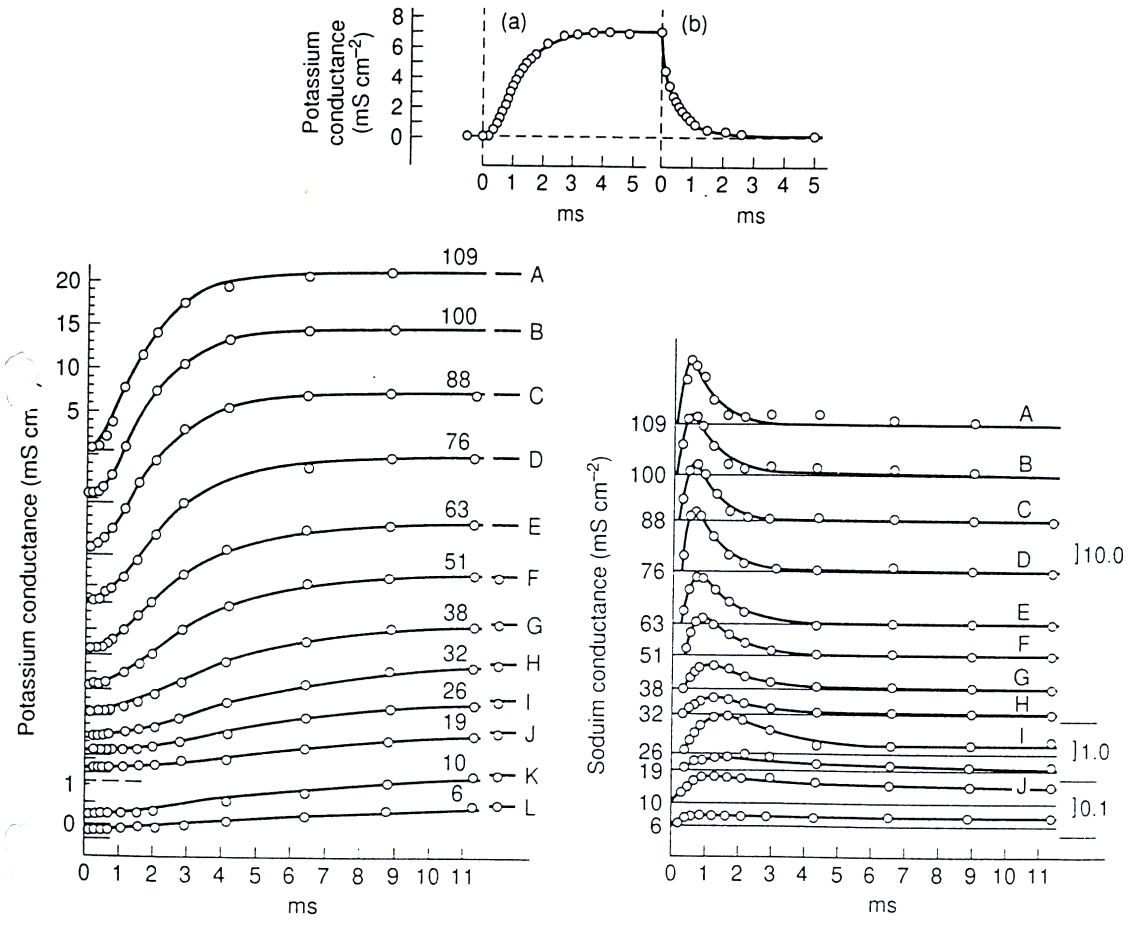


Figure 4.10: Conductances over time

Experimental result:

- g_K behaves sigmoidal for positive voltage step, without inflection point for negative steps
- g_{Na} biphasic

Ansatz:
Choose differential equation for g_K and g_{Na}

Potassium conductivity

- Sigmoidal increase: 1. order ODE
- Relaxation decrease: another 1. order ODE
- Ingenious ansatz

$$\begin{aligned} g_K &= \bar{g}_K n^4, \quad \bar{g}_K = const, \quad n \subset [0,1] \\ \dot{n} &= \alpha_n(v)(1-n) - \beta_n(v)n \end{aligned} \tag{14}$$

- Speculation by Hodgkin & Huxley: "may be given a physical basis":

  Pottasium can pass the membrane if four independent, identical entities are at a certain place ("for example inside")

  - n is the fraction "at a certain place" (open)
  - $1-n$ the rest (closed)
  - $\alpha_n(v)$ und $\beta_n(v)$ are the voltage-dependent transition rates

- Rephrase eq. (14):

$$\tau_n(v)\,\dot{n} = n_\infty(v) - n \tag{15}$$

With

$$n_\infty(v) = \frac{\alpha_n(v)}{\alpha_n(v)+\beta_n(v)} \quad \text{asymptotic state} \tag{16}$$

$$\tau_n(v) = \frac{1}{\alpha_n(v)+\beta_n(v)} \quad \text{time scale} \tag{17}$$

Proof:

$$\begin{aligned}\frac{1}{\alpha_n(v)\beta_n(v)}\,\dot{n} &= \frac{\alpha_n(v)}{\alpha_n(v)+\beta_n(v)} - n \\ \dot{n} &= \alpha_n(v) - (\alpha_n(v)+\beta_n(v))n \\ \dot{n} &= \alpha_n(v)(1-n) - \beta_n(v)n\end{aligned}$$

The other way around:

$$\alpha_n(v) = n_\infty(v)/\tau_n(v) \tag{18}$$
$$\beta_n(v) = (1-n_\infty(v))/\tau_n(v) \tag{19}$$

- Voltage steps:
  - Upwards:
    At $t=0$, step: v from 0 to v_s ($n(0)=0$)
    Solution of eq. (15) yields:

$$n(t) = n_\infty(v_s)\left[1-\exp\left(\frac{-t}{\tau_n(v_s)}\right)\right] \tag{20}$$

    * Monotonously increasing
    * Monotonously decreasing slope
    * Raise to the power of 4: $g_K(t) = \bar{g}n^4(t)$ gives sigmoidal behavior
  - Downwards from v_s to 0

$$n(t) = n_\infty(v_s)\exp\left(\frac{-t}{\tau_n(0)}\right) \tag{21}$$

    Raise to the power of 4: $g_K(t) = \bar{g}n^4(t)$ monotonously decreasing, without inflection point

- Determination of $\alpha_n(v)$ and $\beta_n(v)$:
  - For many voltage steps, fit eqs. (20, 21). Yields $n_\infty(v)$ and $\tau_n(v)$
  - With eqs. (18, 19)

$$\begin{aligned}\alpha_n(v) &= n_\infty(v)/\tau_n(v) \\ \beta_n(v) &= (1-n_\infty(v))/\tau_n(v)\end{aligned}$$

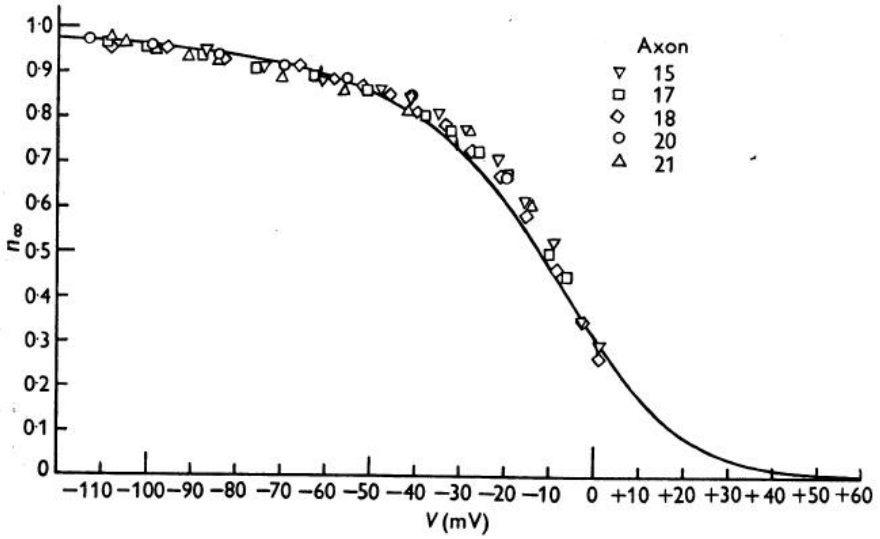


Figure 4.11: $n_\infty(v)$

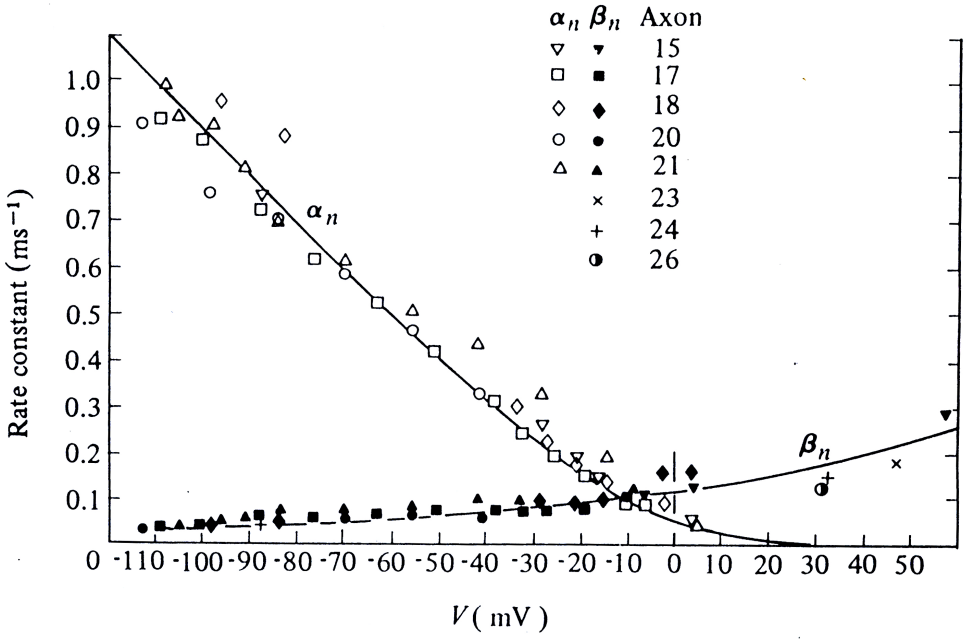


Figure 4.12: $\alpha_n(v), \beta_n(v)$

WS 8

- Non-trivial result:
  - It could have been variable between different axons
  - There could have been hysteresis
- Parameterise the result

$$\begin{aligned} \alpha_n(v) &= 0.01 \frac{10 - \nu}{\exp\left(\frac{10-\nu}{10}\right) - 1} \\ \beta_n(v) &= 0.125 \exp\left(-\frac{\nu}{80}\right) \end{aligned}$$

  - $\beta_n(v)$ purely phenomenological
  - $\alpha_n(v)$ motivated from movement of charged particles in membranes [33]

To be remembered:

- Ansatz comprises $\alpha_n(v)$, $\beta_n(v)$, i.e. voltage dependent quantities
- *In vivo*, a change of $n(t)$ results in a change of $v(t)$ and therby a change of $\alpha_n(v)$, $\beta_n(v)$
- By voltage clamp technique, $v(t)$ is fixed
- By different clamped voltages v, $\alpha_n(v)$, $\beta_n(v)$ are sampled

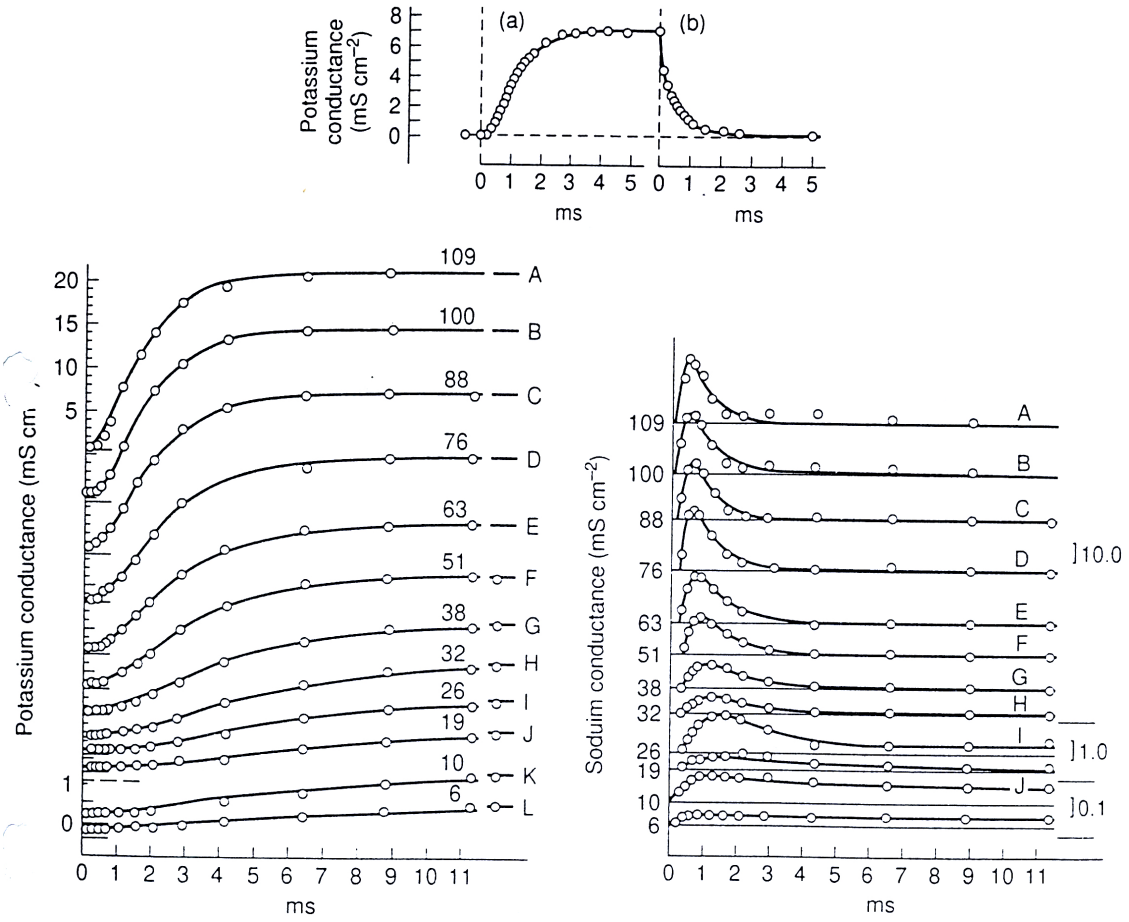


Figure 4.13: Conductivities again

Sodium conductivity

- Biphasic: at least 2. order differential equation
- Ingenious ansatz:

$$\begin{aligned} g_{Na} &= \bar{g}_{Na} m^3 h, \quad \bar{g}_{Na} = const, \quad m, h \subset [0,1] \\ \dot{m} &= \alpha_m(v)(1-m) - \beta_m(v)m \\ \dot{h} &= \alpha_h(v)(1-h) - \beta_h(v)h \end{aligned}$$

- Speculation by Hodgkin & Huxley:

– m "activating molecules", fast, open with increasing v:

$$\frac{\partial \alpha_m(v)}{\partial v} > 0 > \frac{\partial \beta_m(v)}{\partial v}$$

– h "inactivating molecules", slow, close with increasing v:

$$\frac{\partial \beta_h(v)}{\partial v} > 0 > \frac{\partial \alpha_h(v)}{\partial v}$$

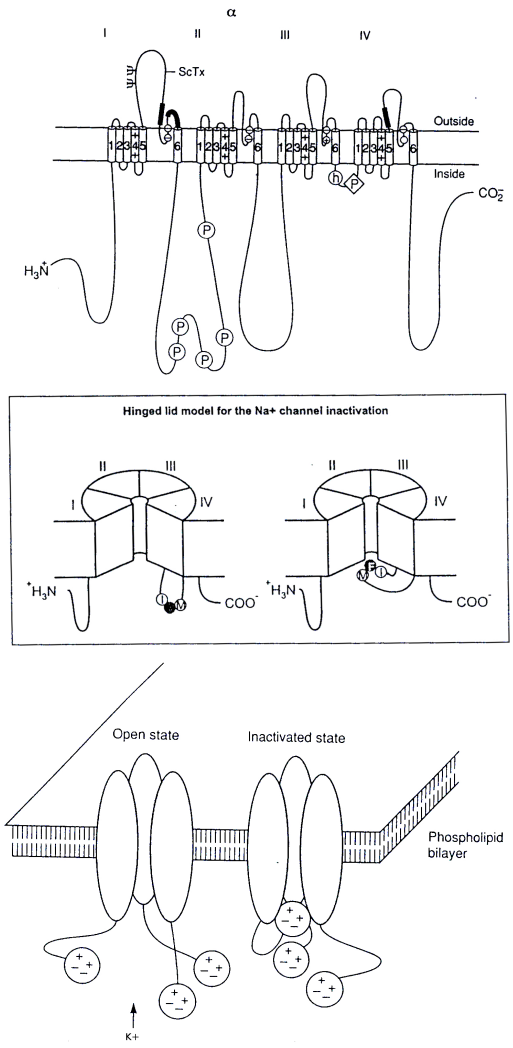


Figure 4.14: Inactivating particle

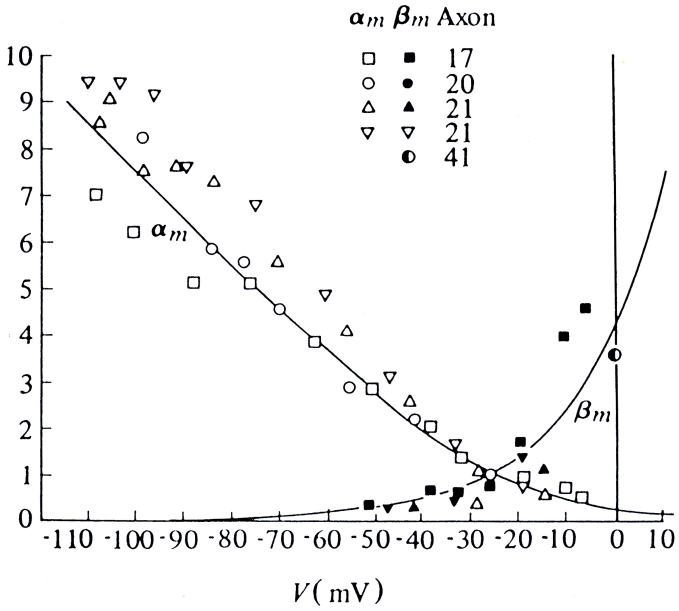


Figure 4.15: $\alpha_m(v)$, $\beta_m(v)$ curves

Central point of HH-model: Determination of $\dot{g}(v)$

Das Hodgkin-Huxley Modell:

$$
\begin{aligned}
C_m\dot{v} &= -\bar{g}_K n^4(v - v_K) - \bar{g}_{Na} m^3 h(v - v_{Na}) - g_L(v - v_L) + I_{app} \\
\dot{n} &= \alpha_n(v)(1 - n) - \beta_n(v)n \\
\dot{m} &= \alpha_m(v)(1 - m) - \beta_m(v)m \\
\dot{h} &= \alpha_h(v)(1 - h) - \beta_h(v)h
\end{aligned}
$$

with

$$\alpha_n \sim \alpha_m \sim \beta h \tag{22}$$

$$\beta_n \sim \beta_m \sim \alpha_h \tag{23}$$

$$\alpha_n = 0.01 \frac{10 - v}{\exp\left(\frac{10-v}{10}\right) - 1}$$

$$\beta_n = 0.125 \exp\left(-\frac{v}{80}\right)$$

$$\alpha_m = 0.1 \frac{25 - v}{\exp\left(\frac{25-v}{10}\right) - 1}$$

$$\beta_m = 4 \exp\left(-\frac{v}{18}\right)$$

$$\alpha_h = 0.07 \exp\left(-\frac{v}{20}\right)$$

$$\beta_h = \frac{1}{\exp\left(\frac{30-v}{10}\right) + 1}$$

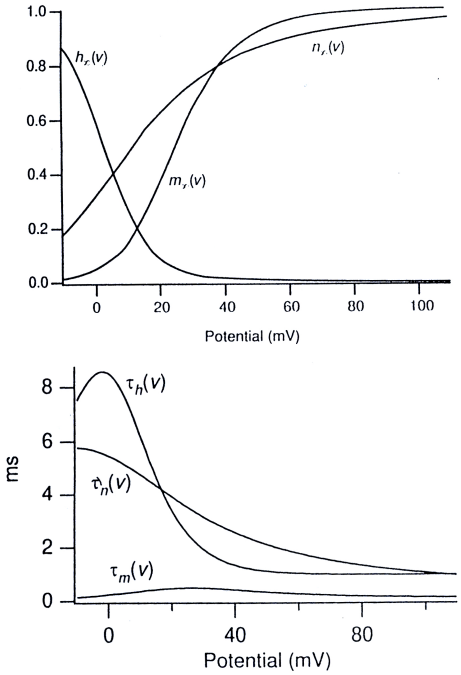


Figure 4.16: Steady state and time constants

The mechanism:

- Central: Separation of time scales : $\tau_m(v) \ll \tau_n(v), \tau_h(v)$
- Sufficiently strong stimulus (I_{app})
- Fast activation of sodium-channels (m)
- "Autocatalytic" increase of m: Inward-current of sodium, strong increase
- Little by little, inactivation of sodium channels starts (h) and activation of pottasium channels (n).
- pottasium channels: Outward-current, strong decrease and undershoot
- As soon as v at initial value, n goes to 0.

Four phases:

- Upwards (m)
- Interplay of m, h, n
- Refractory (h still small), no stimulus can reactivate, biological meaning see below
- Recovery (on the way back to initial situation), sufficiently strong stimulus can reactiviate

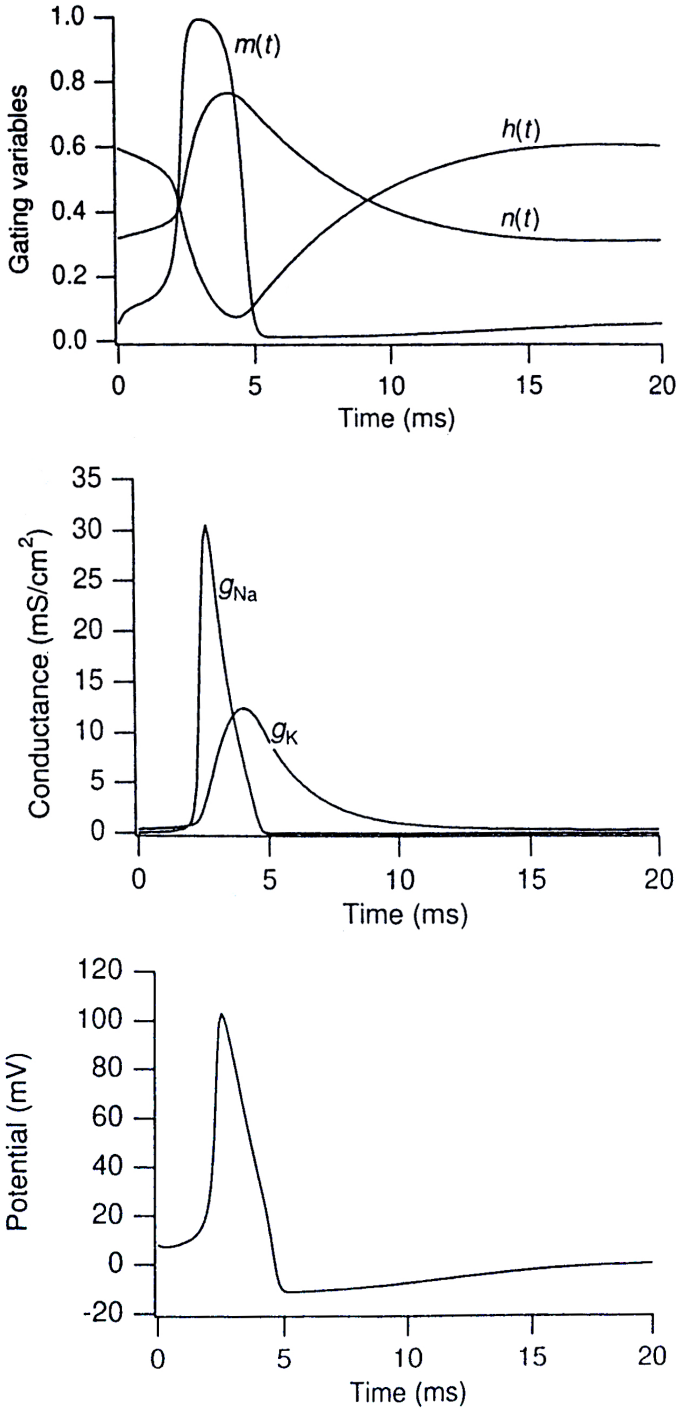


Figure 4.17: Time dependence of m, h, n, and gs and V

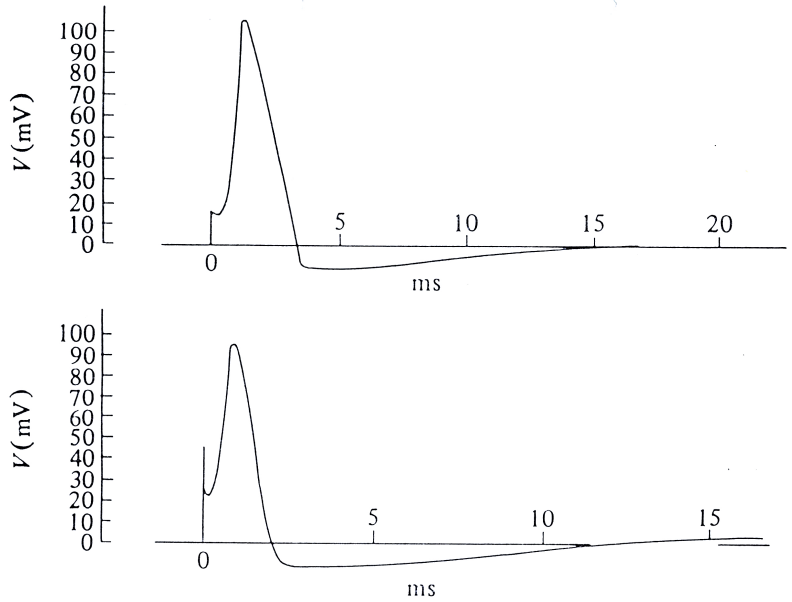


Figure 4.18: Comparison between experiment und simulation

Mechanism for continuous spiking:

- Sufficiently strong I_{app} results in restart during recovery period

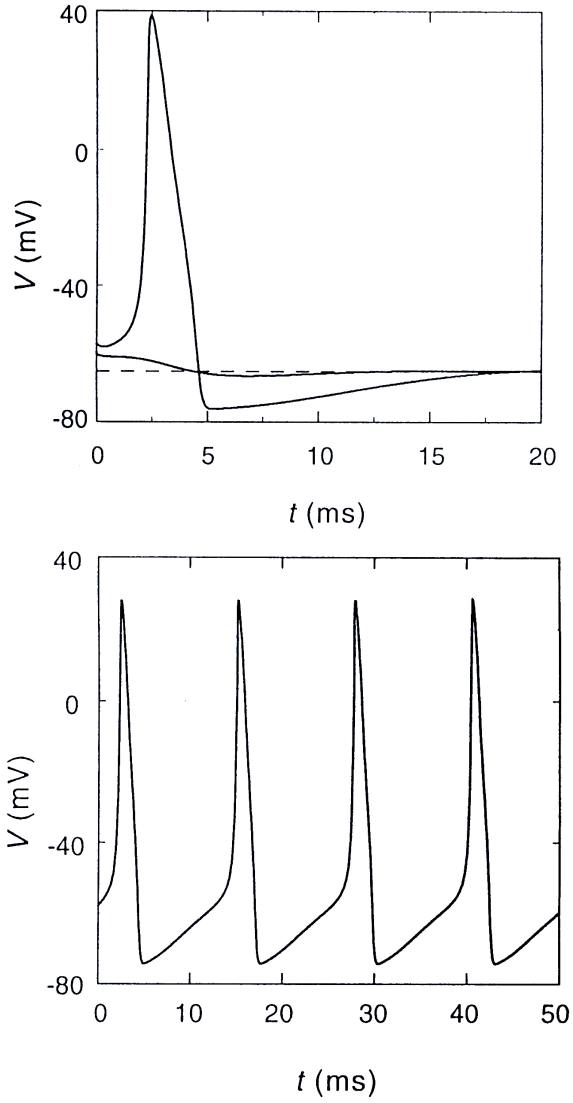


Figure 4.19: Spike train

Summary HH-model, for m & h respectively

- Input:
$$\dot{n} = f(\alpha(v), \beta(v), n) \tag{24}$$
- Result: $\dot{v} = g(n, v)$

- This in turn changes $\alpha(v), \beta(v)$ in eq. (24)
- Also predicts spreads of action potentials correctly, see below

Molecular understanding of ion channels much later, see *Nature* 2003 [46, 47]. 4/19

4.2 FitzHugh-Nagumo Model

- Simplyfied HH-model for sodium channels
- Including the blocking mechanism
- Clearly pointing to the mechanism [26, 77]

"Model of a model"

- v potential, scaled to $v = 0$: rest potential
- $v = a$ potential, above which the neuron fires.
- $v = 1$ potential, at which all sodium channels are open
- The model:
$$\dot{v} = v(a - v)(v - 1)$$
does the job
  - $v = 0$ stable fixed point
  - $v = a$ unstable fixed point
  - $v = 1$ stable fixed point

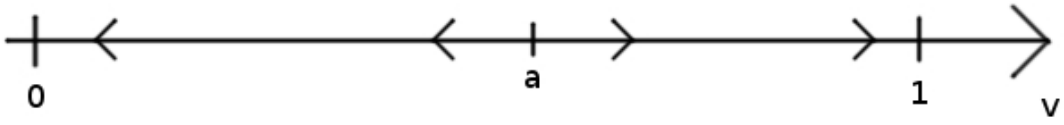


Figure 4.20: v-behavior

  - For $0 < v < a$, v goes back to $v = 0$

  - For $a < v < 1$, v goes to $v = 1$ and stops

  One needs a blocking mechanism w.

  - No blocking, if $v = 0$
  - Increasing blocking if $v \to 1$

- The model:

$$\dot{w} = \epsilon(v - \gamma w)$$

  Stable points

  - w fix: $w = v/\gamma$
  - $v = 0$ $w = 0$
  - $v = 1$ $w = 1/\gamma$

- ϵ determines convergence velocity towards stable points

  For small ϵ, process is slow.

- Effect of blocking on v : $\dot{v} = -w$

The FitzHugh-Nagumo model:

$$\begin{aligned} \dot{v} &= v(a - v)(v - 1) - w \ + I_{app} \\ \dot{w} &= \epsilon(v - \gamma w) \end{aligned}$$

Cubic form of rhs. motivated by HH-equations

Phase space behavior, part II after fixed point behavior:

- Null cline: Curve in phase space with $\dot{x} = 0$

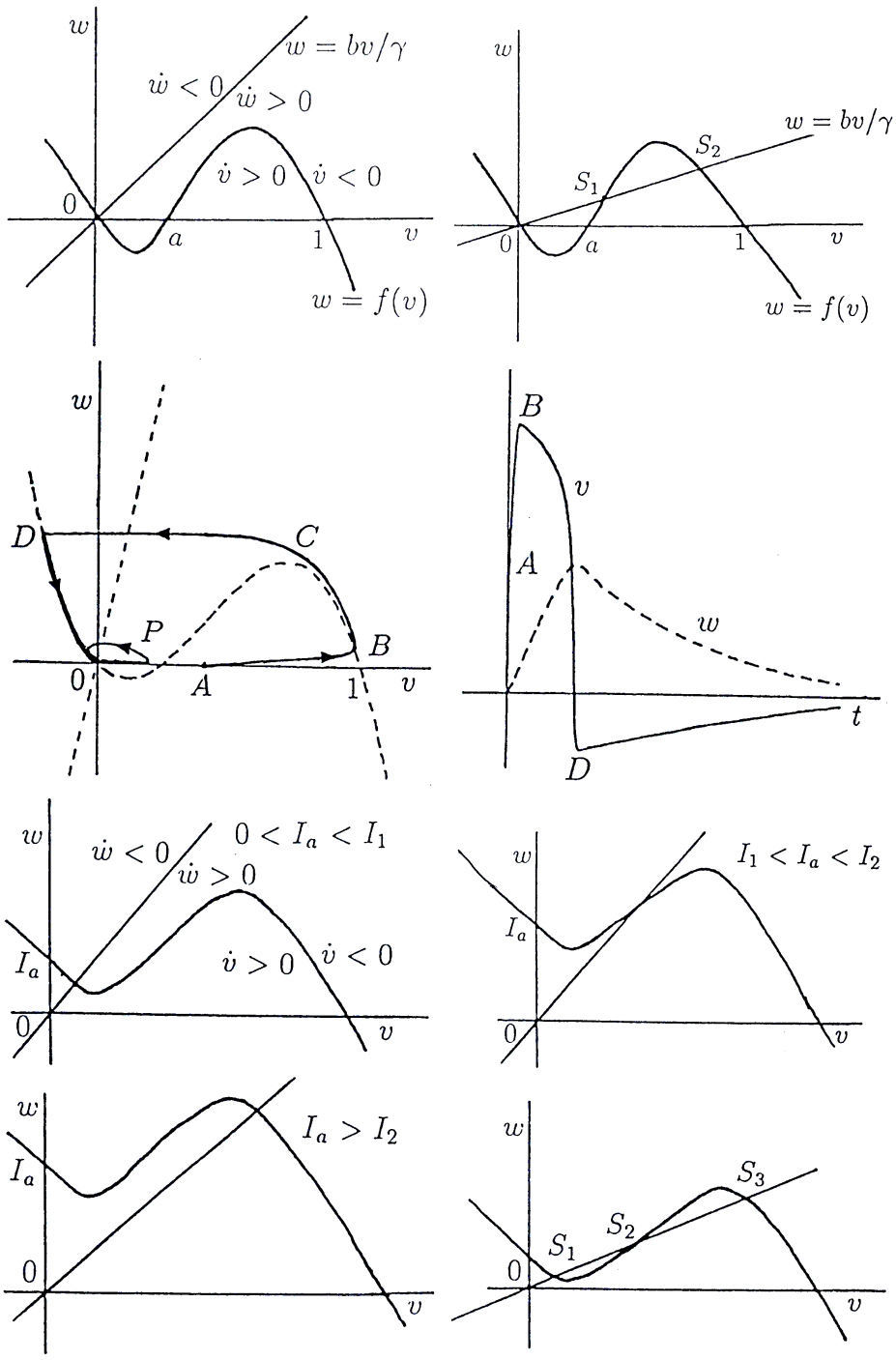


Figure 4.21: Behaviour in phase space

- Subthreshold
- Suprathreshold
- Periodic firing

4.3 Hindmarsh-Rose Model

- Often observed: Bursting behavior, i.e. grouping of action potential spikes
- This can be reproduced by Hindmarsh-Rose model, 1984 [38]

$$\begin{aligned} \dot{x} &= y + ax^2 - bx^3 - z + I_{app} && \text{fast sodium} \\ \dot{y} &= c - dx^2 - y && \text{fast pottasium} \\ \dot{z} &= r(s(x - x_r) - z) && \text{slow rest} \end{aligned}$$

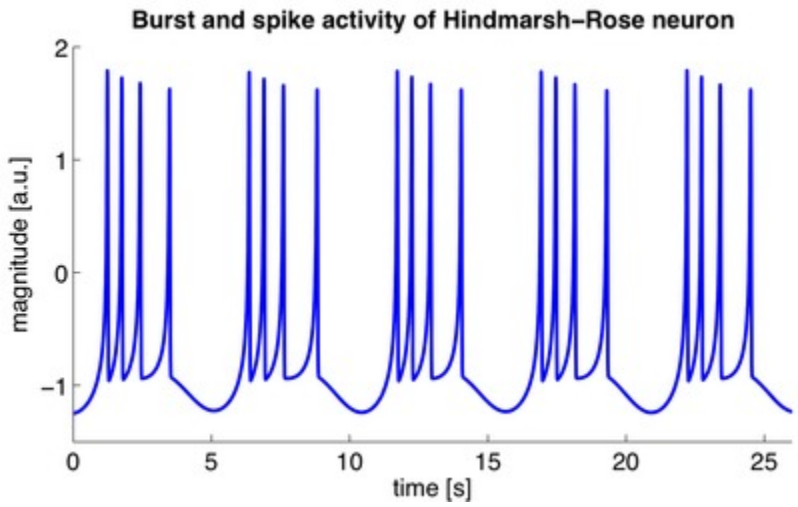


Figure 4.22: Neural bursting in HR model

- For certain parameters, HR-models exhibits chaotic behavior, i.e. sensitivity to initial conditions.
- THE toy model for chaotic neural dynamics.

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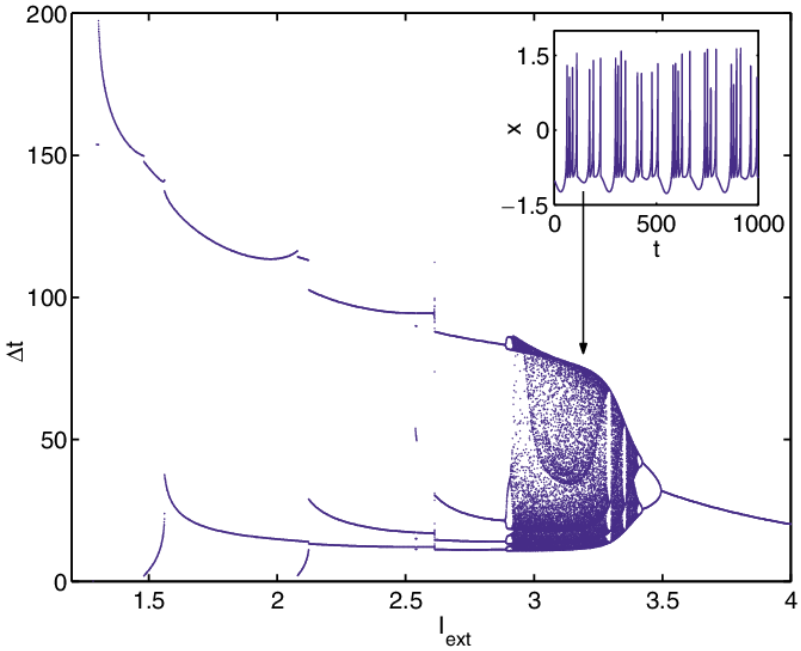

Figure 4.22: Chaos in HR-model

4.4 Spread of action potentials

Similar to infection models, HH, FH & HR can be formulate spatially.

Here for HH

- Remove space clamp
- Cable-Equation
  - Describes poorly isolated (transatlantic telegraph) cables
  - Lord Kelvin, 1855, formerly William Thomson
  - Based on Kirchoff's law

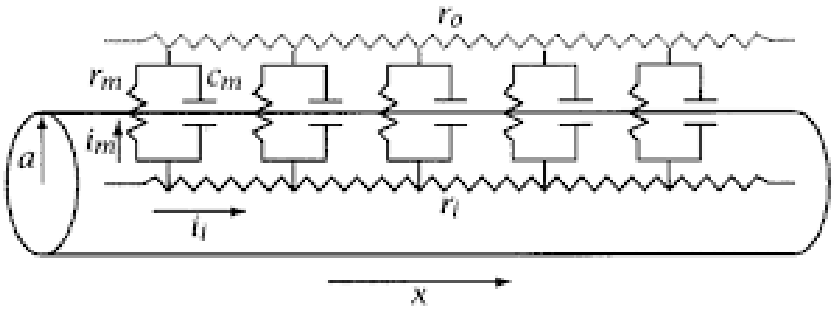

Figure 4.6 Diagram for current flow in a uniform cylinder such as an axon or segment of dendrite.

  - a radius, R resistance of poor isolation
    x: along the cable, I current across the isolation

$$I(x) = \frac{a}{2R}\frac{\partial^2}{\partial x^2}V(x)$$

    Here: open ion channels are the poor isolation

- Yields

$$C_m\dot{v} = \frac{a}{2R}\frac{\partial^2}{\partial x^2}v - \bar{g}_K n^4(v - v_K) - \bar{g}_{Na}m^3h(v - v_{Na}) - g_L(v - v_L) + I_{app}$$

  a partial differential equation.

- As for SIR model assuption; $v(x,t) = v(z)$ mit $z = x - ct$

- Result:

$$\frac{\partial^2 v}{\partial x^2} = \frac{1}{c^2}\frac{\partial^2 v}{\partial t^2}$$

- ODE with wave solution = Spread of action potentials

Big picture

- Function of the refractory period: Action potentials must not propagate backwards
- Remember: Epidemic wave can not propagate backwards due to lack of infectious & susceptibles, $R_0 < 1$ in the back of the infection
- For action potentials due to lack of activatable neurons, since refractory

Important:

- Spread of action potential is <u>not</u> driven by potential difference between the beginning and the end of the axon.
- No electrical current flows along the axon, but potential differences between inside and outside of the axon
- There is no $R = U/I \Longrightarrow$, no heat dissipation by R
- Dissipation of the brain: 60 W.
- Difference to computer where dissipative heating is a major challenge

Lessons learned

- HH model derived from non-physiological experiments
  - Separate analysis of sodium and pottasium channels
  - Space clamp technique
  - Voltage clamp technique
  - Voltage step experiments
- Desribes very accurately action potentials of neurons
- Hodgkin-Huxley Modell is one of the highlights of mathematical biology
- Developed very close to data
- FithHugh-Nagumo model nails down the mechanism
- Hindmarsh-Rose model describes bursting and chaotic behavior

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5 Pattern Formation

5.1 Turing Mechanisms

Nice summary [75]
Motivating example :

- How the leopard got his spots?

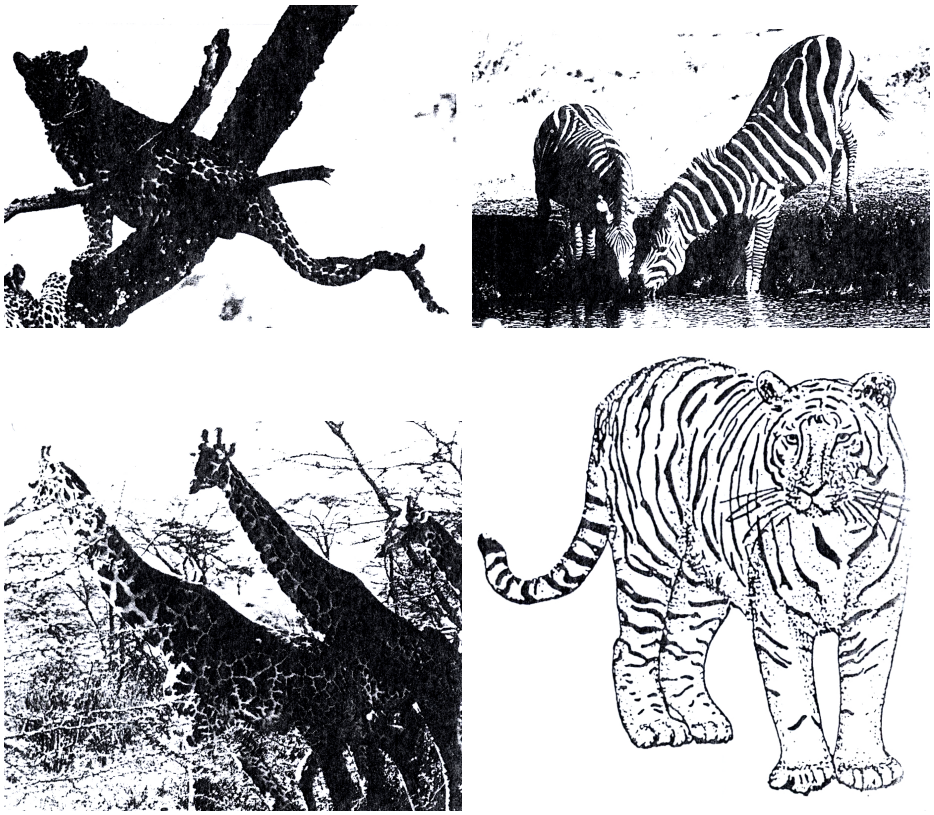

Figure 5.1: Leopard, zebra, giraffe, lion fur

- Remember: We only have 23.000 genes: pattern can not be encoded genetically
- Mathematically:

  Wave phenomenon in literal sense, not edge as in SIR models

1952: Turing's developmental biology pattern formation theory [108]

- Not a data-based model
- General principle
- Biological realisation was long debated, first convincing example 2006: [101]

Central: "Morphogene"

- Morpho = Morphology
- Rough idea: Two catalysts, enzymes, that can diffuse and react
- "Activator" stimulates spots
- "Inhibitor" suppresses spots
- Dynamics of activator and inhibitor forms "prepattern"
- Depending on their local concentration the cells latter differentiate specifically
- Process takes place during certain period of embryogenesis

Illustration [74] :

- Consider a dry forest
- Randomly distributed fire fighters with helicopters
- Randomly distributed little fires (activator) which grow slowly (diffusion)
- Fire fighters (inhibitor) diffuse fast with helicopters and extinguish fires
- Result: Patches of burned and green forest: A pattern
- Does only work if inhibitor diffuses faster than activator

5.1.1 Theory

The model with $c_i = c_i(x, y, t) \in R^+$ $[Mol/m^2]$ in area B:

$$\begin{aligned} \dot{c}_1 &= f(c_1, c_2) + D_1 \nabla^2 c_1 \quad \text{activator} \\ \dot{c}_2 &= g(c_1, c_2) + D_2 \nabla^2 c_2 \quad \text{inhibitor} \end{aligned}$$

By this model, Turing invented reaction-diffusion systems in 1952.

Dimensionless version:

- Characteristic scales:
  - L: spatial scale of B
  - T: temporal scale of the reactions
- With
  - $\gamma = L^2/D_1 T$
    describes ratio of reaction and diffusion effects
    Remember $[D] = m^2/s$
  - $d = D_2/D_1$

$$\begin{aligned} \dot{u} &= \gamma f(u, v) + \nabla^2 u \\ \dot{v} &= \gamma g(u, v) + d\, \nabla^2 v \end{aligned}$$

Boundary conditions at ∂B with $\vec{n}$ outwards normal vector

$$\text{zero flux} : (\vec{n}\vec{\nabla})u = (\vec{n}\vec{\nabla})v = 0$$

Meaning: Massive walls, no influences from outside, no escape from the inside

Conditions for the Turing mechanism:

[1.] $\exists$ spatially homogeneous stationary state (u_0, v_0) as positive solution of $f(u_0, v_0) = g(u_0, v_0) = 0$

[2.] (u_0, v_0) is stable in the absense of diffusion

[3.] (u_0, v_0) gets unstable under diffusion

If one of the conditions is not fulfilled the process does not follow the Turing mechanism

To be noted

- Condition [3.] is the basis for the final pattern
- In [2.] & [3.] linear (un)stability analysis will be employed
- Cool idea: Typically, diffusion destroys patterns, here it creates them
- If a partial differential equation does not fulfill the conditions it can still be a cool PDE, possibly also produce patterns. But not by the Turing mechanism
- Initially not clear whether Turing mechanism can be realised by any biological process.

Therefore:

The Turing analysis

Given a concrete system with spezified $f(u,v)$, $g(u,v)$ and d
$f(u,v)$ and $g(u,v)$ might be parametrised:

$$f(u,v) = f(u,v,p_f), \qquad g(u,v) = g(u,v,p_g) \qquad \text{see Chap. 5.1.2}$$

[1.]

- Determine spatially homogeneous stationary state (u_0, v_0) as solution of the algebraic equations $f(u_0, v_0) = g(u_0, v_0) = 0$.
- If no positive solution exists, system is out of the race to produce a Turing pattern
- If a positive solution exists, go to [2.]

[2.]

Without diffusion, the systems reads

$$\dot{u} = \gamma f(u,v), \quad \dot{v} = \gamma g(u,v)$$

Consider stability:

- Linearise at stationary state (u_0, v_0) with:

$$\vec{w} = \begin{pmatrix} u - u_0 \\ v - v_0 \end{pmatrix} \Longrightarrow \dot{w} = \gamma A w, \text{ with } A = \begin{pmatrix} f_u & f_v \\ g_u & g_v \end{pmatrix}\Big|_{u_0,v_0}$$

Linear system: $\Longrightarrow w \propto e^{\lambda t}$

$$\lambda_{1,2} \text{ from } |\gamma A - \lambda \mathbb{1}| = 0$$

- Yields:

$$\lambda_{1,2} = \frac{1}{2}\gamma \left[(f_u + g_v) \pm \sqrt{(f_u + g_v)^2 - 4(f_u g_v - f_v g_u)} \right]$$

Stable if $Re(\lambda_{1,2}) < 0$, thus:

$$f_u + g_v = tr\, A < 0, \quad f_u g_v - f_v g_u = |A| > 0 \qquad (25)$$

Meaning:

Gives restrictions on possible models and their parameters

- If eqs. (25) hold, go to [3.]

[3.]

- Switch diffusion on:

$$\dot{w} = \gamma A w + D\nabla^2 w, \quad D = \begin{pmatrix} 1 & 0 \\ 0 & d \end{pmatrix} \qquad (26)$$

  - Consider time-independent solution of the spatial eigenvalue problem:

$$\nabla^2 W(r) + k^2 W(r) = 0 \qquad (27)$$

  - Note: In 1D for interval [0,a] :

$$W(x) \propto \cos(n\pi x/a) \text{ with } n \in \mathbb{N}, \text{ fulfills zero flux condition}$$

Eigenvalue $k = n\pi/a$ is called wave number, $1/k \propto$ wavelength

– **Separation ansatz**

$$w(r,t) = \sum_k c_k e^{\lambda_k t} W_k(r), \quad c_k \text{ from initial state } w(r,0)$$

Insert in eq. (26), cancel down $e^{\lambda_k t}$ and c_k.
For each k, since W_ks orthogonal, it holds :

$$\lambda(k) W_k = \gamma A W_k + D\nabla^2 W_k$$

With eq. (27)

$$\lambda(k) W_k = \gamma A W_k - D k^2 W_k$$

– Determine $\lambda_{1,2}(k)$ from

$$|\lambda \mathbb{1} - \gamma A + D k^2| = 0$$

Yields:

$$\lambda^2 + \lambda[k^2(1+d) - \gamma(f_u + g_v)] + h(k^2) = 0 \tag{28}$$

with

$$h(k^2) = dk^4 - \gamma(df_u + g_v)k^2 + \gamma^2|A|$$

– Solutions unstable, if $Re(\lambda)$ from eq. (28) > 0.

- **Conditions for pattern formation**

  – Unstability under diffusion needs $Re(\lambda(k)) > 0$, for some $k \neq 0$.
  2 possibilities:
  1: $[k^2(1+d) - \gamma(f_u + g_v)] < 0$
  2: $h(k^2) < 0$

  – Since from eq. (25) $(f_u + g_v) < 0$ and $k^2(1+d) > 0 \ \forall \ k \neq 0$ anyway, possibility 1 drops out

  Thus

$$h(k^2) = dk^4 - \gamma(df_u + g_v)k^2 + \gamma^2|A| < 0$$

From eq. (25): $|A| > 0$, ergo: only chance to become negative :

$$\boxed{\begin{aligned} d\, f_u + g_v &> 0 \\ \Longrightarrow d &\neq 1, \text{ since } f_u + g_v < 0 \end{aligned}} \tag{29}$$

Consequence: f_u and g_v have different signs

– Realistic models: $f_u > 0$, since activator activates itself autocatalytically, remember the fire.

Consequence: $g_v < 0 \Longrightarrow$

$$\boxed{d > 1 : D_2 > D_1}$$

– Eq. (29) is necessary, but not sufficient
Minimum of $h(k^2)$:

$$h_{\min} = \gamma^2 \left[|A| - \frac{(d\, f_u + g_v)^2}{4d} \right], \quad k^2_{min} = \gamma \frac{(d\, f_u + g_v)}{2d} \tag{30}$$

Thus $h(k^2) < 0$, if:

$$\boxed{\frac{(d\, f_u + g_v)^2}{4d} > |A|}$$

At the critical point, bifurcation, qualitative change of behavior:

- At the bifurcation:

$$|A| = \frac{(d\, f_u + g_v)^2}{4d}$$

- Fixes critical ratio of diffusion coefficients d_c (> 1):

$$|A| = f_u g_v - f_v g_u = \frac{(d_c\, f_u + g_v)^2}{4 d_c}$$

- critical wave number by eq. (30):

$$k_c^2 = \gamma \frac{(d_c f_u + g_v)}{2d_c} = \gamma \sqrt{\frac{|A|}{d_c}} \tag{31}$$

k-range of unstable modes

- When ever $h(k^2) < 0$ the respektive mode are unstable:
- for $d > d_c$ roots k_1^2, k_2^2
- Unstable for $k \in [k_1^2 : k_2^2]$

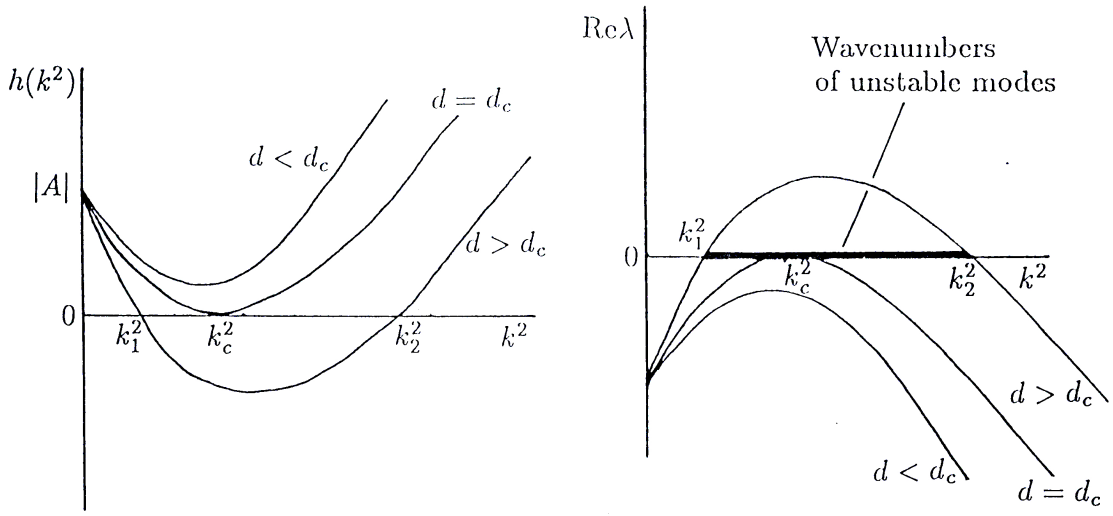

Figure 5.2: The dispersion relation

About dispersion relations

- "Classical" case: $\omega(k)$. Light in vacuum $\omega = ck$, wave packages are stable
  If relation is not linear, wave packages disperse
  ω: time, k: space
- Remember classical mechanics, Noether theorem

  - Time (invariance) and energy are coupled
  - Spatial (invariance) and momentum are coupled

- Remember quantum mechanics I: uncertainty relation
  - $\Delta E\,\Delta t \geq \hbar/2$: Time and energy are coupled
  - $\Delta x\,\Delta p \geq \hbar/2$: Space and momentum are coupled
- Remember quantum mechanics II: Einstein and de Broglie
  - $E = \hbar\omega$: Time and energy are coupled
  - $p = \hbar k$: Space and momentum are coupled
- In general: Products with the unit of action are coupled. Action is the only non-intuitive unit in classical mechanics :-)
- Thus also $E(p)$ is called a dispersion relation
- Here: $Re(\lambda)(k)$ describes temporal evolution for given wave number

Note:

- $h(0) = |A| > 0$, corresponds to condition [2.]
- Unstable range of k does not start at $k = 0$ and does not go to $k = \infty$. Only this can give a "pattern"
- Pattern not strictly periodic since many k^2s$\in [k_1^2 : k_2^2]$ contribute
- Initial conditions: Random spatial fluctuations.

  They determine c_ks in separation ansatz for $w(r,t)$

  $\Longrightarrow$ All furs of one species share the same over all characteristics but look different in the details

5. half week/17

Summary of the requirements on $f(u,v,p_f)$, $g(u,v,p_g)$ and d:

$f_u + g_v < 0,$	$f_u g_v - f_v g_u > 0$	from stability without diffusion
$d\,f_u + g_v > 0$	$(d\,f_u + g_v)^2 > 4d\,\lvert A\rvert$	from unstability with diffusion

End of Turing analysis

So far linear first order approximation

- Linear approximation: For $Re(\lambda(k)) > 0$ exponential increase
- Solution will leave range where linear approximation holds
- Non-linear effects take over and freeze the pattern ... or ...
- ... stops, when "certain period in embryogenensis" is over
- Remark: Consider imaginary part of λ:
  If $Im(\lambda(k)) \neq 0 \Longrightarrow$ temporal oscillations

Typically, diffusion acts stabilising, since smearing out
Turing shows:

- If for $D_1 = D_2 = 0$ the system shows to a spatially homogeneous stable fixed point ...
- ... then diffusion with $D_1 < D_2$ can lead to spatially inhomogeneous patterns
- Short range activation, long range inhibition, serves for patterns in the medium range of wave numbers
  Remember the fire fighters
- Diffusion-driven unstability: Turing unstability
  Small spatial disturbances grow to patterns
- Symmetry break of the translation/rotation invariance of the stable homogeneous solution under conditions [2.] & [3.]
- Other mechanims for pattern formation in PDEs, especially complex Ginzburg-Landau equation[3] :

$$\dot{A} = A - (1 - ib)|A|^2 A + (1 + ia)\nabla^2 A$$

  - Eckhaus Unstability

[3]Not to be confused with the Ginzburg-Landau theory of phase transitions, superconductivity

– ZigZag Unstability

– Benjamin-Feir Unstability

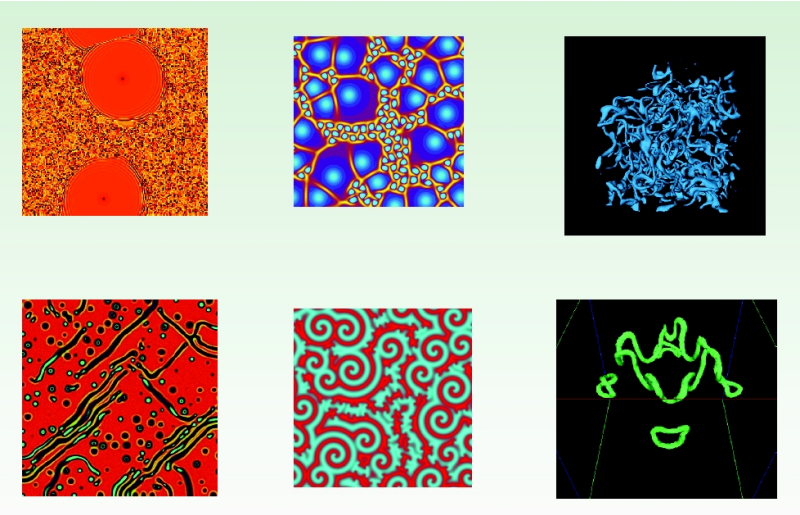

Figure 5.3: Complex Ginzburg-Laundau equation

To be remembered:
Fundamental difference between the Hodgkin-Huxley and the Turing strategy.
For discussion HH vs. Turing modelling strategy, see [116]

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5.1.2 Example for Turing Analysis

Toy model, Schnackenberg, 1973 [92]
1D:

$$\begin{aligned} \dot{u} &= \gamma f(u,v,p_f) + u_{xx} = \gamma(a - u + u^2 v) + u_{xx} \\ \dot{v} &= \gamma g(u,v,p_g) + d v_{xx} = \gamma(b - u^2 v) + d v_{xx} \end{aligned}$$

[1.] Does homogeneous positive stationary state exist ?

$$\begin{aligned} 0 &= a - u + u^2 v \\ 0 &= b - u^2 v \end{aligned}$$

Yields:

$$u_0 = a + b, \quad v_0 = \frac{b}{(a+b)^2}, \quad b > 0, a + b > 0$$

Constraints on the parameters

At the stationary state

$$f_u \Big|_{(u_0,v_0)} = -1+2u_0v_0 = -1+2(a+b)\frac{b}{(a+b)^2} = -1+\frac{2b}{a+b} = -\frac{a+b}{a+b}+\frac{2b}{a+b} = \frac{b-a}{a+b}$$

$$f_v \Big|_{(u_0,v_0)} = (a+b)^2 > 0, \quad g_u \Big|_{(u_0,v_0)} = \frac{-2b}{a+b} < 0, \quad g_v \Big|_{(u_0,v_0)} = -(a+b)^2 < 0$$

Because of the necessity of different signs of f_u and g_v, it follows $b > a$

[2.] Stable without diffusion ?

Conditions on $f(u, v)$ and $g(u, v)$ require

$$\begin{aligned} f_u + g_v < 0 &\implies (a+b)^3 > b - a \\ f_u g_v - f_v g_u > 0 &\implies (a+b)^2 > 0 \end{aligned}$$

[3.] Unstable with diffusion ?

Conditions on $f(u, v)$ and $g(u, v)$ require

$$\begin{aligned} df_u + g_v > 0 &\implies d(b-a) > (a+b)^3 \\ (df_u + g_v)^2 - 4d(f_u g_v - f_v g_u) > 0 &\implies [d(b-a) - (a+b)^3]^2 > 4d(a+b)^4 \end{aligned}$$

This fixes the Turing space of admissible parameters for Turing mechanism/pattern.

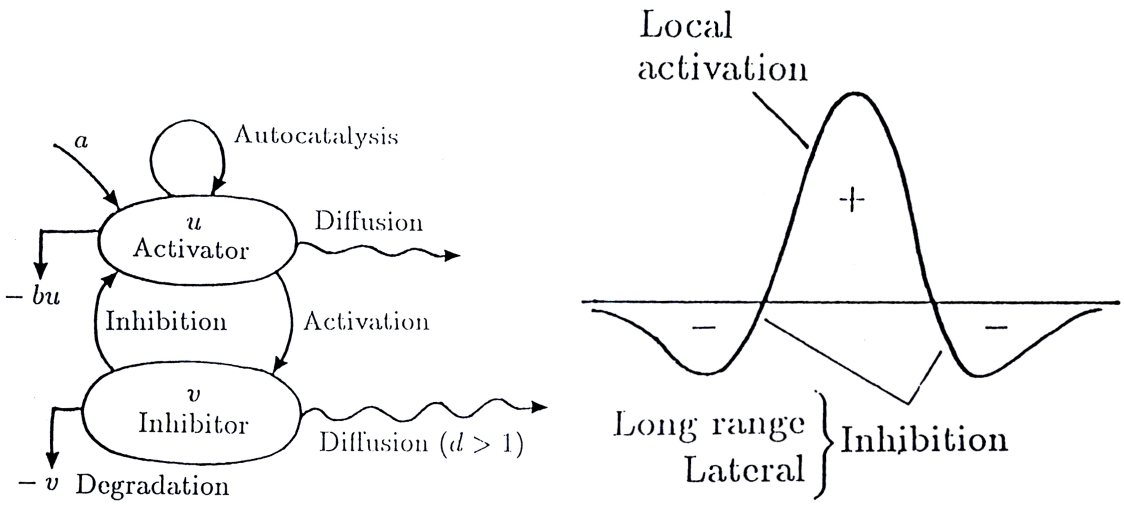


Figure 5.4: Short-range activation, long range inhibition

5.1.3 Gierer-Meinhardt Models

- Concrete example in Turing 1952 was unbiological und non-intiutive

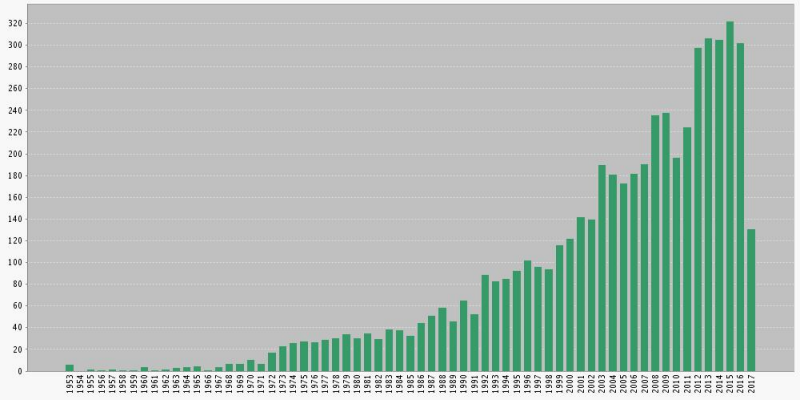


Figure 5.5: References to Turing 1952 paper, a sleeping beauty

- Gierer-Meinhardt models, 1972 [29, 68]: A step towards biology and intuition
- 2 classes of models/mechanisms

Remember, from condition [2.]

$$f_u > 0, \quad g_v < 0, \quad f_u g_v - f_v g_u > 0$$

Ergo:

Either

(i.) $f_v < 0$ and $g_u > 0$

or

(ii.) $f_v > 0$ and $g_u < 0$

(i) Activator-Inhibitor System

$$\begin{aligned} \dot{u} &= \sigma_u + \rho_u \frac{u^2}{(1+\kappa_a u^2)v} - \mu_u u + D_u \nabla^2 u \\ \dot{v} &= \sigma_v + \rho_v u^2 - \mu_v v + D_v \nabla^2 v \end{aligned}$$

Check for $f_v < 0$ and $g_u > 0$

$$\begin{aligned} f_v \Big|_{(u_0,v_0)} &= -\rho_u \frac{u_0^2}{(1+\kappa_a u_0^2)v_0^2} < 0 \\ g_u \Big|_{(u_0,v_0)} &= 2\rho_v u > 0 \end{aligned}$$

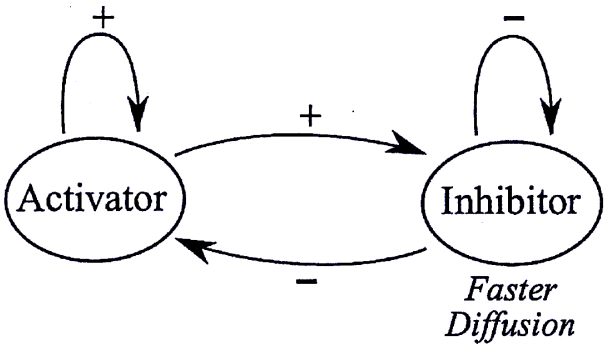


Figure 5.6: Activator-inhibitor system

(ii) Activator-Substrate System

$$\begin{aligned} \dot{u} &= \sigma_u + \rho_u \frac{u^2 v}{1 + \kappa_u u^2} - \mu_u u + D_u \nabla^2 u \\ \dot{v} &= \sigma_v - \rho_v \frac{u^2 v}{1 + \kappa_u u^2} - \mu_v v + D_v \nabla^2 v \end{aligned}$$

Check for $f_v > 0$ and $g_u < 0$, o.k.

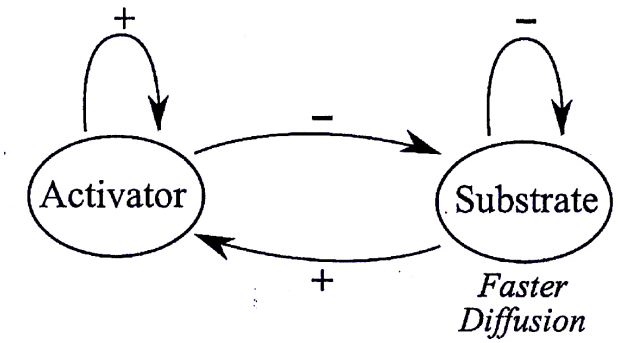


Figure 5.7: Activator-substrate system

5.1.4 Some solutions

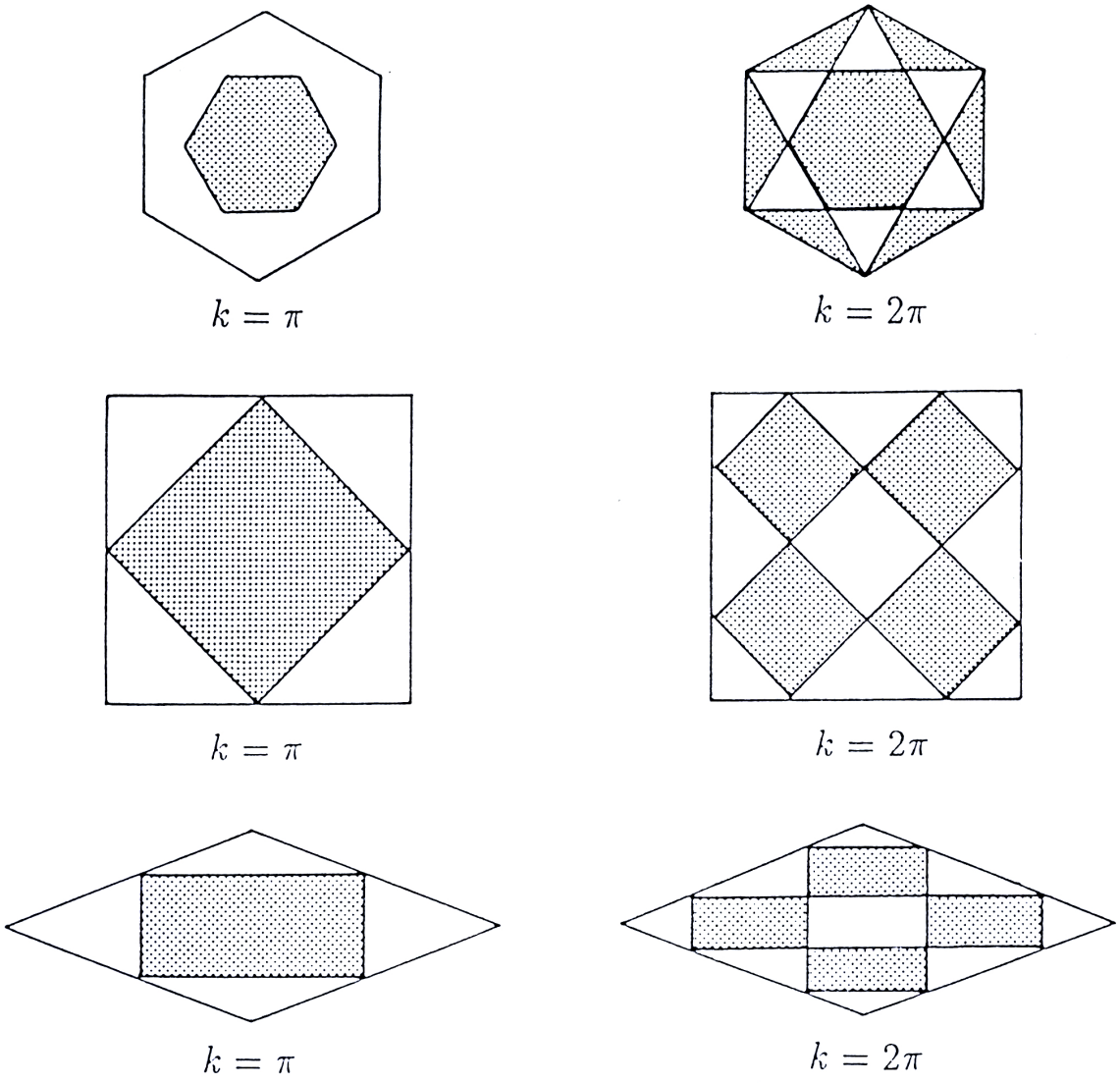


Figure 5.8: Geometry determines solutions

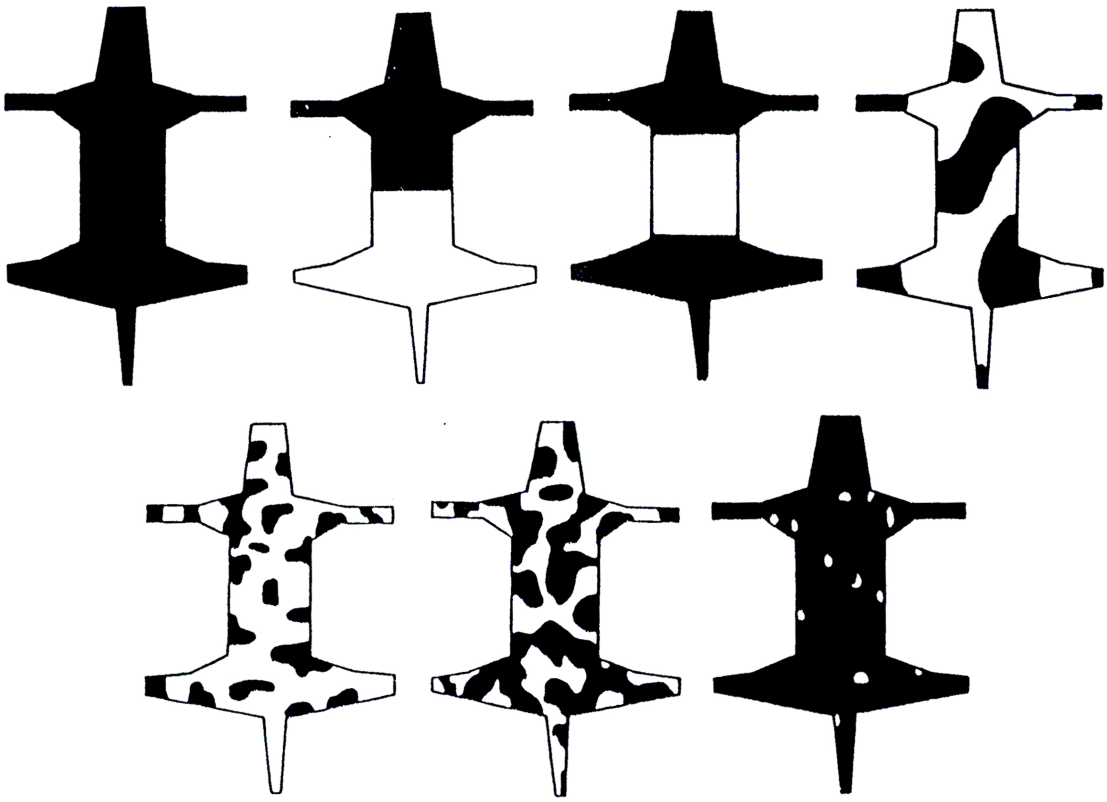


Figure 5.9: Surface scale effect, from small to large, and rescaled

Gives argument for uniform fur of mouse und elefant, but spotted for leopard

5.1.5 Comparison to reality

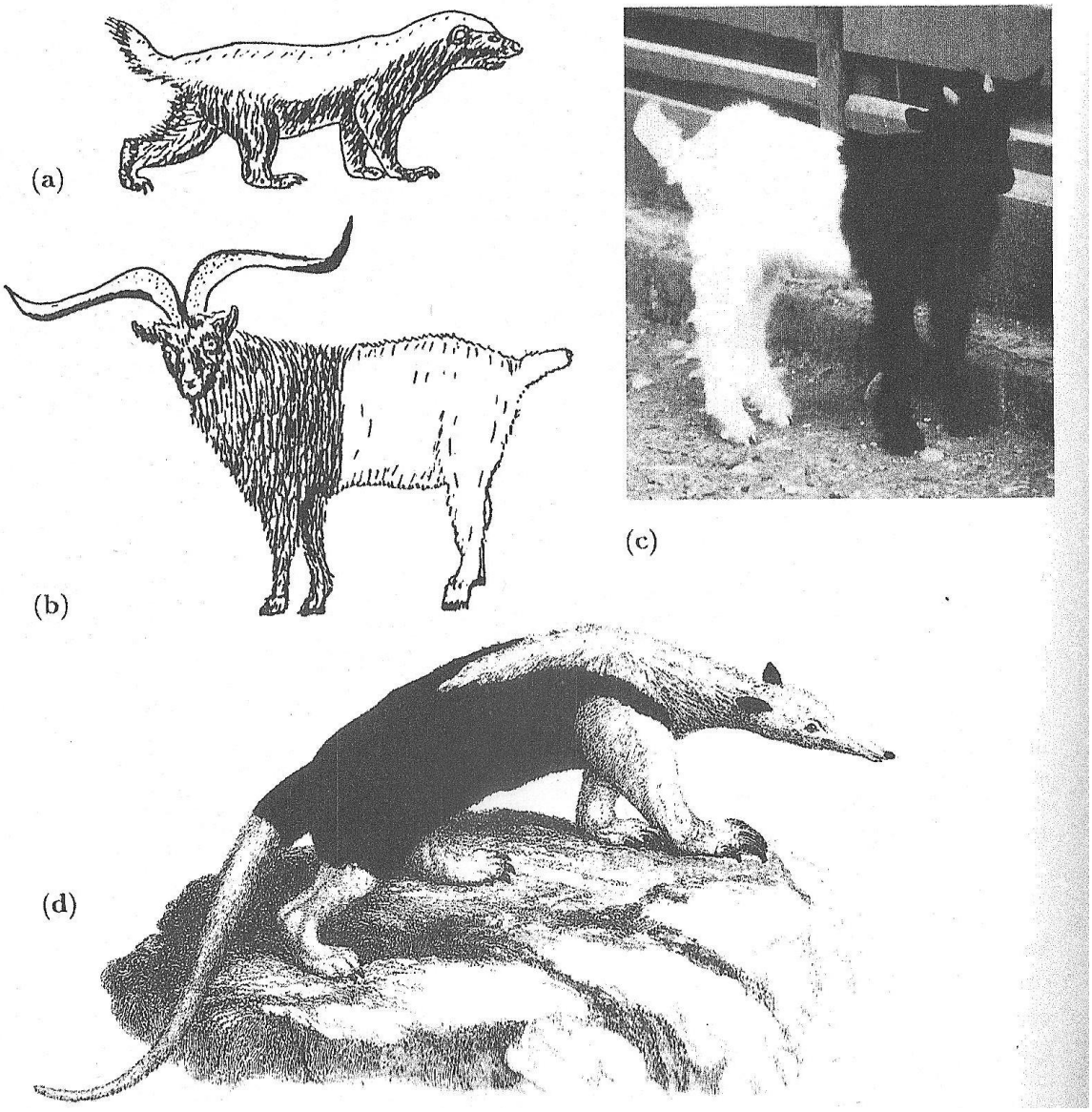


Figure 5.10: (b) *Capra aegagrus hircus*, goat, entrance Mundenhof to the left

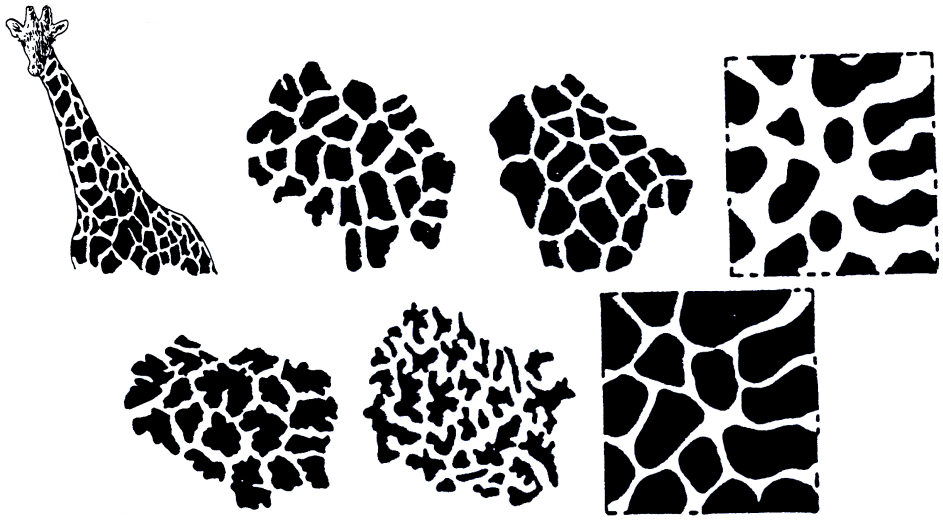


Figure 5.11: Giraffe

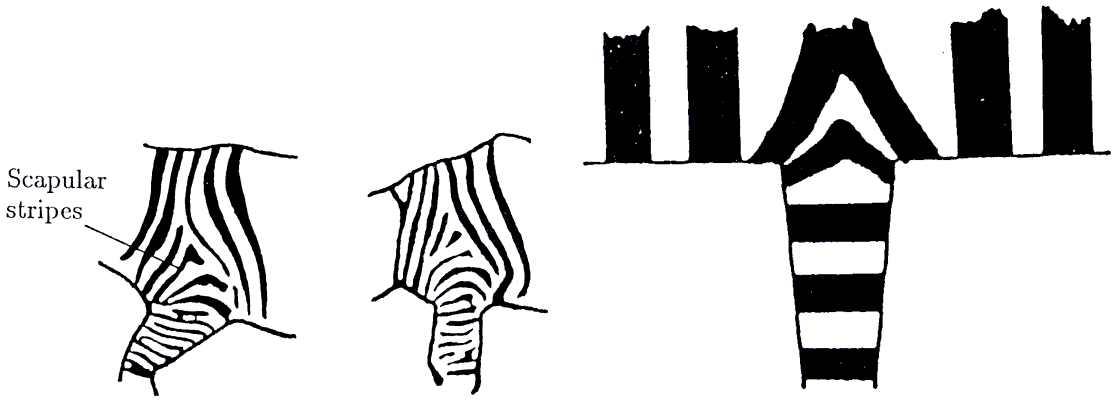


Figure 5.12: Zebra

Analogy to standing waves. If geometry is essentially 1 D (leg), there are only 1 D patterns

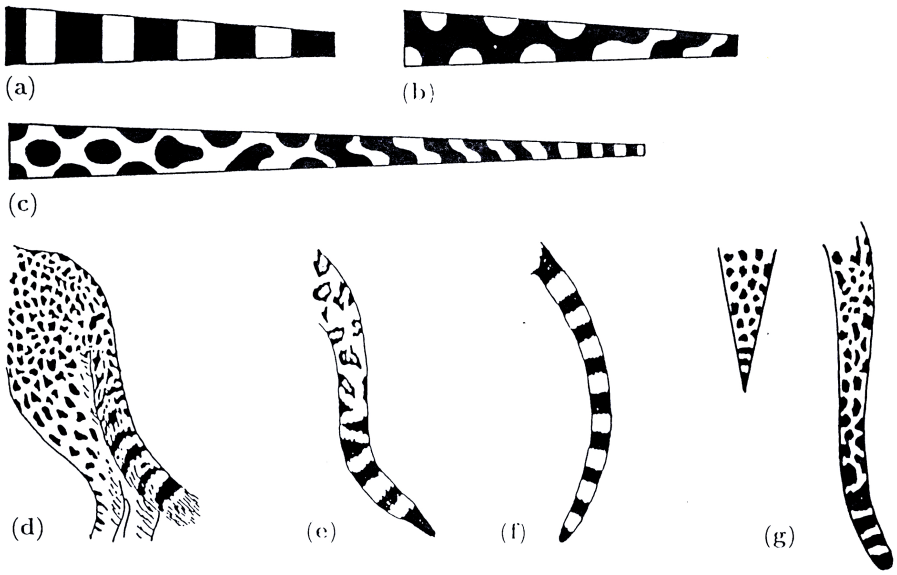
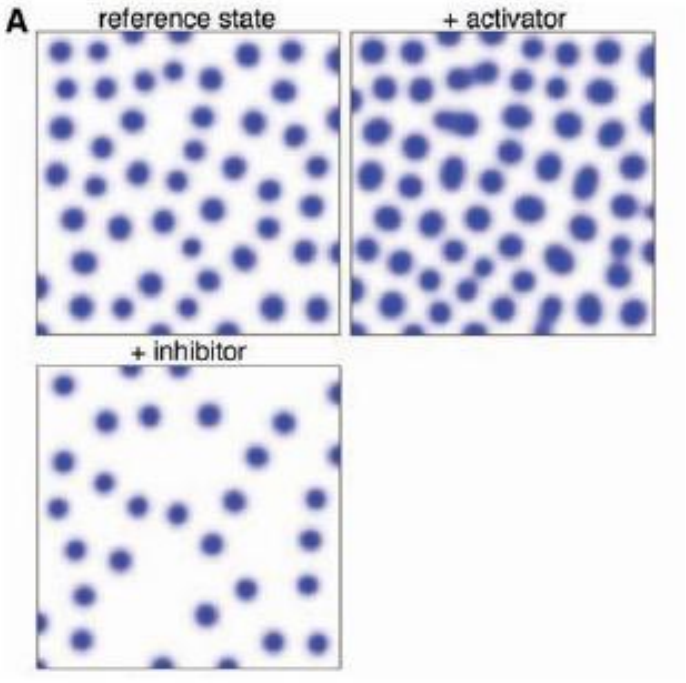


Figure 5.13: Tails

- True model predictions:
  - Anmial with spots on their body can show striped tails ...
  - ... but animal with striped bodies must not have spotted tails

From Sick et al. [101], 2006

- Activator: WNT
- Inhibitor: DKK, Dickkopf = pighead



5.2 Accurate cell division

Accurate cell division
[83, 44] EMBO J paper

- Zellzyklus E. Coli
- Wo ist die Mitte ?
- Beobachtung: MinC, MinD, MinE oszillieren
- Im Mittel erhöhte MinE Konzentration in der Mitte

Modell:

$$\begin{aligned}
\frac{d\rho_D}{dt} &= -\frac{\sigma_1}{1+\sigma_1'\rho_e}\,\rho_D + \sigma_2\rho_e\rho_d + D_D\,\frac{\partial^2\rho_D}{\partial x^2} \\
\frac{d\rho_d}{dt} &= \frac{\sigma_1}{1+\sigma_1'\rho_e}\,\rho_D - \sigma_2\rho_e\,\rho_d \\
\frac{d\rho_E}{dt} &= \frac{\sigma_4}{1+\sigma_4'\rho_D}\,\rho_e + \sigma_3\rho_D\,\rho_E + D_E\,\frac{\partial^2\rho_E}{\partial x^2} \\
\frac{d\rho_e}{dt} &= -\frac{\sigma_1}{1+\sigma_4'\rho_D}\,\rho_e + \sigma_3\rho_D\,\rho_E
\end{aligned}$$

Irgendwann mal ausbauen ...

Lessons learned:

- Turing model is a conceptional model
  Short range activation, long range inhibition
- Diffusion driven instability
  - [1] Homogenous, positive, stationary state
  - [2] Stable without diffusion
  - [3] Unstable with diffusion
- Counter-intuitive because usually diffusion destroys structure
- Gierer-Meinhardt brings it closer to biology
- Discussion: HH-Strategy vs. Turing Strategy

5/19

5M/20

6 Enzyme Dynamics

- Transition from Part I Mathematical Biology to Part II Systems Biology. Here: single enzymes, there networks of enzymes

- Remember enzymes as morphogenes from Turing
- Important in whole cell biology, from metabolism, Chap. 9 to biotechnology

"Law" of mass action
Consider two substances, that react to become a third one

$$A + B \xrightarrow{k} C \tag{32}$$

Rate k determines produktion rate $\frac{dC}{dt}$ and is a product of:

- Number of collisions of A and B per time interval: $\propto [A][B]$
- Probability that in case of a collision the activation energy, free energy barrier, is exceeded

Yields:

$$\frac{d[C]}{dt} = k[A][B] \tag{33}$$

Identification of scheme (32) with eq. (33) is the "law" of mass action
No fundamental law, rather as Ohm's law

- Holds in general only for elementary reactions
- Often good effective description, e.g.

$$2H_2 + O_2 \rightarrow 2H_2O$$

  Elementary reactions:

  - $H_2 \rightarrow 2H$ (ignition)
  - $H + O_2 \rightarrow OH + O$
  - $O + H_2 \rightarrow OH + H$
  - $OH + H_2 \rightarrow H_2O + H$

- Does not hold for

– very high concentrations, molecular crowding effects lead to

$$\frac{d\,[C]}{dt} = k[A]^{\alpha}[B]^{\beta}$$

– diffusion-limited reactions
Reaction-diffusion system

– very low concentrations, "concentration" loses meaning
Discrete dynamics, Gillespie algorithm [30], Chap. 12.1

Many (in principle all) reactions are reversible:

$$A + B \underset{k_-}{\overset{k_+}{\rightleftarrows}} C$$

Leads to:

$$\frac{d\,[C]}{dt} = -k_-[C] + k_+[A][B]$$

In equilibrium :

$$k_-[C]_{eq} = k_+[A]_{eq}[B]_{eq}$$

Since $T_0 = [A] + [C] = \text{const}$

$$[C]_{eq} = T_0\,\frac{[B]_{eq}}{K_{eq} + [B]_{eq}}$$

$K_{eq} = k_-/k_+$: equilibrium constant

Most relevant deviation from law of mass action: Enzyme dynamics

- Enzymes: Proteins that catalyse reactions
- Catalysis: Reduction of activation energy

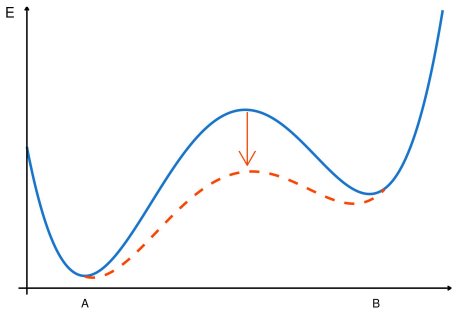


Figure 6.1: Catalyst reduces activation energy

- Example: Sugar and cigarette ash
- Accelerates reactions in both directions, typically one preferred
- Catalyst is not used up in reaction
- Action by e.g.:
  - Abolishment of electrostatic repulsion between reactants
  - Break open of bonds in molecules
- Enzyme are typically highly specific
- Acceleration of reaction velocity by up to 10^7
- Substrates: Victims of enzymes
- In general: enzyme concentrations small, since highly effective
- In general: enzymes are larger molecules than substrates
  Nice exception: Chap. 10.4 MAP-Kinase, where substrates become enzymes

Exhaustive literature: Dixon, Webb [18]

Most important example:

6.1 Michaelis-Menten Kinetik

Original paper from 1913: [69]
With S: substrate, E: enzyme, P: product

$$S + E \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} C \xrightarrow{k_2} P + E$$

- Motivated by: Enzyme Invertin catalyses substrate saccharose into products glucose and fructose.
- P is removed rapidly $\Longrightarrow$ second step is uni-directional

With $s = [S]$, $c = [C]$, ... and law of mass action for all reactions:

$$\begin{aligned} \dot{s} &= k_{-1}c - k_1\, se \qquad (34) \\ \dot{e} &= (k_{-1} + k_2)c - k_1\, se \\ \dot{c} &= k_1\, se - (k_{-1} + k_2)c \\ \dot{p} &= k_2 c \qquad (35) \end{aligned}$$

with conserved quantities $e_T = e + c$ and $s_T = s + c + p$, there are two independent differential equations

- Initial setting: 4 equations
- 2 conserved quantities $\Longrightarrow$ 2 equations
- Goal: 1 equation for product production rate $\dot{p}$ in dependence on substrate s
- Or: Direct relation between s in rhs of eq. (34) and $\dot{p}$ in eq. (35)
- $\Longrightarrow$ 1 more assumption is necessary
- If an assumption is not fulfilled, it is an approximation, good or bad, it depends

Two ansätze:

- Steady-state approximation (original version by MM)
- Quasi-steady-state approximation (Briggs/Haldane, 1925 [13])

Steady-state approximation

- Assumption: $\dot{s} = 0$

  Substrate is continuously resupplied

- Eq. (34) yields:

$$k_1\, se = k_{-1} c$$

  With $e = e_T - c$, if follows:

$$\begin{aligned} k_1 s e_T - k_1 s c &= k_{-1} c \\ k_1 s e_T &= c\,(k_{-1} + k_1 s) \\ c &= \frac{k_1 s e_T}{k_{-1} + k_1 s} \end{aligned}$$

  with Michaelis-Menten constant $K_s = k_{-1}/k_1$

$$c = \frac{e_T s}{K_s + s}$$

- For the velocity V of the final reaction, i.e. productions rate $\dot{p}$ of p:

$$V = \dot{p} = k_2 c = k_2 \frac{e_T s}{K_s + s} = \frac{V_{max} s}{K_s + s} \tag{36}$$

  with $V_{max} = k_2 e_T$

- Note: Enzyme and complex dynamics has disappeared.

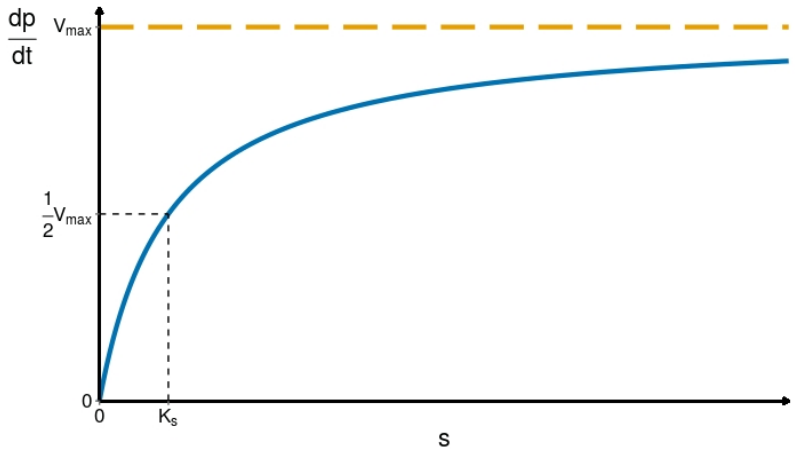


Figure 6.2: Michaelis-Menten kinetics

- For small substrate concentrations: linear
- For large substrate concentrations: Saturation at V_{max}
  All enzyme bound in complex c.
- Scale is fixed by K_s: For $s = K_s$ follows $V = V_{max}/2$
- $V_{max} = k_2 e_T$: Dissociation reaction $C \xrightarrow{k_2} P + E$ is rate-limiting
- Initial step of derivation $k_1\, se = k_{-1} c$ only true for continuous supply, a flux balance or steady state equilibrium
- Otherwise it is an approximation, the steady-state approximation

Quasi-Steady-State Approximation

Assumption: Rates for creation and decay of complex c are essentially equal

- Meaning:

$$\dot{c} \approx 0$$

  For clarity, dimensionsless variable:

$$\sigma = \frac{s}{s_T}, \quad \chi = \frac{c}{e_T}, \quad \tau = k_1 e_T t, \quad \kappa = \frac{k_{-1} + k_2}{k_1 s_T}, \quad \epsilon = \frac{e_T}{s_T}, \quad \alpha = \frac{k_{-1}}{k_1 s_T}$$

- With $e = e_T - c$ and $p = s_T - s - c$, this leads to:

$$\begin{aligned} \frac{d\,\sigma}{d\tau} &= -\sigma + \chi(\sigma + \alpha) \\ \epsilon\,\frac{d\chi}{d\tau} &= \sigma - \chi(\sigma + \kappa) \end{aligned} \tag{37}$$

But:

- Enzymes are very efficient
- their concentration typically small compared to concentrations of substrates

Thus:

$$\epsilon = \frac{e_T}{s_T} \ll 1 \approx 10^{-2} - 10^{-7}$$

Consequence:

- Eq. (37) is fast
- χ stays always close to equilibrium, acts adiabatically
- especially if σ (former s) is changing. Difference to steady-state approximation
- Separation of time scales
- Remember blocking variable w of FitzHugh-Nagumo - model, exactly the other way round

Quasi-Steady-State Approximation:

- Set $\epsilon\,\frac{d\chi}{d\tau} = 0$
- That is <u>not</u> the same as $\frac{d\chi}{d\tau} = 0$, but equivalent to: $\frac{dc}{dt}$, the above assumption

Quasi-Steady-State approximation means:

- χ is changing, ...
- ... but on the manifold : $0 = \sigma - \chi(\sigma + \kappa)$
- <u>Separation of time scales</u>

QSS approximation holds if

- ϵ small
- $\frac{d\chi}{d\tau}$ is in the order of 1

Then:

$$\begin{aligned} \chi &= \frac{\sigma}{\sigma+\kappa} \\ \frac{d\,\sigma}{d\tau} &= -\frac{(\kappa-\alpha)\sigma}{\sigma+\kappa} \end{aligned}$$

In original variables

$$V = \dot{p} = \frac{k_2 e_T s}{K_m + s} = \frac{V_{max} s}{K_m + s} \tag{38}$$

$$c = \frac{e_T s}{K_m + s}$$

with Michaelis-Menten constant $K_m = \frac{k_{-1}+k_2}{k_1}$

- This is a simple example of "Singular Pertubation Theory"
- Structure of equation identical to steady-state approximation eq. (36), only

$$K_m = \frac{k_{-1}+k_2}{k_1} \quad \text{instead of} \quad K_s = \frac{k_{-1}}{k_1}$$

- Small difference not important, since equation is considered as independent
- This explains why steady-state approximation is good even if the assumption $\dot{s} = 0$ is strongly violated.
- Note: Now 2 parameters: V_{max}, K_m, instead of originally 3: k_1, k_{-1}, k_2

Historical remark:

- Determination of V_{max} and K_m without computer:
  Lineweaver-Burk-plots: Invert eq. (38):

$$\frac{1}{V} = \frac{1}{V_{max}} + \frac{K_m}{V_{max}} \frac{1}{s}$$

- Measure V for different s
- Determine $\frac{1}{V_{max}}$ and $\frac{K_m}{V_{max}}$ from linear regression
- Solve for K_m and V_{max}

Examples for more complex enzyme reactions

- Reversible production of product

$$S + E \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} C \underset{k_{-2}}{\overset{k_2}{\rightleftarrows}} P + E$$

  leads to

$$V = \dot{p} = \frac{V^+_{max} s/K_{mS} - V^-_{max} p/K_{mP}}{1 + s/K_{mS} + p/K_{mP}}$$

  with V^+_{max}, V^-_{max}, K_{mS}, K_{mP} as usual, appropriately adjusted

- Uni-directional bi-molecular reaction

$$S_A + S_B + E \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} C \overset{k_2}{\longrightarrow} P + E$$

  leads with $a = [S_A]$, $b = [S_B]$ to

$$V = \dot{p} = \frac{V_{max} ab}{K_{mA} K_{mB} + K_{mA} a + K_{mB} b + ab}$$

- and much more complicated ...

6/17

6.2 Enzyme Inhibition

- Enzyme inhibitors reduce catalytic effect.
- Irreversible Inhibitors set enzyme activity to 0

  Examples:

  - Cyanide: blocks enzyme Cytochrome-C oxidase, cells can not take up oxygen
  - Many nerve gases

In the following:

- Competitive inhibition
- Allosteric inhibition

Competitive Inhibitors

- Other substances that can also bind to catalytic active binding site of enzyme
- Similar to original substrate, key-lock principle
- Substrate has to compete

Simplest example:

$$\begin{array}{rcl} S + E & \overset{k_1}{\underset{k_{-1}}{\rightleftarrows}} & C_1 \xrightarrow{k_2} P + E \\ I + E & \overset{k_3}{\underset{k_{-3}}{\rightleftarrows}} & C_2 \end{array}$$

Analysis as above with quasi steady state approximation and $i \gg e$, i.e. i=const:

$$\begin{aligned} c_1 &= \frac{K_i\, e_T\, s}{K_m i + K_i s + K_m K_i} \\ c_2 &= \frac{K_m\, e_T\, i}{K_m i + K_i s + K_m K_i} \end{aligned}$$

with

$$K_m = \frac{k_{-1} + k_2}{k_1}, \quad K_i = \frac{k_{-3}}{k_3}$$

Velocity V of the reaction :

$$V = \dot{p} = k_2 c_1 = \frac{k_2 K_i e_T s}{K_m i + K_i s + K_m K_i} = \frac{V_{max}\, s}{K_m(1 + i/K_i) + s}$$

Thus:

Competitive inhibitor causes:

- Increase of Michaelis-Menten-constant K_m by a factor of $1 + i/K_i$
- No chance in maximum velocity V_{max}

Allosteric Inhibitors

- Enzyme has numerous binding sites, not only enzymatic active ones
- Binding of substance at an inactive binding site changes conformation of the enzyme
- That can inhibit enzyme activity
- These inactive bindings sites are called allosteric or regulatory
- Allosteric inhibitors typically not similar to substrate
- allosteric (greek): at a different place.
  Inhibition at a different place from the active one

Simplest case:

- One enzymatic binding site
- One allosteric binding site, sets enzymatic activity to zero

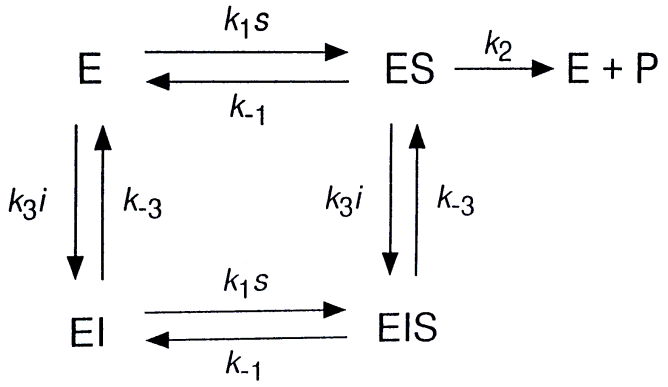


Figure 6.3: Wiring of allosteric inhibition

Analysis in steady state approximation (in QSS approximation more complicated result):

$$V = \frac{V_{max}}{1 + i/K_i} \frac{s}{K_s + s}$$

with

$$K_s = \frac{k_{-1}}{k_1}, \quad K_i = \frac{k_{-3}}{k_3}, \quad V_{max} = k_2 e_T$$

Thus :

Allosteric inhibitor causes:
• No change of Michaelis-Menten-constant
• Reduction of V_{max} by a factor of $1 + i/K_i$

To remember:

Competitive und allosteric inhibitors can be discriminated by their effects on V_{max} and K_m

Short test 5F/20

6.3 Cooperativity

Often:

- Enzyme has several enzymatic active binding sites
- Sustrate binding to one can influence enzymatic activity of the others

Simplest example: Two identical, symmetric bindings sites:

$$S + E \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} C_1 \xrightarrow{k_2} P + E$$

$$S + C_1 \underset{k_{-3}}{\overset{k_3}{\rightleftarrows}} C_2 \xrightarrow{k_4} P + C_1$$

Quasi-steady-state approximation, $dc_i/dt = 0$

$$\begin{aligned} c_1 &= \frac{K_2 e_T s}{K_1 K_2 + K_2 s + s^2} \\ c_2 &= \frac{e_T s^2}{K_1 K_2 + K_2 s + s^2} \end{aligned}$$

with

$$K_1 = \frac{k_{-1} + k_2}{k_1}, \quad K_2 = \frac{k_{-3} + k_4}{k_3}$$

Velocity of the reaction:

$$V = \dot{p} = k_2 c_1 + k_4 c_2 = \frac{(k_2 K_2 + k_4 s) e_T s}{K_1 K_2 + K_2 s + s^2}$$

Consider two extreme cases:

- No interaction

  $k_1 = 2k_3$, $k_{-3} = 2k_{-1}$, $k_4 = 2k_2$, $K = K_1 = K_2$

  $$V = \frac{2k_2 e_T (K + s) s}{K^2 + 2Ks + s^2} = 2\frac{k_2 e_T s}{K + s}$$

  Rate twice as high as for single binding site, makes sense

- Extreme-cooperation
  - Binding to one site renders the other infinitely fast
  - Modelling: $k_3 \longrightarrow \infty$, $k_1 \longrightarrow 0$, but $k_1 k_3 = const$
  - Analogously $K_1 \longrightarrow \infty$, $K_2 \longrightarrow 0$, $K_1 K_2 = const = K_m^2$

  yields:

$$V = \frac{k_4 e_T s^2}{K_m^2 + s^2} = \frac{V_{max} s^2}{K_m^2 + s^2}$$

  Only k_4 in V_{max}, makes sense

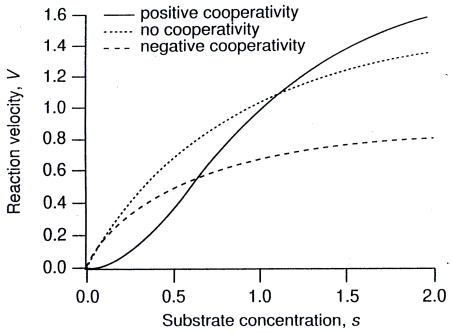


Figure 6.4: Positive & negative cooperativity

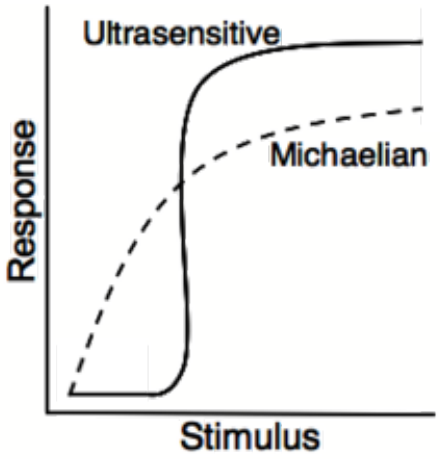
For n binding sites with

$$K_1 \longrightarrow \infty, \quad K_i \longrightarrow 0, \quad K_1 K_i = const, \quad K_m^n = \prod_i K_i :$$

follows

$$V = \frac{V_{max} s^n}{K_m^n + s^n}$$

a sharper and sharper sigmoidal curve.



- Leads to ultra-sensitivity.
  Important for noise suppression, drawing
- For fits to empirical data, estimated n is called Hill-coefficient
  It holds: Hill-coefficient $\leq$ number of binding sites

More detailed models :

- Monod-Wyman-Changeux model, 1965 [73], nice review [16]
- Koshland-Nemethy-Filmer model, 1966 [60]

Lessons learned:

- Michaelis-Menten kinetics is the most important deviation from law of mass action
- Inhibitory effects can be discriminated by their effects on V_{max} and K_m
- Cooperativity can lead to ultra-sensitivity

6/19

7. half week/17

7 Ein ganz besondrer Saft

Reminder:

- Ideal gas:
$$PV = nkT \text{ oder } P = ckT$$
- Mixture of gases with portions x_i:
Partial pressure : $P_i = x_i P$
- Border gas (with P_is) to liquid (c_is) :
$c_i = \sigma_i P_i$
σ_i: solubility,
- For historical reasons: Results reported in partial pressure

7.1 Hemoglobin and Myoglobin

Solubility in blood of

- CO_2: $3.3 \times 10^{-5}\ Molar/mmHg$
- O_2: $1.4 \times 10^{-6}\ Molar/mmHg$

Factor: 20

- CO_2 can be transported dissolved in the blood
- O_2 needs a carrier

Transport of oxygen:

- From the lung into the body: Red blood cells, erythrocytes, no genes
Transport protein: Hemoglobin
- Within the muscles: Myoglobin

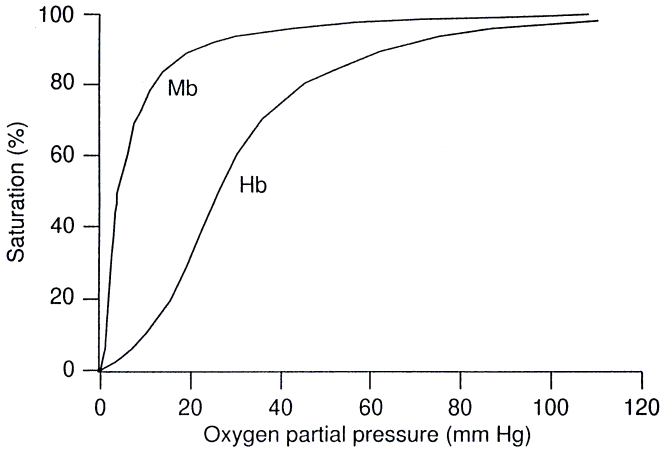


Figure 7.1: Saturation curves for hemoglobin and myoglobin

- Partial pressure of oxygen in the lung: 100 mm Hg.
  $\Longrightarrow$ Hemoglobin saturated
- Mean partial pressure of O_2 in muscle: 40 mm Hg
  $\Longrightarrow$ O_2 goes from hemoglobin to myoglobin
- Sudden need for O_2: partial presses drops to, say, 20 mm Hg
  $\Longrightarrow$ Large transfer of O_2 into the muscle

Makes sense !

The mechanism:

Myoglobin (Mb):

- Myoglobin has one heme complex that can bind one O_2 molecule
  Bound complex: Oxymyoglobin

$$O_2 + Mb \underset{k_-}{\overset{k_+}{\rightleftarrows}} Mb\,O_2$$

- Law of mass action

$$[\dot{O}_2] = -k_+[Mb][O_2] + k_-[Mb\,O_2]$$

- In steady state:

$$k_+[O_2][Mb] = k_-[Mb\,O_2] \quad \Longrightarrow \quad [Mb\,O_2] = \frac{1}{K}[O_2][Mb], \quad K = \frac{k_-}{k_+}$$

- Portion Y of occupied Mb binding sites

$$Y = \frac{[Mb\,O_2]}{[Mb] + [Mb\,O_2]} = \frac{[O_2]}{K + [O_2]}$$

- From concentration to partial pressure: $[O_2] = \sigma_{O_2} P_{O_2}$, with, $K_p = K/\sigma_{O_2}$ yields:

$$Y = \frac{P_{O_2}}{K_p + P_{O_2}}$$

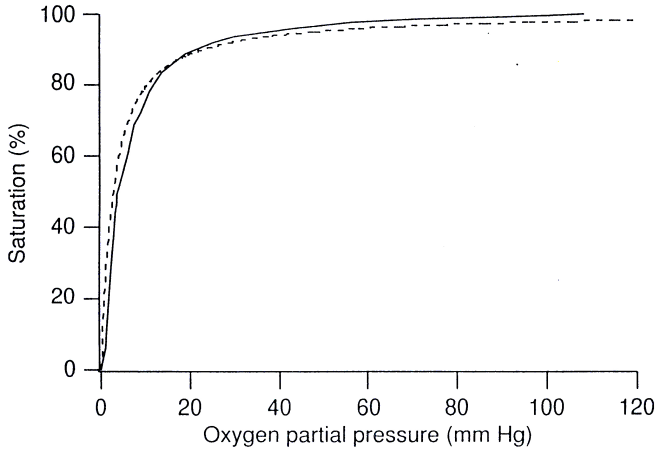


Figure 7.2: Comparison: Myoglobin saturation curves: measured vs. model

- Modell fits the data
- $K = 2.6\sigma_{O_2}$ mm Hg

Hemoglobin (Hb):

Hemoglobin has four heme complexes, each can bind one O_2 molecule.

(i) Simplest model

- "One-shot" binding

$$4\,O_2 + Hb \quad \underset{k_-}{\overset{k_+}{\rightleftarrows}} \quad Hb\,(O_2)_4$$

- Law of mass action:

$$[\dot{Hb}] = -k_+[Hb][O_2]^4 + k_-[Hb\,(O_2)_4]$$

- Portion Y of occupied Hb binding sites

$$Y = \frac{[Hb\,(O_2)_4]}{[Hb] + [Hb\,(O_2)_4]} = \frac{[O_2]^4}{K^4 + [O_2]^4}, \quad K^4 = \frac{k_-}{k_+}$$

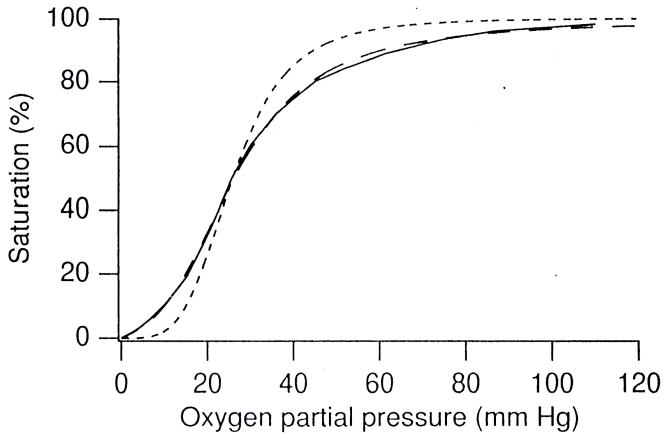


Figure 7.3: Comparison: Hemoglobin measured vs. "One-shot", formal, detailed model

- Model does not fit the data

(ii) Formal model

- Fit formally:

$$\frac{[O_2]^n}{K^n + [O_2]^n}$$

  Remember: n Hill-Coefficient

- Yields: $n = 2.5$ and $K = 26\sigma$ mm Hg
  $\Longrightarrow$ At least three binding sites

- Model fits the data, but no theoretical basis for this model

(iii) Detailed model

- Elementary reactions, with $H_j = Hb(O_2)_j$:

$$O_2 + H_{j-1} \underset{k_{-j}}{\overset{k_{+j}}{\rightleftarrows}} H_j, \qquad j = 1, 2, 3, 4$$

- In steady state

$$[H_j] = \frac{k_{+j}}{k_{-j}}[H_{j-1}][O_2] = \frac{[H_{j-1}][O_2]}{K_j}, \quad K_j = k_{-j}/k_{+j}$$

- Portion Y of occupied Hb binding sites

$$Y = \frac{\sum_{j=1}^{4} jH_j}{4\sum_{j=0}^{4} H_j}$$

- Insert steady state conditions:

$$Y = \frac{\sum_{j=1}^{4} j\alpha_j[O_2]^j}{4\sum_{j=0}^{4} \alpha_j[O_2]^j}$$

  with

$$\alpha_j = \prod_{i=1}^{j} K_i^{-1}, \quad \alpha_0 = 1$$

- Fitting to the empirical curve yields
  - $K_1 = 45.9\sigma$ mm Hg
  - $K_2 = 23.9\sigma$ mm Hg
  - $K_3 = 23.1\sigma$ mm Hg
  - $K_4 = 1.5\sigma$ mm Hg

  Notice: $K_4 \ll K_1$, K_2, K_3
- This means:
  - If three O_2 are bound there is a high affinity to bind a fourth one.
  - Or, if all four binding sites are occupied, dissolution of the first one is most difficult
  - Stamp example
  - Makes sense: Ensures save transport of saturated hemoglobin in the blood and fast release at the muscle if release is started
  - Note: Not a cooperativity in strict sense as for enzymes
  - Mechanism of positive cooperativity is not completely understood, but well described by Monod-Wyman-Changeux model

Mother and fetus have different hemoglobins, fetal hemoglobin has higher O_2 affinity

The crocodile [37]:

- Crocodiles can stay under water for up to one hour
- They have a special hemoglobin with a binding site for bicarbonate.
- Bicarbonate: Salt of carbon dioxide
- Bicarbonate accumulates while not breathing
- By allosteric regulation this decreases the binding affinity for oxygen, squeezing out the last O_2 molecules

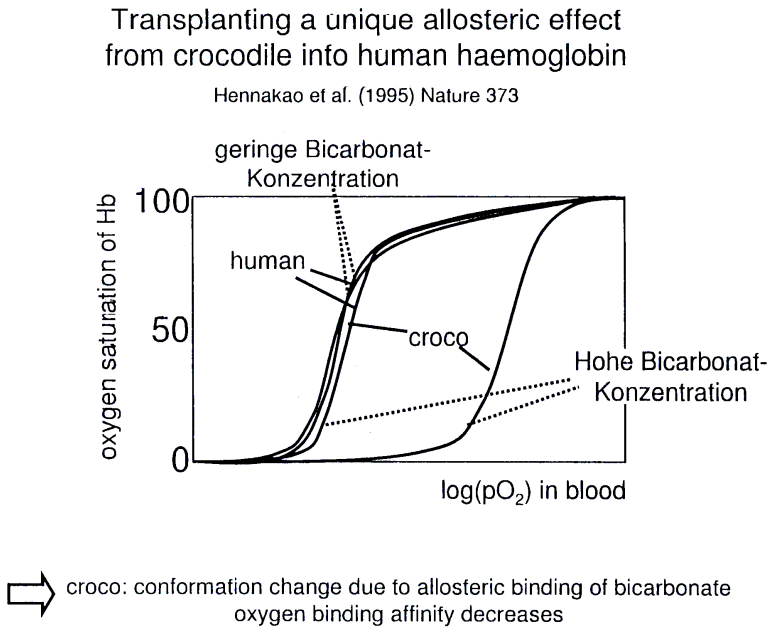


Figure 7.4: Crocohemoglobin

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7.2 Facilitated Diffusion

Reminder:

- Fick's law
  - concentration u
  - production rate f
  - flux J

  Continuity equation

  $$\dot{u} = f - \nabla J$$

  Fick's law :

  $$J = -D\nabla u$$

  with diffusion coefficient D, yields

$$\dot{u} = f + \nabla(D\nabla u)$$

If D constant

$$\dot{u} = f + D\nabla^2 u$$

remember: heat equation

- Mass dependency of D, Einstein 1906 [19]:

  For large spheres

  $$D = \frac{kT}{6\pi\mu r}, \quad \mu \text{ viscosity}, \quad r \text{ radius}$$

  Since

  $$M = \frac{4}{3}\pi r^3 \rho$$

  from radius r to mass M:

  $$D = \frac{kT}{3\mu}\left(\frac{\rho}{6\pi^2 M}\right)^{1/3}$$

  Densities ρ of large proteins are essentially identical: The larger the protein, the slower it diffuses

Facilitated Diffusion

The phenomenon:

- Myoglobin: molecular weight: 16890, diffusion constant: $D = 4.4 \times 10^{-7}\, cm^2/s$
  Oxygen: molecular weight: 32, $D = 1.2 \times 10^{-5}\, cm^2/s$
- Factor: 30
- Flux of O_2 in muscle is much higher in presence of myoglobin
- At first glance: counter-intuitive

The model:

- Consider: 1 D
- $s = [O_2]$, $m = [Mb]$, $c = [Mb\,O_2]$
  D_m, $D_c \ll D_s$
- Reaction-diffusion system:

$$\frac{\partial s}{\partial t} = D_s \frac{\partial^2 s}{\partial x^2} - f \tag{39}$$

$$\frac{\partial m}{\partial t} = D_m \frac{\partial^2 m}{\partial x^2} - f \tag{40}$$

$$\frac{\partial c}{\partial t} = D_c \frac{\partial^2 c}{\partial x^2} + f \tag{41}$$

  with f uptake rate of O_2 into Mb.

- Last subsection

$$O_2 + Mb \underset{k_-}{\overset{k_+}{\rightleftarrows}} Mb\,O_2$$

  Law of mass action:

$$f = -k_- c + k_+ sm$$

- Boundary conditions:
  - $x \in [0, L]$, $x = 0$: $s(0) = s_0$, $x = L$: $s(L) = s_L$, $s_0 > s_L$
  - Mb and $Mb\,O_2$ can not leave the muscle:

$$\frac{\partial m}{\partial x} = \frac{\partial c}{\partial x} = 0 \quad \text{for } x = 0 = L$$

- Since $m + c = m_T$, eq. (40) is superfluous.
- Concentration of myoglobin is large

Analysis:

- Stationary State:

$$\dot{s} = 0, \quad \dot{c} = 0 \quad \Longrightarrow \quad D_s s_{xx} + D_c c_{xx} = 0$$

Integration with respect to x:

$$D_s s_x + D_c c_x = -J$$

Integration constant J: Flux of oxygen

Another integration:

$$J = \frac{D_s}{L}(s_0 - s_L) + \frac{D_c}{L}(c_0 - c_L), \quad c_0, c_L \text{ so far unknown} \tag{42}$$

- Transform to dimensionless variables

$$\sigma = \frac{k_+}{k_-}s, \quad \chi = \frac{c}{m_T}, \quad y = \frac{x}{L}$$

Inserted in eqs. (39, 41) yields

$$\epsilon_1 \sigma_{yy} = \sigma(1 - \chi) - \chi = \epsilon_2 \chi_{yy}$$

with

$$\epsilon_1 = \frac{D_s}{m_T k_+ L^2}, \quad \epsilon_2 = \frac{D_c}{k_- L^2}$$

Experimental values for D_s, m_T, k_+, ...

$$\epsilon_1 \approx 10^{-7}, \quad \epsilon_2 \approx 10^{-4}$$

$\Longrightarrow$ Quasi-steady-state approximation

$$c = m_T \frac{s}{K + s}, \quad \text{with } K = k_-/k_+$$

Insert in eq. (42)

$$
\begin{aligned}
J &= \frac{D_s}{L}(s_0 - s_L) + \frac{D_c}{L} m_T \left(\frac{s_0}{K + s_0} - \frac{s_L}{K + s_L} \right) \\
&= \frac{D_s}{L}(s_0 - s_L) \left(1 + \frac{D_c}{D_s} \frac{m_T K}{(K + s_0)(K + s_L)} \right) \\
&= \frac{D_s}{L}(s_0 - s_L)(1 + \mu\rho)
\end{aligned}
$$

with

$$
\rho = \frac{D_c}{D_s} \frac{m_T}{K}, \quad \mu = \frac{K^2}{(K + s_0)(K + s_L)}
$$

- Interpretation:
  - Without myoglobin $\rho = 0 \Longrightarrow$ pure Fick's diffusion
  - With myoglobin flux is increased by factor $\mu\,\rho$
  - Effect is largest for small concentrations of O_2, then μ close to maximum of 1, experimental data: 0.1
  - Experimental data: $\rho = 500$
  - Overall effect: 50 times increase of flux
  - Summary:
    * Suck of left
      Concentration of O_2 high, affinity of myoglobin to bind O_2 high
    * Spit out right
      Concentration of O_2 low, affinity of myoglobin to bind O_2 low

Critical discussion: [49], Review [118]

Lessons learned:

- Binding of O_2 to hemoglobin is most popular example for cooperativity. Although hemoglobin is not an enzym
- Facilitated Diffusion: Diffusion of O_2 in muscle much faster in presence of rather slowly diffusing myoglobin

Part II
... to Systems Biology

8 Introduction

Literature:

- H. Kitano: Foundations of Systems Biology, 2001 [57]
- Basics of biochemistry: H. Rehm, F. Hammar: Biochemie light, 2001 [88]
- Control theorie: K. Zhou and J.C. Doyle and K. Glover, Robust and optimal control, 1996 [122]
- Metabolism:

  R. Heinrich, S. Schuster: The Regulation of Cellular Systems, 1996 [36]

  D. Fell: Understanding the Control of Metabolism, 1997 [22]
- E.O. Voit: Computational Analysis of Biochemical Systems, 2000 [112]
- C.P. Fall et al.: Computational Cell Biology, 2002 [20]
- E. Klipp et al.: Systems Biology in Practice [59]
- L. Alberghina, H. Westerhoff: Systems Biology [1]
- U. Alon: Introduction to Systems Biology and the Design Principles of Biological Networks [2]
- Z. Szallasi, J. Stelling, V. Periwal: System Modelling in Cellular Biology [107]
- J. Paulsson, J. Elf: Stochastic Modeling in Systems Modeling in Cellular Biology [78]

Systems biology in general

Basic research:

- 2001: First human genome sequenzed, 10 years, 3 bn. $, today: 1 week, 1000 $
- Sequenced genome (ca. 24.000 genes) does not explain (dys)function

- Function determined by regulation
- Regulation = Interaction and dynamics
- Function: Property of a dynamic network of proteins
- Can not be understood by intuitive reasoning
- Systems biology: Understanding of cellular processes based on mathematical modelling of the networks

  "Systems" from Systems Science: Determination of properties of models

Example:

- How does the cell make decisions
  - grow ?
  - proliferate ?
  - divide ?
  - die, apoptosis ?
- and that in a noisy environment ?

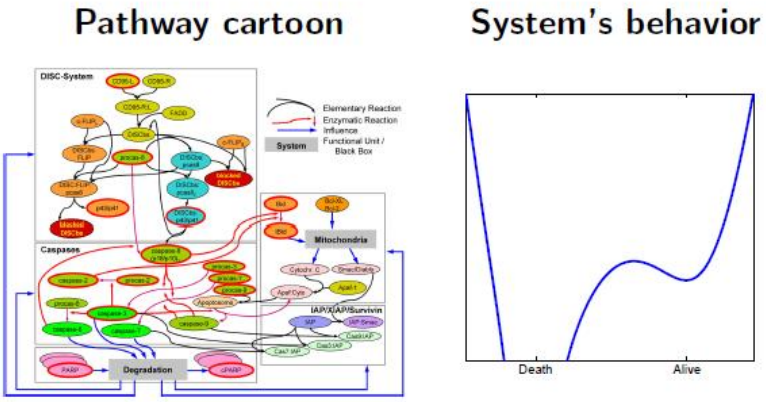


Figure 8.1: Apoptosis, threshold behavior, one-way bistable

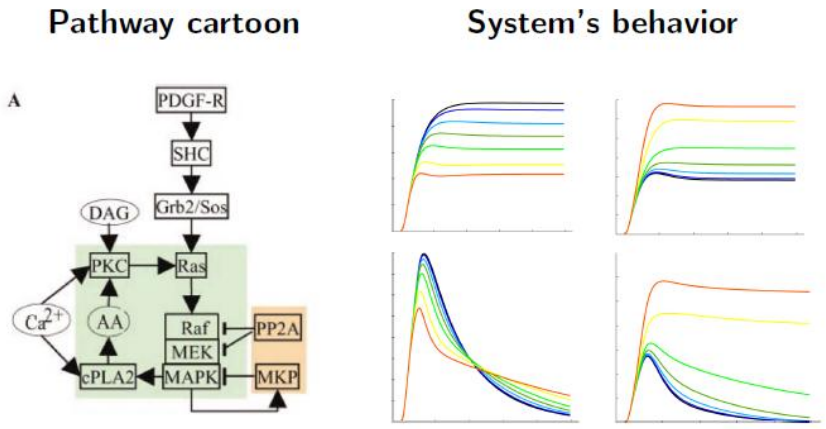


Figure 8.2: MAP kinase, parameters & time scales important

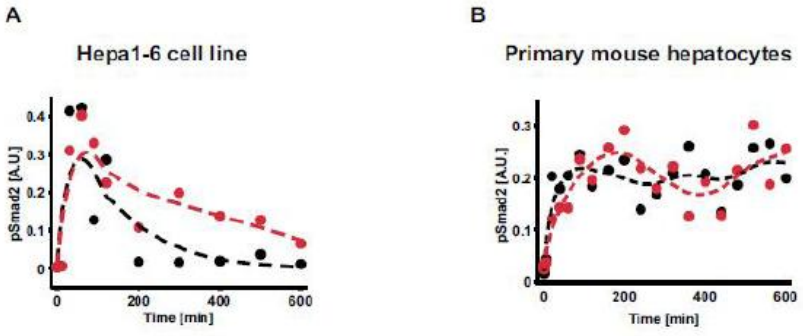


Figure 8.3: Same pathway different behavior, biological example

Medicine (applied biology):

- Drug development becomes more and more expensive and less and less efficient
- 1 drug: 10 years, 1 billion € / $
- Quantitative mathematical & mechanistic understanding should help

Central goals :

- Understanding of function. "Function" does not make sense in physics.
  "Why ?"-questions
  Makes sense in biology due to evolution
  - Ever since there are genes, there is mutation, run faster, bite harder
  - If there is competion, this leads to selection
- Understand robustness [58, 103, 105] Phenotypical stability under disturbances
  - of the environment
  - by intrinsic stochastic effects
  - by extrinsic stochastic effects
- Render drug interventions rational

Three main fields of cell/systems biology:

- Metabolism
  - Fluxes of matter
  - Globally conserved quantities
  - Stationary state is of interessant

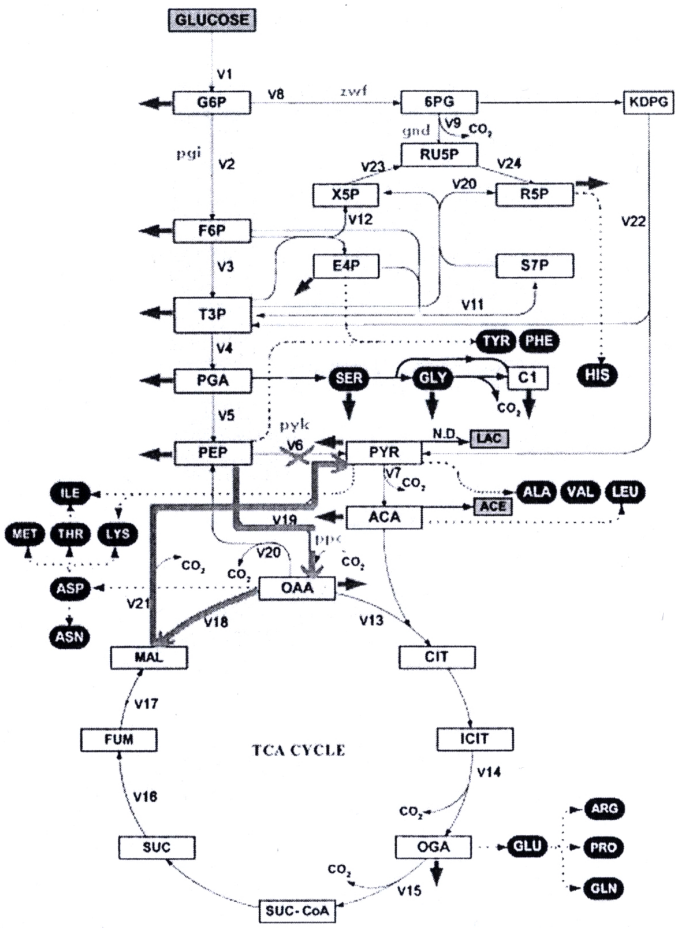


Figure 8.4: Metabolic pathway

- Signal transduction from outside the cell to the DNA
  - Flux of information
  - Locally conserved quantities
  - Transient states are of interest

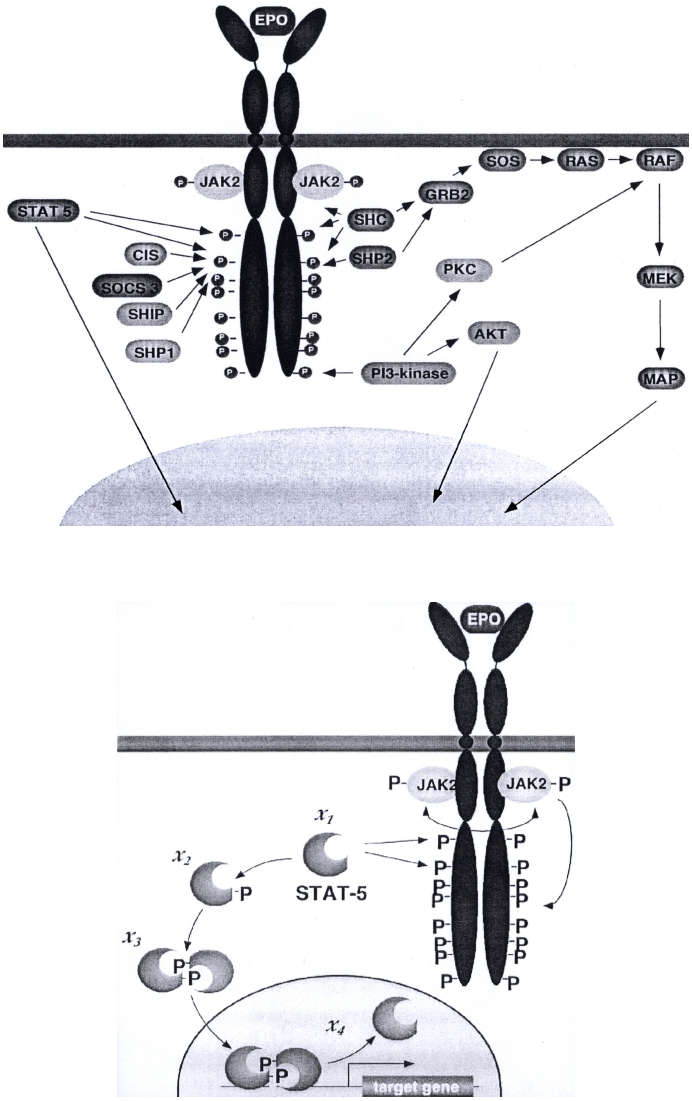


Figure 8.5: Signaling pathways

- Gene regulation
  - No conserved quantities
  - Everything is transient

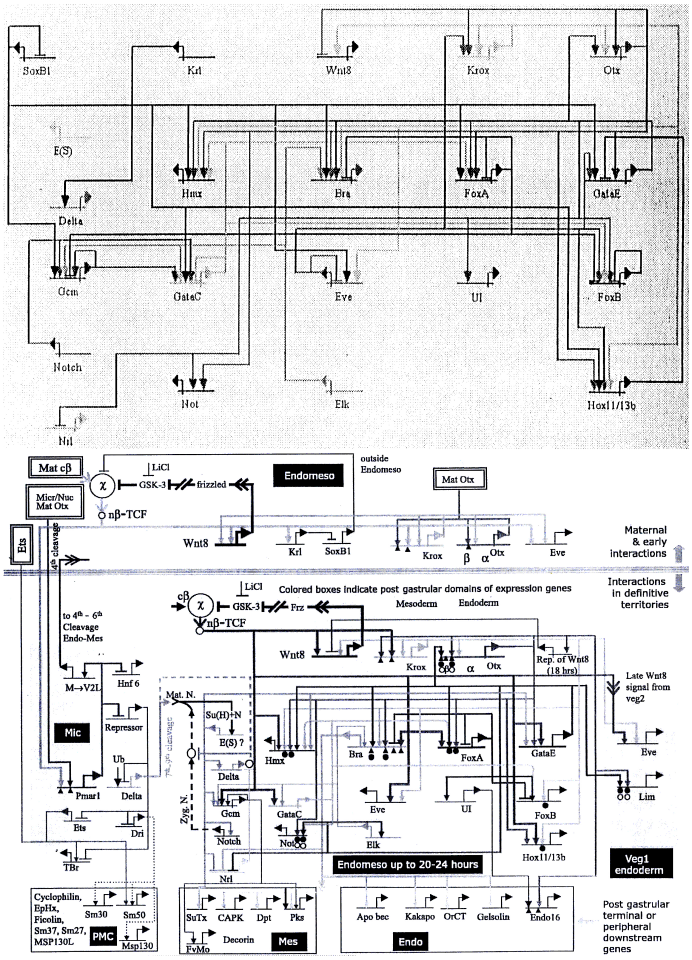


Figure 8.6: Gene regulation

- *In vivo* everything interacts, but typically acts on different time scales

Two lines of attack:

- Discover general principles
  - Robustness
  - Qualitative vs. quantitative
    - Is structure of the network central ? [115]
    - or the specific parameters ? [34, 58]

- Build concrete models of concrete networks [106, 5, 62]

Born to early:

- Norbert Wiener (1894-1964)

  Cybernetics, or Control and Communication in the Animal and the Machine. 1948 [117]

- Ludwig von Bertalanffy (1901-1972)

  Zu einer allgemeinen Systemlehre, Biologia Generalis. 1948 [114]

- Fürs Gemüt: Lessons from the past [116]

8.1 A little bit cell biology, biochemistry & molecular biology

Best Book: [88]

Central dogma of molecular biology

- DNA made out of four nucleobases (A, C, G, T)

  RNA made out of four nucleobases (A, C, G, U)

  Protein made out of 21 amino acids

  Three nucleobases code for one amino acid

- Central dogma: DNA makes RNA, RNA makes protein

- From DNA to RNA: transcription

- From RNA to protein: translation

- From DNA to protein: expression

- Nowadays: It is much more complicated

Biology:

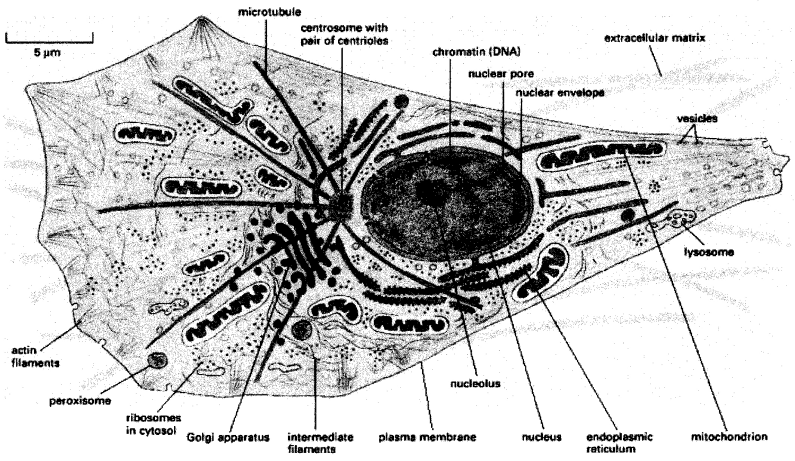


Figure 8.7: The cell, fundamental building block of life

- Prokaryotes & eukaryotes
- Mitochondrium, ribosomes, Golgi-apparatus, endoplasmatic reticulum
- Genes: ORFs, Promotors
- Metabolism: ATP, amino acids
- Gene regulation: Transcription factors

Experimental methods:

- Southern blot: DNA detection
  Northern blot: RNA detection
  Western blots: protein detection
- DNA chips, deep sequencing
- Microscopy:
  Green Fluorescent Protein
  FRAP Fluorescence Recovery after Photobleaching
  FRET Förster/fluorescence resonance energy transfer
  FLIM Fluorescence-lifetime imaging microscopy

- Mass spectroscopy

  Highly sensitive method for protein/metabolite quantification

Important: Never get confused from unknown names and abbreviations 8/17
7F/20

9 Metabolismus

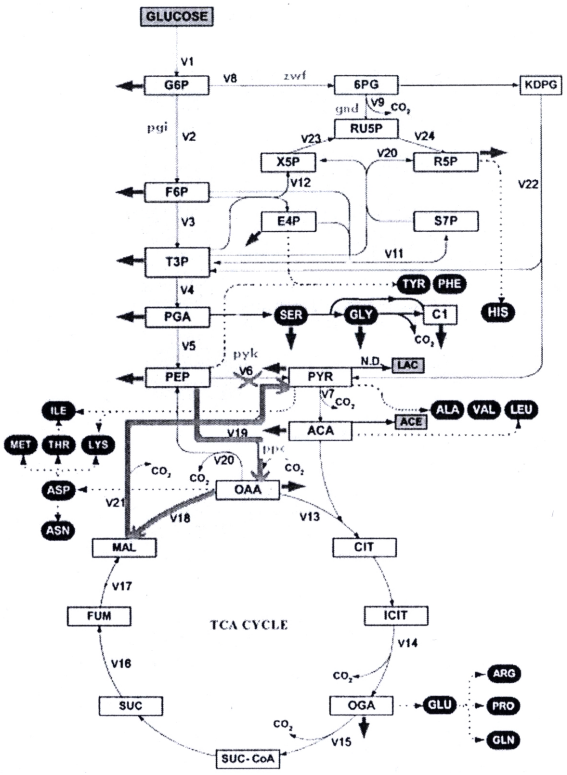


Figure 9.1: Example of a metabolic network

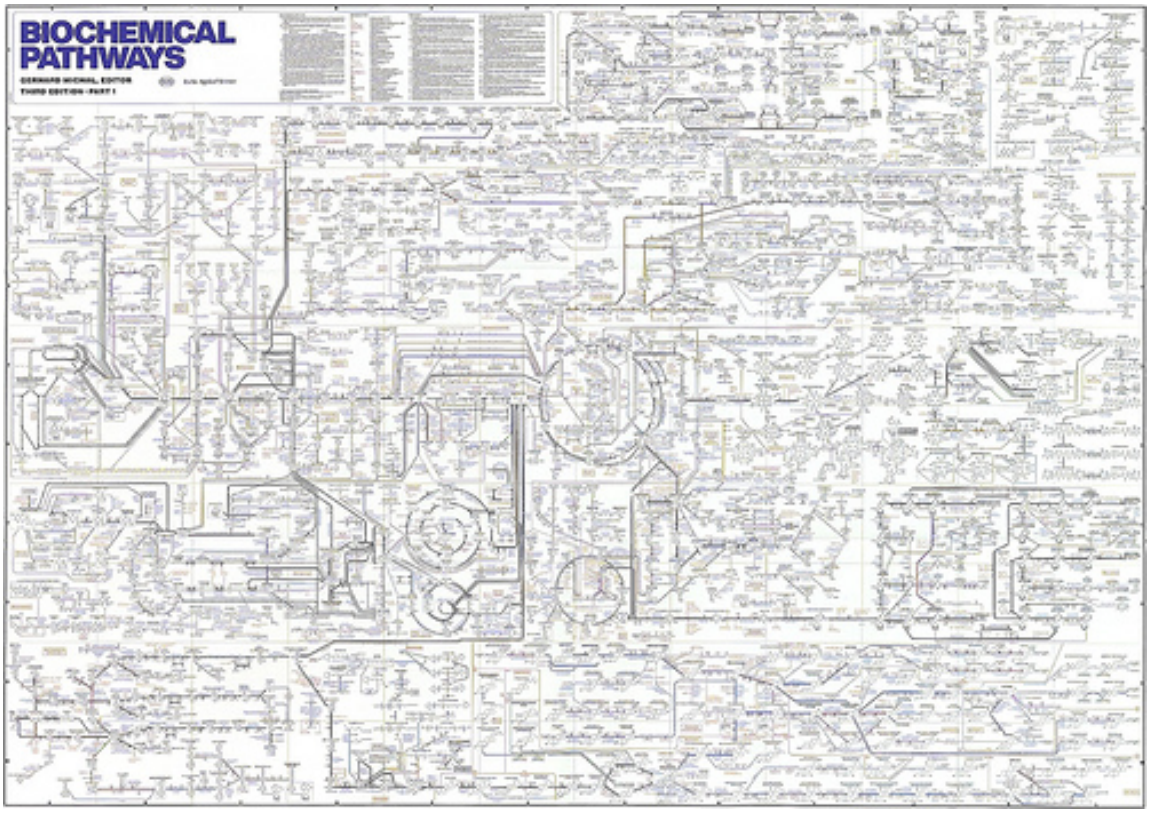


Figure 9.2: Böhringer map

- All reactions are mediated by enzymes

  $\Longrightarrow$ Metabolic networks are determined by the involved enzymes

- Enzymes are given by expressed genes

- If all expressed enzyme genes are known, structure of metabolic network is known

Two questions:

- How does the enzymes control substrate concentrations and fluxes ?

- Which paths through the network are possible ?

9.1 Metabolic Control Theory

From single enzymes á la Sec. 6 Enzyme Dynamics to networks of enzym-mediated reactions

Literature:

- R. Heinrich, S. Schuster: The Regulation of Cellular Systems, 1996 [36]
- D. Fell: Understanding the Control of Metabolism, 1997 [22]

Questions:

- Which reaction determines the flux how strongly ?
- Is there a rate limiting step ? The "old dogma"

  Remember Michalis-Menten: $C \overset{k_2}{\to} P$. $V_{max} = k_2\, e_T$
- Which enzymes are efficient drug targets ?

Notation:

- Concentration of metabolites: S as substrate
- Any kind of parameter: p
- Velocity of single reaction: $v(S, p)$

  Example Michaelis-Menten

$$v(S, p) = \frac{V_{max}\, S}{K_m + S}$$

- Stoichiometric matrix N

$$S \underset{v_4}{\overset{v_1}{\rightleftarrows}} S_1 \underset{v_5}{\overset{v_2}{\rightleftarrows}} S_2 \underset{v_6}{\overset{v_3}{\rightleftarrows}} P$$

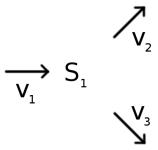
$$\dot{S}_1 = v_1 - v_2 - v_4 + v_5, \quad \dot{S}_2 = v_2 - v_3 - v_5 + v_6$$

$$N = \begin{pmatrix} 1 & -1 & 0 & -1 & 1 & 0 \\ 0 & 1 & -1 & 0 & -1 & 1 \end{pmatrix}$$

N fixes the topology of the network

Sometimes to & back reactions are united in a single reaction

- Other examples
  - Branched network:



Branched network

$$\dot{S}_1 = v_1 - v_2 - v_3 \qquad N = (1\ -1\ -1)$$

  - Water

$$2H_2 + O_2 \rightarrow 2H_2O$$
$$N = (\,2\ 1\,)$$

- Stoichiometric matrix typically describes only internal metabolites. External metabolites can be involved in other reaction are taken as known

Thus dynamics read:

$$\frac{dS_i}{dt} = \sum_{j=1}^{r} n_{ij} v_j(S, p)$$

or more compact:

$$\dot{S} = N\, v$$

Important:

- Non-linear in S & p
- but linear in v

From now on: Consider system in stationary state:

$$N\,v = 0$$

Makes sense for metabolism: Stationary flux through the system[4]

$$J = J(S(p), p) = J(p)$$

An example:

- Consider

$$S \underset{k_1^-}{\overset{k_1^+}{\rightleftarrows}} X \underset{k_2^-}{\overset{k_2^+}{\rightleftarrows}} P$$

  with

$$v_1 = k_1^+ S - k_1^- X \quad \text{and } v_2 = k_2^+ X - k_2^- P$$

- Thus:

$$\dot{X} = v_1 - v_2, \quad N = (1 \;\; -1)$$

  Stationary state:

$$N\,v = 0 \quad \Longrightarrow v_1 = v_2 \quad \text{has to hold for a linear chain}$$

- From $v_1 = v_2$ follows

$$X = \frac{k_1^+ S + k_2^- P}{k_1^- + k_2^+}$$

  and

$$J = v_1 = v_2 = k_1^+ S - k_1^- \frac{k_1^+ S + k_2^- P}{k_1^- + k_2^+} = \frac{k_1^+ k_2^+ S - k_1^- k_2^- P}{k_1^- + k_2^+} \tag{43}$$

  - Flux in dependence from input & output (and parameters), remember MM
  - Will be generalized below, see eq. (44)

[4]Makes absolutely no sense for signalling and gene regulation

- $J = 0$ for

$$k_1^+ k_2^+ S = k_1^- k_2^- P$$

$$\frac{P}{S} = \frac{k_1^+}{k_1^-}\frac{k_2^+}{k_2^-}, \quad q_1 q_2 = q \text{ equilibrium constants}$$

Control coefficients:

- What change if something changes ?
- What changes if a parameter is slightly perturbed

(Relative) flux control coefficients

$$C_k^{J_j} = \lim_{\Delta v_k \to 0} \frac{\Delta J_j / J_j}{\Delta v_k / v_k} = \frac{\partial \ln J_j}{\partial \ln v_k}$$

- Nature is logarithmic. We detect relative changes of stimuli S: $\Delta S/S$, Weber-Fechtner law
- $C_k^{J_j} = x$ means, that a change of v_k by 1% causes a chance of J_j by x%
- Change of v_k depends on change of parameter $p_{k'}$, e.g. for Michaelis-Menten V_{max} or K_m
- Thus, in fact:

$$C_k^{J_j} = \frac{v_k}{J_j}\frac{\partial J_j / \partial p_{k'}}{\partial v_k / \partial p_{k'}}$$

(Relative) concentration control coefficients:

- Analogous:

$$C_k^{S_i} = \lim_{\Delta v_k \to 0} \frac{\Delta S_i / S_i}{\Delta v_k / v_k} = \frac{v_k}{S_i}\frac{\partial S_i / \partial p_{k'}}{\partial v_k / \partial p_{k'}} = \frac{\partial \ln S_i}{\partial \ln v_k}$$

- Controll coefficients are global properties or systems' properties : What happens here if I change something there

Concrete determination

- Can in general not be determined analytically
- Numerically:
  - Calculate J_j or S_i in undisturbed system
  - Disturbe system slighty, calculate $\tilde{J}_j$ or $\tilde{S}_i$
  - Take difference, see exercise

Summation theorems

Controll coefficients are not independent

Reminder:
Theorem about homogeneous functions (Euler, 1707-1783)

- Assume

$$f(\lambda x_1, \lambda x_2, \ldots, \lambda x_n) = \lambda^\mu f(x_1, x_2, \ldots, x_n)$$

  $f(.)$ homogeneous of degree μ

- Theorem

$$\sum_{i=1}^{n} \frac{\partial f(x_1, x_2, \ldots, x_n)}{\partial x_i} \frac{x_i}{f(x_1, x_2, \ldots, x_n)} = \mu$$

- Proof:

  Differentiate assumption with respect to λ

$$\sum_{i=1}^{n} \frac{\partial f(\lambda x_1, \lambda x_2, \ldots, \lambda x_n)}{\partial(\lambda x_i)} x_i = \mu \lambda^{\mu-1} f(x_1, x_2, \ldots, x_n)$$

  Set $\lambda = 1$

$$\sum_{i=1}^{n} \frac{\partial f(x_1, x_2, \ldots, x_n)}{\partial x_i} x_i = \mu f(x_1, x_2, \ldots, x_n)$$

  Dividing by $f(x_1, x_2, \ldots, x_n)$ proofs the theorem

- Often reaction velocities are linear in enzyme concentration, as for Michaelis-Menten

$$v = k_2 \frac{e_T s}{K_s + s} = \frac{V_{max} s}{K_s + s}, \quad \text{with } V_{max} = k_2 e_T = k_2 E$$

- Then:

$$\frac{\partial v_k}{\partial E_k} = \frac{v_k}{E_k}$$

and for controll coefficients hold:

$$C_k^{J_j} := \frac{\partial \ln J_j}{\partial \ln v_k} = \frac{v_k}{J_j}\frac{\partial J_j}{\partial v_k} = \frac{E_k}{J_j}\frac{\partial J_j}{\partial E_k} = \frac{\partial \ln J_j}{\partial \ln E_k} =: C_{E_k}^{J_j}$$

$C_k^{S_i}$ analogous

- General setting:

$$v_j = E_j g_j(S_1, \ldots, S_n)$$

In stationary state:

$$\sum_{j=1}^{r} n_{ij} v_j = \sum n_{ij} E_j g_j = 0$$

Change of all enzyme concentrations by a factor λ: $E_j \to \lambda E_j$ cancels out
Thus, stationary metabolite concentrations do not change

$$S_i(\lambda E_1, \ldots, \lambda E_r) = \lambda^0 S_i(E_1, \ldots, E_r)$$

Homogeneous of degree 0

- Differentiate with respect to λ, right hand side = 0

$$\sum_j \frac{\partial S_i}{\partial(\lambda E_j)} \frac{\partial(\lambda E_j)}{\partial \lambda} = \sum_j \frac{\partial S_i}{\partial(\lambda E_j)} E_j = 0$$

Consider $\lambda = 1$ and divide by S_i yields:

$$\sum_j \frac{E_j}{S_i}\frac{\partial S_i}{\partial E_j} = \sum_j C_{E_j}^{S_i} = 0$$

> The sum of all concentration control coefficients of a substrate is zero
> Consequence: There must be positive and negative ones

For flux control coefficient:

- Change of enzyme concentration causes:

  $$J_i(\lambda E_1, \ldots, \lambda E_r) = \lambda^1 J_i(E_1, \ldots, E_r)$$

  Homogeneous of degree 1

- Differentiate with respect to λ

  $$\sum_j \frac{\partial J_i}{\partial(\lambda E_j)}\frac{\partial(\lambda E_j)}{\partial \lambda} = \sum_j \frac{\partial J_i}{\partial(\lambda E_j)} E_j = J_i$$

- Set $\lambda = 1$ and divide by J_i yields:

  $$\sum_j \frac{E_j}{J_i}\frac{\partial J_i}{\partial E_j} = \sum_j C_{E_j}^{J_i} = 1$$

> The sum of all flux control coefficients of a flux is one

In branched pathways, $C_{E_j}^{J_i}$ can be negative

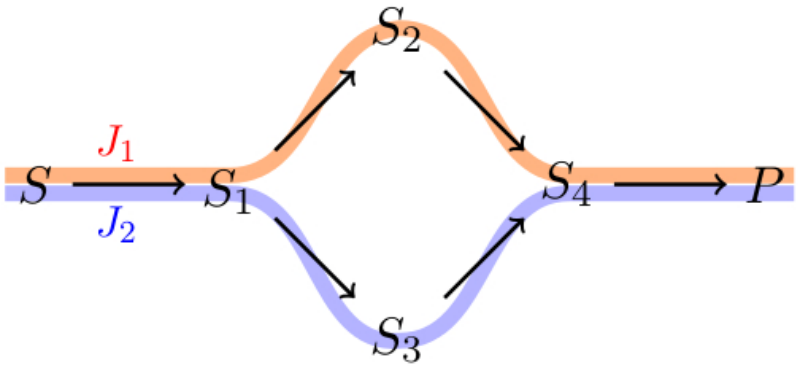


Figure 9.3: Negative flux control coefficients

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If control coefficients are determined empirically, if $\sum C^{S_i,J_j} \neq \{0,1\}$ points to uncomplettness of the system. At least in principle.

Example : Un-branched chain

- Consider:

$$S_0 \overset{v_1}{\underset{\longleftarrow}{\longrightarrow}} S_1 \overset{v_2}{\underset{\longleftarrow}{\longrightarrow}} S_2 \overset{v_3}{\underset{\longleftarrow}{\longrightarrow}} \ldots S_{n-1} \overset{v_n}{\underset{\longleftarrow}{\longrightarrow}} P$$

  Forward and backward reaction between to substrates considered as one flux

  $\Longrightarrow$ Velocity of reaction is function of substrate and product:

$$v_i = v_i(S_{i-1}, S_i)$$

- Assumption: Linear kinetics

$$v_i = k_{+i} S_{i-1} - k_{-i} S_i, \qquad \text{with inverse equilibrium constant } q_i = k_{+i}/k_{-i}$$

  yields for flux in generalisation of eq. (43)

$$J = \frac{S_0 \prod_{j=1}^{n} q_j - P}{\sum_{j=1}^{n} \frac{1}{k_{+j}} \prod_{m=j}^{n} q_m} \tag{44}$$

- For control coefficients, change k_{+i}, k_{-i} such that q_i stays constant

$$C_i^J = \frac{v_k}{J} \frac{\partial J/\partial p_{k'}}{\partial v_k/\partial p_{k'}}$$

follows:

$$C_i^J = \frac{\frac{1}{k_{+i}} \prod_{j=i}^{n} q_j}{\sum_{j=1}^{n} \frac{1}{k_{+j}} \prod_{m=j}^{n} q_m} \tag{45}$$

- Note:
  - Control coefficients C_i^J have direct relation to $\frac{1}{k_{+i}}$
  - But: Control coefficents of each reaction depend on all other reactions.
  - The "old dogma", that the slowest reaction determines the overall reaction velocity does not hold
- Consider relaxation time of enzyme:

$$\tau_i = \frac{1}{k_{+i} + k_{-i}}$$

Eq. (45) becomes

$$C_i^J = \frac{\tau_i(1+q_i) \prod_{j=i+1}^{n} q_j}{\sum_{j=1}^{n} \tau_j(1+q_j) \prod_{m=j+1}^{n} q_m} \tag{46}$$

Consequences:

- For $q_i = 1$ follows

$$C_i^J = \frac{\tau_i}{\sum_{j=1}^{n} \tau_j}$$

closest the "old dogma"

- Consider last control coefficient of chain of three reactions

$$C_3^J = \frac{\tau_3(1+q_3)}{\tau_1(1+q_1)q_2q_3 + \tau_2(1+q_2)q_3 + \tau_3(1+q_3)}$$

For τ_3, $q_3 = \text{const.}$, $q_1 \to \infty$ or $q_2 \to \infty$ follows $C_3^J \to 0$, independent from τ_3

Thus: Reactions downstream of irreversible reaction have no flux control, no matter how slow they are

- In general: Control coefficients depend not only on the reaction velocity of an enzyme but also on its postion in the chain
- Consider control coefficients of successive reactions. From eq. (46) follows:

$$\frac{C_i^J}{C_{i+1}^J} = \frac{\tau_i(1+q_i)}{\tau_{i+1}(1+q_{i+1})}\, q_{i+1}$$

Typically $q_j > 1$

$\Longrightarrow$ Tendency, that control coefficents are larger at the beginning than at the end of the chain

Controll coefficients in optimal states

- Maximising flux is an important evolutionary optimisation criterion

$$J \to Max.$$

- But: limited amount of enzymes

Constraint for optimisation

$$\sum_l E_l = E_{tot} = const.$$

- Lagrange multiplier

Optimise:

$$J^* = J + \lambda \left(\sum_l E_l - E_{tot} \right)$$

Yields for any pair i, j

$$\frac{\partial J^*}{\partial E_i} = \frac{\partial J}{\partial E_i} + \lambda = 0, \quad \frac{\partial J^*}{\partial E_j} = \frac{\partial J}{\partial E_j} + \lambda = 0$$

Thus

$$\frac{\partial J}{\partial E_i} = \frac{\partial J}{\partial E_j}$$

Un-normalised flux controll coefficients must be equal

- Normalisation

$$\frac{1}{E_i}\left(\frac{E_i}{J}\frac{\partial J}{\partial E_i}\right) = \frac{1}{E_j}\left(\frac{E_j}{J}\frac{\partial J}{\partial E_j}\right)$$

Thus

$$\frac{C_i^J}{C_j^J} = \frac{E_i}{E_j}$$

control coefficients must be distributed as enzyme concentrations.

By summation theorem follows:

$$C_i^J = \frac{E_i}{\sum_j E_j}$$

Further examples

- Maximal fast relaxation to equilibrium
- Maximising the growth rate

To be extended: Spatial effects diffusion Control always ≤ 0.5 [80] 8M/20

9.2 Elementary Mode Analysis

First paper 1994 [96], nice review [94]

Null-Space Ansatz

Metabolic system in steady state

$$N\, v(S, p) = 0$$

- Parameters known: Determine S, in general a non-linear problem
- Parameters unknown: Determine v, a linear problem

$$N\,v = 0$$

- Typically, an under-determined linear system, luckily
- But it gives constraints.
- Example: Linear chain:
  - All reactions velocities must be identical
  - But specific value is not specified

From now on, slight abuse of notation: Reaction velocity denoted by flux

Relations between fluxes given by

$$N\,K = 0$$

with K, matrix with maximum rank

The columns of kernel of the stoichiometric matrix determine the possible fluxes

Example:

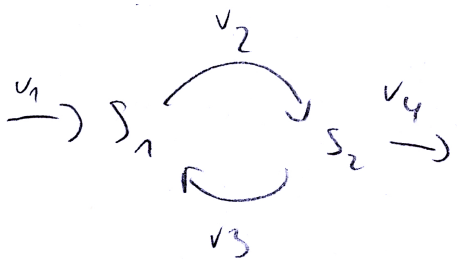

Figure 9.4

- Stoichiometric matrix

$$N = \begin{pmatrix} 1 & -1 & 1 & 0 \\ 0 & 1 & -1 & -1 \end{pmatrix}$$

Possible K

$$K = \begin{pmatrix} 1 & 0 \\ 1 & 1 \\ 0 & 1 \\ 1 & 0 \end{pmatrix}$$

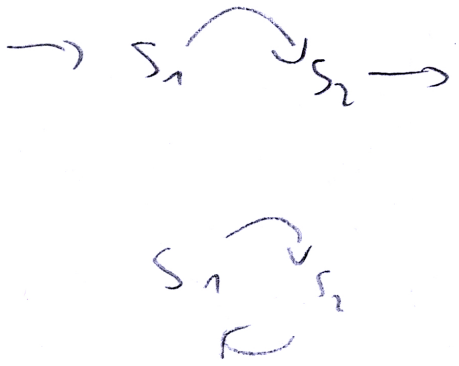

Figure 9.5

- Columns of K present possible paths through the network
  Each realisation is a linear combination of the column vectors

$$\begin{pmatrix} v_1 \\ v_2 \\ v_3 \\ v_4 \end{pmatrix} = \begin{pmatrix} 1 & 0 \\ 1 & 1 \\ 0 & 1 \\ 1 & 0 \end{pmatrix} \begin{pmatrix} \lambda_1 \\ \lambda_2 \end{pmatrix} = \begin{pmatrix} \lambda_1 \\ \lambda_1 + \lambda_2 \\ \lambda_2 \\ \lambda_1 \end{pmatrix}$$

Enzyme subsets:

- Enzymes that work in a fixed ratio
- Proportional rows of K give enzyme subset.
- Example

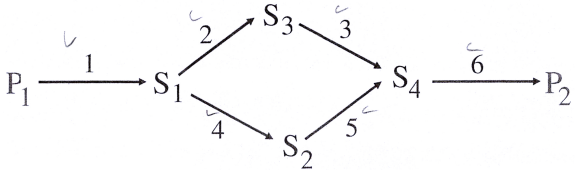

Figure 9.6

$$N = \begin{pmatrix} 1 & -1 & 0 & -1 & 0 & 0 \\ 0 & 0 & 0 & 1 & -1 & 0 \\ 0 & 1 & -1 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 1 & -1 \end{pmatrix}$$

$$K = \begin{pmatrix} 1 & 1 \\ 1 & 0 \\ 1 & 0 \\ 0 & 1 \\ 0 & 1 \\ 1 & 1 \end{pmatrix}$$

Enzyme Subsets: {1,6} {2,3}, {4,5}

Disadvantages of null-space ansatz:

- In general no unique solution
- Base vectors not necessarily maximum simple
- Might violate irreversible reactions
- Might describe knock-outs not correctly

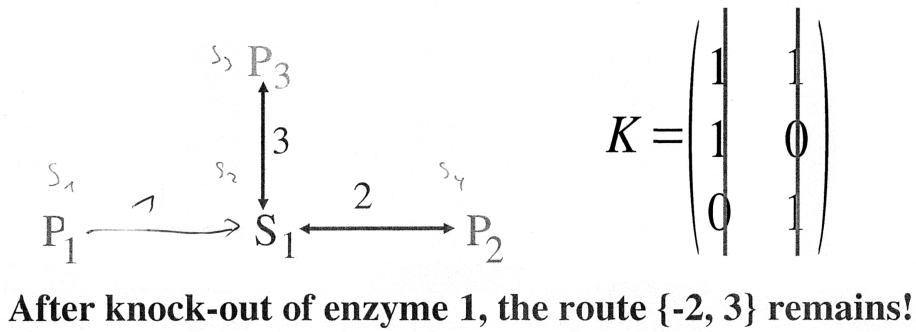

Figure 9.7: After knock-out of enzyme 1, route 2-3 remains active

Therefore: **Elementary mode analysis** [93, 95, 97]

Definition elementary mode v^*

(i) $Nv^* = 0$

(ii) v^* treates irreversible reaktions correctly $v_{irr} > 0$

(iii) v^* can not be reduced
meaning there is no $\tilde{v}^*$ with

- $\tilde{v}^*$ fulfills (i), (ii)
- $\tilde{v}^*$ has zeros where v^* has zeros and at least one more

One can show

- Elementary modes are unique up to scaling
- All realisable flux distributions are positive linear combinations of the elementary modes

$$v = \sum_k a_k \, v_k^*, \quad a_k \geq 0$$

- Elementary modes define a cone in the space of reactions
- All possible reactions lie within the cone

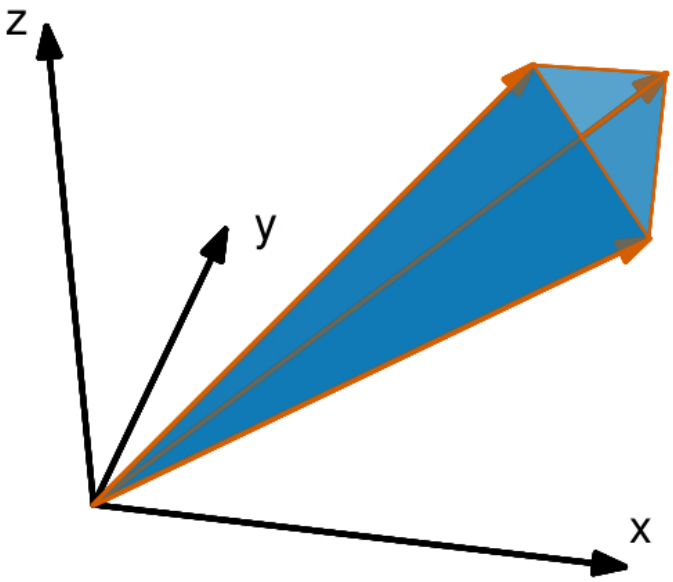

Figure 9.8: Axes: Reaction rates of enzymes

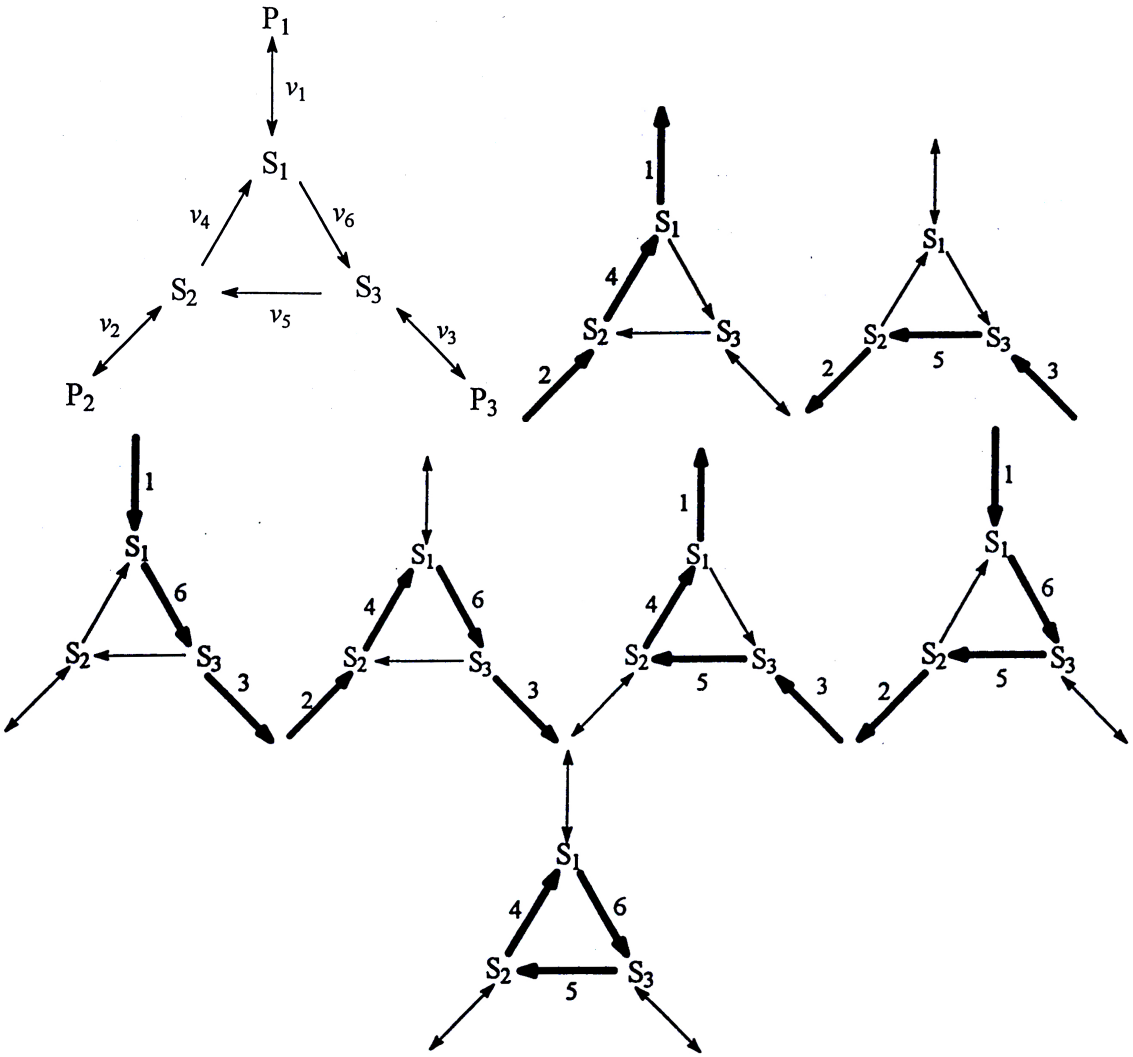

Figure 9.9: Examples for elementary modes

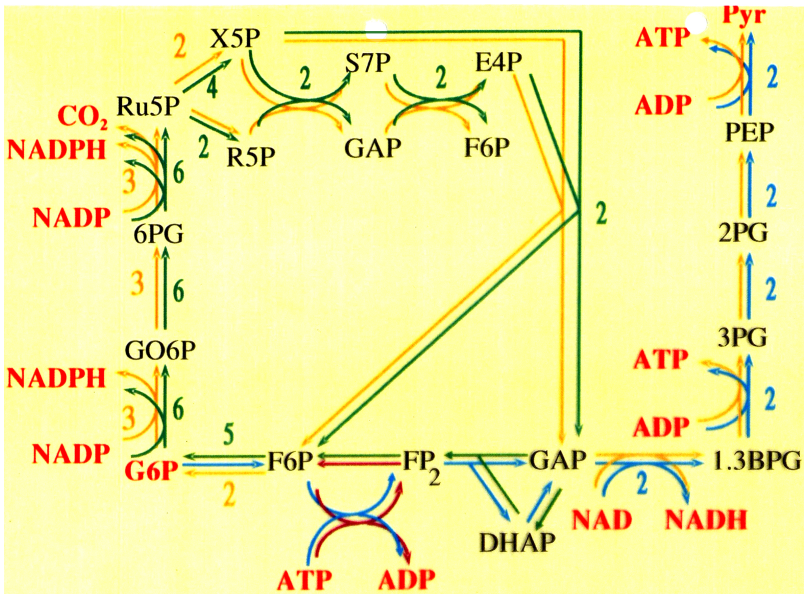

Figure 9.10: Example elementary modes

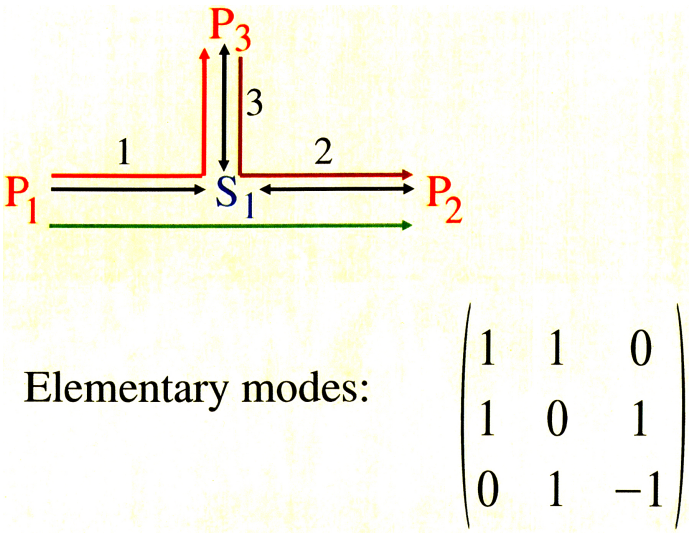

Figure 9.11: Describes knock-outs correctly

- Describes knock-outs correctly

Determination of elementary modes

- Analogous to Gauß-Jordan elimination
- Identity matrix I, form $(N^T : I)$
- Paarwise combination of rows, such that maximum number of columns of N^T become null vectors
- Transformed I gives elementary modes

Application [94]

- Why we can not produce sugar from fett

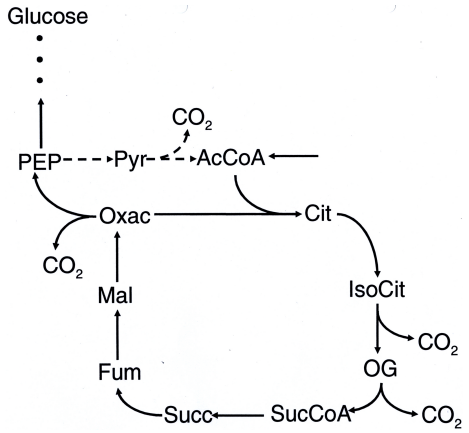

Figure 9.12: Human situation

  - There is a connection from AcCoA stemming from fatty acids to glucose, but it not realisable
  - There is only one elementary mode

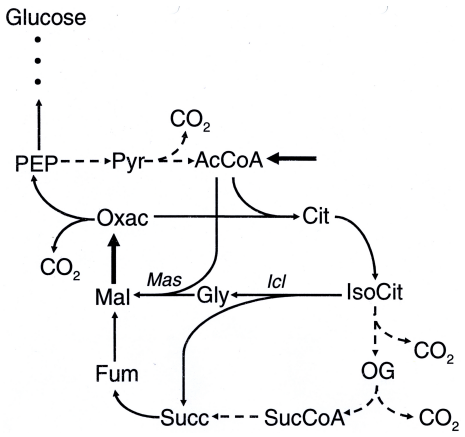

Figure 9.13: Plant situation, remember: they have more genes than we

- There is a shunt
- The connection from AcCoA to glucose is realisable

Other applications :

- Investigation of robustness [104]
- Optimisation of pathways [98]

Related conzept: Extremal pathway analysis
Treats reversible reactions differently

- Elementary mode analysis typically unites to and back reactions
- Extremal pathway analysis treats them separated

9.3 Flux Balance Analysis

Next time

Lessons learned

- Metabolic control theory: Summation theorems, give relations between components and systems behavior
- Allow for insights even if the fluxes are not expicitely known as functions of the parameters
- Elementary mode analysis reaveals realisable paths through the network

8F/20
9/17

10 Signal transduction

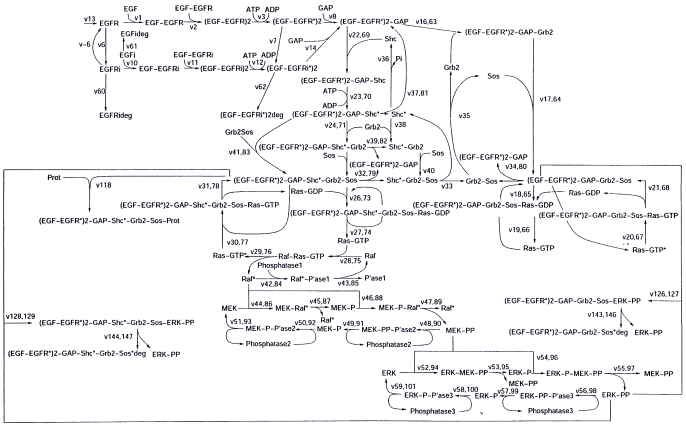

Figure 10.1: MAP kinase pathway

Networks are complex.
But networks are structured by motifs, building blocks:

- Feedback loops
- Feed-forward loops
- Zero-order ultrasensitivity
- Phosphorylation cascades

- Nice overview: "Sniffers, buzzers ..." [109]

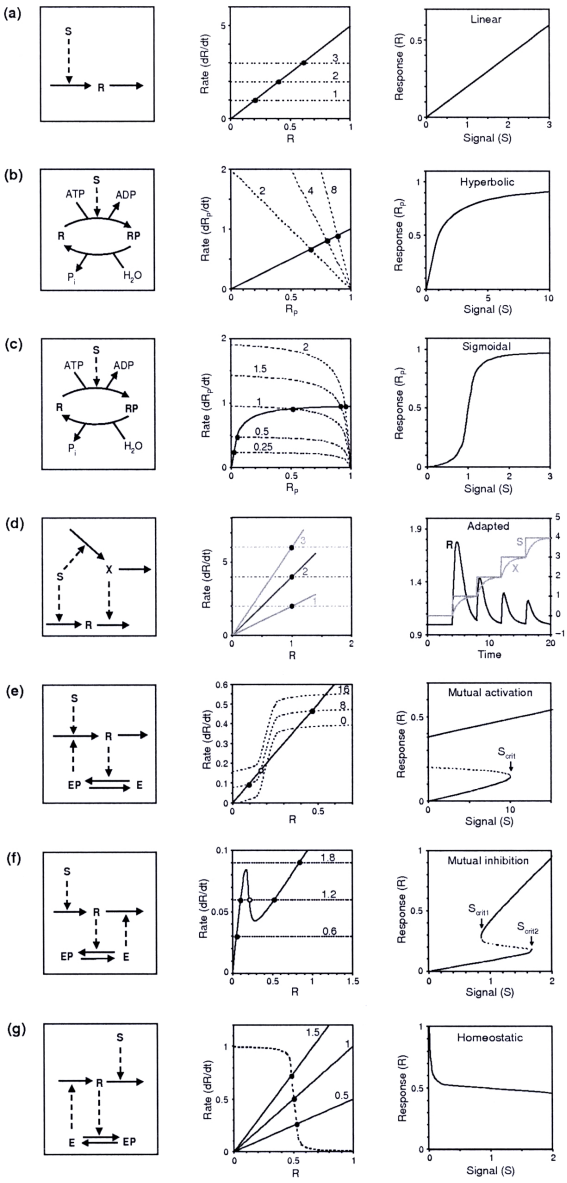

Figure 10.2: "Sniffers, buzzers ..."

10.1 Feedback-Loops

Negative Feedback-Loops

Literature:

- Review "Feedback for physicists: a tutorial essay on control" [4]

Proportional feedback[5]

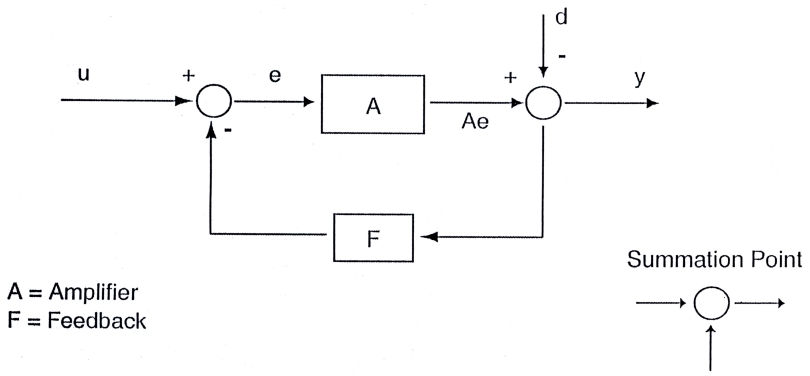

Figure 10.3: Proportional negative feedback [91]

- System described by, for now $d = 0$:

$$\begin{aligned} y &= Ae \\ e &= u - Fy \end{aligned}$$

Elimination of e, to obtain input/output relationship, remember Michaelis-Menten :

$$y = A(u - Fy)$$

$$y = \frac{A}{1 + AF}\, u, \qquad \text{or simply } y = Gu$$

- with G: Closed-loop amplification factor.

[5]Feedback loops were first introduced for amplifiers. Feedback loops in biology

- But:

$$G = \frac{A}{1 + AF} < A$$

Thus, why negative feedback ?

Four reasons

(i) Control of amplification by feedback

For

$$\underline{\text{loop-gain}}\ AF \gg 1 \quad \Longrightarrow \quad G \approx \frac{A}{AF} = \frac{1}{F}$$

$\Longrightarrow$ Feedback determines amplifier properties

A might be complicated, F can be simple

(ii) Robust against variations of amplifier

How do changes of the amplifier effect closed-loop amplification factor G ?

$$\frac{\partial G}{\partial A} = \frac{\partial}{\partial A}\frac{A}{1 + AF} = \frac{1}{(1 + AF)^2}$$

$\Longrightarrow$ Sensitivity decreases with increasing loop-gain

In relative units

$$\frac{A}{G}\frac{\partial G}{\partial A} = \frac{1}{1 + AF}$$

Thus:

$$\frac{\Delta G}{G} = \frac{1}{1 + AF}\frac{\Delta A}{A}$$

(iii) Linearisation of the system

Consider non-linear amplifier $A(u)$:

$$G(u) = y = A(e), \quad e = u - Fy = u - FG(u)$$

yields:

$$G(u) = A(u - FG(u))$$

Differentiate

$$G'(u) = A'(u - FG(u))(1 - FG'(u))$$

Solve for G'

$$G' = \frac{A'}{1 + A'F}$$

For $A'F \gg 1$ follows:

$$G'(u) \approx \frac{1}{F}$$

$\Longrightarrow$ The amplifier becomes linear

(iv) Robust against disturbances of the output

Now, switch on disturbances of the output, i.e. $d \neq 0$

$$\begin{aligned} y &= Ae - d \\ e &= u - Fy \end{aligned}$$

Elimination of e yields:

$$y = \frac{Au - d}{1 + AF}$$

Sensitivity against disturbances of the output

$$\frac{\partial y}{\partial d} = -\frac{1}{1 + AF}$$

$\Longrightarrow$ Eduction/further processing of the output does not disturb the system for large loop-gain

Negative feedback leads to modularisation

This can not be overestimated. Only therfor we can talk about subsystems

- Subsystem is first order
- Interaction with other subsystems is 2. order

Comparison to brain research, especially frontal brain, place of the higher brain functions

- Interaction seems to be the leading term
- Breakdown in moduls not possible
- One has to deal with whole complexity in first place

For all of this holds:

- Robust yet fragile
- Shift of control from A to F
- Consider airplanes
  - Airplanes of brothers Wright was not robust against crosswind, but robust againt breakdown of the electronics (since not present)
  - Airbus is robust against crosswind, but not against breakdown of electronics

Consequences for drug development:

- Never target inside a negative feedback loop !

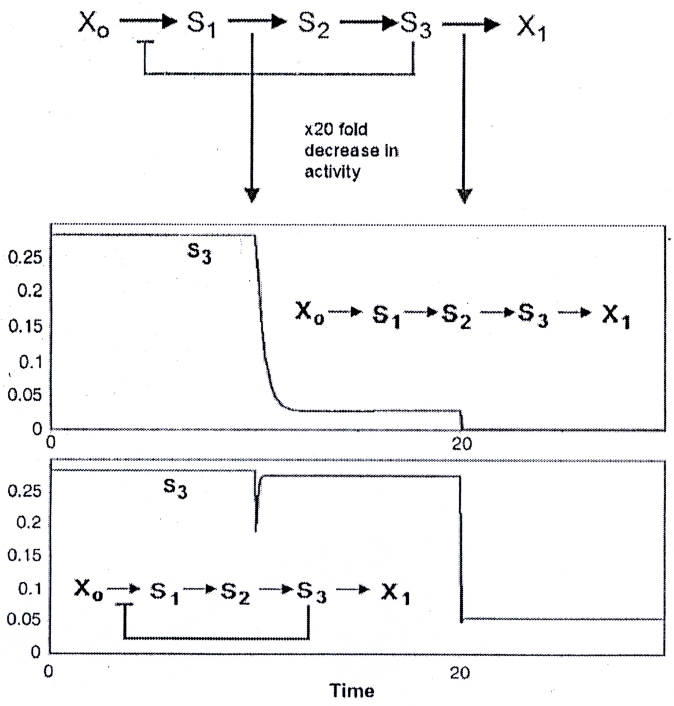

Figure 10.4: Never target inside a negative feedback loop !

Amplification is not always the goal, see Chap. 13.1 Chemotaxis

Proportional negative feedback does not allow for perfect tracking [4]

$$y_\infty = \frac{A}{1+AF}\, u_\infty, \quad y_\infty < u_\infty \qquad \text{for large loop-gain } AF$$

So far static, now consider dynamics:

- Negative Feedback can lead to overshoot oscillations
  Example:
  Temperature of the water while taking a shower
- Simple example:

$$\begin{aligned} \dot{x} &= -ax - by \\ \dot{y} &= cx - dy \end{aligned}$$

Interpretation:

- y is positively regulated by x
- x is negatively regulated by y
- Both are negatively auto-regulated

Linear system:

- $Tr = -a - d$ determines auto-regulation
- $Det = ad + bc$ determines feedback-regulation

Oscillation if $Tr^2 < 4\,Det$: Strong negative feedback can cause oscillations

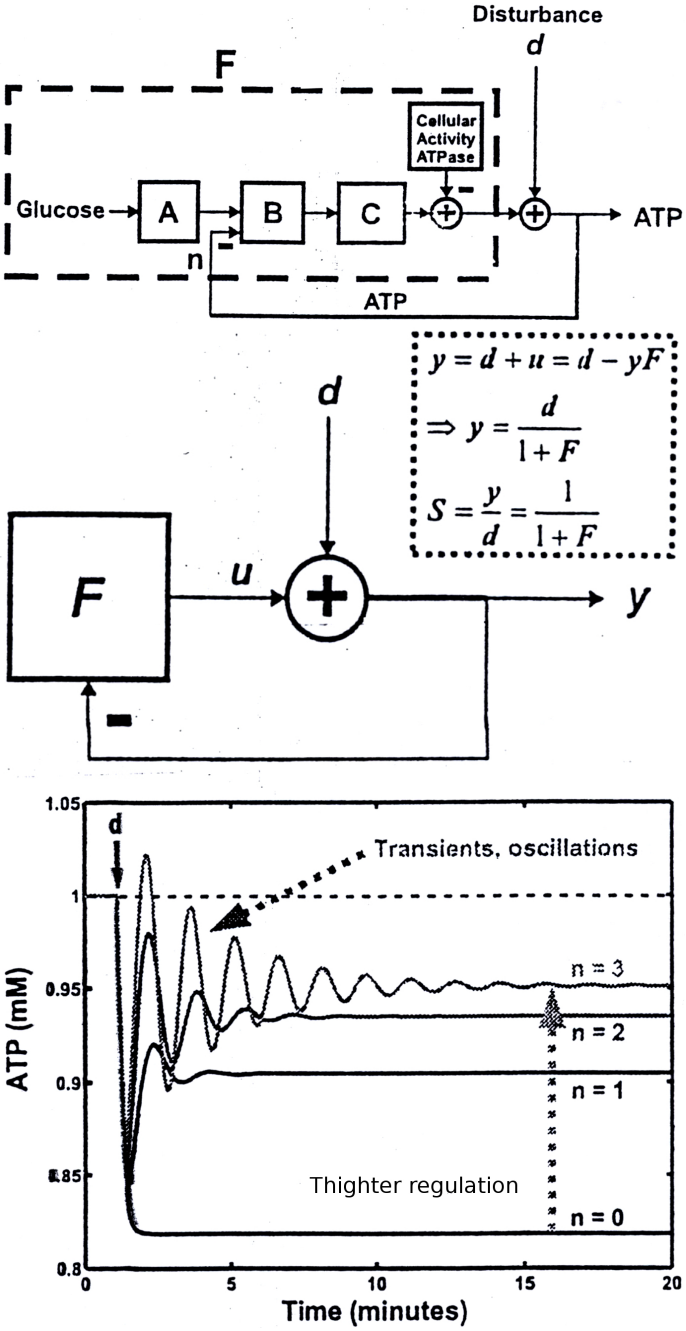

Figure 10.5: Oscillations in negative feedbacks

- For wings of airplanes this can be catastrophic

Integral negative feedback

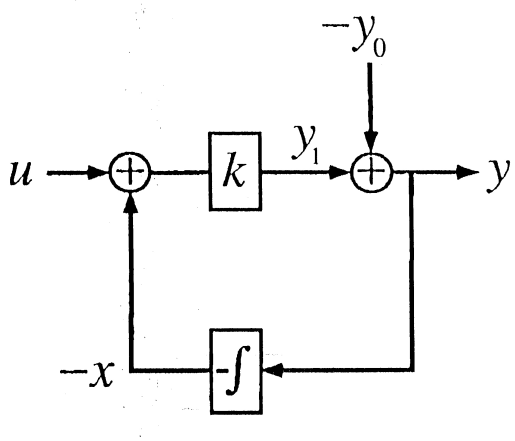

Figure 10.6: Integral negative feedback [121]

- Heater: Temperature is integral over applied energy (in 1. order)
- Serves for perfectes tracking.

$$\dot{y}(t) = -\frac{1}{\tau}y(t) + \frac{K_i}{\tau^2}\int_{-\infty}^{t}[u_\infty - y(t')]dt'$$

Differentiate:

$$\ddot{y}(t) = -\frac{1}{\tau}\dot{y}(t) + \frac{K_i}{\tau^2}[u_\infty - y(t')]$$

Stationary solution: $y_\infty = u_\infty$

- see Chap. 13.1 Chemotaxis

In summary PID negative feedback

- P: proportional: Considers current deviation
- I: integral: Forms a memory of past deviations
- D: differential: Looks at rate of change, predicts future behavior

Negative feedback can accelerate signal transduction [90]

Positive Feedback-Loops

Literature: [109, 25, 24, 120]

Simple example, roughly here, have fun in the exercise

- Protein 1 inhibits protein 2
- Protein 2 inhibits protein 1
- $- \times - = +$
- Both proteins with synthesis and degradation

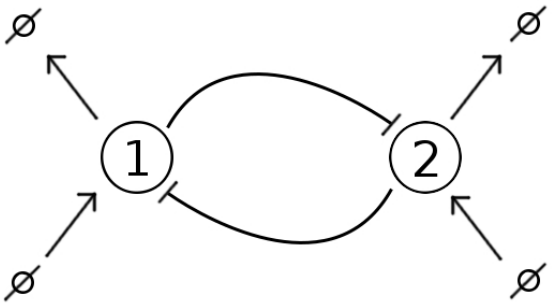

Figure 10.7: Two mutually inhibiting proteins

- Let protein 2 be "stronger"
- Stably protein 2 high, protein 1 low
- Increase synthesis of protein 1, until it overwhelms protein 2
- Now, stably protein 2 low, protein 1 high
- Decrease synthesis rate again
- Result: Hysteresis, a memory

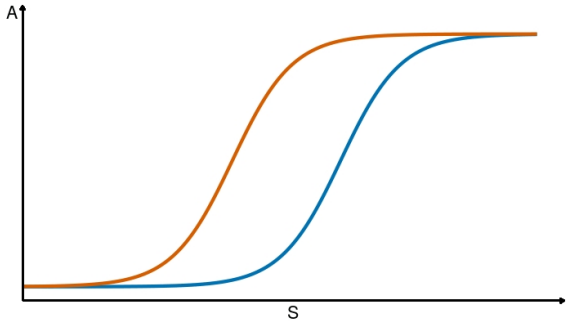

Figure 10.8: Hysteresis in a positive feedback

Effects of negative and positive feedbacks loops in signalling pathways

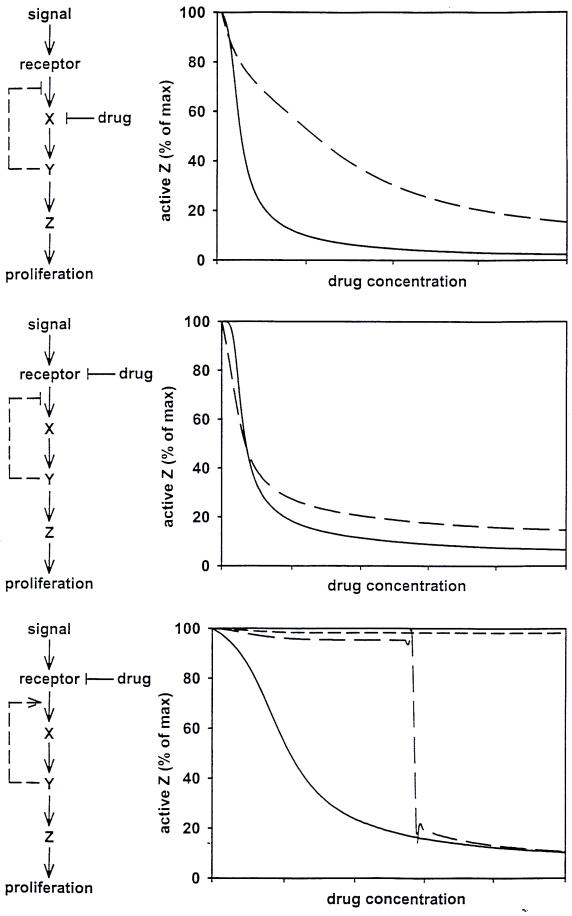

Figure 10.9: Negative and positive feedbacks, dashed lines if feedback is active

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10.2 Feed-forward Loops

Also important in gene regulatory networks

Literature: [99, 66, 70]

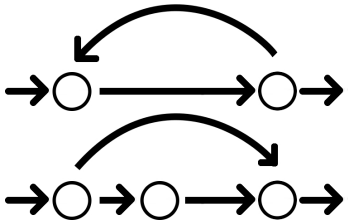


Figure 10.10: Feedback and feed-forward loops

Discrimination: coherent and incoherent feed-forward loops

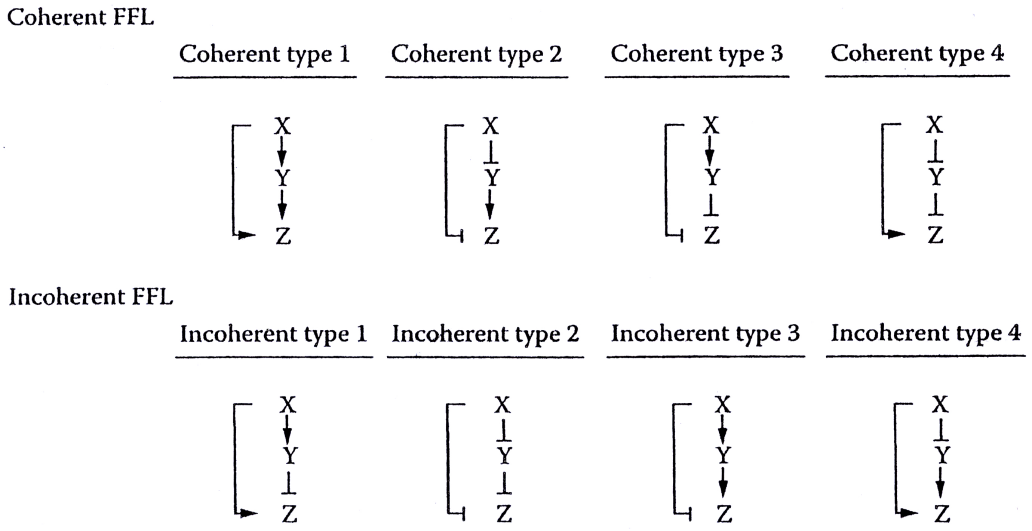


Figure 10.11: The FFL loops

Possible action on the target: logical AND or OR

Coherent Feed-forward Loops

Consider type 1 coherent feed-forward loop with logical AND

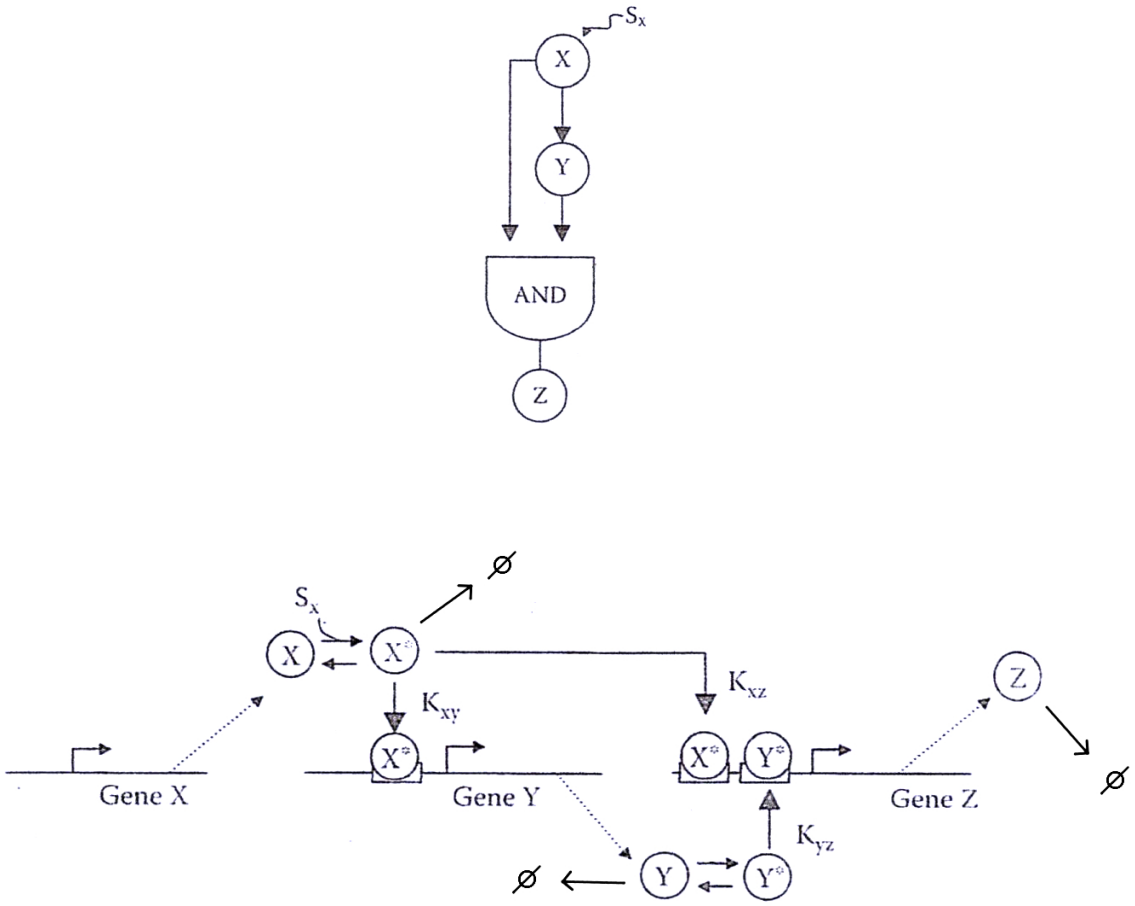


Figure 10.12: Biological realisation of type 1 FFL with logical AND

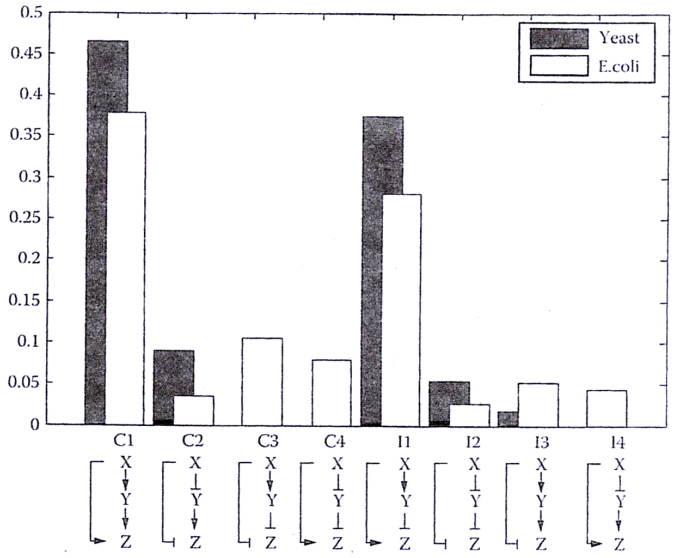


Figure 10.13: Biological realisations

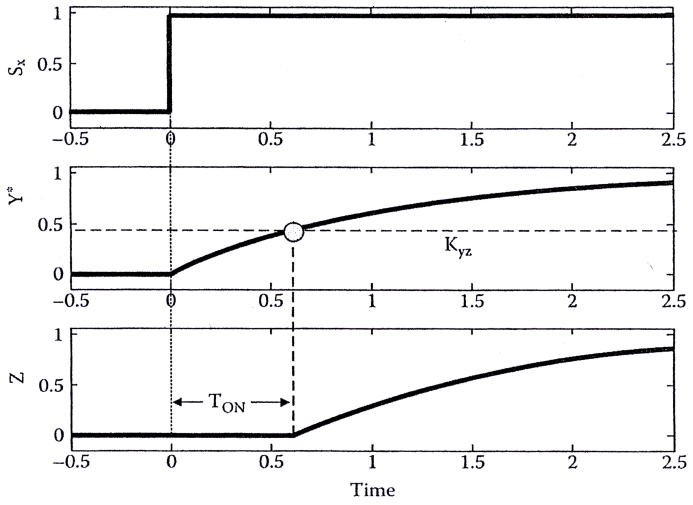


Figure 10.14: Delay in activation

Delay in activation

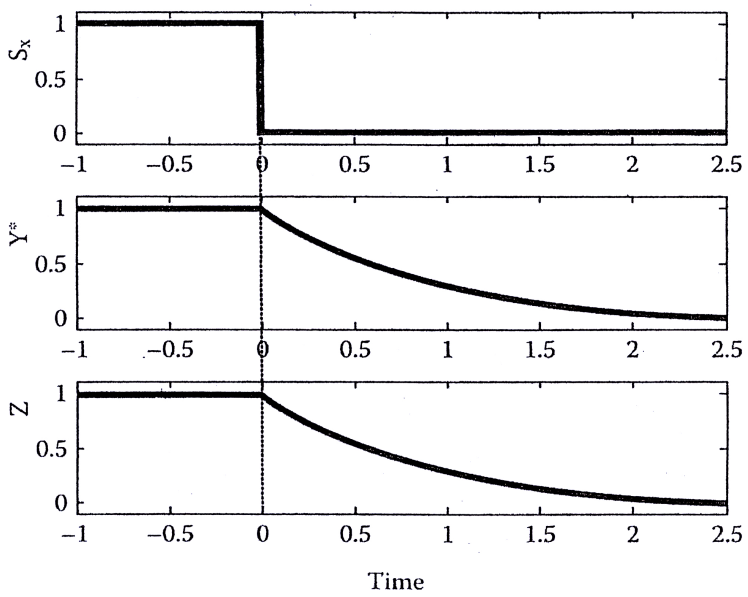


Figure 10.15: No delay in deactivation

No delay in deactivation

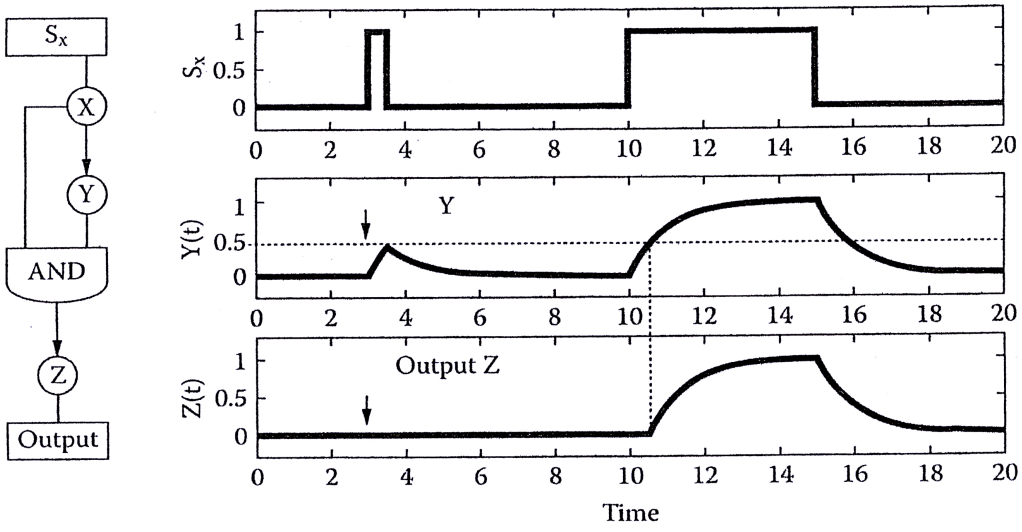


Figure 10.16: Elevator door effect, light barrier

Sign-dependent delay element, Elevator door effect

Robust aganist fluctuations in inactive state

Consider type-1 coherent feed-forward with logical OR

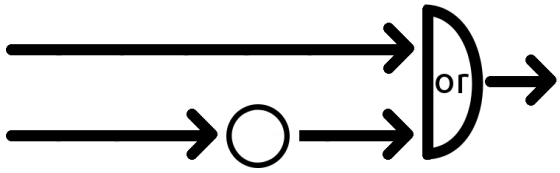


Figure 10.17: Type-1 coherent feed-forward with logical OR

Robust against fluctuations in active state

Incoherent Feed-forward Loops

Consider type-1 incoherent feed-forward loop with logical AND

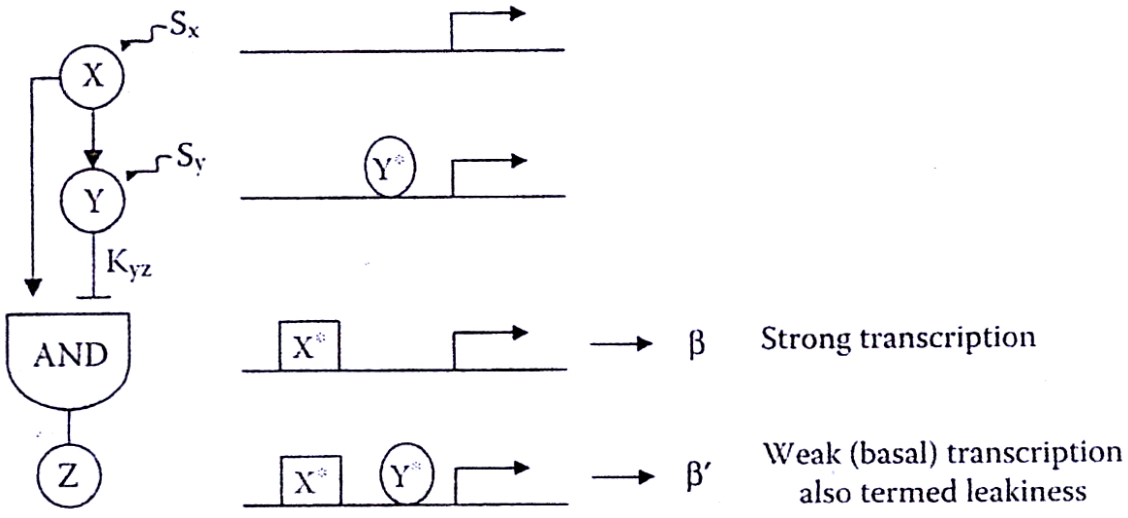


Figure 10.18: Type-1 incoherent FFL logical AND

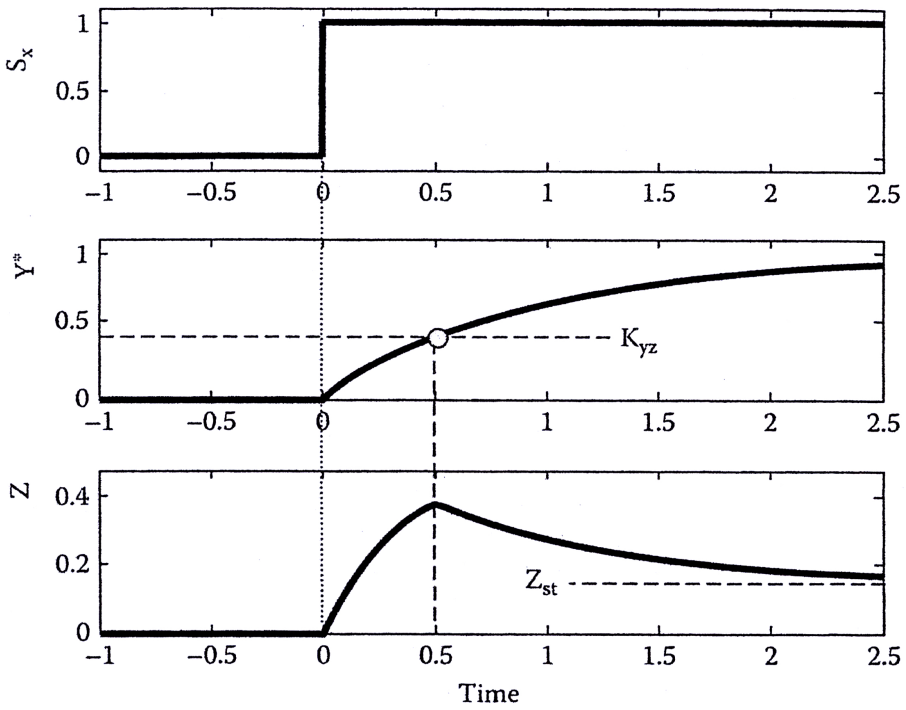


Figure 10.19: Puls generator

- Pulse generator
- Several of them with different times for maxima regulate just in time gene expression [50]

To extend:

- Logarithmic Weber-Fechtner law by feedforward-loop

10.3 Zero-order ultrasensitivity

Remark on sniffers slide

Reversible modifications of proteins T are ubiquitous regulatory mechanism

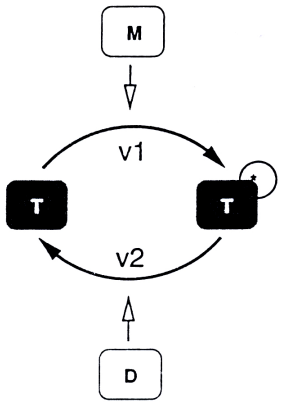


Figure 10.20: Reversible phosphorylation

Simplest case [31, 32]

- Enzymes that modify (M) and demodify (D) the protein
- Phosphorylation by kinases
- Dephosphorylisation by phosphatases

$$\dot{T}^* = v_1 - v_2$$

$$v_1 = \frac{k_1\, M\, T}{K_1 + T}$$

$$v_2 = \frac{k_2\, D\, T^*}{K_2 + T^*}$$

With

$$T + T^* = T_{tot}$$

$$v_1 = \frac{k_1\, M\, (T_{tot} - T^*)}{K_1 + (T_{tot} - T^*)}$$

follows:

$$v_1 = \frac{k_1\, M\, (1 - T^*/T_{tot})}{K_1/T_{tot} + (1 - T^*/T_{tot})}$$

$$v_2 = \frac{k_2\, D\, (T^*/T_{tot})}{K_2/T_{tot} + (T^*/T_{tot})}$$

Both only depend on T^*.

Steady state is given by intersection.

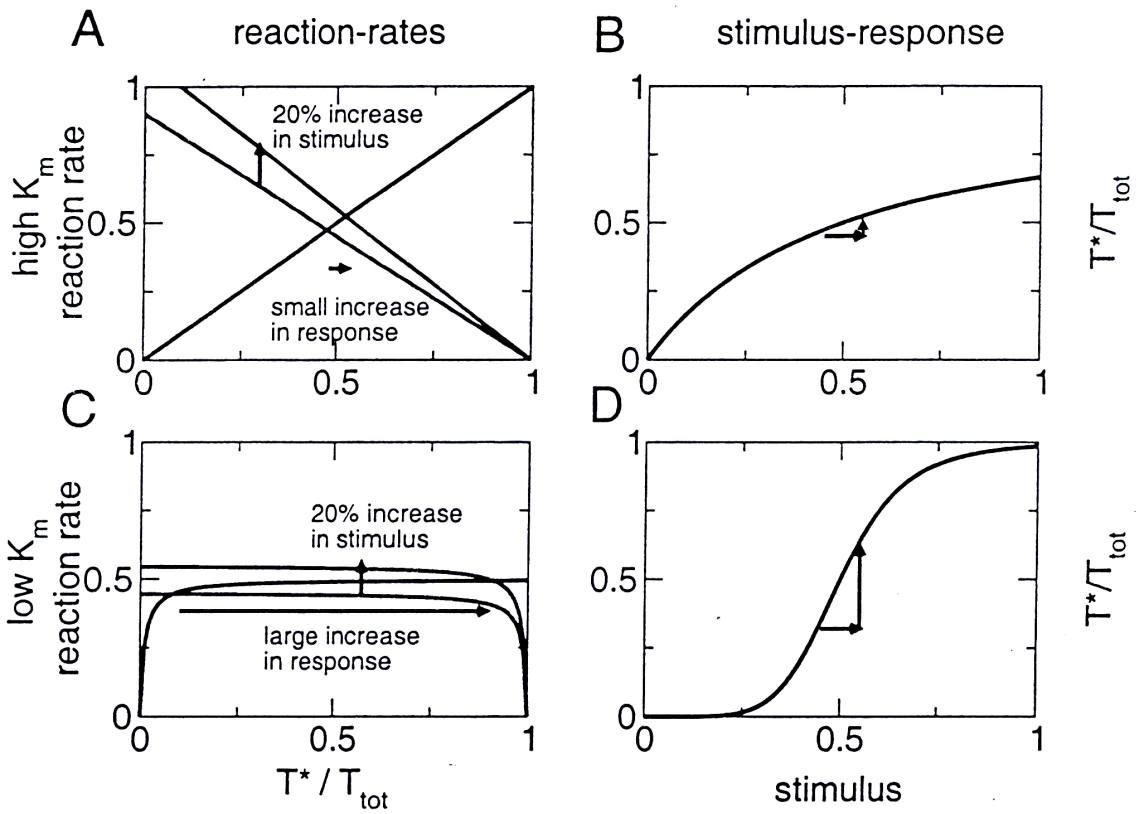


Figure 10.21: Zero-order ultrasensitivity

- Enzymes work in saturation, "zero order" reactions
- "Zero order ultrasensitivity" = Threshold behavior, robustness against noise

- Critical discussion [9]

10M/20

10.4 Phosphorylation Cascades

The most famous one: MAP Kinase cascade

Literature: MAP Kinase [23, 45, 56, 7, 8]

- MAP Kinase cascade: Mitogen activated protein kinase cascade
- Kinase: Phosphorylates a protein
- Mitogen: induces mitosis, mitosis: cell division

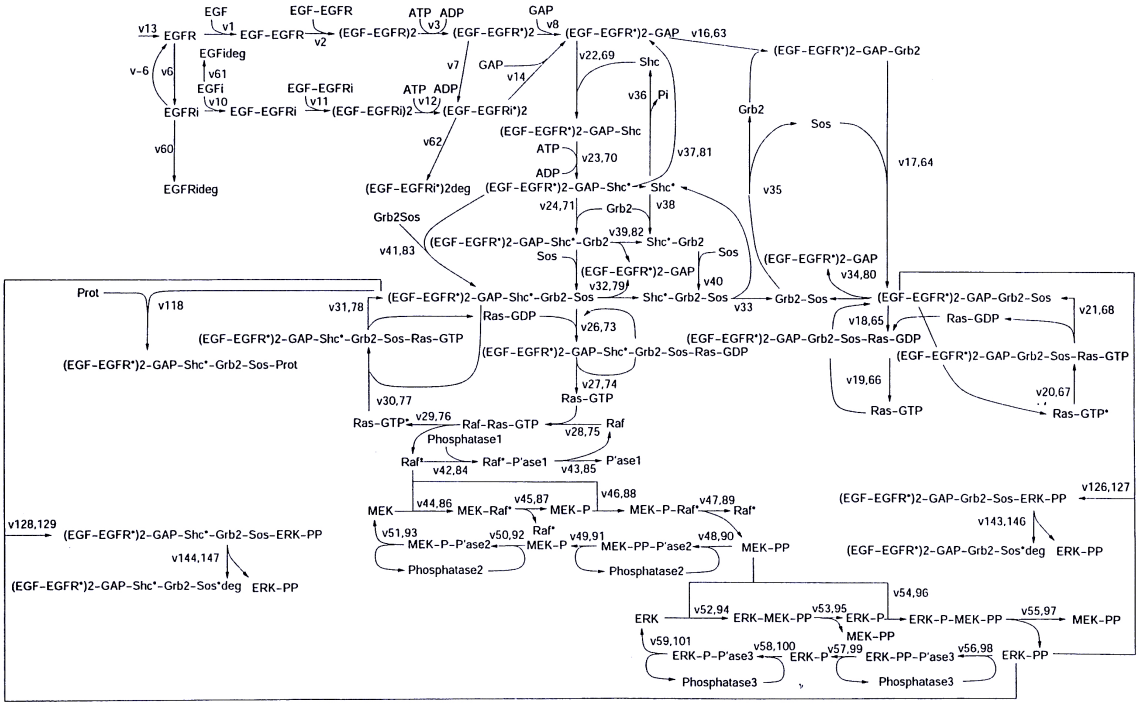


Figure 10.22: The complex picture

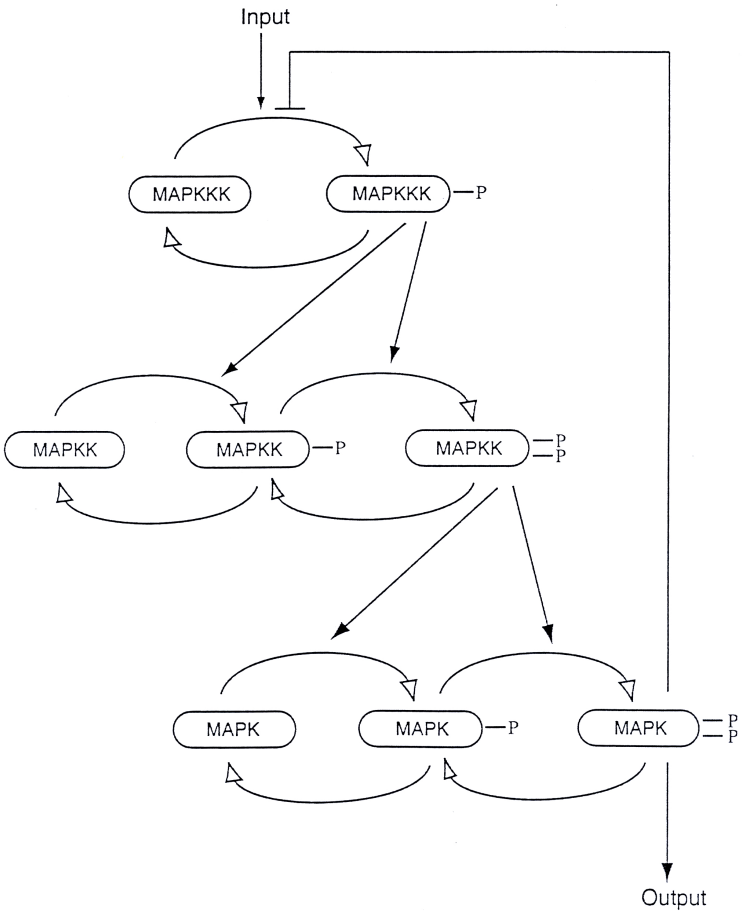


Figure 10.23: A simplifed scheme

Static Situation [23]

- Three times Michaelis-Menten gives sigmoidal
- As ultrasensitivity for cooperativity, robust against fluctuations in input if not close to the threshold

Dynamic situation [35]

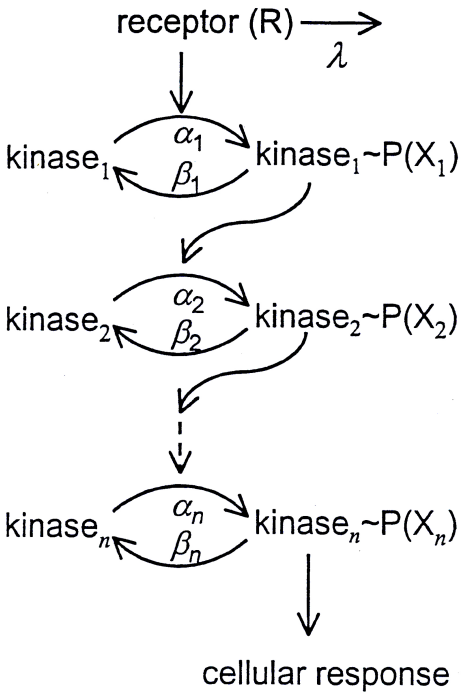


Figure 10.24: A very simplified MAP kinase scheme, we already know what the feedback does

Note: Substrates become enzymes (kinases)

Notation:

- $\tilde{x}_i$: non-phosphorylated (inactive) kinase
- x_i: phosphorylated (active) kinase, $x_i = 0$ for $t < 0$
- $c_i = \tilde{x}_i + x_i$: total
- $R(t)$: Receptor activation

Assumptions:

- Concentration of substrates smaller than Michaelis-Menten constants
  $\Longrightarrow$ Mass action kinetics

- Phosphatases are constant

  $\Longrightarrow$ Dephosphorylisation proportional to x_i

- Receptor activiation $R(t) = 0$ for $t < 0$ and

$$R(t) = R\exp(-\lambda t) \quad \text{for } t > 0$$

WS 19

The dynamics

- First reaction:

$$\dot{x}_1 = \tilde{a}_1 R(t)\tilde{x}_1 - b_1 x_1$$

  downstream:

$$\dot{x}_i = \tilde{a}_i x_{i-1}\tilde{x}_i - b_i x_i$$

- With $c_i = \tilde{x}_i + x_i$ und $a_i = c_i\tilde{a}_i$

$$\dot{x}_1 = a_1 R(t)\left(1 - \frac{x_1}{c_1}\right) - b_1 x_1 \tag{47}$$

  for downstream reactions

$$\dot{x}_i = a_i x_{i-1}\left(1 - \frac{x_i}{c_i}\right) - b_i x_i \tag{48}$$

  Note: $x_i(0) = x_i(\infty) = 0$

Characteristic quantities:

- Signaling time:

$$\tau_i = \frac{T_i}{I_i}, \quad \text{with } I_i = \int_0^\infty x_i(t)\,dt, \quad T_i = \int_0^\infty t x_i(t)\,dt$$

- Signal duration:

$$\vartheta_i = \sqrt{\frac{Q_i}{I_i} - \tau_i^2}, \quad \text{mit } Q_i = \int_0^\infty t^2 x_i(t)\,dt$$

- Signal amplitude:

$$S_i = \frac{I_i}{2\vartheta_i}$$

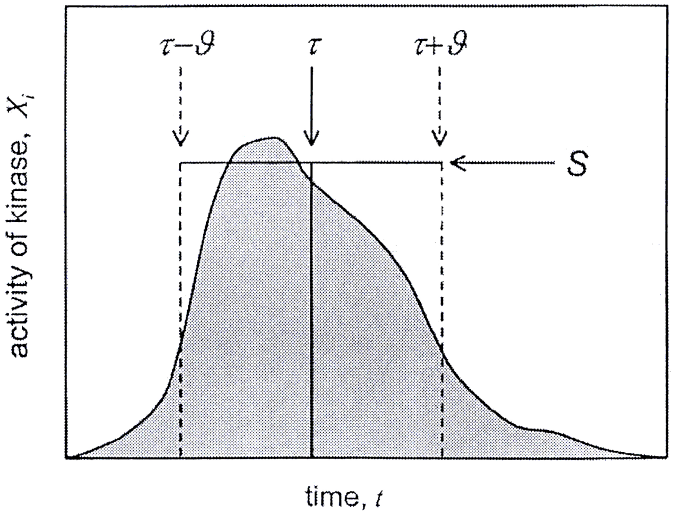


Figure 10.25: The characteristic quantities: Time τ_i, duration ϑ_i, and amplitude S_i

Consider: Weakly activited pathway: $x_i \ll c_i$

Eqs. (47, 48) become

$$\begin{aligned} \dot{x}_1 &= a_1 R(t) - b_1 x_1 \\ \dot{x}_i &= a_i x_{i-1} - b_i x_i \end{aligned} \tag{49}$$

The quantities τ_i, ϑ_i, S_i can be calculated analytically

- Signaling time τ_i
  - From receptor activation $R(t) = R\,\exp(-\lambda t)$ follows:
    - $I_0 = R/\lambda$
    - $T_0 = R/\lambda^2$
    - $\tau_0 = 1/\lambda$

– Eq. (49) yields:

$$I_i = \frac{a_i}{b_i} I_{i-1} \tag{50}$$

since

$$I_i = \int_0^\infty x_i(t)\,dt = \frac{a_i}{b_i}\int_0^\infty x_{i-1}\,dt - \frac{1}{b_i}\underbrace{\int_0^\infty \dot{x}_i\,dt}_{=0} = \frac{a_i}{b_i} I_{i-1}$$

Thus:

$$\boxed{I_n = \frac{R}{\lambda}\prod_{i=1}^{n}\frac{a_i}{b_i}}$$

– Multiply eq. (49) by t and integrate over t yields

$$\int_0^\infty t\,\dot{x}_i\,dt = a_i\int_0^\infty t\,x_{i-1}(t)\,dt - b_i\int_0^\infty t\,x_i(t)\,dt$$

LHS: Partial integration:

$$\int_0^\infty t\,\dot{x}_i\,dt = [t\,x_i]_0^\infty - \int x_i\,dt = -I_i$$

Results in:

$$I_i = -a_i T_{i-1} + b_i T_i \tag{51}$$

– Divide eq. (51) by I_i and complement 1

$$1 = -a_i\frac{T_{i-1}I_{i-1}}{I_{i-1}I_i} + b_i\frac{T_i}{I_i}$$

Remember definition $\tau_i = \frac{T_i}{I_i}$ and eq. (50)

– Yields:

$$1 = -a_i\tau_{i-1}\frac{b_i}{a_i} + b_i\tau_i$$

Recursion equation for τ_i

$$\tau_i = \tau_{i-1} + \frac{1}{b_i}$$

– Thus:

$$\tau_n = \frac{1}{\lambda} + \sum_{i=1}^{n} \frac{1}{b_i}$$

Signalling time depends only on *pari passu* phosphatases.

- Signaling duration ϑ_i
  - Multiply eq. (49) by t^2
  - Integration yields:
    $$2T_i = -a_i Q_{i-1} + b_i Q_i$$
  - Leads to
    $$\vartheta_i^2 = \vartheta_{i-1}^2 + \frac{1}{b_i^2}$$
    and finally to

$$\vartheta_n = \sqrt{\frac{1}{\lambda^2} + \sum_{i=1}^{n} \frac{1}{b_i^2}}$$

Signalling duration depends on *pari passu* phosphatases.

- Analogously signaling amplitude S_i

$$S_n = \frac{\frac{R}{2} \prod_{i=1}^{n} \frac{a_i}{b_i}}{\sqrt{1 + \lambda^2 \sum_{i=1}^{n} \frac{1}{b_i^2}}} = \frac{\frac{R}{2} \prod_{i=1}^{n} \frac{a_i}{b_i}}{\lambda \vartheta_n} \tag{52}$$

Interpretation:

- Kinases have no influence on signalling time und duration
- High amplitudes by fast kinases and slow phosphatases

  Kinases have larger effect on amplitudes as phosphatases, since the latter are in denominator and in the nominator
- Phosphatases have negative effect on all quantities

  Ergo: High amplitudes only to the expence of high signalling time and duration

- It holds $\tau_{i+1} > \tau_i$, $\vartheta_{i+1} > \vartheta_i$
- Relation between S_{i+1} and S_i: Anything goes
- Experimentally validated [43], see also [42]

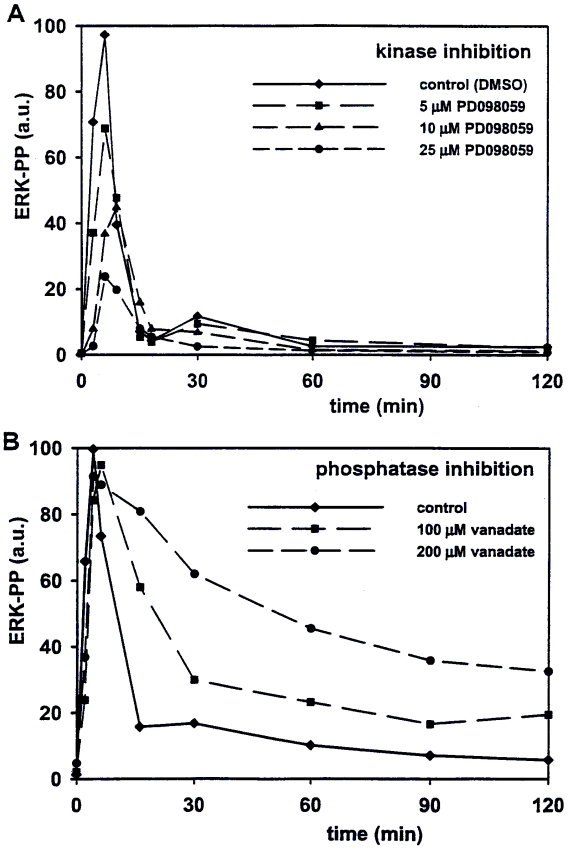


Figure 10.26: Experimental validation

Amplification[6] :
From eq. (52), $S_{i+1} > S_i$, if

$$b_i < a_i \sqrt{1 - \frac{1}{a_i^2 \vartheta_{i-1}^2}}$$

[6]Remember: Amplification is not necessarily the goal of signalling, but MAP kinase cascade is typically amplifying

- Phosphatases must be slower than kinases, makes sense
- If duration of the previous step long: phosphatases can be a little bit faster

  Since signalling duration ϑ_i increases with i: Amplification better late in cascade

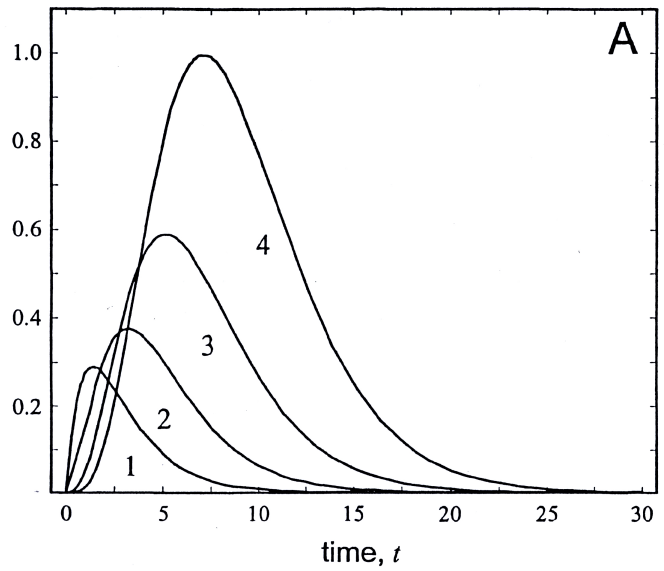


Figure 10.27: Parameters fixed, longer cascade

Counter-acting effects:
Longer cascades ...

- ... cause higher signalling time and duration
- ... allow for distribution of amplification with faster phosphatases in the single steps

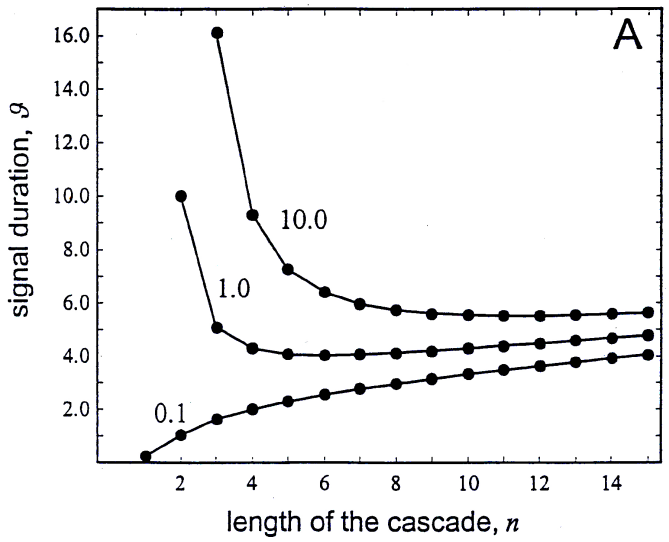


Figure 10.28: Signalduration in dependence on length of cascade and amplification factor

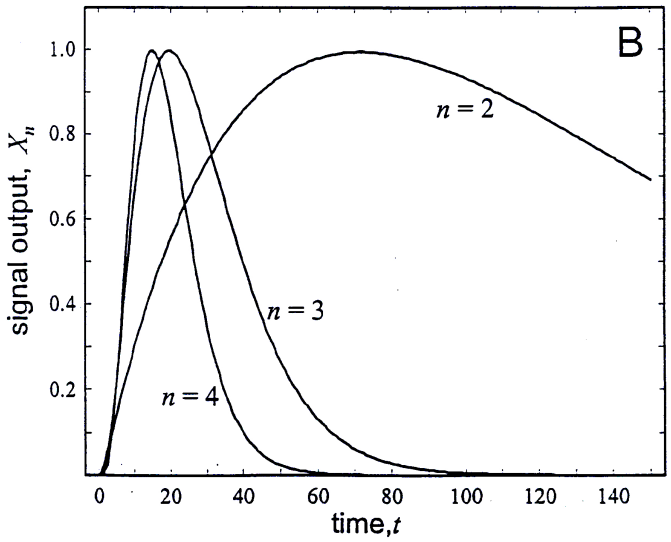


Figure 10.29: Effect of longer cascades

- Longer cascades enable sharper and faster signals.

- Explanation for biological fact of cascade with multiple (three) steps

Big Picture:

- Systems Biology: Use modules to understand biological systems
- Synthetic Biology: Use modules to design artificial biological systems

WS 20
10F/20

11 Parameter Estimation in Dynamical Systems 10/17

- In general, parameters are unknown and can not be measured directly
- Idea: Estimate parameters from time resolved data

Needs three ingredients

- Parameter estimation theory
  What is a "good" estimator ?
- Optimization algorithms
  Non-linear problem
  $\Longrightarrow$ Estimation has to be done numerically
- Statistics
  How well are parameters determined by the data, confidence intervals ?

In our case

- Dynamics:
$$\dot{\vec{x}} = \vec{f}(\vec{x}, \vec{p}, \vec{u}), \quad \vec{x} \in \mathbb{R}^n_+, \quad \vec{u} \text{ external stimuli}$$
- Observations
  - Typically not all components can be measured
  - Or, only combinations of them
  - Measurements often on relative scale
  - Measurements are noisy

Thus, observations:

$$\vec{y}(t_i) = \vec{g}(\vec{x}(t_i), \vec{p}) + \vec{\epsilon}(t_i), \quad \vec{\epsilon}(t_i) \sim N(0, \Sigma_i), \quad \vec{y} \in \mathbb{R}_+^m$$

with $m < n$

- Parameter estimation in nonlinear, partially observed, noisy, non-autonomous, stiff, sparse dynamical systems

11.1 Parameter Estimation Theory

Two fundamentally different approaches

- Frequentists' approach

  There are true parameters. With increasing number of data there is a chance to determine them more and more exactly

- Bayesian approach

  Parameters are random variables. They have a distribution

  Prior knowledge can be incorporated

Maximum likelihood estimation

Assume the probability distribution of possible data x given parameter a is given by $p(x, a)$

- a is known and fixed
- For all possible x, $p(x, a)$ determines their probability of occurence
- It holds

$$\int_{-\infty}^{\infty} p(x, a)\, dx = 1$$

For parameter estimation, data x_i, $i = 1, \ldots, N$ is given, a is unknown

- Data x_i are known and fixed
- a is unknown
- Idea: Read $p(x_i, a)$ in dependence on a

- It holds
$$\int_{-\infty}^{\infty} p(x,a)\,da \neq 1$$
$p(x,a)$ in dependence on a is not a probalility.
- It is called <u>likelihood</u> $L(a)$
- Choose a such that the probability for the observed data, the likelihood, is maximum
$\Longrightarrow$ Maximum likelihood estimation
- For a single given data point x
$$L(a) = p(x,a)$$
For N data points
$$L(a) = \prod_{i=1}^{N} p(x_i,a)$$
- Maximizing products (numerically) is no fun
- Good news: The value of a that maximizes $L(a)$ stays the same if one maximizes twice the logarithm of $L(a)$, the log-likelihood $LL(a)$
$$LL(a) = \sum_{i=1}^{N} \log p(x_i,a)$$
- Typically minus the log-likehood is considered and minimized and ...
- ... to maximize confusion again called the likelihood

Towards our setting

- Special case:
For independent Gaussian distributed data, a: the mean μ. σ^2 assumed to be known

$$p(x_i, \mu) = \frac{1}{\sqrt{2\pi}\sigma} e^{-\frac{(x_i-\mu)^2}{2\sigma^2}}$$

Likelihood:

$$L(\mu) = \prod_{i=1}^{N} \frac{1}{\sqrt{2\pi}\sigma} e^{-\frac{(x_i-\mu)^2}{2\sigma^2}}$$

- Minus twice the log-likelihood

$$-2LL(\mu) = \text{const.} \ + \sum_{i=1}^{N} \frac{(x_i - \mu)^2}{\sigma^2}$$

Here, $-2LL(\mu)$ is called $\chi^2(\mu)$ since it is χ^2-distributed for the true μ

$$''\chi^2_r = \sum_{i=1}^{r} N(0,1)^{2''}$$

- For Gaussian distributed errors minimising weighted least squares is the maximum likelihood estimator
- Otherway around: If you use weighed least squares you have (implicitely) assumed Gaussian errors
- In general

$$\chi^2(p) = \sum_{i=1}^{N} \frac{(x_i - \text{model}\,(p))^2}{\sigma^2}$$

- Summary

Dynamics:

$$\dot{\vec{x}} = \vec{f}(\vec{x}, \vec{p}, \vec{u}), \quad \vec{x} \in \mathbb{R}^n_+$$

Observations:

$$\vec{y}(t_i) = \vec{g}(\vec{x}(t_i), \vec{p}) + \vec{\epsilon}(t_i), \quad \vec{\epsilon}(t_i) \sim N(0, \Sigma_i), \quad \vec{y} \in \mathbb{R}^m_+$$

Minus twice the log-likelihood, χ^2

$$\chi^2(\vec{p}, \vec{x}(t_0)) = \sum_{i=1}^{N} \sum_{j=1}^{M} \left(\frac{(y_j^D(t_i) - g_j(\vec{x}(t_i; \vec{p}, \vec{x}(t_0))}{\sigma_{ij}} \right)^2 \tag{53}$$

WS 21

11.2 Optimization algorithms

The bible for numerics: The Numerical Recipes [81]

- Optimization problem eq. (53) can not be solved analytically, but need to be solved numerically
- Optimization problem is non-linear

  $\Longrightarrow$ There will be local optima

Two general classes of optimizers

- Deterministic 'local' optimisers
  - Take an initial parameter guess and run down the hill
  - Apply gradient and curvature information, see below
  - Use several different initial parameter guesses to find the global optimum
- Stochastic 'global' optimisers
  - Take an initial parameter guess and apply heuristic search strategy
  - Central: Allow with a certain probability to run up the hill to escape local optima
  - Simulated annealing, genetic algorithm
  - Problem: Magic parameters that correspond to gradient an curvature

9/19

How to determine a good optimizer [87]

- Start the optimizer multiple time with different initial guesses
- Sort the final results by their likelihood
- Since one can in general only expect convergence to a local optimum, at least steps in the sorted likelihood should appear.

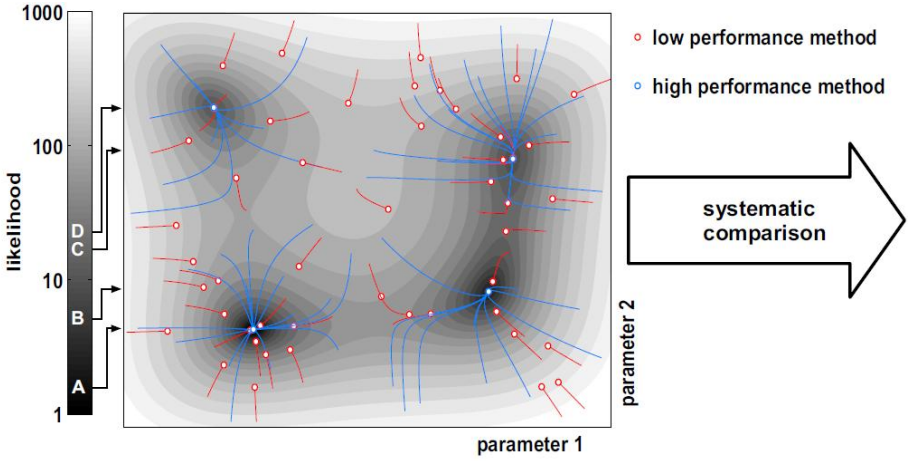


Figure 11.1: Likelihood landscape of the Himmelblau function

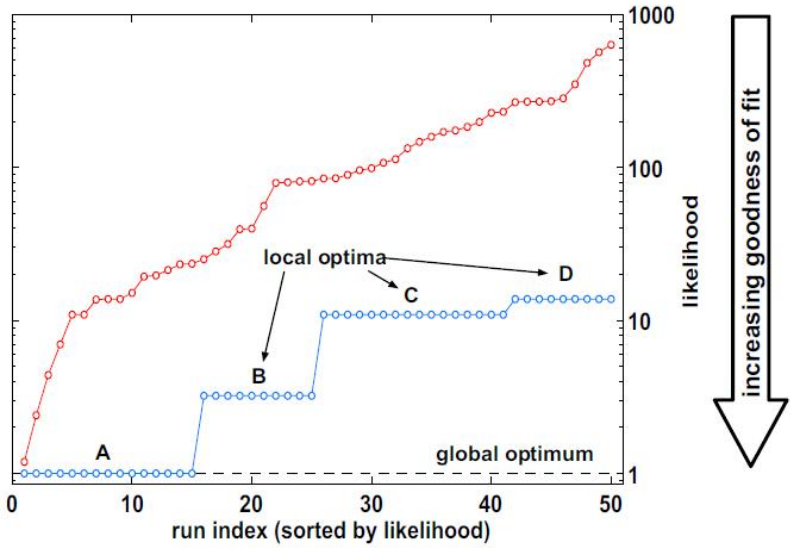


Figure 11.2: Sorted -log-likelihood values

Deterministic optimisation/minimisation algorithms

Simplest version: Steepest descent

- Follow the negative gradient

$$p_{i+1} = p_i - \lambda \nabla \chi^2(p_i) \tag{54}$$

- Choice of λ unclear
- Line search algorithm

$$\arg\min_{\lambda} \chi^2(p_i - \lambda \nabla \chi^2(p_i))$$

Observation:

- If one is close to the optimum, χ^2 is a parabola, $\Delta p = p_{i+1} - p_i$

$$\chi^2(p_i + \Delta p) \approx \chi^2(p_i) + \nabla \chi^2(p_i)\Delta p + \frac{1}{2}\Delta p^T H(p_i)\Delta p \tag{55}$$

with Hessian

$$H(p) = \frac{\partial^2 \chi^2(p)}{\partial p_i \partial p_j}$$

Minimum of RHS of eq. (55), derivative with respect to Δp equals 0

$$0 = \nabla \chi^2(p_i) + H(p_i)\Delta p \Longrightarrow \Delta p = -H^{-1}(p_i)\nabla \chi^2(p_i)$$

- Minimum can be reach in a single Newton-step by

$$p_{min} = p_i - H^{-1}(p_i)\nabla \chi^2(p_i) \tag{56}$$

A zoo of optimization algorithms

- Steepest descent, line search
- Conjugate gradients

  Choose iteratively orthogonal gradients with respect to the metric induced by the Hessian
- Quasi-Newton method

  Calculating of Hessian is expensive: Approximates Hessian iteratively based on gradients
- Trust-region method

  Checks, for which region the quadratic approximation is good

- Levenberg-Marquard method for least squares problems $y = y(x_i, p)$

$$\chi^2(p) = \sum_i \frac{(y_i - y(x_i, p))^2}{\sigma_i^2}$$

  - Do a mixture of a steepest descent and approximative Newton step. Gradient:

$$\frac{\partial \chi^2}{\partial p_k} = -2 \sum_{i=1}^{N} \frac{y_i - y(x_i, p)}{\sigma_i^2} \frac{\partial y(x_i, p)}{\partial p_k}$$

    Hessian:

$$\frac{\partial^2 \chi^2}{\partial p_k \partial p_l} = 2 \sum_{i=1}^{N} \frac{1}{\sigma_i^2} \left(\frac{\partial y(x_i, p)}{\partial p_k} \frac{\partial y(x_i, p)}{\partial p_l} - (y_i - y(x_i, p)) \frac{\partial^2 y(x_i, p)}{\partial p_k \partial p_l} \right)$$

    If model is correct, the second term should be small. Neglect it. Convention :

$$\beta_k = -\frac{1}{2} \frac{\partial \chi^2(p)}{\partial p_k}, \quad \alpha_{kl} = \frac{1}{2} \frac{\partial^2 \chi^2(p)}{\partial p_k \partial p_l}$$

  - With $\delta p_l = (p_{i+1} - p_i)_l$, eq. (56) becomes

$$\sum_{l=1}^{M} \alpha_{kl} \delta p_l = \beta_k \tag{57}$$

  - Note : Steepest Descent given by:

$$\delta p_l = \text{const } \beta_l \tag{58}$$

  - Idea Levenberg-Marquardt algorithm:
    - Far away from optimum, Newton-step eq. (57) might be bad.
    - Take gradient-step Gl. (54). How to choose "const" ?
    - $\chi^2(p)$ dimension-less, dimension $[\beta_l]$ = dimension $[1/\delta p_l]$, consider eq. (57) $\Longrightarrow$
      $1/\alpha_{ll}$ is candidat for scaling.

* To be on the save side, step not too large, choose $\lambda \gg 1$

$$\delta p_l = \frac{1}{\lambda \alpha_{ll}} \beta_l \quad \text{or} \quad \lambda \alpha_{ll} \delta p_l = \beta_l \tag{59}$$

– Combine gradient step Gl. (59) and Newton-step Gl. (57) by

$$\begin{aligned} \alpha'_{jj} &= \alpha_{jj}\,(1+\lambda) \\ \alpha'_{jk} &= \alpha_{jk}, \quad \text{für } j \neq k \end{aligned}$$

yields:

$$\sum_{l=1}^{M} \alpha'_{kl} \delta p_l = \beta_k \tag{60}$$

Interpretation:

* If λ large $\Longrightarrow$ α'_{kl} diagonal-dominated $\Longrightarrow$ small gradient step
* For $\lambda \to 0$, Newton-step

Procedere:

1. Choose initial choice for p, Calculate $\chi^2(p)$
2. Choose small λ, e.g. $\lambda = 0.001$. Expresses hope
3. Solve eq. (60) and calculate $\chi^2(p + \delta p)$
4. If $\chi^2(p + \delta p) \geq \chi^2(p)$, reject δp, choose $\lambda = 10\lambda$, go to 3
5. If $\chi^2(p + \delta p) < \chi^2(p)$, accept δp, choose $\lambda = 0.1\lambda$, go to 3.
6. At optimum, $\chi^2(p + \Delta p) = \chi^2(p)$, λ will increase
7. Terminate optimisation if $\lambda > 10^6$

Interpretation:

If Newton step

– successful, more of it

– not successful, choose (save) gradient step

- If χ^2 does not decrease for a proposed δp give more weight to a smaller steepest descent step

- If χ^2 decreases, give more weight to the approximative Newton step

Deterministic 'local' optimisers in our case $y = g(x, p)$ require derivatives

$$\frac{dg}{dp} = \frac{\partial g}{\partial x}\frac{\partial x}{\partial p} + \frac{\partial g}{\partial p}, \qquad \frac{\partial g}{\partial x}, \frac{\partial g}{\partial p} \quad \text{no problem}$$

- Finite difference

$$\frac{\partial x(t,p)}{\partial p_i} \approx \frac{x(t,p) - x(t,p+he_i)}{h},$$

  Two error sources:

  - Discretisation error h
  - Different step size controls for integrating $x(t,p)$ and $x(t,p+he_i)$
  - Uncontrollable

- Sensitivity equations

$$\frac{d}{dt}\frac{\partial x}{\partial p} = \frac{\partial \dot{x}}{\partial p} = \frac{\partial f(x,p)}{\partial p} = \frac{\partial f}{\partial x}\frac{\partial x}{\partial p} + \frac{\partial f}{\partial p}$$

  Can be integrated in parallel with the dynamics

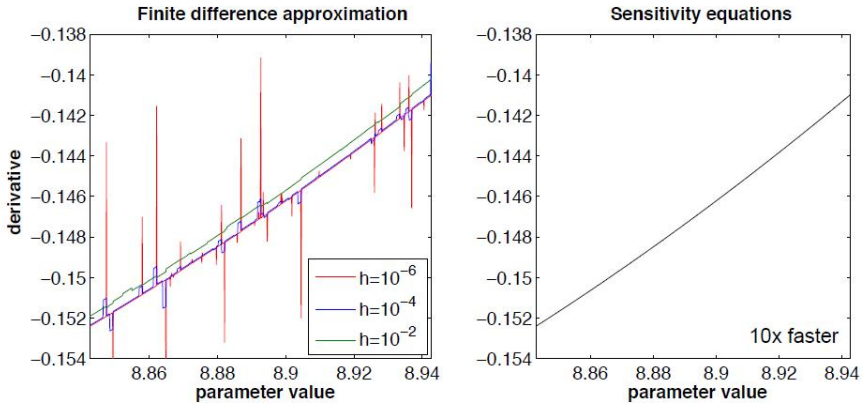


Figure 11.3: Finite differences vs. sensitivity equations

WS 21
10.5/17
11M/20

11.3 Statistics

Optimisation algorithms deliver a point estimate, a number

- What is the uncertainty of that number ?

Random variable

- Something that has a distribution $p(x)$
- Expectation value of random variable

$$\langle x \rangle = \int dx\, p(x)\, x$$

  Expectation value is a number.

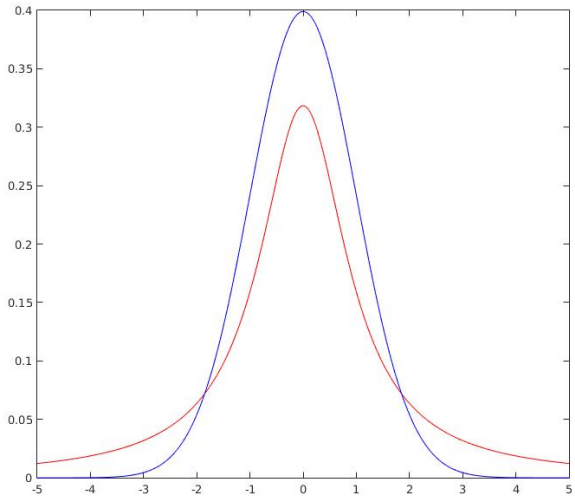
Examples

- Gaussian, normal distribution: $N(\mu, \sigma^2)$

$$p_N(x) = \frac{1}{\sqrt{2\pi}\sigma} e^{-\frac{(x-\mu)^2}{2\sigma^2}}$$

- Cauchy distribution, see Sec. 3.3.2 Spatial effects in SIR models

$$p_{Cauchy}(x, a, \gamma) = \frac{1}{\pi} \frac{\gamma^2}{(x-a)^2 + \gamma^2}$$

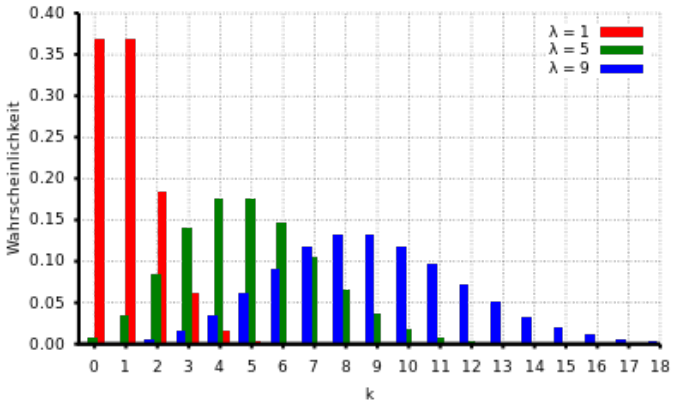


Cauchy-distribution (red) compared to normal distribution (blue)

- Poisson-distribution

$$P(k, \lambda) = \frac{e^{-\lambda}\lambda^k}{k!}, \quad k \in \mathbb{N}_0$$

  - Probability for k events in a time interval
  - λ: Average number of event in time interval
  - Important for point processes with constant rate, think of photon counting processes, e-mails per hour, fireing neurons.



Poisson-distribution for different λ

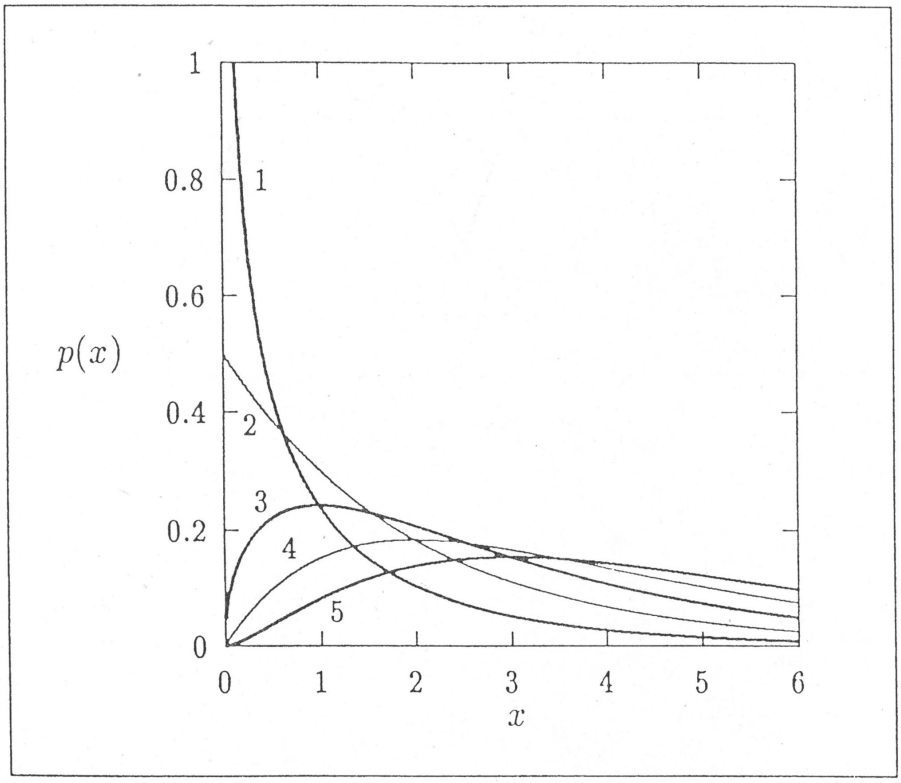
It holds

$$\mu = \sigma^2 = \lambda$$

- χ^2_r distribution with r degrees of freedom

  χ^2_r is sum of r independent squared standard Gaussian random variables

$$''\chi^2_r = \sum_{i=1}^{r} (N_i(0,1)^2)''$$



χ^2_r-distribution with $r = 1, 2, 3, 4, 5$ degrees of freedom

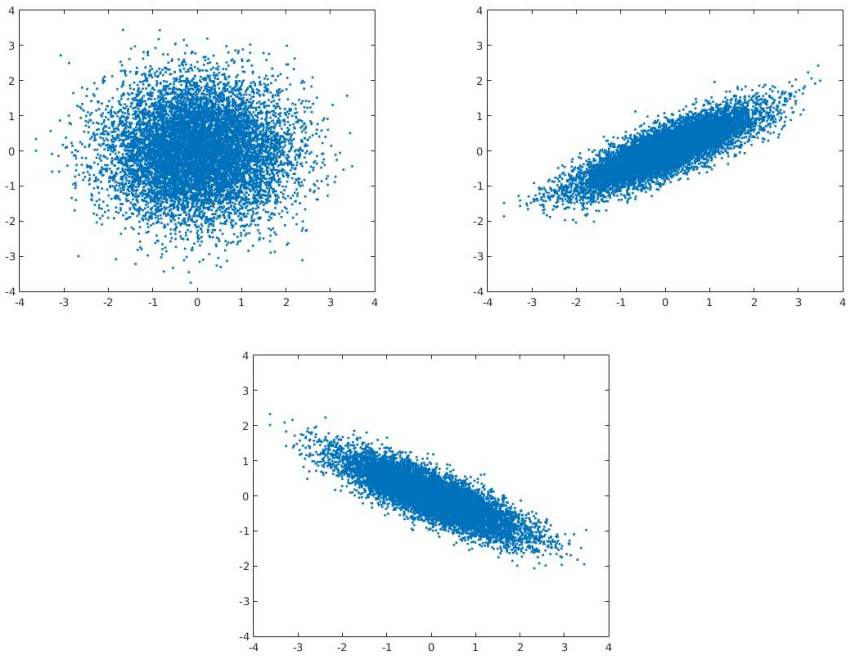
- Multivariate Gaussian distribution

$$p(\vec{x}) = \frac{1}{(2\pi)^{d/2}\sqrt{|\Sigma|}} \exp\left(-\frac{1}{2}(\vec{x}-\vec{\mu})^T\Sigma^{-1}(\vec{x}-\vec{\mu})\right), \qquad d = \dim(\vec{x})$$

with covariance matrix Σ

$$\Sigma = \langle(\vec{x}-\vec{\mu})(\vec{x}-\vec{\mu})^T\rangle$$

Describes correlations between the components



$2d$-normally distributed random numbers with

$$\Sigma_1 = \begin{pmatrix} 0.7 & 0 \\ 0 & 0.7 \end{pmatrix}, \quad \Sigma_2 = \begin{pmatrix} 0.7 & 0.4 \\ 0.4 & 0.7 \end{pmatrix}, \quad \Sigma_3 = \begin{pmatrix} 0.7 & -0.4 \\ -0.4 & 0.7 \end{pmatrix}$$

- Many more

Note: <u>An estimator is a random variable</u>

- Whenever one estimates a parameter from new data, the point estimate will be different since the noise realisation will be different

Definitions

- True parameter : p_0
- Estimator for parameter : $\hat{p}$
- Bias of estimator: $\langle \hat{p} \rangle - p_0$, how wrong in the mean
- Variance of estimator : $\langle (\hat{p} - \langle \hat{p} \rangle)^2 \rangle$, how variable

- Mean square error : $\langle(\hat{p} - p_0)^2\rangle$ = bias^2 + variance of estimator
- Confidence interval: Region around $\hat{p}$, in which true value p_0 lies with a certain probability

Example:

- Estimate the mean μ of a Gaussian $N(\mu, \sigma^2)$ from N data x_i, σ^2 assumed to be known
- $$p_N(x) = \frac{1}{\sqrt{2\pi\sigma^2}} e^{-\frac{(x-\mu)^2}{2\sigma^2}}$$

  Log-likelihood $L(\mu)$, neglect constant terms:

  $$L(\mu) = -\sum_{i=1}^{N} \frac{(x_i - \mu)^2}{2\sigma^2}$$

- Taking derivative, setting it to zero:

  $$\frac{dL(\mu)}{d\,\mu} = \sum_{i=1}^{N} \frac{(x_i - \mu)}{\sigma^2} \stackrel{!}{=} 0$$

- MLE:

  $$\hat{\mu} = \frac{1}{N} \sum_{i=1}^{N} x_i$$

- $\hat{\mu}$ is unbiased

  $$< \hat{\mu} >= \frac{1}{N} \sum_{i=1}^{N} < x_i >=< x >= \mu$$

- Variance of $\hat{\mu}$

  $$Var(\hat{\mu}) = \frac{1}{N^2} \sum_{i=1}^{N} Var(x_i) = \frac{1}{N} Var(x) = \frac{1}{N}\sigma^2$$

- Standard error of the mean

$$\sigma(\hat{\mu}) = \sqrt{\frac{1}{N}}\,\sigma$$

- Confidence interval

$$\left[\hat{\mu} - \sqrt{\frac{1}{N}}\,\sigma, \hat{\mu} + \sqrt{\frac{1}{N}}\,\sigma\right]$$

  Variance:

  –

$$p_N(x) = \frac{1}{\sqrt{2\pi\sigma^2}} e^{-\frac{(x-\mu)^2}{2\sigma^2}}$$

  – Assume μ is known
    Log-likelihood

$$L(\sigma^2) = -\frac{N}{2}\log(2\pi\sigma^2) - \frac{1}{2\sigma^2}\sum_i (x_i - \mu)^2$$

  – Take derivative, set it to zero and solve

$$\hat{\sigma}^2 = \frac{1}{N}\sum_i (x_i - \mu)^2$$

  – If μ is also estimated, plug in $\hat{\mu}$
  – Estimator is biased
  – Un-biased estimator

$$\hat{\sigma}^2 = \frac{1}{N-1}\sum_i (x_i - \hat{\mu})^2$$

    One degree of freedom is "burned" for estimating μ

What is the distribution of the maximum likelihood estimator ?

- Central limit theorem:

  The sum of random variables with finite moments converges to a Gaussian distribution

- Assumption: True parameter not at the boundary of parameter space

  Asymptotically, MLE is Gaussian distributed as

$$\sqrt{N}(\hat{p} - p_0) \sim \mathcal{N}(0, \Sigma) \quad \text{Statisticians}$$

$$(\hat{p} - p_0) \sim \mathcal{N}(0, \frac{\Sigma}{N}) \quad \text{Physicists}$$

  with

$$\Sigma = -N \left(\frac{\partial^2 L(\hat{p})}{\partial p_i \partial p_j} \right)^{-1} \tag{61}$$

  Proof: Estimation is always some kind of averaging

- Discuss true parameter at the boundary of parameter space
- Result does not depend on the distribution of the noise, e.g. also holds for Cauchy distributed random variables.
- Right hand side of eq. (61) is called Cramér-Rao bound or Fisher Information Matrix

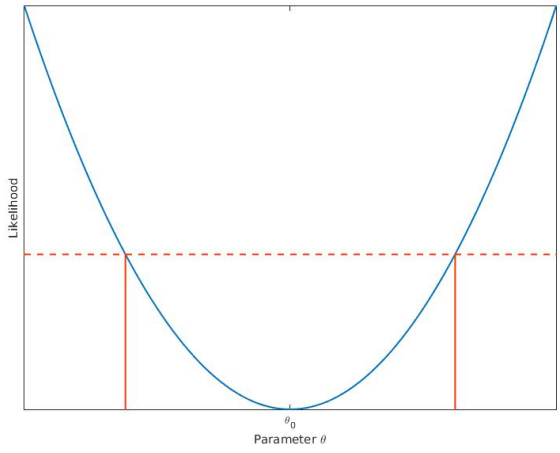


Figure 11.4: Confidence intervals based on Fisher Information Matrix

- MLE is most efficient, all other estimator have larger variance, and, thus confidence intervals. They do not reach Cramér-Rao bound

  MLE makes most out of the data

For mean:

$$\frac{dL(\mu)}{d\,\mu} = \sum_{i=1}^{N} \frac{(x_i - \mu)}{\sigma^2}$$

$$\frac{d^2L(\mu)}{d\mu^2} = -N\frac{1}{\sigma^2}$$

$$\Sigma = -N\left(\frac{\partial^2 L(\hat{p})}{\partial p_i \partial p_j}\right)^{-1} = \sigma^2 \tag{62}$$

As above, Standard error of the mean

$$\sigma(\hat{\mu}) = \sqrt{\frac{1}{N}}\,\sigma$$

Model selection

- Typically, true model structure is not known
- Nested models: model 1 is simplifcation of model 2

  Example:

  - One parameter fixed to a certain value
- Non-nested models: model 1 and model 2 are just different

  Example: Two different mechanisms to describe the system

  Newton vs. Einstein

Likelihood ratio test

- Assume the model is true, r parameters

- Then, the (log-)likelihood ratio is distributed as

$$2\left[L(\hat{p}) - L(p_0)\right] \sim \chi^2_r \quad . \tag{63}$$

  Difference of log-likelihoods is log-*ratio* of the likelihoods

  Meaning: The fit will always be better than the truth, over-fitting

- Proof

$$\begin{aligned} L(p_0) &= L(\hat{p}) + \frac{\partial L(\hat{p})}{\partial\, p_i}(p_0 - \hat{p}) + \\ &\quad \frac{1}{2}(p_0 - \hat{p})^T \frac{\partial^2 L(\hat{p})}{\partial p_i \partial p_j}(p_0 - \hat{p}) + \mathcal{O}(|p_0 - \hat{p}|^3) \quad . \end{aligned}$$

  - 2. term RHS $= 0$ since MLE.
  - Neglect terms of higher order
  - Σ^{-1} rotates out the correlations of $\hat{p}$, normalises to unit variance
  - 3. term of RHS is χ^2_r
  - Solve for $2(L(\hat{p}) - L(p_0))$

WS 22

Consider two nested models

- Assumption, null hypothesis: The smaller model 1 with r_1 parameters is a justified simplification of the larger model 2 with r_2 parameters
- Occam's razor: Take the smaller one
- Same idea of calculation, but more complicated leads to

$$2\left[L(\hat{p}_2) - L(\hat{p}_1)\right] \sim \chi^2_{r_2 - r_1} \quad . \tag{64}$$

Interpretation

- Larger model has more degrees of freedom
- Will slightly over-fit the data
- Eq. (64) says, how much over-fitting is fine
- If assumption not true, likelihood ratio will be larger as allow by eq. (64)

- Basis for a statistical test to reject the null hypothesis

Profile likelihood

- Strong asymptotic assumptions for the Fisher Information Matrix based confidence intervals: Quadratic approximation based on point estimate and its curvature must hold
- For linear regression models approximation holds globally
- For non-linear, it depends
- Note: In our setting

$$\begin{aligned} \dot{x} &= f(x,p) \\ y(t_i) &= g(x(t_i),p) + \epsilon(t_i) \end{aligned}$$

  solution only linear in the parameters if $f(x,p) = const.$

  Even for linear dynamics the solution, exponential, is non-linear in the parameters.

- If asymptotics hold, two possibilities
  - Quadratic: Finite confidence intervals
  - Flat: Parameter can not be determined: Structural non-identifiable
    - Parameter can not be determined because of model structure
    - (Trivial) example
      $$y = (ab)x$$
    - (Highly) non-trivial examples for partially observed differential equation
- Not invariant under reparametrisation

  Transformation of parameters, e.g. taking logarithm

  $\Longrightarrow$ Confidence intervals does not change according to transformation

Alternative:

- Profile Likelihood

$$PL(p_i) = \max_{p_{j\neq i}} L(p)$$

  Scan each parameter, reoptimise the others

- For χ^2 fitting

$$PL(p_i) = \min_{p_{j\neq i}} \chi^2(p)$$

- Confidence intervals given by

$$2(L(\hat{p}) - PL(p_i)) \leq \chi^2_{(1-\alpha,1)}$$

  Since this a likelihood ratio test with one degree of freedom !

- For χ^2 fitting

$$PL(p_i) - \chi^2(\hat{p}) \leq \chi^2_{(1-\alpha,1)}$$

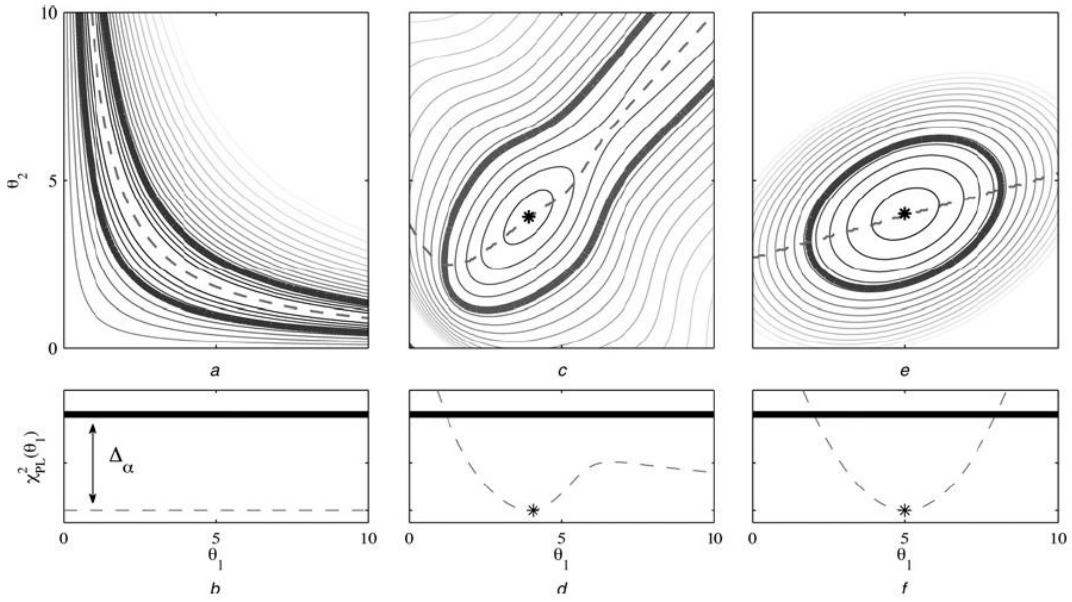


Figure 11.5: Profile Likelihood, typical behaviours

Properties:

- Much weaker asymptotic assumptions than Fisher Information Matrix based confidence intervals.

  Convexity of likelihood sufficient.

- Invariant under reparametrisation
- Allows for insights when quadratic approximation does not hold

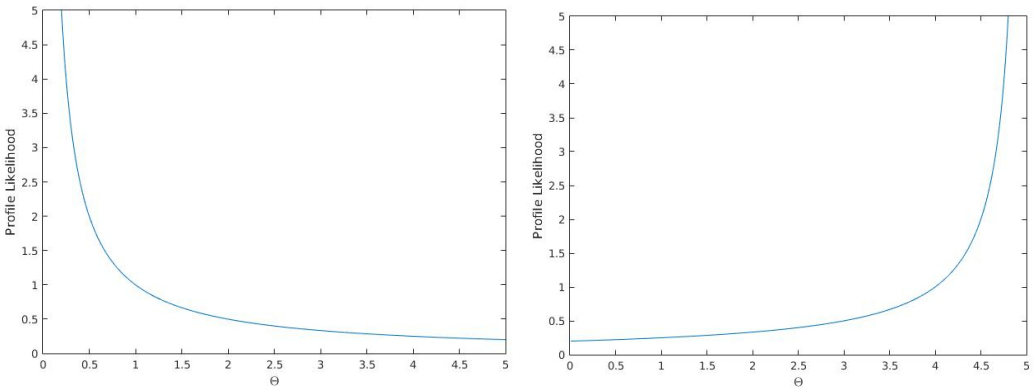


Figure 11.6: Lower or upper bound, can not be treated by Fisher Information matrix, see exercise

- Allows for definition of practical non-identifiability [85]:
  - Profile likelihood not flat, but no bounded confidence intervals
  - A problem that can often be solved with more data
- Formal definition of structural non-identifiability
  - For two parameter sets $\vec{p_1}$ and $\vec{p_2}$ it holds $\vec{g}(\vec{x}, \vec{p_1}) = \vec{g}(\vec{x}, \vec{p_2})$
  - Or positivily. Structural identifiable if for $\vec{p_1} \neq \vec{p_2}$ it holds $\vec{g}(\vec{x}, \vec{p_1}) \neq \vec{g}(\vec{x}, \vec{p_2})$
  - Cure: Reduce dimension of $\vec{f}$ and/or increase dimension of $\vec{g}$
- The basis for experimental design [84, 86] and/or model reduction [64]

If parameters are not well determined, in turn, model predictions will not be well determined.

Goal: Tailor the model complexity to the information content of the data 10/19

11.4 General Considerations

G.E.P. Box: "All models are wrong but some are useful" [11]

- What is a useful model ?

First, what is a good model ?

- too simple model
  can not fit the data
- too large model
  overfits the data, parameters and predictions not well determined
- good model
  fits the data, parameters and predictions well determined

A good model has the chance to become a useful model

A useful model

- captures the main effects, neglects the rest
- makes testable predictions
- delivers insights

Important:

- The goal of modelling can not be to get a "copy" the biological system
- Goethe: If I draw my dog exactly as he is, I have a second dog, but not a piece of art.
- The same holds for modelling in cell biology

Lessons learned:

- Maximum likelihood estimation with Gaussian distributed errors is equivalent to weighted least squares minimisation and vice versa
- Parameter estimation in nonlinear, partially observed, noisy, non-autonomous, stiff, sparse dynamical systems
- MLE is asymptotically Gaussian distributed no matter how the data are distributed
- Profile likelihood highy informative alternative to asymptotic confidence intervals
- All models are wrong, but some are useful

11/17
12M/20

12 Genetic networks

Nice review [102, 17]

- Number of genes: typically 2
- number of mRNA: $\mathcal{O}(100)$
- number of proteins up to $\mathcal{O}(10^6)$
- For proteins, notion of "concentration" makes sense, deterministic continuous ordinary differential equations make sense
- For mRNA, deterministic description by ODE questionable [61]
- For genes, it surely does not make any sense
- In general for "population dynamics" with few players, discreteness and stochasticity has to be taken into account

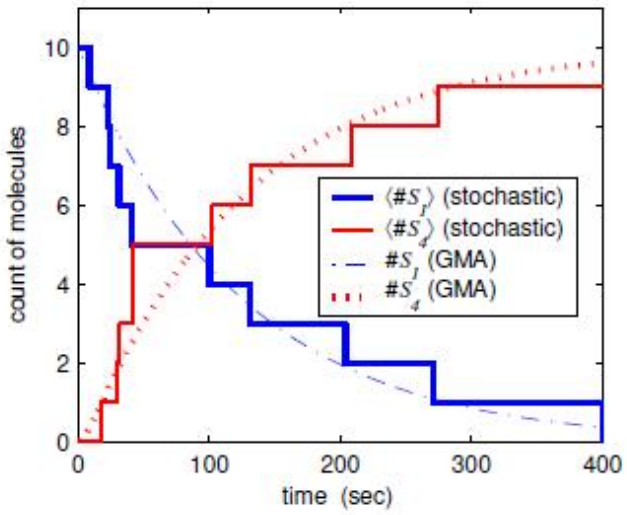


Figure 12.1: Discrete and stochastic dynamics with few players

Questions:

- How to simulate a discrete states system ?
- What is the substitute for rate constants ?

The answer: The Gillespie-algorithm

- Takes into account the stochastic nature of the reactions
- Simulation of single trajectories that are valid realisations of the underlying stochastic process

12.1 Gillespie-Algorithm

Literature:

- Original paper 1976 [30]
- Further developments : [28, 67, 82]
- Critical discussion of assumptions and interpretation [119]

Let S be a species and

$$P_n(t) = Prob(\#S = n \text{ at } t)$$

Consider:

- Propensity $a(.)$: Probability per time unit for change of state
- Influx to $P_n(t)$

$$n - \nu_\mu \overset{a_\mu(n-\nu_\mu)}{\longrightarrow} n$$

  with $a_\mu(n - \nu_\mu)$ the rate for a change by ν_μ, given the state was in $n - \nu_\mu$

- Efflux from $P_n(t)$

$$n \overset{a_\mu(n)}{\longrightarrow} n + \nu_\mu$$

  with $a_\mu(n)$ the rate for a change by ν_μ, given state was in n

With this, the Chemical Master Equation follows:

$$\dot{P}_n = \sum_{\mu=1}^{\infty} a_\mu(n - \nu_\mu)P_{n-\nu_\mu} - a_\mu(n)P_n$$

In general

- More than one species: $P(S_1, S_2, \ldots, S_K)$
- Many possible reactions $R_1, R_2, \ldots, R_M$
- No analytical solution

Gillespie-Algorithm: Instead of analytical solution

- Simulate many trajectories
- Obtain results by averaging
- One can show: Gillespie algorithm produces the correct distributions $P_n(t)$

Strategy of Gillespie-algorithm

- When will a next reaction take place ?

- Which reaction is the next one ?

Central quantity: Reaction-probability function $P(i,\tau)$

$P(i,\tau)d\tau$: Probability for reaction R_i in time interval $(t+\tau, t+\tau+d\tau)$, given system is in state $S(t)$ for $(t, t+\tau)$

$$P(i,\tau)d\tau = P_0(\tau)\, P_i(d\tau) \tag{65}$$

with

- $P_i(d\tau) = a_i d\tau$: Probability that reaction R_i takes place in time interval $(t+\tau, t+\tau+d\tau)$.
- $P_0(\tau)$: Probability that given state $S(t)$ no reaction takes place in interval $(t, t+\tau)$

Probability that some reaction takes place in interval $d\tau$:

$$\sum_{i=1}^{M} a_i d\tau$$

Define:

$$a^* = \sum_{i=1}^{M} a_i$$

- Probability for no reaction in interval $d\tau : 1 - a^* d\tau$

  Thus

$$P_0(\tau + d\tau) = P_0(\tau)(1 - a^* d\tau) = P_0(\tau) - a^* P_0(\tau) d\tau$$

- Yields differential equation

$$\dot{P}_0 = -a^* P_0$$

  with solution

$$P_0(\tau) = e^{-a^*\tau}$$

  In summary, with eq. (65):

$$P(i,\tau) = a_i e^{-a^*\tau}$$

When will a next reaction take place and which ?

- When ?

  Sum over all reactions

$$\bar{P}(\tau) = \sum_{i=1}^{M} P(i,\tau) = a^* e^{-a^*\tau}$$

  yields with $\bar{P}(\tau)d\tau$ probability for a next reaction in interval $(t+\tau, t+\tau+d\tau)$

- Which ?

  Given a reaction happens in the interval, the conditional probability

$$\tilde{P}(i|\tau) = \frac{P(i,\tau)}{\bar{P}(\tau)} = \frac{a_i e^{-a^*\tau}}{a^* e^{-a^*\tau}} = \frac{a_i}{a^*}$$

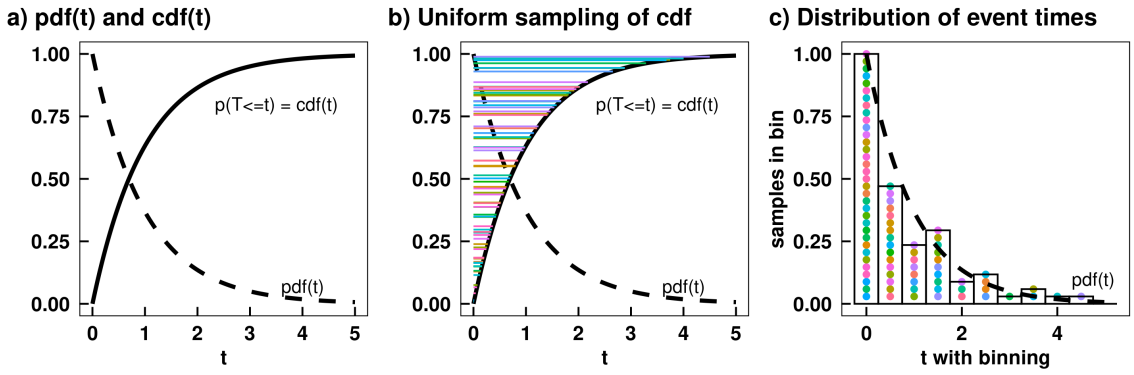
  gives the probability that is reaction i.

On the way to the algorithm

- When ?
  - The cumulative distribution $F(t)$ for $\bar{P}(\tau)$ reads:

$$F(t) = \int_0^t \bar{P}(\tau)\, d\tau = a^* \int_0^t e^{-a^*\tau} d\tau = 1 - e^{-a^* t}$$

  - Let r_1 be uniformly distributed random number in interval $[0, 1]$
  - If one chooses t, such that $F(t) = r_1$, the probability density of t is the one of $\bar{P}(\tau)$



Uniformly distributed random variables fed into the inverse of the cumulative distribution follow the originally probability distribution.

- Thus t is given by

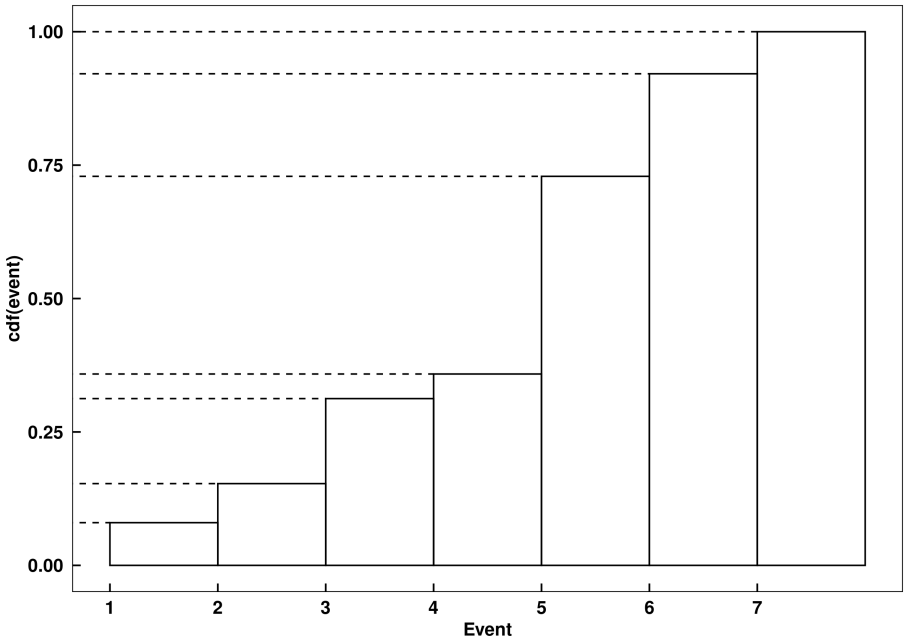
$$t = F^{-1}(r_1) = \frac{1}{a^*} \ln\left(\frac{1}{1 - r_1}\right)$$

- Since r_1 is uniformly distributed as $1 - r_1$ is, for the random variable of the time t of the next reaction holds

$$t = F^{-1}(r_1) = \frac{1}{a^*} \ln\left(\frac{1}{r_1}\right) = -\frac{1}{a^*} \ln r_1$$

- Which reaction
  - Let r_2 be a uniformly distributed random number in $[0, 1]$
  - Which reaction j happens is determined by

$$\sum_{i=1}^{j-1} \frac{a_i}{a^*} \leq r_2 < \sum_{i=1}^{j} \frac{a_i}{a^*}$$



The larger a_i, the larger the probability to be chosen for the next reaction

Determination of the propensities a_i

- $c_i\,dt$: Probability that a certain single reaction R_i takes place in next time step dt
- h_i: Number of combinations of reactants
- $a_i dt = h_i c_i\,dt$: Probability of reaction R_i in next time step
- Determine c_i and h_i such that stochastic and determinsistic dynamics coincide for $\#S_i \to \infty$
- Examples:

Reaction R_i	c_i	h_i
$S_1 \overset{k}{\to} \ldots$	k	$\#S_1$
$S_1 + S_2 \overset{k}{\to} \ldots$	k/V	$\#S_1 \cdot \#S_2$
$2S_1 \overset{k}{\to} \ldots$	$2k/V$	$\frac{1}{2}\#S_1 \cdot (\#S_1 - 1) = \begin{pmatrix} \#S_1 \\ 2 \end{pmatrix}$

The algorithm:

1. Initialisation
   - Set $t = 0$
   - Choose number of molecules $\#S_i$
2. Calculate propensities
   - $a_i = h_i c_i$
   - Calculate $a^* = \sum_{i=1}^{N} a_i$
3. Draw two uniformly distributed random numbers r_1, r_2
   - Determine $\tau = -1/a^* \ln r_1$
   - Determine j such that

$$\sum_{i=0}^{j-1} \frac{a_i}{a^*} \leq r_2 < \sum_{i=1}^{j} \frac{a_i}{a^*} \qquad \text{with } a_0 = 0$$

4. Update

   - Update the number of molecules according to the reaction scheme
   - Set $t = t + \tau$
   - Go to 2

A little mystery:

Remember relation between quantum mechanics and classical mechanics:

- Quantum mechanics is (believed to be) fundamental, classical mechanics is a limit case
- But in practise:
- Formulate classical theory, Hamilton function ...
- Replace x, p, E, ... by operators, Poisson brackets by commutators
- There is no "in first place" quantum mechanics

Here the same

- Stochastic process is fundamental, deterministic dynamics a limit case
- But: No first-principle derivation of propensity a_i possible
- "Backwards" from deterministic rate k_i to stochastic a_i such that they coincide for large N

10.5/19
11.5/17
12F/20

13 Worked examples

13.1 Chemotaxis

Talk: Chemotaxis

13.2 JAK-STAT Signalling

Talk: JAK-STAT signalling

13.3 Towards Medical Applications

Talk: Towards medical applications

Question time

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