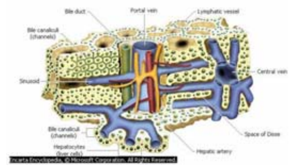
Systems Biology

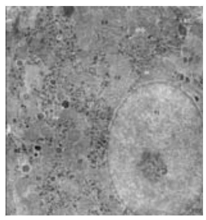
An introduction to dynamic pathway modelling

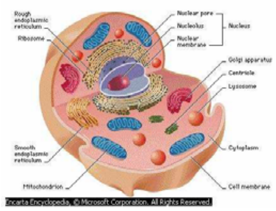
Olaf Wolkenhauer

www.sbi.uni-rostock.de

From cells to organisms!?





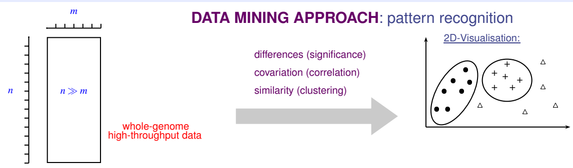


... the cell is not a soup of molecules.

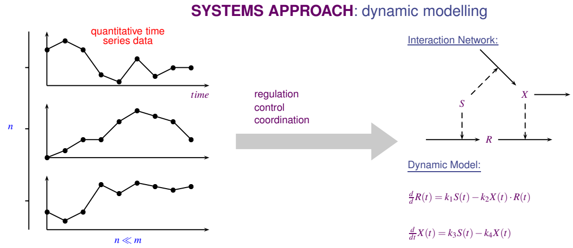
... structural versus functional organisation!

Mining vs. Systems Approaches

DATA MINING APPROACH: pattern recognition



SYSTEMS APPROACH: dynamic modelling



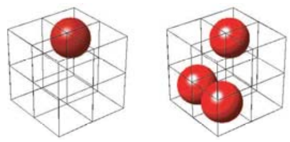
$\frac{d}{dt}R(t) = k_1 S(t) - k_2 X(t) \cdot R(t)$

$\frac{d}{dt}X(t) = k_3 S(t) - k_4 X(t)$

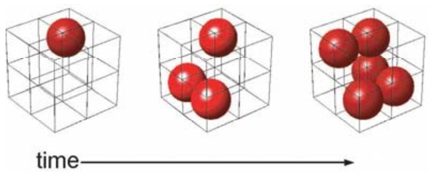
✘ *There is no such thing as a "holistic approach".*
✘ *There is no such thing as a "hypothesis-free fishing expeditions".*

Mining vs Systems Approach

Comparing two data sets (cell lines, genomes,...), there are $2^8 = 256$ pattern to discern:



... considering *signals*, for only 3 time points, there are 256^3, i.e., > 16M trajectories:



... it is systems dynamics that gives rise to biological function!

Causation is an explanation of change

Example: Protease cleaving peptide bonds in a substrate protein:

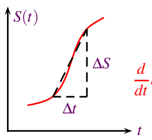
"Rate of proteolysis is proportional to amount of substrate"

Changes in substrate concentration:

$$\frac{d}{dt}S = -k_p S(t)$$

- $S(t)$ → variable (changing)
- k_p → parameter (fixed value)

... an *ordinary differential equation* (ODE).

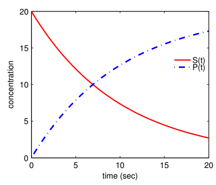


$$\frac{d}{dt}S = \lim_{\Delta t \to 0} \frac{\Delta S}{\Delta t}$$

State **of the system:**

$$S(t) = S_0 \cdot e^{-k_p t}$$

$$P(t) = S_0 (1 - e^{-k_p t})$$



Differential Equation Modelling

Pathways: *Networks* of *catalysed* biochemical reactions:

$$S + E \underset{k_2}{\overset{k_1}{\rightleftarrows}} SE \overset{k_3}{\longrightarrow} P + E$$

$R_1 : S + E \overset{k_1}{\longrightarrow} SE$, $v_1 = k_1[E][S]$.

$R_2 : SE \overset{k_2}{\longrightarrow} E + S$, $v_2 = k_2[SE]$.

$R_3 : SE \overset{k_3}{\longrightarrow} E + P$, $v_3 = k_3[SE]$.

Mathematical Model:

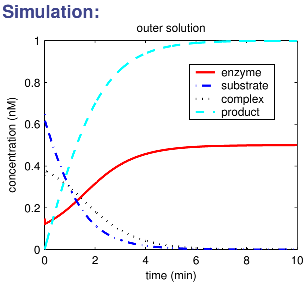
$$\frac{d[E]}{dt} = -k_1[E][S] + k_2[SE] + k_3[SE]$$

$$\frac{d[S]}{dt} = -k_1[E][S] + k_2[SE]$$

$$\frac{d[SE]}{dt} = k_1[E][S] - k_2[SE] - k_3[SE]$$

$$\frac{d[P]}{dt} = k_3[SE] .$$

Simulation:



MAPK π-Calculus Model

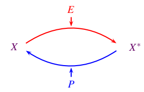
```
new KKK:<> new KKKst:<> new E1:<> new E2:<>
new KK:<> new KK_P:<> new KK_PP:<> new KKPse:<>
new K:<> new K_P:<> new K_PP:<> new KPse:<>
new a1:1.0:<<>> new k1:1.0:<> new a2:1.0:<<>> new k2:1.0:<>
new a3:1.0:<<>> new k3:1.0:<> new a4:1.0:<<>> new k4:1.0:<>
new a5:1.0:<<>> new k5:1.0:<> new a6:1.0:<<>> new k6:1.0:<>
new a7:1.0:<<>> new k7:1.0:<> new a8:1.0:<<>> new k8:1.0:<>
new a9:1.0:<<>> new k9:1.0:<> new a10:1.0:<<>> new k10:1.0:<>
new spike:<<>,int> (* a spike #2 high of #1 molecules *)
( !spike(a,n); if n=0 then () else (a<> | spike<a,n-1>)
| !KKK();
new d1:1.0:<>
(a1<d1>;(d1<>;KKK<> + k1<>;KKKst<>))
| !KKKst();
new d2:1.0:<>
(a2<d2>;(d2<>;KKKst<> + k2<>;KKK<>) +
a3(d3);(d3();KKKst<> + k3();KKKst<>) +
a5(d5);(d5();KKKst<> + k5();KKKst<>))
| !E1();
a1(d1);(d1();E1<> + k1();E1<>)
| !E2();
a2(d2);(d2();E2<> + k2();E2<>)
| !KK();
new d3:1.0:<>
(a3<d3>;(d3<>;KK<> + k3<>;KK_P<>))
| !KK_P();
new d4:1.0:<>
new d5:1.0:<>
(a4<d4>;(d4<>;KK_P<> + k4<>;KK<>) +
a5<d5>;(d5<>;KK_P<> + k5<>;KK_PP<>))
| !KK_PP();
new d6:1.0:<>
```

```
(a6<d6>;(d6<>;KK_PP<> + k6<>;KK_P<>) +
a7(d7);(d7();KK_PP<> + k7();KK_PP<>) +
a9(d9);(d9();KK_PP<> + k9();KK_PP<>))
| !KKPse();
a4(d4);(d4();KKPse<> + k4();KKPse<>) +
a6(d6);(d6();KKPse<> + k6();KKPse<>)
| !K();
new d7:1.0:<>
(a7<d7>;(d7<>;K<> + k7<>;K_P<>))
| !K_P();
new d8:1.0:<>
new d9:1.0:<>
(a8<d8>;(d8<>;K_P<> + k8<>;K<>) +
a9<d9>;(d9<>;K_P<> + k9<>;K_PP<>))
| !K_PP();
new d10:1.0:<>
(a10<d10>;(d10<>;K_PP<> + k10<>;K_P<>))
| !KPse();
a8(d8);(d8();KPse<> + k8();KPse<>) +
a10(d10);(d10();KPse<> + k10();KPse<>)
| E1<> (* input signal *) | E2<> | KKPse<> | KPse<>
| spike<KKK,100> | spike<KK,100> | spike<K,100> )
```

What is a *useful* model?

Michaelis-Menten Modelling

Activation of protein X by enzyme E:



... constant concentration for phosphatase P.

Reaction model:

$$X + E \underset{k_2'}{\overset{k_1}{\rightleftharpoons}} X^* + E\,, \qquad X^* + P \xrightarrow{k_2'} X + P$$

... leading to:

$$\frac{d}{dt}x = k_1 e(t)\tilde{x}(t) - k_2' P x(t)\,. \quad \text{Let } k_2 \doteq k_2' P\text{:} \quad \frac{d}{dt}x = k_1 e(t)\big(\bar{x} - x(t)\big) - k_2 x(t)$$

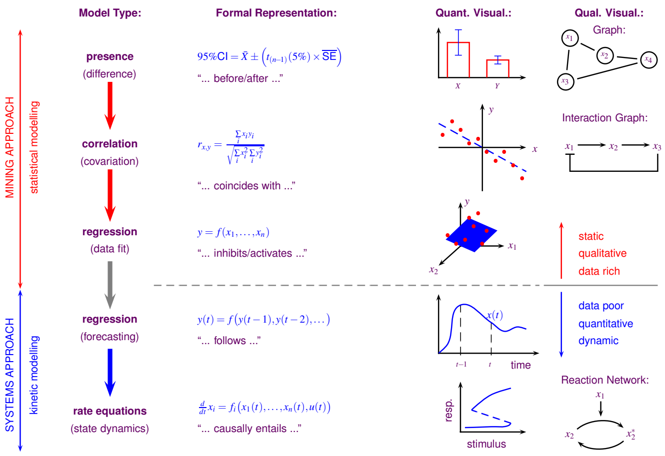
Michaelis-Menten model:

$$X + E \underset{d_1}{\overset{a_1}{\rightleftharpoons}} XE \xrightarrow{k_1} X^* + E\,, \qquad X^* + P \underset{d_2}{\overset{a_2}{\rightleftharpoons}} X^*P \xrightarrow{k_2} X + P$$

... Michaelis-Menten constants $K_{m1} = \frac{d_1+k_1}{a_1}$, $K_{m2} = \frac{d_2+k_2}{a_2}$ ... leading to:

$$\frac{d}{dt}x = \frac{k_1 e(t)\big(\bar{x} - x(t)\big)}{K_{m1} + \big(\bar{x} - x(t)\big)} - \frac{k_2 x(t)}{K_{m2} + \big(\bar{x} - x(t)\big)}\,.$$

Classification of Models



Mass Action Modelling

Pathways: *Networks* of *catalysed* biochemical reactions:

$$R_\mu \;:\; l_{1\mu}X_1 + \dots + l_{N\mu}X_N \xrightarrow{k_\mu} r_{1\mu}X_1 + \dots + r_{N\mu}X_N \tag{1}$$

X_μ : i-th chemical species, $i = 1, \dots, N$

R_μ : μ-th elementary reaction, $\mu = 1, \dots, M$

$l_{i\mu}, r_{i\mu}$: stoichiometric coefficients (whole numbers)

k_μ : rate constant for reaction channel μ

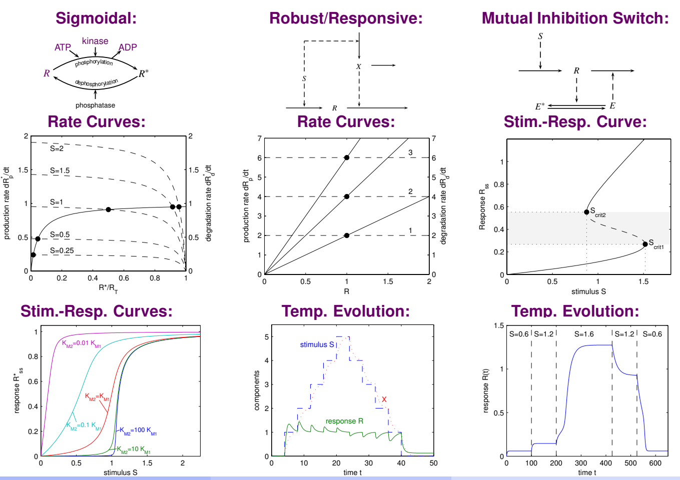
Changes: ... in the molecular population of X_i:

$$\delta_{i\mu} = r_{i\mu} - l_{i\mu} = \begin{cases} -l_{i\mu} & \text{if } X_i \text{ is a reactant in } R_\mu, \\ +r_{i\mu} & \text{if } X_i \text{ is a product in } R_\mu, \\ 0 & \text{otherwise.} \end{cases}$$

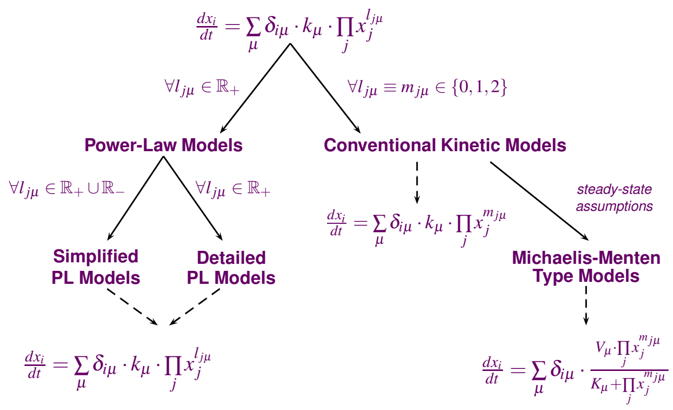
Differential Equation Model (ODEs):

$$\frac{d}{dt}x_i = \sum_{\mu=1}^{M} \delta_{i\mu} k_\mu \prod_{j=1}^{N} x_j^{l_{j\mu}}$$

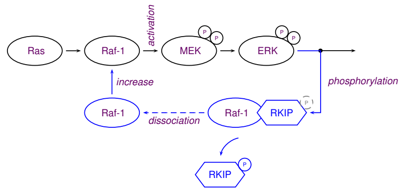
Dynamic Motifs

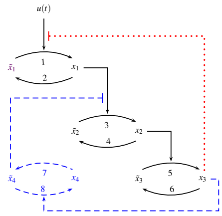


Overview ODE Modelling Strategies



RKIP Regulation of the Ras/Raf/MEK/ERK Pathway





Mathematical model:

$$\frac{d}{dt}x_1 = \underbrace{\frac{k_1 u(t)(\tilde{x}_1 - x_1(t))}{K_{m1} + (\tilde{x}_1 - x_1(t))}}_{\text{phosphorylation}} - \underbrace{\frac{k_2 x_1(t)}{K_{m2} + x_1(t)}}_{\text{dephosphorylation}}$$

$$\frac{d}{dt}x_2 = \frac{k_3 x_1(t)(\tilde{x}_2 - x_2(t))}{K_{m3} + (\tilde{x}_2 - x_2(t))} - \frac{k_4 x_2(t)}{K_{m4} + x_2(t)}$$

$$\frac{d}{dt}x_3 = \frac{k_5 x_2(t)(\tilde{x}_3 - x_3(t))}{K_{m5} + (\tilde{x}_3 - x_3(t))} - \frac{k_6 x_3(t)}{K_{m6} + x_3(t)}$$

RKIP:

$$\frac{d}{dt}x_4 = \frac{k_7 x_3(t)(\tilde{x}_4 - x_4(t))}{K_{m7} + (\tilde{x}_4 - x_4(t))} - \frac{k_8 x_4(t)}{K_{m8} + x_4(t)}$$

Functional Organisation: Feedback Dynamics

The Claim:

> The cell's functioning is realised through feedback interactions

The Argument:

1. To *control*, *regulate*, *adapt* or *coordinate* whatever, ...
2. ... there must exist a *goal* or *objective*, which we refer to as a *function*.
3. In order to induce or prevent *change*, information of the *state* of the system must be *fed back*.
4. Feedback implies a *before* and *after*,
5. ... which is why we cannot avoid *dynamic systems theory*.

> It is feedback that gives rise to *dynamic principles*, including robust-, responsive- and harmonious behavior

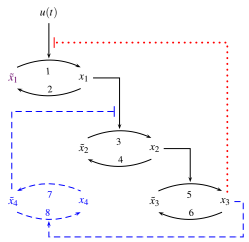
RKIP Regulation of the Ras/Raf/MEK/ERK Pathway

Positive feedback through RKIP:

$$\frac{d}{dt}x_2 = \frac{k_3 x_1(t)\left[1/\left(1+\left[\frac{\tilde{x}_4 - x_4(t)}{K_P}\right]^p\right)\right](\tilde{x}_2 - x_2(t))}{K_{m3} + \tilde{x}_2 - x_2(t)} - \frac{k_4 x_2(t)}{K_{m4} + x_2(t)}$$

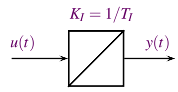
Negative feedback:

$$\frac{d}{dt}x_1 = \frac{k_1 u(t)\left[1/\left(1+\left[\frac{x_3(t)}{K_N}\right]^n\right)\right](\tilde{x}_1 - x_1(t))}{K_{m1} + \tilde{x}_1 - x_1(t)} - \frac{k_2 x_1(t)}{K_{m2} + x_1(t)}$$

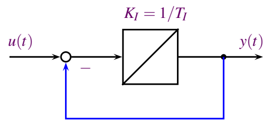


The Role of Feedback Dynamics

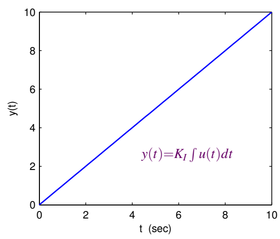
Stimulus $u(t)$, response $y(t)$:



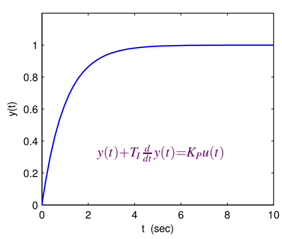
Adding a *negative* feedback loop:



Step response:

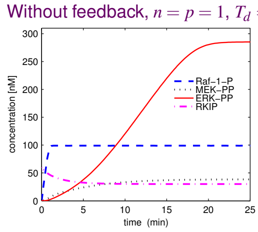


Step response:

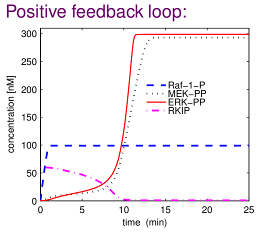


The Role of Feedback in Signalling Pathways

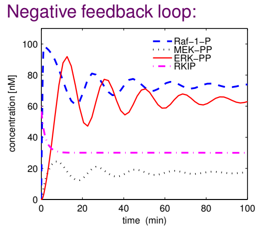
Without feedback, $n = p = 1$, $T_d = 0$:



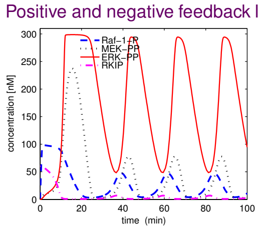
Positive feedback loop:



Negative feedback loop:

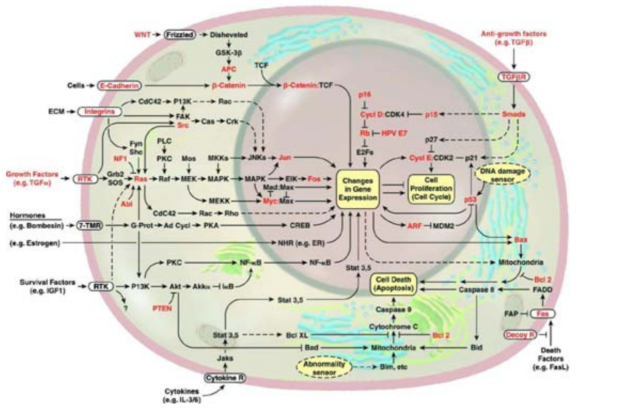


Positive and negative feedback loops:



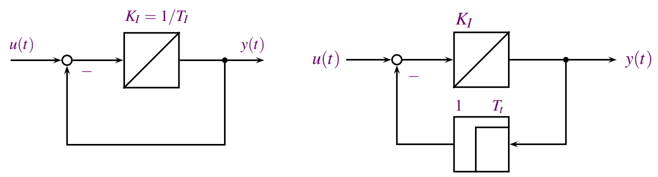
Abstraction: Pathways

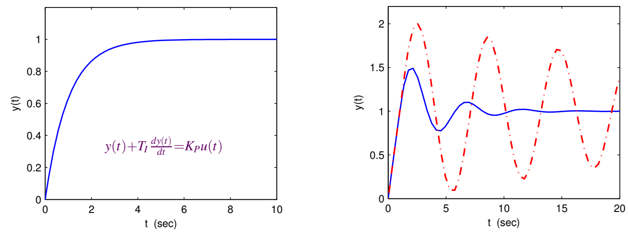
... networks of biochemical reactions:



Picture from D.Hanahan and R.A.Weinberg "The hallmarks of cancer", *Cell*, 11(2000): 57-70

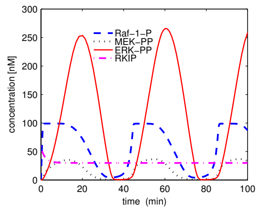
The Role of Delays



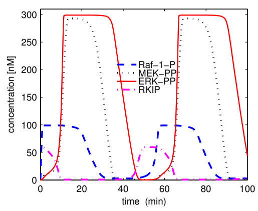


The Role of Oscillations and Ultrasensitivity

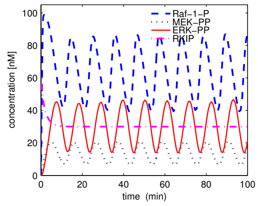
Neg. feedback, $n = p = 1$, $T_d = 10$min:



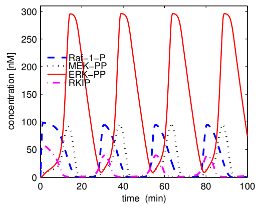
Pos. and neg. feedback:



Neg. feedback, $n = 2$, $p = 1$, $T_d = 0$:



Pos. and neg. feedback:



Coordination: Cross-Talk among Pathways