DYNAMICS AND DESIGN OF CELLULAR NETWORKS

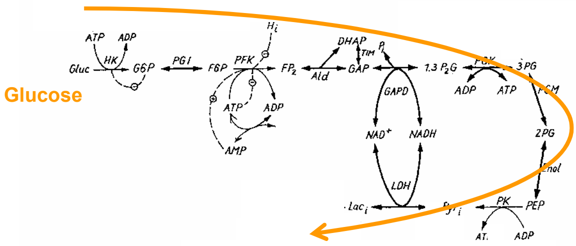
Reinhart Heinrich

**Institute of Biology/Theoretical Biophysics
Humboldt-University, Berlin**

**FEBS Advanced Course, Systems Biology
Gosau, March 12, 2005**

$$\xrightarrow{1} X \xrightarrow{2} Y \dashrightarrow \;\; \dashrightarrow Z \xrightarrow{r}$$

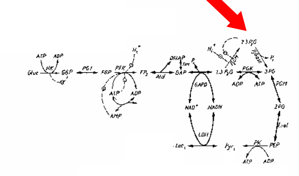
Glycolysis



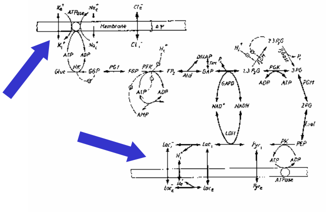
Glucose

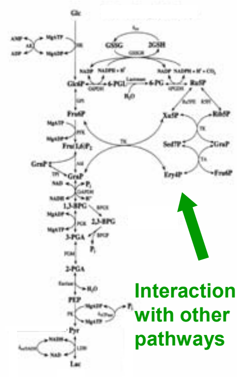
2 x Lactate   2 x ATP

Branches



Coupling to membrane transport





Interaction with other pathways

MOST SIMPLE METABOLIC PATHWAY

substrate

i -1 ↓

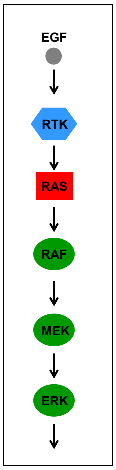
metabolite$_{i-1}$(X$_{i-1}$)

i ↓

metabolite$_i$ (X$_i$)

i +1 ↓

product



PATHWAYS OF SIGNAL TRANSDUCTION

---

multiple phosphorylations

G-proteins

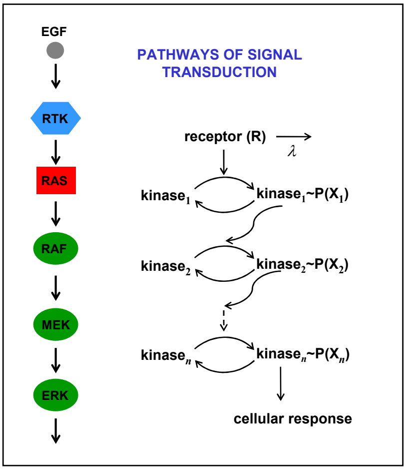
adaptors

scaffolds

exchange factors

feedback

etc....



PATHWAYS OF SIGNAL TRANSDUCTION

receptor (R) → λ

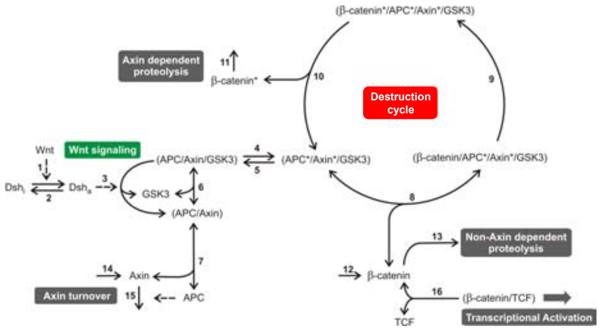
kinase$_1$ ⇄ kinase$_1$~P(X$_1$)

kinase$_2$ ⇄ kinase$_2$~P(X$_2$)

kinase$_n$ ⇄ kinase$_n$~P(X$_n$)

cellular response

Wnt-SIGNALING-PATHWAY

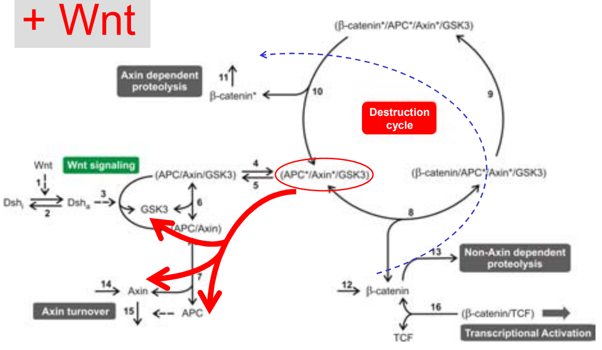


Lee, Krüger, Salic, Kirschner, Heinrich,
PLoS 2003,
Genome Informatics, 2004

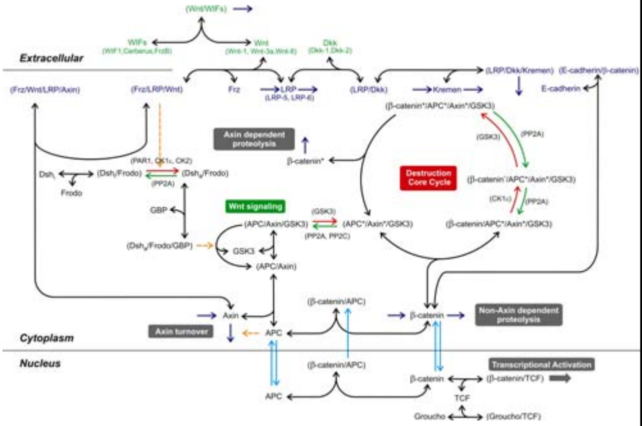
Functioning of the pathway

β–CATENIN HIGH

+ Wnt



Wnt-signaling: extended scheme



RELEVANCE

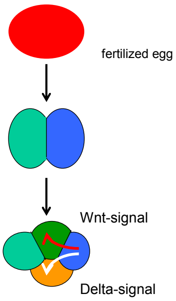
THE WNT-PATHWAY

In vertebrate development: induction of primary body axis

Organ formation, limb development

Morphogenesis

Unphysiological activation of the Wnt-pathway leads to tumor formation (e.g. colorectal cancer)



Wnt-signaling and cancer

Wnt

Frizzled

Dishevelled

APC

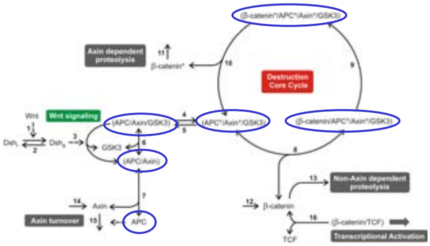
Axin

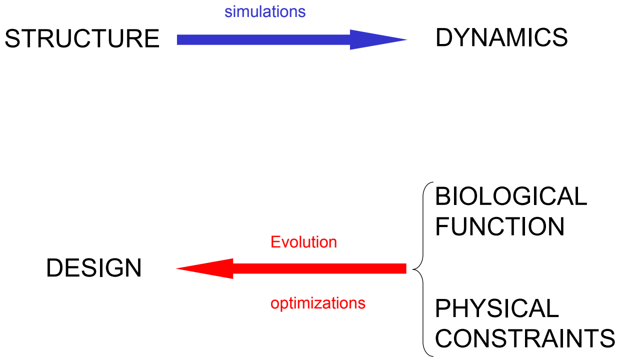
β-catenin

GSK3

PP2A

~85%of all sporadic and hereditary colorectal cancers show loss of APC function (mutation cluster region, MCR, codons ~1250-1500)





simulations

STRUCTURE → DYNAMICS

BIOLOGICAL FUNCTION

DESIGN ← PHYSICAL CONSTRAINTS

Evolution

optimizations

DYNAMICS AND CONTROL

$$\xrightarrow{v_1} S_1 \xrightarrow{v_2} S_2 \xrightarrow{v_3}$$

$$\frac{dS_1}{dt} = v_1 - v_2$$

$$\frac{dS_2}{dt} = v_2 - v_3$$

metabolite concentrations

stoichiometric coefficients

reaction rates

$$\frac{dS_i}{dt} = \sum_{j=1}^{r} n_{ij} v_j \qquad \frac{dS}{dt} = N \cdot v$$

$$v = (v_1, \ldots, v_r)^T \qquad v = v(S, p)$$

10-100 differential equations

high number of variables

nonlinearity

regulatory loops

separation of time constants

kinetic parameters often unknown

$$\xrightarrow{v_1} S_1 \xrightarrow{v_2} S_2 \xrightarrow{v_3}$$

$$\frac{d\,S_1}{dt} = v_1 - v_2$$

$$\frac{d\,S_2}{dt} = v_2 - v_3$$

metabolite concentrations

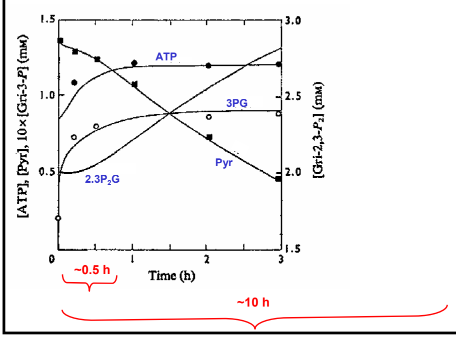
stoichiometric coefficients

reaction rates

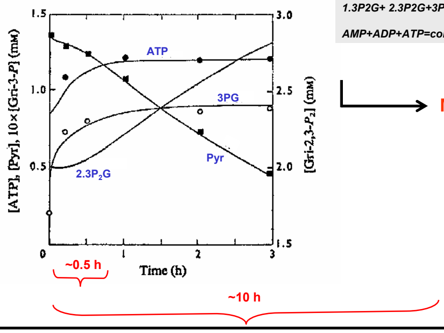
$$\frac{dS_i}{dt} = \sum_{j=1}^{r} n_{ij} v_j \qquad \frac{d\,S}{dt} = N \cdot v$$

$$v = (v_1, \ldots, v_r)^T \qquad v = v(S, p)$$

TIME DEPENDICIES OF GLYCOLYTIC METABOLITES



TIME DEPENDICIES OF GLYCOLYTIC METABOLITES



separation of time scales
quasi-steady states

+

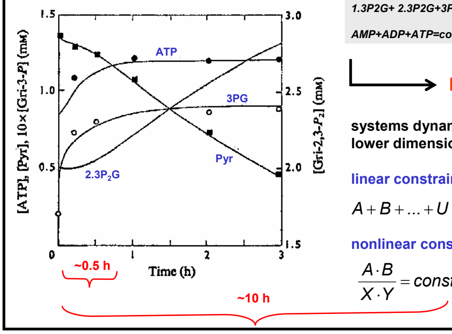
conservation quantities

1.3P2G+ 2.3P2G+3PG+2PG+PEP+Pyr+NADH=const

AMP+ADP+ATP=const

→ **MODEL REDUCTION**

REDUCING COMPLEXITY



separation of time scales
(time hierarchy) quasi-steady states

+

conservation quantities

1.3P2G+ 2.3P2G+3PG+2PG+PEP+Pyr+NADH=const

AMP+ADP+ATP=const

→ **MODEL REDUCTION**

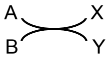
systems dynamics in a subspace of lower dimension

linear constraints

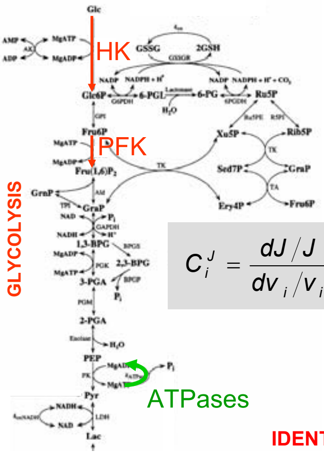
$$A + B + \ldots + U + V = const$$

nonlinear constraints

$$\frac{A \cdot B}{X \cdot Y} = const$$



REDUCING COMPLEXITY



$$C_i^J = \frac{dJ/J}{dv_i/v_i}$$

$$C_{HK}^J = 0.34$$

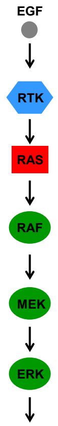
$$C_{PFK}^J = 0.18$$

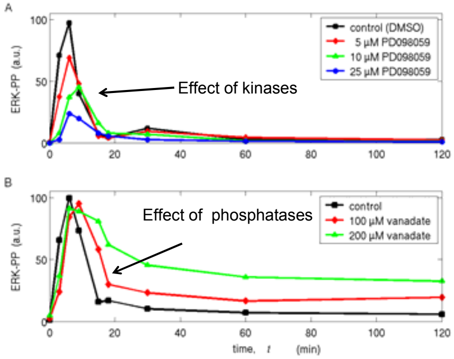
$$C_{ATPase}^J = 0.48$$

$$\sum_{k=1}^{r} C_k^J = 1 \qquad \sum_{k=1}^{r} C_k^S = 0$$

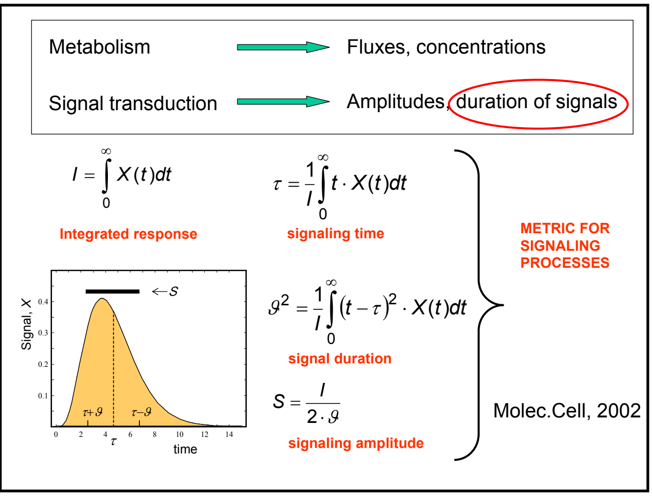
IDENTIFICATION OF KEY STEPS

SIGNAL TRANSDUCTION PATHWAYS





J.J.Hornberg et al. FEBS Journal, (2005)



Metabolism → Fluxes, concentrations

Signal transduction → Amplitudes, duration of signals

$$I = \int_0^\infty X(t)dt$$

Integrated response

$$\tau = \frac{1}{I}\int_0^\infty t \cdot X(t)dt$$

signaling time

$$\vartheta^2 = \frac{1}{I}\int_0^\infty (t-\tau)^2 \cdot X(t)dt$$

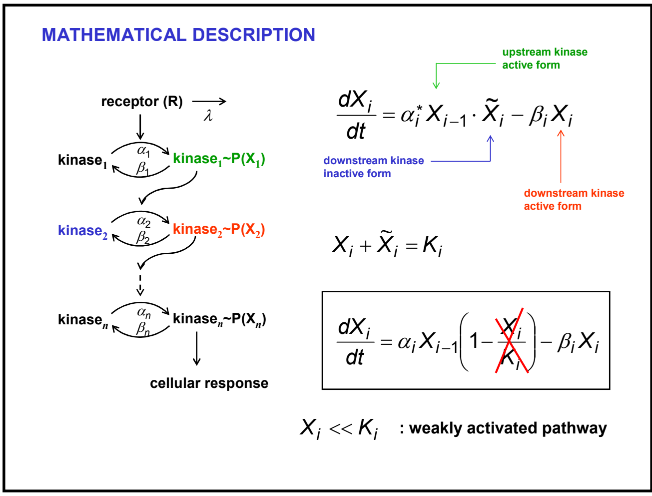
signal duration

$$S = \frac{I}{2 \cdot \vartheta}$$

signaling amplitude

METRIC FOR SIGNALING PROCESSES

Molec.Cell, 2002



MATHEMATICAL DESCRIPTION

upstream kinase active form

$$\frac{dX_i}{dt} = \alpha_i^* X_{i-1} \cdot \tilde{X}_i - \beta_i X_i$$

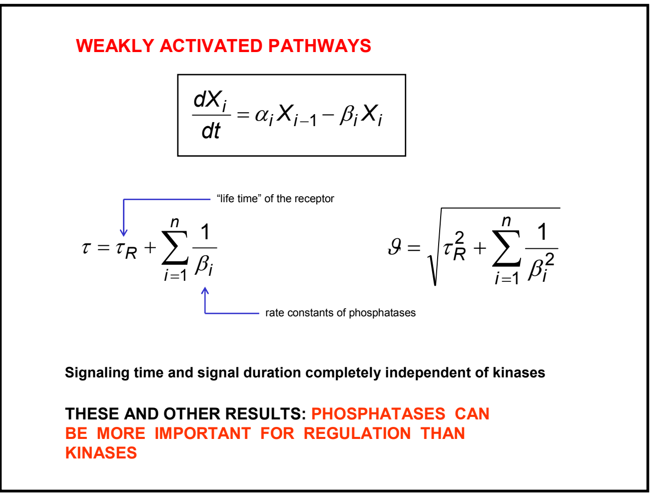
downstream kinase inactive form

downstream kinase active form

$$X_i + \tilde{X}_i = K_i$$

$$\boxed{\frac{dX_i}{dt} = \alpha_i X_{i-1}\left(1 - \cancel{\frac{X_i}{K_i}}\right) - \beta_i X_i}$$

$X_i << K_i$ **: weakly activated pathway**



WEAKLY ACTIVATED PATHWAYS

$$\boxed{\frac{dX_i}{dt} = \alpha_i X_{i-1} - \beta_i X_i}$$

"life time" of the receptor

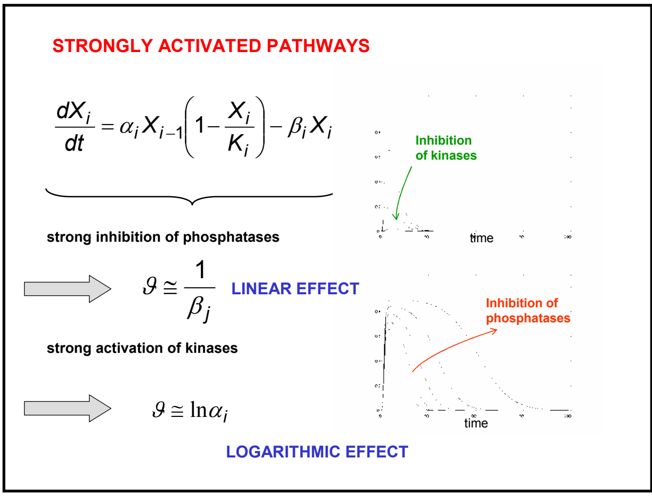
$$\tau = \tau_R + \sum_{i=1}^{n} \frac{1}{\beta_i}$$

rate constants of phosphatases

$$\vartheta = \sqrt{\tau_R^2 + \sum_{i=1}^{n} \frac{1}{\beta_i^2}}$$

Signaling time and signal duration completely independent of kinases

THESE AND OTHER RESULTS: PHOSPHATASES CAN BE MORE IMPORTANT FOR REGULATION THAN KINASES



STRONGLY ACTIVATED PATHWAYS

$$\underbrace{\frac{dX_i}{dt} = \alpha_i X_{i-1}\left(1 - \frac{X_i}{K_i}\right) - \beta_i X_i}$$

strong inhibition of phosphatases

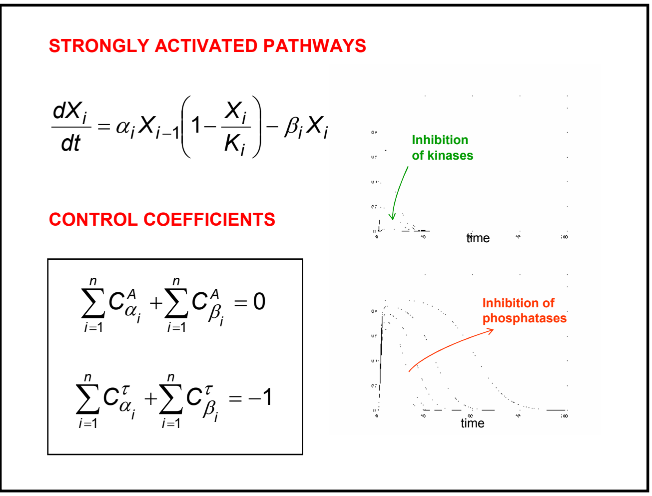
$$\vartheta \cong \frac{1}{\beta_j}$$

LINEAR EFFECT

strong activation of kinases

$$\vartheta \cong \ln \alpha_i$$

LOGARITHMIC EFFECT

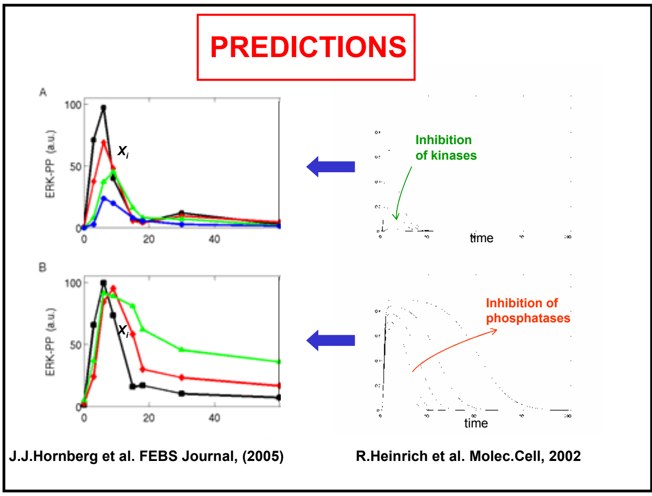


STRONGLY ACTIVATED PATHWAYS

$$\frac{dX_i}{dt} = \alpha_i X_{i-1}\left(1 - \frac{X_i}{K_i}\right) - \beta_i X_i$$

CONTROL COEFFICIENTS

$$\boxed{\begin{gathered}\sum_{i=1}^{n} C^A_{\alpha_i} + \sum_{i=1}^{n} C^A_{\beta_i} = 0 \\ \sum_{i=1}^{n} C^\tau_{\alpha_i} + \sum_{i=1}^{n} C^\tau_{\beta_i} = -1\end{gathered}}$$

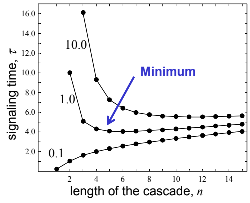


PREDICTIONS

J.J.Hornberg et al. FEBS Journal, (2005)

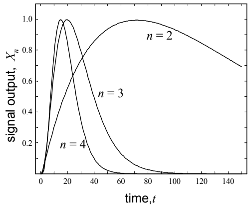
R.Heinrich et al. Molec.Cell, 2002

SIGNALS CAN BE FASTER TRANSMITTED THROUGH LONGER CHAINS



$$\tau = \tau_R + \sum_{i=1}^{n} \frac{1}{\beta_i}$$

$$S \propto \frac{\alpha_1 \alpha_2 \ldots \alpha_n}{\beta_1 \beta_2 \ldots \beta_n}$$

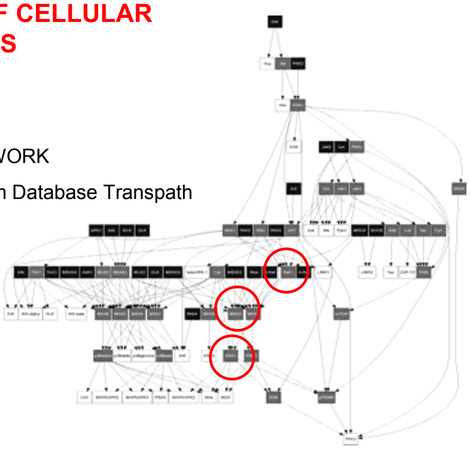


ONE REASON WHY MAPK – PATHWAY 3-4 KINASES ??

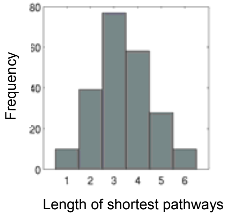
DESIGN OF CELLULAR NETWORKS

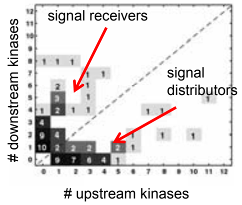
KINASE NETWORK

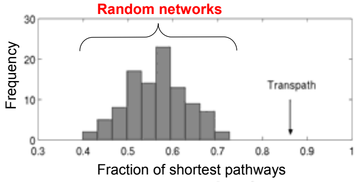
Retreaved from Database Transpath



DESIGN OF KINASE NETWORKS

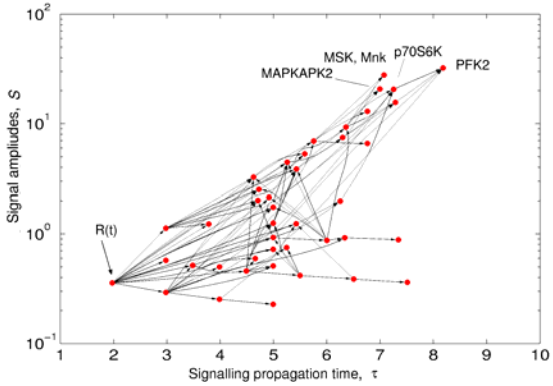






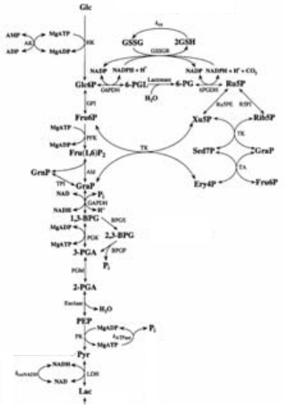
Binder & Heinrich (2004) Genome Informatics.Vol. 15

DYNAMICS OF LARGE SCALE SIGNALING NETWORKS



DESIGN OF CELLULAR NETWORKS

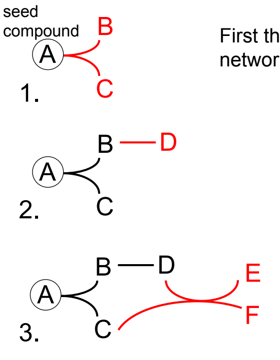
$$\longrightarrow S_1 \longrightarrow S_2 \longrightarrow$$



MAIN FEATURE OF ANY METABOLIC NETWORK NETWORK:

Occurrence of one reaction depends generally on the occurrence of other reactions

STRUCTURAL ANALYSIS OF METABOLISM BY "NETWORK EXPANSION"



etc.

First three generations of an expanding network

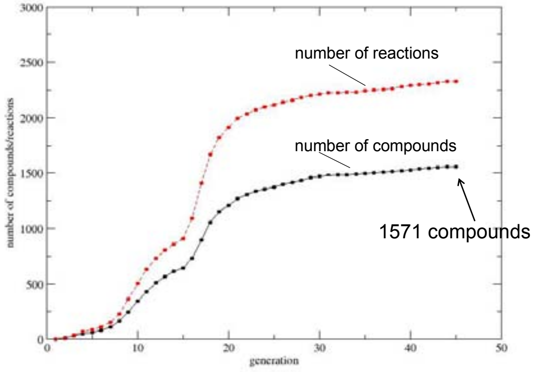
STARTING POINT: set of initial compounds (seed) plus set of possible reactions

LARGE SCALE ANALYSIS

KEGG Database: 5311 reactions, 4587 compounds

EXPANSION OF ATP

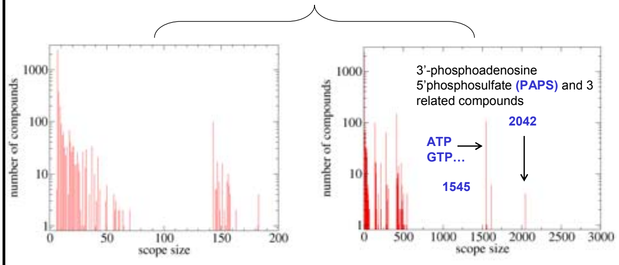
Handorf, Ebenhöh, Heinrich, 2004

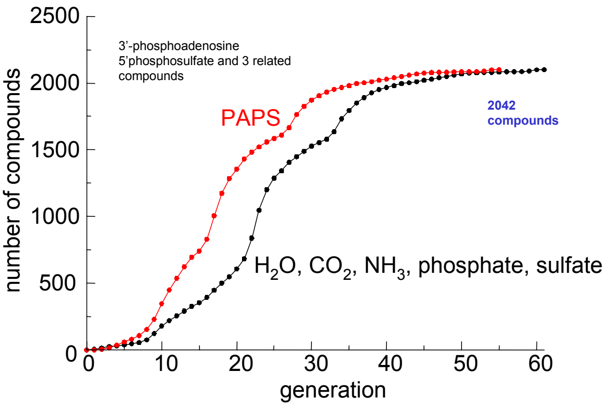


Scope Σ_A of compounds

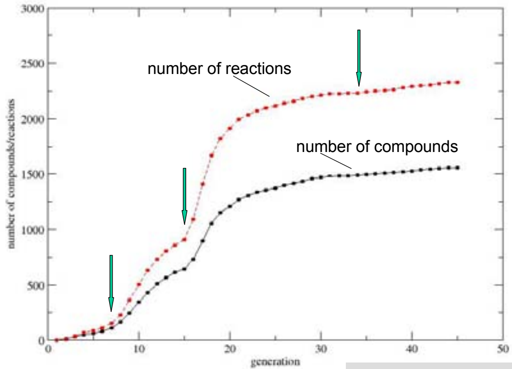
The scope of a compound A is the set of all compounds that can be reached by an expansion starting from A

Scopes sizes of all metabolic compounds





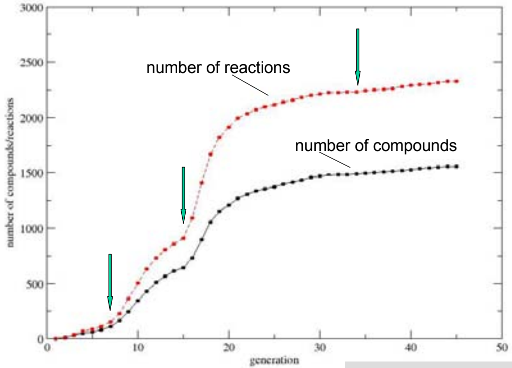
KEGG-Database: 5161 reactions and 4450 compounds



Seed compound: ATP

T. Handorf, O.Ebenhöh, R. Heinrich A. (2004), Genome Informatics Series, Vol. 15

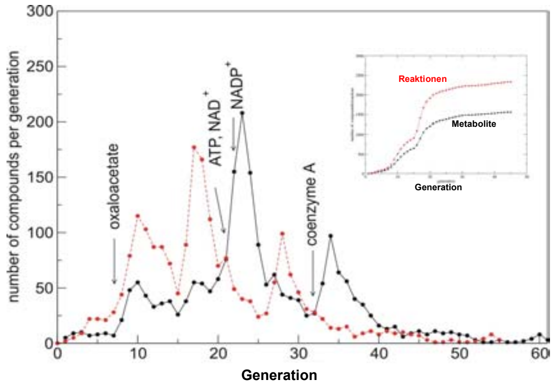
KEGG-Database: 5161 reactions and 4450 compounds



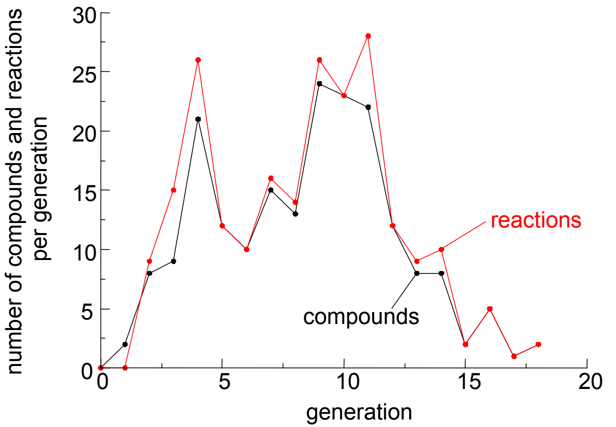
Seed compound: ATP

T. Handorf, O.Ebenhöh, R. Heinrich A. (2004), Genome Informatics Series, Vol. 15

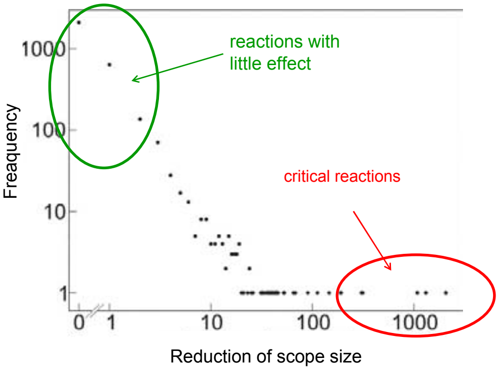
Expansion of {H_2O, CO_2, NH_3, H_3PO_4, H_2SO_4 }



expansion process starting from glucose

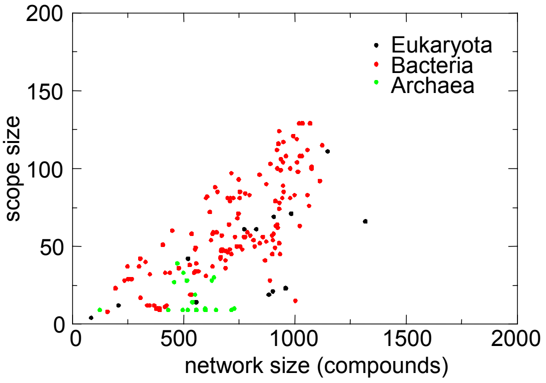


Robustness against single enzyme deletion



---

scope size of ATP in 180 different species



Two posters on network expansion:

P-P12: Scopes: A new concept for the structural analysis of metabolic networks

(T.Handorf, O.Ebenhöh, R. Heinrich)

P-P09: Phylogenetic analysis based on structural information of metbolic networks

(O.Ebenhöh, T. Handorf, R. Heinrich)

HUMBOLDT-UNIVERSITY

Thomas Höfer
Roland Krüger
Bernd Binder
Oliver Ebenhöh
Edda Klipp (MPI)
Stefan Schuster (Jena)
Thomas Handorf

HARVARD MEDICAL SCHOOL, BOSTON

Tom A. Rapoport
Marc Kirschner
Benjamin G. Neel
Lew Cantley
Adrian Salic
Ethan Lee

BOSTON UNIVERSITY

Charles DeLisi

KYOTO UNIVERSITY

Minoru Kanehisa

BIOCENTRUM AMSTERDAM

Hans Westerhoff
Roel van Driel

UNIVERSITY BORDEAUX

Jean-Pierre Mazat
Christine Reder