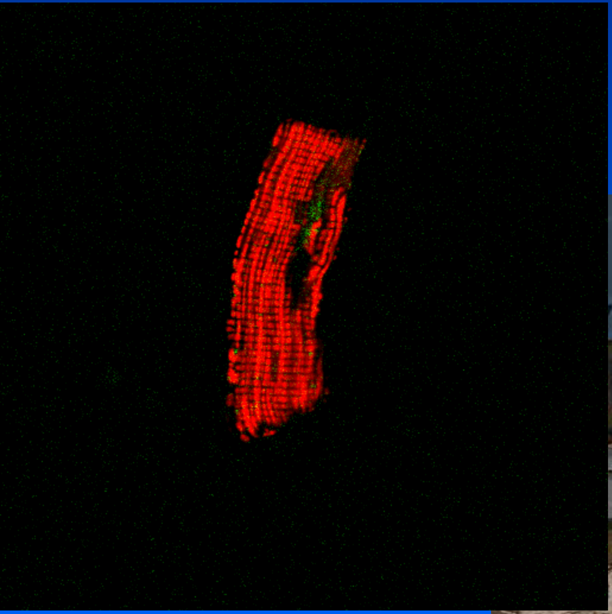
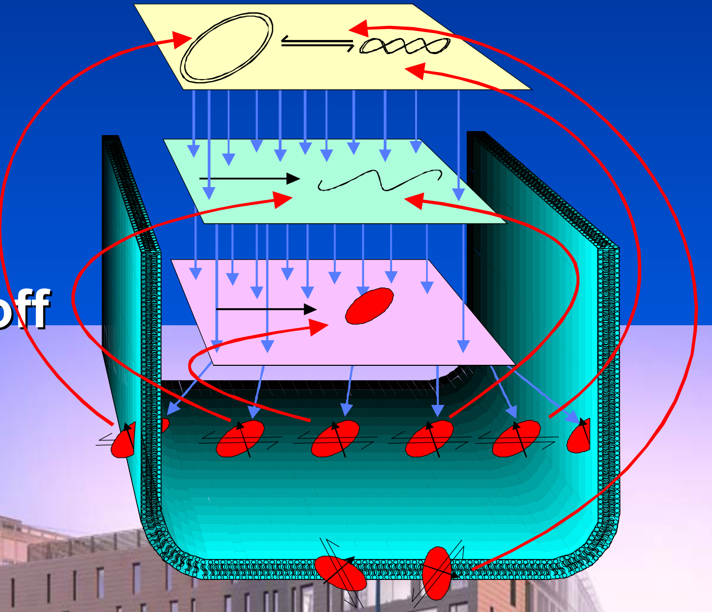
Systems Biology
Signaling where to go





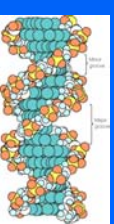
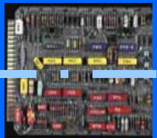
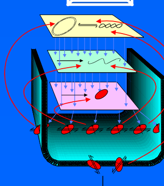
Hans V. Westerhoff
and
friends

November 22, 2005
Oxford

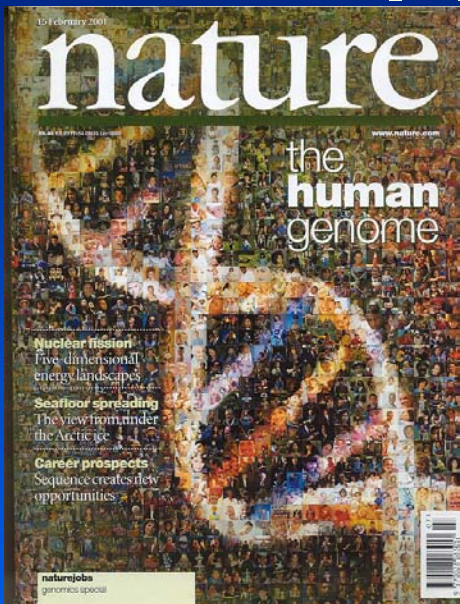
BioCentrum Amsterdam and Manchester Interdisciplinary BioCentre

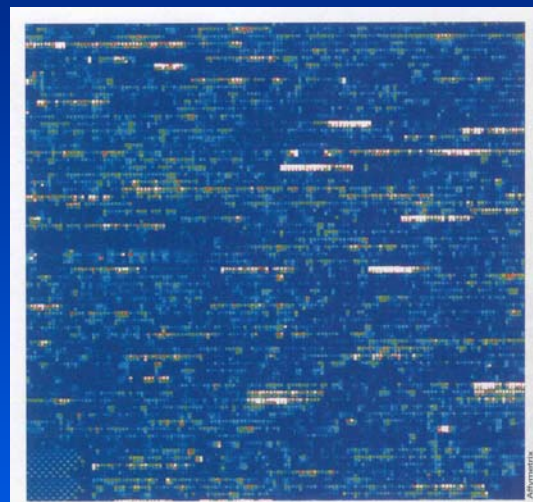
Systems Biology: signaling where to go

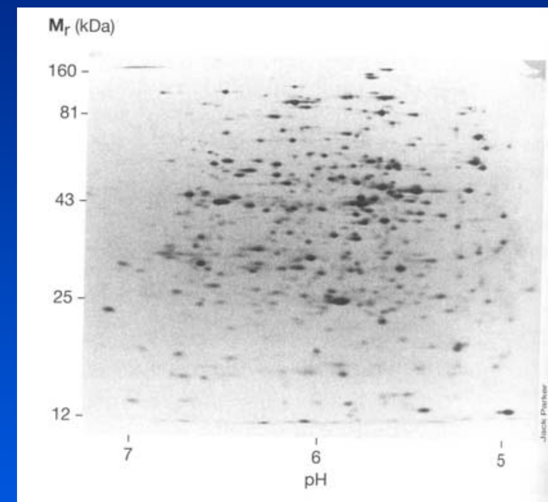
- Interactions & loops & emergence
- Towards applications: Network-based drug design anti-parasites
- Silicon cells
- Systems Biology a science: laws and principles
- Improved understanding of multifactorial disease
- Two paradigms for anti tumor drugs
- What regulates function? Gene expression or metabolism?

Sequence, transcriptome, proteome, metabolome, ...

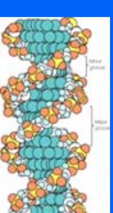


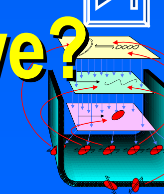




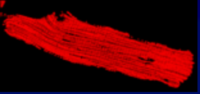
Soon we will know all molecules and their abundances……

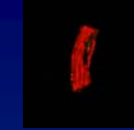
So, we will understand all the facts, or shall we?



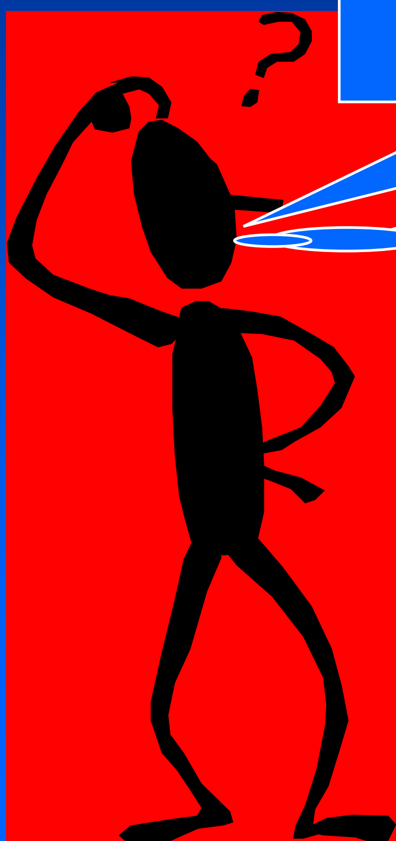



Transcrip



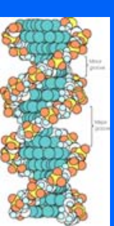


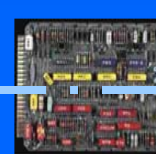
Systems Biology then?

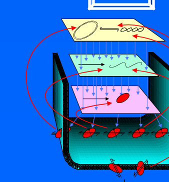


But ‘this is only more computing’…..

and ‘high throughput experiments’…….



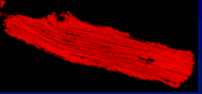


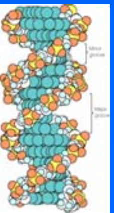


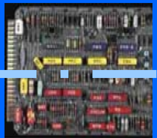
Signaling where to go.....

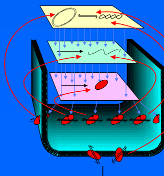
- The essence of Systems Biology is not in computing or in high throughput experimentation

- The essence is:
- The emergent properties of the networks
- The laws and principles that govern how these arise from the interactions





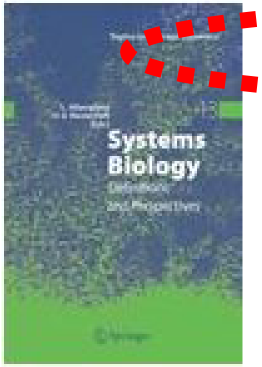




How do I know?

Systems Biology defined by example

by many Systems Biologists



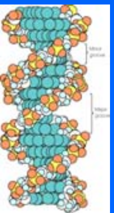
Systems Biology
Definitions and Perspectives
Series: Topics in Current Genetics, Vol. 13
Alberghina, Lilia; Westerhoff, H.V. (Eds.)
2005, Approx. 425 p. 88 illus., 10 in colour., Hardcover
ISBN: 3-540-22968-X
Online version available

Online orders shipping within 2-3 days.

About this book | Table of contents

About this book

For life to be understood and disease to become manageable, the wealth of postgenomic data now needs to be made dynamic. This development requires systems biology, integrating computational models for cells and organisms in health and disease; quantitative experiments (high-throughput, genome-wide, living cell, in silico); and new concepts and principles concerning interactions. This book defines the new field of systems biology and discusses the most efficient experimental and computational strategies. The benefits for industry, such as the new network-based drug-target design validation, and testing, are also presented.



Westerhoff et al.,

Systems Biology is not: genome-wide molecular biology or computing

but it is not just Physics either

The beauty of Physics is:

Cause 1

↓

Effect 1 = Cause 2

↓

Effect 2

The reality of Biology is:

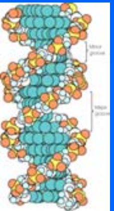
Cause 1 = Effect 0

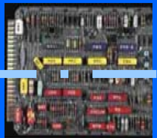
↓

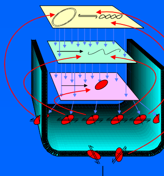
Effect 1 = Cause 2

↓

Effect 2 = Cause 0







(The reality of Modern Physics is☺☺:)

Cause 1 = Effect 0

↓

Effect 1 = Cause 2

↓

Effect 2 = Cause 0

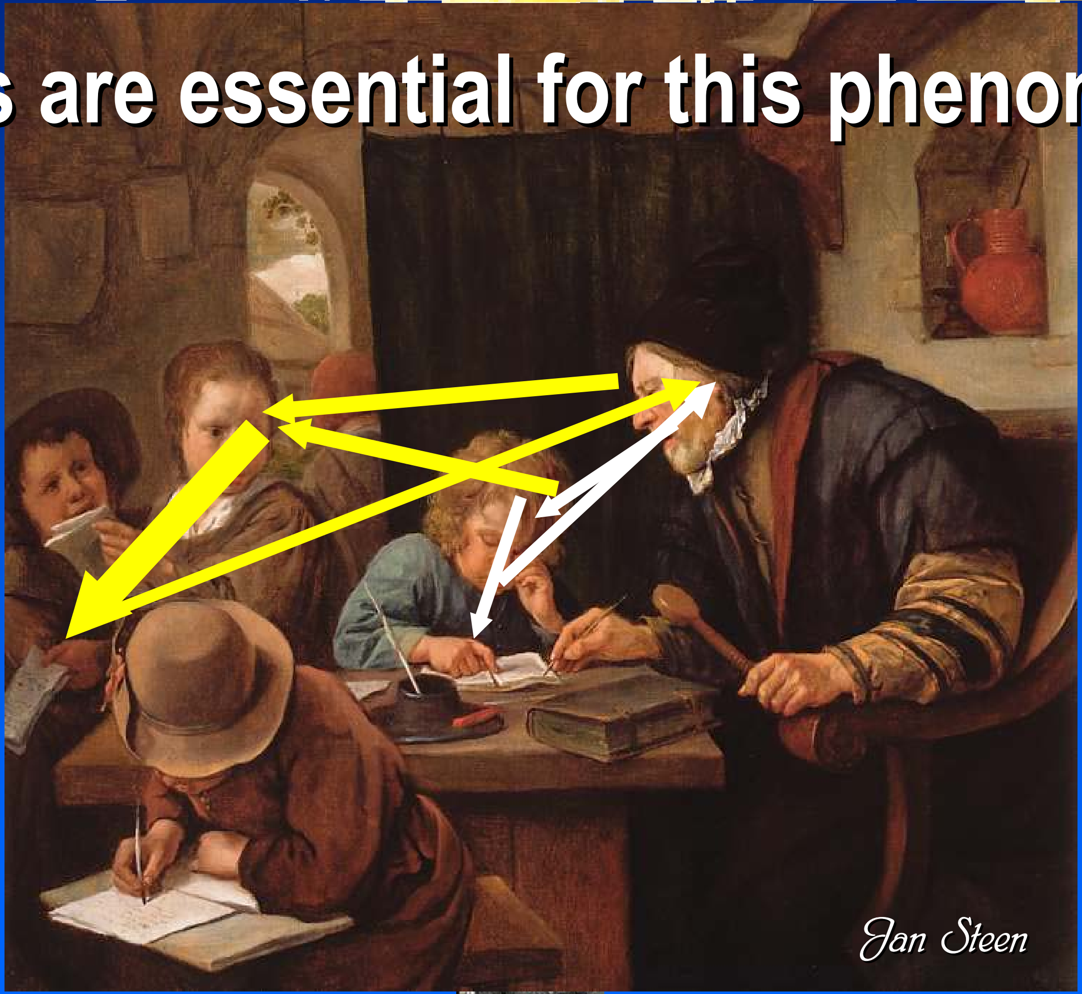
What is it that we are looking for then?

Life arises not just in the isolated molecules but in their communication

And loops are essential for this phenomenon

Life arises not just in the isolated molecules but in their communication

And loops are essential for this phenomenon



Where is the rub?
of Systems' Biology?

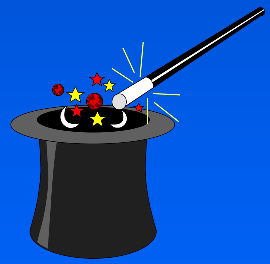
The properties that arise

in nonlinear interactions

....

Through the
dynamic-
dynamic modes:

The loops



We need to
understand/manage
these modes

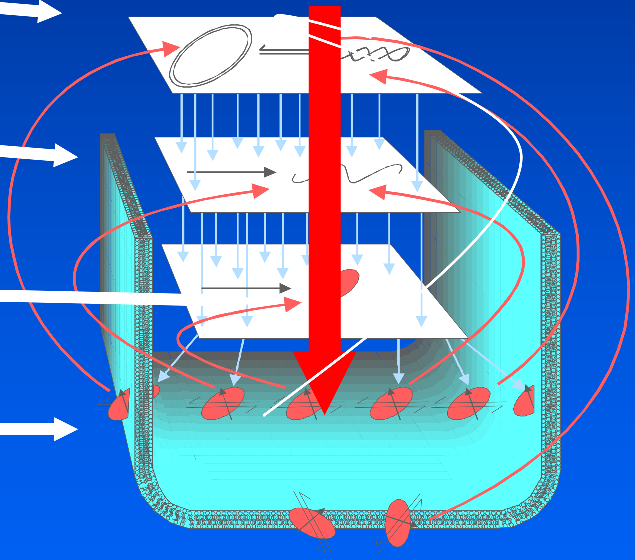
Dogma of molecular biology

Genome

Transcriptome

Proteome

Metabolome



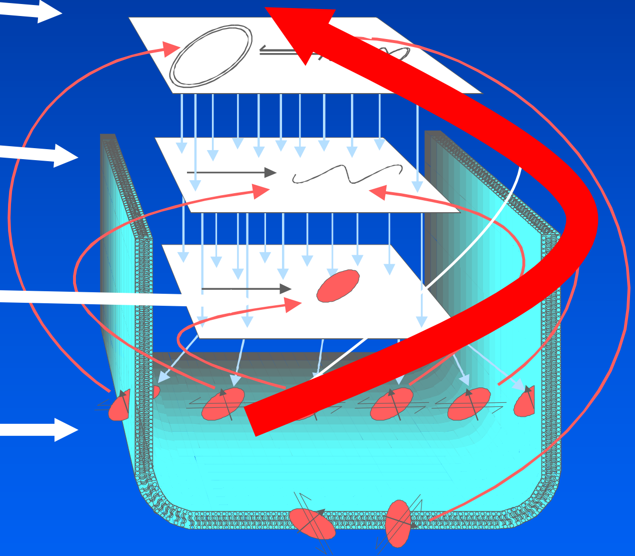
Monod: lac operon

Genome

Transcriptome

Proteome

Metabolome



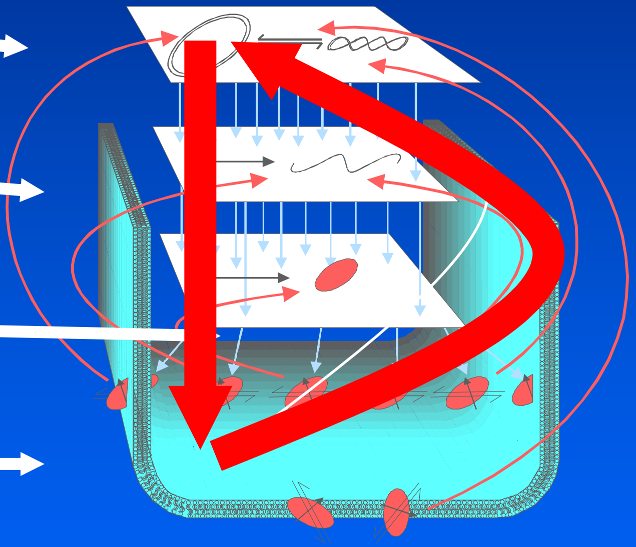
True Cell Biology

Genome

Transcriptome

Proteome

Metabolome



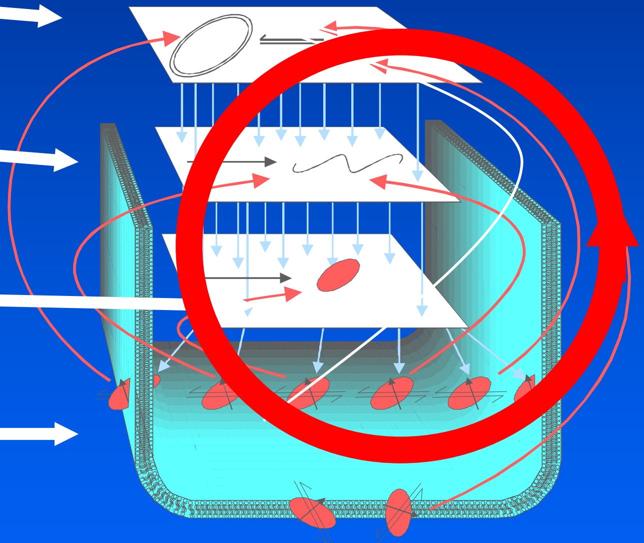
Integrative Systems Biology:
How to deal with circular causality

Genome

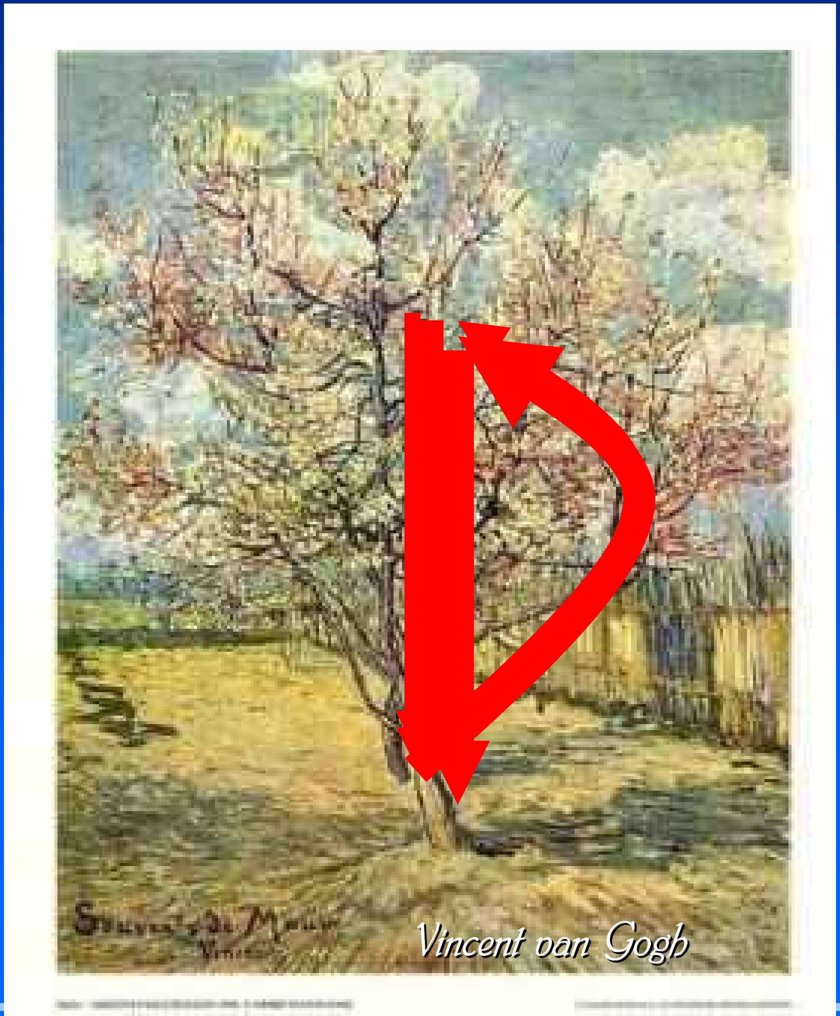
Transcriptome

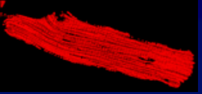
Proteome

Metabolome



Systems Biology should deal with circular causality

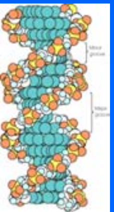


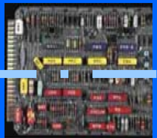


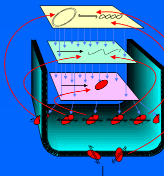
Does it always do so ………???

- Correlations
- Bayesian networks ??? (without the feedback loops?????)

- Feedback & loops not often dealt with explicitly

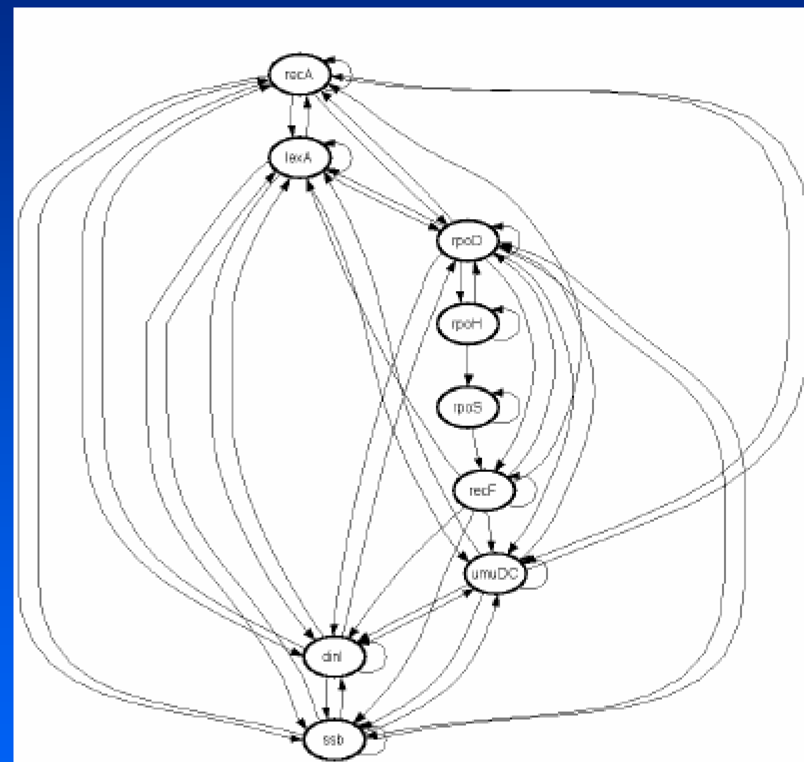




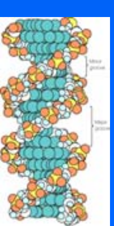


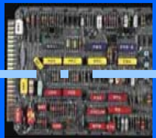
Loops are essential for Systems Biology and approaches *do* exist

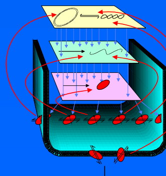
$$R^X_X = A \cdot r^X_X$$

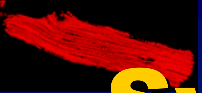


Kholodenko, B. N., Kiyatkin, A., Bruggeman, F. J., Sontag, E., Westerhoff, H. V. & Hoek, J. B. (2002). Untangling the wires: A strategy to trace functional interactions in signaling and gene networks. *Proc Natl Acad Sci U S A* 99(20), 12841-6.



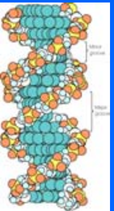


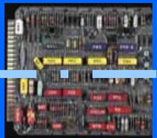


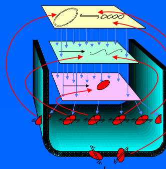


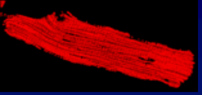
Systems Biology: signaling where to go

- Interactions & loops & emergence ✓
- Towards applications: Network-based drug design anti-parasites
- Silicon cells
- Systems Biology a science: laws and principles
- Improved understanding of multifactorial disease
- Two paradigms for anti tumor drugs
- What regulates function? Gene expression or metabolism?



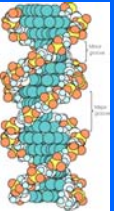


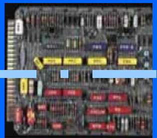


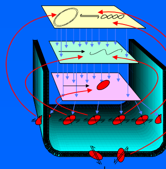


Systems Biology is a Science ....

- Definitions
- Principles/laws
- Validation
- Utilization







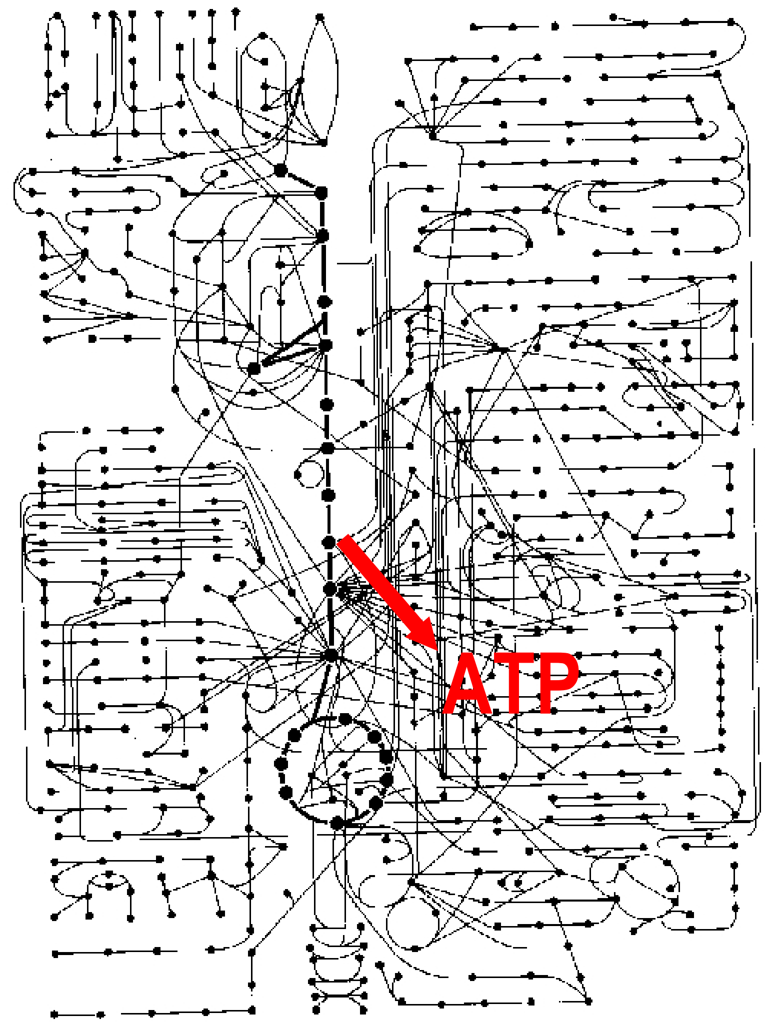
Rational (?) drug design

- Design inhibitor for the enzyme

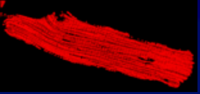
Elementary mode, minimum cut set versus dynamic modeling

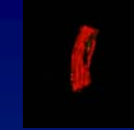
- Works for deletion mutants
- To kill parasites/tumor cells inhibitors will have to be used
- These do not inhibit by 100 %

- Dynamic model needed



A chart illustrating the chemical reactions that interconvert small molecules in cells.

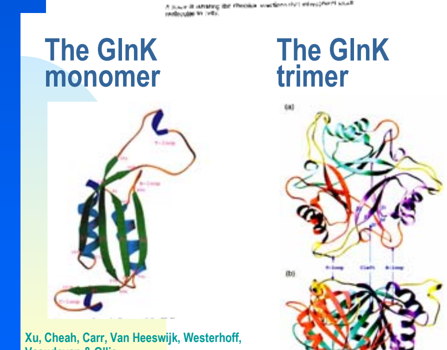




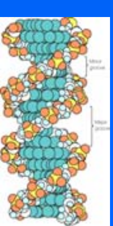
Paradigm 1:
Network based Rational drug design first!

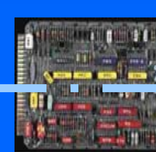
- Figure out which enzyme should be inhibited to kill the parasite/tumor

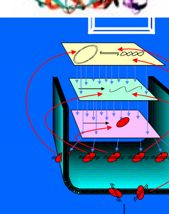
- Only then:
- Design inhibitor for the enzyme



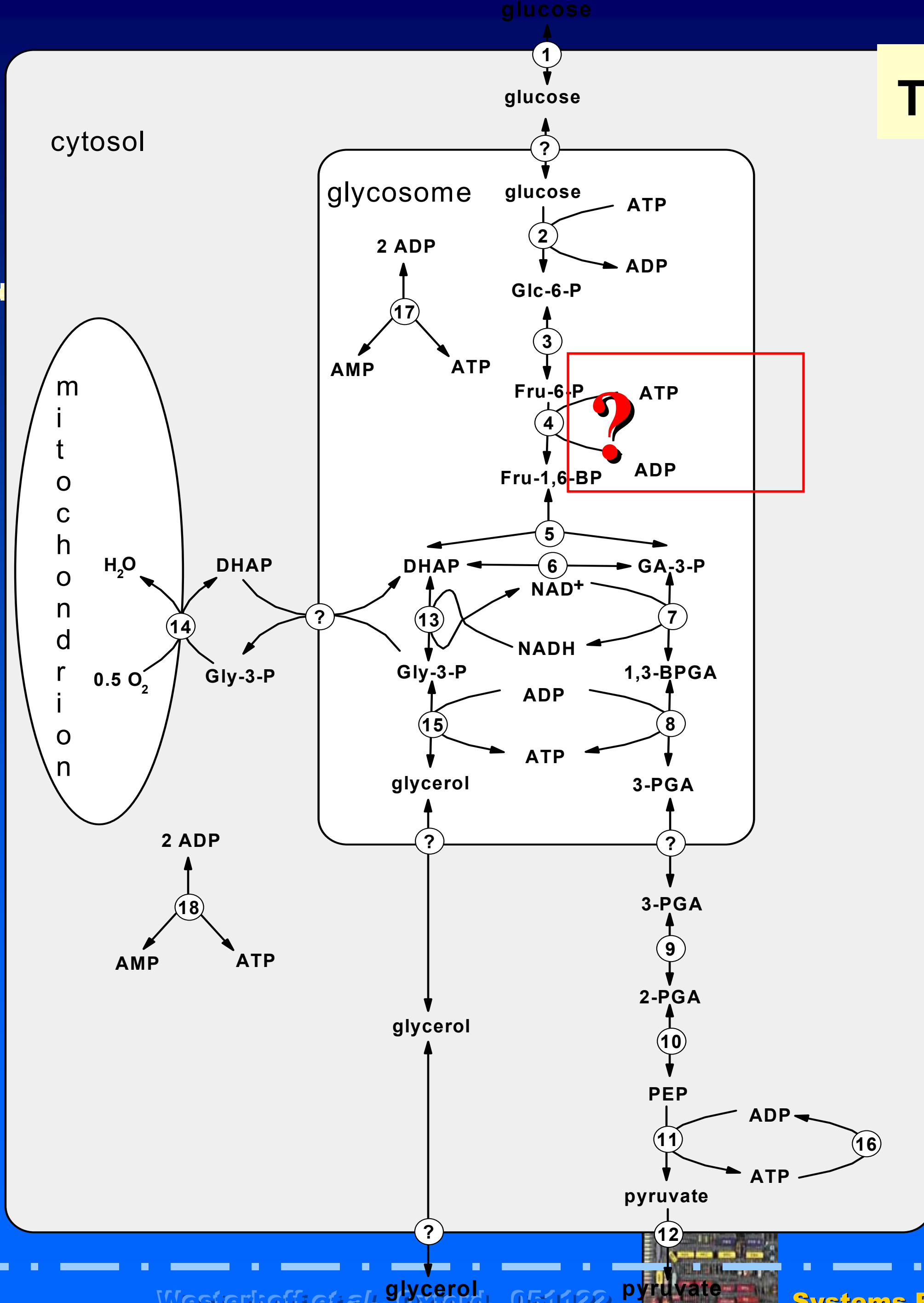
Xu, Cheah, Carr, Van Heeswijk, Westerhoff, Vasudevan & Ollis







Trypanosome metabolism

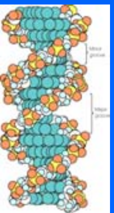


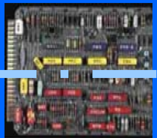
Network-based drug design:

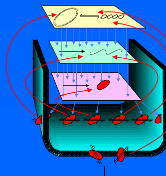
Where is the best target?

Network based drug design

- Kinetics of individual enzymes
- **Calculate which reactions control (limit) the flux**
- **Design an inhibitor for those reactions**







The silicon cell approach

http://www.siliconcell.net/

SiC!: The Silicon Cells

A silicon cell is a precise replica of (part of) a living cell. It is based on experimentally determined rate laws and parameter values, *i.e.* only on data, not on fitted values or assumptions. It merely calculates the system biology implications of the molecular properties that are already known. The international silicon cell program thereby differs (i) from the *Virtual Cell*, which collects software that can be used to calculate what happens in cells, (ii) from the *E-Cell* in that it uses precise and experimentally determined kinetics, (iii) from the San Diego initiative in that it calculates kinetics, rather than analyzing which pathways are possible or actually used.

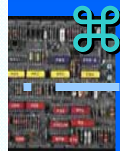
At present silicon cells exist for glycolysis in yeast, trypanosomes, *E. coli*, erythrocytes, EGF induced signal transduction, for histone-gene expression in early development. Most of these can be found on the ready-to-use website (also ideal for teaching purposes) pioneered by Jacky Snoep.

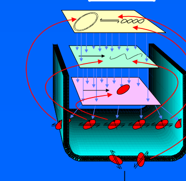
- Amsterdam Silicon cell papers
- The Amsterdam Silicon Cells programme
- YSiC: the Yeast Silicon Cell, a planned European Consortium
- Silicon Cell ready to use.: the website with silicon cells that can be run over the web.

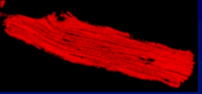
Please contact us when interested in joining this international consortium.

Towards the System Biology site

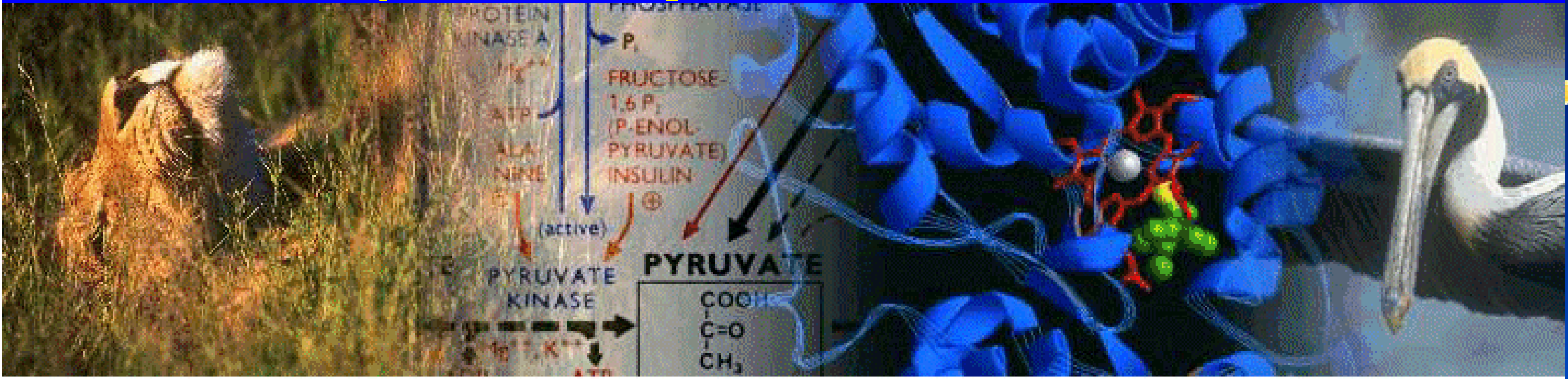
- If important properties stem from the interactions, then ..
- If we know the components and the interaction properties…
- We should be able to calculate important properties
- And by checking these, verify we understand the biology.
- Or discover new mechanisms!







JWS Online Cellular Systems Modelling



Home **Model Database** **Site information** **Forums**

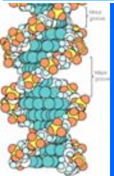
Linked to *FEBS Journal* and *Microbiology*

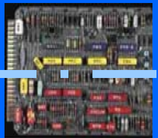
New! **Our discussion forums are now live: try the Forum pages.**

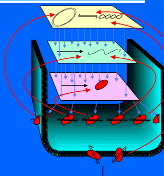
2002/12/03: The Applets have been upgraded to use the Sun Microsystems JRE 1.4 or higher

www.siliconcell.net

Site last updated: 03 December 2002







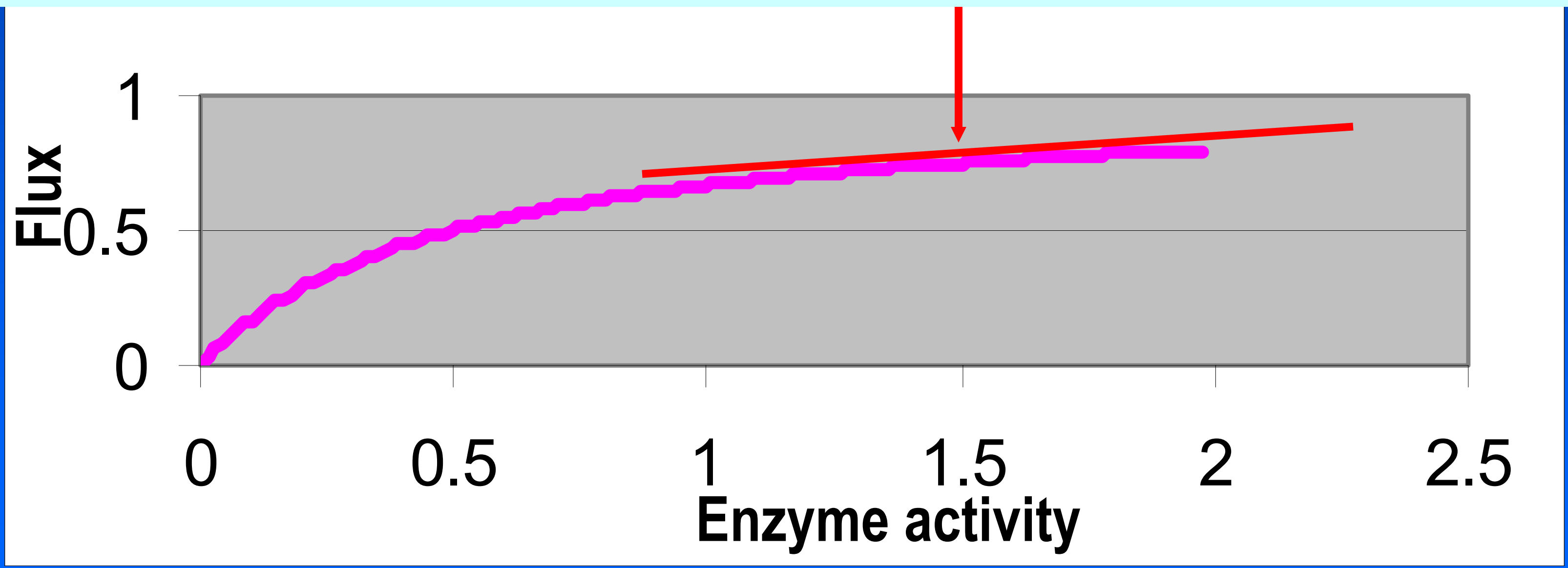
Let us try…

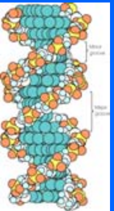
http://www.siliconcell.net

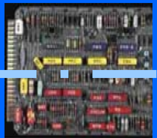
http://localhost/index.html

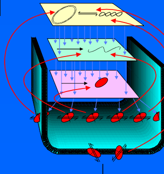
How to measure whether an enzyme is limiting the flux

$$C_i^J \equiv \frac{percentage\ decrease\ in\ flux J}{percentage\ decrease\ in\ enzyme\ activity}$$



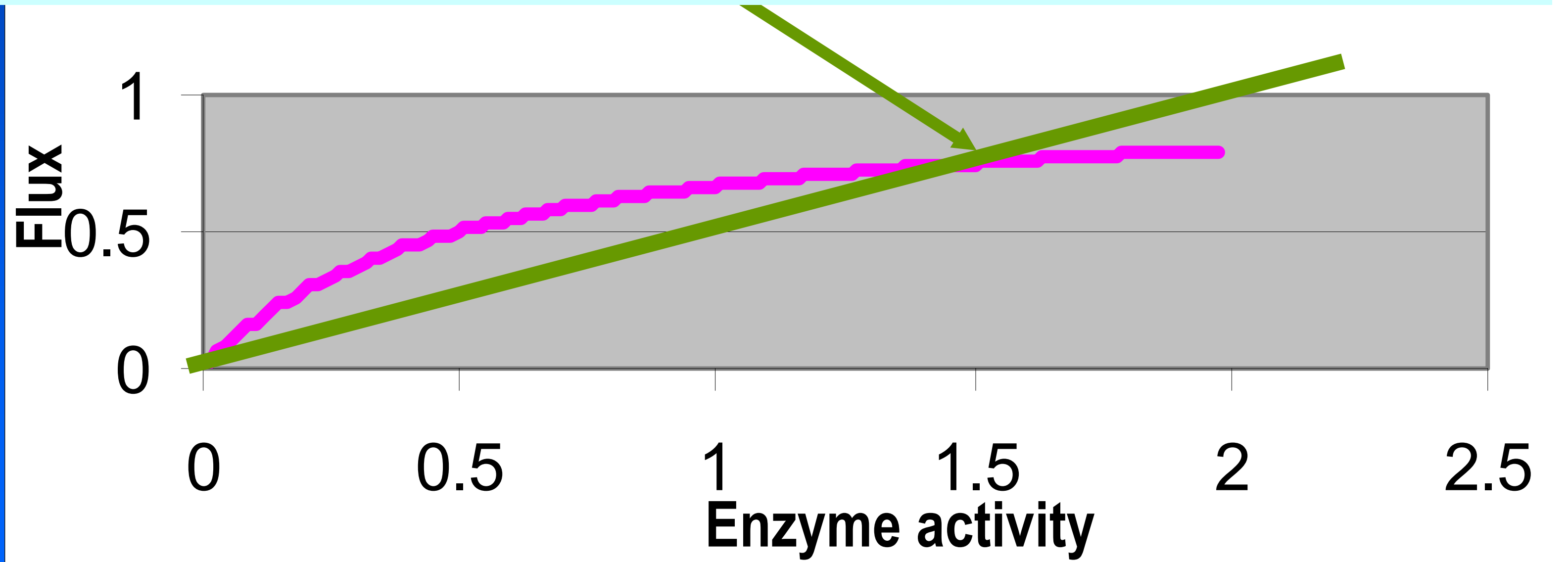






A truly rate limiting step has C=1

$$C_i^J \equiv \frac{10\%\ decrease\ in\ flux J}{10\%\ decrease\ in\ enzyme\ activity} = 1$$



How to measure whether an enzyme is limiting the flux

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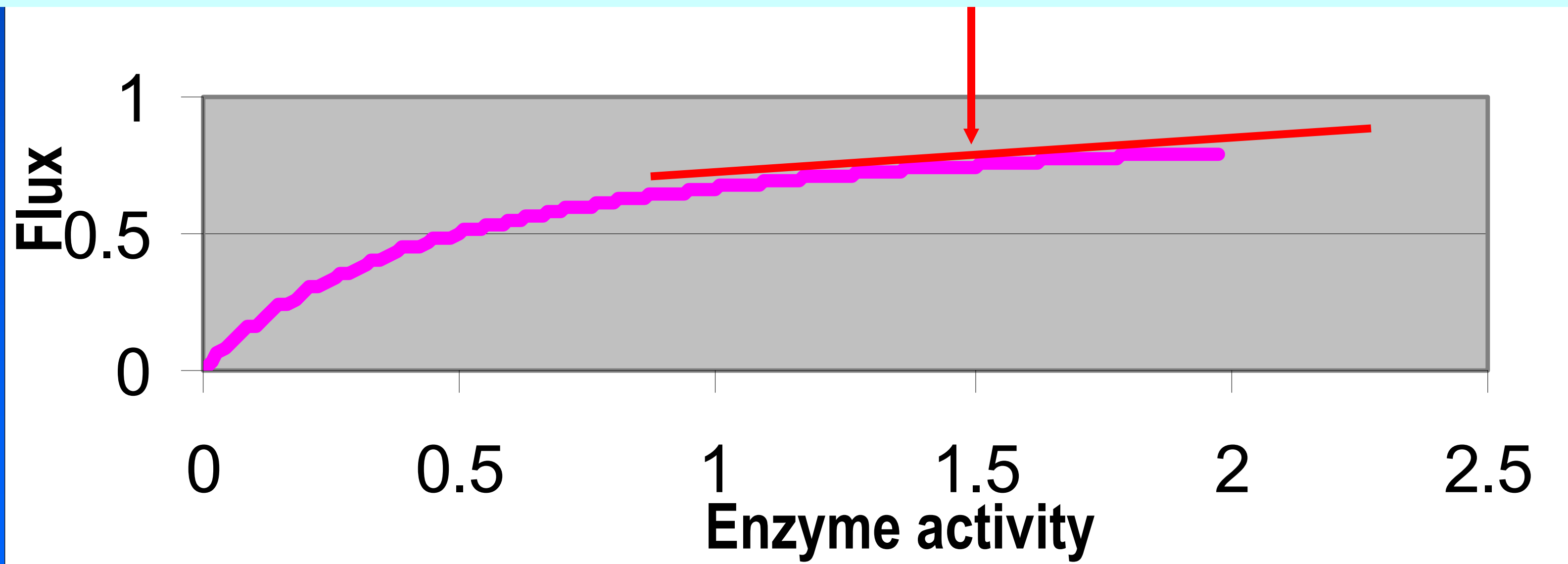
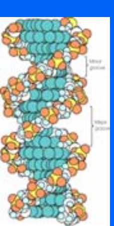
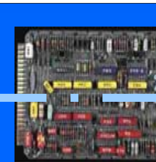
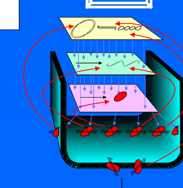


Definition of how important a process is for function: flux-control coefficient

Relative change in flux caused by unit specific activation of an enzyme, at steady state

$$C_{e_i}^{J} = \left(\frac{d \ln |J|}{d \ln e_i} \right)_{steady\,state} = \frac{dJ / J}{de_i / e_i} = \frac{\text{'}\%dJ\text{'}}{\text{'}1\%de_i}$$

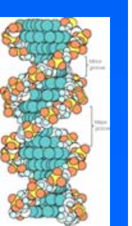
dlne$_i$: activity (rate) modulation of process i

Control coefficient

- Control of a system property by a component activity
- Importance of component activity for that system property

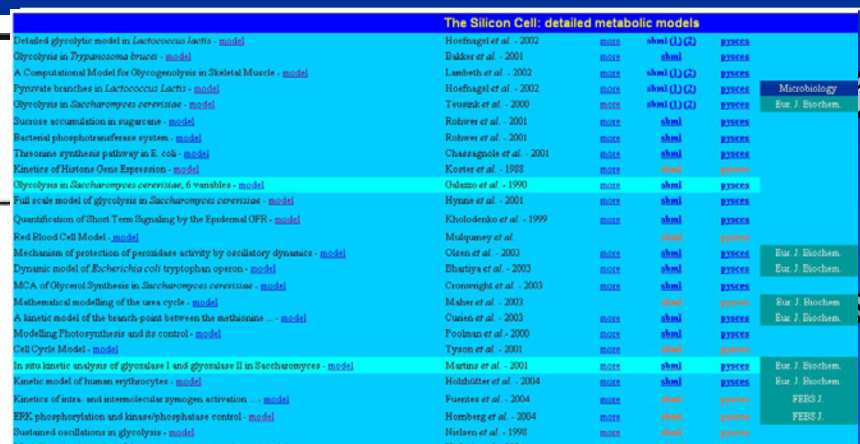
Control of glycolysis

Reaction	glucose Γ/K_{eq}
Glucose transport	$9.2 \cdot 10^{-3}$
HK ?	$<< 10^{-3}$
PFK ?	$<< 10^{-3}$
ALD	0.17
GAPDH	0.20
PGK	$3.4 \cdot 10^{-3}$
PYK ?	$<< 10^{-3}$
Pyruvate transport	$<< 10^{-3}$
GDH	$9.1 \cdot 10^{-3}$
GPO	$<< 10^{-3}$
ATP utilization	

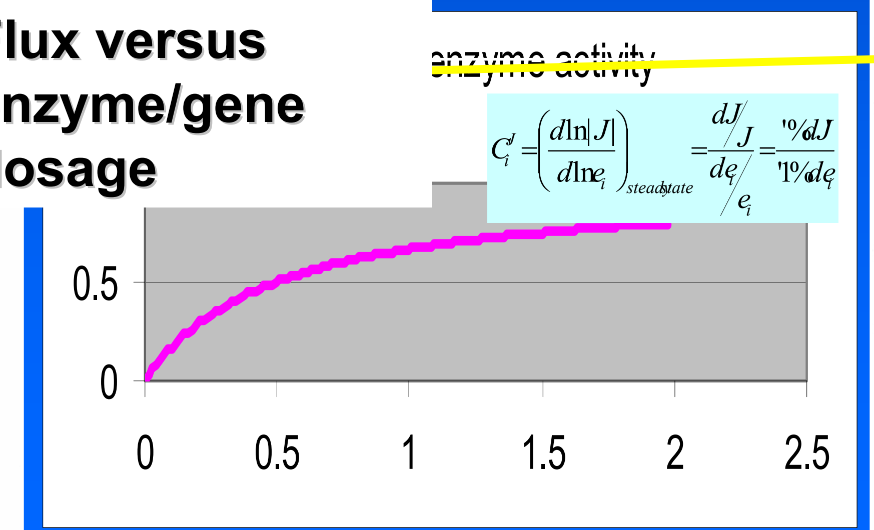


Silicon trypanosome: flux control is distributed **with some focus on transporter**

Reaction	8 mM glucose	
	C_i^J	Γ/K_{eq}
Glucose transport	0.63	[illegible]
HK	0.04	$<< 10^{-3}$
PFK	0.01	$<< 10^{-3}$
ALD	0.10	[illegible]
GAPDH	0.09	[illegible]
PGK	0.06	$3.4 \cdot 10^{-3}$
PYK	0.01	$<< 10^{-3}$
Pyruvate transport	0.00	$<< 10^{-3}$
GDH	0.06	$9.1 \cdot 10^{-3}$
GPO	0.01	$<< 10^{-3}$
ATP utilization	0.00	

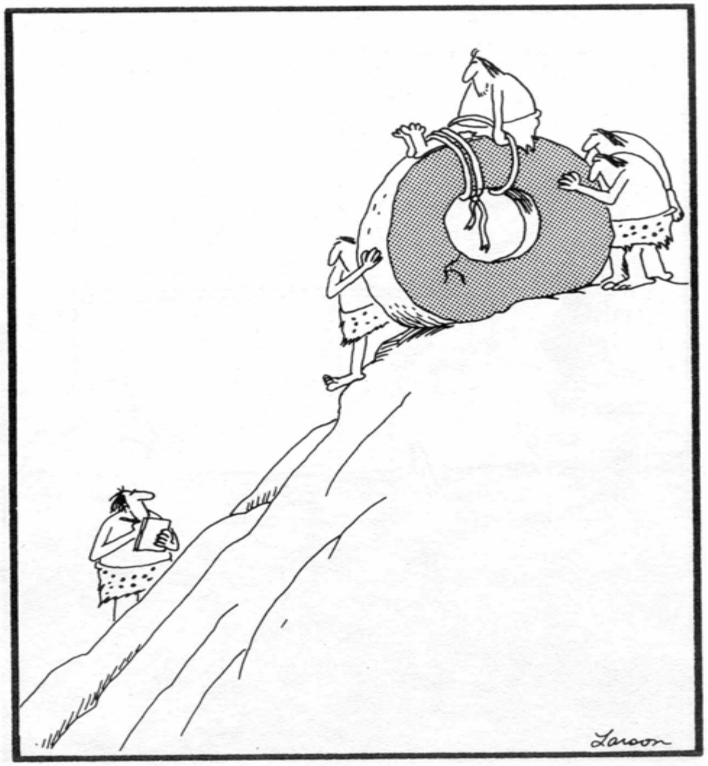


Flux versus enzyme/gene dosage

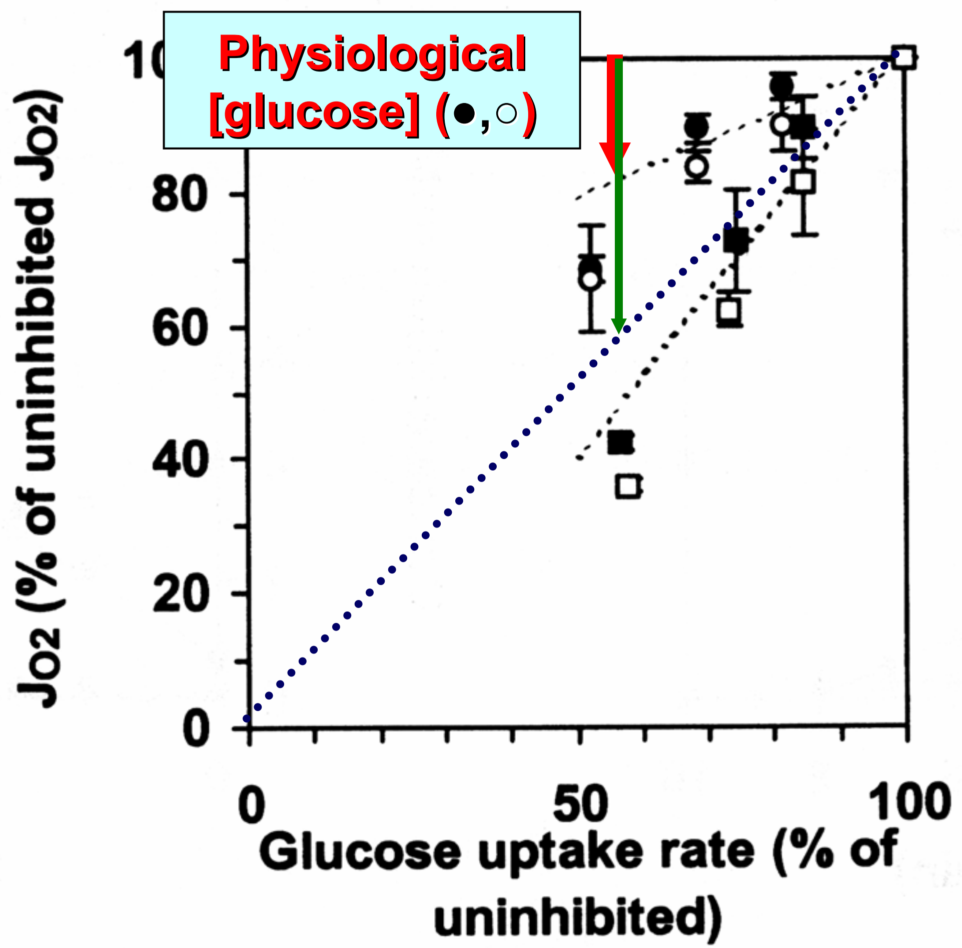


$$C_i^J = \left(\frac{d\ln|J|}{d\ln e_i}\right)_{steady state} = \frac{dJ/J}{de_i/e_i} = \frac{\%dJ}{1\%de_i}$$

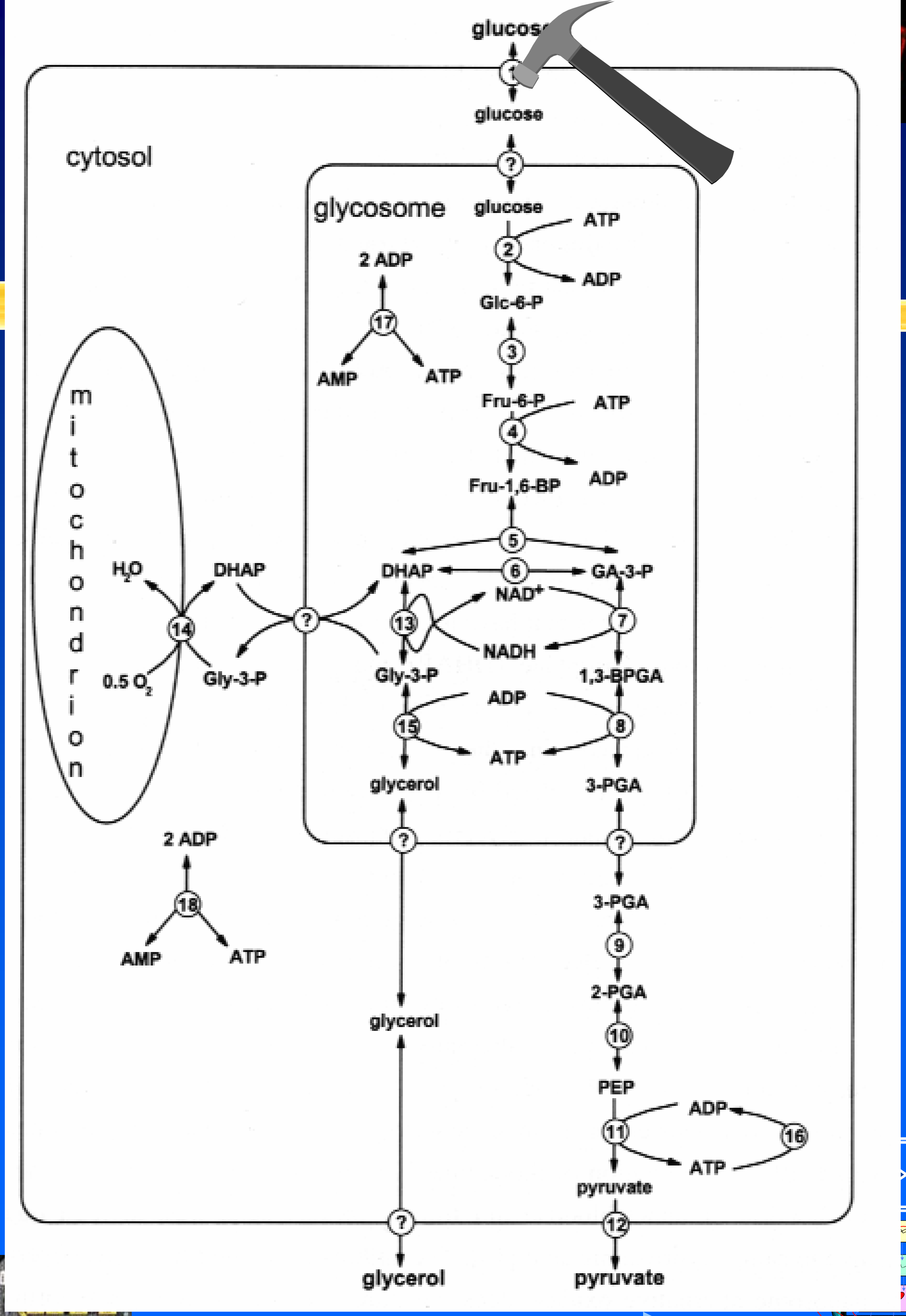
Experimental validation: control by transport indeed approximately 0.5



Early experiments in transportation



Where to target drugs?



The glucose transporter

Drug-target paradigm 2 (parasites)

- Inhibit the step with the highest control on vital flux of parasite

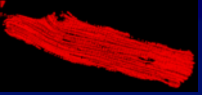
However: genomics shows.....

High homology between parasites and host:

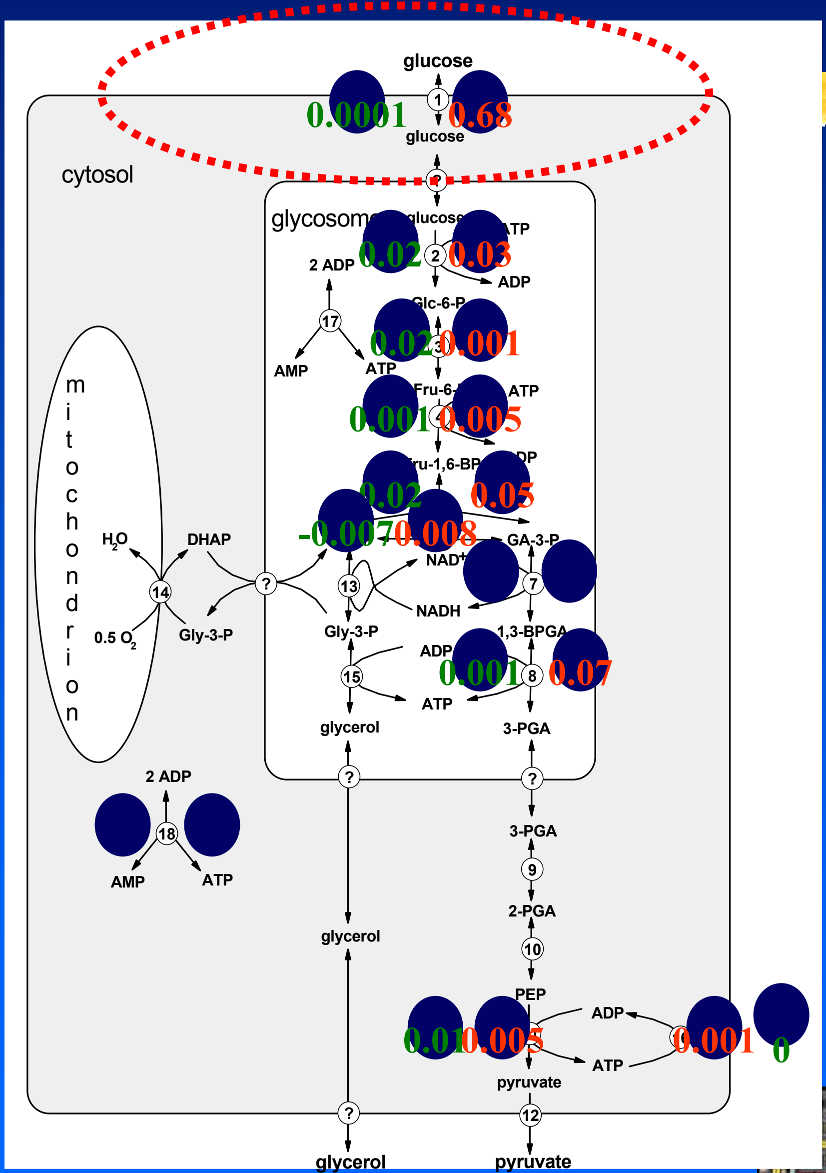
⇒PARADIGM 2 may not always work

Drug-target paradigm 3 (parasites)

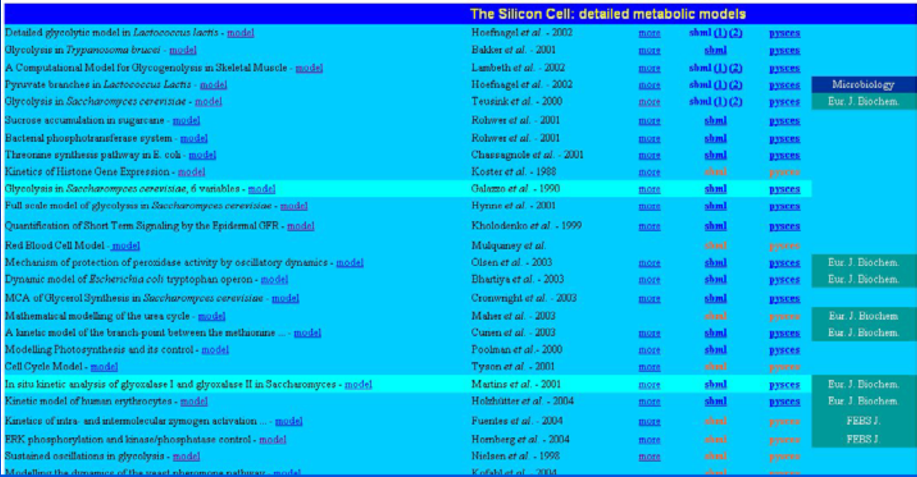
⌘Inhibit the step with the highest diffrerence in control on vital flux between parasite and host



Control over the ATP synthesis flux



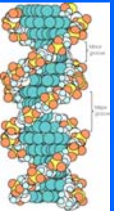
Erythrocyte model | Trypanosome model

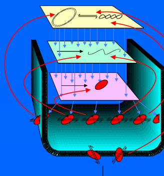


The Silicon Cell: detailed metabolic models

Detailed glycolytic model in *Lactococcus lactis* - model	Hoefnagel *et al.* - 2002	more	sbml (1) (2)	pysces	
Glycolysis in *Trypanosoma brucei* - model	Bakker *et al.* - 2001	more	sbml	pysces	
A Computational Model for Glycogenolysis in Skeletal Muscle - model	Lambeth *et al.* - 2002	more	sbml (1) (2)	pysces	
Pyruvate branches in *Lactococcus Lactis* - model	Hoefnagel *et al.* - 2002	more	sbml (1) (2)	pysces	Microbiology
Glycolysis in *Saccharomyces cerevisiae* - model	Teusink *et al.* - 2000	more	sbml (1) (2)	pysces	Eur. J. Biochem.
Sucrose accumulation in sugarcane - model	Rohwer *et al.* - 2001	more	sbml	pysces	
Bacterial phosphotransferase system - model	Rohwer *et al.* - 2001	more	sbml	pysces	
Threonine synthesis pathway in E. coli - model	Chassagnole *et al.* - 2001	more	sbml	pysces	
Kinetics of Histone Gene Expression - model	Koster *et al.* - 1988	more	sbml	pysces	
Glycolysis in *Saccharomyces cerevisiae*, 6 variables - model	Galazzo *et al.* - 1990	more	sbml	pysces	
Full scale model of glycolysis in *Saccharomyces cerevisiae* - model	Hynne *et al.* - 2001	more	sbml	pysces	
Quantification of Short Term Signaling by the Epidermal GFR - model	Kholodenko *et al.* - 1999	more	sbml	pysces	
Red Blood Cell Model - model	Mulquiney *et al.*		sbml	pysces	
Mechanism of protection of peroxidase activity by oscillatory dynamics - model	Olsen *et al.* - 2003	more	sbml	pysces	Eur. J. Biochem.
Dynamic model of *Escherichia coli* tryptophan operon - model	Bhartiya *et al.* - 2003	more	sbml	pysces	Eur. J. Biochem.
MCA of Glycerol Synthesis in *Saccharomyces cerevisiae* - model	Cronwright *et al.* - 2003	more	sbml	pysces	
Mathematical modelling of the urea cycle - model	Maher *et al.* - 2003		sbml	pysces	Eur. J. Biochem.
A kinetic model of the branch-point between the methionine ... - model	Curien *et al.* - 2003	more	sbml	pysces	Eur. J. Biochem.
Modelling Photosynthesis and its control - model	Poolman *et al.* - 2000	more	sbml	pysces	
Cell Cycle Model - model	Tyson *et al.* - 2001	more	sbml	pysces	
In situ kinetic analysis of glyoxalase I and glyoxalase II in Saccharomyces - model	Martins *et al.* - 2001	more	sbml	pysces	Eur. J. Biochem.
Kinetic model of human erythrocytes - model	Holzhütter *et al.* - 2004	more	sbml	pysces	Eur. J. Biochem.
Kinetics of intra- and intermolecular zymogen activation ... - model	Fuentes *et al.* - 2004	more	sbml	pysces	FEBS J.
ERK phosphorylation and kinase/phosphatase control - model	Hornberg *et al.* - 2004	more	sbml	pysces	FEBS J.
Sustained oscillations in glycolysis - model	Nielsen *et al.* - 1998	more	sbml	pysces	
Modelling the dynamics of the yeast pheromone pathway - model	Kofahl *et al.* - 2004		sbml	pysces	

Glucose transport has high control over the ATP synthesis flux in the parasite, but not in the erythrocyte!



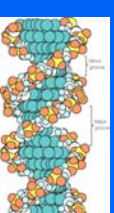


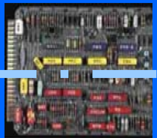
Good news: it delivers

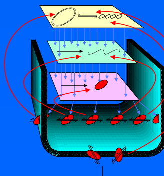
Bad (?) News: we need to make silicon cells of more host tissues

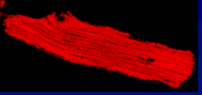
Systems Biology: signaling where to go

- Interactions & loops & emergence
- Towards applications: Network-based drug design anti-parasites
- Silicon cells
- Systems Biology a science: laws and principles
- Improved understanding of multifactorial disease
- Two paradigms for anti tumor drugs
- What regulates function? Gene expression or metabolism?



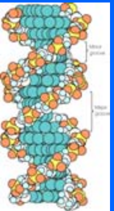


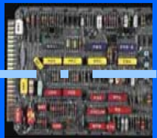


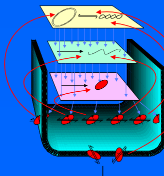


Systems Biology is a Science ……………………………

- ⌘Definitions
- ⌘Principles/laws
- ⌘Validation
- ⌘Utilization





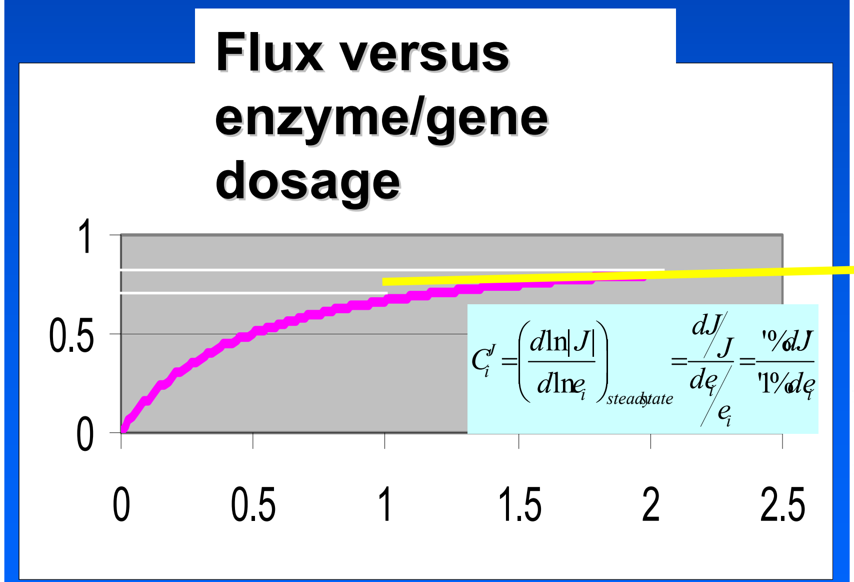


Looking for a principle

Where did the 1 go?
(of THE rate limiting step
/
total limitation/importance)

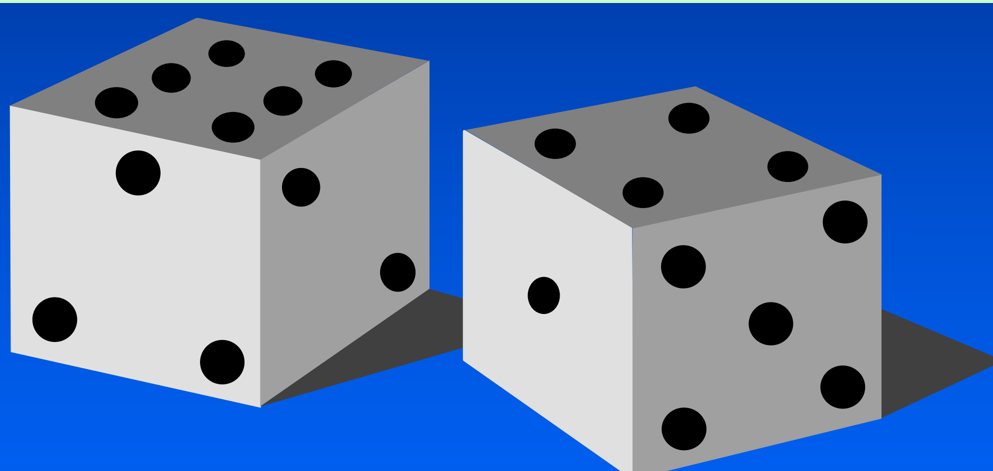
Silicon trypanosome: total flux control is 1

Reaction	8 mM glucose C_i^J	Γ/K_{eq}
Glucose transport	**0.63**	$9.2 \cdot 10^{-3}$
HK	0.04	$<< 10^{-3}$
PFK	0.01	$<< 10^{-3}$
ALD	**0.10**	0.17
GAPDH	**0.09**	0.20
PGK	**0.06**	$3.4 \cdot 10^{-3}$
PYK	0.01	$<< 10^{-3}$
Pyruvate transport	0.00	$<< 10^{-3}$
GDH	**0.06**	$9.1 \cdot 10^{-3}$
GPO	0.01	$<< 10^{-3}$
ATP utilization	[illegible]	
	1.01	

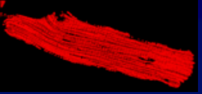


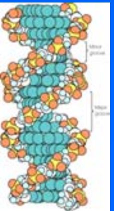
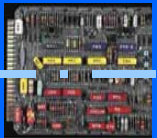
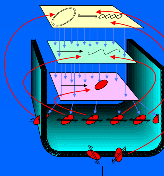
The first law of Systems Biology: summation law for flux control

$$C^{J}_{e_1} + C^{J}_{e_2} + C^{J}_{e_3} + \ldots\ldots\ldots + C^{J}_{e_n} = 1$$



Implication: steady-state flux control need not be in single step; can be distributed, but must sum to 1

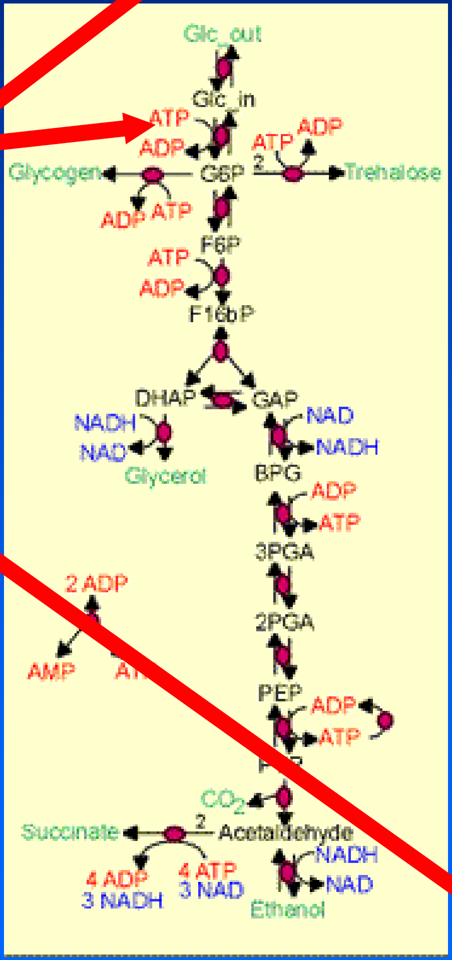


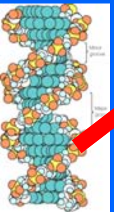




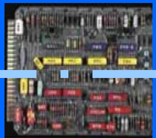
The old principle:

- The first irreversible step in the pathway is the sole rate-limiting (important) step

- Is this correct?

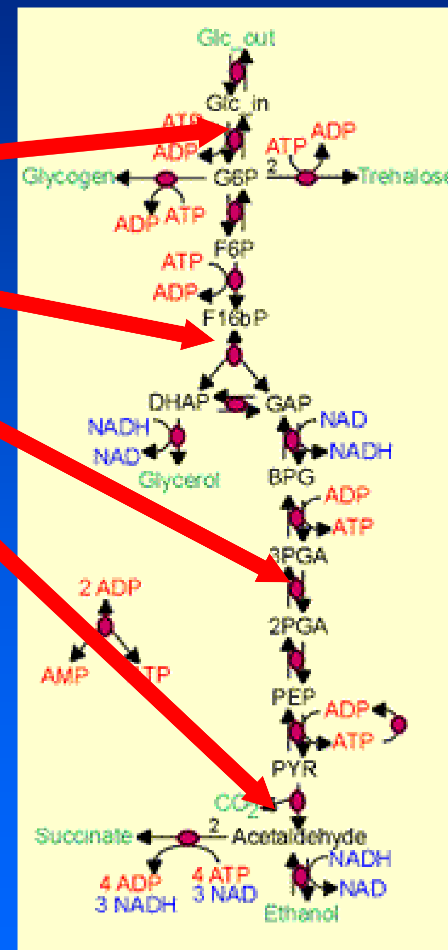


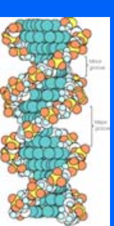


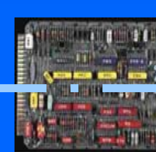


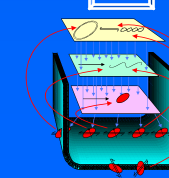
The new law:

- Total control is 1
- Control may be distributed
- Intuitive proof:
  - increase all enzymes by 1 %
  - Steady state maintained and flux up by 1 %



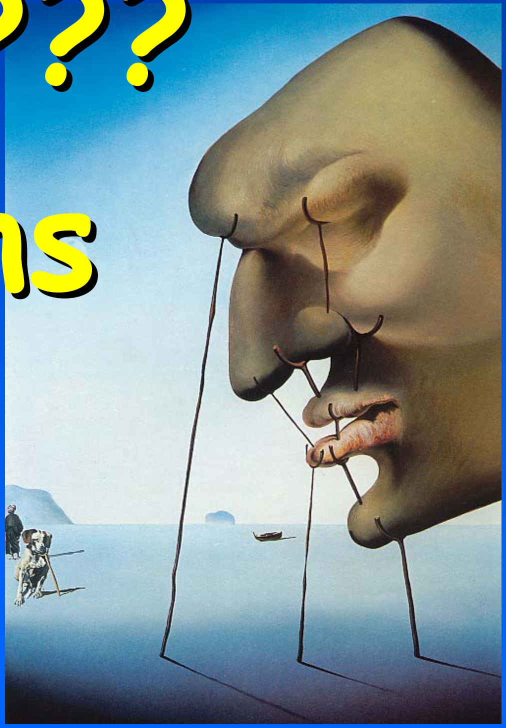






Integrative Systems Biology:

Laws in Biology???
With implications



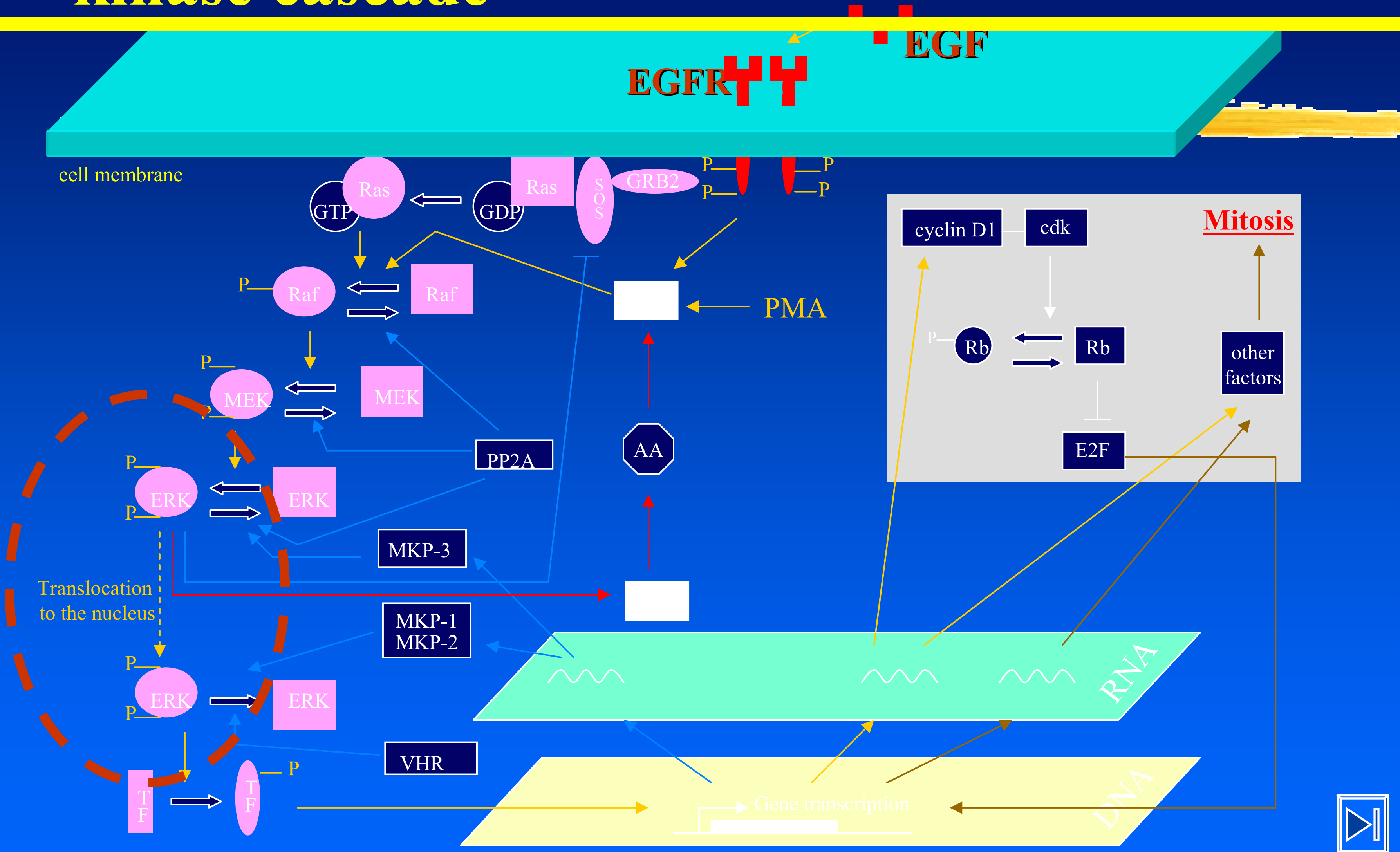
Drug-target paradigm 2 (parasites)

- Inhibit the step with the highest control on vital flux of parasite

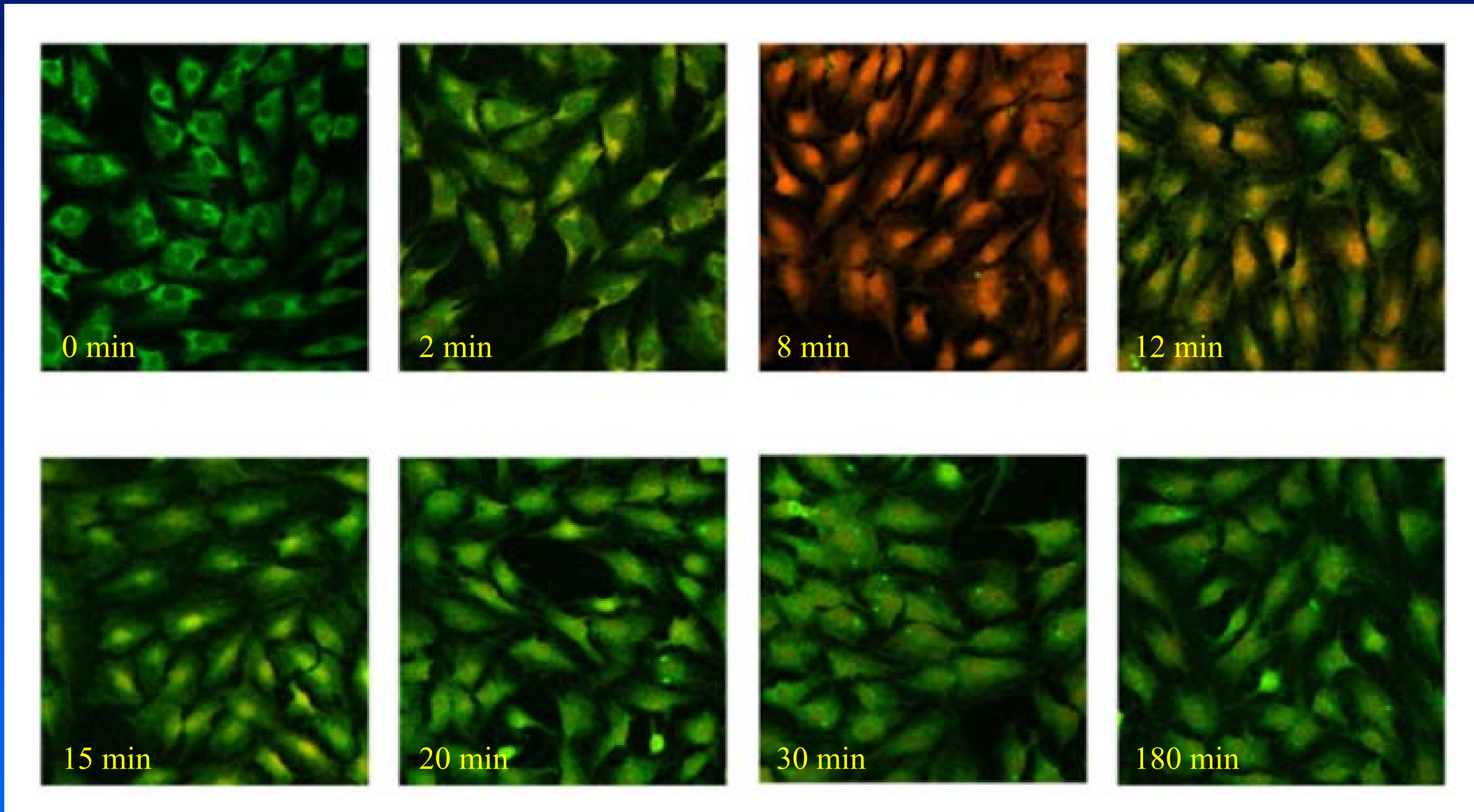
Principles

- We want more!

From EGF to Mitogen-activated protein kinase cascade

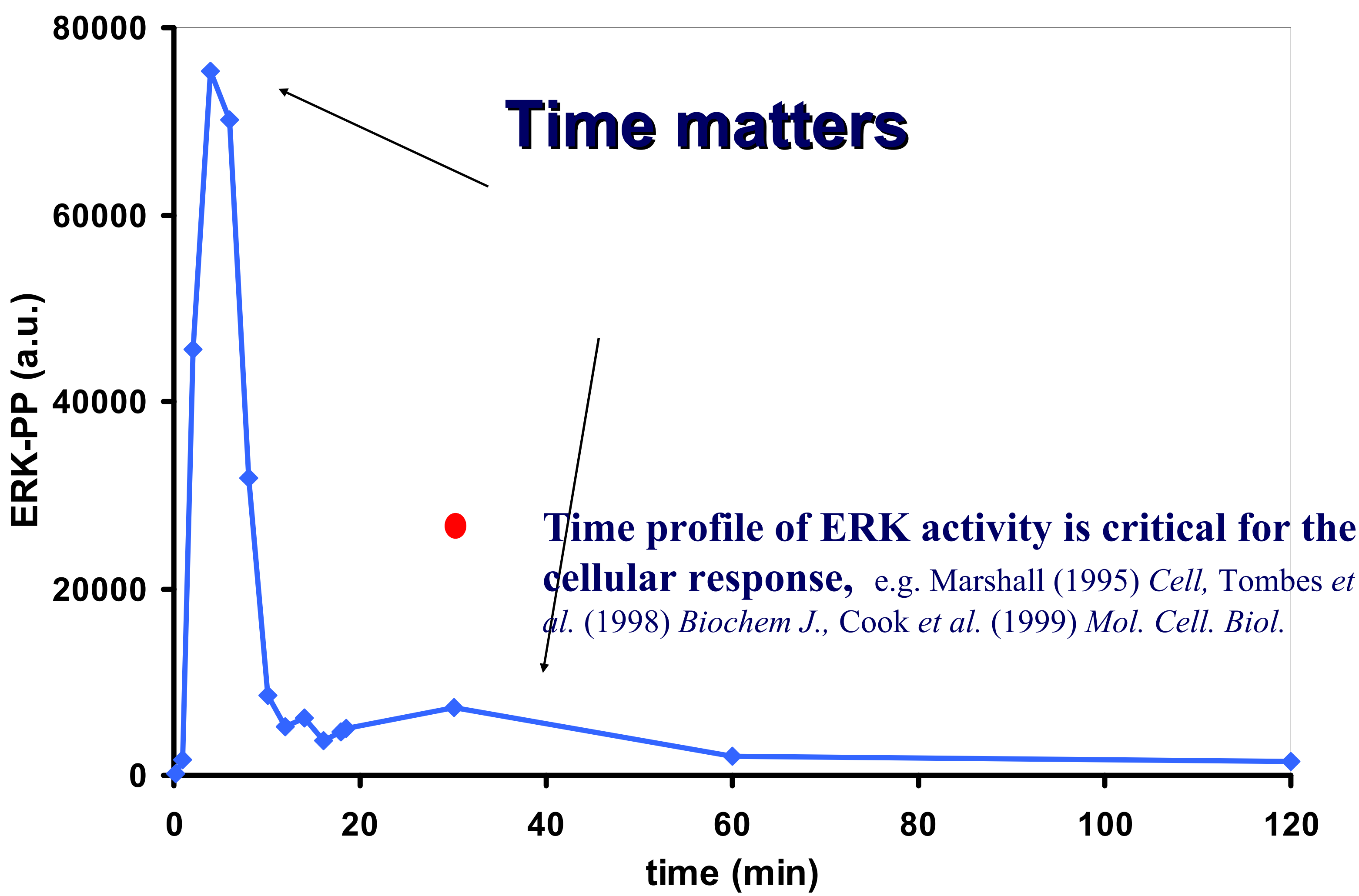


ERK-PP in single cells upon EGF stimulation



Green: total ERK
Red: ERK-PP

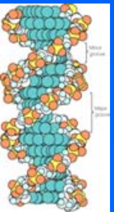
ERK-PP profile upon EGF stimulation

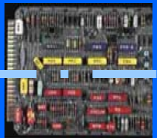


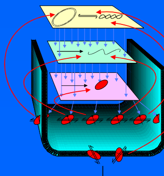
- **Time profile of ERK activity is critical for the cellular response,** e.g. Marshall (1995) *Cell,* Tombes *et al.* (1998) *Biochem J.,* Cook *et al.* (1999) *Mol. Cell. Biol.*

Systems Biology is a Science

- Definitions
- Principles/laws
- Validation
- Utilization

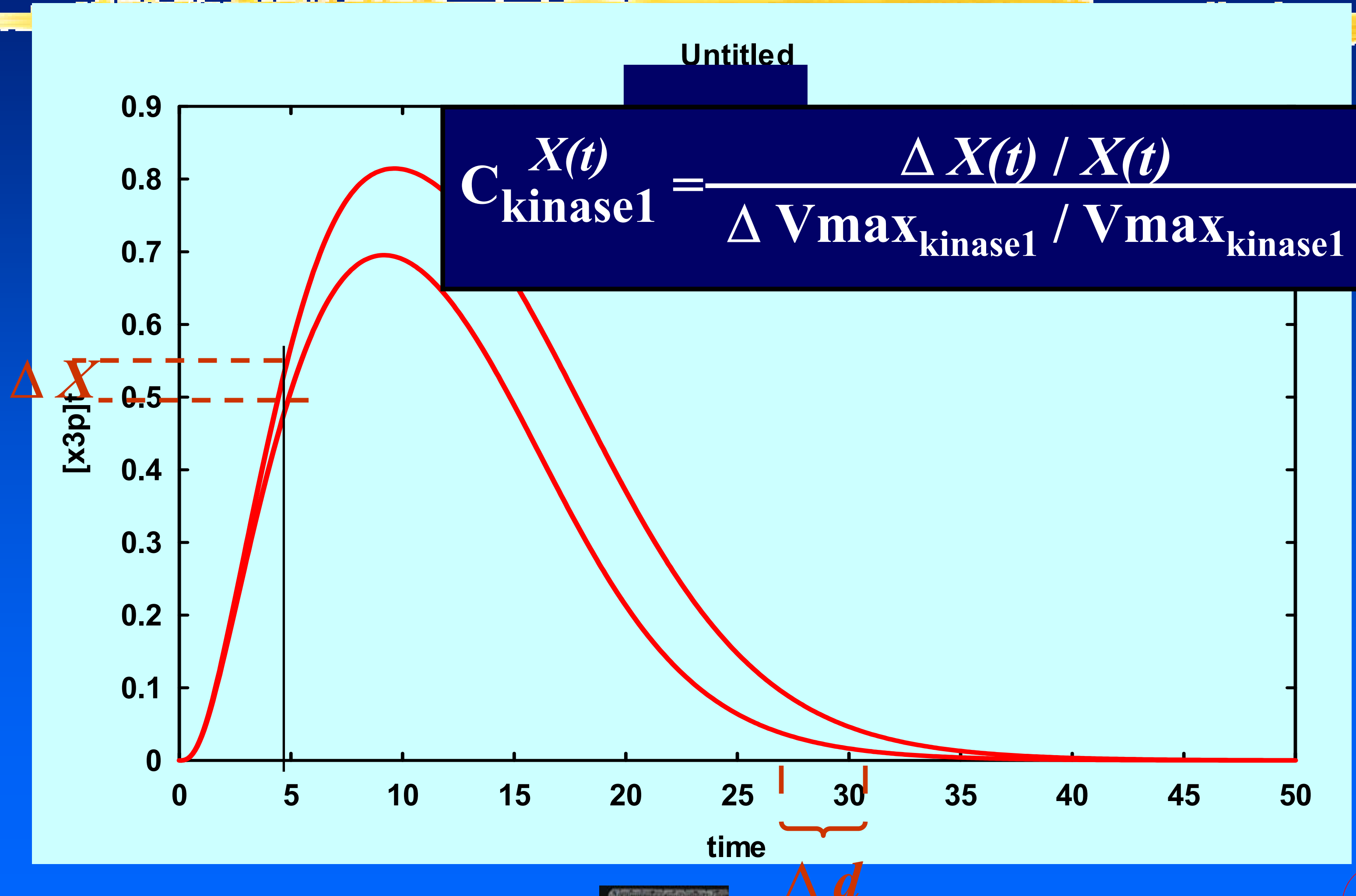






Control coefficient:

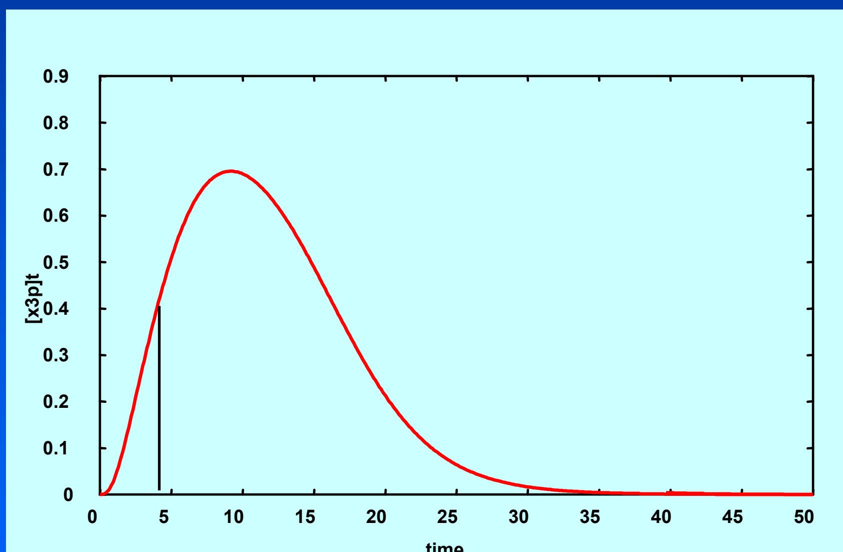
relative change in concentration caused by a relative change in kinase activity



$$C^{X(t)}_{kinase1} = \frac{\Delta X(t) / X(t)}{\Delta Vmax_{kinase1} / Vmax_{kinase1}}$$

Control coefficient

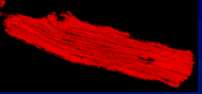
relative change in concentration (or duration or area under the curve caused by a relative change) in kinase activity



$$C^{[X(t)]}_{V_{\max,i}} = \frac{d\ln[X(t)]}{d\ln V_{\max,i}}$$

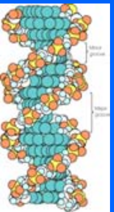
Science .....

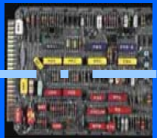
- Definitions
- Principles/laws
- Validation

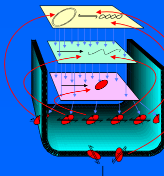


Huh, just sensitivity coefficients ....

- Can you give a law they should obey?

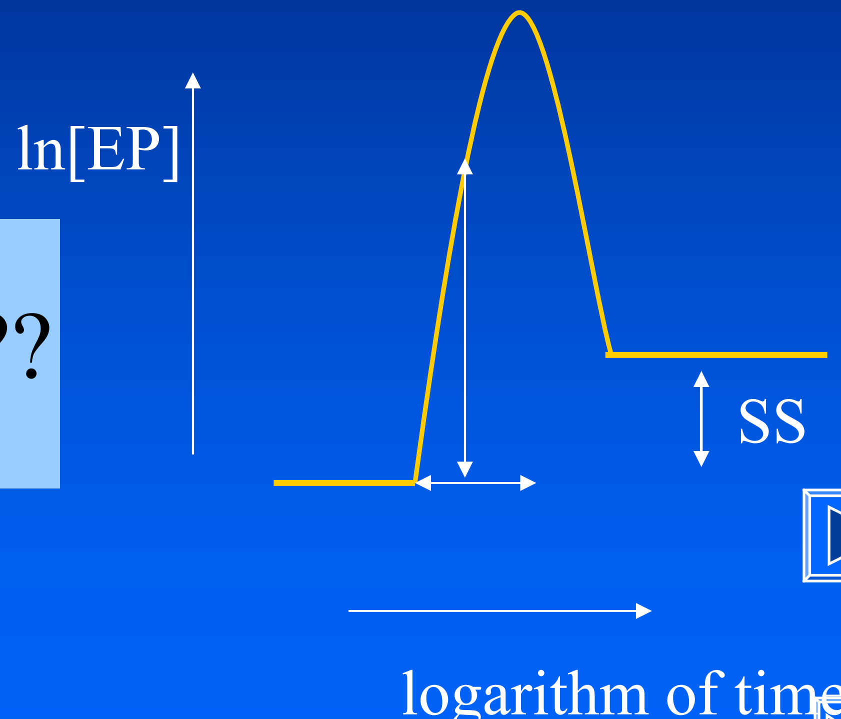






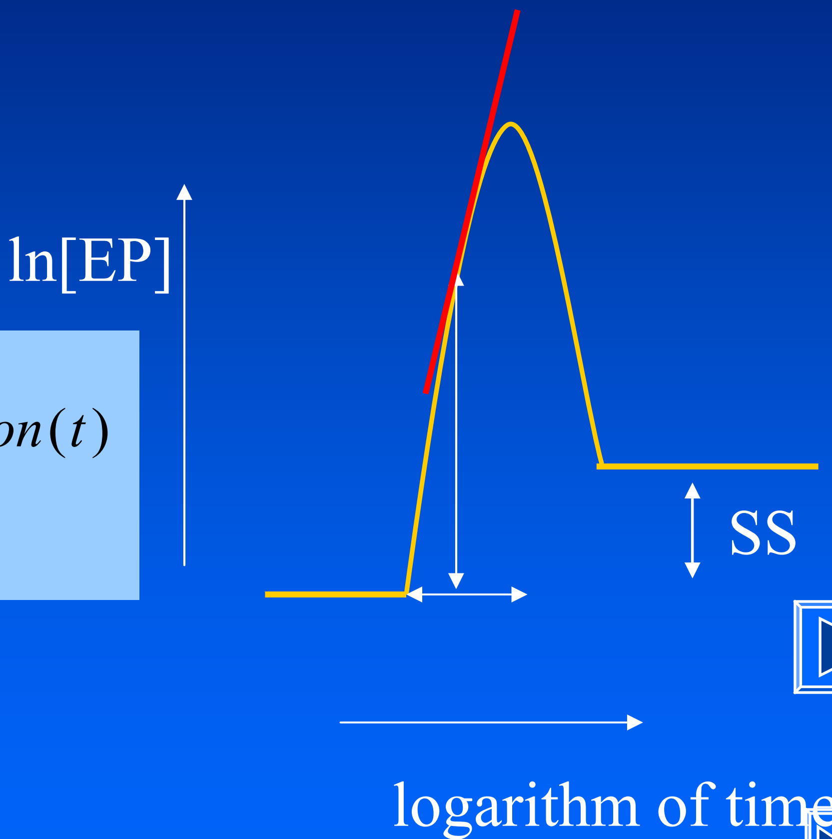
Signal transduction:
New laws (with proofs)

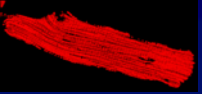
$$\sum_{i=1}^{n} C_i^{concentration(t)} = ???????$$



Signal transduction: New law

$$\sum_{i=1}^{n} C_i^{concentration(t)} = C_t^{concentration(t)}$$





Time + rates transformation invariance

$$\frac{\partial c_i}{\partial \alpha_t \cdot t} = \sum_{j=1}^{n} N_{ij} \cdot \alpha_j \cdot v_j(c_k)$$

$$c_i' \equiv c_i(\alpha_j v_j, \alpha_t t, c_k(0))$$

c_i' are the concentrations c_i after transformation

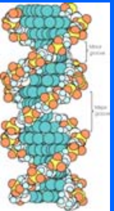
$$c_i' = c_i(\lambda^1 \cdot v_j, \lambda^{-1} \cdot t, \lambda^0 \cdot c_k(0))$$

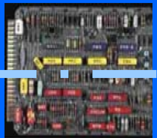
λ: Special transformation

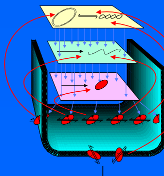
$$\cancel{\lambda} \cdot \frac{\partial c_i'}{\partial t} = \sum_{j=1}^{n} N_{ij} \cdot \cancel{\lambda} \cdot \alpha_j \cdot v_j(c_k')$$

c(t) is invariant to this transformation

$$c_i' \equiv c_i(\lambda^{+1} \cdot v_j, \lambda^{-1} \cdot t) = c_i(v_j, t)$$



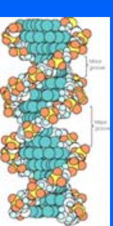


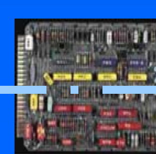


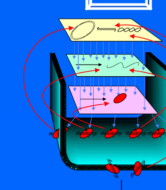
Euler's theory of homogeneous functions

$$g(\lambda^{\beta_1} \cdot p_1, \ldots\ldots, \lambda^{\beta_n} \cdot p_n) = \lambda^{\gamma} \cdot g(p_1, \ldots, p_n)$$

$$\sum_{i=1}^{n} \beta_i \cdot \frac{d \ln g}{d \ln p_i} = \gamma$$







Euler's theory of homogeneous functions

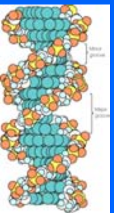
$$g(\lambda^{\beta_1} \cdot p_1,\ldots\ldots,\lambda^{\beta_n} \cdot p_n) = \lambda^{\gamma} \cdot g(p_1,\ldots,p_n)$$

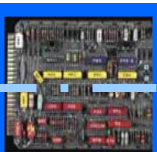
$$\sum_{i=1}^{n} \beta_i \cdot \frac{d \ln g}{d \ln p_i} = \gamma$$

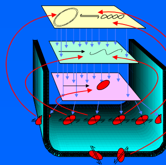
$$g(\lambda^{1} \cdot p_1,\ldots\ldots,\lambda^{-1} \cdot p_n) = \lambda^{0} \cdot g(p_1,\ldots,p_n)$$

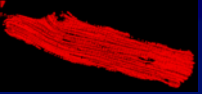
$$+1 \cdot \frac{d \ln g}{d \ln p_1} + \ldots + -1 \cdot \frac{d \ln g}{d \ln p_n} = 0$$

$$C_1^g + \ldots - C_n^g = 0$$









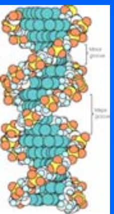
Euler's theory of homogeneous functions

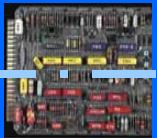
$$g(\lambda^{1} \cdot p_1, \ldots\ldots, \lambda^{-1} \cdot p_1) = g(p_1, \ldots, p_n)$$

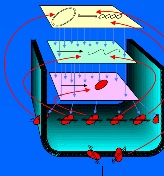
$$c_i' = c_i(\lambda^{+1} \cdot v_j, \lambda^{-1} \cdot t) = c_i(v_j, t)$$

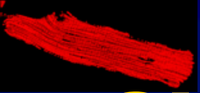
$$C_1^g + \ldots - C_n^g = 0$$

$$C_{vj}^c + \ldots - C_t^c = 0$$





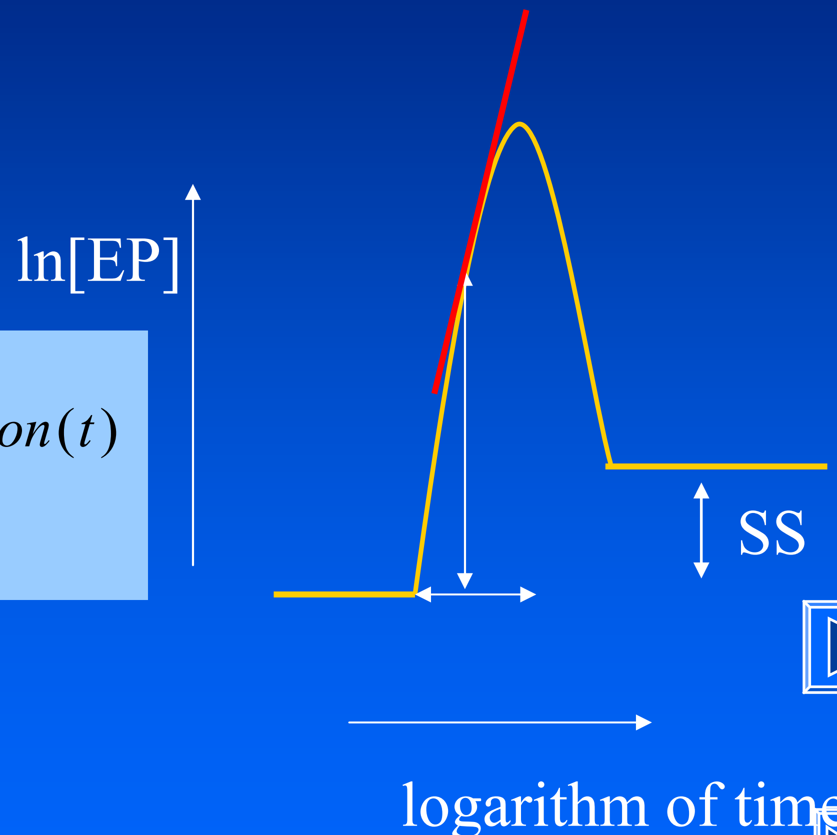


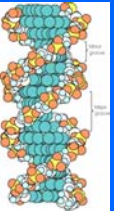


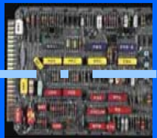
Signal transduction: New law (with proof)

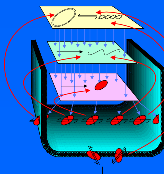
$$C^{c}_{vj} + \ldots. - C^{c}_{t} = 0$$

$$\sum_{i=1}^{n} C_i^{concentration(t)} = C_t^{concentration(t)}$$



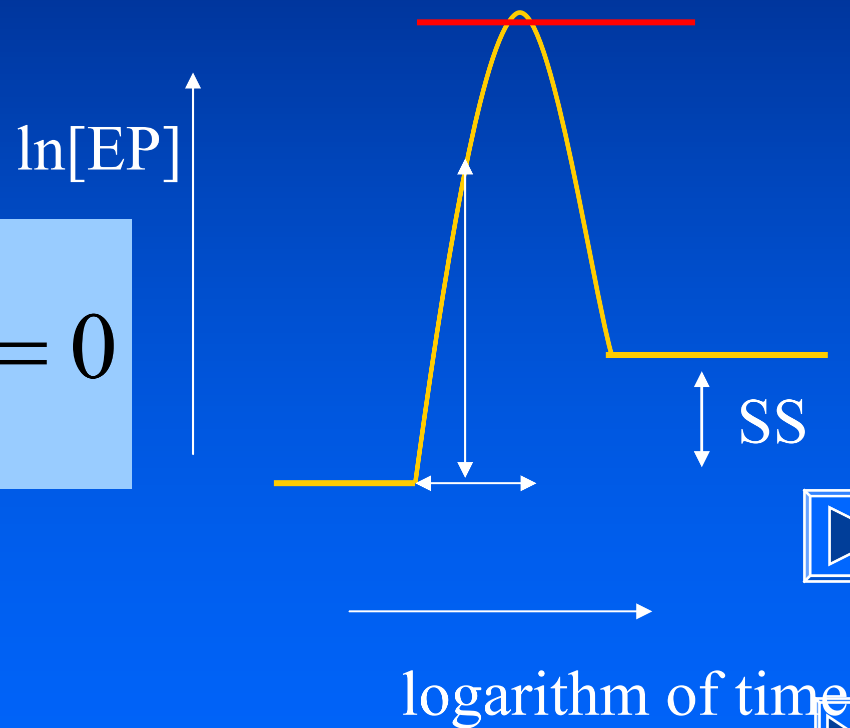




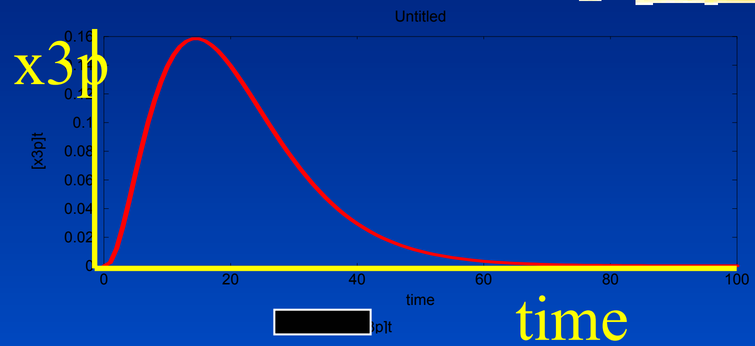


Signal transduction: New law (with proof) for amplitude

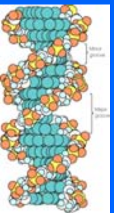
$$\sum_{i=1}^{n} C_i^{amplitude(t)} = C_t^{amplitude(t)} = 0$$

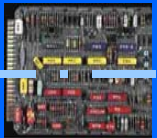


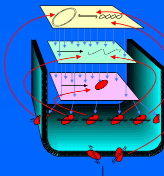
Control of kinases and phosphatases on signaling; Three level cascade *in silico*



Control on amplitude	kinases			phosphatases				Sum
	1	2	3	1	2	3	R	
	0.17	0.26	0.45	-0.14	-0.19	-0.36	-0.18	**0.01**







The new law as principle

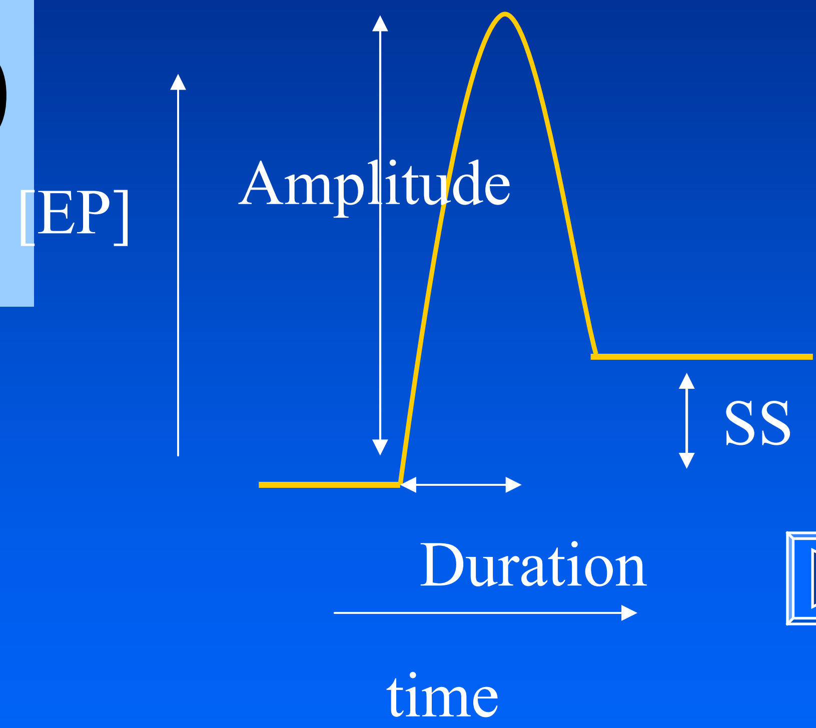
$$\sum_{i=1}^{n} C_i^{concentration(t)} = C_t^{concentration(t)}$$

- Kinases together are equally important for amplitude as the phosphatases together (sum=0)
- **Kinases together are more important for concentration in the increasing phase (sum = positive)**
- **Phosphatases together are more important for concentration in the decreasing phase (sum =negative)**

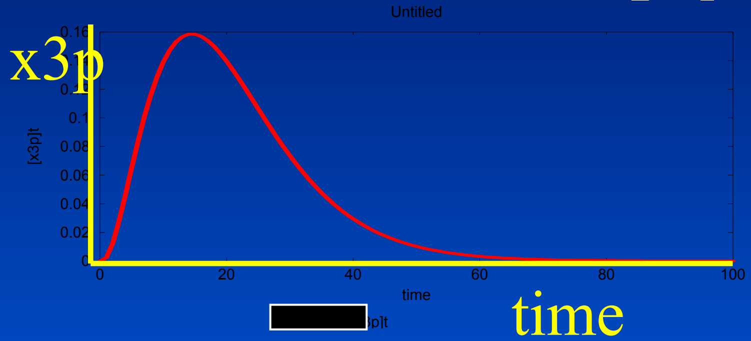
Signal transduction: New laws

$$\sum_{i=1}^{n} C_i^{Amplitude} = 0$$

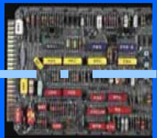
$$\sum_{i=1}^{n} C_i^{Duration} = -1$$

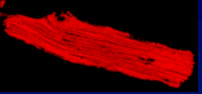


Control of kinases and phosphatases on signaling; Three level cascade *in silico*



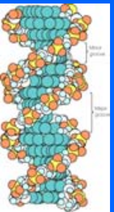
	kinases			phosphatases				Sum
	1	2	3	1	2	3	R	
Amplitude	0.17	0.26	0.45	-0.14	-0.19	-0.36	-0.18	**0.01**
Duration	0.06	0.09	0.12	-0.46	-0.37	-0.34	-0.12	**-1.02**

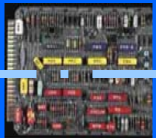


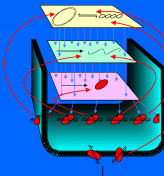


The new laws as principles

- Kinases together are equally important for amplitude as the phosphatases together (sum=0)
- Phosphatases together are more important for duration (sum =-1)



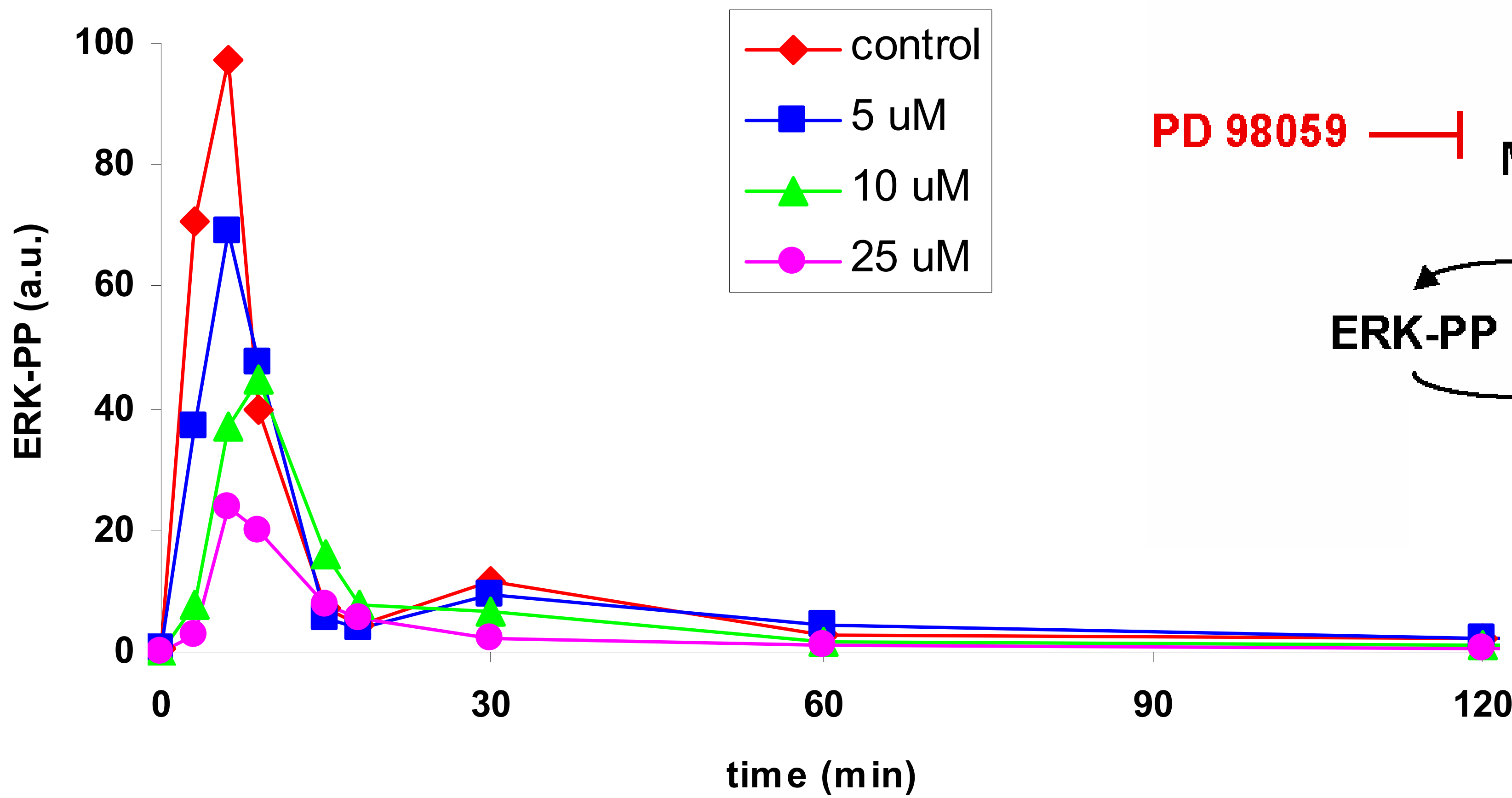


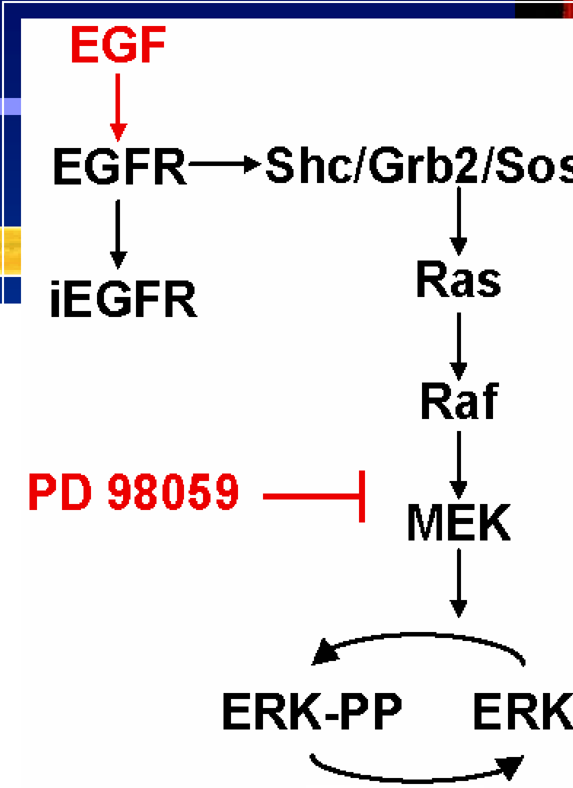


The new law as principle

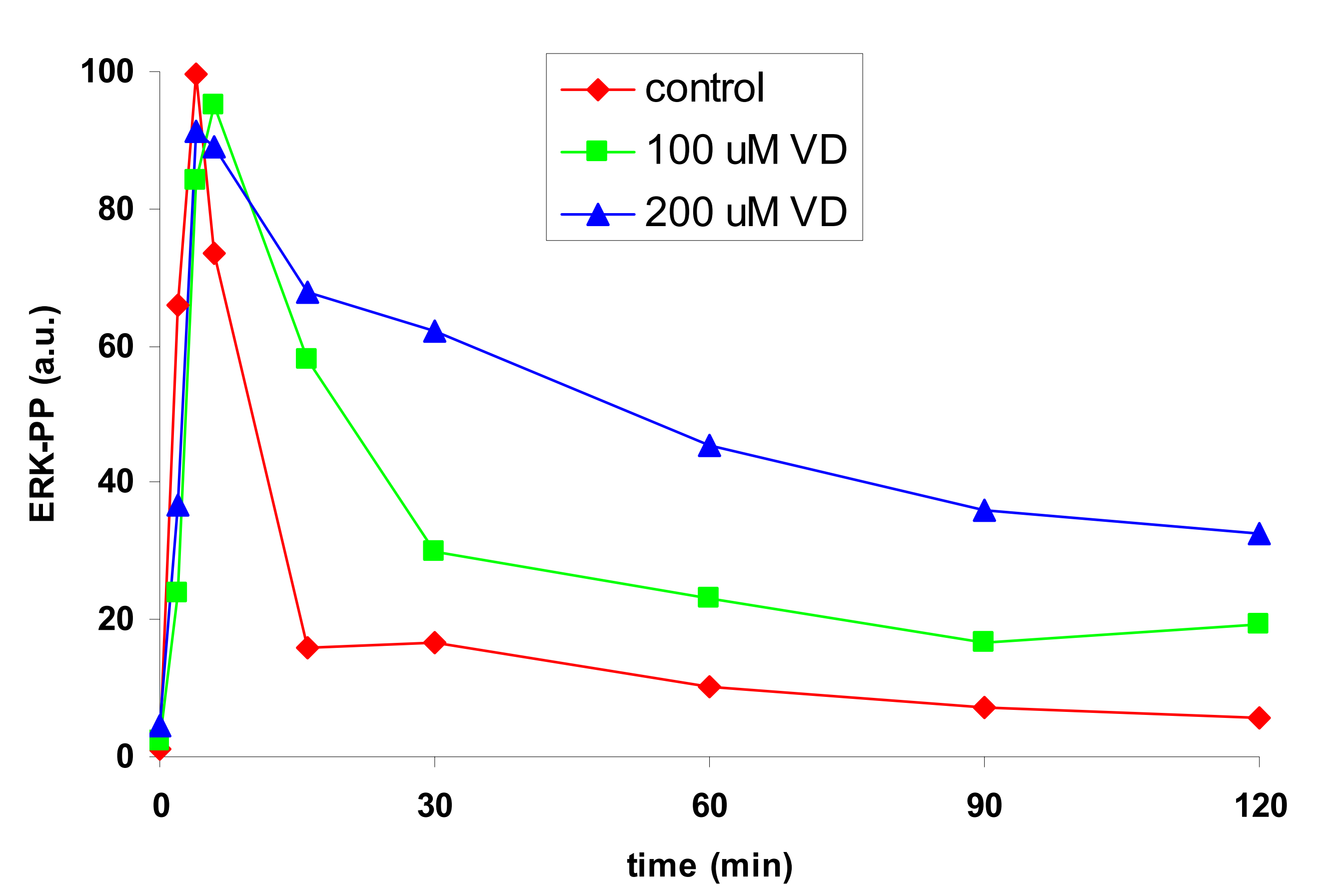
- Kinases together are equally important for amplitude as the phosphatases together (sum=0)
- Phosphatases are more important for duration (sum=-1)
- Kinases together are more important for concentration in the increasing phase (sum = positive)
- Phosphatases together are more important for concentration in the decreasing phase (sum =negative)

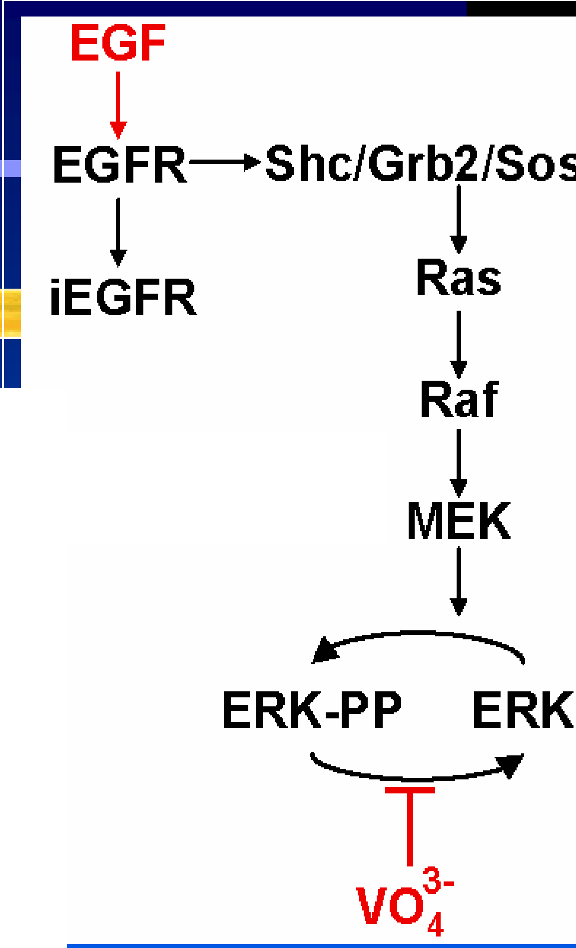
Kinases more important for increasing phase
Experimental validation: MEK inhibition





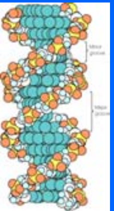
Experimental validation: phosphatases important for decreasing phase PTP inhibition

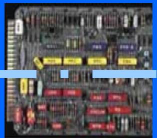


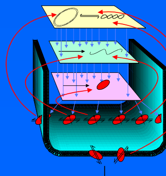


Systems Biology is a Science ....

- ⌘Definitions
- ⌘Principles/laws
- ⌘Validation
- ⌘Utilization







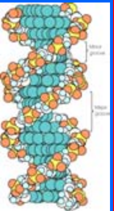
Systems Biology then?

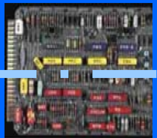
But 'this is only more computing'.....

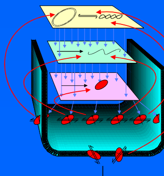
and 'high throughput experiments'.......

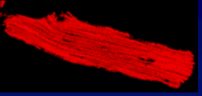
$$\sum^{n} C_i^{concentration(t)} = C_t^{concentration(t)}$$

and now this b…. Maths as well?.......





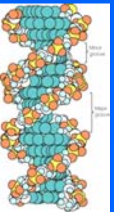


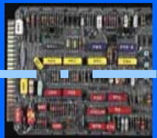


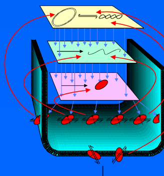
What was this mathematics good for?

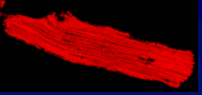
$$\sum_{i=1}^{n} C_i^{concentration(t)} - C_t^{concentration(t)} = 0$$

- To show that some Systems Biology derives from Mathematics, not from experiments: extra power
- To show what one should sum over, i.e.
- Not 'just sensitivity coefficients': a special subset related to the two main principles of biochemistry/molecular biology



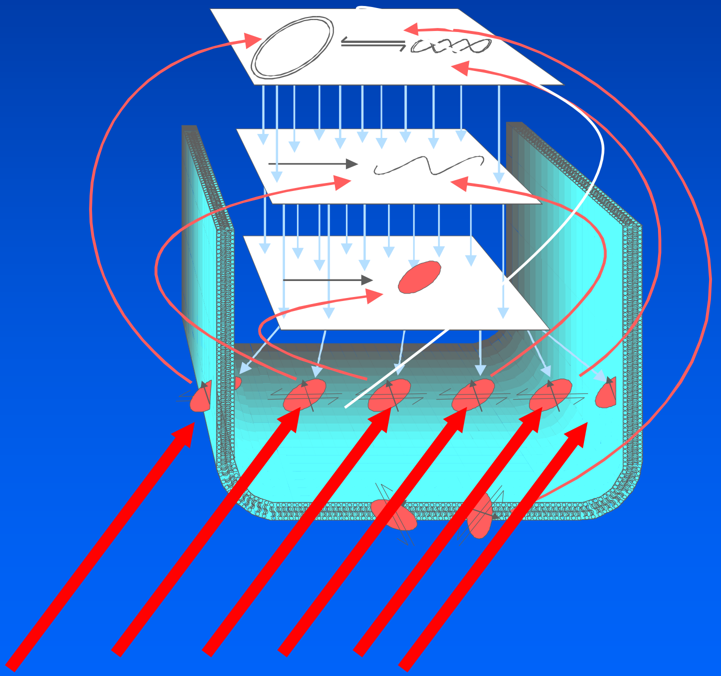


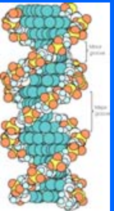


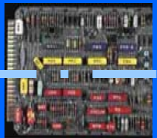


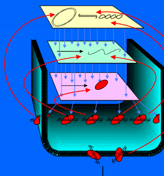
Paradigm of biochemistry

- Every process is carried out (catalyzed) by a protein (enzyme)



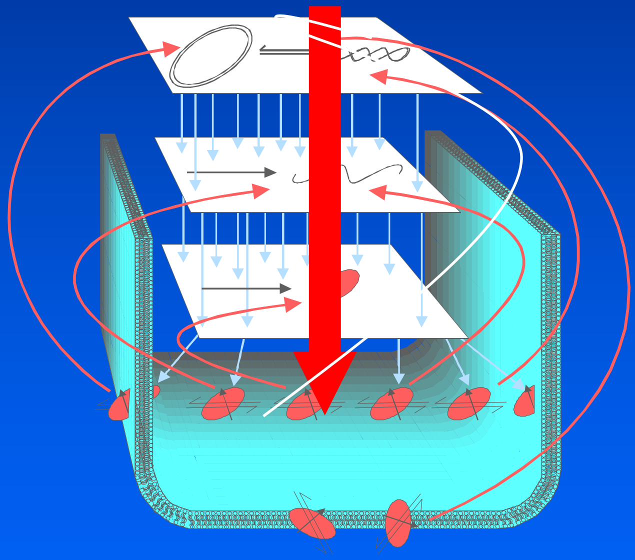






Paradigm of molecular biology

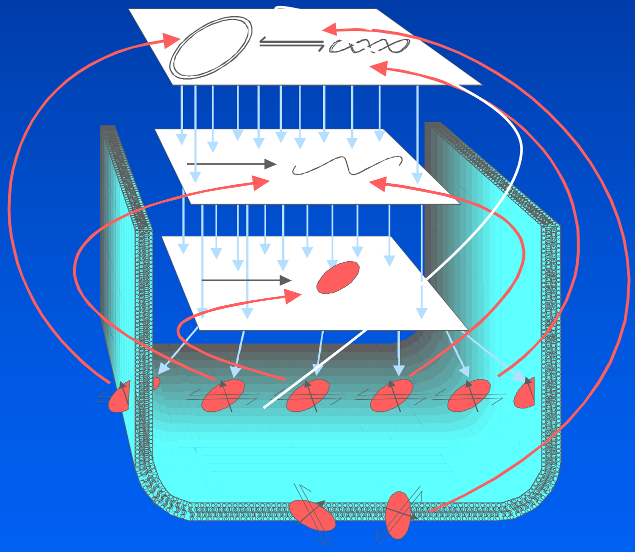
- Every protein is encoded by a gene

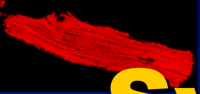


Paradigm of systems biology

- Every system property is determined by all the processes
- This then relates every systems property to proteins and genes

$$\sum_{i=1}^{n} C_i^{concentration(t)} = C_t^{concentration(t)}$$





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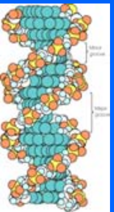
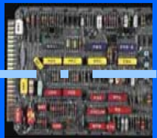
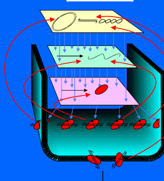
- Interactions & loops & emergence ✓
- Towards applications: Network-based drug design anti-parasites ✓
- Silicon cells ✓
- Systems Biology a science: laws and principles ✓
- Improved understanding of multifactorial disease
- Two paradigms for anti tumor drugs
- What regulates function? Gene expression or metabolism?



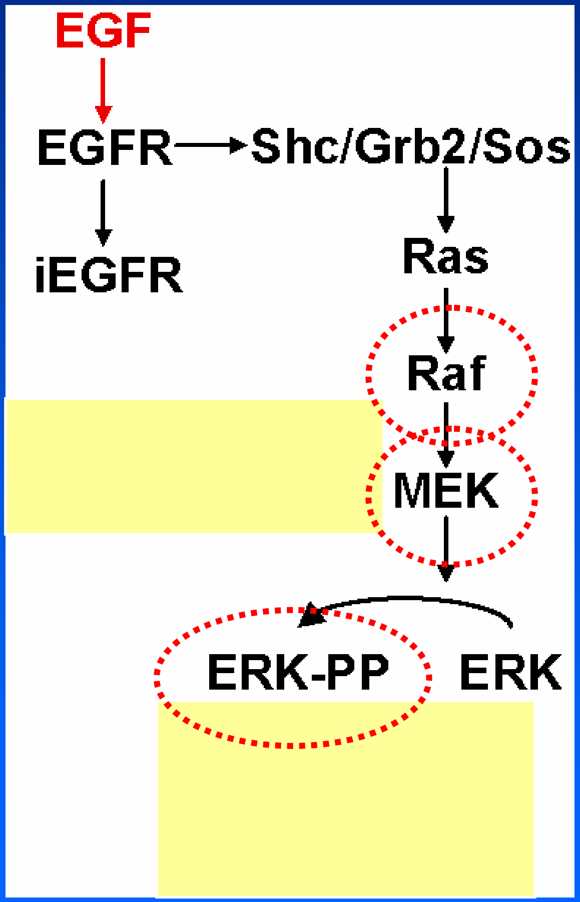


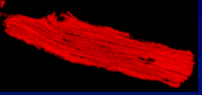


Your suspicions about the importance of the oncogene

- Search for the gene that causes cancer
- Implication: the sole target?

- **Your suspicion:**
- **Biology is more subtle than this**



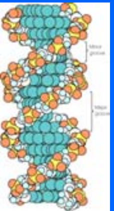


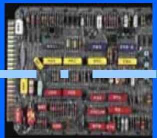
Suggestion from Systems Biology

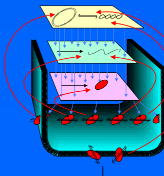
⌘Control not in a single gene, but distributed

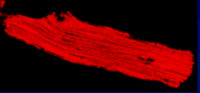
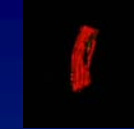
⌘Bad news?: all genes are oncogenes?

⌘Again perhaps: against you intuition; Biology is less random than this

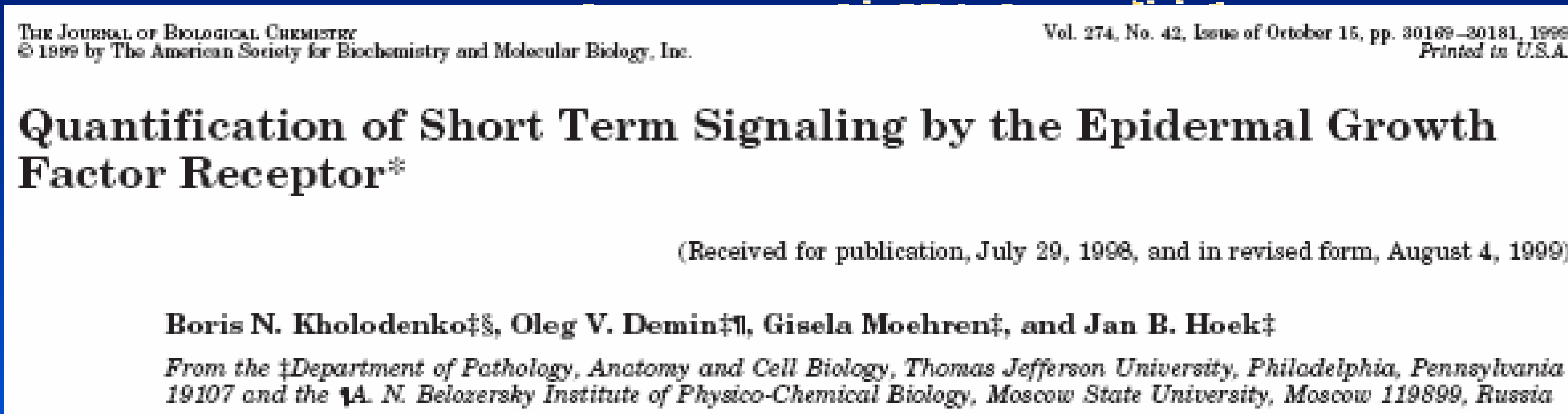






Example: model of signaling from EGFR to Ras


THE JOURNAL OF BIOLOGICAL CHEMISTRY
Vol. 274, No. 42, Issue of October 15, pp. 30169–30181, 1999
Printed in U.S.A.

Quantification of Short Term Signaling by the Epidermal Growth Factor Receptor*

(Received for publication, July 29, 1998, and in revised form, August 4, 1999)

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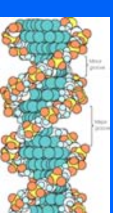
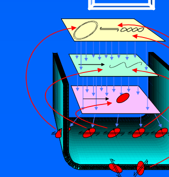
Silicon Cell website

www.jjj.bio.vu.nl

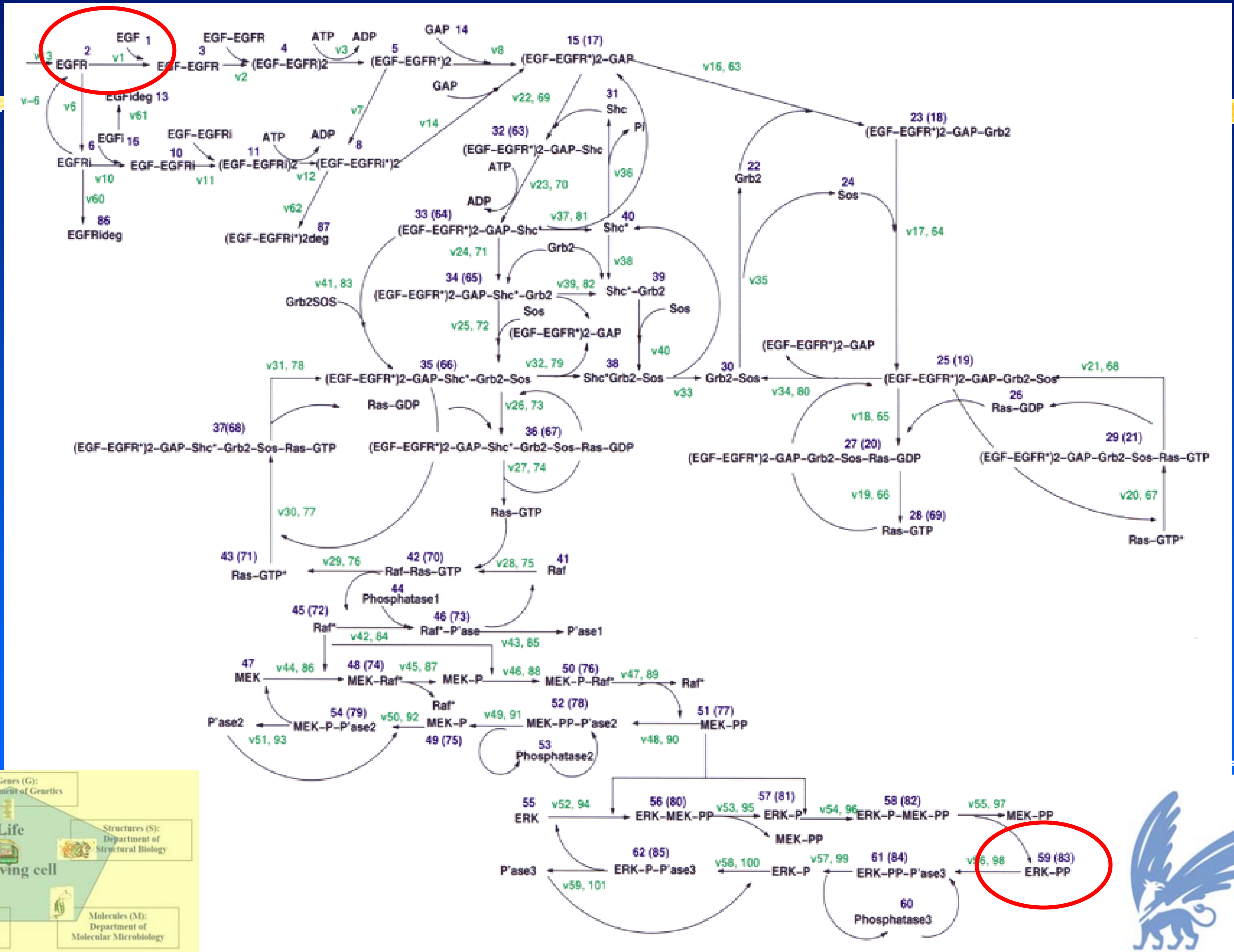
Olivier and Snoep (2004) Bioinformatics
Snoep and Westerhoff (2005) Curr. Genomics

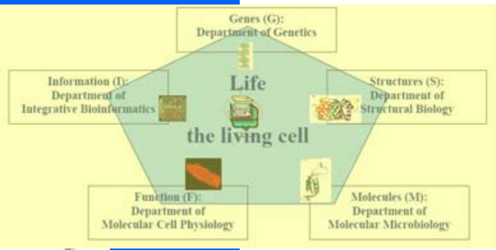




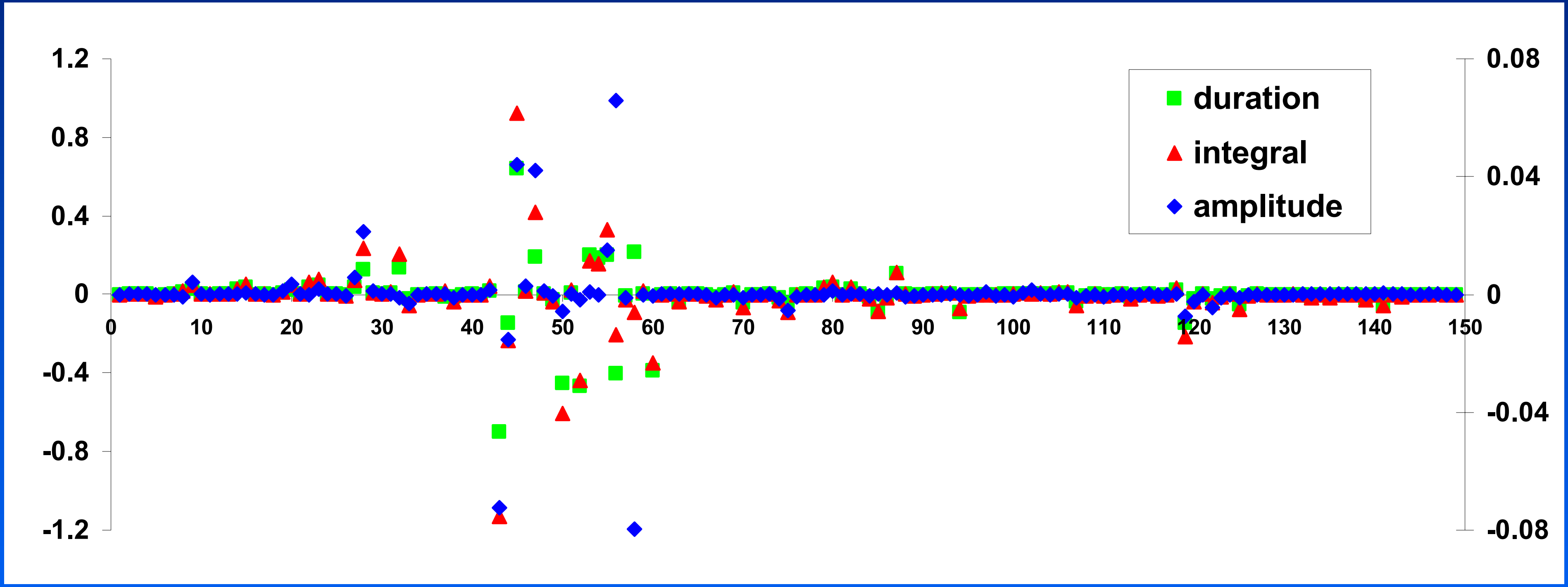
Detailed kinetic model of signaling by EGF

Schoeberl *et al.* (2002)





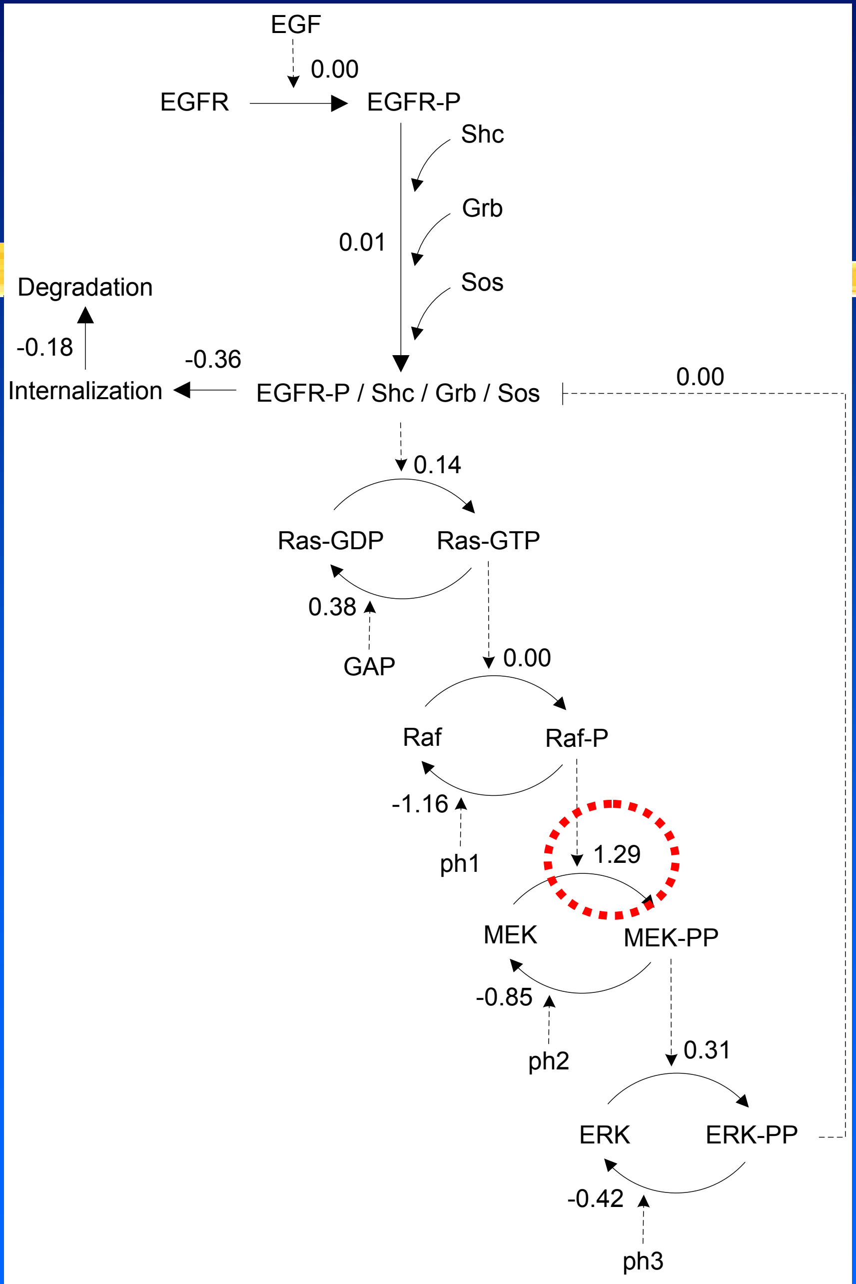
Is control completely dispersed?: No!!



MAP kinase signaling: who is in control?

Mutations of the *BRAF* gene in human cancer

Helen Davies[1,2], Graham R. Bignell[1,2], Charles Cox[1,2], Philip Stephens[1,2], Sarah Edkins[1], Sheila Clegg[1], Jon Teague[1], Hayley Woffendin[1], Mathew J. Garnett[3], William Bottomley[1], Neil Davis[1], Ed Dicks[1], Rebecca Ewing[1], Yvonne Floyd[1], Kristian Gray[1], Sarah Hall[1], Rachel Hawes[1], Jaime Hughes[1], Vivian Kosmidou[1], Andrew Menzies[1], Catherine Mould[1], Adrian Parker[1], Claire Stevens[1], Stephen Watt[1], Steven Hooper[3], Rebecca Wilson[3], Hiran Jayatilake[4], Barry A. Gusterson[5], Colin Cooper[6], Janet Shipley[6], Darren Hargrave[7], Katherine Pritchard-Jones[7], Norman Maitland[8], Georgia Chenevix-Trench[9], Gregory J. Riggins[10], Darell D. Bigner[10], Giuseppe Palmieri[11], Antonio Cossu[12], Adrienne Flanagan[13], Andrew Nicholson[14], Judy W. C. Ho[15], Suet Y. Leung[16], Siu T. Yuen[16], Barbara L. Weber[17], Hilliard F. Seigler[18], Timothy L. Darrow[18], Hugh Paterson[3], Richard Marais[3], Christopher J. Marshall[3], Richard Wooster[1,6], Michael R. Stratton[1,4] & P. Andrew Futreal[1]



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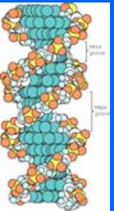
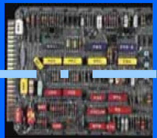
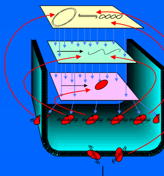
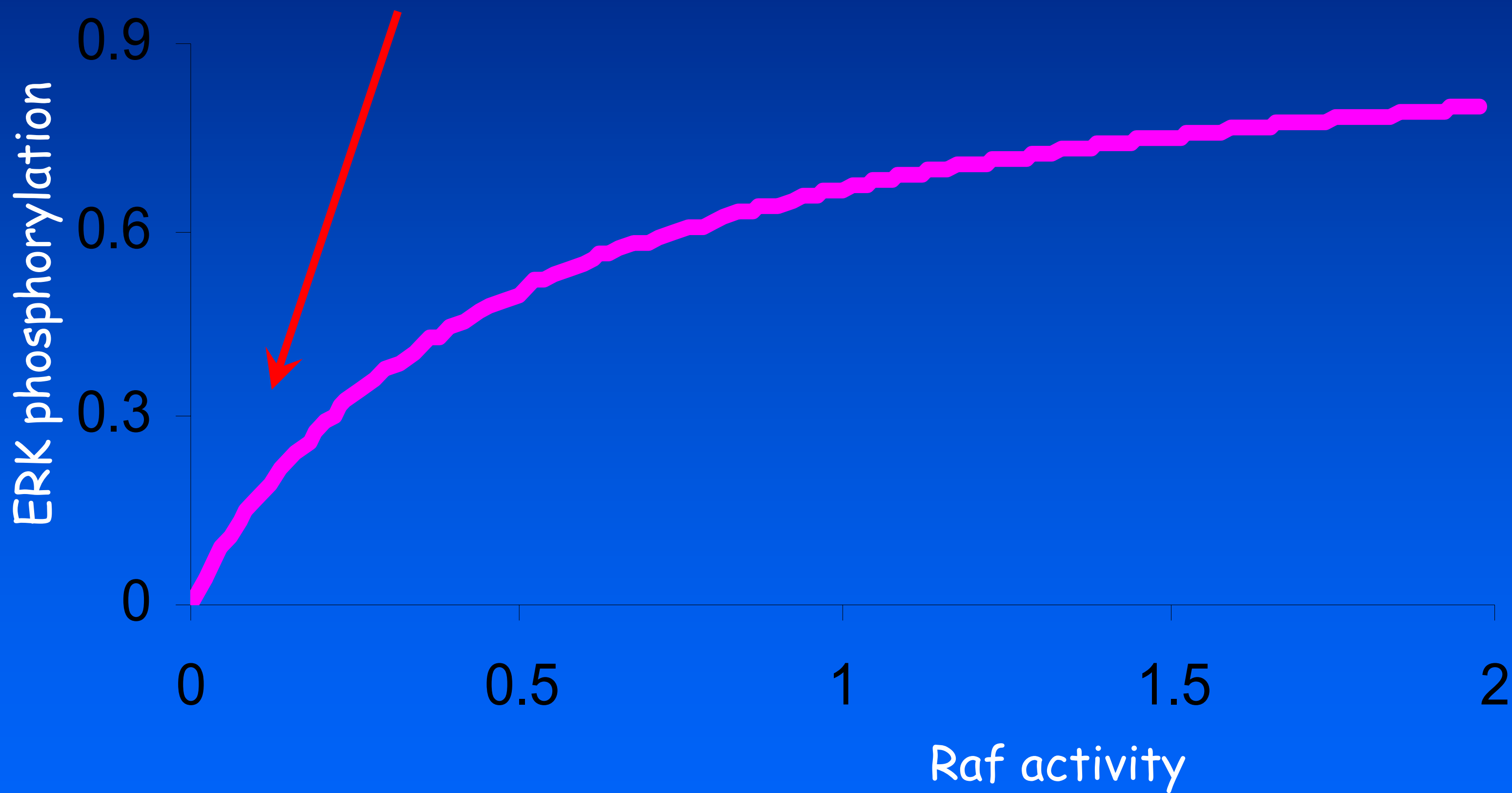




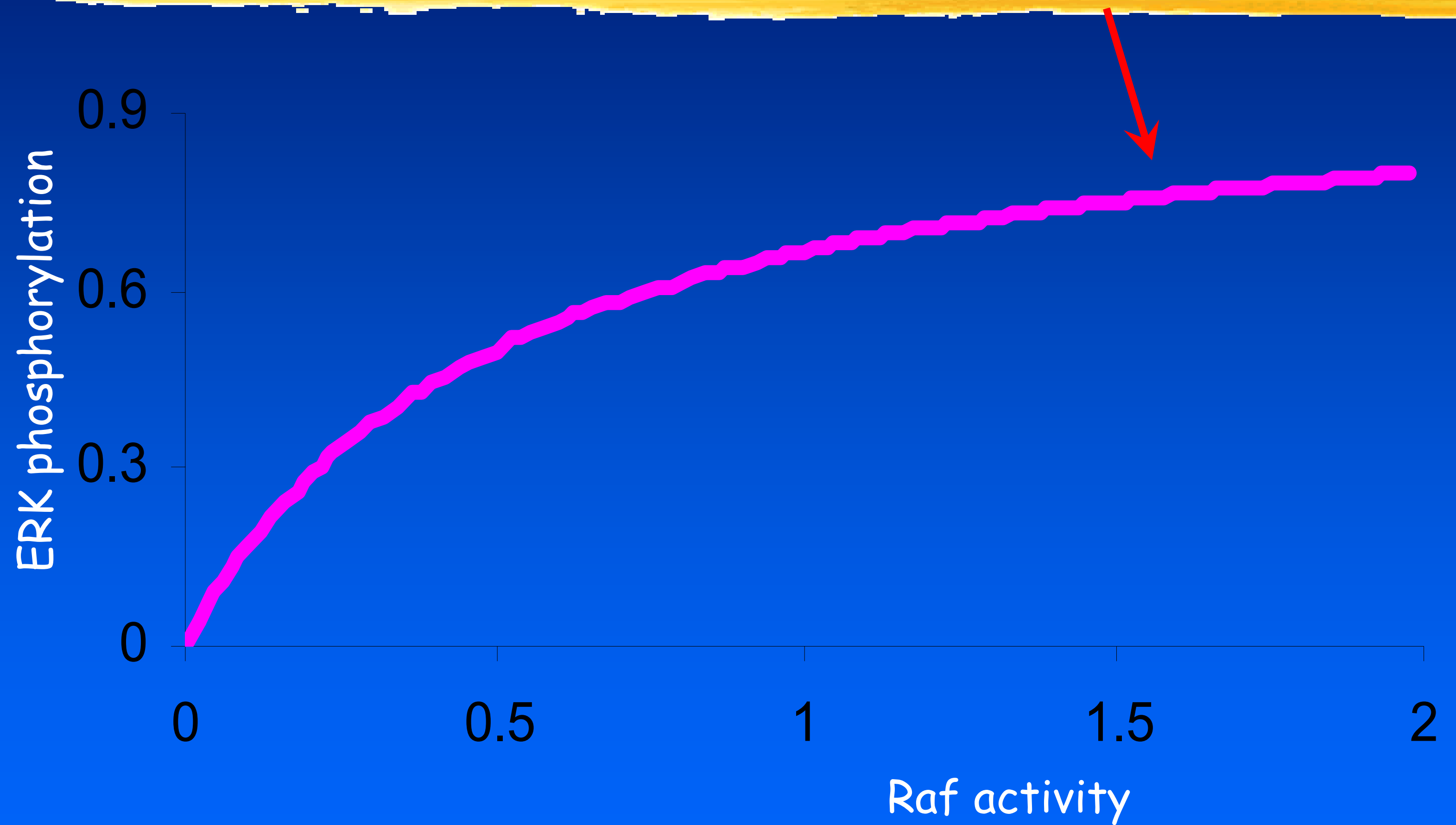
Towards further drug discovery/selection paradigms....

Raf has high control

Enzyme is important



However, once mutated...



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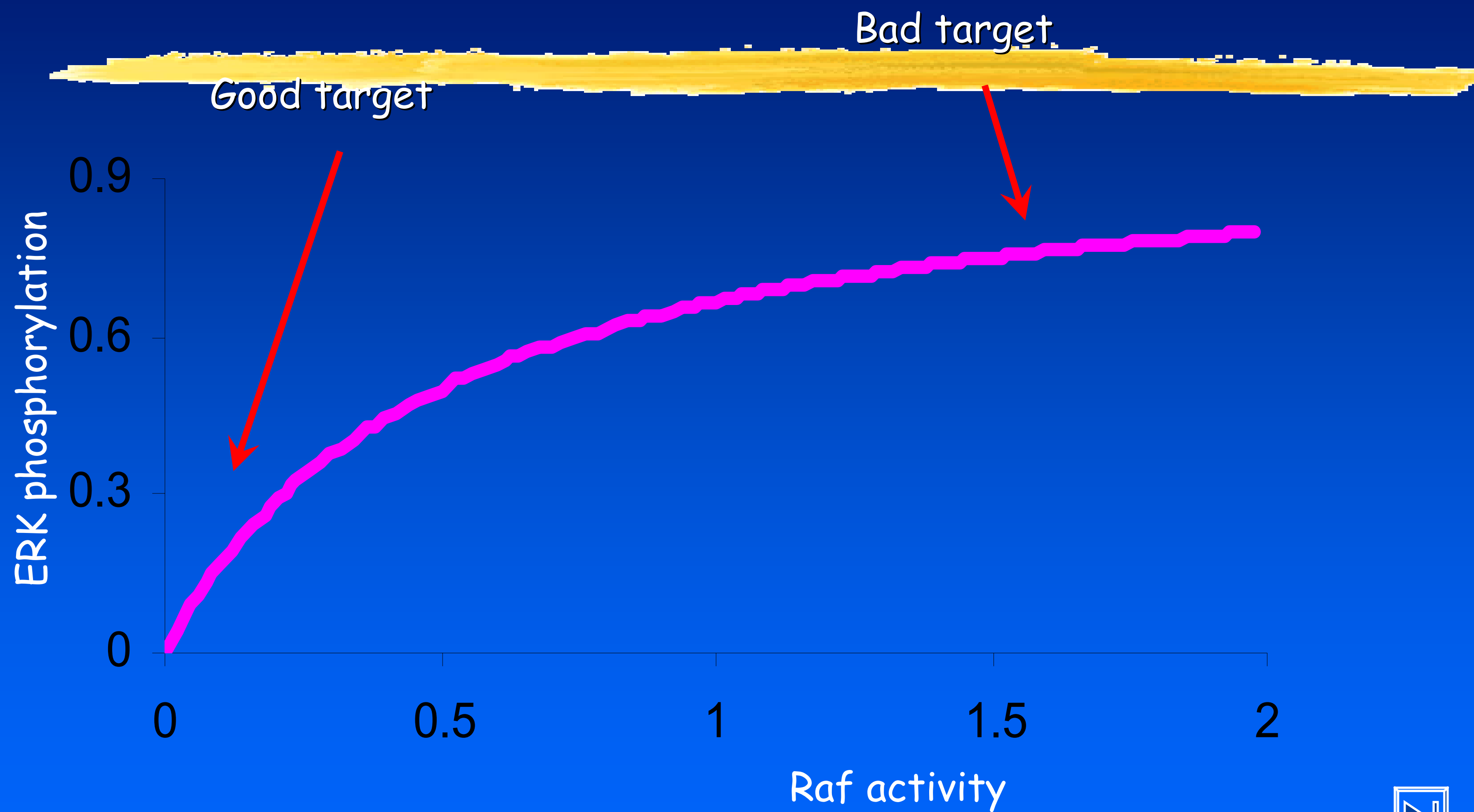
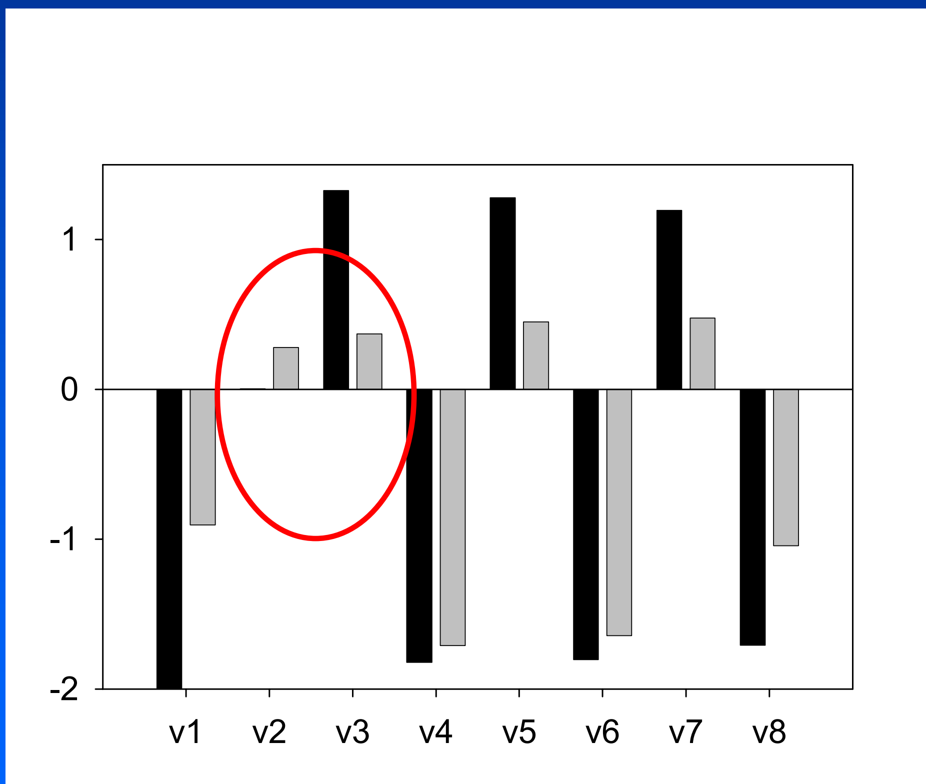
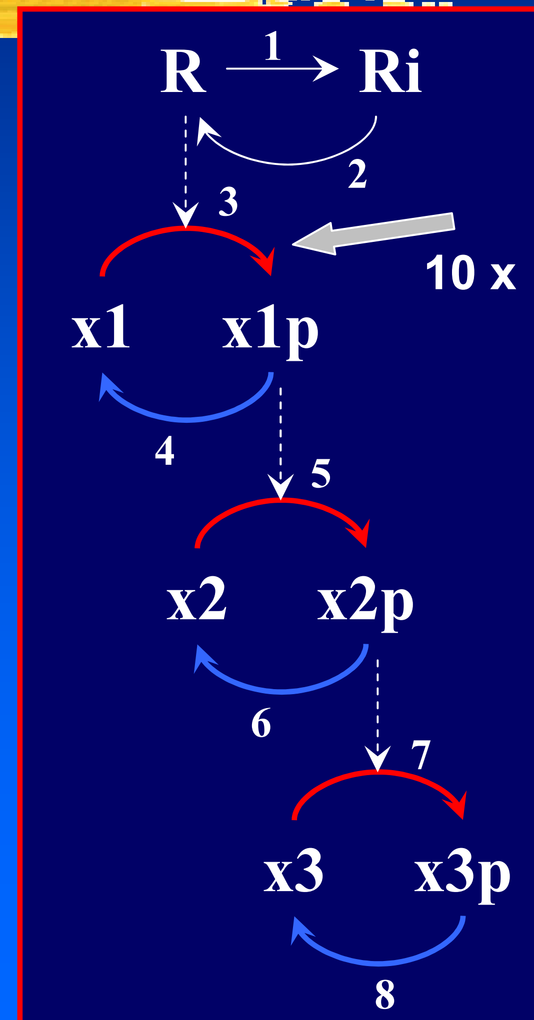


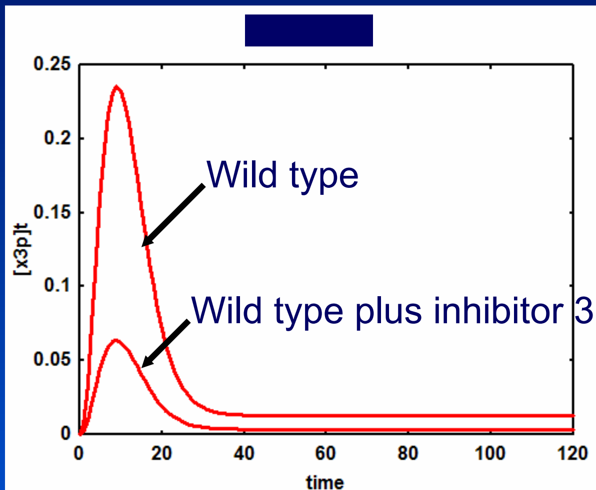
Can a mutation redistribute control?

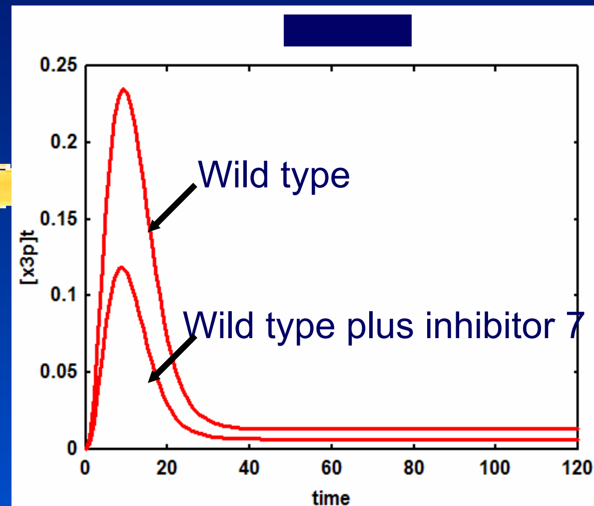


normal mutation



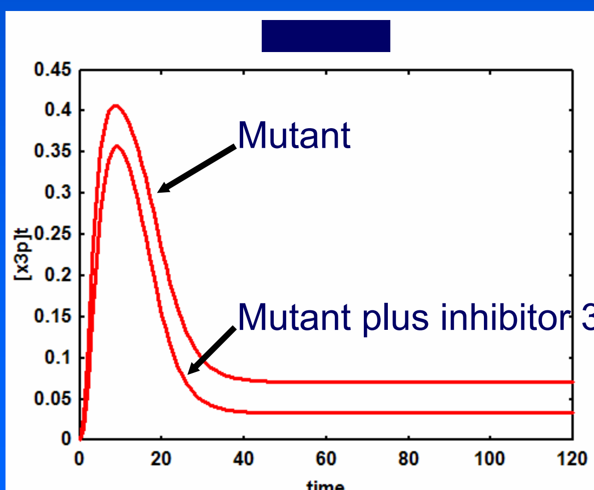
Not step 3 but step 7 should be inhibited

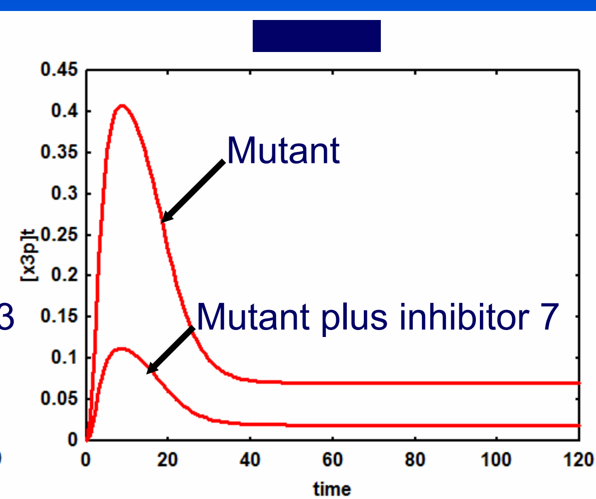


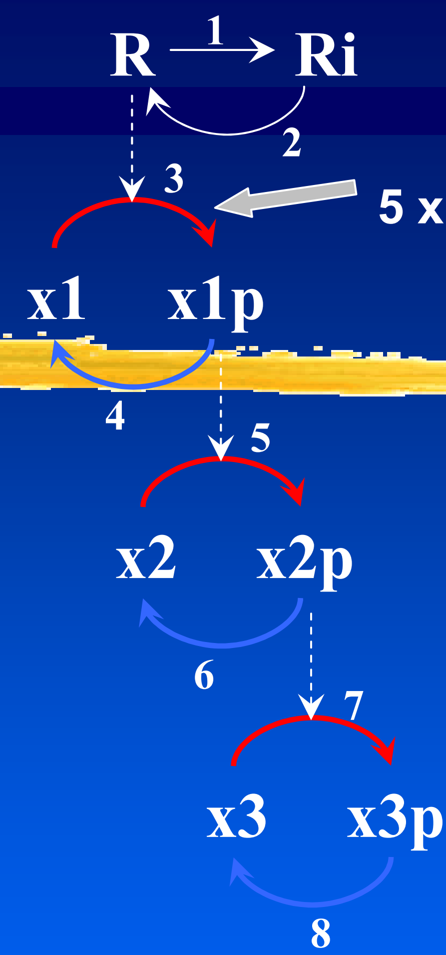


Inhibitor of reaction 3

Inhibitor of reaction 7







Drug-target paradigm 4 (oncogenesis)

- Inhibit a step different from the process enhanced by oncogenesis

Drug-target paradigm 4 (oncogenesis)

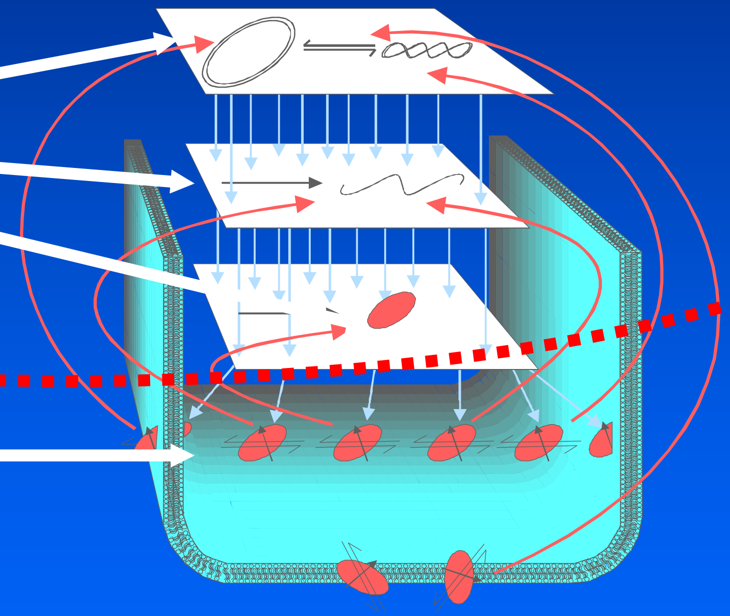
- Inhibit a step different from the process enhanced by oncogenesis

- Is this always a good paradigm?

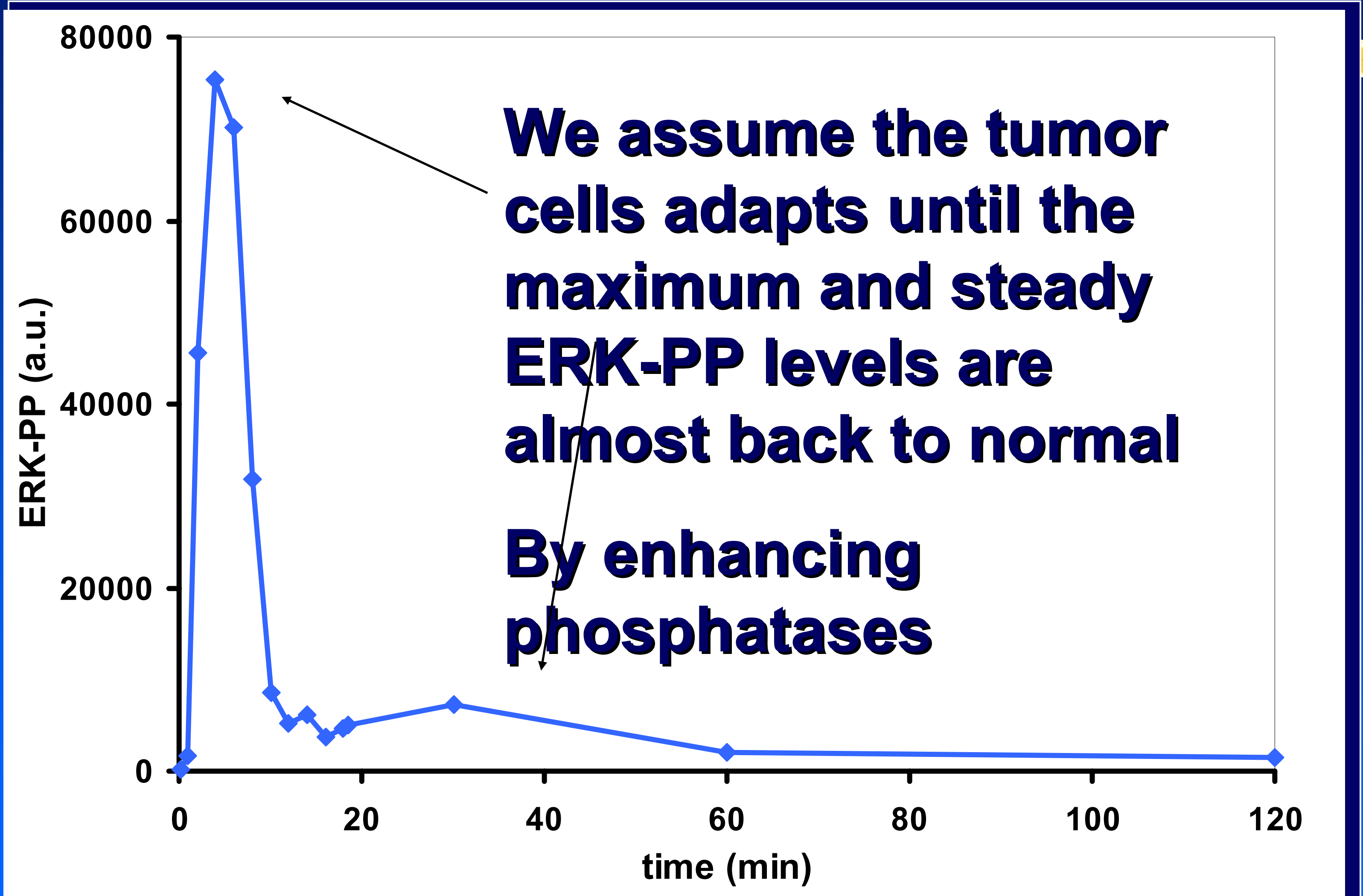
There are other players: adaptation

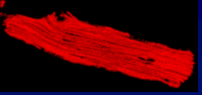
Hierarchical

Metabolic



ERK-PP profile upon EGF stimulation



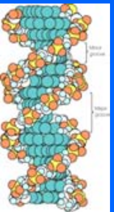
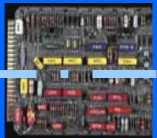
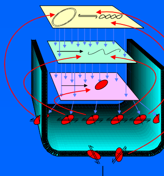



Using the laws:

- Kinase and phosphatases have equal control on amplitude and steady state

- But phosphatases have more control on duration and area under the curve

- Hence the tumor should be disadvantaged in the latter

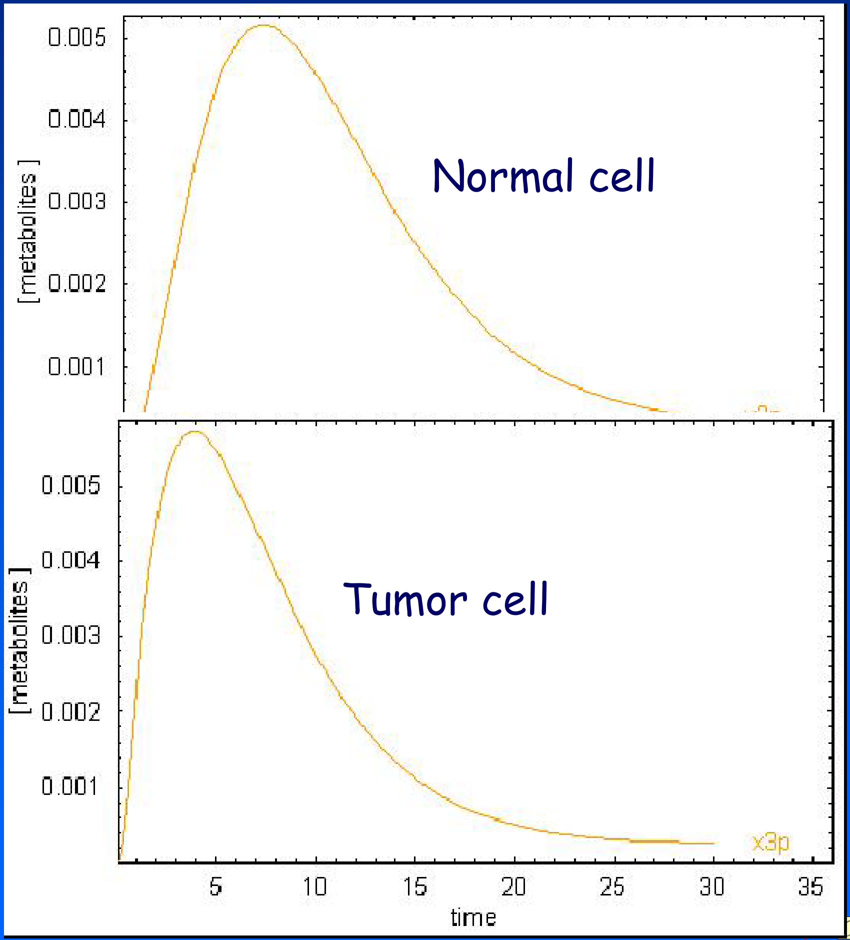




Normal cell and adapted tumor cell (bottom) both in the presence of kinase inhibitor

Amplitude the same: drug would have no effect

But:

Time matters................



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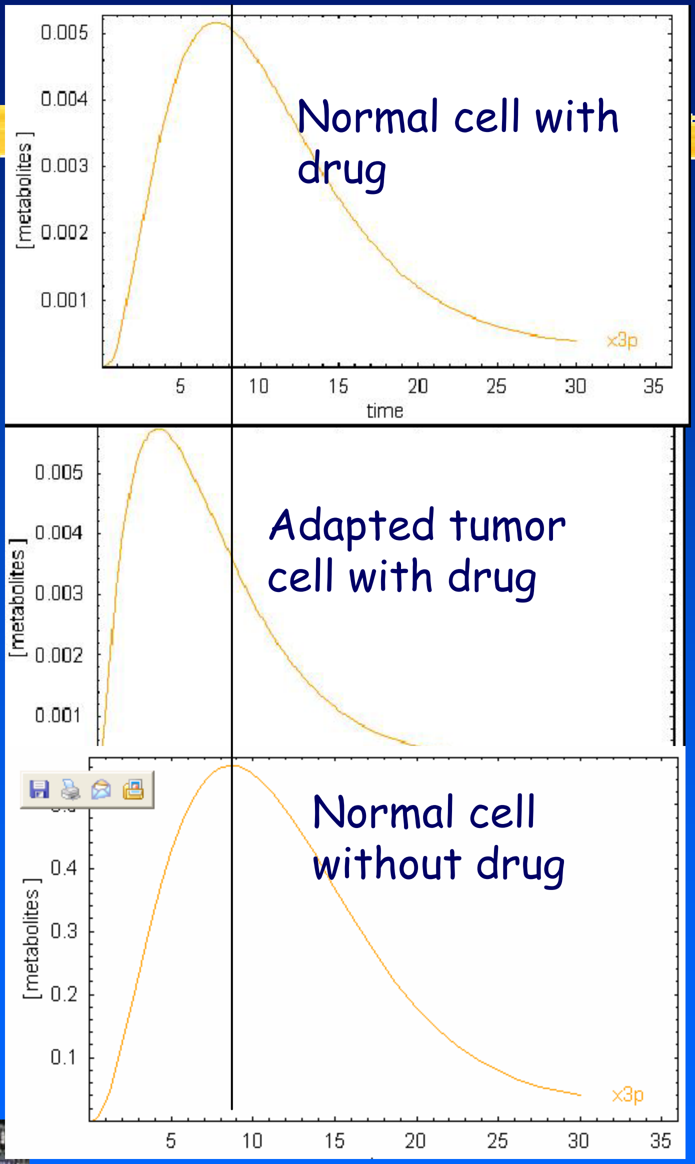
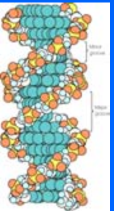
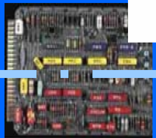
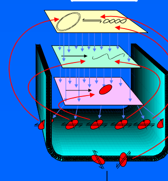
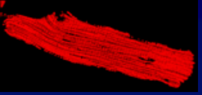




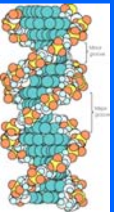


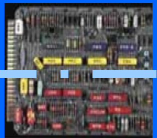


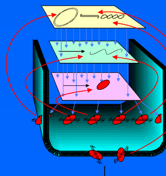


Drug-target paradigm 5 (oncogenesis)

- Inhibit a step enhanced by oncogenesis if the tumor cell has adapted strongly







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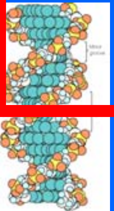
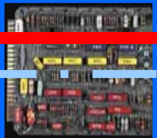
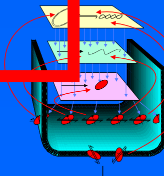






Control $\neq$ Regulation

Control: that what limits the phenomenon

Regulation: what the cell actually uses to change the phenomenon

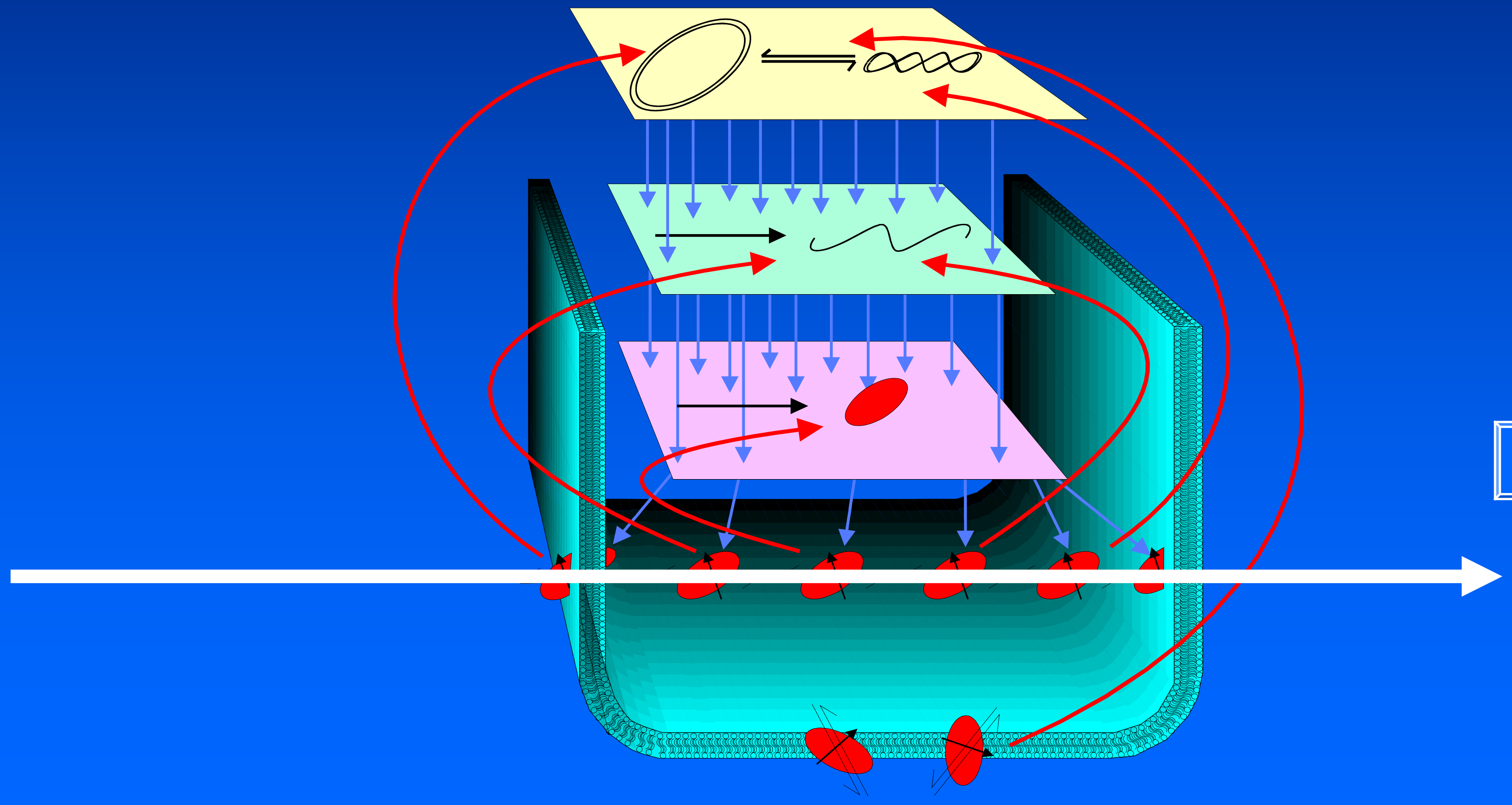
Does the cell regulate its flux??????? Yes it does

But how does the cell regulate itself?

Through gene expression or through metabolic regulation?

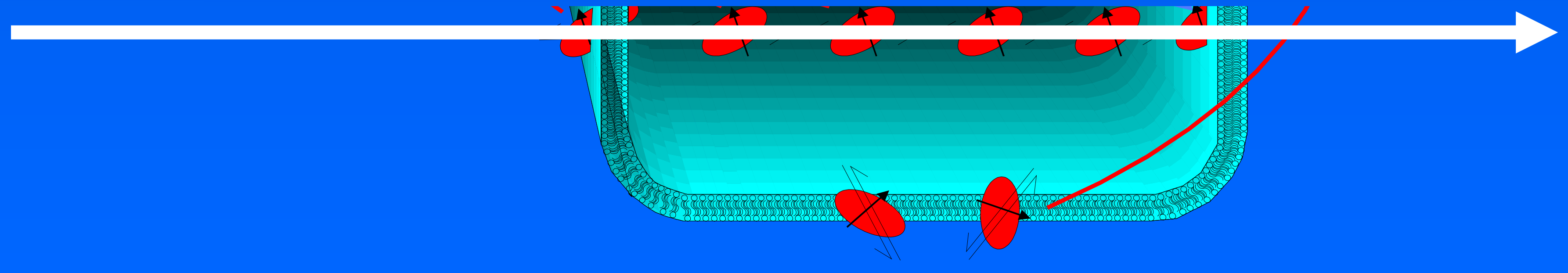
Hierarchies in regulation:

Genes versus metabolites: - ?



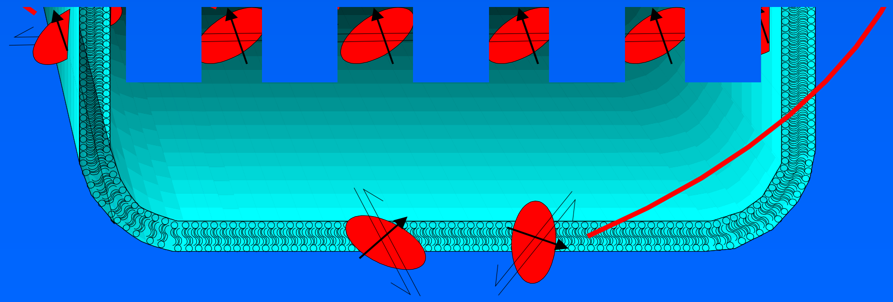
Hierarchies in regulation:

Genes versus metabolites : 0-1?



Hierarchies in regulation:

Genes versus metabolites: 2-1?



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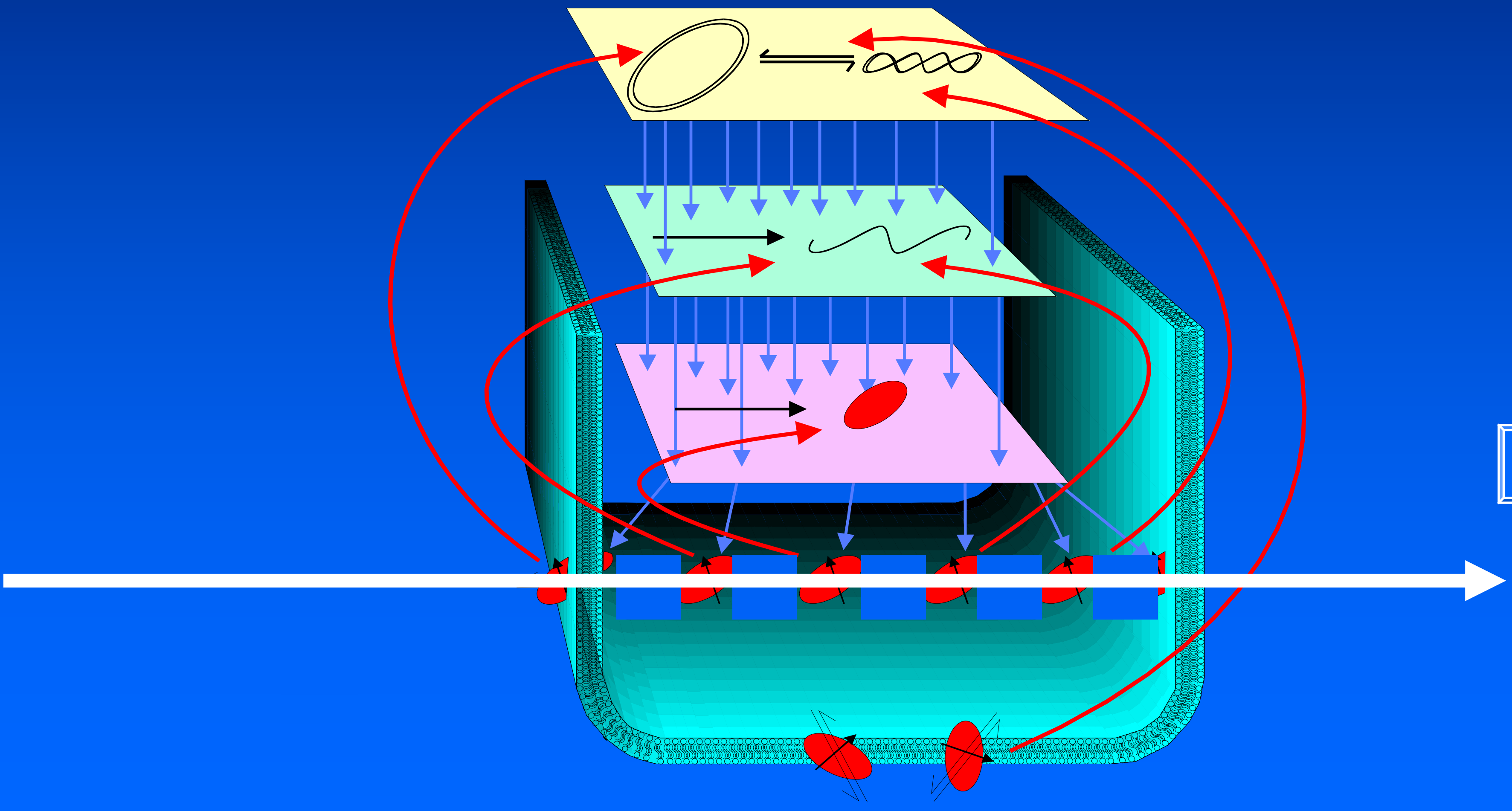


How much hierarchical, how much metabolic (direct) regulation of each step?

and

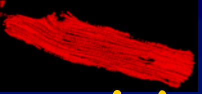
How can one figure this out?

How much of function is regulated hierarchically, how much directly?

$$v = v(e, X) = e \cdot \upsilon(X)$$

Hierarchical

Metabolic/direct



How much of function is regulated hierarchically, how much directly?

$$v = v(e, X) = e \cdot \upsilon(X)$$

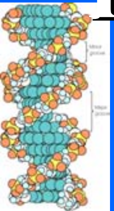
$$\Delta \ln(J) = \Delta \ln(v) = \Delta \ln(e) + \Delta \ln(\upsilon(X))$$

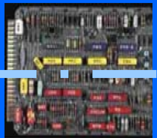
$$1 = \frac{\Delta \ln(v)}{\Delta \ln(J)} = \frac{\Delta \ln(e)}{\Delta \ln(J)} + \frac{\Delta \ln(\upsilon(X))}{\Delta \ln(J)}$$

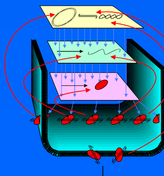
$$1 = \frac{\Delta \ln(v)}{\Delta \ln(J)} = \rho_h + \rho_m$$

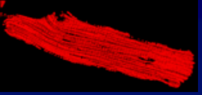
Hierarchical

Metabolic/direct





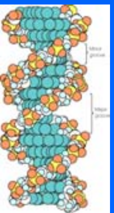




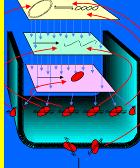
Systems Biology law for hierarchical regulation:

A total of 100 % regulation is distributed between metabolic and hierarchical regulation:

$$1 = \frac{\Delta \ln v}{\Delta \ln J} = \rho_h + \rho_m$$



$$\rho_h \equiv \frac{\Delta \ln e}{\Delta \ln J} \cong \frac{\textit{fold change in amount of enzyme}}{\textit{fold change of flux through it}}$$

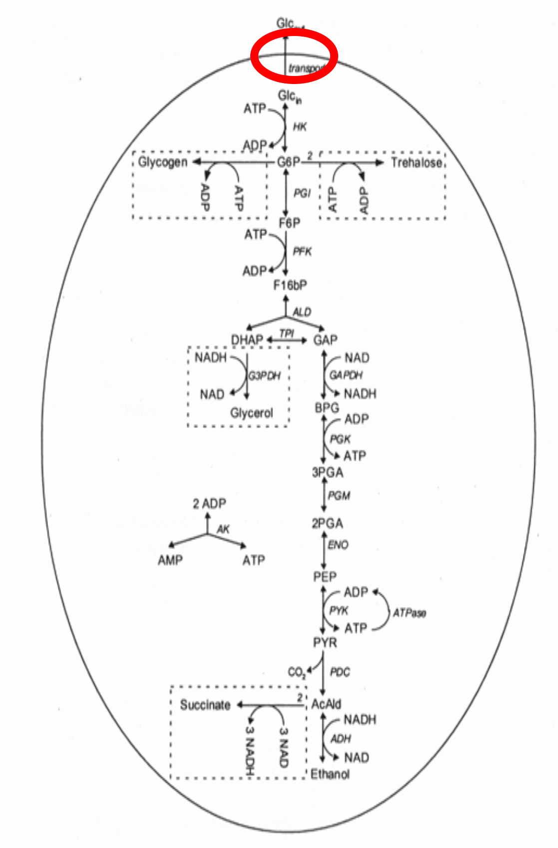


How does the cell **regulate** the transporter flux?

Through gene expression

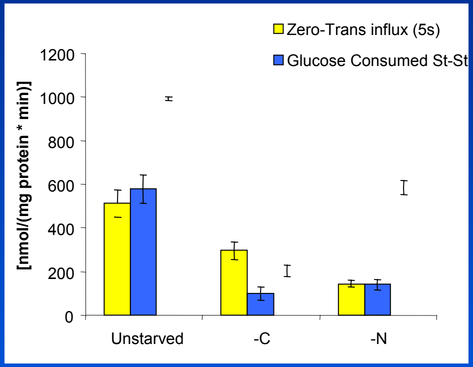
Or

Through metabolic regulation?



Regulation of the loss of transport capacity by yeast upon starvation

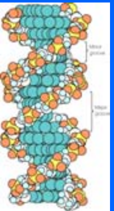
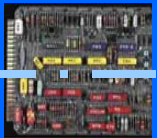
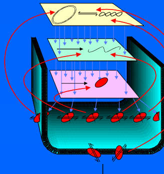
	Carbon starvation	Nitrogen starvation
$\Delta\ln$(transport activity)	-0.5	-1.3
$\Delta\ln(J_{glucose})$	-1.8	-1.4
$\rho_{hierarchical}$	31 %	91 %
$\rho_{metabolic}$	69 %	9 %

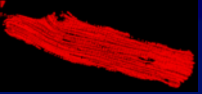


Gene expression regulated in N-starvation; largely metabolically regulated in C starvation

(Down-) regulation of glycolysis during starvation

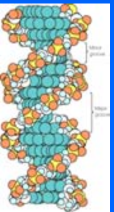
	Unstarved	N-starved	C-starved
Glucose	-0.62 ± 0.03	-0.16 ± 0.02	-0.17 ± 0.03
Glycerol	0.13 ± 0.01	0.06 ± 0.01	0.04 ± 0.00
Ethanol	1.04 ± 0.03	0.49 ± 0.05	0.33 ± 0.05
Trehalose	0.00 ± 0.00	-0.01 ± 0.00	0.00 ± 0.00
Glycogen	0.00 ± 0.00	-0.03 ± 0.01	0.00 ± 0.00

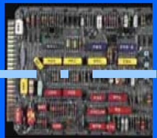




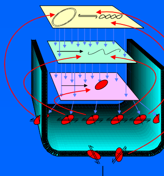


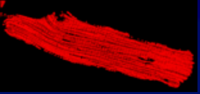
Regulation is not all through gene expression….. and we can readily determine how much of it is

	Carbon starvation		
	ρ_h	SEM	ρ_m
GLT	0.4	0.1	0.6
HK	0.1	0.0	0.9
PGI	0.0	0.0	1.0
PFK	0.4	0.4	0.6
ALD	0.0	0.2	1.0
TPI	−0.4	0.2	1.4
GAPDH	0.1	0.0	0.9
PGK	−0.3	0.1	1.3
PGM	0.0	0.0	1.0
ENO	0.3	0.1	0.7
PK	0.1	0.0	0.9
PDC	0.1	0.0	0.9
ADH	−1.3	0.2	2.3



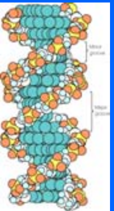


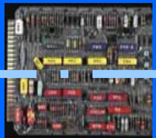


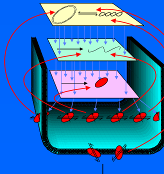


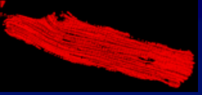
Regulation is diverse

	Carbon starvation		
	ρ_h	SEM	ρ_m
GLT	0.4	0.1	0.6
HK	0.1	0.0	0.9
PGI	0.0	0.0	1.0
PFK	0.4	0.4	0.6
ALD	0.0	0.2	1.0
TPI	−0.4	0.2	1.4
GAPDH	0.1	0.0	0.9
PGK	−0.3	0.1	1.3
PGM	0.0	0.0	1.0
ENO	0.3	0.1	0.7
PK	0.1	0.0	0.9
PDC	0.1	0.0	0.9
ADH	−1.3	0.2	2.3



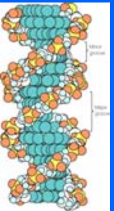


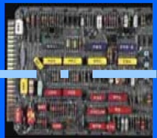


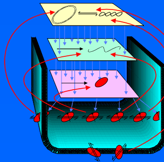


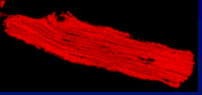
No one regulated entirely through gene expression

	Carbon starvation		
	ρ_h	SEM	ρ_m
GLT	0.4	0.1	0.6
HK	0.1	0.0	0.9
PGI	0.0	0.0	1.0
PFK	0.4	0.4	0.6
ALD	0.0	0.2	1.0
TPI	−0.4	0.2	1.4
GAPDH	0.1	0.0	0.9
PGK	−0.3	0.1	1.3
PGM	0.0	0.0	1.0
ENO	0.3	0.1	0.7
PK	0.1	0.0	0.9
PDC	0.1	0.0	0.9
ADH	−1.3	0.2	2.3



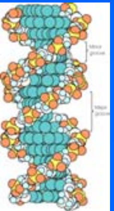


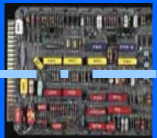


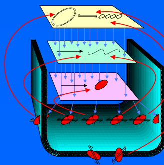


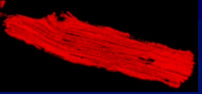
Glucose transporter half through gene expression:

	Carbon starvation		
	ρ_h	SEM	ρ_m
GLT	0.4	0.1	0.6
HK	0.1	0.0	0.9
PGI	0.0	0.0	1.0
PFK	0.4	0.4	0.6
ALD	0.0	0.2	1.0
TPI	−0.4	0.2	1.4
GAPDH	0.1	0.0	0.9
PGK	−0.3	0.1	1.3
PGM	0.0	0.0	1.0
ENO	0.3	0.1	0.7
PK	0.1	0.0	0.9
PDC	0.1	0.0	0.9
ADH	−1.3	0.2	2.3



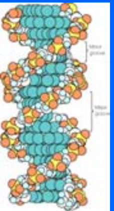


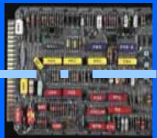


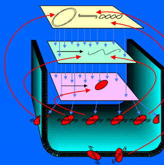


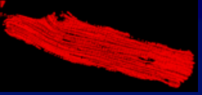
Aldolase only metabolically:

	Carbon starvation		
	ρ_h	SEM	ρ_m
GLT	0.4	0.1	0.6
HK	0.1	0.0	0.9
PGI	0.0	0.0	1.0
PFK	0.4	0.4	0.6
ALD	0.0	0.2	1.0
TPI	−0.4	0.2	1.4
GAPDH	0.1	0.0	0.9
PGK	−0.3	0.1	1.3
PGM	0.0	0.0	1.0
ENO	0.3	0.1	0.7
PK	0.1	0.0	0.9
PDC	0.1	0.0	0.9
ADH	−1.3	0.2	2.3



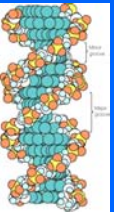


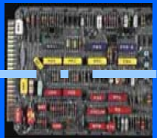


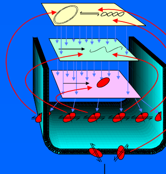


ADH homeostated through gene expression

	Carbon starvation		
	ρ_h	SEM	ρ_m
GLT	0.4	0.1	0.6
HK	0.1	0.0	0.9
PGI	0.0	0.0	1.0
PFK	0.4	0.4	0.6
ALD	0.0	0.2	1.0
TPI	−0.4	0.2	1.4
GAPDH	0.1	0.0	0.9
PGK	−0.3	0.1	1.3
PGM	0.0	0.0	1.0
ENO	0.3	0.1	0.7
PK	0.1	0.0	0.9
PDC	0.1	0.0	0.9
ADH	−1.3	0.2	2.3

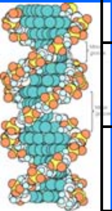


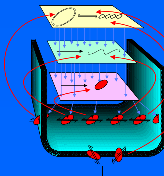




Sacharomyces cerevisiae: regulation of fermentative capacity; experimental

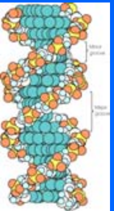
	Nitrogen starvation				Carbon starvation		
	ρ_h	SEM	ρ_m		ρ_h	SEM	ρ_m
GLT	1.2	0.1	-0.2		0.4	0.1	0.6
HK	1.0	0.2	0.0		0.1	0.0	0.9
PGI	0.8	0.3	0.2		0.0	0.0	1.0
PFK	0.4	0.2	0.6		0.4	0.4	0.6
ALD	1.1	0.5	-0.1		0.0	0.2	1.0
TPI	0.1	0.9	0.9		-0.4	0.2	1.4
GAPDH	0.7	0.5	0.3		0.1	0.0	0.9
PGK	0.0	0.2	1.0		-0.3	0.1	1.3
PGM	1.0	0.4	0.0		0.0	0.0	1.0
ENO	0.4	0.5	0.6		0.3	0.1	0.7
PK	1.4	0.3	-0.4		0.1	0.0	0.9
PDC	2.3	0.6	-1.3		0.1	0.0	0.9
ADH	1.7	0.4	-0.7		-1.3	0.2	2.3

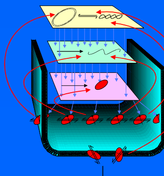




1. **Exclusively hierarchical** regulation $\rho_h = 1$

	Nitrogen starvation				Carbon starvation		
	ρ_h	SEM	ρ_m		ρ_h	SEM	ρ_m
GLT	1.2	0.1	-0.2		0.4	0.1	0.6
HK	1.0	0.2	0.0		0.1	0.0	0.9
PGI	0.8	0.3	0.2		0.0	0.0	1.0
PFK	0.4	0.2	0.6		0.4	0.4	0.6
ALD	1.1	0.5	-0.1		0.0	0.2	1.0
TPI	0.1	0.9	0.9		-0.4	0.2	1.4
GAPDH	0.7	0.5	0.3		0.1	0.0	0.9
PGK	0.0	0.2	1.0		-0.3	0.1	1.3
PGM	1.0	0.4	0.0		0.0	0.0	1.0
ENO	0.4	0.5	0.6		0.3	0.1	0.7
PK	1.4	0.3	-0.4		0.1	0.0	0.9
PDC	2.3	0.6	-1.3		0.1	0.0	0.9
ADH	1.7	0.4	-0.7		-1.3	0.2	2.3





2. **Exclusively metabolic** regulation $\rho_h = 0$

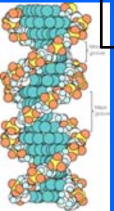
	Nitrogen starvation				Carbon starvation		
	ρ_h	SEM	ρ_m		ρ_h	SEM	ρ_m
GLT	1.2	0.1	-0.2		0.4	0.1	0.6
HK	1.0	0.2	0.0		0.1	0.0	0.9
PGI	0.8	0.3	0.2		0.0	0.0	1.0
PFK	0.4	0.2	0.6		0.4	0.4	0.6
ALD	1.1	0.5	-0.1		0.0	0.2	1.0
TPI	0.1	0.9	0.9		-0.4	0.2	1.4
GAPDH	0.7	0.5	0.3		0.1	0.0	0.9
PGK	0.0	0.2	1.0		-0.3	0.1	1.3
PGM	1.0	0.4	0.0		0.0	0.0	1.0
ENO	0.4	0.5	0.6		0.3	0.1	0.7
PK	1.4	0.3	-0.4		0.1	0.0	0.9
PDC	2.3	0.6	-1.3		0.1	0.0	0.9
ADH	1.7	0.4	-0.7		-1.3	0.2	2.3

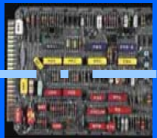
3. **Mixed regulation** $0<\rho_h<1$

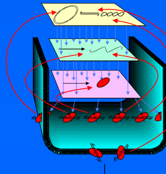
	Nitrogen starvation				Carbon starvation		
	ρ_h	SEM	ρ_m		ρ_h	SEM	ρ_m
GLT	1.2	0.1	-0.2		0.4	0.1	0.6
HK	1.0	0.2	0.0		0.1	0.0	0.9
PGI	0.8	0.3	0.2		0.0	0.0	1.0
PFK	0.4	0.2	0.6		0.4	0.4	0.6
ALD	1.1	0.5	-0.1		0.0	0.2	1.0
TPI	0.1	0.9	0.9		-0.4	0.2	1.4
GAPDH	0.7	0.5	0.3		0.1	0.0	0.9
PGK	0.0	0.2	1.0		-0.3	0.1	1.3
PGM	1.0	0.4	0.0		0.0	0.0	1.0
ENO	0.4	0.5	0.6		0.3	0.1	0.7
PK	1.4	0.3	-0.4		0.1	0.0	0.9
PDC	2.3	0.6	-1.3		0.1	0.0	0.9
ADH	1.7	0.4	-0.7		-1.3	0.2	2.3

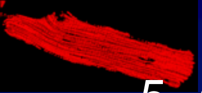
4. Superhierarchical regulation V_{max} dominating $\rho_h > 1$

	Nitrogen starvation				Carbon starvation		
	ρ_h	SEM	ρ_m		ρ_h	SEM	ρ_m
GLT	1.2	0.1	-0.2		0.4	0.1	0.6
HK	1.0	0.2	0.0		0.1	0.0	0.9
PGI	0.8	0.3	0.2		0.0	0.0	1.0
PFK	0.4	0.2	0.6		0.4	0.4	0.6
ALD	1.1	0.5	-0.1		0.0	0.2	1.0
TPI	0.1	0.9	0.9		-0.4	0.2	1.4
GAPDH	0.7	0.5	0.3		0.1	0.0	0.9
PGK	0.0	0.2	1.0		-0.3	0.1	1.3
PGM	1.0	0.4	0.0		0.0	0.0	1.0
ENO	0.4	0.5	0.6		0.3	0.1	0.7
PK	1.4	0.3	-0.4		0.1	0.0	0.9
PDC	**2.3**	**0.6**	**-1.3**		0.1	0.0	0.9
ADH	**1.7**	**0.4**	**-0.7**		-1.3	0.2	2.3



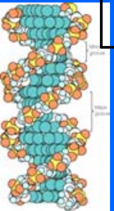


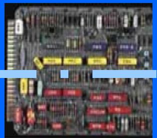


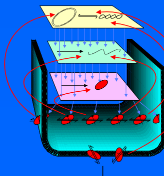


5. Antagonistic regulation interaction dominating $\rho_h < 0$

	Nitrogen starvation				Carbon starvation		
	ρ_h	SEM	ρ_m		ρ_h	SEM	ρ_m
GLT	1.2	0.1	-0.2		0.4	0.1	0.6
HK	1.0	0.2	0.0		0.1	0.0	0.9
PGI	0.8	0.3	0.2		0.0	0.0	1.0
PFK	0.4	0.2	0.6		0.4	0.4	0.6
ALD	1.1	0.5	-0.1		0.0	0.2	1.0
TPI	0.1	0.9	0.9		-0.4	0.2	1.4
GAPDH	0.7	0.5	0.3		0.1	0.0	0.9
PGK	0.0	0.2	1.0		-0.3	0.1	1.3
PGM	1.0	0.4	0.0		0.0	0.0	1.0
ENO	0.4	0.5	0.6		0.3	0.1	0.7
PK	1.4	0.3	-0.4		0.1	0.0	0.9
PDC	2.3	0.6	-1.3		0.1	0.0	0.9
ADH	1.7	0.4	-0.7		-1.3	0.2	2.3

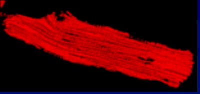






Is there a rule here?

Comparative Systems Biology

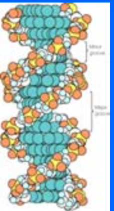
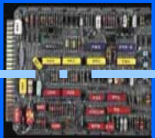
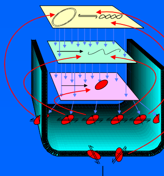



Comparative Systems Biology

Relative abundance of four types of regulation

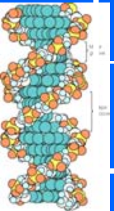
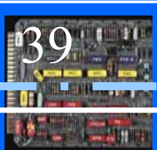
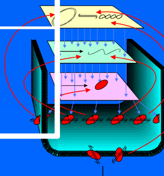
Species	Regulation type			
	supermetabolic ($\rho_h < -0.2$)	metabolic ($-0.2 < \rho_h < 0.2$)	shared ($0.2 < \rho_h < 0.8$)	hierarchical ($0.8 < \rho_h < 1.2$)
T. brucei	6	7	3	1
L. donovani	7	2	1	2
T. vaginalis	1	8	3	0

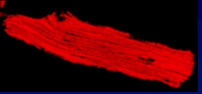
Numbers of enzymes that show negative hierarchical or supermetabolic, regulation ($\rho_h < -0.2$), metabolic regulation ($-0.2 < \rho_h < 0.2$), regulation shared between the hierarchical and metabolic routes ($0.2 < \rho_h < 0.8$) and hierarchical regulation ($0.8 < \rho_h < 1.2$). Super-hierarchical regulation (i.e. when enzyme activity increases more than proportionally as compared to the flux ($\rho_h > 1.2$) occurred only at the higher fluxes. When highest and second highest fluxes are compared it was found in eight out of 29 cases of *T. brucei* and *L. donovani* combined and in nine out of 12 for *T. vaginalis*.

Type of regulation by number of glycolysis steps

Organism	Condition	supermetabolic	metabolic	mixed	hierarchical	superhierarchical
T. brucei	Glucose limited chemostat	6	7	3	1	0
L. Donovani	Glucose limited chemostat	7	2	1	2	0
T. vaginalis	Glucose limited chemostat	1	8	3	0	0
S. cerevisiae	Glucose starvation	3	7	3	0	0
S. cerevisiae	N starvation	0	2	3	5	3
Total		17	26	13	8	3
%		25	39	19	12	4



Is there a rule here?

- All types
- In all organisms
- Metabolic regulation dominates
- In all organisms/conditions examined

Type of regulation by number of glycolysis steps

Organism	Condition	supermetabolic	metabolic	mixed	hierarchical	superhierarchical
T. brucei	Glucose limited chemostat	6	7	3	1	0
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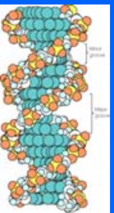
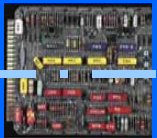
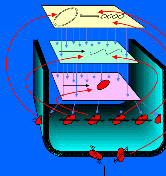
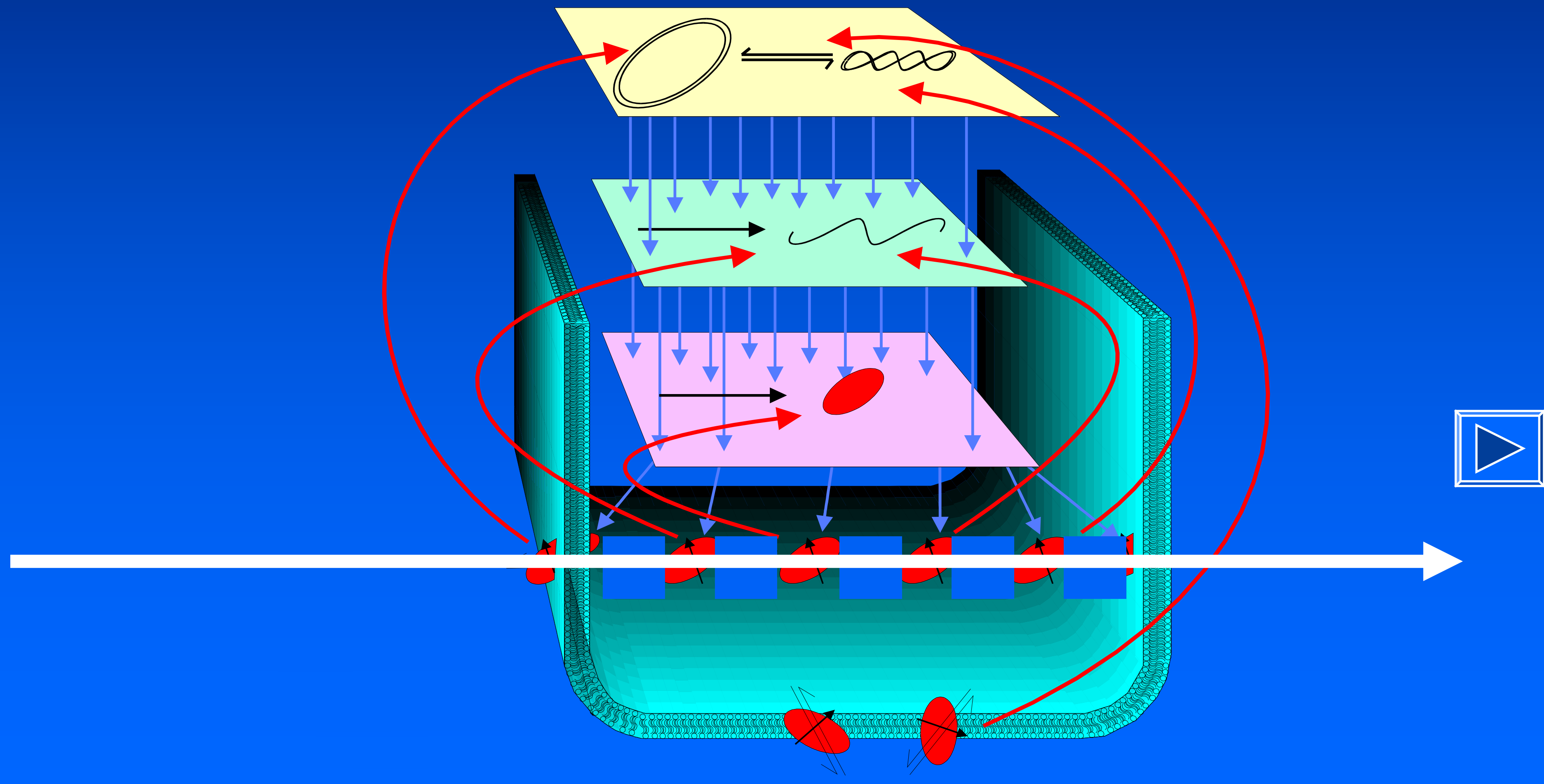






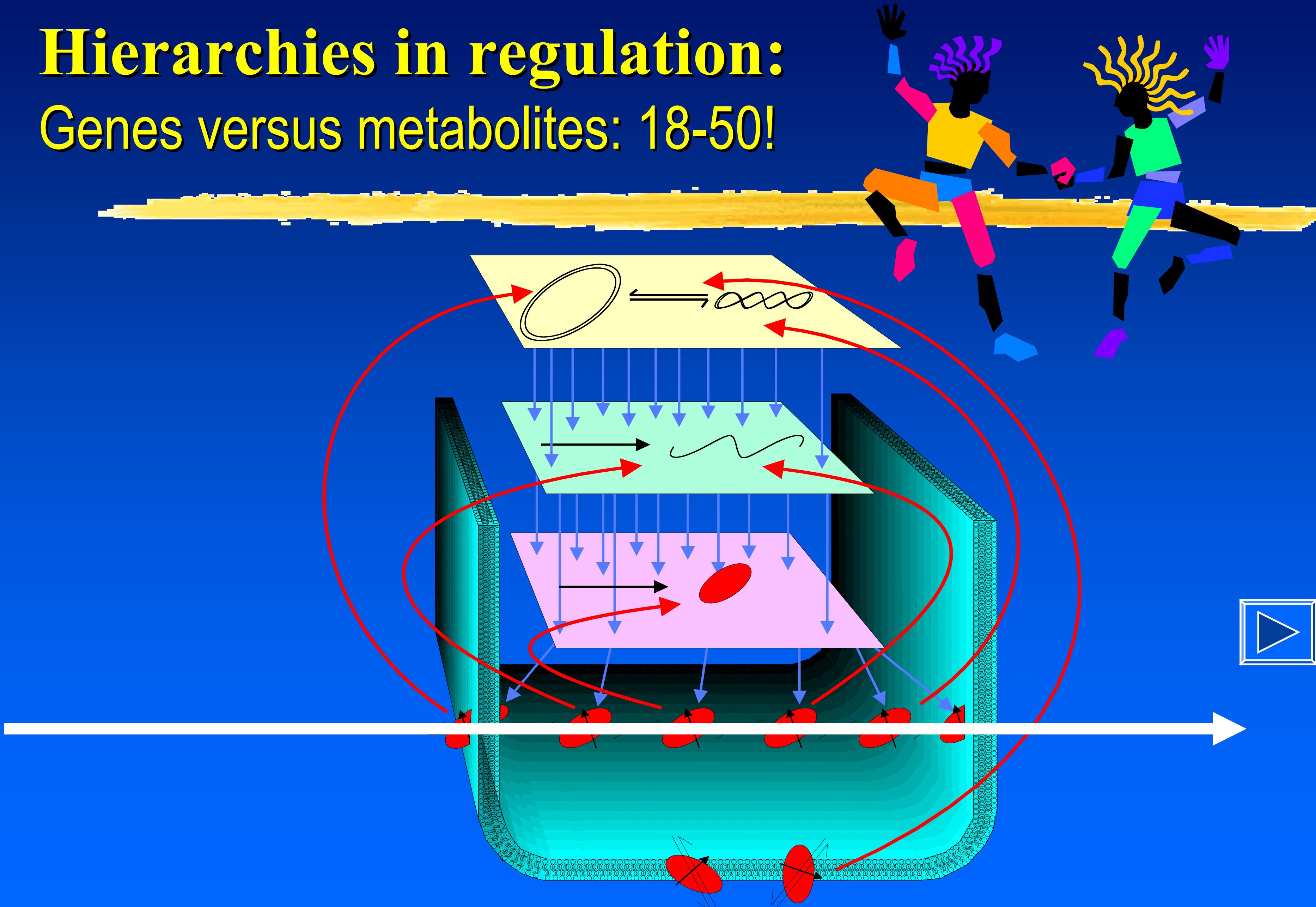
Hierarchies in regulation:

Genes versus metabolites: 2-1?



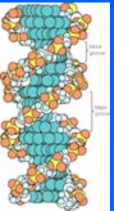
Hierarchies in regulation:

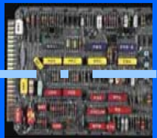
Genes versus metabolites: 18-50!



Systems Biology: signaling where to go

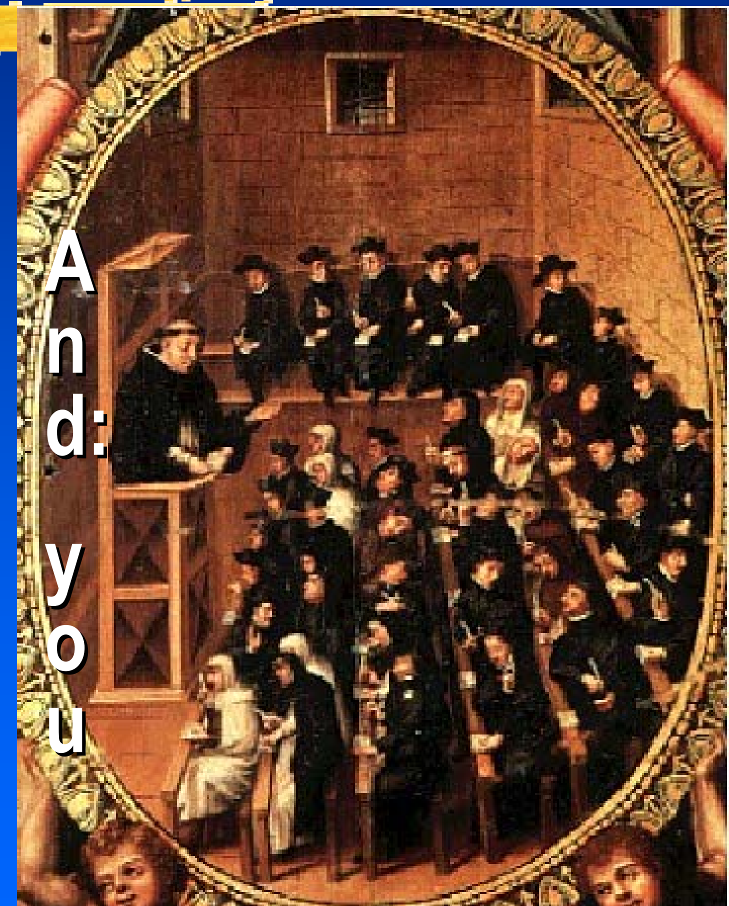
- Interactions & loops & emergence ✓
- Towards applications: Network-based drug design anti-parasites ✓
- Silicon cells ✓
- Systems Biology a science: laws and principles ✓
- Improved understanding of multifactorial disease ✓
- Two paradigms for anti tumor drugs ✓
- What regulates function? Gene expression or metabolism? ✓



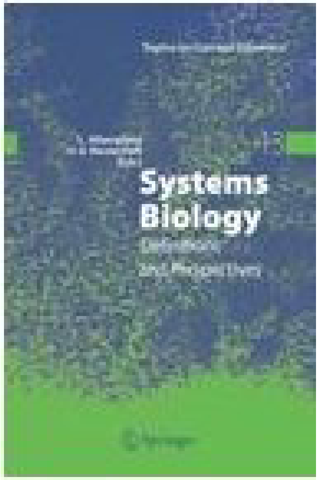


Thanks to:

Barbara M. Bakker
Frank Bruggeman
Jorrit Hornberg
Jan Lankelma
Sergio Rossell
Jacky L. Snoep
Paul Michels (Brussels)
Benno ter Kuile (New York)
and many others



My patient audience



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Alberghina, Lilia; Westerhoff, H.V. (Eds.)
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About this book

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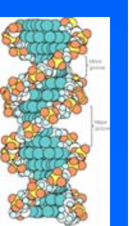

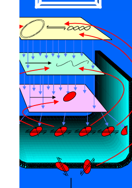

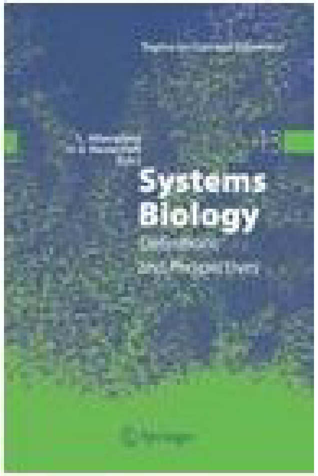

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