Robust systems in control

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Gosau
FEBSysBio2007

Hans V. Westerhoff, Frank Bruggeman
&
friends

Netherlands' Institute for Systems Biology and Manchester Center for Integrative Systems Biology

2nd FEBS Advanced Lecture Course on
Systems Biology:
From Molecules to Life
Gosau, Austria, EU, March 10-16, 2007

First part: methodology

- Systems Biology as methodology:
  - Precise definition of biological concepts
  - Qualitative biological understanding through quantification
  - Silicon cell/JWS
  - Generality: mathematical proof & thought experiments
  - A definition of robustness

Middle part: tutorial

- Calculating robustness
- Falsifying proposed constant robustness
- Searching for new general principles
- How to enhance robustness; a paradoxical principle

Third part: results

- Biochemical networks are highly robust
- Robustness is not conserved
- ..... is conserved
- Robustness through fragility
- Robustness and signal transduction
- Robustness as disease

To deal with Biological Systems.....

We should engage in Systems Biology

How important is Systems Biology?

Most remaining diseases are

Systems Biology (network) diseases

Cf. Adriano Henney

To cure the network

One should deal with the network

An enormous paradigm shift

Cf. Lee Hood

Health and disease

- Classical:
- Disease is .... dysfunction

- Novel:
- Disease is .... failure to be robust,
- (or failure to be fragile.....)

Assets of Systems Biology

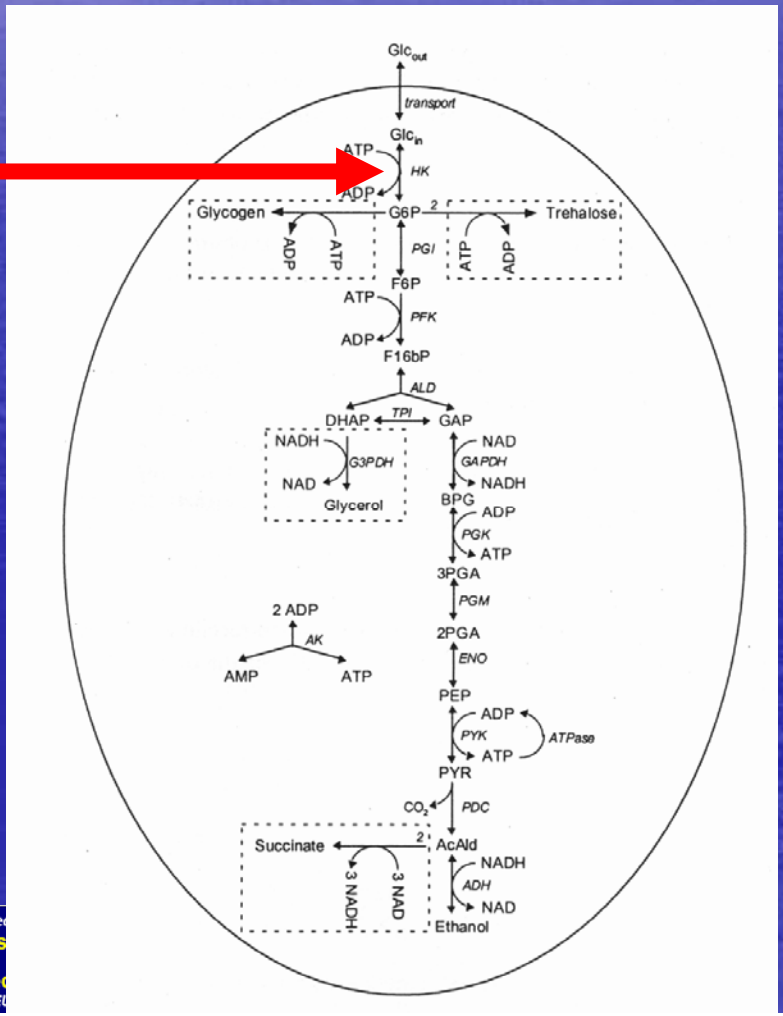
- It is non dogmatic (neither reductionist nor holist)
- It does not evade the complexity of the real world
  - (one should simplify as much as possible but not more; Einstein)
- It adds precision to biology and this may enable one to solve issues that could not be solved before

Example of non dogmatic and precise nature of Systems Biology

- Biochemistry/molecular biology:
  - 'the rate limiting step is the first irreversible step in the pathway'
- Systems Biology:
  - Control may be distributed:

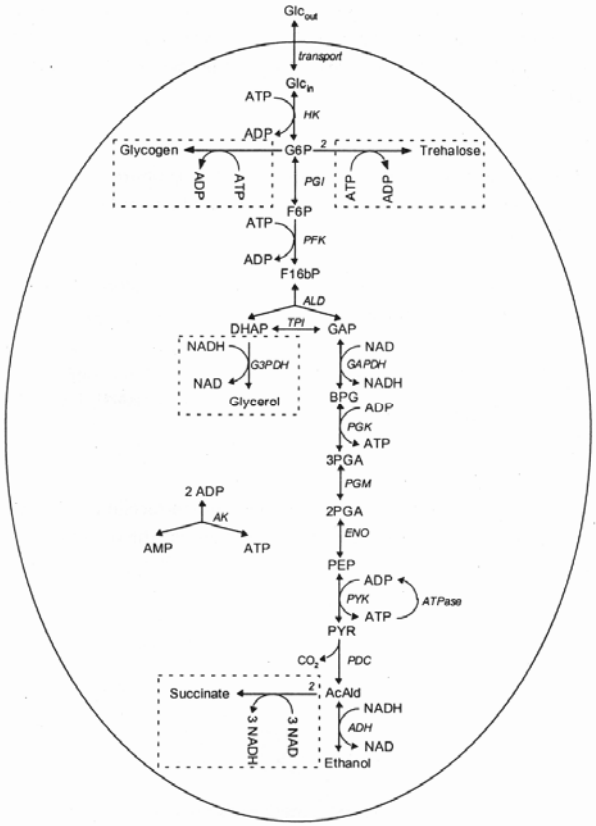
$$C_1^J + C_2^J + C_3^J + C_4^J = 1$$

The rate-limiting step



‘Criteria’ for limitation originally in use

- There is only one
- Irreversible step
- First step
- Most regulated step
- When deleted, flux stops
- When inhibited flux decreases
- I like (work on) the enzyme, therefore it must be important



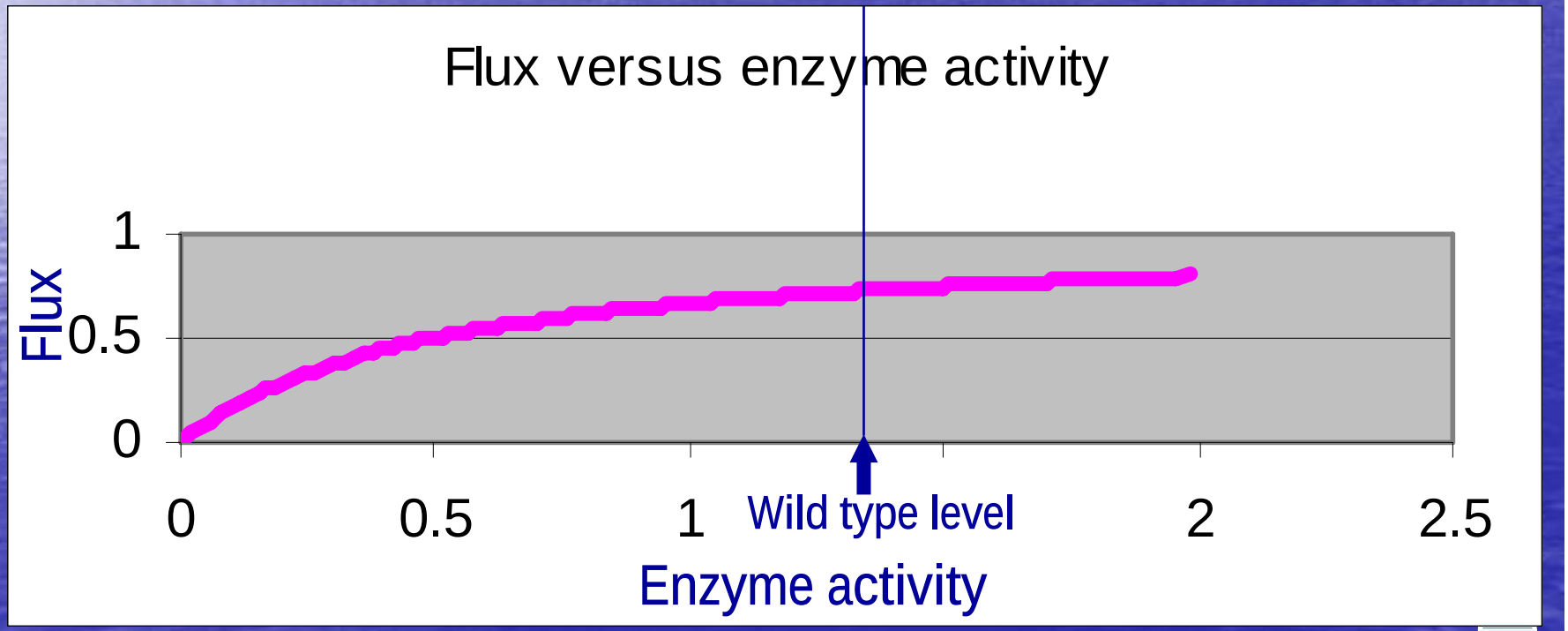
Problems arising

- **More than one step was proposed to be the only rate-limiting step**
- **Criteria were muddy**

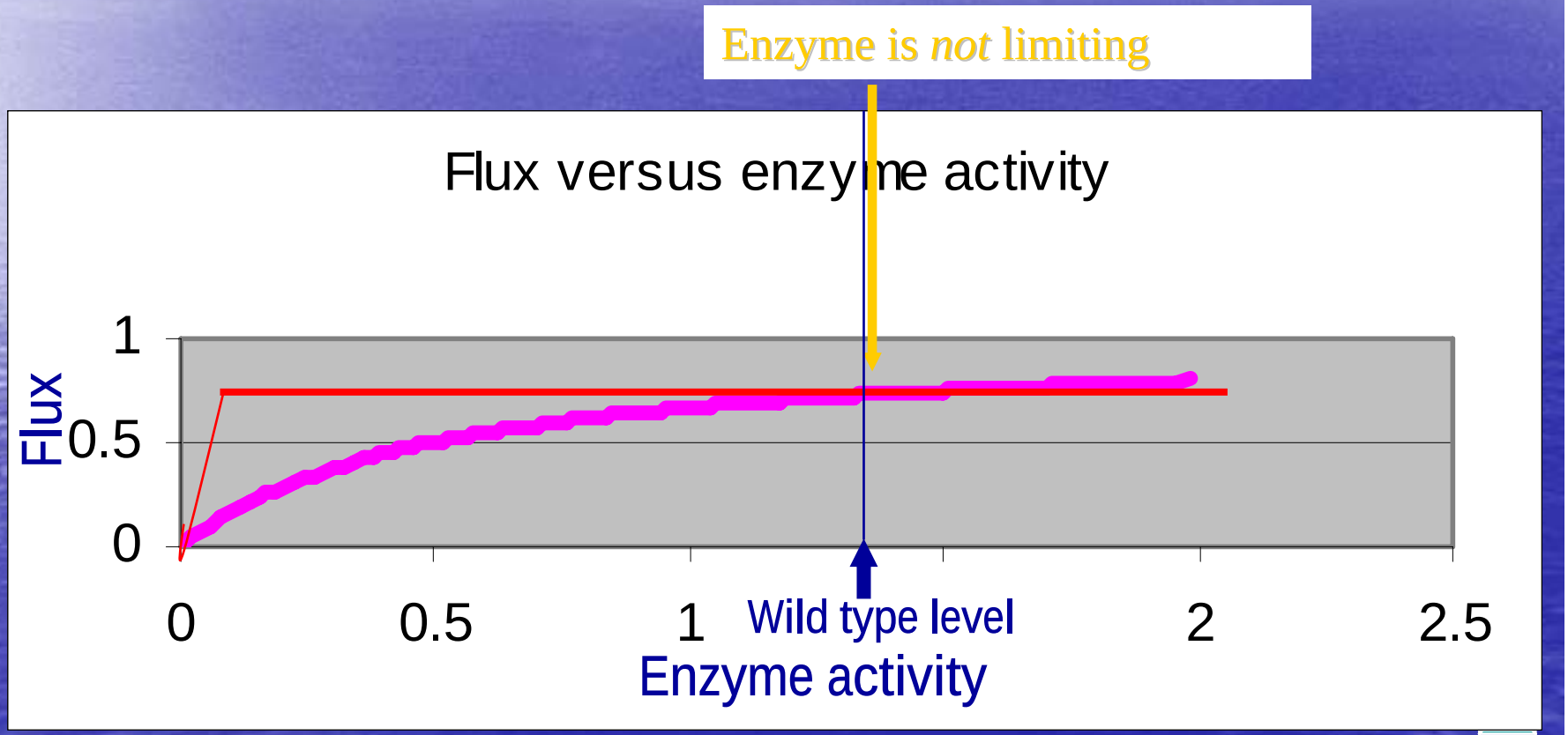
A good definition

- Should enable us to figure out which of these definitions (if any) is right
- Should even enable us to find that there is no rate-limiting step at all...

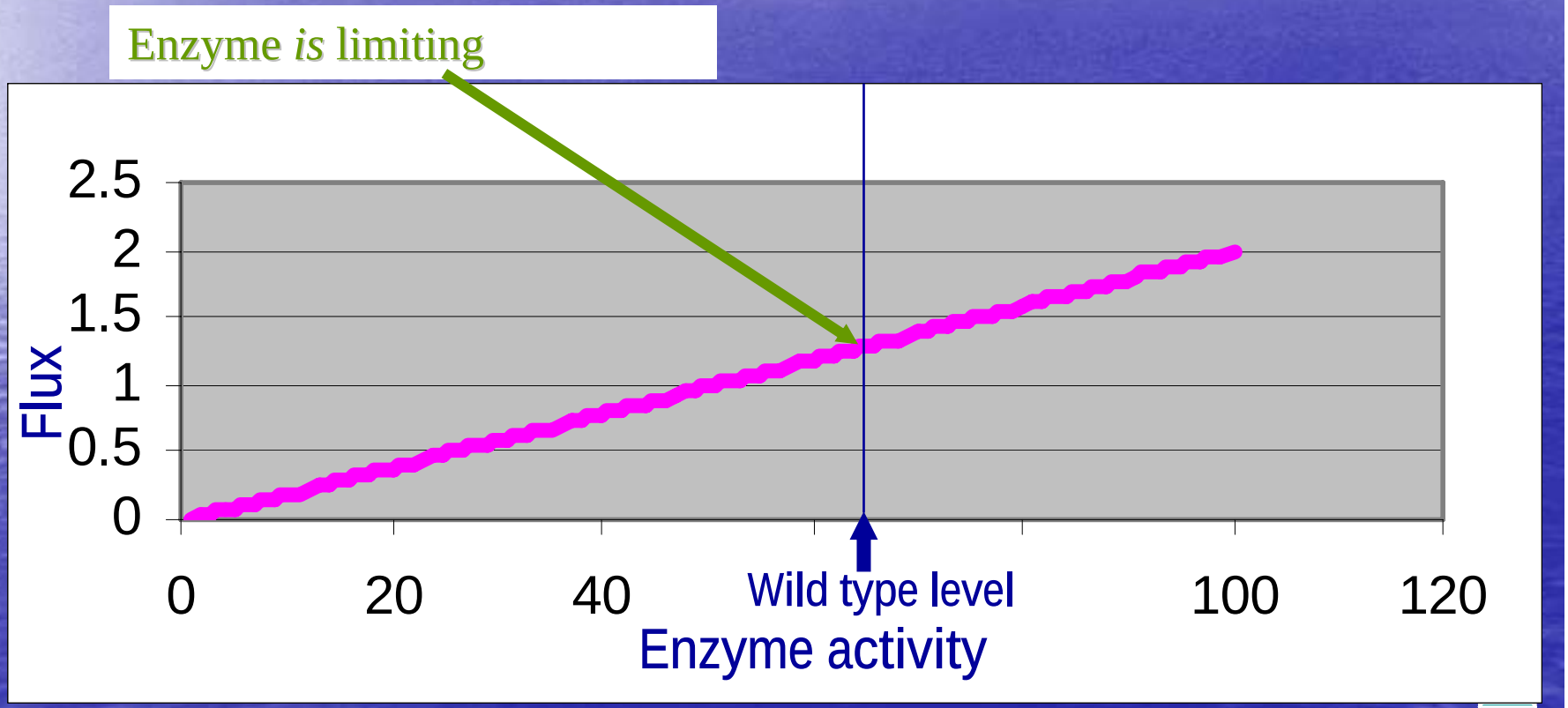
How to measure whether a component is limiting = controlling ??



How to measure whether a component is limiting:

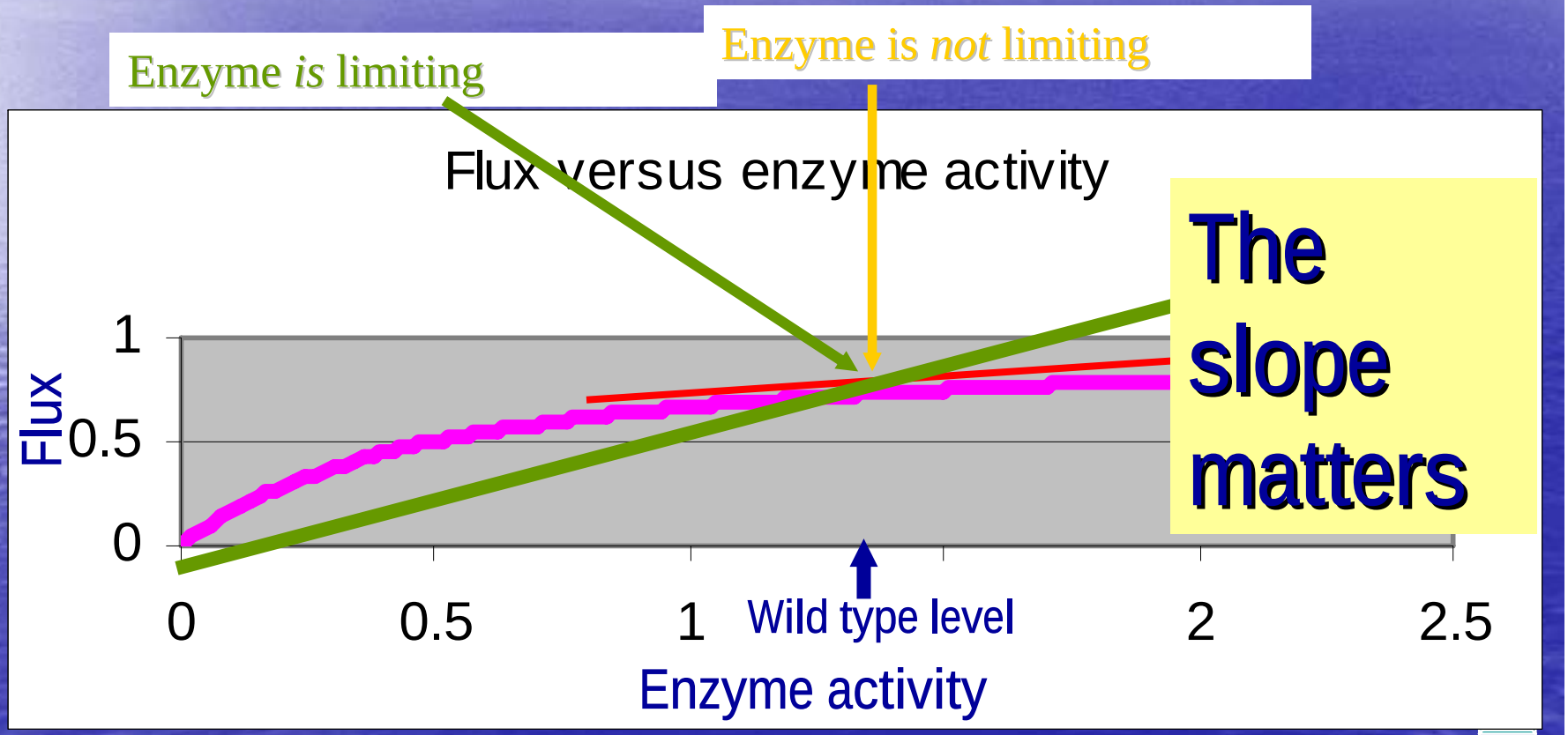


The rate-limiting step: flux proportional to enzyme activity; 1 % decrease in flux for 1 % decrease in enzyme activity, C=1



How to measure whether an component is limiting:

the Control coefficient



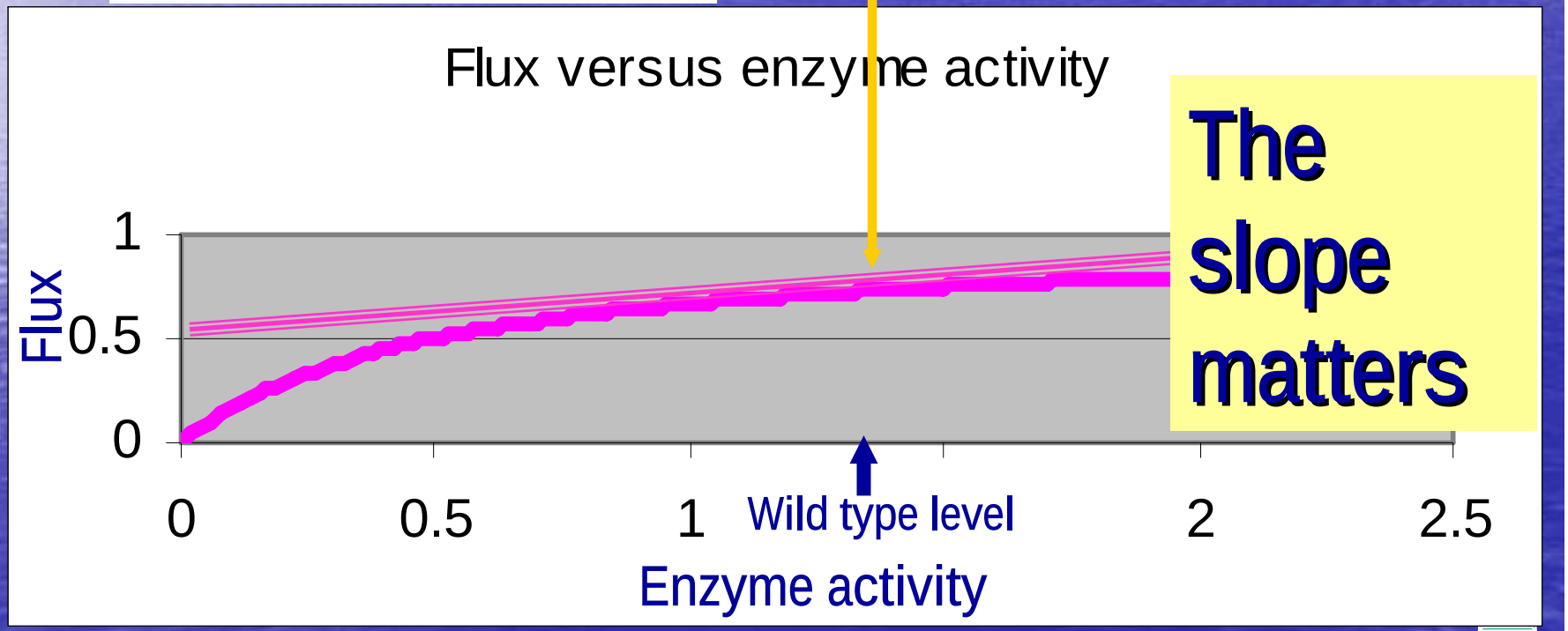
How to measure whether an component is limiting:

the Control coefficient

$$slope = \frac{dJ}{de}$$

s limiting

Enzyme is somewhat limiting



The slope matters

Disadvantage

$$slope = \frac{dJ}{de}$$

- dJ: nmol/min/mgdryweight
- de: mg protein

- Control changes when expressed per gram protein

Relative changes

$$slope = \frac{dJ / J}{de / e}$$

- dJ/J: dimensionless
- de/e: dimensionless

- Control changes when expressed per gram protein

Flux Control Coefficient

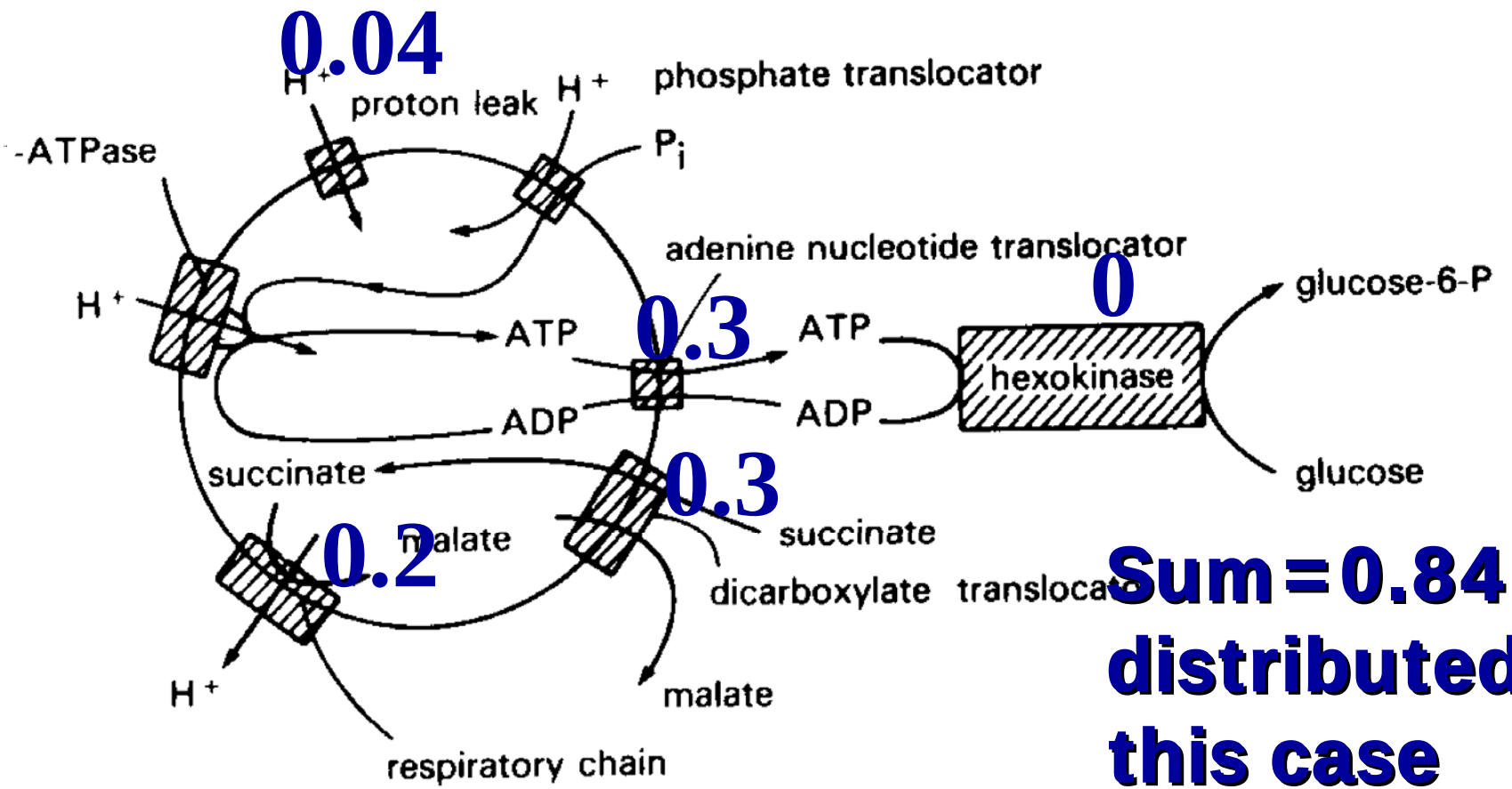
- Control coefficient: alternative expressions

$$C_i^J \equiv \frac{dJ/J}{de_i/e_i} = \left(\frac{d\ln(J)}{d\ln(e_i)}\right)_{steadystate} = \left(\frac{d\log(J)}{d\log(e_i)}\right)_{steadystate}$$

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

Cf. Jannie Hofmeyr

Surprise: nobody and everyone was right: distributed control



Sum = 0.84; distributed in this case

Qualitative conclusion

Control may be distributed

Asset of Systems Biology

Discover qualitative properties

By being sufficiently more precise (quantitative)

First part: methodology

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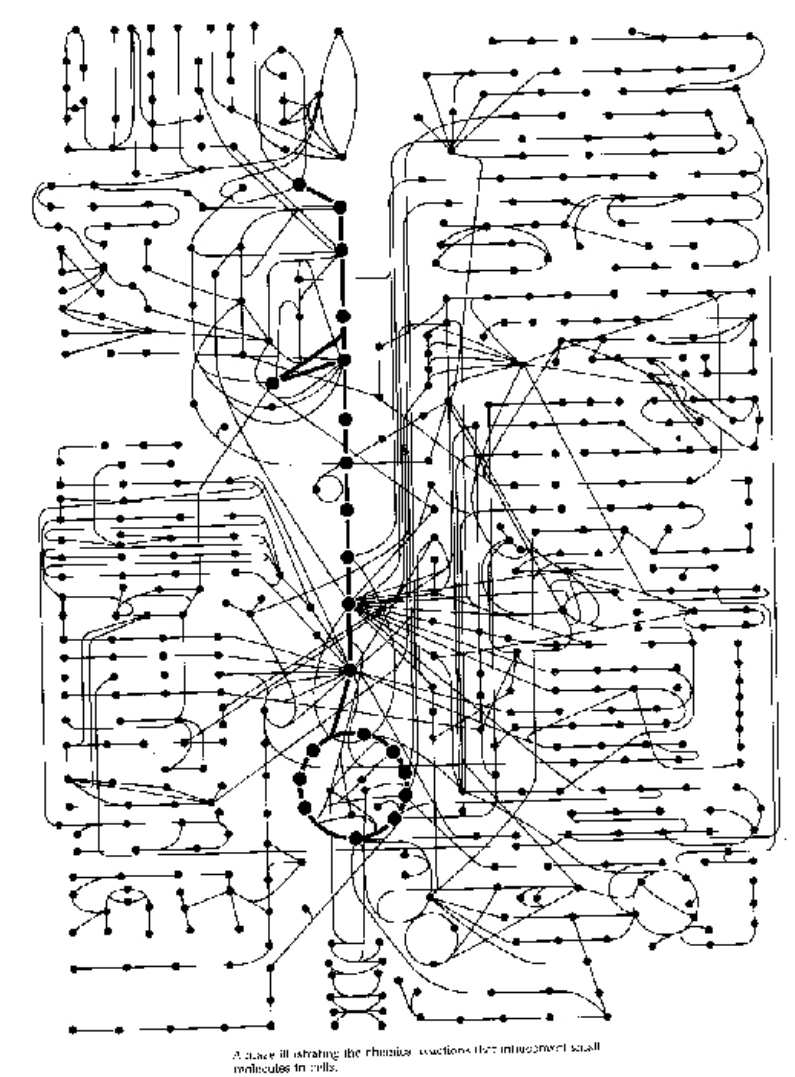
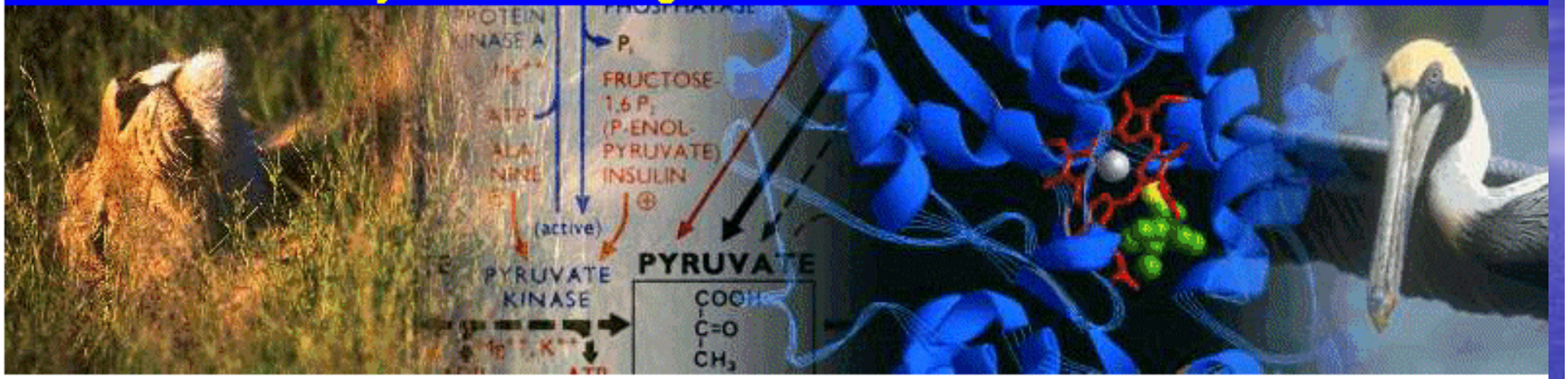
Is control distributed?



We can now calculate this for some cases using the silicon cell

JWS Online Cellular Systems Modelling



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Linked to *FEBS Journal* and *Microbiology*

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

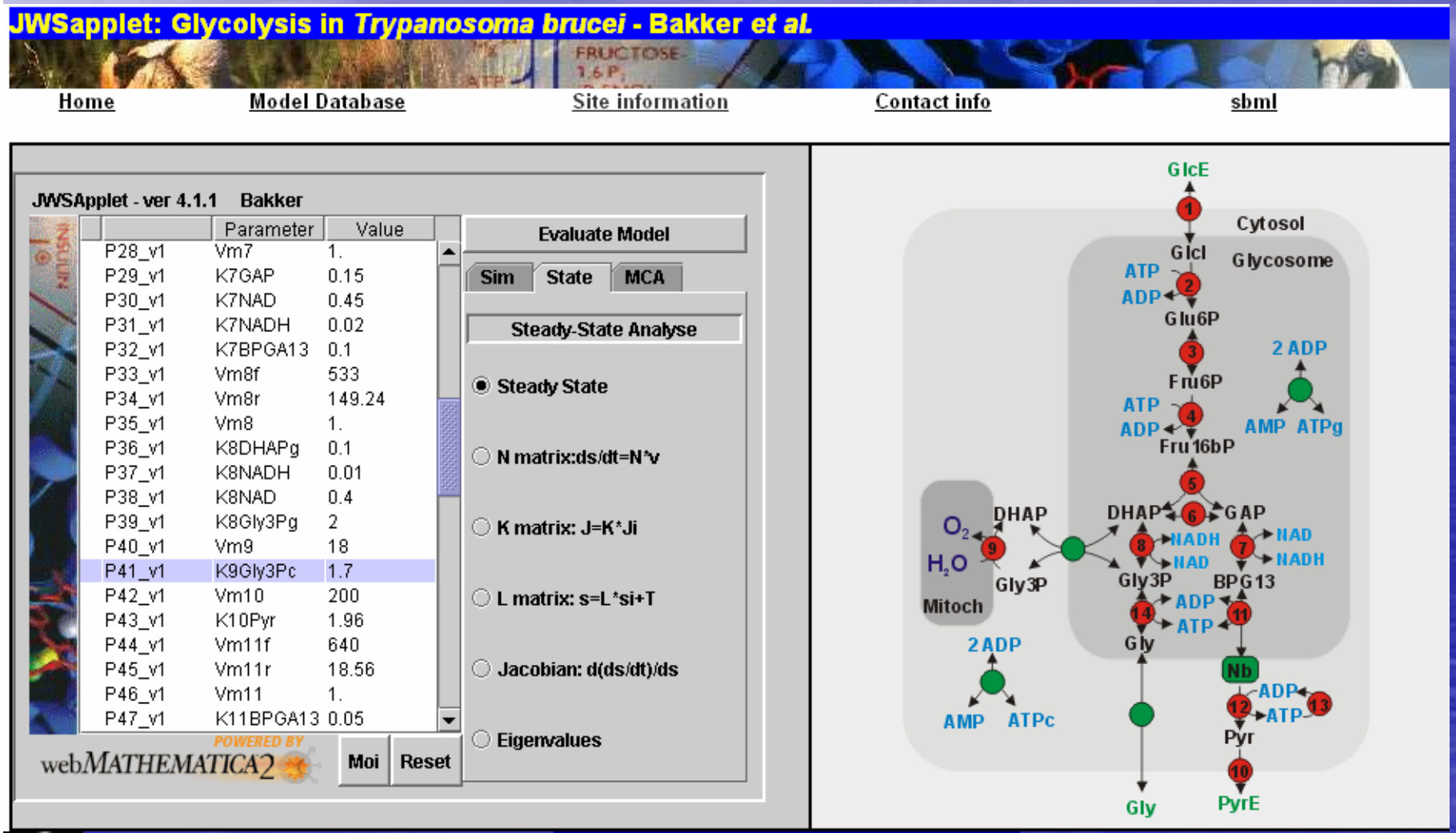
2002/12/03: The Applets have been upgraded to use the Sun Microsystems JRE 1.4 or higher

www.siliconcell.net

Site last updated: 03 December 2002

Cf. Jacky Snoep

Silicon cell live models: http://www.jjj.bio.vu.nl



In one case

Control is distributed

(and in fact in many other cases)

Silicon cell……

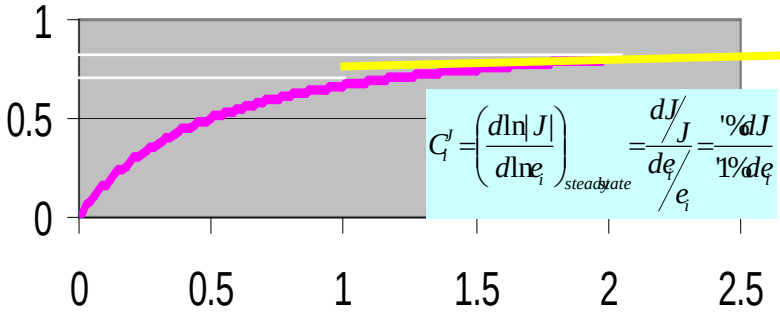
As complex as reality

‘Therefore not useful’ (??)

Where did the 1 go?

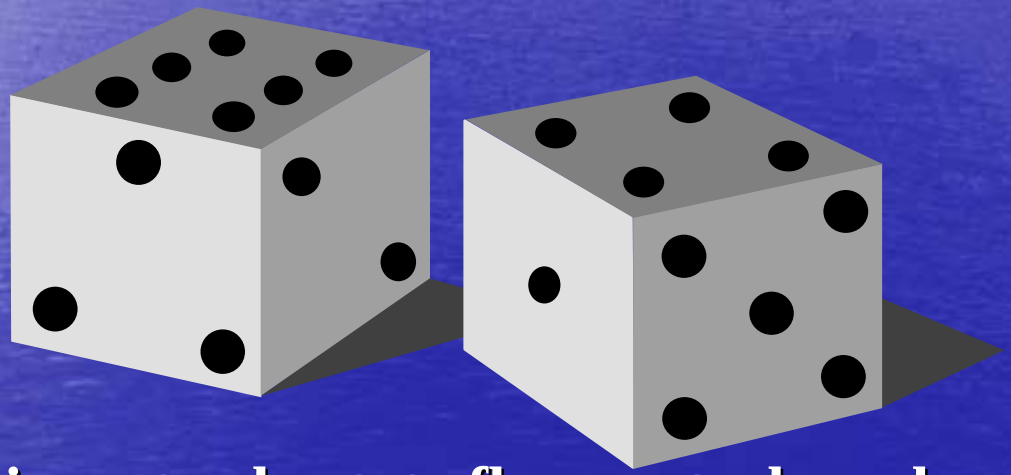
Reaction	4 mM glucose C_i^J	4 mM glucose Γ/K_{eq}	5 mM glucose C_i^J	5 mM glucose Γ/K_{eq}	8 mM glucose C_i^J	8 mM glucose Γ/K_{eq}
Glucose transport					**0.63**	$9.2 \cdot 10^{-3}$
HK					0.04	$<< 10^{-3}$
PFK					0.01	$<< 10^{-3}$
XLD					**0.10**	0.17
GAPDH					**0.09**	0.20
PGK					**0.06**	$3.4 \cdot 10^{-3}$
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					0.00	

Flux versus enzyme/gene dosage



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

$$C_1^J + C_2^J + C_3^J + \ldots\ldots\ldots + C_n^J = 1$$



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

Silicon cell…….

Made a discovery

…….

This is a true story:

Kacser & Burns and for other theorems:

Van Dam et al.

Bruggeman et al.

Systems Biology

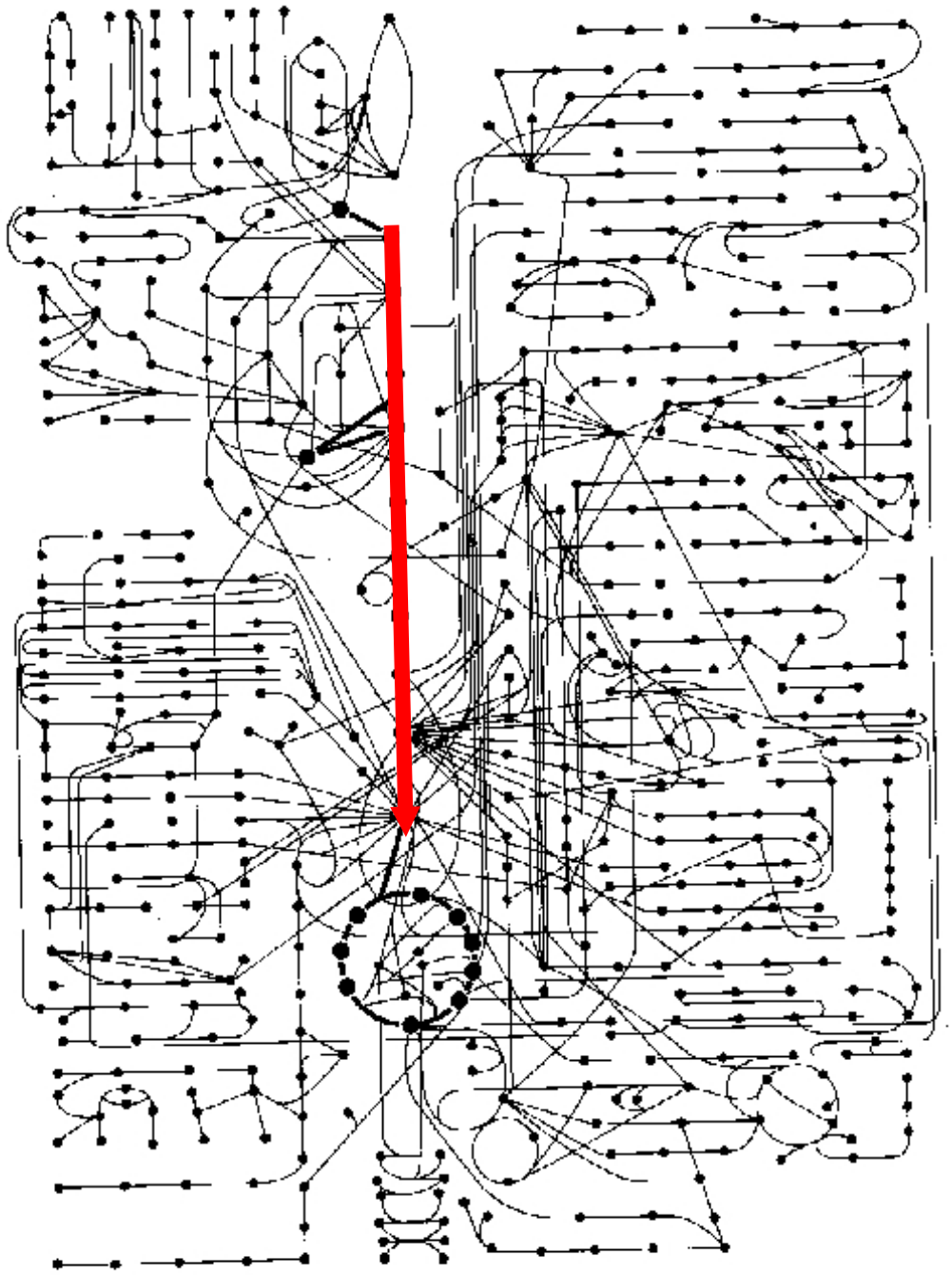
The Life of Biology

The quantitative experimentation of biochemistry/biophysics

The precision of physics

The certainty/generality of mathematics

Cf. Guy Shinar



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

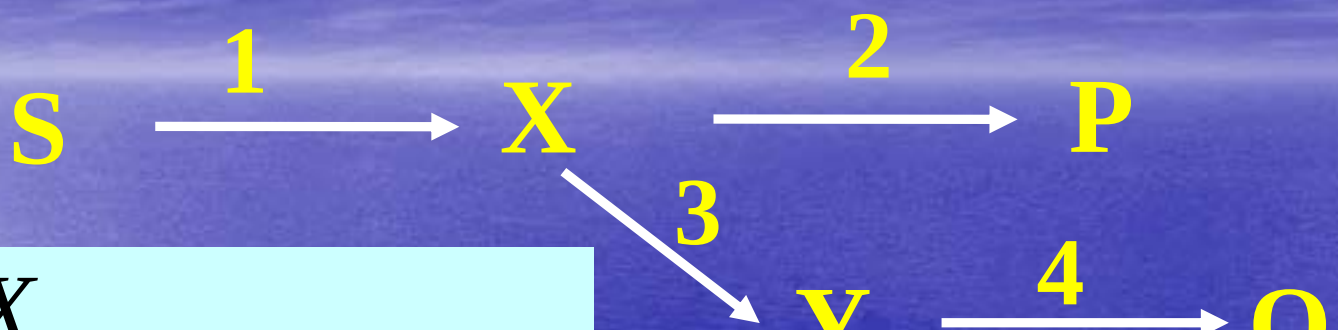
MANCHESTER 1824

Ein Gedanken Experiment

A thought experiment

Intuitive proof of the summation law

- C^J_1 = the percentage increase in steady state flux if one activates only enzyme 1, keeping all other parameters constant
- $C^J_1 + C^J_2$ = the percentage increase in steady state flux if one activates both enzyme 1 and enzyme 2 by 1 %, keeping all other parameters constant
- $C^J_1 + C^J_2 + C^J_3 + \ldots + C^J_n$ = the percentage increase in steady state flux if one activates all enzymes by 1 %, keeping all other parameters constant = ????

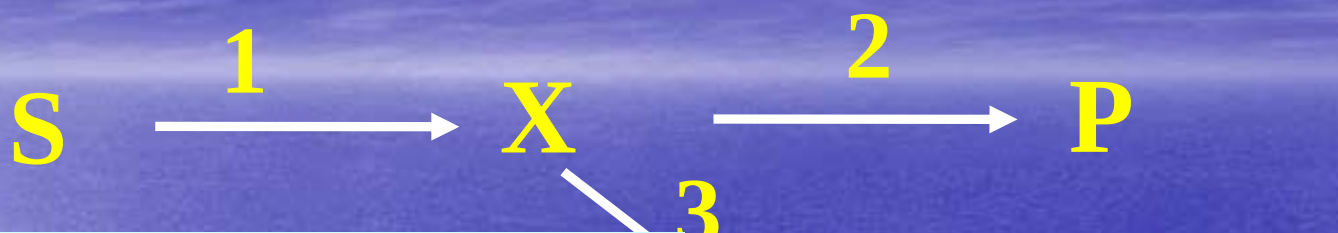


$$\frac{dX}{dt} = v_1 - v_2 - v_3$$

$$\frac{dX}{dt} = 100 - 70 - 30 = 0$$

$$\frac{dX}{dt} = 110 - 77 - 33 = ?$$

Cf. Ursula Kummer, Frank Bruggeman



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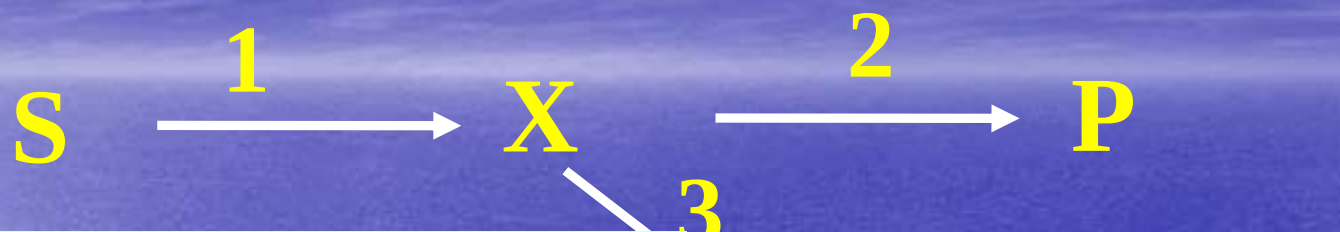

$$\frac{dX}{dt} = v_1 - v_2 - v_3$$

$$\frac{dX}{dt} = 100 - 70 - 30 = 0$$

$$\frac{dX}{dt} = 110 - 77 - 33 = 0$$

Steady state is established immediately

No change in [X]

Same percentage change in fluxes

Laws of Systems Biology: summation law for flux control...and..

$$C_1^J + C_2^J + C_3^J + C_4^J = \frac{10\%}{10\%} = 1$$

Laws of Systems Biology: summation law for flux control...and.. concentration control

$$C_1^J + C_2^J + C_3^J + C_4^J = \frac{10\%}{10\%} = 1$$

$$C_1^X + C_2^X + C_3^X + C_4^X = \frac{0\%}{10\%} = 0$$

Laws of Systems Biology: summation law for flux control...and.. concentration control... and noise control

$$C_1^J + C_2^J + C_3^J + C_4^J = \frac{10\%}{10\%} = 1$$

$$C_1^{\sigma_x} + C_2^{\sigma_x} + C_3^{\sigma_x} + C_4^{\sigma_x} = \frac{0\%}{10\%} = 0$$

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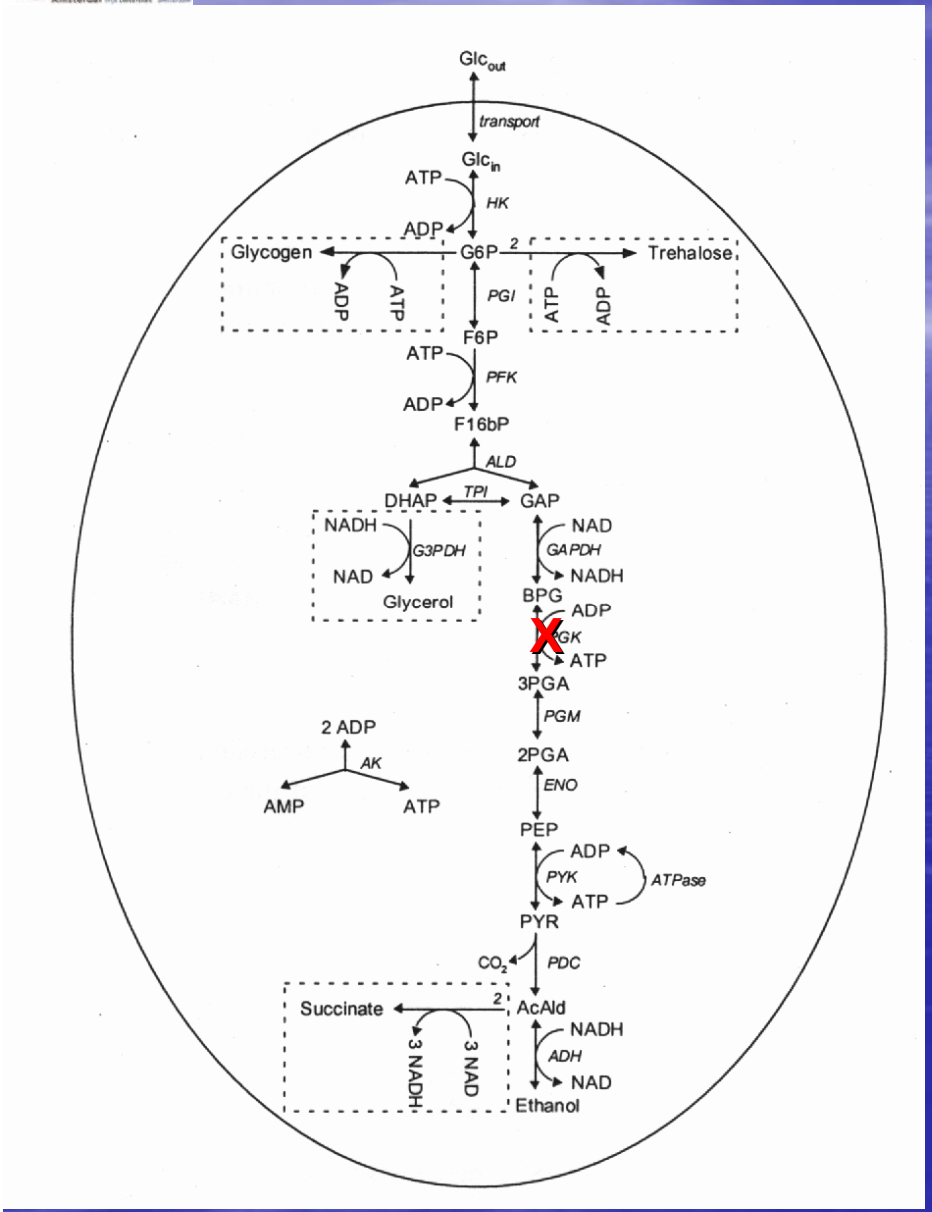
To understand robustness / health

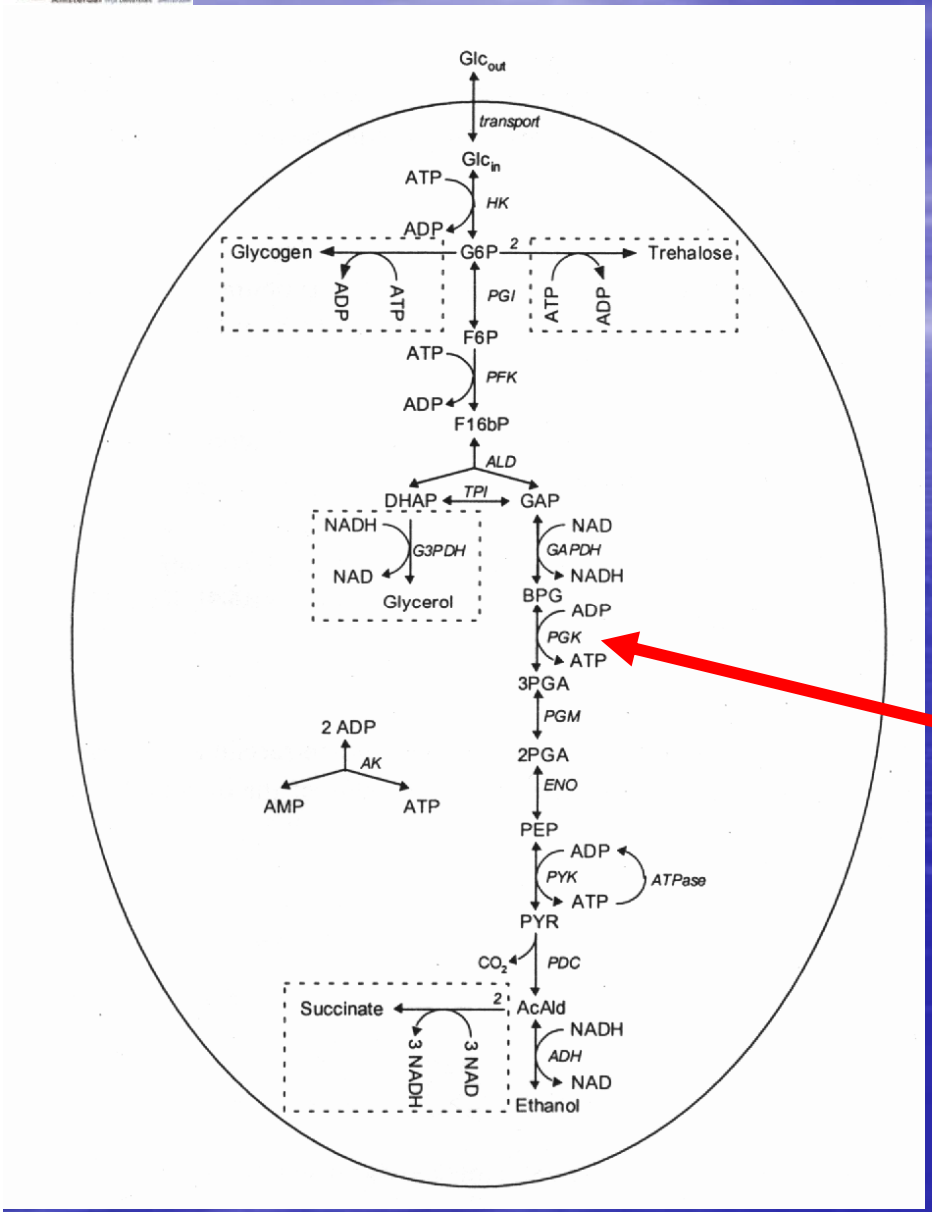
We need a definition of robustness / health



Example:

Robustness of the flux

When enzyme activities are eliminated



Example:

Robustness of the flux

When enzyme activities are eliminated

When enzyme activities are perturbed

Definition of robustness

In the tutorial

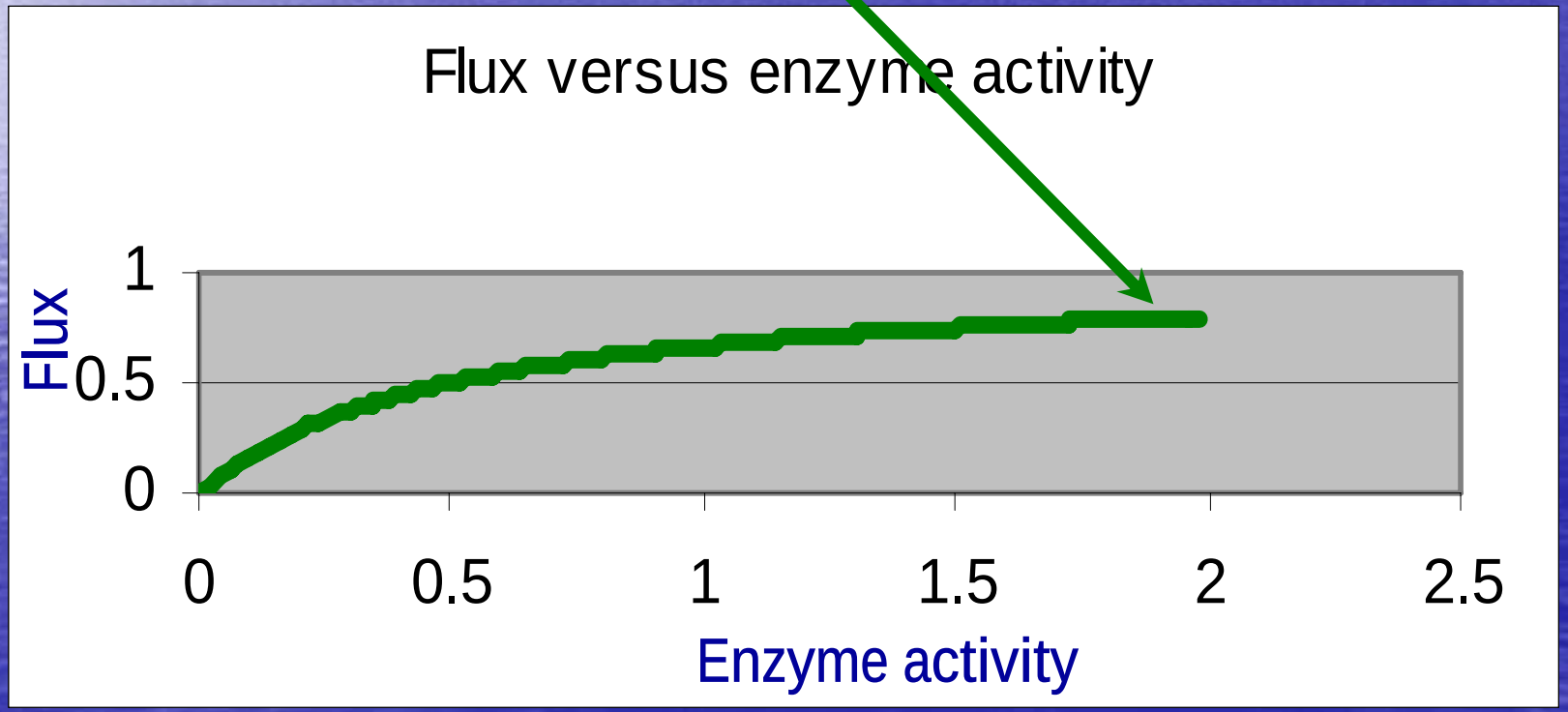
Coffee & tutorial time!

Definition of robustness vis-a-vis a perturbation

How robust is a function with respect to a perturbation in a property?

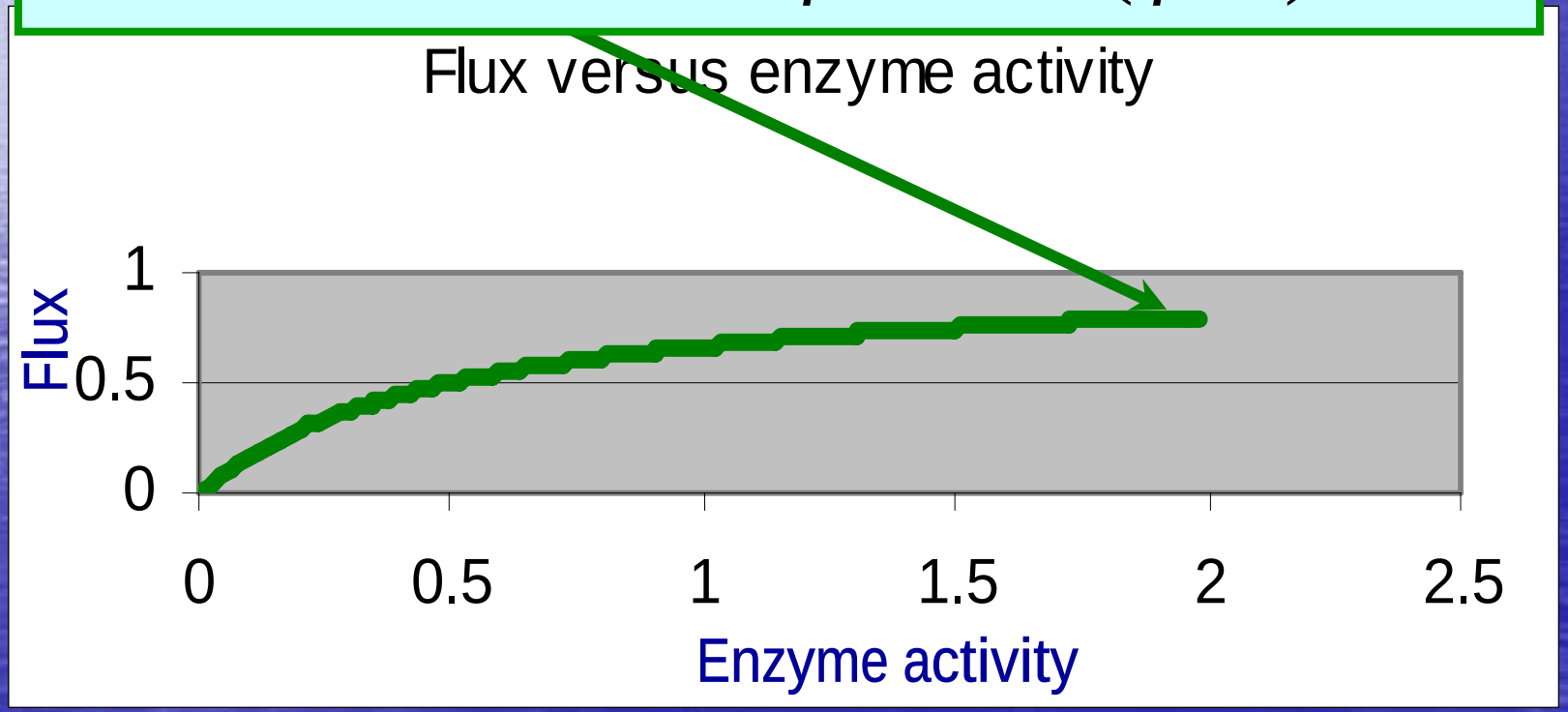
By what percentage can I perturb that function and change system function by only 1 %?

An example of robustness



An example of robustness

$$\Re_{e_i}^{J} \equiv \frac{5\%\ decrease\ in\ enzyme\ activity}{1\%\ decrease\ in\ \ function\ (\ flux)\ J} = 5$$



An example of robustness

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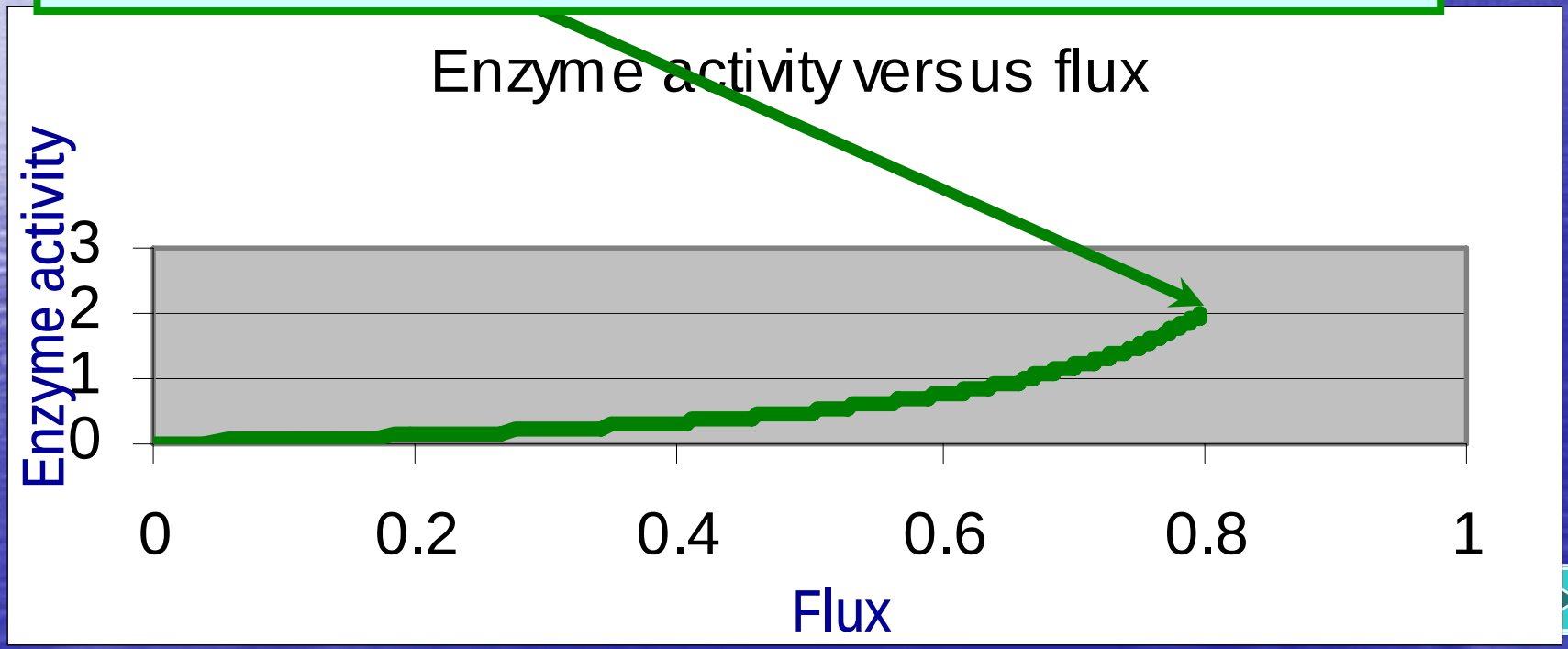
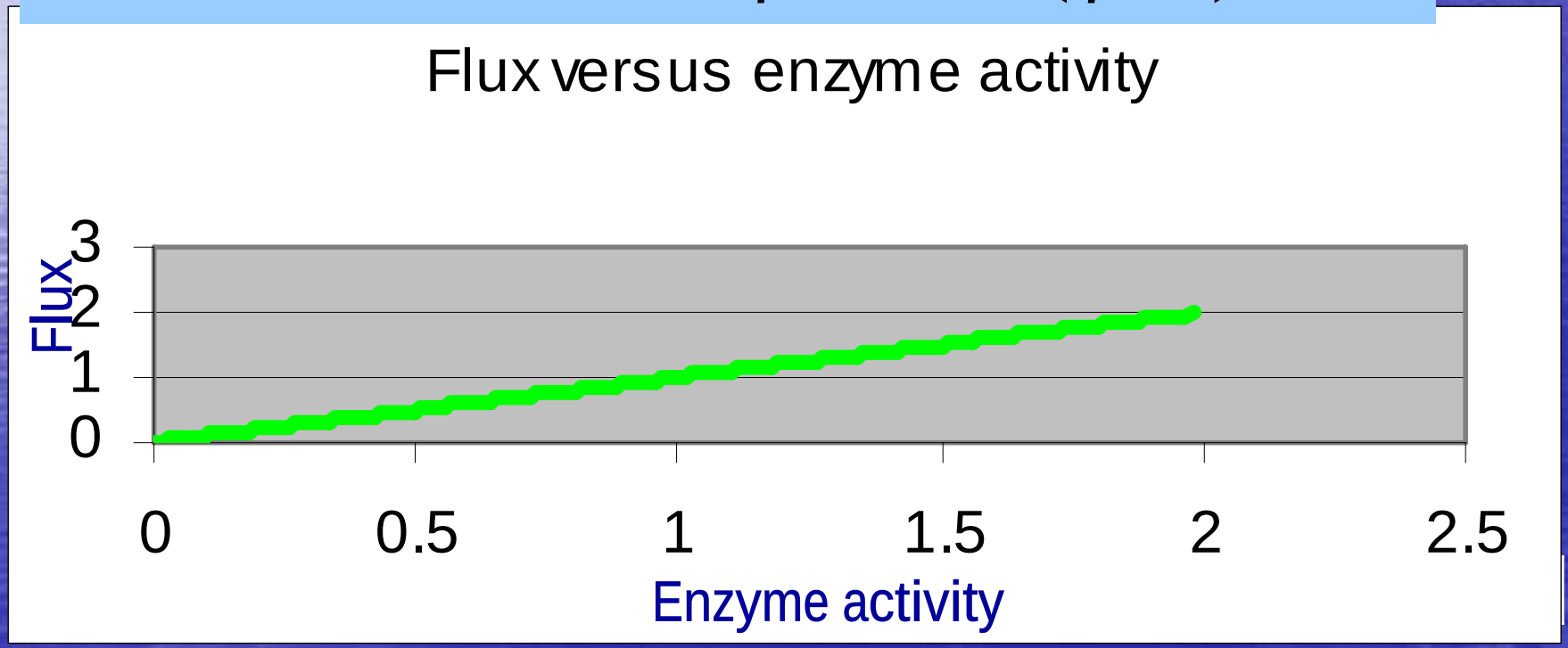


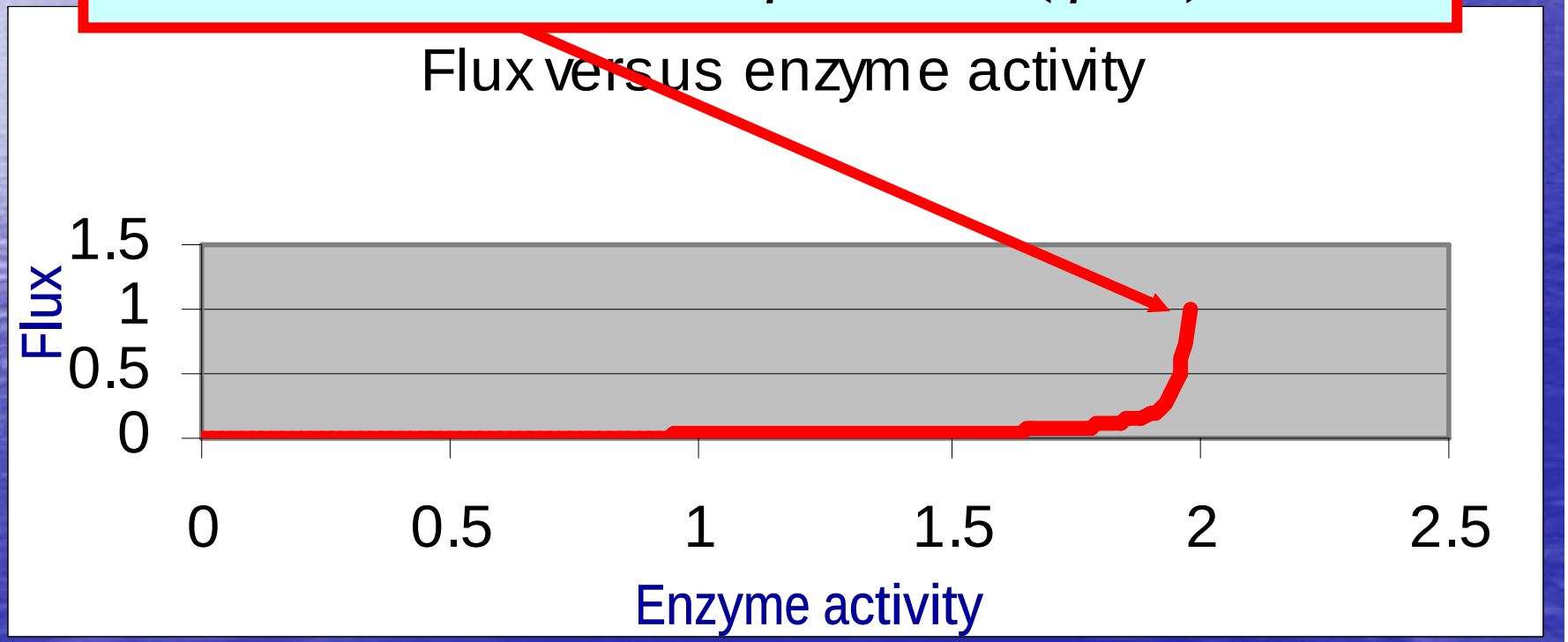
Low robustness of processes in isolation

$$\Re_{e_i}^{J} \equiv \frac{1\%\ decrease\ in\ enzyme\ activity}{1\%\ decrease\ in\ \ function\ (\ flux)\ J} = 1$$



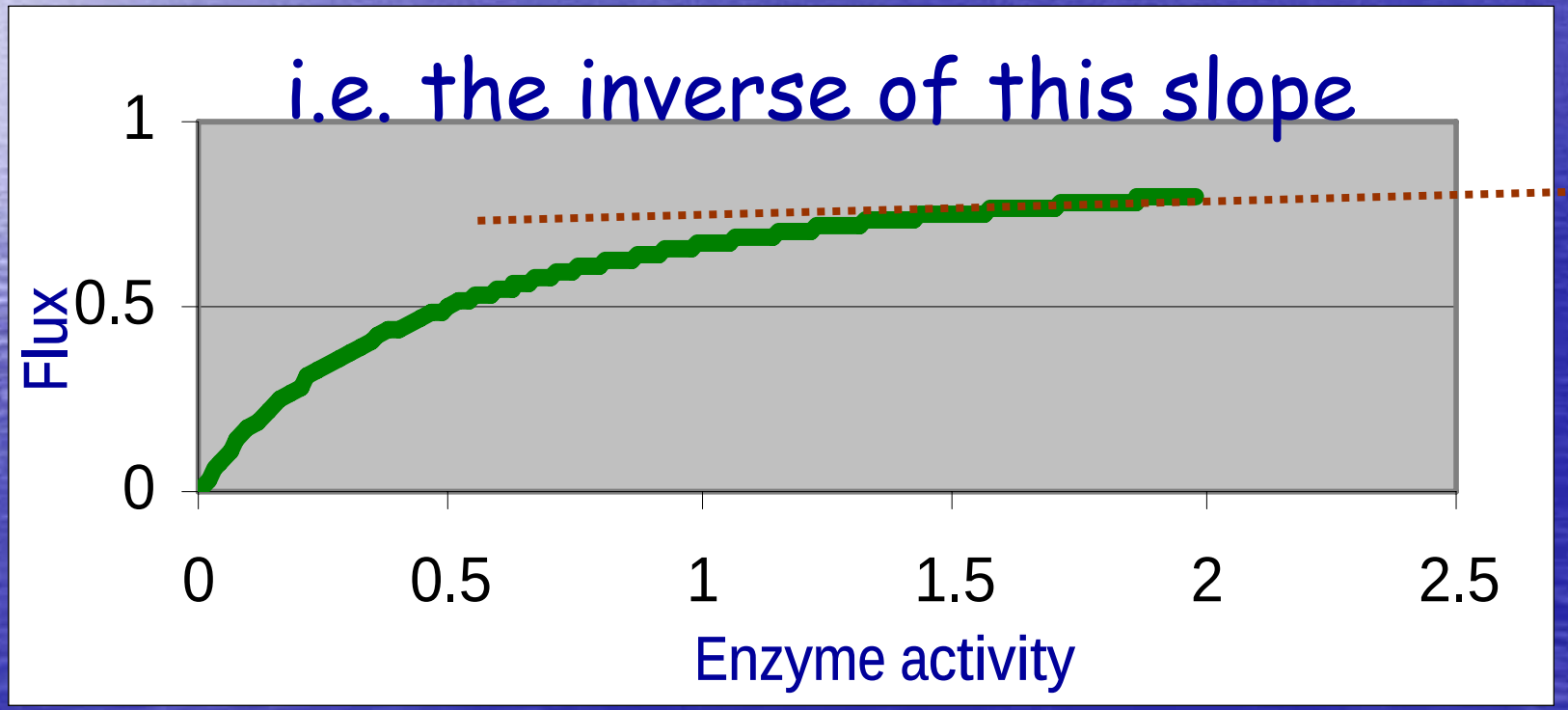
An example of lack of robustness (fragility)

$$\Re_{e_i}^{J} \equiv \frac{0.1\%\ decrease\ in\ enzyme\ activity}{1\%\ decrease\ in\ \ function\ (\ flux)\ J} = 0.1$$

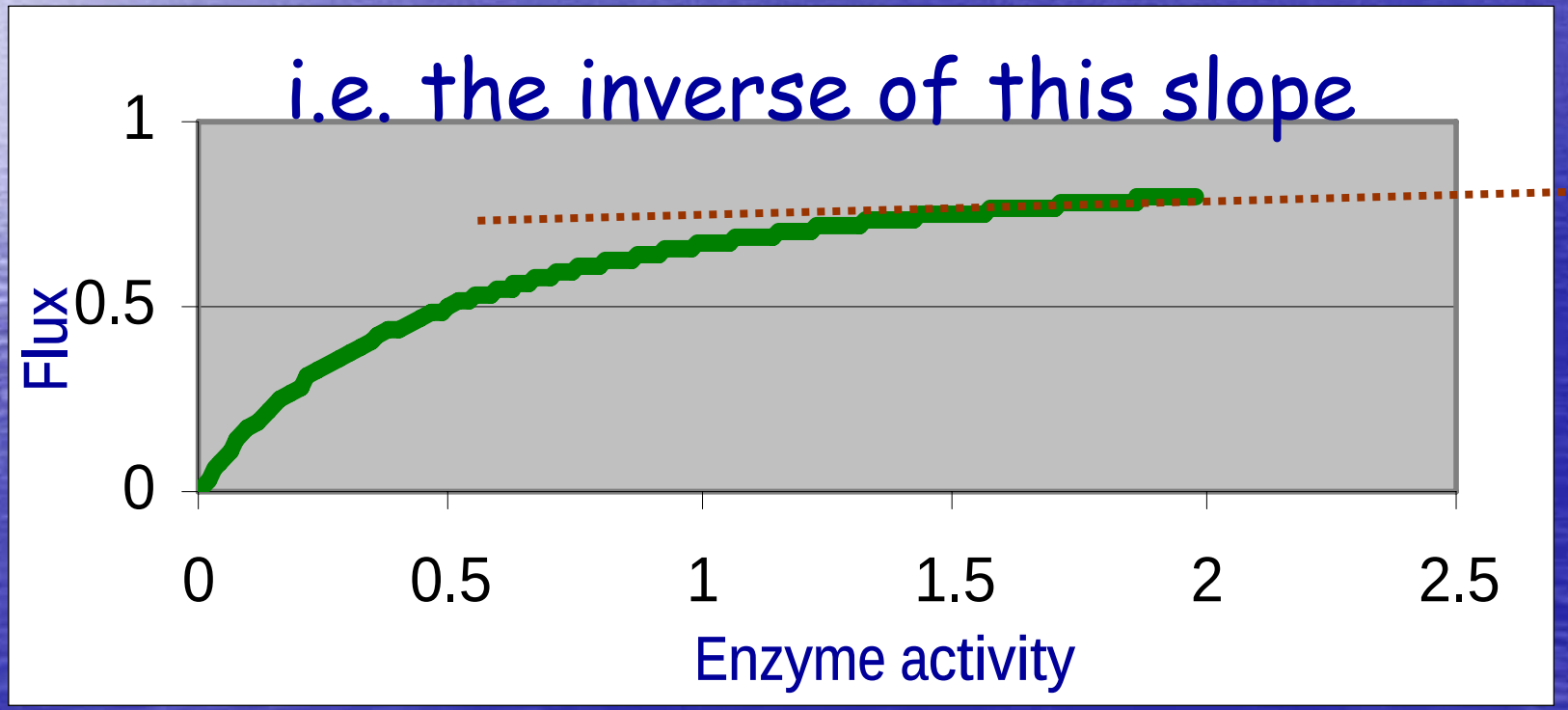


More precise definition of robustness

$$\Re_{e_i}^{function_j} \equiv \left(\frac{\partial enzyme_i / enzyme_i}{\partial function_j / function_j} \right)_{all\ other\ parameters} = \left(\frac{\partial \ln enzyme_i}{\partial \ln function_j} \right)_{all\ other\ parameters} = 1/\left(\frac{\partial \ln function_j}{\partial \ln enzyme_i} \right)_{all\ other\ parameters}$$

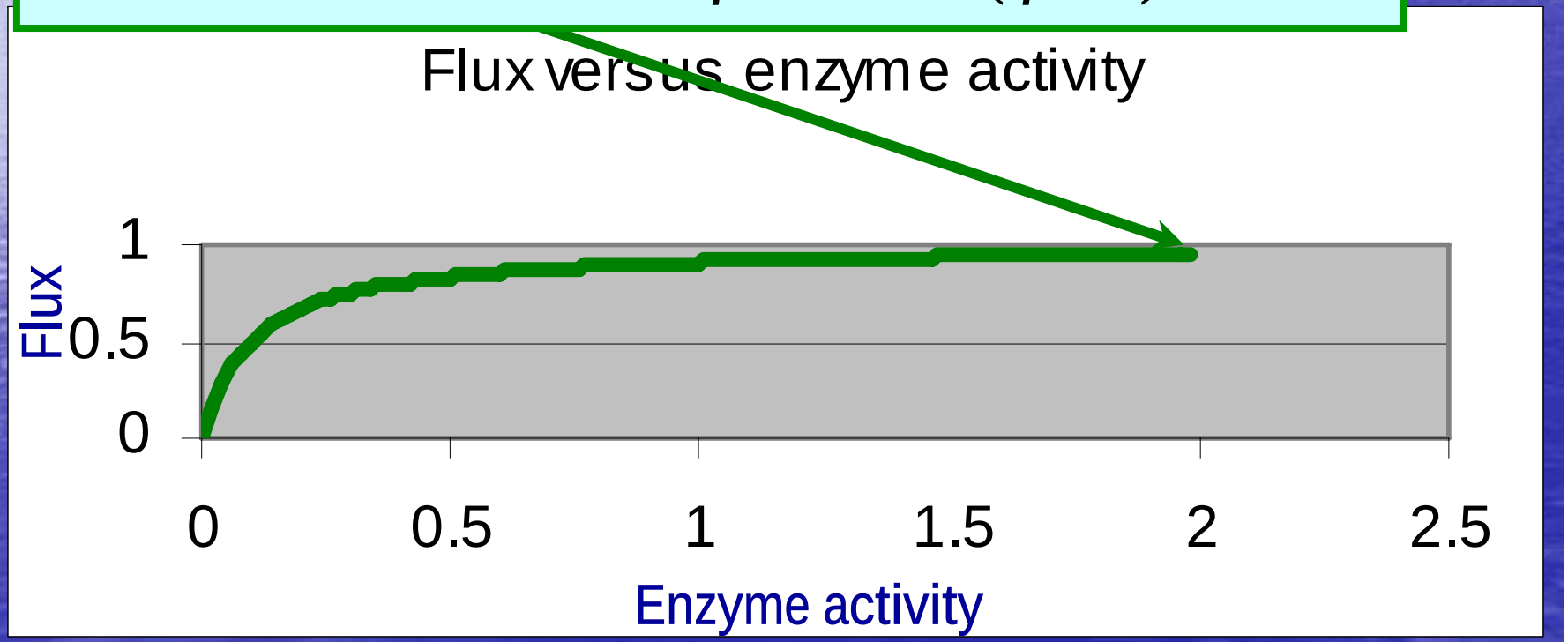


More precise definition of robustness



An example of high robustness

$$\Re_{e_i}^{J} \equiv \frac{23\%\ decrease\ in\ enzyme\ activity}{1\%\ decrease\ in\ \ function\ (\ flux)\ J} = 23$$



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An example of high robustness

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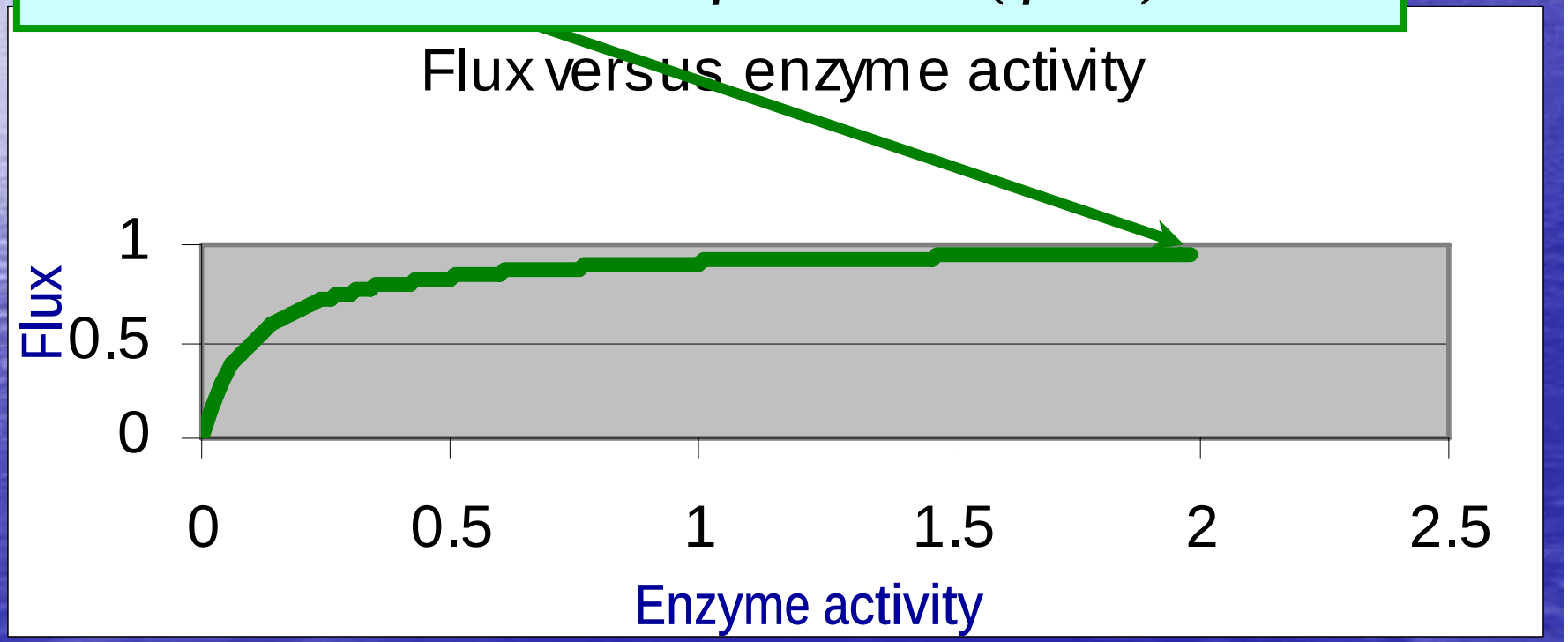
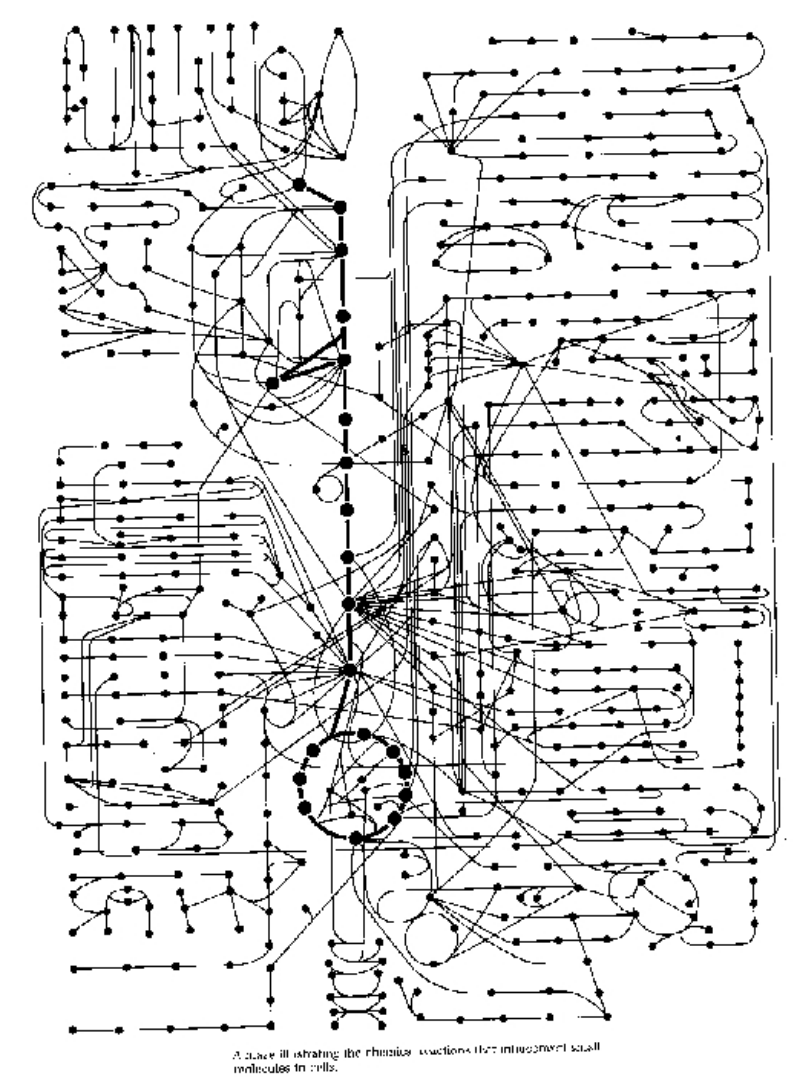


Robustness

- There is more than one definition:
  - John Doyle's/Kitano definition: frequency domain
  - Robustness vis-à-vis gene deletion
  - Guy Shinar: variation of concentration of protein form with total concentration of that protein
  - This one: steady state function with respect to parameters, such as catalytic activities

But cells and tissues may not be classical, e.g. they are networks



We can now calculate this for some cases using the silicon cell

T-L03-Toward the theory of biological robustness and its application to drug design

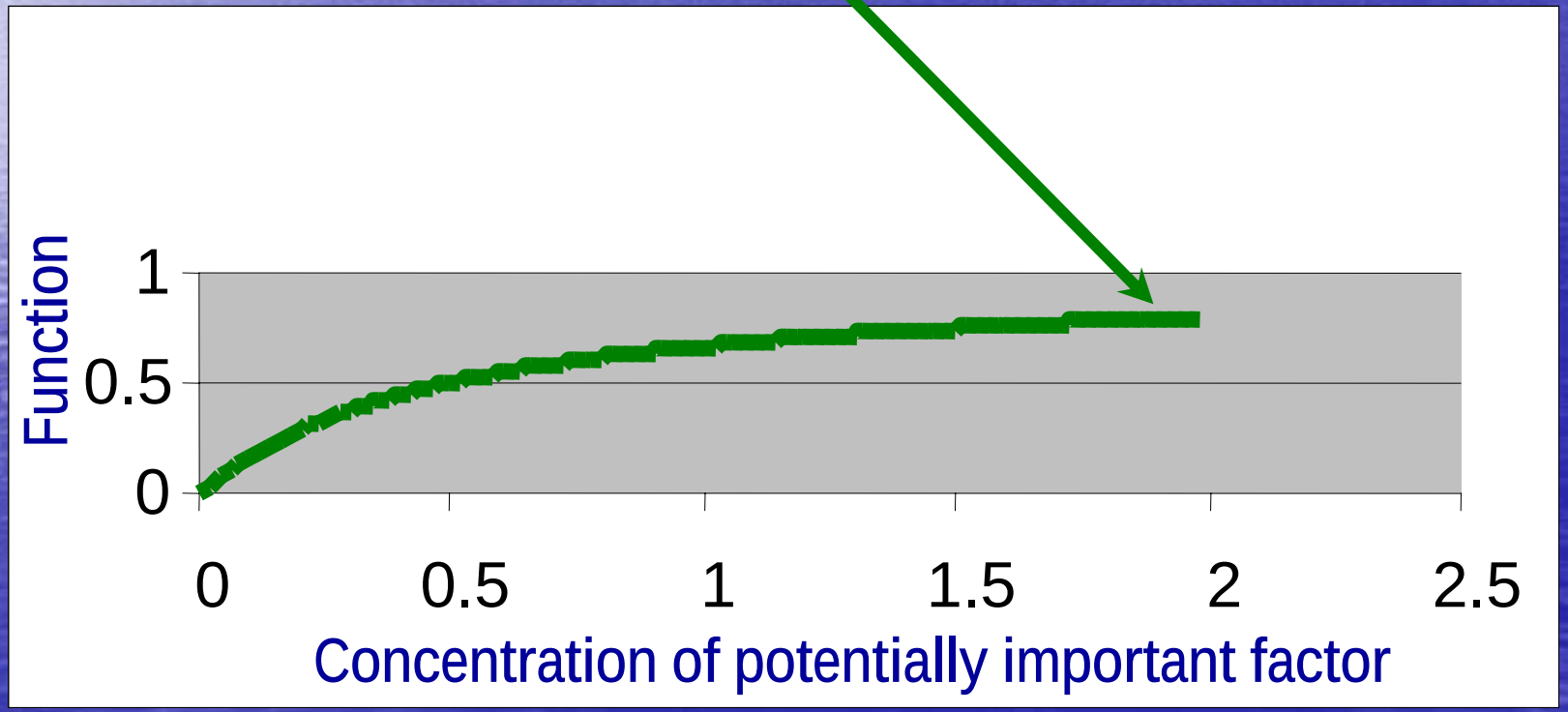
Hiroaki Kitano

Sony Computer Science Laboratories, Inc., The Systems Biology Institute, Department of Cancer Systems Biology, The Cancer Institute

Robustness is a ubiquitously observed property of biological systems. It is considered to be a fundamental feature of complex evolvable systems. It is attained by several underlying principles that are universal to both biological organisms and sophisticated engineering systems. Robustness facilitates evolvability and robust traits are often selected by evolution. Such a mutually beneficial process is made possible by specific architectural features observed in robust systems. But there are trade-offs between robustness, fragility, performance and resource demands, which explain system behaviour, including the patterns of failure. Insights into inherent properties of robust systems will provide us with a better understanding of complex diseases and a guiding principle for therapy design.

Many potential drugs that target causative disease genes have been found to be less effective than hoped, or to cause significant side-effects. The intrinsic robustness of living systems against various perturbations is a key factor that prevents such compounds from being successful. By studying complex network systems and reformulating control and communication theories that are well established in engineering, a solid theoretical foundation for a system to control the robustness of living systems, particularly at the cellular level, could be developed. Here, I use examples from drugs currently on the market to illustrate the concept of robustness and then discuss how greater consideration of the importance of robustness could influence the design of drugs that are ultimately intended to control complex systems.

An example of robustness

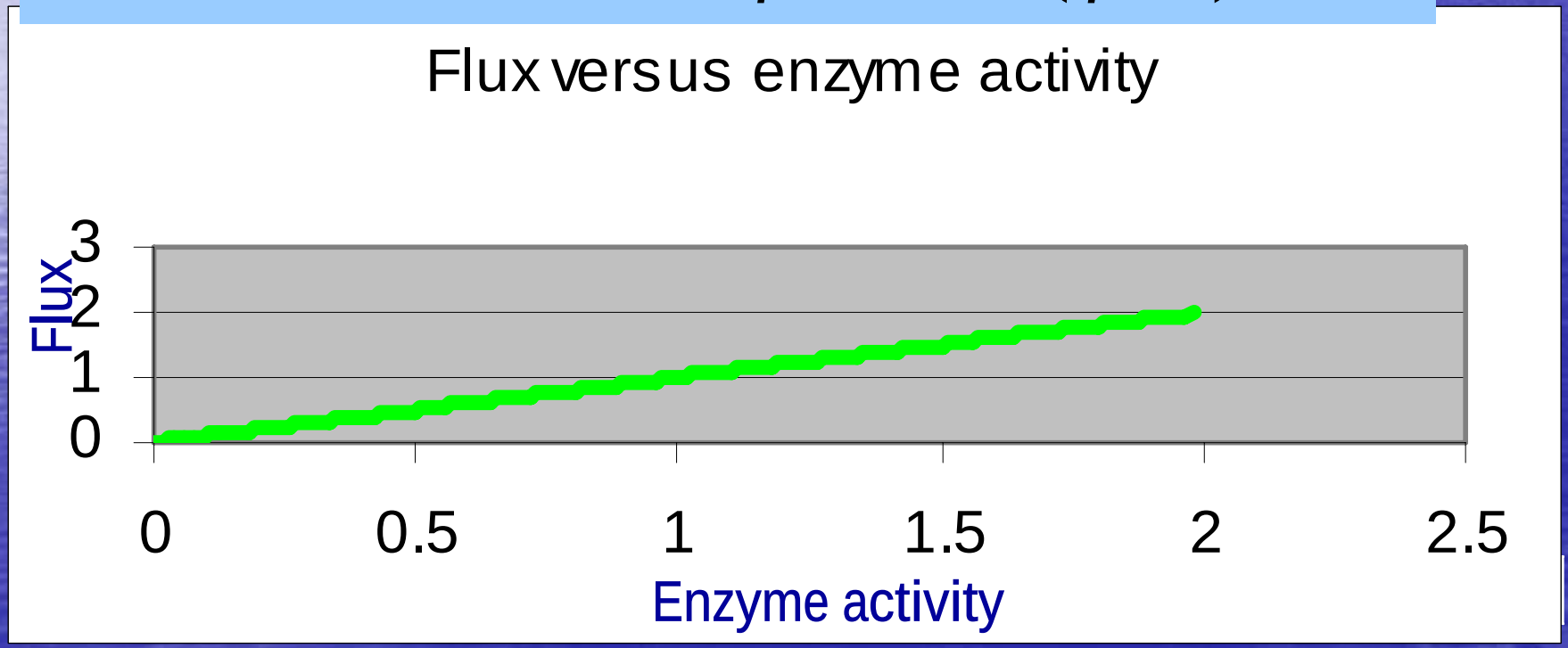


Definition of robustness

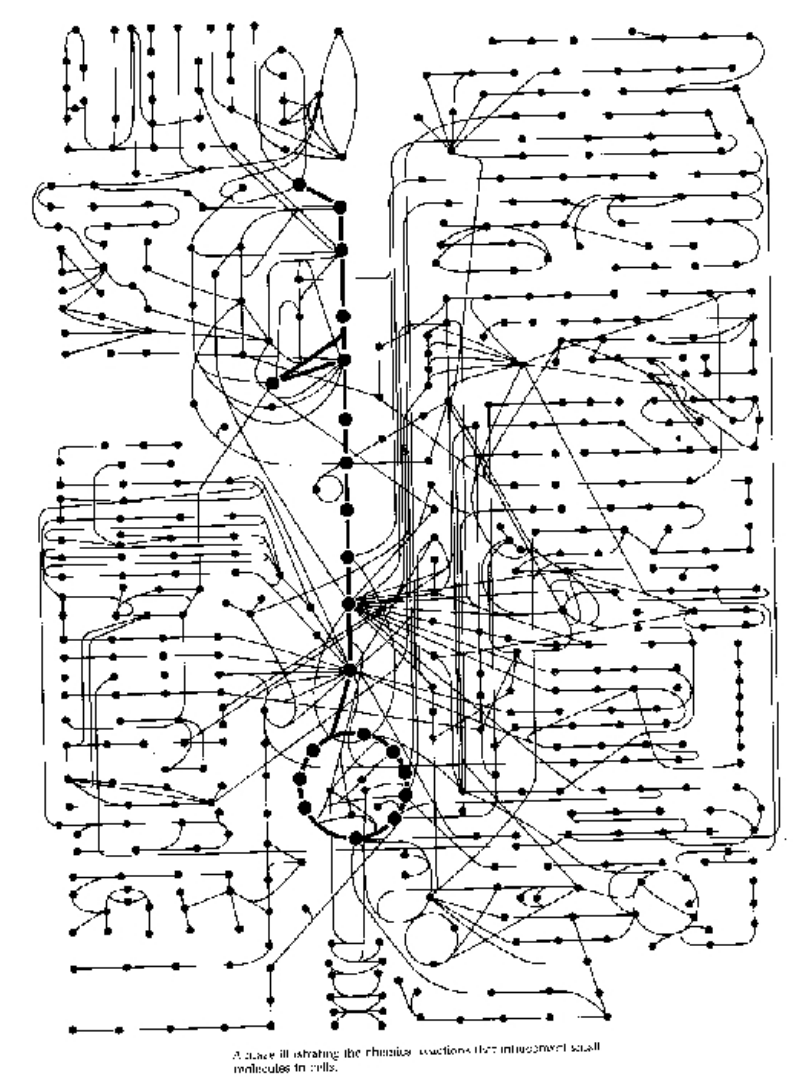
By what percentage can I perturb a component process of the system and affect system function by only 1 %?

Processes in isolation have a robustness of 1

$$\Re_{e_i}^{J} \equiv \frac{1\%\ decrease\ in\ enzyme\ activity}{1\%\ decrease\ in\ \ function\ (\ flux)\ J} = 1$$

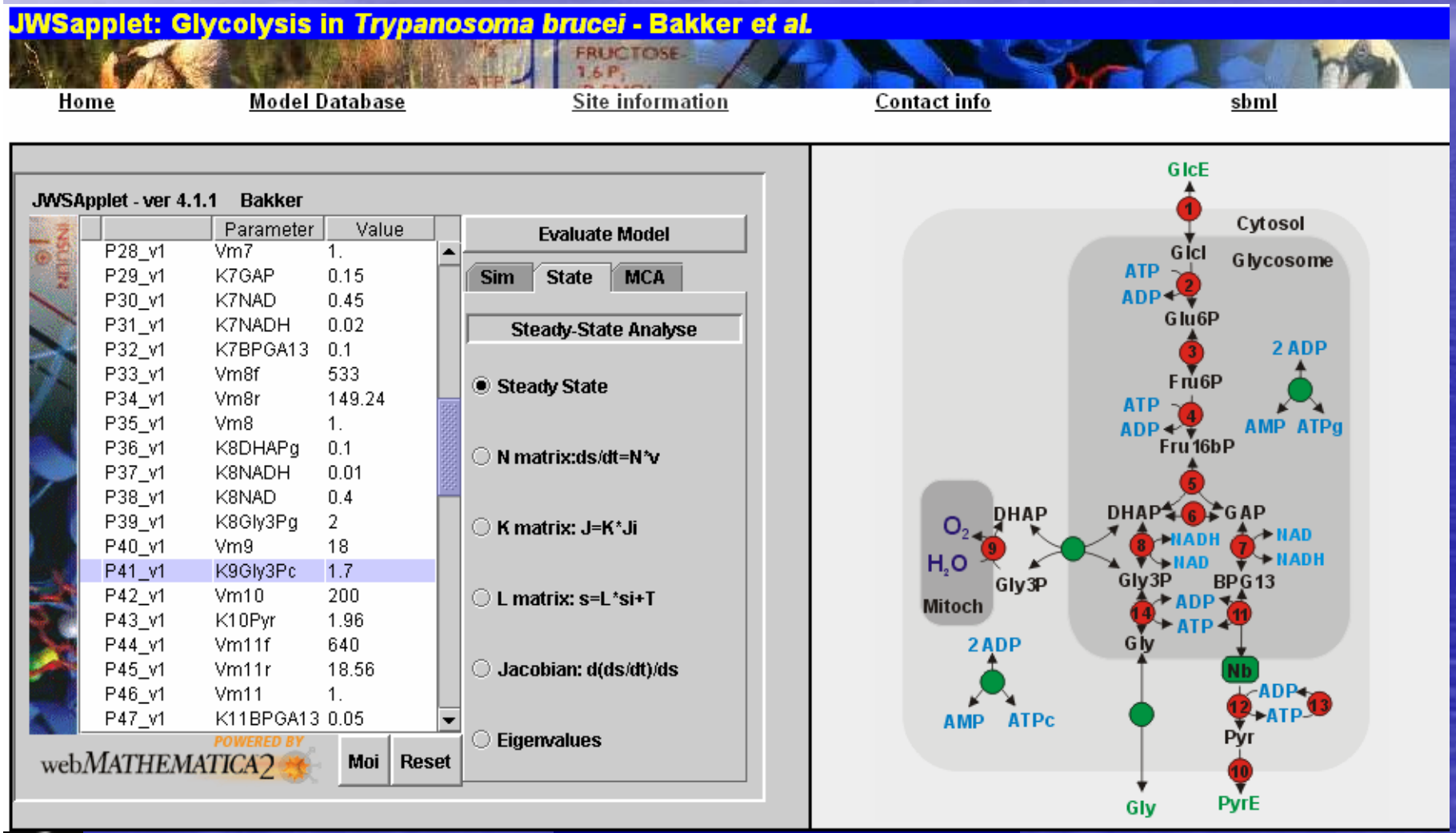


Cells and tissues are systems



Let us see whether they tend to be more robust than processes in isolation

Silicon cell live models: jjj.bio.vu.nl



Assignments

1. Calculate robustnesses for silicon cell flux with respect to reactions
2. Add them up
3. Vary one of the activities
4. Do the same
5. Is total robustness constant?
6. Take the inverses.
7. Repeat

Middle part: tutorial

- Calculating robustness ☑
- Falsifying proposed constant robustness ☑
- Searching for new theorems ☑
- How to enhance robustness; a paradoxical principle ☑

Third part: results

- Are biochemical networks robust?
- Is robustness conserved ?
- ..... is conserved
- Robustness through fragility
- Robustness and signal transduction
- Robustness as disease

End of tutorial

T-L03-Toward the theory of biological robustness and its application to drug design

Hiroaki Kitano

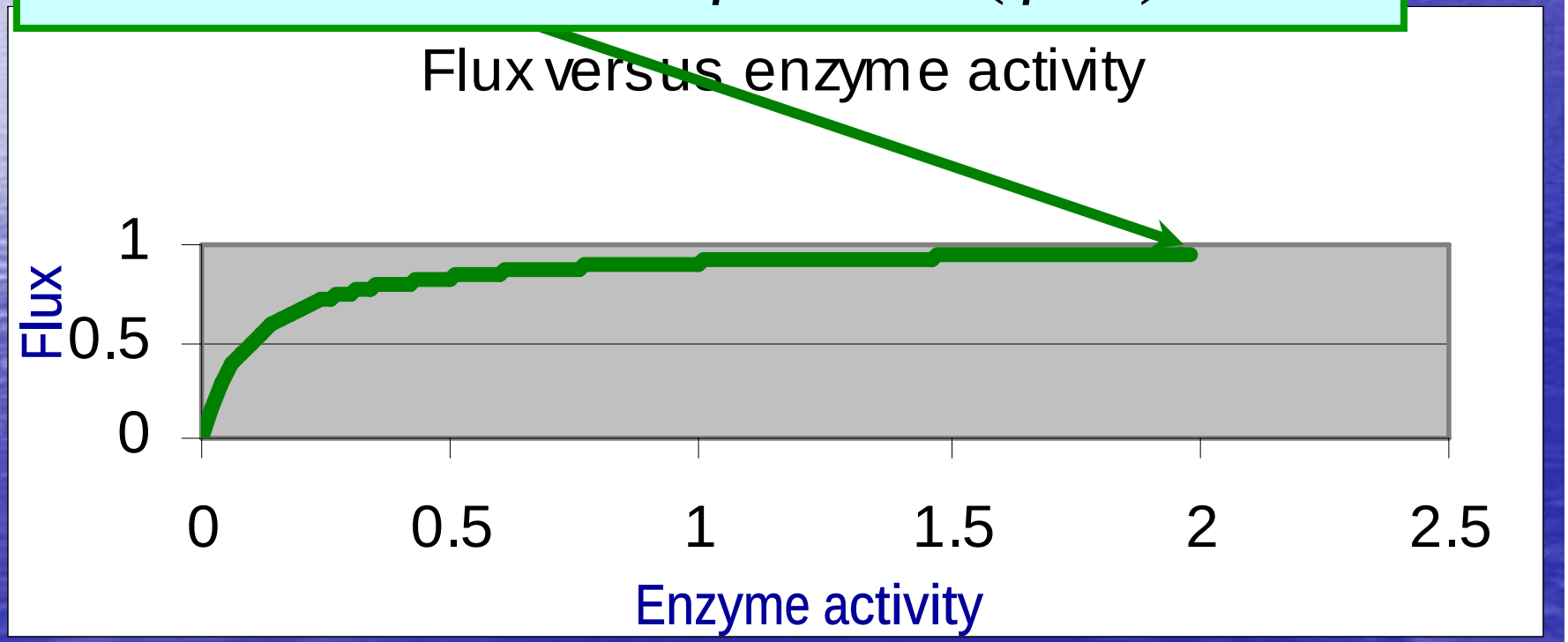
Sony Computer Science Laboratories, Inc., The Systems Biology Institute, Department of Cancer Systems Biology, The Cancer Institute

Robustness is a ubiquitously observed property of biological systems. It is considered to be a fundamental feature of complex evolvable systems. It is attained by several underlying principles that are universal to both biological organisms and sophisticated engineering systems. Robustness facilitates evolvability and robust traits are often selected by evolution. Such a mutually beneficial process is made possible by specific architectural features observed in robust systems. But there are trade-offs between robustness, fragility, performance and resource demands, which explain system behaviour, including the patterns of failure. Insights into inherent properties of robust systems will provide us with a better understanding of complex diseases and a guiding principle for therapy design.

Many potential drugs that target causative disease genes have been found to be less effective than hoped, or to cause significant side-effects. The intrinsic robustness of living systems against various perturbations is a key factor that prevents such compounds from being successful. By studying complex network systems and reformulating control and communication theories that are well established in engineering, a solid theoretical foundation for a system to control the robustness of living systems, particularly at the cellular level, could be developed. Here, I use examples from drugs currently on the market to illustrate the concept of robustness and then discuss how greater consideration of the importance of robustness could influence the design of drugs that are ultimately intended to control complex systems.

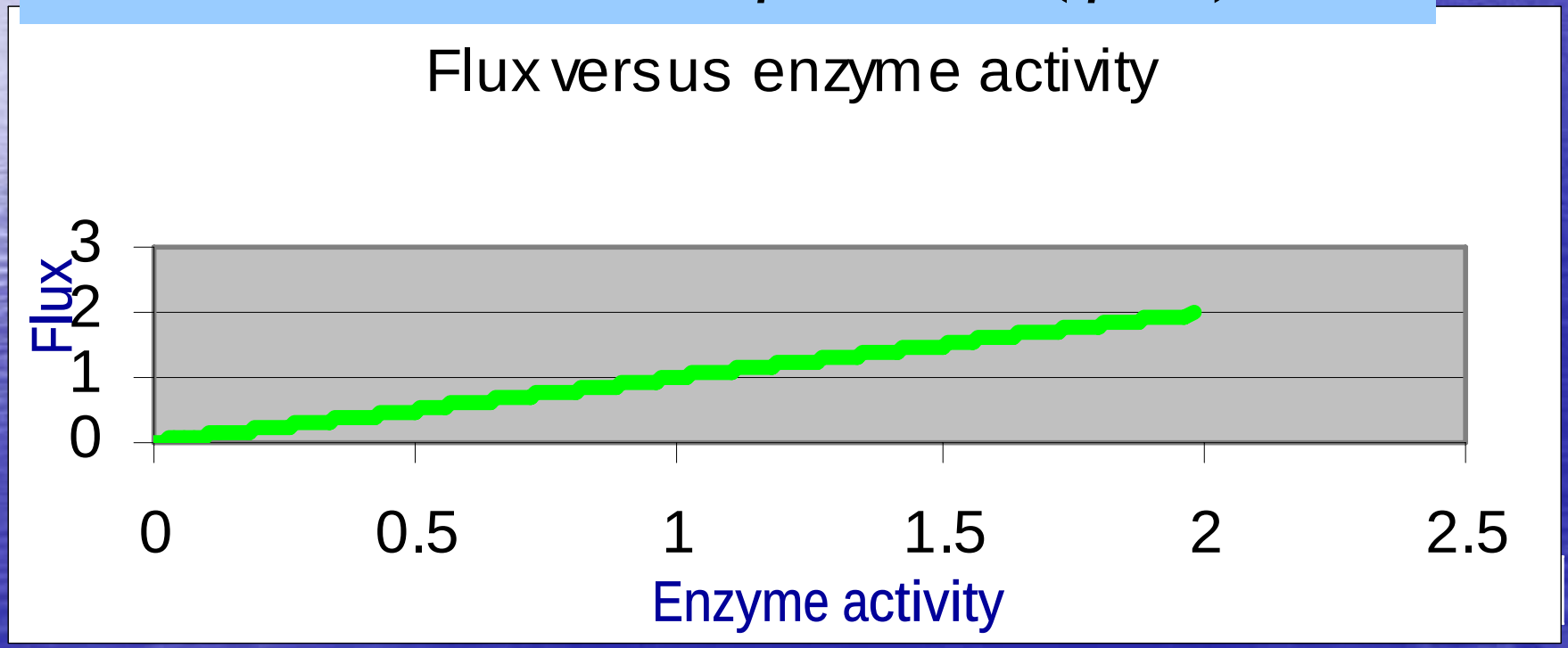
An example of high robustness

$$\Re_{e_i}^{J} \equiv \frac{23\%\ decrease\ in\ enzyme\ activity}{1\%\ decrease\ in\ \ function\ (\ flux)\ J} = 23$$



Processes in isolation have a robustness of 1

$$\Re_{e_i}^{J} \equiv \frac{1\%\ decrease\ in\ enzyme\ activity}{1\%\ decrease\ in\ \ function\ (\ flux)\ J} = 1$$



Robustness of vital flux of Trypanosomes vis-à-vis perturbations of glycolytic steps

step	Robustness
Glctr	1.1
GAPdh	42
HK	42
PGI	1546
PFK	234
ALD	38
TPI	482
GDH	66
GPO	-251
PGK	61
PK	691
ATPase	2744
GlyK	389
Sum	**6085**

Average robustness = 470 >>>1

Networking increases robustness

470 fold in this case

Third part: results

- Biochemical networks are highly robust 
- Is robustness conserved ?
- ..... is conserved
- Robustness through fragility
- Robustness and signal transduction
- Robustness as disease

Is robustness conserved?

Does total robustness remain constant when system is made more robust vis-à-vis perturbation of one of its steps?

Total robustness is not conserved

step		double glucose transporter
Glucose transport	1.1	87.8
GAPdh	42	4
HK	42	20
PGI	1546	412
PFK	234	56
ALD	38	3
TPI	482	64
GDH	66	6
GPO	-251	-15
PGK	61	7
PK	691	73
ATPase	2744	313
GlyK	389	26
Sum	**6085**	**1055**

Robustness is *not* constant

Third part: results

- Biochemical networks are highly robust 
- Robustness is not conserved ? 
- ..... is conserved
- Robustness through fragility
- Robustness and signal transduction
- Robustness as disease

Robustness is not conserved

But fragility is

Sum over all fragilities=inverse robustnesses = 1

step	1/robustness	1/robustness (doubled glc transporter)
Glucose transport	0.887	0.011
GAPdh	0.024	0.249
HK	0.024	0.051
PGI	0.001	0.002
PFK	0.004	0.018
ALD	0.026	0.354
TPI	0.002	0.016
GDH	0.015	0.166
GPO	-0.004	-0.068
PGK	0.016	0.144
PK	0.001	0.014
ATPase	0	0.003
GlyK	0.003	0.039
Sum	**0.999**	**0.999**

Definition of fragility

$$Fragility \equiv \frac{1}{\Re_{e_i}^{J}} \equiv C_{e_i}^{J}$$

Systems Biology principle concerning robustness

$$\sum_{i=1}^{n} \frac{1}{\Re_{e_i}^{J}} \equiv 1$$

Third part: results

- Biochemical networks are highly robust
- Robustness is not conserved ?
- Fragility is conserved
- Robustness through fragility
- Robustness and signal transduction
- Robustness as disease

Implications

- **If the robustness vis-à-vis an already fragile step is decreased, average robustness may increase**
- **Sacrifice principle: robustness through fragility**

By decreasing robustness vis-à-vis one step one can increase the total robustness

step	Robustness	Robustness double glc transporter
Glctr	1.1	87.8
GAPdh	41.6	4
HK	42.4	19.7
PGI	1545.9	411.5
PFK	233.6	56.2
ALD	38.3	2.8
TPI	481.9	63.7
GDH	65.7	6
GPO	-250.7	-14.8
PGK	61	6.9
PK	691.3	72.6
ATPase	2743.5	313
GlyK	389.4	25.5
Sum	**6085**	**1054.9**

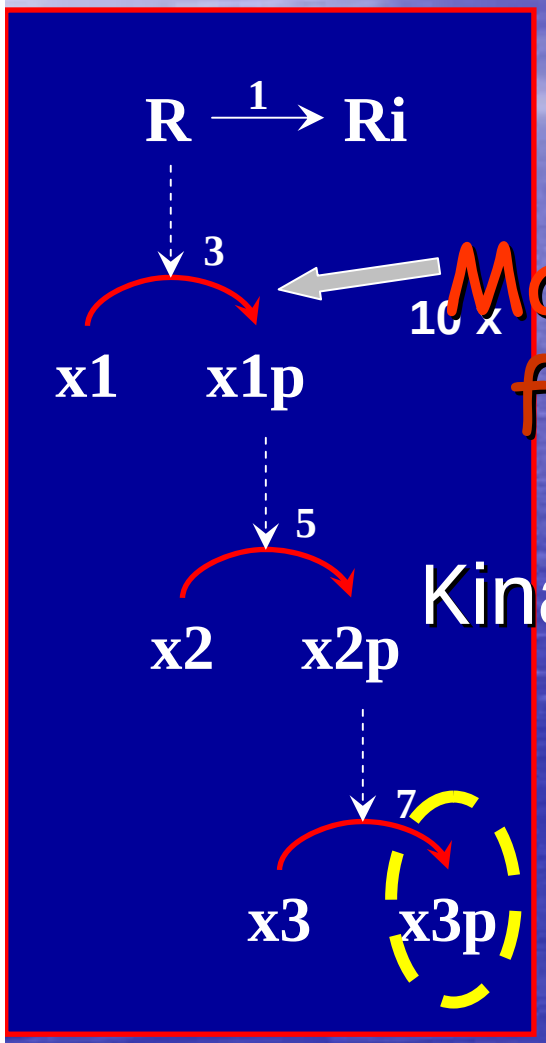
Perhaps this is why robust systems tend to have Achilles heels

....

which should be the better drug targets

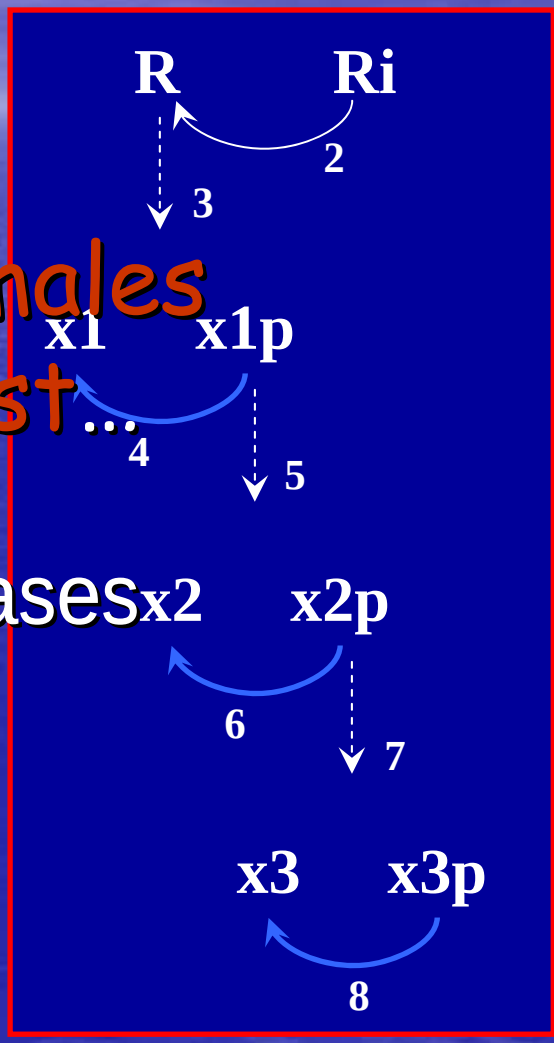
Third part: results

- Biochemical networks are highly robust
- Robustness is not conserved ?
- Fragility is conserved
- Robustness through fragility
- Robustness and signal transduction
- Robustness as disease

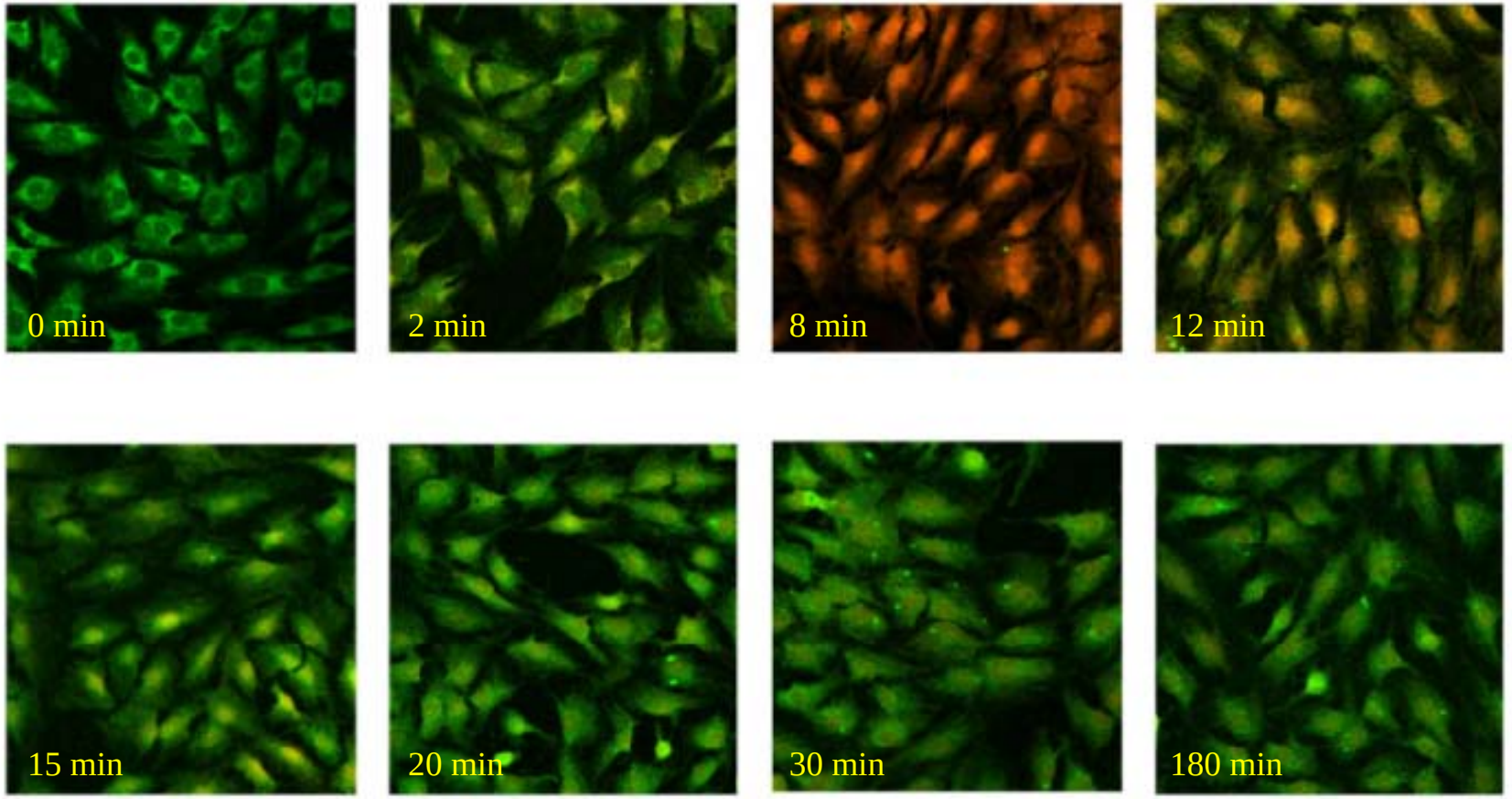


Males versus the females
fragile versus robust...

Kinases versus phosphatases

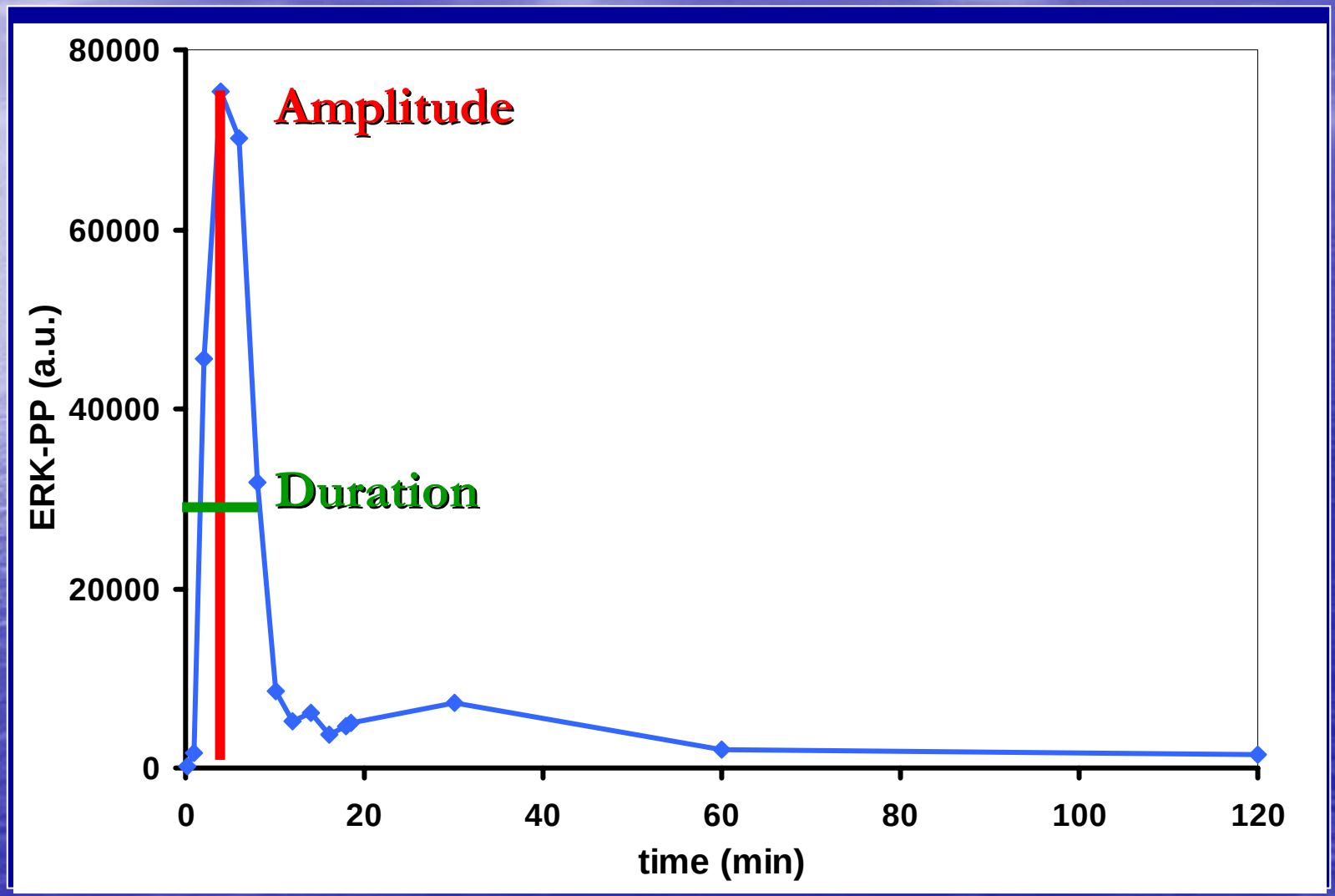


P in single cells upon EGF stimulation



Green: total ERK
Red: ERK-PP

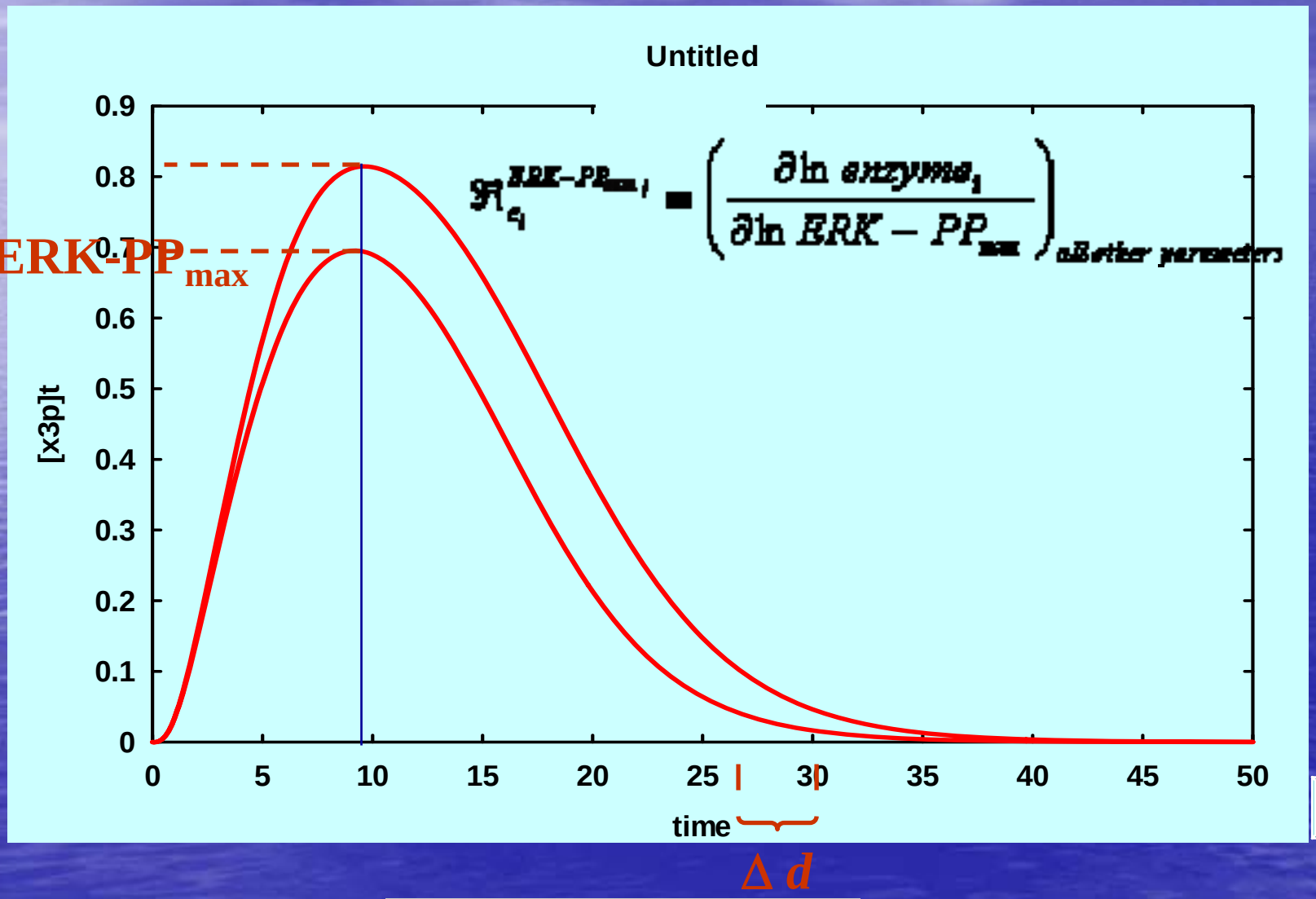
ERK-PP profile upon EGF stimulation



Research questions

- To which perturbations are duration and amplitude robust (fragile)?
- Are these the same perturbations?

Robustness of ERK-PP *vis-à-vis* perturbation



Robustness of ERK-PP amplitude in model MAP kinase pathway: mostly robust

	kinases			phosphatases				Sum
	1	2	3	1	2	3	R	
Amplitude	6	4	2	-7	-5	-3	-6	**-9**

Duration robustness in model MAP kinase pathway

	kinases			phosphatases				Sum
	1	2	3	1	2	3	R	
Amplitude	6	4	2	-7	-5	-3	-6	**-9**
Duration	17	11	8	-2	-3	-3	-8	**20**

33

52

Research questions

- To which perturbations is this signal transduction robust (fragile)? **Most**
- Are these the same perturbations? No

Robustness depends on function considered and is not conserved

	kinases			phosphatases				Sum
	1	2	3	1	2	3	R	
Amplitude	6	4	2	-7	-5	-3	-6	**-9**
Duration	17	11	8	-2	-3	-3	-8	**20**

33

52

Systems Biology principle: total amplitude fragility = conserved and zero

$$\sum_{i=1}^{n} \frac{1}{\Re_{e_i}^{amplitude}} \equiv 0$$

Research questions

- To which perturbations is this signal transduction robust (fragile)? **Most**
- Does robustness differ for the various aspects of the signal? **Yes**

- **Do you believe this?**

Systems Biology principles concerning robustness differ

$$\sum_{i=1}^{n} \frac{1}{\Re_{e_i}^{amplitude}} \equiv 0$$

$$\sum_{i=1}^{n} \frac{1}{\Re_{e_i}^{duration}} \equiv -1$$

Robustness depends on function considered and is not conserved

	kinases			phosphatases				Sum
	1	2	3	1	2	3	R	
Amplitude	6	4	2	-7	-5	-3	-6	**-9**
Duration	17	11	8	-2	-3	-3	-8	**20**

33

52

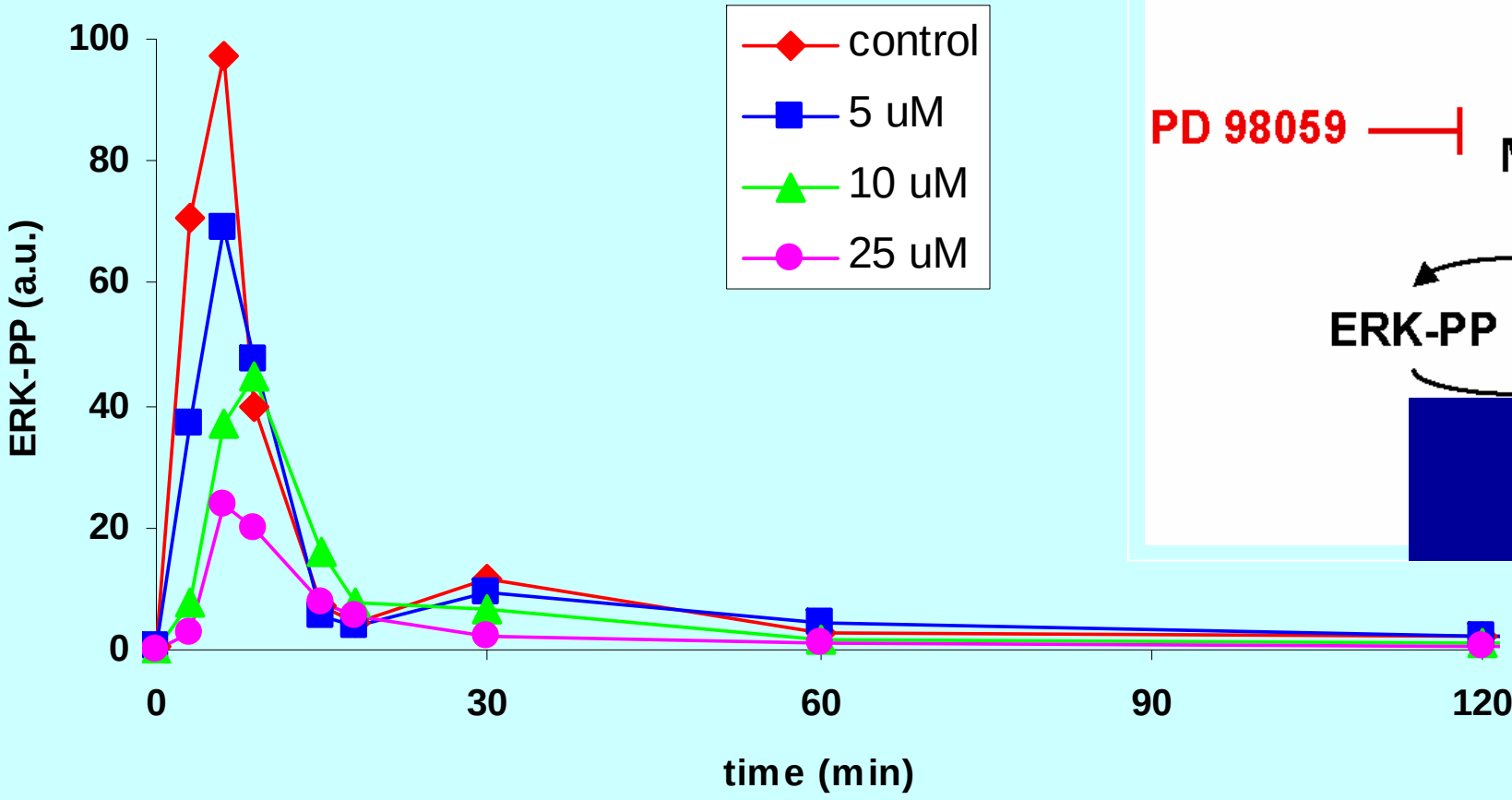
Duration robust *vis-à-vis* kinase perturbation, fragile *vis-à-vis* phosphatase perturbation

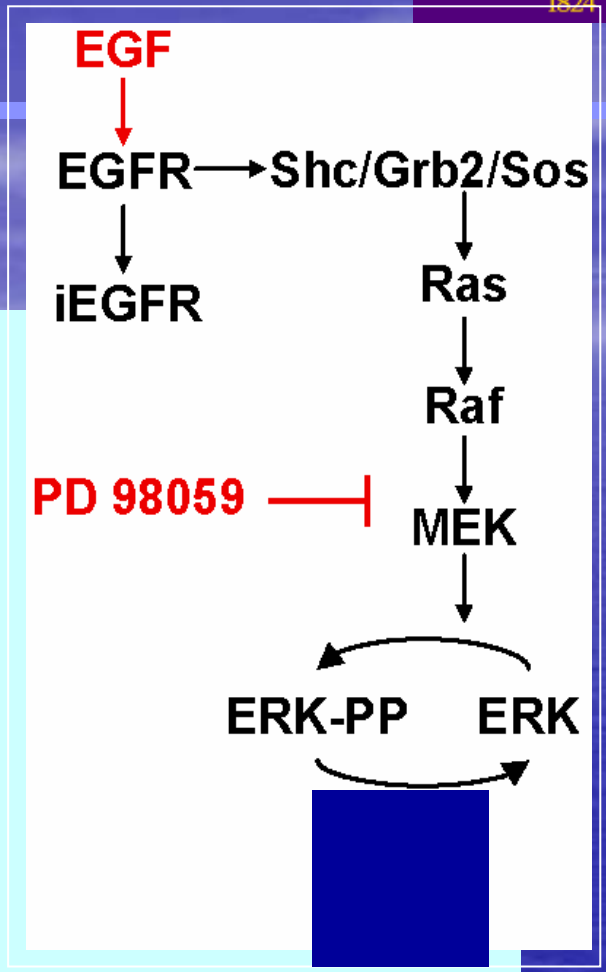
	kinases			phosphatases				**Sum**
	1	2	3	1	2	3	R	
Amplitude	6	4	2	-7	-5	-3	-6	**-9**
Duration	17	11	8	-2	-3	-3	-8	**20**

33

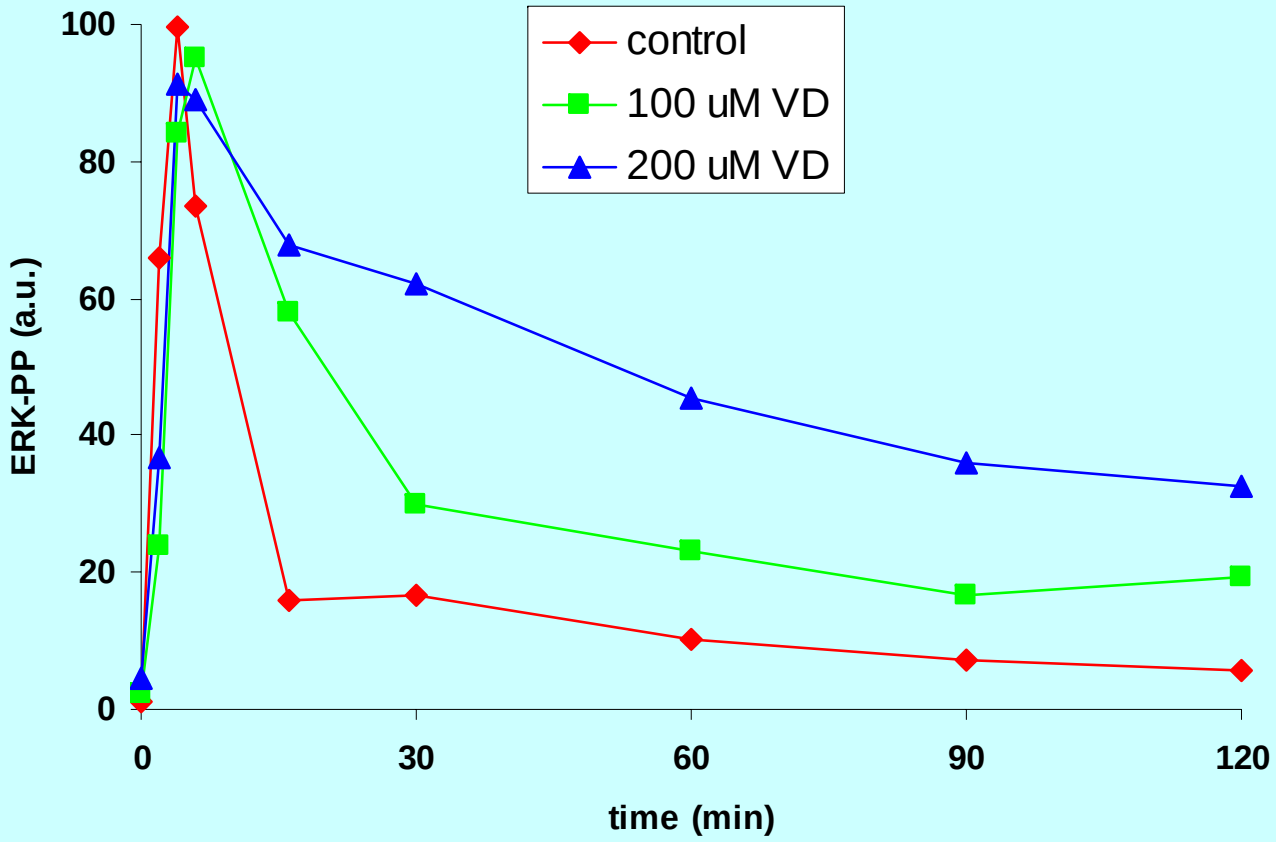
52

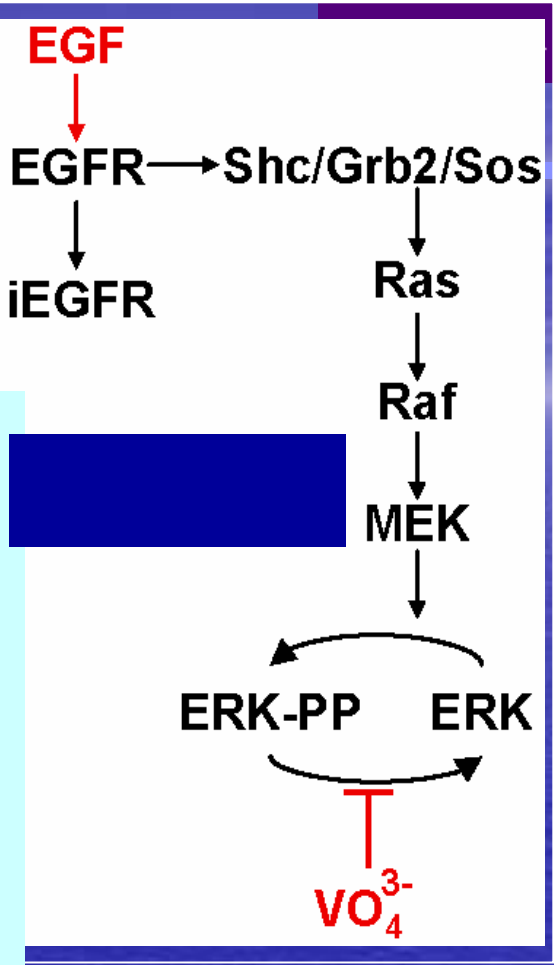
Duration is more robust *vis-à-vis* kinases than vis-à-vis phosphatase perturbation





Duration is more robust *vis-à-vis* kinases than vis-à-vis phosphatase perturbation

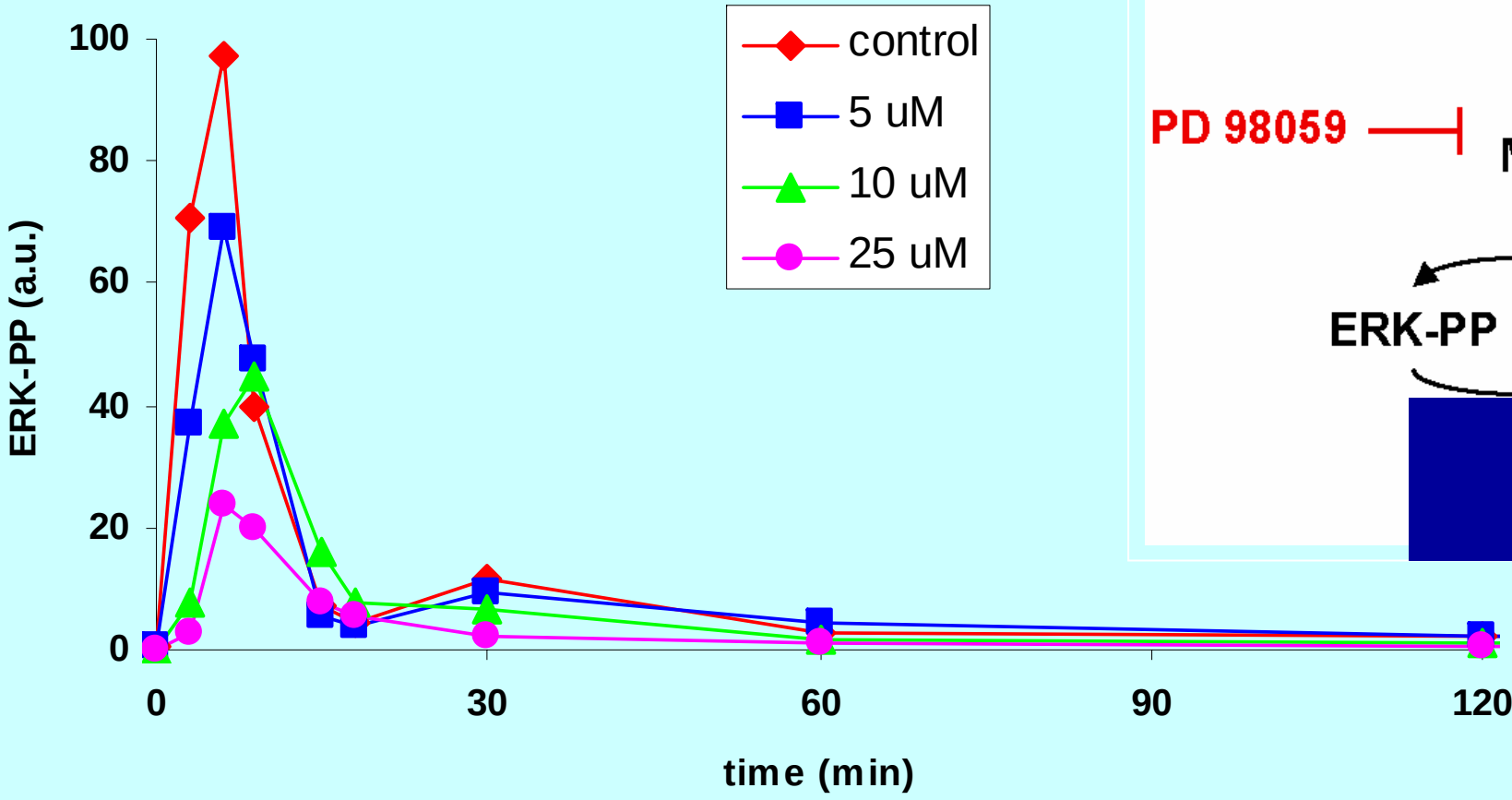


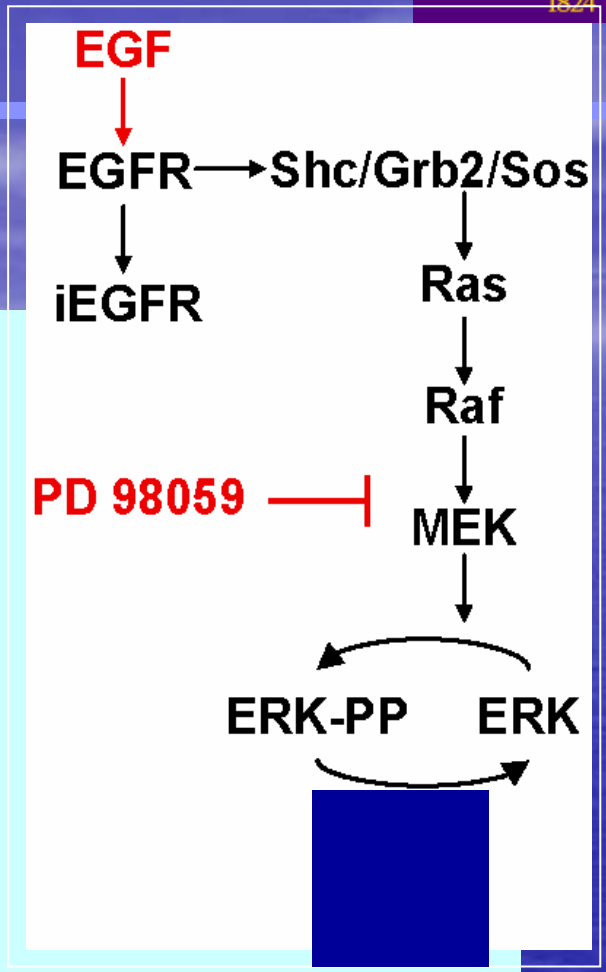


Amplitude is less robust vis-à-vis kinase perturbation than is duration

	kinases			phosphatases				**Sum**
	1	2	3	1	2	3	R	
Amplitude	6	4	2	-7	-5	-3	-6	**-9**
Duration	17	11	8	-2	-3	-3	-8	**20**

Duration is more robust *vis-à-vis* kinases than vis-à-vis phosphatase perturbation





Third part: results

- Biochemical networks are highly robust
- Robustness is not conserved ?
- Fragility is conserved
- Robustness through fragility
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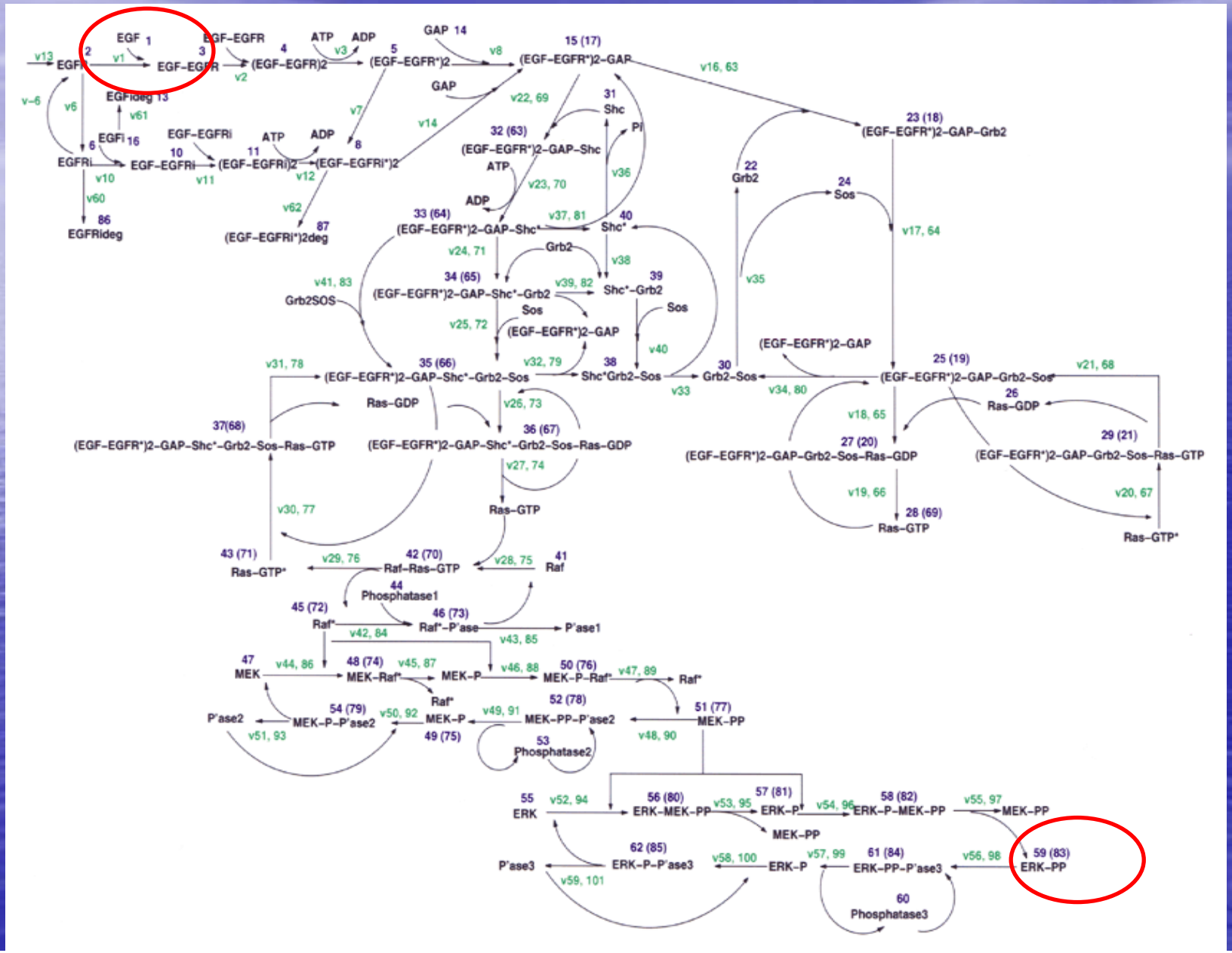
Oncogenesis

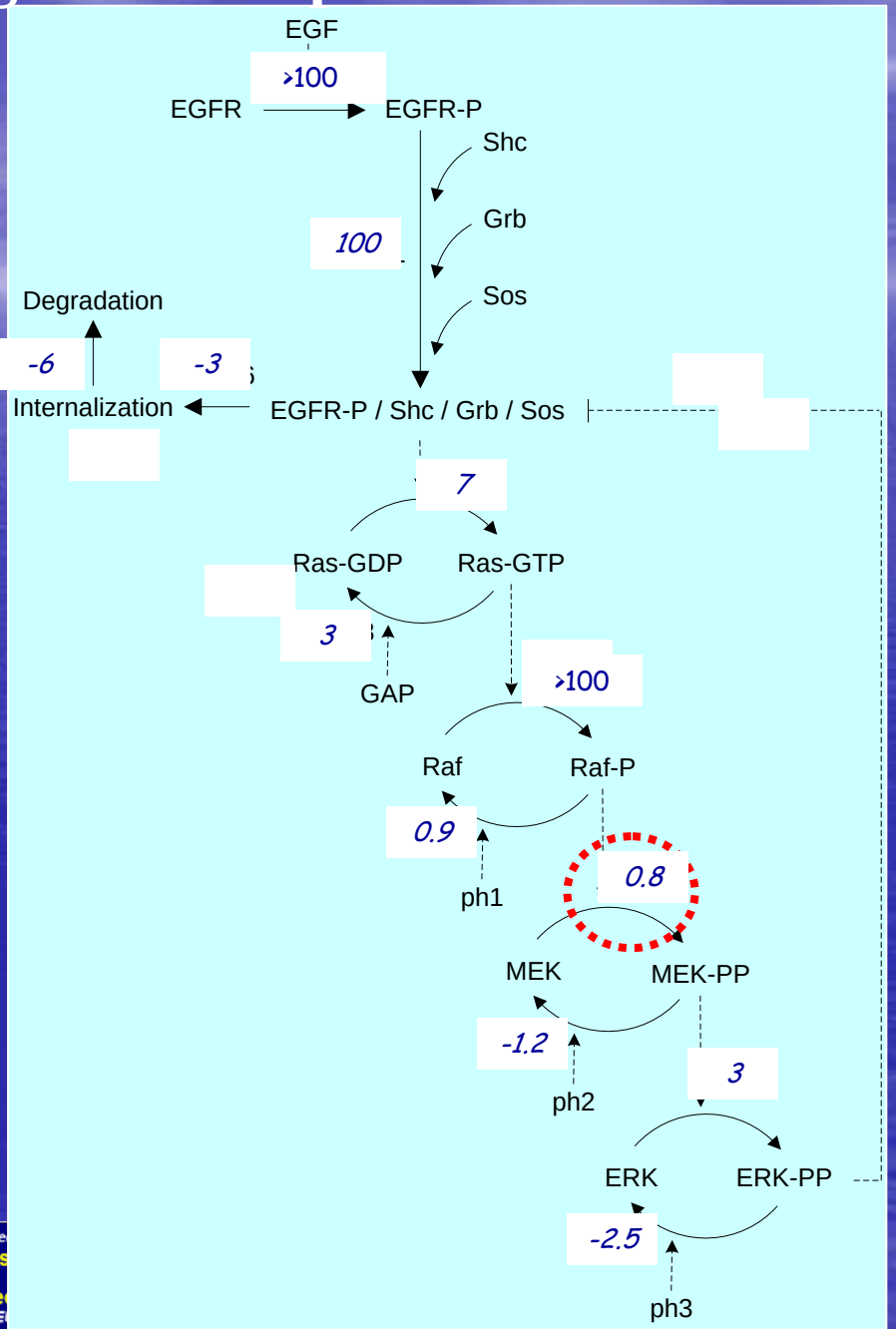
Which type of step is amplified?
Robust or fragile?

Detailed kinetic model of signaling by EGF

Schoeberl *et al.* (2002)



MAP kinase signaling: which steps are robust?



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]

Oncogenes may affect fragile steps

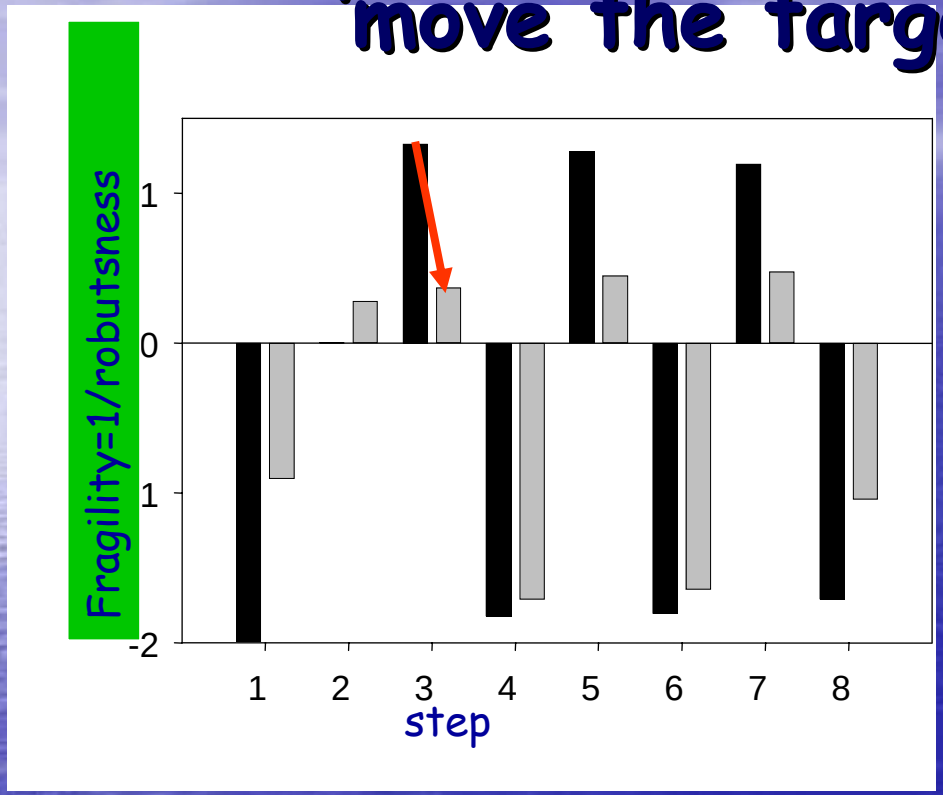
and make the cells more robust:

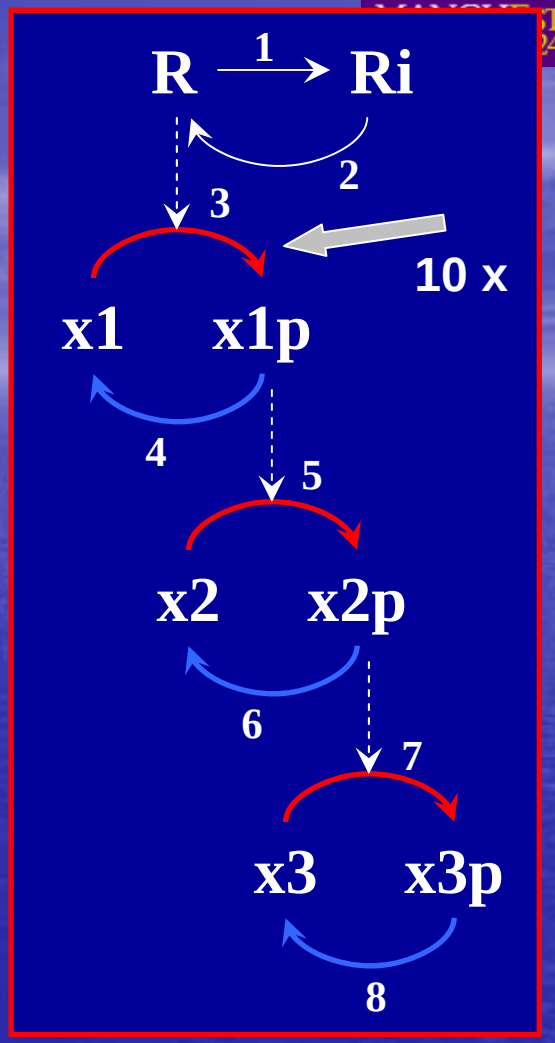
robustness as disease

Drug designers

do not like moving targets

Does the mutation change fragility, hence 'move the target'?





normal mutant

Yes: 3 less fragile; 2 more fragile

Hence: tumor cell less fragile towards mutated step

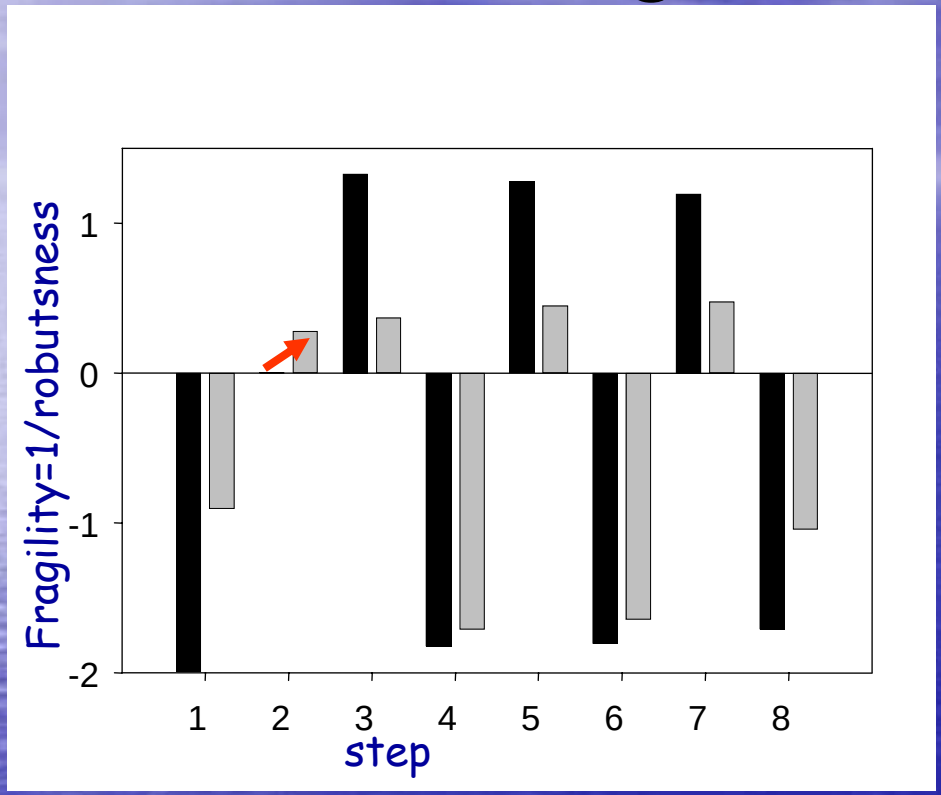
Oncogenes affect fragile steps

- And increase the robustness of that step:
- That step is not a good target
- Tumor cell is more robust with respect to the process amplified by the oncogenesis, but is likely to be less robust on average
- Some other steps must be more fragile

Function should have become more fragile towards another step in the network

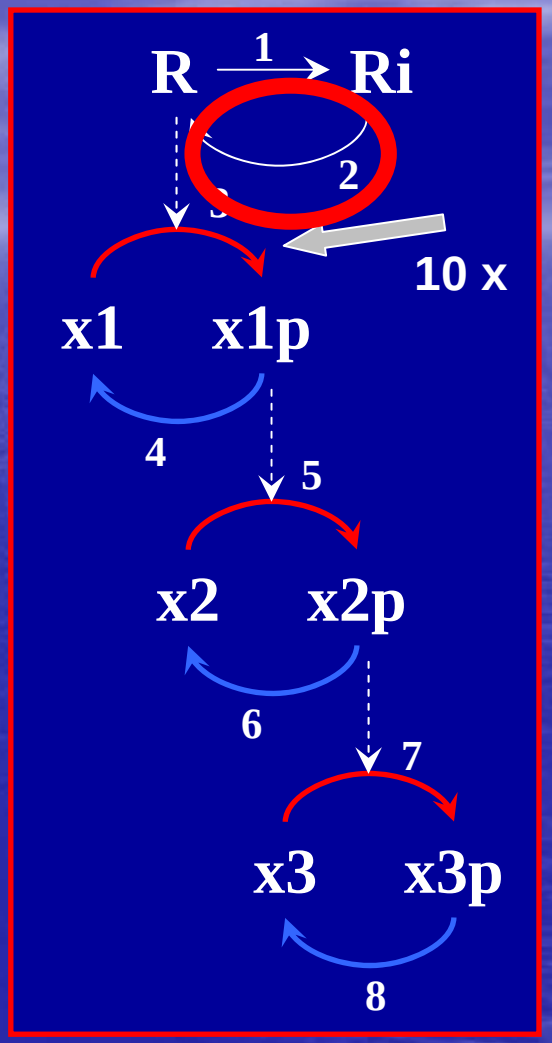
That should be the drug target

Step 2 has become more fragile



normal mutation

Yes: 3 less fragile; 2 more fragile



Hence: tumor cell less sensitive to inhibitor of amplified step: Not step 3 but step 2 is the preferred target!!

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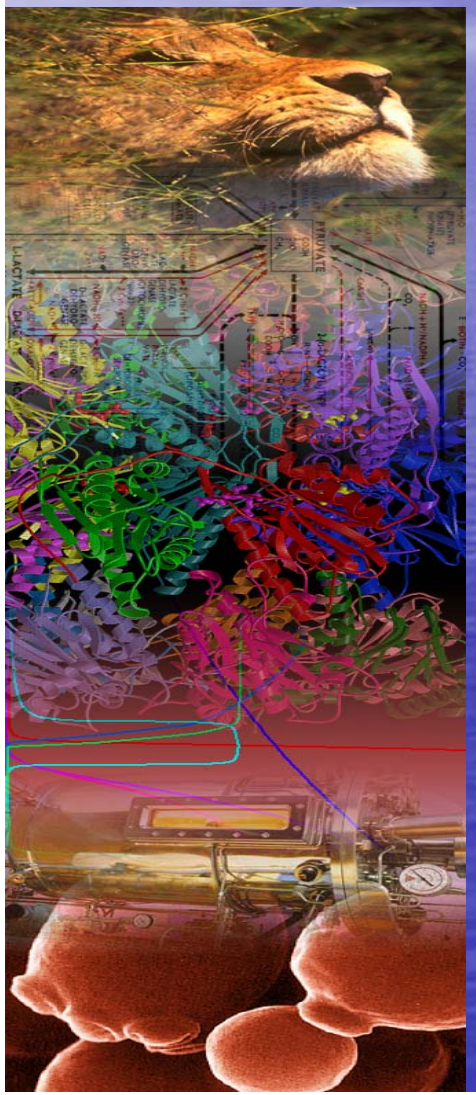
Systems Bio

Integrative Syste



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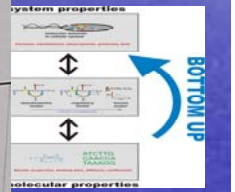

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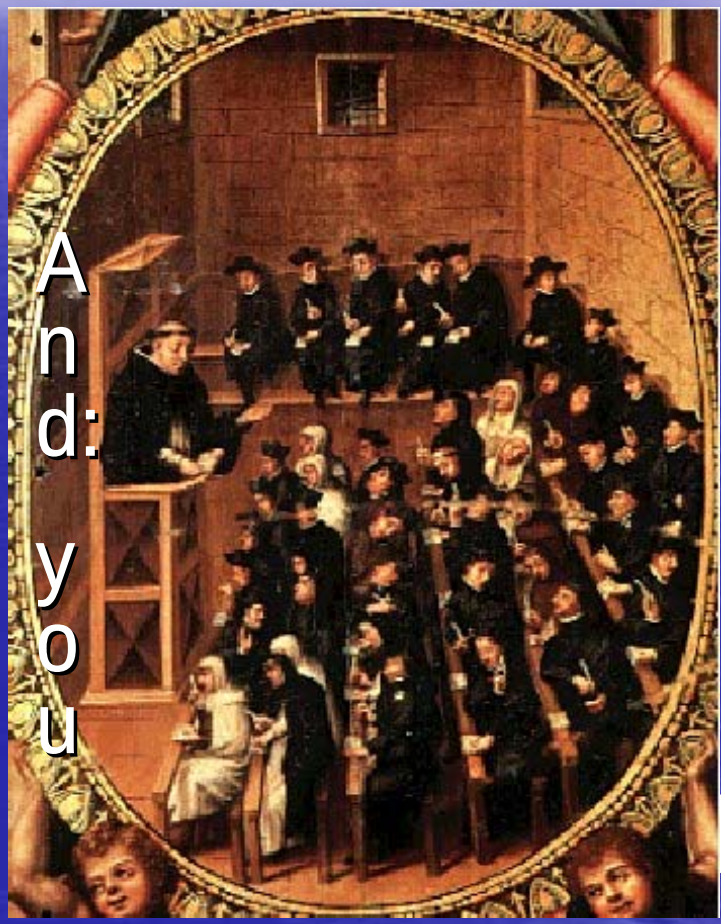
Thanks to:

Barbara Bakker
Frank Bruggeman
Jacky L. Snoep

and many others



And: you

My patient audience

Moving targets