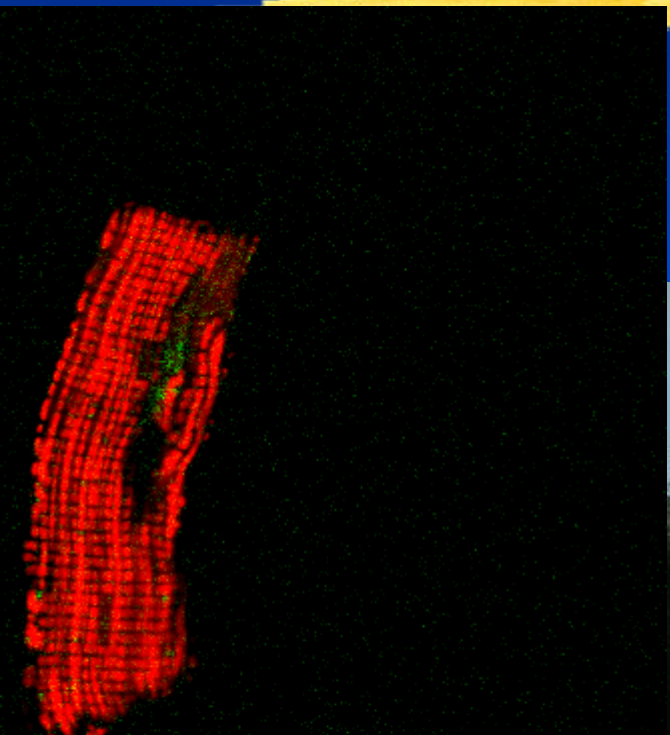
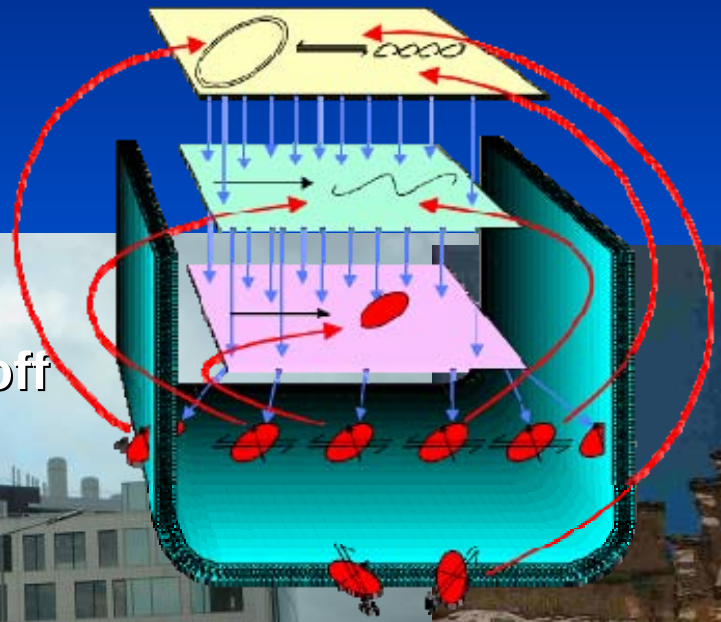
Emerging Principles : a theory for robustness





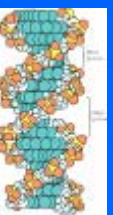
Hans V. Westerhoff
and
friends

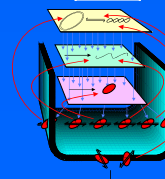
Manchester Centre for Integrative Systems Biology and BioCentrum Amste

12 October, ICSB2006
Yokohama

Opening lecture Hiroaki Kitano

- We need a theory for systems biology, notably for robustness
- Robustness is a system property
- Is robustness conserved?
- Trade-off between robustness and fragility (exact?)

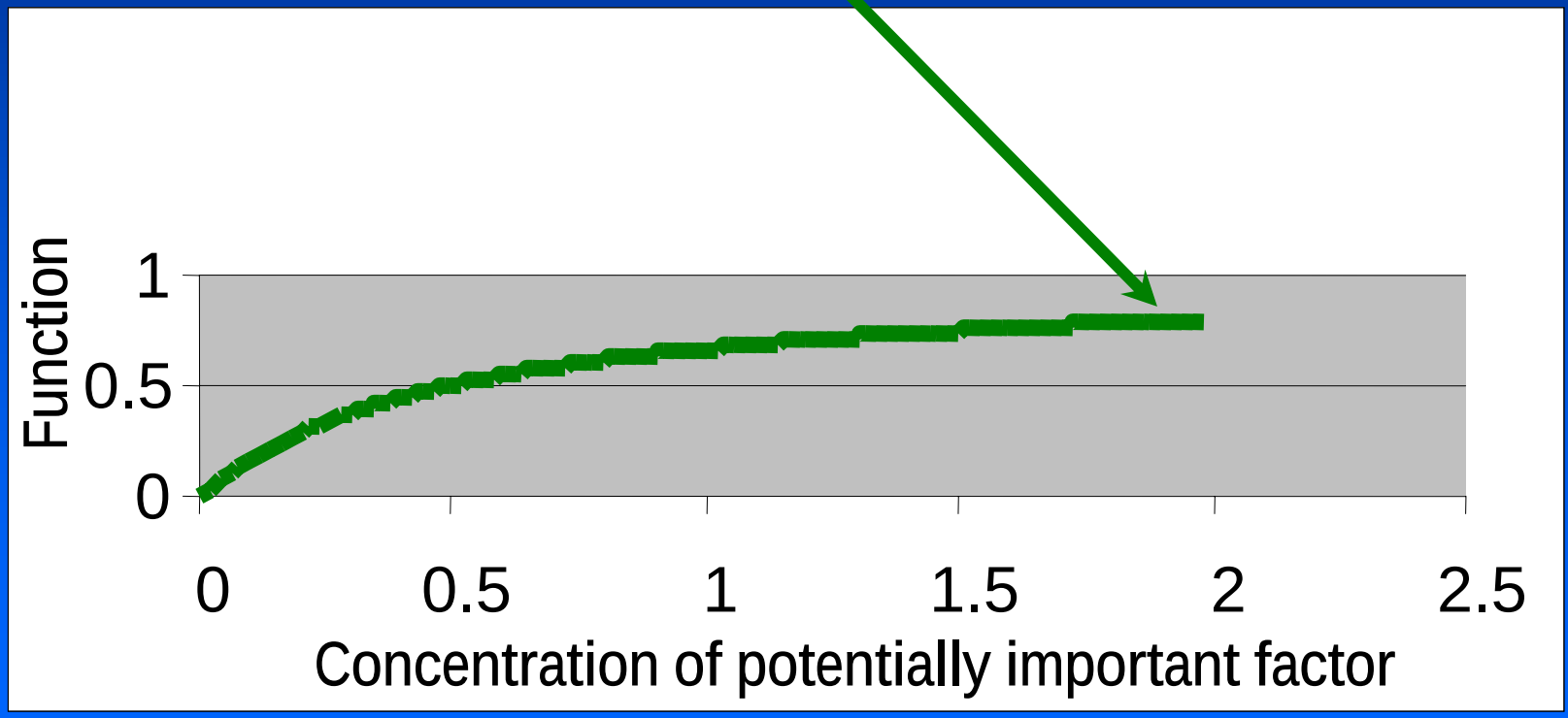




For a theory of robustness

We need a definition of robustness

An example of robustness



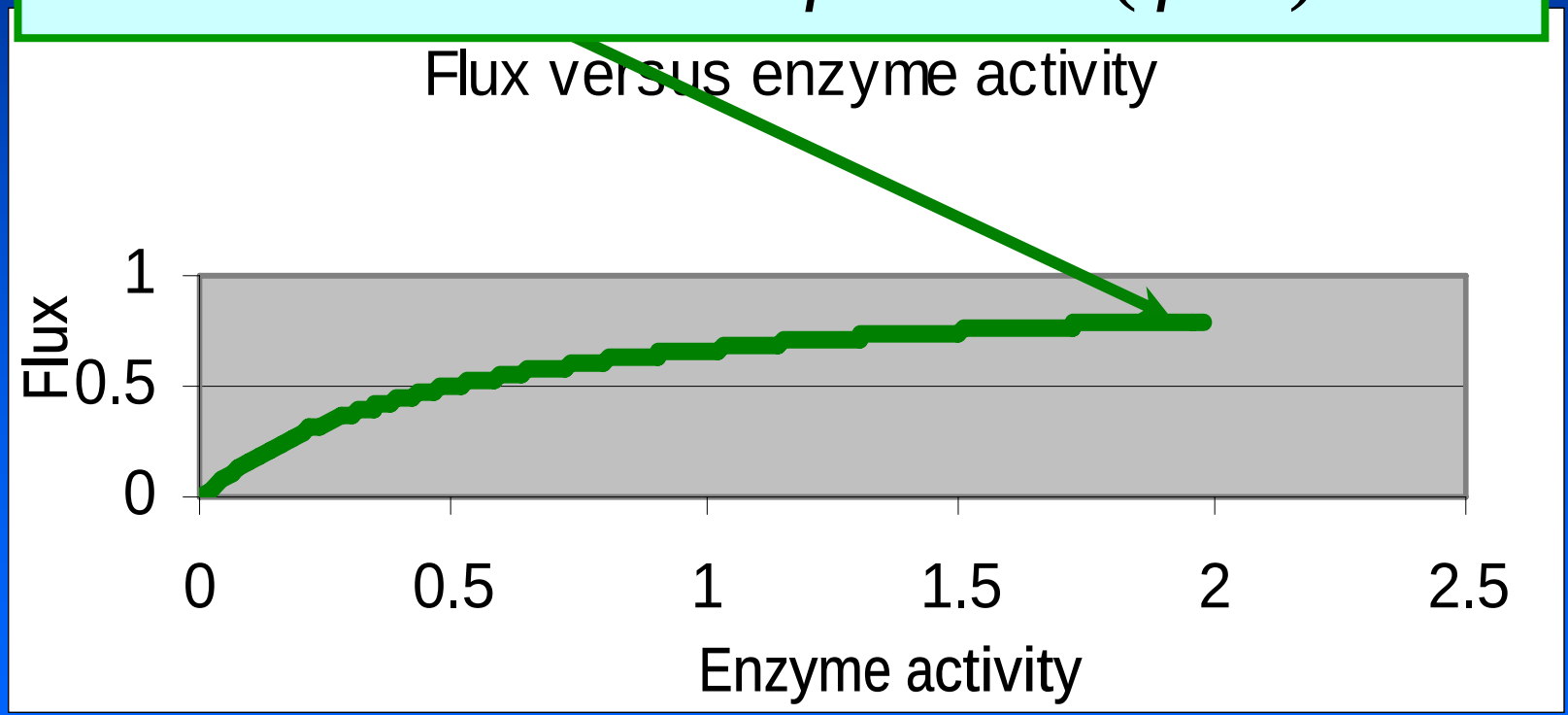
Definition of robustness *vis-à-vis* a perturbation

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

By what percentage can I perturb that property and still affect system function by only 1 %?

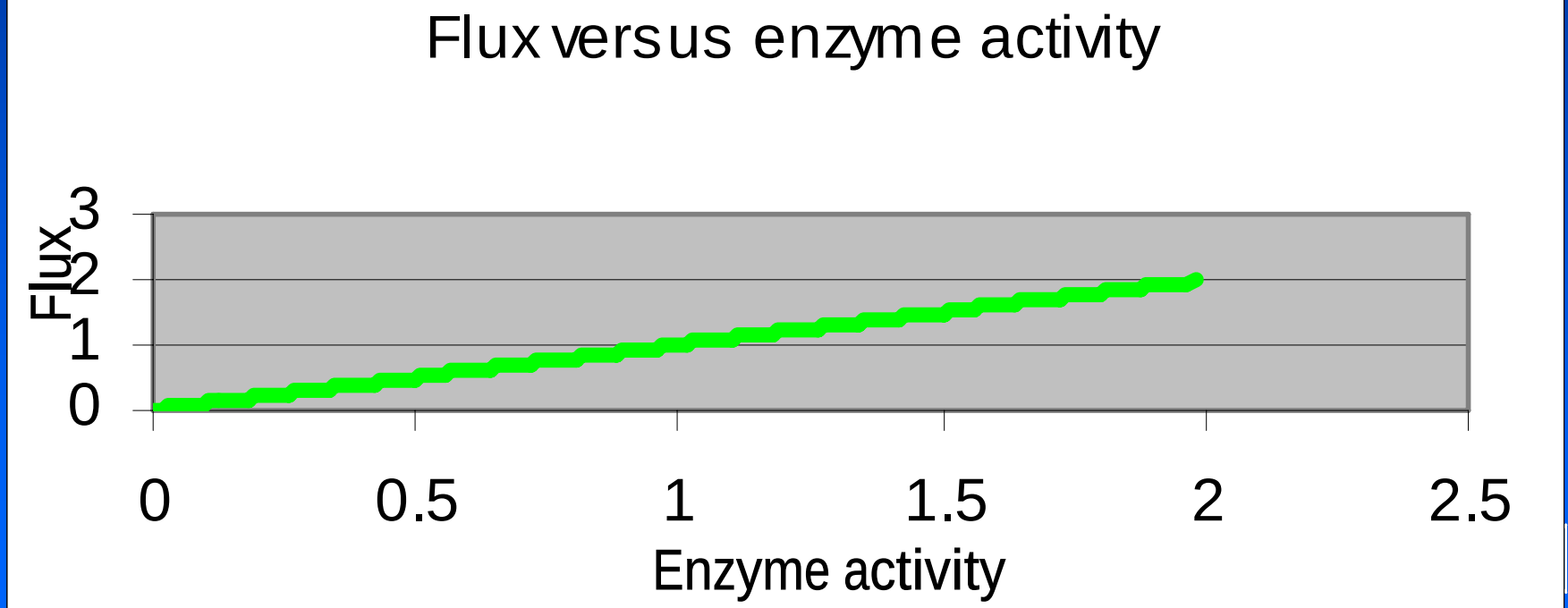
An example of robustness

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



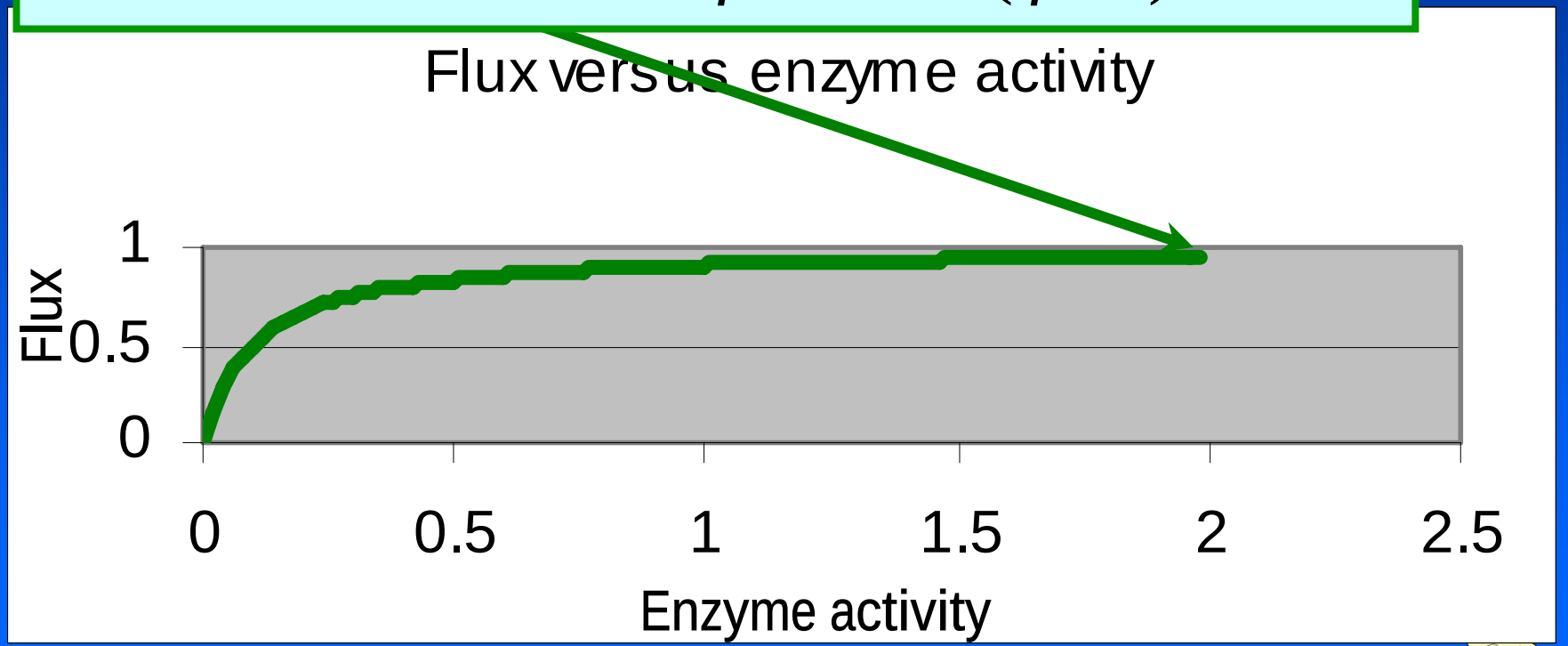
Robustness is a system property: Low robustness of processes in isolation

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



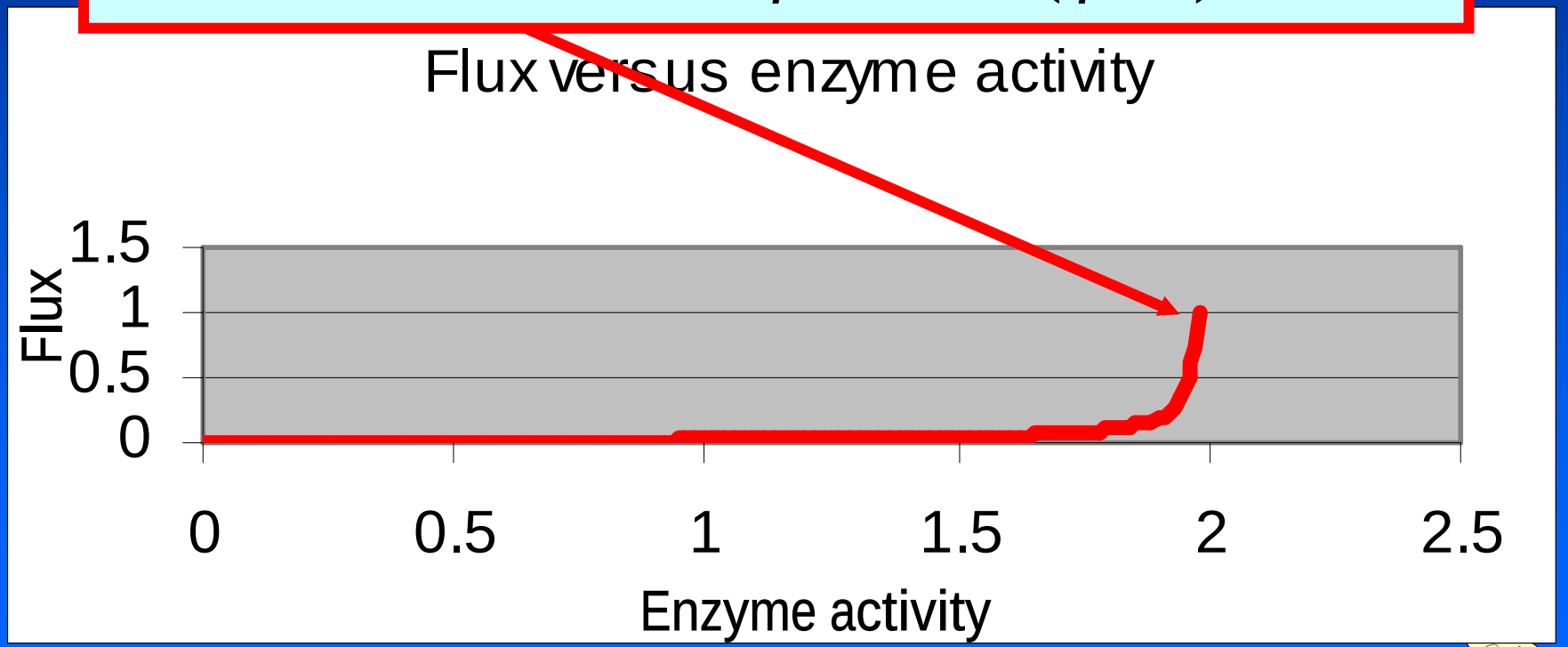
An example of high robustness

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



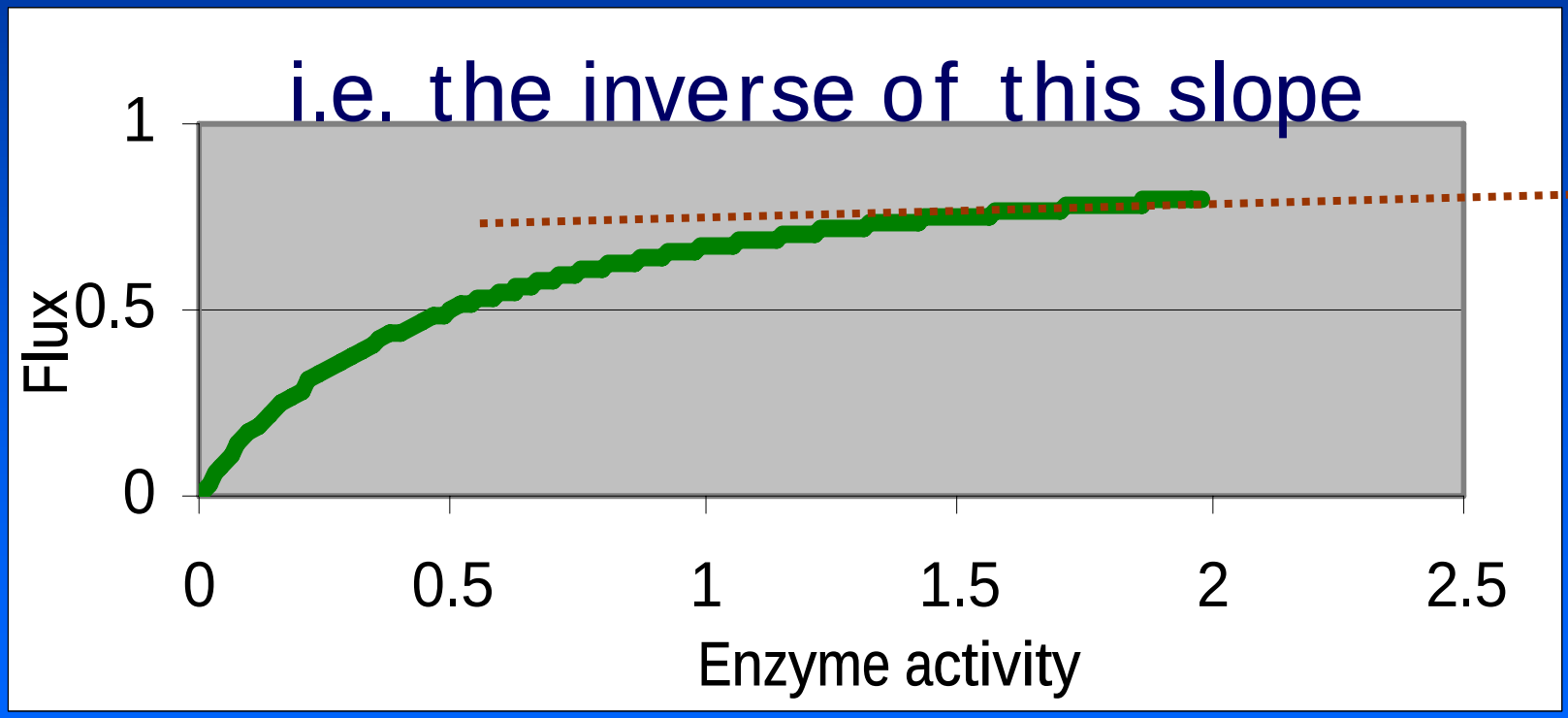
An example of lack of robustness (fragility)

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



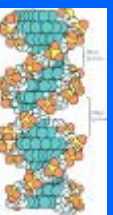
More precise definition of robustness

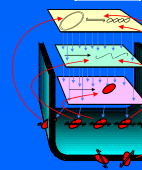
$$\Re_{e_i}^{function_j} \equiv \left(\frac{\partial enzyme_i / enzyme_i}{\partial function_j / function_j} \right)_{all\ other\ parameters} = \left(\frac{\partial \ln enzyme_i}{\partial \ln function_j} \right)_{all\ other\ parameters} = 1 / \left(\frac{\partial \ln function_j}{\partial \ln enzyme_i}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



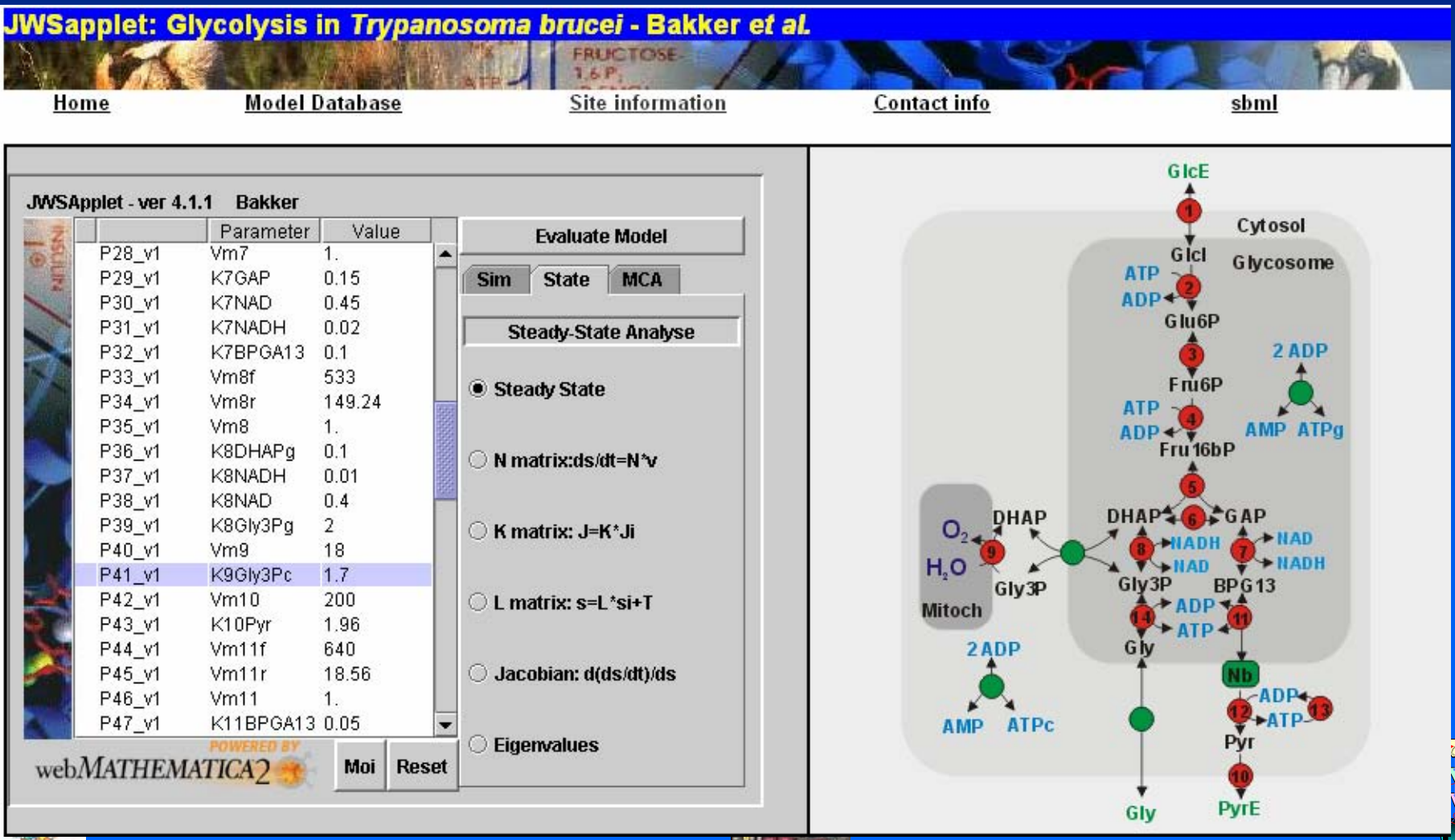
Robustness

- There is more than one definition
- E.g. John Doyle's definition: frequency domain
- This one: steady state function with respect to parameters, such as catalytic activities





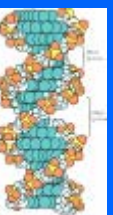
Are robustnesses large?
Silicon cell live models: jjj.bio.vu.nl

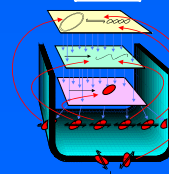


Robustness of vital flux of Trypanosomes *vis-à-vis* perturbation of various glycolytic steps

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

Yes, most robustnesses are large; average is 468 here





Systems Biology: principles

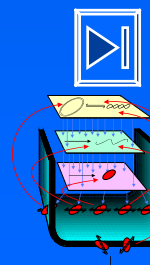
Are there any principles vis-à-vis this robustness?

Is robustness conserved?

Is robustness conserved? (e.g. when making the most fragile step robust)

step	Robustness	Robustness double glc transporter
Glctr	1.1	88
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 (average)	**6085 (468)**	**1055(81)**

No, robustness is not conserved



No principles then?

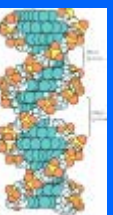
Yes, there is one!

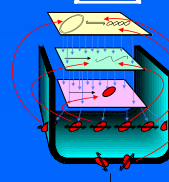
Sum over all inverse robustnesses = 1

step	1/robustness	1/robustness (doubled glc transporter)
Glctr	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**

Systems Biology principle concerning robustness

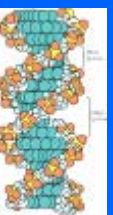
$$\sum_{i=1}^{n} \frac{1}{\Re_{e_i}^{J}} \equiv 1$$

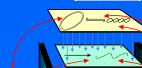




Implications

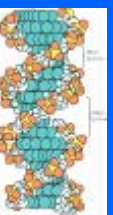
- Flux robustnesses can be homogeneous (robustness the same *vis-à-vis* all enzyme perturbations) or heterogeneous
- Average robustness is higher when robustness is heterogeneous
- By increasing fragility *vis-à-vis* one step one can increase the average robustness
- Lowest robustness is best drug target





Opening lecture Hiroaki Kitano

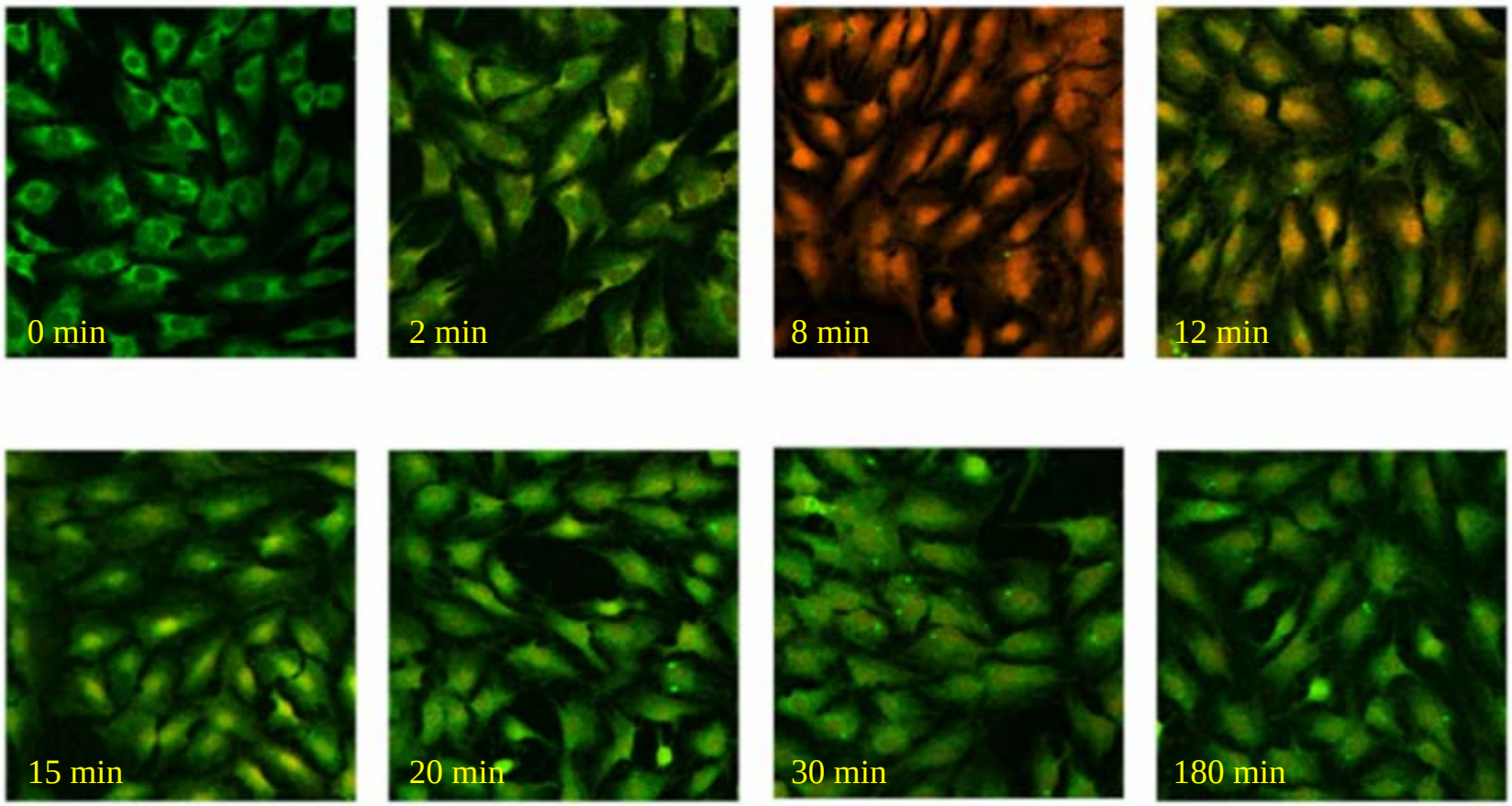
- We need a theory for systems biology, notably for robustness
- Robustness is a system property
- Is robustness conserved? X
- Trade-off between robustness and fragility (exact?) X



Robustness of ERK phosphorylation

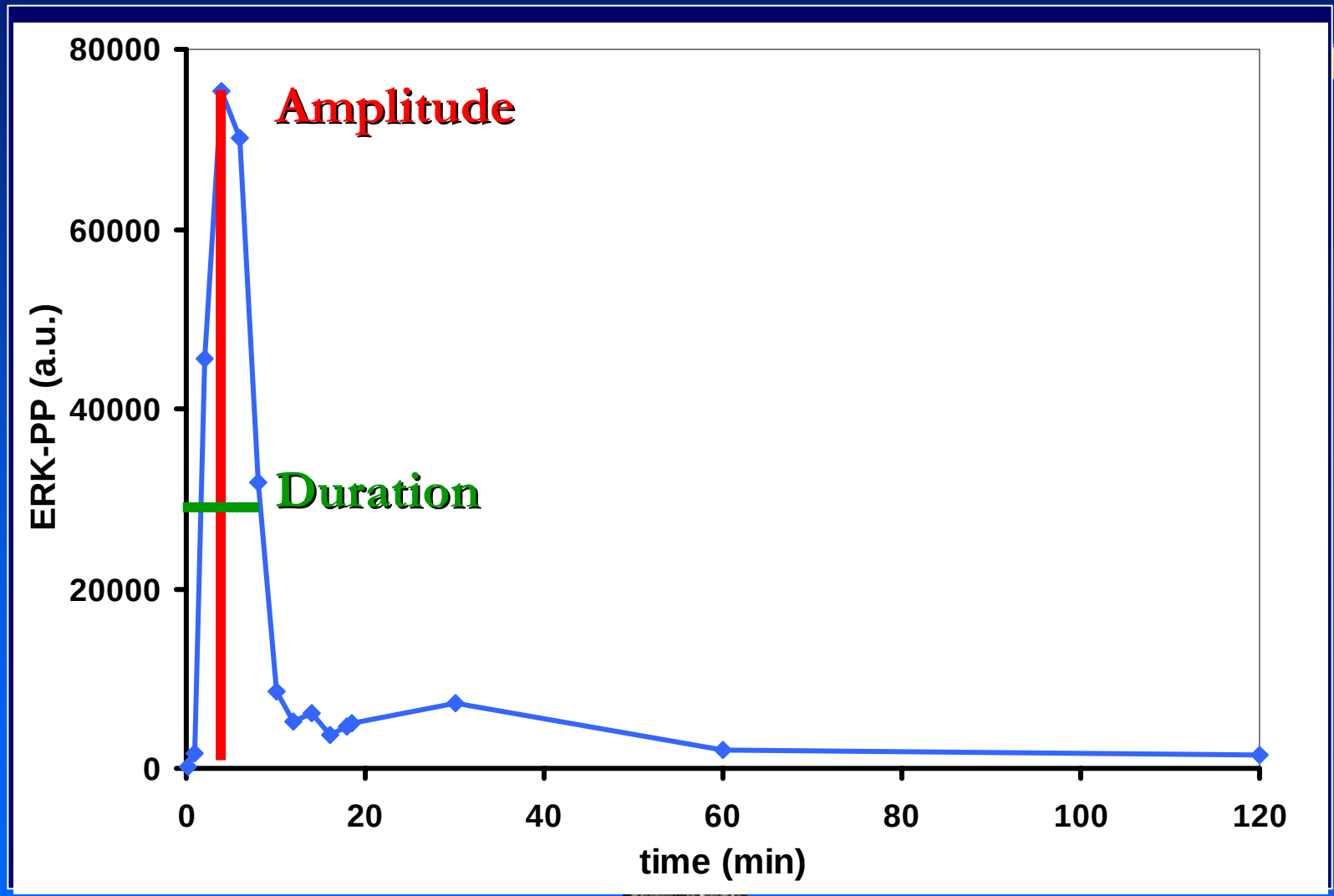
EGF initiated signal transduction

ERK-PP in single cells upon EGF stimulation



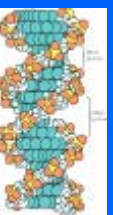
Green: total ERK
Red: ERK-PP

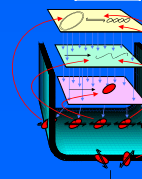
ERK-PP profile upon EGF stimulation



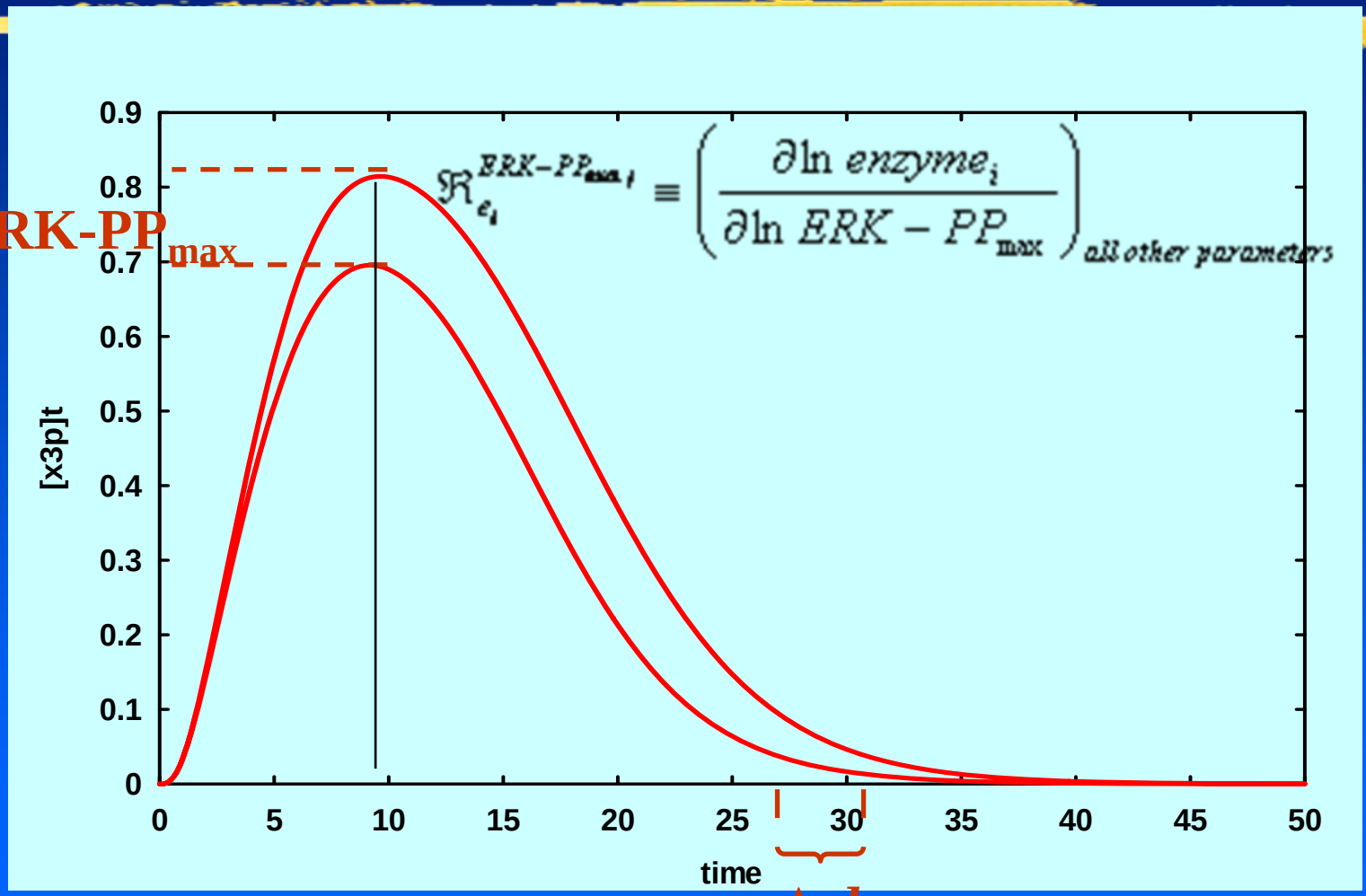
Research questions

- To which perturbations is this signal transduction robust (fragile)?
- Does this differ for the various aspects of the signal?
- Are there generic principles here?





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



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

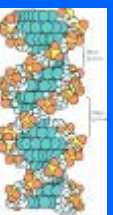
	kinases			phosphatases				Sum
	1	2	3	1	2	3	R	
Amplitude	6	4	2	-7	-5	-3	-6	**-9**

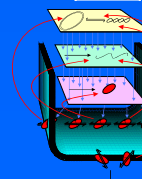
Duration robustness in model MAP kinase pathway

	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**

Research questions

- To which perturbations is this signal transduction robust (fragile)? **Most**
- Does robustness differ for the various aspects of the signal?
- Are there generic principles here?



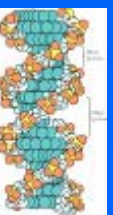


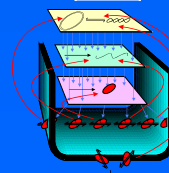
Robustness depends on function considered and is not conserved

	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**

Systems Biology principle concerning robustness

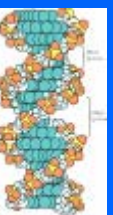
$$\sum_{i=1}^{n} \frac{1}{\Re_{e_i}^{amplitude}} \equiv 0$$

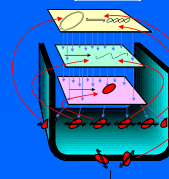




Research questions

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

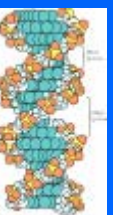


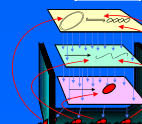


Systems Biology principles concerning robustness differ

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

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





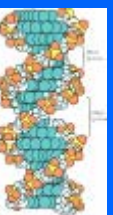
Incidentally, the math behind these theorems....

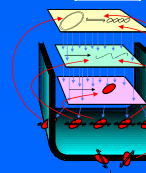
Metabolic Control Analysis

Fragility *vis-à-vis* kinases and phosphatase perturbation?

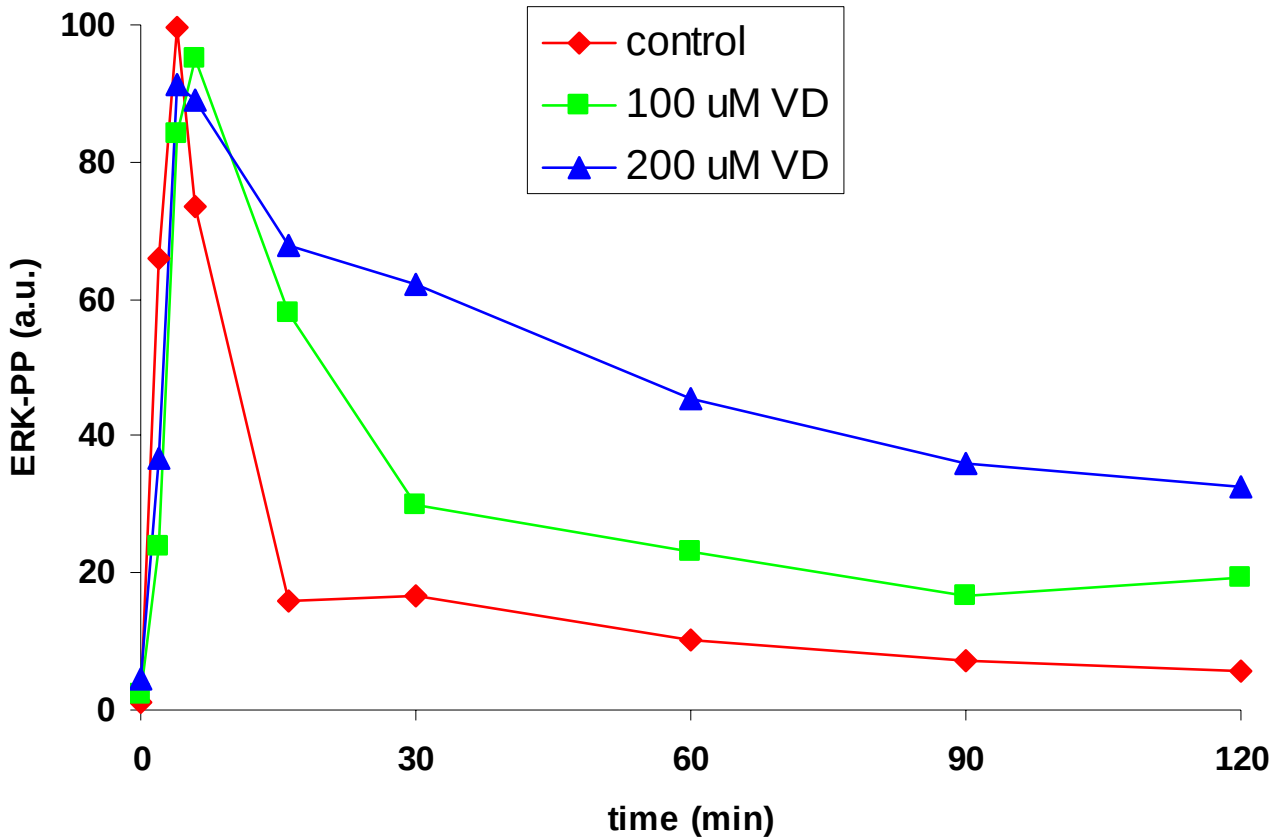
- Duration more than amplitude is fragile *vis-à-vis* phosphatase perturbation

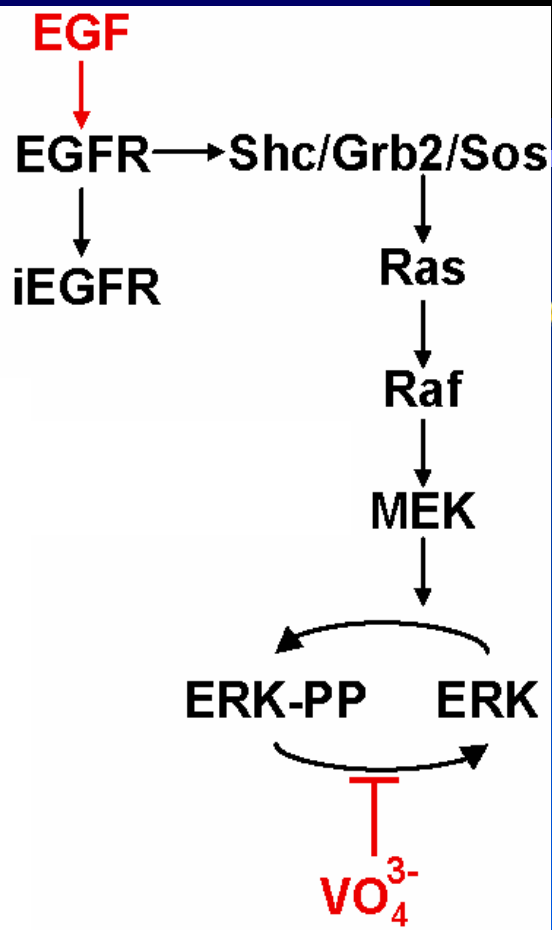
- Amplitude more than duration is fragile *vis-à-vis* kinase perturbation



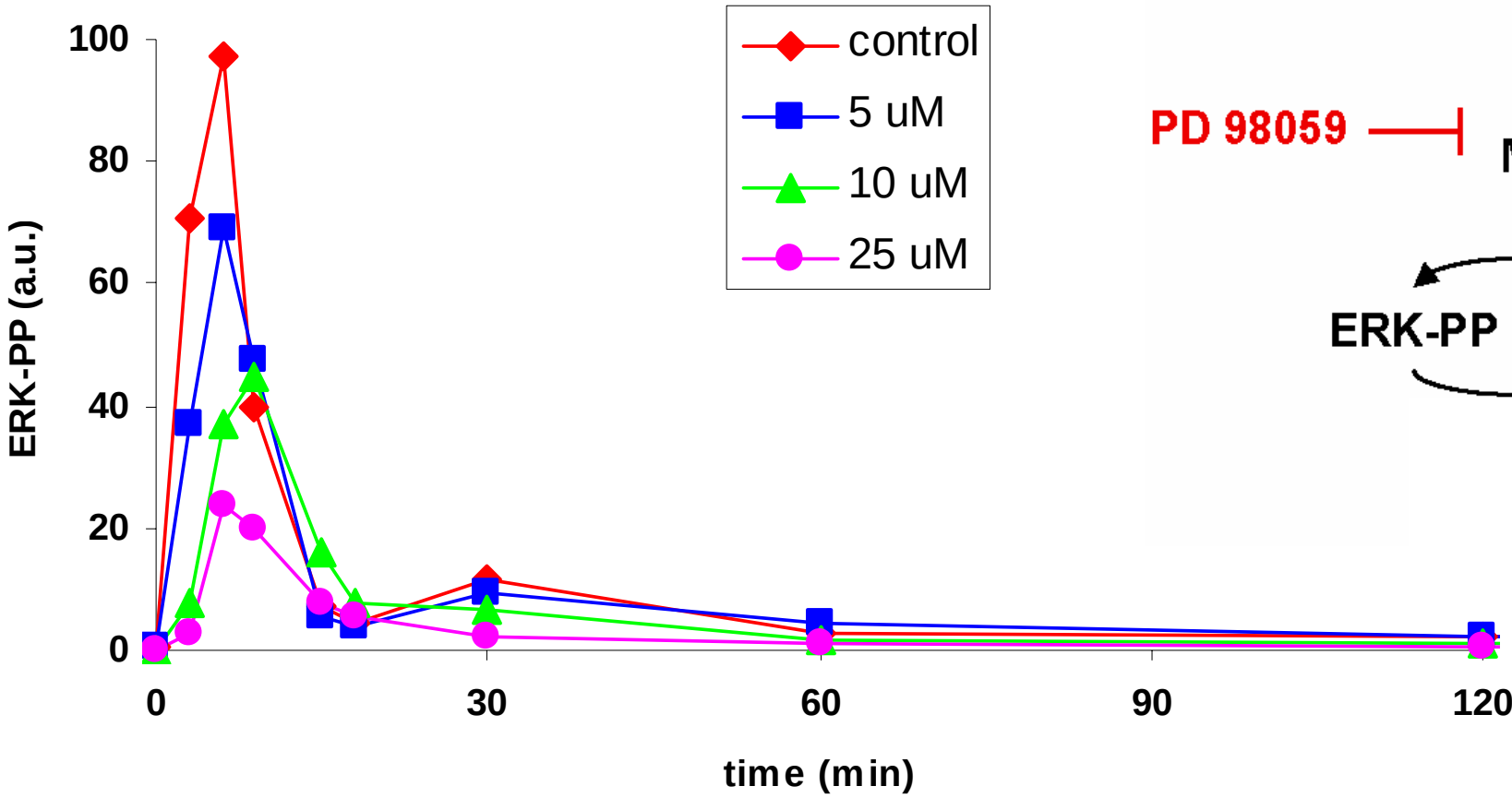


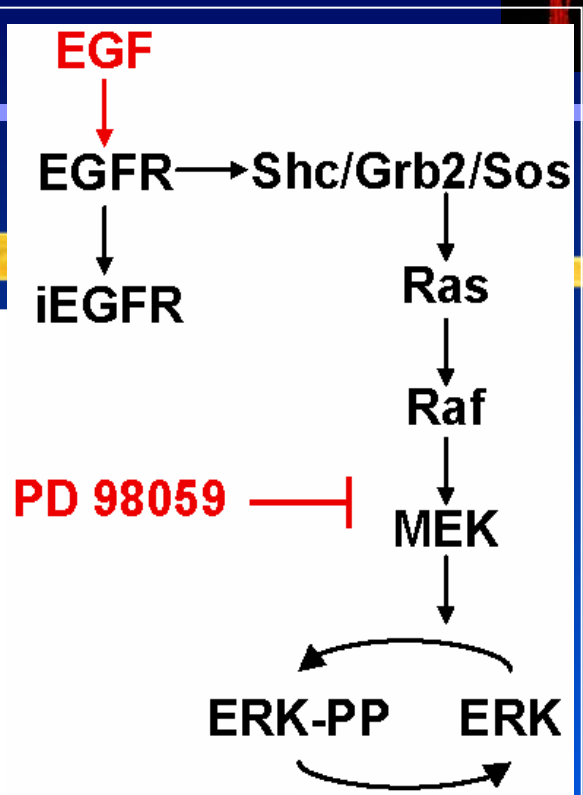
Duration more than amplitude is fragile *vis-à-vis* phosphatases





Amplitude more than duration is fragile *vis-à-vis* kinases

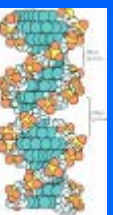


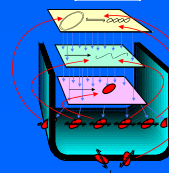


Is it all true?

- Duration fragility resides more in phosphatases

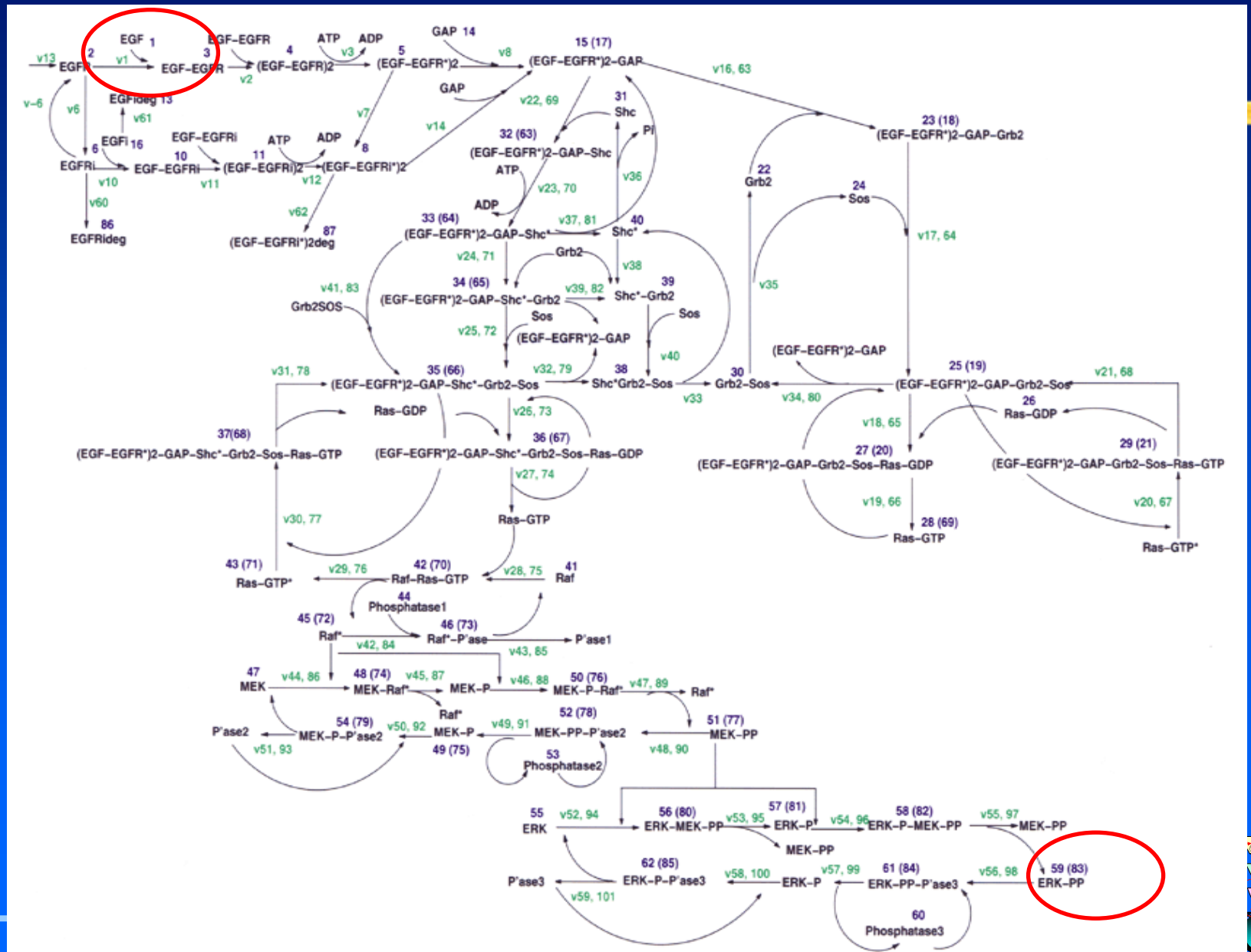
- Amplitude more fragile vis-à-vis kinase activity



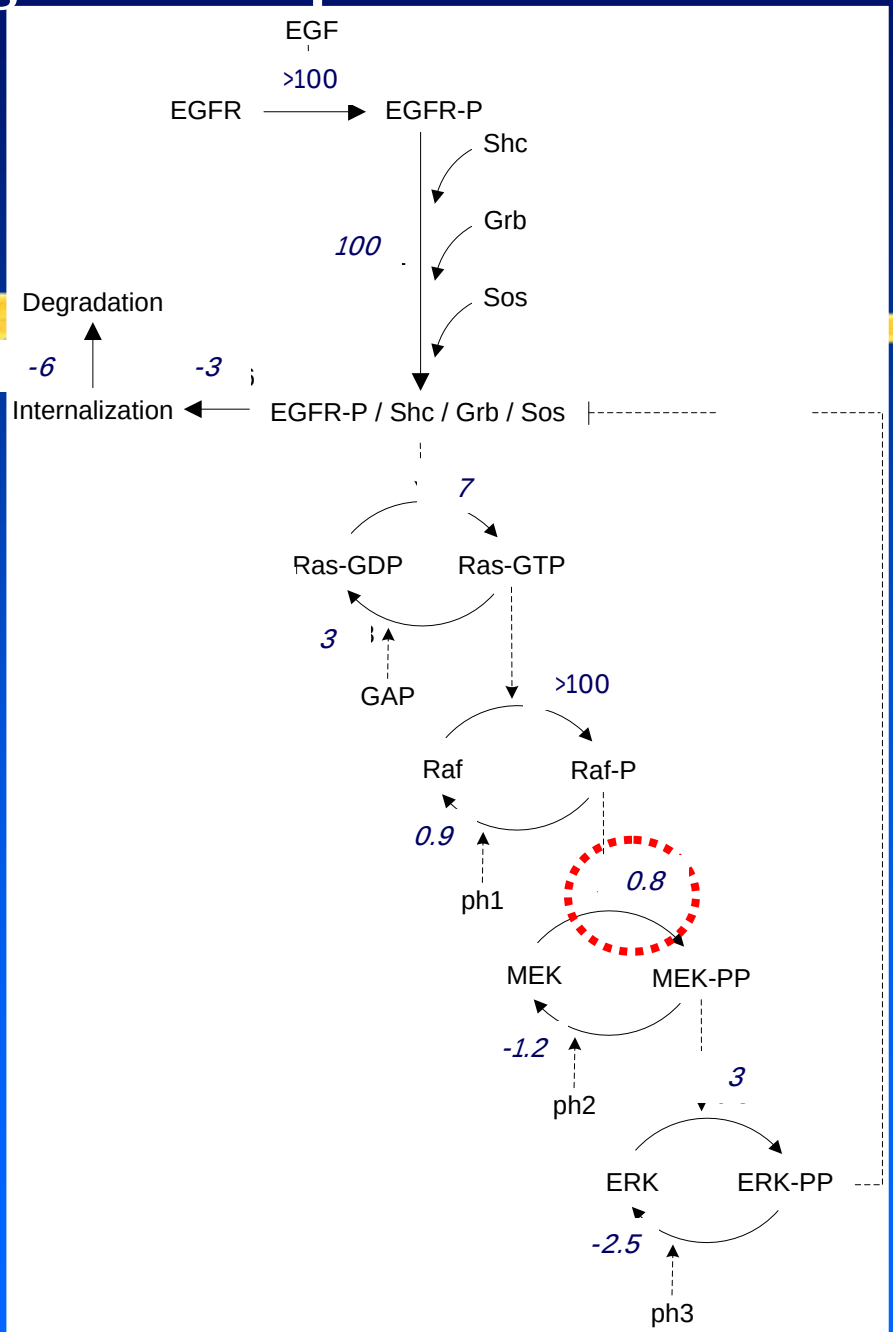


Detailed kinetic model of signaling by EGF

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]

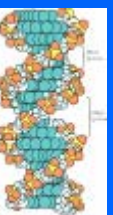
Oncogenes affect steps for which the system is least robust

And increase the robustness

Tumor cell is more robust

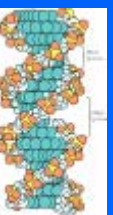
Emerging Principles of Living Systems: Robustness

- Robustness, a quantitative definition
- Example: robustness of the vital flux of Trypanosomes
  - Robustness is not conserved
  - General principle 1: fluxes
- Robustness in signal transduction
  - General principle 2: amplitude
  - Duration fragile *vis-à-vis* phosphatases perturbation more than kinase perturbation
  - Amplitude also fragile *vis-a-vis* kinase perturbation
- Oncogenes: may act to enhance robustness



Opening lecture Hiroaki Kitano

- We need a theory for systems biology, notably for robustness
- Robustness is a system property
- Is robustness conserved?
- Trade-off between robustness and fragility (exact?)
- **Hiroaki was right!**



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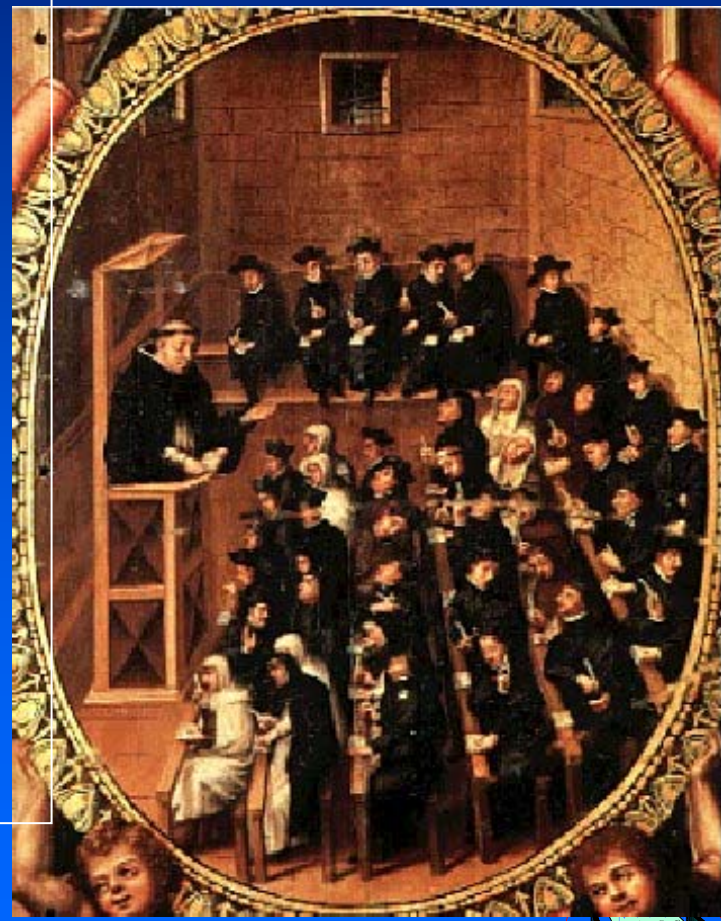
Jacky Snoep

and many others



2nd FEBS Advanced Course Systems Biology

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