institut non linéaire de nice SOPHIA ANTIPOLIS UMR6618

CNRS CENTRE NATIONAL DE LA RECHERCHE SCIENTIFIQUE

Université Nice SOPHIA ANTIPOLIS

Effets de rétroaction dans les cascades de signalisation intracellulaire

Jacques-Alexandre Sepulchre

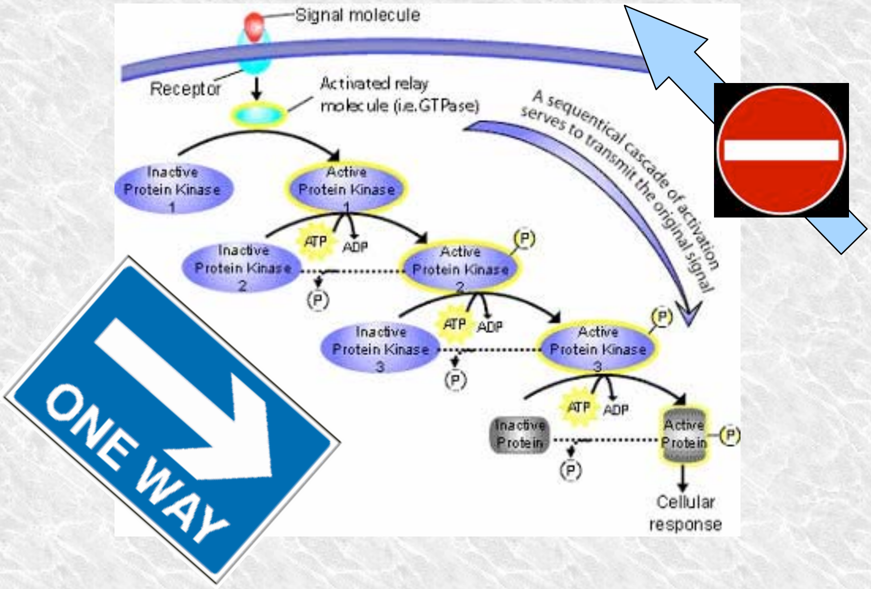
Institut Non Linéaire de Nice (INLN)

In collab. with Alejandra VENTURA,

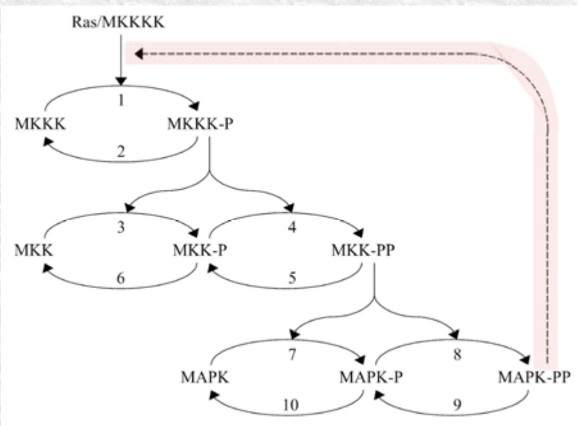
Postdoc in the lab of Sofia MERAJVER
Cancer Center, University of Michigan

To appear in *PLoS Computational Biology* March/April 2008.

The concept of signaling cascades

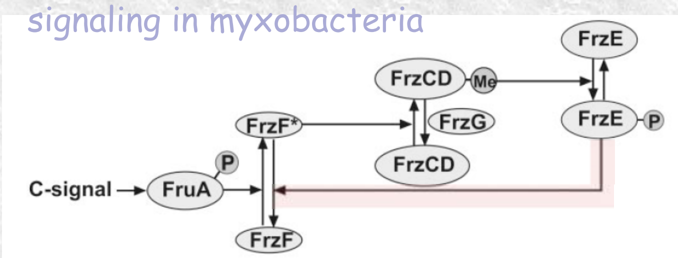


MAPK



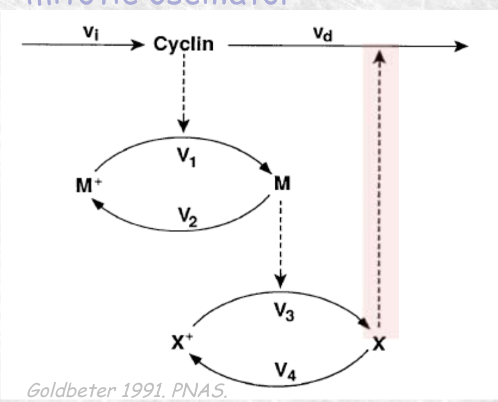
Kholodenko 2000. FEBS.

signaling in myxobacteria



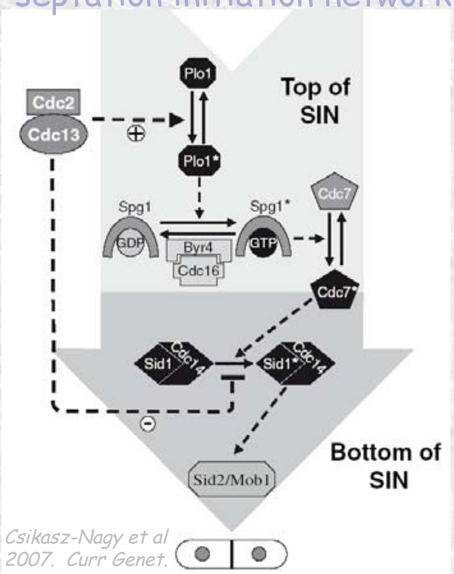
Igoshin et al 2004. PNAS.

mitotic oscillator



Goldbeter 1991. PNAS.

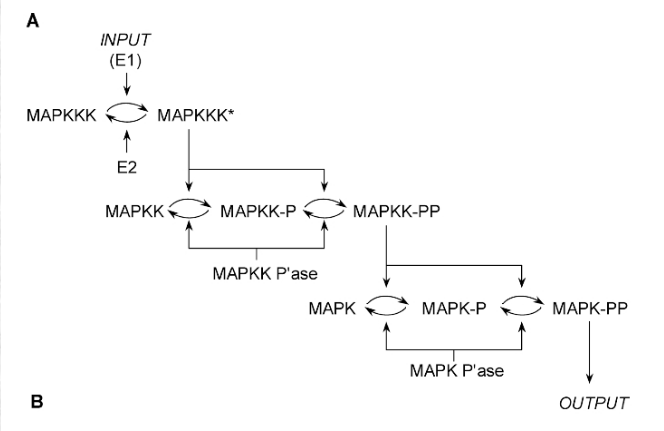
septation initiation network



Csikasz-Nagy et al 2007. Curr Genet.

The concept of signaling cascades

A paradigm: the MAPK's cascade

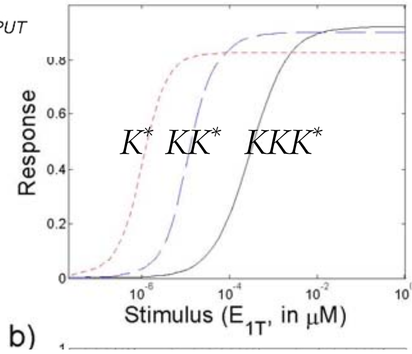


Example:

Raf

Mek

Erk



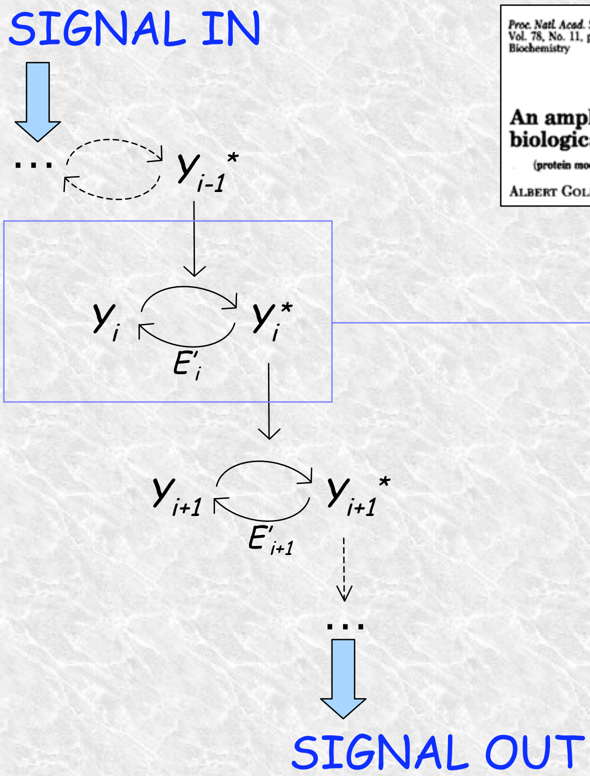
Objectives of this talk

1. A short review of the math modeling of signaling cascades :

2. A new system of equations which challenges the concept of only unidirectional « cascades »

3. Towards experimental confrontation ?

Modeling the basic unit of the cascade

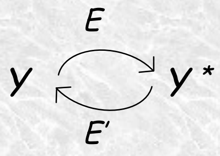


Proc. Natl. Acad. Sci. USA
Vol. 78, No. 11, pp. 6840–6844, November 1981
Biochemistry

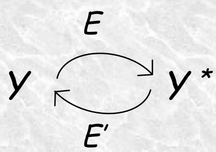
An amplified sensitivity arising from covalent modification in biological systems

(protein modification/metabolic regulation/switch mechanism/enzyme cascades)

ALBERT GOLDBETER† AND DANIEL E. KOSHLAND, JR.



The Goldbeter-Koshland model



$$Y + E \underset{d}{\overset{a}{\rightleftharpoons}} C \xrightarrow{k} Y^* + E$$

$$Y^* + E' \underset{d'}{\overset{a'}{\rightleftharpoons}} C' \xrightarrow{k'} Y + E'$$

+6 variables
- 3 conservation laws
- 2 quasi-steady state approximations

(Y_T in large excess over E_T and E'_T)

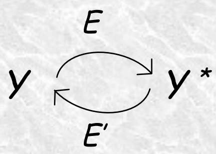
$$\dot{y}^* = V\frac{y}{K+y} - V'\frac{y^*}{K'+y^*}$$

$$y^* + y = 1$$

$$V \propto E_T$$

$$V' \propto E'_T$$

The Goldbeter-Koshland model



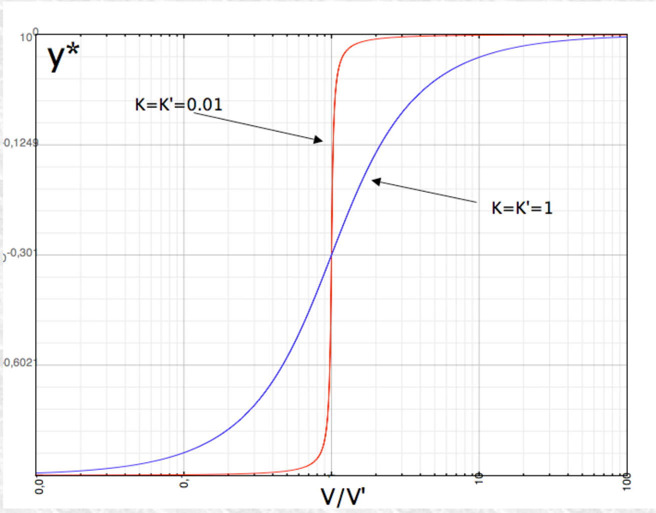
$$Y + E \underset{d}{\overset{a}{\rightleftharpoons}} C \overset{k}{\longrightarrow} Y^* + E$$

$$Y^* + E' \underset{d'}{\overset{a'}{\rightleftharpoons}} C' \overset{k'}{\longrightarrow} Y + E'$$

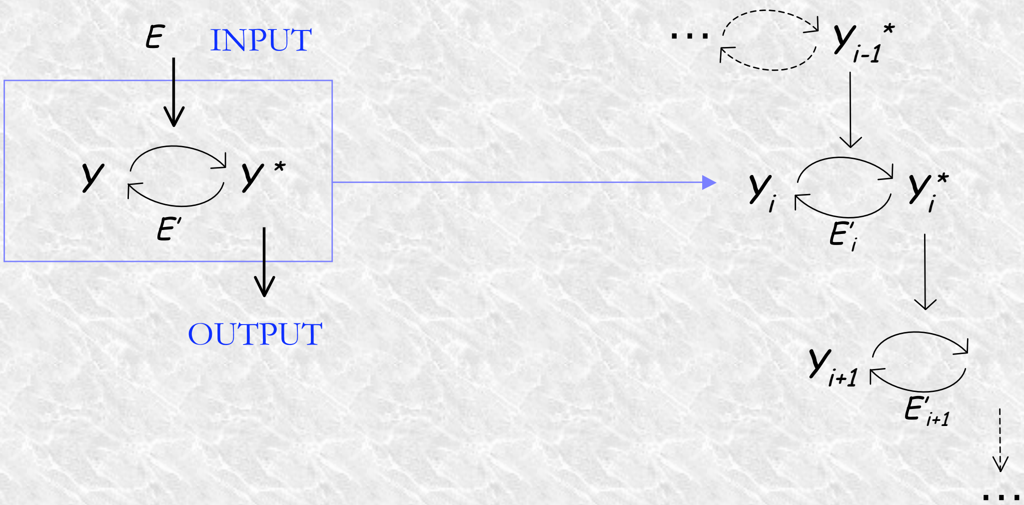
$$\dot{y}^* = V \frac{y}{K + y} - V' \frac{y^*}{K' + y^*}$$

$$y^* + y = 1$$

Ultrasensitivity



Phenomenological extension of the GK model

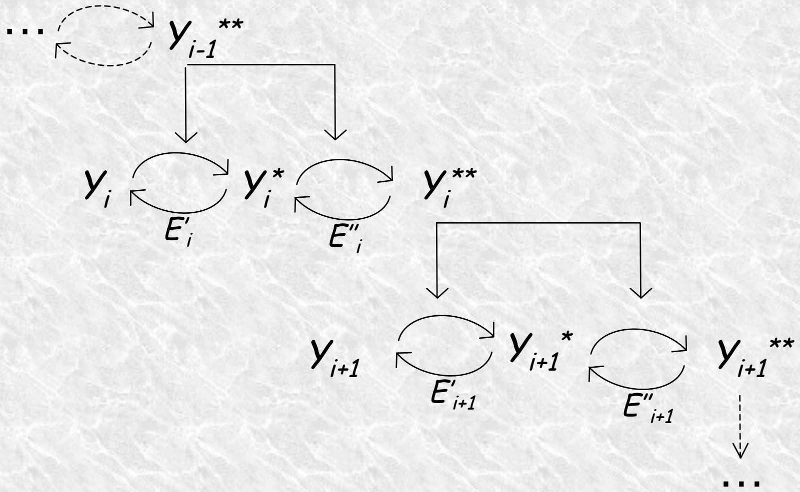


Goldbeter and Koshland, 1981
Goldbeter, 1991
Igoshin et al, 2004,
Csikasz-Nagy et al., 2007

$$\dot{y}_i^* = U_i \, y^*_{i-1} \frac{y_i}{K_i + y_i} - V'_i \frac{y_i^*}{K'_i + y_i^*}$$

$$y_i^* + y_i = 1$$

Extension to the doubly phosphoryl. cascade



$$\dot{y}_i^{**} = V_i\, y_{i-1}^{**} \frac{y_i^*}{K_i + y_i^*} - V_i'' \frac{y_i^{**}}{K_i'' + y_i^{**}}$$

$$\dot{y}_i = V_i' \frac{y_i^*}{K_i' + y_i^*} - V_i\, y_{i-1}^{**} \frac{y_i}{K_i + y_i}, \qquad y_i + y_i^* + y_i^{**} = 1$$

(Kholodenko,2000, Angeli et al, 2004, Giuraniuc et al, 2007)

Various simplifications

$$\dot{y}_i^* = U_i\, y^*_{i-1} \frac{y_i}{K_i + y_i} - V_i' \frac{y_i^*}{K_i' + y_i^*}$$

$$y_i^* + y_i = 1$$

$$K_i >> 1, \quad K_i' >> 1,$$
$$\dot{y}_i^* = \alpha_i y^*_{i-1}\, y_i - \beta_i y_i^*$$

Heinrich, Neel, Rapoport, *Math. Models of protein kinase Signal transduction*, Mol. Cell (2002)

$$K_i >> 1, \quad K_i' >> 1, \quad y_i = 1 - y_i^* \approx 1,$$
$$\dot{y}_i^* = \alpha_i y^*_{i-1} - \beta_i y_i^*$$

Chaves et al. (2004)
Chaves et Sontag, 2006

Incidence graph

$$\dot{x}_i = F_i(\ldots, x_j, \ldots)$$

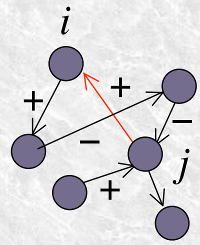
$$\Delta \dot{x}_i = \frac{\partial F_i}{\partial x_j}(x)\, \Delta x_j + \cdots$$

$$J_{ij}(x) = \frac{\partial F_i}{\partial x_j}(x)$$

describes the (instantaneous) *influence* of unit j on unit i

Gives a signed and oriented graph:

The INCIDENCE GRAPH

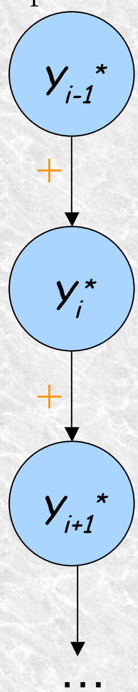


Incidence graph of cascades and consequences

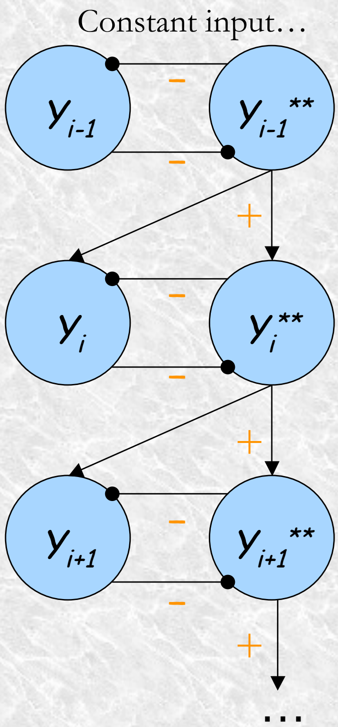
$$\dot{y}_i{}^* = U_i\, y^*_{i-1} \frac{y_i}{K_i + y_i} - V_i' \frac{y_i{}^*}{K_i' + y_i{}^*}$$

$$y_i{}^* + y_i = 1$$

Only (feedforward) positive interactions



Incidence graph of the MAPK's cascades



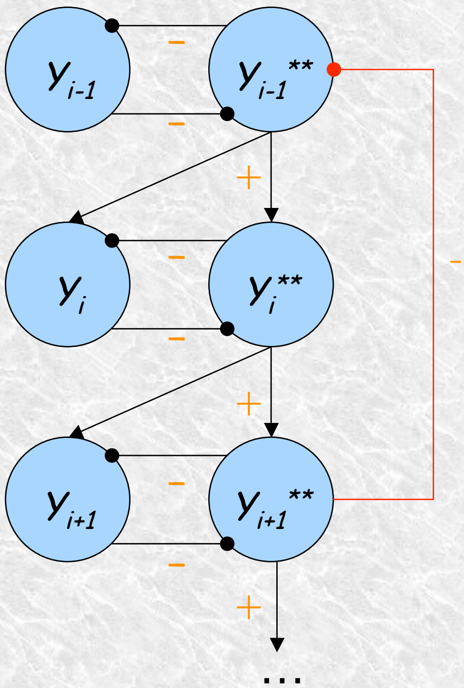
Only (feedforward) positive interactions

+ implicit positive feedback loops

gives possibly *bistability*

Cf. Angeli et al. (PNAS, 2004)
The bistability in MAPK's is proven
using the property *monotone* system,

Incidence graph of the MAPK's cascades



Only (feedforward) positive interactions

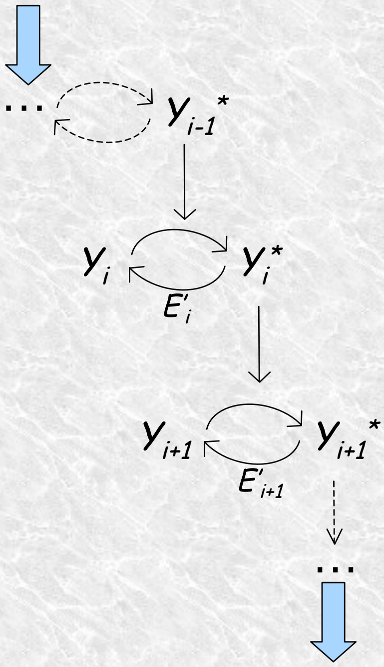
+ implicit positive feedback loops

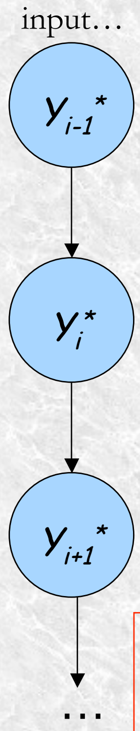
gives possibly *oscillations* only

If there is an explicit negative feedback

Kholodenko (2000)
Gouzé (1998), Hirsh (1985)

Conclusion: the concept of cascade implies…





No feedback:
Feedforward network

In presence of ultrasensitivity:
« Dominoes effect »
(Gonze, Goldbeter (2000))

No retrograde effect

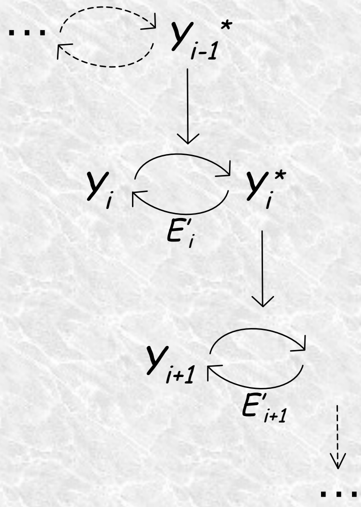
$$\dot{y}_i^* = V_i\, y^*_{i-1} \frac{y_i}{K_i + y_i} - V_i' \frac{y_i^*}{K_i' + y_i^*}$$

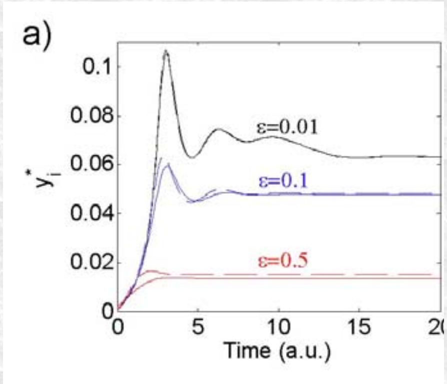
$$y_i^* + y_i = 1$$

Objectives

1. A short review of the math modeling of signaling cascades :
2. A new system of equations which challenges the concept of only unidirectional « cascades »
3. Towards experimental confrontation ?

Existence of damped oscillations in the mechanistic model

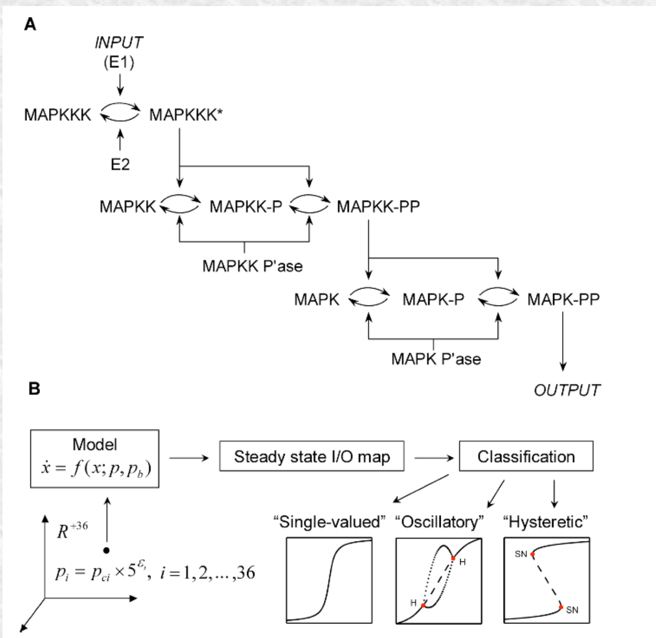




$$\varepsilon = \frac{E'_T}{Y_T}$$

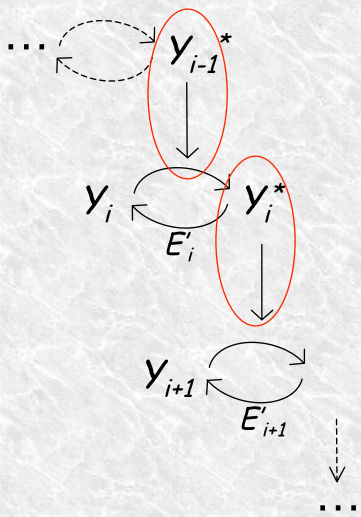
Autonomous oscillations in the MAPK cascade

Qiao et al., (PLoS sept. 2007)



82%   9%   9%

Perturbation analysis of the mechanistic model



$$\begin{aligned}
\frac{d[Y_i^*]}{dt} &= k_i[C_i] - a_i'[Y_i^*][E_i'] + d_i'[C_i'] - a_{i+1}[Y_{i+1}][Y_i^*] \\
&\quad +(k_{i+1}+d_{i+1})[C_{i+1}] \\
\frac{d[C_i]}{dt} &= a_i[Y_i][Y_{i-1}^*] - (k_i+d_i)[C_i] \\
\frac{d[C_i']}{dt} &= a_i'[Y_i^*][E_i'] - (k_i'+d_i')[C_i']
\end{aligned}$$

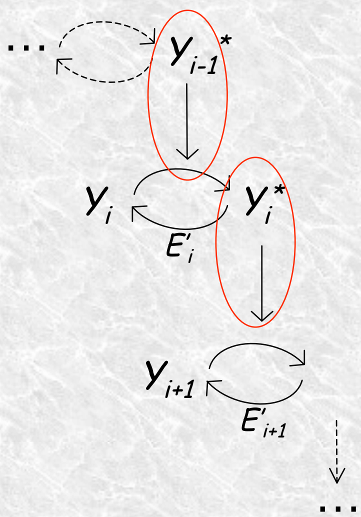
Conservation: $Y_{iT} = Y_i + \underline{Y_i^* + C_{i+1}} + C_i + C_i'$

New variable: $X_i = Y_i^* + C_{i+1}$

Small parameters:

$$\epsilon_i = \frac{E'_{iT}}{Y_{iT}}, \qquad \eta_i = \frac{Y_{i-1,T}}{Y_{iT}}, \qquad \mu_i = \frac{k_i}{k_i'}$$

A new reduced 1-variable model of the chain



$$\begin{aligned}
\dot{x}_i &= \frac{\epsilon_i k_i'}{\epsilon k'}\left(\frac{\mu_i\eta_i}{\epsilon_i} c_i - \frac{a_i' Y_{iT}}{k_i'}(x_i - c_{i+1})e_i' + \frac{d_i'}{k_i'}c_i'\right) \\
\epsilon\,\dot{c}_i &= \frac{a_i Y_{iT}}{k'}\left(y_i(x_{i-1}-c_i) - K_i c_i\right) \\
\epsilon\,\dot{c}_i' &= \frac{a_i' Y_{iT}}{k'}\left((x_i - c_{i+1})e_i' - K_i' c_i'\right)
\end{aligned}$$

$\varepsilon_i \rightarrow 0$

$\mu_i \eta_i \sim \varepsilon_i$

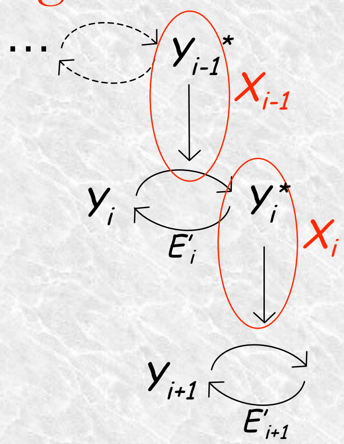
$$\dot{x}_i = V_i\, x_{i-1}\frac{y_i}{K_i + y_i} - V_i' \frac{x_i}{K_i'(1+\frac{y_{i+1}}{K_{i+1}}) + x_i}$$

$$x_i + y_i + \eta_i x_{i-1}\frac{y_i}{K_i + y_i} + O(\varepsilon_i) = 1$$

Extensions of the GK model to signaling chains

$$\dot{y}_i^* = V_i\, y^*_{i-1} \frac{y_i}{K_i + y_i} - V_i' \frac{y_i^*}{K_i' + y_i^*}$$

$$y_i^* + y_i = 1$$



$$\dot{x}_i = V_i\, x_{i-1} \frac{y_i}{K_i + y_i} - V_i' \frac{x_i}{K'_{eff,i} + x_i},$$

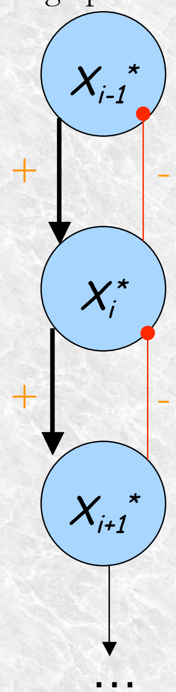
$$K'_{eff,i} = K_i'\left(1 + \frac{y_{i+1}}{K_{i+1}}\right)$$

$$x_i + y_i + \eta_i x_{i-1} \frac{y_i}{K_i + y_i} + O(\varepsilon_i) = 1$$

Negative backward feedback from the following cycle in the chain due to complex sequestration

Extensions of the GK model to signaling chains

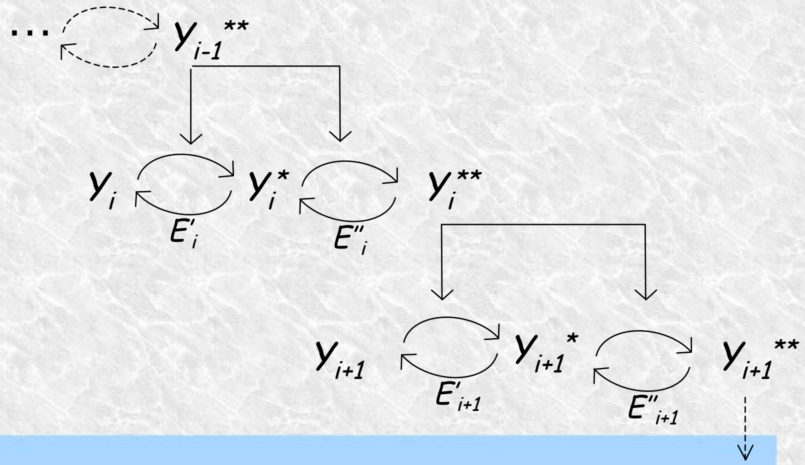
Incidence graph



$$\dot{x}_i = V_i\, x_{i-1} \frac{y_i}{K_i + y_i} - V_i' \frac{x_i}{K'_{eff,i} + x_i}$$

$$x_i + y_i + \eta_i x_{i-1} \frac{y_i}{K_i + y_i} + O(\varepsilon_i) = 1$$

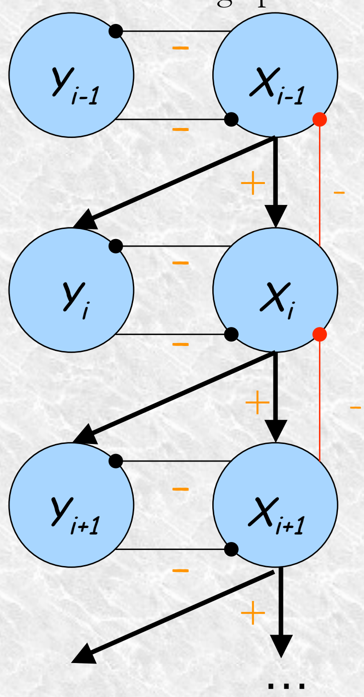
Extensions of the GK model to MAPK chain



$$\dot{x}_i = V_i\, x_{i-1} \frac{y_i^*}{K_{eff,i} + y_i^*} - V_i'' \frac{x_i}{K''_{eff,i} + x_i}$$

$$\dot{y}_i = V_i' \frac{y_i^*}{K'_{eff,i} + y_i^*} - V_i\, x_{i-1} \frac{y_i}{K_{eff,i} + y_i}$$

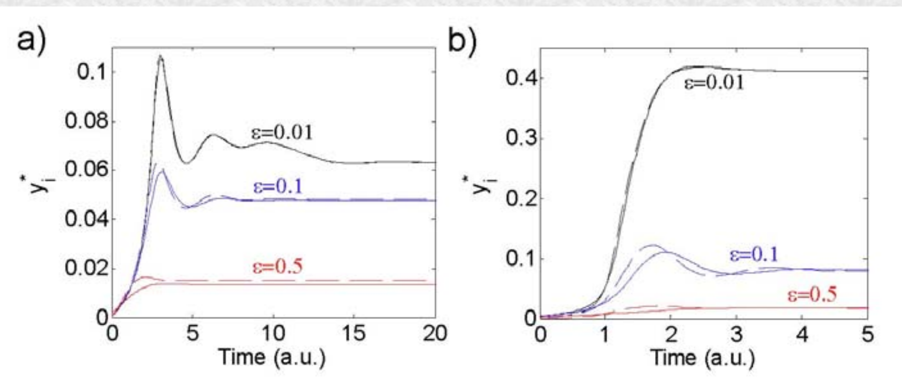
Incidence graph

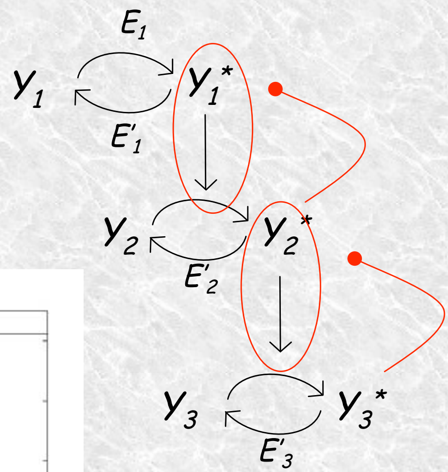


Properties revealed by the overlooked feedback

Damped temporal oscillations

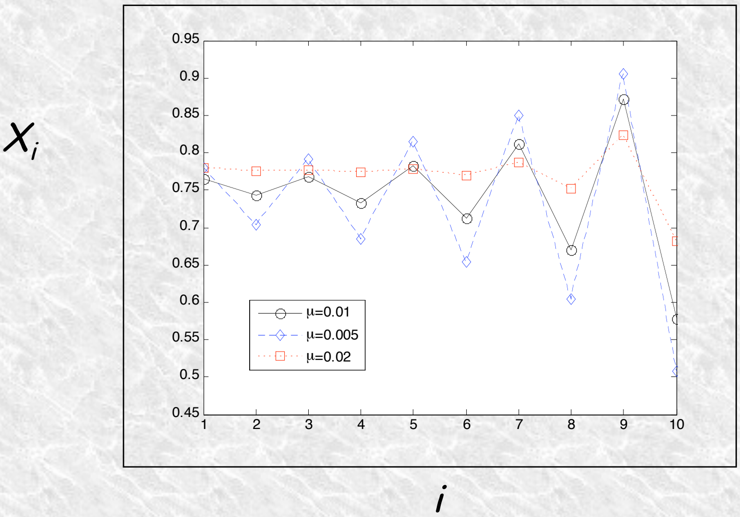
$\eta_i \sim \varepsilon_i$ $\mu_i \sim \varepsilon_i$

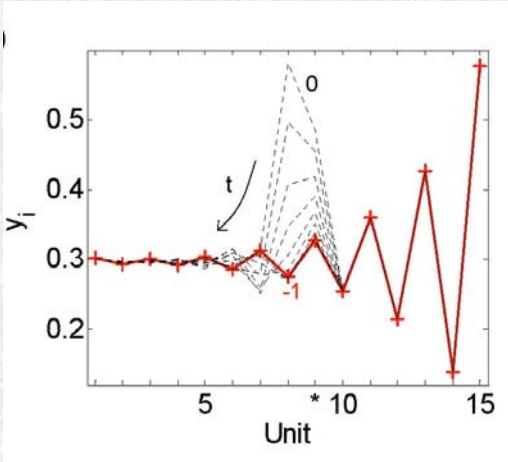




Properties revealed by the overlooked feedback

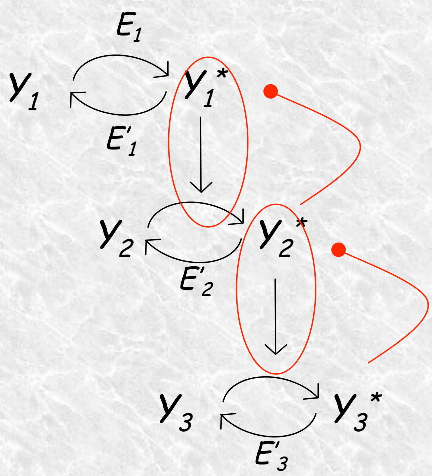
Non monotonous « spatial » profile and retrograde propagation

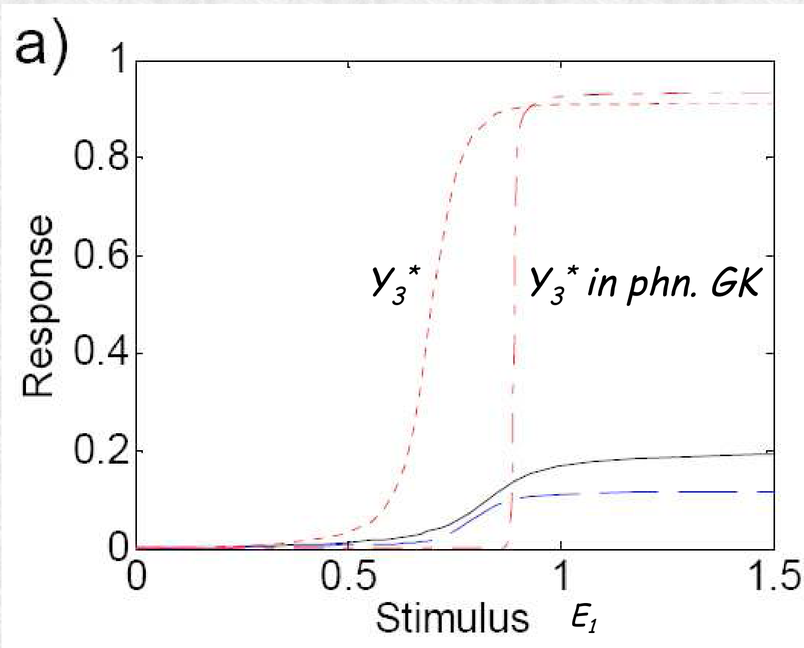




Rem: Stationary states of the reduced model are identical to the mechanistic (complete) system

Attenuation of ultrasensitivity





Rem: Stationary states of the reduced model are identical to the mechanistic (complete) system

Objectives

1. A short review of the math modeling of signaling cascades :

2. A new system of equations which challenges the concept of only unidirectional « cascades »

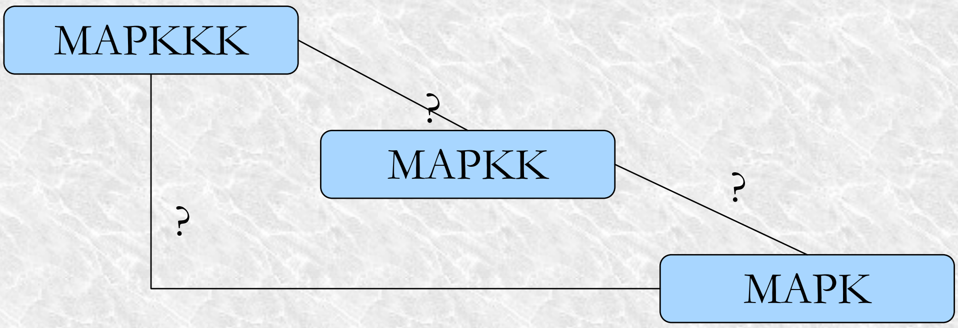
3. Towards experimental confrontations ?

    1) Modular Response Analysis

    2) Prediction of stimulus-response curves

Modular Response Analysis method (MRA)

Kholodenko et al. (PNAS, 2002):



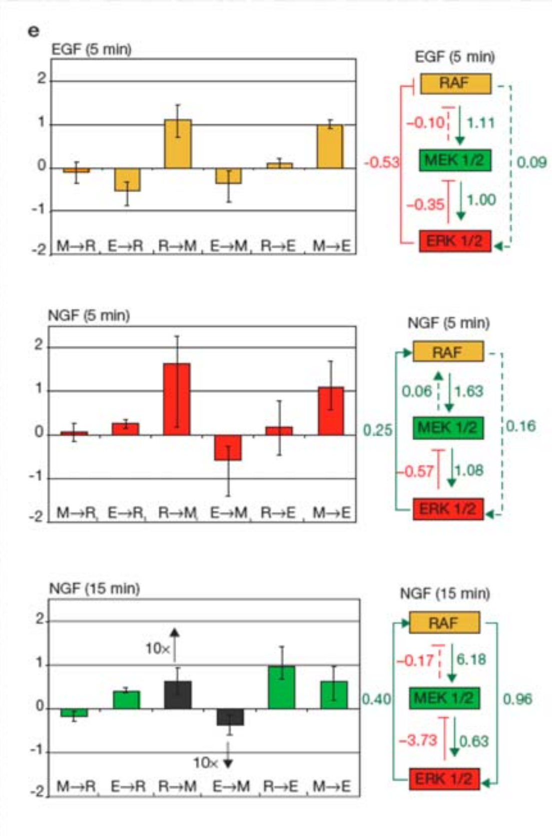
Modular Response Analysis:
-perturb each module separatly
-compute the global response coefficients:

$$R_{ij} = \frac{1}{x_i}\frac{dx_i}{dp_j}$$

-Deduce the local response matrix:

$$r_{ij} = -(R^{-1}_{ii})^{-1} R^{-1}_{ij} = -\left(x_j \frac{\partial f_i}{\partial x_j}\right) \Big/ \left(x_i \frac{\partial f_i}{\partial x_i}\right)$$

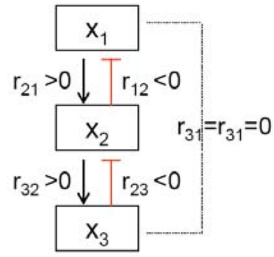
Santos, Verveer and Bastiaens, *Nat. Cell Biol.* (2007)



Our computation

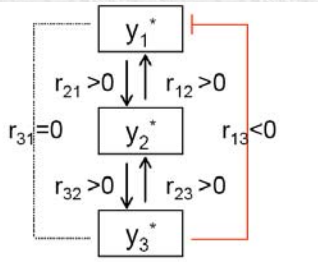
'total' active enzyme

r_{11} -1	r_{12} -1.50	r_{13} 0
r_{21} 0.05	r_{22} -1	r_{23} -0.01
r_{31} 0	r_{32} 0.03	r_{33} -1

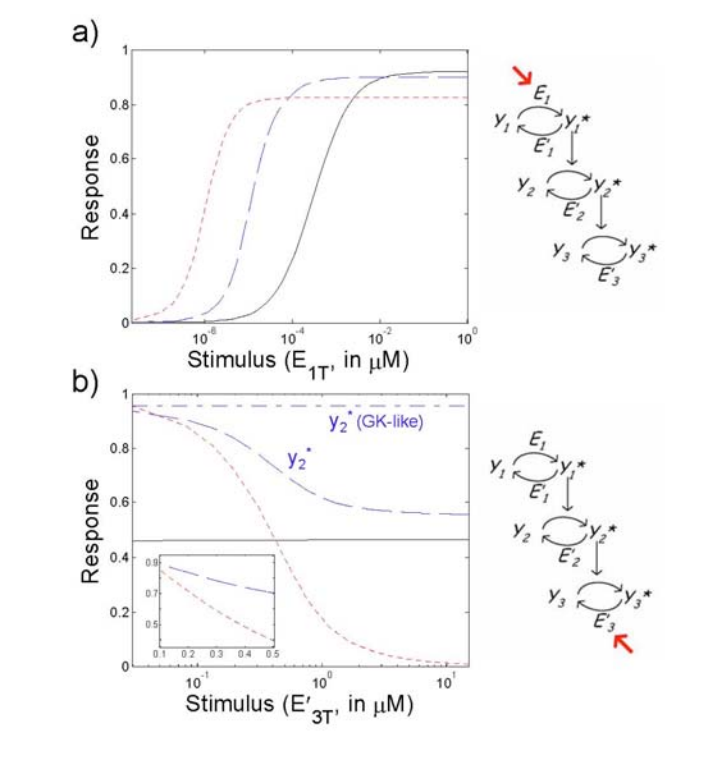


'free ' active enzyme

r_{11} -1	r_{12} 1.63	r_{13} -1.20
r_{21} 0.05	r_{22} -1	r_{23} 0.73
r_{31} 0	r_{32} 0.02	r_{33} -1



Prediction of a reverse stim-resp curve



Y_1 = *Raf*

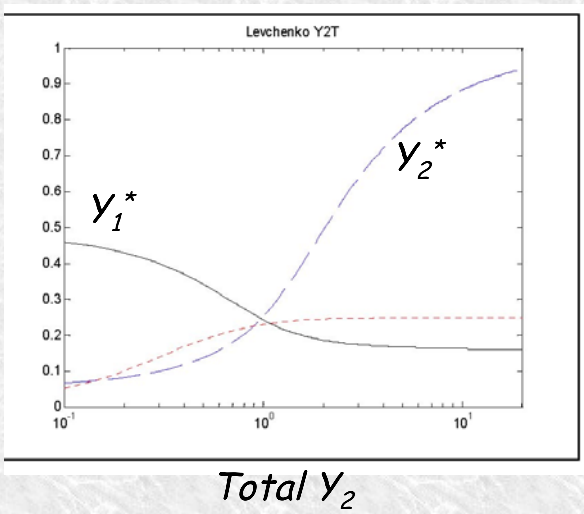
Y_2 = *Mek*

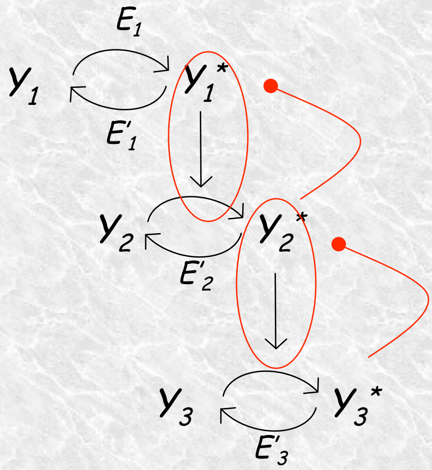
Y_3 = *Erk*

(Using the Huang-Ferrel, PNAS 1996, data parameters for the vertebrate Erk1/Erk2 MAPK cascade)

Prediction of reverse stim-resp curves

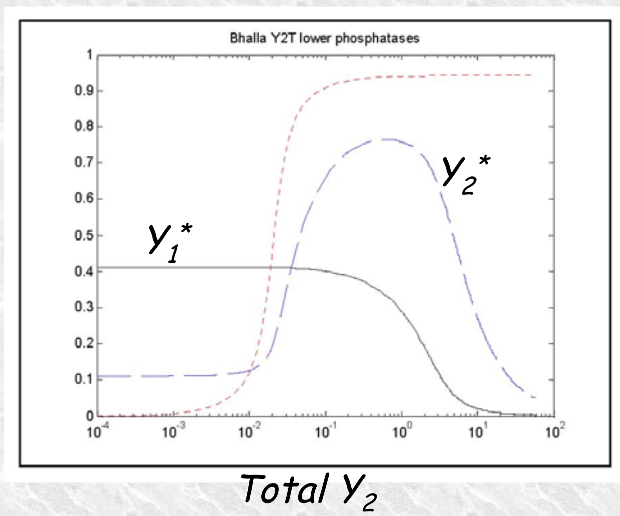
Using parameter of D. Levchenko, PNAS 1998
MAPK in the pheromone pathway in yeast

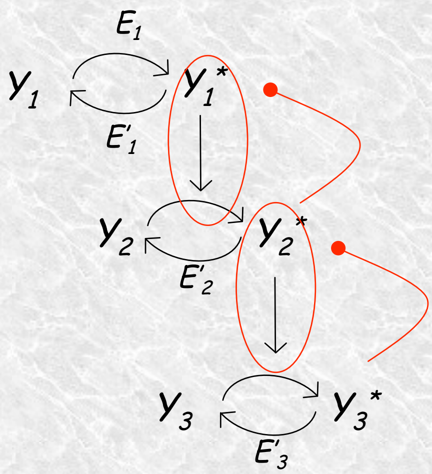




Prediction of reverse stim-resp curve

Using parameter of Bhalla and Iyengar, Science 1999
MAPK pathway in neurons.





Conclusions

1. A new model for signaling cascade with 1-variable per cycle highlights the effect of a backward feedback due to protein sequestration.

2. There are various consequences of this backward feedback, e.g. possibily of temporal and « pathway » oscillations.

3. We predict the possibility of reverse stimulus-response curves.

Applications for crosstalk ?