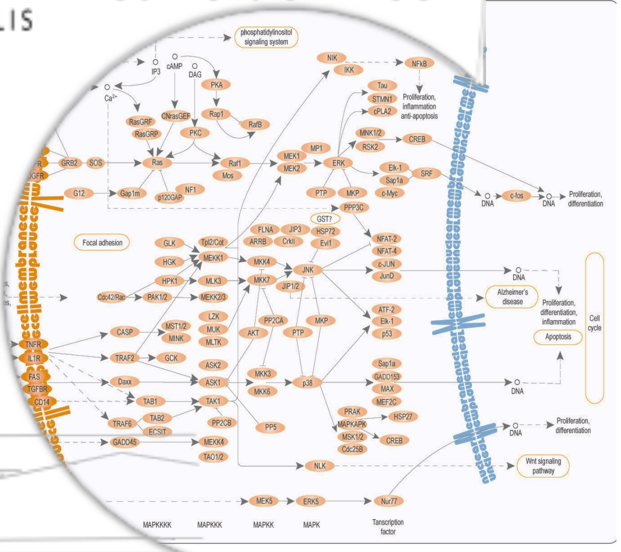
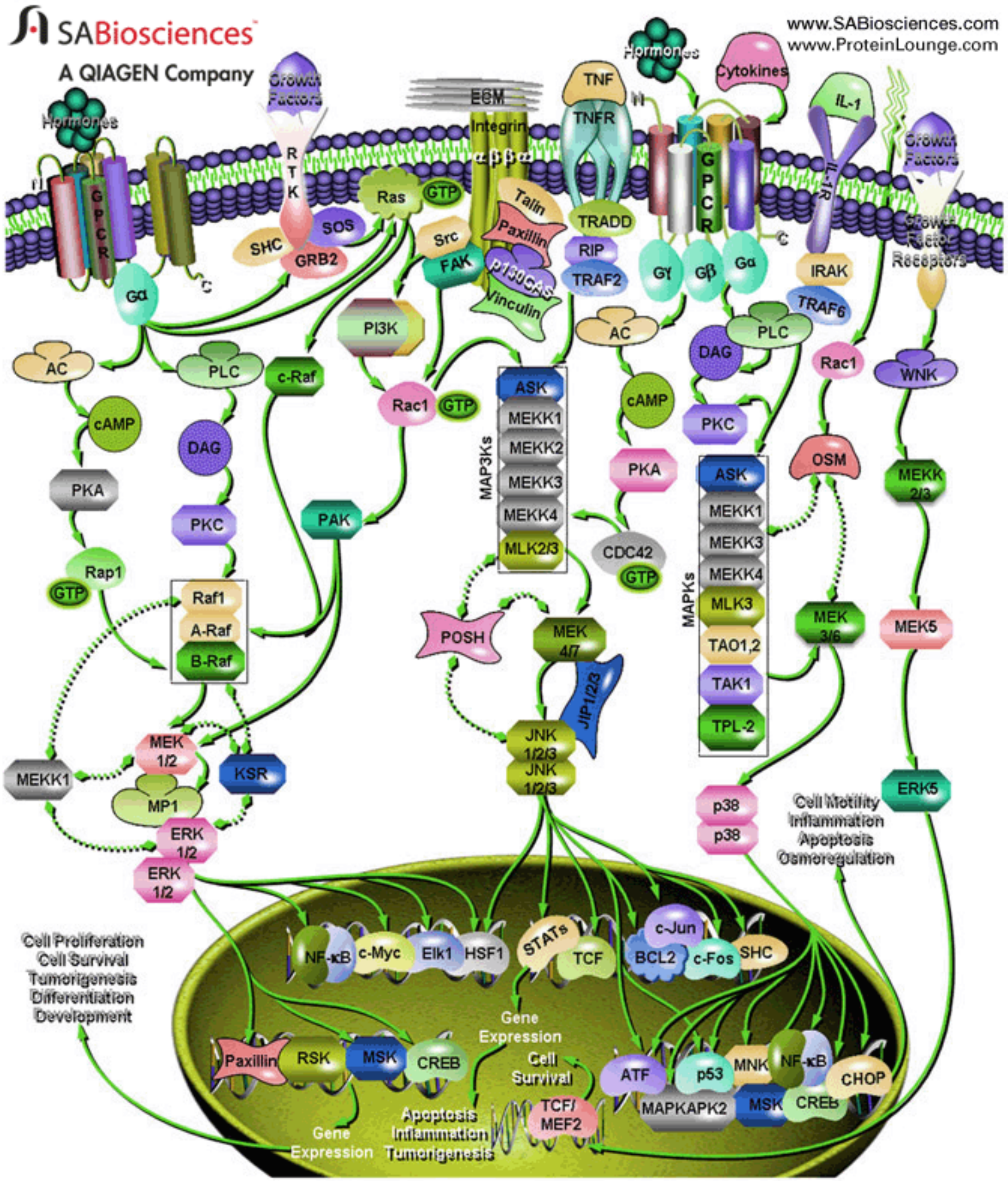
Institut Non Linéaire de Nice

Un grain de sel de la physique non linéaire dans la soupe moléculaire d'une cellule vivante

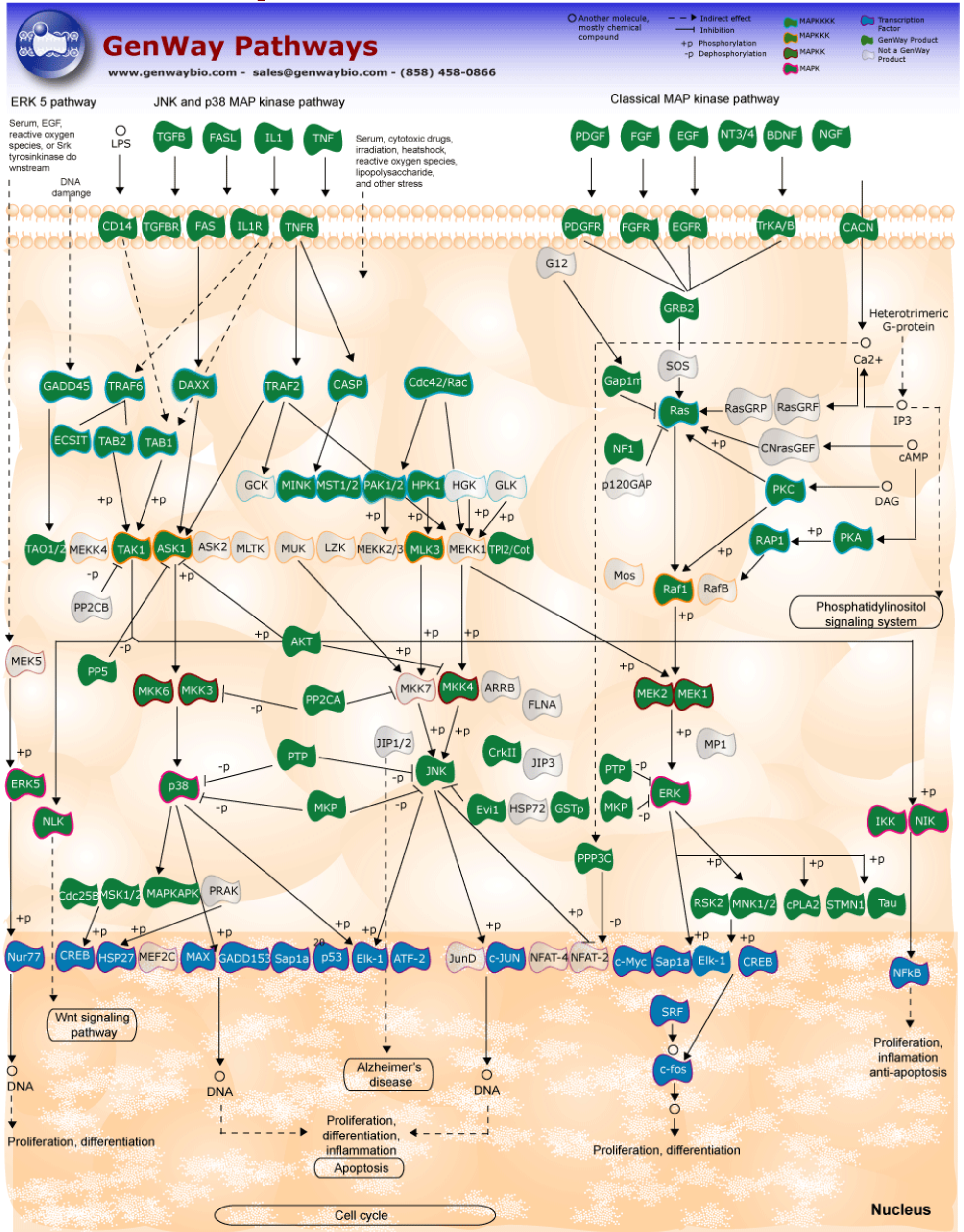


Jacques-Alexandre SEPULCHRE

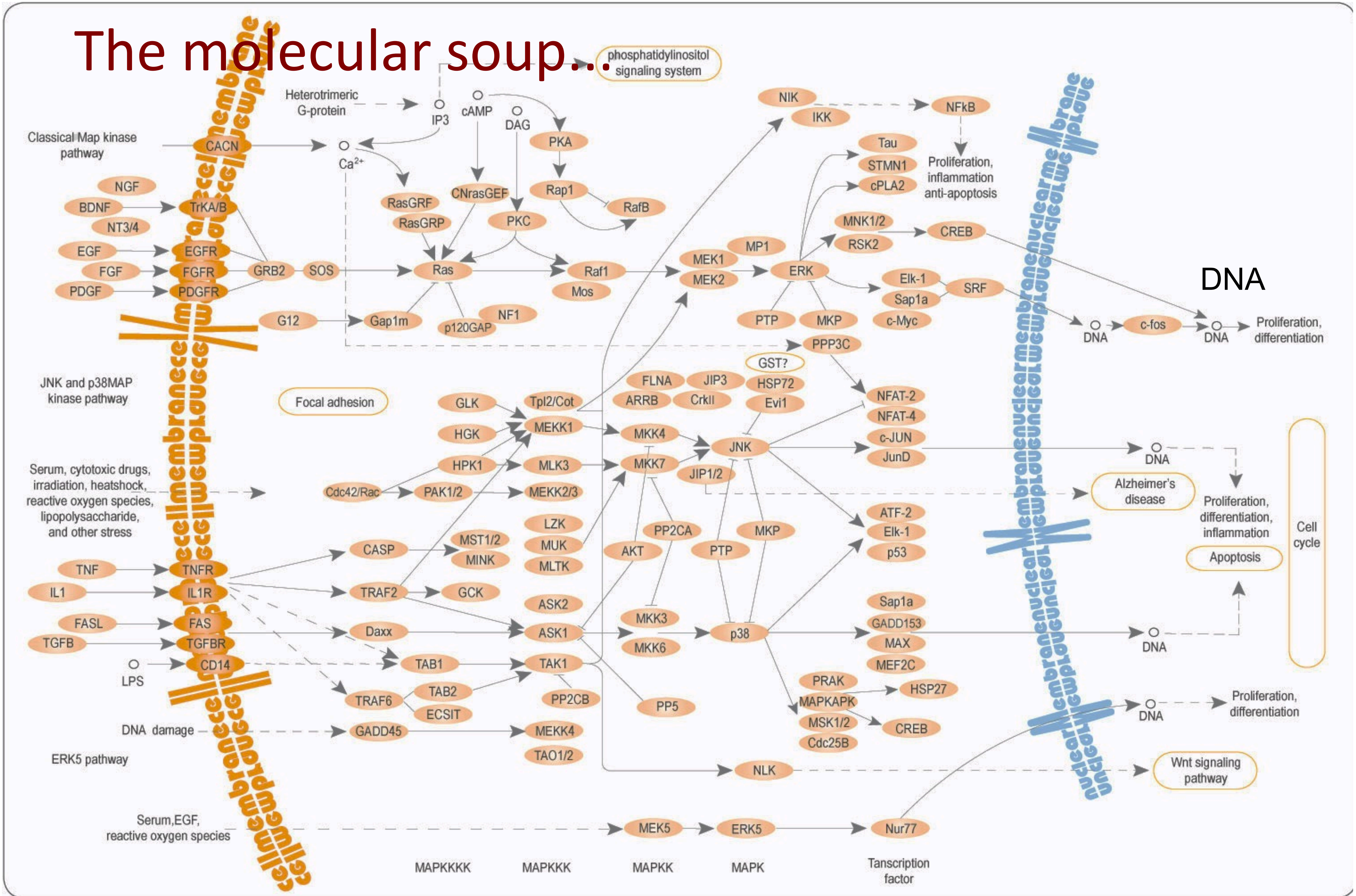
The molecular soup...



The molecular soup...



The molecular soup…



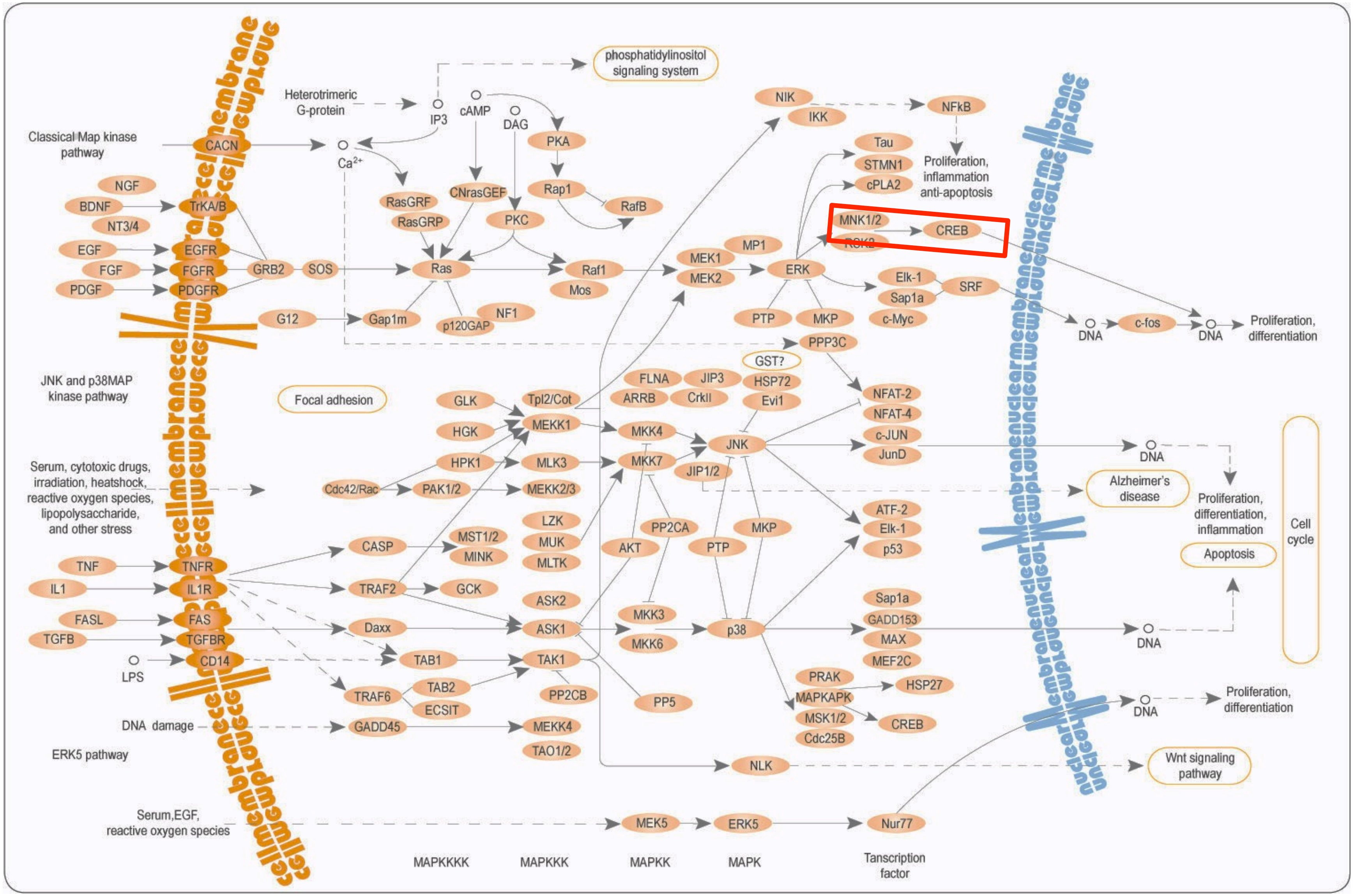
Plan

1. Some principles of the modeling of intracellular biochemical kinetics by coupled ODEs

2. Optimal response of genetic expression under periodic stimulations

3. Onset of autonomous periodic oscillations in signaling cascades

1. Some principles of the modeling…



1. Some principles of the modeling…

Enzymatic activation (e.g. phosphorylation)

$$MNK + CREB \longleftrightarrow C \longleftrightarrow MNK + CREB^*$$

$$P + CREB^* \longleftrightarrow C^* \longleftrightarrow P + CREB$$

$$\Rightarrow \quad \frac{d[CREB]}{dt} = \dots$$

$$\frac{d[C]}{dt} = \dots, \quad \frac{d[C^*]}{dt} = \dots$$

a) Kinetics associated with the *law of mass action* (→ 3 var.)

b) Kinetics associated with the Michaelis-Menten approximation (→ 1 var.)

$$x = \frac{[CREB^*]}{[CREB]_{total}},$$

$$\frac{dx}{dt} = k[MNK]_{total} \frac{(1-x)}{K+(1-x)} - k'[P]_{total} \frac{x}{K'+x}$$

Rem : an enzymatic activation involves often a double phosphorylation

1. Some principles of the modeling…

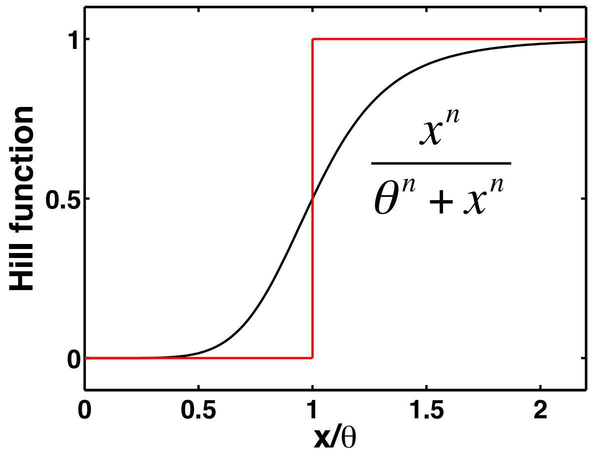
Activation of a gene by a transcription factor

$$n\,CREB^{*} + DNA + polymerase + nucleotids \longrightarrow n\,CREB^{*} + DNA + polymerase + mRNA$$

$$mRNA + ribosomes + amino - acids \longrightarrow mRNA + ribosomes + protein$$

Phenomenological kinetics with a Hill function :

$$\frac{dA}{dt} = \beta \frac{x^n}{\theta^n + x^n} - \alpha A$$



Approximation : $\frac{x}{\theta^n + x^n} \approx H(x-\theta)$

1. Some principles of the modeling…

Activation of a gene by a transcription factor

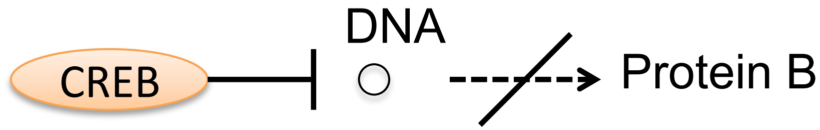
$$n\,CREB^* + DNA + polymerase + nucleotids \longrightarrow n\,CREB^* + DNA + polymerase + mRNA$$

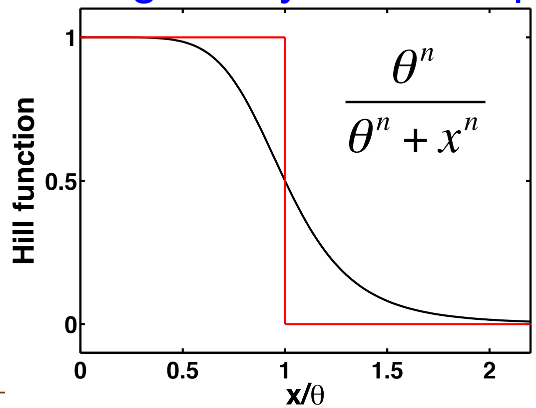
$$mRNA + ribosomes + amino - acids \longrightarrow mRNA + ribosomes + protein$$

Phenomenological kinetics with a Hill function :

$$\frac{dA}{dt} = \beta \frac{x^n}{\theta^n + x^n} - \alpha A$$

Repression of a gene by a transcription factor:





$$\frac{dB}{dt} = \beta \frac{\theta^n}{\theta^n + x^n} - \alpha B$$

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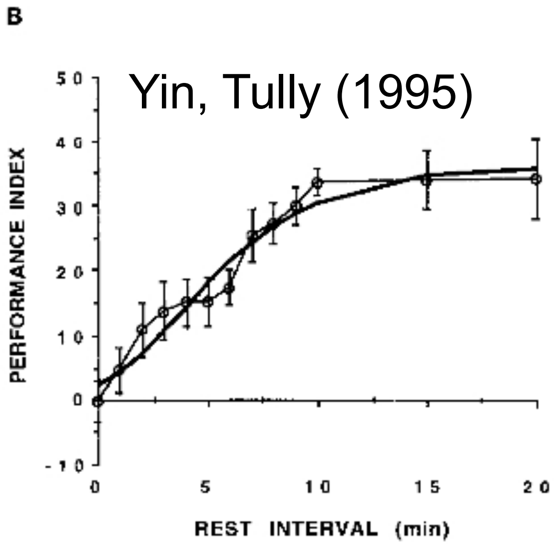
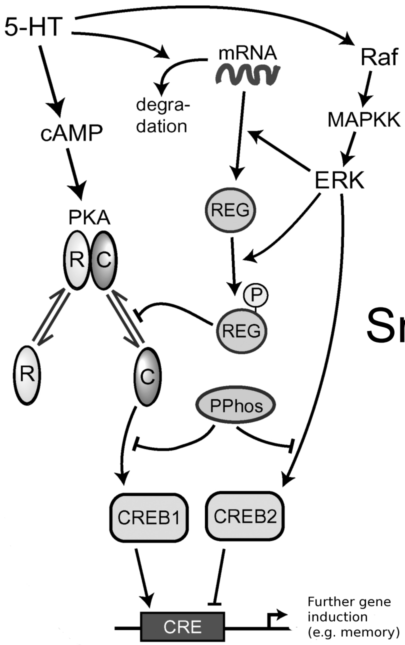
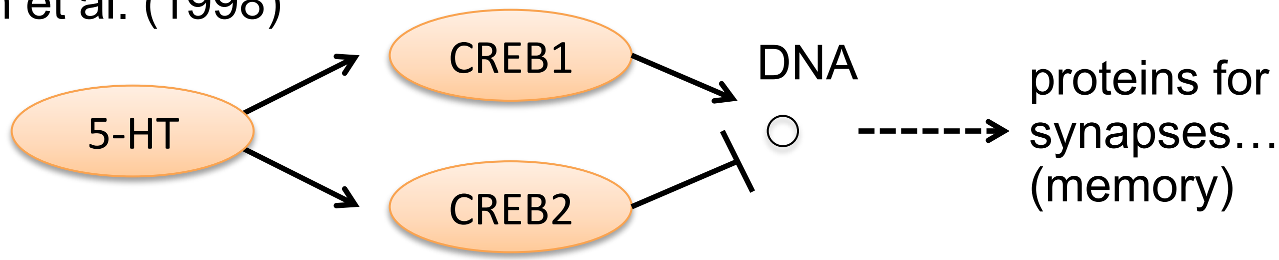
2. Optimal response of genetic expression under periodic stimulation

Context : periodic stimulations associated with the formation of memory … in the drosophila.

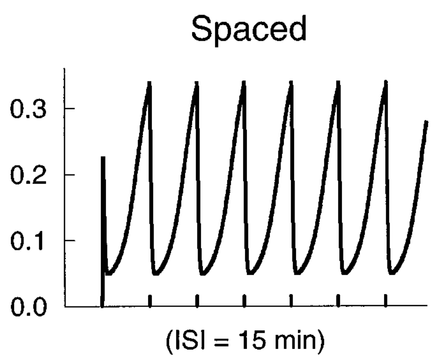


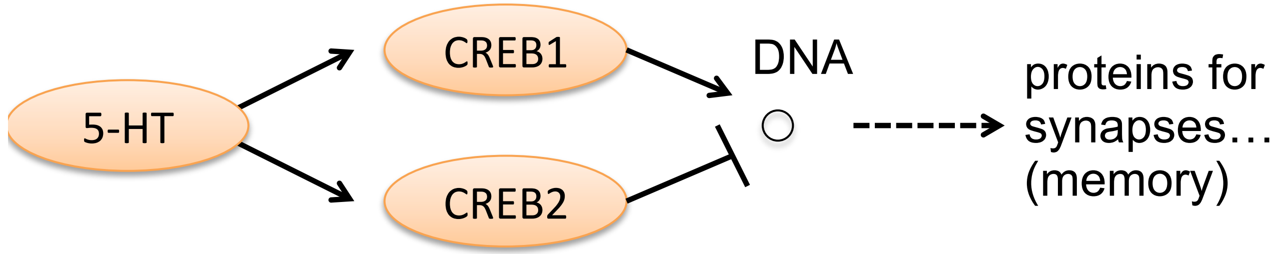


Smolen et al. (1998)



Qualitative modeling (Smolen et al, , *Am J Physiol Cell Physiol, 1998*)





$$\frac{d[AP]}{dt} = k_{A,f}(t)\,\frac{2A_{tot} - [AP]}{2A_{tot} - [AP] + K_{A,ph}} - k_{A,b}\,\frac{[AP]}{[AP] + K_{A,deph}} \quad (A1)$$

$$\frac{d[AA]}{dt} = -k_{1,f}\,[AA]\,G_{free} + k_{1,b}\,[AAB] \quad (A2)$$

where $[AAB] = A_{tot} - [AA]$.

$$r_{Rep} = k_{Rep}\,\frac{[AAB]\,[AP]}{A_{tot}} \quad (A9)$$

$$\frac{d[Rep]}{dt} = r_{Rep} - [Rep] \quad (A11)$$

$$\frac{d[L1]}{dt} = \frac{r_{L1}}{(1 + [Rep]^2/K_{Rep}^{\,2})} - [L1] \quad (A12)$$

$G_{tot} = 0.1$	$A_{tot} = 1.0$	$R_{tot} = 3.0$
$K_{A,ph} = 20.0$	$K_{A,deph} = 20.0$	$k_{A,b} = 0.7\ min^{-1}$
$k_{R,b} = 7.0\ min^{-1}$	$k_{1,f} = 10.0\ min^{-1}$	$k_{1,b} = 10.0\ min^{-1}$
$K_{R,ph} = 10.0$	$K_{R,deph} = 10.0$	$k_{2,f} = 10.0\ min^{-1}$
$k_{2,b} = 1.0\ min^{-1}$	ISI varies	$k_{A,max} = 30\ min^{-1}$
$k_{R,max} = 30\ min^{-1}$	$\tau_1 = 4.0$ min	$\tau_2 = 4.0$ min

$$r_{R,ph} = k_{R,f}(t)\,\frac{2[RR] + [RRP]}{2[RR] + [RRP] + K_{R,ph}} \quad (A3)$$

$$r_{R,deph} = k_{R,b}\,\frac{2[RRPP]+[RRP]}{2[RRPP]+[RRP]+K_{R,deph}} \quad (A4)$$

$$\frac{d[RR]}{dt} = -\,r_{R,ph}\,\frac{2[RR]}{2[RR] + [RRP]} + r_{R,deph}\,\frac{[RRP]}{2[RRPP] + [RRP]} \quad (A5)$$

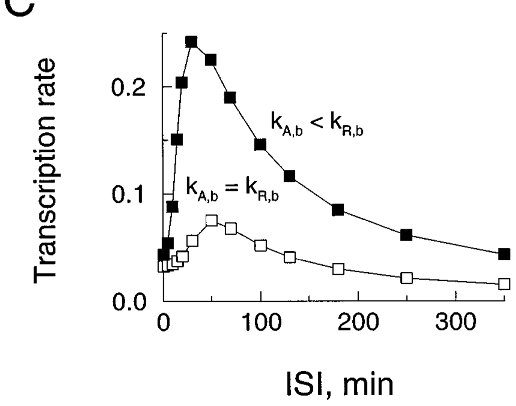
$$\frac{d[RRP]}{dt} = r_{R,ph}\,\frac{2[RR]}{2[RR] + [RRP]} - r_{R,deph}\,\frac{[RRP]}{2[RRPP] + [RRP]} - r_{R,ph}\,\frac{[RRP]}{2[RR] + [RRP]} + r_{R,deph}\,\frac{2[RRPP]}{2[RRPP] + [RRP]} \quad (A6)$$

$$\frac{d[RRPP]}{dt} = r_{R,ph}\,\frac{[RRP]}{2[RR] + [RRP]} - r_{R,deph}\,\frac{2[RRPP]}{2[RRPP] + [RRP]} - k_{2,f}\,[RRPP]\,G_{free} + k_{2,b}\,[RRPPB] \quad (A7)$$

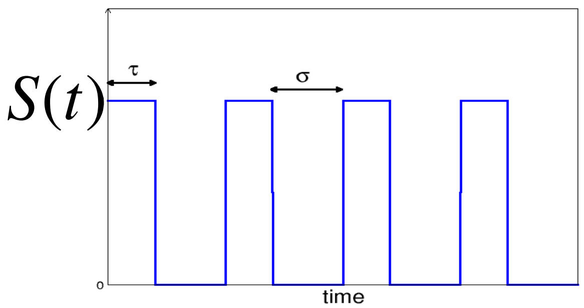
$$\frac{d[RRPPB]}{dt} = k_{2,f}\,[RRPP]\,G_{free} - k_{2,b}\,[RRPPB] \quad (A8)$$

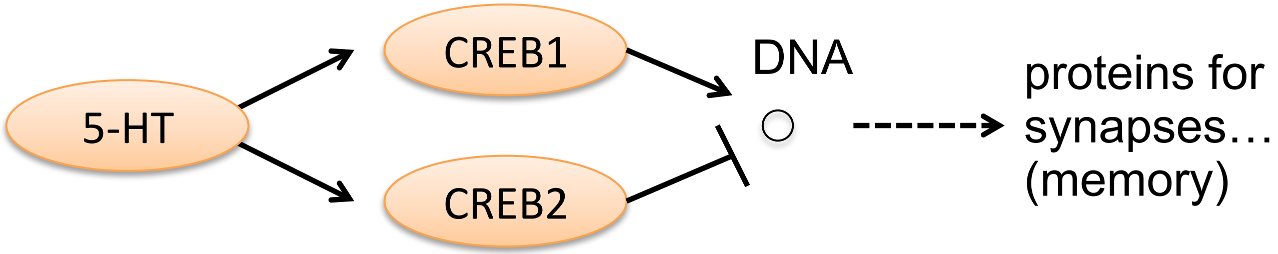
Result :
« frequency selectivity »
In the gene response

C



Qualitative modeling (A. Cournac and JAS, *BMC Systems Biol., 2009*)





$$\dot{x} = k\ S(t)(x_{tot} - x) - k'\ x$$

$$\dot{y} = k\ S(t)(y_{tot} - y) - k'\ y$$

$$\dot{z} = \beta\ H(x - \theta_1)H(\theta_2 - y) - \alpha\ z$$

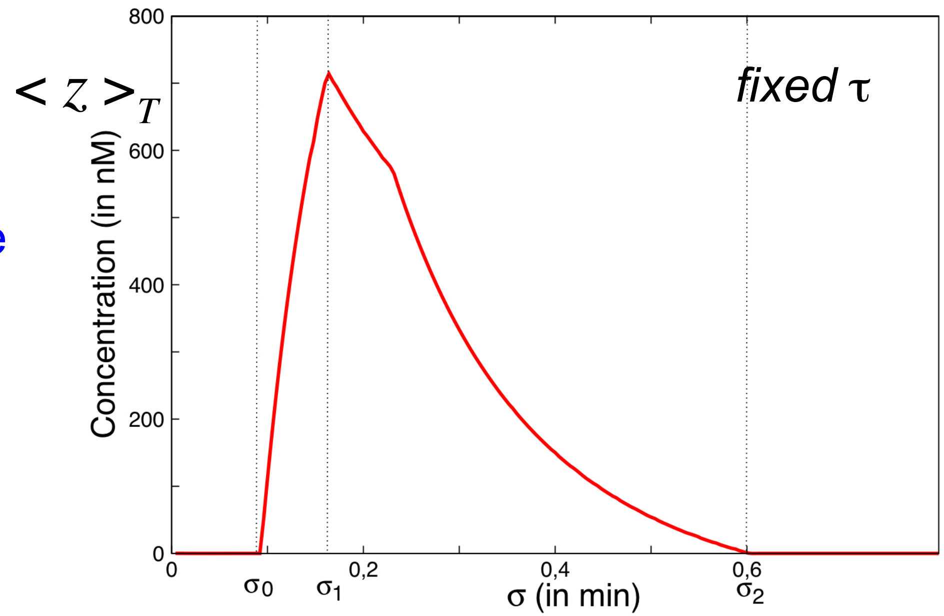
Result :
interspike selectivity
In the gene response

Some benefits of the simplified modeling:

- Analytical calculations are made possible

- Highlight the role of repressor,
(and a closed link with the IFFL of U. Alon)

- Highlight the role of the interspike rather than the frequency of the simulus



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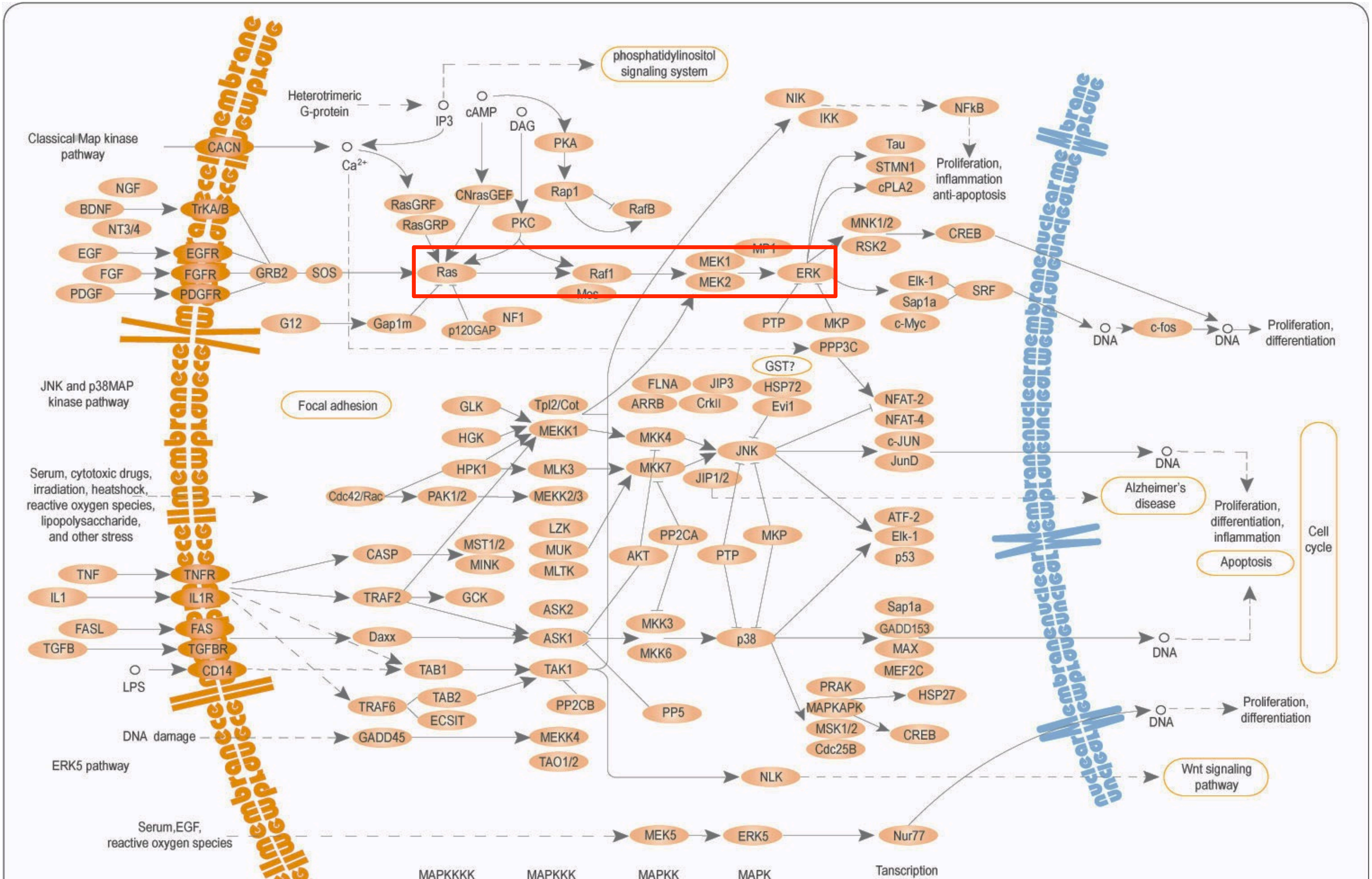
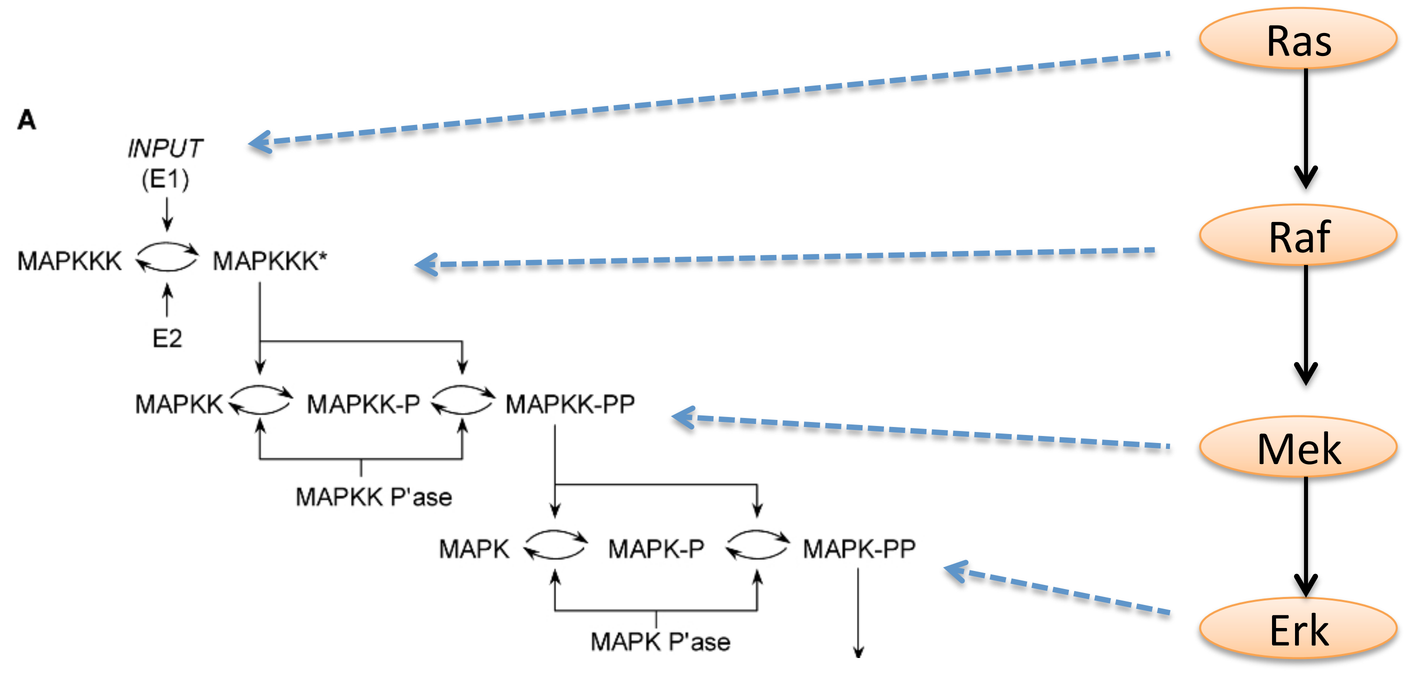
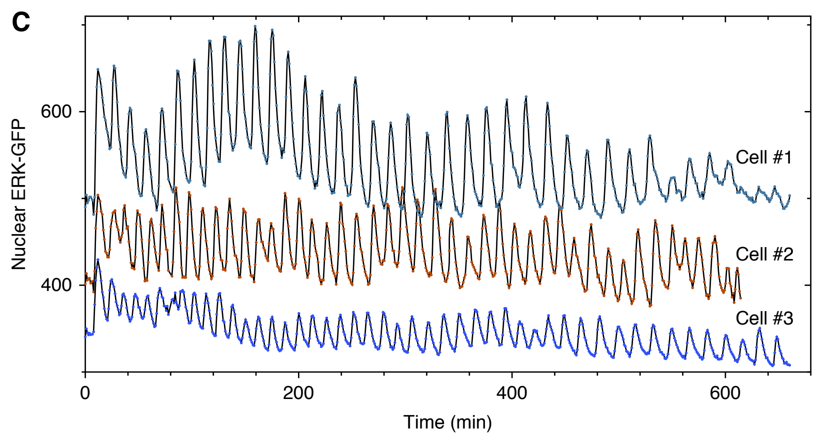
3. Periodic oscillations in signaling cascades



Autonomous oscillations in MAPK cascade

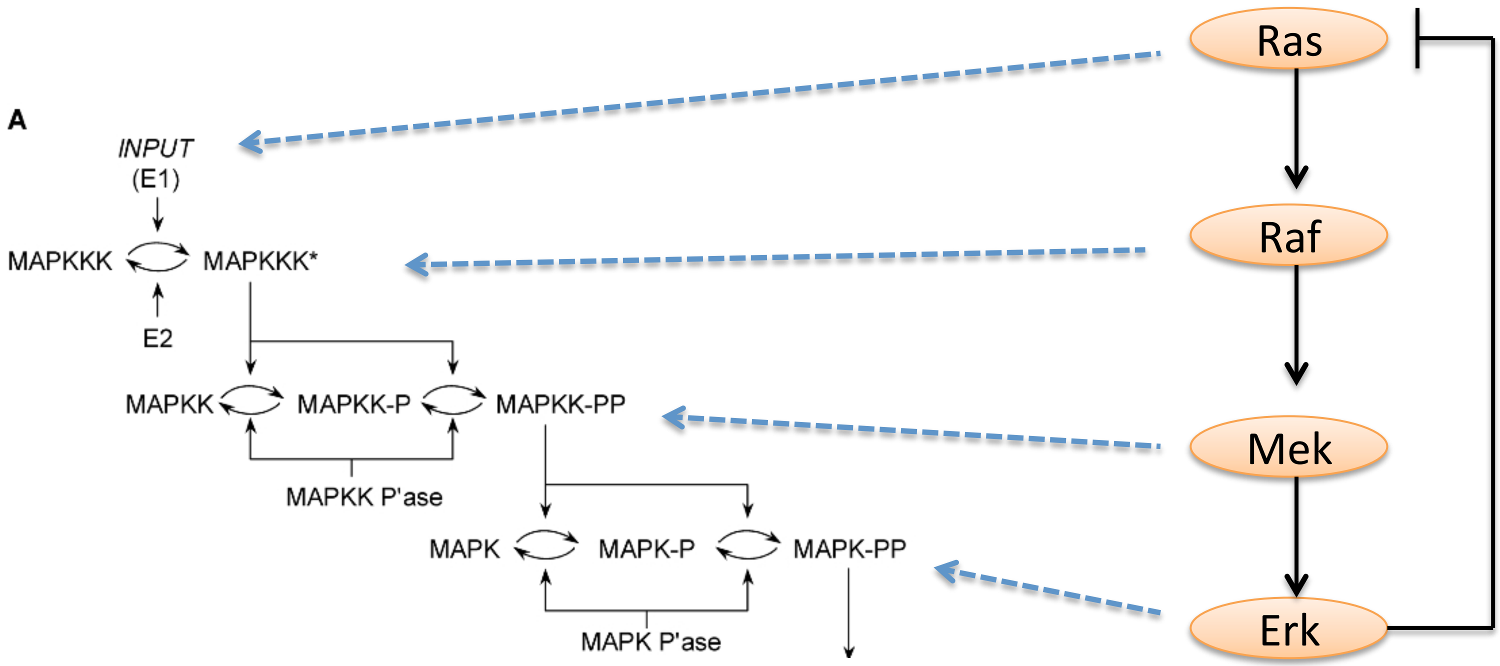




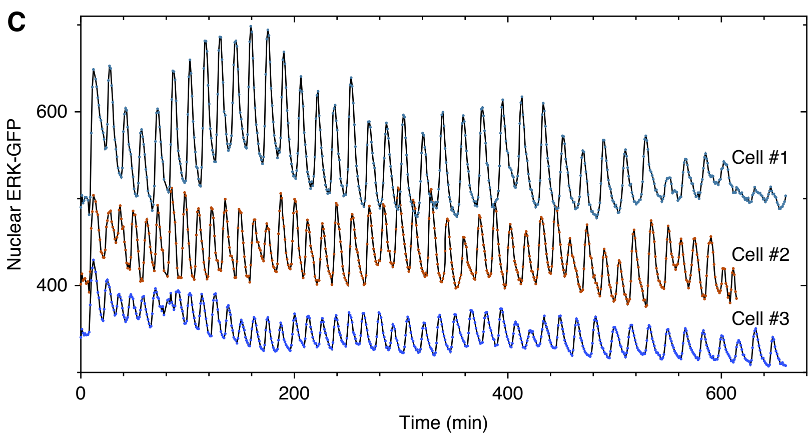
Rapid and sustained nuclear–cytoplasmic ERK oscillations induced by epidermal growth factor

Shankaran et al. Mol. Syst. Biol. 2009.

Autonomous oscillations in MAPK cascade



(negative feedback loop)



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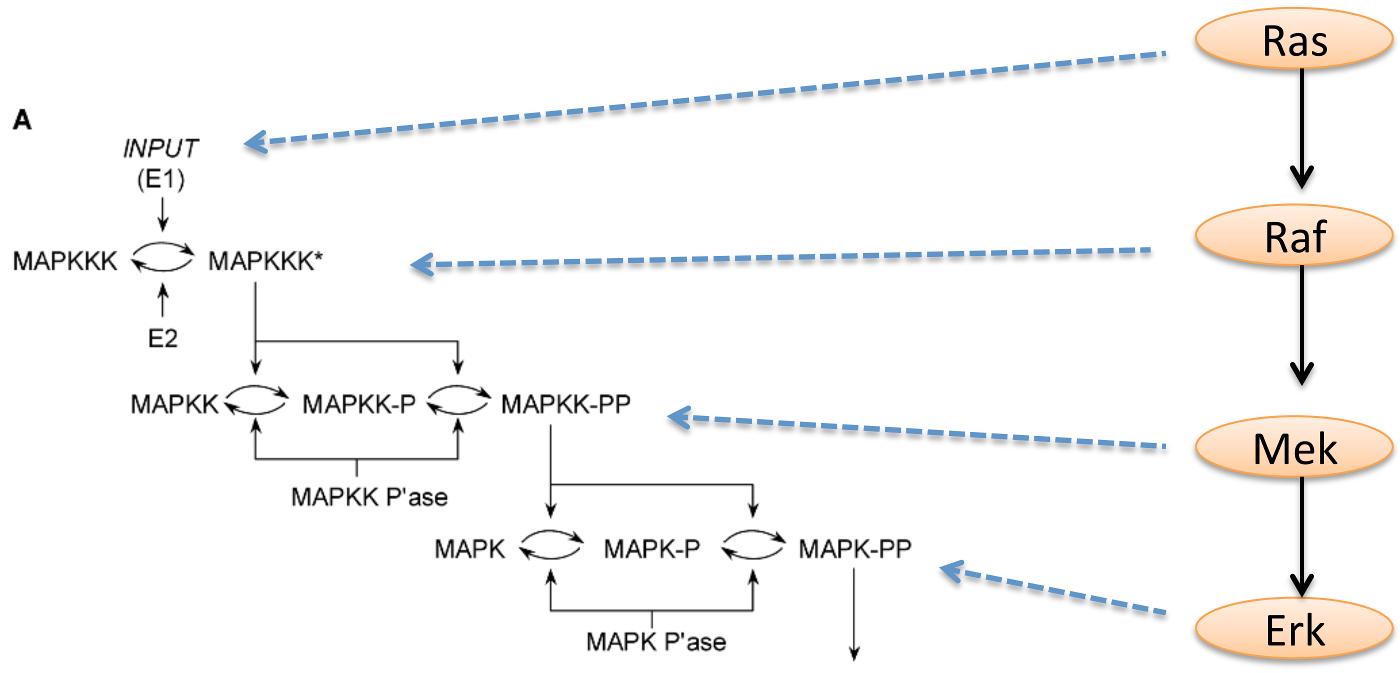
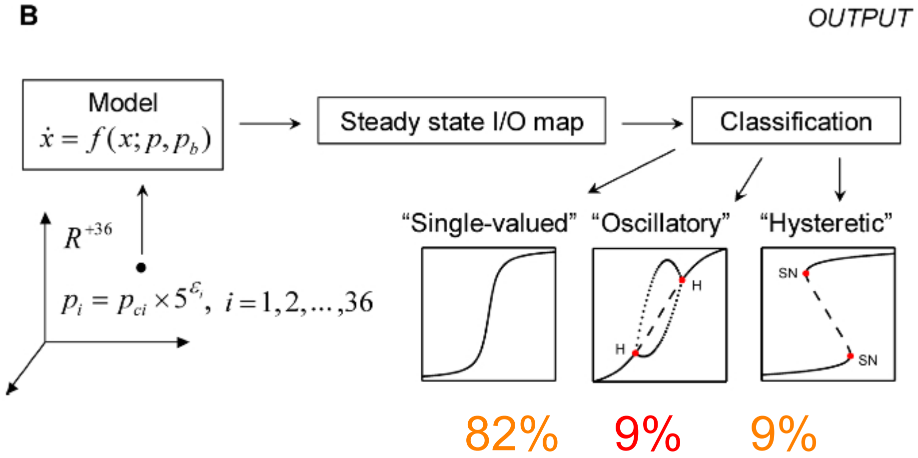
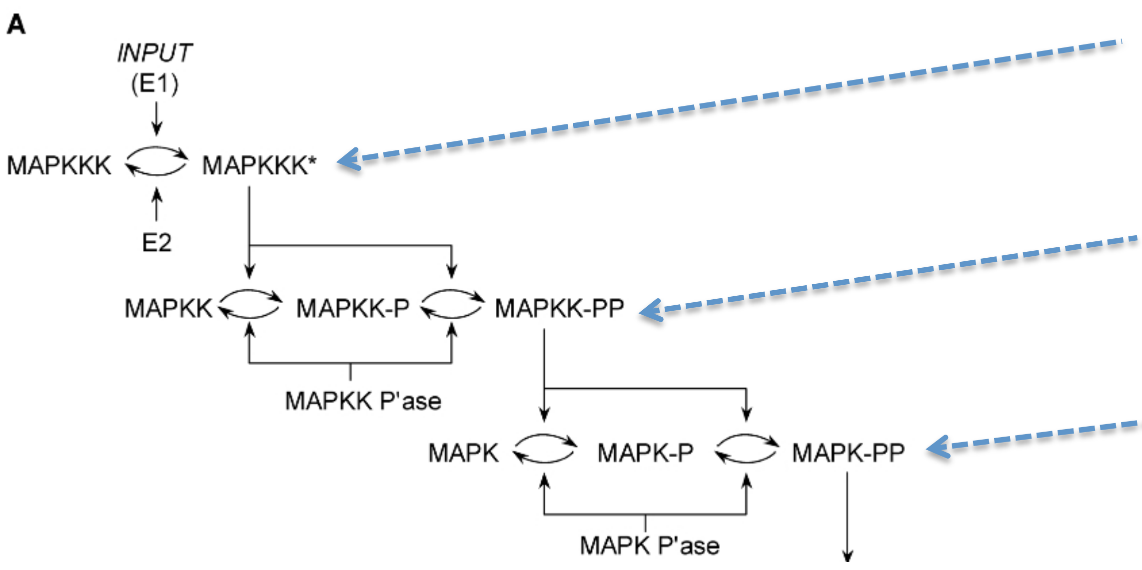




Qiao et al., (PLoS sept. 2007)

Autonomous oscillations in MAPK cascade



$$\dot{y}_1^* = V_1 \frac{y_1}{K_1 + y_1} - V_1' \frac{y_1^*}{K_1' + y_1^*}$$

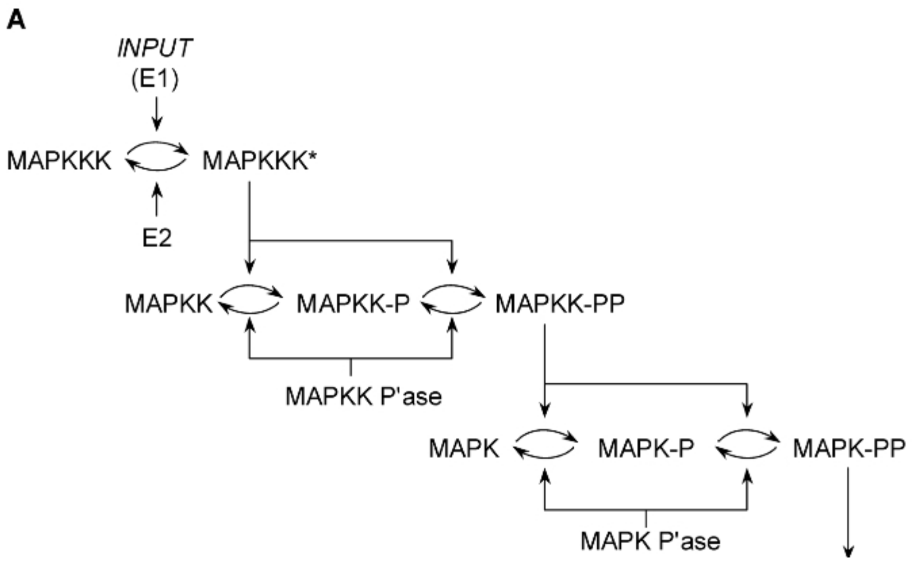
$$\dot{y}_2^* = V_2 y_1^* \frac{y_2}{K_2 + y_2} - V_2' \frac{y_2^*}{K_2' + y_2^*}$$

$$\dot{y}_3^* = V_3 y_2^* \frac{y_3}{K_3 + y_3} - V_3' \frac{y_3^*}{K_3' + y_3^*}$$

$$with \quad y_i = 1 - y_i^*$$

(e.g. Kholodenko,2000, Angeli et al, 2004, Giuraniuc et al, 2007)

Autonomous oscillations in MAPK cascade



Results from a rigorous perturbation scheme
(Ventura, JAS, PLoS CB 2008)

$$\dot{x}_1 = V_1 E_1 \frac{y_1}{K_1 + y_1} - V_1' \frac{x_1}{K_1'(1 + y_2 / K_2) + x_1}$$

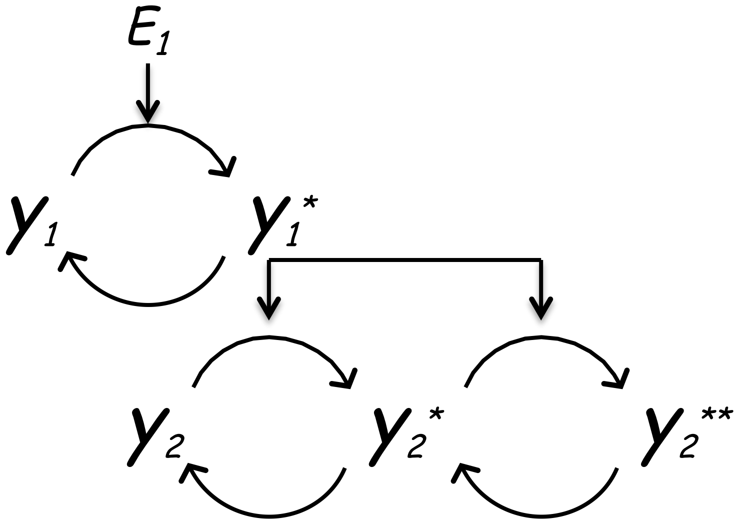
$$\dot{x}_2 = V_2 x_1 \frac{y_2}{K_2 + y_2} - V_2' \frac{x_2}{K_2'(1 + y_3 / K_3) + x_2}$$

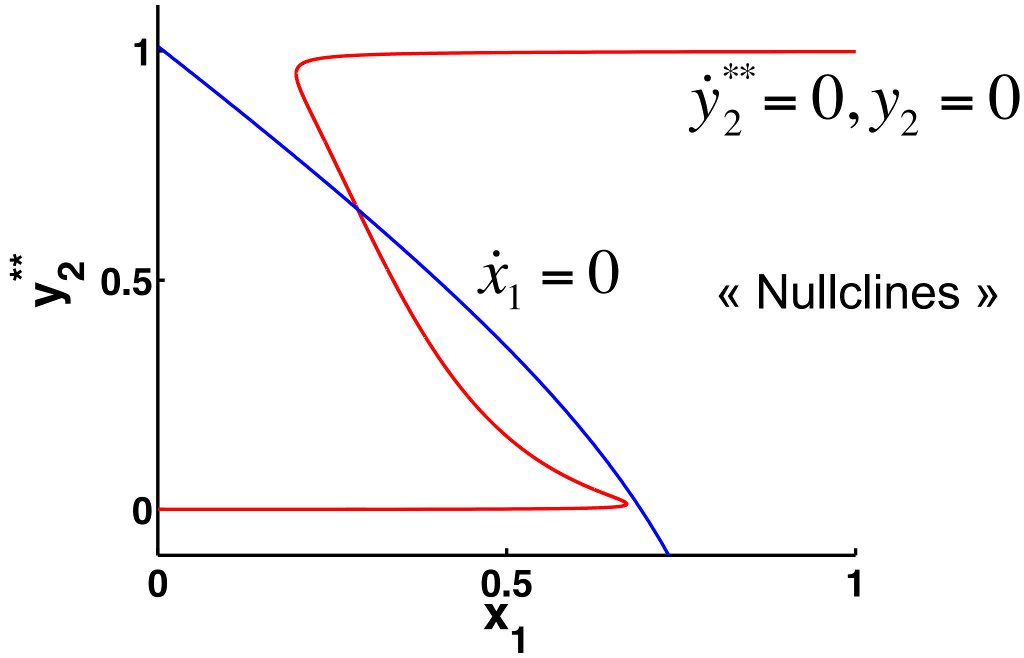
$$\dot{x}_3 = V_3 x_2 \frac{y_3}{K_3 + y_3} - V_3' \frac{x_3}{K_3' + x_3}$$

$$with \quad y_i = 1 - x_i \quad and \quad x_i = y_i^*(1 + y_{i-1} / K_{i-1})$$

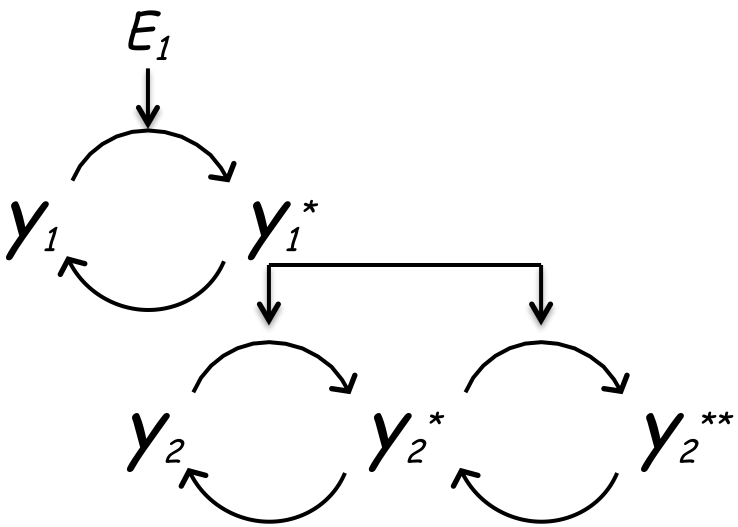
There is a intrinsic negative feedback

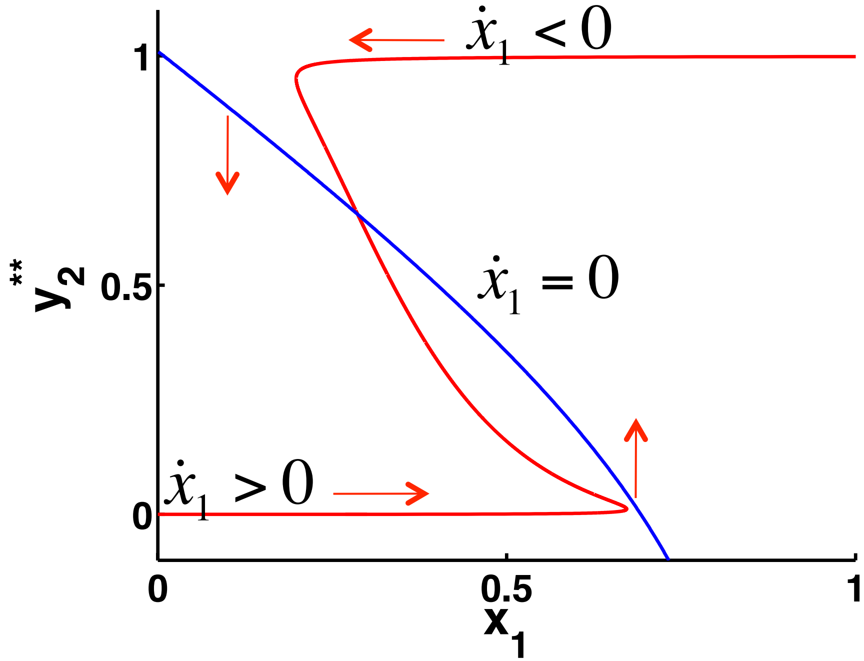
Autonomous oscillations in MAPK cascades



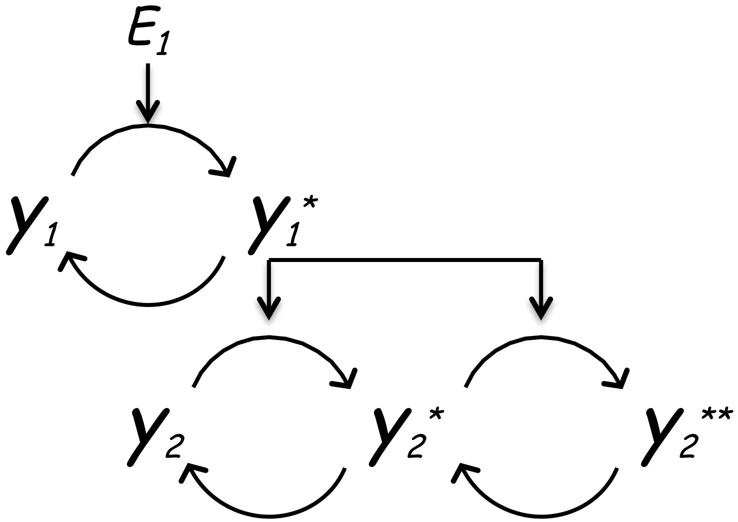


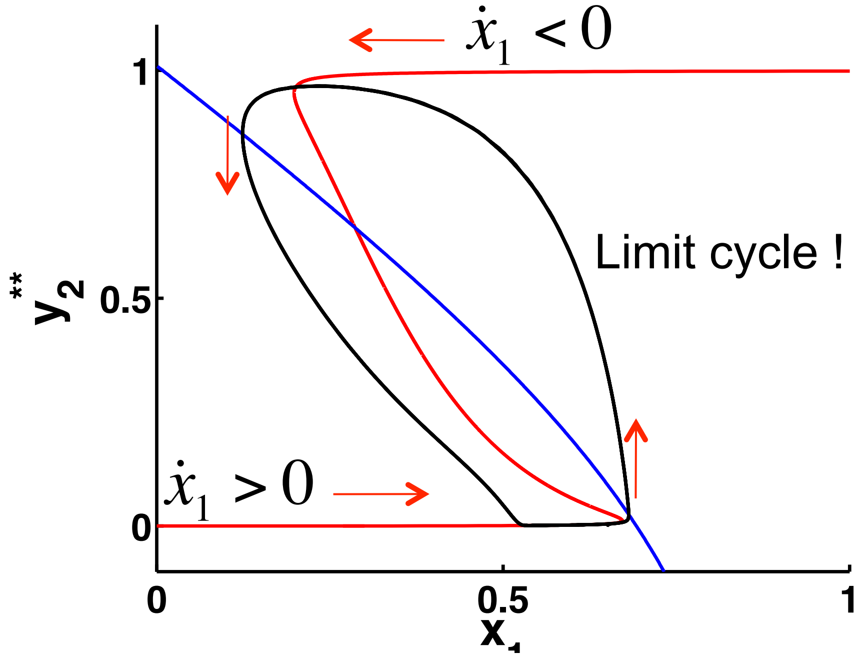
Autonomous oscillations in MAPK cascades



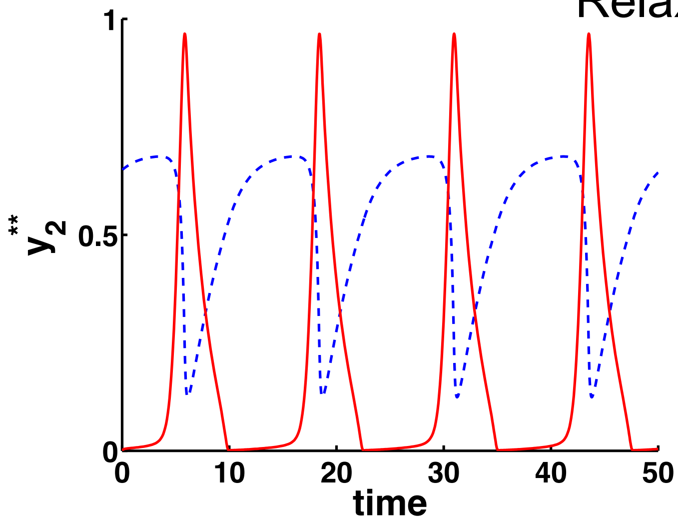


Autonomous oscillations in MAPK cascades





Relaxation oscillations



Bifurcations:

- Supecritical Hopf bifurcation
- Saddle-node bifurcation on a cycle

Conclusion : via 2 study cases, we saw that

1. Periodic pulsatile stimulations of gene network motifs can lead to optimal response in the production of proteins. (Possible applications to memory formation)

2. A negative retroactivity exists in signaling cacades. It leads to the possibility of autonomous oscillations in (MAPK) signaling pathways.

We conclude that the « relevant » level of modeling is not absolute:

- Looking for a « minimal » model allows one to better understand (and control) the underlying mechanisms

- This form of reductionism can typically be brought up by physicists !

Acknowledgements

Study case 1

Axel COURNAC, LPTMC (postdoc), Univ. Pierre et Marie Curie

Study case 2

Alejandra VENTURA, University of Buenos Aires, Argentina (main collaboration)

Sofia MERAJVER, Cancer Center, University of Michigan