On the equilibria of the MAPK cascade in Xenopus oocyte

Christophe Russo
Biological Nanosystems group, IRI-CNRS; and Laboratoire de la régulation des signaux de division, Université de Lille 1

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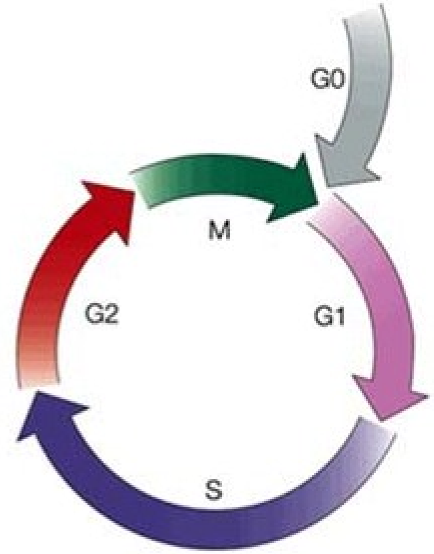
Cell cycle

- Sequence of events driving cell division
- Each step needs the accomplishment of the previous one



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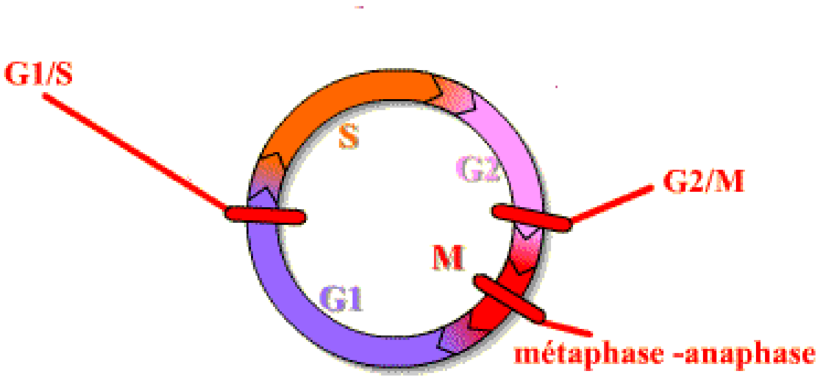
Constraints on the cell cycle

- Compartmentalize space to keep the internal and external functions
- Interaction with outer space
- Keep memory of the Chemical kinetics
- transmission of genetic “information”

Notion of checkpoint

- Check ‘quality’ of cellular processes /events before progression into the next phase



www.snv.jussieu.fr/.../images/cycle-points2.gif

- Interruption when :
  - DNA is damaged (G1/S)
  - There is replication error (G2/M)
  - Chromosomes are not aligned at the mitotic plate

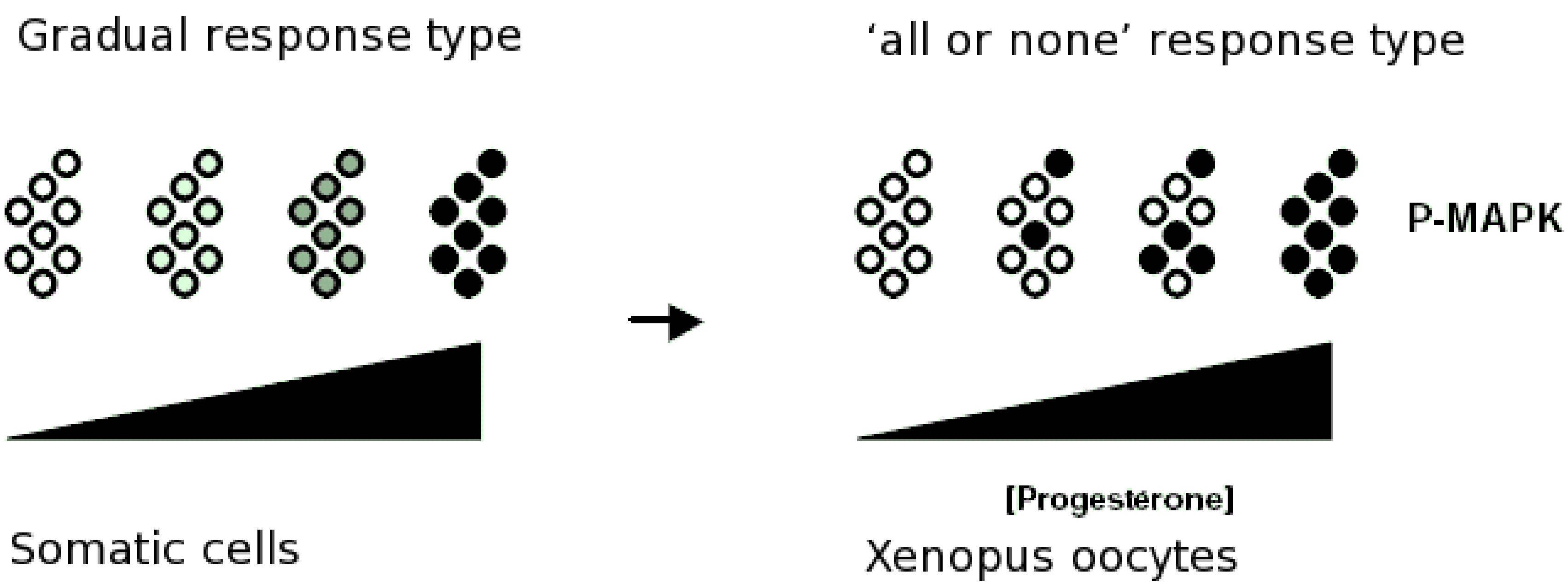
Why focusing on MAPK ?

- Any MAPK pathway disturbance leads to disease / catastrophic cell events (i.e. Cell division)
- Play crucial roles during cell cycle :
  - G1/S transition
  - G2/M transition
  - Spindle Assembly Checkpoint

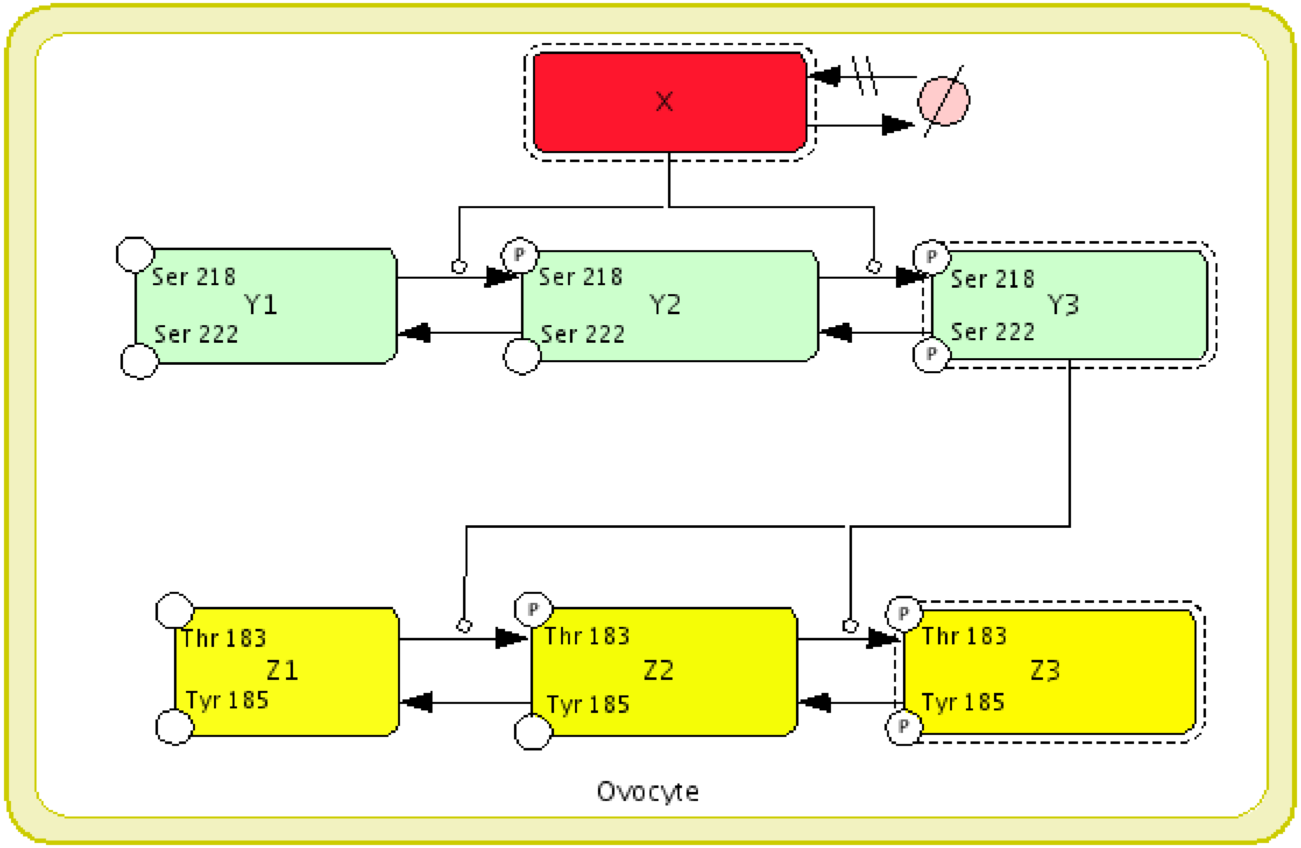
MAPK : 4 different pathways

Mitogen Signal	*Osmotic choc*	*Stress*	*Mitogen signals*
Growth Factors	*Cytokines*	*Cytokines*	*Oxydative Stress*
			Hyperosmolarity
Mos / Raf MEKK			
MEK 1, 2	MEK 3, 4, 6	MEK 4 (JNKK1), MEK7 (JNKK2)	MEK 5
MAPK (ERK) 1, 2	p38MAPK	SAPK, JNK	ERK 5 (BMK)
p90RSK, Elk1	MAPKAP Kinase-2	Jun	MEF-2C
Proliferation *Differenciation*	*Spindle assembly checkpoint (M phase) Response to stress ; Inflammation ; Apoptosis*	*Inflammation ; Apoptosis*	*Differenciation*

MAPK in *Xenopus* oocyte



Modeling of MOS/MEK/ERK



Kinetic equations

$$\dot{y}_1 = \frac{V_6 y_2}{K_6 + y_2} - \frac{V_3 x y_1}{K_3 + y_1}$$

$$\dot{y}_2 = -(\dot{y}_1 + \dot{y}_3)$$

$$\dot{y}_3 = \frac{V_4 x y_2}{K_4 + y_2} - \frac{V_5 y_3}{K_5 + y_3}$$

$$\dot{z}_1 = \frac{V_{10} z_2}{K_{10} + z_2} - \frac{V_7 y_3 z_1}{K_7 + z_1}$$

$$\dot{z}_2 = -(\dot{z}_1 + \dot{z}_3)$$

$$\dot{z}_3 = \frac{V_8 y_3 z_2}{K_8 + z_2} - \frac{V_9 z_3}{K_9 + z_3}$$

Analytical solution (1)

- Redefining variables : $x' \equiv \frac{V_3}{V_6} x\,, \quad y_i \equiv y'_i y_T\,, \quad i = 1, 2, 3$
- We find : $\frac{y_T}{V_6} \dot{y}'_1 = \frac{y'_2 y_T}{K_6 + y'_2 y_T} - x' \frac{y'_1 y_T}{K_3 + y'_1 y_T}$
- With Angeli parameters : $K_3 = K_6 = y_T$
- Equations become : $\dot{y}_1 = \frac{y_2}{1 + y_2} - x \frac{y_1}{1 + y_1}$

  $t' = (V_6 / y_T) t$

- Same with Y2 and Y3 $V_3 = V_4, V_5 = V_6$

  $K_3 = K_4 = K_5 = K_6 = y_T$

Analytical solution (2)

- Same strategy with Zi variables but new parameters :

$$v \equiv \frac{V_7}{V_{10}} y_T \,, \quad \tau \equiv \frac{V_6}{V_{10}} \frac{z_T}{y_T}$$

- Example for Z1 :

$$\tau \dot{z}_1 = \frac{z_2}{1+z_2} - v y_3 \frac{z_1}{1+z_1}$$

- And with :

$$K_7 = K_8 = K_9 = K_{10} = z_T$$

$$V_7 = V_8, V_9 = V_{10}$$

we find the same results for Z2 and Z3

Analytical solution (3)

- Equations are in a homogeneous form in the variables :

$$w_i \equiv \frac{y_i}{1+y_i}, \quad q_i \equiv \frac{z_i}{1+z_i}$$

- Time derivative Wi :

$$\dot{w}_i = \frac{\dot{y}_i}{(1+y_i)^2}$$

and similar for Qi

Analytical solution (4)

- Model written into a simpler form :

$$
\begin{aligned}
\dot{w}_1 &= (1-w_1)^2(w_2 - xw_1) \\
\dot{w}_2 &= (1-w_2)^2(xw_1 + w_3 - xw_2 - w_2) \\
\dot{w}_3 &= (1-w_3)^2(xw_2 - w_3) \\
\tau\dot{q}_1 &= (1-q_1)^2(q_2 - sq_1) \\
\tau\dot{q}_2 &= (1-q_2)^2(sq_1 + q_3 - q_2(1+s)) \\
\tau\dot{q}_3 &= (1-q_3)^2(sq_2 - q_3)
\end{aligned}
$$

- Where :

$$s \equiv v\frac{w_3}{1-w_3}$$

Fixed-point conditions (1)

- Stationary Solutions when : $$\dot{w}_i = \dot{q}_i = 0$$
- So for Wi variables : $$w_3 = x w_2 = x^2 w_1$$
- For the Qi variables : $$q_3 = s q_2 = s^2 q_1$$
- Constraints of Yi and Zi conservation bring in term of W1 : $$\frac{w_1}{1-w_1} + \frac{w_2}{1-w_2} + \frac{w_3}{1-w_3} = 1$$

Fixed-point conditions (2)

- Constraints incorporated in earlier equation in W1 :

$$4x^3w_1^3 - 3x(1+x+x^2)w_1^2 + 2(1+x+x^2)w_1 - 1 = 0$$

- Solutions for Wi :

$$w_1 = \frac{1}{2}\frac{1}{1+x+x^2}$$

$$w_2 = \frac{1}{2}\frac{x}{1+x+x^2}$$

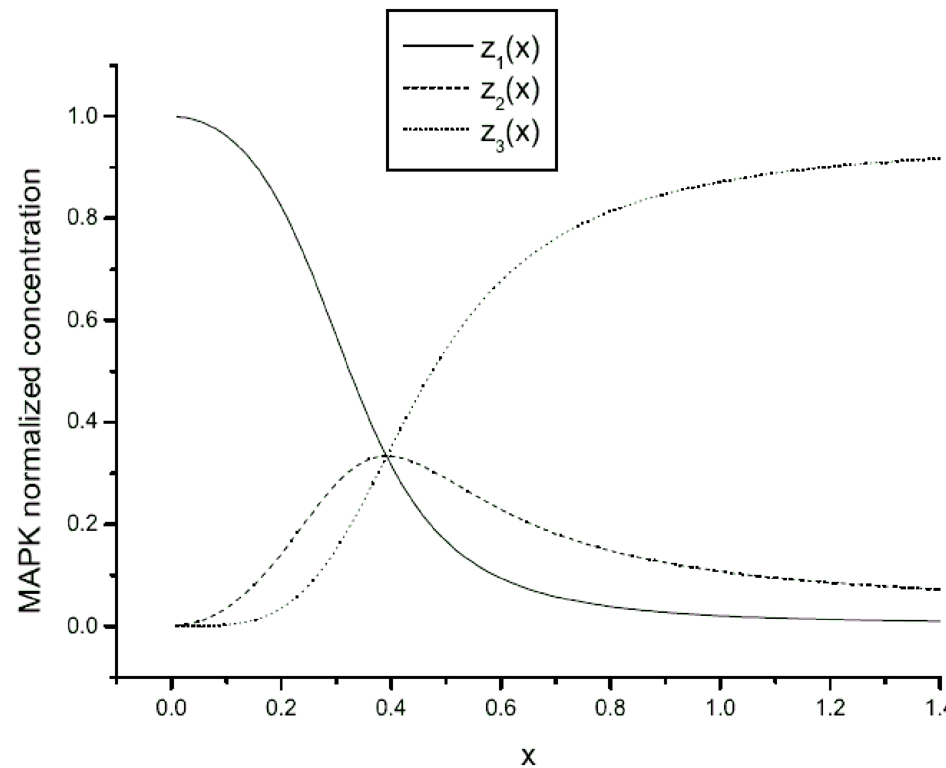
$$w_3 = \frac{1}{2}\frac{x^2}{1+x+x^2}$$

Variation of MAPK (Z3)

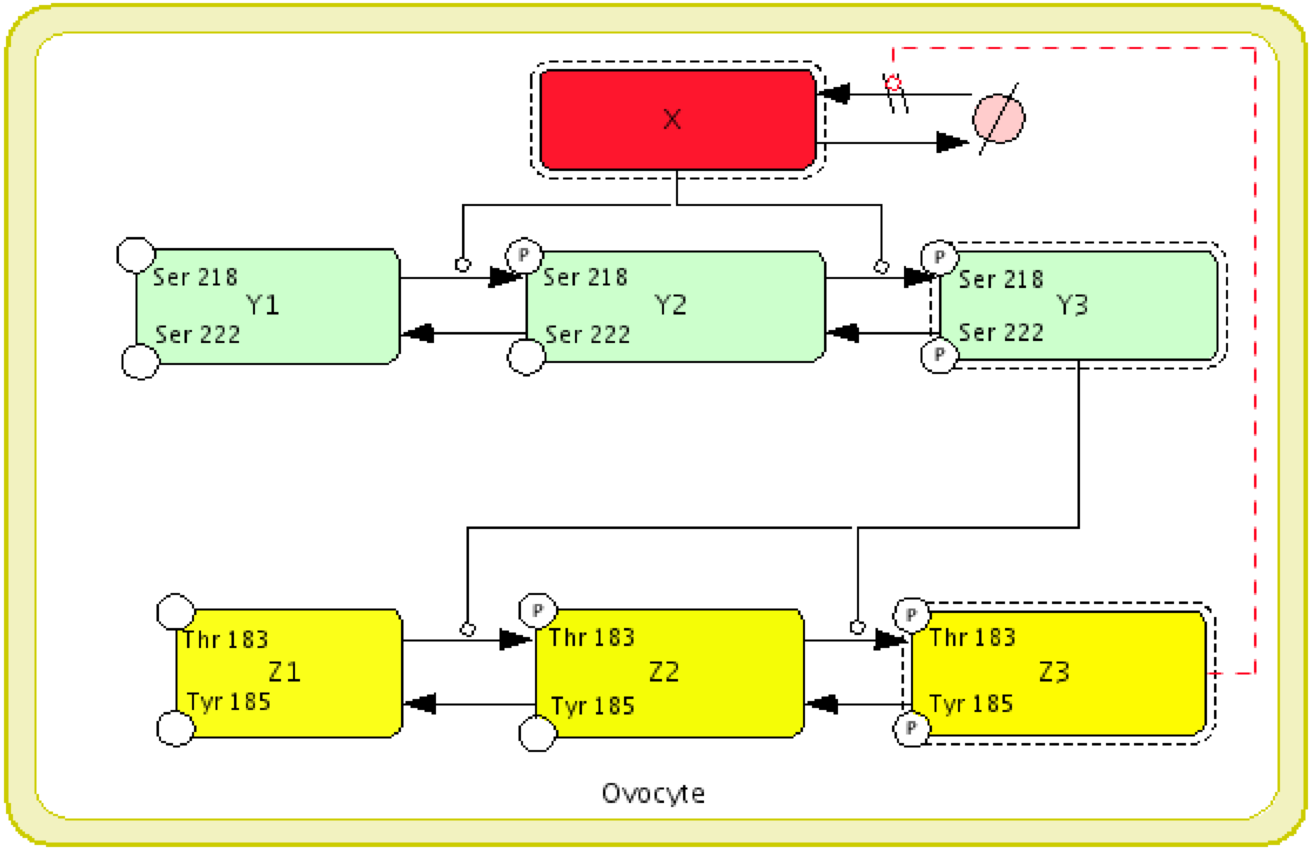
- From Q3 we find value of Z3in function of X :

$$z_3 = \frac{s^2}{2(1+s+s^2)}$$

- As s is function of X we see a sigmoidal function with a Hill coefficient equal to 4 that correspond to known results



Model with feed-back loop



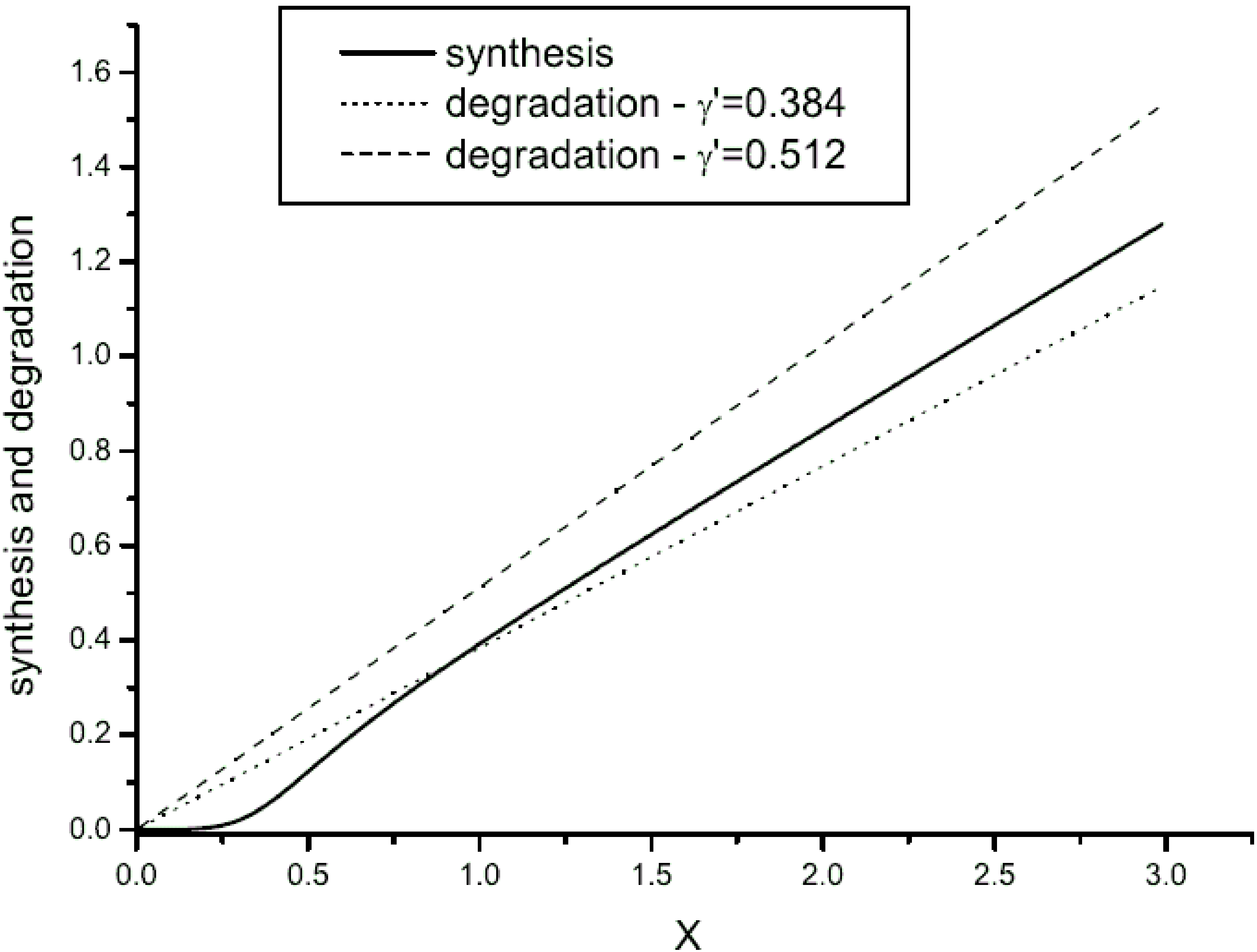
Kinetic with a feed-back loop

- Dynamic evolution of Mos protein (X) for Angeli :

$$\dot{x} = -\gamma \frac{x}{K_2 + x} + \tilde{V}_0 z_3(x) x + \tilde{V}_1$$

- Simplified form :

$$\dot{x} = -\gamma x + \tilde{V}_0 z_3(x) x$$



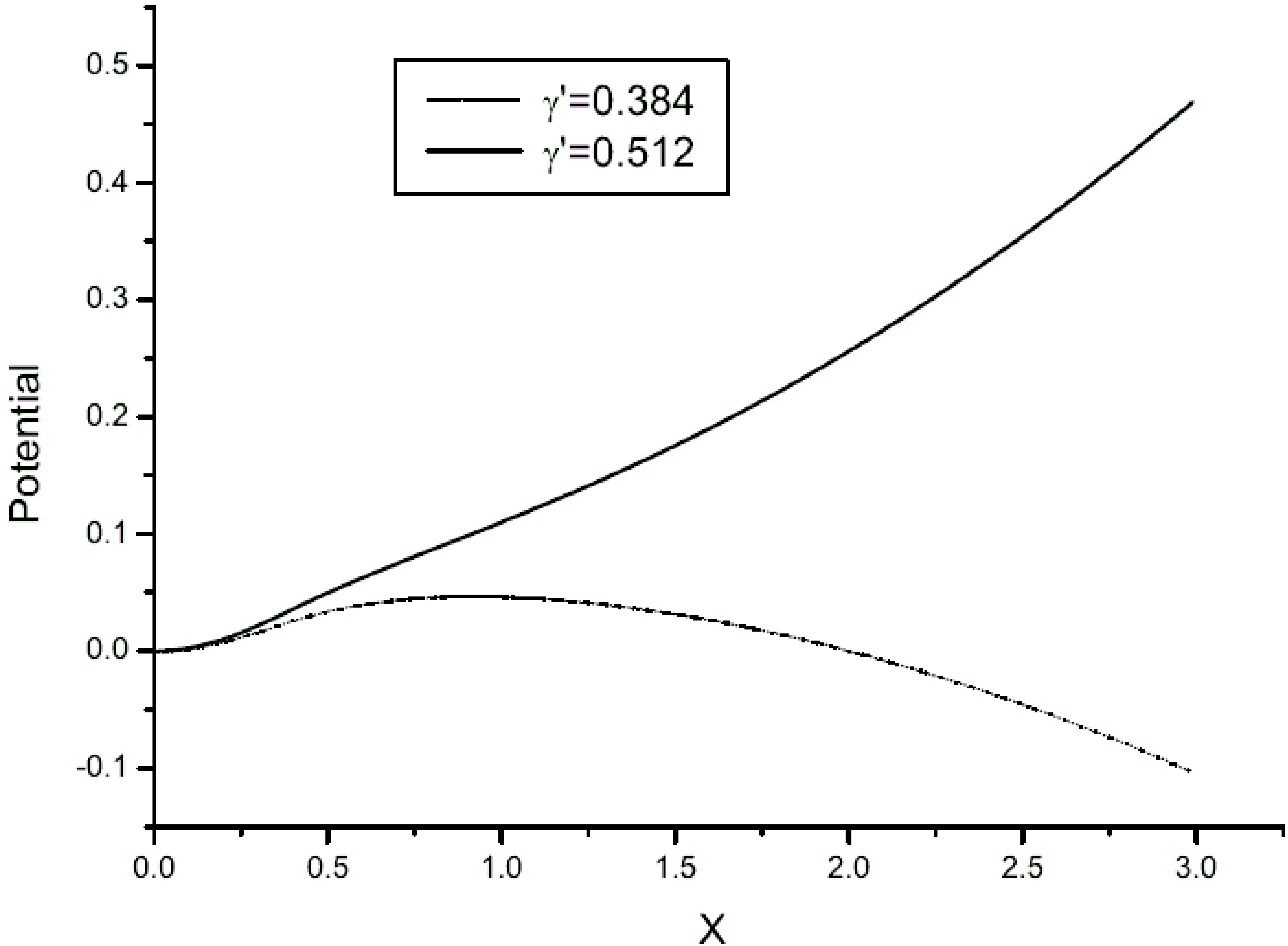
synthesis
degradation - γ'=0.384
degradation - γ'=0.512
synthesis and degradation
X
0.0
0.2
0.4
0.6
0.8
1.0
1.2
1.4
1.6
0.0
0.5
1.0
1.5
2.0
2.5
3.0

Angeli 's feedback-loop

- If we define a mechanical potential named W(x) :

$$\dot{x} = -\frac{dW}{dx}$$

- Because of Z3 and X inter-dependence we now use numerical calculation



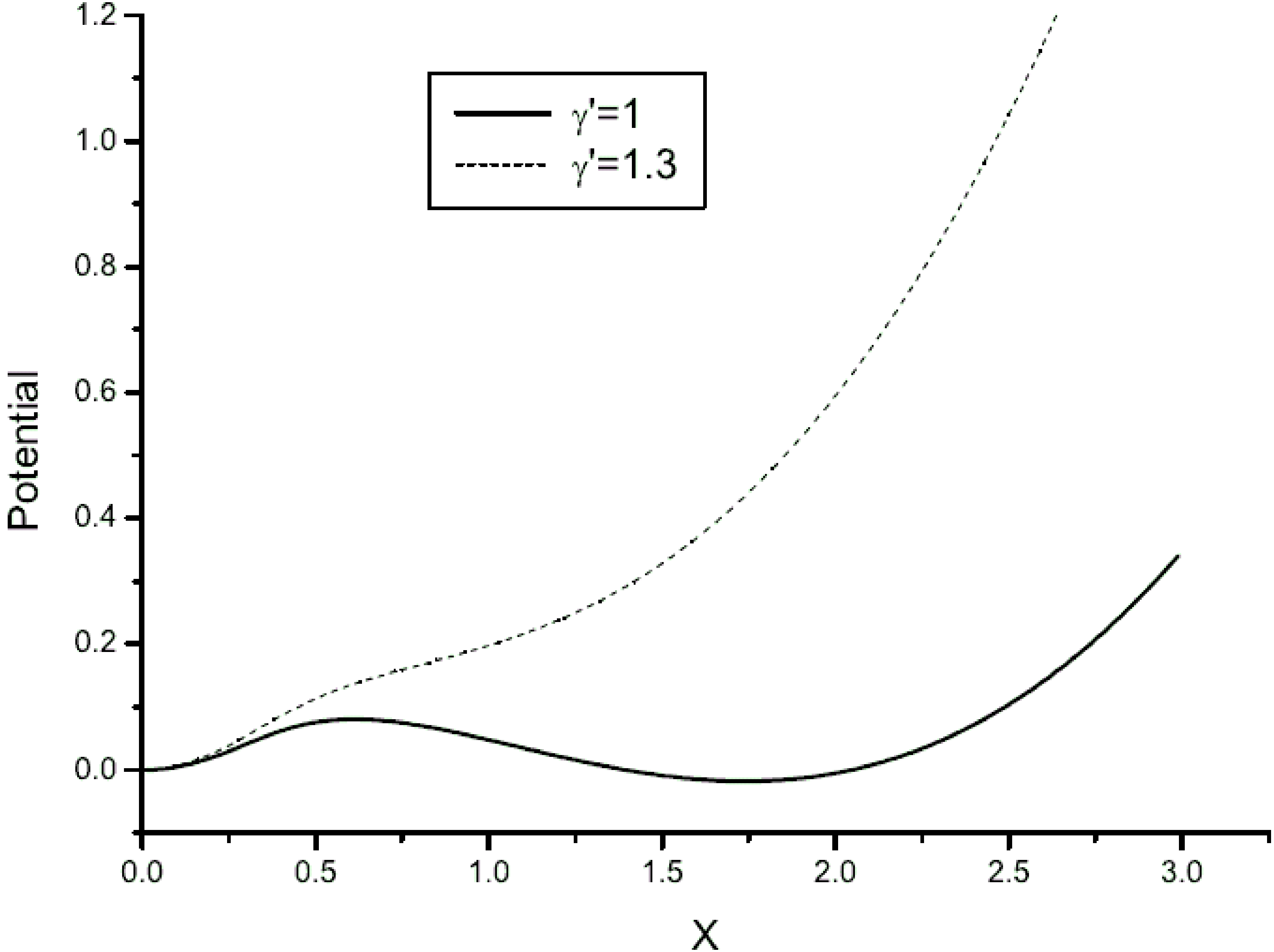
γ'=0.384
γ'=0.512
Potential
X
0.5
0.4
0.3
0.2
0.1
0.0
-0.1
0.0
0.5
1.0
1.5
2.0
2.5
3.0

Modification of the feed-back loop

- If we use this new equation :

$$\dot{x} = -\gamma x + \frac{\tilde{V}_0 z_3(x) x}{\tilde{K} + x}$$

- We find 2 stable solutions and 1 unstable solution (see next page)



γ'=1
γ'=1.3
Potential
X
1.2
1.0
0.8
0.6
0.4
0.2
0.0
0.0
0.5
1.0
1.5
2.0
2.5
3.0

Conclusion

- Even for Michaelis-Mentens kinetics we can find analytical result
- Caution when modeling feed-back loop - between MAPK and MOS - which turns the cascade to a switch as expected for the biological behaviour

Perspectives

- Further models which will take into account of the dynamics of the MOS synthesis
- Study new interactions between proteins within the cascade, given new experimental observations

Reference

- D. Angeli, J. E. Ferrell Jr., and E. D. Sontag, **Detection of multistability, bifurcations, and hysteresis in a large class of biological positive-feedback systems,** *PNAS*, February 17, 2004; 101(7): 1822 – 1827

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