Building and Simulating Models using COPASI

Files and supporting materials are available at:
http://www.ebi.ac.uk/biomodels/courses/20160706/

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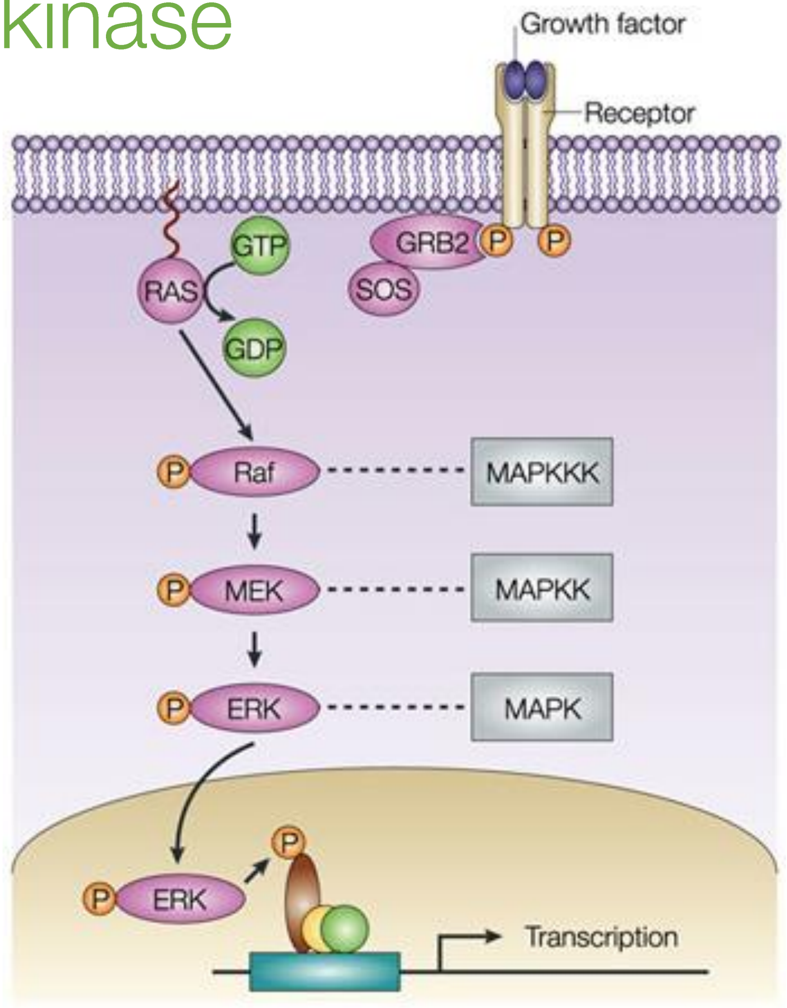
EMBL-EBI

Mitogen activated protein kinase

- Mitogen activated protein kinase (MAPK) cascades are ubiquitous signalling modules that couple receptor mediated events at the cell surface to cytoplasmic and nuclear effectors.
- MAPK signalling cascades – signal-relay mechanism involves sequential phosphorylation of three kinases (Ser/Thr protein kinases).
- Involved in many cellular processes such as cell proliferation, differentiation, movement, survival etc.). Widely conserved among eukaryotes.
- The cascade arrangement has important consequences for the dynamics (like switch or all-or-none and oscillatory activation pattern) of MAPK signaling



Nature Reviews | Molecular Cell Biology

http://www.nature.com/nrm/journal/v5/n6/box/nrm1400_BX1.html

Exercises

1. **MAPK cascade - Ultrasensitivity :**

   Huang CY, Ferrell JE Jr. Ultrasensitivity in the mitogen-activated protein kinase cascade. Proc Natl Acad Sci U S A. 1996 Sep 17;93(19):10078-83. (http://www.ebi.ac.uk/biomodels-main/BIOMD0000000009)

2. **MAPK cascade - Oscillations :**

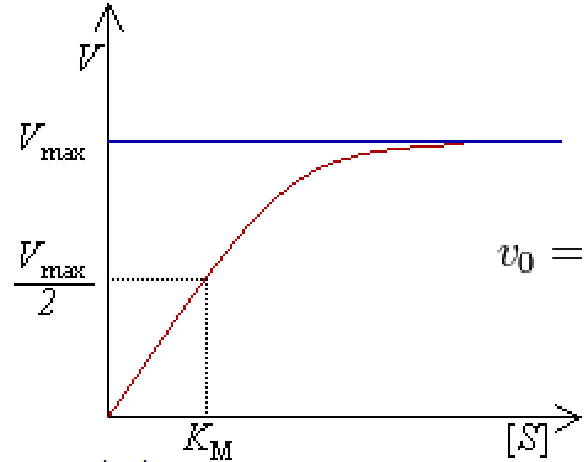
   Kholodenko BN. Negative feedback and ultrasensitivity can bring about oscillations in the mitogen-activated protein kinase cascades. Eur J Biochem. 2000 Mar;267(6):1583-8. (http://www.ebi.ac.uk/biomodels-main/BIOMD0000000010)

3. **MAPK double phosphorylation – Bistability:**

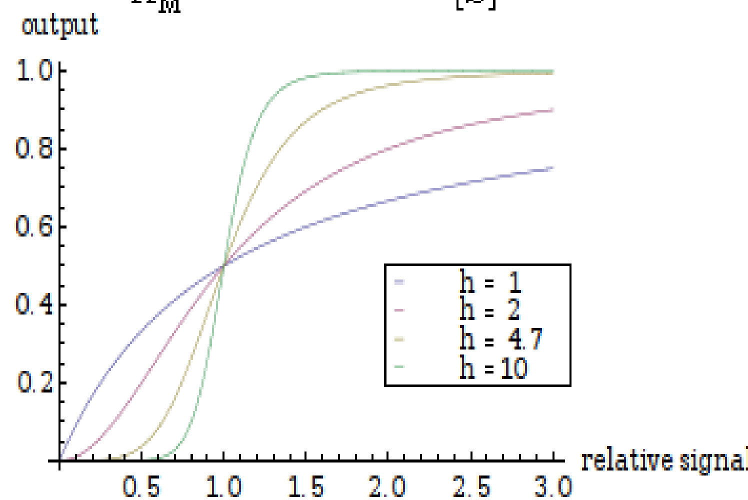
   Markevich NI, Hoek JB, Kholodenko BN. Signalling switches and bistability arising from multisite phosphorylation in protein kinase cascades. J Cell Biol. 2004 Feb 2;164(3):353-9. (http://www.ebi.ac.uk/biomodels-main/BIOMD0000000027)

1. Huang and Ferrell (1996) – Ultrasensitivity in MAPK cascade

- Ultrasensitivity: an output signal being more sensitive to a small change in stimulus strength, resulting in a sigmoidal (S-shaped) response curve, steeper than an a classical Michaelis' Menton curve.
- Can be compared with Hill's equation, where h>1 indicates ultrasensitvity.
- Most common mechanism for Ultrasensitivity – cooperratvity (eg. binding of haemoglobin to its substrates.
- Also arises when enzyme cycles operate near saturation and when the stimulus impinge upon multiple steps of an enzyme cascade (eg. MAPK cascade)

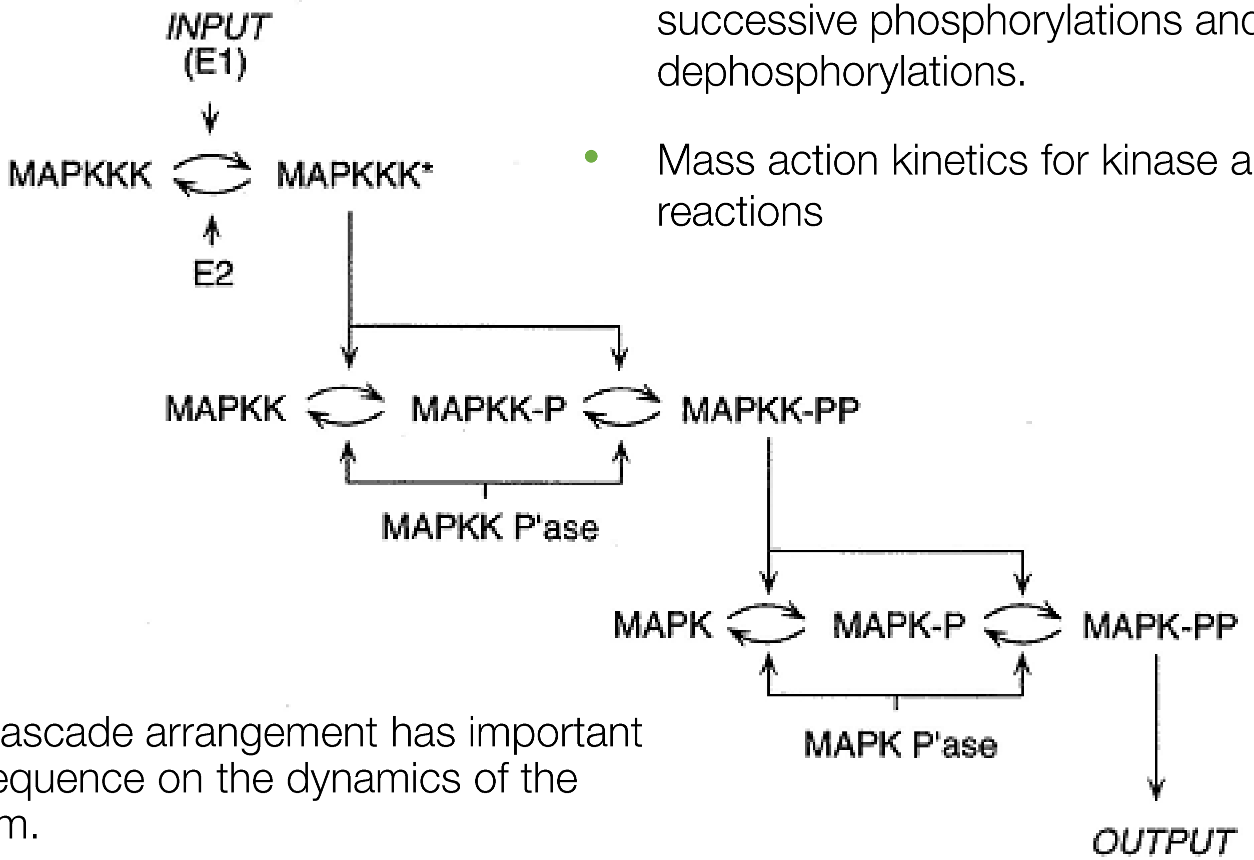


$$v_0 = \frac{v_{max}[S]}{K_M + [S]}$$



$$out = s^h / (1 + s^h)$$

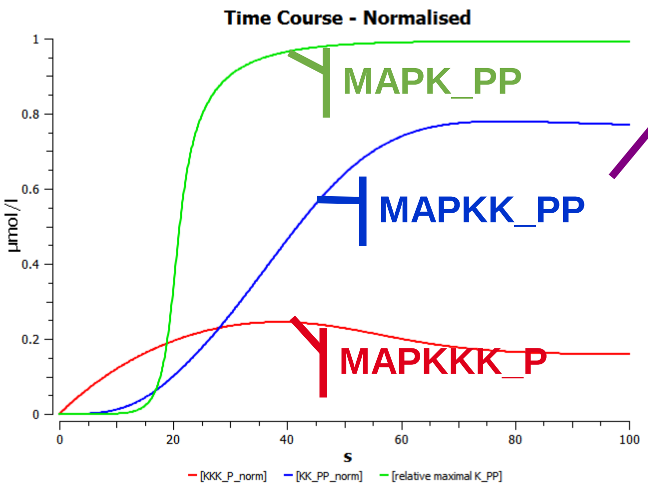
1. Huang and Ferrell (1996) – Ultrasensitivity in MAPK cascade



- The cascade is modelled as a simple linear chain of successive phosphorylations and dephosphorylations.
- Mass action kinetics for kinase and phosphatase reactions
- The cascade arrangement has important consequence on the dynamics of the system.

1. Huang and Ferrell (1996) – Ultrasensitivity in MAPK cascade;

What do we infer from the model?

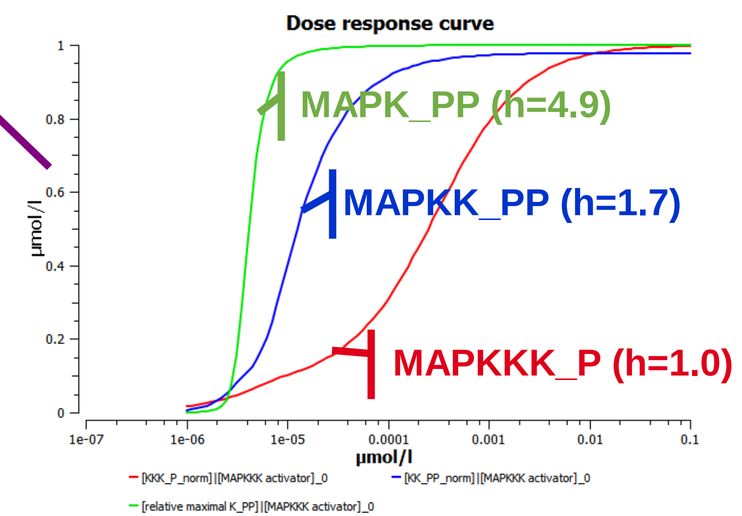


The temporal sequence of kinase activation, from MAPKKK to the final effector MAPK.

Increase in sensitivity along the levels of the cascade; MAPK reaches its maximal level before MAPKKK.

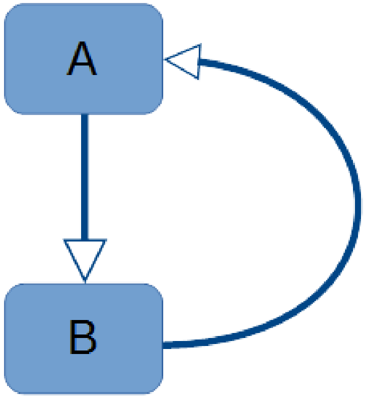
The dose-response curves (varying stimulus E1, i.e. Ras (MAPKKK_activator) predicted to be sigmoidal

- MAPK - Hill's coefficient nearly 5 (steepest).
- MAPKK – Hill's coefficient 1.7
- MAPKKK – linear Michaelis-Menton enzyme

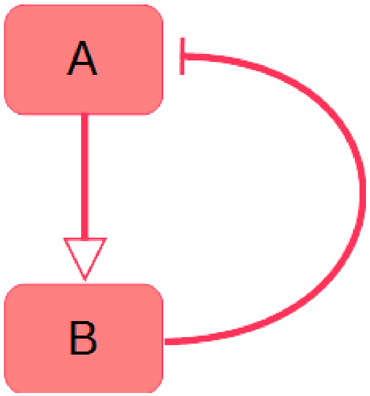


2. Kholodenko (2000) –Ultrasensitivity & Negative feedback -> Oscillation in MAPK cascade

- Feedback loops:
  - Positive feedback: increase or activation of a downstream element, causing the same effect (i.e. increase or activation) to an upstream element, in a sequence of biological process.



  - Negative feedback: increase or activation of a downstream element, causing an opposite effect (i.e. decrease or inactivation) to an upstream element, in a sequence of biological process.



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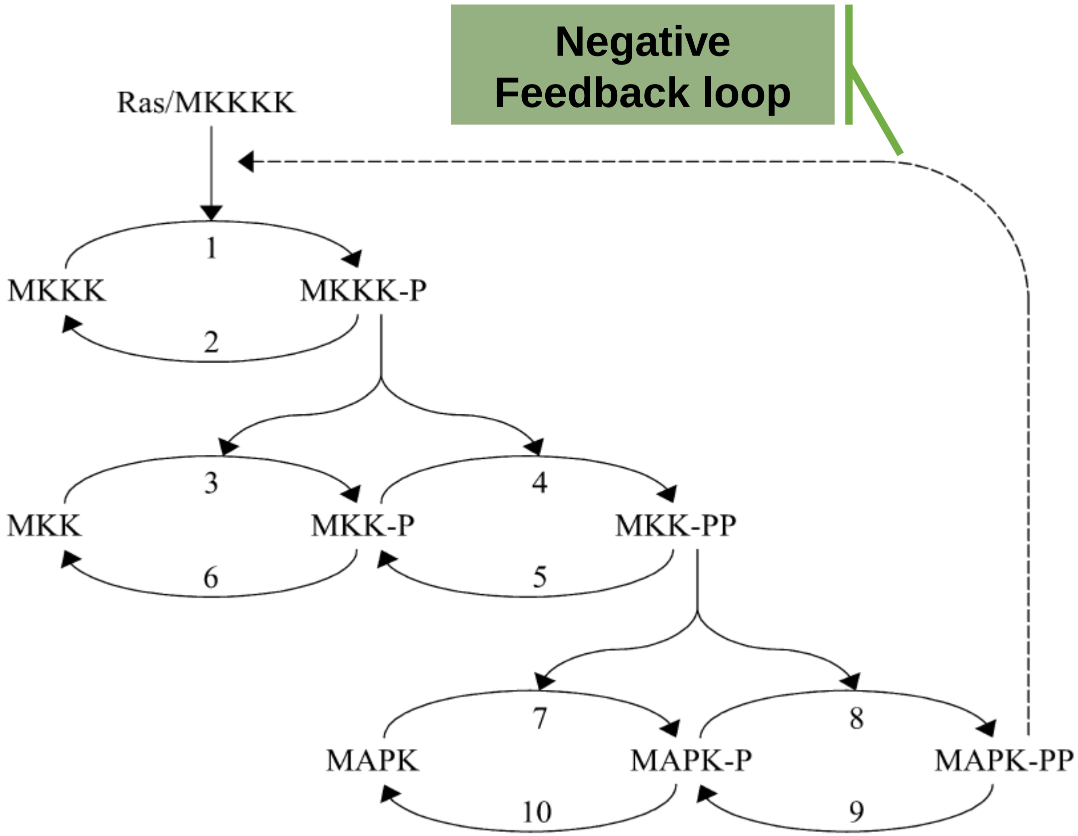

- Cascade modelled as a linear chain of successive phosphorylations and dephosphorylations
- Inhibitory phosphorylation of SOS by MAPK (ERK), switches off Ras signalling. Indeed, whereas activated Raf (MAPKKK) brings in ERK activation, ERK mediated inhibition of Raf stimulation by SOS decrease ERK phosphorylation.
- Michaelis Menten kinetics for kinase and phosphatase reactions

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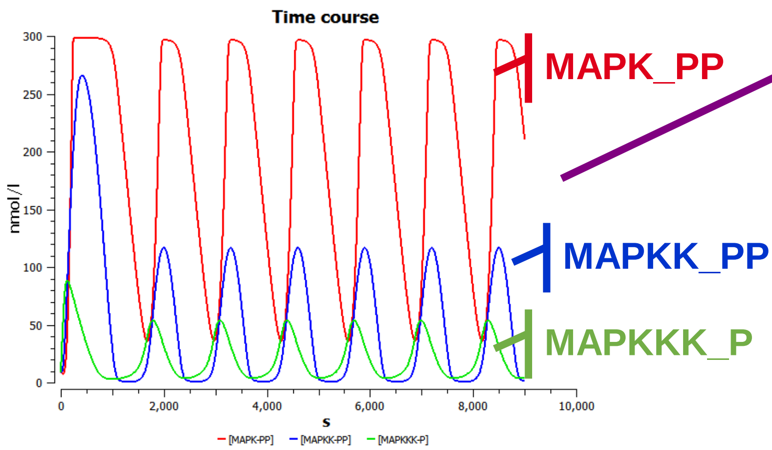
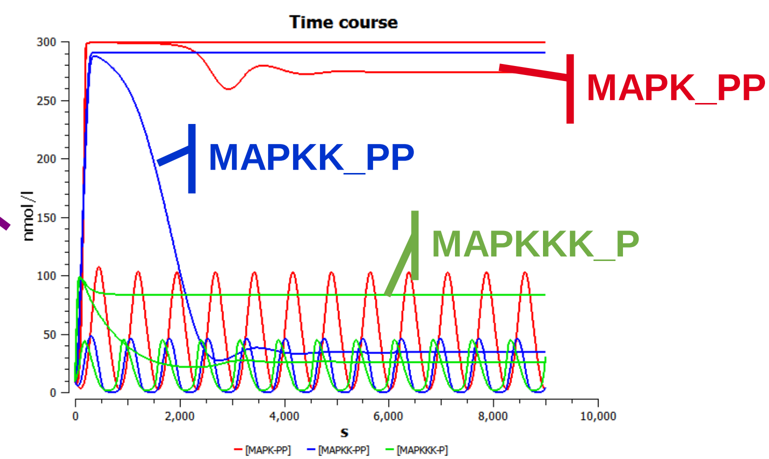


With a simple negative feedback, the system exhibits oscillatory behaviour under constant stimulation. i.e. The combination of ultrasensitivity and negative feedback brings sustained biochemical oscillations.

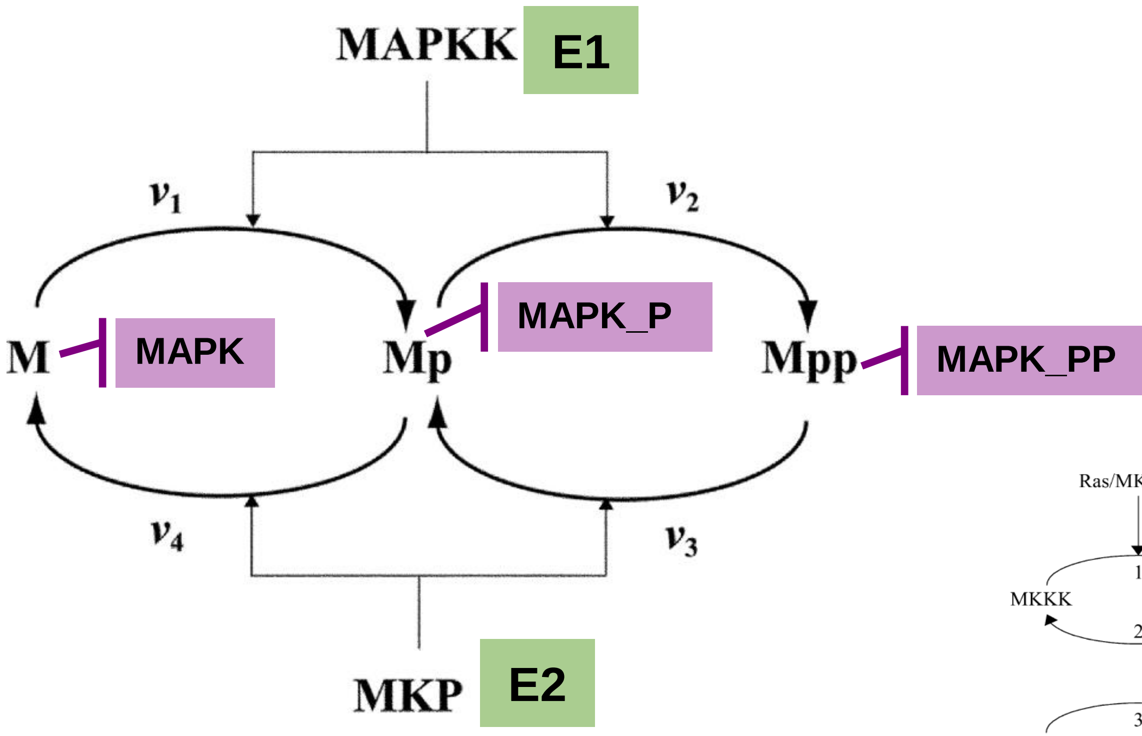
With smaller inhibition constants (Ki), the coupling between ERK and Raf decreases. The frequency of oscillations increases.

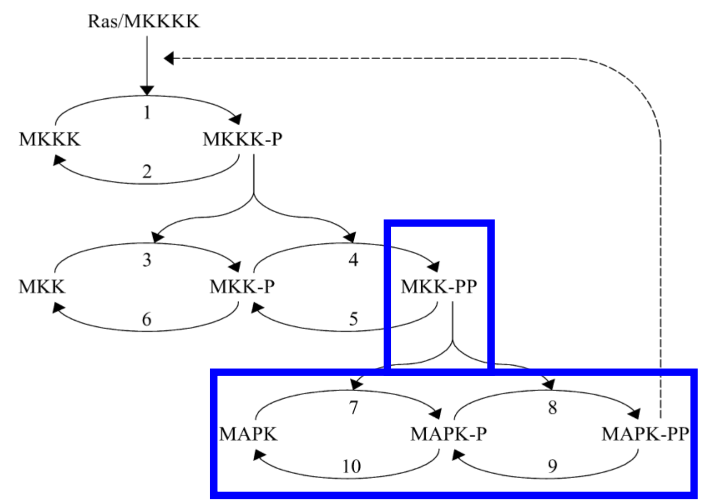
The oscillatory behaviour at values of Ki between 25 and 27



3. Markevich et al. (2004) – double phosphorylation causes bistability

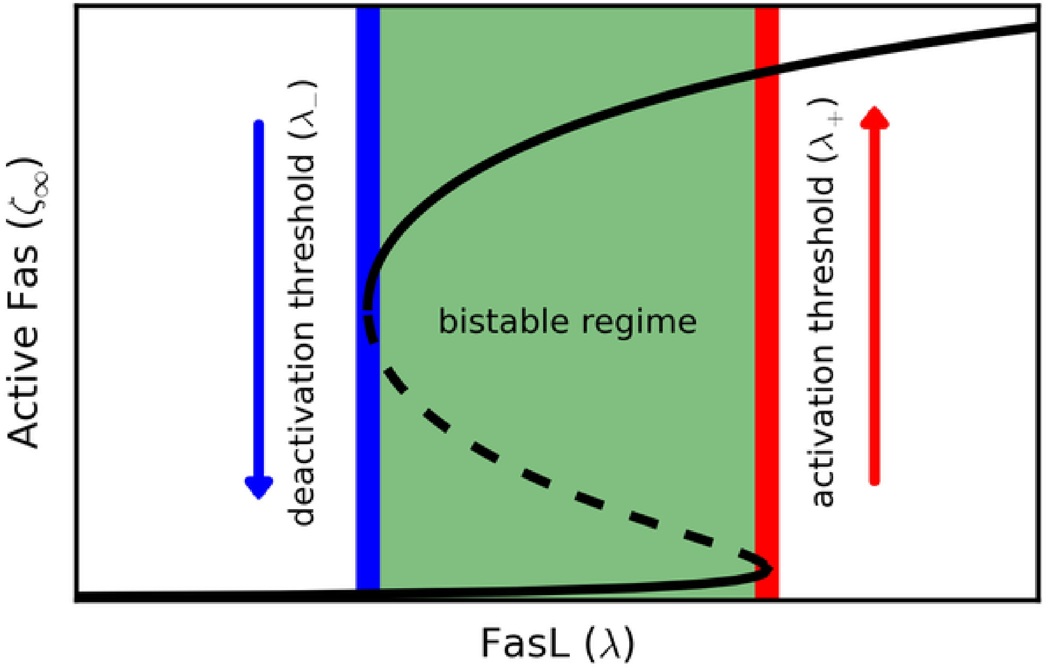
- This model demonstrates that both dual and multisite modification cycles can display bistability and hysteresis.





Bistability

- Over a certain region of signal, a system shows two steady states
- The system can switch state, either if the signal goes over the activation or fall under the deactivation threshold
- The system exhibits a memory effect, also known as hysteresis



Kenneth L. Ho, Heather A. Harrington: Bistability in Apoptosis by Receptor Clustering; PLos Comp. Biol. 2010 6(10): e1000956.

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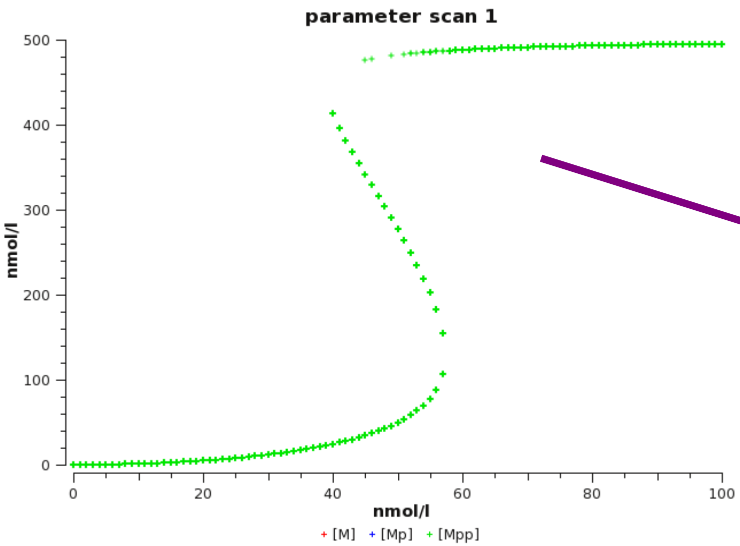
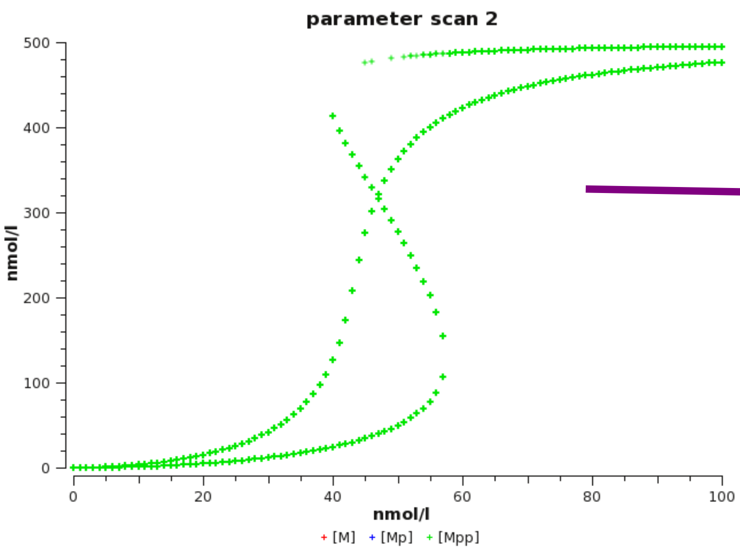


Stimulus strength (MAPKK from 0 to 100) against MAPK activity:

MAPK activity works like a switch with a memory: i.e. MAPK activity not only depend on the stimulus strength (MAPKKK), but also on the prior state of MAPK (hysteresis).



Dependence of bistability on Km1:

The size of the bistable region depends on the value of Km1. Further analysis of the system showed that Km1 has to be smaller than Km2 i.e. the first phosphorylation step has to saturate at much lower concentrations of M than the second.