Modeling Signaling Pathways using COPASI

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EMBL-EBI
13th April, 2010

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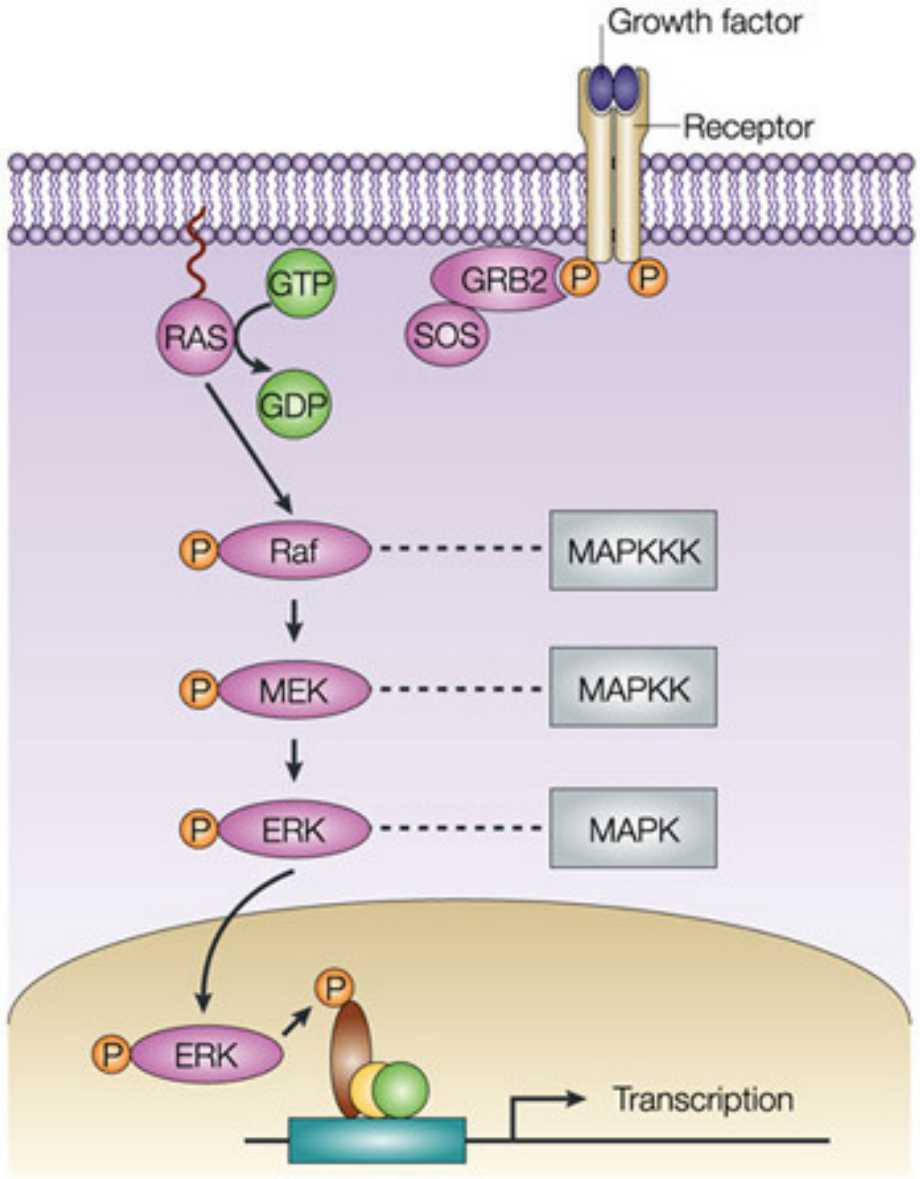
Mitogen activated protein kinase cascade

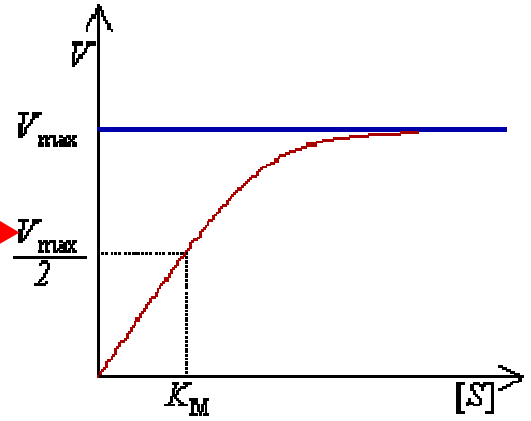
- Mitogen activated protein kinase (MAPK) cascades are ubiquitous signaling modules that couple receptor mediated events at the cell surface to cytoplasmic and nuclear effectors.
- In mammalian cells, one well characterized Signal transduction pathways – links the activated receptor tyrosine kinases (RTKs) to the MAPK cascades.
- In response to stimuli, phosphorylated RTKs complexed with GRB2, recruit the cytoplasmic guanine nucleotide exchange protein Son of Sevenless (SOS), to the cell membrane, which activates the membrane bound GTPase RAS.
- Activated RAS triggers the activation of MAPKKK (Raf).
- MAPK signaling cascades – signal-relay mechanism involves sequential phosphorylation of three kinases (Ser/Thr protein kinase).
- Involve 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



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

Ultrasensitivity

- Some enzymes exhibit stimulus/response curves that are steeper (at the high stimulus level) or less steep (at the low stimulus level) than the Michaelis-Menten Curve.

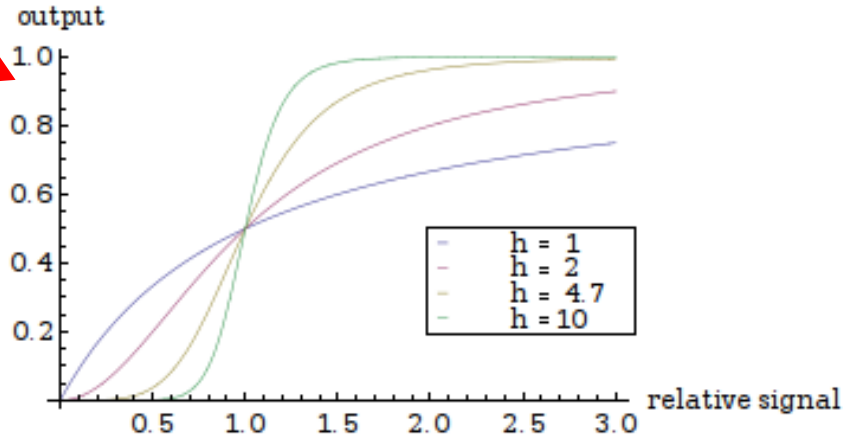


$$v_0 = \frac{v_{max}[S]}{K_M + [S]}$$

- Goldbeter and Koshland have termed these responses as 'Ultrasensitivity' – emphasizing the fact that the upstroke of the stimulus/response curve is steeper than that of a hyperbolic Michaelis-Menton enzyme.

- Thus, highly ultrasensitive enzymes tend towards all-or-none, switch-like response.

- Ultrasensitivity also arises when enzyme cycle operates near saturation (zero-order ultrasensitivity) and when stimuli impinge upon multiple steps of a enzyme cascade (multistep ultrasensitivity). Can be compared to Hill functions (out= $s^h/(K^h+s^h)$, in which h>1 means ultrasensitivity.



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

Evolution of MAPK models

Signaling Pathway Models

MINIREVIEWS

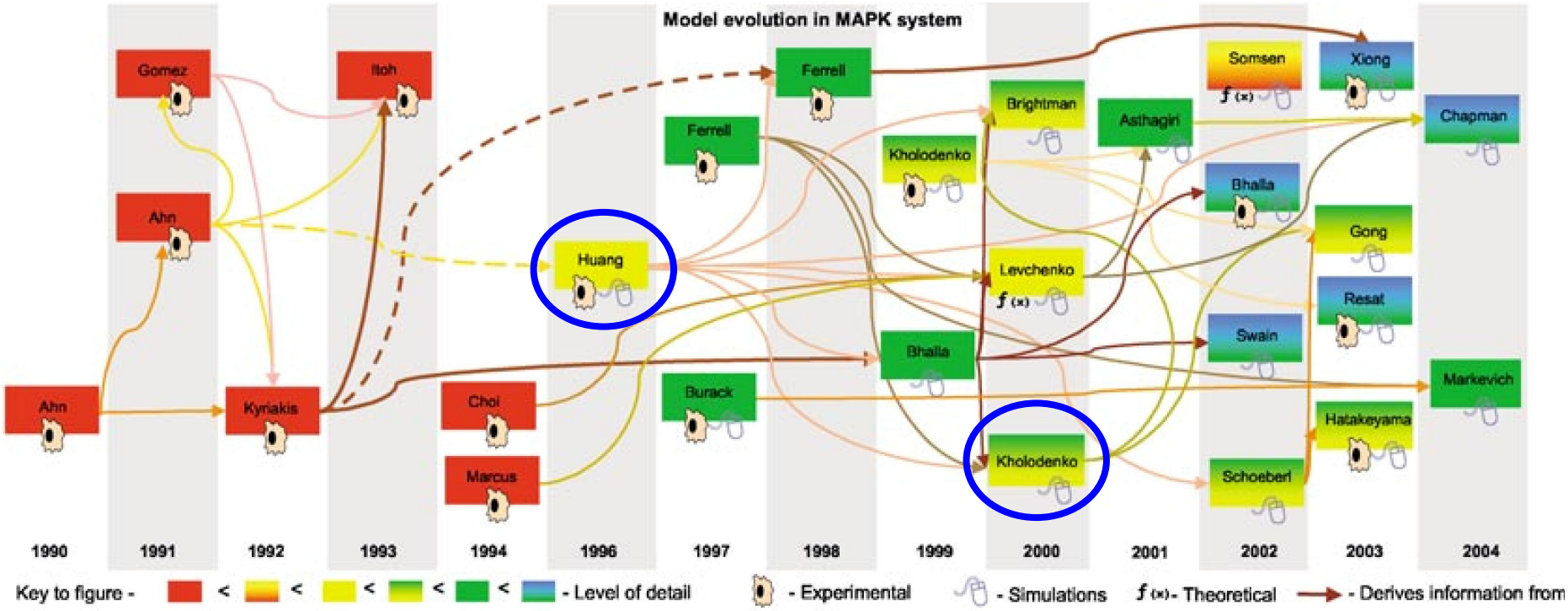
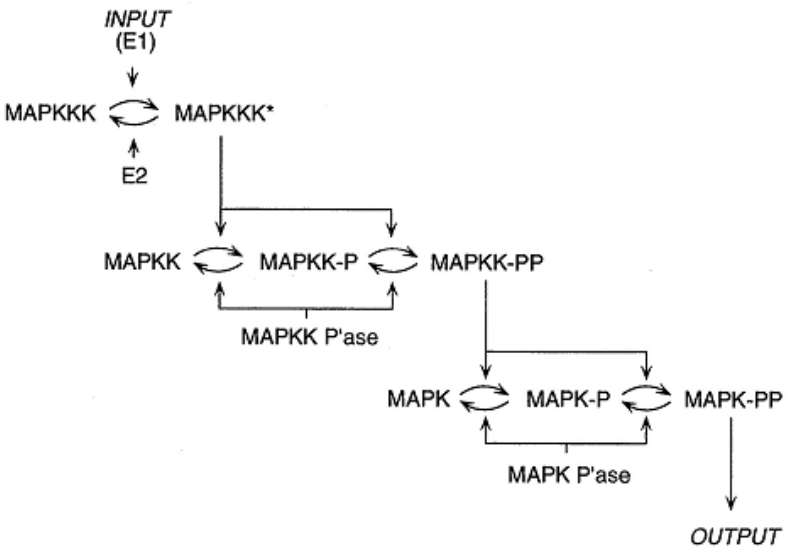


Figure 3. *Evolution of modeling, with modeling in MAPK taken as an example. Models are arranged chronologically from left to right by the year of their publication. Each model considered is represented by a box, and the color in the box is indicative of the level of detail incorporated in the model. The classification of the levels is in accordance with the criteria detailed in Table 1 (also see text). The boxes are color coded in increasing order of detail, red being the lowest and blue being the highest. The icon at the base of the box indicates the approach adopted by the study for modeling. The connections to each model indicates important source of starting information. All connections originating from a single model are represented by a single color.*

Vayttaden SJ, Ajay SM, Bhalla US. A spectrum of models of signaling pathways. Chembiochem. 2004 Oct 4;5(10):1365-74.

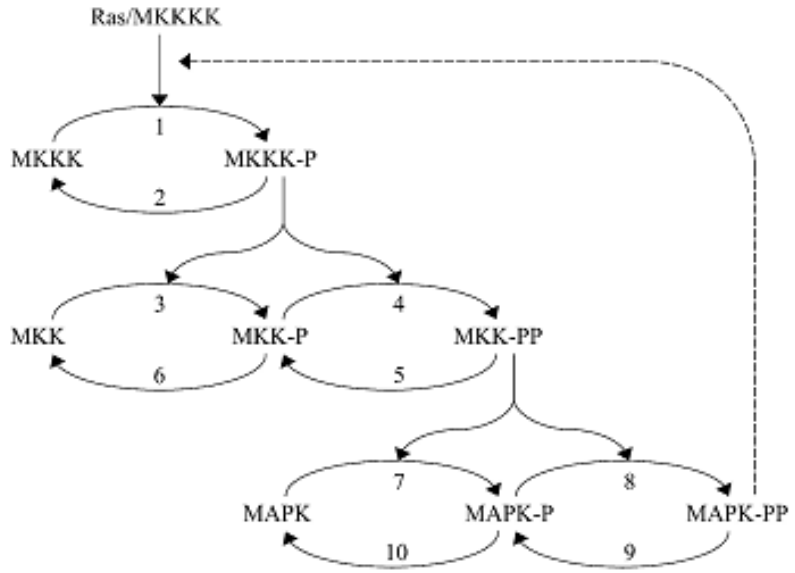
MAPK cascades

Huang and Ferrell, 1996



- The rate equations of the cascade was solved numerically.
- The dose response curves for MAPK, MAPKK, MAPKKK are predicted to be sigmoidal (ultrasensitive), with MAPK curve predicted to the steepest.
- Parameters and concentrations were roughly estimated from the experimental result.
- The experimental result in Xenopus *laevis* oocytes reproduced the predicted result.

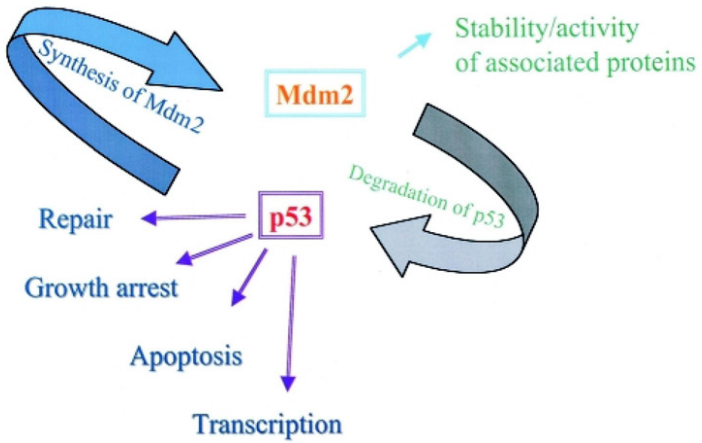
Kholodenko, 2000



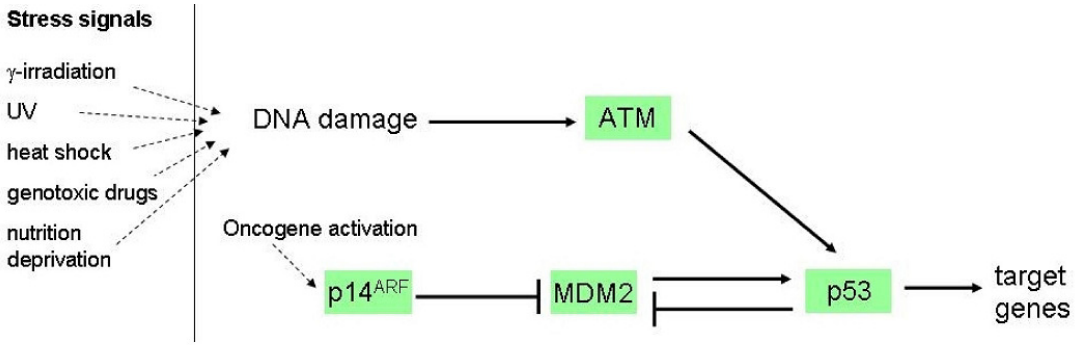
- Inhibitory phosphorylation of SOS by p42/p44 MAPK (ERK) provides a mechanism for switching off Ras signaling. This inhibition creates a negative-feedback in the MAPK cascade.
- Indeed, whereas tyrosine phosphorlated Raf brings ERK activation, ERK mediated inhibition of Raf stimulation by SOS decrease ERK phosphorylation.
- Combination of negative feedback and ultrasensitivity brings in sustained biochemical oscillation.

..and additional exercises for those who are interested..

p53/Mdm2 circuit - p53 stabilization, Proctor and Gray, 2008



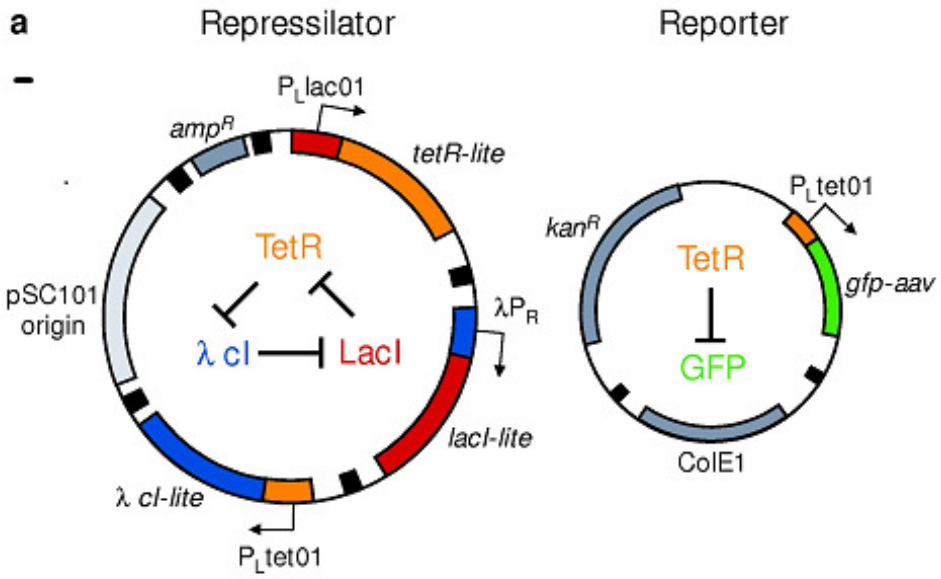
Major activities implicated for p53 and Mdm2 are illustrated. Figure taken from Alarcon-Vargas and Ronai, 2002



Network diagram of p53 signaling pathway. Figure taken from Proctor and Gray, 2008

- The p53 protein is a sequence-specific DNA binding transcription factor which is encoded by TP53 gene (in human) located on the short arm of chromosome 17.
- Three major functions of p53: growth arrest, DNA repair and apoptosis.
- In normal cell, p53 concentration is regulated by Mdm2 (negatively regulated) since, excess of p53 may accelerate the aging process by excessive apoptosis.
- In stressed cell: Its important function in response to DNA damage is to induce cell growth arrest, to allow DNA repair to take place, by which it prevents tumour growth (p53 also called as tumour suppressor). If the DNA repair fails, it initiates Apoptosis. DNA damage sensed by kinases like ATM and nucleolar protein ARF inhibits Mdm2 binding to p53 resulting in p53 stabilization and hence it initiates growth arrest and activates transcription of protein involved in DNA repair.
- Here, we will see two models: 1) p53 stabilization by ARF and 2) p53 stabilization by ATM. DNA damage is initiated by irradiation (IR=2dGy for 1 minute at time t=1hour).

A synthetic oscillatory network, Elowitz and Leibler, 2000



The repressilator network. The repressilator is a cycle negative feedback loop composed of three repressor genes and their corresponding promoters, as shown schematically in the centre of the left-hand plasmid.

- Designed and constructed a synthetic network which involves three transcriptional repressor system in e.coli to show the oscillatory behaviour.
- Loop of 3 transcriptional repressors each controlling the next – negative feedback.
- Here, we could see the oscillatory behaviour of the repressor proteins "LacI", "cI" and "TetR". Also, can see what happens when altering some of the key parameters.