Review

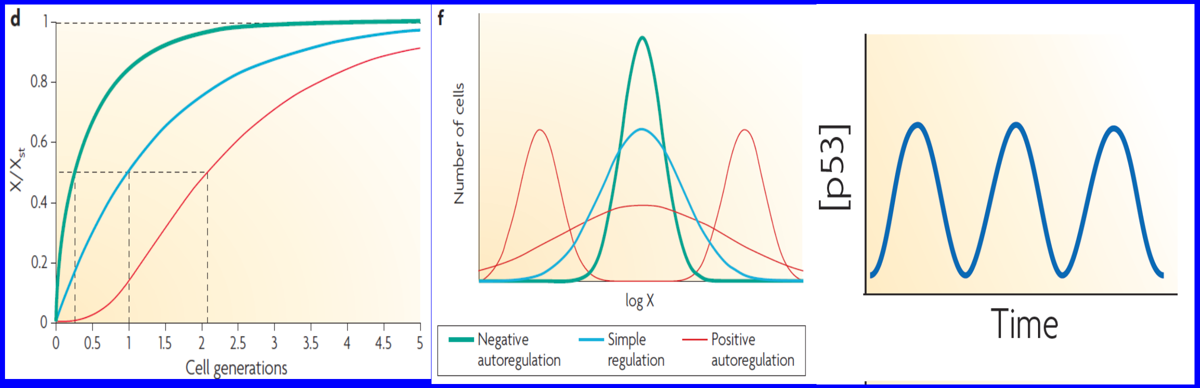
Equation of gene regulation

$$\frac{dY}{dt} = f(X^*) - k_d * Y$$

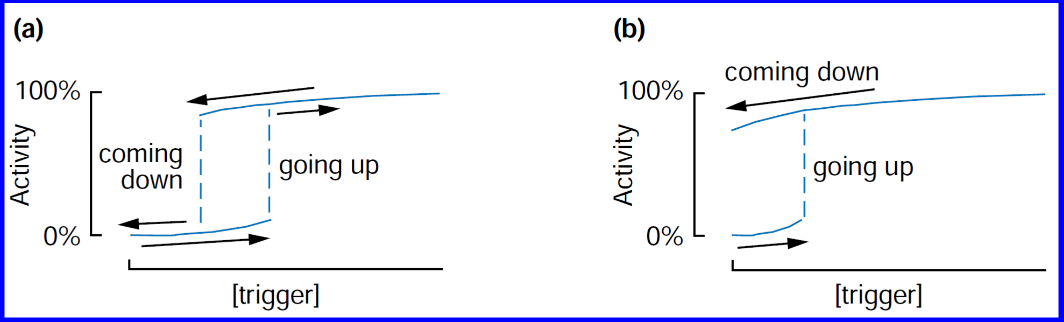
$$f(X^*) = \beta_0 + \frac{\beta X^{*n}}{K^n + X^{*n}} \qquad f(X^*) = \frac{\beta K^n}{K^n + X^{*n}}$$

Feedback loops

NFL：Speeding response time; Noise repressor; Oscillator



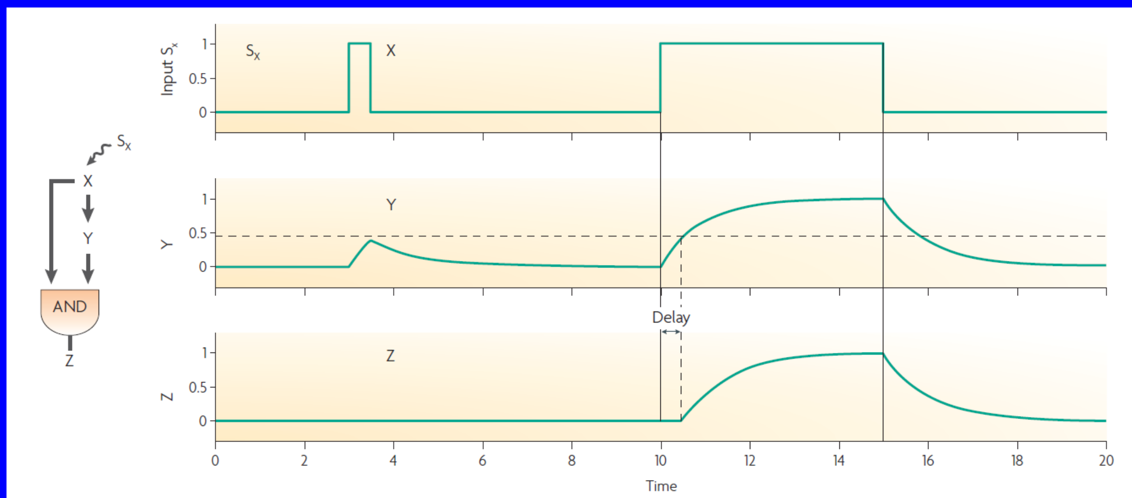
PFL: Bistable switch;
Cell memory



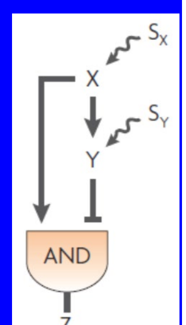
Review

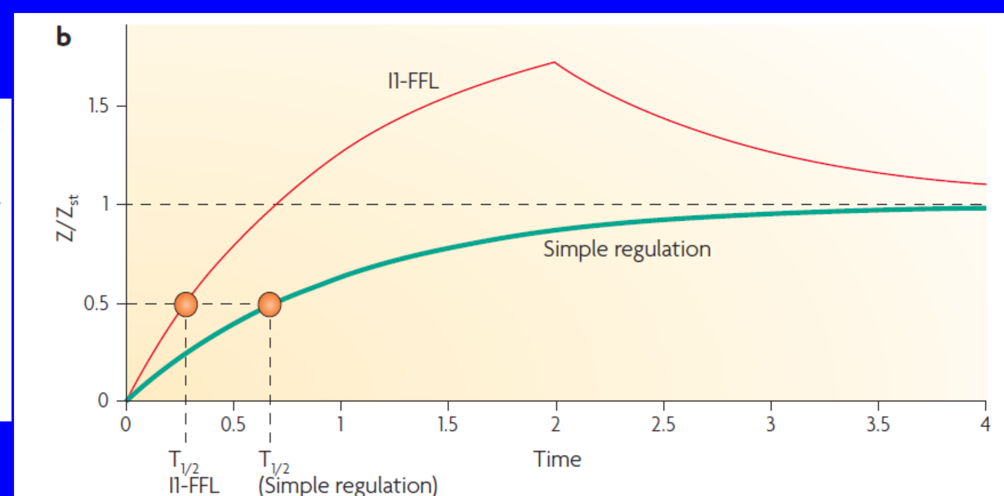
Feedforward loops

C1-FF L: a sign sensitive filter



I1-FFL: a pulse generator and response accelerator





Chapter 2:Cell signaling network

Outline

- Concept , Properties and Examples
- Modeling the dynamics of cell signaling network

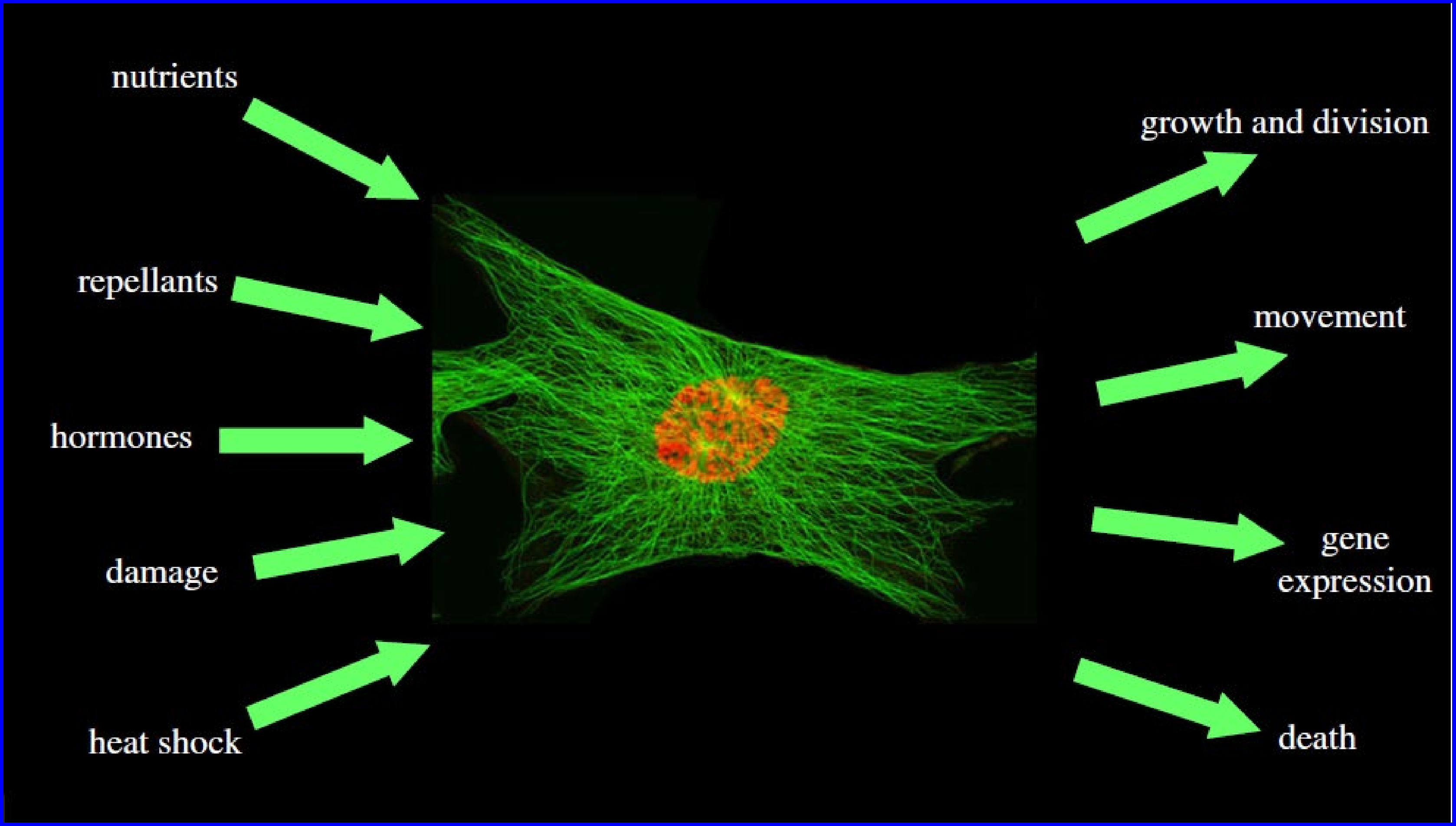
2.1 Cell signaling network

——Concept, dynamical properties and examples

2.1.1 Concepts

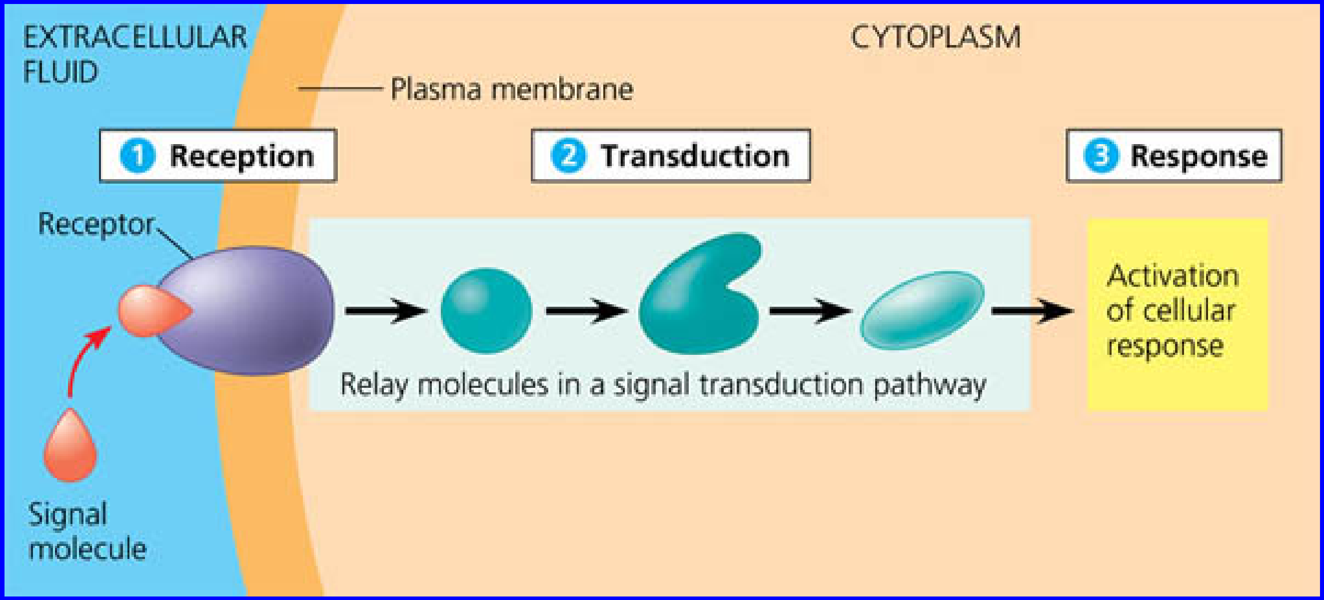
- Cell signaling networks ——A complex protein network senses information about the intracellular and extracellular environment (input), processes the information, and triggers a response (output). It is composed of interconnected cell signaling pathways.

Batchelor E, Loewer A, Lahav G. Nat Rev Cancer. 2009; **9**(5): 371-7.



The cell is an information-processing system!

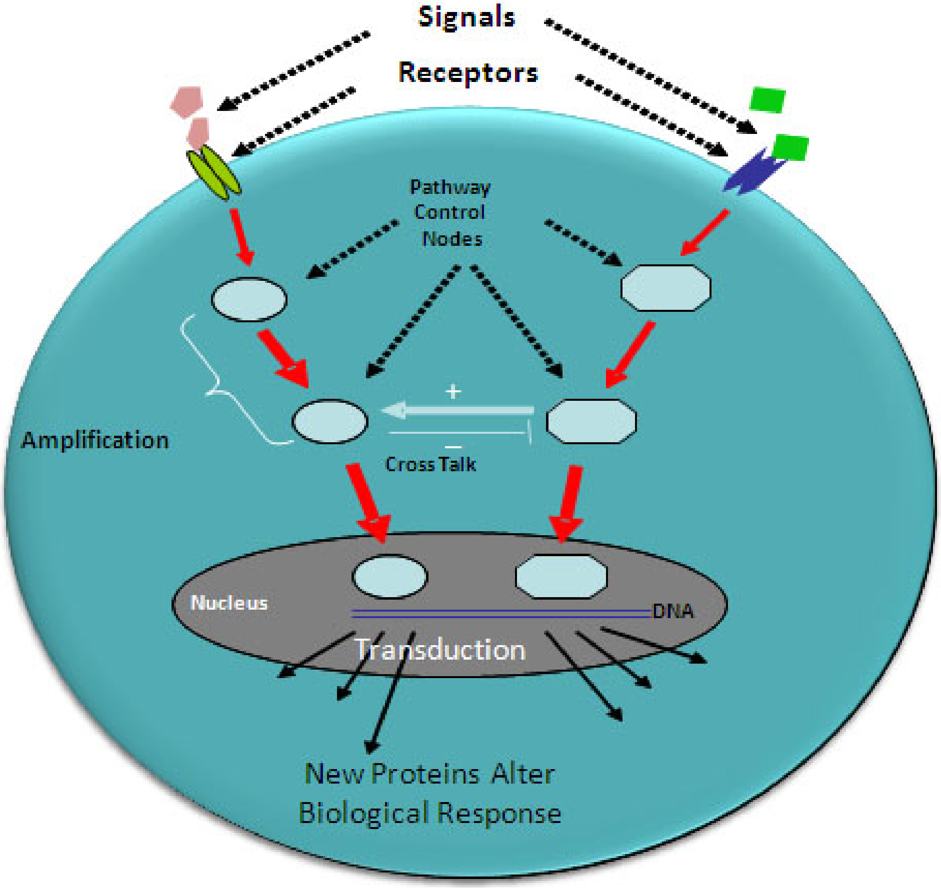
Three steps of cell signaling

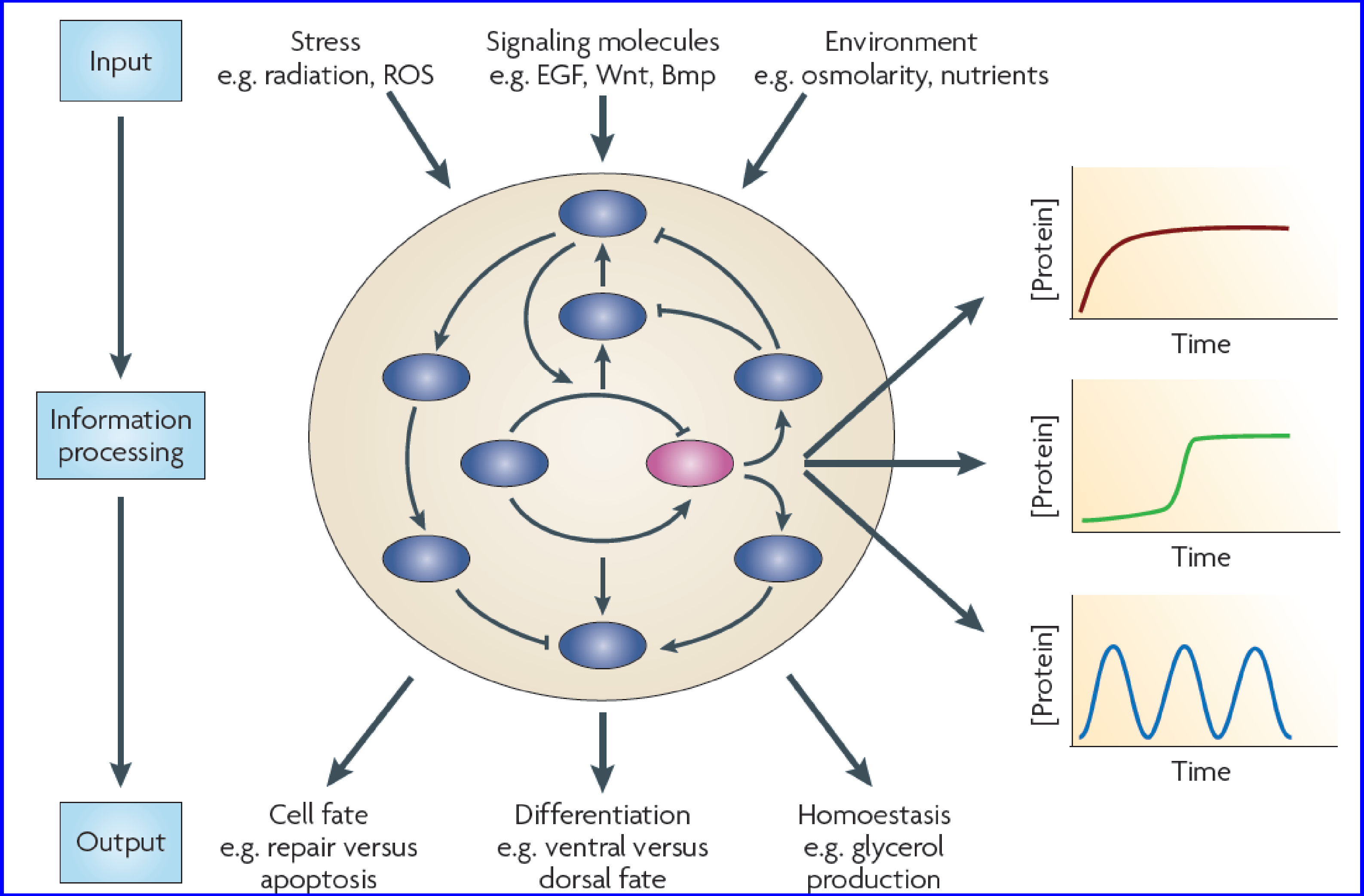


Signal Transduction Pathways

Signal Transduction Pathways are inter-connected networks of proteins that control a cell's response to change by signaling the production of new proteins.

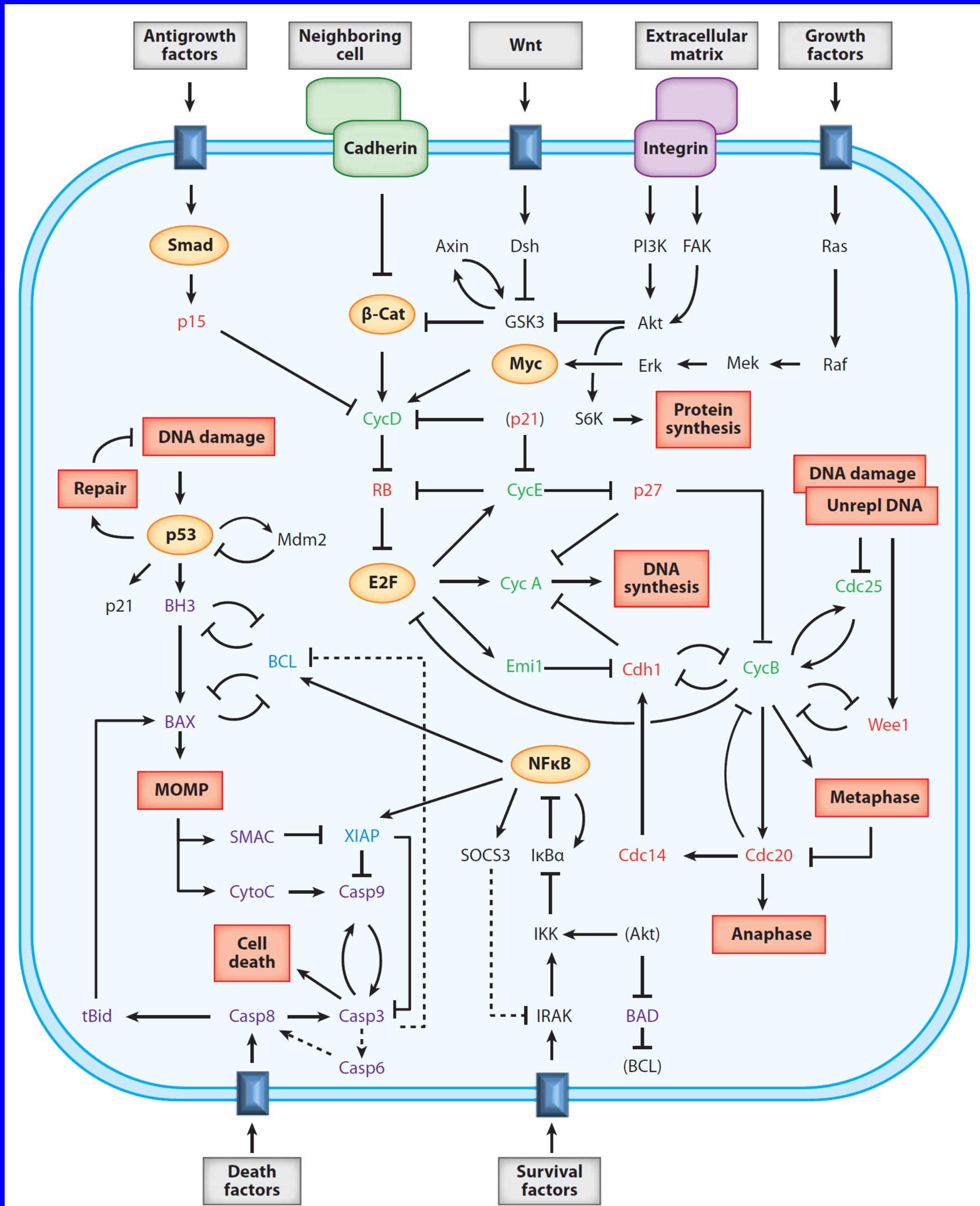
Pathways direct the physical and chemical processes of cells by activating the transcription of new proteins.





Cell signaling network

Batchelor E, Loewer A, Lahav G. Nat Rev Cancer. 2009; **9**(5): 371-7.

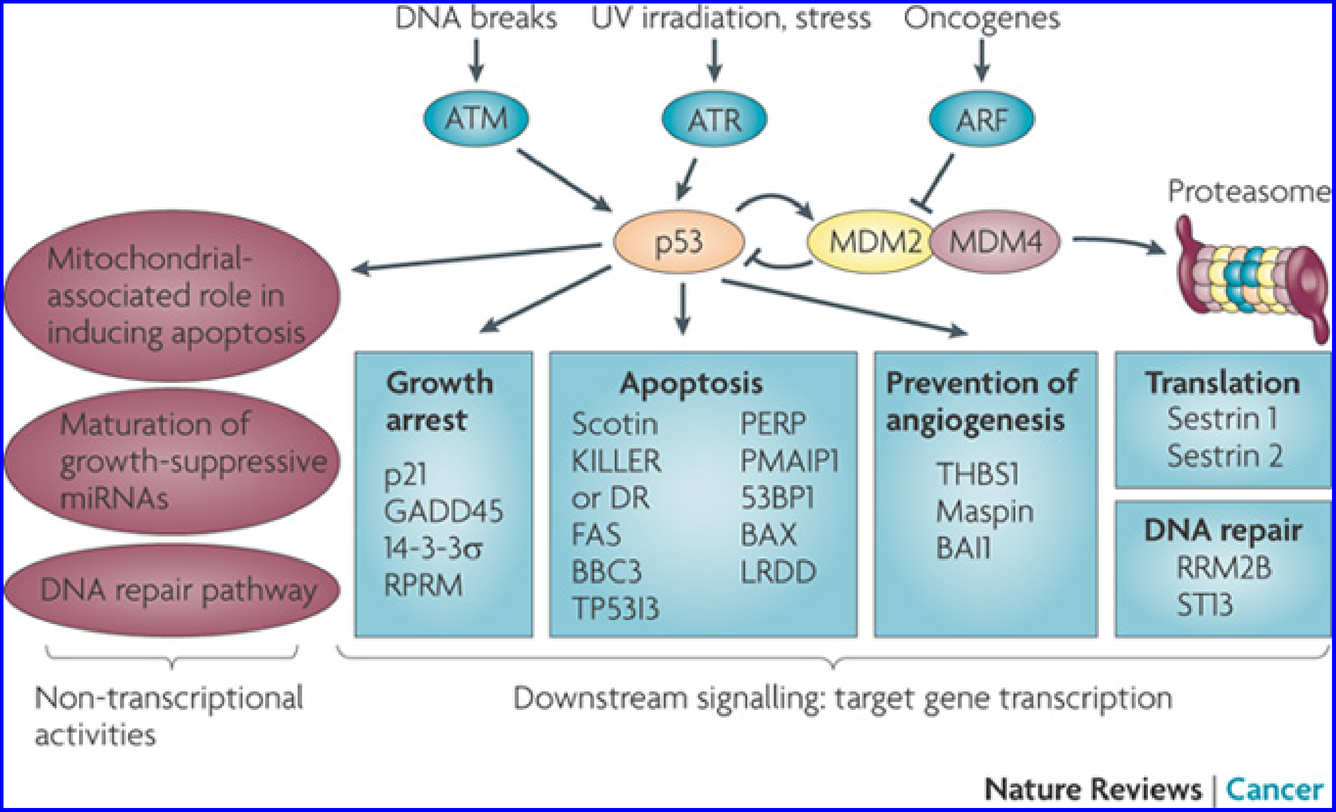


Some representative information-processing systems in a cell.

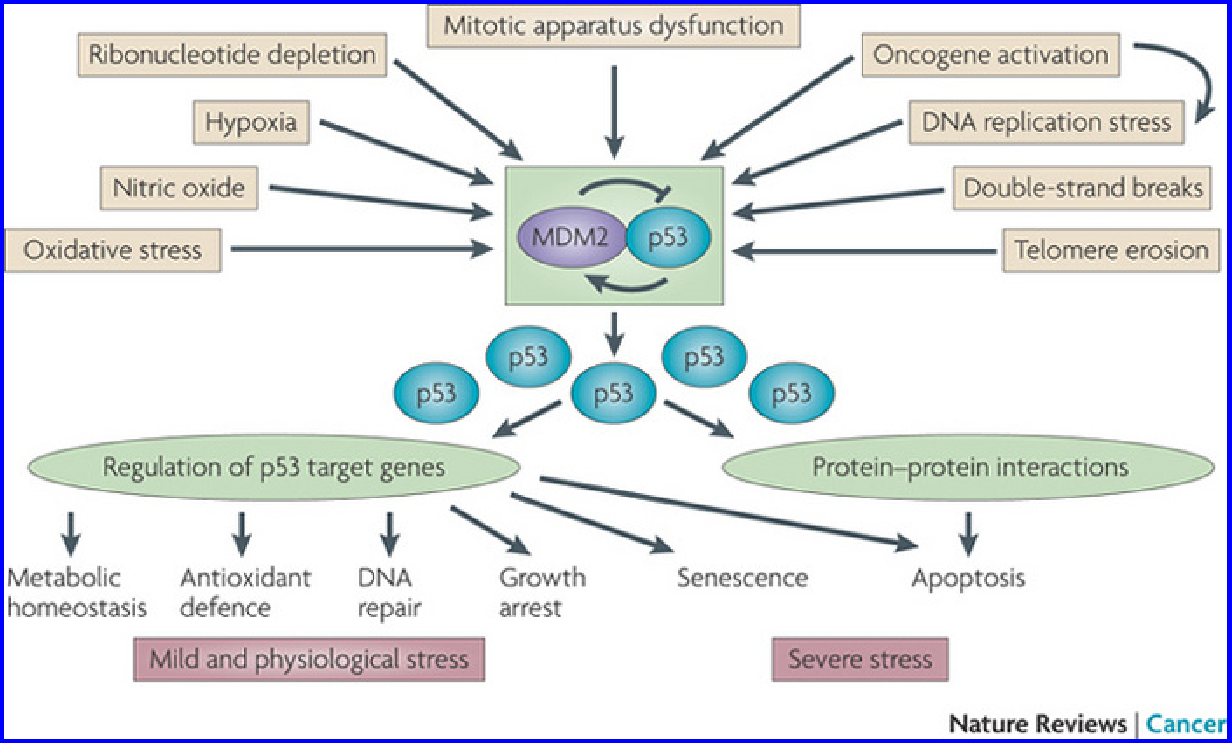
Tyson JJ, Novak B. Annual Review of Physical Chemistry. 2009; **61**(1).

2.1.2 Some cell signaling networks

P53 signaling network



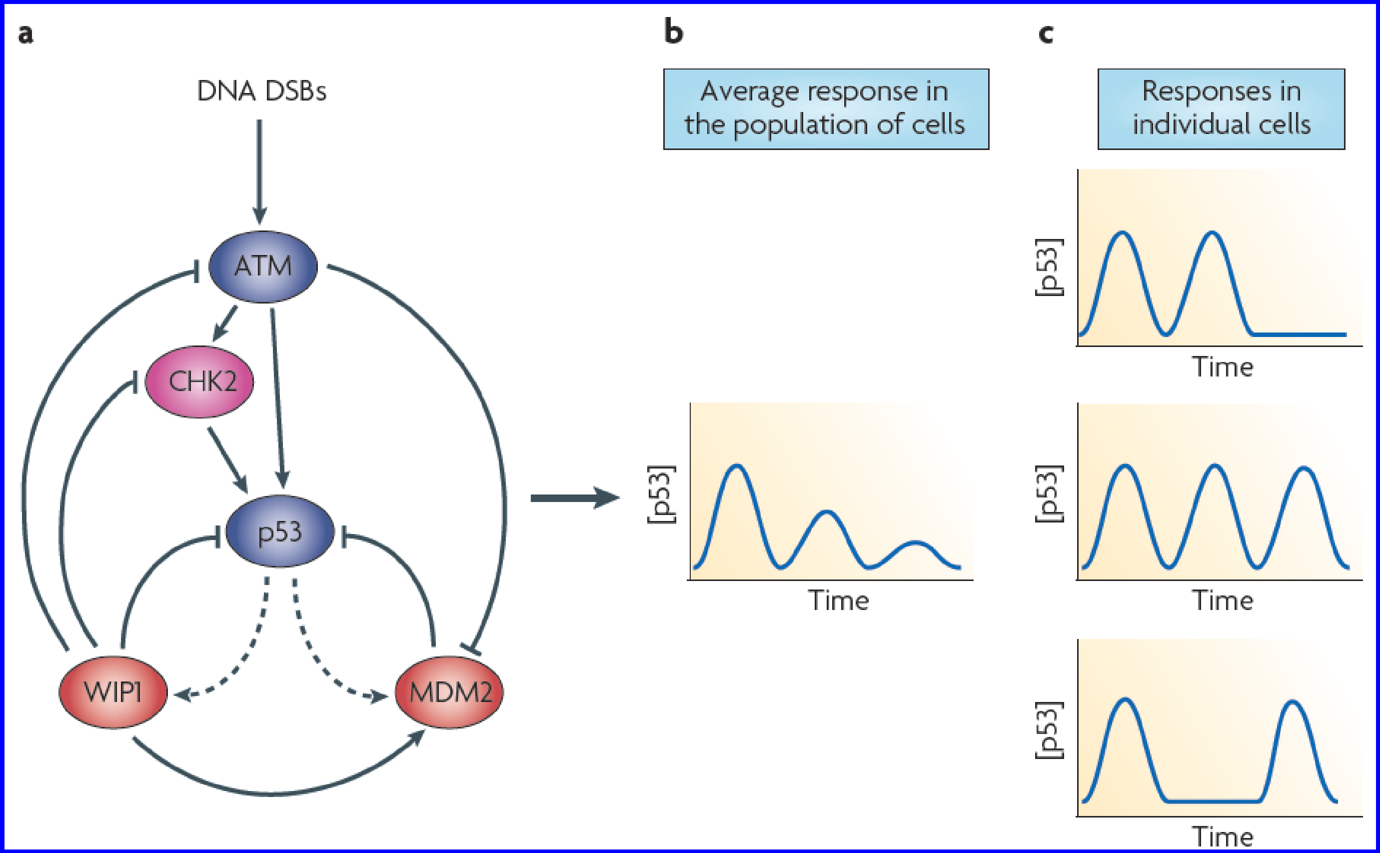
Christopher J. Brown, Sonia Lain, Chandra S. Verma, Alan R. Fersht & David P. Lane Nature Reviews Cancer 9, 862-873 (December 2009)



Simplified scheme of the p53 pathway

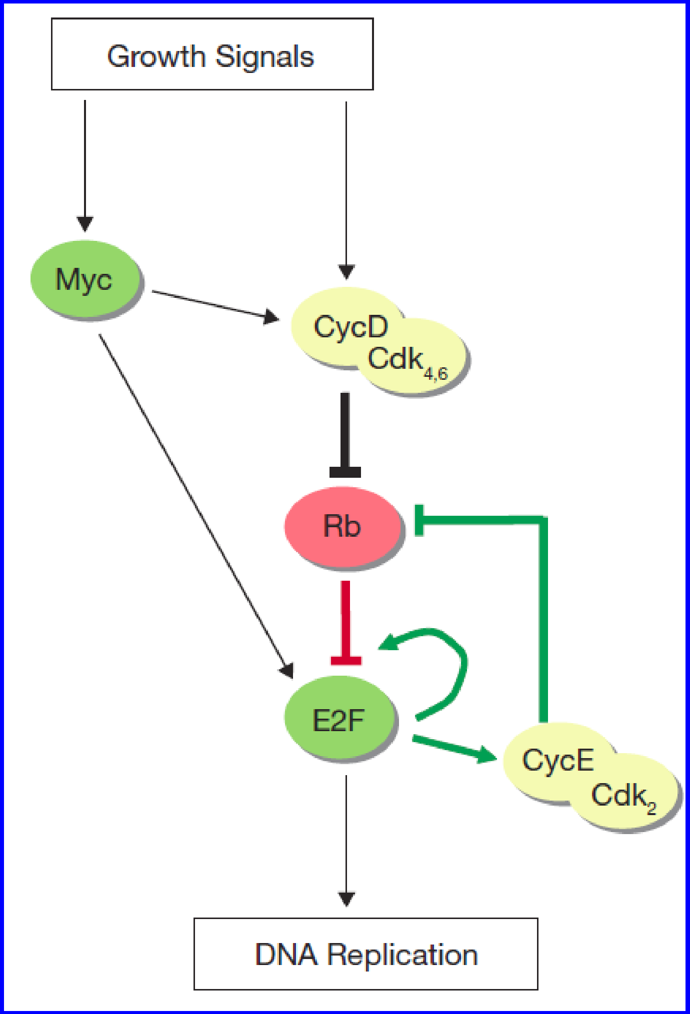
Levine, A. J. & Oren, M. *Nature Reviews Cancer* **9**, 749-758 (2009)

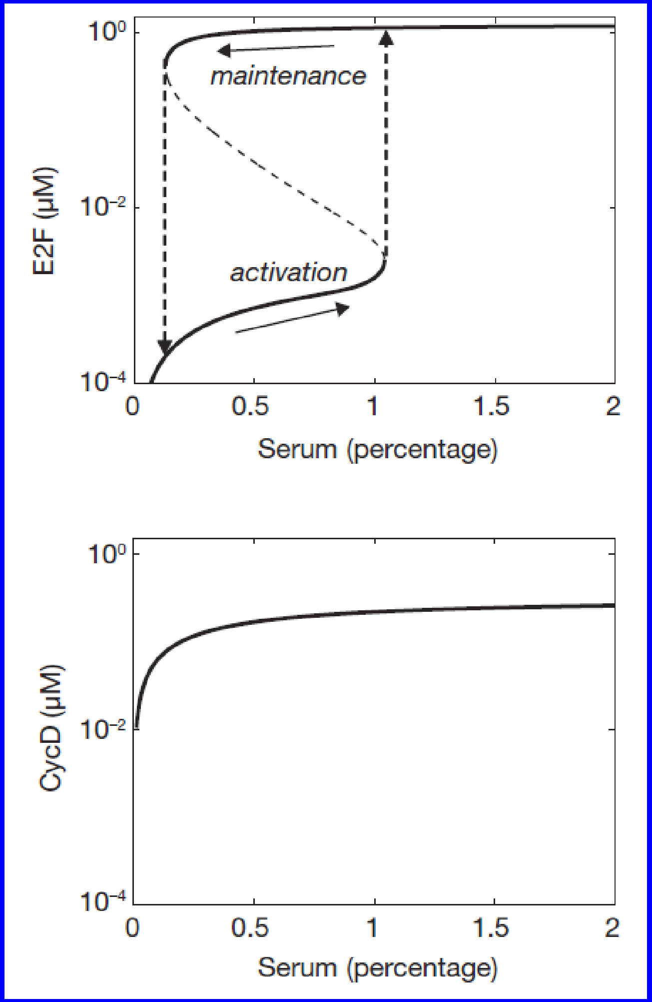
p53 dynamics: oscillation



P53 shows damped oscillations at population level, while shows undamped pulses in single cells.

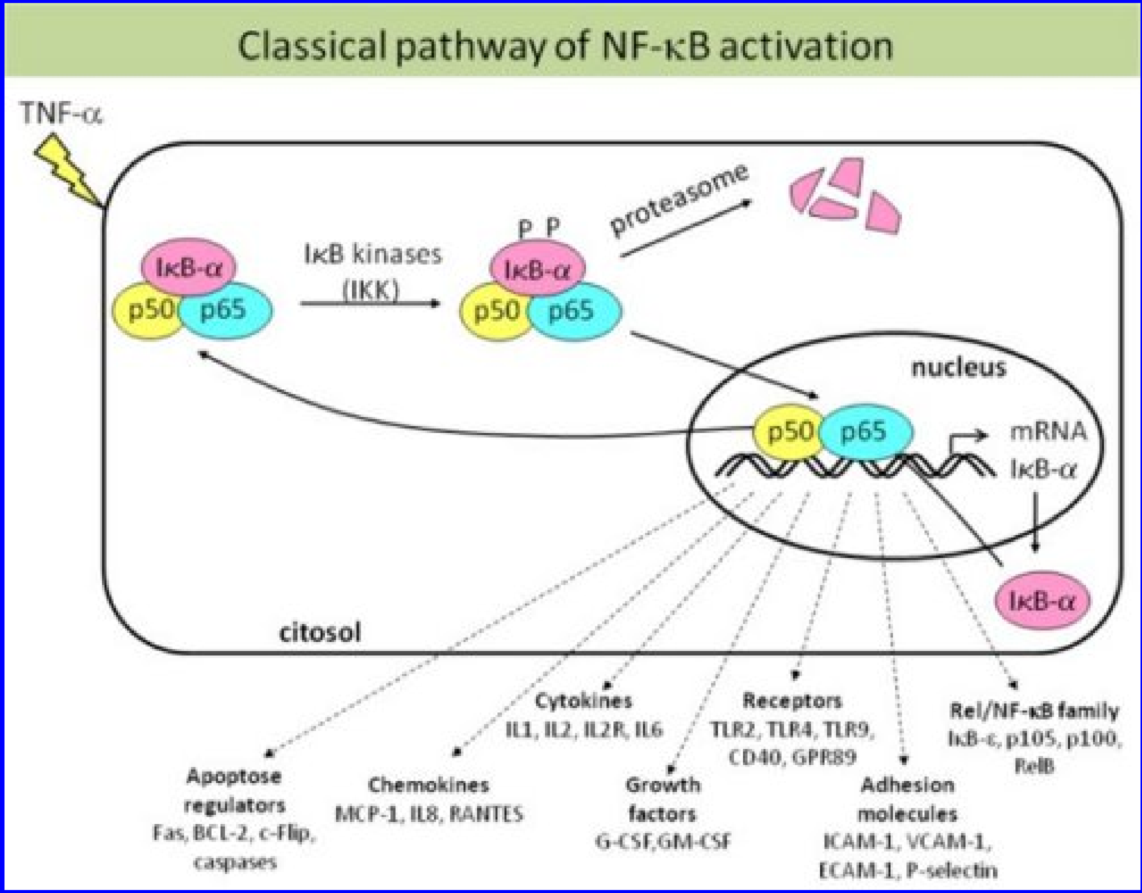
Rb/E2F1: cell proliferation

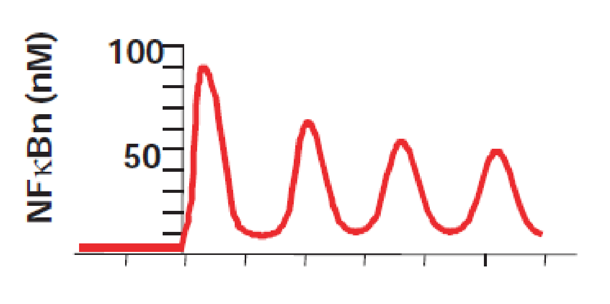




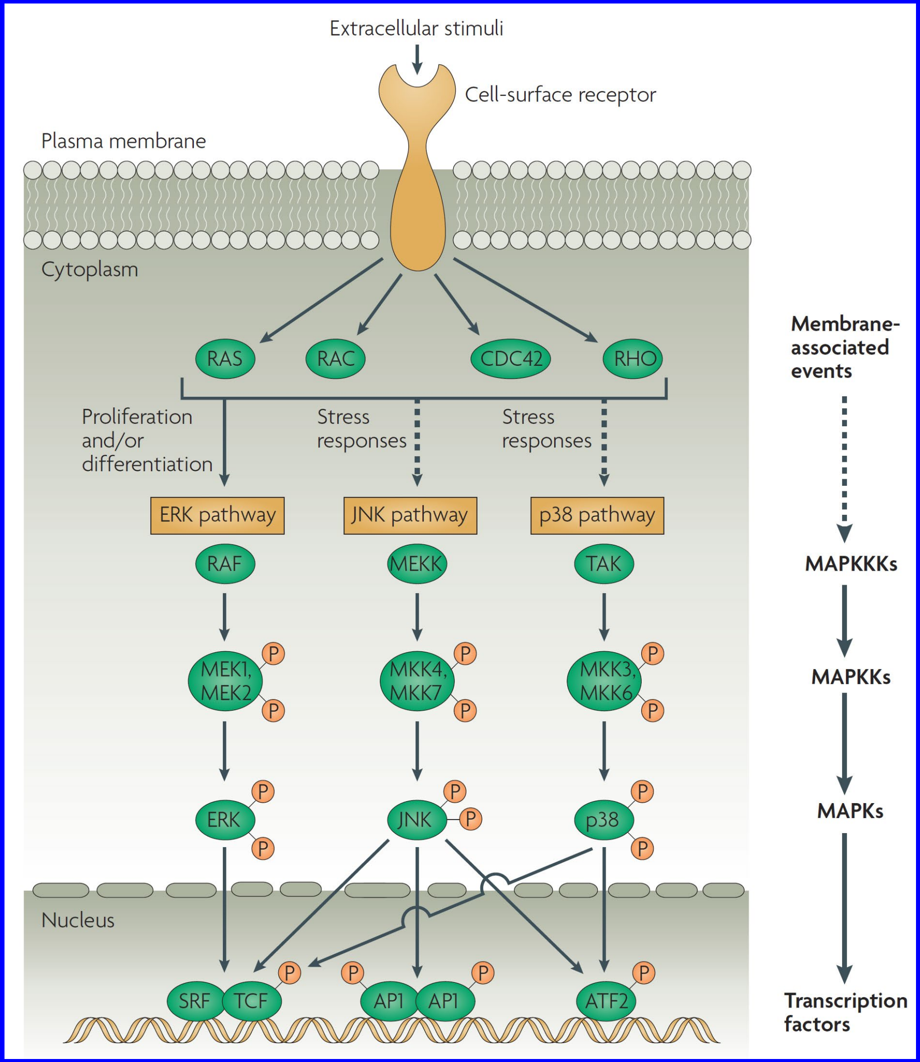
Yao, G., T. J. Lee, et al. (2008). Nat Cell Biol **10**(4): 476-482.

$NF - \kappa B$: immune and inflammatory responses



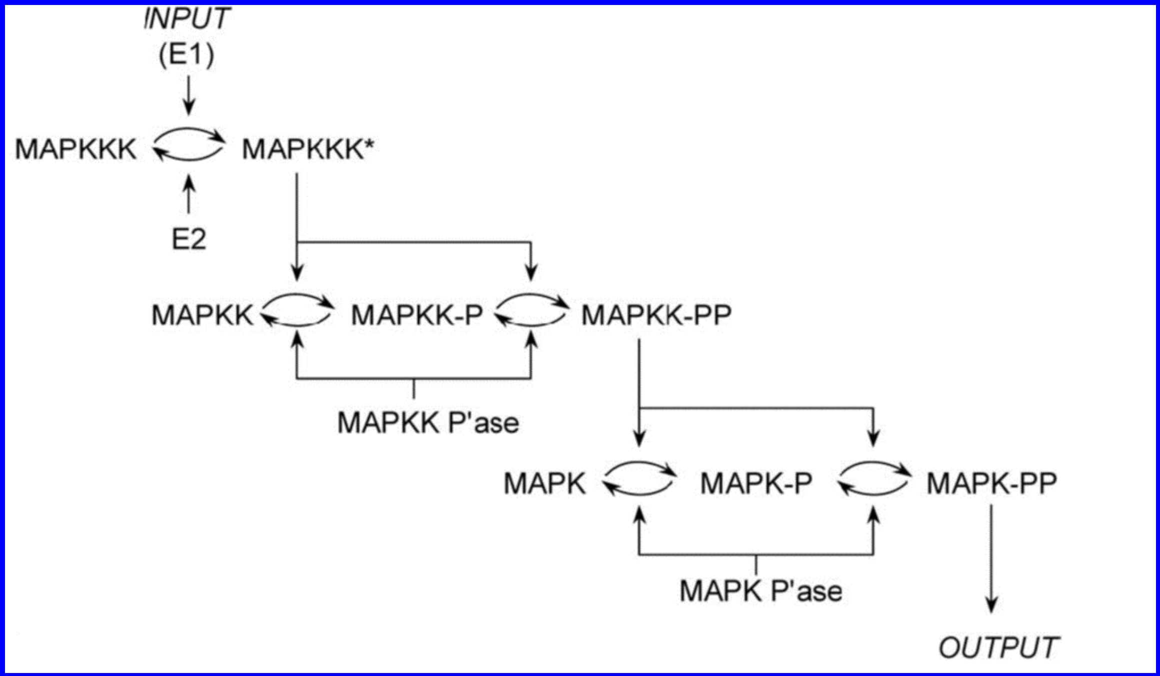


Mitogen-Activated Protein Kinase (MAPK) : cell growth, proliferation

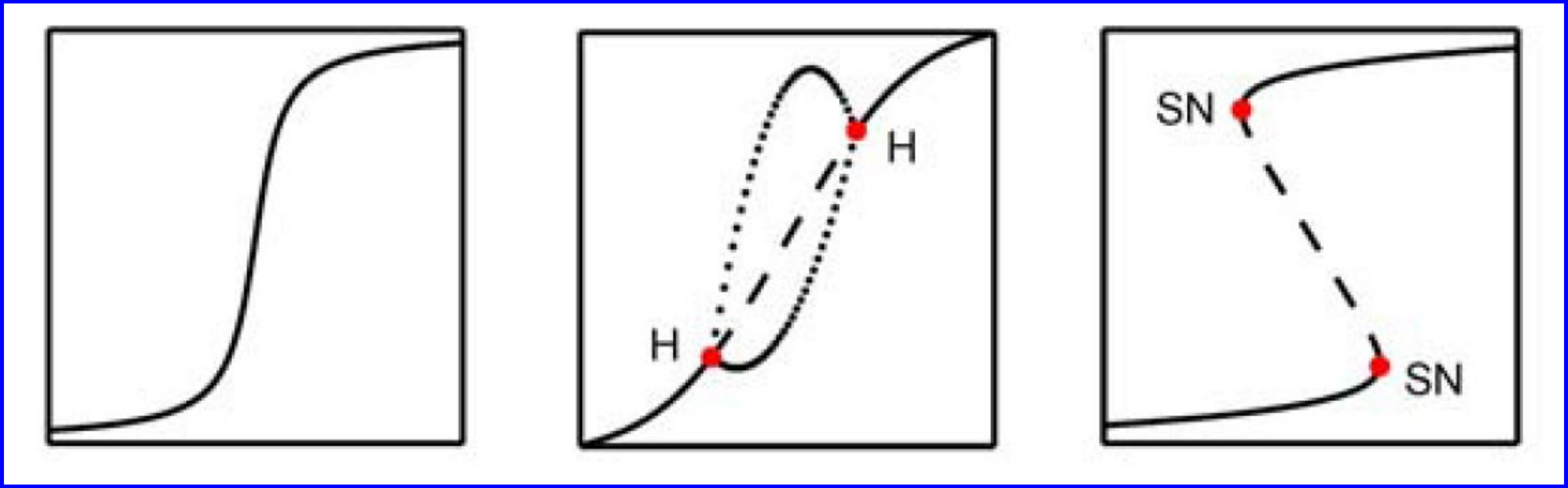


Wagner, E. F. and A. R. Nebreda (2009). Nat Rev Cancer **9**(8): 537-549.

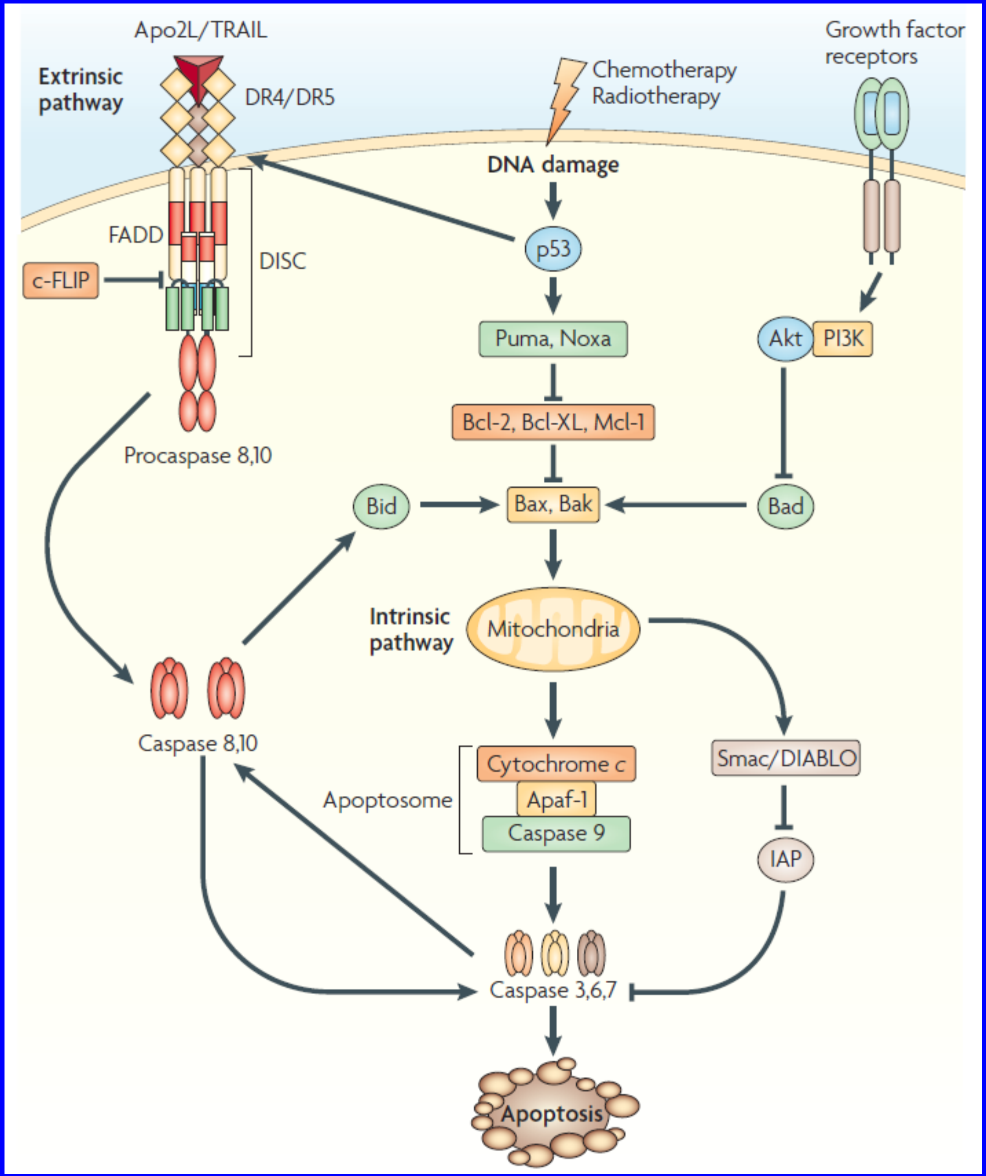
Dynamics of MAPK pathway



Qiao, L., R. B. Nachbar, et al. (2007). PLoS Computational Biology **3**(9): e184.



Apoptosis induction pathway



DISC：Death-inducing signaling complex

Key steps in apoptotic signaling pathways

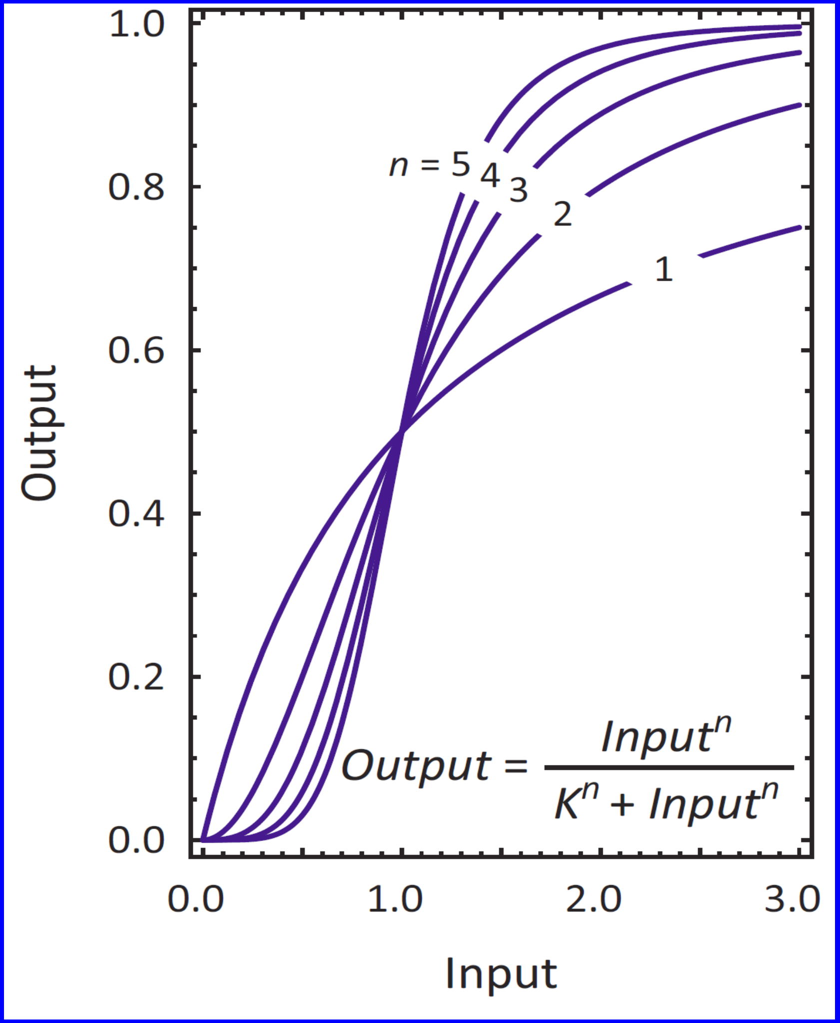
Ashkenazi, A. (2008). Nat Rev Drug Discov 7(12): 1001-1012.

2.1.3 Dynamical properties

- Ultrasensitivity
- Bistability
- Oscillation
- Adaptation

Ultrasensitivity

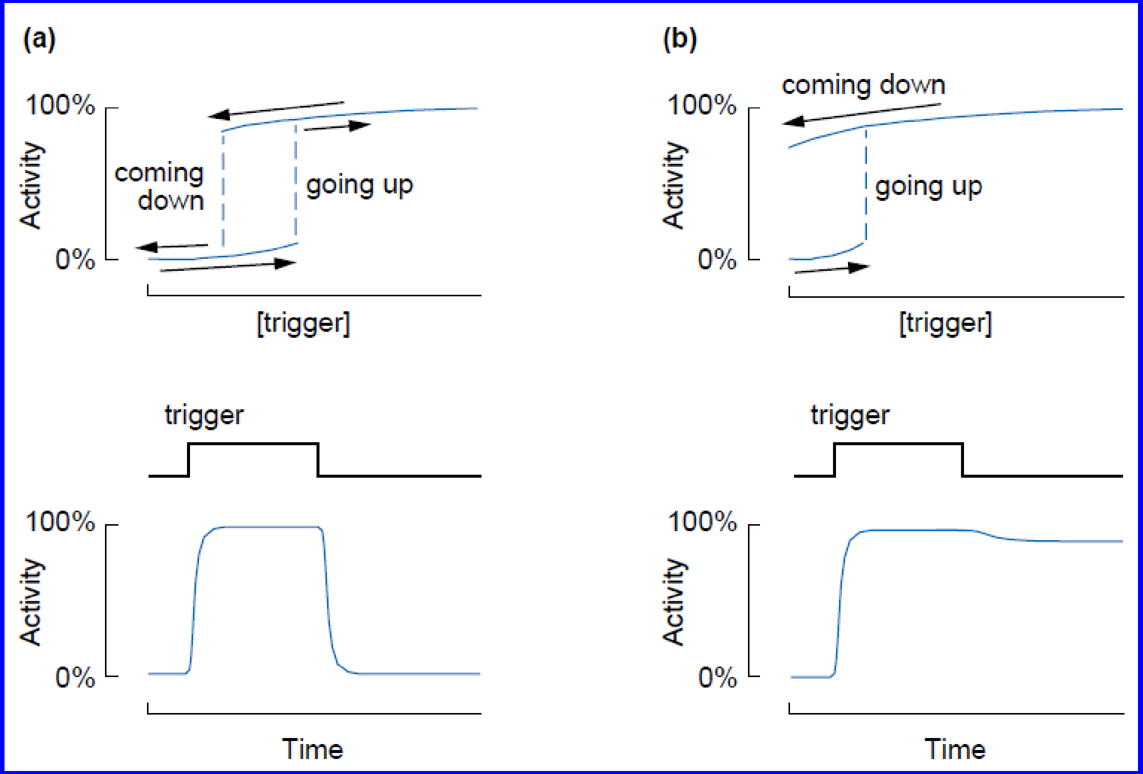
- **Ultrasensitivity** describes an output response that is more sensitive to stimulus change than the hyperbolic Michaelis-Menten response.



Bistability

Bistability: having two stable steady states for a single value of the input, as contrasted with a monostable response.

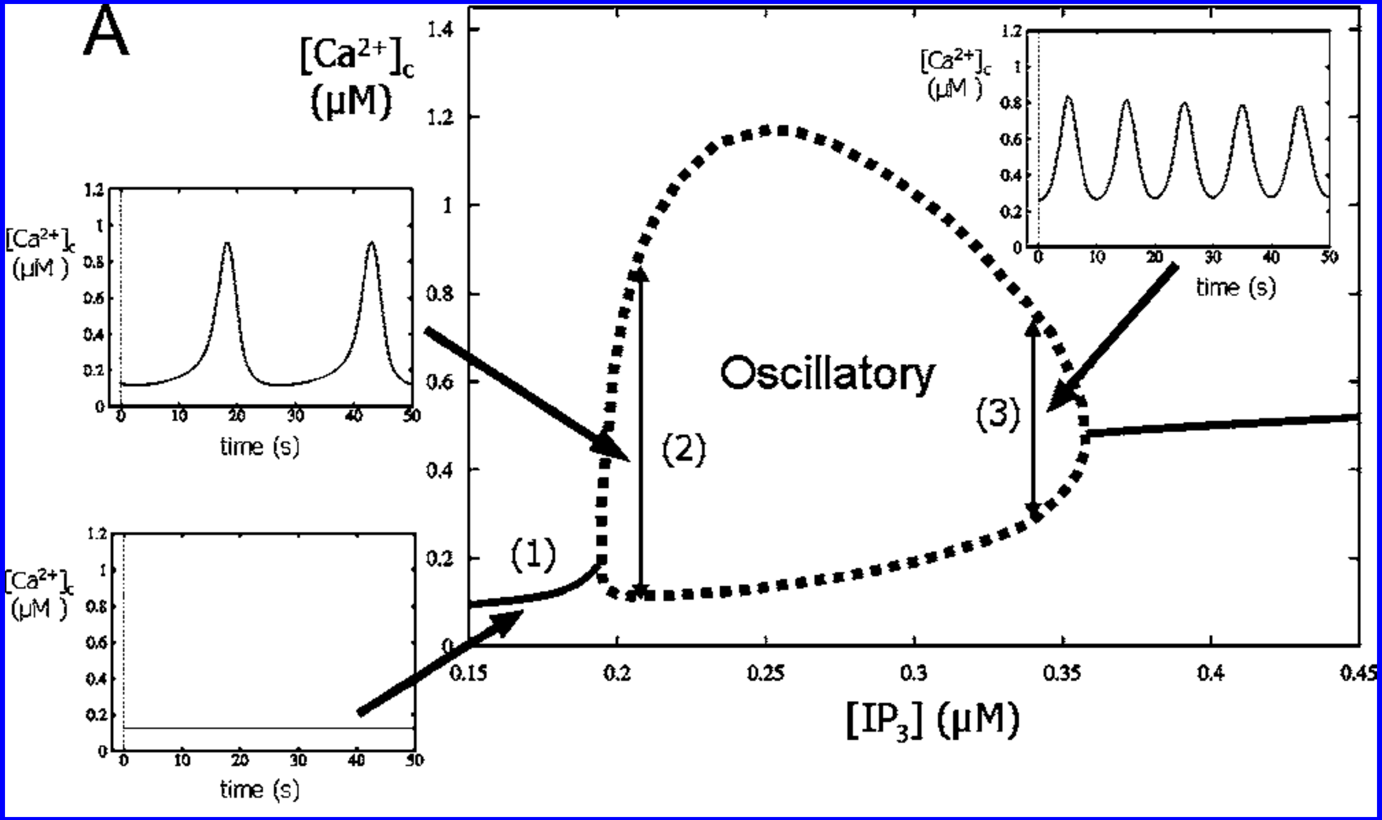
Hysteresis and irreversibility in bistable signaling circuits



Hu, J. S., L. T. Doan, et al. (2008). PNAS.105(9): 3398-3403.

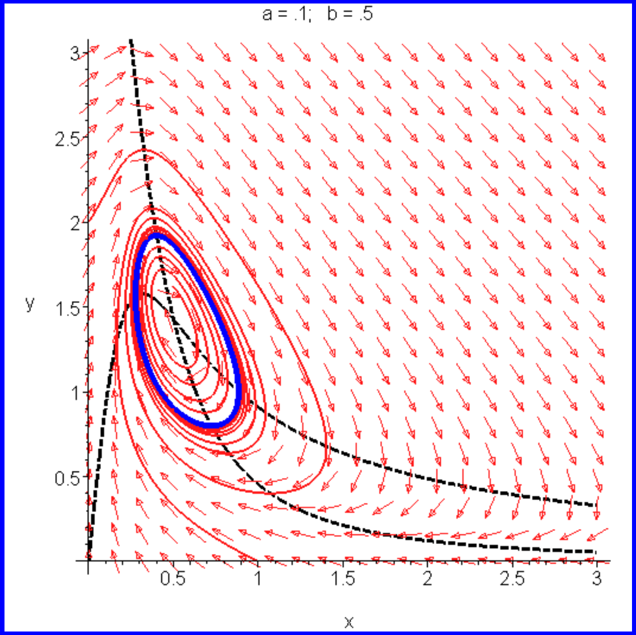
Oscillation

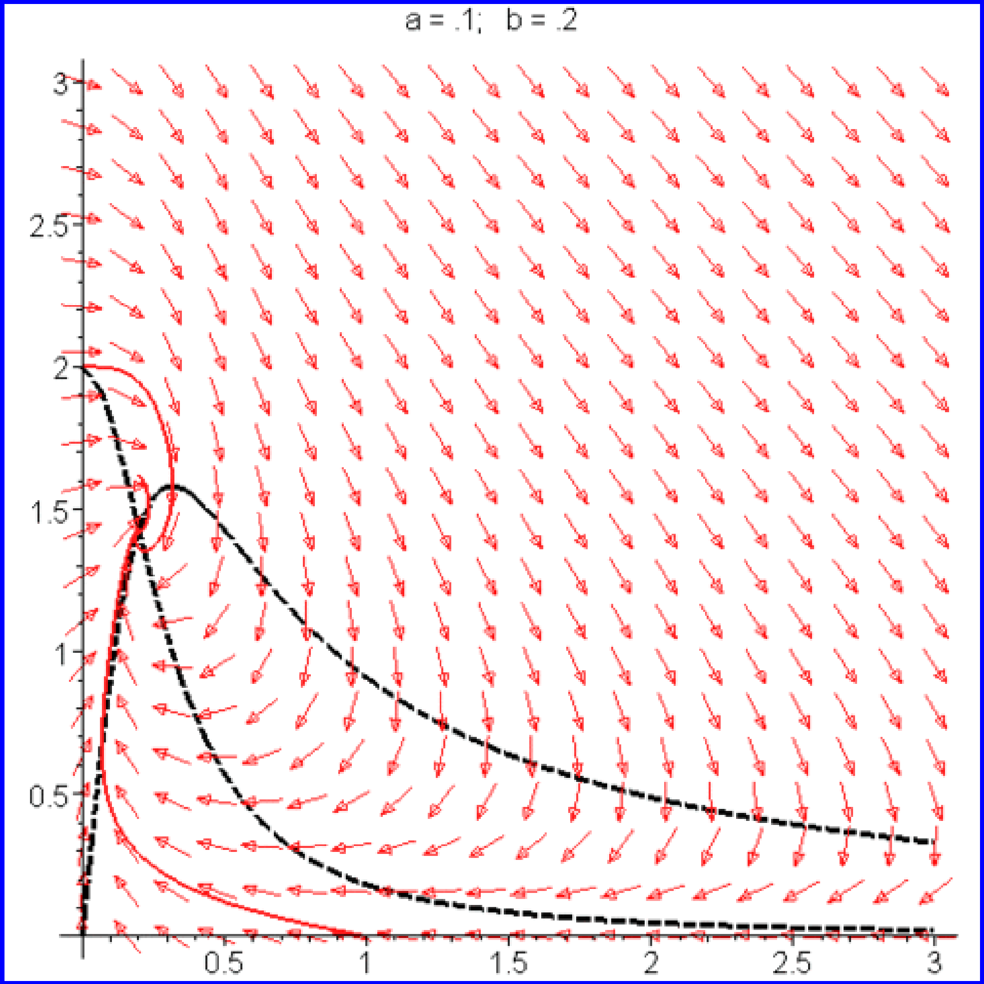
Oscillations are an important type of cell signaling characterized by the periodic change of the system in time.



$$\frac{dx}{dt} = -x + ay + x^2 y$$

$$\frac{dy}{dt} = b - ay - x^2 y$$

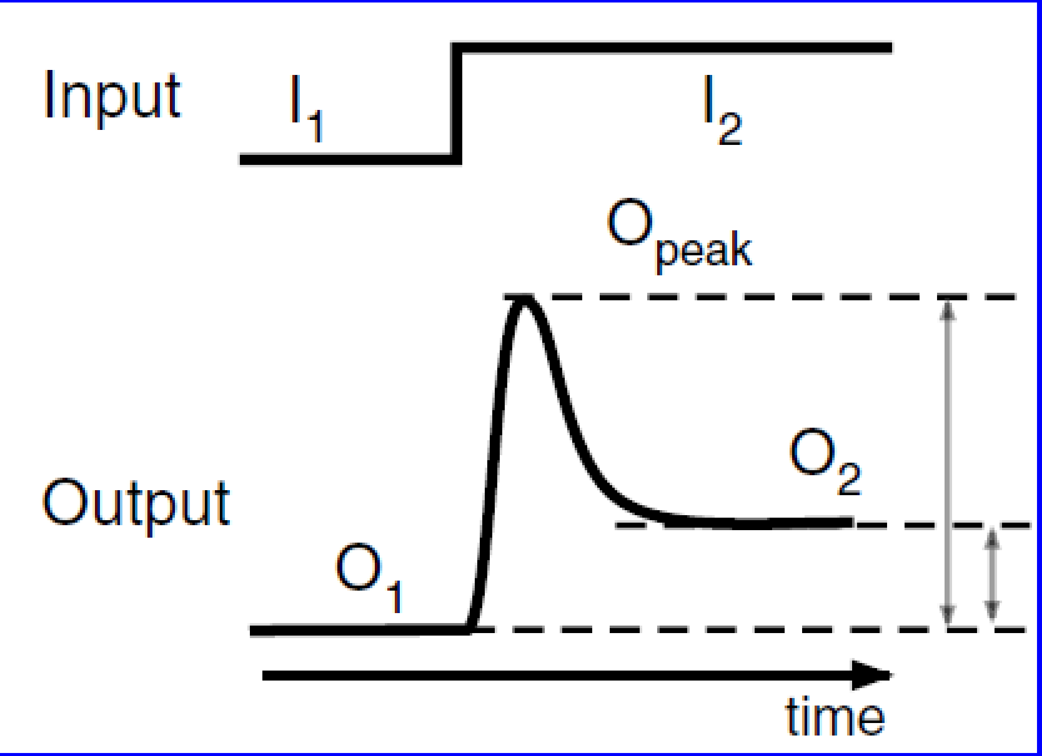




Adaptation

Adaptation—the ability to reset themselves after responding to a stimulus.

Ma, W., A. Trusina, et al. (2009). Cell.**138**(4): 760-773.



2.2 Dynamics of cell signaling networks

- Simulation tools

- Bifurcation theory

2.2.1 Simulation tools

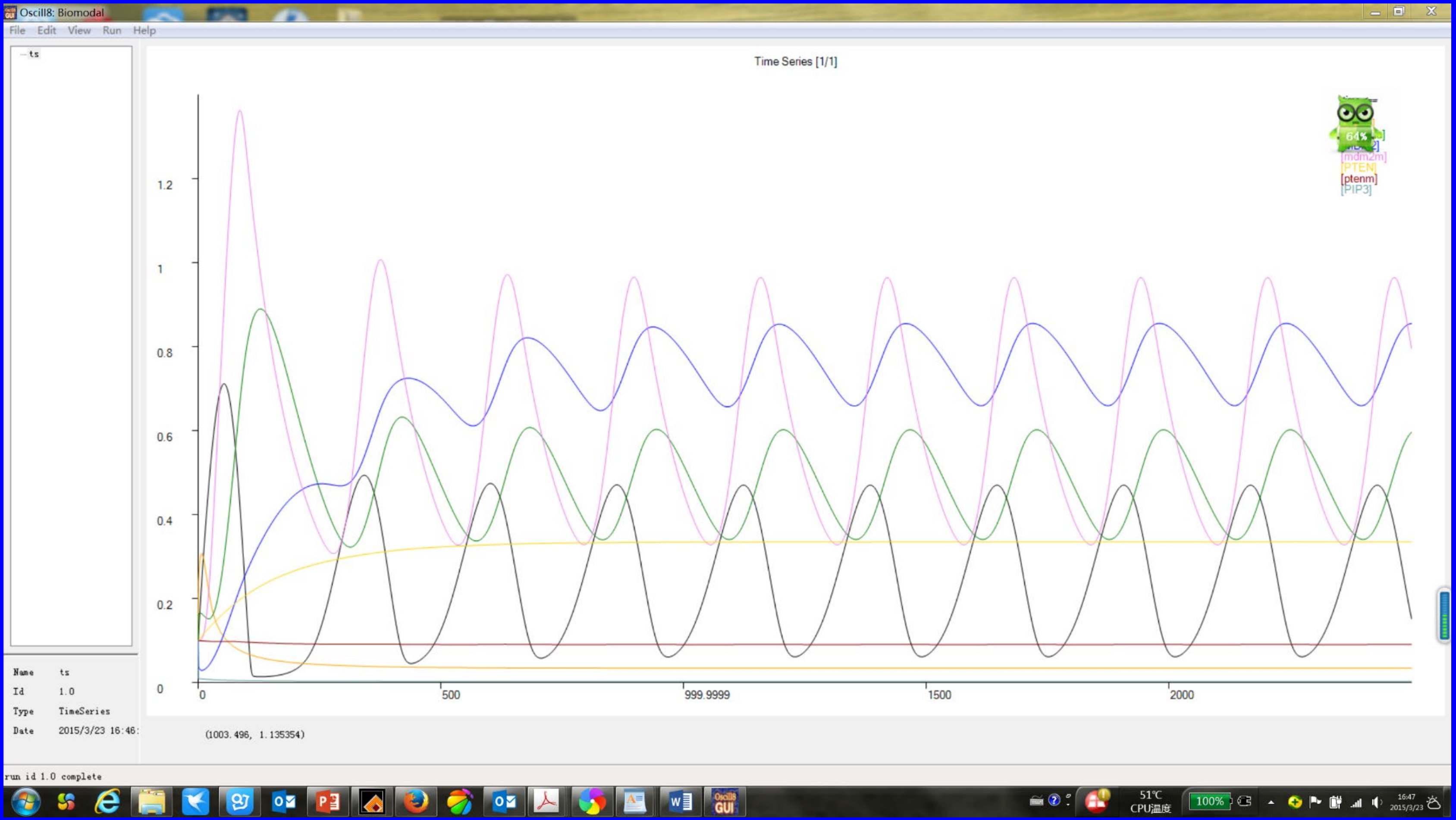
- Oscill8

Oscill8 is a suite of tools for analyzing dynamical systems which concentrates on understanding how the dynamical behavior depends on the parameters using bifurcation theory and reaction network theory.

http://sourceforge.jp/projects/sfnet_oscill8/

ODE file

```
# test
x'=a1*(1-x)-b1*x*(v*y)^r1/(k1+(v*y)^r1)
y'=a2*(1-y)-b2*y*x^r2/(k2+x^r2)
par v=0, a1=1, a2=1, b1=200
par b2=10, k1=30, k2=1, r1=4, r2=4
init x=0.1, y=0.1
done
```


Oscill8: Biomodal
File Edit View Run Help
ts
Time Series [1/1]
1.2
1
0.8
0.6
0.4
0.2
0
0
500
999.9999
1500
2000
64%
[mdm2m]
[PTEN]
[ptenm]
[PIP3]
Name ts
Id 1.0
Type TimeSeries
Date 2015/3/23 16:46:
(1003.496, 1.135354)
run id 1.0 complete
51℃
CPU温度
100%
16:47
2015/3/23

Other simulation tools

- Xpp/Xppaut

http://www.math.pitt.edu/~bard/xpp/xpp.html

- Matlab

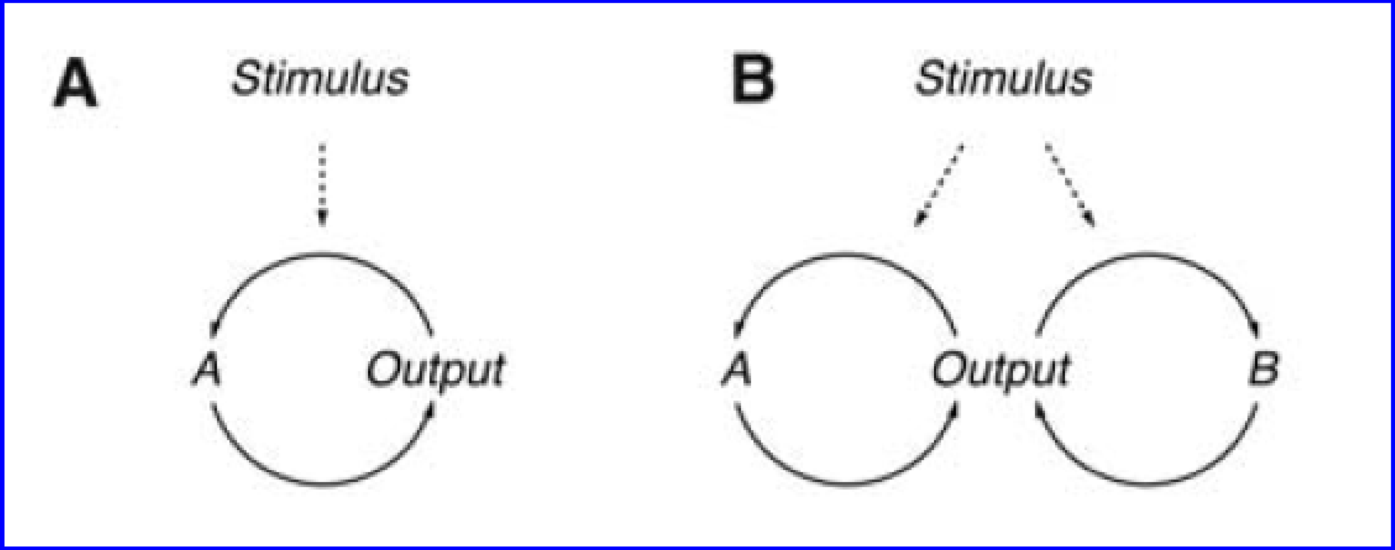
Graphing software

Origin 8

Assignment 1

Reproducing Figs 2C-G in the following paper:

Brandman, O., J. E. Ferrell, Jr., et al. (2005). "Interlinked Fast and Slow Positive Feedback Loops Drive Reliable Cell Decisions." Science 310(5747): 496-498.



1) One loop

$$\frac{dOUT}{dt} = k_{out\_on} * A * (1 - OUT) - k_{out\_off} * OUT + k_{out\_min}$$

$$\frac{dA}{dt} = \left[stimulus * \frac{OUT^n}{OUT^n + ec_{50}^n} * (1 - A) - A + k_{min}\right] * \tau_A$$

2) Two loops

$$\frac{dOUT}{dt} = k_{out\_on} * (A + B) * (1 - OUT) - k_{out\_off} * OUT + k_{out\_min}$$

$$\frac{dA}{dt} = \left[stimulus * \frac{OUT^n}{OUT^n + ec_{50}^n} * (1 - A) - A + k_{min}\right] * \tau_A$$

$$\frac{dB}{dt} = \left[stimulus * \frac{OUT^n}{OUT^n + ec_{50}^n} * (1 - B) - B + k_{min}\right] * \tau_B$$

$k_{out\_on} = 2$, $k_{out\_off} = 0.3$, $k_{out\_min} = 0.001$, $k_{min} = 0.01$, $n = 3$, $ec_{50} = 0.35$. For a fast loop, $\tau = 0.5$. For a slow loop, $\tau = 0.008$. The equations were solved numerically with Matlab 7.0.