Systems Biology Across Scales: A Personal View
XXII. Building elements for Biological circuits

Sitabhra Sinha

IMSc Chennai

Elements of biological circuits

Figures and text from
Tyson, Chen & Novak, "Sniffers, buzzers, toggles and blinkers," *Curr. Opin. Cell Biol.* **15**:221 (2003).

A molecular network looks strikingly similar to the wiring diagram of a modern electronic gadget. Instead of resistors, capacitors and transistors hooked together by wires, one sees genes, proteins and metabolites hooked together by chemical reactions and intermolecular interactions.

• Complex molecular networks, like electrical circuits, seem to be constructed from simpler modules: sets of interacting genes and proteins that carry out specific tasks and can be hooked together by standard linkages.

• Simple signalling pathways can be embedded in networks using positive and negative feedback to generate more complex behaviours — toggle switches and oscillators — which are the basic building blocks of the exotic, dynamic behaviour shown by nonlinear control systems.

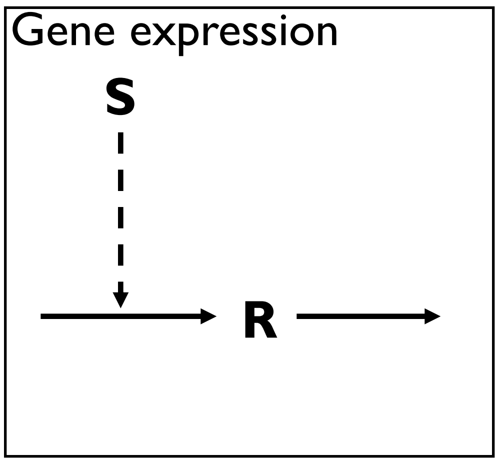
Simple modules for building complex dynamic networks

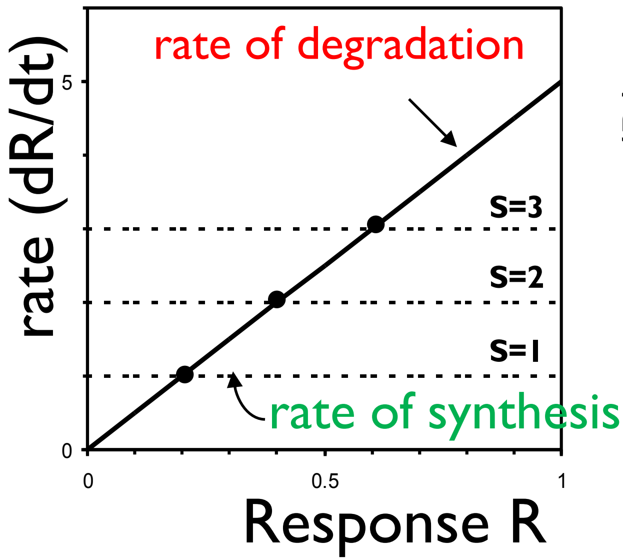
- Linear and hyperbolic signal response : graded & reversible
- Sigmoidal response: reversible but abrupt (“buzzer”)
- Perfectly adapted response: transient response (“sniffer”)
- Positive feedback : discontinuous switch
  - hysteresis
  - mutual activation (“one way” switch)
  - mutual inhibition (“toggle” switch)
- Negative feedback
  - homeostasis
  - oscillations (“blinker”)

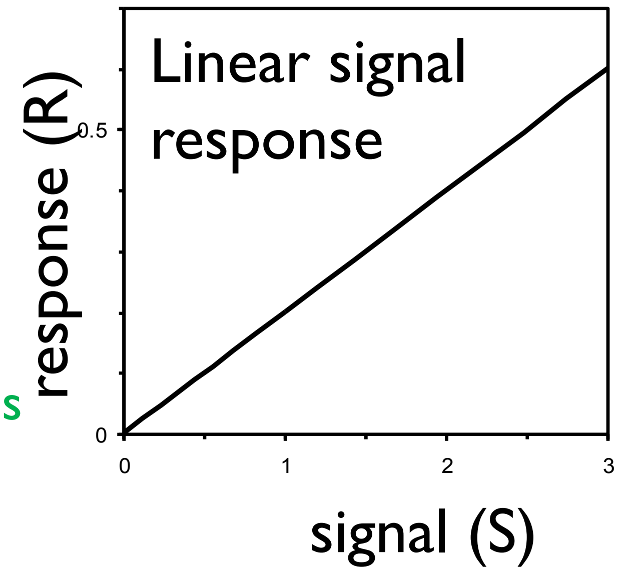
Protein synthesis and degradation

S = signal concentration (e.g., concentration of mRNA)

R = response magnitude (e.g., concentration of protein)





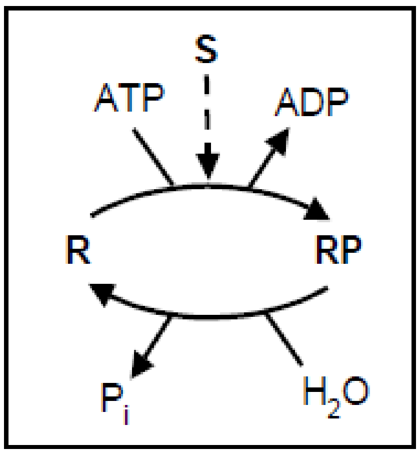


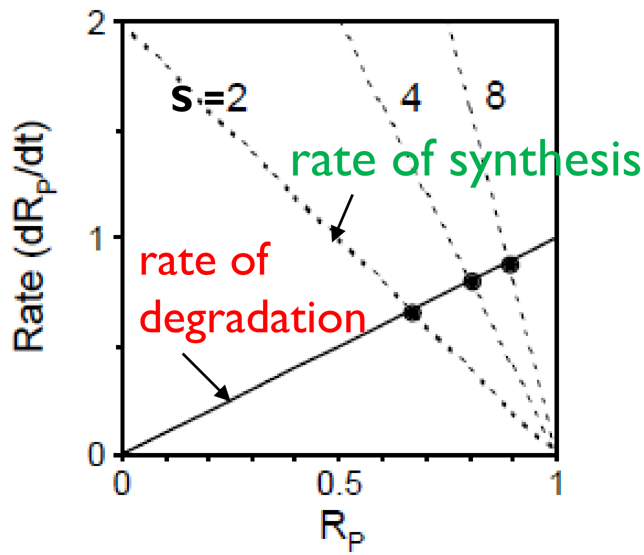
$$\frac{dR}{dt} = k_0 + k_1 S - k_2 R,$$

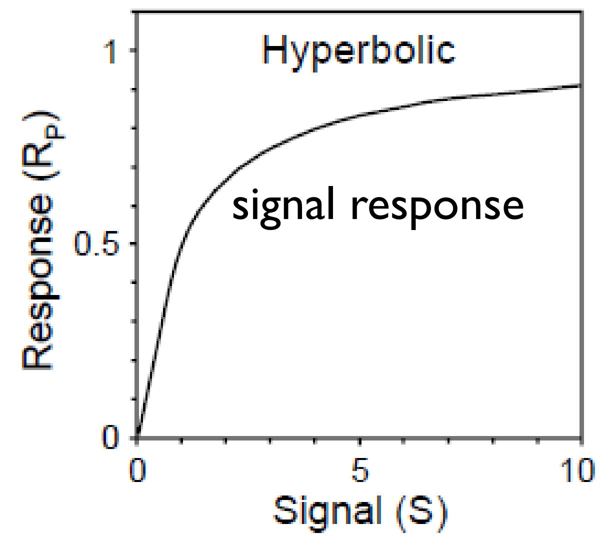
Steady-state solution $$R_{ss} = \frac{k_0 + k_1 S}{k_2}$$

Protein Phosphorylation/Dephosphorylation

R = unphosphorylated protein
R_P = phosphorylated protein
$R_T = R + R_P$ = total protein concentration







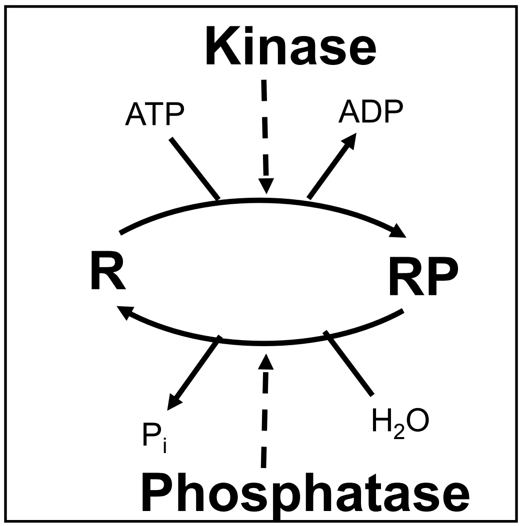
$$\frac{dR_P}{dt} = k_1 S(R_T - R_P) - k_2 R_P$$

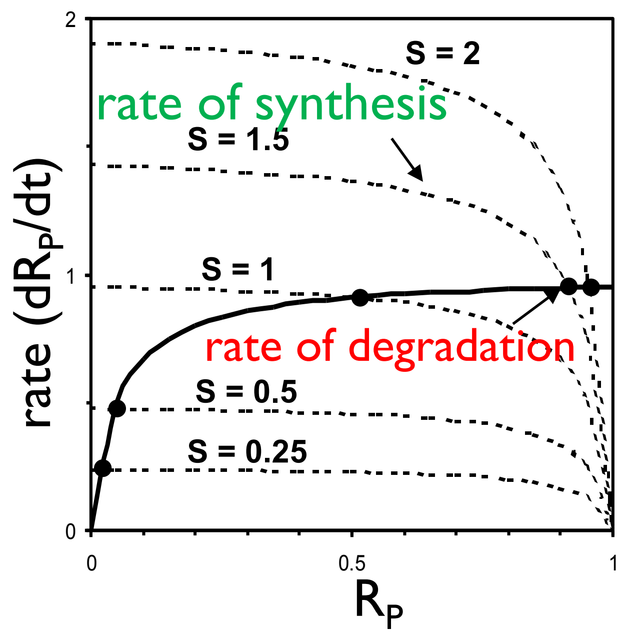
Steady-state solution $$R_{P,ss} = \frac{R_T S}{(k_2/k_1) + S}$$

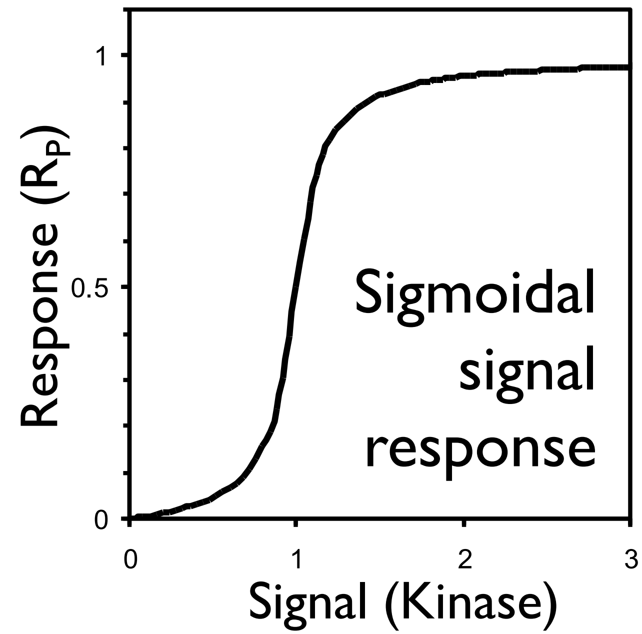
Protein Phosphorylation/Dephosphorylation Michelis-Menten kinetics

Switch-like response or zero-order ultrasensitivity (“buzzer”)

Goldbeter & Koshland, PNAS 78, 6840 (1981)







$$\frac{dR_P}{dt} = \frac{k_1 S(R_T - R_P)}{K_{m1} + R_T - R_P} - \frac{k_2 R_P}{k_{m2} + R_P}$$

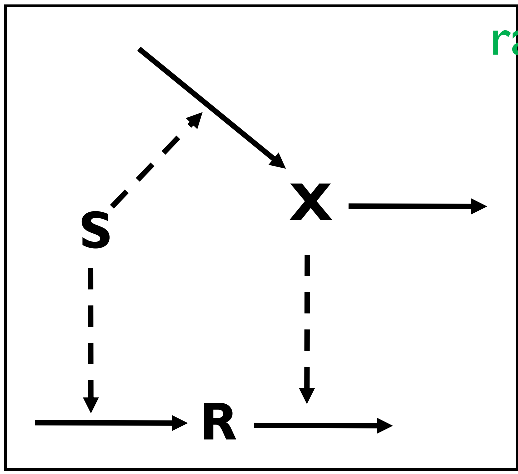
Steady-state concn is a solution of

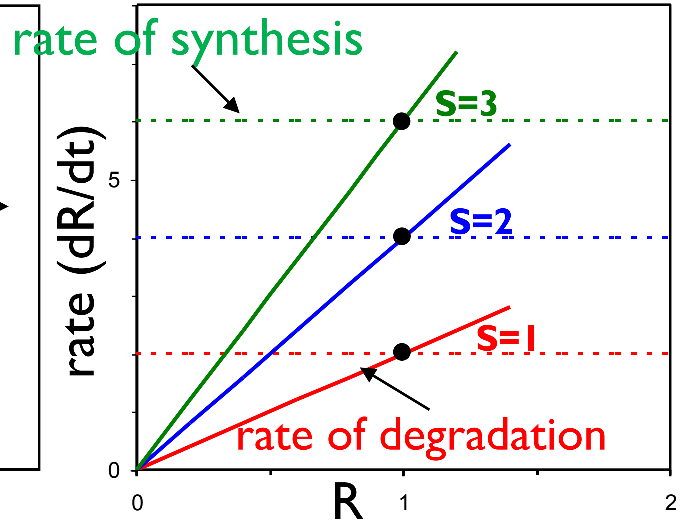
$$k_1 S(R_T - R_P)(K_{m2} + R_P) = k_2 R_P(K_{m1} + R_T - R_P)$$

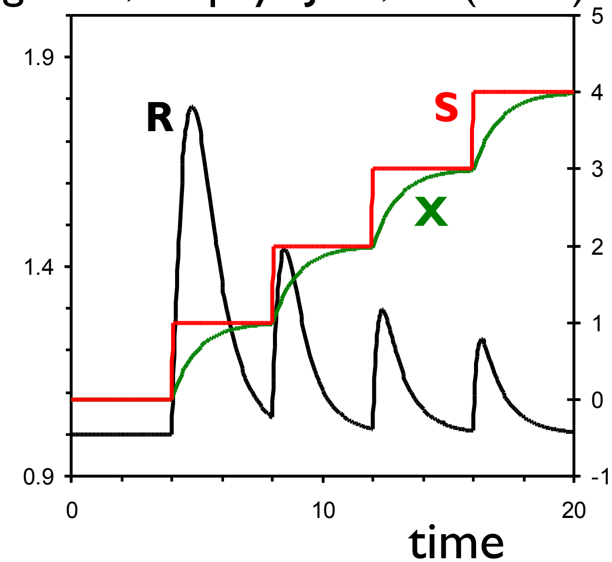
Perfectly adapted signal response (“sniffer”)

by supplementing the simple linear response element with a second signaling pathway (via species X)

Levchenko & Iglesias, Biophys J 82, 50 (2002)







Perfect adaptation: Although the signaling pathway exhibits a transient response to changes in signal strength, its steady-state response

$$\frac{dR}{dt} = k_1 S - k_2 X \cdot R \qquad R_{ss} = \frac{k_1 k_4}{k_2 k_3}$$

$$\frac{dX}{dt} = k_3 S - k_4 X \qquad X_{ss} = \frac{k_3 S}{k_4}$$

R_{ss} is independent of S

Typical of chemotactic systems responding to abrupt changes but insensitive to a constant signal

Feedback

some component of a response pathway may feed back on the signal.

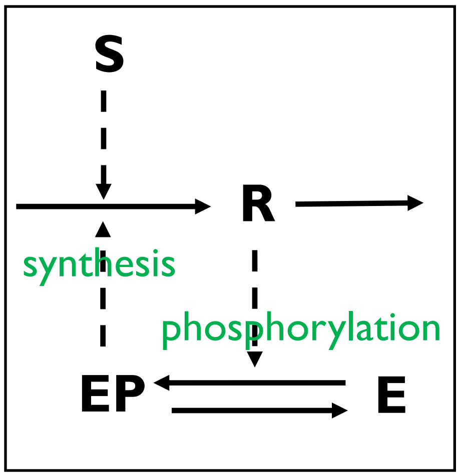
Feedback can be

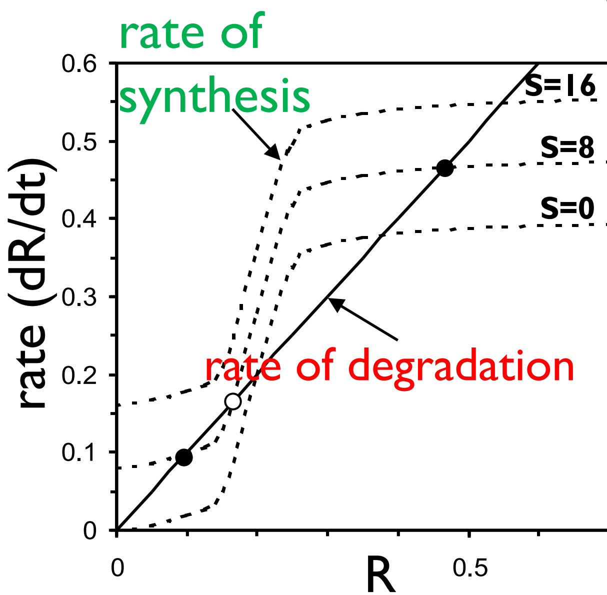
- positive,
- negative or
- mixed

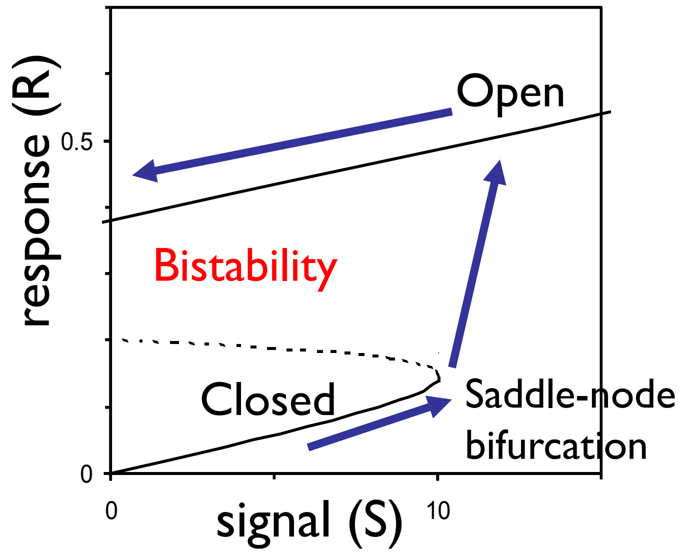
Positive Feedback: Mutual activation

- R activates protein E by phosphorylation
- EP enhances the synthesis of R

Griffith, J Theor Biol 20, 202 (1968)







Discontinuous switch: cellular response changes abruptly and irreversibly as signal magnitude crosses a critical value.

$$\frac{dR}{dt} = k_0 E_P(R) + k_1 S - k_2 X \cdot R$$

$$E_P(R) = G(k_3 R, k_4, J_3, J_4)$$

Irreversible switch (“fuse”): once response goes to high, it remains there even when signal becomes low

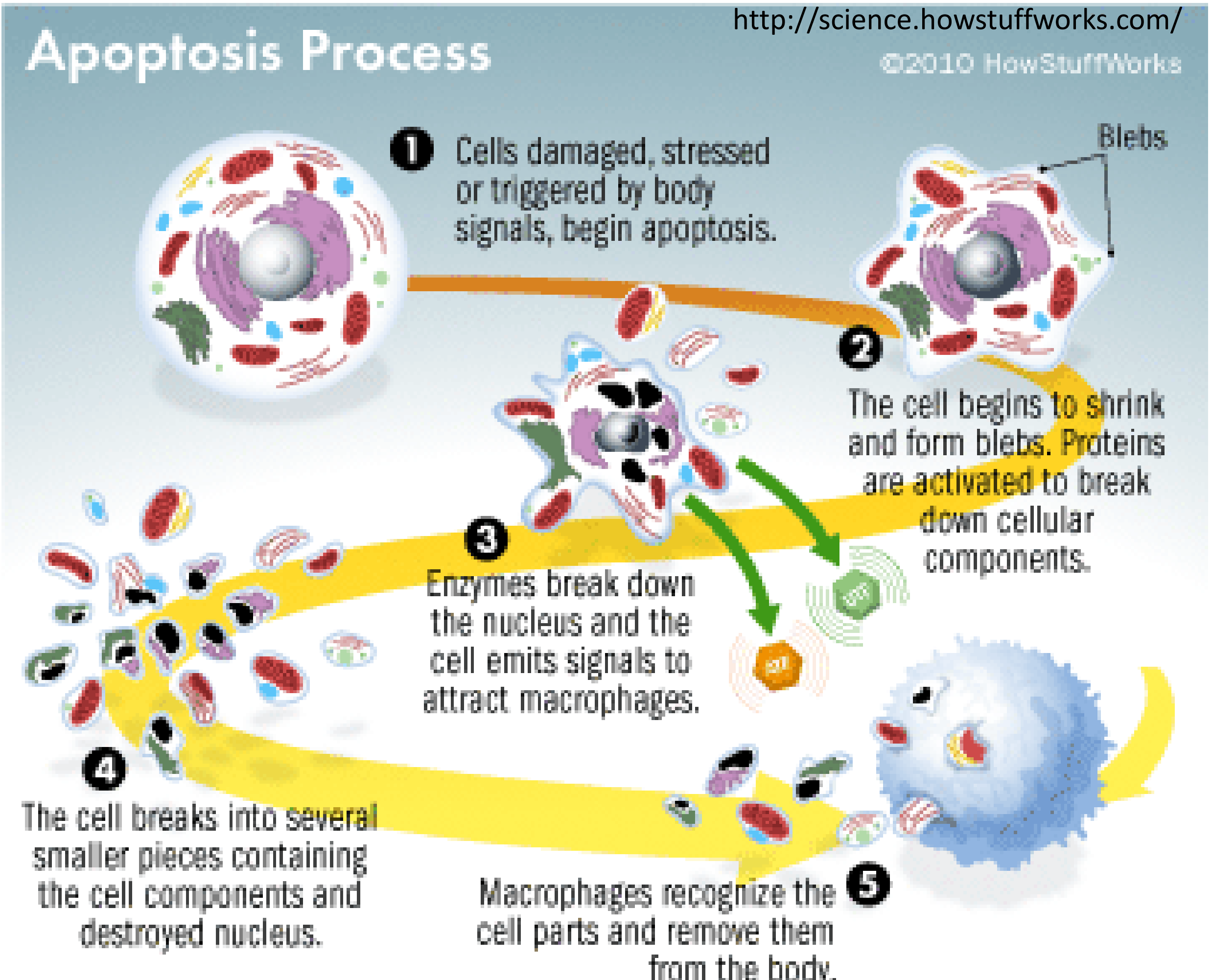
One-way switch ("fuse")

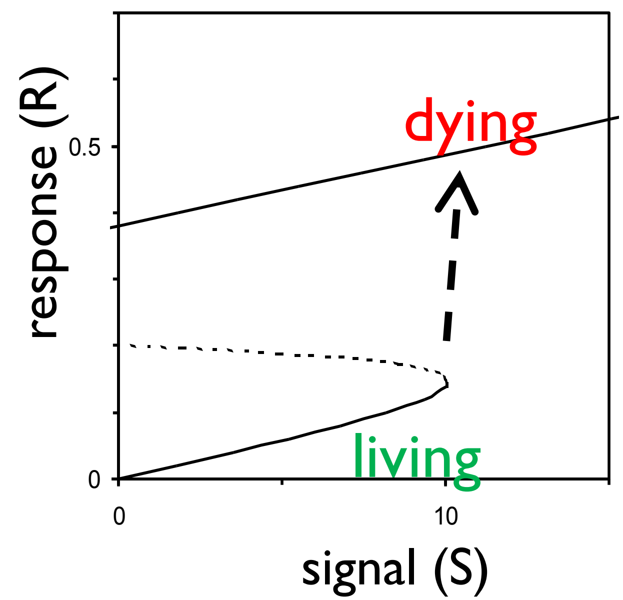
One-way switches presumably play major roles in developmental processes characterized by a "point of no return"

Laurent & Kellershohn, Trends Biochem Sci 24, 418 (1999)

Example: Apoptosis (Programmed Cell Death)

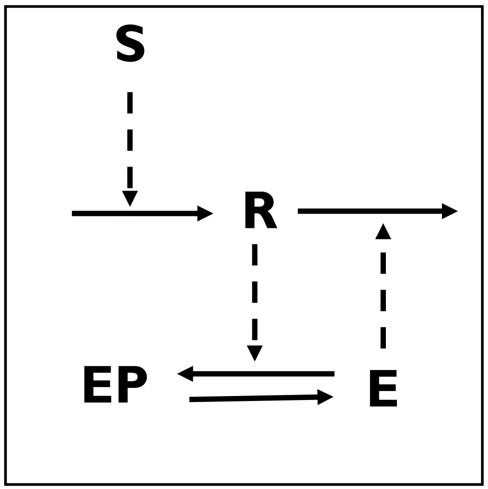
http://science.howstuffworks.com/

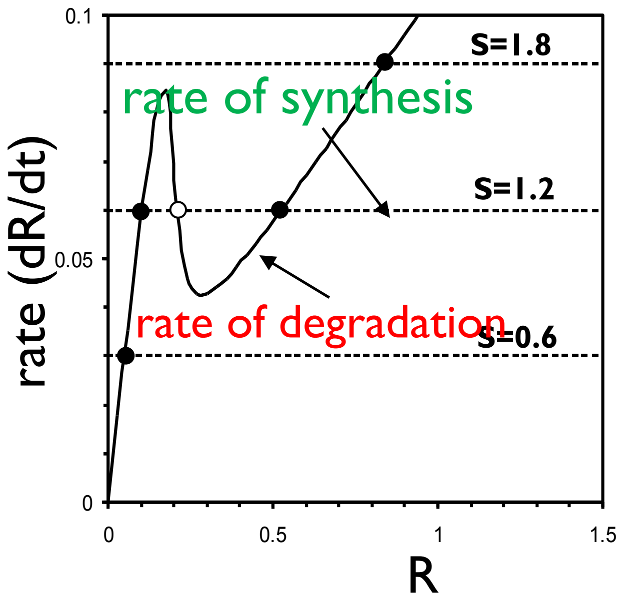


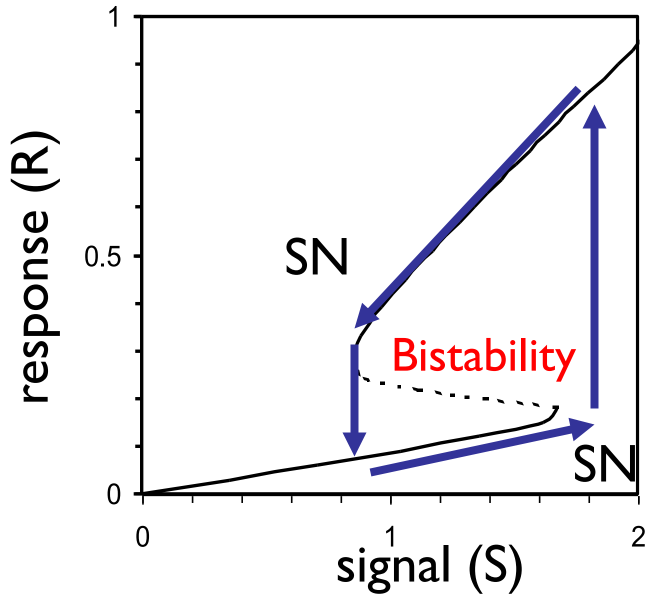


Positive Feedback: Mutual inhibition

- R inhibits E
- E promotes the degradation of R







$$\frac{dR}{dt} = k_o + k_1 S - k_2 R - k_2' E(R) \cdot R$$

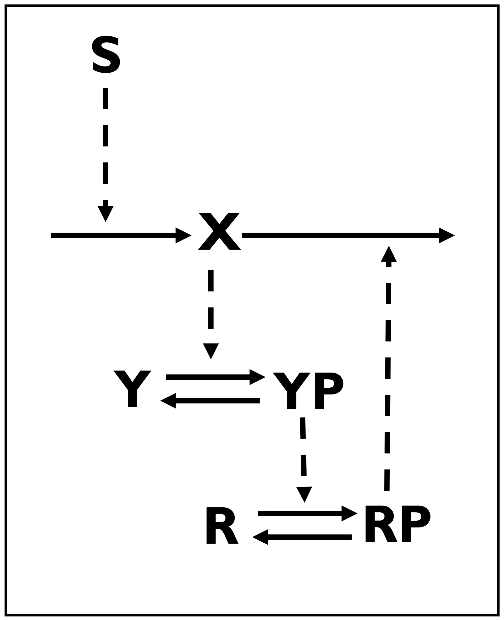
$$E(R) = G(k_3, k_4 R, J_3, J_4)$$

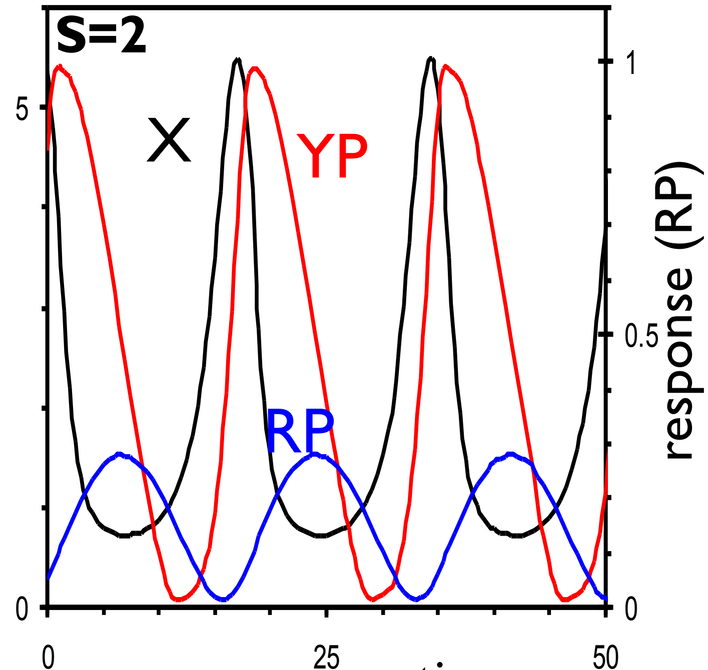
Toggle switch: if the signal is increased beyond a critical value the system will switch to a high state and if signal decreases enough, the switch will go back to the low state but in bistable region will display hysteresis (state depends on how signal is changed – increased or decreased)

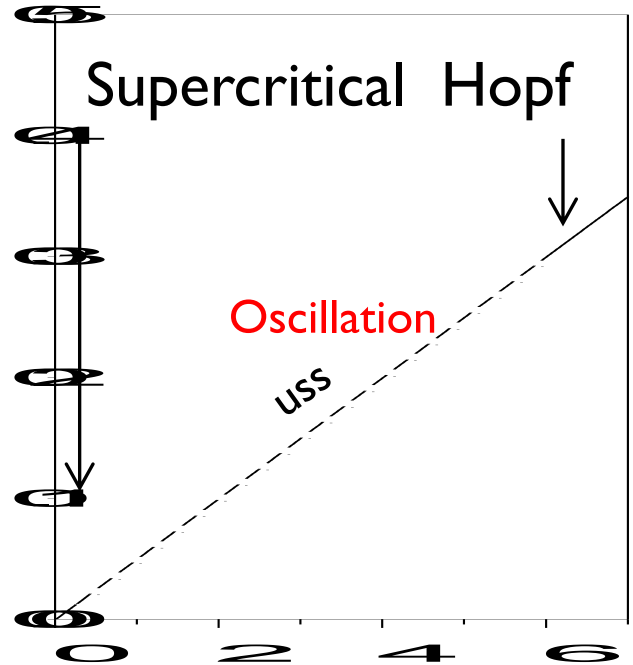
Negative Feedback Oscillator

RP activates the degradation of X

Goodwin, Nature 209, 479 (1966)







$$\frac{dX}{dt} = k_0 + k_1 S - k_2 X + k_2' R_P \cdot X$$

$$\frac{dY_P}{dt} = \frac{k_3 X (Y_T - Y_P)}{K_{m3} + Y_T - Y_P} - \frac{k_4 Y_P}{K_{m4} + Y_P}$$

$$\frac{dR_P}{dt} = \frac{k_5 Y_P (R_T - R_P)}{K_{m5} + R_T - R_P} - \frac{k_6 R_P}{K_{m6} + R_P}$$

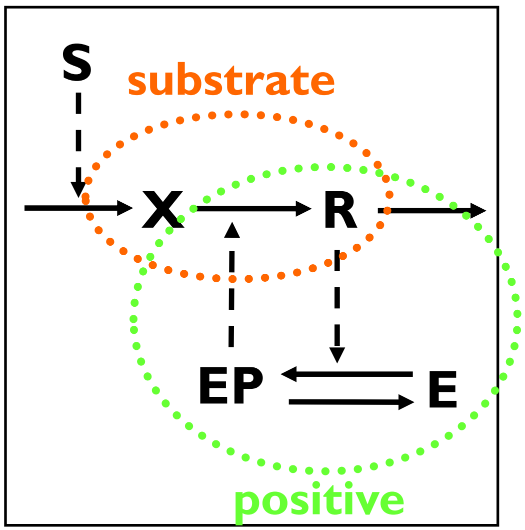
Negative feedback has been proposed as a basis for oscillations in protein synthesis

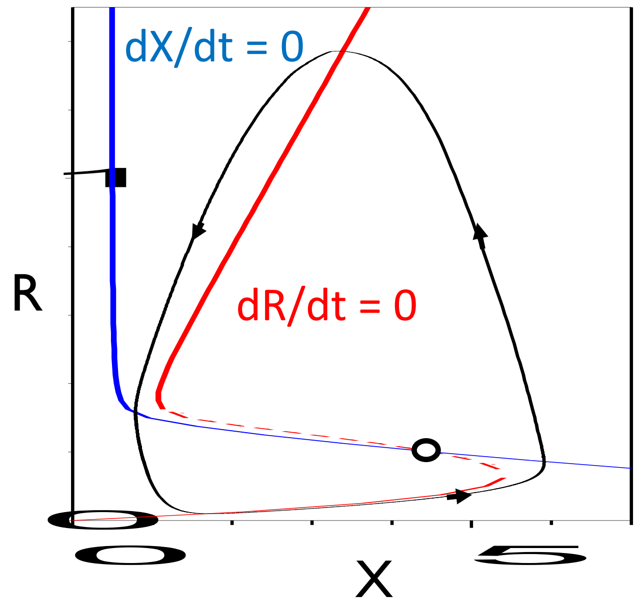
Repressilator (Elowitz & Leibler): artificial oscillating genetic network consisting of 3 operons that repress one another in a loop.

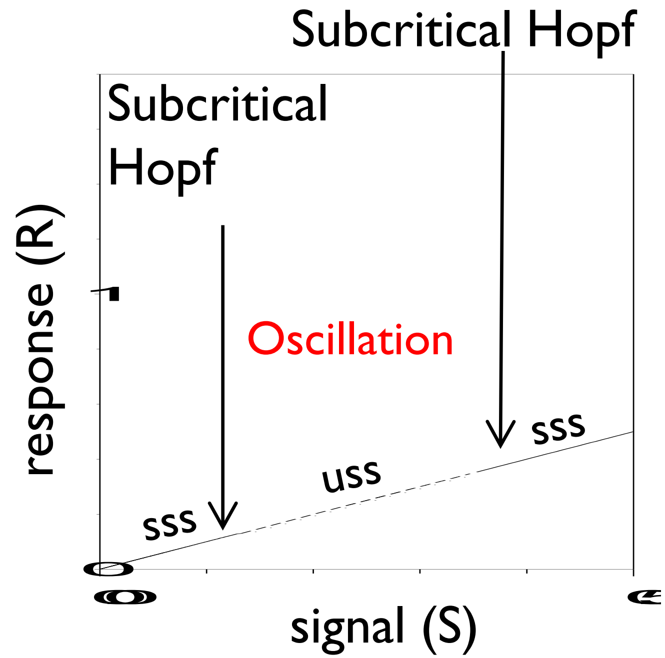
Substrate Depletion Oscillator

Oscillations via positive & negative feedback

+ve feedback creates a bistable system and –ve feedback drives the system back and forth between the two stable steady states







$$\frac{dX}{dt} = k_1 S - [k_0' + k_0 E_P(R)] \cdot X$$

$$\frac{dR}{dt} = [k_0' + k_0 E_P(R)] \cdot X - k_2 R$$

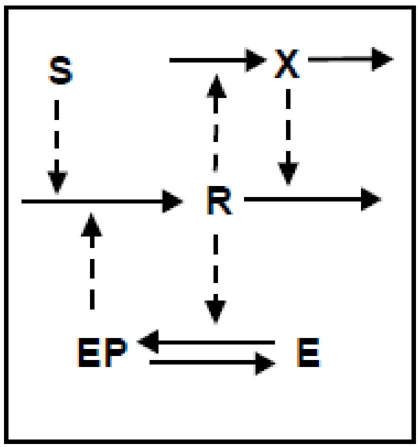
$$E_P(R) = G(k_3 R, k_4, J_3, J_4)$$

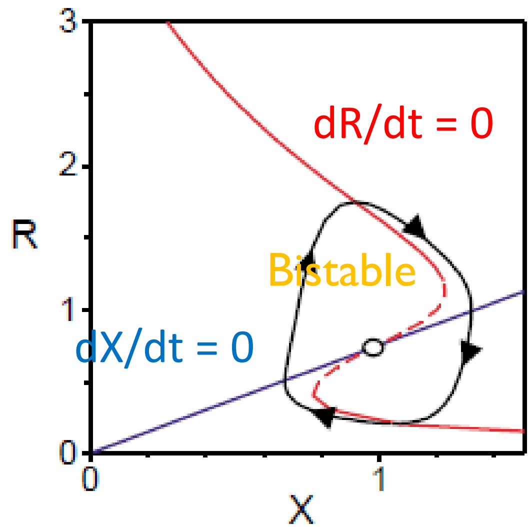
X is converted into R in an autocatalytic process. Initially, X is abundant and R is scarce. As R builds up, production of R accelerates until there is an explosive conversion of the entire pool of X into R. Then the autocatalytic reaction shuts off for lack of substrate, X. R is degraded, and X must build up again before another burst of R is produced.

Activator-Inhibitor Oscillator

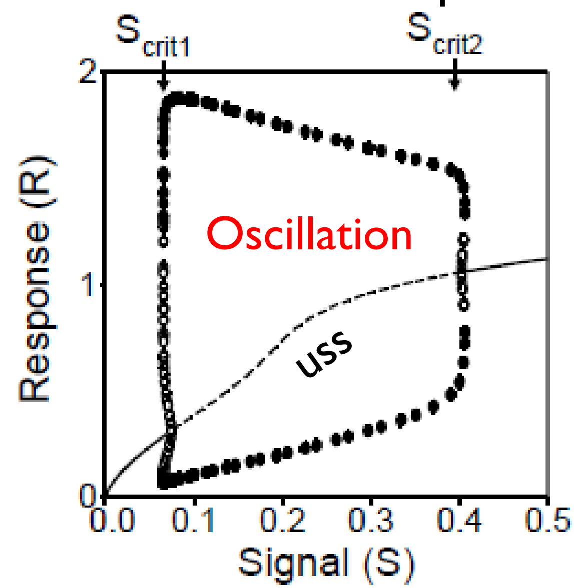
R is created in an autocatalytic process, then it promotes the production of an inhibitor, X, which speeds up R removal. First, R builds up, then comes X to force R back down, then X disappears and R can rise again.

Goldbeter, *Biochemical oscillations and cellular rhythms* (1997)





Subcritical Hopf



$$\frac{dR}{dt} = k_o E_P(R) + k_1 S - k_2 R - k_2' X \cdot R$$

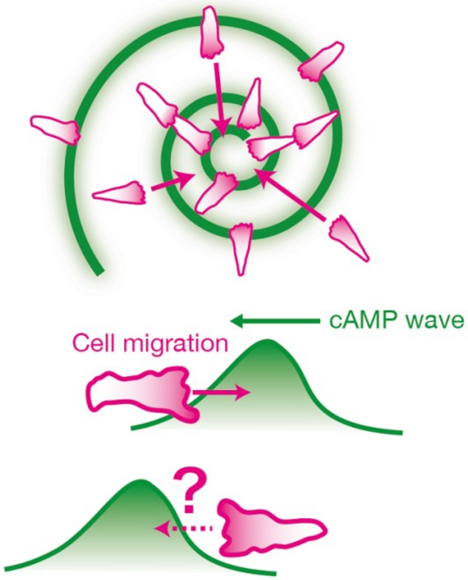
$$\frac{dX}{dt} = k_5 R - k_6 X$$

$$E_P(R) = G(k_3 R, k_4, J_3, J_4)$$

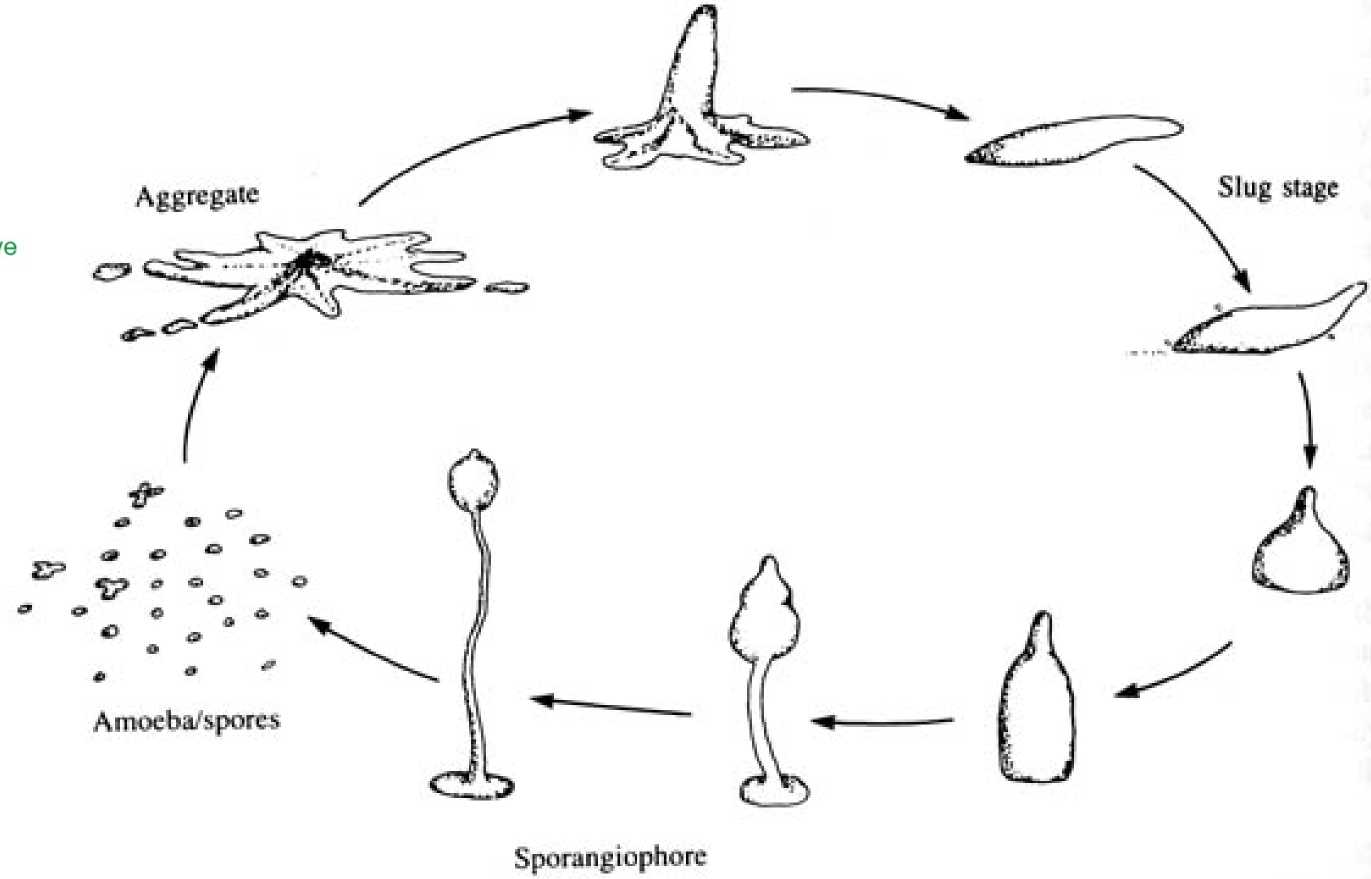
Example: cyclicAMP production in slime mold

External cAMP binds to a surface receptor, stimulates adenylate cyclase to produce and excrete more cAMP. At the same time, cAMP-binding pushes the receptor into an inactive form. After cAMP falls off, the inactive form slowly recovers its ability to bind cAMP and stimulate adenylate cyclase again.

cyclicAMP oscillations in slime mold

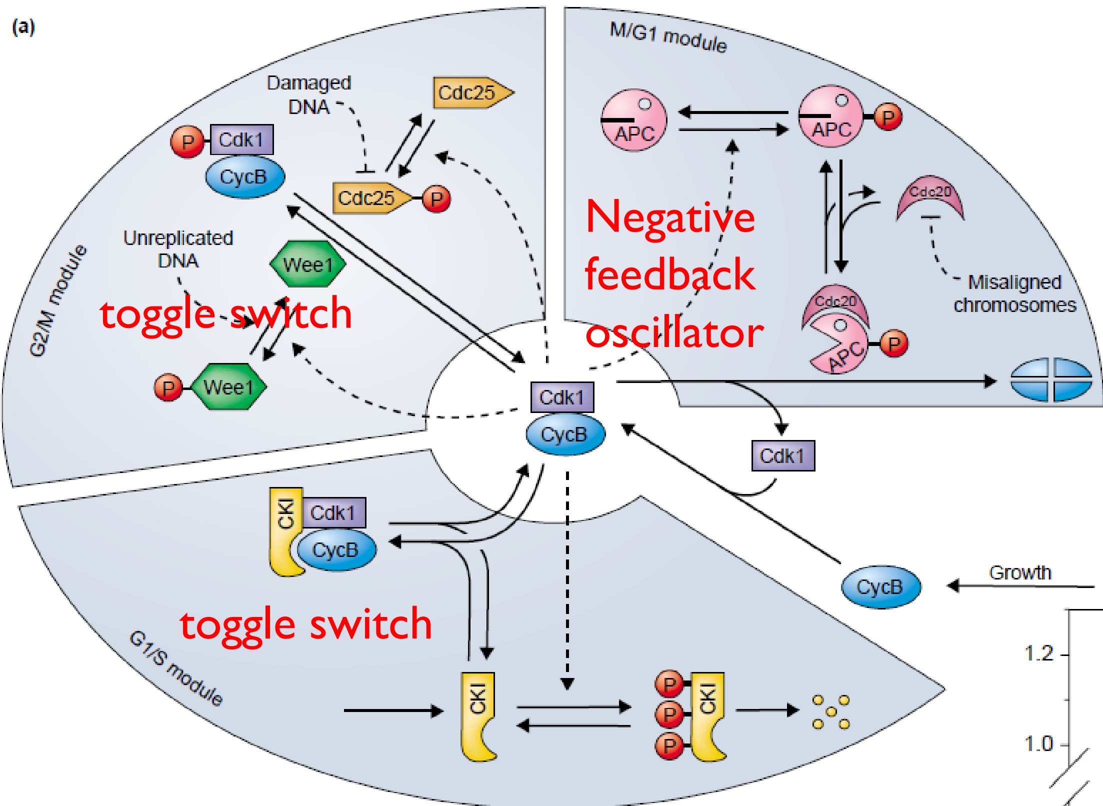


www.u-tokyo.ac.jp



http://zool33.uni-graz.at/

Cell-cycle regulation in eukaryotes



Cyclin-dependent kinase (Cdk) network regulating DNA synthesis and mitosis