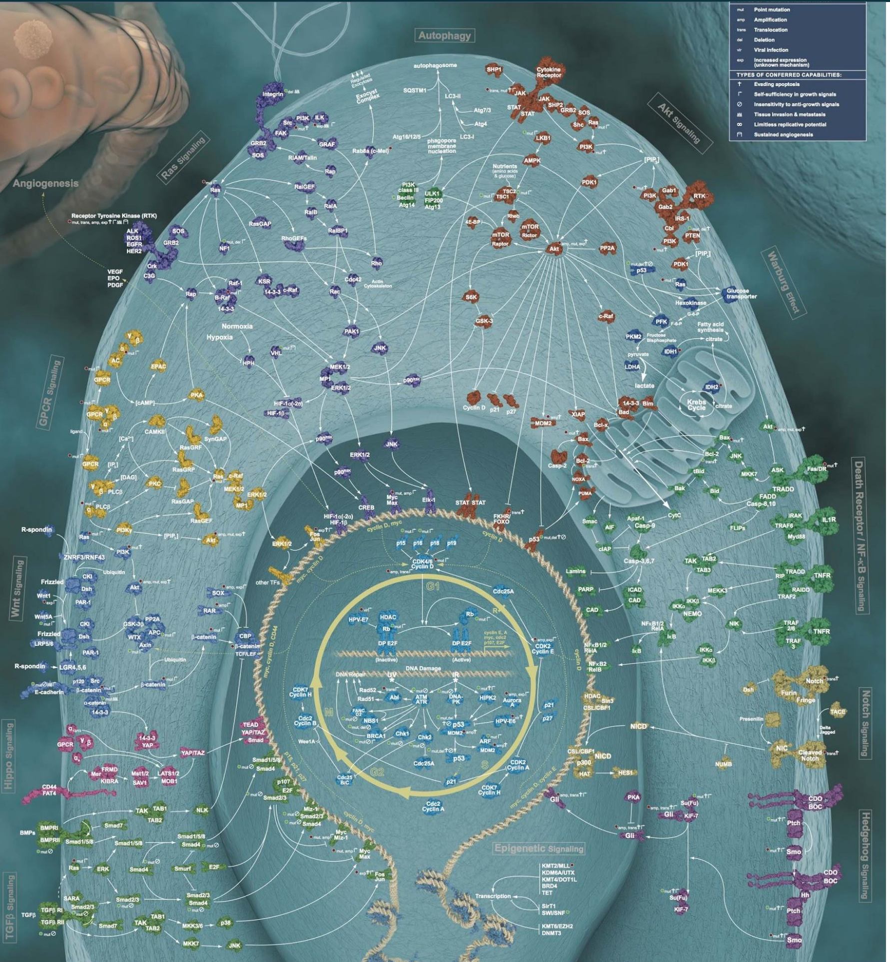
Week 13: Modeling regulatory pathways

- Modeling simple motifs
- State spaces, vector fields, and bifurcations
- Application to modeling the cell cycle

Cellular signaling and regulatory pathways



Cell physiology is governed by complex assemblies of interacting proteins carrying out most of the interesting jobs in a cell, such as metabolism, DNA synthesis, movement and information processing.

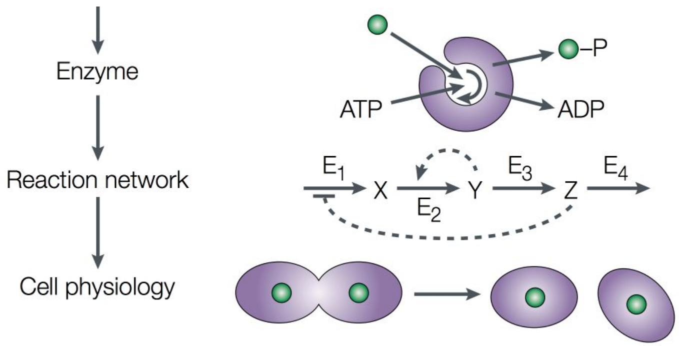
These processes are orchestrated by signaling and regulatory networks.

media.cellsignal.com

Computational molecular biology

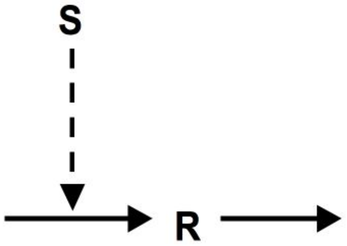
Take a cellular process and...

1. Draw a **wiring diagram** representing the signaling and regulatory interactions between underlying proteins.
2. Convert the diagram to a system of **(differential/difference/Boolean) equations**.
3. **Simulate the system** (along with optimal parameters) to understand its temporal/spatial properties and how they relate to the process being modelled...
4. **Make predictions** about molecular and process-level behavior in unobserved scenarios including the effect of mutations.

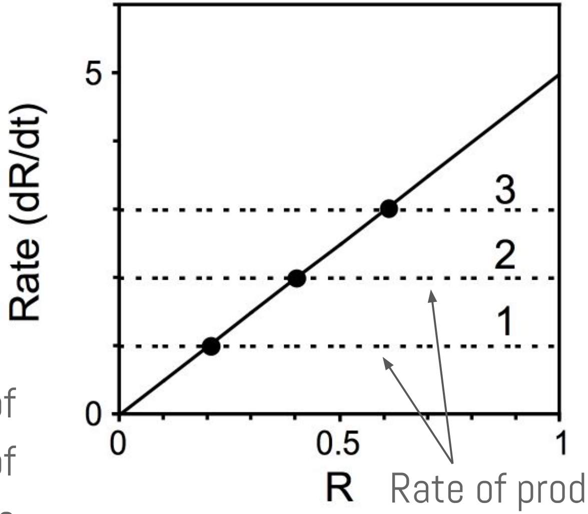


Tyson (2001) Nat. Rev. Mol. Cel. Biol.

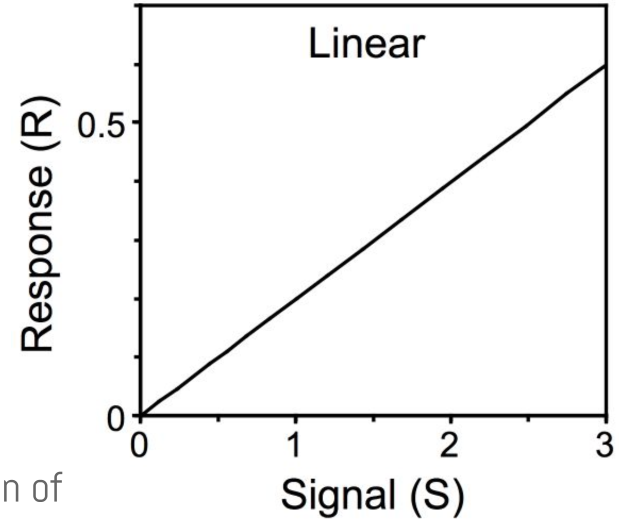
Modeling the dynamical systems: linear response



Rate of removal of response



Rate of production of response for various values of signal strength S



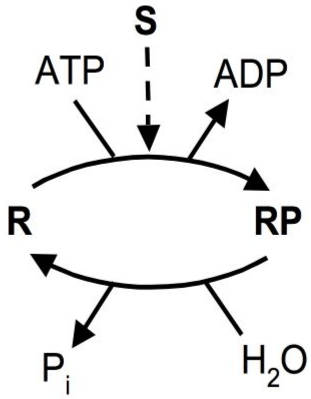
$$\frac{dR}{dt} = k_0 + k_1 S - k_2 R$$

Steady-state solution

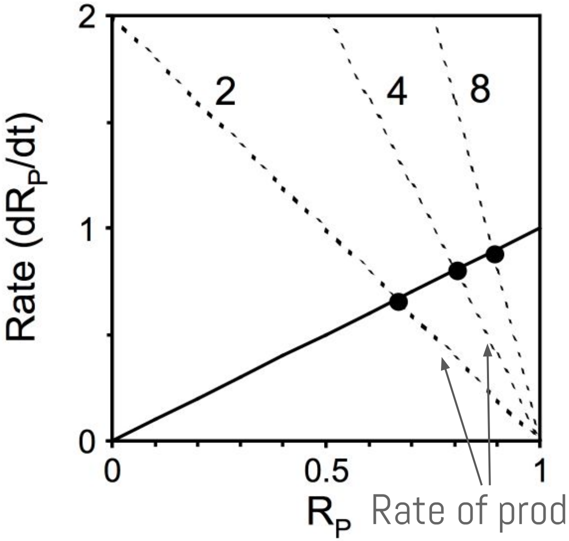
$$R_{ss} = \frac{k_0 + k_1 S}{k_2}$$

Tyson (2003) Curr. Opin. Cell Biol.

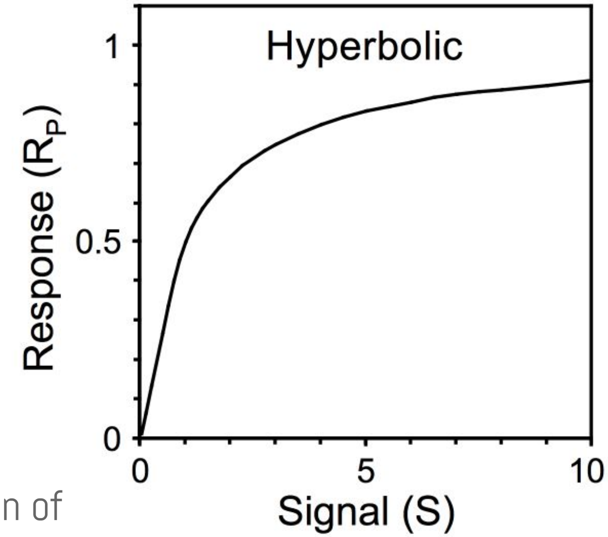
Modeling the dynamical systems: hyperbolic response



Rate of removal of response R_p



Rate of production of response R_p for various values of signal strength S



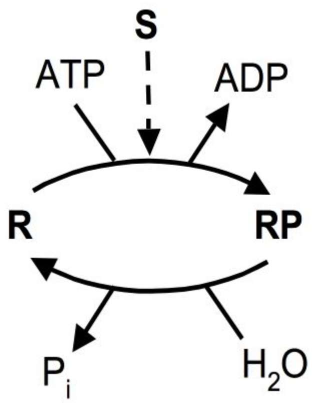
$$R_T = R + R_P$$

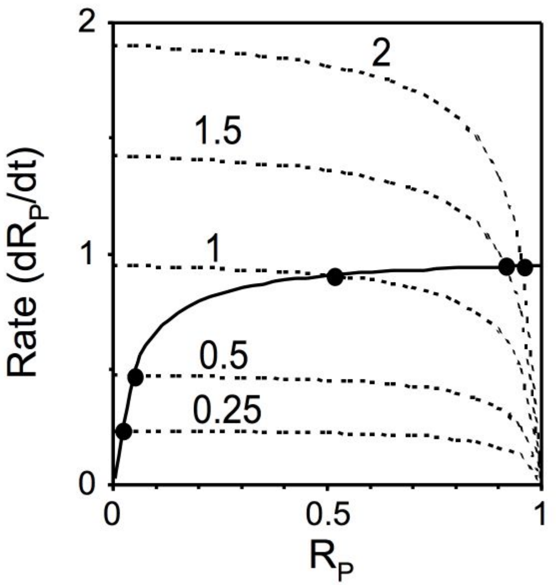
$$\frac{dR_P}{dt} = k_1 S(R_T - R_P) - k_2 R_P$$

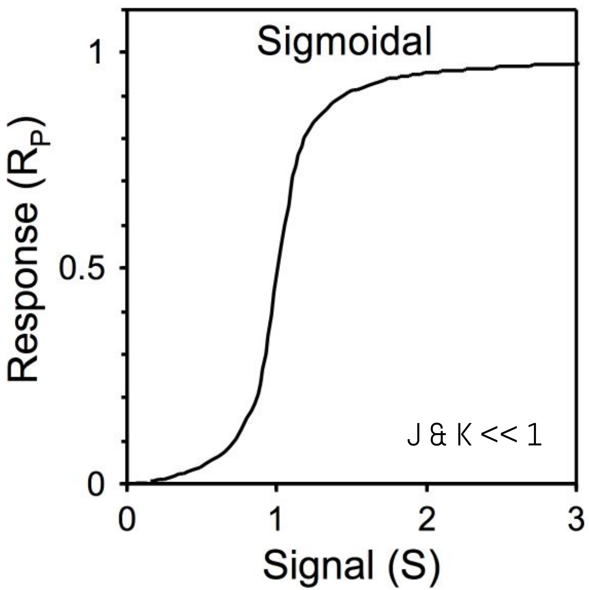
Steady-state solution $$R_{P,ss} = \frac{R_T S}{(k_2/k_1) + S}$$

Tyson (2003) Curr. Opin. Cell Biol.

Modeling the dynamical systems: sigmoidal response







Zero-order ultrasensitivity

$$R_T = R + R_P$$

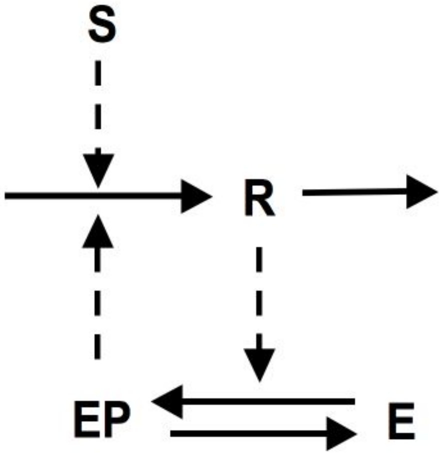
$$\frac{dR_P}{dt} = \frac{k_1 S(R_T - R_P)}{K_{m1} + R_T - R_P} - \frac{k_2 R_P}{k_{m2} + R_P}$$

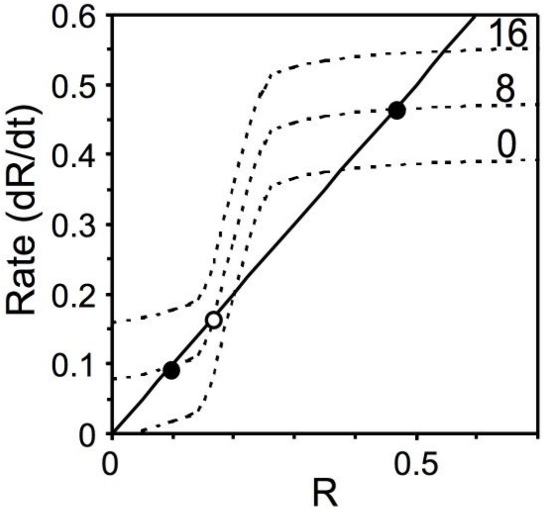
Steady-state solution

$$\frac{R_{P,ss}}{R_T} = G(k_1, S, k_2, \frac{K_{m1}}{R_T}, \frac{K_{m2}}{R_T})$$

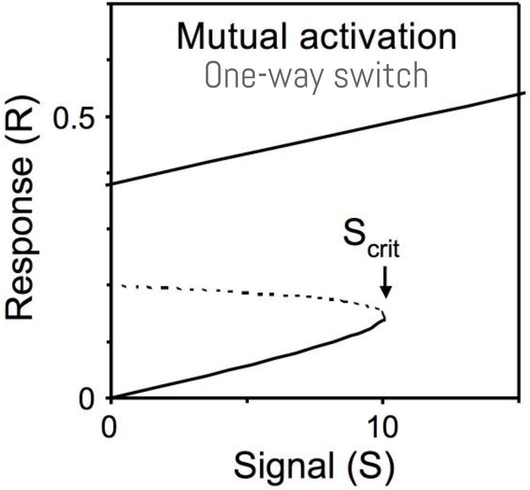
Tyson (2003) Curr. Opin. Cell Biol.

Modeling the dynamical systems: positive feedback





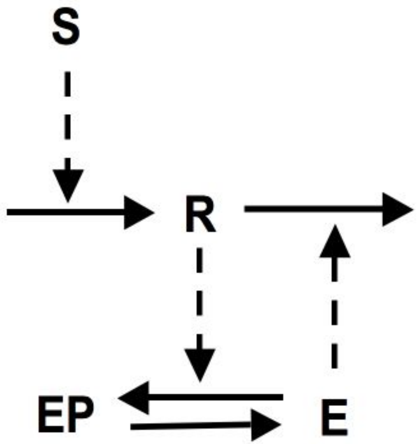
One-way switch

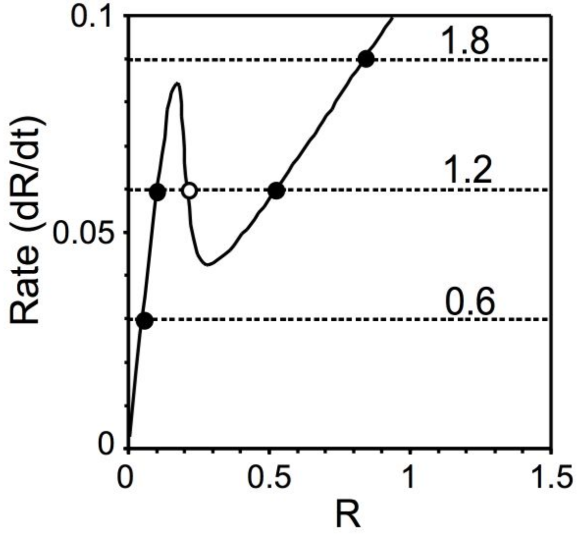


1-parameter bifurcation diagram

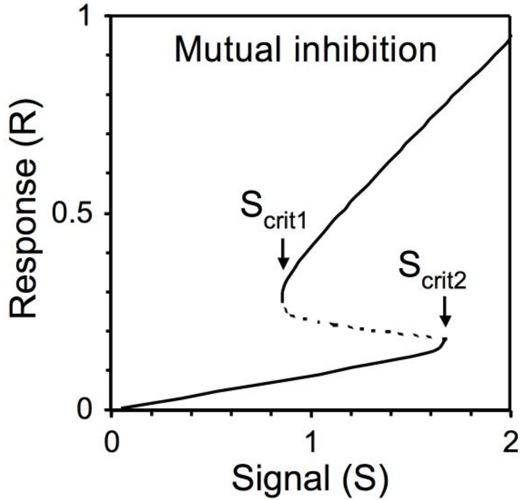
Tyson (2003) Curr. Opin. Cell Biol.

Modeling the dynamical systems: positive feedback





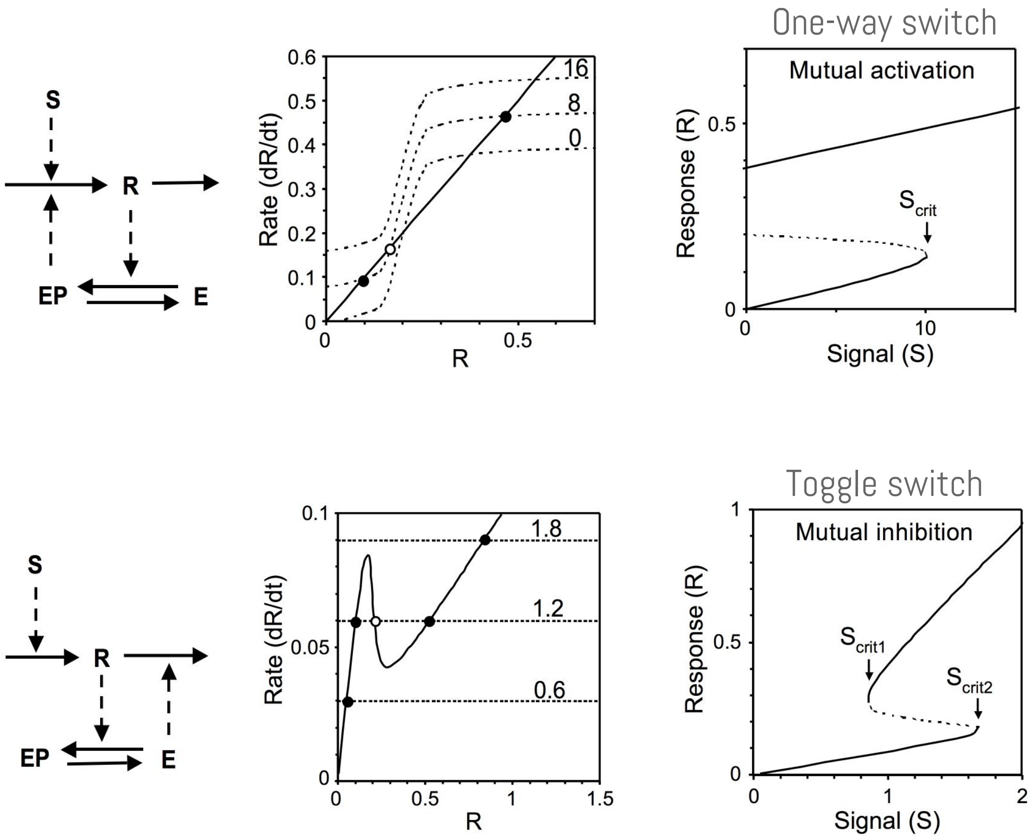
Toggle switch



1-parameter bifurcation diagram

Tyson (2003) Curr. Opin. Cell Biol.

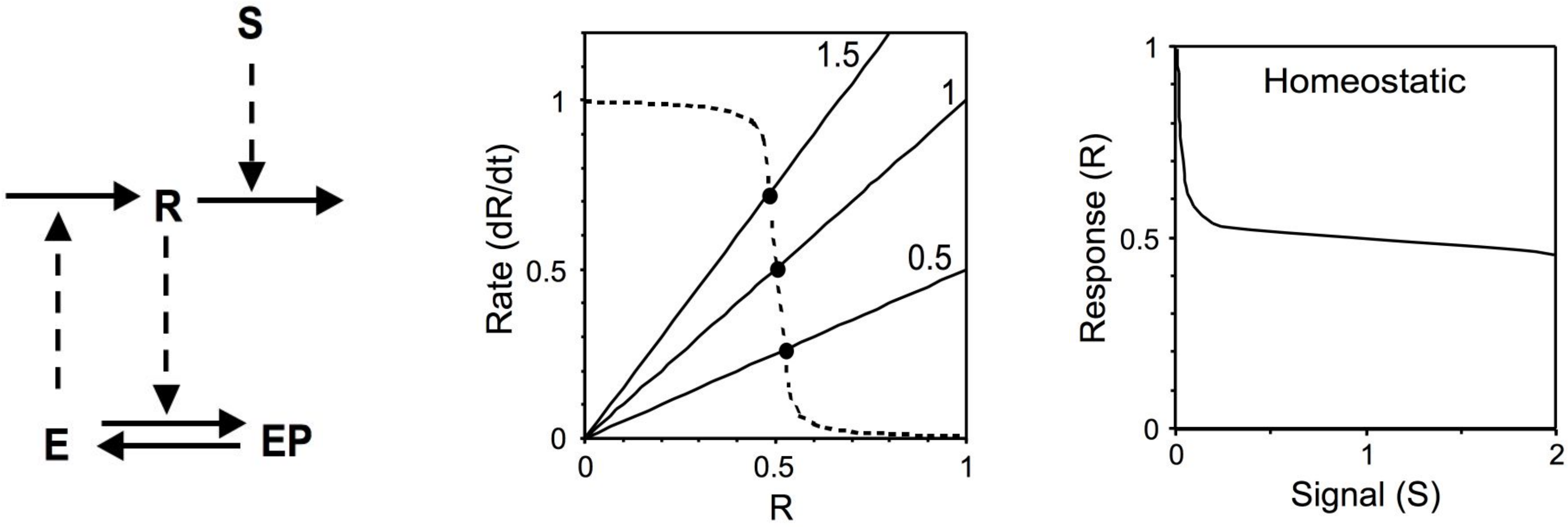
Modeling the dynamical systems: positive feedback



- Irreversible
- Bistable
    - Between 0 & S_{crit} (bifurcation point) and
    - Between S_{crti1} & S_{crit2}
- Undergoes a bifurcation:
    - In this case, a saddle-node bifurcation.

Tyson (2003) Curr. Opin. Cell Biol.

Modeling the dynamical systems: negative feedback



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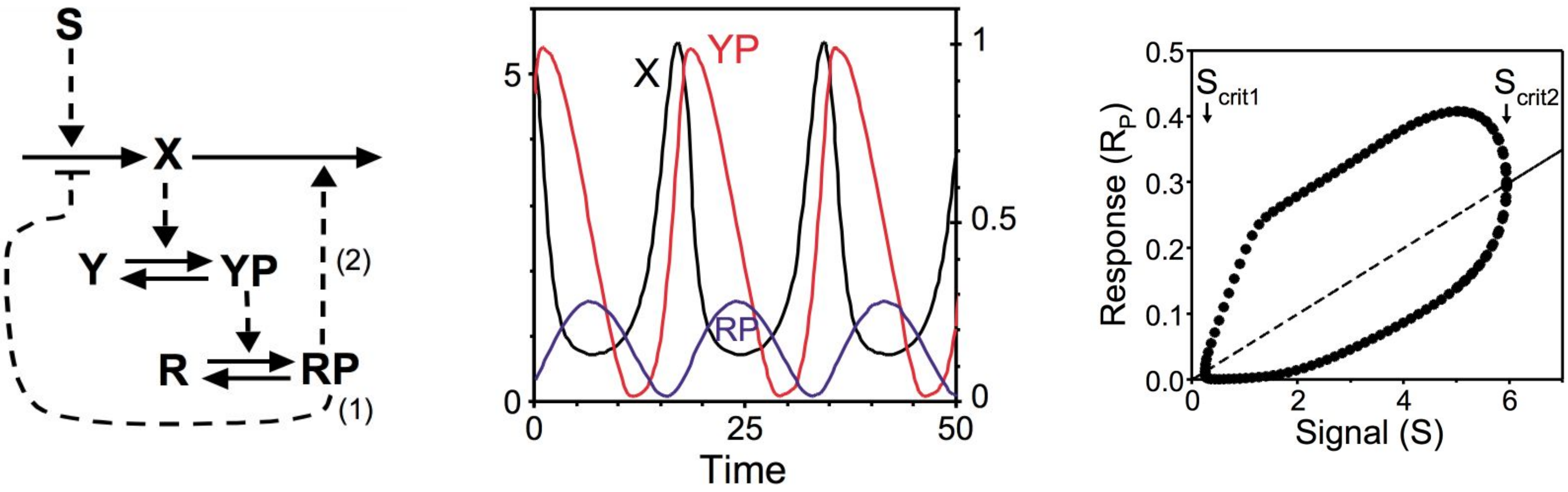
Modeling the dynamical systems: negative feedback



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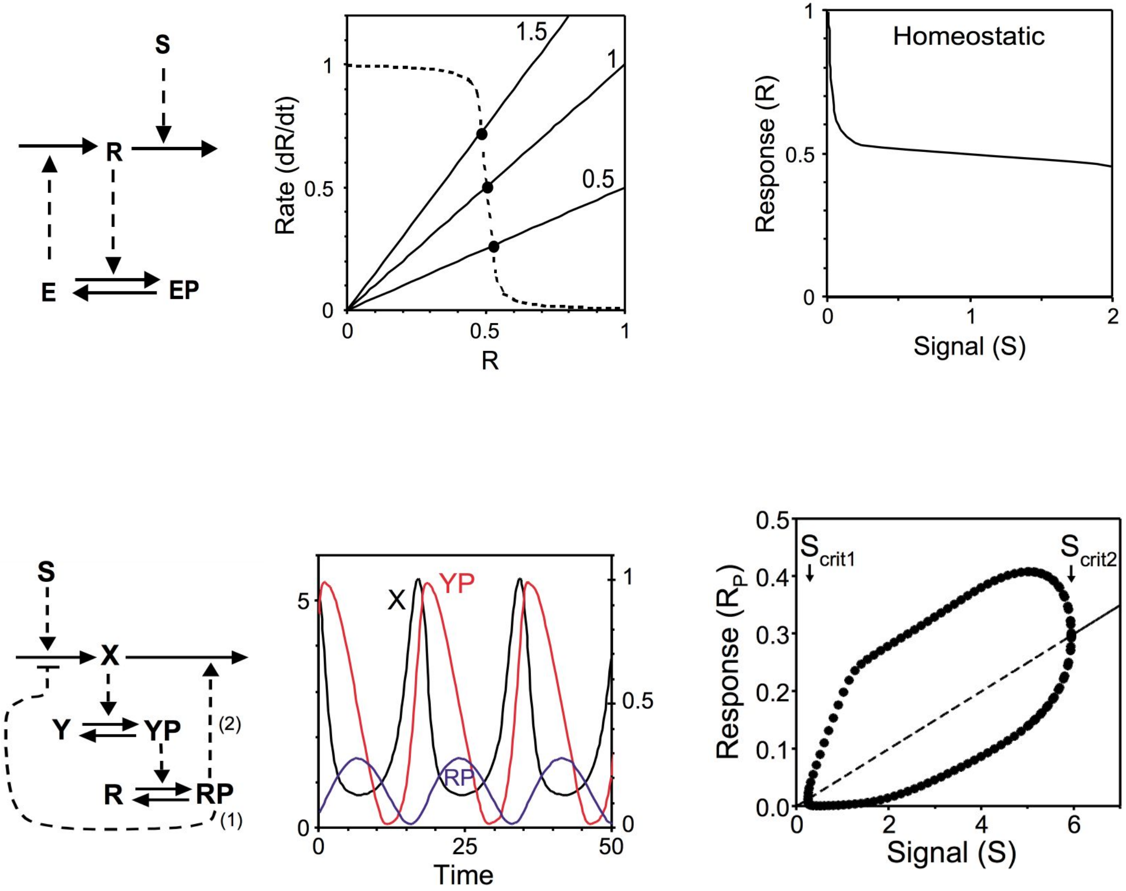
Modeling the dynamical systems: negative feedback



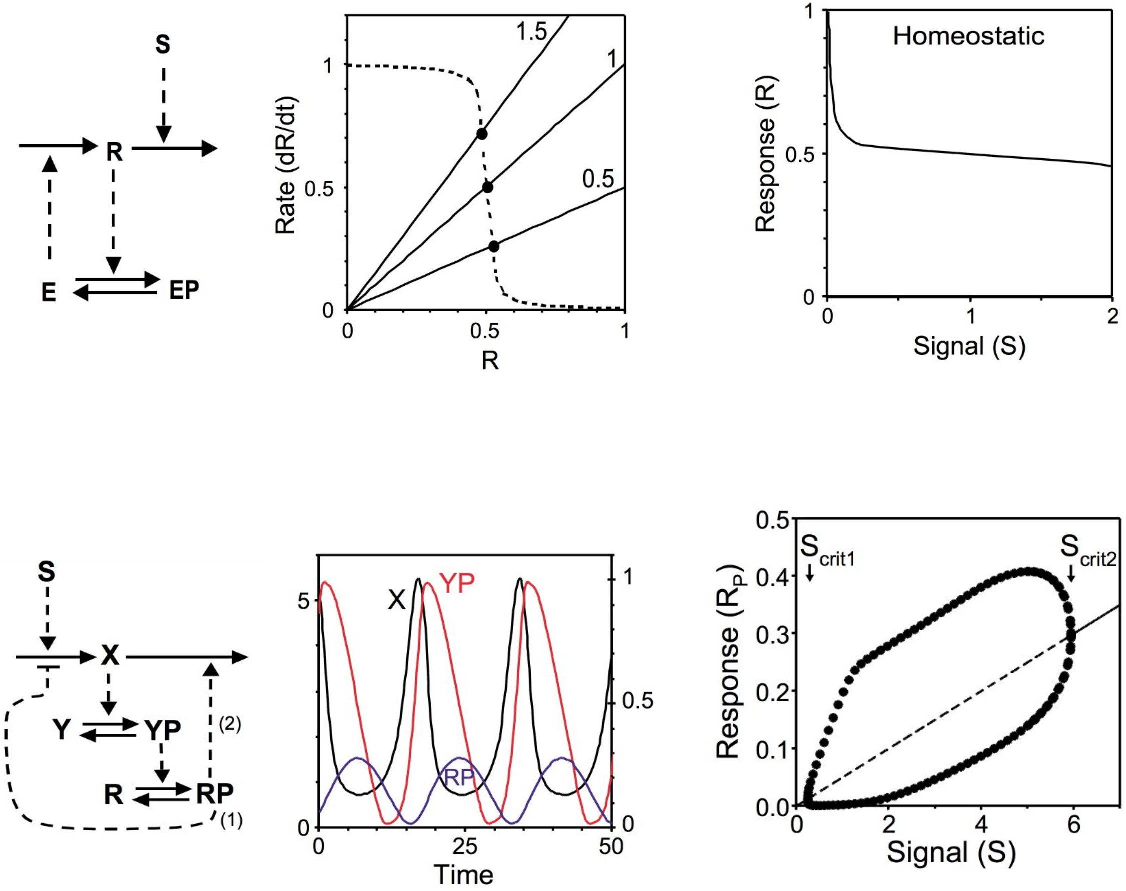
Negative feedback can also create an oscillatory response.

- $X \longrightarrow R \twoheadrightarrow X$

This results in **damped oscillations** to a stable steady state.

Tyson (2003) Curr. Opin. Cell Biol.

Modeling the dynamical systems: negative feedback



Sustained oscillations require at least three components:

- $X \rightarrow Y \rightarrow R \twoheadrightarrow X$

Third component (Y) introduces a time delay in the feedback loop, causing the system to repeatedly over- & undershoot its steady state.

Tyson (2003) Curr. Opin. Cell Biol.