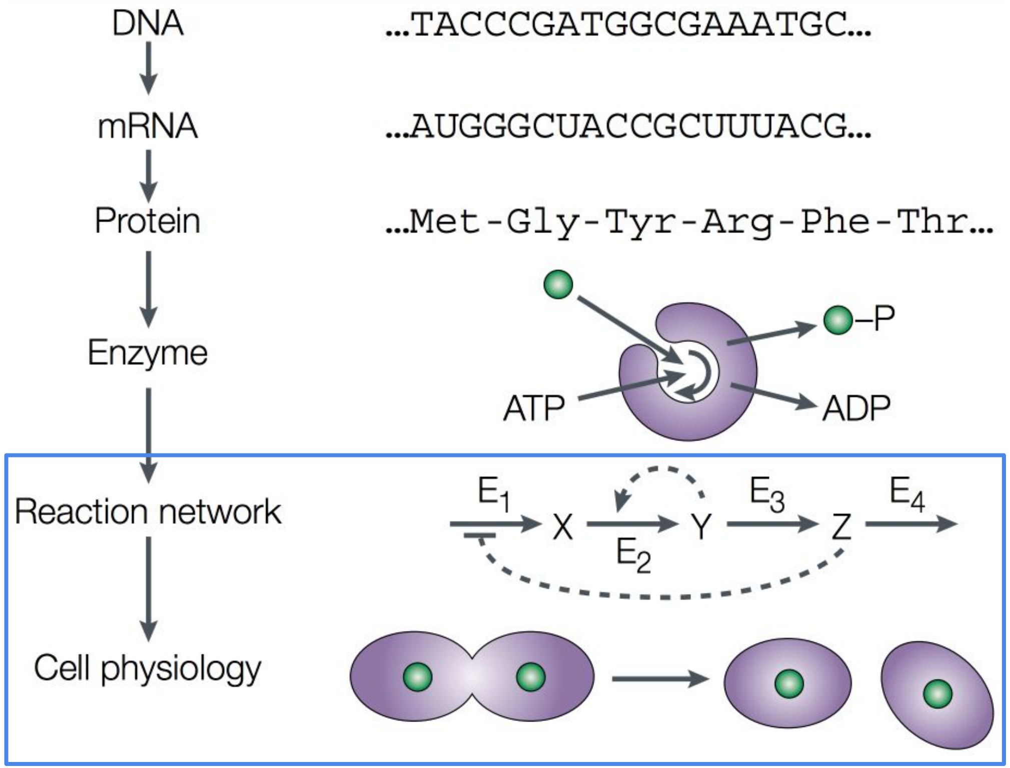
Modeling cellular pathways

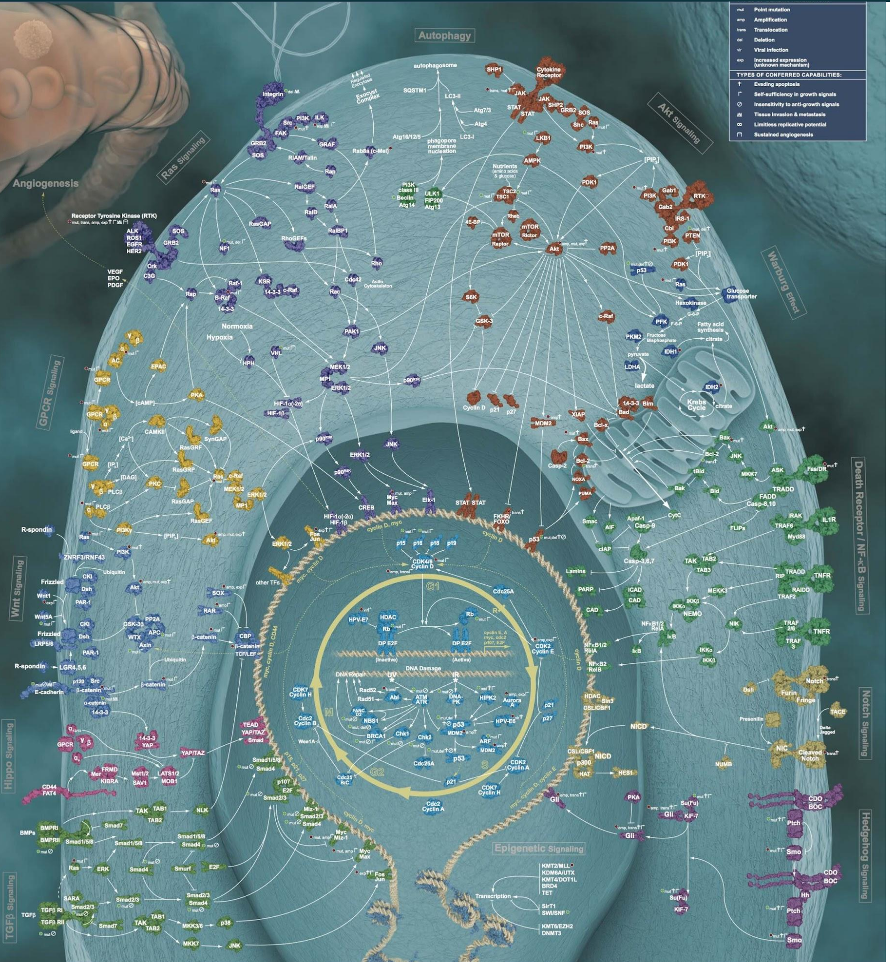
- Modeling simple motifs
- State spaces, vector fields, and bifurcations
- Application to modeling the cell cycle

Next level of hierarchy



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

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.

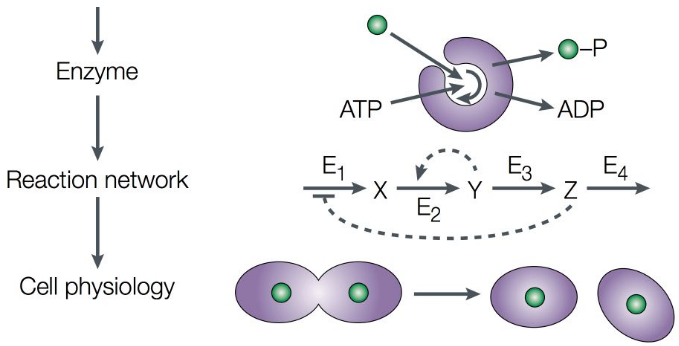
These processes are orchestrated by signaling and regulatory networks.

media.cellsignal.com

Computational molecular biology

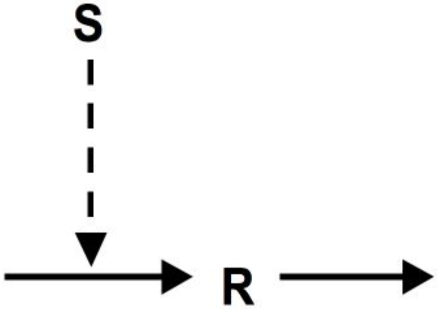
Take a cellular process and...

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 **finding 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.

Linear response



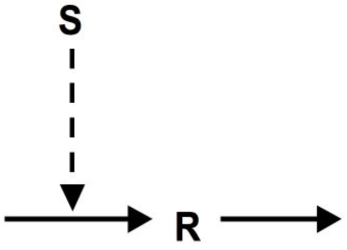
$$\frac{dR}{dt} = k_0 + k_1 S - k_2 R$$

Steady-state solution

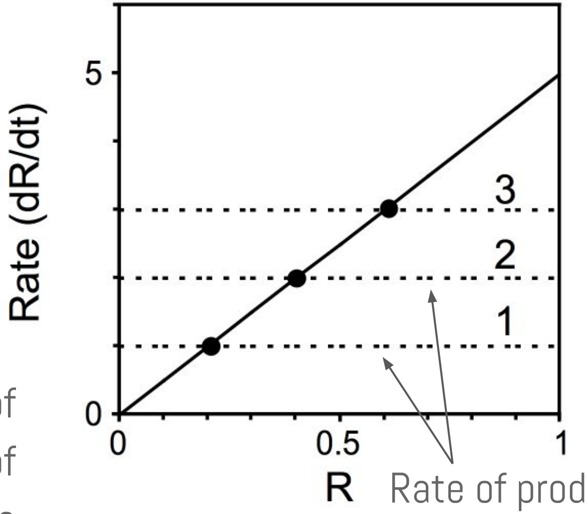
$$R_{ss} = \frac{k_0 + k_1 S}{k_2}$$

Tyson (2003) Curr. Opin. Cell Biol.

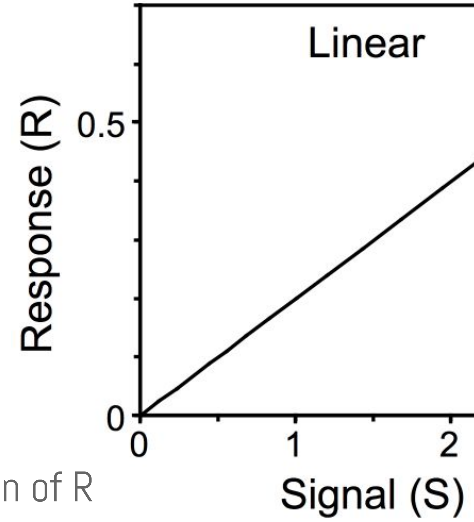
Linear response



Rate of removal of response



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



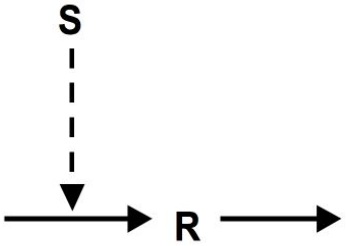
$$\frac{dR}{dt} = k_0 + k_1 S - k_2 R$$

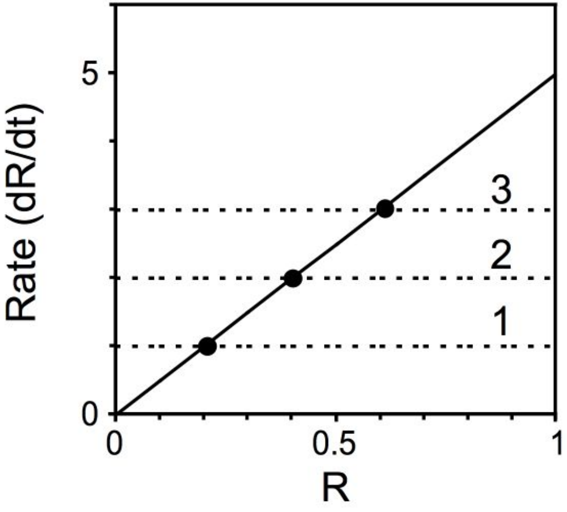
Steady-state solution

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

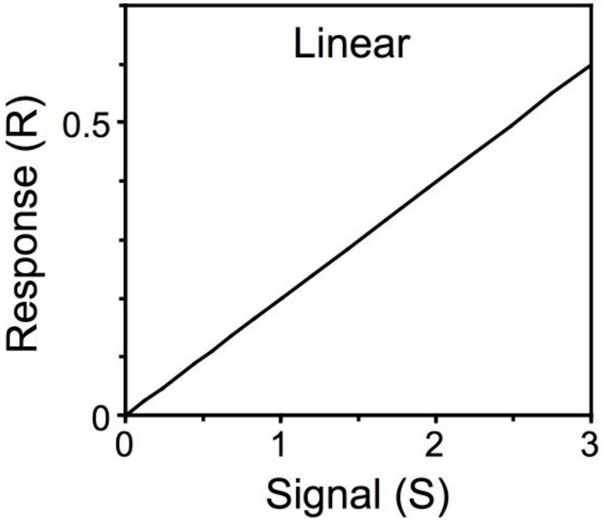
Tyson (2003) Curr. Opin. Cell Biol.

Linear response





Rate curve



Signal-response curve

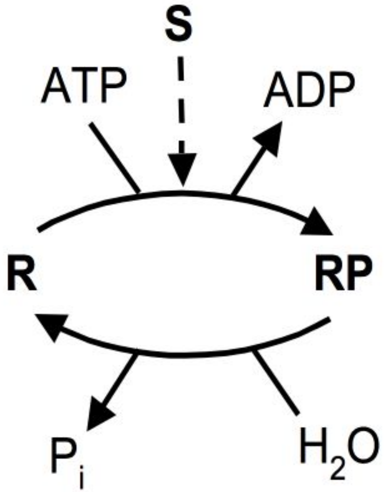
$$\frac{dR}{dt} = k_0 + k_1 S - k_2 R$$

Steady-state solution

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

Tyson (2003) Curr. Opin. Cell Biol.

Hyperbolic response



$$R_T = R + R_P$$

$$\frac{dR_P}{dt} = k_1 S R - k_2 R_P$$

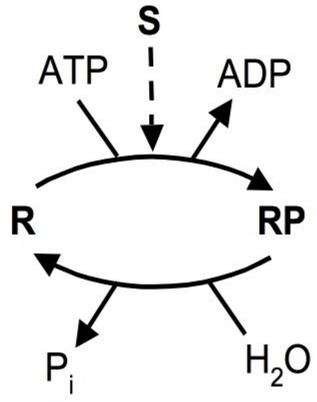
$$= k_1 S (R_T - R_P) - k_2 R_P$$

Steady-state solution

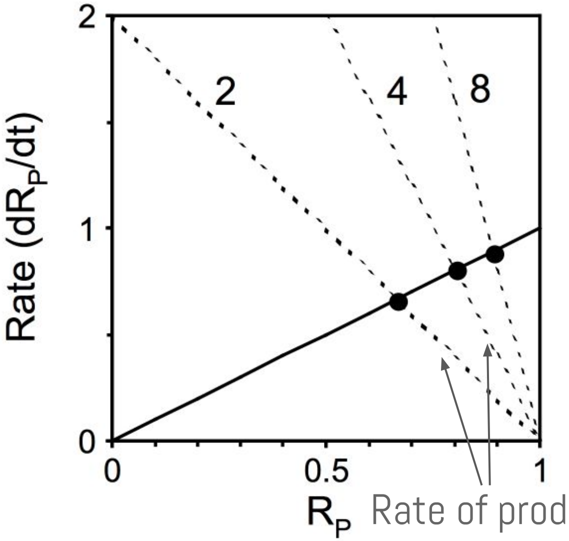
$$R_{P,ss} = \frac{R_T S}{(k_2/k_1) + S}$$

Tyson (2003) Curr. Opin. Cell Biol.

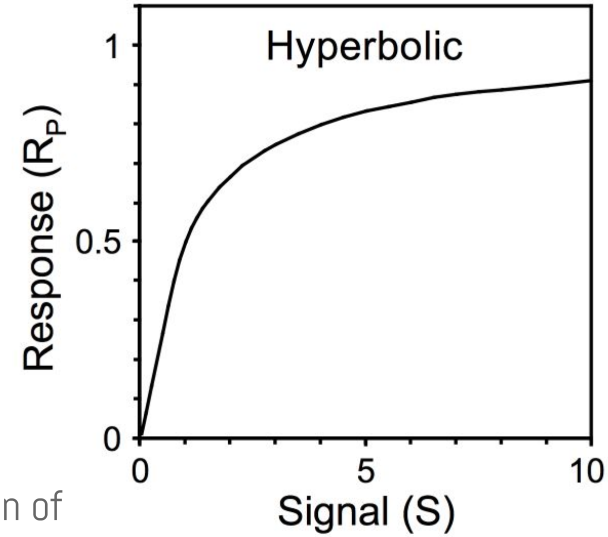
Hyperbolic response



Rate of removal of response R_p



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



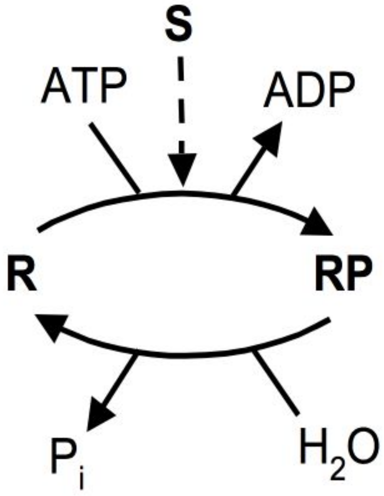
$$R_T = R + R_P$$

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

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

Tyson (2003) Curr. Opin. Cell Biol.

Hyperbolic response



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Steady-state solution

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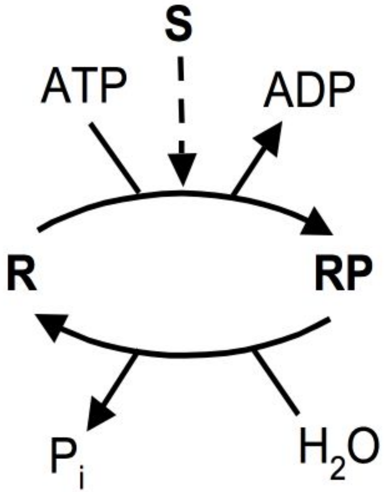
Sigmoidal response



$$R_T = R + R_P$$

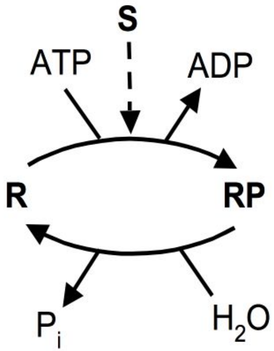
$$\frac{dR_P}{dt} = \frac{k_1 S (R_T - R_P)}{K_{m1} + R_T - R_P} - \frac{k_2 R_P}{k_{m2} + R_P}$$

Michaelis-Menten kinetics:

- One of the best-known models for enzyme kinetics
- Assumes that enzyme concentration is much less than the substrate concentration.

Tyson (2003) Curr. Opin. Cell Biol.

Sigmoidal response



$$R_T = R + R_P$$

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

Steady-state solution

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

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

Physiologically meaningful solution w/ $0 < R_P < R_T$

Goldbeter-Koshland function: graded & reversible

$$G(u,v,J,K) = \frac{2uK}{v - u + vJ + uK + \sqrt{(v - u + vJ + uK)^2 - 4(v-u)uK}}$$

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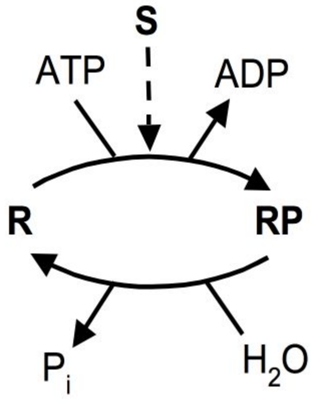
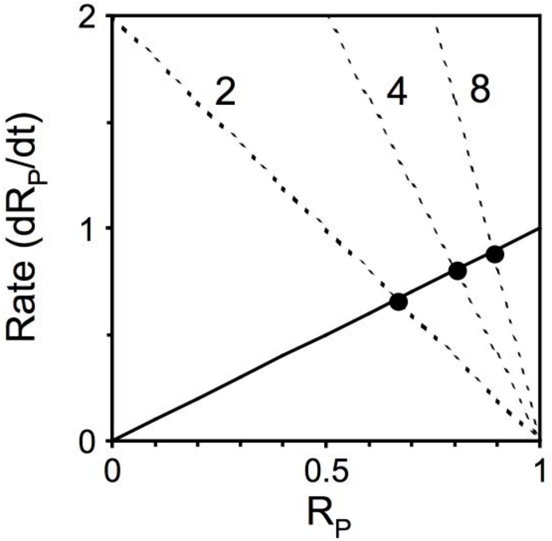
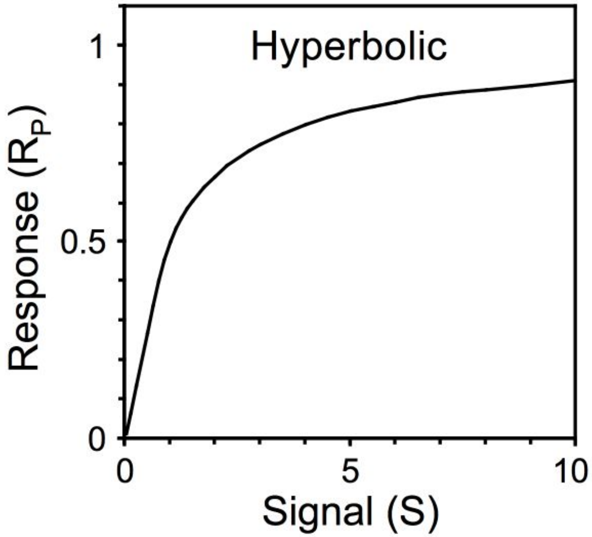
Hyperbolic response







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

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

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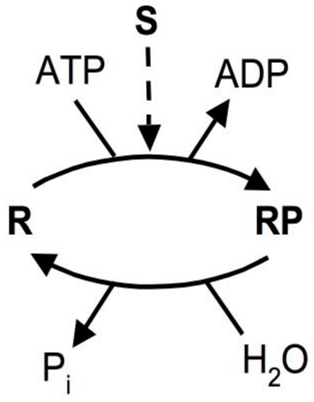
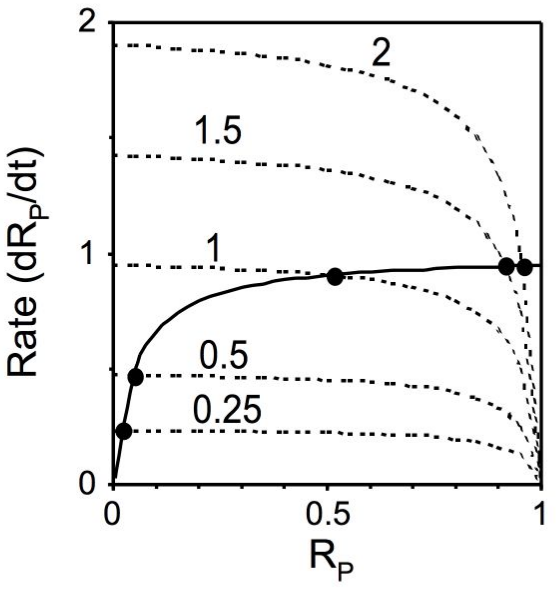
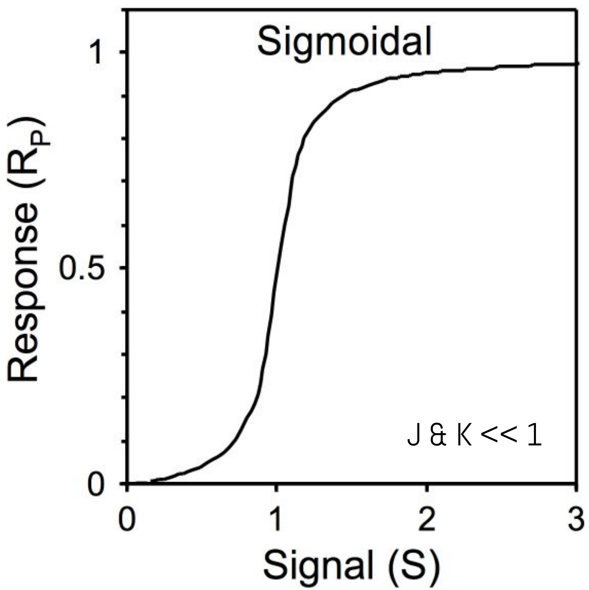
Sigmoidal response







Zero-order ultrasensitivity

$$R_T = R + R_P$$

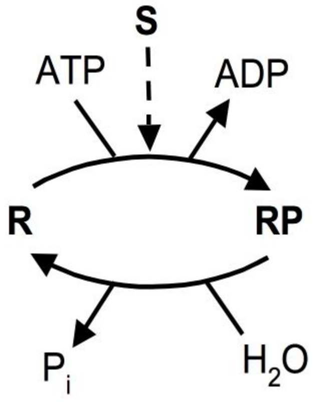
$$\frac{dR_P}{dt} = \frac{k_1 S(R_T - R_P)}{K_{m1} + R_T - R_P} - \frac{k_2 R_P}{k_{m2} + R_P}$$

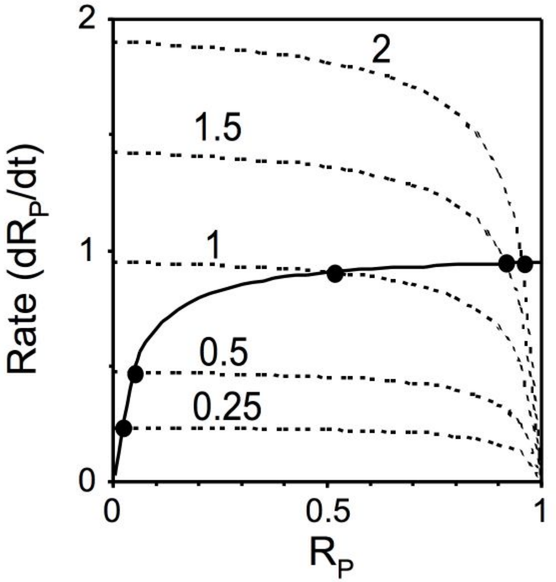
Steady-state solution

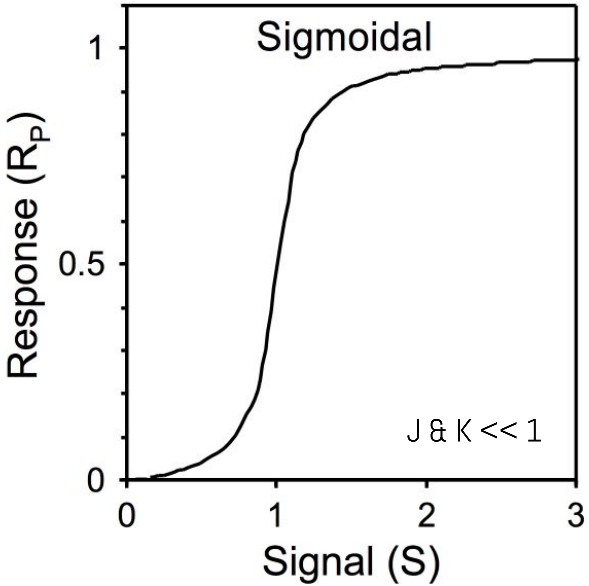
$$\frac{R_{P,ss}}{R_T} = G(k_1, S, k_2, \frac{K_{m1}}{R_T}, \frac{K_{m2}}{R_T})$$

Tyson (2003) Curr. Opin. Cell Biol.

Sigmoidal response





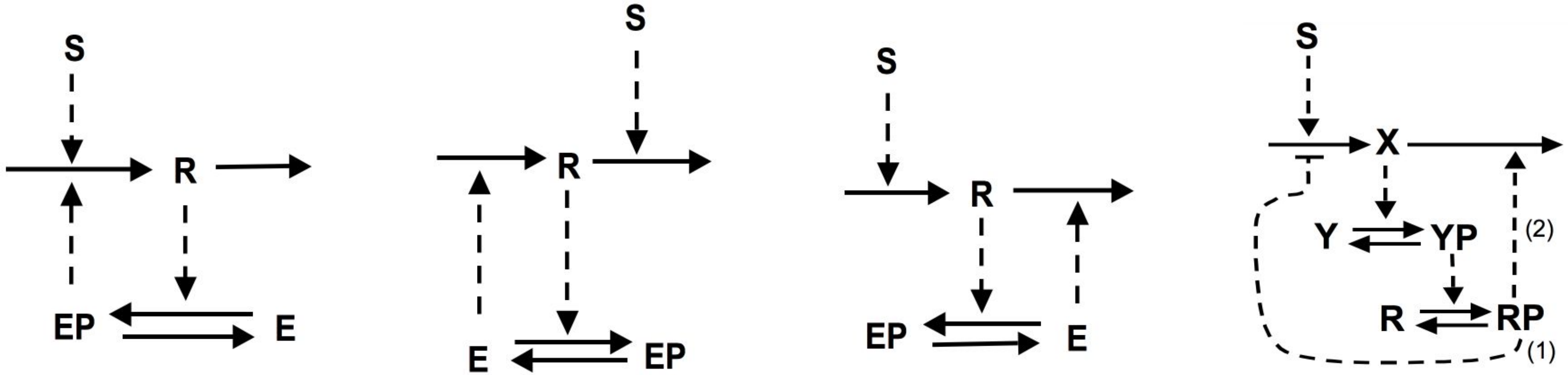


Zero-order ultrasensitivity

Just like the linear and hyperbolic responses, the sigmoid response is **graded** & **reversible**, but, unlike the other two, it is also **abrupt**.

Tyson (2003) Curr. Opin. Cell Biol.

Feedback loops



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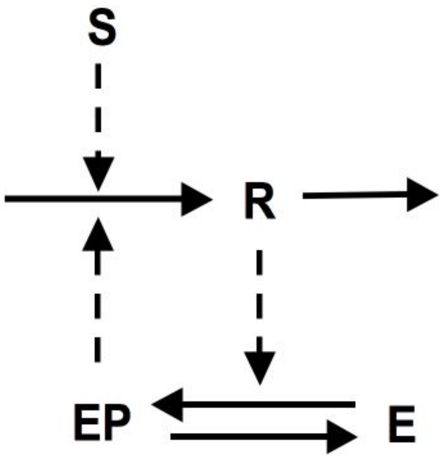
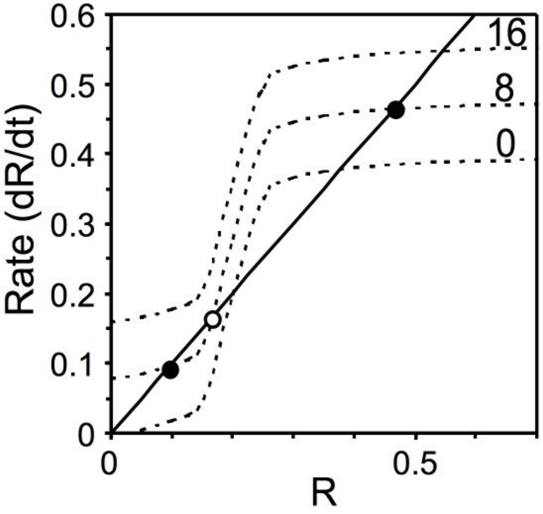
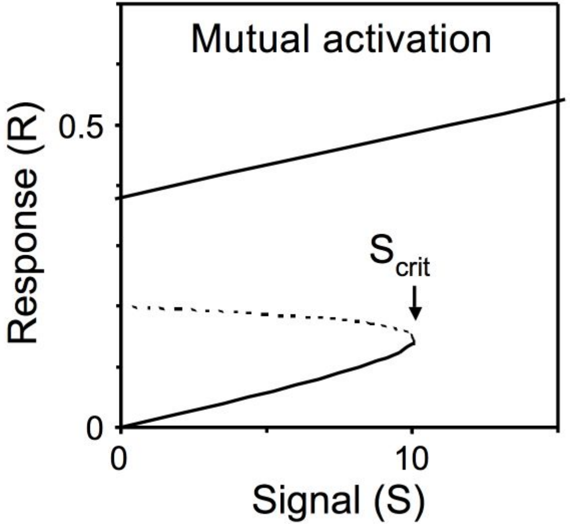
Positive feedback loop





One-way switch



1-parameter bifurcation diagram

Bifurcation: A sudden 'qualitative' change in the behavior of a dynamical system caused by a small smooth change made to the parameter values.

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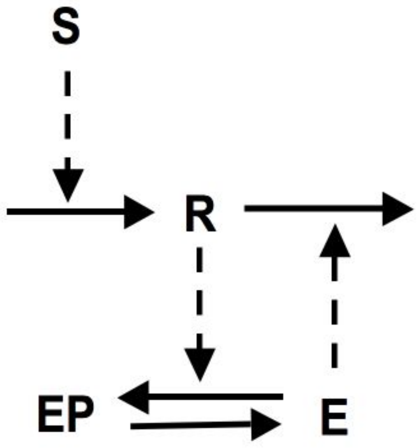
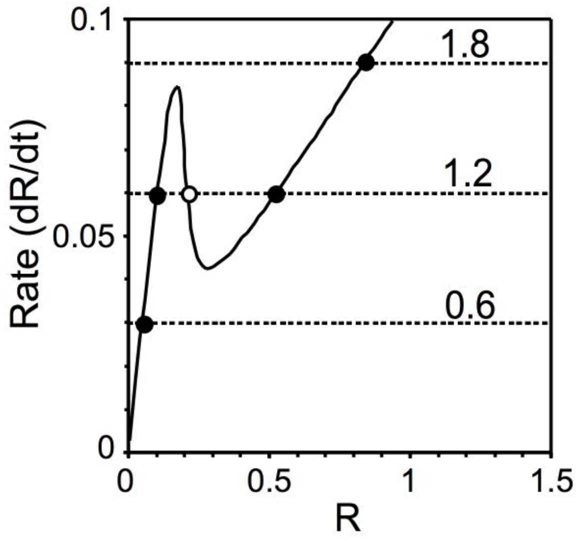
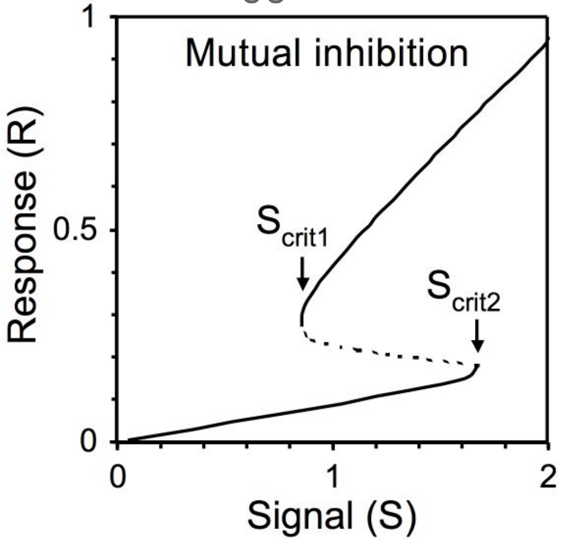
Positive feedback loop





Toggle switch



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Positive feedback loop

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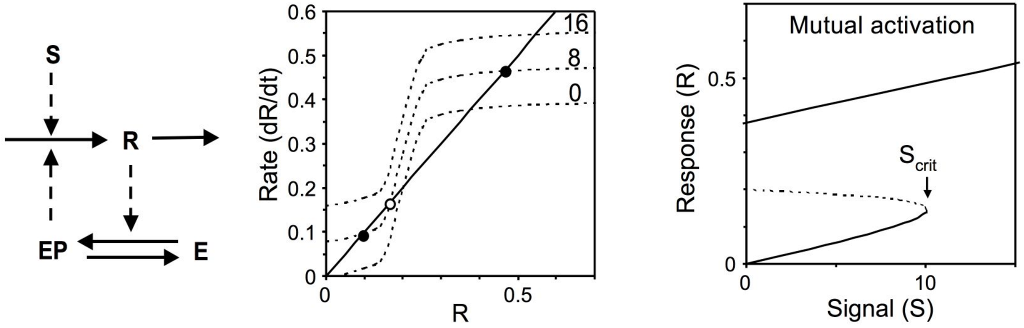
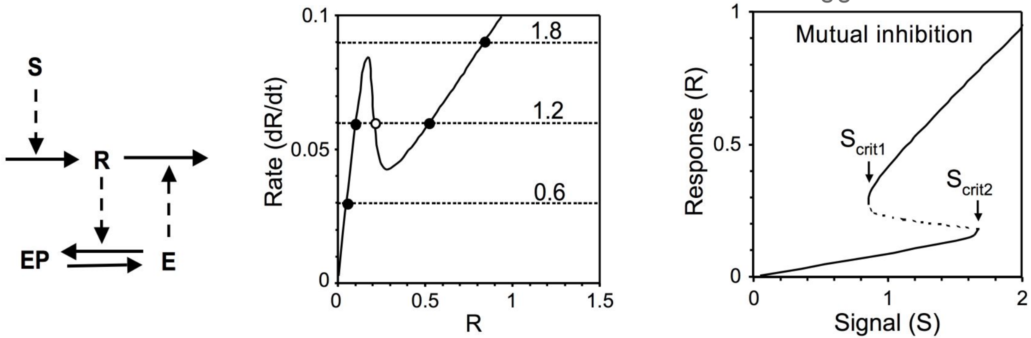


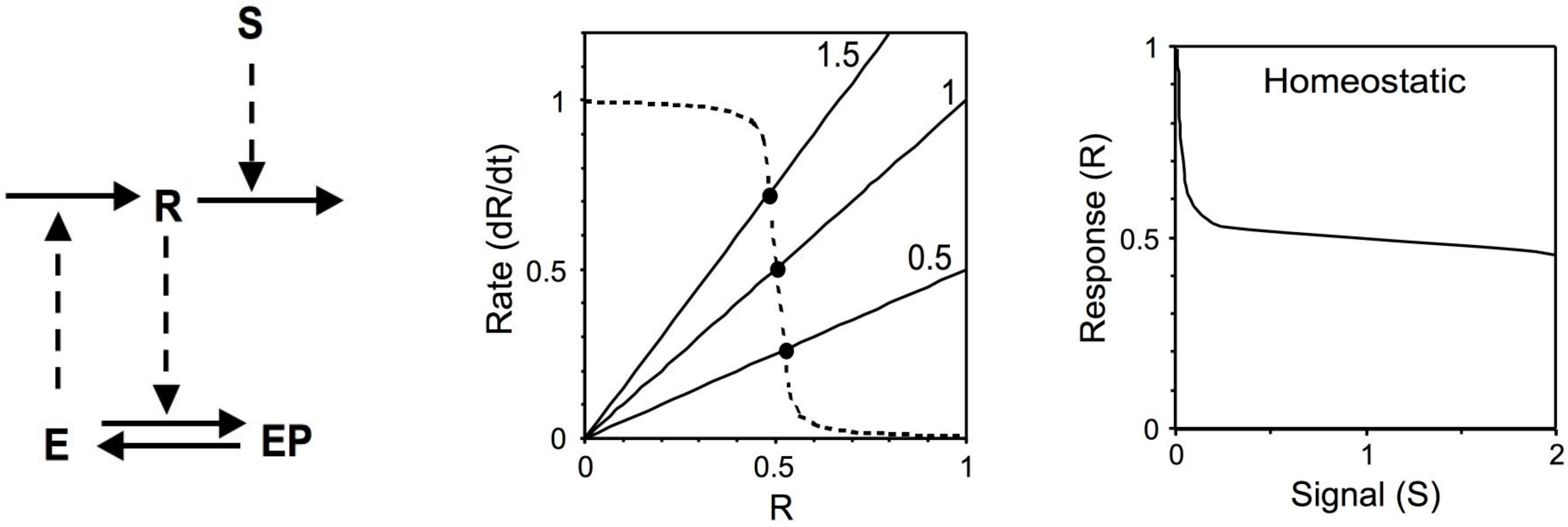
Toggle switch



- 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.

Negative feedback loop



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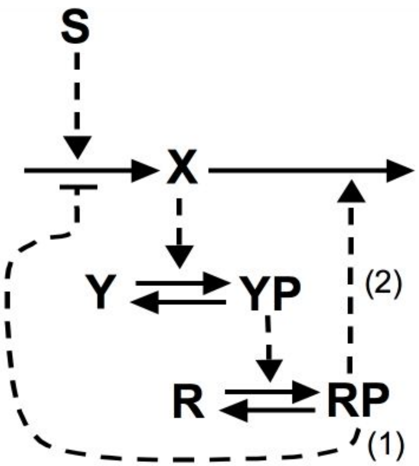
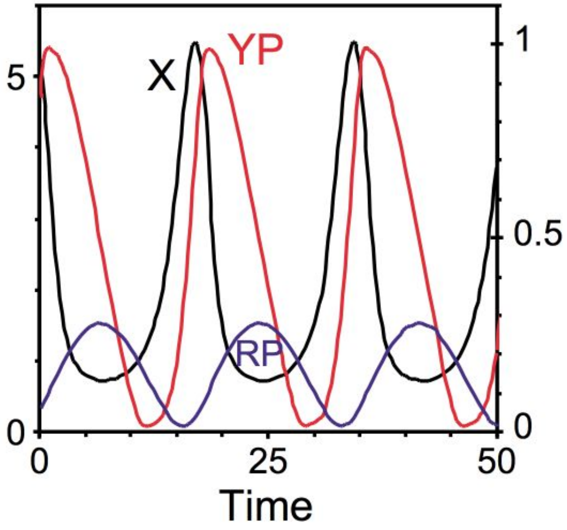
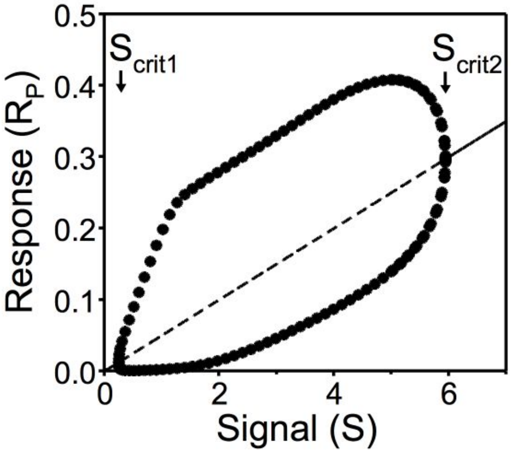
Negative feedback loop







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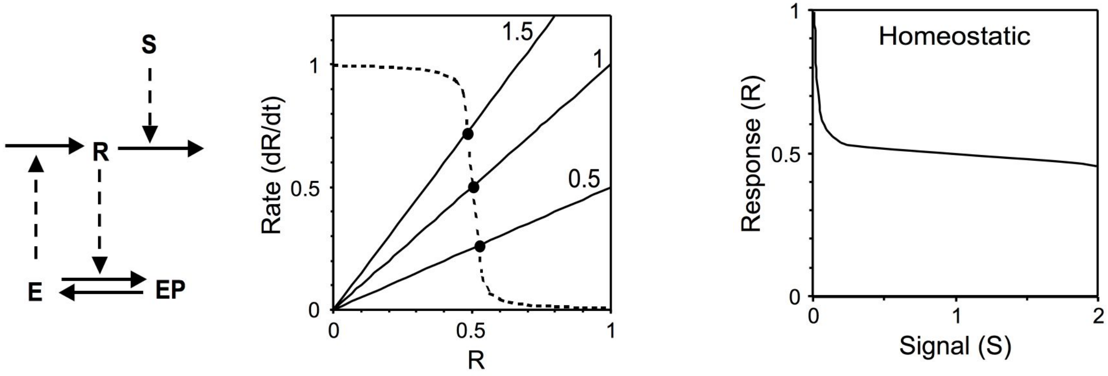
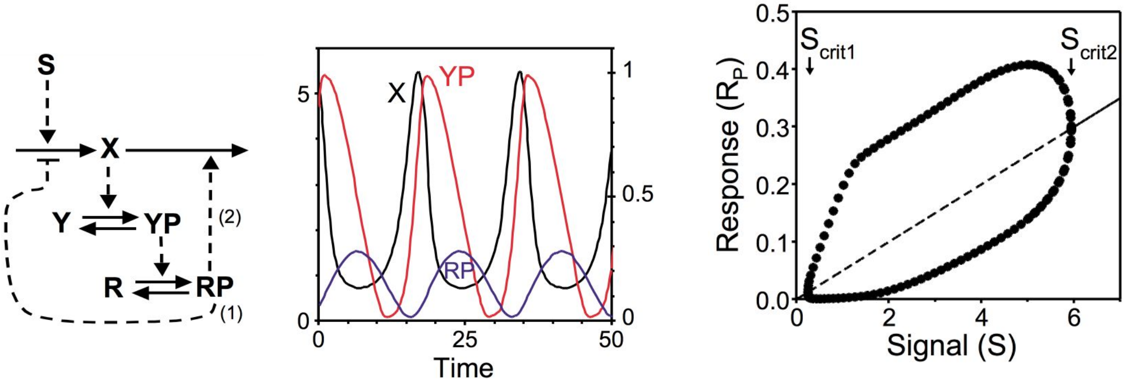
Negative feedback loop





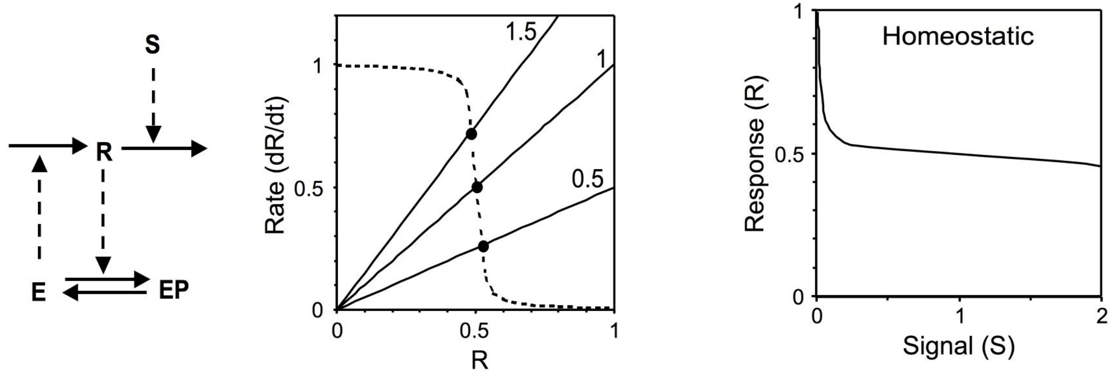
Negative feedback can also create an oscillatory response.

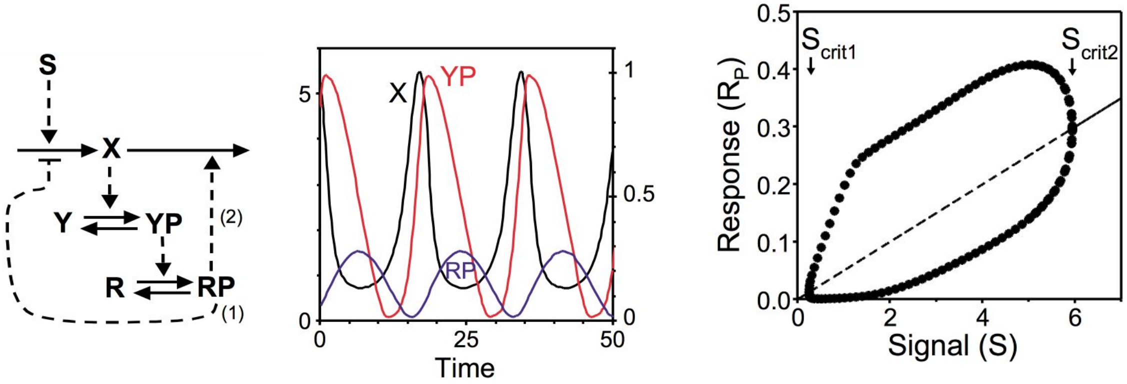
- $X \rightarrow R \twoheadrightarrow X$

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

Tyson (2003) Curr. Opin. Cell Biol.

Negative feedback loop





Sustained oscillations require at least three components:

- $X \longrightarrow Y \longrightarrow R \twoheadrightarrow X$

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.