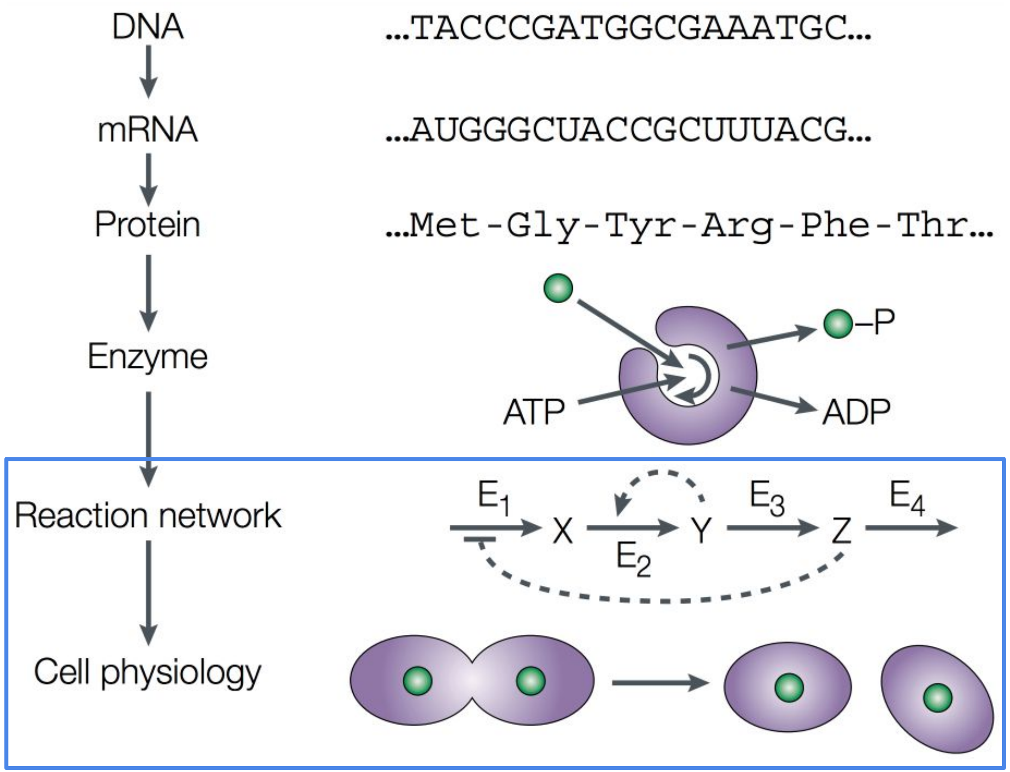
Week 13: Modeling regulatory pathways

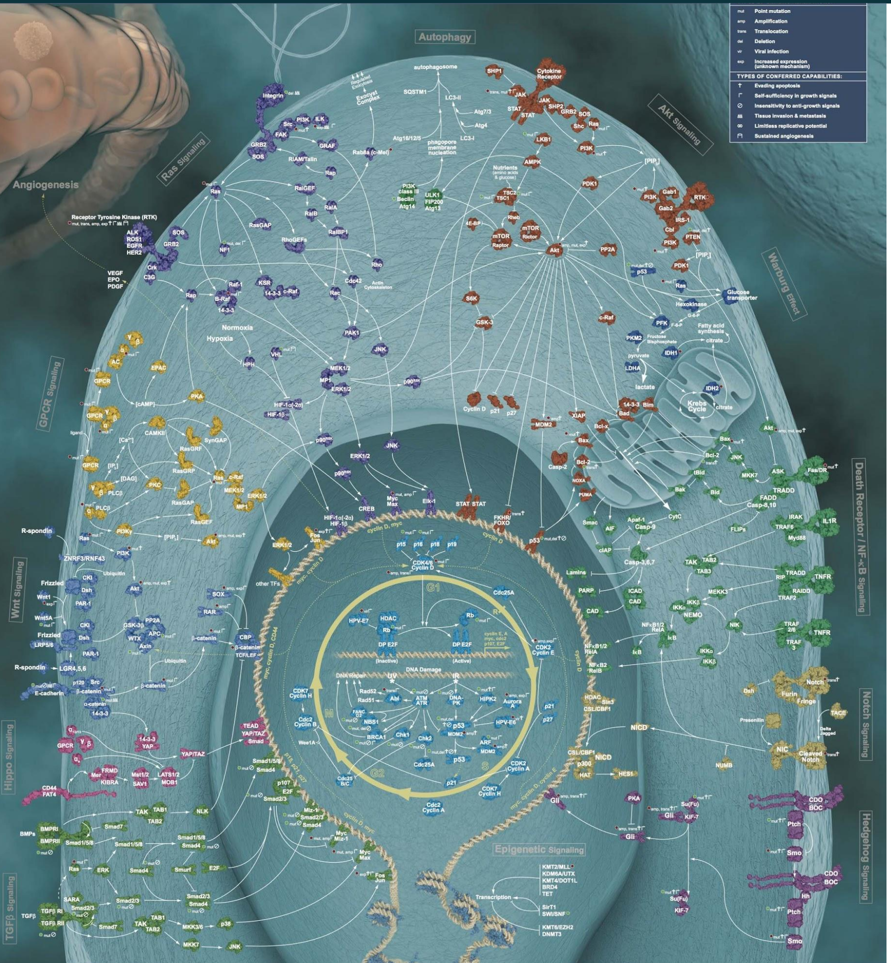
- Modeling simple motifs
- State spaces, vector fields, and bifurcations
- Application to modeling the cell cycle

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.

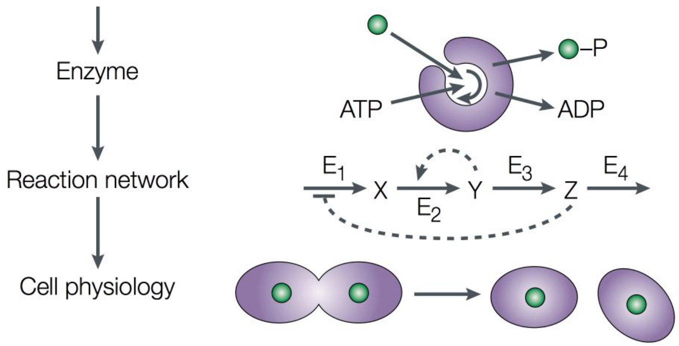
These processes are orchestrated by signaling and regulatory networks.

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 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.



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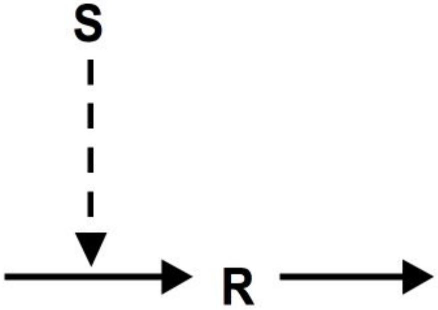
Modeling the dynamical systems: linear response



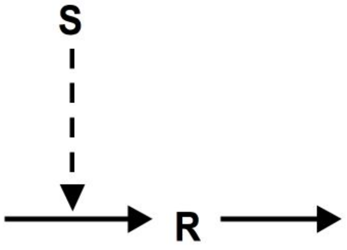
$$\frac{dR}{dt} = k_0 + k_1 S - k_2 R$$

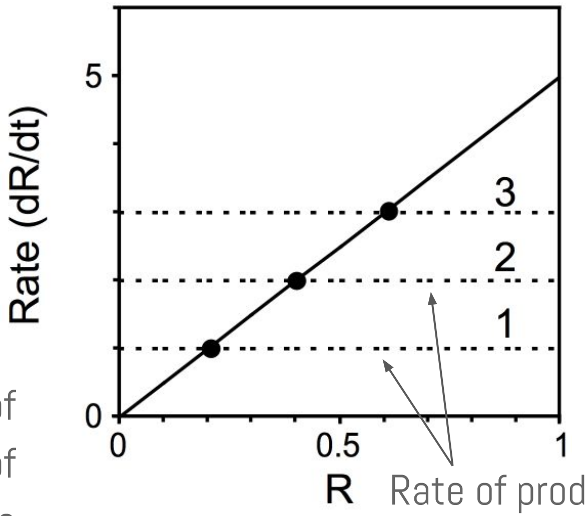
Steady-state solution

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

Tyson (2003) Curr. Opin. Cell Biol.

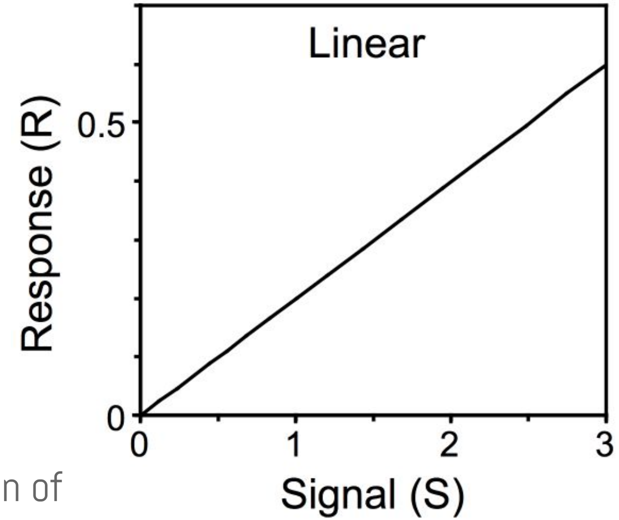
Modeling the dynamical systems: linear response





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

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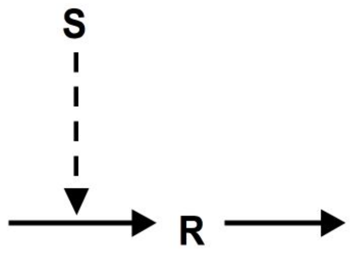
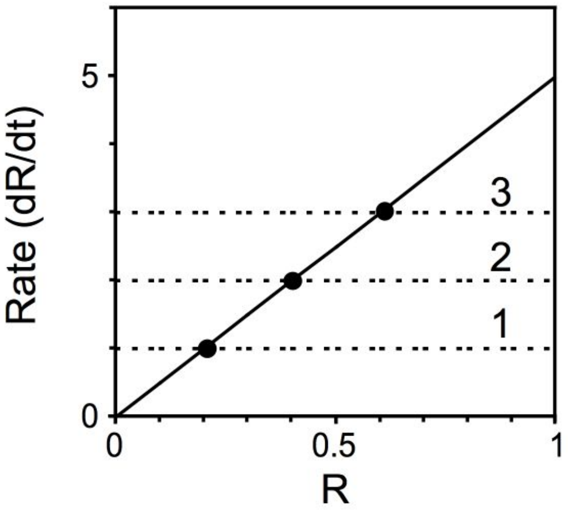
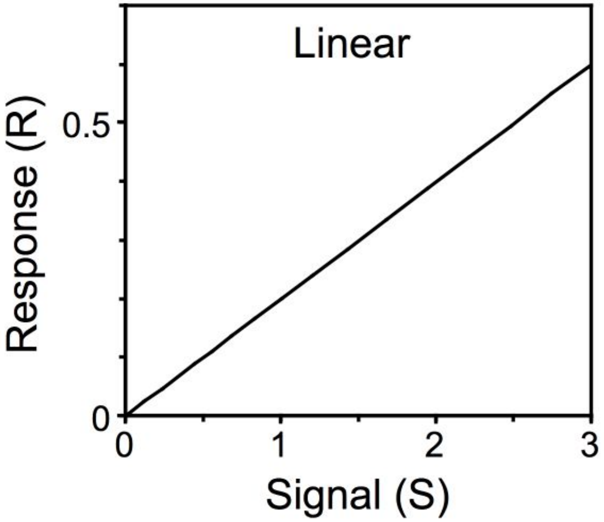
Modeling the dynamical systems: linear response





Rate curve



Signal-response curve

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

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

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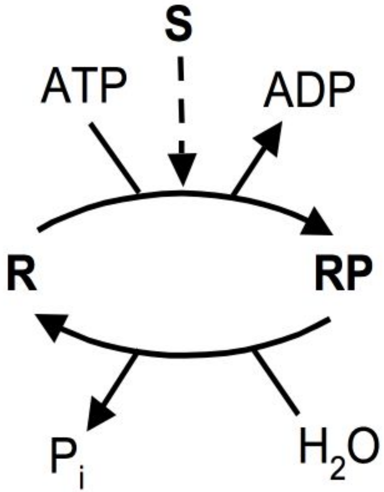
Modeling the dynamical systems: hyperbolic response



$$R_T = R + R_P$$

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

Steady-state solution

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

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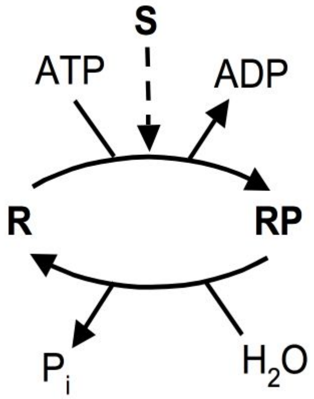
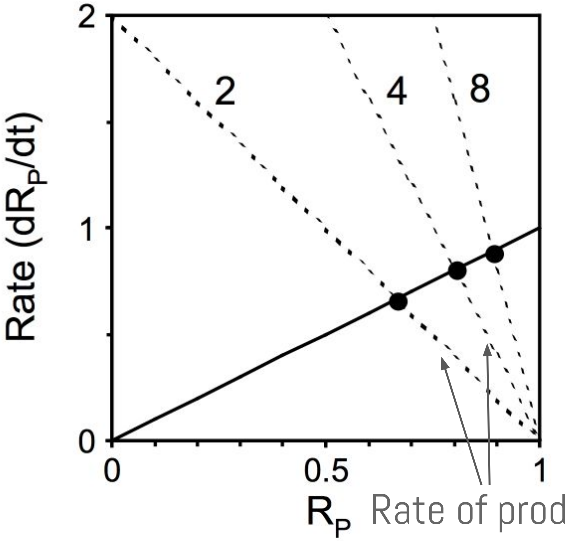
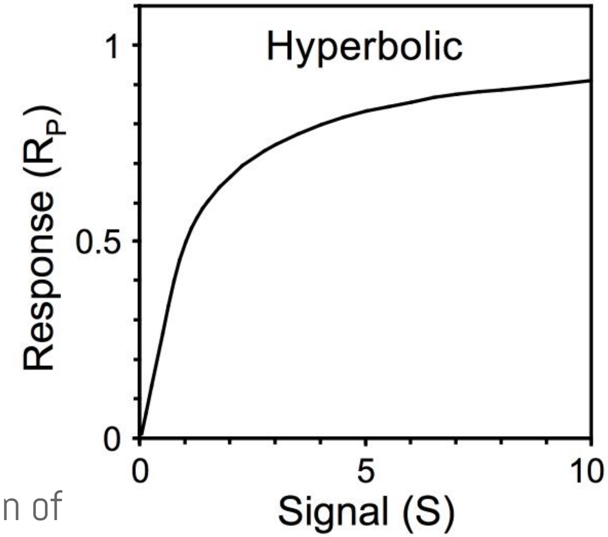
Modeling the dynamical systems: hyperbolic response



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

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

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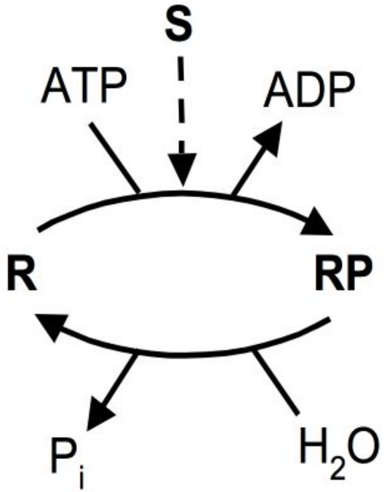
Modeling the dynamical systems: hyperbolic response



$$R_T = R + R_P$$

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

Steady-state solution

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

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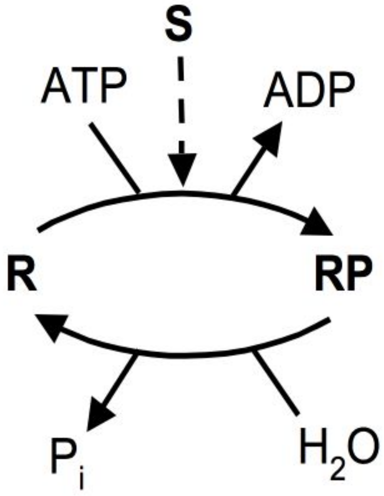
Modeling the dynamical systems: sigmoidal response



$$R_T = R + R_P$$

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

Michaelis-Menten kinetics:

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

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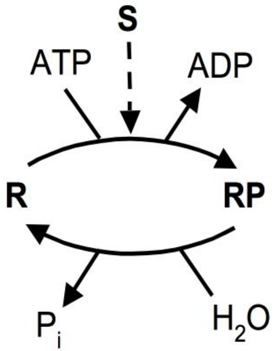
Modeling the dynamical systems: sigmoidal response



$$R_T = R + R_P$$

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

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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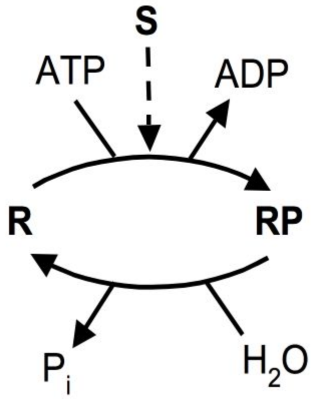
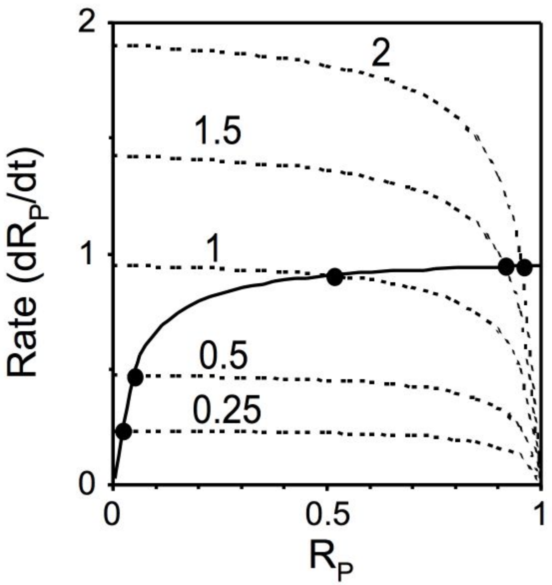
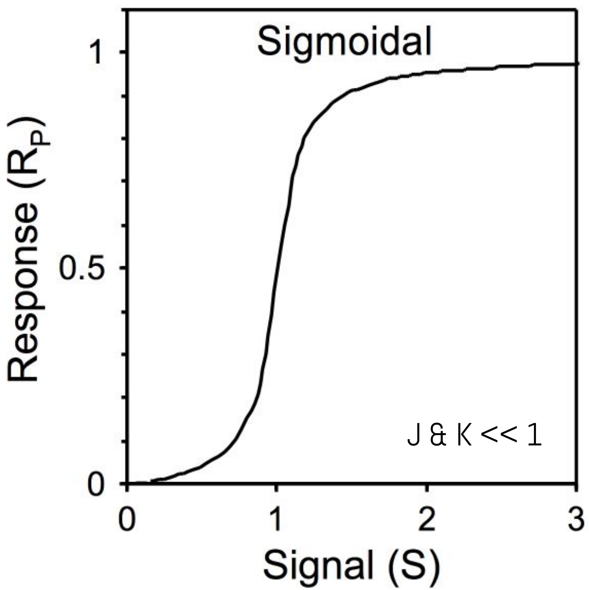
Modeling the dynamical systems: sigmoidal response







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

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

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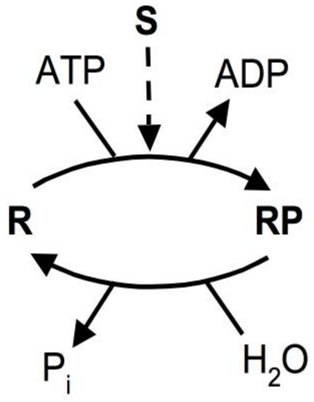
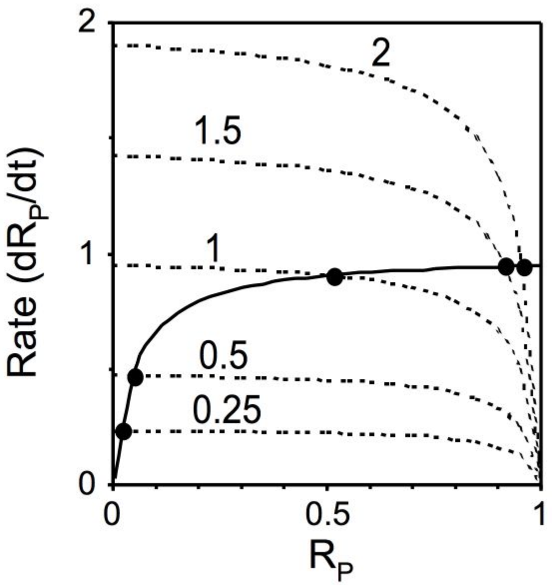
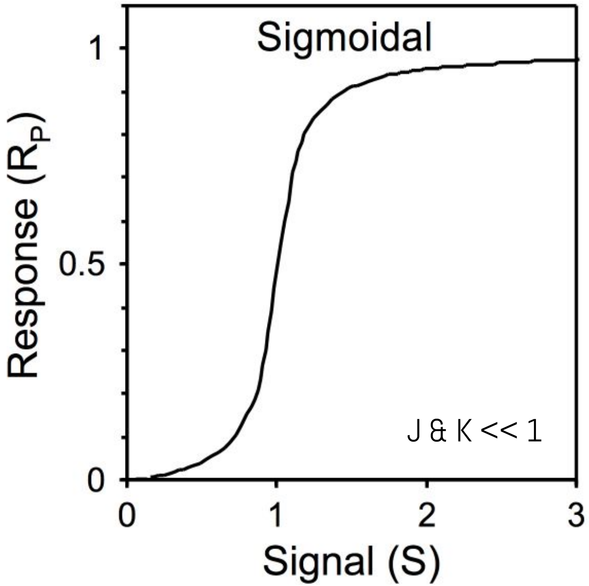
Modeling the dynamical systems: sigmoidal response







Zero-order ultrasensitivity

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

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