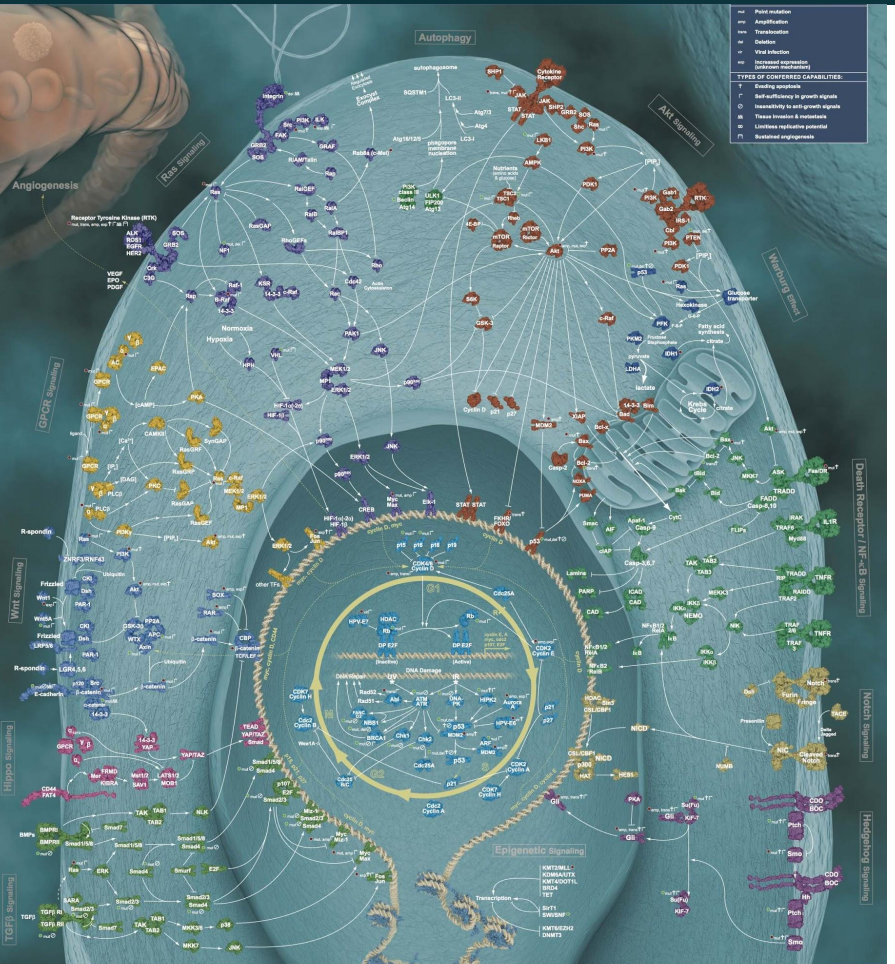
Lecture 12: Modeling cellular pathways

- 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 carry out most of the interesting jobs in a cell, such as metabolism, DNA synthesis, movement and information processing.

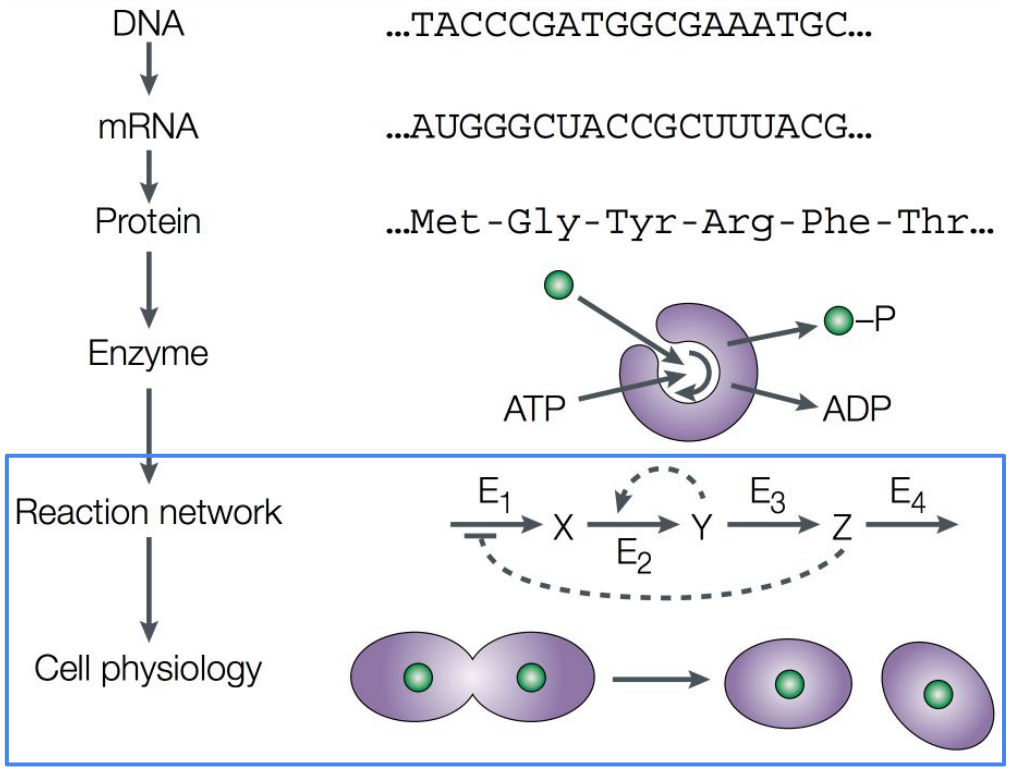
These processes are orchestrated by signaling and regulatory networks.

media.cellsignal.com

Computational molecular biology

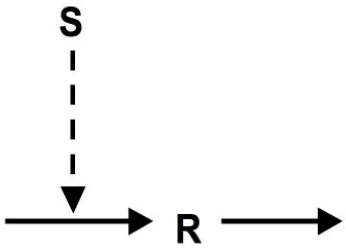
Can we take a cellular process and…

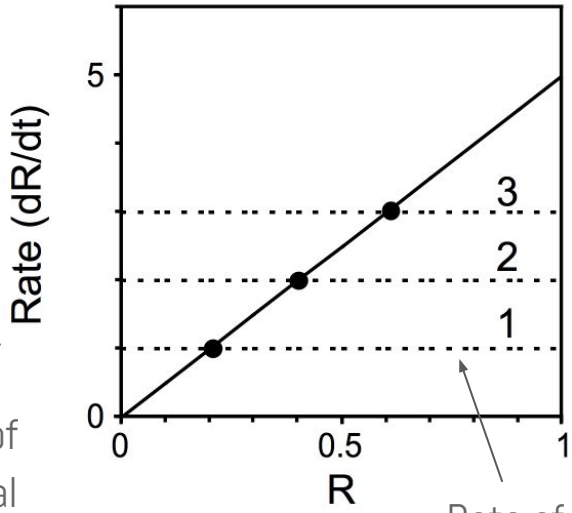
1. Draw a wiring diagram representing the signaling and regulatory interactions between underlying proteins…
2. Convert the diagram to a system of (differential/difference/Boolean) equations…
3. Simulate the system (along with optimal parameters) to understand its temporal/spatial properties and how 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.

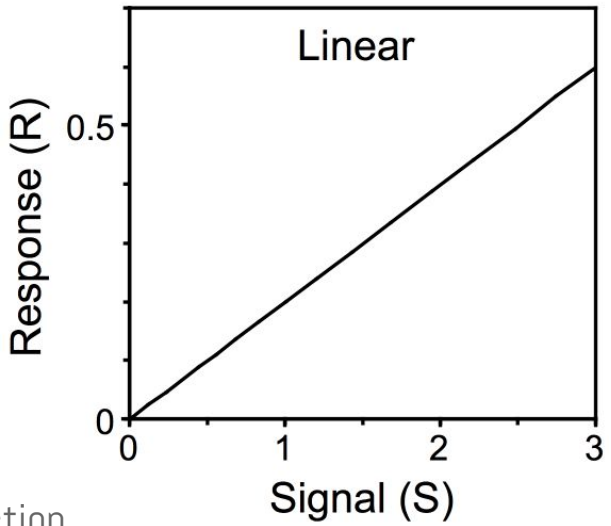
Modeling the dynamical systems: linear response





Rate of removal

Rate of production as a function of S

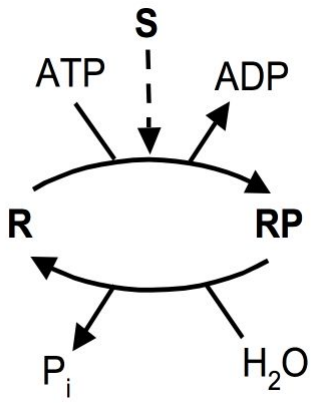


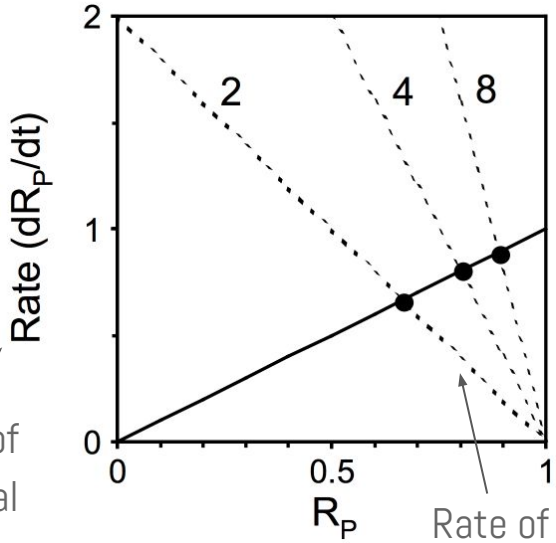
$$\frac{dR}{dt} = k_0 + k_1 S - k_2 R$$

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

Tyson (2003) Curr. Opin. Cell Biol.

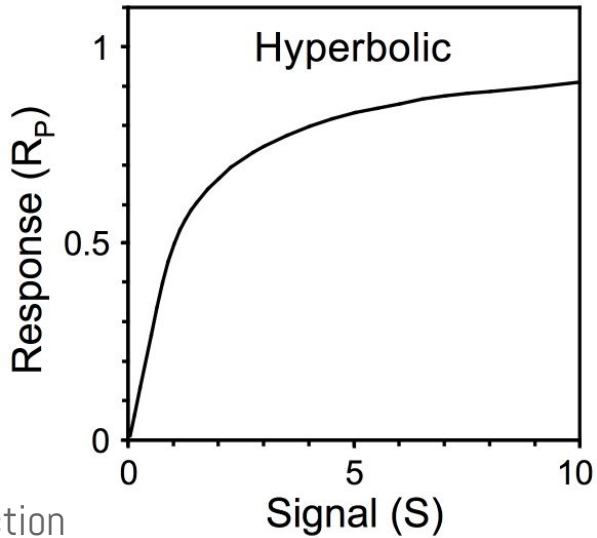
Modeling the dynamical systems: hyperbolic response





Rate of removal

Rate of production as a function of S



$$R_T = R + R_P$$

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

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

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

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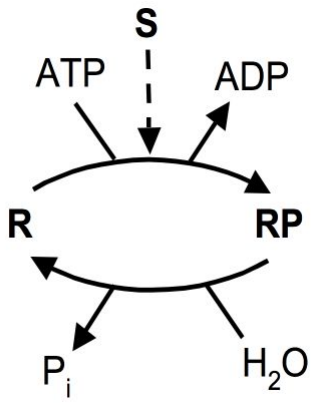
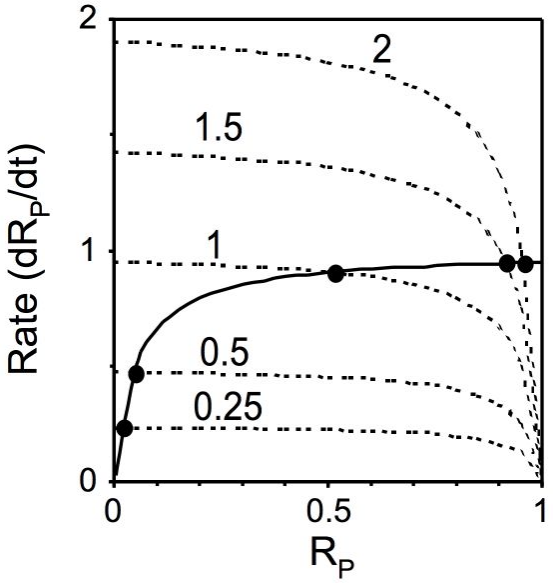
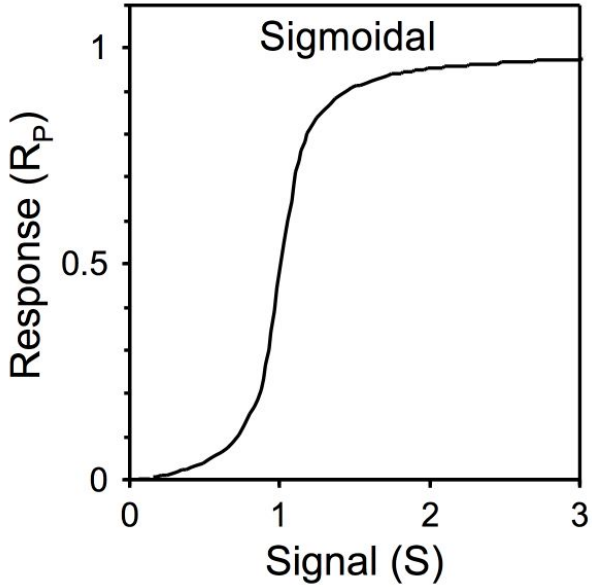
Modeling the dynamical systems: sigmoidal response







$$R_T = R + R_P$$

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

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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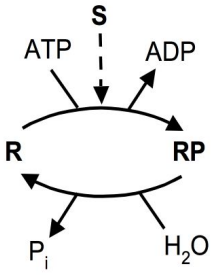
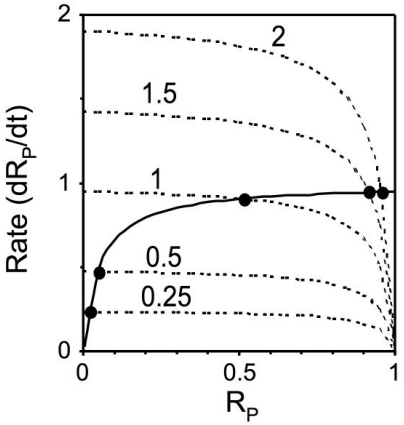
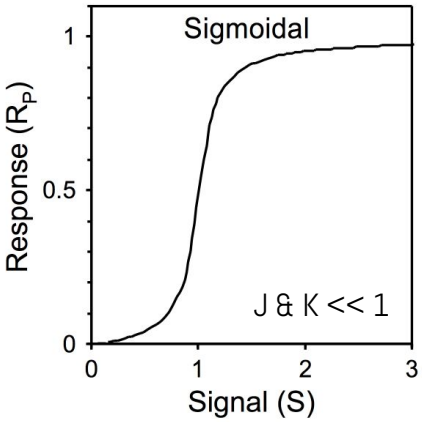
Modeling the dynamical systems: sigmoidal response







$$R_T = R + R_P$$

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

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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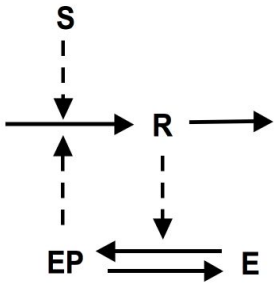
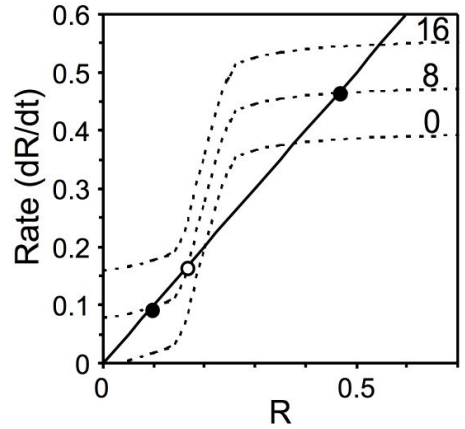
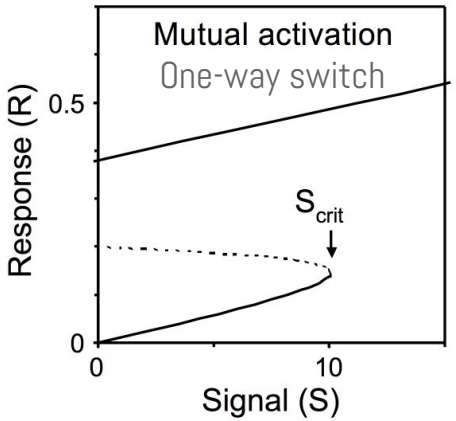
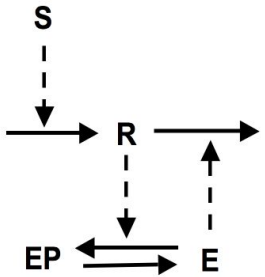
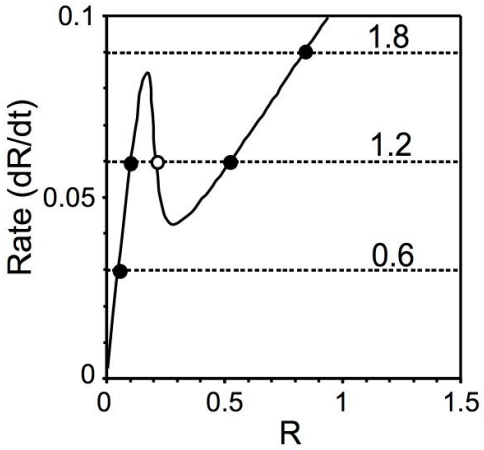
Modeling the dynamical systems: positive feedback

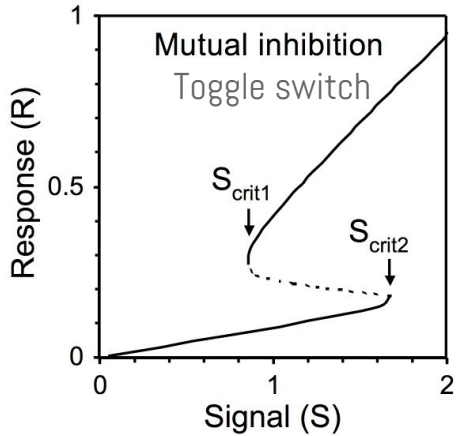












1-parameter bifurcation diagram

System is:

- Irreversible
- bistable b/w 0 & S_{crit} (birfurcation point) and b/w S_{crti1} & S_{crit2}
- In this case: saddle-node bifurcation.

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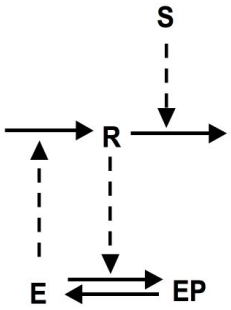
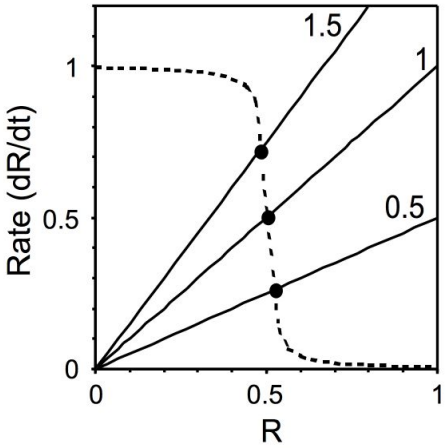
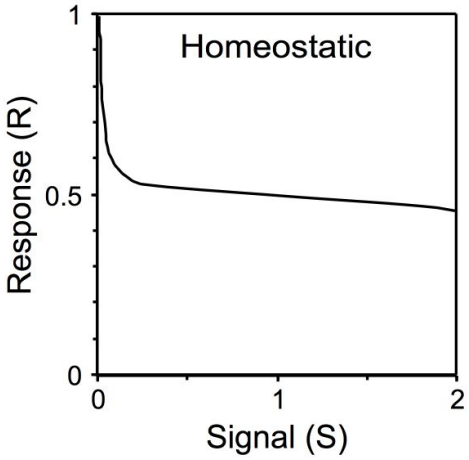
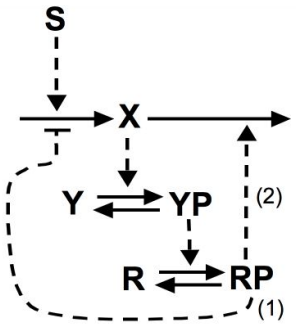
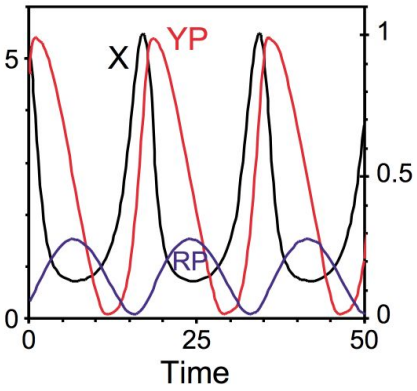
Modeling the dynamical systems: negative feedback

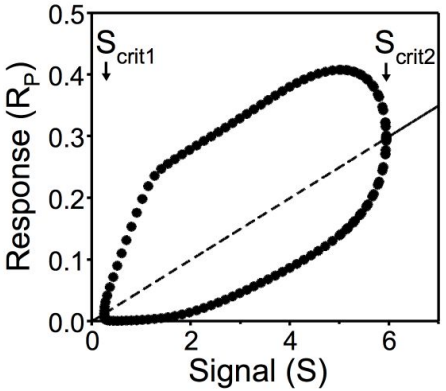












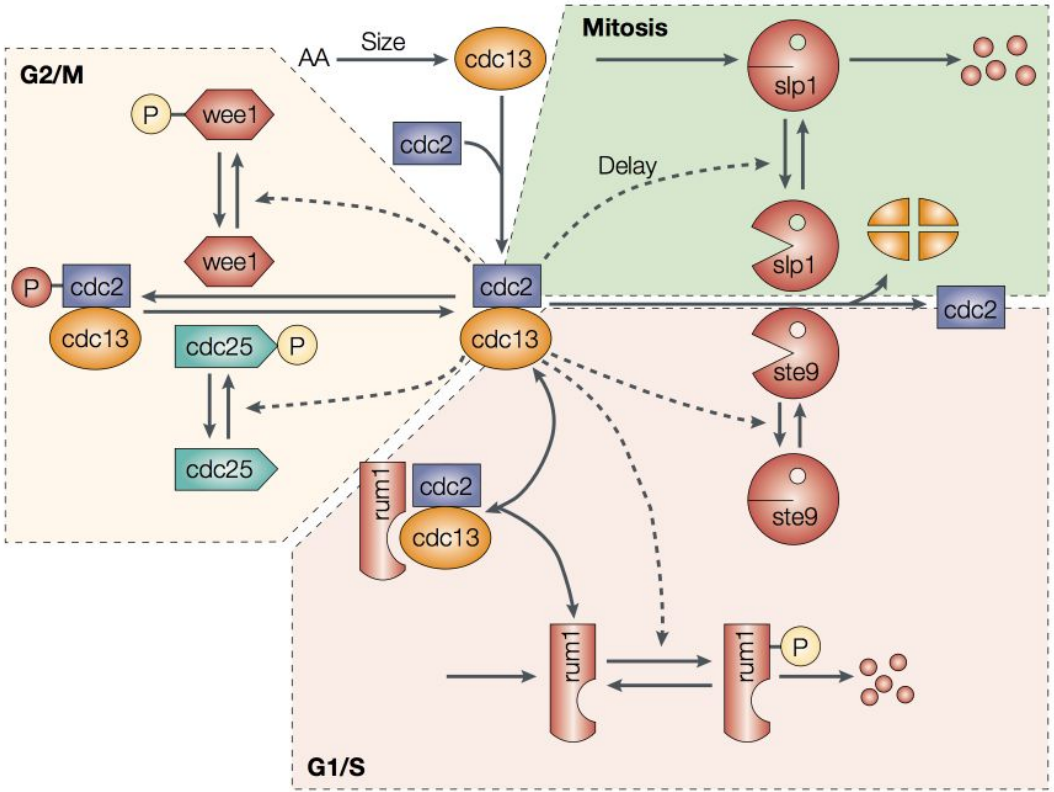
–ve feedback can also create an oscillatory response.

X ⟶ R ↠ X (damped oscillations to a stable steady state).

Sustained oscillations require at least three components: X ⟶ Y ⟶ R ↠ 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.

The cell-cycle control system in fission yeast



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

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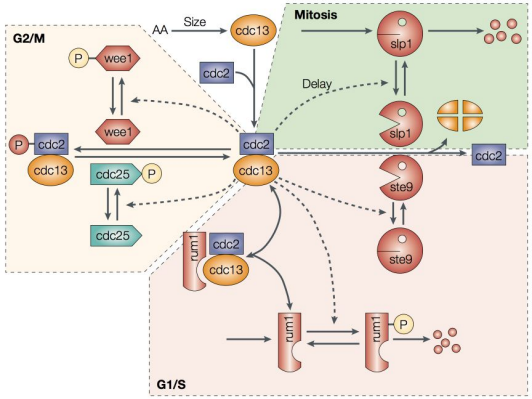
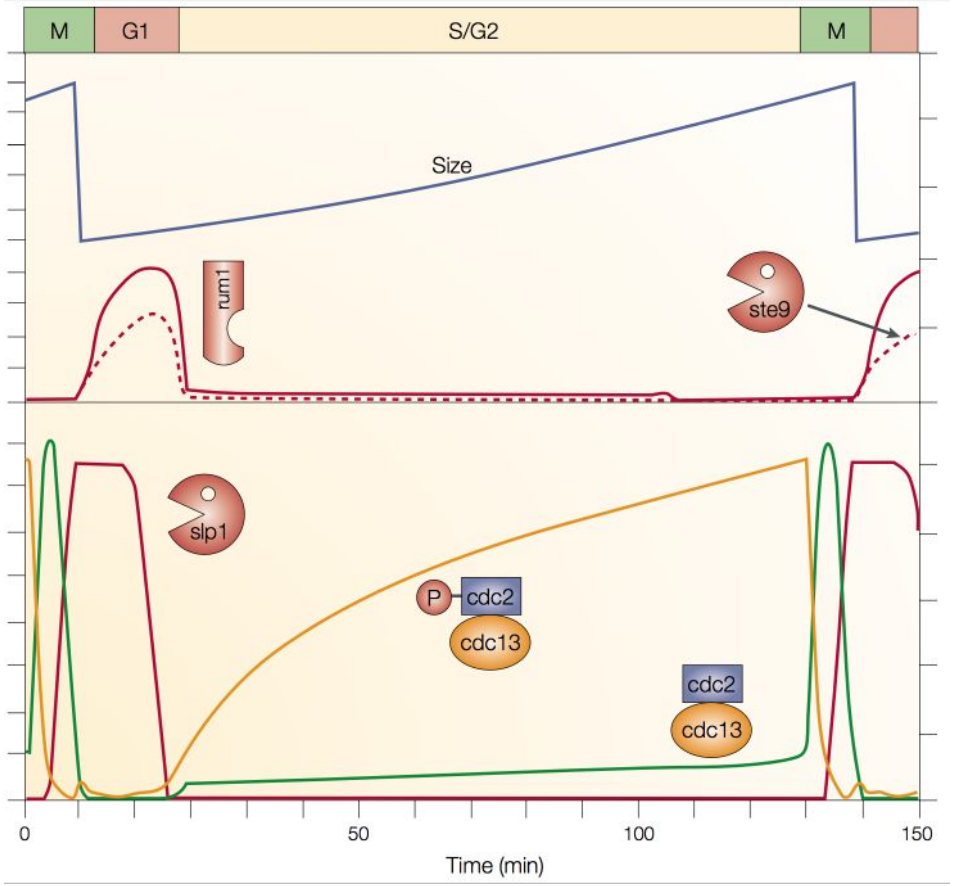


Fission yeast	Budding yeast	Frog egg	Mammal	Generic role
cdc2	Cdc28	Cdk1,2	Cdk1,2	Cyclin-dependent kinase
cdc13	Clb1–6	Cyclin A,B,E	Cyclin A,B,E	Cyclins
rum1	Sic1	Xic1	$p27^{Kip1}$	Stoichiometric inhibitor
ste9	Cdh1	Fizzy-related	Cdh1	APC auxiliary
slp1	Cdc20	Fizzy	$p55^{cdc}$	APC auxiliary
wee1	Swe1	Wee1	Wee1	Tyrosine kinase
cdc25	Mih1	Cdc25C	Cdc25C	Tyrosine phosphatase

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

Modeling the cell-cycle control system in fission yeast



Write the full set of differential equations that describe the wiring diagram.

Perform numerical integration of these equations to get time courses.

'Size' refers to the number of ribosomes per nucleus.

Notice the brief G1 phase, when ste9 is active and rum1 is abundant. After a long S/G2 phase, during which cdc2 is tyrosine phosphorylated, the cell enters M phase, when cdc25 removes the inhibitory phosphate group. After some delay, slp1 activates and degrades cdc13. As cdc2–cdc13 activity falls, the cell exits mitosis. Size decreases twofold at nuclear division.

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

State spaces and vector fields

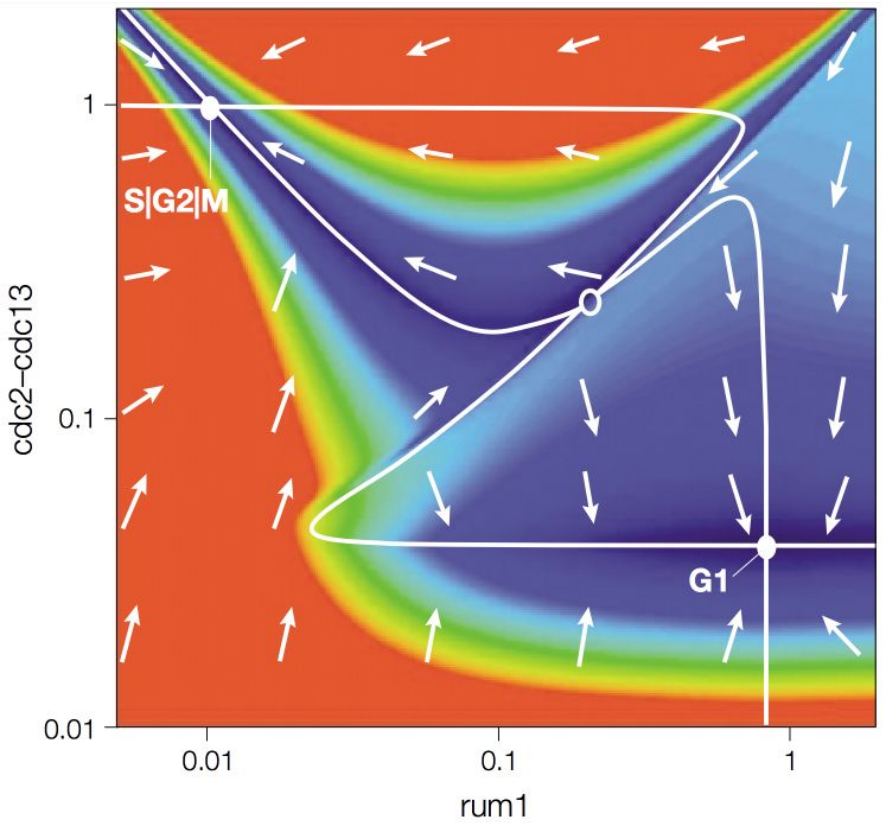
At any given point, the differential equations determine how fast the state of the system is changing

- they associate to each point an arrow, which indicates the direction and magnitude of the rates of change of [cdc2–cdc13] and [rum1].

The collection of arrows at every point in **state space** defines the **vector field** of the dynamical system.

Direction: arrow; Magnitude: color (red, fast; blue, slow)

Two curves: the vector field is either horizontal or vertical. Within the regions bounded by these curves, all arrows lie in the same quadrant of compass directions.



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

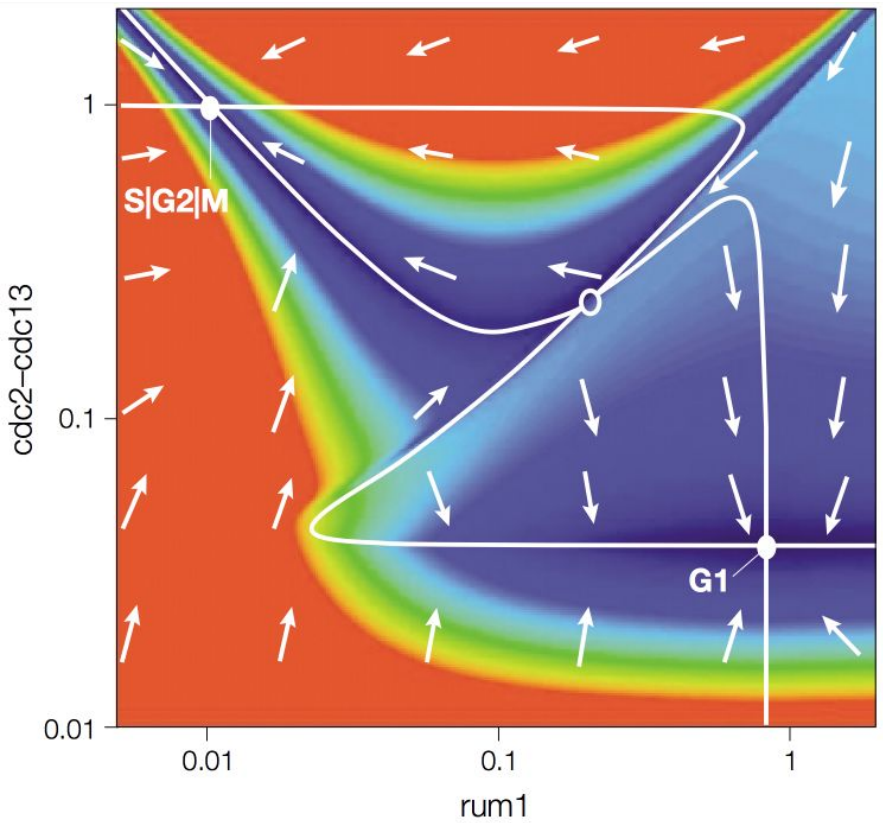
State spaces and vector fields

Knowing the vector field, one can predict the response of the control system to any initial condition - simply pick a starting point and follow the arrows.

In this case, the dynamical system has two attractors (●); in the vicinity of a stable steady state, all arrows point towards the steady state.

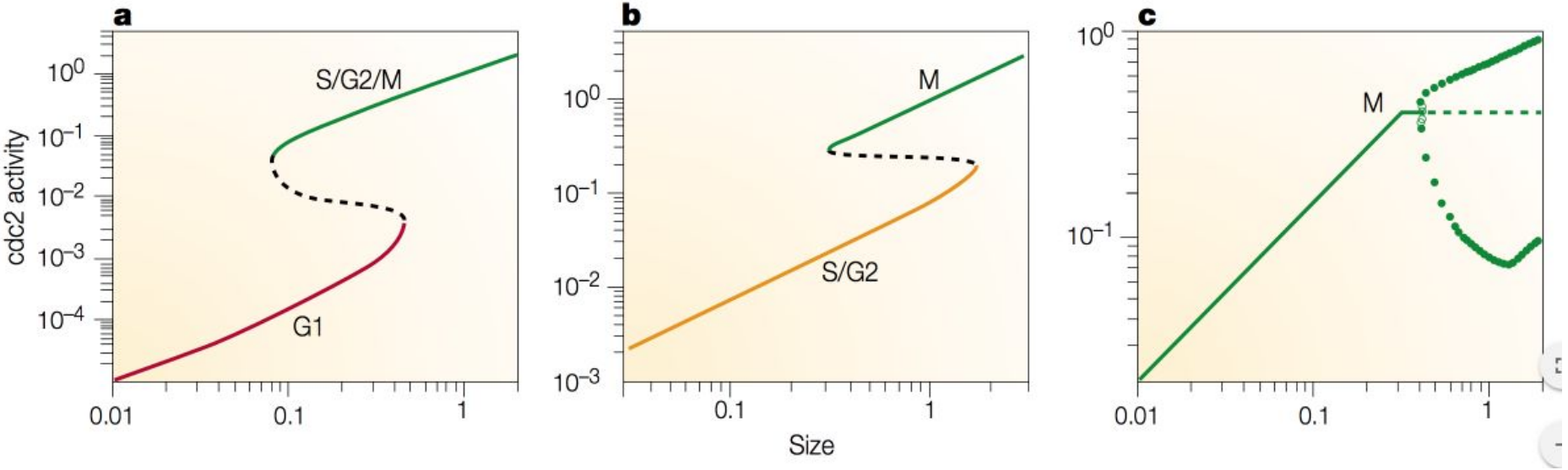
The intermediate steady state (o) is an unstable saddle point (attractive in two directions and repelling in all others).

The 'state-space' idea is readily generalized to any number of dynamical variables, but the vector field is hard to visualize in 3 or more dimensional state space.



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

Bifurcation diagrams for the three control modules of the cell cycle



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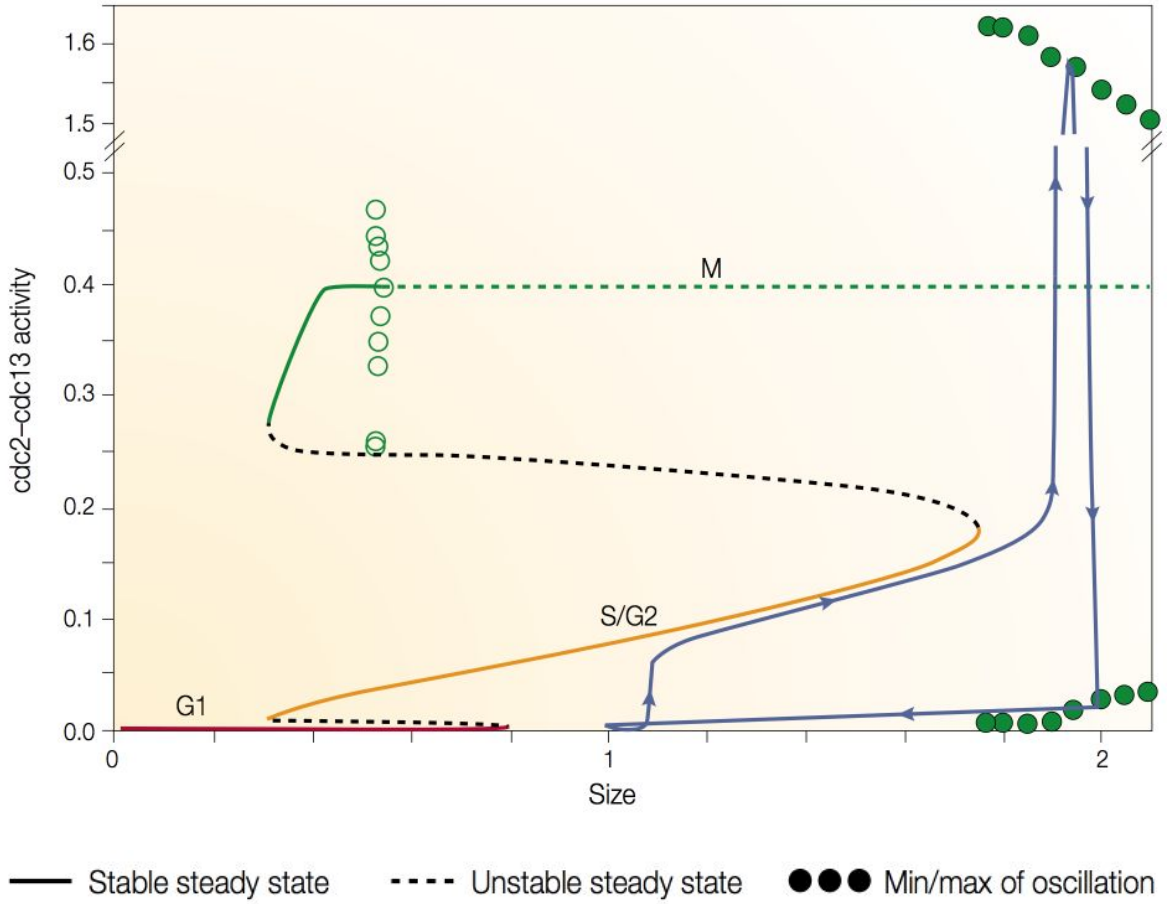
Bifurcation diagram for the full cell-cycle control network



Composite of the 3 diagrams: not a simple sum of the bifurcation diagrams of modules. (e.g. oscillations around the M state)

Blue line: Cell-cycle orbit from time course data.

At small cell size, all three modules support stable steady states.

The cell-cycle orbit follows the attractors of the control system.

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

Broad ideas

Kinetic modelling and bifurcation theory provide a precise, mathematical connection between the molecular networks and cellular physiology.

Can be used to make powerful predictions.

Several modeling strategies:

- Rate equations
- Boolean (& hybrid) modeling
- Stochastic simulations