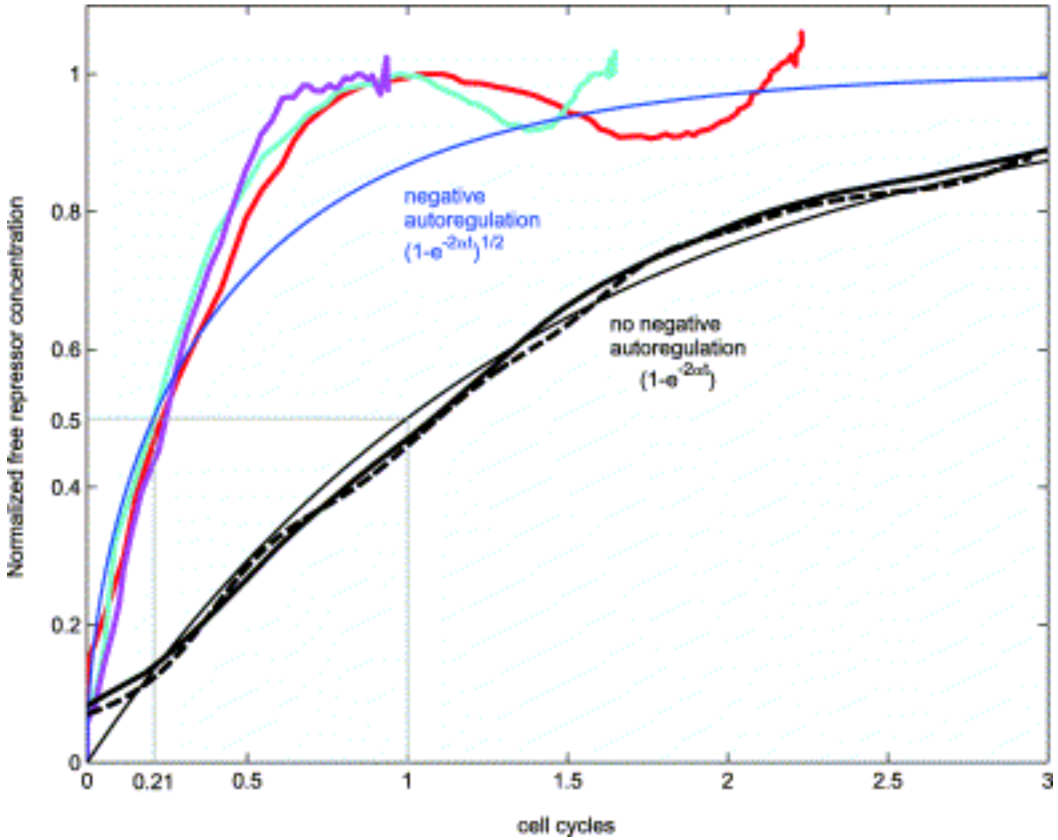
Systems Biology – Lecture 3

Positive feedback, bistability, differentiation, and oscillations

In the last lecture, we saw how negative feedback speeds up response times



Rosenfeld et al. 2002

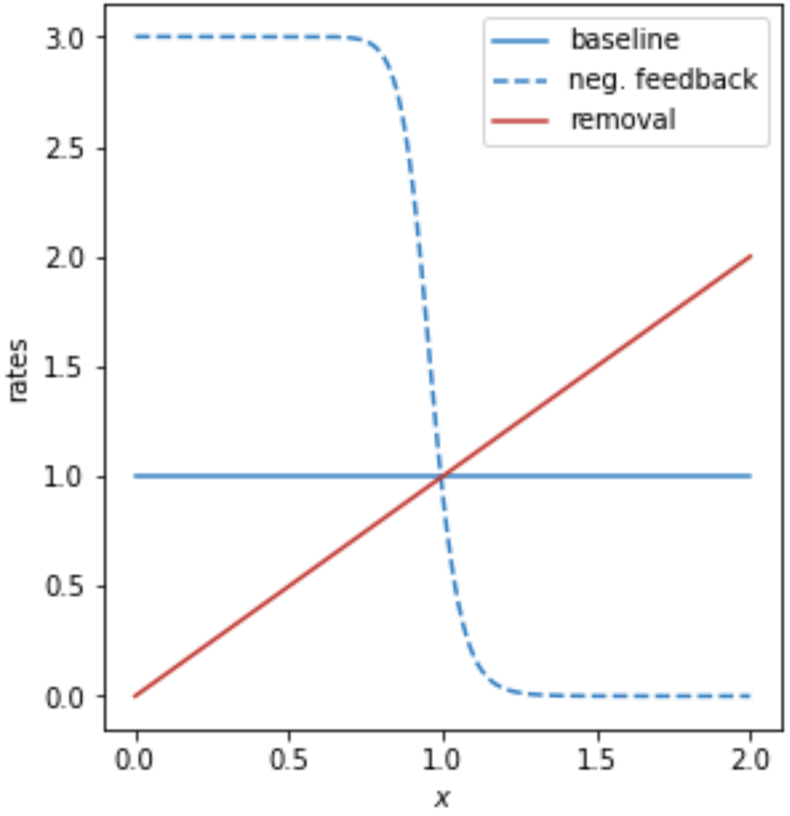
The speed-up of responses can be captured by rate plots

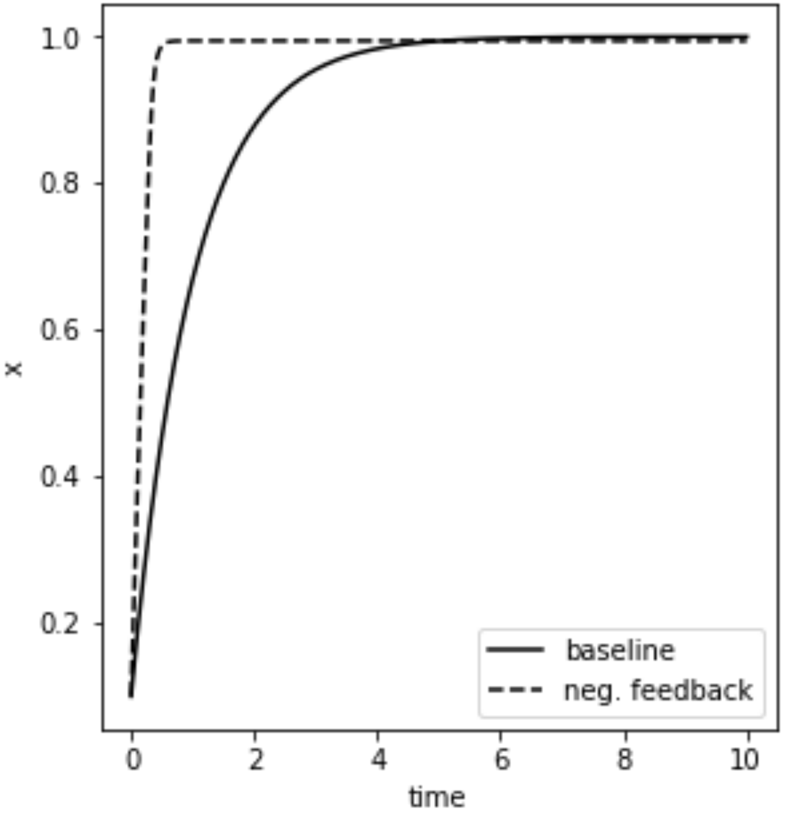
Baseline model:

$$\dot{x} = \alpha - \gamma x$$

Neg. feedback:

$$\dot{x} = V \frac{k^n}{k^n + x^n} - \gamma x$$





What about positive feedback?

Baseline model:

$$\dot{x} = \alpha - \gamma x$$

Neg. feedback:

$$\dot{x} = V \frac{k^n}{k^n + x^n} - \gamma x$$

Pos. feedback:

$$\dot{x} = V \frac{x^n}{k^n + x^n} - \gamma x$$

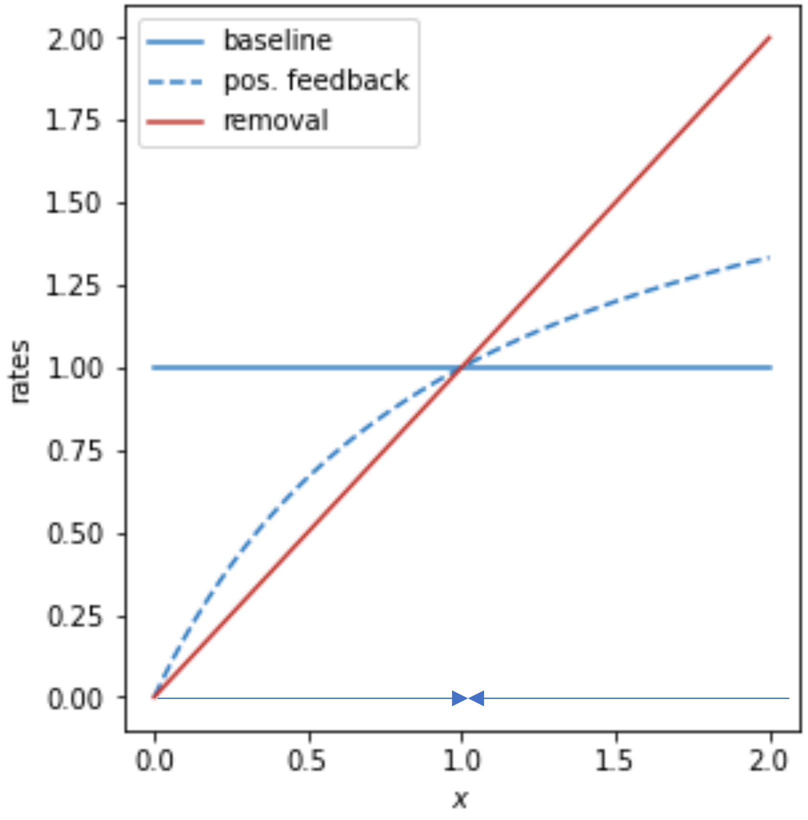
Linear (n=1) positive feedback slows down responses, and stabilizes $x = 0$

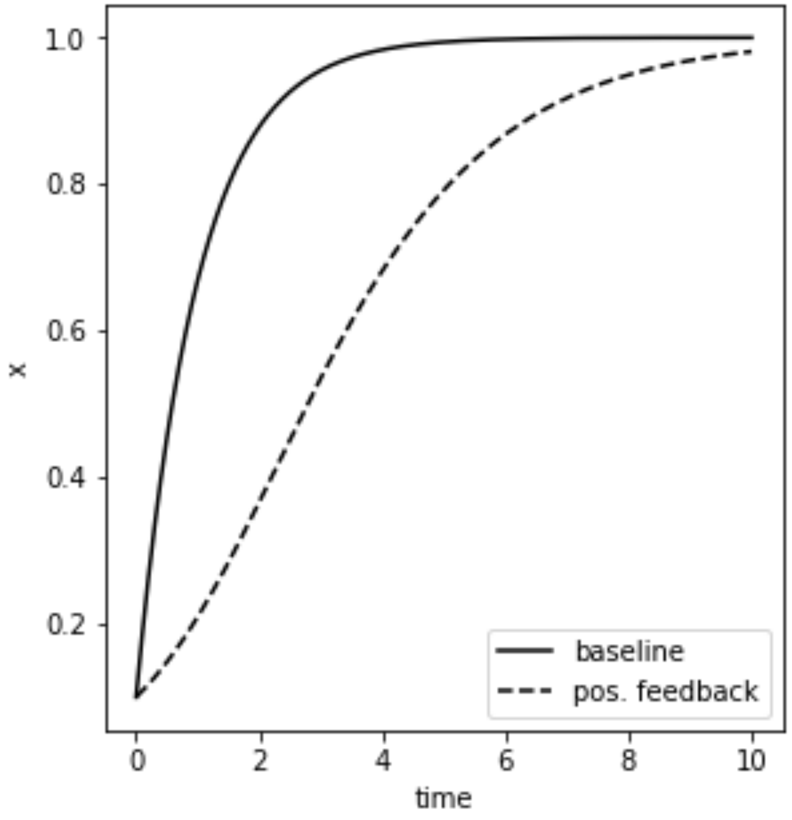
Baseline model:

$$\dot{x} = \alpha - \gamma x$$

Linear pos. feedback:

$$\dot{x} = V\frac{x}{k + x} - \gamma x$$





Another way to look at the dynamics of the convergence to steady-state is to consider the potential

$$\dot{x} = -\frac{\partial U}{\partial x}$$

For a simple production-removal system, we have a quadratic potential

$$\dot{x} = -\frac{\partial U}{\partial x}$$

$$U_{base}(x) = -\alpha x + \frac{\gamma x^2}{2} + C$$

Steady-states are local minima of the potential

$$\dot{x} = -\frac{\partial U}{\partial x}$$

$$U_{base}(x) = -\alpha x + \frac{\gamma x^2}{2} + C$$

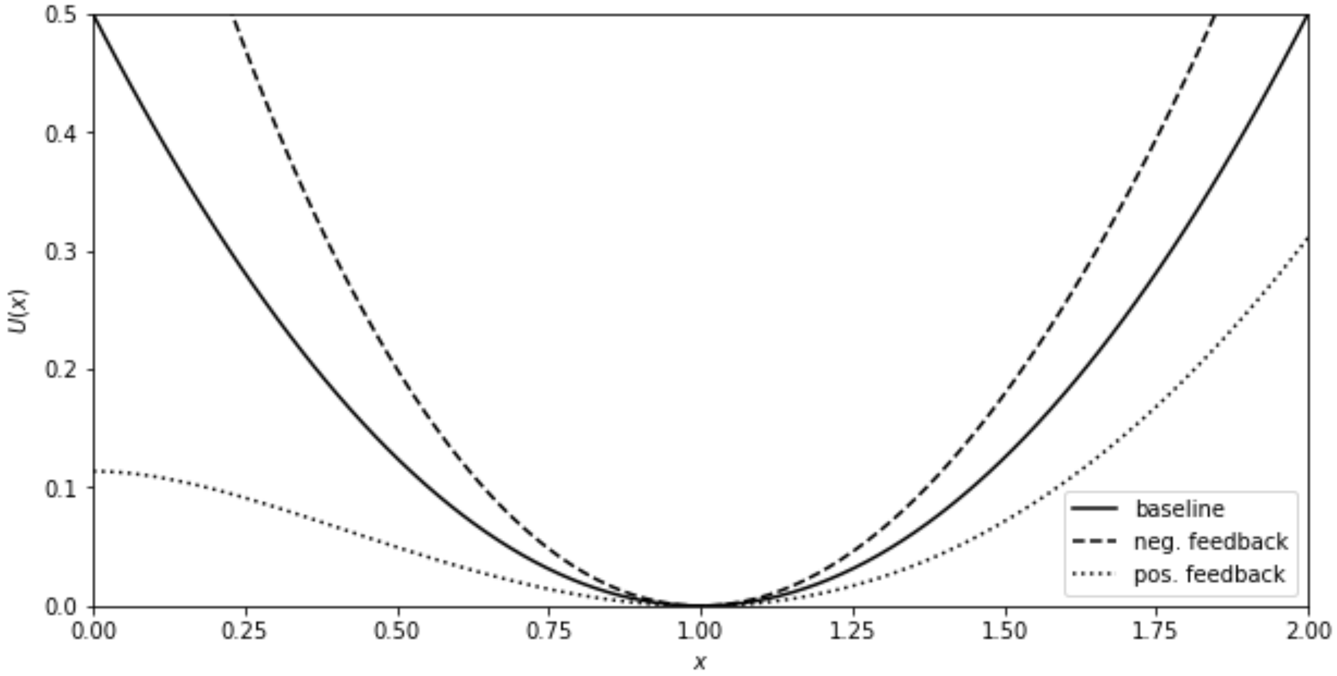
Positive and negative feedback make the potential shallower/steeper

$$\dot{x} = -\frac{\partial U}{\partial x}$$

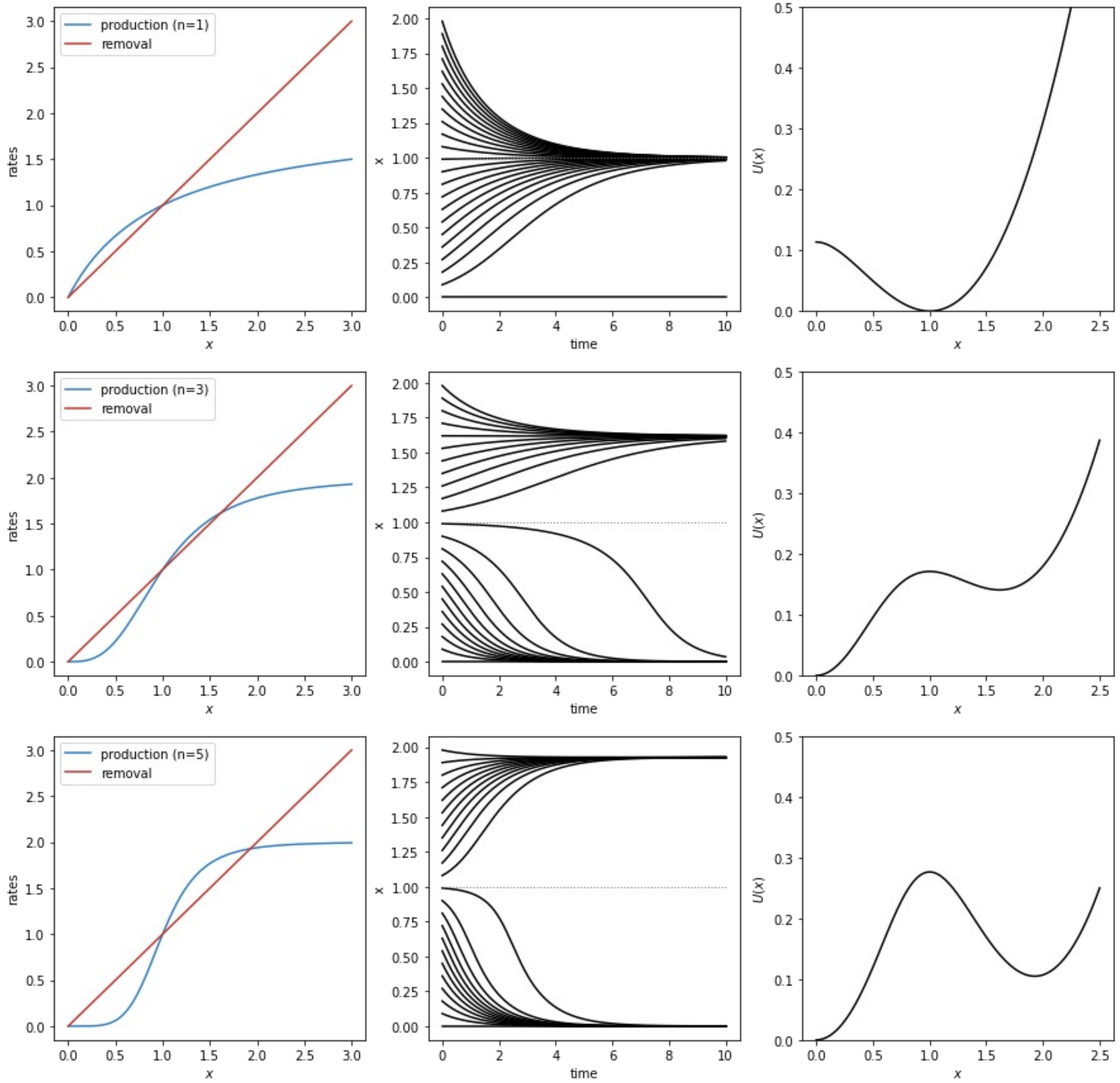
$$U_{base}(x) = -\alpha x + \frac{\gamma x^2}{2} + C$$

$$U_{neg}(x) = -k\,V\log(k+x)\ + \frac{\gamma x^2}{2} + C$$

$$U_{pos}(x) = k\,V\log(k+x)\ - Vx + \frac{\gamma x^2}{2} + C$$



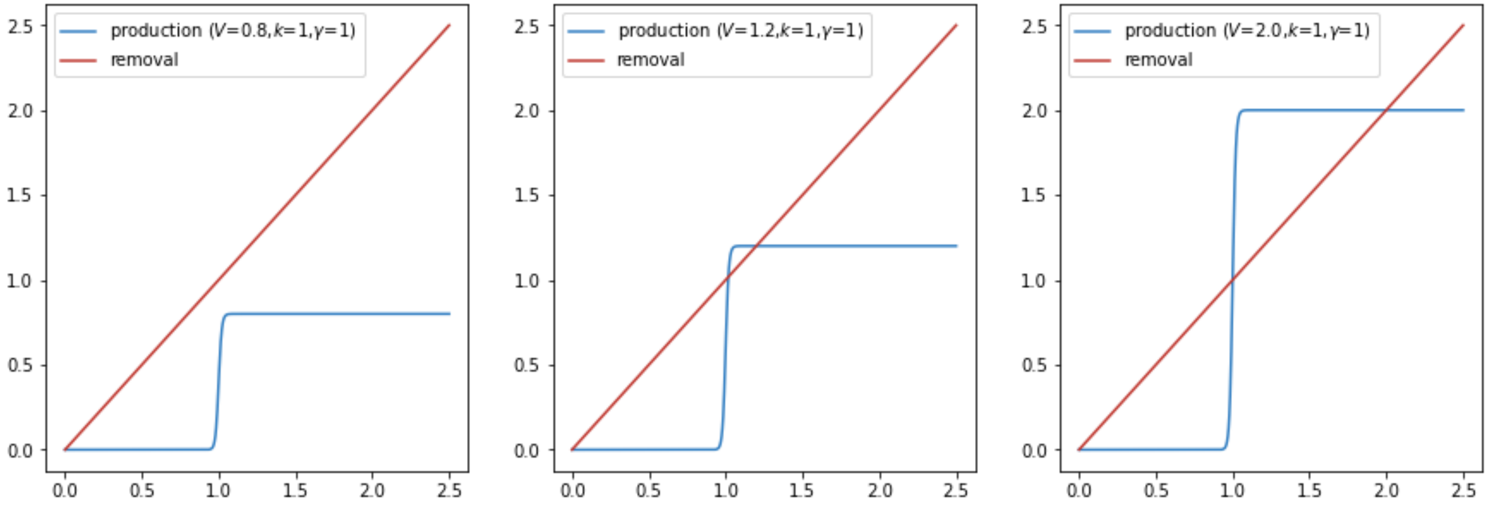
Cooperative positive feedback can destabilize the system to the extent that new steady-states are formed **(bistability)**



Bistability depends on parameter values

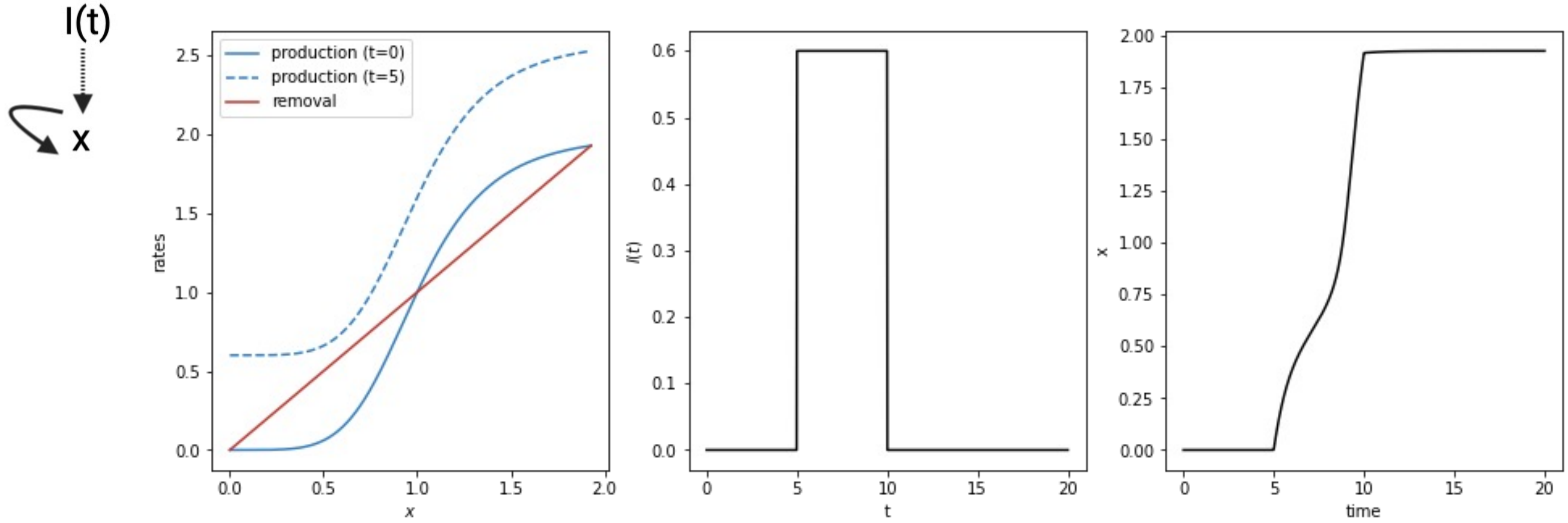
$$\dot{x} = V\frac{x^n}{k^n + x^n} - \gamma x, \mathrm{n} \gg 1$$

- Curves intersect at $x = 0$, and then possibly at $x \approx k$ and $x \approx \frac{V}{\gamma}$
- Bistability requires that these would be solutions, i.e. that $V \gtrapprox \gamma k$

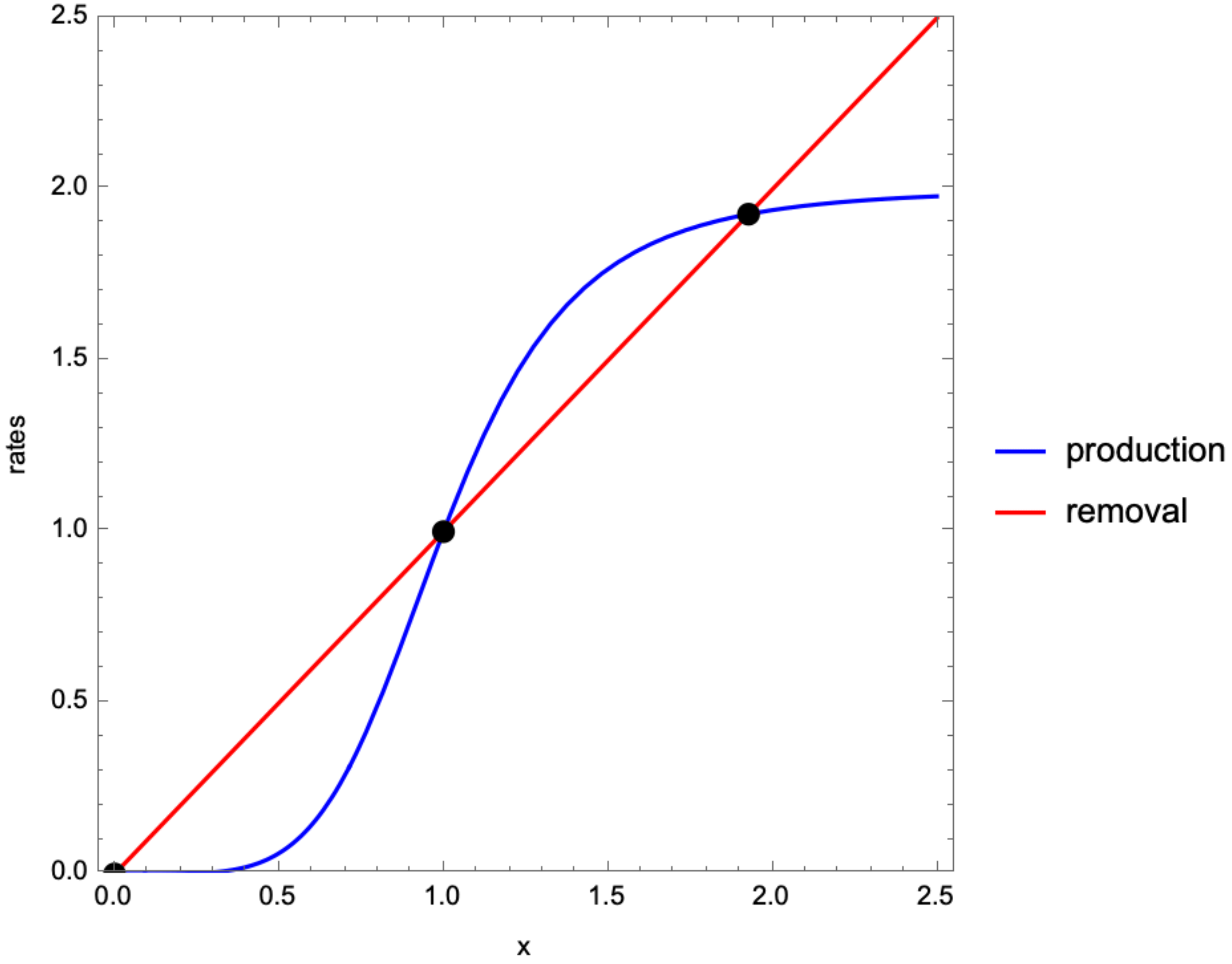


Bistable switches can act as long-term memory units

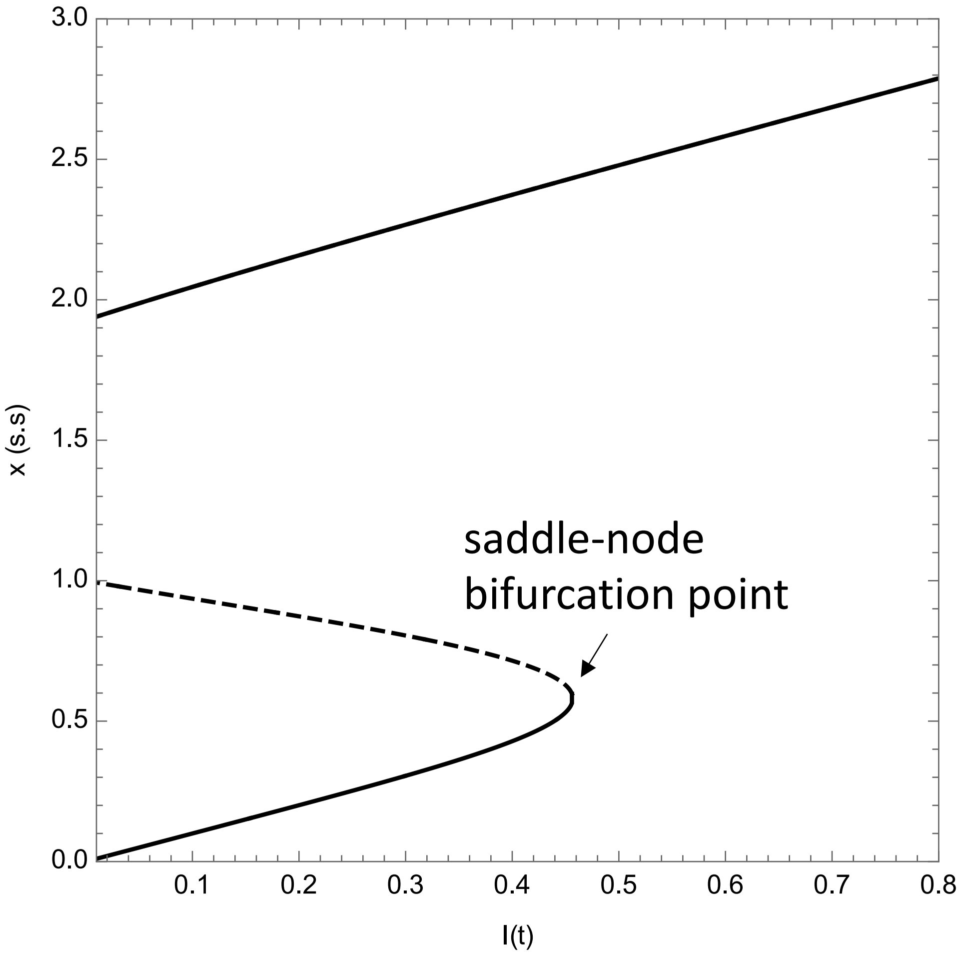
$$\dot{x} = I(t) + V\frac{x^n}{k^n + x^n} - \gamma x$$



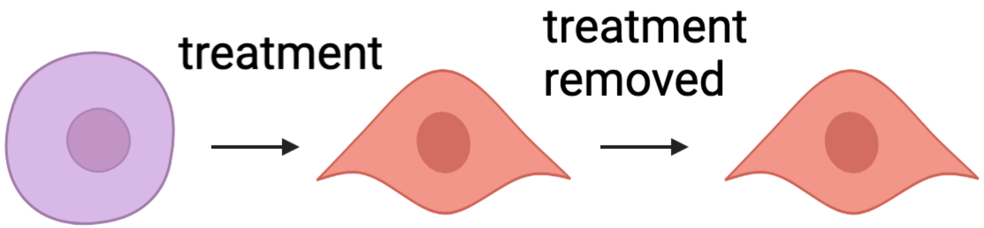
The process of the creation / elimination of (pairs of) fixed points is known as a saddle-node bifurcation



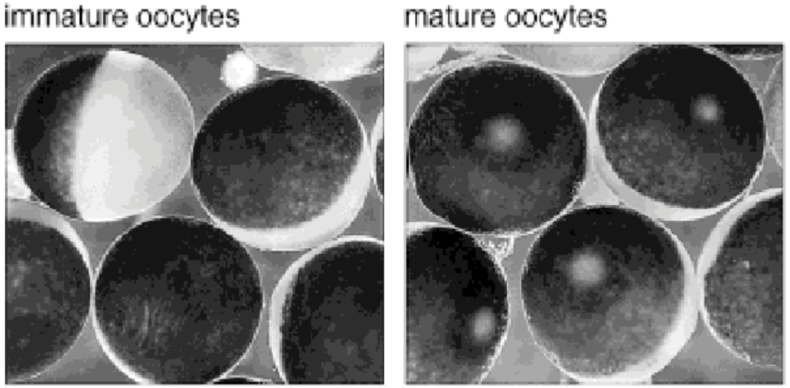
The input *I* acts as a control parameter for the saddle node bifurcation



Bistable switches are a simple model for cell fate induction

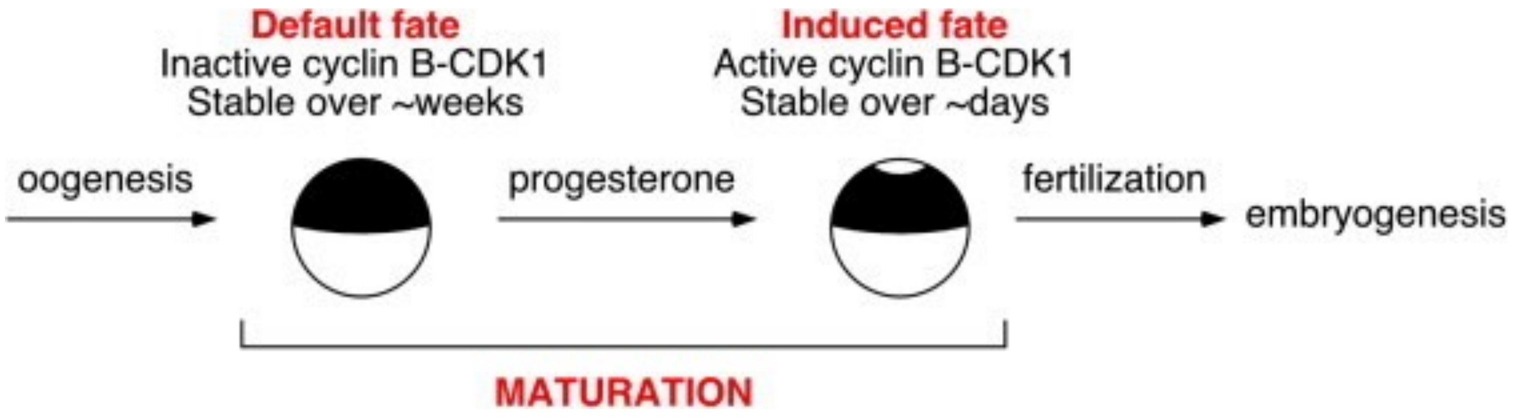


Oocyte in *Xenopus* maturation is a model for cell fate induction



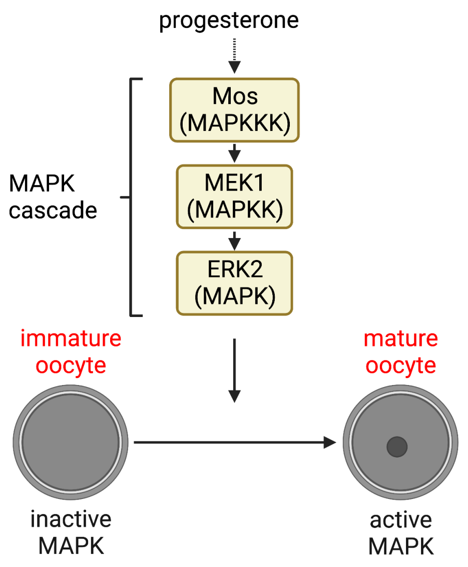
Ferrell JE Jr. Xenopus oocyte maturation: new lessons from a good egg. Bioessays. 1999

Xenopus oocyte maturation occurs following a transient increase in progesterone levels



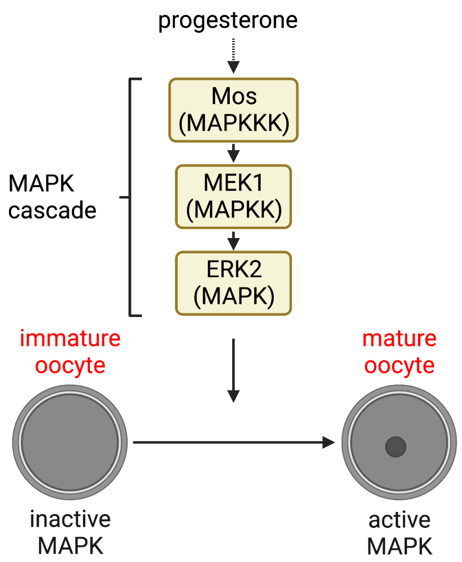
Ferrell JE Jr, Pomerening JR, Kim SY, Trunnell NB, Xiong W, Huang CY, Machleder EM. Simple, realistic models of complex biological processes: positive feedback and bistability in a cell fate switch and a cell cycle oscillator. FEBS Lett. 2009

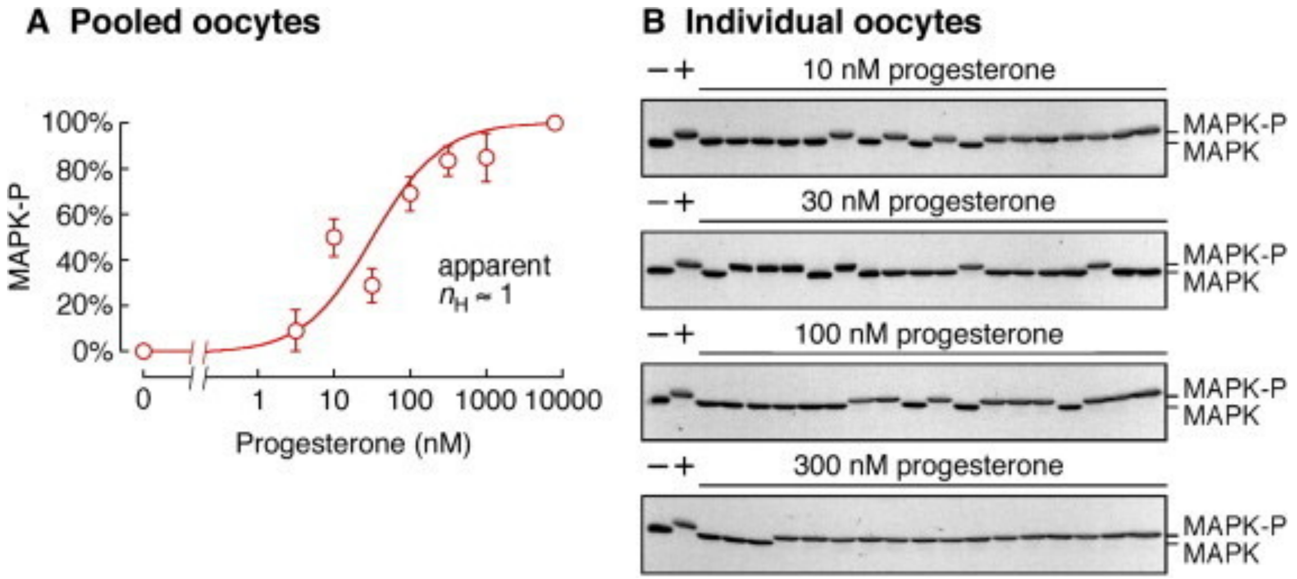
Xenopus oocyte maturation is controlled by activation of the MAP pathway



Adapted from Ferrell, Systems Biology of Cell Signaling, 2022

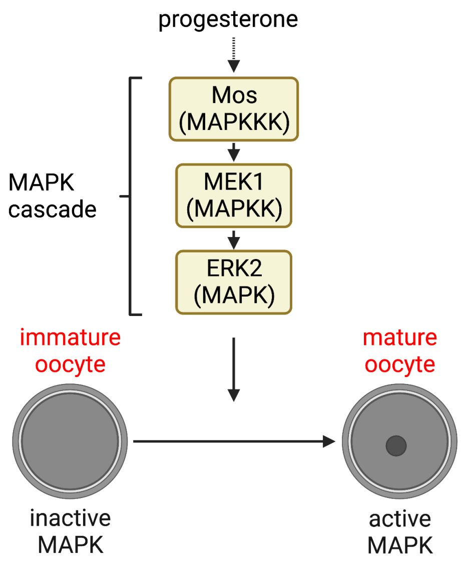
*A*ctivation of the MAPK pathway is all-or-none, which is puzzling in a linear signalling cascade

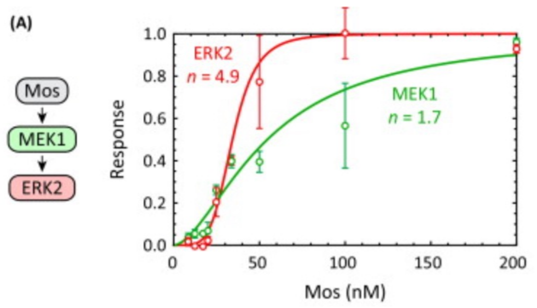




Ferrell JE Jr, Pomerening JR, Kim SY, Trunnell NB, Xiong W, Huang CY, Machleder EM. Simple, realistic models of complex biological processes: positive feedback and bistability in a cell fate switch and a cell cycle oscillator. FEBS Lett. 2009

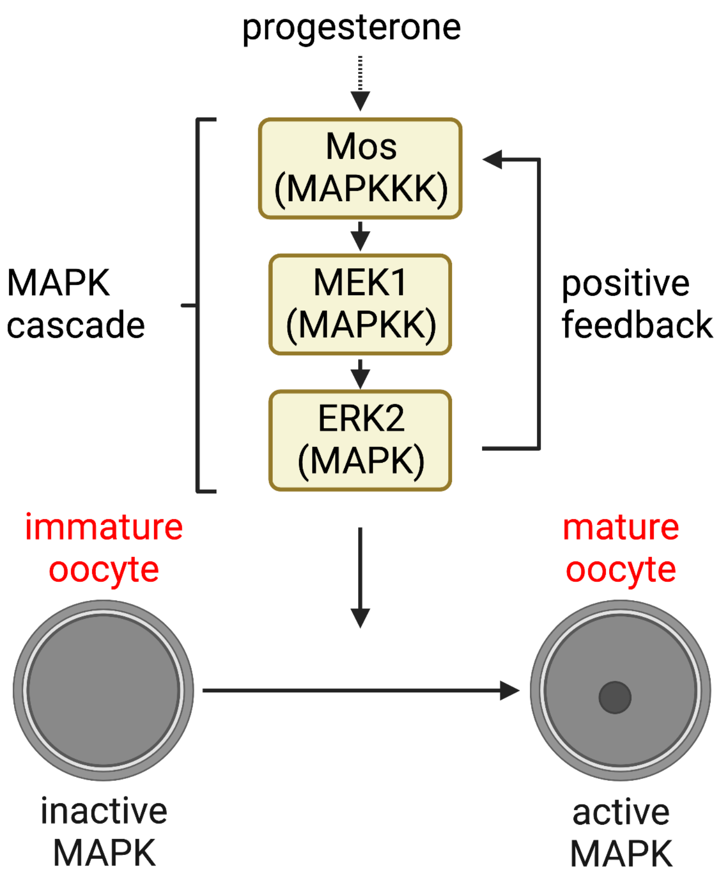
Activation in the MAPK pathway is highly cooperative

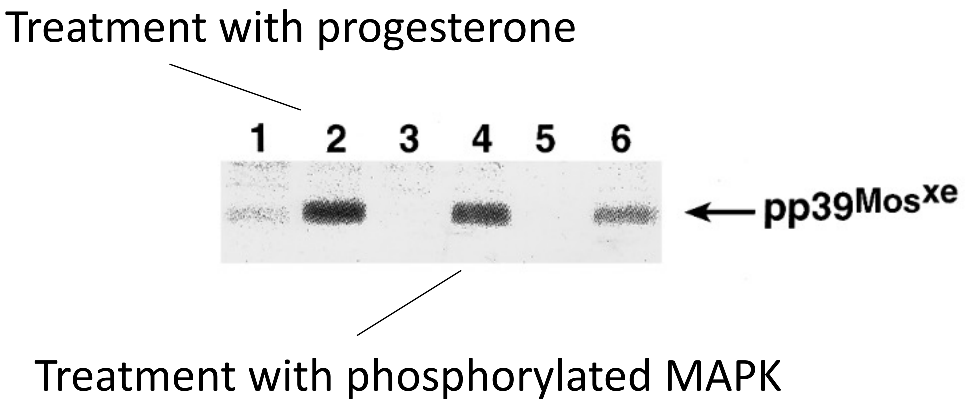




Ferrell and Ha, Trends Biochem. Sci. 2014

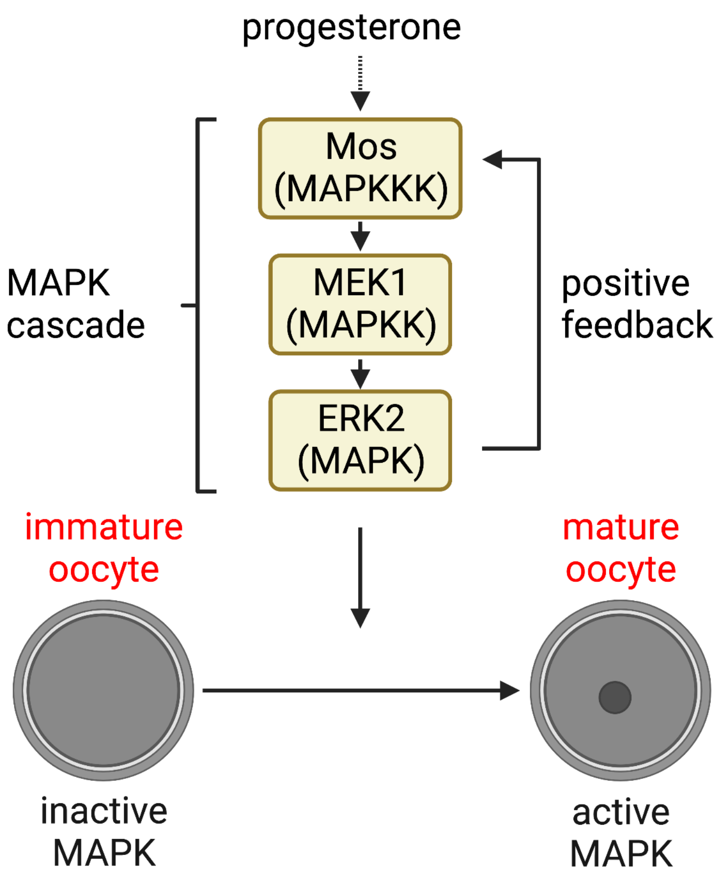
Activation of the MAPK cascade increases the accumulation of Mos2, resulting in positive feedback

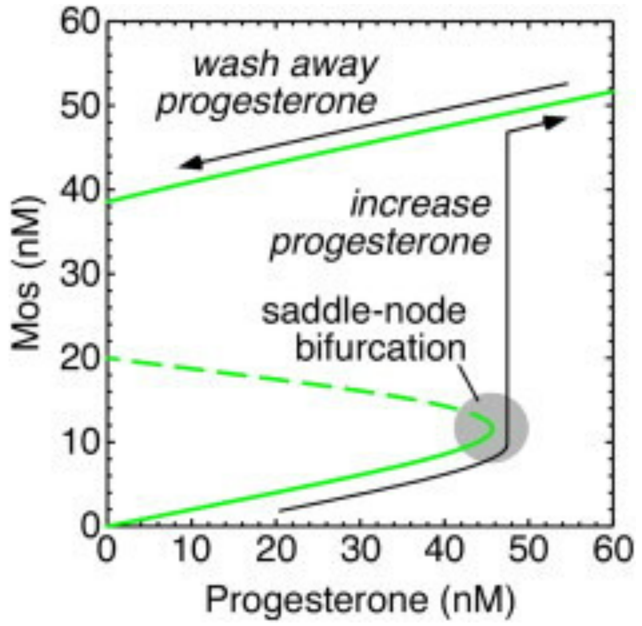




Matten WT, Copeland TD, Ahn NG, Vande Woude GF. Positive feedback between MAP kinase and Mos during Xenopus oocyte maturation. Dev Biol. 1996

Coopertive dynamics and positive feedback result in a bistable switch with irreversible activation



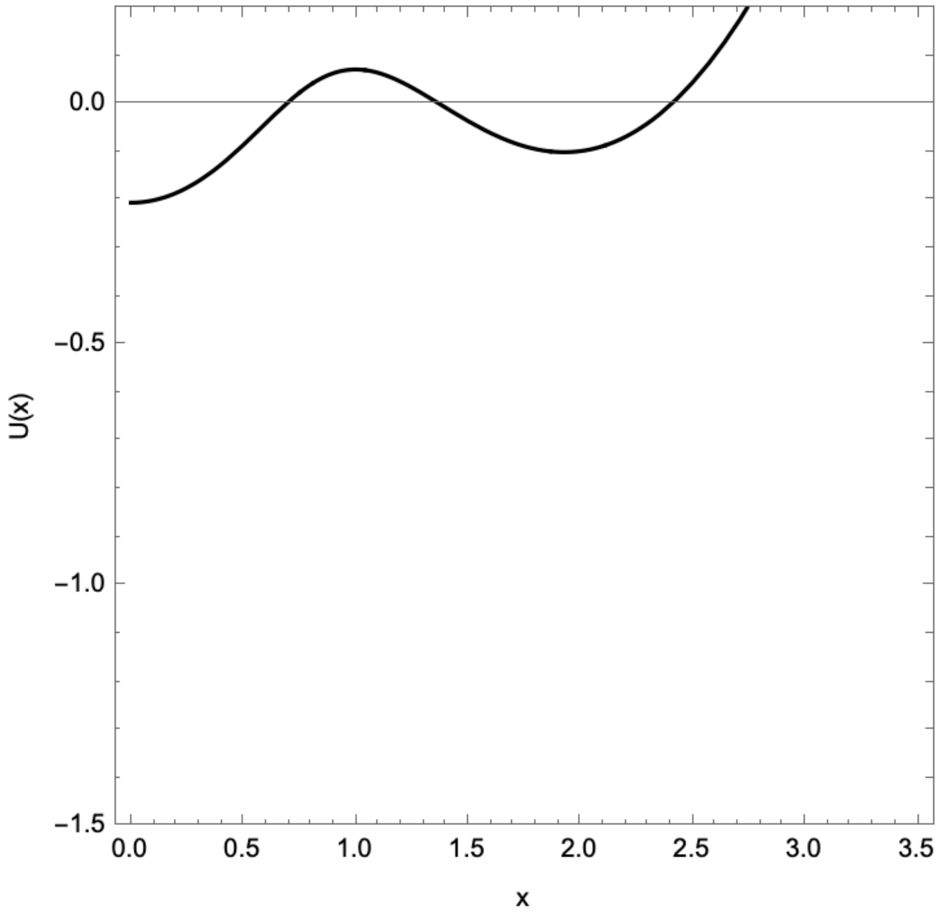


Ferrell JE Jr, Pomerening JR, Kim SY, Trunnell NB, Xiong W, Huang CY, Machleder EM. Simple, realistic models of complex biological processes: positive feedback and bistability in a cell fate switch and a cell cycle oscillator. FEBS Lett. 2009

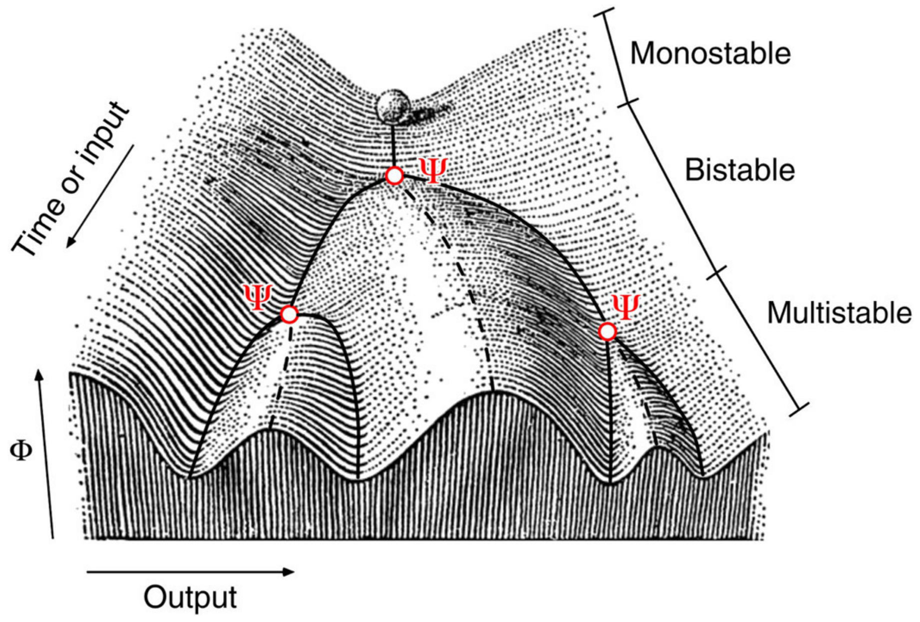
Interim summary

- Positive feedback can slow down responses
- Cooperative positive feedback generates multistability
- A simple (1d) circuit with cooperative positive feedback can act as a memory unit for transient stimulus

The bifurcation can be captured by changes to a potential landscape

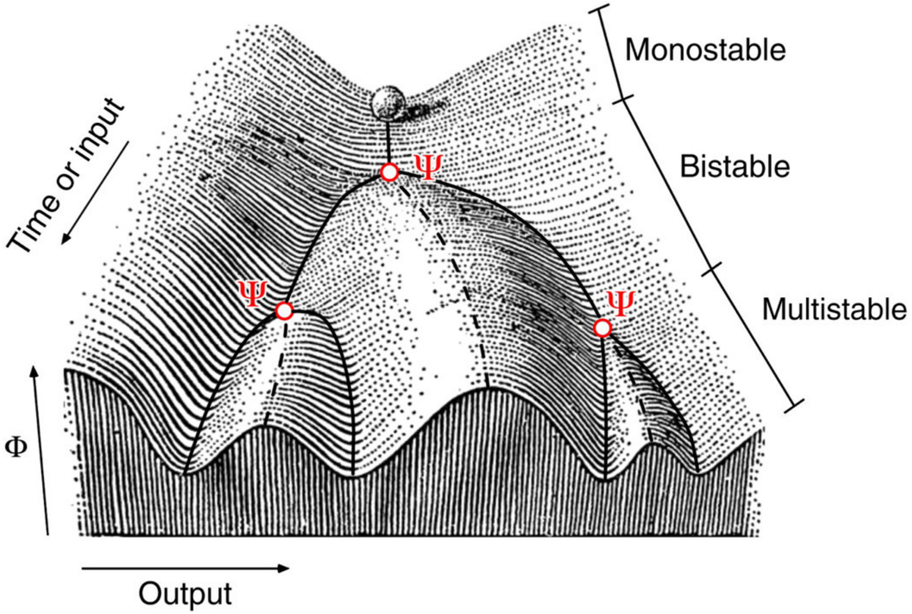


A classic and common conceptual framework / metaphor for cellular differentiation is the Waddington landscape



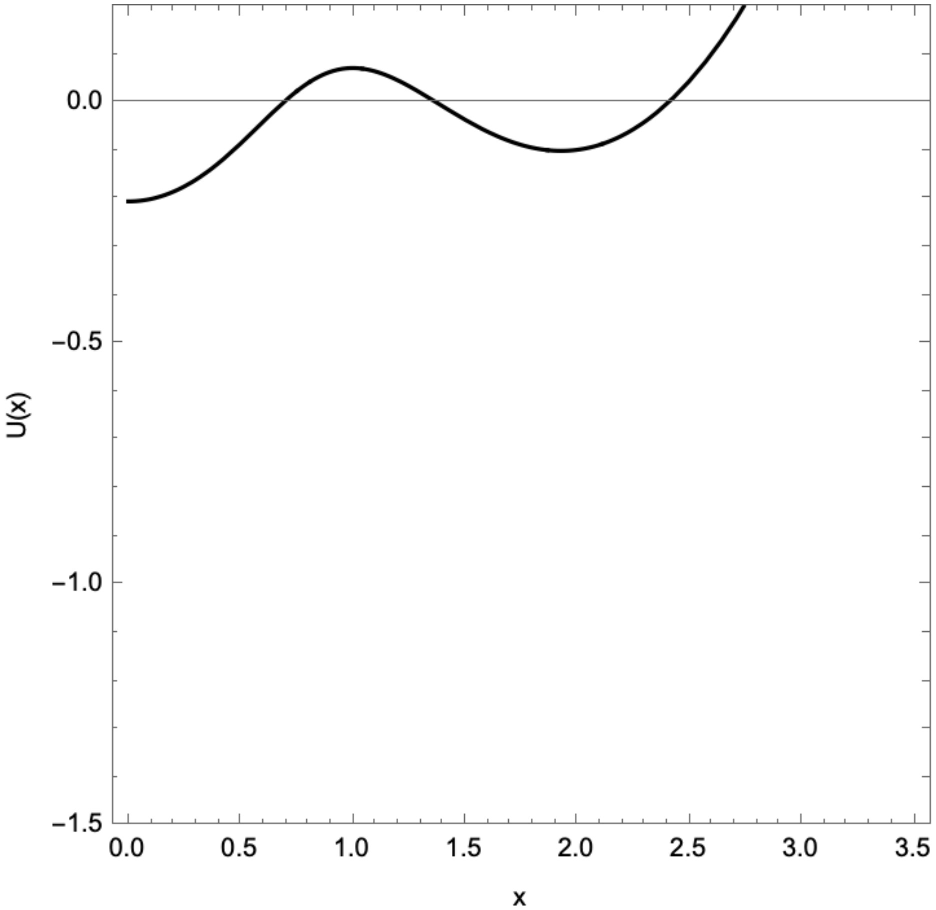
Ferrell JE Jr. Bistability, bifurcations, and Waddington's epigenetic landscape. Curr Biol. 2012

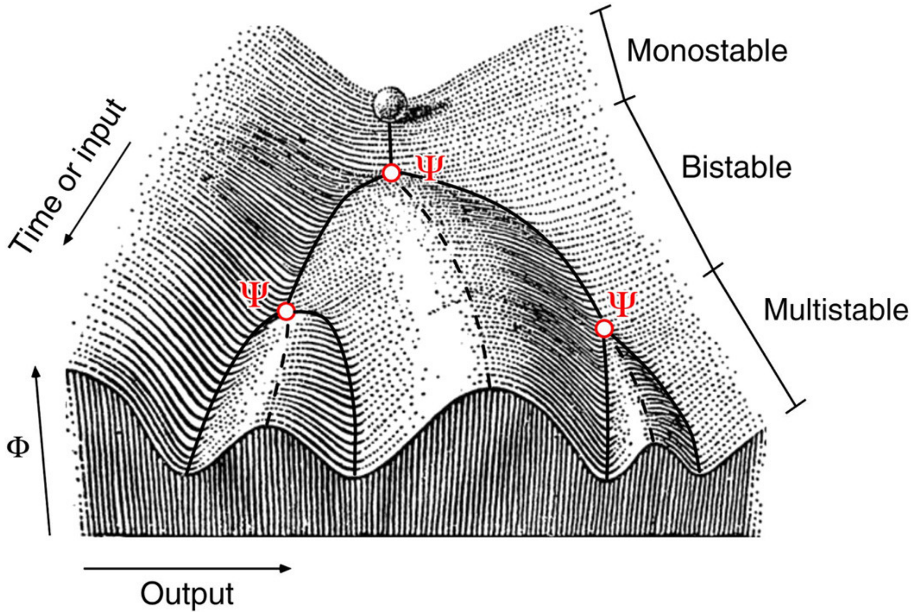
From the perspective of dynamical systems, we can think of the Waddington landscape as changes in the potential landscape with time/input



Ferrell JE Jr. Bistability, bifurcations, and Waddington's epigenetic landscape. Curr Biol. 2012

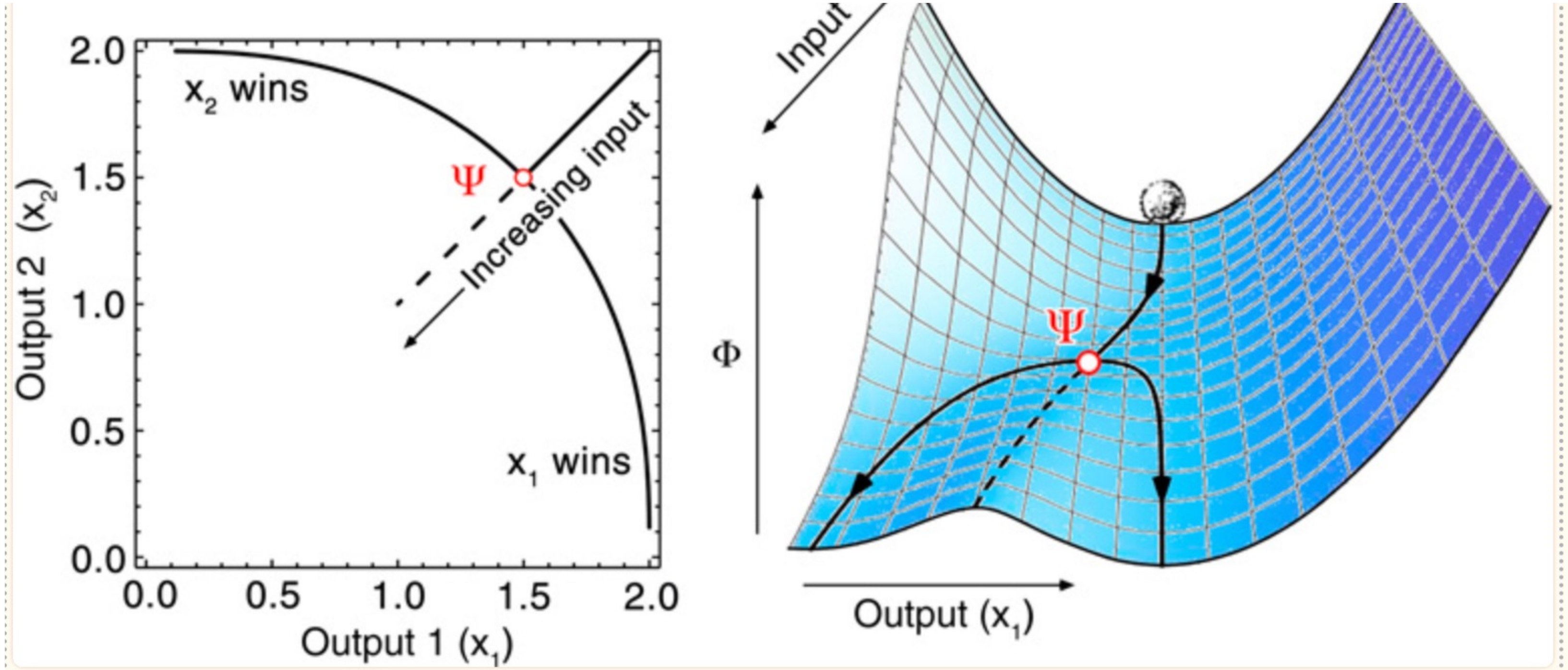
Cell-fate induction through saddle-node bifurcations **does not** correspond to the bifurcations of the Waddington landscape





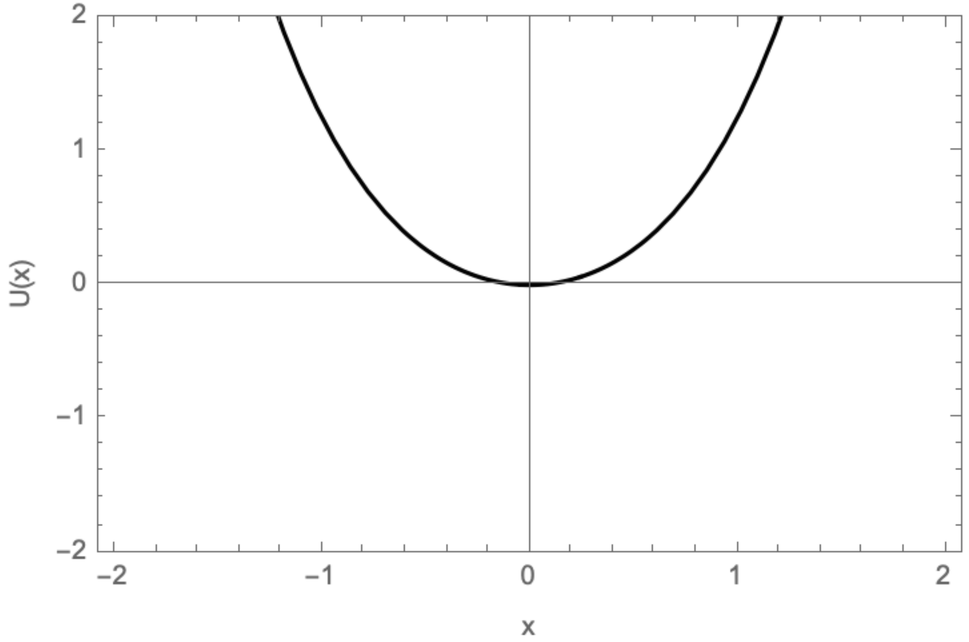
Ferrell JE Jr. Bistability, bifurcations, and Waddington's epigenetic landscape. Curr Biol. 2012

Bifurcations as in the Waddington lanscape correspond to pitchfork bifurcations, which rely on symmetry and are commonly observed in physics

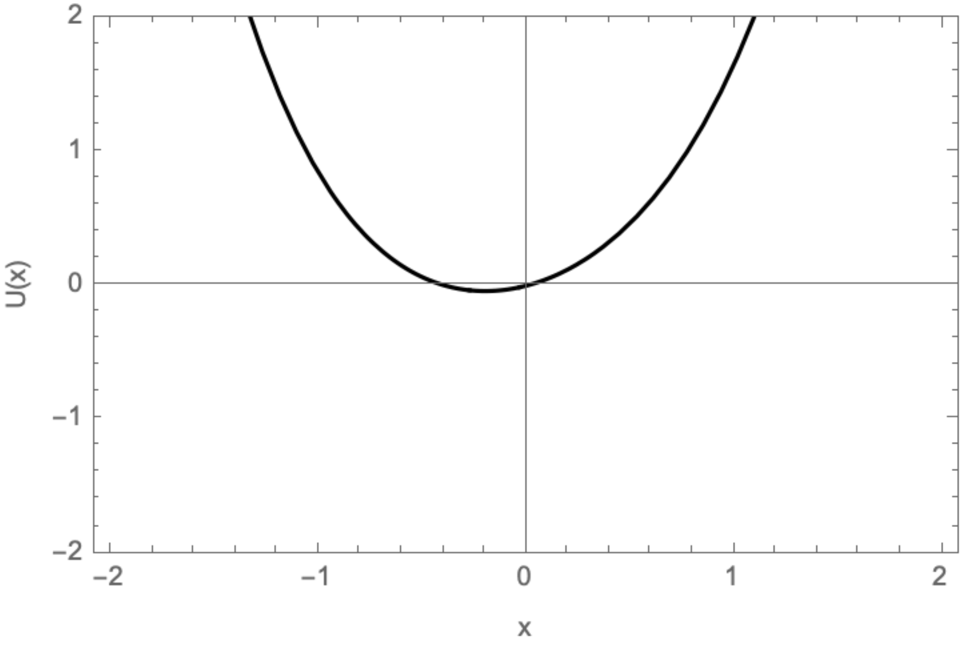


Ferrell JE Jr. Bistability, bifurcations, and Waddington's epigenetic landscape. Curr Biol. 2012

Supercritical pitchfork bifurcation is given by the normal form $\dot{x} = rx - x^3$



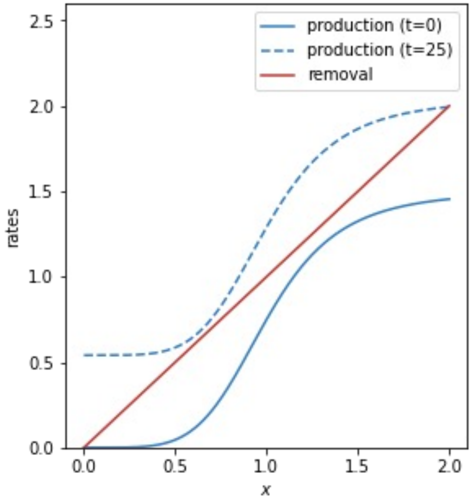
Slight disturbances to symmetry transform a pitchfork bifurcation to a saddle-node bifurcation

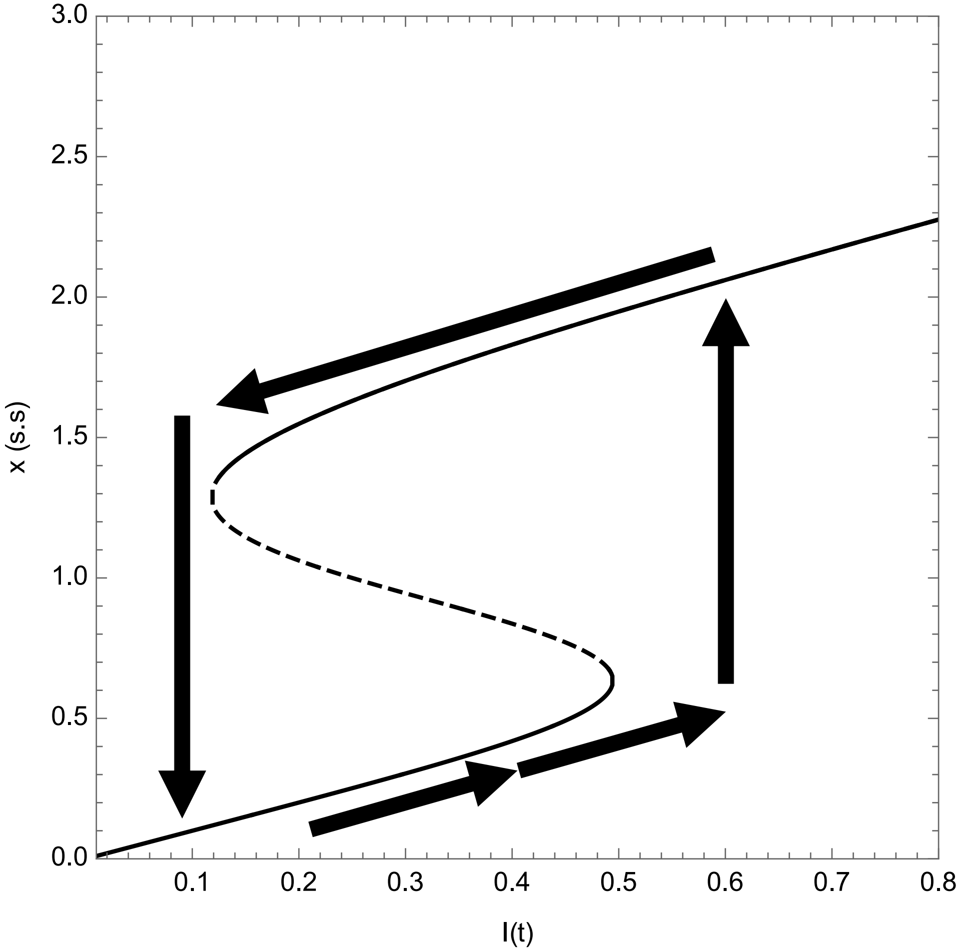


Interim summary

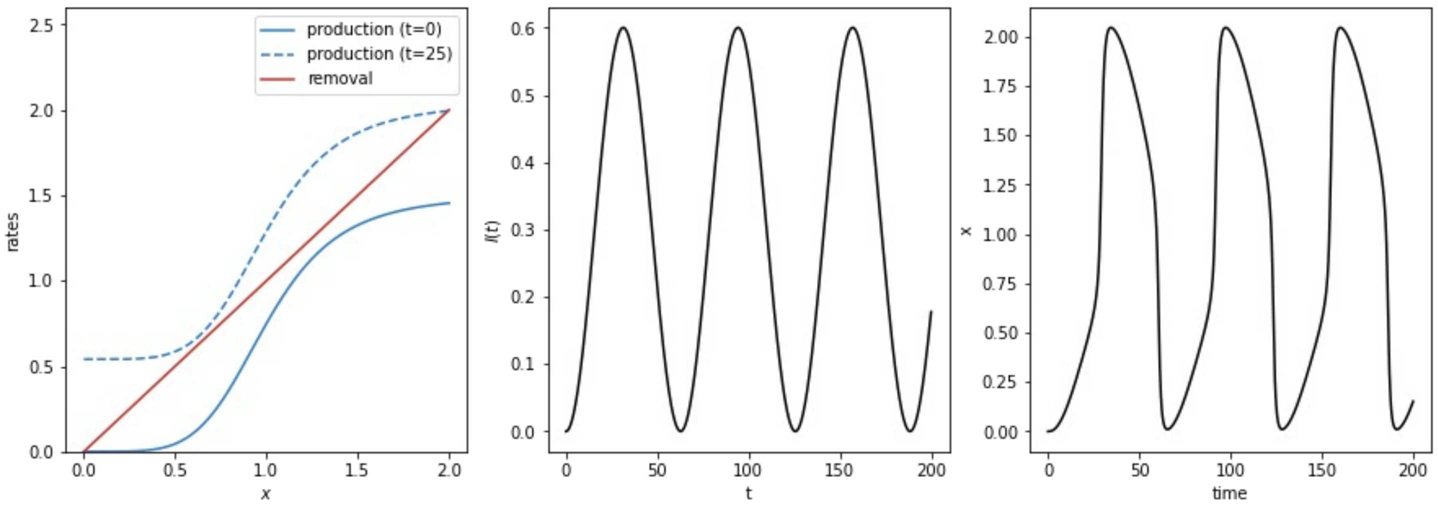
- Cell-fate induction involves a saddle node bifurcation
  - dynamics are captured by the normal form $\dot{x} = x^2 - r$ (where *r* is the distance from bifurcation)
- Potential landscape: disappearance of a valley
- The classic Waddington landscape metaphore involves splitting of valleys, more appropriate to supercritical pitchfork bifurcation
  - Dynamics are captured by $\dot{x} = rx - x^3$
- Pitchfork bifurcation requires symmetry and is structural unstable, saddle node is generic for genetic networks

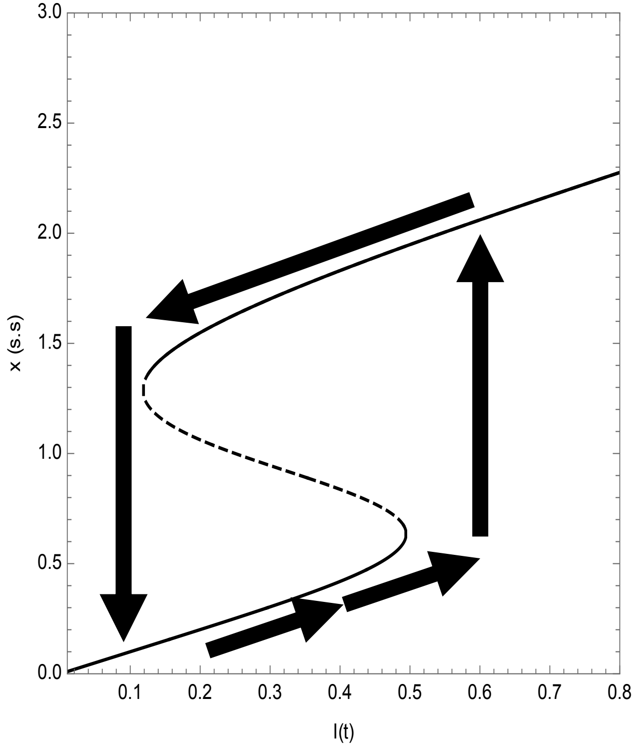
In addition to the irreversible, bistable switch, a reversible hysteretic switch is also a possible regime of the system





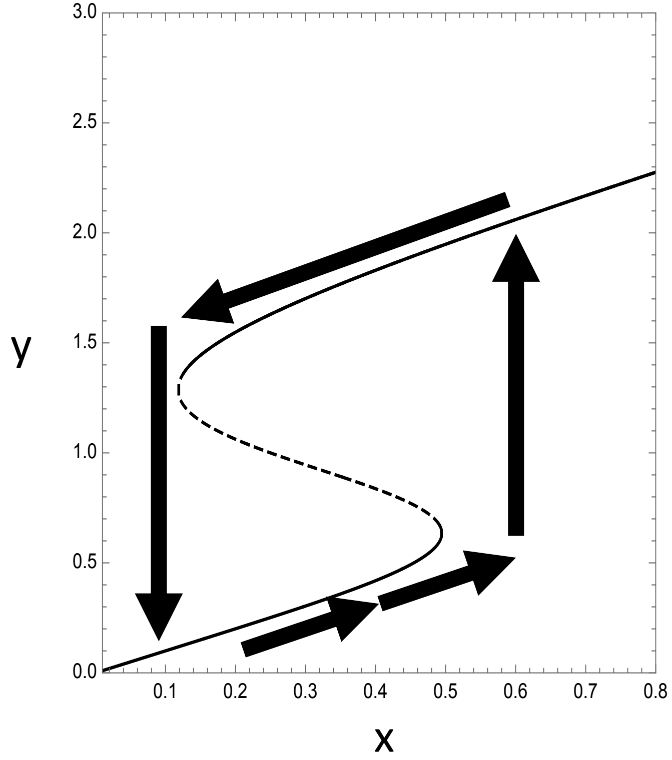
Hysteretic systems have "saw-tooth" dynamics





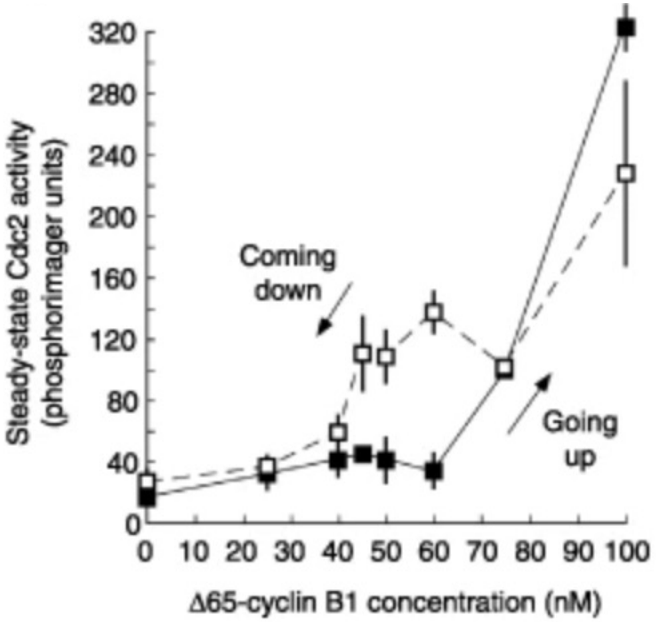
We can imagine, possibly, an oscillator based on hysteretic dynamics

- What if instead of an input, we consider the control parameter as a dynamic variable?
- We now denote this variable as *x* and consider the "output" to be *y*
- *y* is hysteretic and there is negative feedback with *x*
- When *y* is low, *x* is induced, and drives *y* to increase
- When *y* is high, *x* is inhibited and *y* returns to baseline



Oscillatory dynamics of cell division dominates the early development of *Xenopus*

Cyclins, which regulate cell cycle transitions in the *Xenopus* embryo, show hysteretic dynamics



Pomerening et al. Nat. Cell Biology 2003

A simple model that combines positive and negative feedback captures dynamics

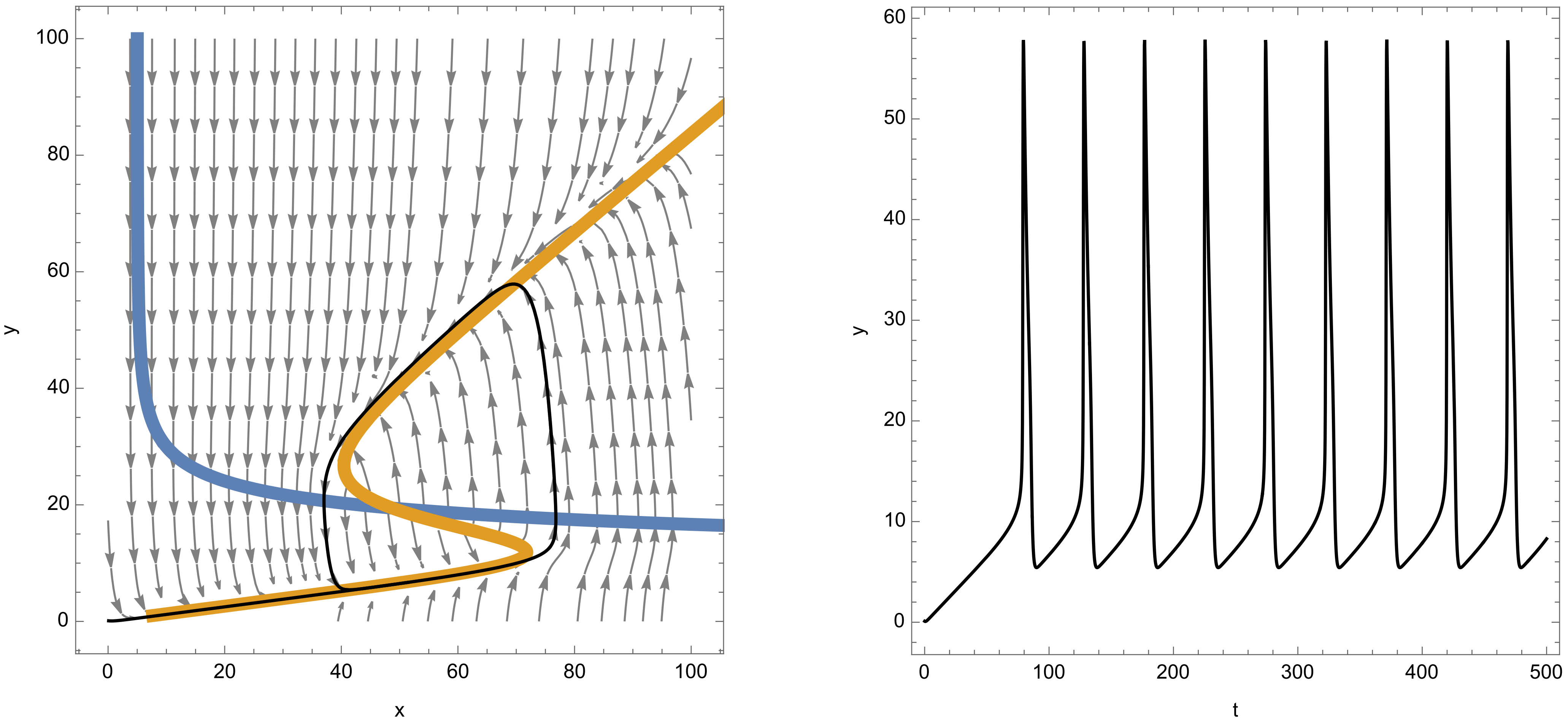
accumulation — switch off

$$\dot{x} = \alpha_1 - \gamma_1 x \frac{y^5}{k_1^5 + y^5}$$

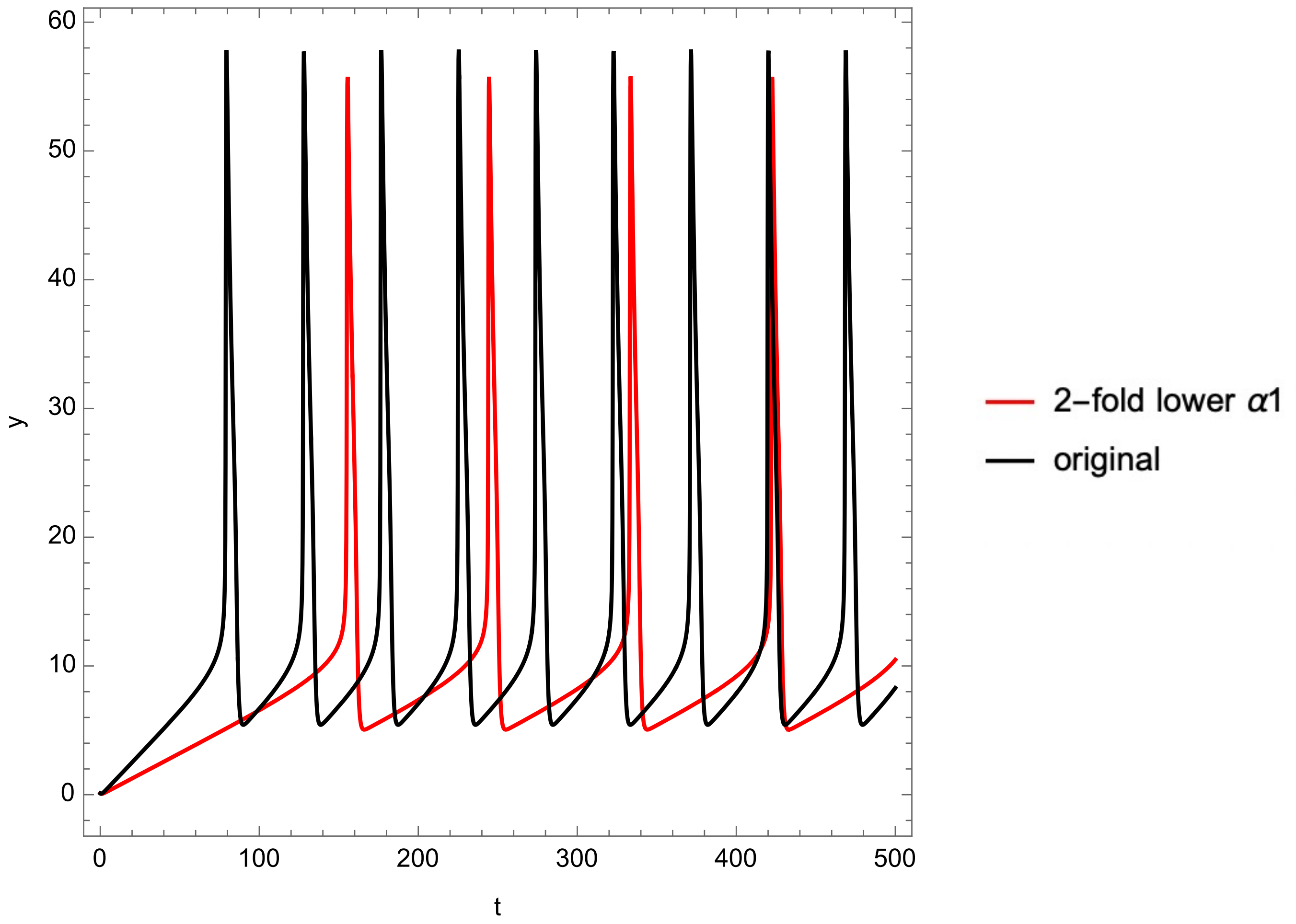
positive feedback — negative feedback

$$\dot{y} = \alpha_2 \left(a + \frac{y^5}{k_2^5 + y^5} \right) (x - y) - \gamma_2 y$$

Model implements a relaxation oscillator

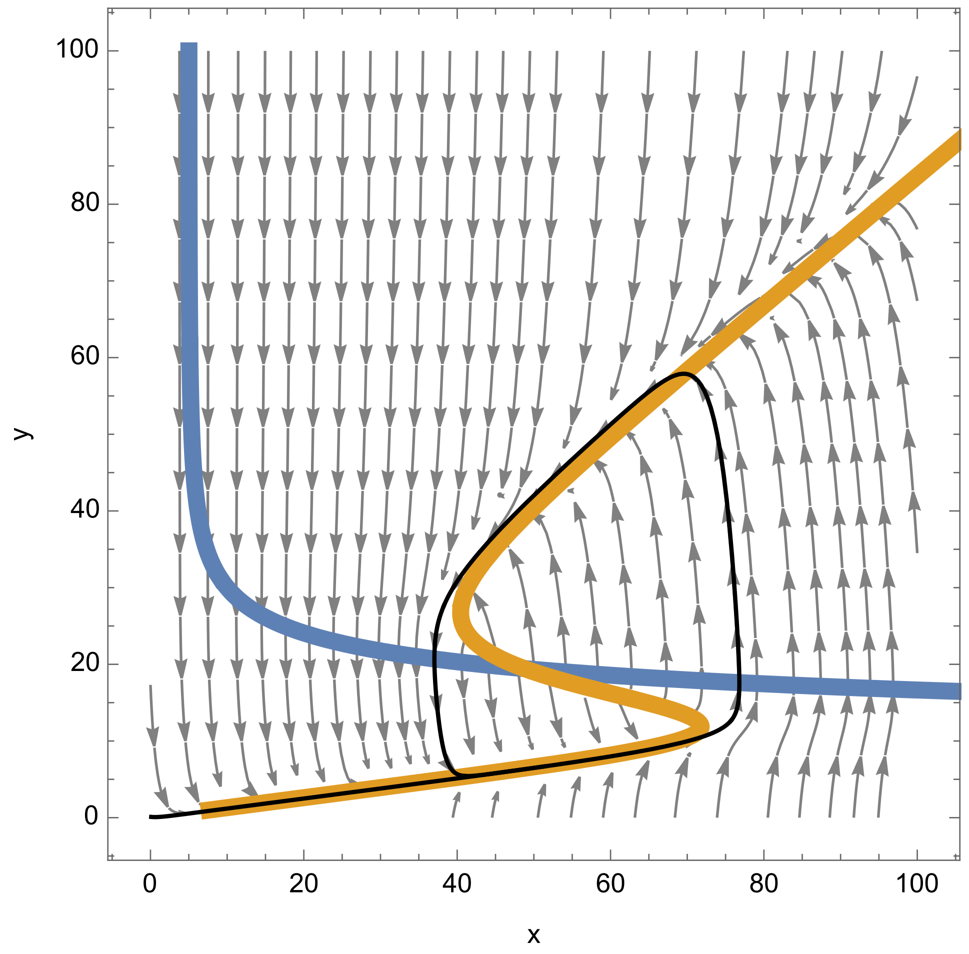


The period of the oscillations can be adjusted by adjusting the production rate of x



Parametrized model has a single unstable fixed point

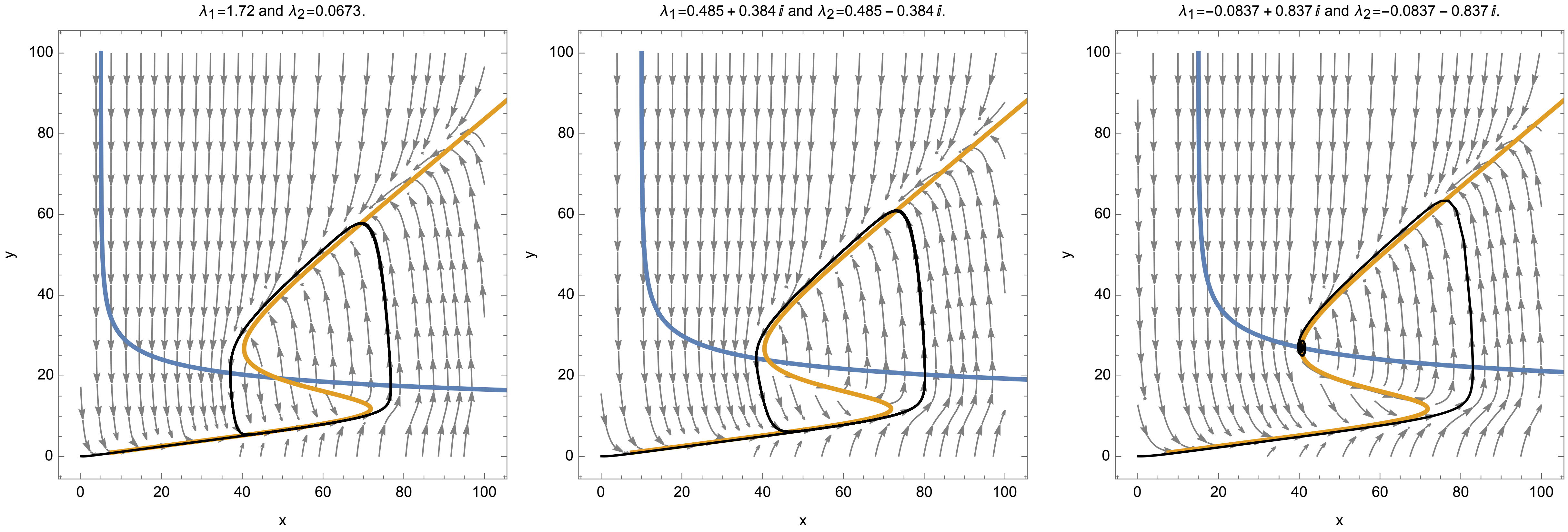
- Nullclines intersect at a single point, the Jacobian has positive real eigenvalues
- Fixed point is therefore unstable



Existence of limit cycle can be inferred from Poincaré–Bendixson theorem

- **If the dynamics on a plane are confined to a closed region without a fixed point, they will converge to a limit cycle**
- Highly applicable to biology, as dynamics are confined to positive number of molecules, and cannot diverge to infinity

Stability depends on model parameters, with a Hopf bifurcation occuring as parameters change



Hopf bifurcation is a simple two dimensional bifurcation where a pair of eigenvalues crosses the real axis together

- Supercritical hopf bifurcation captures a stable fixed point losing stability and becoming a limit cycle
- Normal form (in polar coordinates) $\dot{r} = (\mu - r^2)r, \dot{\theta} = \omega$
  - μ is distance from bifurcation
  - ω is angular velocity

Summary

- Positive feedback destabilizes fixed points and can generate bistability
- Positive feedback allows the long-term stabilization of cell fate after induction
- At the basis of this is a saddle-node bifurcation which creates new fixed points, and may result in an irreversible transition
- Circuits with positive feedback can become hysteretic
- The combination of such hysteretic circuits with negative feedback can result in oscillations with adjustable period