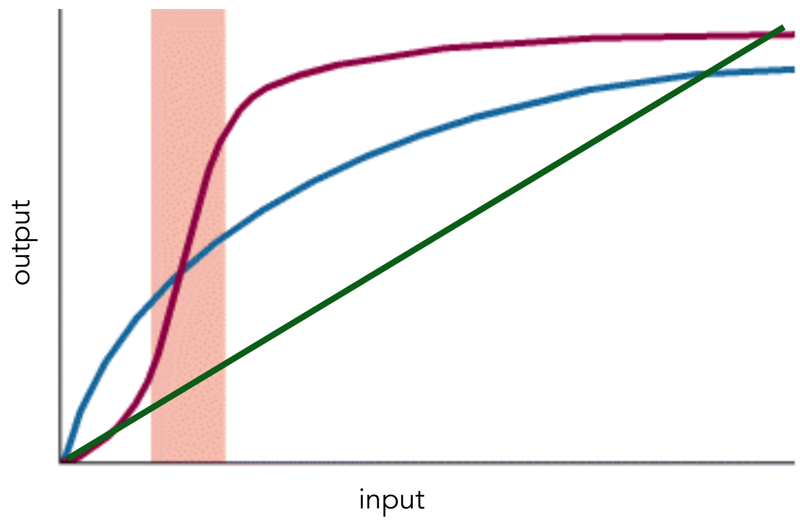
Concepts from non-linear dynamics are used to understand the behaviour of biological systems

The dynamics of biochemical networks are non-linear

Non-linear : the magnitude of an output is not proportionally related to the magnitude of the input



sigmoidal input-output curve

hyperbolic input-output curve

linear input-output curve

There are two ways we specify a dynamical system

System parameters specify the properties of the system, eg temperature, kinetic rates for reacting species such as the V_{max} and K_m for enzyme reactions, system volume

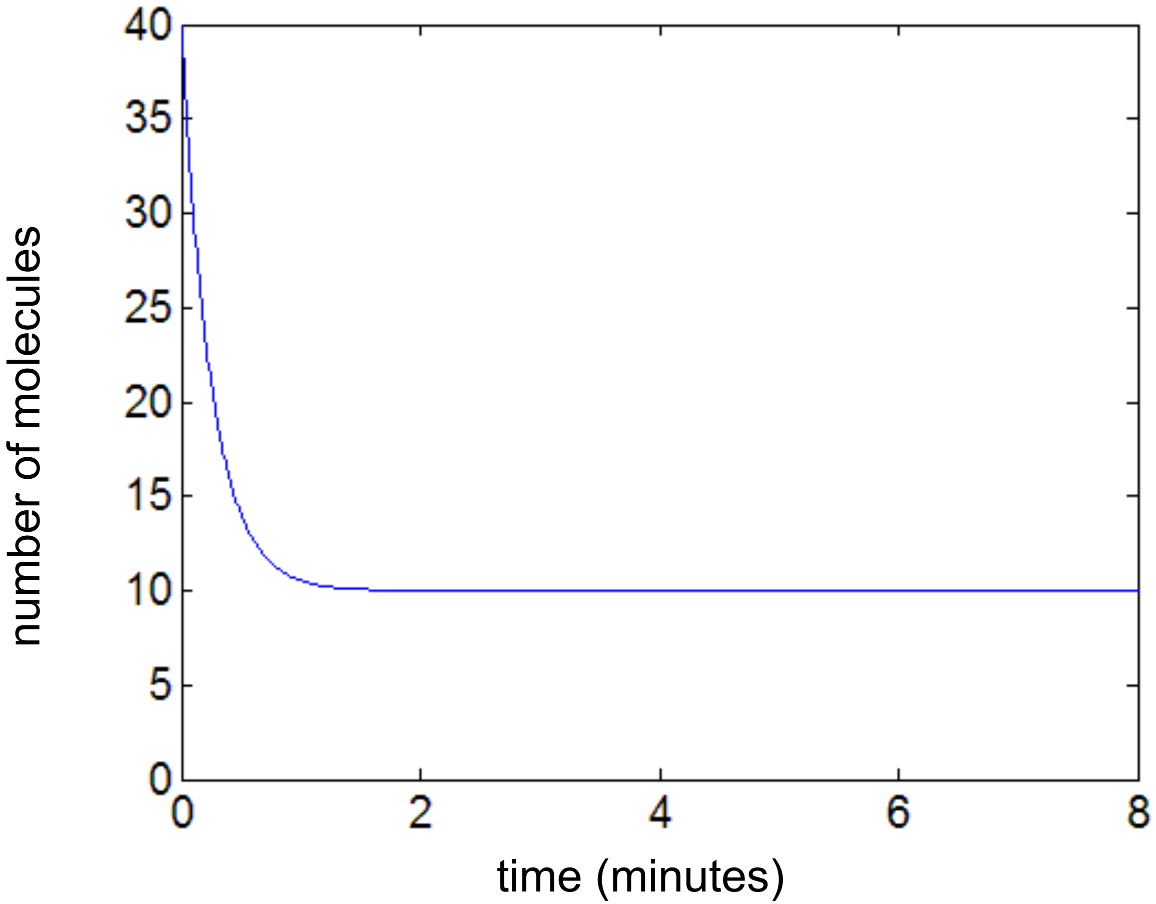
Initial conditions specify the initial values of all components of the system that evolve with time, e.g. initial concentrations of all proteins in a biochemical network

Dynamical systems ultimately tend to attractors

After an initial transient, a dynamical system settles into a long-term behaviour that the system will maintain if undisturbed.

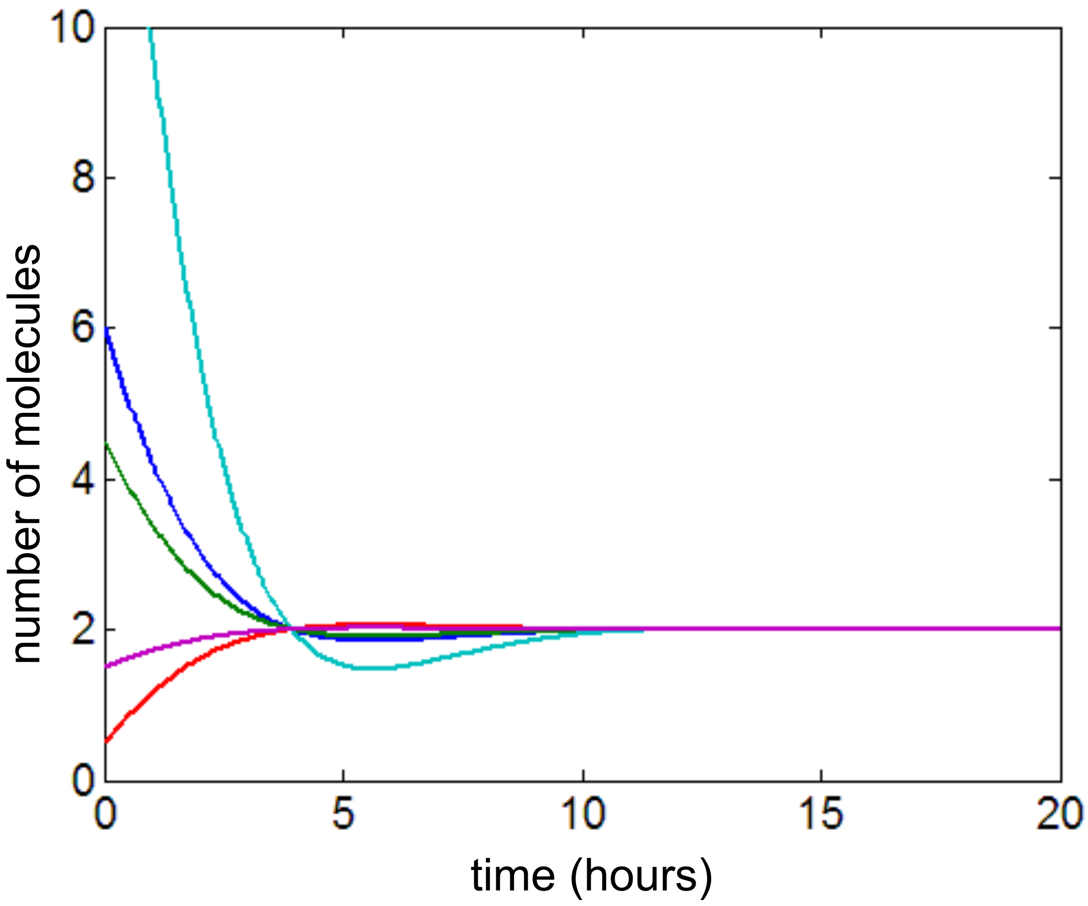
The system has reached an attractor.

e.g.



A steady-state attractor is a common one

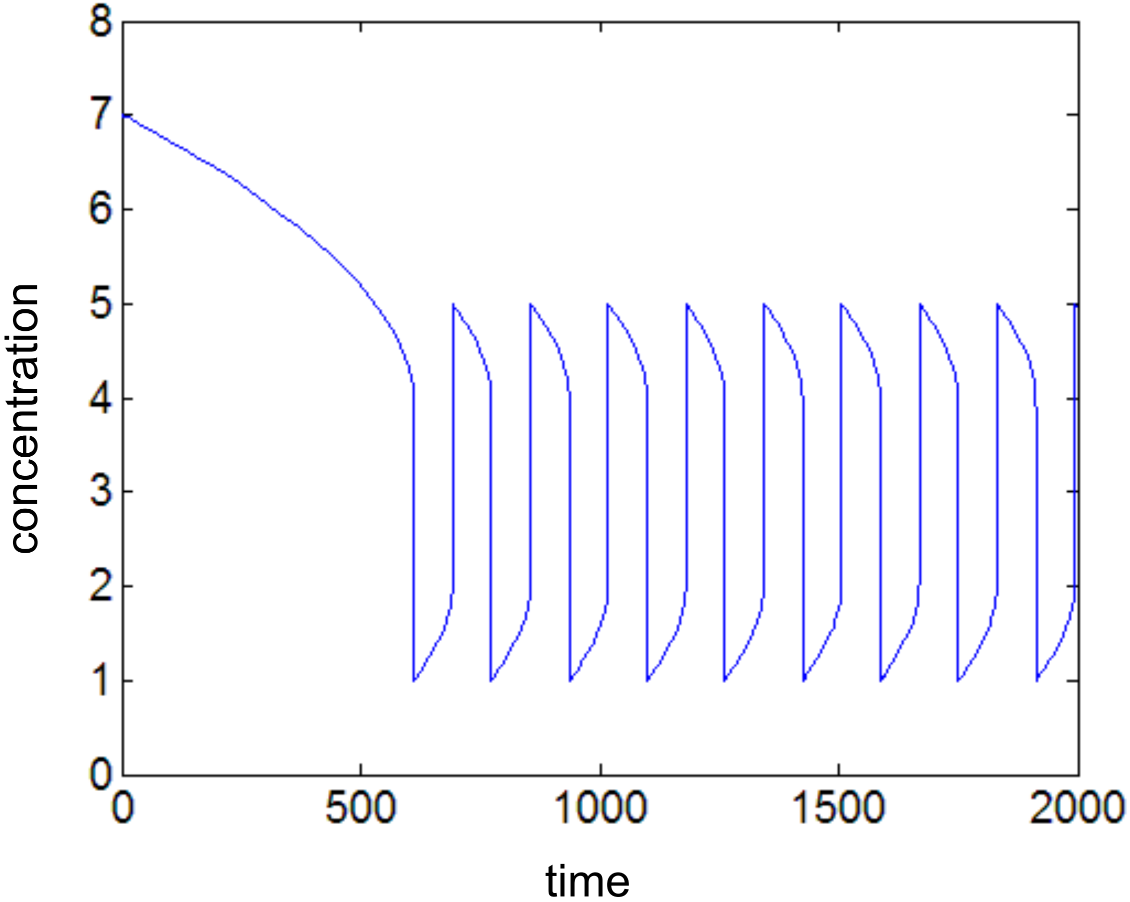
Components of the system eventually no longer change with time: they are *steady*.



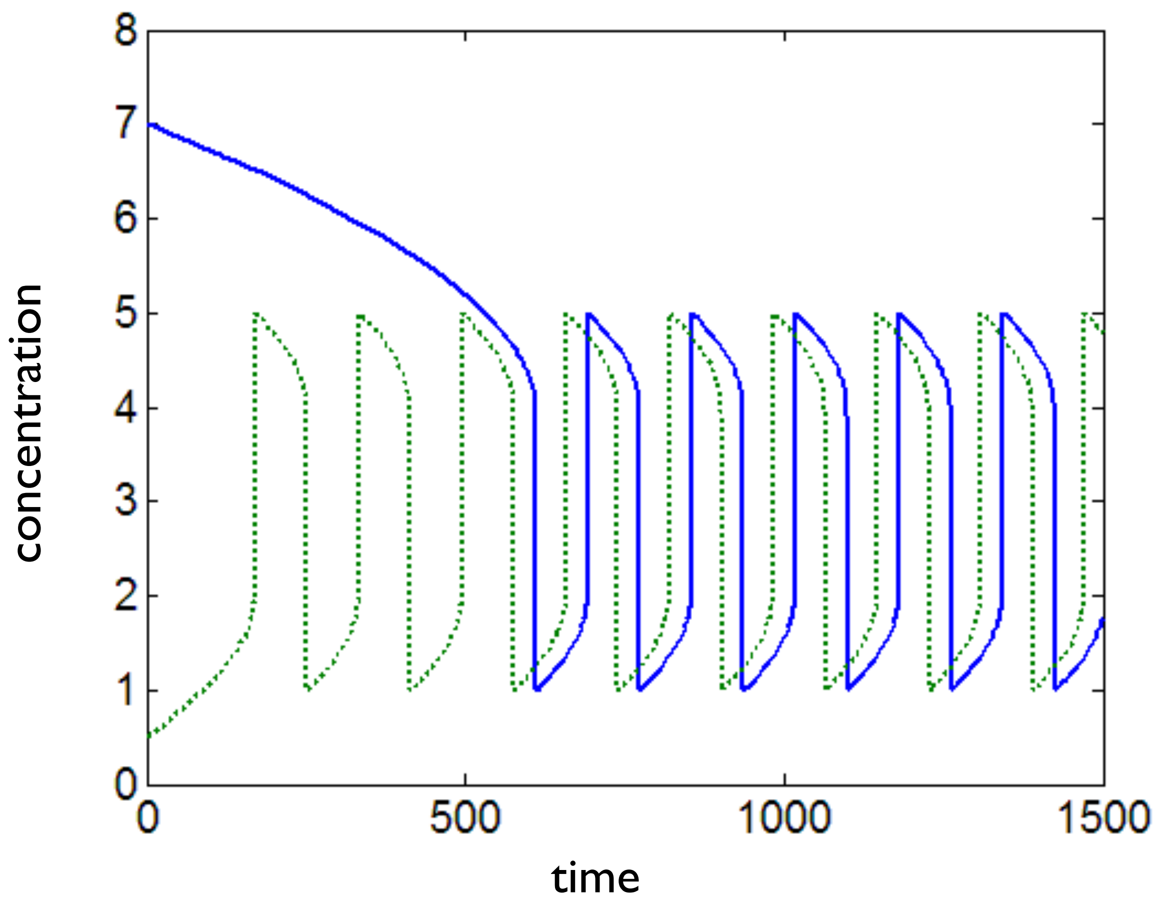
Different initial conditions give the same steady-state behaviour.

The components of a system oscillate at a limit cycle attractor

After some initial behaviour, the system eventually oscillates.



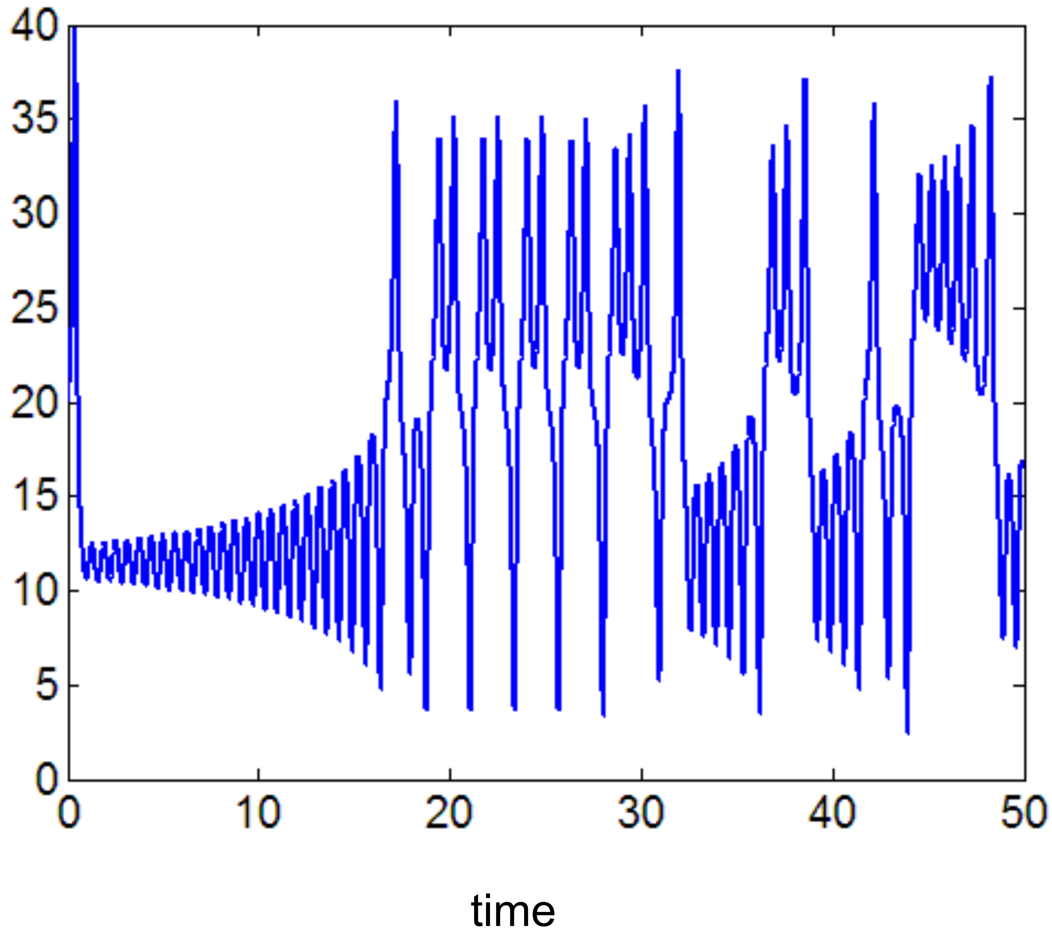
From different initial conditions, the system reaches the limit cycle and oscillates with the same frequency and amplitude.



The time taken to reach the limit cycle is different for different initial conditions.

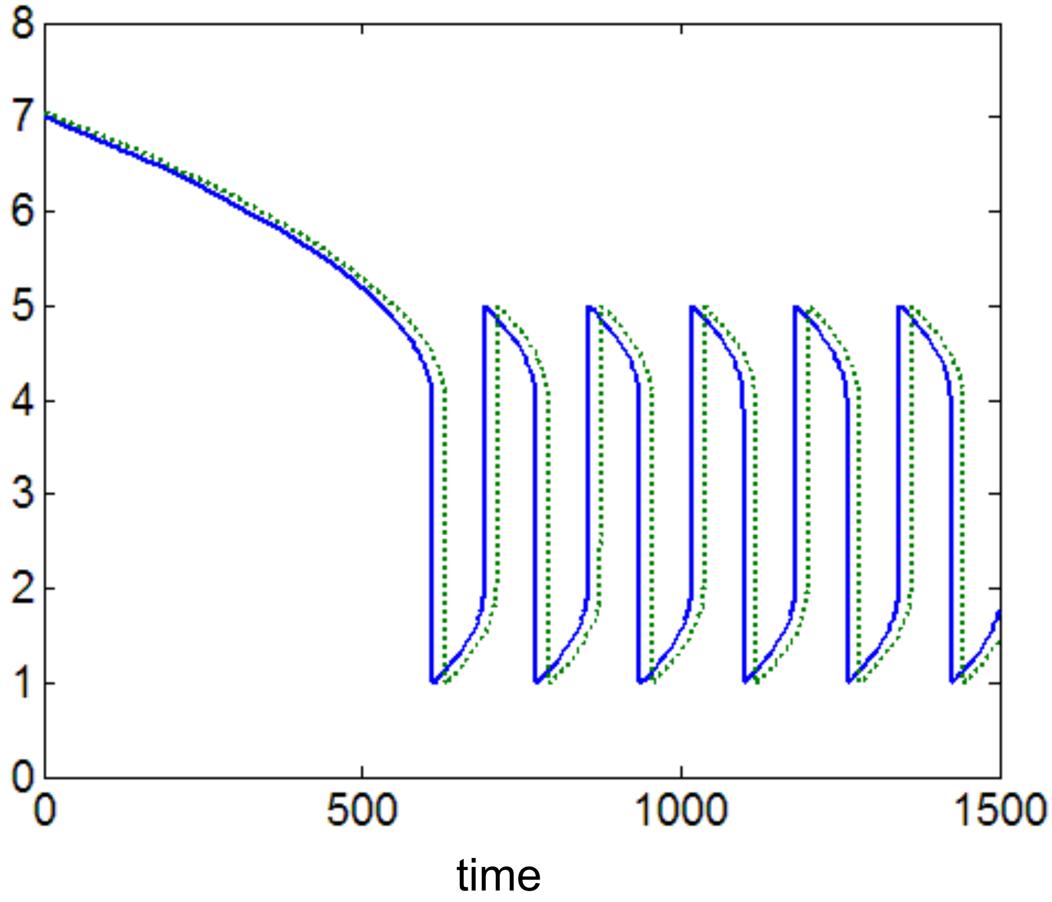
Strange attractors give chaotic dynamics

Chaos is aperiodic, long-term behaviour in a deterministic system that exhibits sensitive dependence on initial conditions.



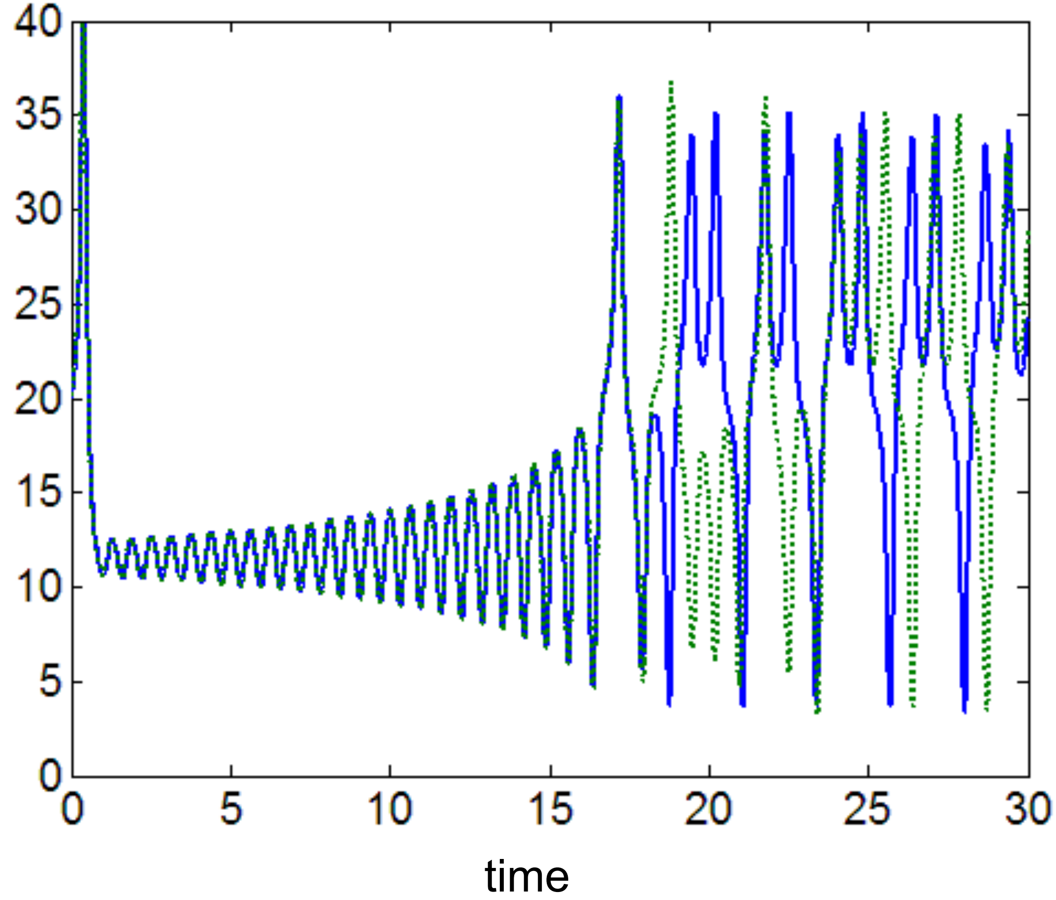
Aperiodic: an irregular oscillation that never exactly repeats

For a limit cycle, there is no sensitive dependence on initial conditions and the dynamics from two similar initial conditions remain closely related.



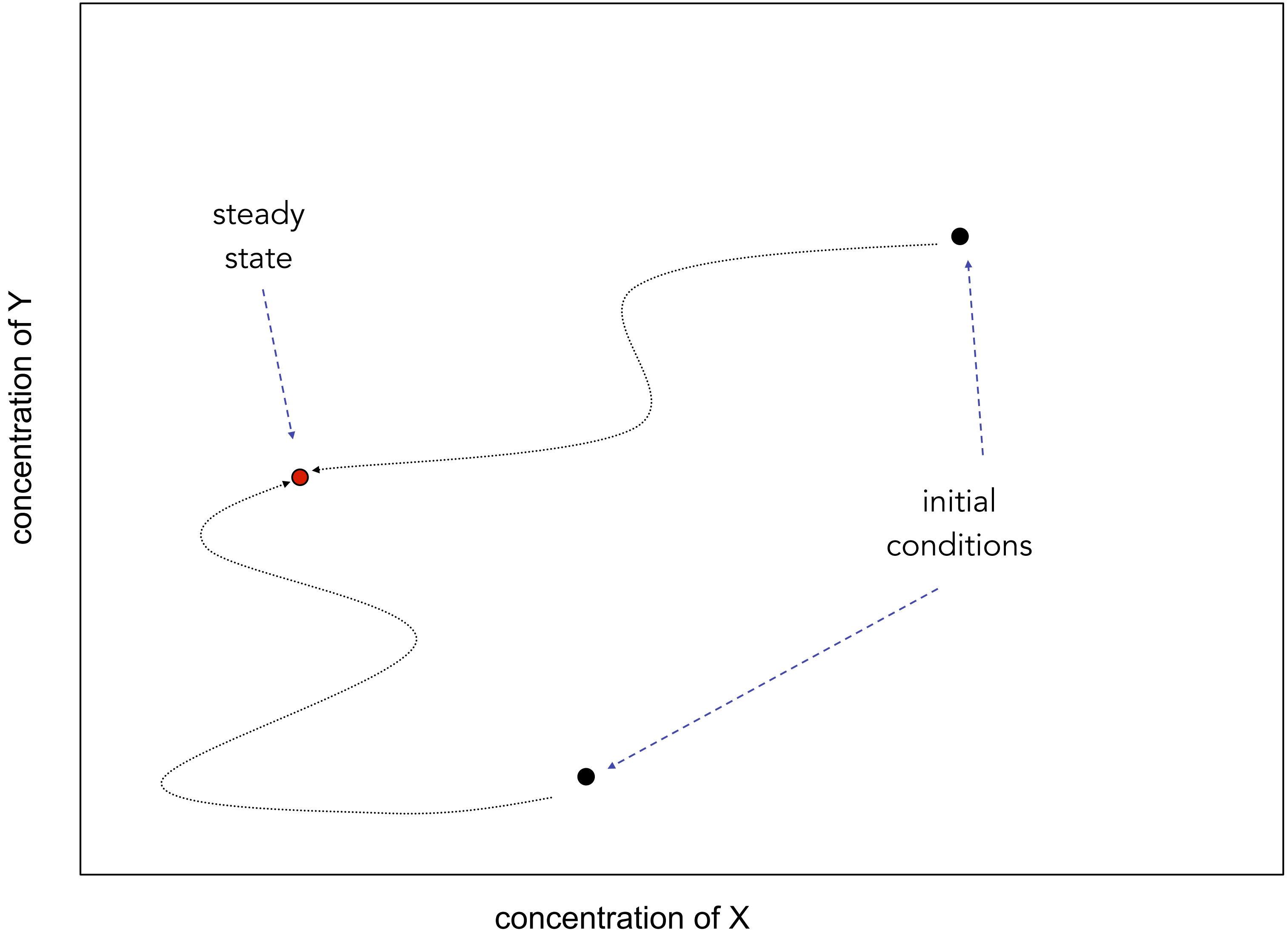
Neighbouring trajectories never substantially separate.

For a strange attractor, there is sensitive dependence on initial conditions, and the dynamics from two similar initial conditions become distinct.

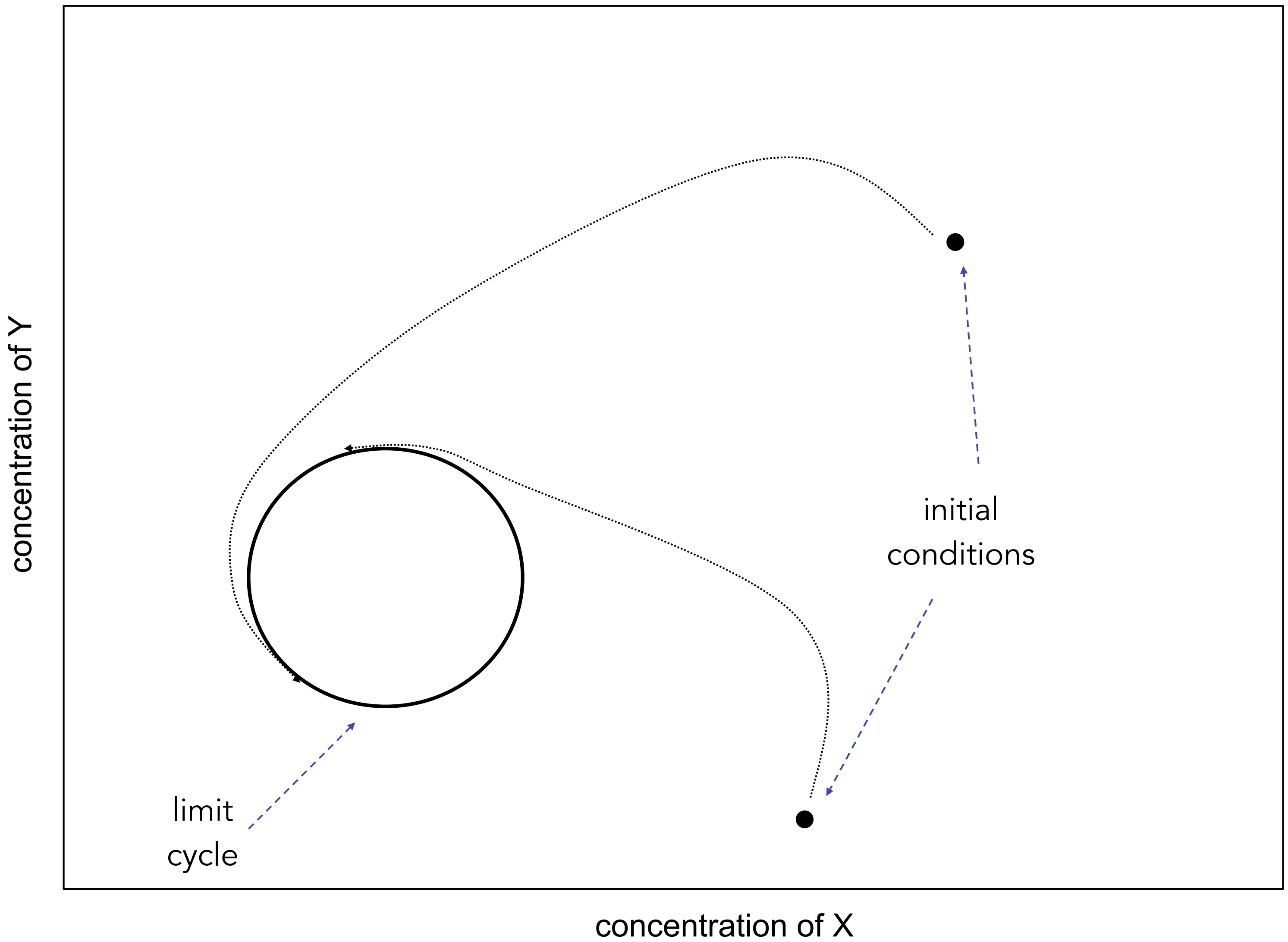


Neighbouring trajectories separate exponentially fast.

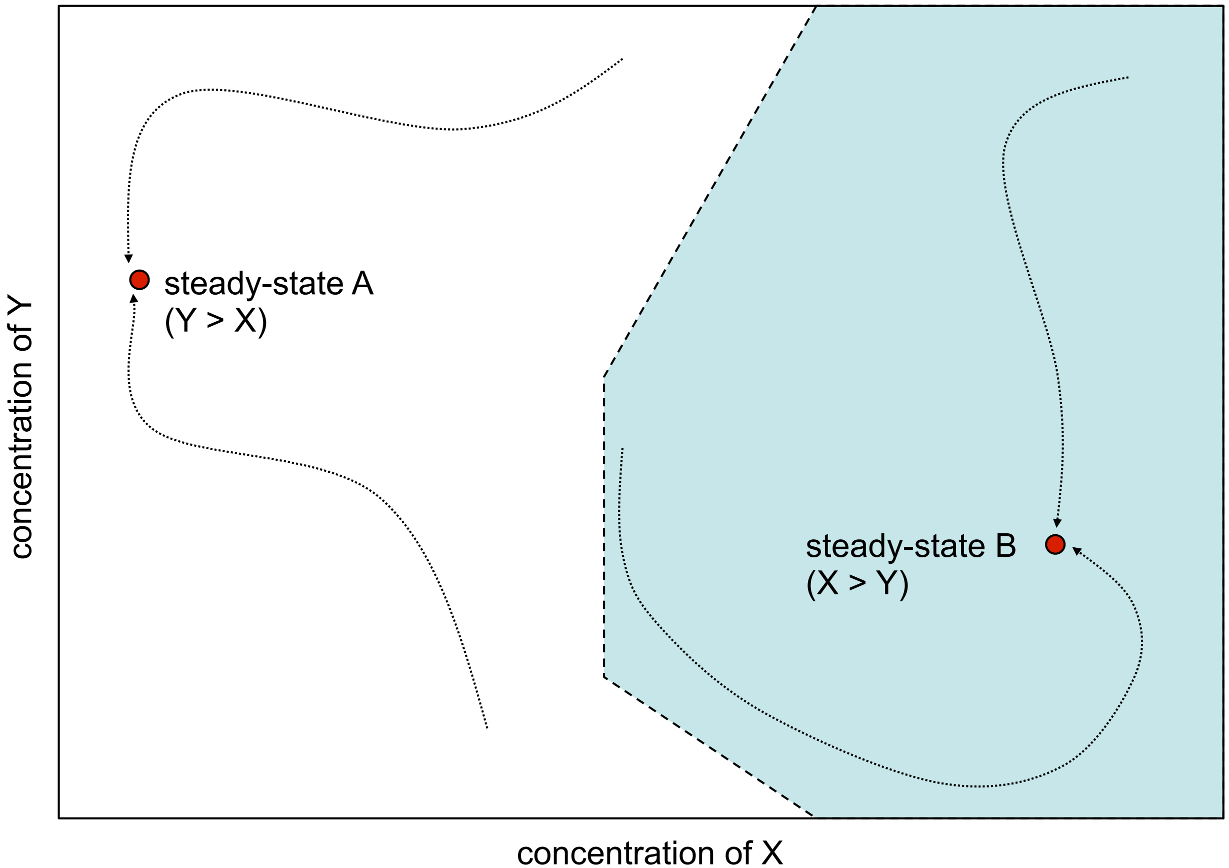
A phase diagram shows the dynamics of a system by plotting the concentration of one system component against another.



A limit cycle appears as a circle in the phase diagram.



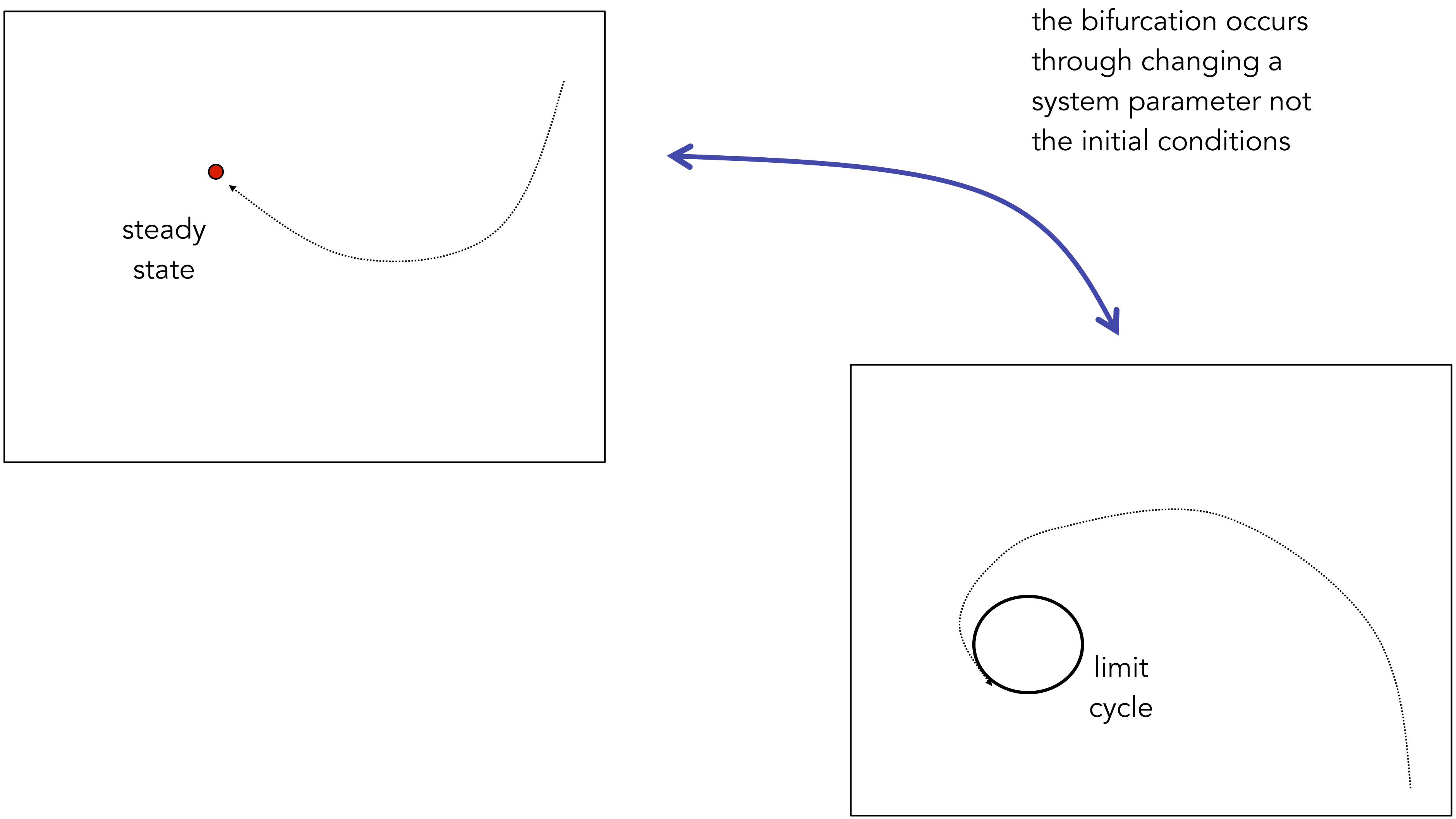
A bistable system has two steady-state attractors



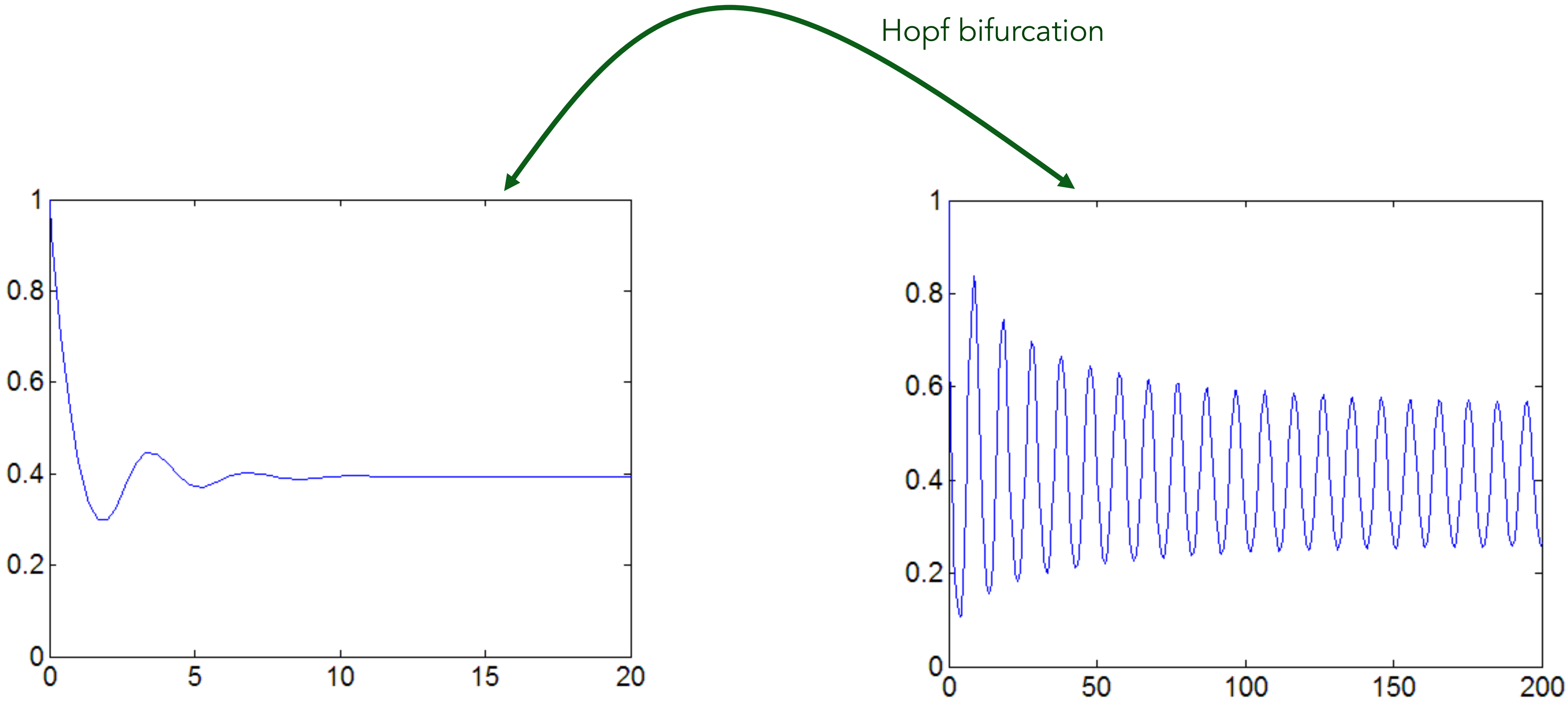
The system tends to either steady-state A or steady-state B depending on the initial conditions.

State A has the white basin of attraction; state B has the blue one.

A bifurcation is a qualitative change in the behaviour of a system



Example: before the bifurcation, a system goes to steady-state; after the bifurcation, the system oscillates

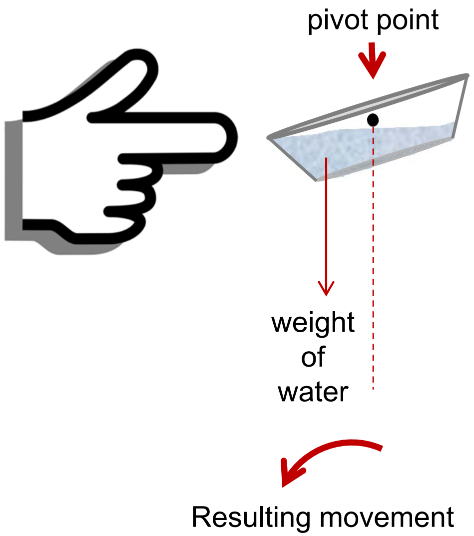


There are multiple different types of bifurcation.

Positive feedback and bistability in MAP kinase pathways generates memory

Positive feedback is a requirement for bistability

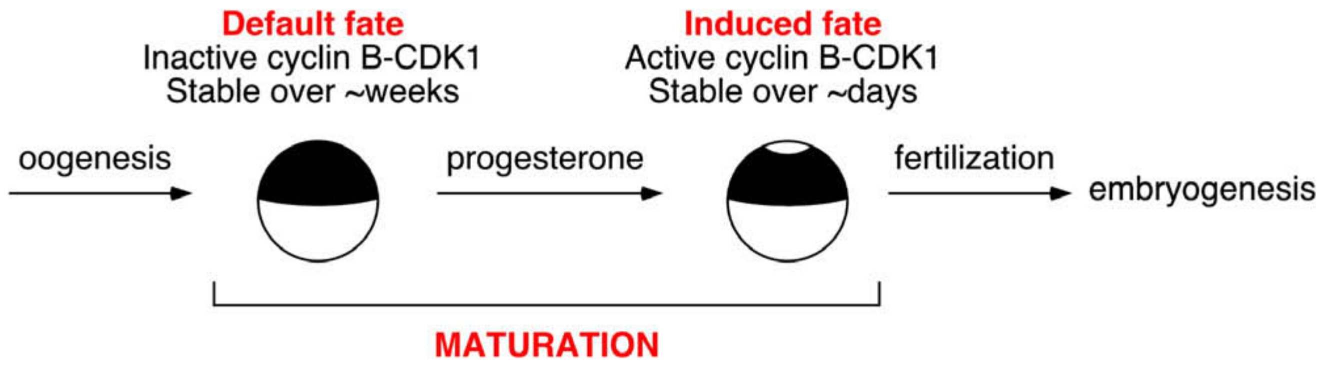
Positive feedback is a “runaway” process, where an effect enhances itself.



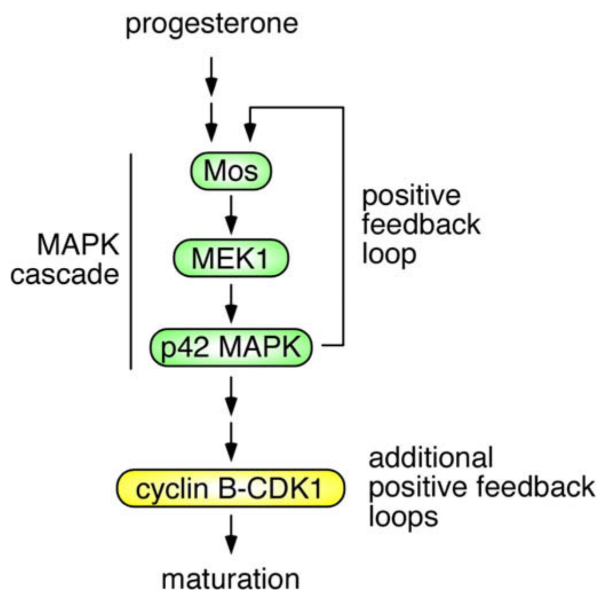
After a small perturbation, water moving tips the bucket and causes the water to move more and so tips the bucket further.

If an increase in the output of the system increases the output of the system still further, then the system has positive feedback.

Bistability underlies the maturation of frog oocytes.



The bistability is generated by an ultrasensitive, MAP kinase cascade and positive feedback.

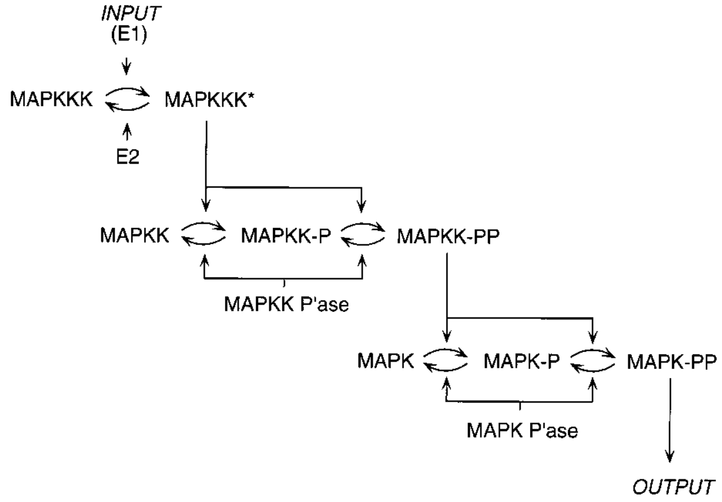


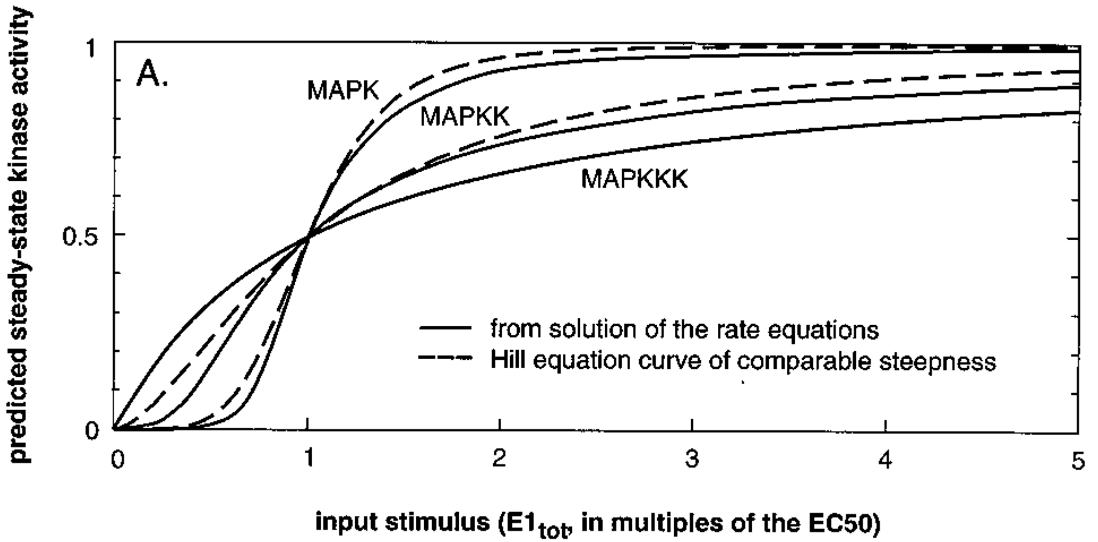
Proc. Natl. Acad. Sci. USA
Vol. 93, pp. 10078–10083, September 1996
Biochemistry

Ultrasensitivity in the mitogen-activated protein kinase cascade

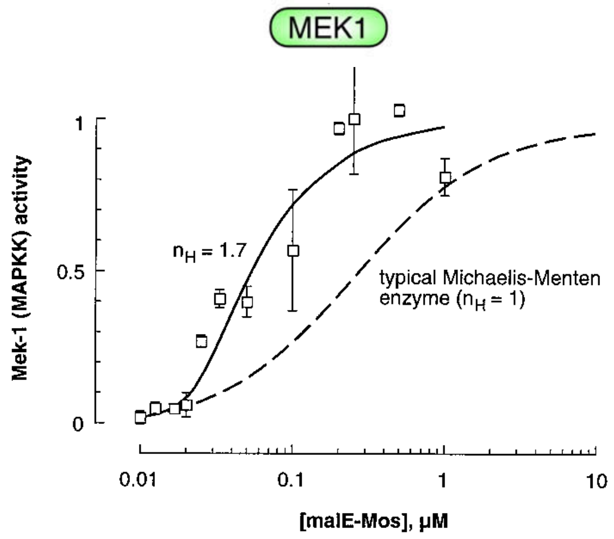
CHI-YING F. HUANG AND JAMES E. FERRELL, JR.†

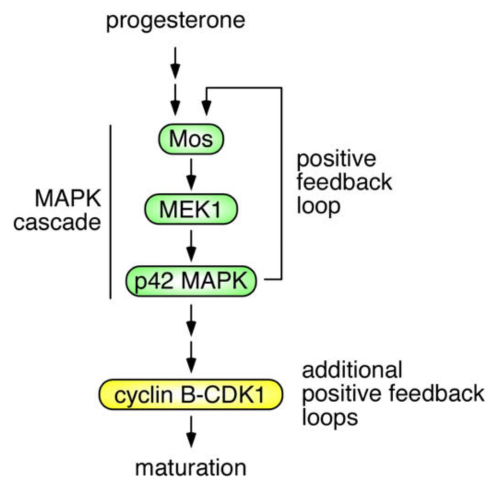
Requiring two phosphorylations to become active and distributive phosphorylation generates an ultrasensitive response that becomes steeper with each step of the cascade.

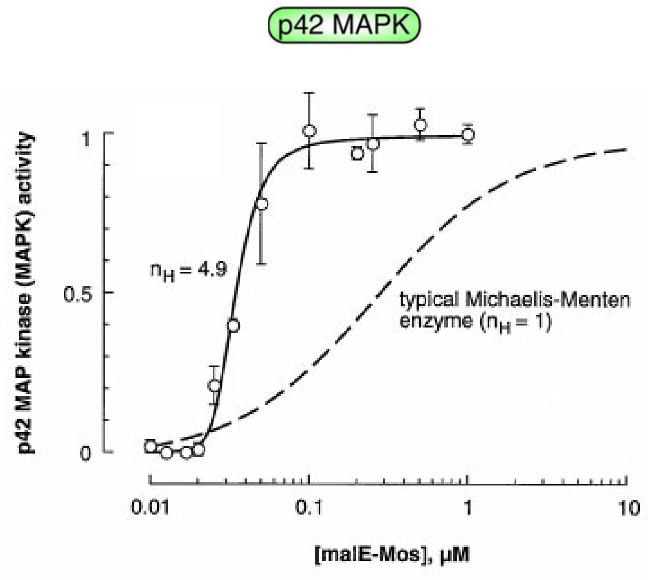




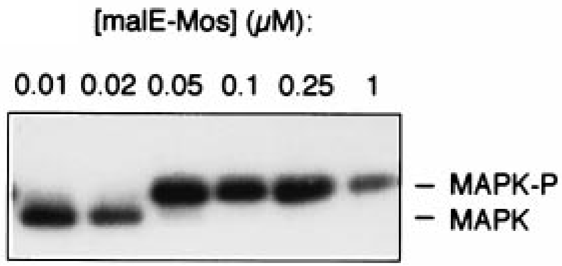
Ultrasensitivity does increase down the MAPK cascade







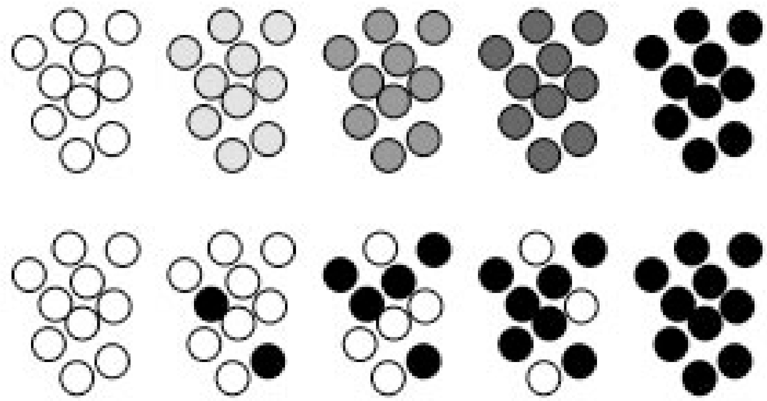
Levels of active kinases were measured using Western blots.



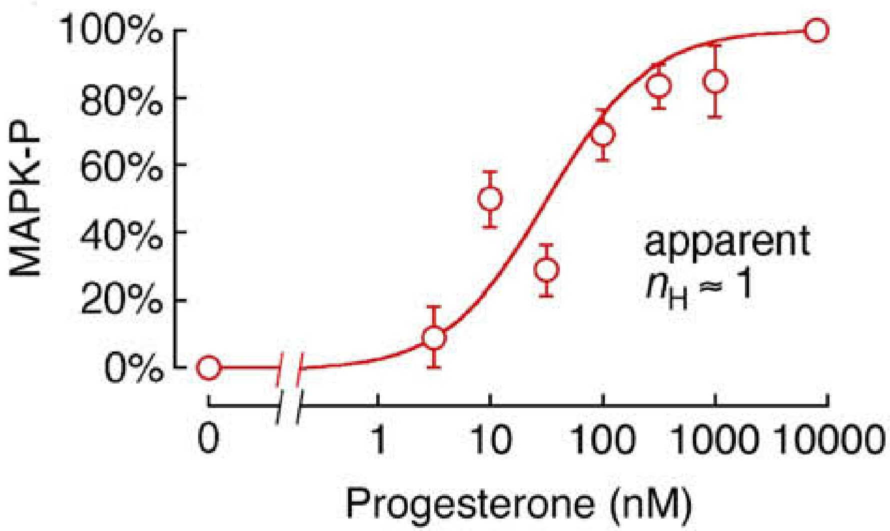
malE-Mos is an exogenously expressed version of Mos.

We need to look at single cells to see switching

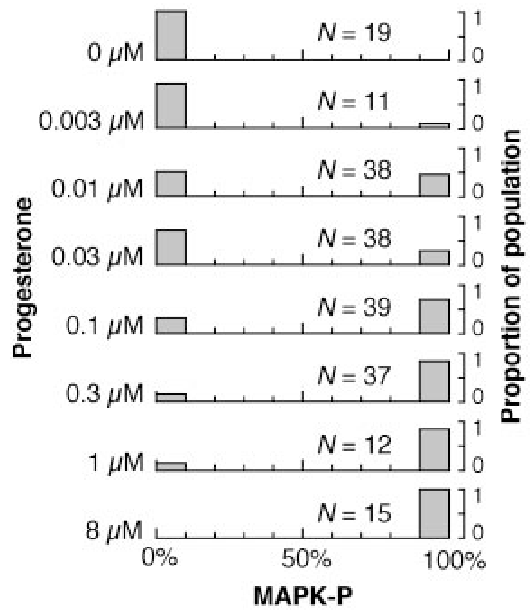
The same average behaviour of a population can be generated by different behaviours in single cells.



Population level measurements of activated MAP kinase

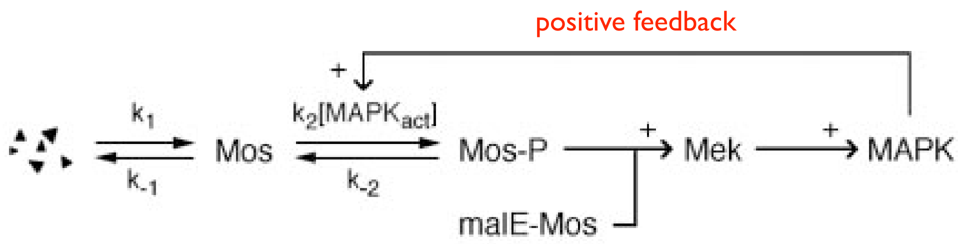


Single-cell level measurements of activated MAP kinase



from Ferrell & Machleder, 1998

Positive feedback is also present and is required for bistable, or “all-or-none”, behaviour

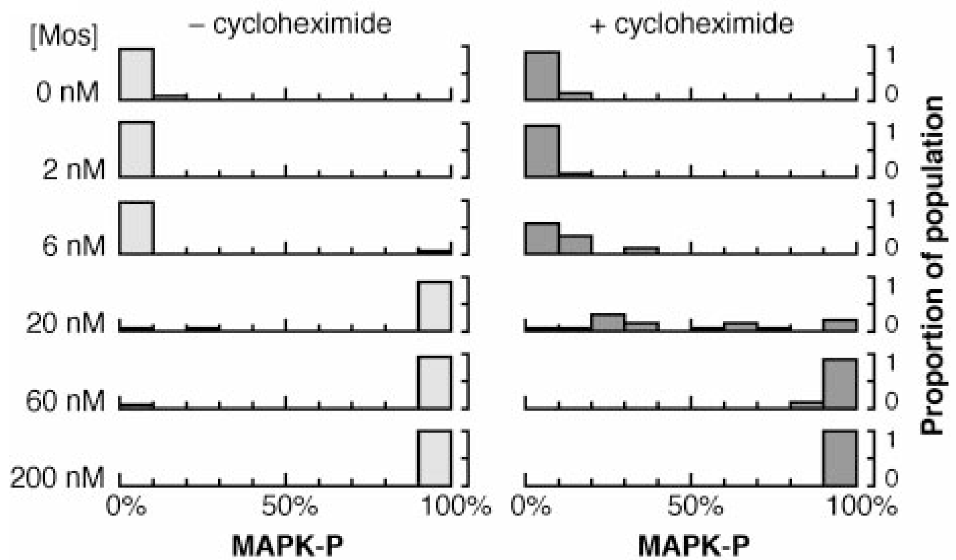


The Biochemical Basis of an All-or-None Cell Fate Switch in *Xenopus* Oocytes

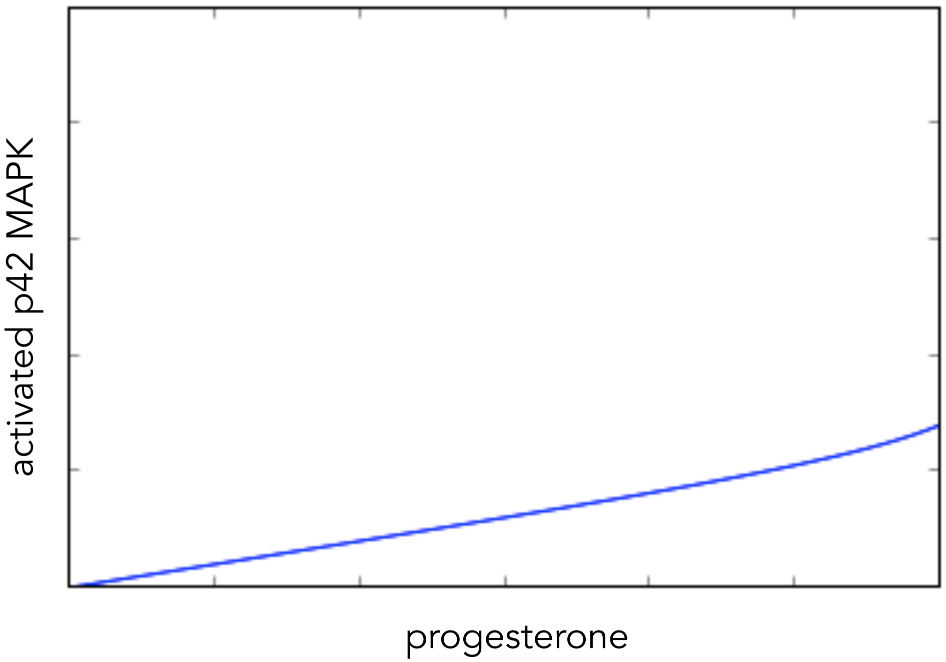
James E. Ferrell Jr.* and Eric M. Machleder

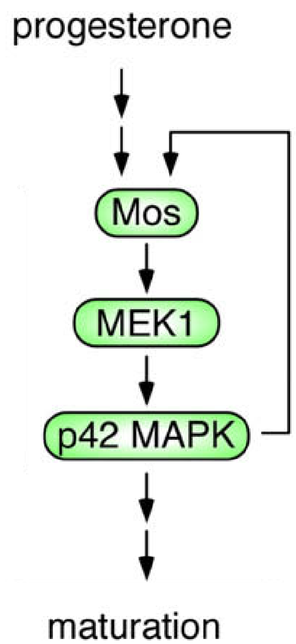
With cycloheximide, which inhibits translation, bistability, but not ultrasensitivity, is lost.

Positive feedback requires the synthesis of new proteins.

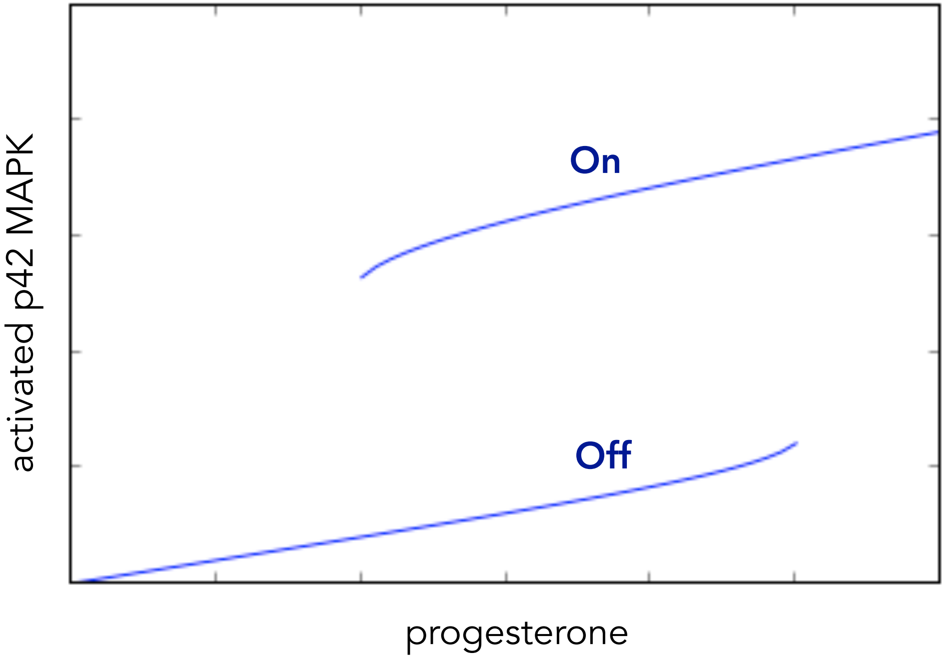


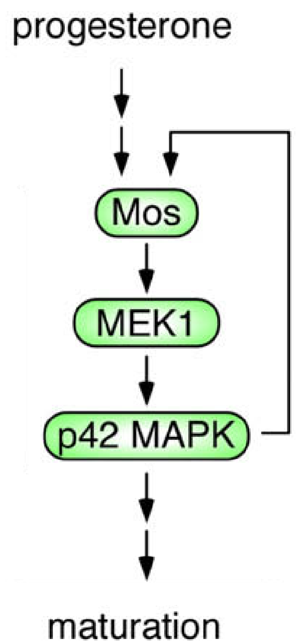
The p42 MAP kinase becomes more active as levels of progesterone increase.



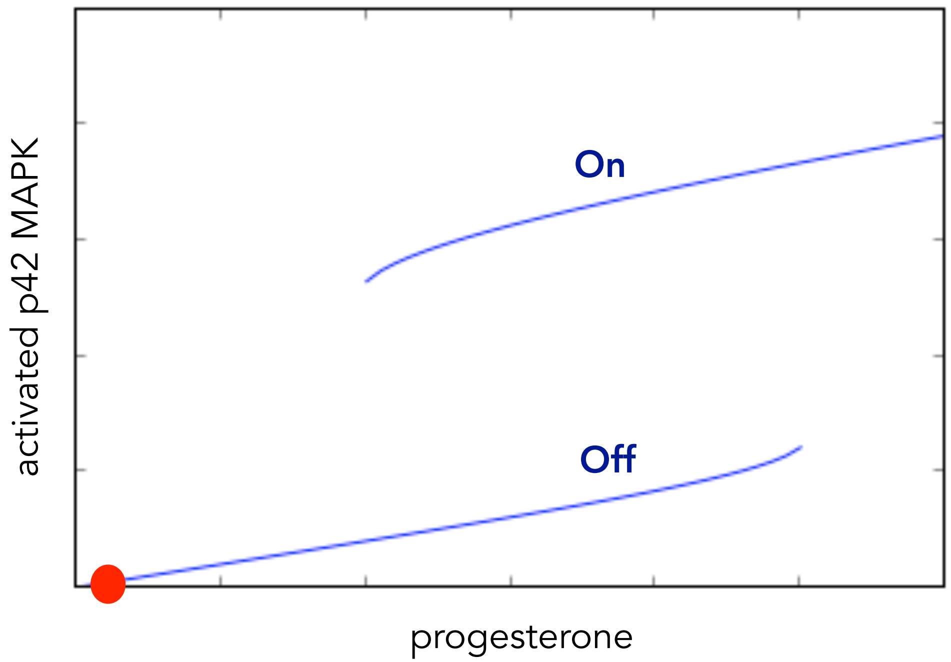


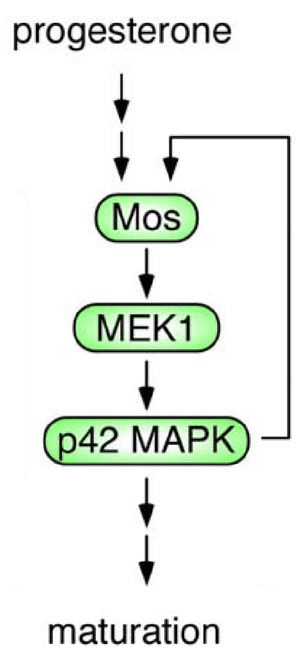
Increasing positive feedback allows the system to become either On or Off





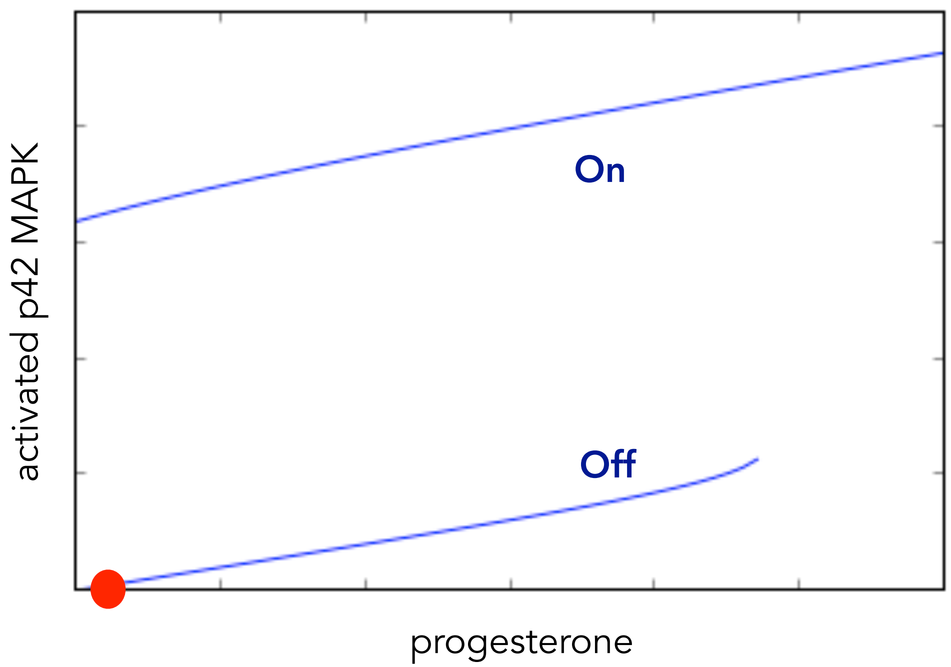
With an On and an Off state possible for the same level of progesterone, the system has memory

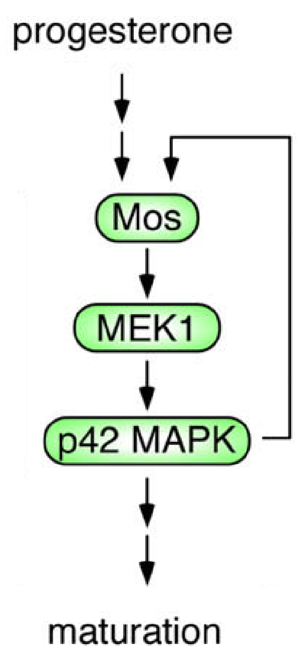




The cell remembers because the level of progesterone at which it jumps to the alternative state depends on whether the cell was initially On or Off.

With strong feedback, the memory can become permanent





Even when levels of progesterone fall to zero, the cell remains On – the cell has differentiated.

By modelling Mos only, we are able to describe the bistability

basal synthesis

positive feedback

degradation

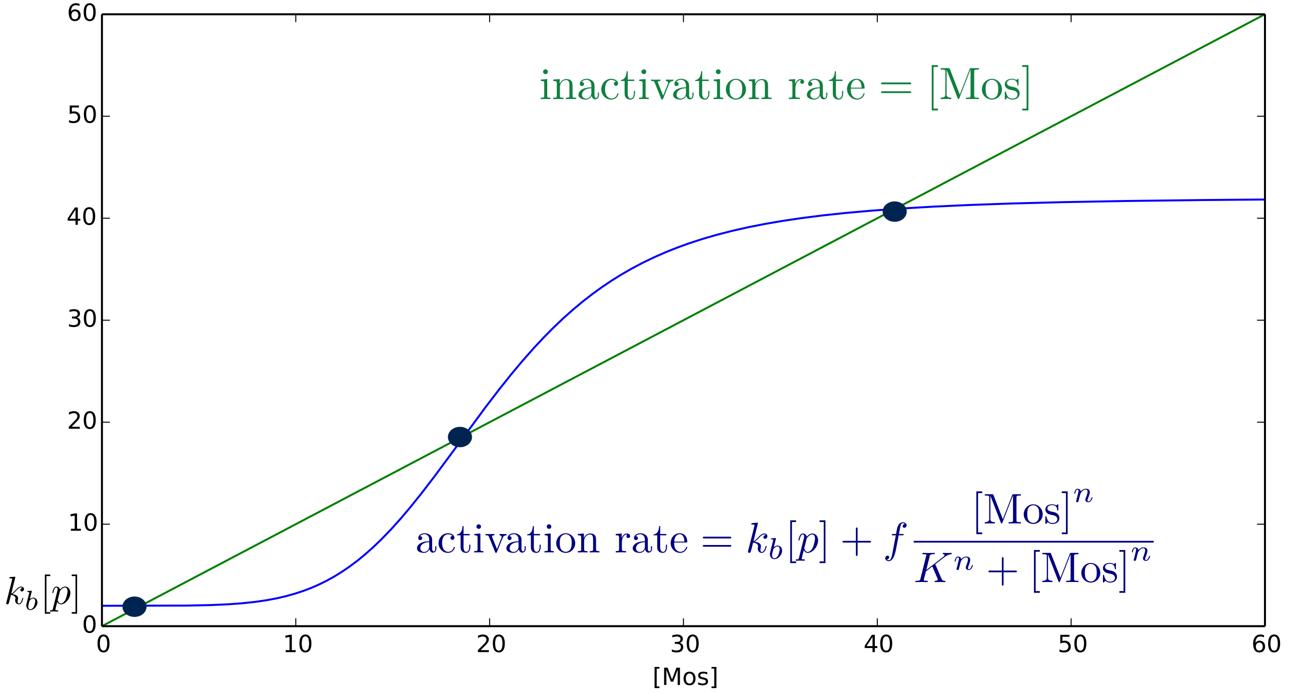
$$\frac{d[\mathrm{Mos}]}{dt} = k_b[p] + f\,\frac{[\mathrm{Mos}]^n}{K^n + [\mathrm{Mos}]^n} - [\mathrm{Mos}]$$

progesterone

The positive feedback is described with a Hill function.

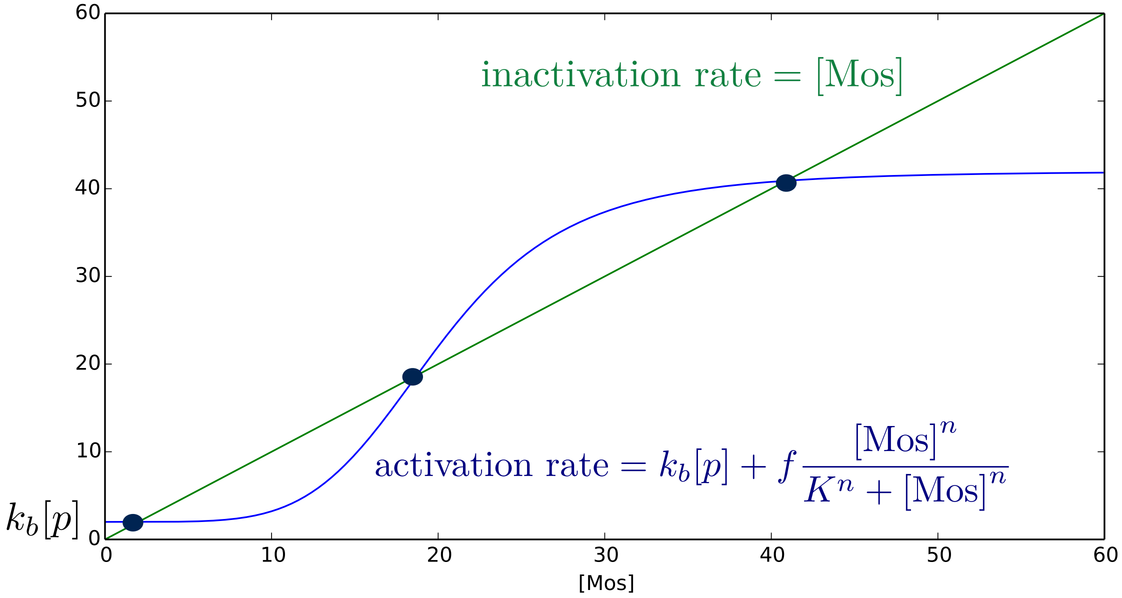
We use a graphical construction to find the steady-state solutions

The system is at steady state when the activation rate of Mos equals its inactivation rate.



There are **three** steady-state solutions.

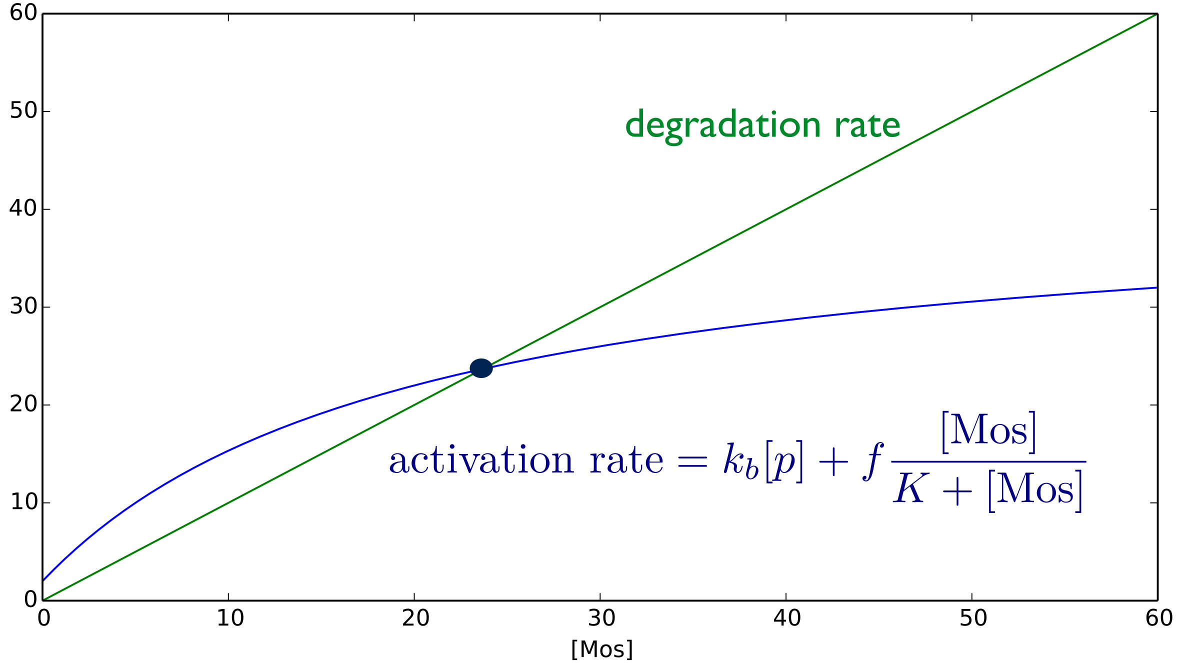
The long-term behaviour will depend on the initial conditions



A phase diagram summarises the possible dynamics.

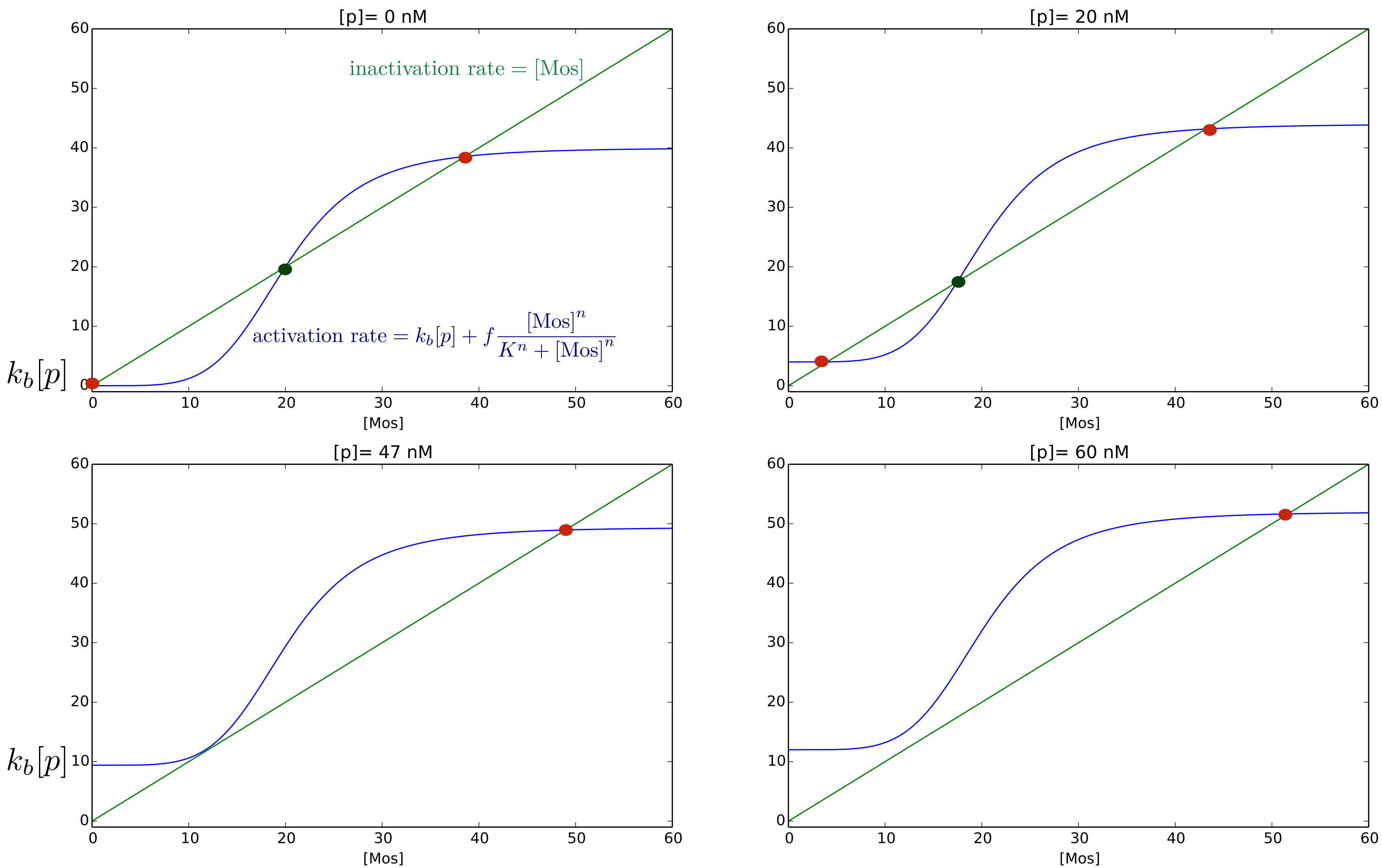
$[p] = 20$ nM

Ultrasensitivity in the positive feedback is necessary for bistability

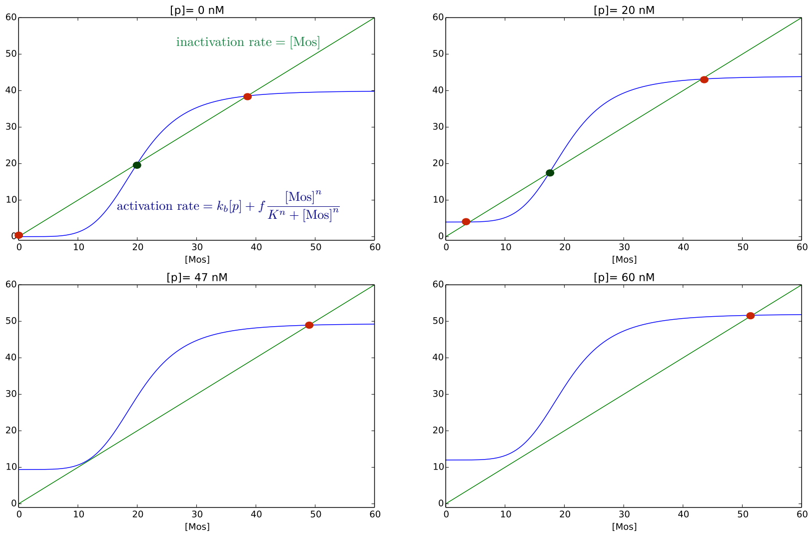


When n=1 and the cascade of kinases is not ultrasensitive, there is only one steady state.

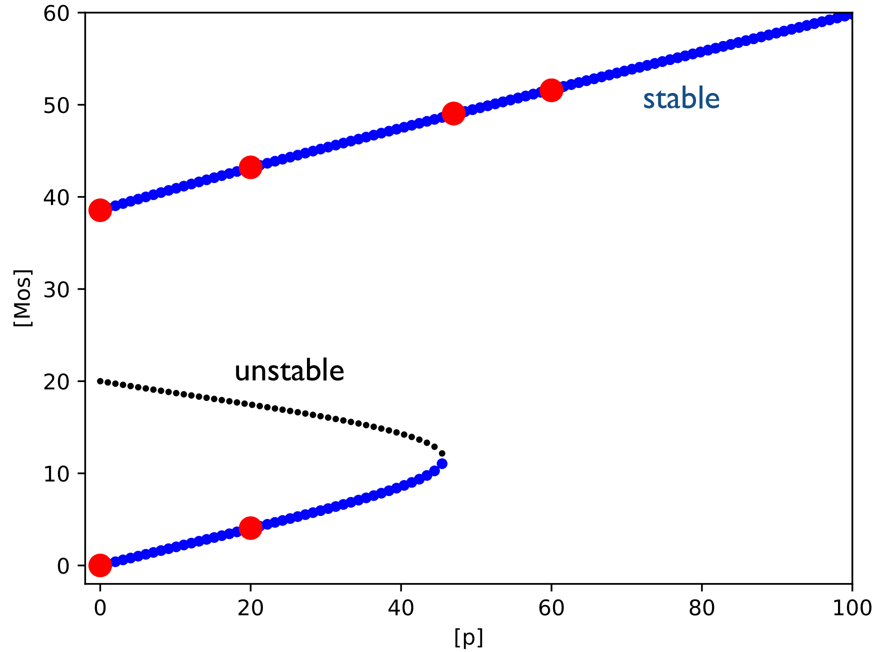
By changing the concentration of pheromone, the system undergoes a bifurcation



A bifurcation diagram shows the steady states as a function of the bifurcation parameter

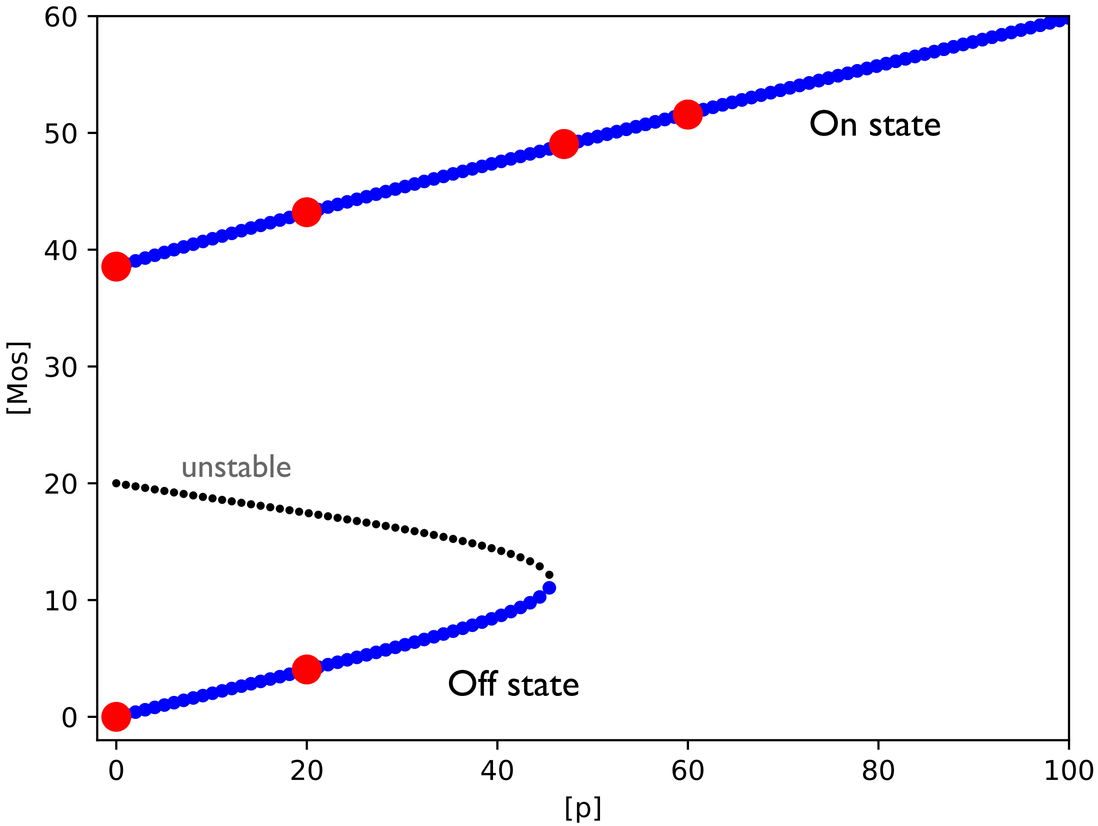


The bifurcation parameter is *[p]* and this type of bifurcation is called a saddle-node bifurcation.



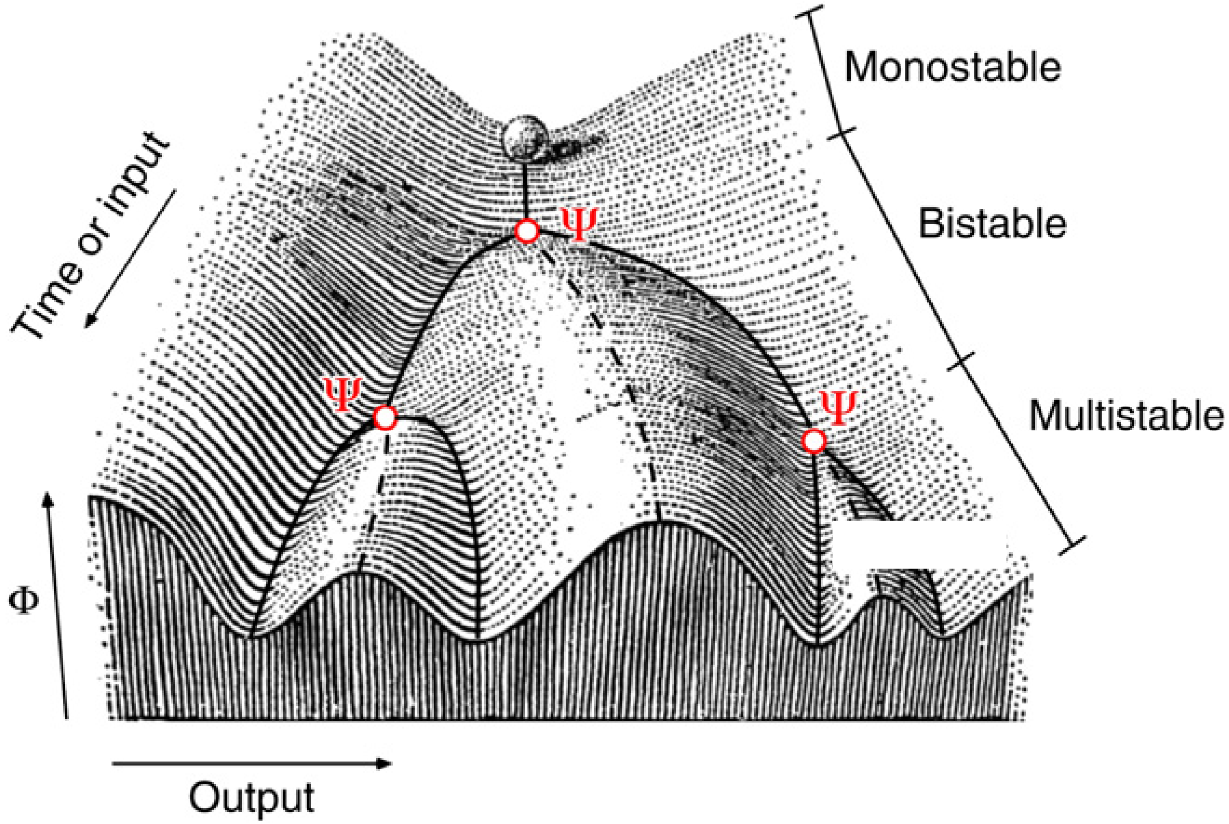
The system has hysteresis and the positive feedback is so strong that there is permanent memory

Hysteresis means history-dependent behaviour

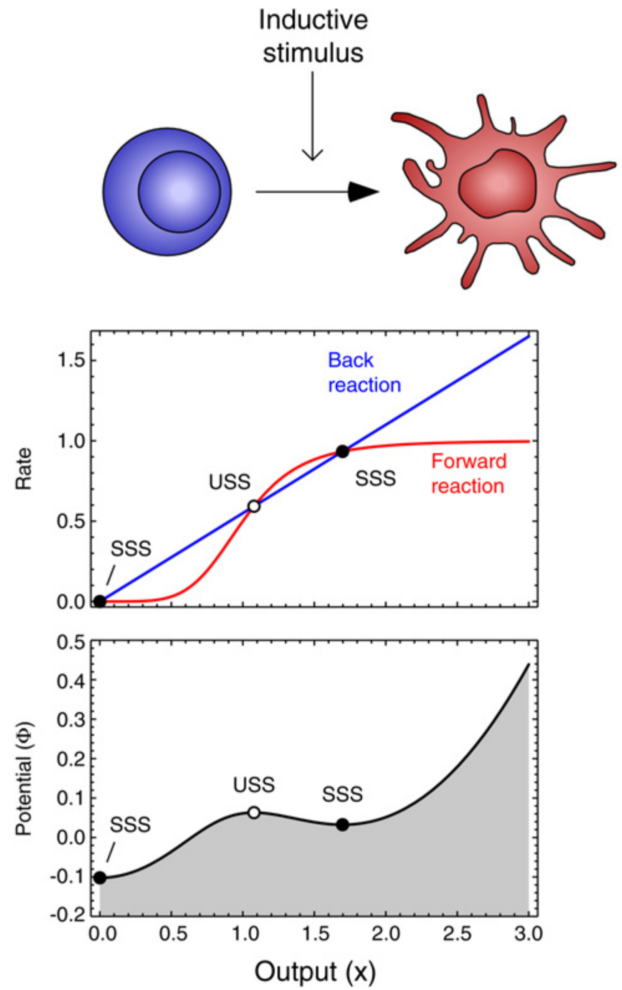


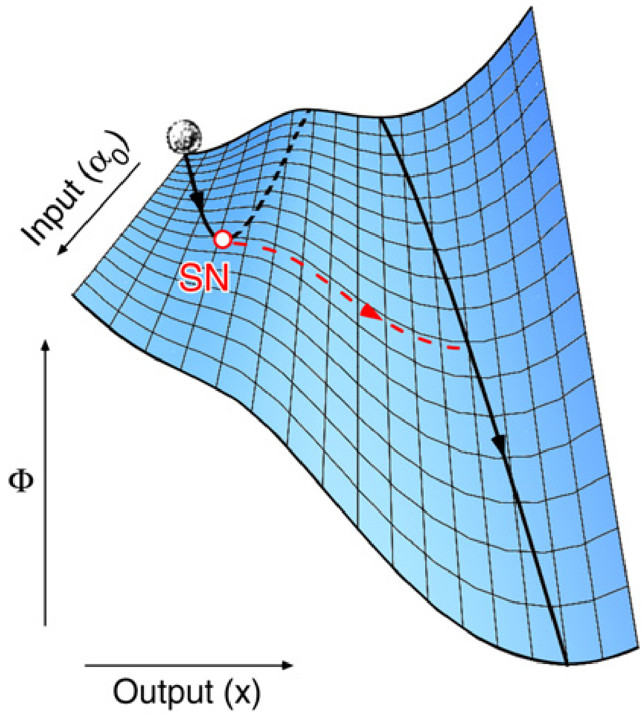
Starting from the Off state as pheromone [p] increases, the system will eventually jump permanently to the On state, remaining there even as [p] decreases.

Waddington's epigenetic landscape illustrates how an undifferentiated cell progresses to one of several possible differentiated states



Differentiation is more likely to occur through saddle-node bifurcations, which cause a valley and a ridge to disappear





$$\frac{dx}{dt} = -\frac{d\Phi}{dx} = k_b[p] + f\,\frac{x^n}{K^n + x^n} - x$$

From Ferrell, 2012