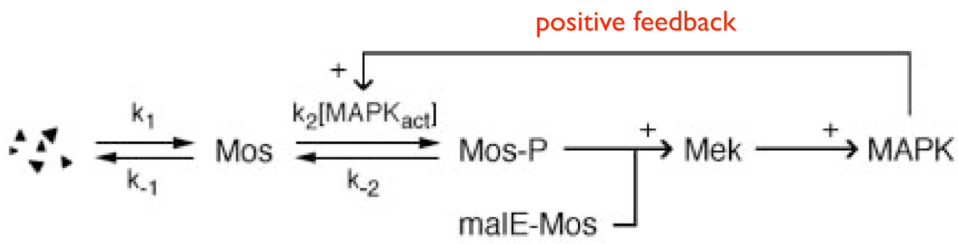
Positive feedback is also present and is required for bistable, or "all-or-none", behaviour

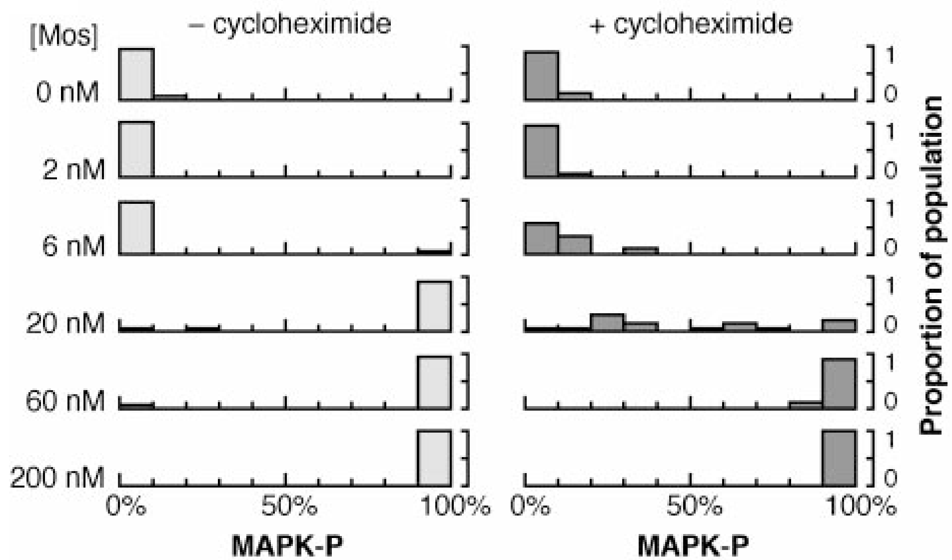


The Biochemical Basis of an All-or-None Cell Fate Switch in *Xenopus* Oocytes

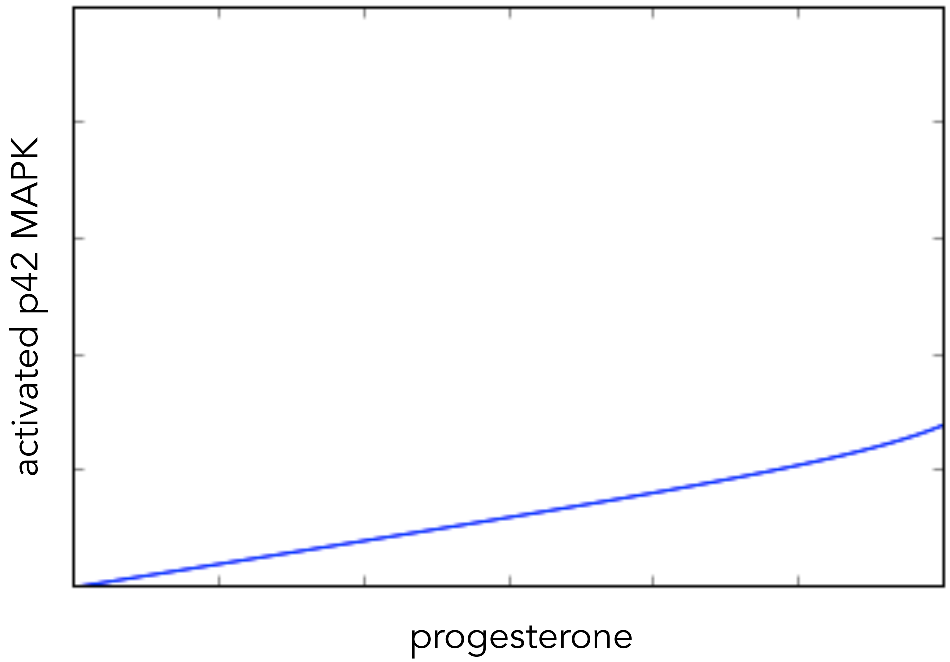
James E. Ferrell Jr.* and Eric M. Machleder

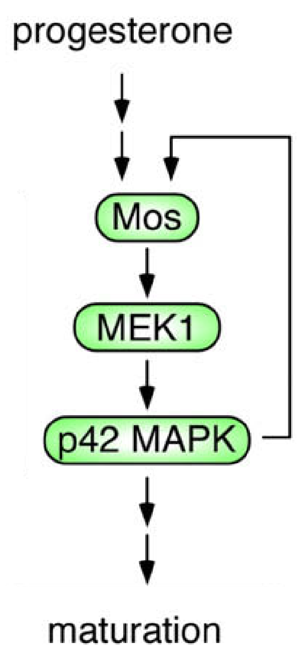
With cycloheximide, which inhibits translation, bistability, but not ultrasensitivity, is lost.

Positive feedback requires the synthesis of new proteins.

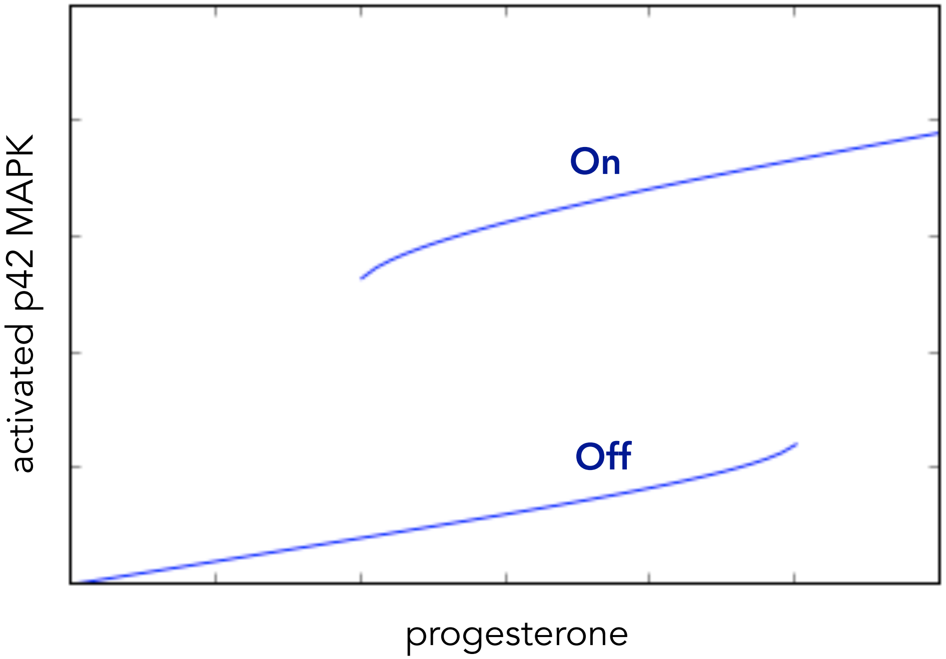


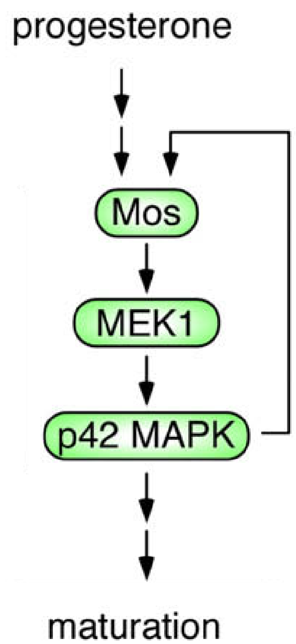
The p42 MAP kinase becomes more active as levels of progesterone increase.



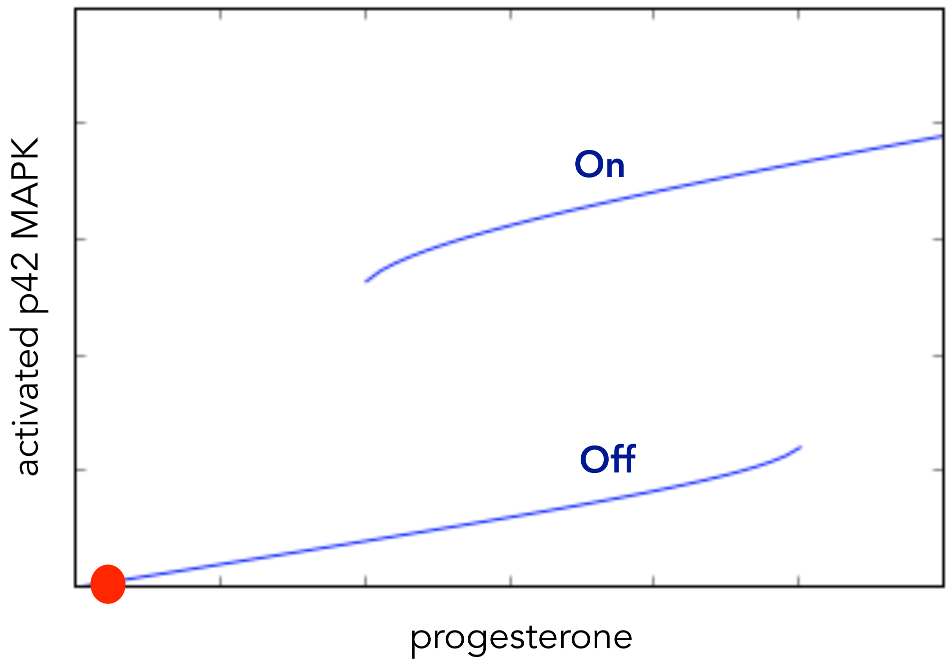


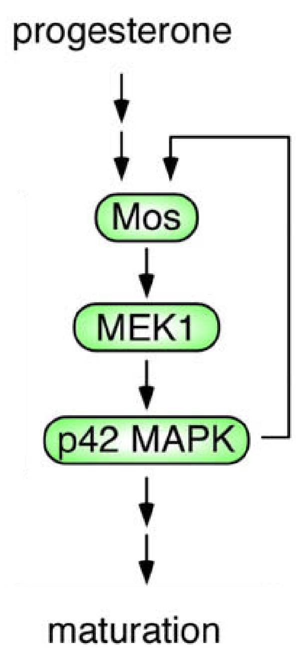
Increasing positive feedback allows the system to become either On or Off





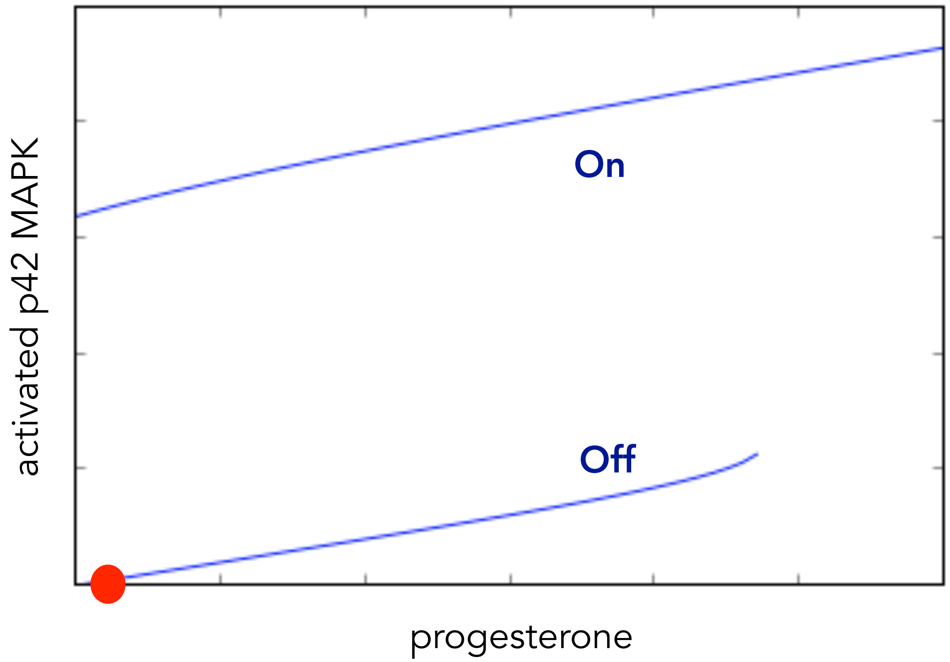
With an On and an Off state possible for the same level of progesterone, the system has memory

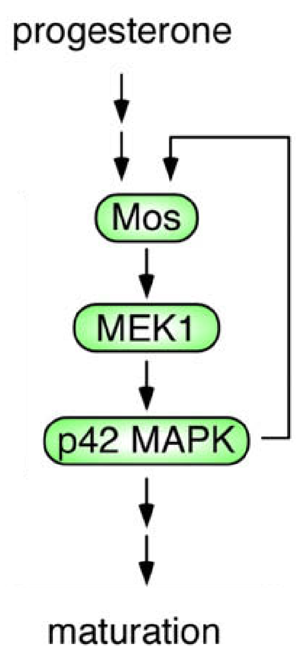




The cell remembers because the level of progesterone at which it jumps to the alternative state depends on whether the cell was initially On or Off.

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

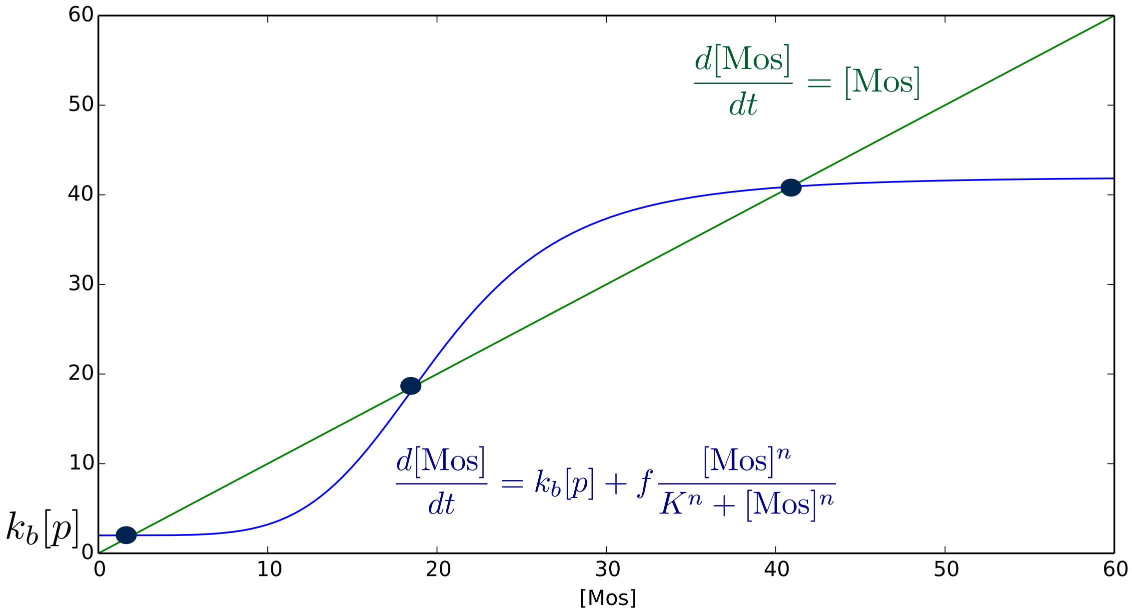
$$\frac{d[\mathrm{Mos}]}{dt} = k_b[p] + f\frac{[\mathrm{Mos}]^n}{K^n + [\mathrm{Mos}]^n} - [\mathrm{Mos}]$$

progesterone

The positive feedback is described with a Hill function.

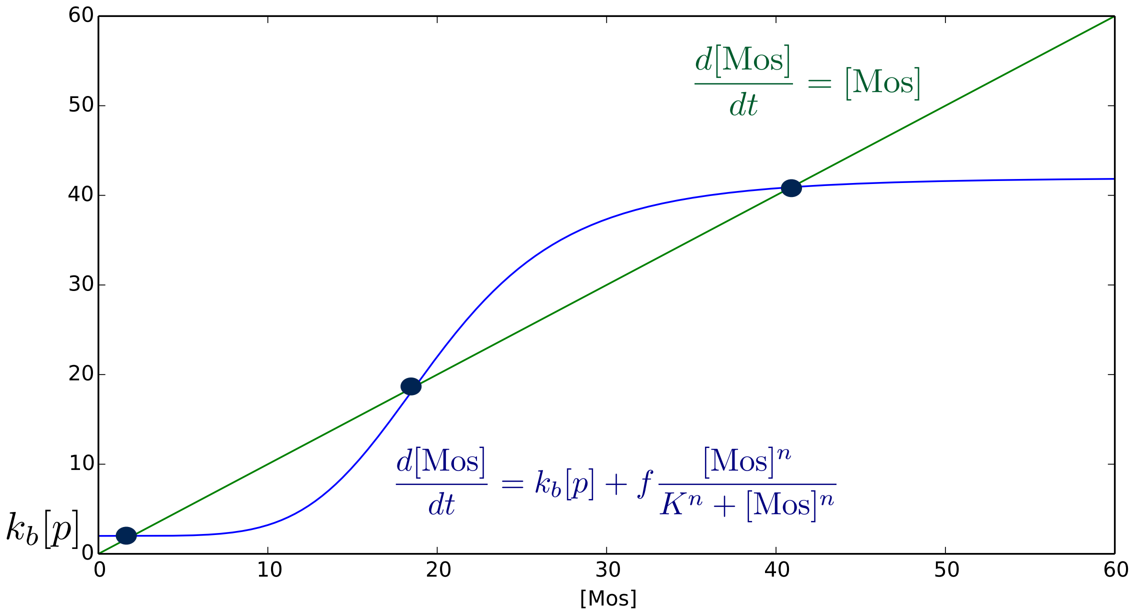
We use a graphical construction to find the steady-state solutions

The system is at steady state when the rate of production of Mos equals its rate of degradation.



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

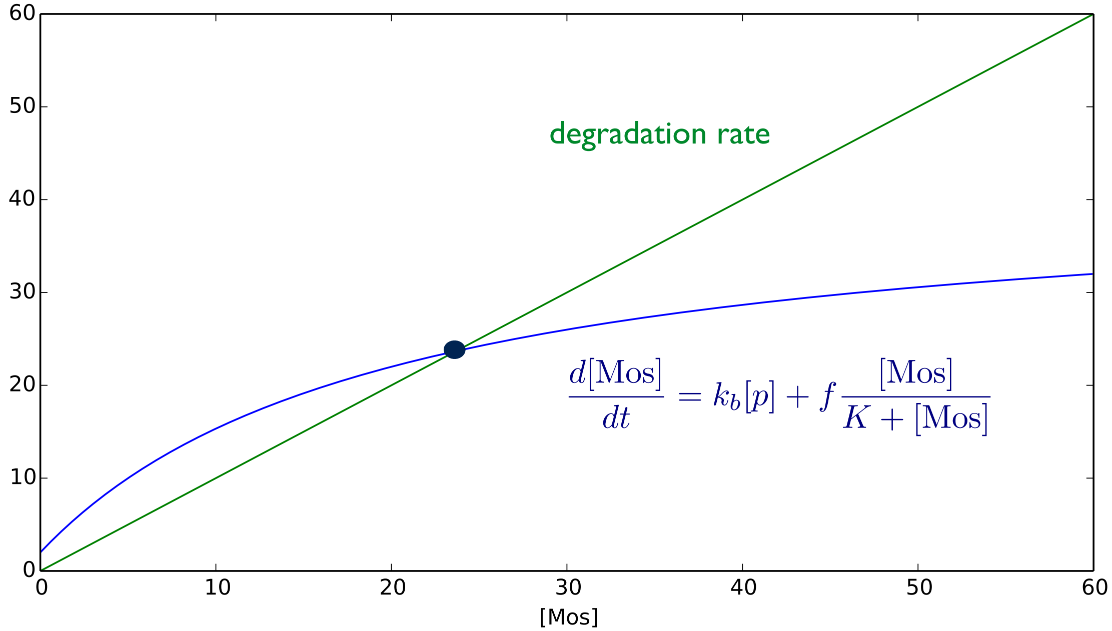
The long-term behaviour will depend on the initial conditions



A phase diagram summarises the possible dynamics.

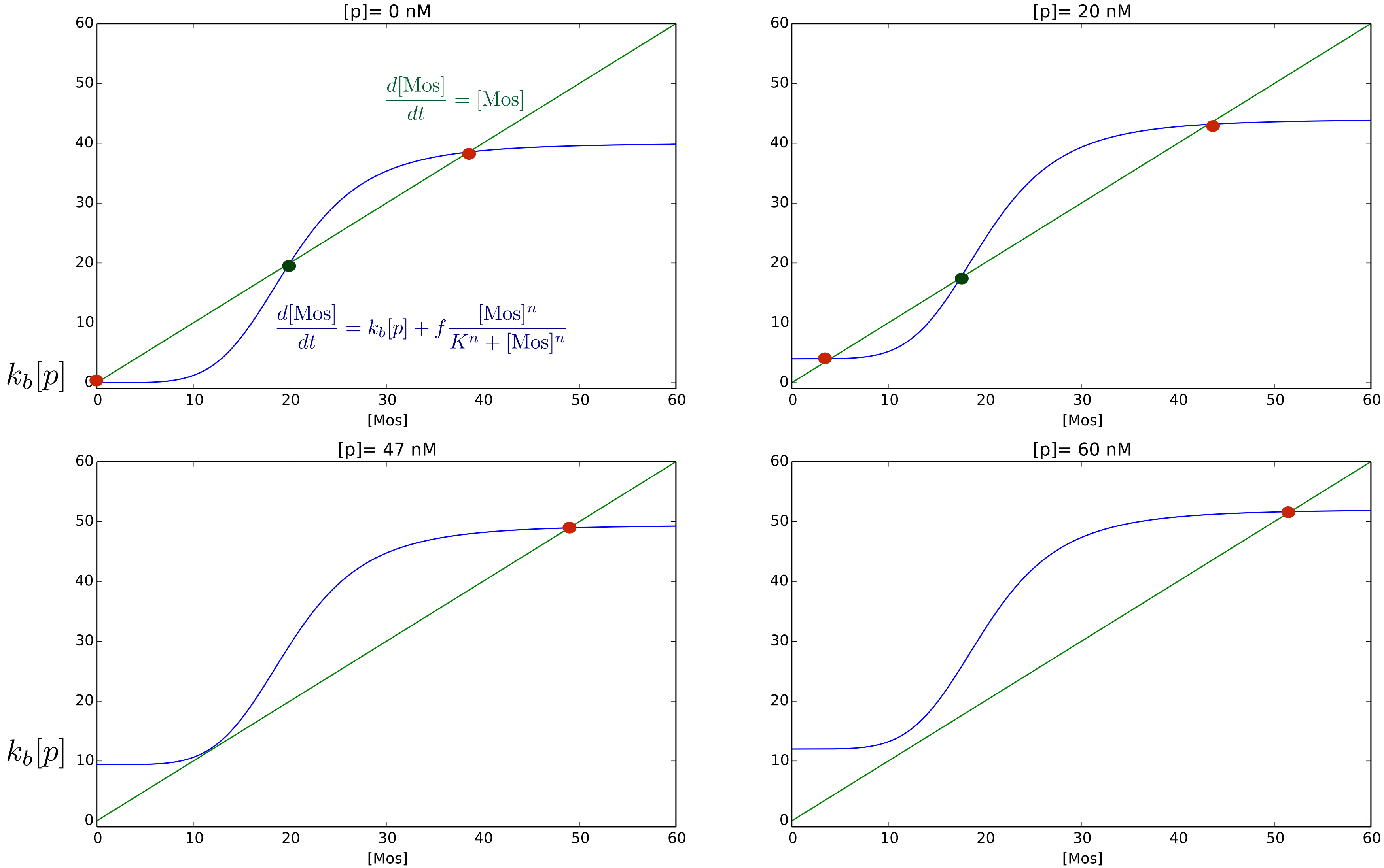
$[p] = 20$ nM

Ultrasensitivity in the positive feedback is necessary for bistability

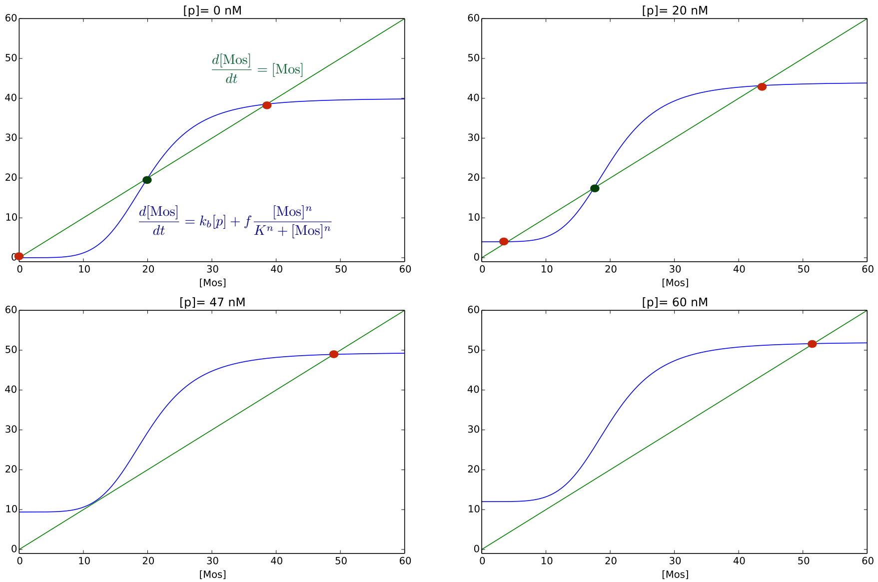


When n=1 and the cascade of kinases is not ultrasensitive, there is only one steady state.

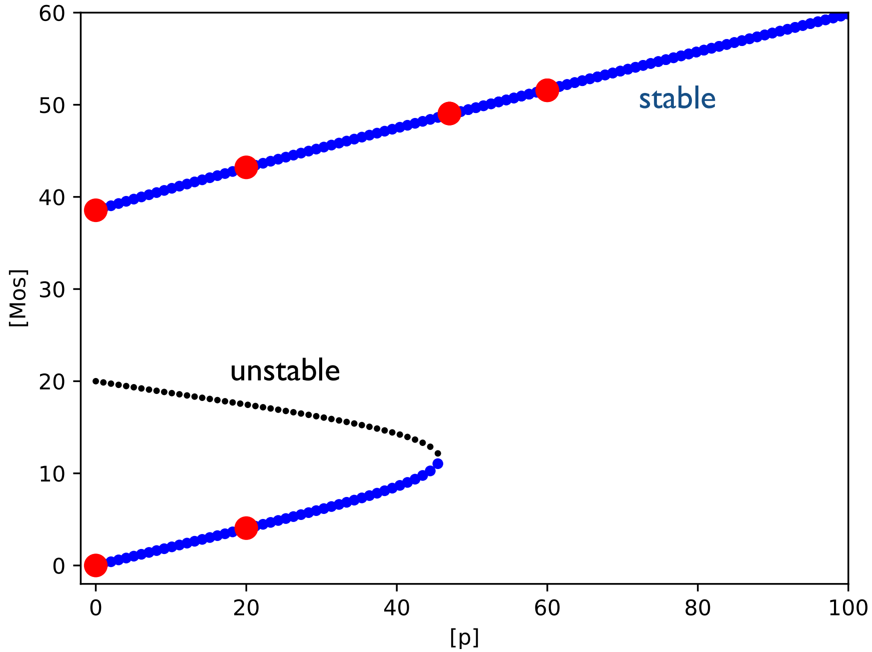
By changing the concentration of pheromone, the system undergoes a bifurcation



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

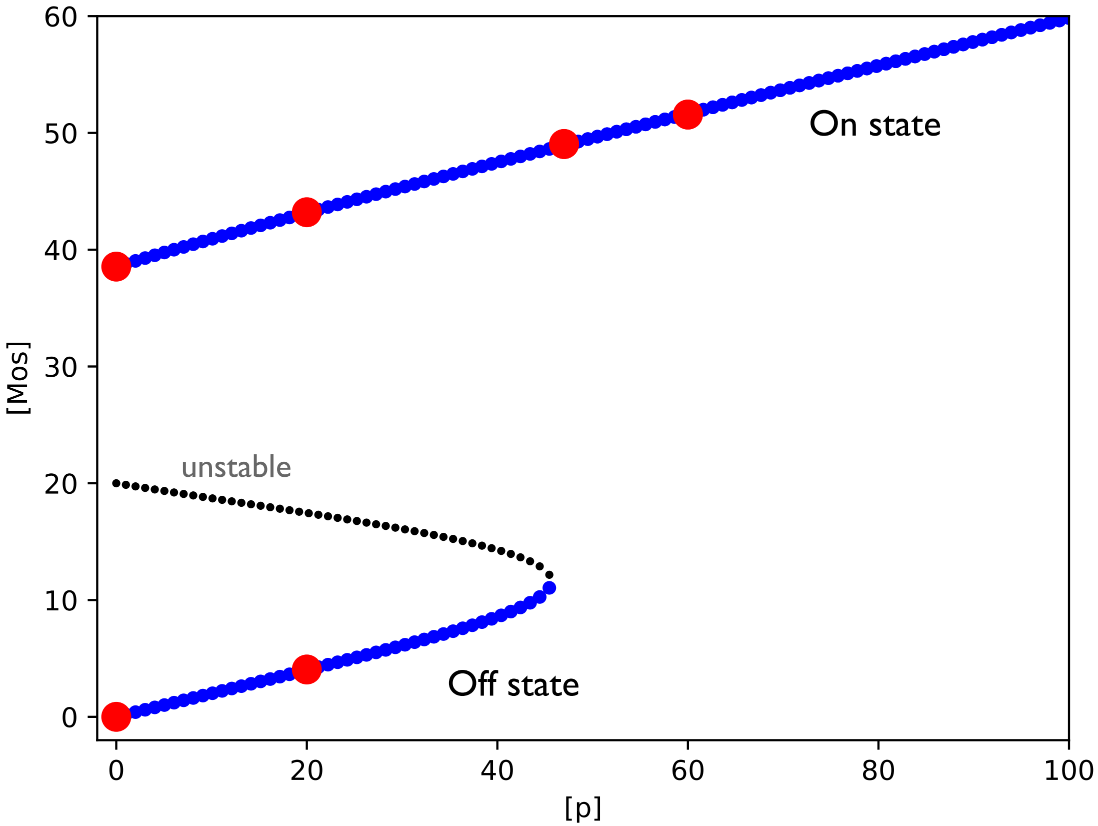


The bifurcation parameter is *[p]* and this type of bifurcation is called a saddle-node bifurcation.



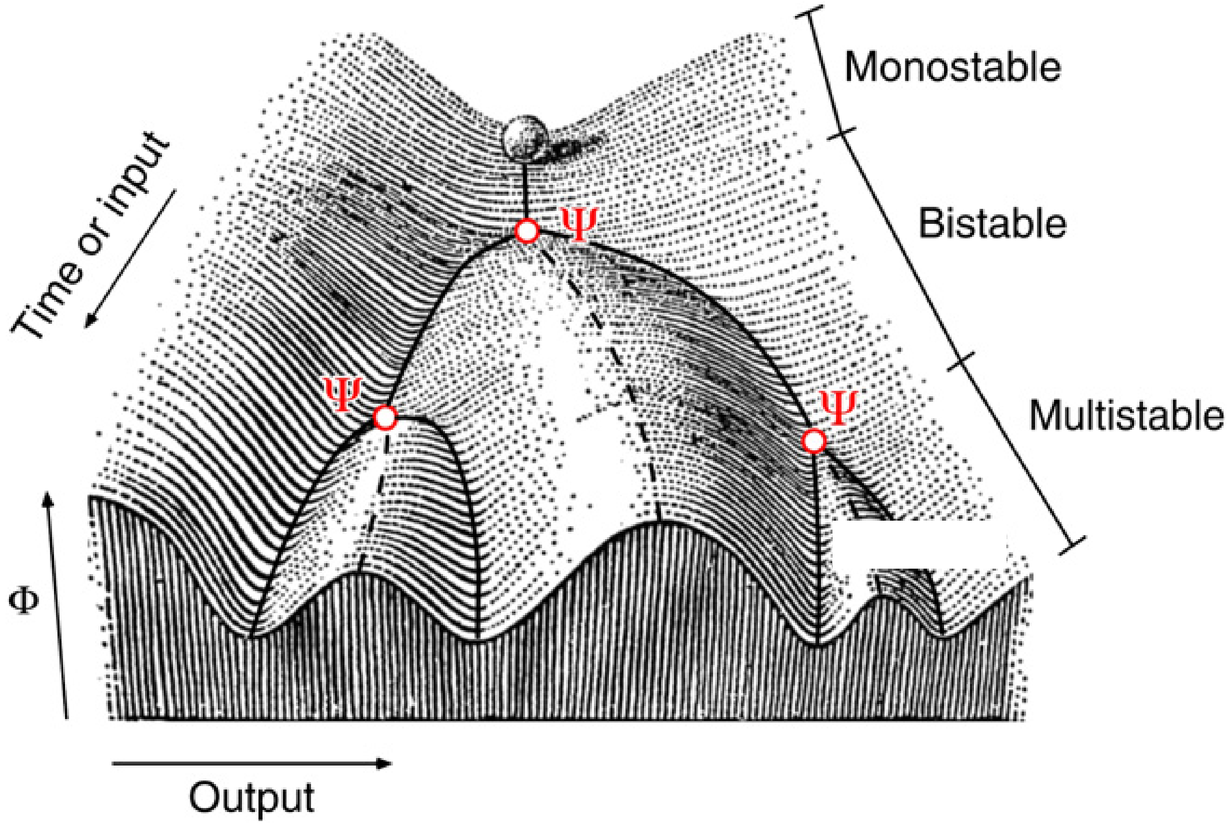
The system has hysteresis and the positive feedback is so strong that there is permanent memory

Hysteresis means history-dependent behaviour

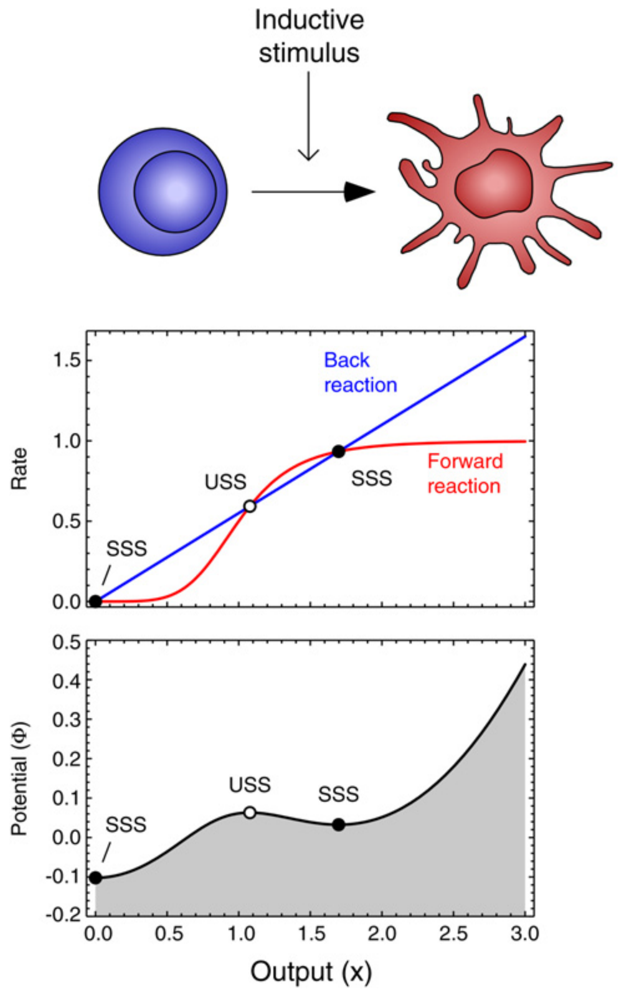


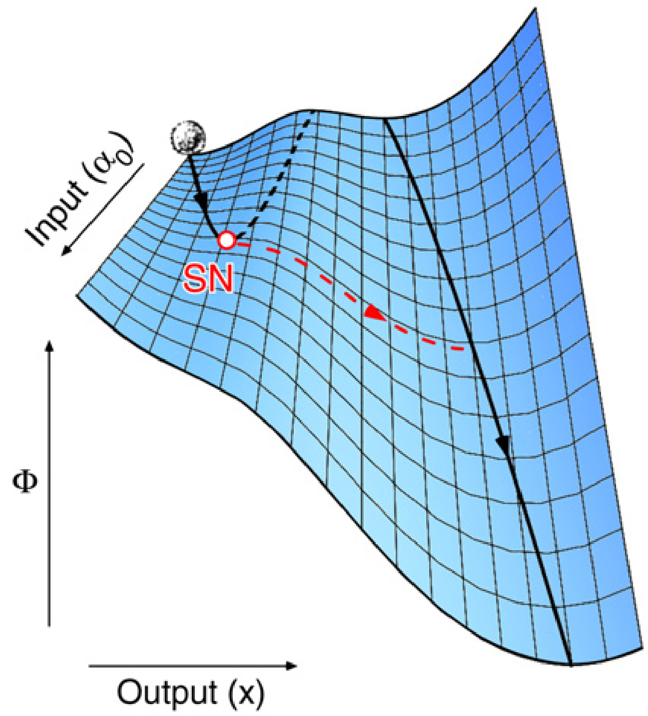
Starting from the Off state as [p] increases, the system will eventually jump permanently to the On state, remaining there even as [p] decreases.

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