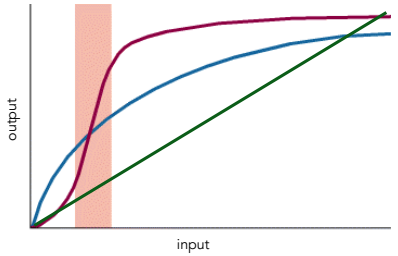
Concepts from non-linear dynamics are used to understand the behaviour of biological systems

The dynamics of biochemical networks is non-linear

Non-linear : the magnitude of an effect 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 types of specifications for a dynamical system

System parameters specify the properties of the system, e.g. temperature, kinetic rates for reacting species (V_{max} and K_m for enzyme reactions), system volume

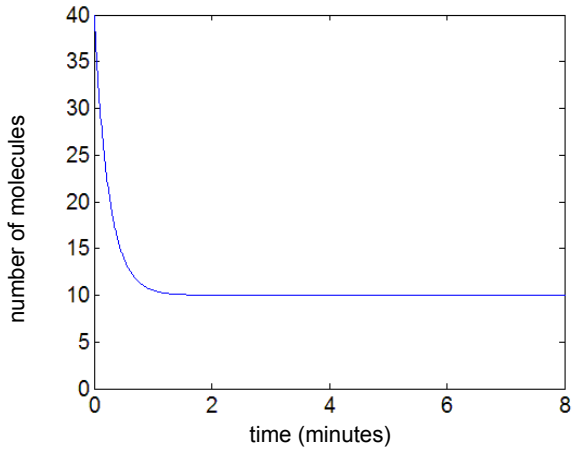
Initial conditions specify the initial values of all components of the system that evolve with time, e.g. initial concentrations of all proteins in a biochemical network

Dynamical systems tend after long times to attractors

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

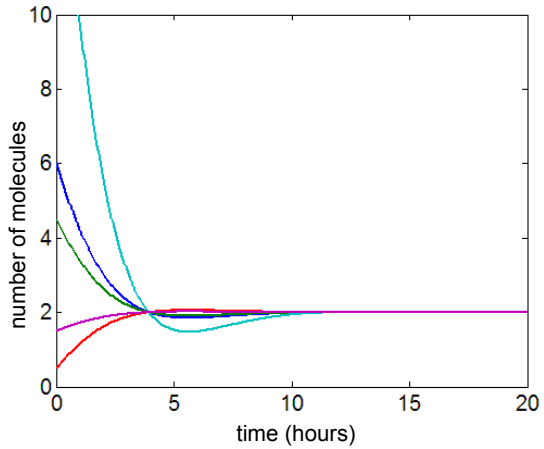
The system has reached an attractor.

e.g.



A steady-state attractor is a common attractor

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

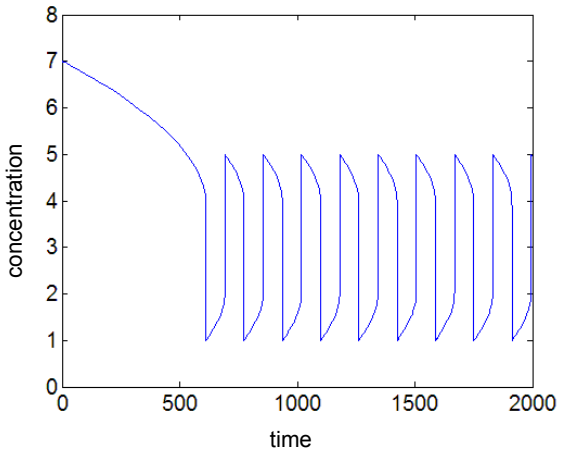


different initial conditions give the same steady state behaviour

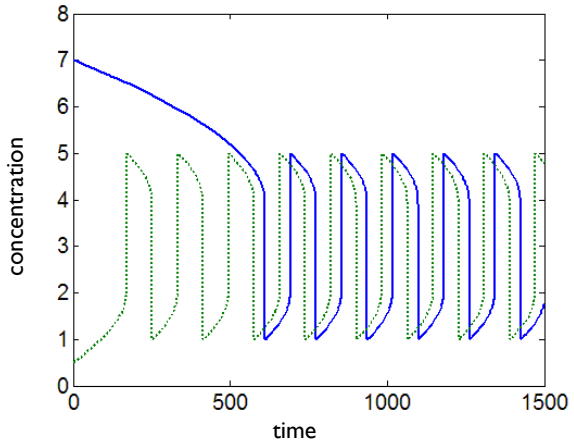
Equilibrium is a special steady-state that consumes no energy (and is the only attractor for such systems).

The components of a system oscillate at a limit cycle attractor

After some initial behaviour, the system eventually oscillates.



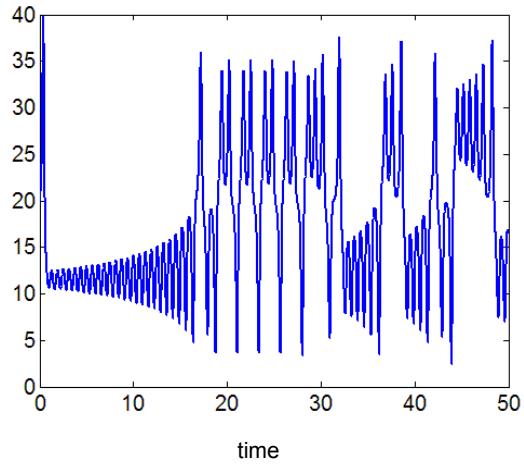
From different initial conditions, the system reaches the limit cycle, and oscillates with the same frequency and amplitude.



The time taken to reach the limit cycle will not be the same in general.

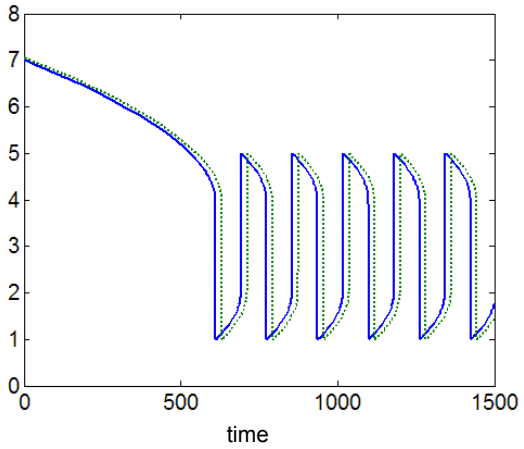
Strange attractors give chaotic dynamics

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



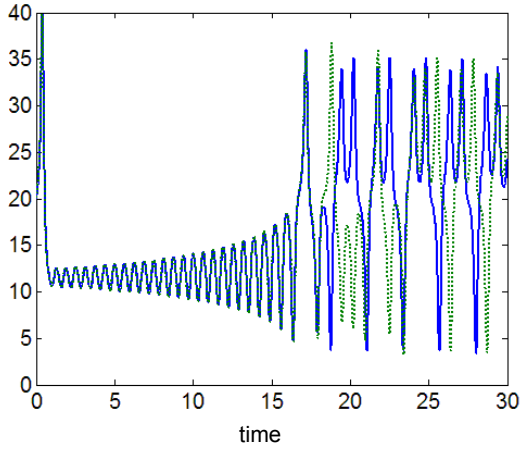
Aperiodic: an irregular oscillation that never exactly repeats

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



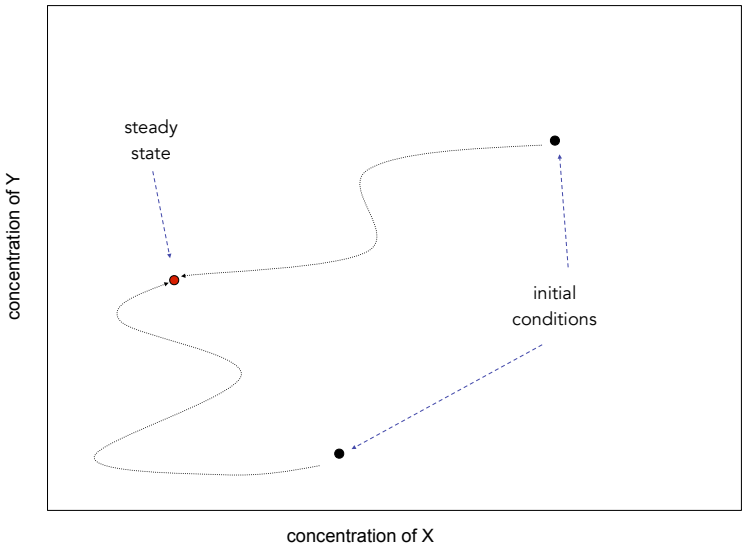
Neighbouring trajectories never significantly separate.

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

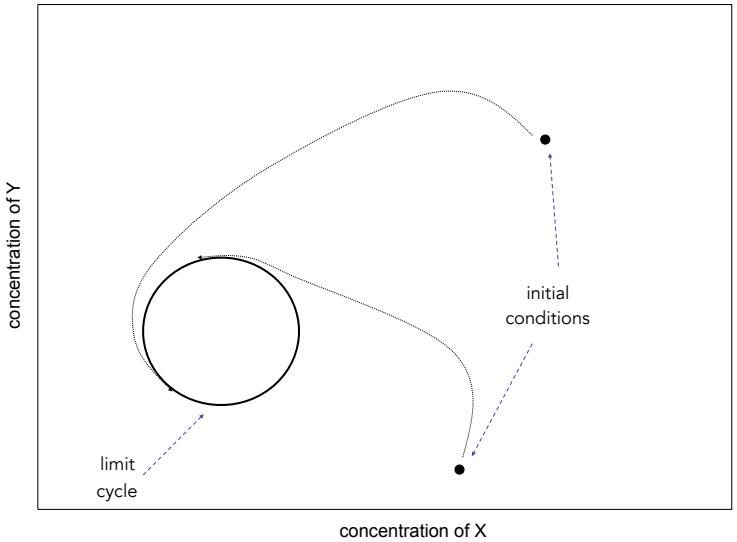


Neighbouring trajectories separate exponentially fast.

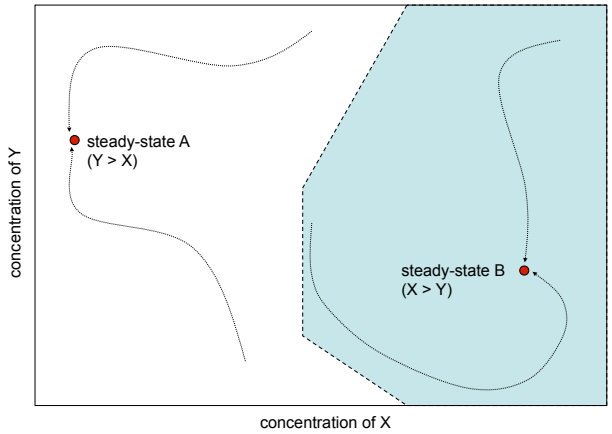
A phase diagram shows the dynamics of a system by plotting the concentration of one system component against another.



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



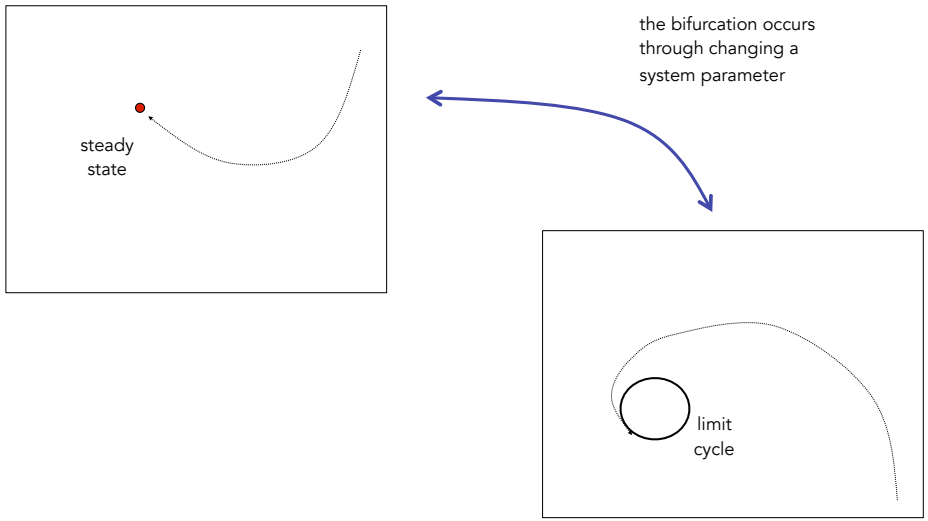
A bistable system has two steady-state attractors



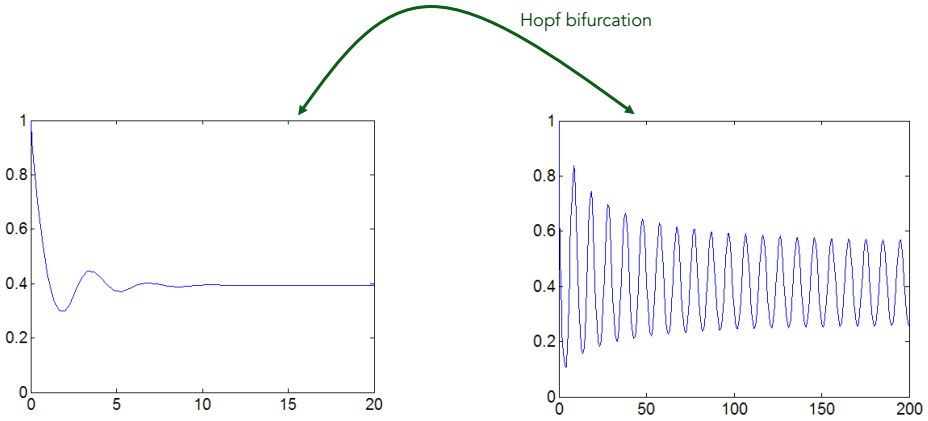
The system tends to either steady-state A or B depending on the initial conditions.

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



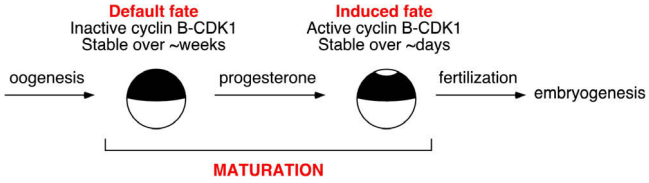
Example: before the bifurcation, a system goes to steady-state; after the bifurcation, the system oscillates



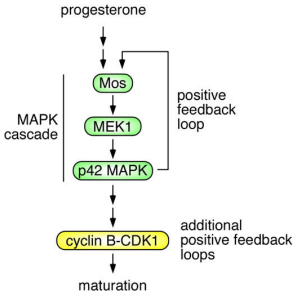
There are multiple different types of bifurcation.

Bistability in MAP kinase pathways

Bistability underlies the maturation of frog oocytes.

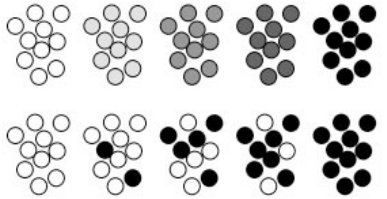


The bistability is generated by an ultrasensitive MAP kinase cascade and positive feedback.

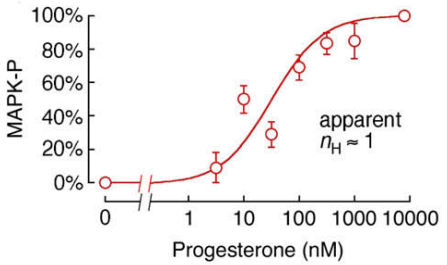


We need to look at single cells to see switching.

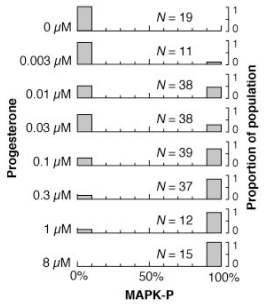
The same average behaviour detected by population-level measurements can be generated by different behaviours at the single-cell level.



Population level measurements of activated MAP kinase



Single-cell level measurements of activated MAP kinase



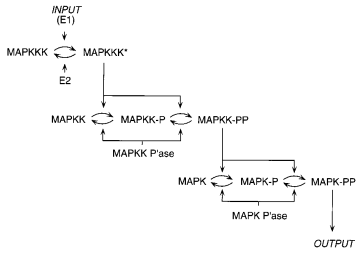
from Ferrell & Machleder, 1998

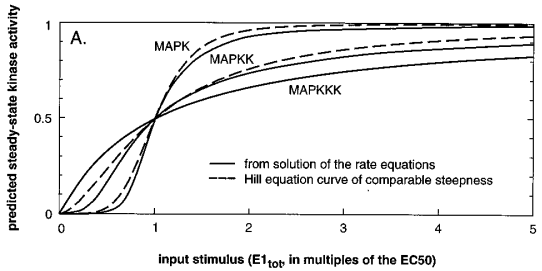
Proc. Natl. Acad. Sci. USA
Vol. 93, pp. 10078–10083, September 1996
Biochemistry

Ultrasensitivity in the mitogen-activated protein kinase cascade

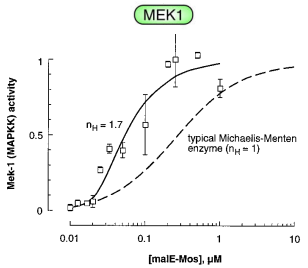
CHI-YING F. HUANG AND JAMES E. FERRELL, JR.†

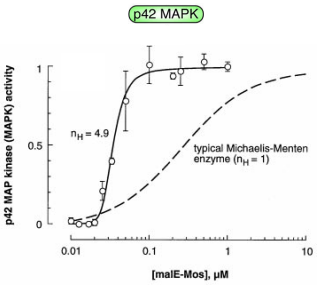
Requiring two phosphorylations for activation and distributive phosphorylation generates a response that becomes more ultrasensitive with each step of the cascade.

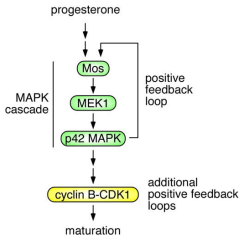




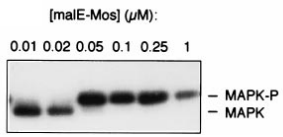
The prediction of ultrasensitivity increasing down the cascade conforms with experiments.







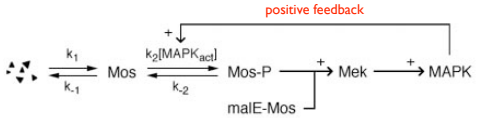
Levels of MAP kinases were measured using Western blots.



malE-Mos is an exogenously expressed version of Mos.

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

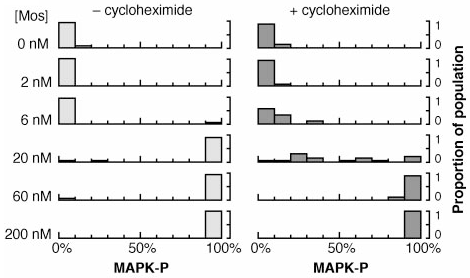
James E. Ferrell Jr.* and Eric M. Machleder



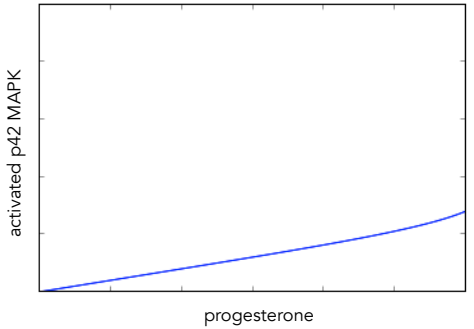
Positive feedback is also present and is required for bistable, or "all-or-none", behaviour.

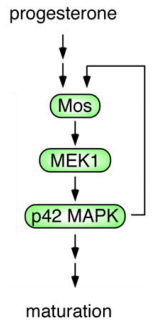
With cycloheximide, which inhibits translation, bistability, but not ultrasensitivity, is lost.

Positive feedback requires the synthesis of new proteins.

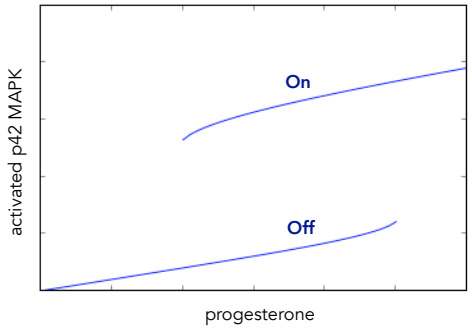


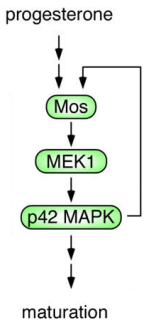
The p42 MAP kinase becomes more active as levels of progesterone increase.



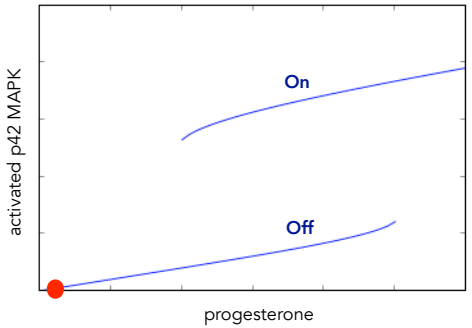


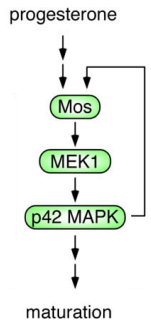
Increasing positive feedback allows the system to become either "on" or "off".





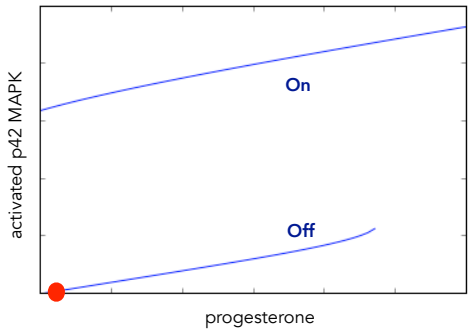
With an "on"and an "off" state possible for the same level of progesterone, the system has memory.



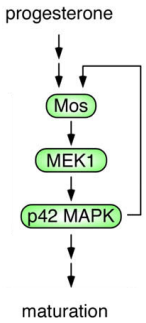


The cell remembers because the level of progesterone at which it jumps to the alternative state depends on whether the cell was initially "on" or "off".

With strong feedback, the memory can become permanent.



Even when levels of progesterone fall to zero, the cell remains "on". The cell has differentiated.



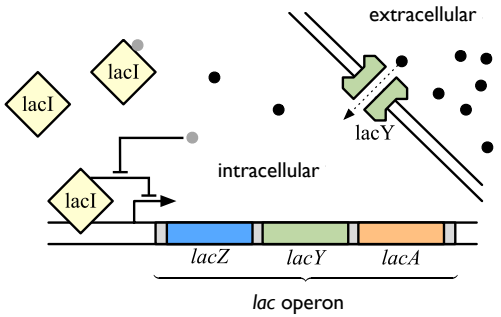
Other examples

Bistable behaviour in a genetic network relies on positive feedback and exhibits hysteresis.

Multistability in the lactose utilization network of *Escherichia coli*

Ertugrul M. Ozbudak[1*], Mukund Thattai[1*], Han N. Lim[1], Boris I. Shraiman[2] & Alexander van Oudenaarden[1]

Positive feedback is through the permease LacY, which acts to increase its own expression.

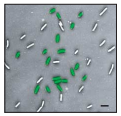


Expression from the network exhibits hysteresis.

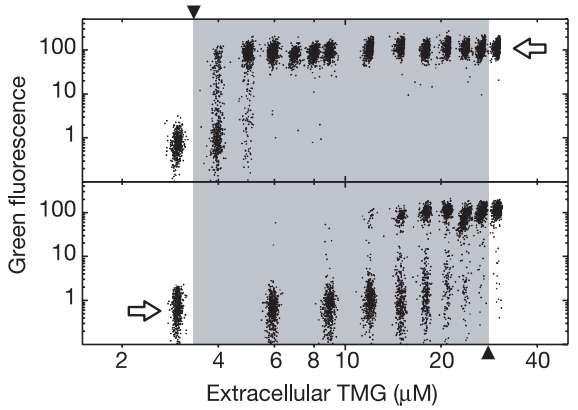
Multistability in the lactose utilization network of *Escherichia coli*

Ertugrul M. Ozbudak[1*], Mukund Thattai[1*], Han N. Lim[1], Boris I. Shraiman[2] & Alexander van Oudenaarden[1]

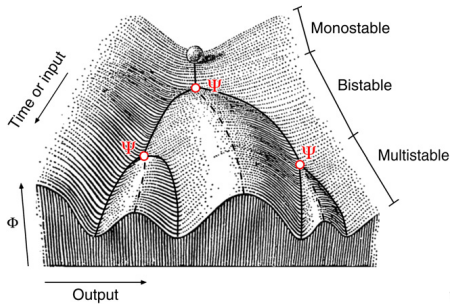
GFP synthesized from a copy of a promoter in the network is used to measure output.



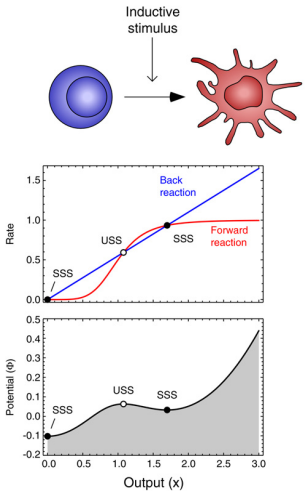
Hysteresis: two different concentrations of inducer (TMG) cause switching of expression

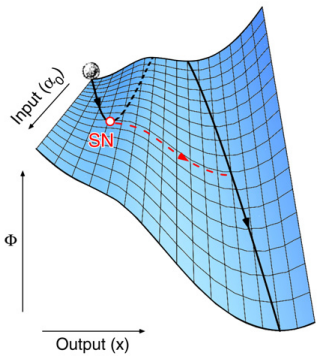


Waddington's epigenetic landscape illustrates how an undifferentiated cell progresses to one of several possible differentiated states



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