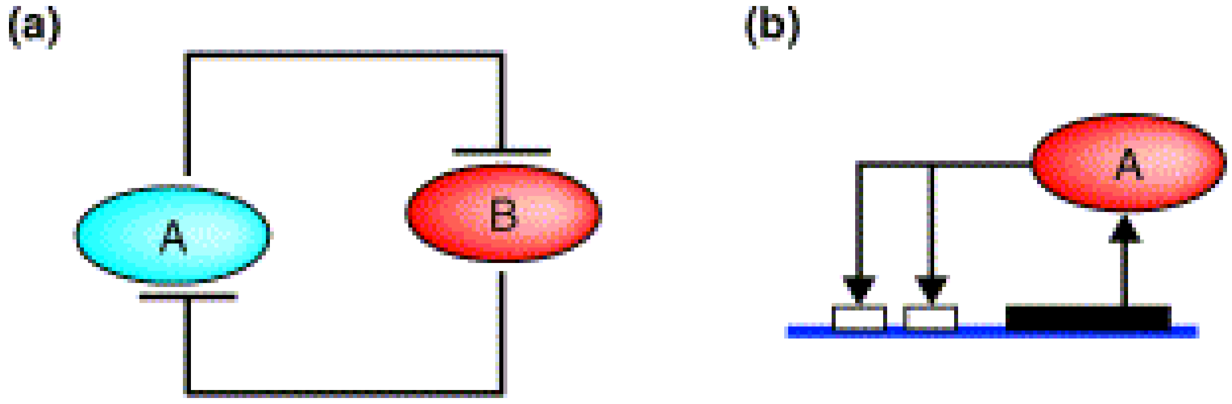
„Self Control is the quality that distinguishes the fittest to survive”

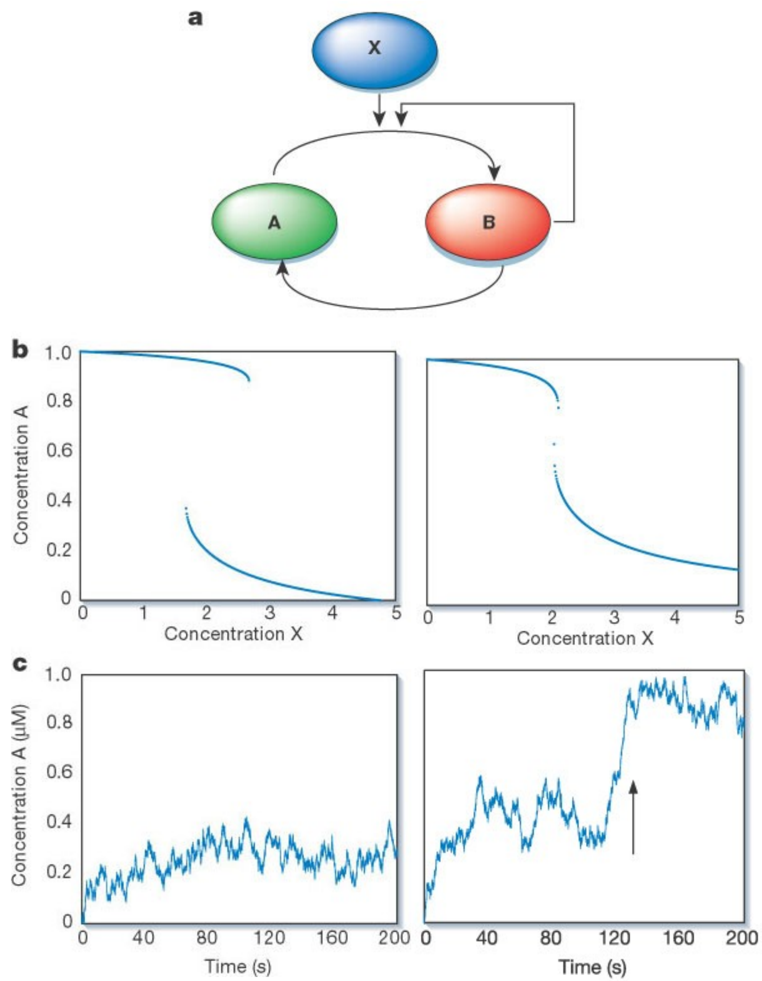
- George Bernard Shaw

More genetic switches



Gen-Regulation with feedback makes a switch

„Robuste“ vs. „ultrasensitive“ Switches



Simple networks with positive feedback

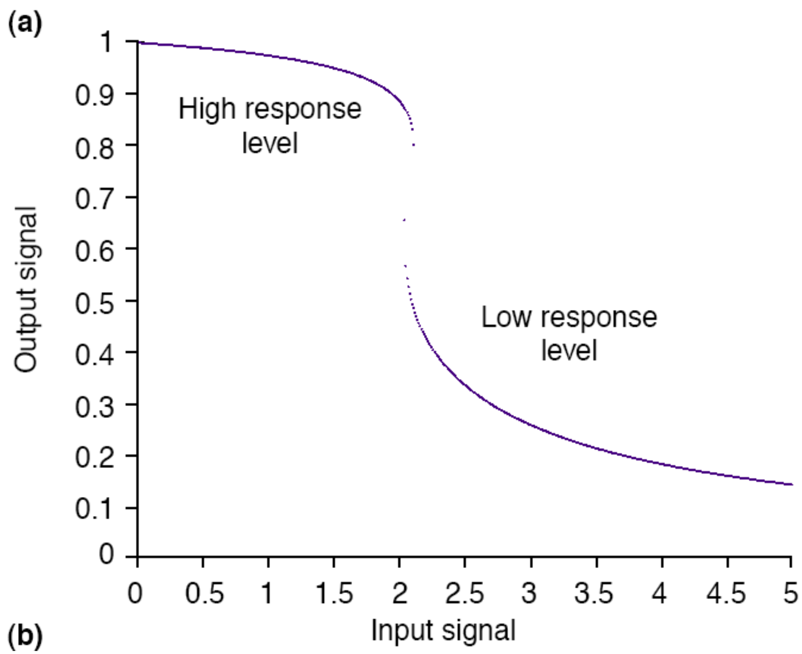
<u>Without hysteresis:</u>
Ultrasensitive switch, noise induced switching

<u>With hysteresis:</u>
Robust against noise (concentration of A stays down if it was down at the beginning)

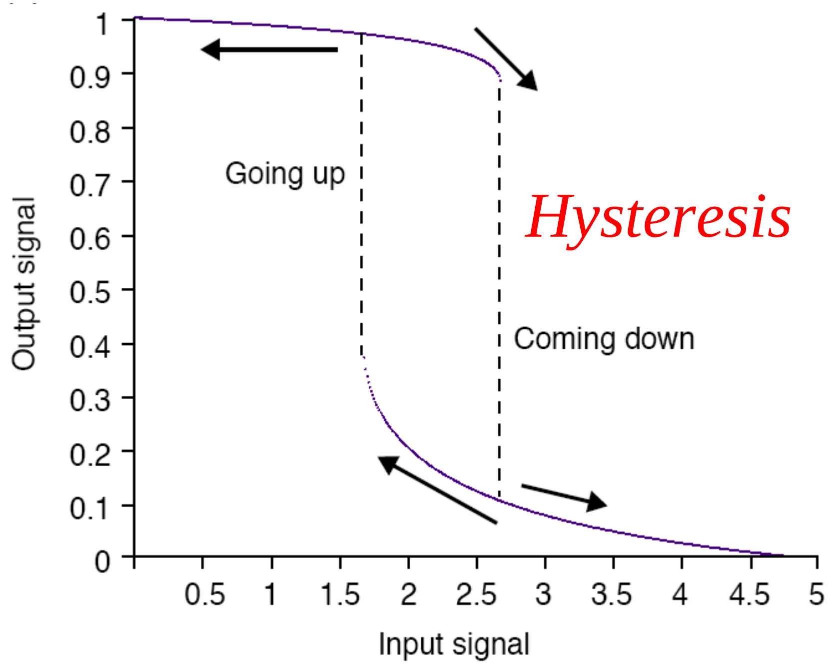
Robust switches/Hysteresis

A simple switch with psoitive feedback loop

memory-less switch



bistable switch

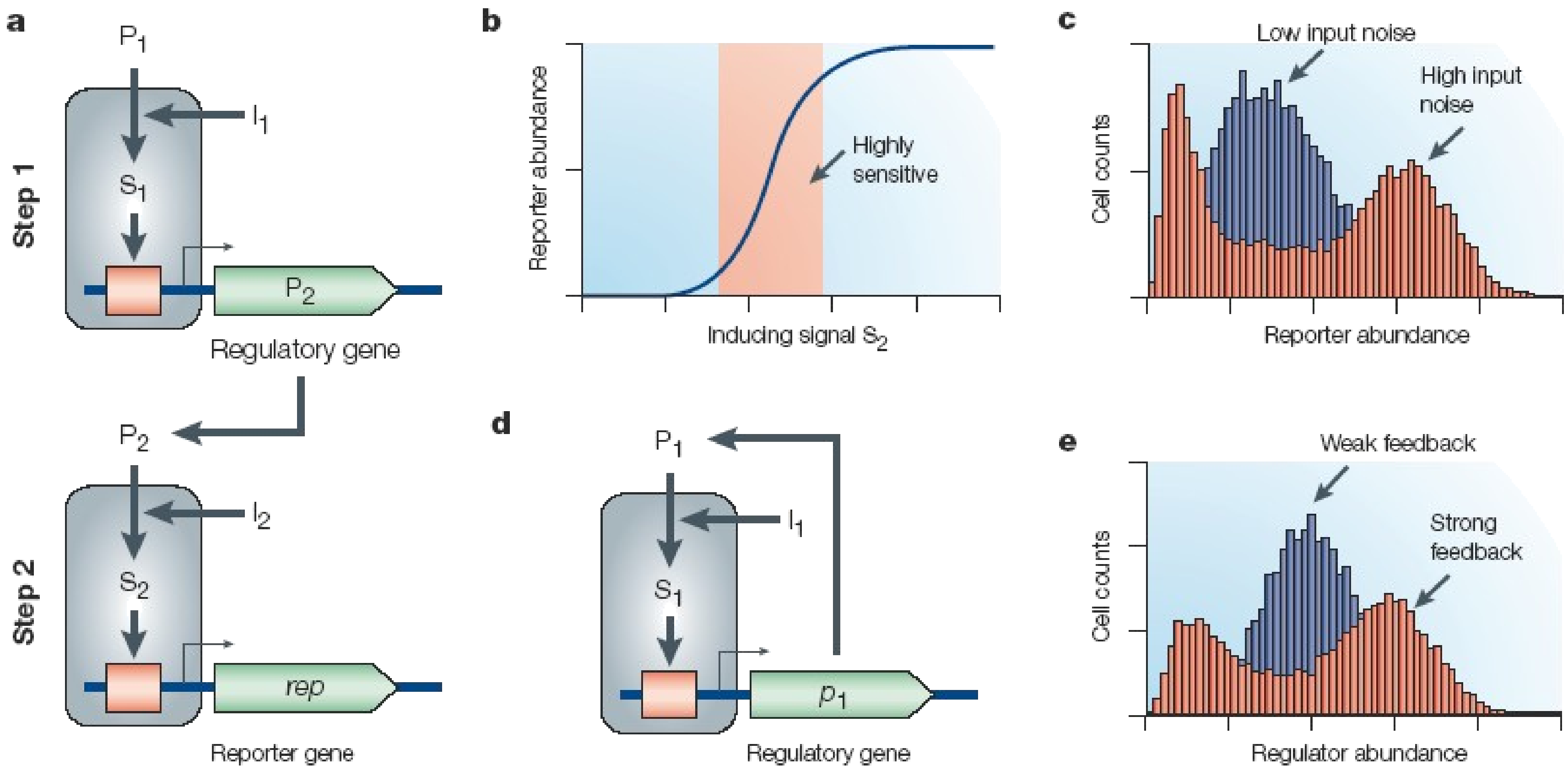


<u>without Hysteresis:</u>
Ultrasensitive switch,
Noise induced switching

<u>With hysteresis:</u>
Robust against noise (concentration of a stays low, if initial concentration is low)

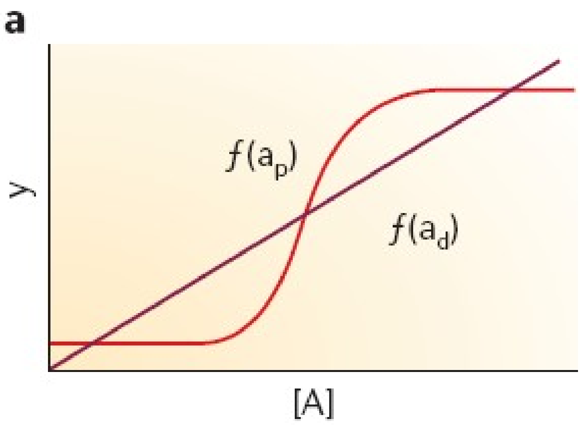
Bistabile Behaviour

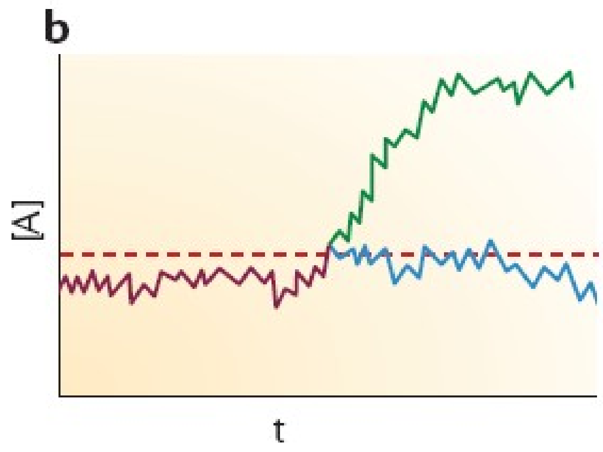
positive feedback loops lead to bistable switches



from: Kaern et al.
Nature Review 2005

Bistable genetic Switches





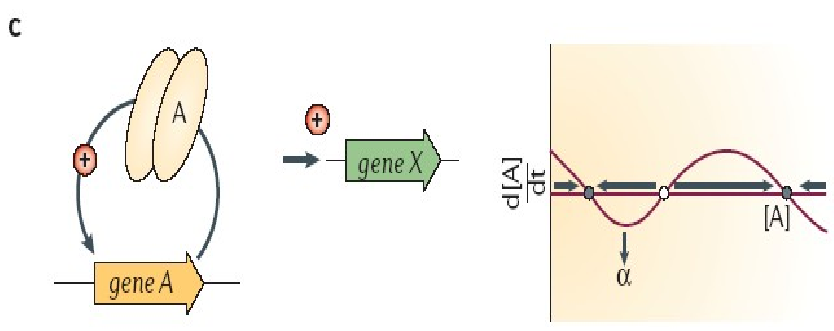
Protein A = key regulator

active when present as a multimer.

multimerization => nonlinear dynamics of the system

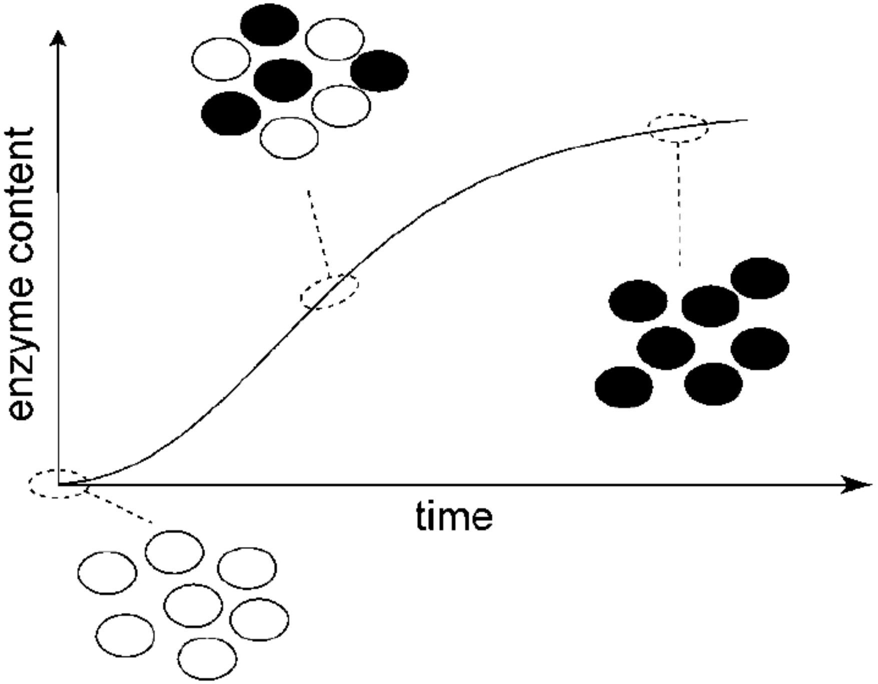
production of A, $f(a_p)$
described by Hill-type function.

deactivation rate,
described by a linear-type function, $f(a_d)$

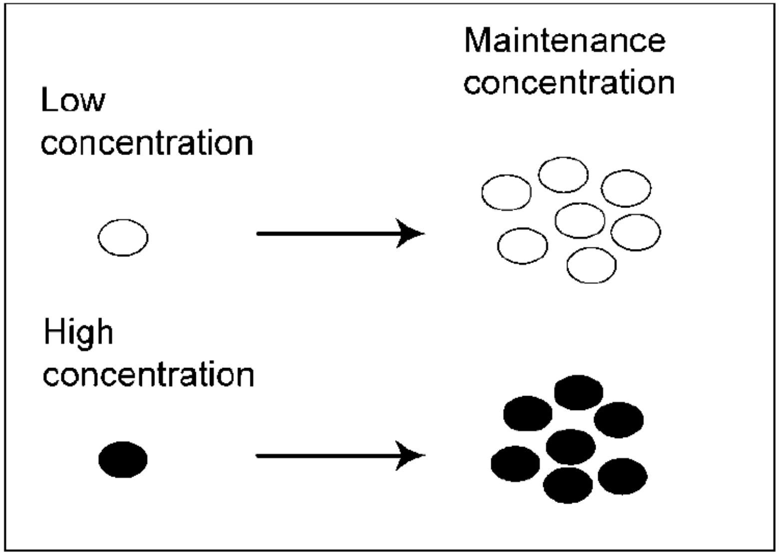


Properties of the *Lac* Network

Induction of the lac synthesis is an all-or-nothing process

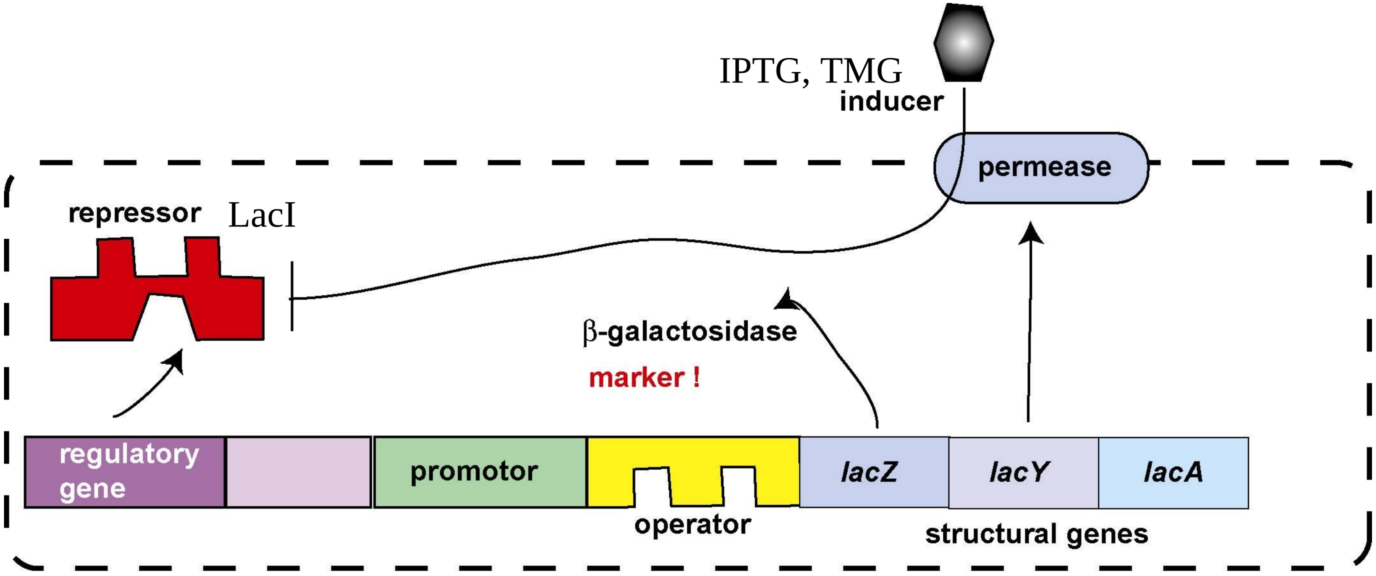


Properties of genetic networks can be inheritied



Novick & Weiner 1957

Gen-Regulation with Feedback: *lac*-Operon

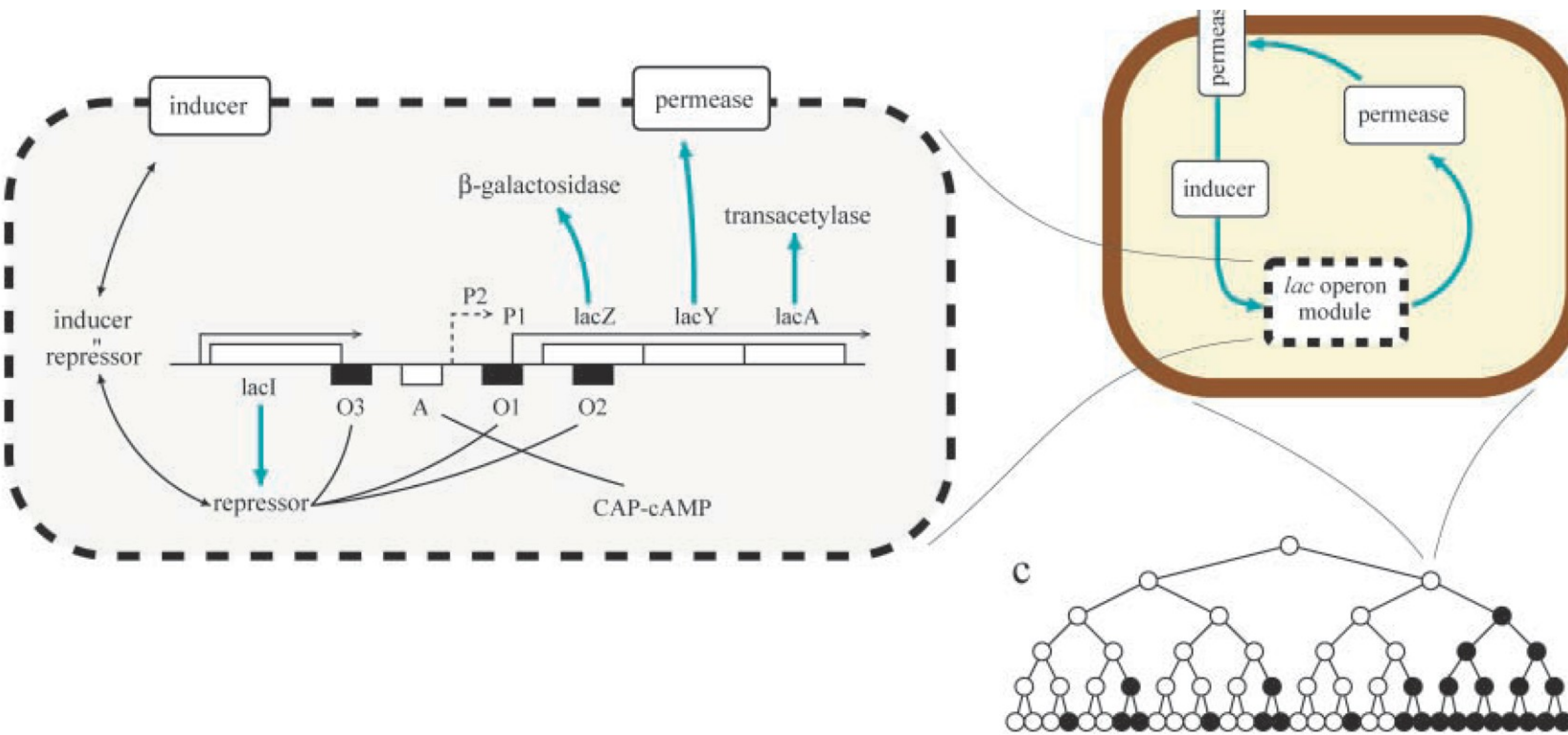


The Lactose degradation pathway

a hierarchic consideration

Molecular interactions

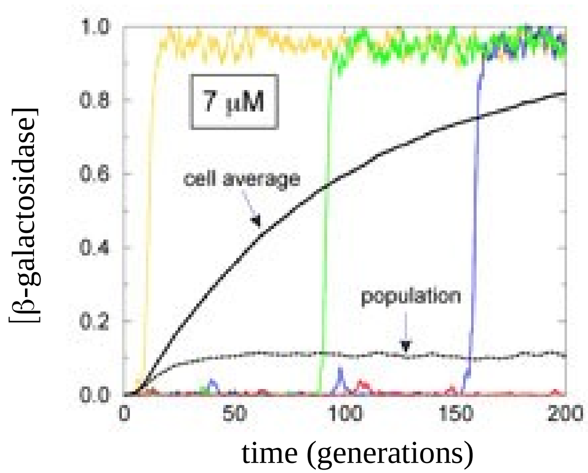
Cellular networks



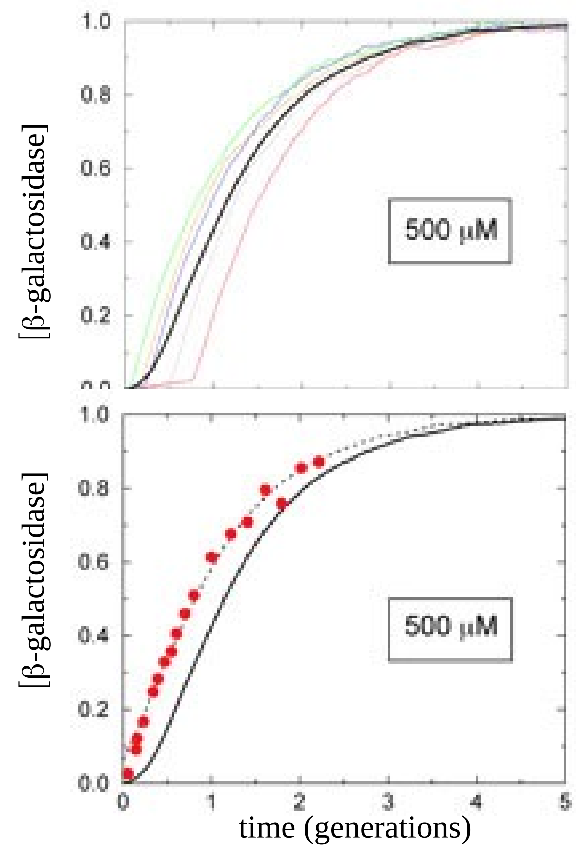
Heterogenity in population dynamics

Time behaviour of the *lac*-Operon switch

Low inductor-concentration :



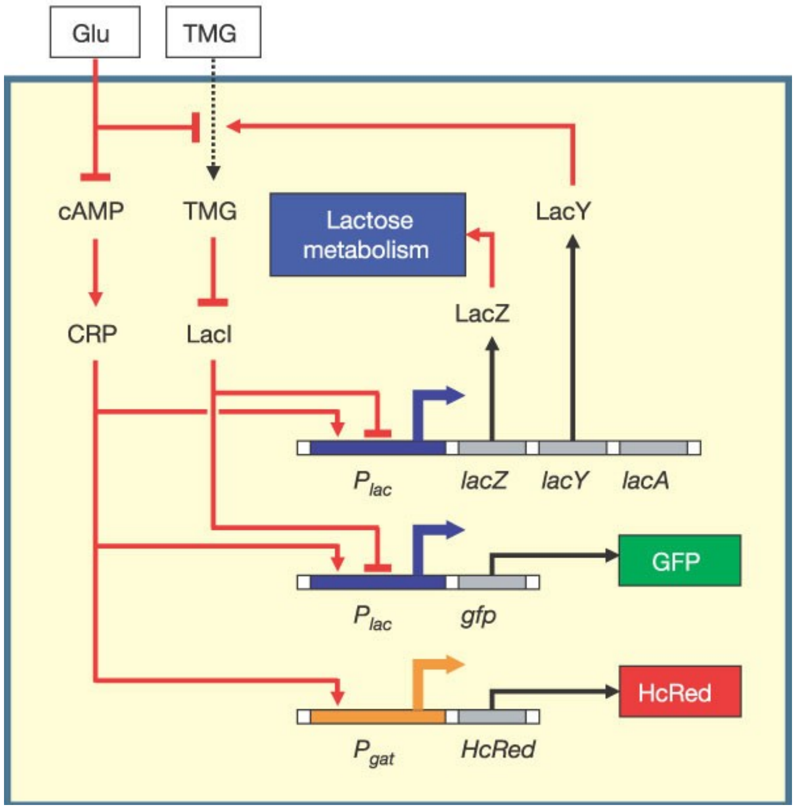
High inductor-concentration :



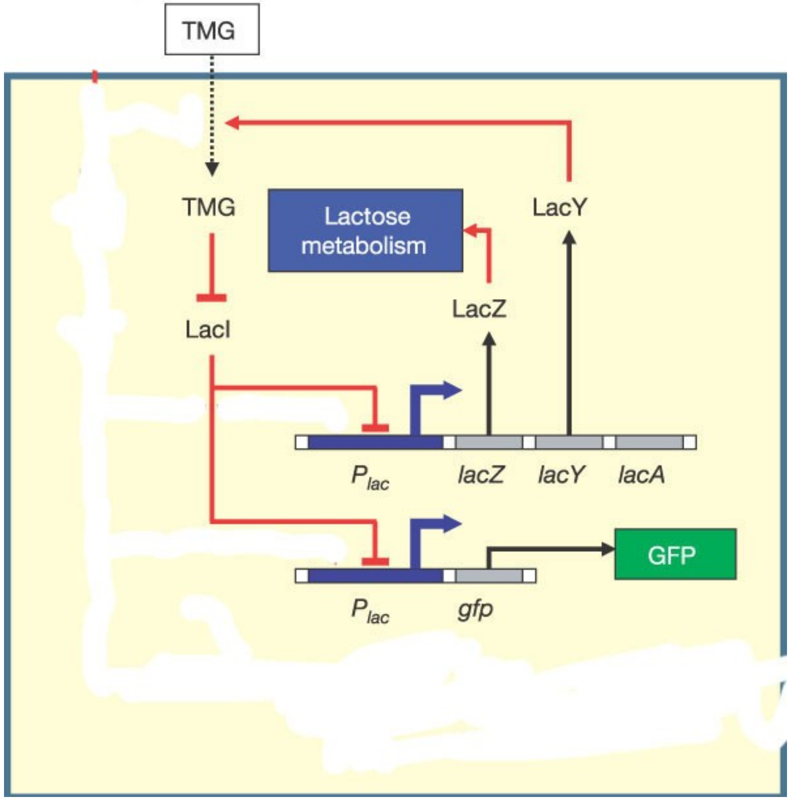
Different colors ⇔different cells
=> Cells don´t switch synchronized!
Solid line: mean value of 2000 cells
Red dots: experiment (Novik, Wiener, PNAS 1957)

Vilar, J.M.G et al, J.Cell Biol. 2003

Model for *lac* Network

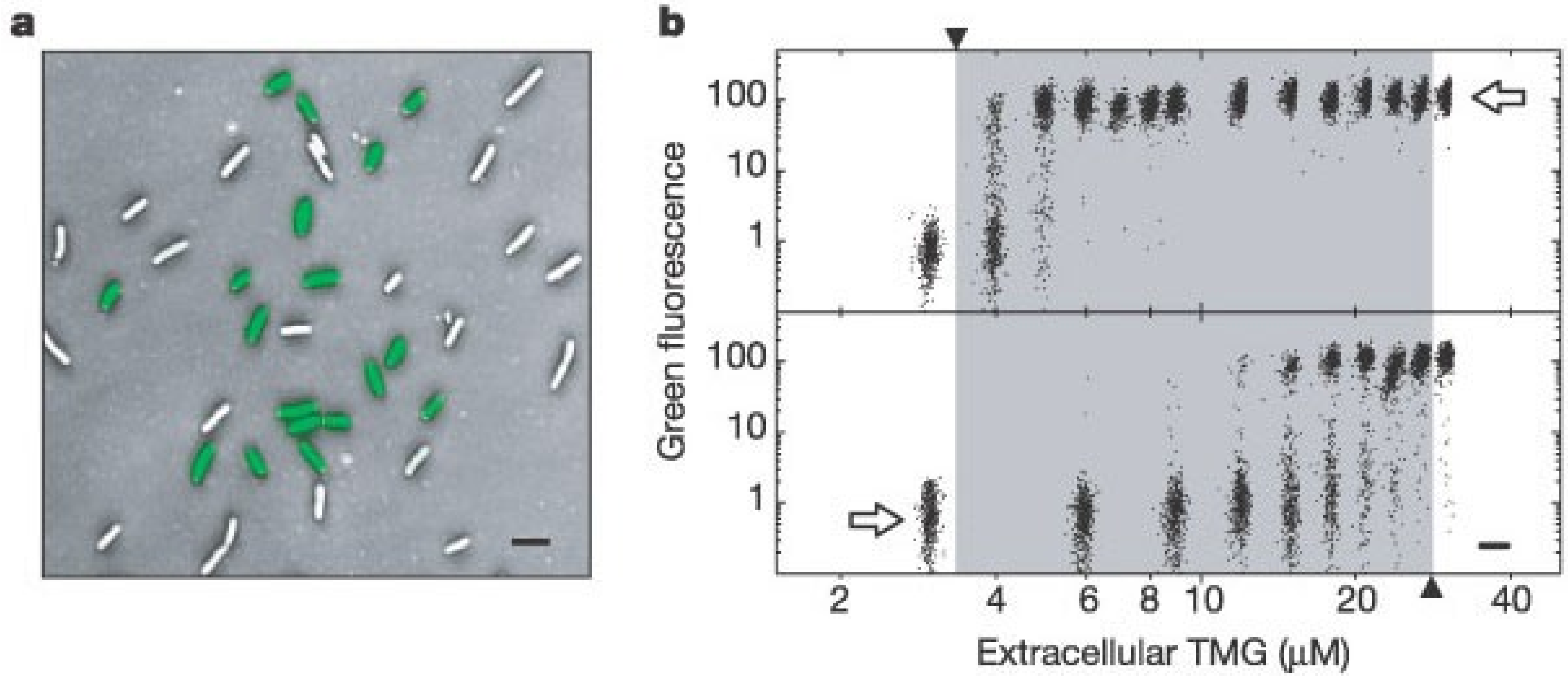


Glukose conc. constant



GFP: reportermolekule, Imaging via Fluorescence
=> The higher the fluorescence signal, the more LacZ,Y is expressed

Experimental prove of a switch with hysteresis



start: not induced

After induction appear two populations:

Induced population: green

Not induced population: white

Bistable area (grey)

Arrow marks the initial condition of bacteria!

State of bacteria depends on the initial state

=> Switch with hysteresis

Ozbudak et al, Nature 2004

Modell for *lac* Network

$$\tau_y \frac{dy}{dt} = \alpha \frac{1}{1 + R/R_0} - y$$

$$\tau_x \frac{dx}{dt} = \beta y - x$$

$$\frac{R}{R_T} = \frac{1}{1 + \left(x/x_0\right)^n}$$

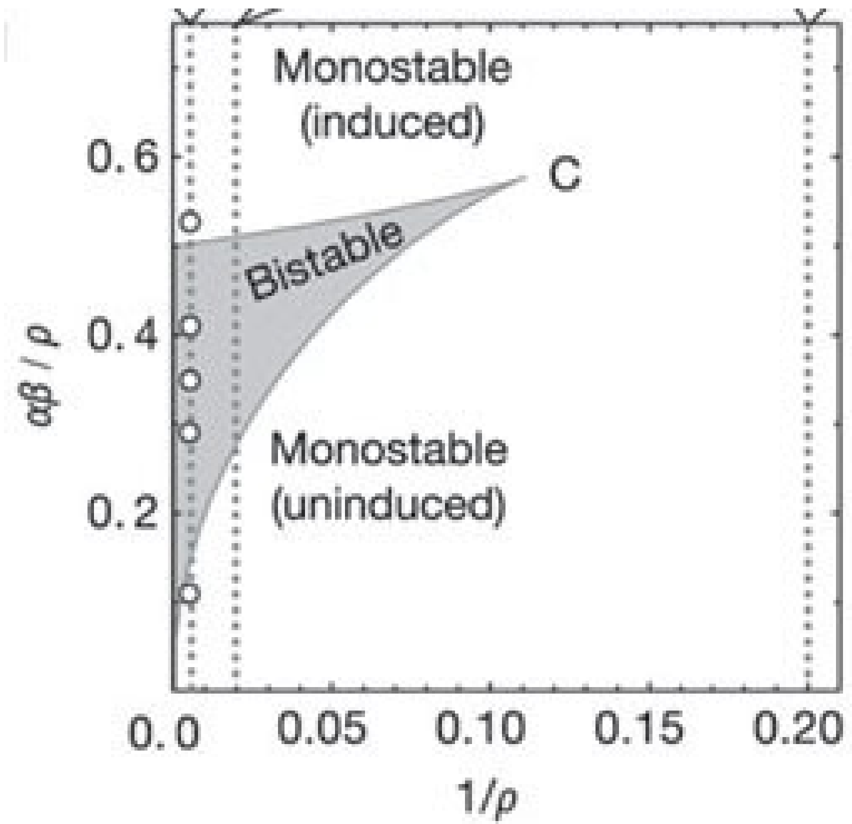
steady state:

$$y = \alpha \frac{1 + (\beta y)^2}{\rho + (\beta y)^2}$$

x: intracellular TMG concentration
y: concentration of LacY (permease) (measured in GFP fluorescence units)
R: concentration of active LacI (repressor)
$\mathbf{R_T}$: total concentration LacI
n: Hill coefficient (LacI is tetrameric, but 1 TMG is sufficient to interfere with LacI activity) $n \approx 2$
α: maximal activity level (if all repressors were inactive)
β: transport rate, TMG uptake rate per LacY
$\rho = 1 + R_T / R_0$: repression factor
$\mathbf{R_0}$: half saturation concentration
$\mathbf{x_0}$: half saturation concentration
$\boldsymbol{\tau_x}, \boldsymbol{\tau_y}$: time constants

Ozbudak et al, Nature 2004

Phase diagramm



- large ρ: discontinous transition from uninduced state to induced state ➔ Phase transition of 1.Order
- small ρ: continous transition form uninduced state to induced state➔ Phase transition of 2.Order
- in wildtype bacteria, only discontinous transitions are observed

=> Create a mutant

α: maximal activity level (if all repressors were inactive)
β: transport rate, TMG uptake rate per LacY
$\rho = 1 + R_T / R_0$: repression factor

Ozbudak et al, Nature 2004

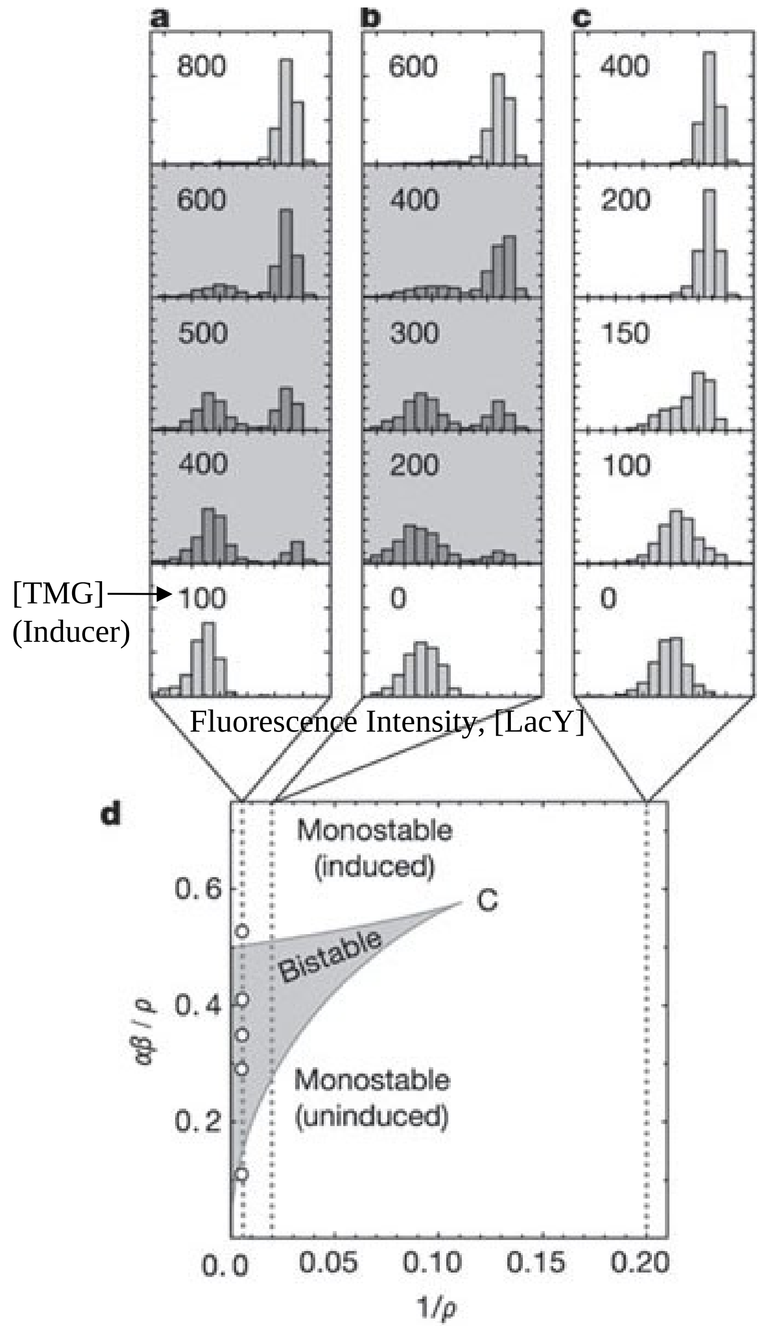
Phase diagram

lowered ρ under Wild Type niveau!

Mutant with additional binding sites for LacI Repressor (b:4, c:25) ➔ reduction of effective LacI (Repressor) concentration ➔ reduction of ρ

Fig c: Continous transition between uninduced and induced state➔NO SWITCH!

(Phase transition of 2.Order)



Dynamics of switch behavior: comparison of experiment (grey bars) and stochastic simulation (red)