The undecided cell

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Memory

How do transient stimuli produce persistent responses?

Anticipation

How does a single cell deal with what happens next?

Memory

How do transient stimuli produce persistent responses?

Anticipation

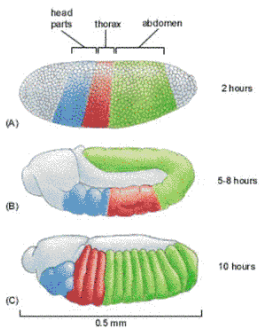
How does a single cell deal with what happens next?

Cellular memory

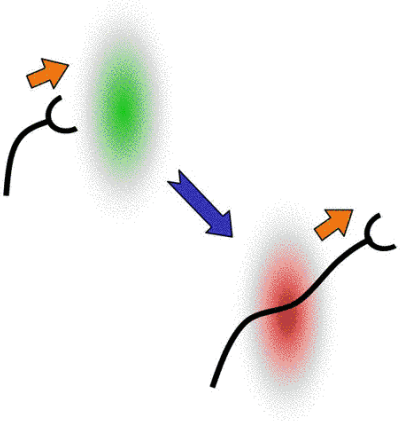
Transient stimuli produce persistent responses

Cell state is sustained though individual molecules turn over

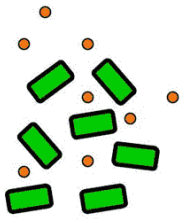
Cell fate switch



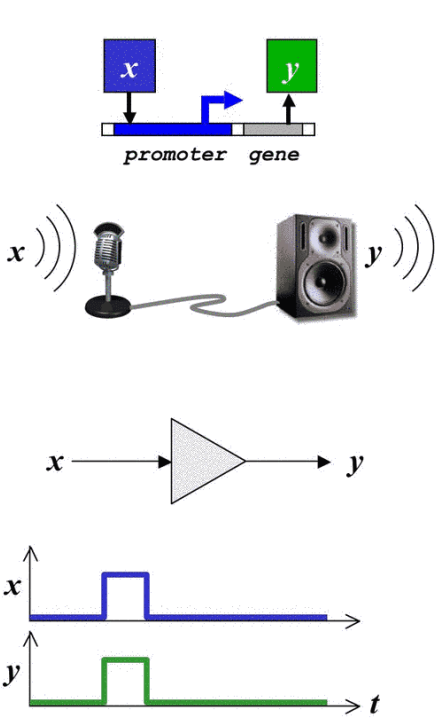
Axon guidance

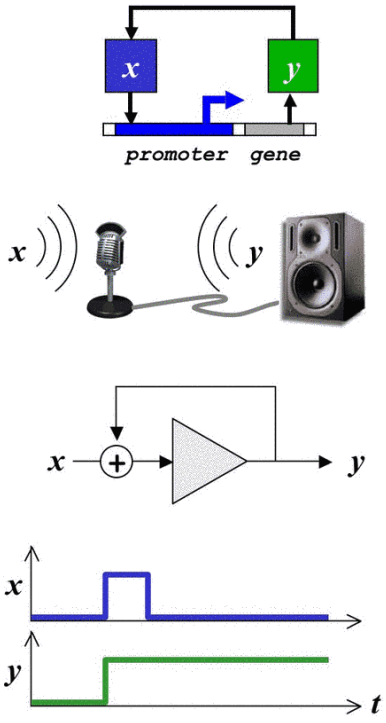


Quorum sensing

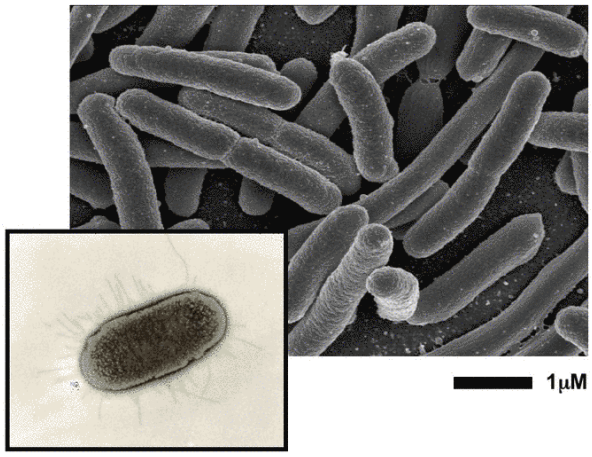


A mechanism for persistence

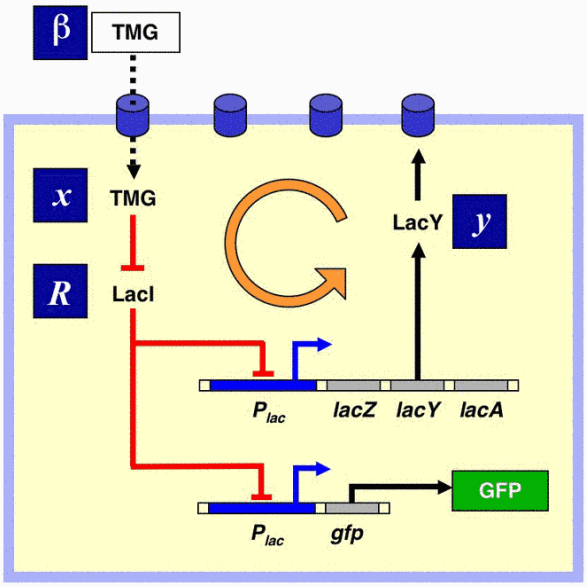




Experiments on the bacterial model system reveal general principles underlying cellular memory



Positive feedback in a bacterial regulatory network



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

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

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

$$\frac{dy}{dt} = f(y) - g(y)$$

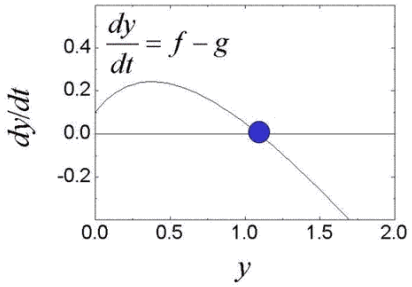
$$\frac{dy}{dt} = \alpha \frac{1+(\beta y)^n}{\rho+(\beta y)^n} - y$$

maximal activation: α

extracellular TMG: β

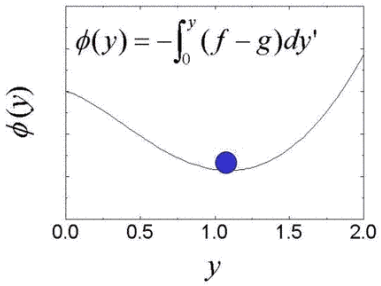
repression factor: $\rho = (1+R_T/R_0)^{-1}$

The *lac* system is bistable

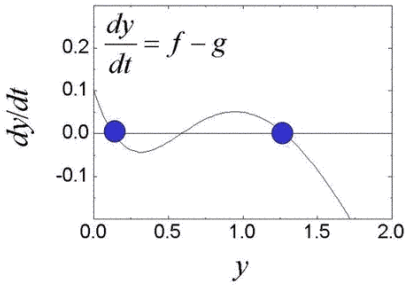


$$\frac{dy}{dt} = \alpha \frac{1+(\beta y)^n}{\rho+(\beta y)^n} - y$$

$n = 1$

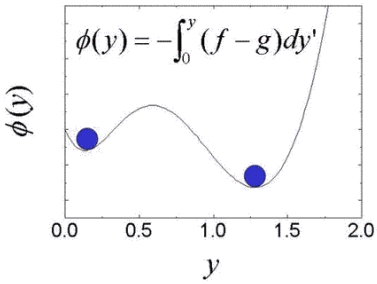


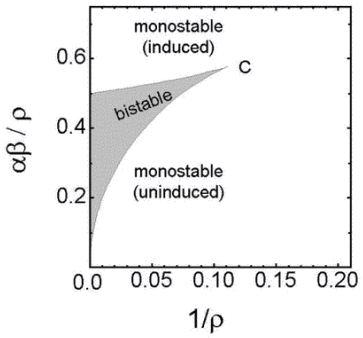
The *lac* system is bistable



$$\frac{dy}{dt} = \alpha \frac{1 + (\beta y)^n}{\rho + (\beta y)^n} - y$$

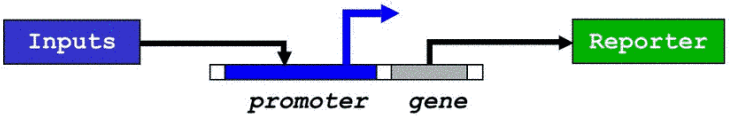
$n = 2$

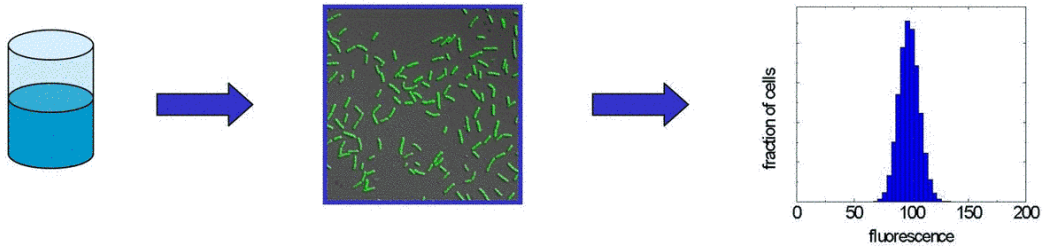




Thattai & Shraiman, Biophys. J. 85, 744 (2003).

Experimental protocol



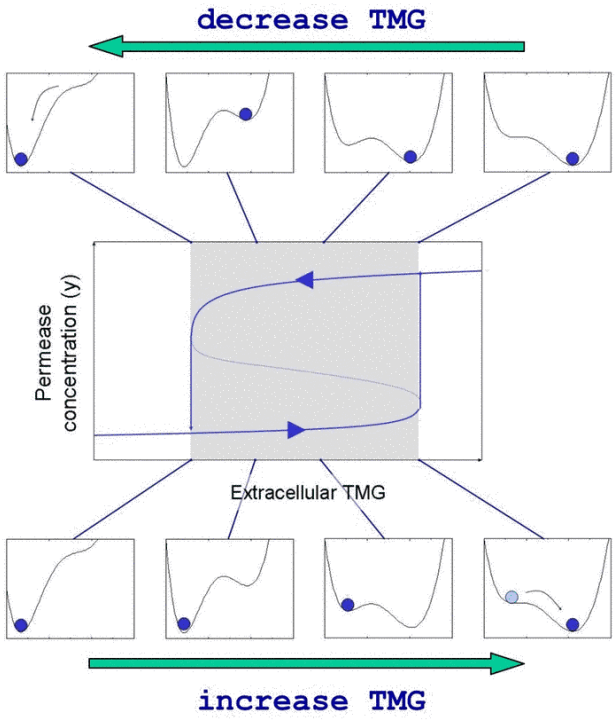


Growth conditions

Fluorescence microscopy

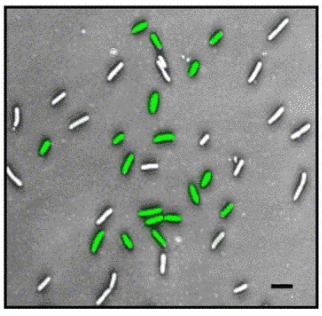
Single cell measurements

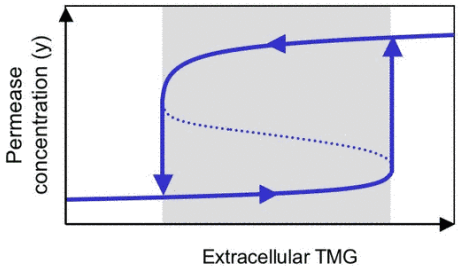
Lesson 1: Bistability allows memory storage

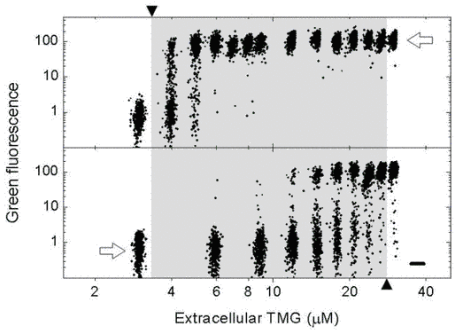


Lesson 1: Bistability allows memory storage

Single cells can be switched on and off

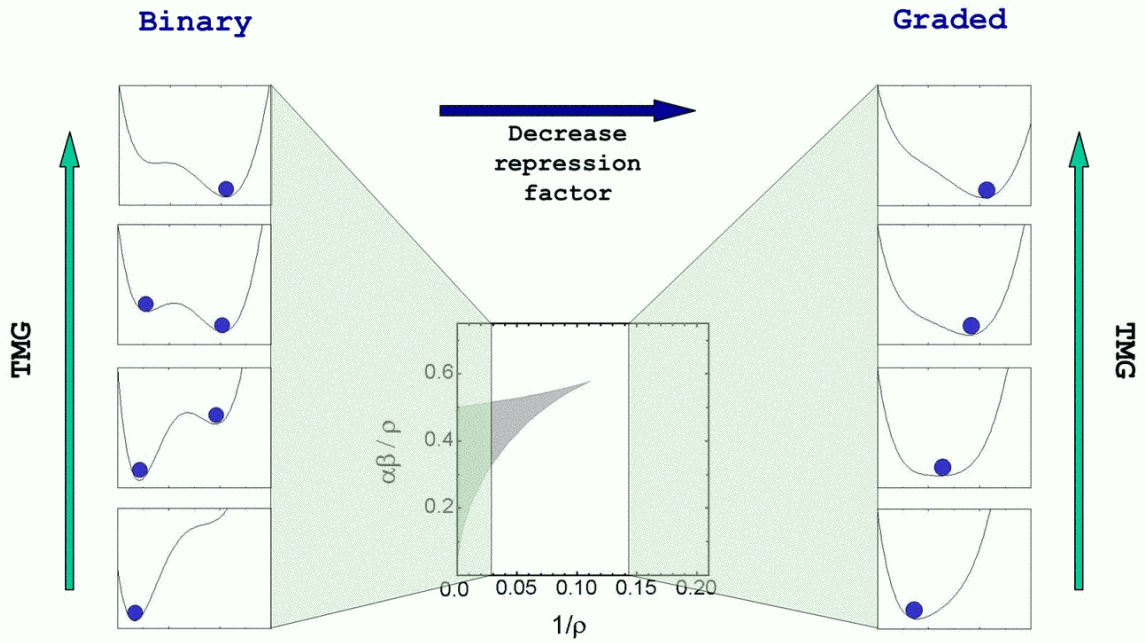




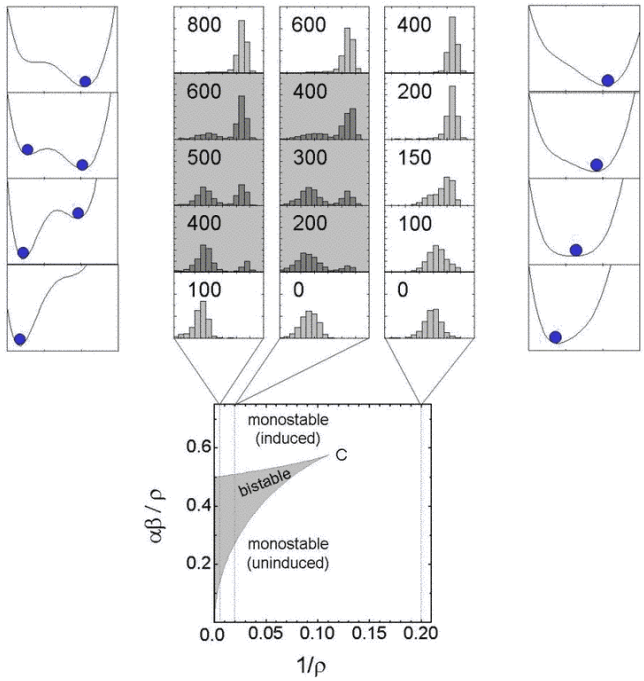


Ozbudak & Thattai et al., Nature 427, 737 (2004).

Lesson 2: System response can be either binary or graded

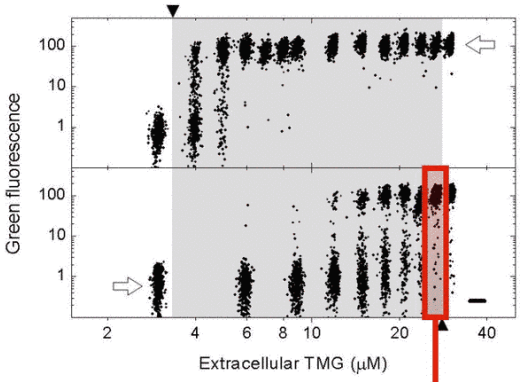


Lesson 2: System response can be either binary or graded

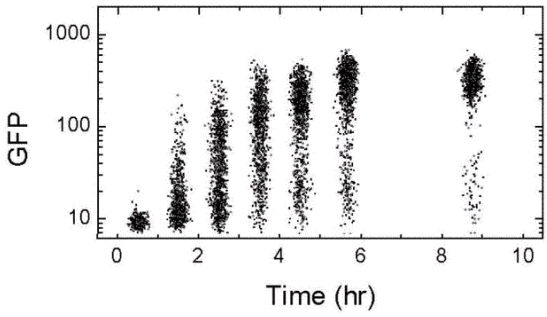


Ozbudak & Thattai et al., Nature 427, 737 (2004).

Lesson 3: The response of individual cells is extremely heterogenous



Non-uniform distribution of permease causes some cells to turn on within minutues while others stay off for several hours



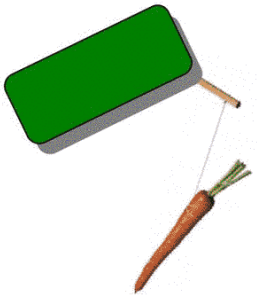
Memory

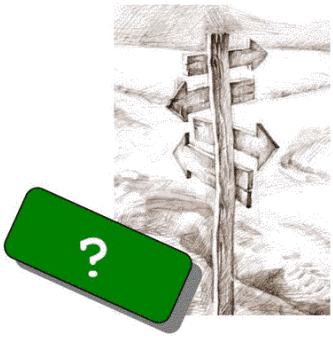
How do transient stimuli produce persistent responses?

Anticipation

How does a single cell deal with what happens next?

What is the resting state of free-living cells?





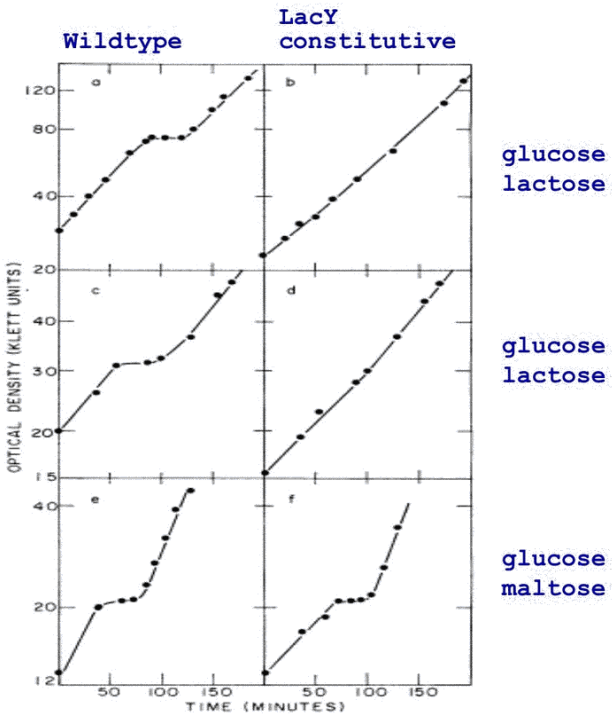
Laboratory conditions

- Time-invariant
- Dominant nutrients
- Small number of genes

Natural environments

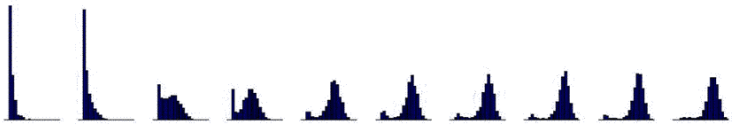
- Fluctuating, uncertain
- Diverse nutrients
- Large number of genes

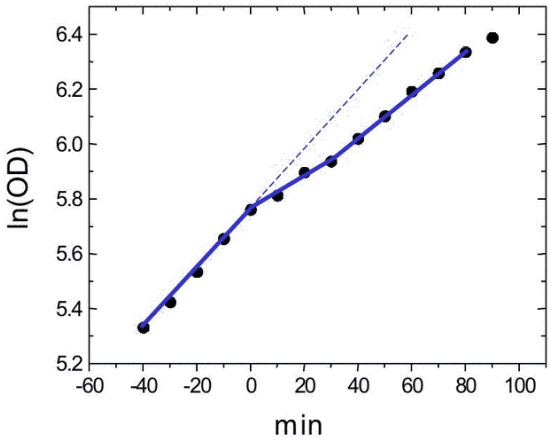
Diauxie



Loomis & Magasanik, J. Bacteriol 93, 1397 (1967).

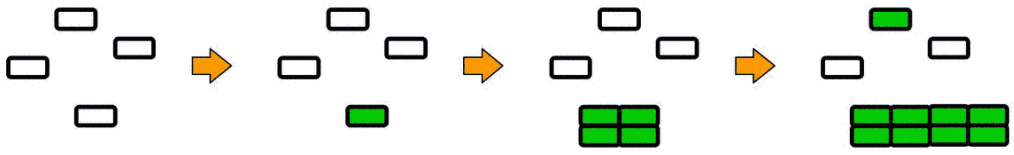
Lag phase arises from heterogeneity





succinate
lactose

A small fraction of rapidly responding cells accounts for a large fraction of the final population



How?

What are the molecular origins of this variability?

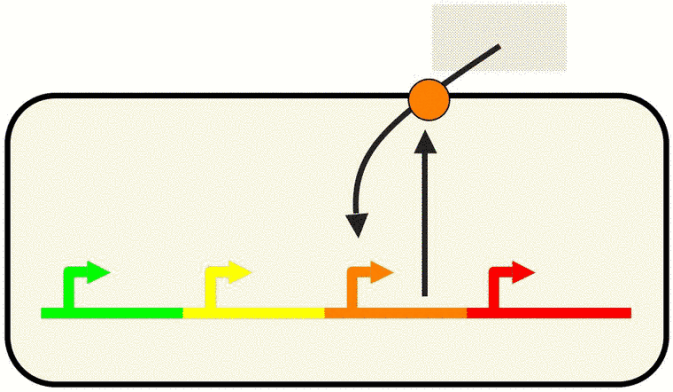
Why?

Is there any reason such a response might be selected for?

Metabolic decisions

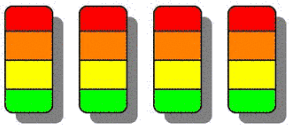
Ecoli has over 200 transporters

Metabolic commitment begins with transporter expression



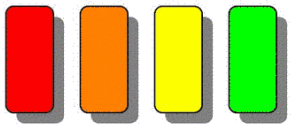
Two strategies for anticipation

homogenous

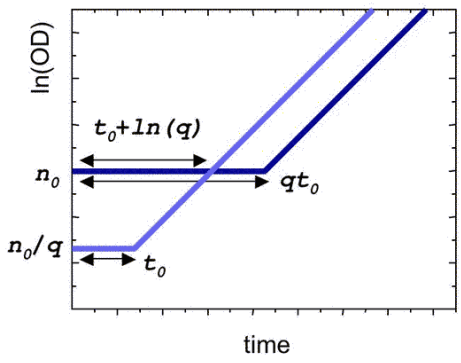


Active fraction: 1
Response time: qt_0

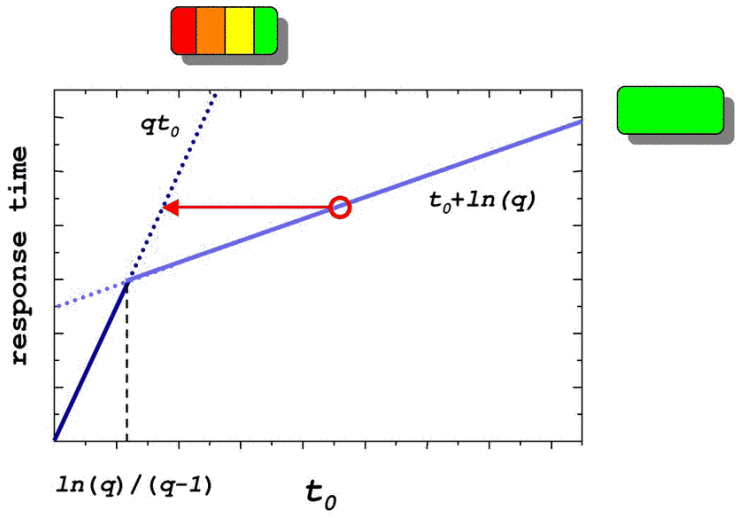
heterogenous



Active fraction: $1/q$
Response time: t_0

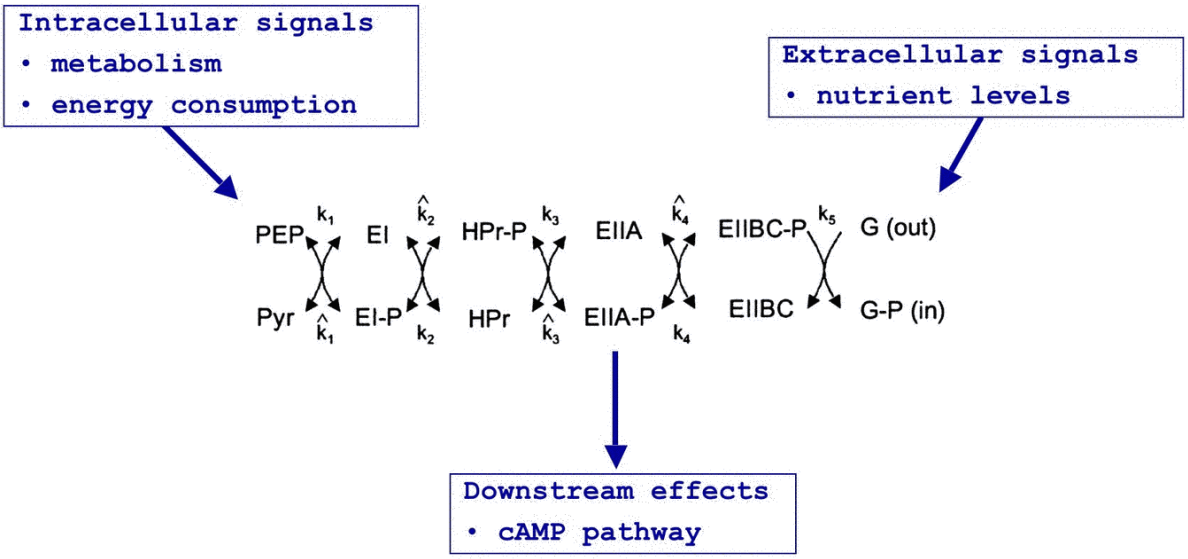


Heterogeneity is the preferred strategy

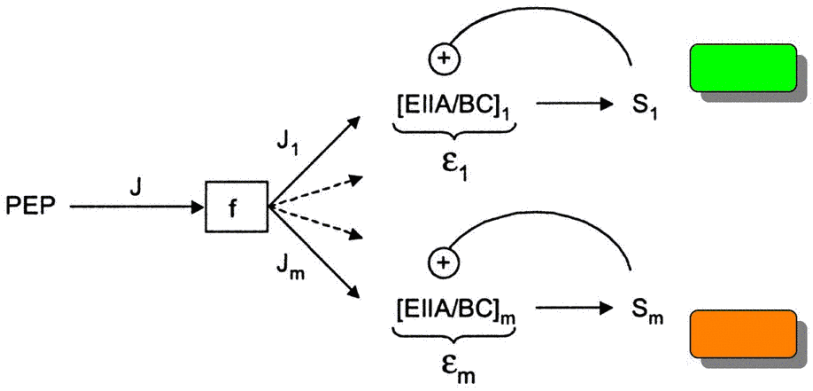


Extreme overproduction of proteins is required if homogenous populations are to match the response characteristics of heterogenous populations

The experimental system: PTS

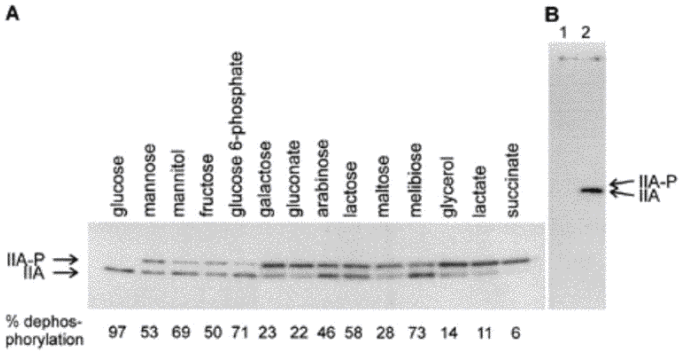


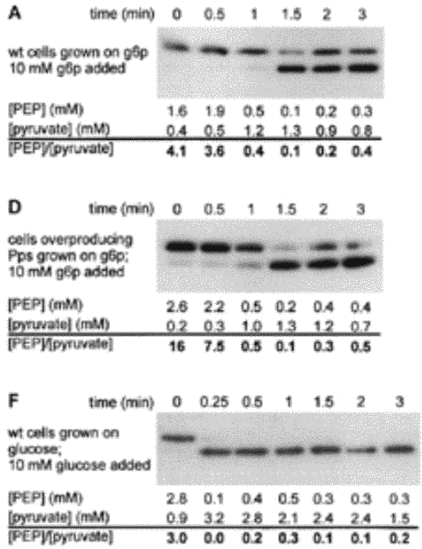
Decision making in the PTS



The system regulates the uptake of multiple carbon sources

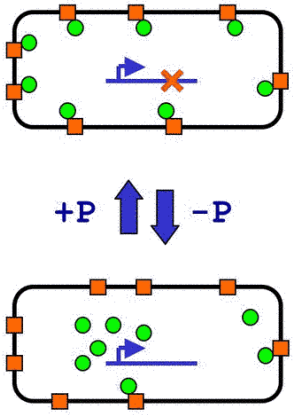
PTS phosphorylation responds to sugar uptake

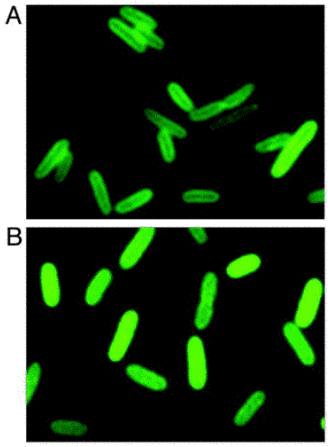




Hogema et al., Mol. Microbiol. 30, 487 (1998).

A reporter for PTS phosphorylation





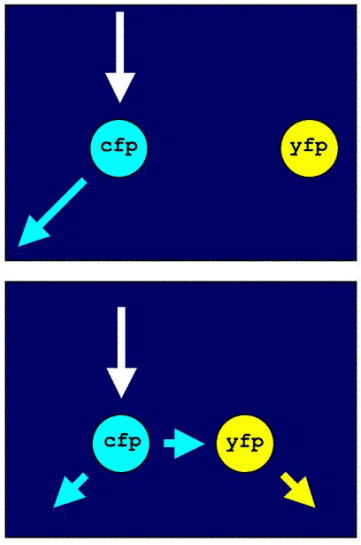
EIIABC^{Bgl} sequesters BglG to the membrane, releasing it upon dephosphorylation

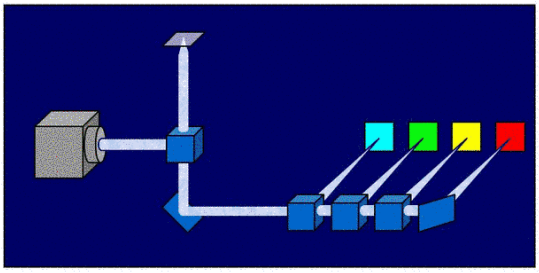
Lopian et al., Proc. Natl. Acad. Sci. USA 100, 7099 (2003)

Forster Resonance Energy Transfer (FRET)

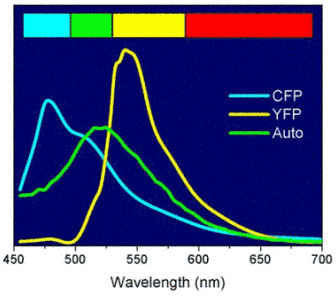
A sensitive quantitative detector of protein-protein interactions

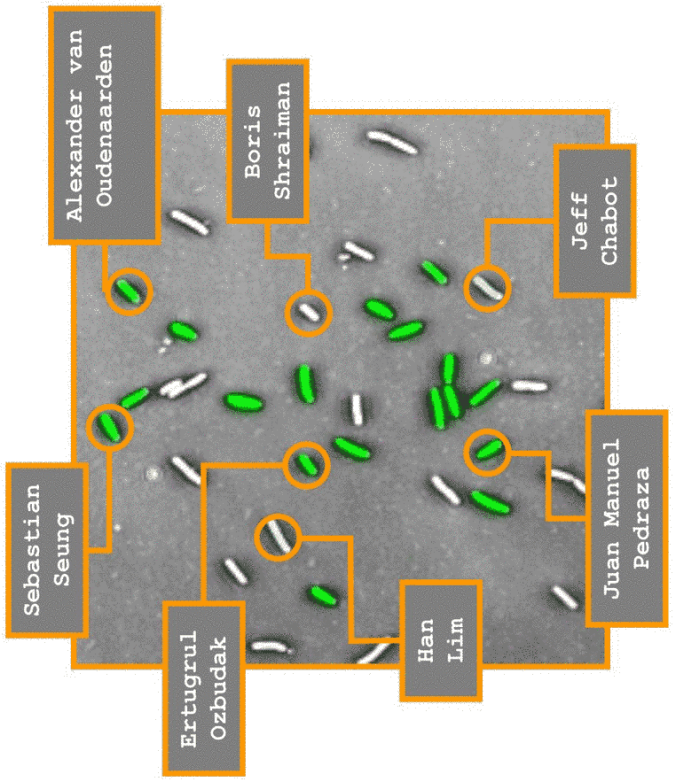
Allows the imaging of rapid signaling dynamics in single cells





Linear extraction of individual spectra




Alexander van Oudenaarden
Boris Shraiman
Jeff Chabot
Sebastian Seung
Juan Manuel Pedraza
Ertugrul Ozbudak
Han Lim