Metabolic Switching in *Escherichia coli*

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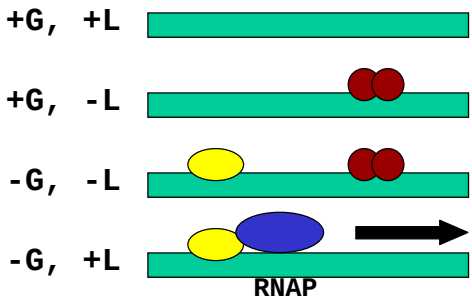
1. Phase diagram of the *lac* operon

The lac operon: A genetic switch

G ↑ ⇒ C (CRP-cAMP) ↓

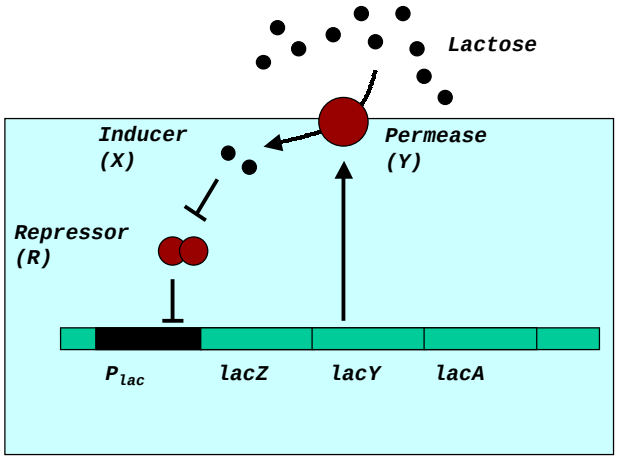
L ↑ ⇒ R (Repressor) ↓



$$\wp(on) = \frac{C}{1 + C + R + RC}$$

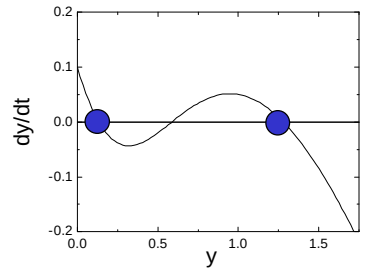
$$\wp(on) = \frac{C}{1 + C}\frac{1}{1 + R}$$

Regulation of lactose uptake: Positive feedback



Multistability in *lac* expression

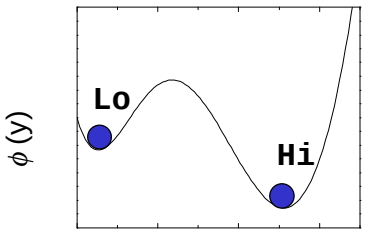
$$\frac{dy}{dt} = A\frac{v + y^2}{1 + v + y^2} - y \qquad A = \frac{\alpha_0 A_0}{\sqrt{R_T}}\frac{C}{1+C}\frac{L}{1+L} \qquad v = \frac{1}{R_T}$$



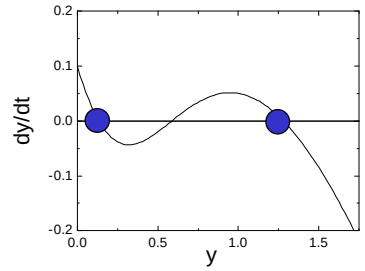
Novick & Weiner. *Proc. Natl. Acad. Sci. USA* 43, 553 (1957).

Multistability in *lac* expression

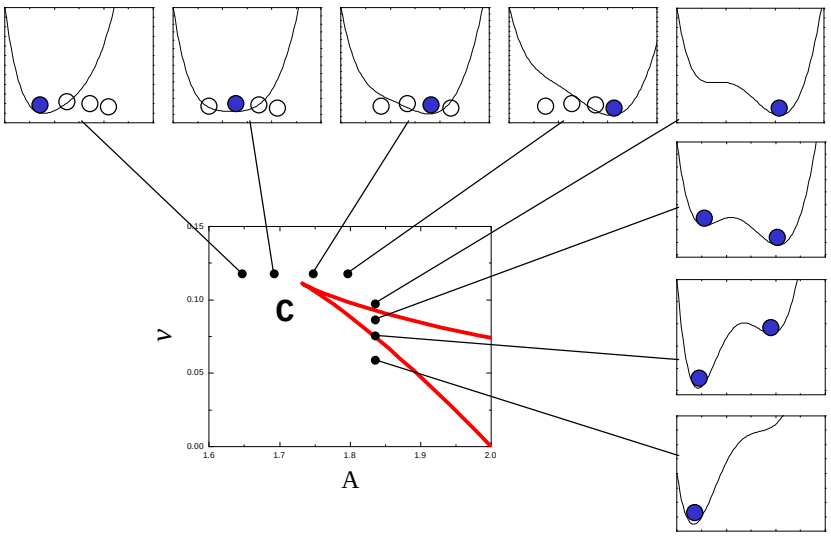
Energy



Dynamics



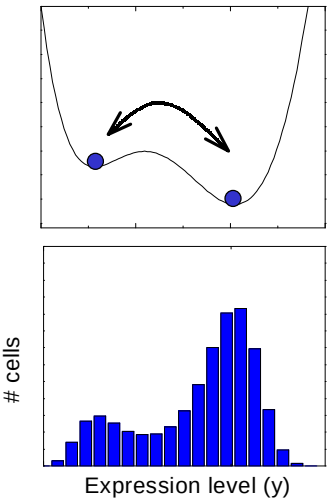
Phase diagram



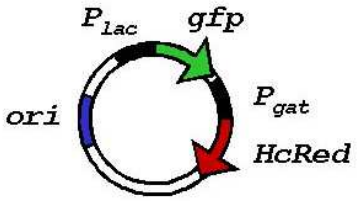
Stochastic transitions

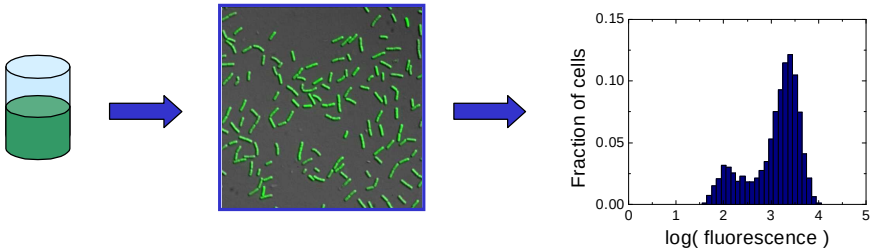
$\varphi(y)$

$e^{-\beta\varphi(y)}$



Experimental protocol

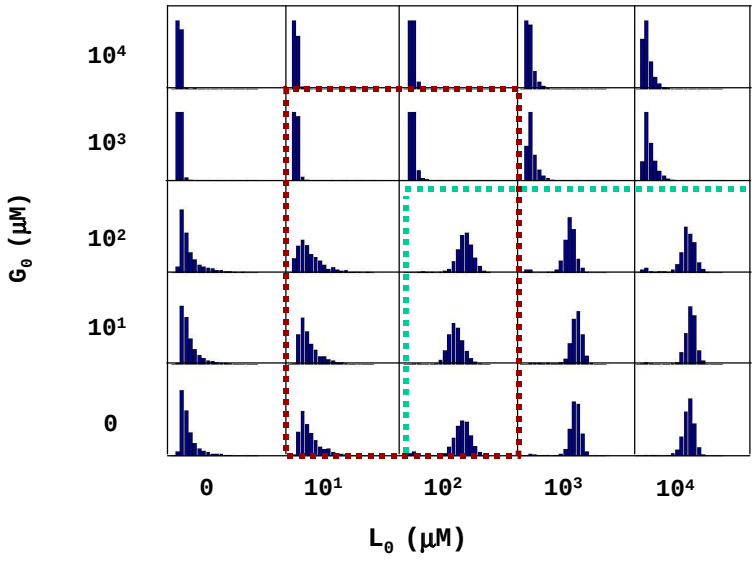


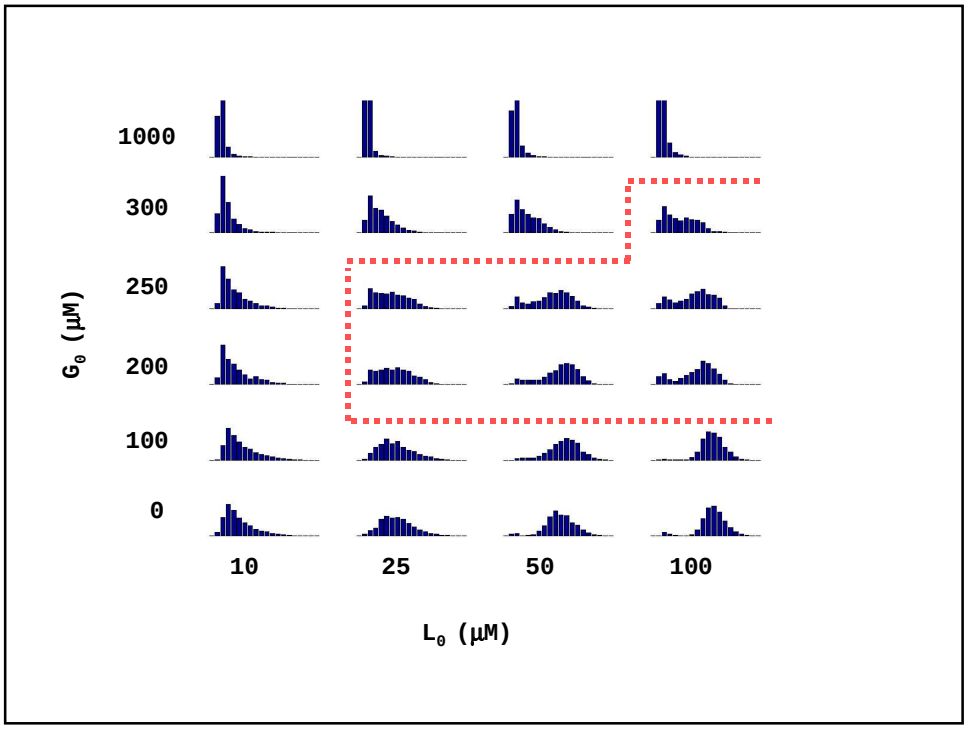


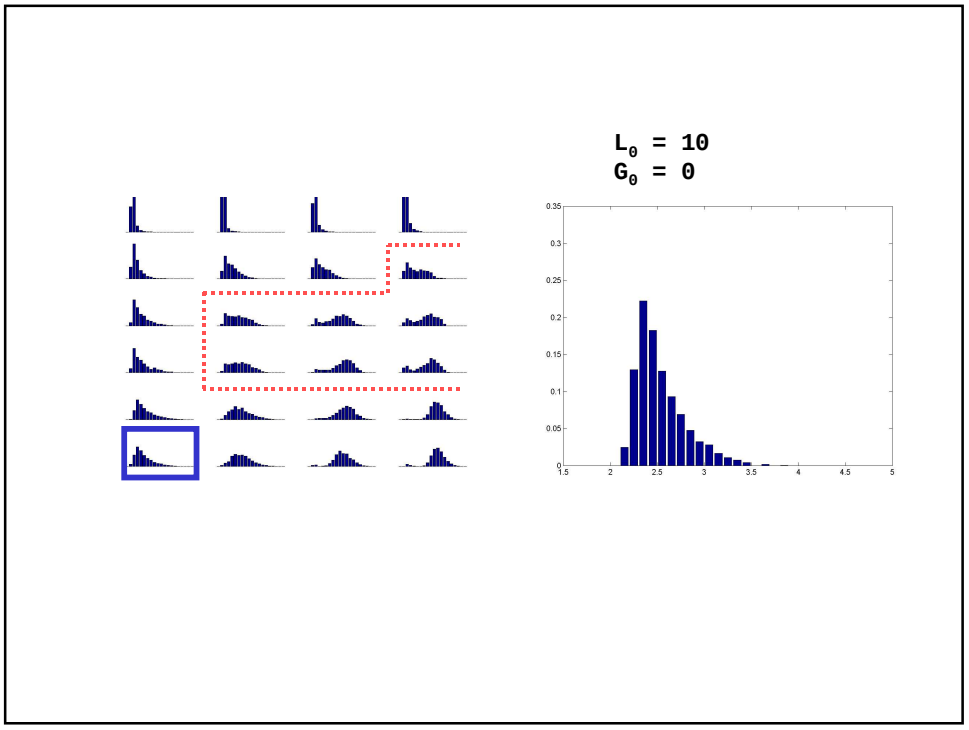
Growth conditions

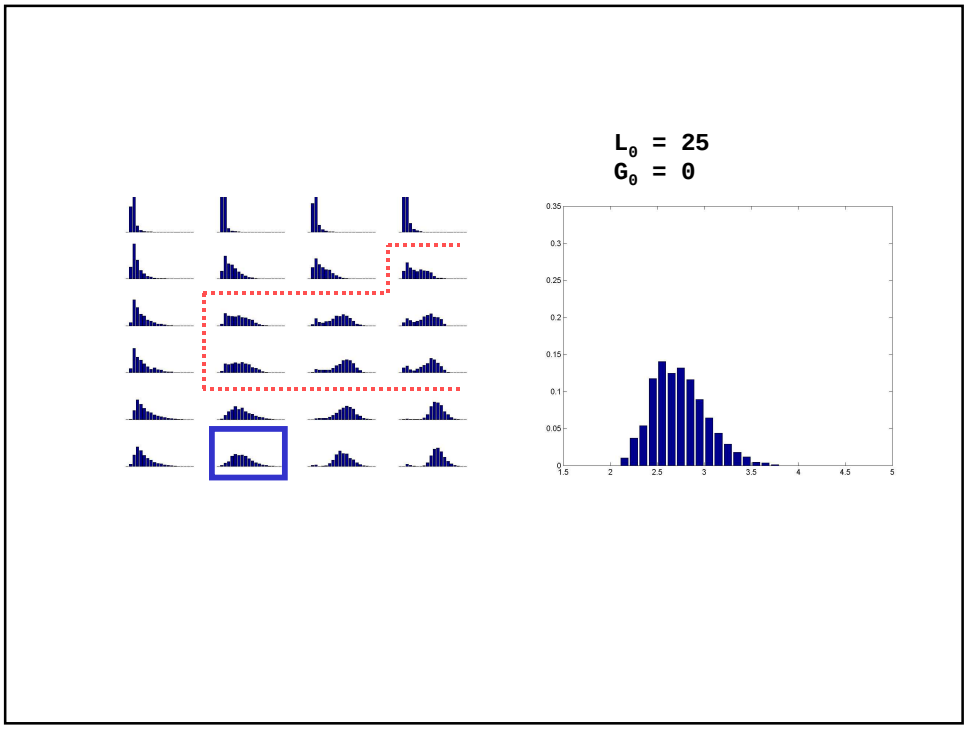
Fluorescence microscopy

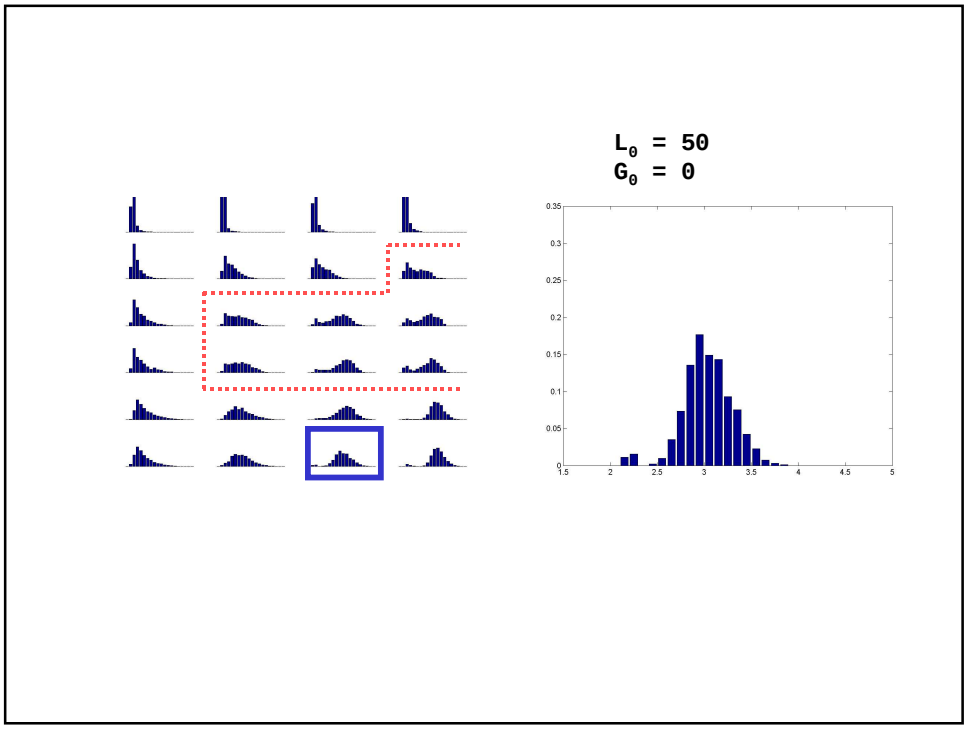
Single cell expression measurements

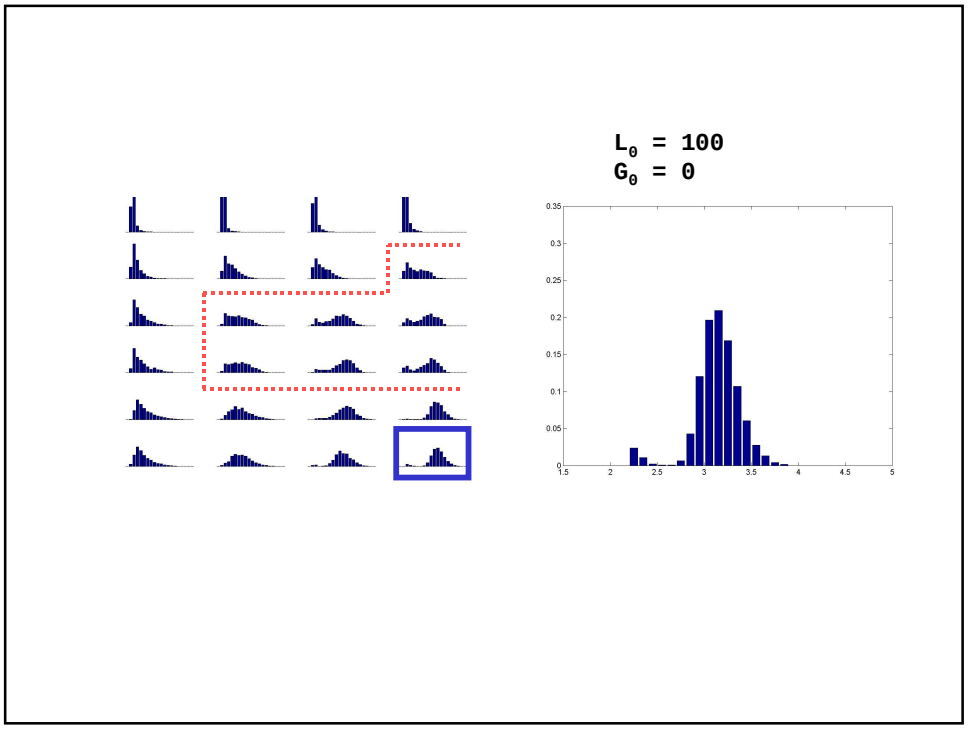


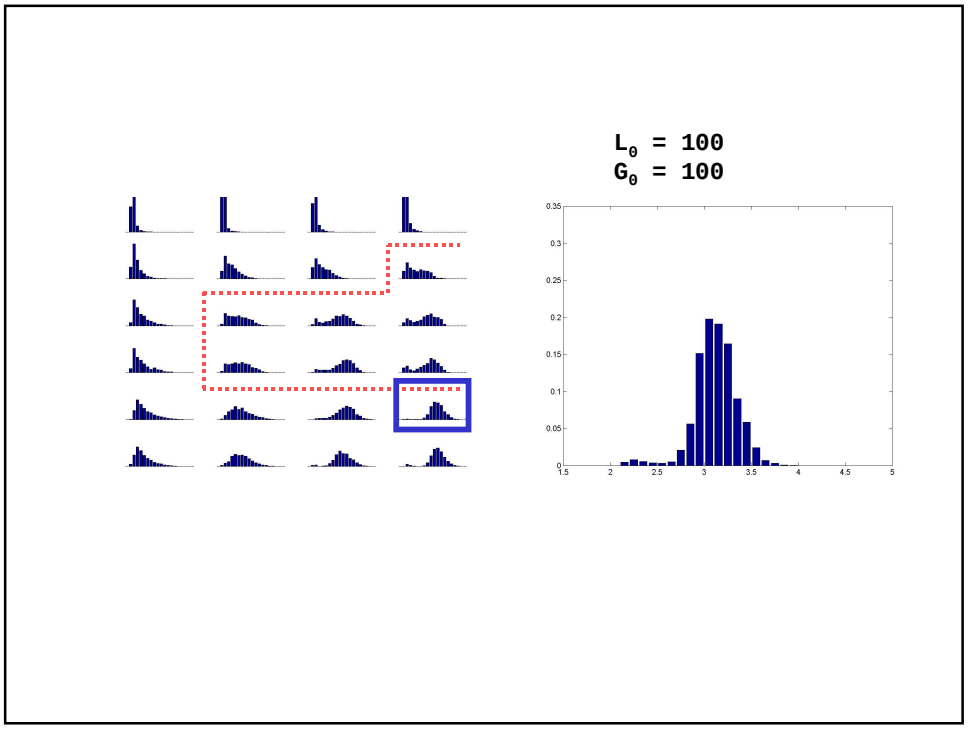

1000
300
250
200
100
0
G_0 (μM)
10
25
50
100
L_0 (μM)

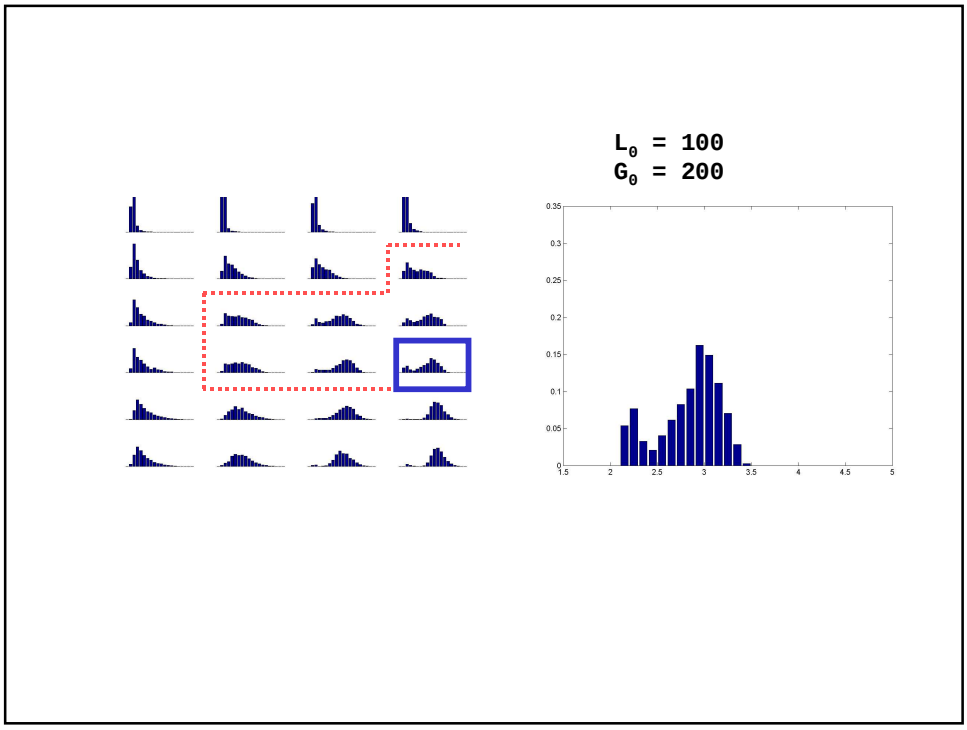

L_0 = 10
G_0 = 0

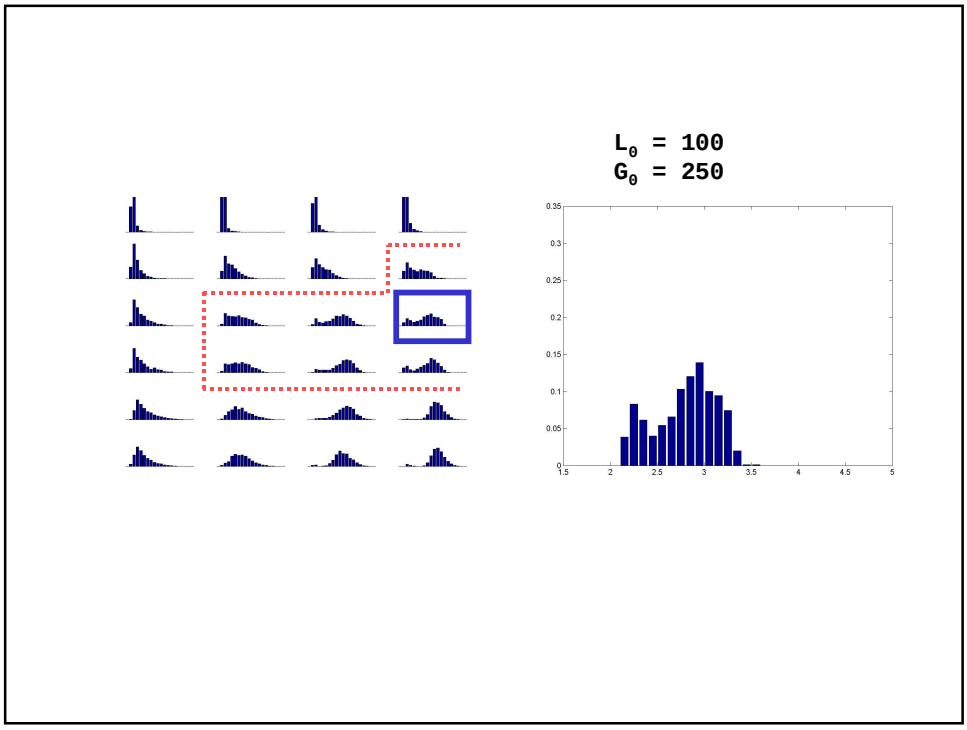

$L_0 = 25$
$G_0 = 0$

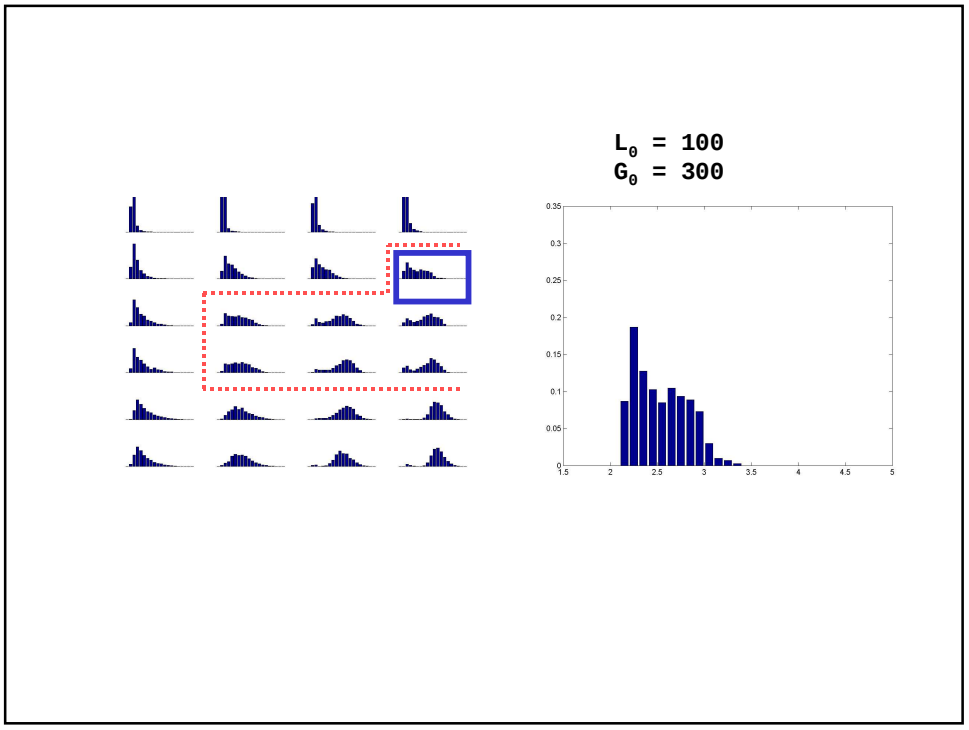

$L_0 = 50$
$G_0 = 0$

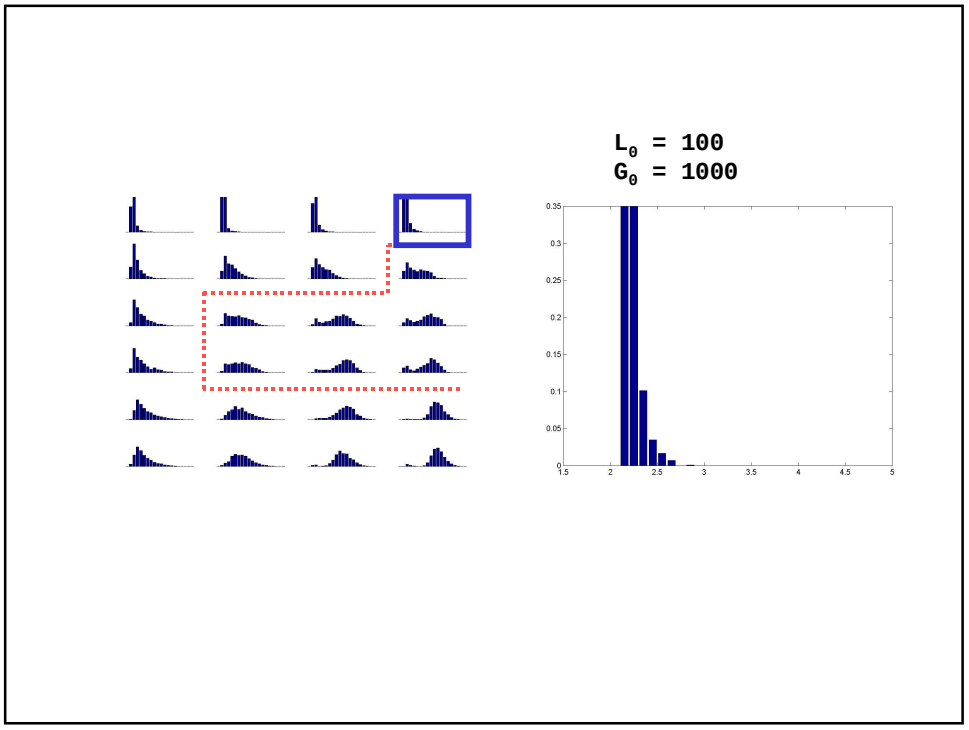

$L_0 = 100$
$G_0 = 0$

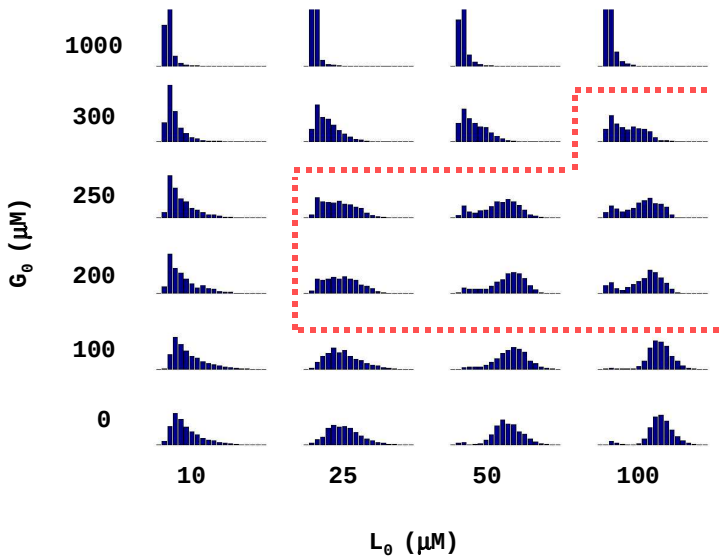

$L_0 = 100$
$G_0 = 100$


$L_0 = 100$
$G_0 = 200$

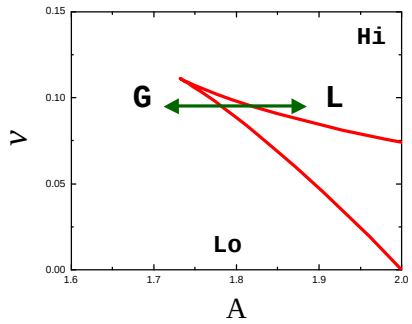

$L_0 = 100$
$G_0 = 250$


L_0 = 100
G_0 = 300


L_0 = 100
G_0 = 1000



Phase diagram as a probe of system structure

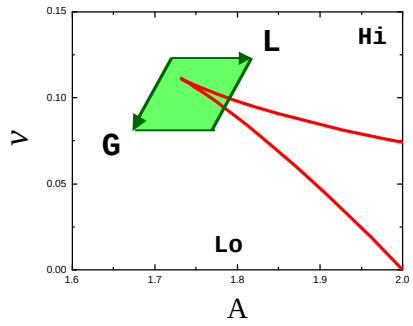


$$\wp(on) = \frac{C}{1 + C + R + RC}$$

$$A = \frac{\alpha_0 A_0}{\sqrt{R_T}} \frac{C}{1+C} \frac{L}{1+L}$$

$$\nu = \frac{1}{R_T}$$

Phase diagram as a probe of system structure



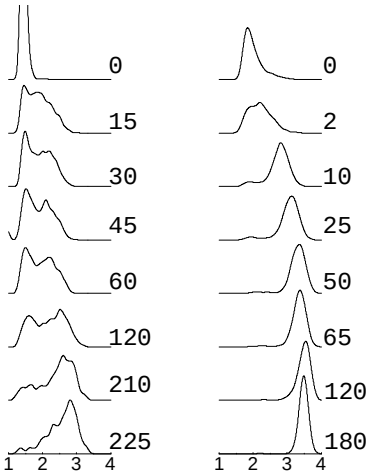
$$\wp(on) = \frac{C}{1 + C + R + RC}$$

$$A = \frac{\alpha_0 A_0}{\sqrt{R_T}} \frac{C}{\sqrt{1+C}} \frac{L}{1+L}$$

$$\nu = \frac{1}{R_T}(1+C)$$

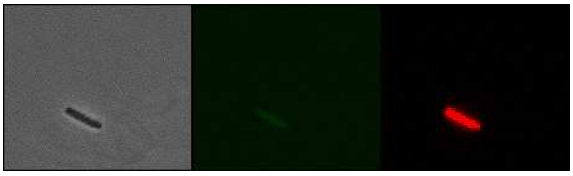
Population distribution dynamics

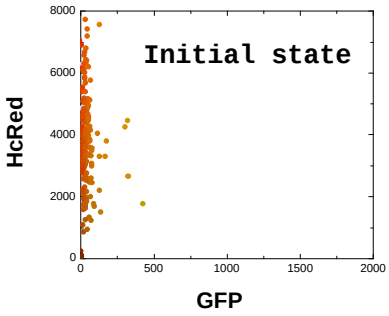
[glucose] = 25 μM
[lactose] = 1 mM

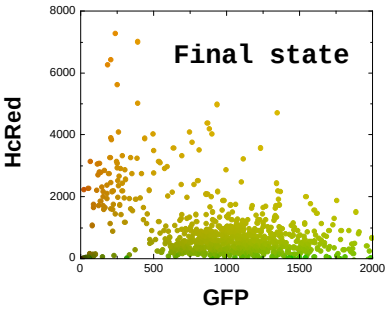


[glucose] = 0 μM
[lactose] = 1 mM

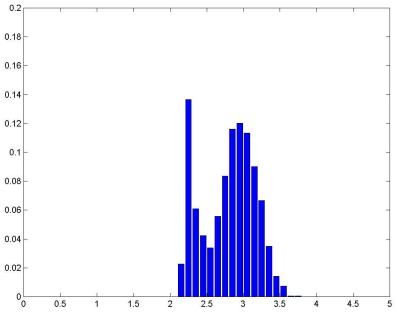
Single cell dynamics

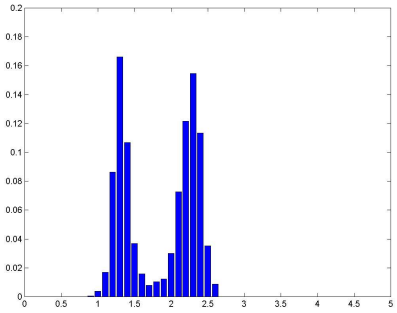






Plasmid noise



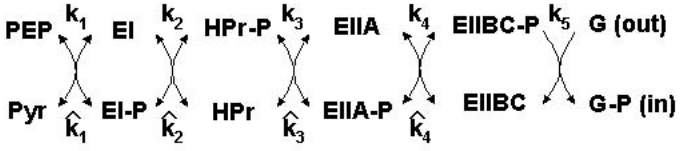


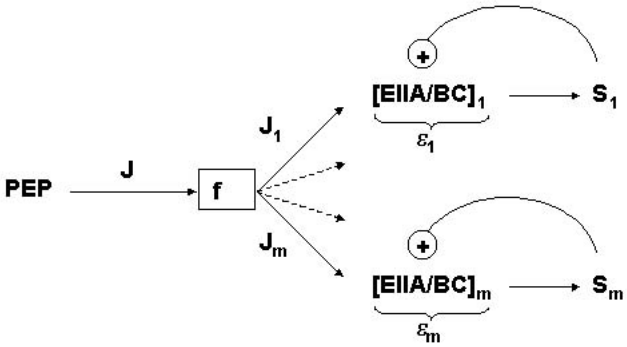
plasmid reporter

chromosomal reporter

2. Switching in the sugar Phosphotransferase system

The Phosphotransferase system

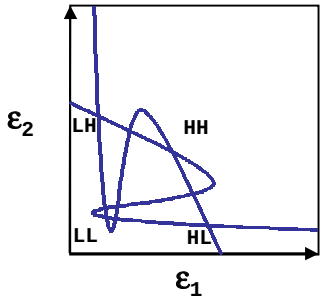




The Phosphotransferase system

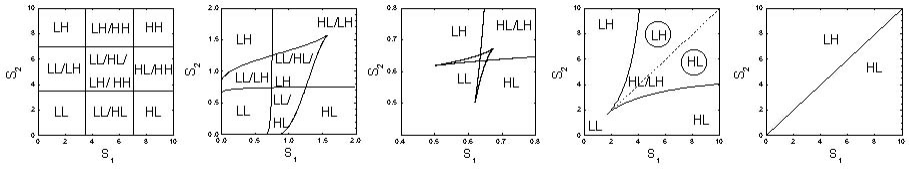
$$\dot{\varepsilon}_i = \nu + \frac{\tau_i}{1+\tau} - \varepsilon_i \qquad \tau_i = \frac{\varepsilon_i^2}{\beta}\frac{S_i}{E_i + S_i} \qquad \tau = \sum_j \tau_j$$

Nullcline analysis: classification of fixed points



Metabolic phase diagrams

System state as a function of sugar concentrations



Independent hysteretic switches

PTS phase diagrams

Optimal metabolism

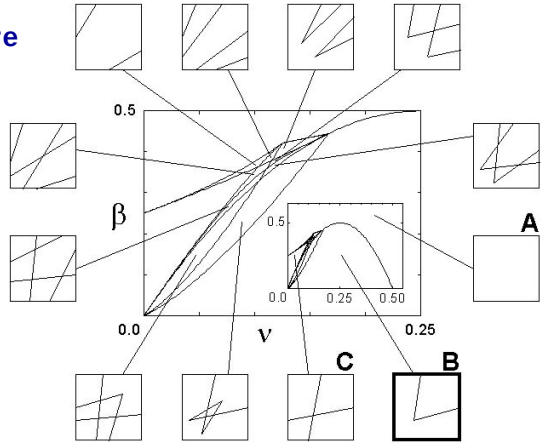
Topological structure of phase diagram defines switching phenotype

Global parameter analysis

Identify all possible switching phenotypes that can be achieved by mutations of PTS

Robust phenotypes are those which occupy large regions of parameter space

Phenotype B performs a winner-take-all operation



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