# Bistability in the *lac* operon

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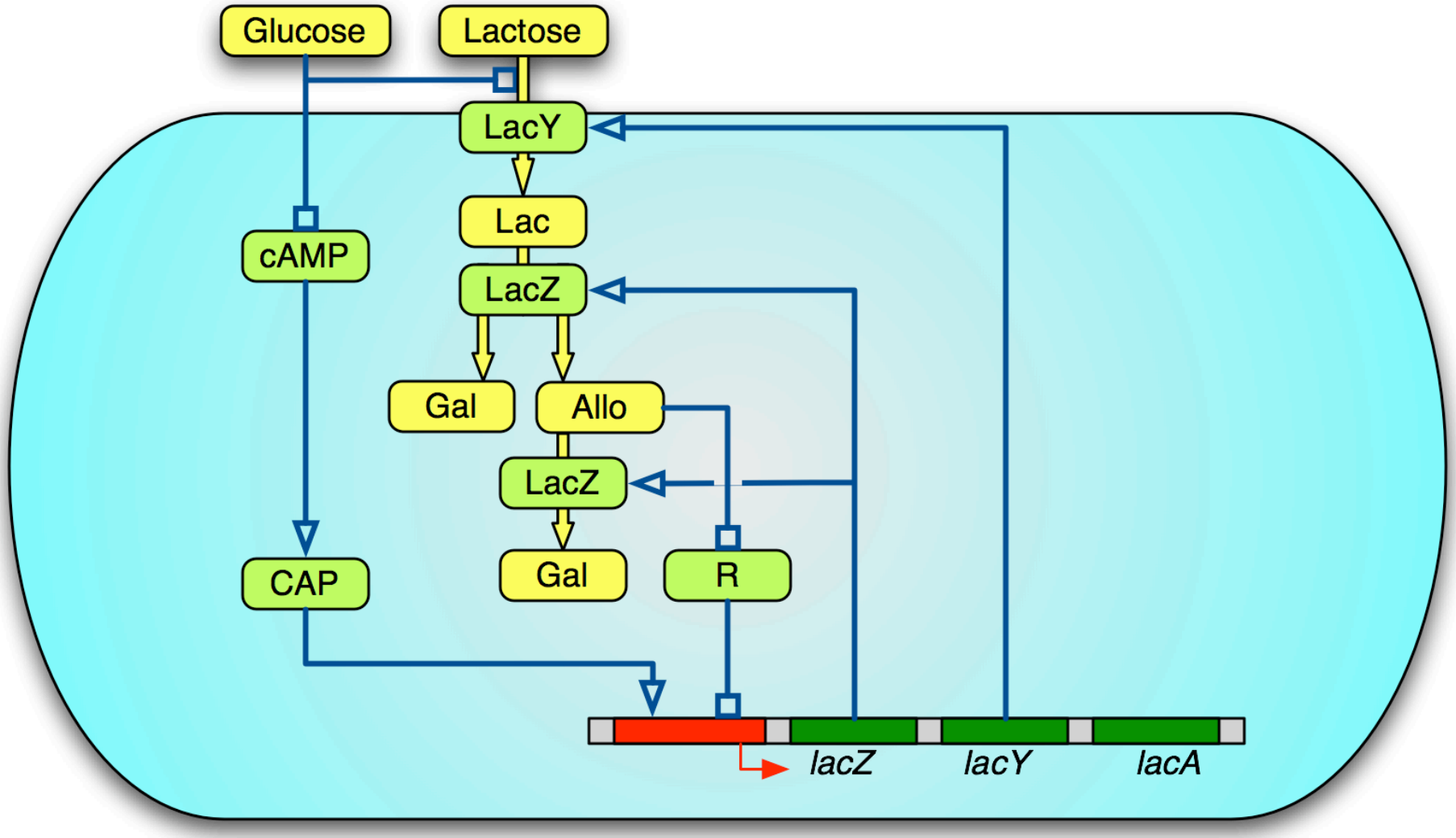
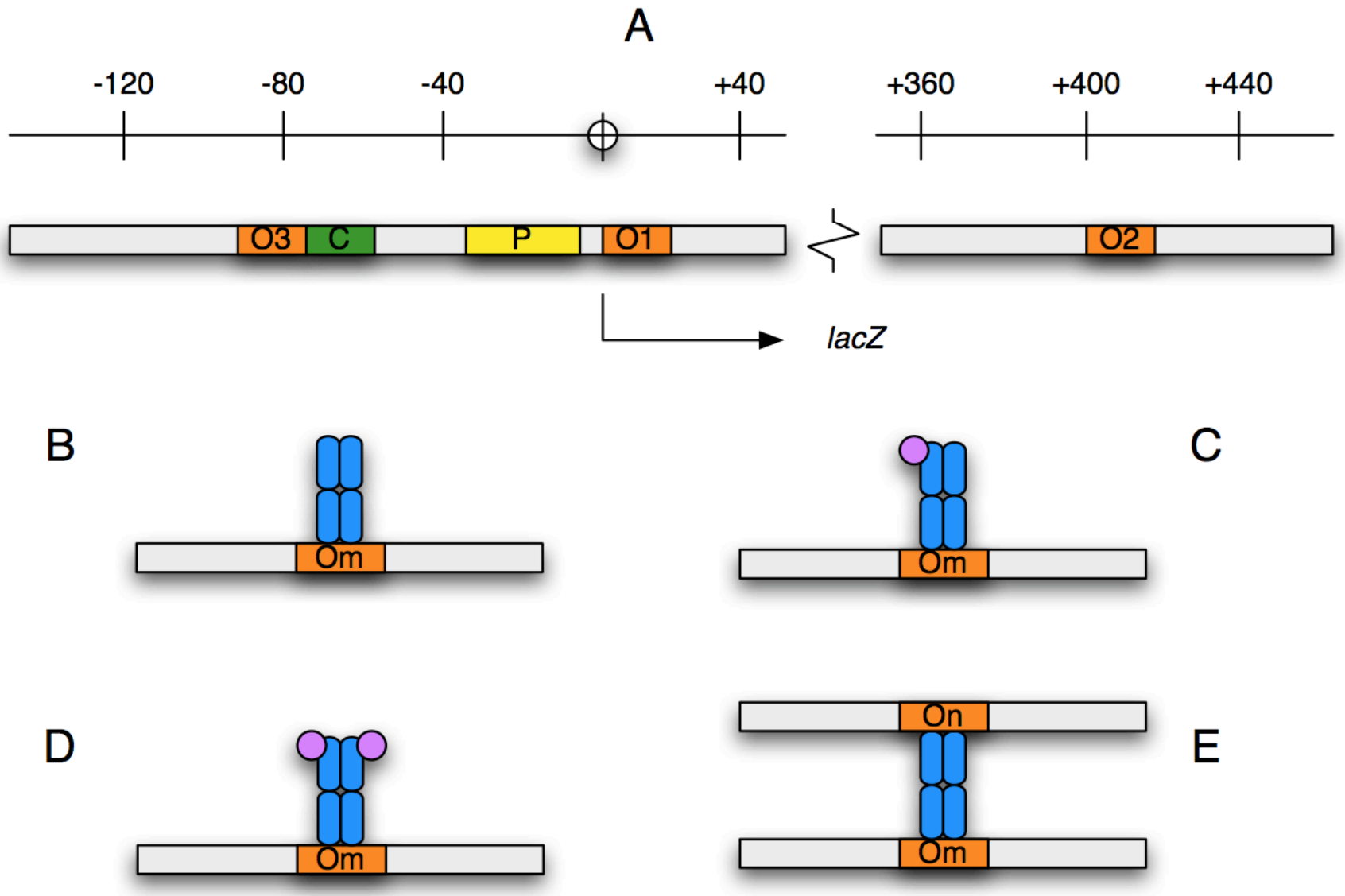
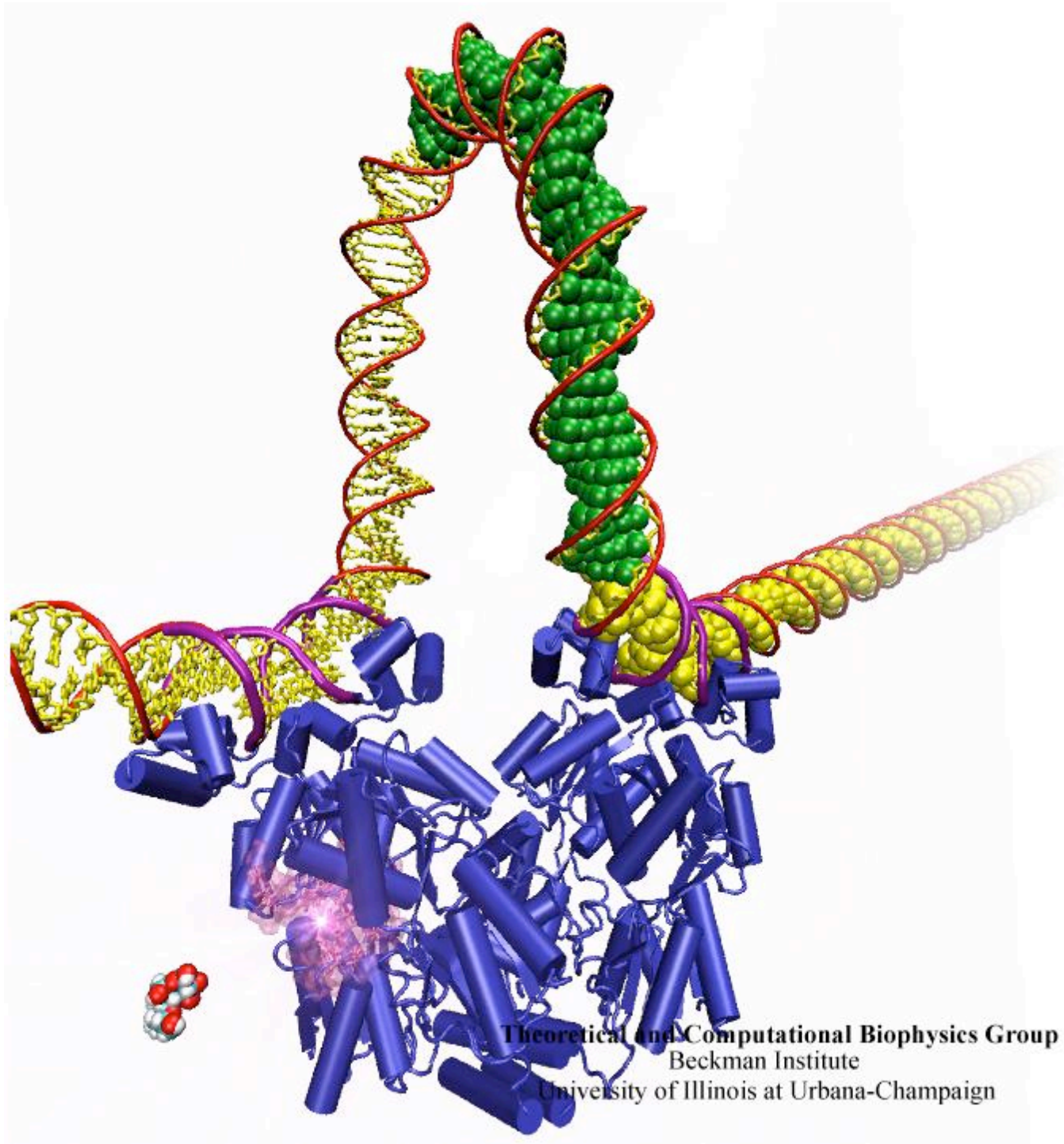
# The lactose operon



# Interaction of the repressor with the *lac* operators

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# The Osbudak et al. Experiment

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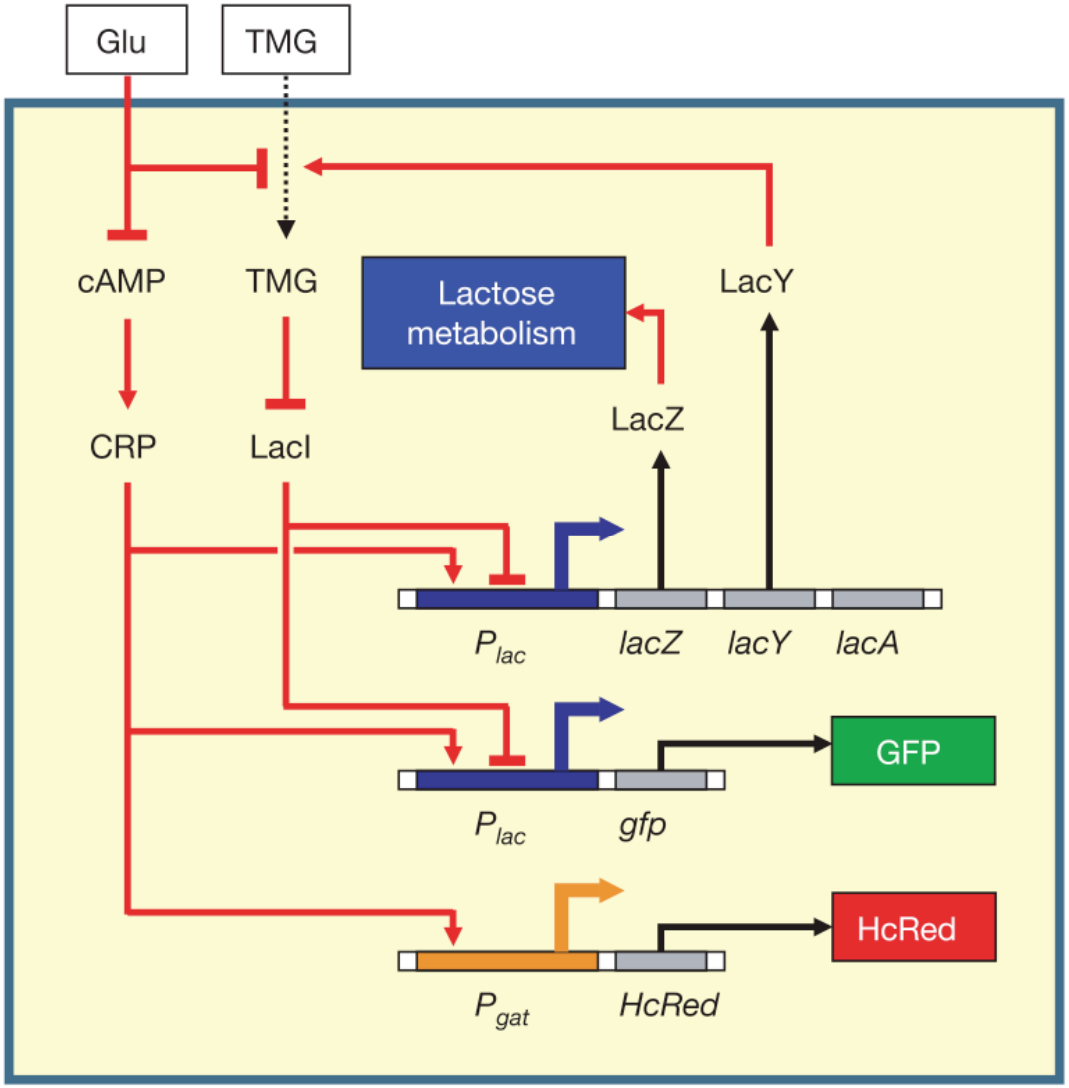
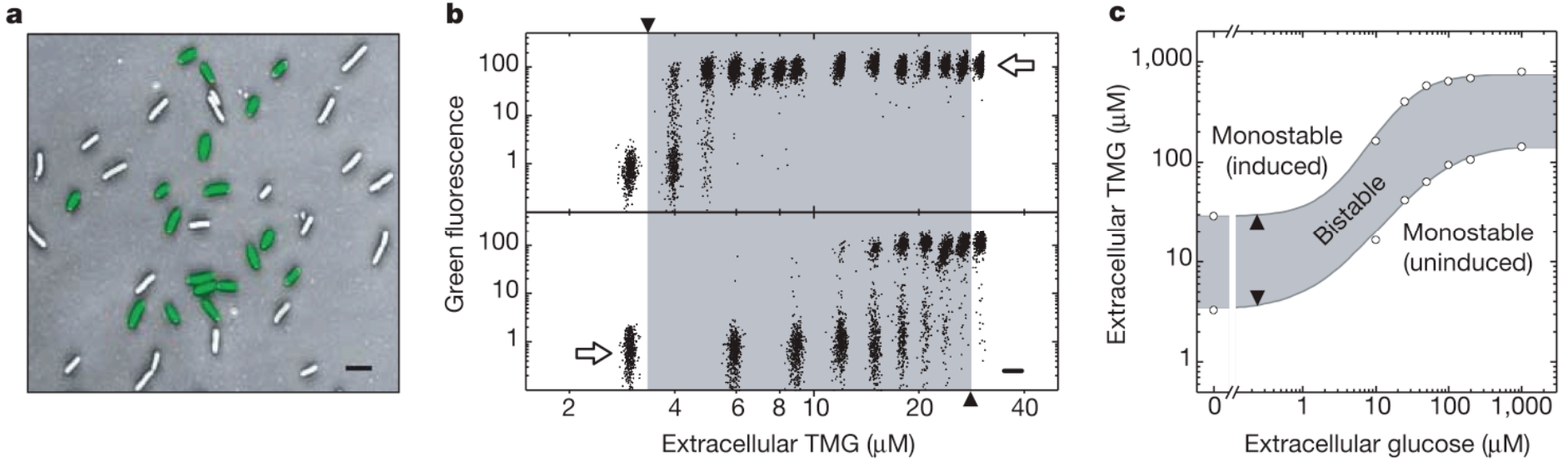



a
b
c
Green fluorescence
100
10
1
100
10
1
2
4
6
8
10
20
40
Extracellular TMG (μM)
Extracellular TMG (μM)
1,000
100
10
1
Monostable
(induced)
Bistable
Monostable
(uninduced)
0
1
10
100
1,000
Extracellular glucose (μM)

# Bistability was not observed when the inducer was lactose

During induction with lactose, initially uninduced cell populations show a transient bimodal distribution of green fluorescence levels at certain glucose concentrations, and a transient unimodal distribution at others. However, the steady state distribution after 4 hours of growth is *always* unimodal, and we never observe hysteresis. By performing extensive measurements, we confirmed this unimodal behaviour to occur for over fifty combinations of glucose and lactose concentrations, upto saturating quantities of each sugar. The difference between the observed responses to TMG and lactose could be due to several causes. First, because lactose is metabolized and therefore affects cell growth rate, it could happen that the induced subpopulation of a bimodal population always grows to dominance. Second, since the metabolism of lactose leads to a drop in CRP-cAMP levels[18], the inducer activity of allolactose might be counteracted to some extent. Third, although an increase in operon expression leads to an increase in lactose uptake and allolactose production, it also leads to an increase in allolactose degradation by β-galactosidase. Intracellular allolactose levels therefore depend very weakly on operon expression levels, reducing the strength of positive feedback and possibly eliminating bistability altogether.

# A mathematical model for the *lac* operon

$$
\begin{aligned}
[\dot{M}] &= k_M[D]\Big(p_{pc}([Ge])\mathcal{P}_R^1([A]) + p_p\mathcal{P}_R^2([A])\Big) - (\gamma_M + \mu)M && (1)\\
[\dot{E}] &= k_E[M] - (\gamma_E + \mu)[E] && (2)\\
[\dot{L}] &= k_L\beta_L([Le])\beta_G([Ge])[Q] - 2\phi_M\mathcal{M}([L])[B] - \mu[L] && (3)\\
[A] &= [L] && (4)\\
[Q] &= [E] && (5)\\
[B] &= [E]/4 && (6)\\
\mu &= \varepsilon\big(J_G([Ge]) + J_L([L])\big) && (7)
\end{aligned}
$$

# Supplementary equations

$$p_{pc}([Ge]) = \frac{p_p\left(1 + p_c([Ge])\left(k_{pc} - 1\right)\right)}{1 + p_p p_c([Ge])\left(k_{pc} - 1\right)} \tag{8}$$

$$p_c([Ge]) = \frac{K_G^{n_h}}{K_G^{n_h} + [Ge]^{n_h}} \tag{9}$$

$$\mathcal{P}_R^1([A]) = \frac{1 + \xi_2 \rho_1([A])}{\prod_{i=1,2,3}\left(1 + \xi_i \rho_1([A])\right) + \sum_{\sigma \in \mathrm{perm}(1,2,3)}\left(1 + \xi_{\sigma_1}\rho_1([A])\right)\xi_{\sigma_2\,\sigma_3}\rho_2([A])} \tag{10}$$

$$\mathcal{P}_R^2([A]) = \frac{\left(1 + \xi_2 \rho_1([A])\right)\xi_3 \rho_1([A]) + \xi_{23}\,\rho_2([A])}{\prod_{i=1,2,3}\left(1 + \xi_i \rho_1([A])\right) + \sum_{\sigma \in \mathrm{perm}(1,2,3)}\left(1 + \xi_{\sigma_1}\rho_1([A])\right)\xi_{\sigma_2\,\sigma_3}\rho([A])_2} \tag{11}$$

$$\rho_1([A]) = \left(\frac{K_A}{K_A + [A]}\right)^2 \tag{12}$$

$$\rho_2([A]) = \left(\frac{K_A}{K_A + [A]}\right)^4 \tag{13}$$

$$\beta_L([Le]) = \frac{[Le]}{\kappa_L + [Le]} \tag{14}$$

$$\beta_G([Ge]) = 1 - \phi_G \frac{[Ge]}{\kappa_G + [Ge]} \tag{15}$$

$$\mathcal{M}([L]) = \frac{[L]}{\kappa_M + [L]} \tag{16}$$

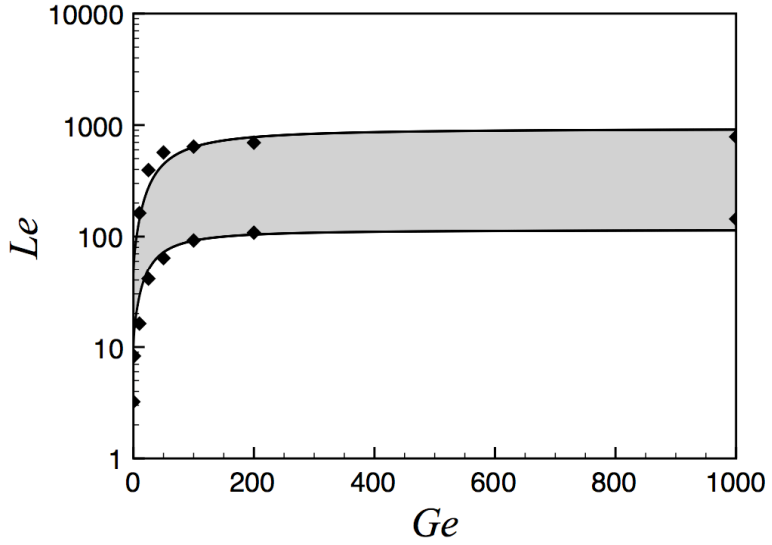
$$J_G([Ge]) = J_G^{\max} \frac{[Ge]}{[Ge] + \Phi_G} \tag{17}$$

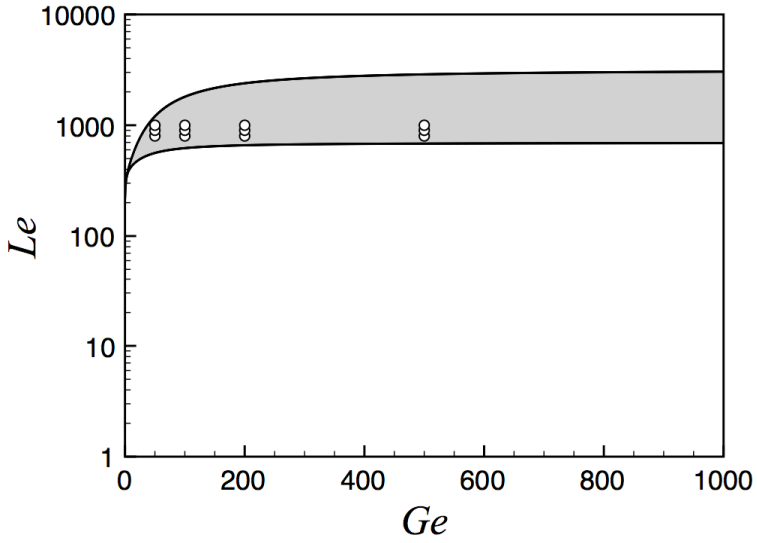
$$J_L([L]) = 4\phi_M \mathcal{M}([L])[B] \tag{18}$$

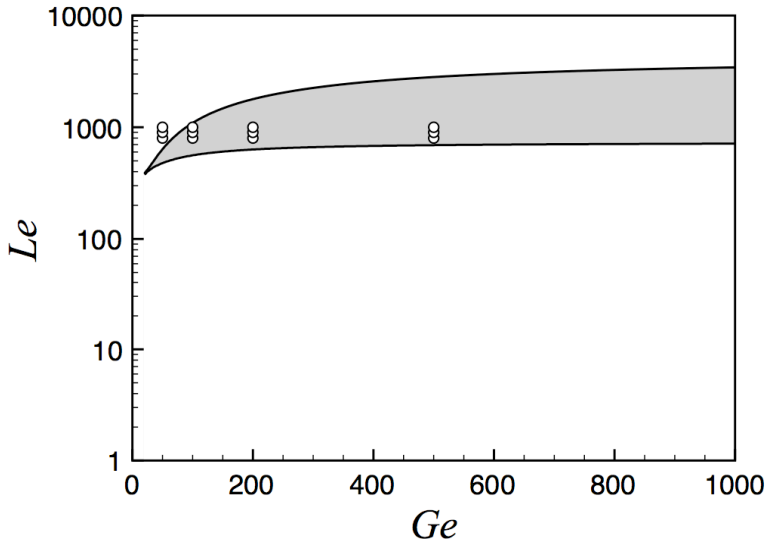
# Parameter Values

| | | | | | |
|---|---|---|---|---|---|
| $[D]$ | $\approx$ | $2\,\mathrm{mpb}$ | $k_M$ | $\approx$ | $0.18\,\mathrm{min}^{-1}$ |
| $\varepsilon$ | $\approx$ | $5.2 \times 10^{-10}\,\mathrm{mpb}^{-1}$ | $\gamma_M$ | $\approx$ | $0.46\,\mathrm{min}^{-1}$ |
| $p_p$ | $\approx$ | $0.127$ | $k_{pc}$ | $\approx$ | $30$ |
| $K_G$ | $\approx$ | $2.6\,\mu\mathrm{M}$ | $n_h$ | $\approx$ | $1.3$ |
| $\xi_1$ | $\approx$ | $17$ | $\xi_2$ | $\approx$ | $0.85$ |
| $\xi_3$ | $\approx$ | $0.17$ | $\xi_{12}$ | $\approx$ | $1261.7$ |
| $\xi_{13}$ | $\approx$ | $430.6$ | $\xi_{23}$ | $\approx$ | $2.4$ |
| $K_A$ | $\approx$ | $?\,\mathrm{mpb}$ | $k_E$ | $\approx$ | $18.8\,\mathrm{min}^{-1}$ |
| $\gamma_E$ | $\approx$ | $0.01\,\mathrm{min}^{-1}$ | $k_L$ | $\approx$ | $6.0 \times 10^4\,\mathrm{min}^{-1}$ |
| $\phi_M$ | $\approx$ | $\in [0, 3.8 \times 10^4]\,\mathrm{min}^{-1}$ | $\kappa_L$ | $\approx$ | $680\,\mu\mathrm{M}$ |
| $\phi_G$ | $\approx$ | $0.35$ | $\kappa_G$ | $\approx$ | $1.0\,\mu\mathrm{M}$ |
| $\kappa_M$ | $\approx$ | $7.0 \times 10^5\mathrm{mpb}$ | $J_G^{\max}$ | $\approx$ | $4.4 \times 10^7\,\mathrm{mpb\,min}^{-1}$ |
| $\Phi_G$ | $\approx$ | $22\,\mu\mathrm{M}$ | | | |

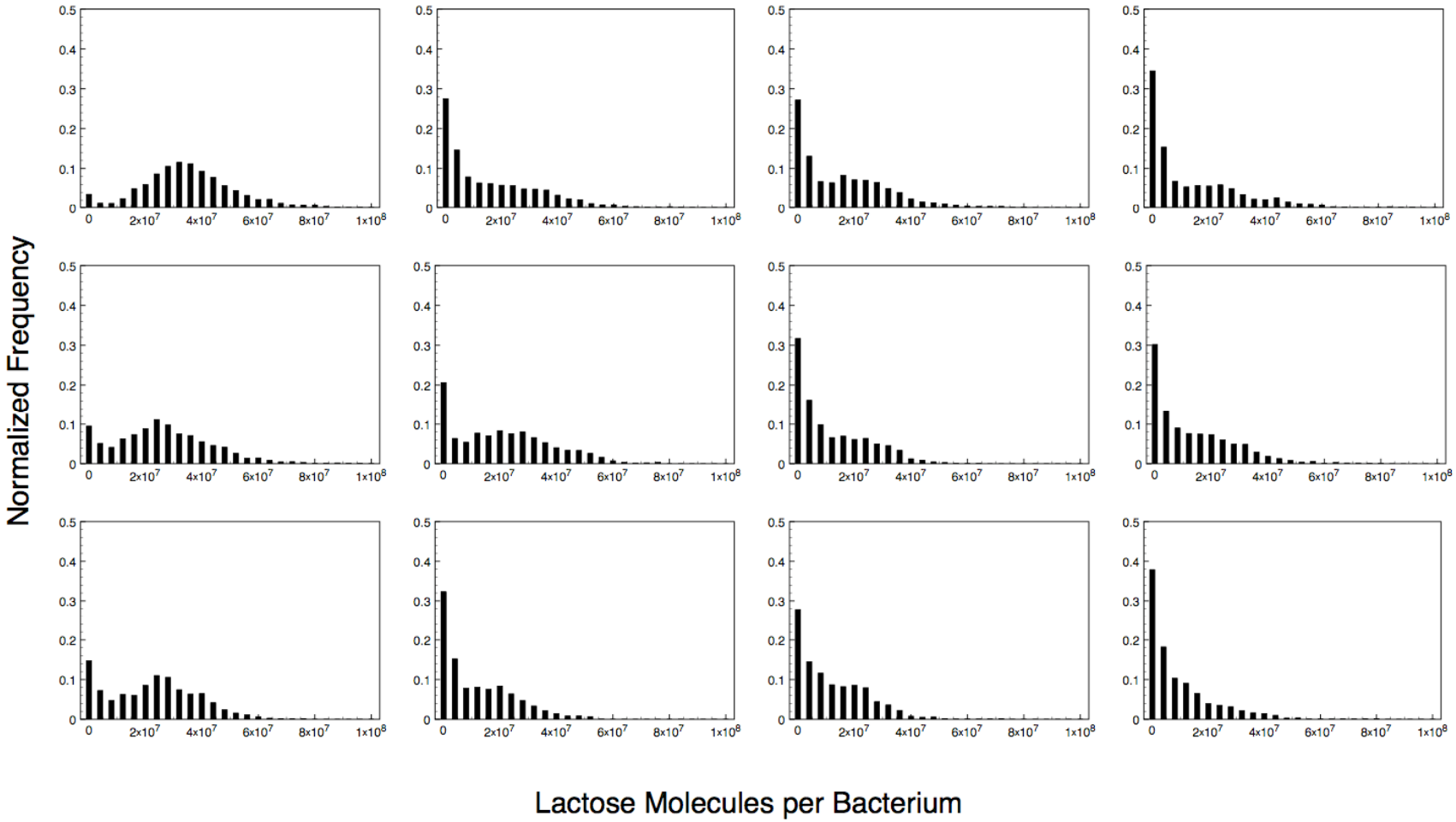
# Bifurcation Diagrams



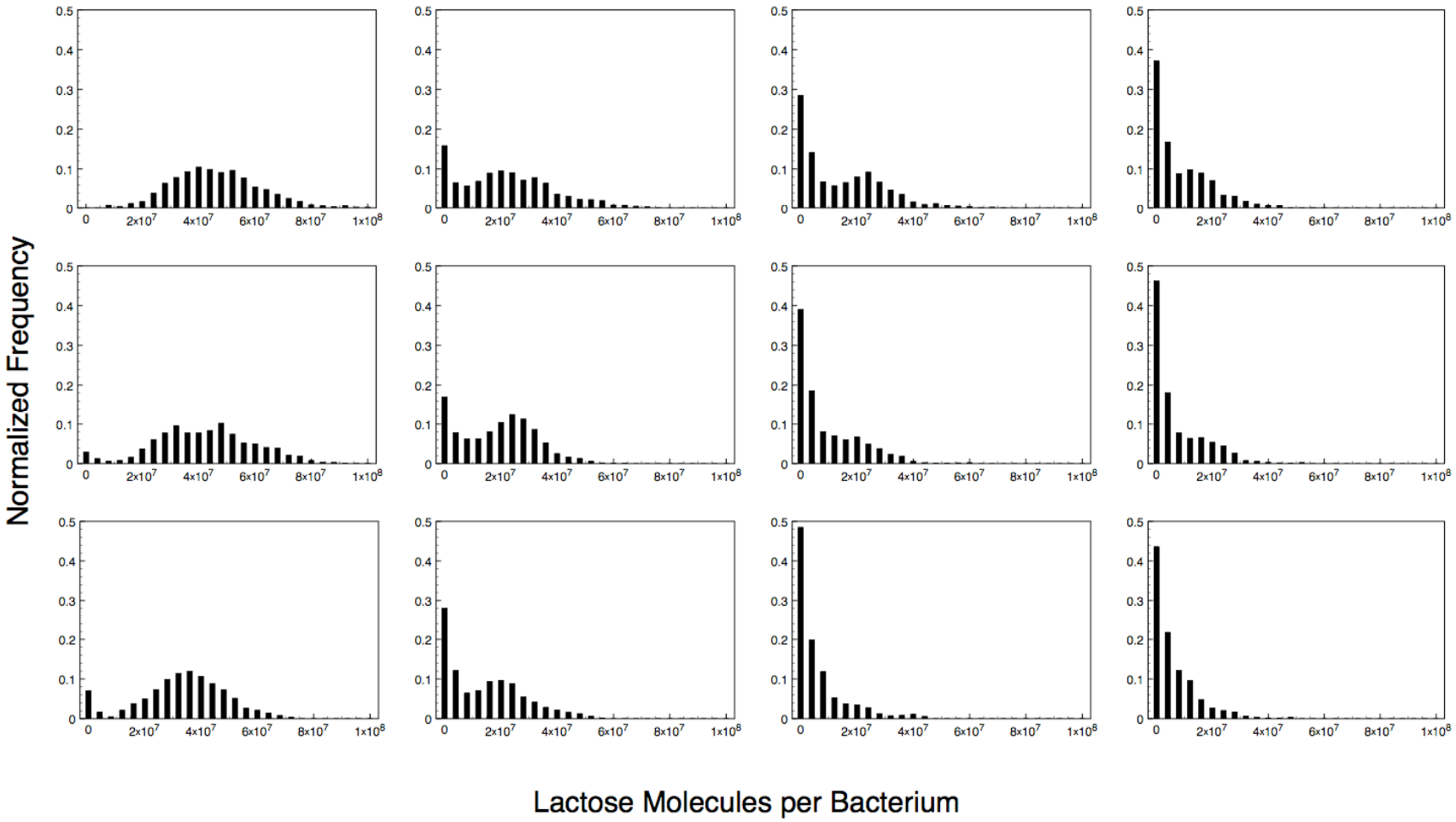
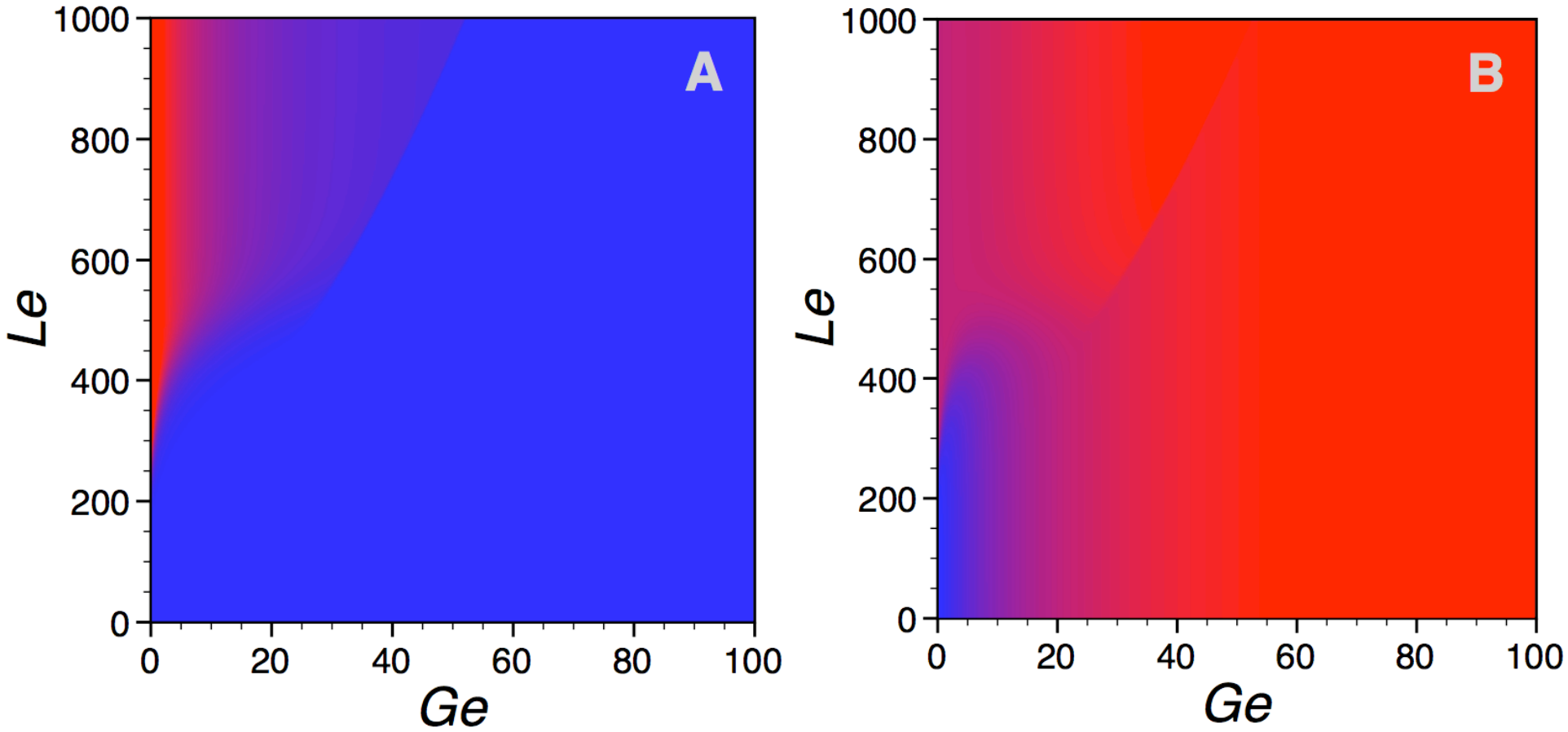



# Constant Growth Rate



# Variable Growth Rate



# Induction Level & Growth Rate