Bistability and a differential equation model of the *lac* operon

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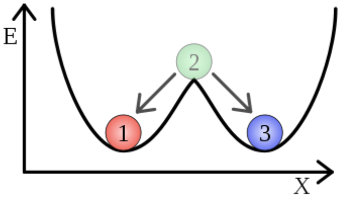

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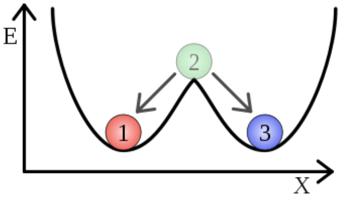

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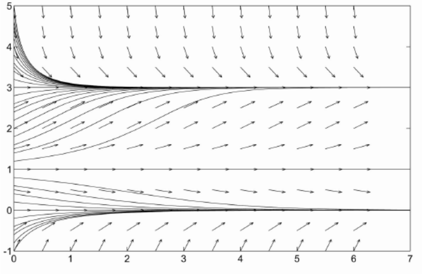

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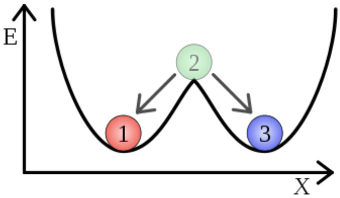

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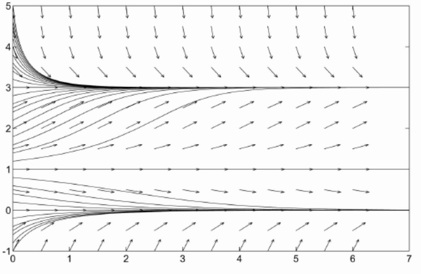

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In the threshold model for population growth, there are three steady-states, $0 < T < M$:

- M = carrying capacity (stable),
- T = extinction threshold (unstable),
- 0 = extinct (stable).

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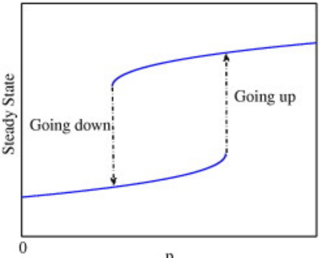

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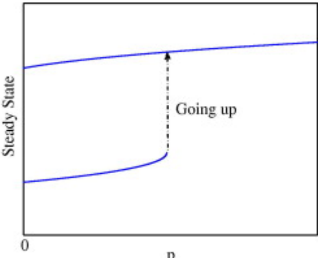

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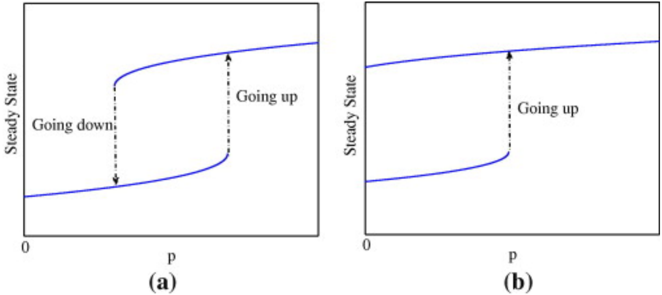

This is reversible bistability. In other situations, it may be irreversible (at right).

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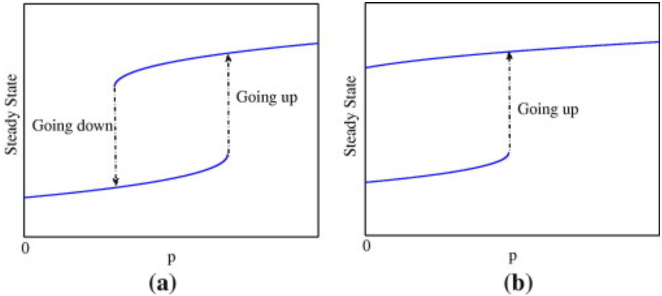

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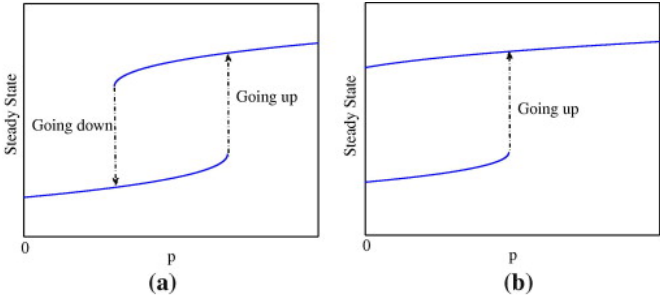

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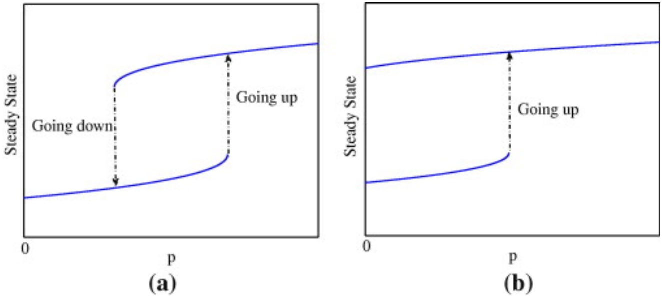

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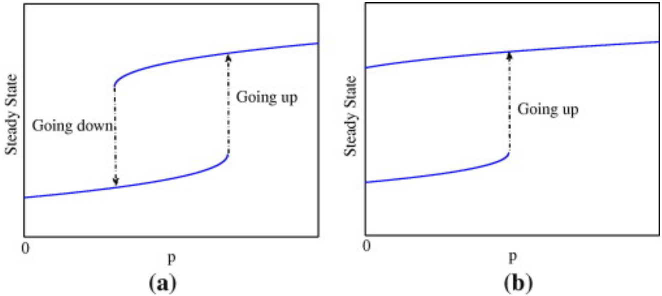

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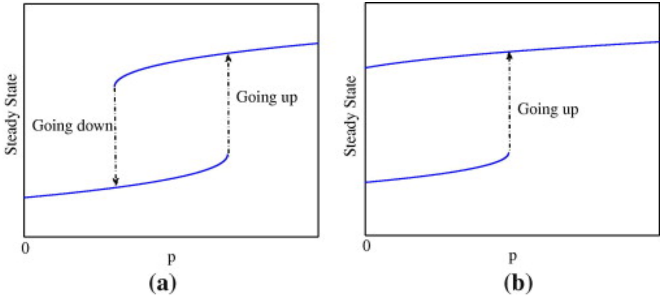

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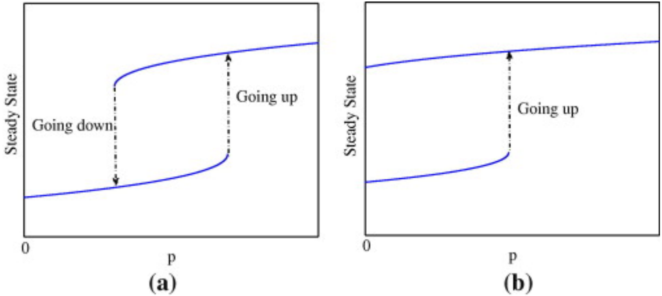

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- If the temperature is $T > 73$, then the AC kicks on.
- If $71 < T < 73$, then we don't know whether the heat or AC was on last.

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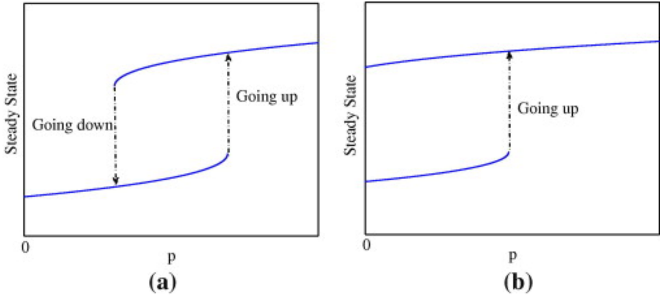

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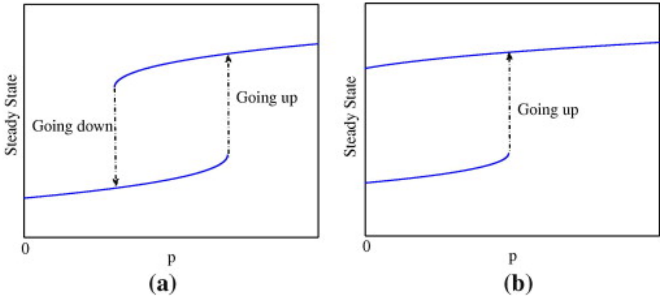

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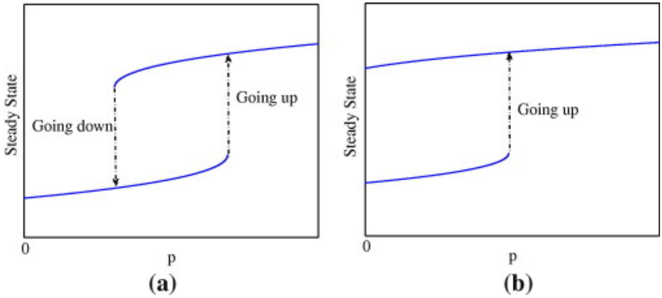

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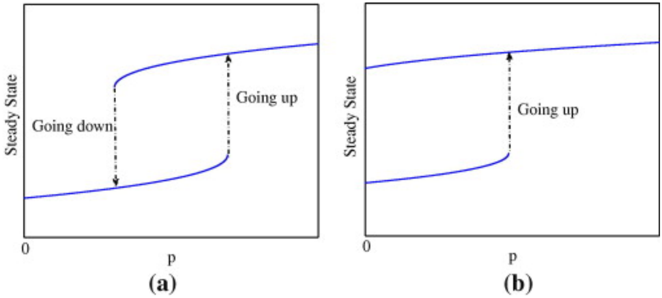

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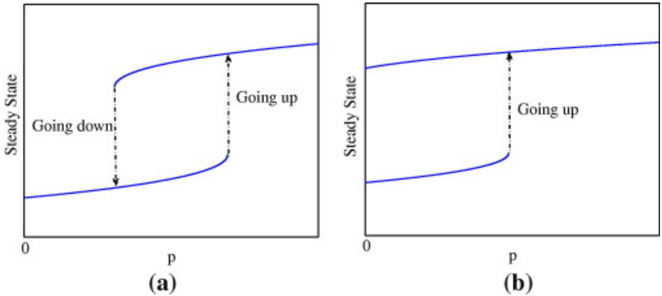

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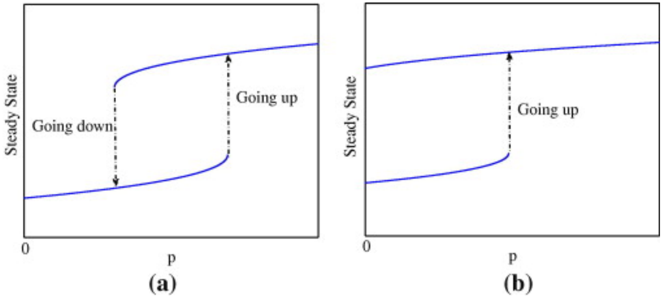

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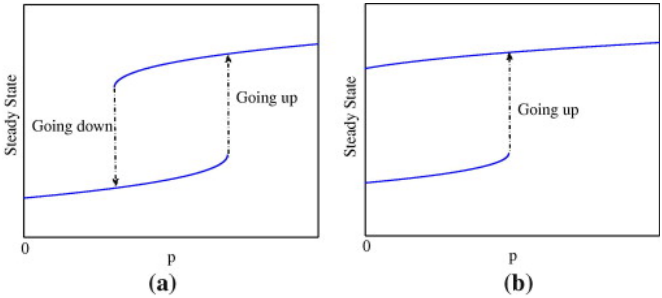

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The region of bistability (L_1, L_2) has both induced and un-induced cells.

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In general, bistable systems tend to have positive feedback loops (in their "wiring diagrams") or double-negative feedback loops (=positive feedback).

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- f is *increasing* in $[A]$, when $[A] \geqslant 0$.
- $\lim\limits_{[A]\to\infty} f([A]) = 1$ "with lots of allolactose, gene expression level is max'ed."

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$$p(t) = e^{-\mu\tau} p(t-\tau).$$

A 3-variable ODE model

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Consider the following 3 quantities, which represent *concentrations* of:

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The model (Yildirim and Mackey, 2004)

$$\begin{aligned}
\frac{dM}{dt} &= \alpha_M \frac{1 + K_1 (e^{-\mu\tau_M} A_{\tau_M})^n}{K + K_1 (e^{-\mu\tau_M} A_{\tau_M})^n} - \widetilde{\gamma}_M M \\
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These are *delay differential equations*, with discrete time delays due to the transcription and translation processes.

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- The term $e^{-\mu\tau_M} A_{\tau_M}$ accounts for the concentration of A at time $t - \tau_M$, and dilution due to bacterial growth.

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ODE for allolactose (A)

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- The second term models loss of allolactose from the chemical reaction $allo \overset{\beta-gal}{\longrightarrow} glucose \ \& \ galactose$.

A 3-variable ODE model

Steady-state analysis

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To find the steady states, we must solve the nonlinear system of equations:

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\begin{aligned}
0 &= \alpha_M \frac{1 + K_1(e^{-\mu\tau_M} A_{\tau_M})^n}{K + K_1(e^{-\mu\tau_M} A_{\tau_M})^n} - \widetilde{\gamma}_M M \\
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Steady states	A^* (mM)	M^* (mM)	B^* (mM)
I.	4.27×10^{-3}	4.57×10^{-7}	2.29×10^{-7}
II.	1.16×10^{-2}	1.38×10^{-6}	6.94×10^{-7}
III.	6.47×10^{-2}	3.28×10^{-5}	1.65×10^{-5}

3-variable ODE model

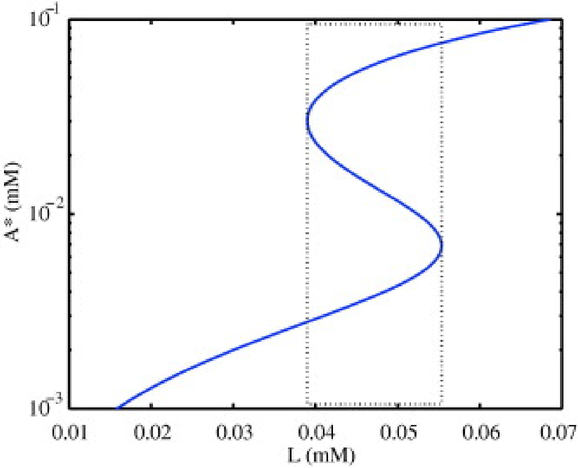

Figure: Bistability is (L, A^*) space. The y-axis is in logarithmic scale. For a range of L concentrations there are three coexisting steady states for the allolactose concentration.

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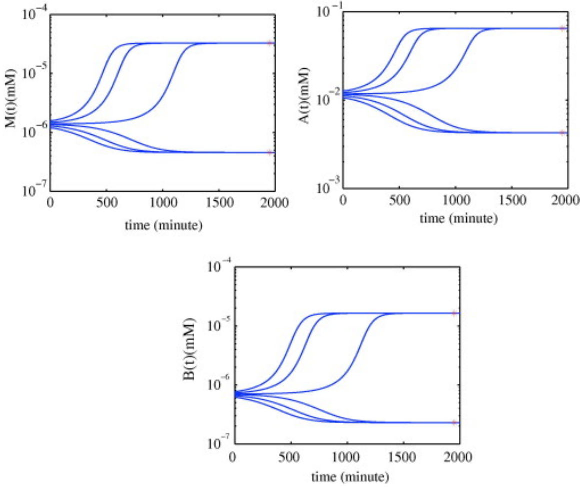

Figure: Time series simulations of mRNA, β-galactosidase and allolactose concentrations. These were produced by numerically solving the 3-variable model using $L = 50 \times 10^{-3}$ mM, which is in the bistable region.

5-variable ODE model

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Consider the following 5 variables, which represent *concentrations* of:

- $M(t) =$ mRNA,
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The model (Yildirim and Mackey, 2004)

$$\begin{aligned}
\frac{dM}{dt} &= \alpha_M \frac{1 + K_1 (e^{-\mu \tau_M} A_{\tau_M})^n}{K + K_1 (e^{-\mu \tau_M} A_{\tau_M})^n} + \Gamma_0 - \widetilde{\gamma}_M M \\
\frac{dB}{dt} &= \alpha_B e^{-\mu \tau_B} M_{\tau_B} - \widetilde{\gamma}_B B \\
\frac{dA}{dt} &= \alpha_A B \frac{L}{K_L + L} - \beta_A B \frac{A}{K_A + A} - \widetilde{\gamma}_A A \\
\frac{dP}{dt} &= \alpha_P e^{-\mu(\tau_B + \tau_P)} M_{\tau_B + \tau_P} - \widetilde{\gamma}_P P \\
\frac{dL}{dt} &= \alpha_L P \frac{L_e}{K_{L_e} + L_e} - \beta_{L_e} P \frac{L}{K_{L_e} + L} - \alpha_A B \frac{L}{K_L + L} - \widetilde{\gamma}_L L
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  is justified by the following:
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  - The 2nd term accounts for loss due to this process being reversible.
  - The 3rd term describes loss due to $lac \xrightarrow{\beta-gal} allo$.
  - the 4th term accounts for loss due to degredation and dilution.

A 5-variable ODE model

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SS's	A^* (nM)	M^* (mM)	B^* (mM)	L^* (mM)	P^* (mM)
I.	7.85×10^{-3}	2.48×10^{-6}	1.68×10^{-6}	1.69×10^{-1}	3.46×10^{-5}
II.	2.64×10^{-2}	7.58×10^{-6}	5.13×10^{-6}	2.06×10^{-1}	1.05×10^{-4}
III.	3.10×10^{-1}	5.80×10^{-4}	3.92×10^{-4}	2.30×10^{-1}	8.09×10^{-3}

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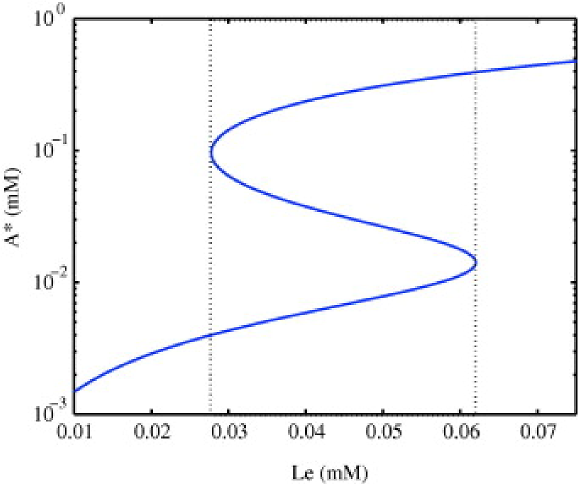

Figure: Bistability is (L, A^*) space. The y-axis is in logarithmic scale. For a range of L_e concentrations there are three coexisting steady states for the allolactose concentration.

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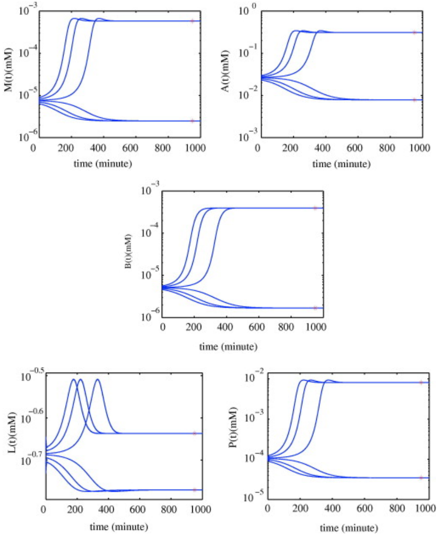

Figure: Time series simulations of mRNA, β-galactosidase and allolactose concentrations. These were produced by numerically solving the 3-variable model using $L_e = 50 \times 10^{-3}$, which is in the bistable region.