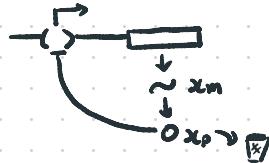


Homework 1.2: Autoactivation, Bistability, leakage

(a)



$$\beta(x) = \alpha_0 + \frac{\beta_0 (x/k)^n}{1 + (x/k)^n} - \gamma x$$

$$\left[\frac{dx}{dt} = \alpha_0 + \frac{\beta_0 (x/k)^n}{1 + (x/k)^n} - \gamma x \right]$$

(b) when $n=1$,

$$\frac{dx}{dt} = \alpha_0 + \frac{\beta_0 x/k}{1 + x/k} - \gamma x$$

Nondimensionalization:

$$\frac{x_d}{t_d} \frac{dx}{dt} = \alpha_0 + \frac{\beta_0 x_d/k \tilde{x}}{1 + x_d/k \tilde{x}} - \gamma x_d \tilde{x}$$

$$\frac{d\tilde{x}}{dt} = \frac{t_d \alpha_0}{x_d} + \frac{\beta_0 t_d}{x_d} \frac{x_d/k \tilde{x}}{1 + x_d/k \tilde{x}} - \gamma t_d \tilde{x}$$

$$\tilde{\alpha} = \frac{\alpha_0}{t_d k} \quad \frac{\beta_0}{t_d k} \quad x_d = k \quad t_d = 1/\gamma$$

$\frac{\beta_0}{\alpha_0}$ is dimensionless but we can call this scaled thing $\tilde{\beta}$ for now

$$\left[\frac{d\tilde{x}}{dt} = \tilde{\alpha} + \tilde{\beta} \frac{\tilde{x}}{1 + \tilde{x}} - \tilde{x} \right]$$

Mathematica:

$$x_{\ominus} = \frac{1}{2} (\tilde{\alpha} + \tilde{\beta} - 1 - \sqrt{4\tilde{\alpha} + (\tilde{\alpha} + \tilde{\beta} - 1)^2})$$

$$x_{\oplus} = \frac{1}{2} (\tilde{\alpha} + \tilde{\beta} - 1 + \sqrt{4\tilde{\alpha} + (\tilde{\alpha} + \tilde{\beta} - 1)^2})$$

Note when $\alpha_0 = 0$, $\tilde{\alpha} = 0$
 $\tilde{\beta} > 0$ since $\frac{\beta_0}{t_d k}$ must always
 $\tilde{\beta} < 0$

when $\alpha_0 > 0$ $\tilde{\alpha} > 0$

$\tilde{\beta} > 0$

when $\alpha_0 = 0$, $x_{\ominus} = 0$

$$x_{\oplus} = \tilde{\beta} - 1$$

$$\begin{cases} x_{\ominus} = 0 \\ x_{\oplus} = \frac{\beta_0}{t_d k} - 1 \end{cases}$$

if $\frac{\beta_0}{t_d k} > 1$. If $\frac{\beta_0}{t_d k} = 1$, then $x_{\oplus} = 0$

when $\alpha_0 > 0$, $x_{\ominus} < 0$ since $4\tilde{\alpha}$ is \oplus form: $\tilde{\beta} - \sqrt{4\tilde{\alpha} + (\tilde{\alpha} + \tilde{\beta} - 1)^2} < 0$

concentrations can't be \ominus

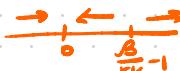
$$x_{\oplus} = \frac{\alpha_0 + \beta_0}{t_d k} - 1 + \sqrt{4\frac{\alpha_0}{t_d k} + \left(\frac{\alpha_0 + \beta_0}{t_d k} - 1\right)^2}$$

Stability of fixed points:

@ $x < 0$, $\frac{dx}{dt} > 0$...

@ $0 < x < \frac{\beta_0}{t_d k} - 1$, $\frac{dx}{dt} < 0$...

@ $x > \frac{\beta_0}{t_d k} - 1$, $\frac{dx}{dt} > 0$...



$x = 0$: stable
 $x = \frac{\beta_0}{t_d k} - 1$: unstable

look @ nondim in the form $\frac{\xi - \zeta}{1 + \xi - \zeta} - \zeta < 0$

opposite of above

$$\textcircled{C} \quad \frac{d\tilde{x}}{dt} = \tilde{\alpha} + \tilde{\beta} \frac{\tilde{x}^n}{1+\tilde{x}^n} - \tilde{x}$$

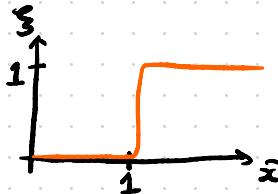
$$\tilde{\alpha} = \frac{\alpha_0}{\gamma K}$$

$$\tilde{\beta} = \frac{\beta_0}{\delta K}$$

$$\tilde{x} = \frac{1}{K} x$$

Graphical analysis

When $n \rightarrow \infty$



$$\tilde{x} < 1 \quad \xi(\tilde{x}) = 0$$

$$\tilde{x} > 1 \quad \xi(\tilde{x}) = 1$$

$$\tilde{x} = 1 \quad \xi(\tilde{x}) = [0,1]$$

$$\text{so when } \tilde{x} < 1: \dot{\tilde{x}}_{st} = \tilde{\alpha}$$

$$\text{when } \tilde{x} > 1: \dot{\tilde{x}}_{st} = \tilde{\alpha} + \tilde{\beta}$$

$$\text{when } \tilde{x} = 1: \frac{d\tilde{x}}{dt} = \alpha - 1 + \frac{\beta}{2}$$

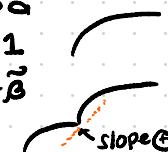
$$\text{then } \frac{d\tilde{x}}{dt} = 0 \text{ when } \alpha = \frac{\beta}{2} + 1$$

$$\text{otherwise } \frac{d\tilde{x}}{dt} > 0$$

when $\tilde{\alpha} < 1$, there is only one fixed point @ $\tilde{\alpha}$

when $\tilde{\alpha} = 1$, if $\tilde{\beta} = 0$ one fixed point @ 1

otherwise $\tilde{\beta} > 0$ fixed point @ $\tilde{\alpha} + \tilde{\beta}$



when $\tilde{\alpha} > 1$, there is one fixed point @ $\tilde{\alpha} + \tilde{\beta}$

* if $\tilde{\alpha} = \frac{\beta}{2} + 1$, another fixed point @ 1

Bistability

$$\text{when } \tilde{\alpha} > 1, \tilde{\alpha} = \frac{\beta}{2} + 1, \quad \frac{\alpha_0}{\gamma K} = 1 \quad \tilde{\alpha} = \frac{1}{2}\beta_0 + \delta K$$

$$x_{st}: 1 \quad \frac{\alpha_0 + \beta_0}{\gamma K}$$

Infinite cooperativity is effectively a really strong action of repression (as soon as one binds, it recruits, but this threshold is essentially where $x_{\tilde{x}} = 1$, or $x = 1/k$), we see that the production and degradation rates fade into irrelevance in terms of response time.

This bistability threshold informs some ideas we could try in the process of design: the γ term can be tuned (through careful dilution??) to equalize the leakage. Binding affinity 'K' can also be tuned. We see that response times are predominantly controlled by the hill coefficient 'n', which can tell us inherently which systems are more regulatable than others.