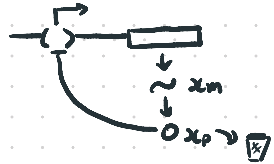
# Homework 1.2: Autoactivation, Bistability, Leakage

**a**




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

$$\boxed{\frac{dx}{dt} = \alpha_0 + \frac{\beta_0 (x/K)^n}{1+(x/K)^n} - \gamma x}$$

**b** when $n=1$,

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

Nondimensionalization:

$$\frac{x_d}{t_d}\frac{d\tilde{x}}{d\tilde{t}} = a_0 + \frac{\beta_0 \, x_d/K \, \tilde{x}}{1+x_d/K\,\tilde{x}} - \gamma x_d \tilde{x}$$

$$\frac{d\tilde{x}}{d\tilde{t}} = \frac{t_d a_0}{x_d} + \frac{\beta_0 t_d}{x_d}\frac{x_d/K\,\tilde{x}}{1+x_d/K\,\tilde{x}} - \gamma t_d \tilde{x}$$

$\boxed{\tilde{\alpha} = \frac{a_0}{\gamma K}}$ $\quad \frac{\beta_0}{\gamma K} \quad x_d = K \quad t_d = 1/\gamma$

$\frac{\beta_0}{\alpha_0}\tilde{\alpha}$ $\quad \boxed{\tilde{\beta} = \frac{\beta_0}{\alpha_0}\tilde{\alpha} = \frac{\beta_0}{\gamma K}}$

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

$$\boxed{\frac{d\tilde{x}}{d\tilde{t}} = \tilde{\alpha} + \tilde{\beta}\frac{\tilde{x}}{1+\tilde{x}} - \tilde{x}}$$

Mathematica:

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

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

Note when $\alpha_0 = 0$, $\tilde{\alpha} = 0$
$\tilde{\beta} > 0$ since $\frac{\beta_0}{\gamma K}$ must always be $\oplus$

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

When $\alpha_0 = 0$, $x_{\ominus} = 0$
$x_{\oplus} = \tilde{\beta} - 1$

$$\boxed{x_{\ominus} = 0 \qquad x_{\oplus} = \frac{\beta_0}{\gamma K} - 1}$$

if $\frac{\beta_0}{\gamma K} > 1$. If $\frac{\beta_0}{\gamma K} = 1$, then $x_{st} = 0$

When $\alpha_0 > 0$, $x_{\ominus} < 0$ since $4\tilde{\alpha}$ is $\oplus$ form: $\heartsuit - \sqrt{4\alpha + \heartsuit} < 0$

concentrations can't be $\ominus$

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

Stability of fixed points: If $\left.\frac{d^2x}{dt^2}\right|_{x_{st}} > 0$ : unstable
$\left.\frac{d^2x}{dt^2}\right|_{x_{st}} < 0$ : stable

$$\boxed{\frac{d^2x}{dt^2} = -\gamma - \frac{\beta_0 x}{K^2\left(1+\frac{x}{K}\right)^2} + \frac{\beta_0}{K\left(1+\frac{x}{K}\right)}}$$

when $x_{st} = 0$, $\left.\frac{d^2x}{dt^2}\right|_0 = -\gamma + \frac{\beta_0}{K}$

when $x_{st} = \frac{\beta_0}{\gamma K} - 1$, $\left.\frac{d^2x}{dt^2}\right|_{x_{st}} = -\gamma - \frac{\beta_0\left(\frac{\beta_0}{\gamma K}-1\right)}{K^2\left(1+\frac{\frac{\beta_0}{\gamma K}-1}{K}\right)^2} + \frac{\beta_0}{K\left(1+\frac{\frac{\beta_0}{\gamma K}-1}{K}\right)}$

Analysis continued...

# Stability Analysis

$\boxed{\text{case}: \alpha_0 = 0}$

From the previous page, if $\left.\frac{d^2x}{dt^2}\right|_{x_{st}}$ $>0$: unstable, $<0$: stable

when $\boxed{x_{st}=0,}$ $\left.\frac{d^2x}{dt^2}\right|_0 = \left[-\gamma + \frac{\beta_0}{K}\right]$

This steady state is stable when $\frac{\beta_0}{K} - \gamma < 0$

OR when $\frac{\beta_0}{\gamma K} < 1$

When this is the case, the other stable point does not exist, so there is always only ever one stable point. This is a beautiful result !!

when $\boxed{x_{st} = \frac{\beta_0}{\gamma K} - 1,}$

$$\left.\frac{d^2x}{dt^2}\right|_{x_{st}} = -\gamma - \frac{\beta_0\left(\frac{\beta_0}{\gamma K}-1\right)}{K^2\left(1+\frac{\frac{\beta_0}{\gamma K}-1}{K}\right)^2} + \frac{\beta_0}{K\left(1+\frac{\frac{\beta_0}{\gamma K}-1}{K}\right)} \;?\; 0$$

This steady state only exists when $\frac{\beta_0}{\gamma K} > 1$

Let's use this condition.

$$-\gamma - \frac{\beta_0\left(\frac{\beta_0}{\gamma K}-1\right)}{K^2\left(1+\frac{\frac{\beta_0}{\gamma K}-1}{K}\right)^2} + \frac{\beta_0}{K\left(1+\frac{\frac{\beta_0}{\gamma K}-1}{K}\right)} \cdot \frac{K\left(1+\frac{\frac{\beta_0}{\gamma K}-1}{K}\right)}{K\left(1+\frac{\frac{\beta_0}{\gamma K}-1}{K}\right)} \;?\; 0$$

$$\frac{\beta_0\left[K+\left(\frac{\beta_0}{\gamma K}-1\right)-\left(\frac{\beta_0}{\gamma K}-1\right)\right]}{K^2\left(1+\frac{1}{K}\left(\frac{\beta_0}{\gamma K}-1\right)\right)^2} \;?\; \gamma$$

$$\frac{\beta_0}{\gamma K}\,\frac{1}{\left(1+\frac{1}{K}\left(\frac{\beta_0}{\gamma K}-1\right)\right)^2} \;?\; 1$$

$$\underbrace{\frac{\beta_0}{\gamma K}}_{<1}\;\underbrace{\frac{1}{\left(1+\frac{1}{K}\underbrace{\left(\frac{\beta_0}{\gamma K}-1\right)}_{\oplus}\right)^2}}_{<1}\Big\}>1 \;-1 \;?\; 0$$

$$\downarrow$$

$$<$$

Therefore, when this fixed point exists, it is stable. When it doesn't exist, 0 is the stable fixed point. There is only ever 1!!

$\boxed{\text{case}: \alpha_0 > 0}$

$x_\ominus < 0$ since $4\tilde{\alpha}$ is $\oplus$ $\rightsquigarrow$ form: $\heartsuit - \sqrt{4\alpha + \heartsuit} < 0$

concentrations can't be $\ominus$

$$\left[\, x_\oplus = \frac{\alpha_0+\beta_0}{\gamma K} - 1 + \sqrt{4\frac{\alpha_0}{\gamma K} + \left(\frac{\alpha_0+\beta_0}{\gamma K} - 1\right)^2} \,\right]$$

There is only one fixed point.

Plugging this in $\frac{d^2x}{dt^2}$ looks too scary.

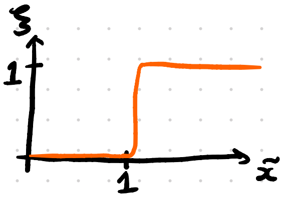
ⓒ $\frac{d\tilde{x}}{dt} = \tilde{\alpha} + \tilde{\beta}\underbrace{\frac{\tilde{x}^n}{1+\tilde{x}^n}}_{\xi} - \tilde{x}$

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

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

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

Graphical Analysis
When $n \to \infty$




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

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

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

∴ when $\tilde{x}<1$: $\tilde{x}_{st} = \tilde{\alpha}$

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

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

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

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

Bistability

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

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

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 = 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 $\gamma$ term can be tuned (through careful dilution??) to equalize the leakage. Binding affintiy 'k' can also be tuned. We see that response times are predominantly controlled by the hill coefficient 'n', which can tell use inherently which systems are more regulatable than others.