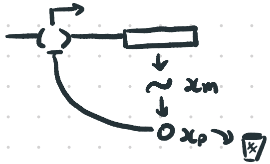
Homework 1.2: Autoactivation, Bistability, Leakage

(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:

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

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

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

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

β_0/α_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 $\alpha_0 = 0$, $x_\ominus = 0$
$x_\oplus = \tilde{\beta} - 1$

$$\boxed{\begin{aligned} x_\ominus &= 0 \\ x_\oplus &= \frac{\beta_0}{\gamma K} - 1 \end{aligned}}$$

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

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

concentrations can't be $\ominus$

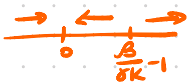
$$\boxed{x_\oplus = \frac{\alpha_0 + \beta_0}{\gamma K} - 1 + \sqrt{4\frac{\alpha_0}{\gamma K} + \left(\frac{\alpha_0+\beta_0}{\gamma K} - 1\right)^2}}$$

Stability of fixed points:

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

@ $0 < x < \frac{\beta}{\gamma K} - 1$, $\frac{dx}{dt} < 0$ look @ nondim in the form $\frac{\xi - \varepsilon}{1+\xi - \varepsilon} - \xi < 0$

@ $x > \frac{\beta}{\gamma K} - 1$, $\frac{dx}{dt} > 0$ opposite of above



$\therefore$ $x = 0$: stable
$x = \frac{\beta}{\gamma K} - 1$: unstable

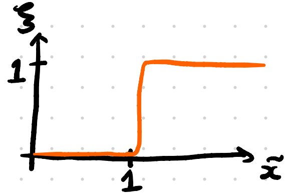
(c) $\frac{d\tilde{x}}{d\tilde{t}} = \tilde{\alpha} + \tilde{\beta}\underbrace{\frac{\tilde{x}^n}{1+\tilde{x}^n}}_{\xi} - \tilde{x}$

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

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

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

Graphical Analysis
when $n \to \infty$



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

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

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

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$\therefore$ 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 $\alpha = \frac{\beta}{2}+1$

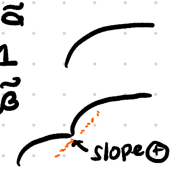
otherwise $\frac{d\tilde{x}}{dt}>0$

I'm not sure what you're getting at here regarding response time. How are you seeing response time in this question?

$\therefore$ 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 γ 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.