LECTURES 23-29: Microbial Growth and Bioreactors

Problem 1: Consider the model of a constant –volume, non-ideally mixed chemostate with sterile feed, consisting of following equations, with initial condition being given by S=X=0 at t=0:

$$\frac{dX}{dt} = \frac{X_m - X}{t_{mix}} + \mu X, \quad (1) \qquad \frac{X_m - X}{t_{mix}} = -\frac{X_m}{\tau}, \quad (2)$$

$$\frac{dS}{dt} = \frac{S_m - S}{t_{mix}} - \mu X, \quad (3) \qquad \frac{S_m - S}{t_{mix}} = \frac{S_0 - S_m}{\tau}, \quad (4)$$

where X and S are the average cell and substrate concentrations in the chemostate, respectively, while X_m and S_m are the mixing-cup cell and substrate concentrations in the chemostate respectively, S_0 is the inlet substrate concentration, t_{mix} and τ are the mixing time and residence time respectively, and μ is the specific growth rate of cells, given by

$$\mu = \frac{\mu_{\max} S}{K_S + S + S^2 / K_I} \quad (5).$$

Obtain the steady states of the above model given by equations (1-5) and examine the stability of each steady-state.

Solution: From equation (2)

$$\frac{X_m - X}{t_{mix}} = -\frac{X_m}{\tau} = -DX_m \qquad (10.1)$$

where D- dilution rate

$$X_m = \frac{X\tau}{\tau + t_{mix}} \qquad (10.2)$$

Using eqn.(10.2) in eqn.(1), we get

$$\frac{dX}{dt} = \mu X - \frac{X}{\tau + t_{mix}} \tag{10.3}$$

$$\frac{dX}{dt} = \left[\mu - \frac{D}{\left(1 + \frac{t_{mix}}{\tau}\right)} \right] X \tag{10.4}$$

Also

$$\frac{S_m - S}{t_{mix}} = \frac{S_0 - S_m}{\tau}$$

or

$$S_m = \frac{\left(S_0 t_{mix} + S\tau\right)}{\tau + t_{mix}} \tag{10.5}$$

Put eqn. (10.5) into given eqn.(3), so we get

$$\frac{dS}{dt} = \frac{D\left(S_0 - S\right)}{\left(1 + \frac{t_{mix}}{\tau}\right)} - \mu X \tag{10.6}$$

and

$$\mu = \frac{\mu_{\max} S + \mu_2}{\left(K_s + S + \frac{S^2}{K_I}\right)} \tag{10.7}$$

Now at S.S

(A) $$\frac{dX}{dt} = 0$$

Therefore from (10.4)

$$\left[\mu - \frac{D}{\left(1 + \frac{t_{mix}}{\tau}\right)}\right] X = 0$$

<u>Case 1</u>: if $X_{ss} \neq 0$ (Non-wash out case)

$$D = \mu\left(1 + \frac{t_{mix}}{\tau}\right)$$

Lets say $$\alpha = \left(1 + \frac{t_{mix}}{\tau}\right) \qquad (\alpha > 1)$$

therefore

$$D = \alpha\mu$$

$$D = \alpha\left(\mu_{\max} S_{ss} + \mu_2\right) \tag{10.8}$$

from eqn.(10.7) and eqn.(10.8)

$$\frac{D}{K_I} S_{ss}^2 + S_{ss}\left(D - \alpha\mu_{\max}\right) + \left(DK_s - \alpha\mu_2\right) = 0 \tag{10.9}$$

$$S_{ss}=\frac{S\left(\alpha\mu_{\max}-D\right)\pm\sqrt{\left(\alpha\mu_{\max}-D\right)^{2}-\frac{4D}{K_{I}}\left(DK_{s}-\alpha\mu 2\right)}}{\frac{2D}{K_{I}}}$$

(10.10)

(provided determinant >0)

and from eqn.(10.6) (at S.S)

$$\frac{D}{\alpha}\left(S_{0}-S_{ss}\right)=\mu X \qquad (10.11)$$

or

$$X=\left(S_{0}-S_{ss}\right) \qquad \left[\because D=\alpha\mu\right]$$

Case 2: Wash out state

$$\text{if} \quad \frac{D}{\alpha} > \mu$$

$$X_{ss} = 0$$

$$S_{ss} = S_0$$

Stability Analysis:

Case 1: $D = \alpha\mu$

Jacobian matrix can be formed as

$$A = \begin{pmatrix} \dfrac{\partial f_1}{\partial X} & \dfrac{\partial f_1}{\partial S} \\ \dfrac{\partial f_2}{\partial X} & \dfrac{\partial f_2}{\partial S} \end{pmatrix}$$

$$\frac{\partial f_1}{\partial X} = \left(\mu - \frac{D}{\alpha} \right) = 0 \ ; \qquad \frac{\partial f_1}{\partial S} = X \frac{\partial \mu}{\partial S}$$

$$\frac{\partial f_2}{\partial X} = -\mu \ ; \qquad \frac{\partial f_2}{\partial S} = -\frac{D}{\alpha} - X \frac{\partial \mu}{\partial S}$$

Now

$$\frac{\partial \mu}{\partial S} = \frac{\mu_{\max}\left(K_s - \frac{S_2}{K_I}\right) - \mu_s\left(1 + \frac{2S}{K_I}\right)}{\left(K_s + S + \frac{S^2}{K_I}\right)^2} \qquad (10.12)$$

$$\therefore A = \begin{pmatrix} 0 & a_{12} \\ a_{21} & a_{22} \end{pmatrix}$$

$$|A - \lambda I| = 0 \qquad \begin{vmatrix} -\lambda & a_{12} \\ a_{21} & a_{22} - \lambda \end{vmatrix} = 0$$

$$\lambda^2 - a_{22}\lambda - a_{12}a_{21} = 0$$

Now by Routh-Hurwitz criteria

$$\begin{vmatrix} \beta 1 & \beta 3 \\ 1 & \beta 2 \end{vmatrix} > 0 \qquad\qquad \beta 1 > 0$$

$$\beta 1 = -a_{22} = \frac{D}{\alpha} + X\frac{\partial \mu}{\partial S}$$

For stability $\beta 1 > 0$

i.e. $\frac{\partial \mu}{\partial S} > 0$

Hence from eqn.(10.14)

$$\mu_{\max}\left(K_s - \frac{S^2}{K_I}\right) - \mu_2\left(1 + \frac{2S}{K_I}\right) > 0$$

Let $\quad \dfrac{\mu_{\max}}{\mu_2} = \mu'_{\max}$

$$\therefore \quad \mu'_{\max}\left(K_s - \frac{S^2}{K_I}\right) - \left(1 + \frac{2S}{K_I}\right) > 0$$

Hence one of the root is

$$\text{root } 1 = \frac{\dfrac{-2}{K_I} + \sqrt{\dfrac{4}{K_I^{\,2}} - \dfrac{4\mu'_{\max}}{K_I}\left(1 - \mu'_{\max} K_s\right)}}{\dfrac{2\mu'_{\max}}{K_I}}$$

So for stability

$$0 < S < \text{root } 1$$

$$\mathrm{S_{ss}} < \frac{\dfrac{-1}{K_I} + \sqrt{1 + \mu'_{\max} K_I \left(\mu'_{\max} K_s - 1\right)}}{\mu'_{\max}} \tag{10.13}$$

Equation (10.13) is the condition for stability.
If S_{ss} satisfies above condition, $\beta_2>0$ also satisfied and the system steady state would be stable.

Case 2: Wash-out state

Here $D > \alpha\mu$ & $X_{ss}=0$ & $S_{ss}=0$

$$\therefore A = \begin{pmatrix} \mu - \dfrac{D}{\alpha} & 0 \\ -\mu & \dfrac{-D}{\alpha} \end{pmatrix}$$

$$|A - \lambda I| = 0 \qquad \begin{vmatrix} \left(\mu - \dfrac{D}{\alpha}\right) - \lambda & 0 \\ -\mu & -D - \lambda \end{vmatrix} = 0$$

$$\lambda^2 + \lambda\left(\frac{2D}{\alpha} - \mu\right) + \frac{D}{\alpha}\left(\frac{D}{\alpha} - \mu\right) = 0$$

$\beta 1$ $\beta 2$ $(\beta 3 = 0)$

So by Routh-Hurwitz criteria

(1) $\beta_1 > 0$
(2) $\beta_1\beta_2 > \beta_3$ $\beta_1\beta_2 > 0$ $\beta_2 > 0$

$$\beta_1 = \frac{2D}{\alpha} - \mu > 0 \qquad \text{because } \frac{D}{\alpha} > \mu$$

$$\beta_2 = \frac{D}{\alpha}\left(\frac{D}{\alpha} - \mu\right) > 0 \qquad \text{because } \frac{D}{\alpha} > \mu$$

Hence this steady state is globally stable.

Problem 2:

The following prey-predator model is used to describe the predation by an amoeba on a bacterium. Obtain analytically the steady states of the model and examine their stability using linear stability analysis. All symbols in the model have their usual meanings.

$$\frac{ds}{dt} = D\left(s_0 - s\right) - \frac{\mu_s\left(s\right)}{Y_S} n_1, \qquad (1)$$

$$\frac{dn_1}{dt} = -Dn_1 + \mu_s\left(s\right) n_1 - \frac{\mu_p\left(n_1\right)}{Y_p} n_2, \qquad (2)$$

$$\frac{dn_2}{dt} = -Dn_2 + \mu_p\left(n_1\right) n_2. \qquad (3)$$

For equation (1), (2) and (3), steady states are

$$D\left(s_0 - s_s\right) - \frac{\mu_s\left(s\right)}{Y_S} n_{1s} = 0, \tag{12.1}$$

$$-Dn_{1s} + \mu_s\left(s\right) n_{1s} - \frac{\mu_p\left(n_{1s}\right)}{Y_p} n_{2s} = 0, \tag{12.2}$$

$$-n_{2s}\left(D - \mu_p\left(n_{1s}\right)\right) = 0 \tag{12.3}$$

from (12.3) $n_{2s} = 0$ or $D = \mu_p\left(n_{1s}\right)$

for $n_{2s} = 0$, from (12.2)

$$-n_{1s}\left(D - \mu_s\left(s\right)\right) = 0$$

$n_{1s} = 0$

Therefore from eqn.(12.1)

$s_s = s_0$

or $\quad D = \mu_s\left(s_s\right)$

$$D = \frac{\mu_{s\max} s_s}{K_s + s_s} \Rightarrow s_s = \frac{DK_s}{\left(\mu_{\max} - D\right)} \qquad (12.4)$$

$\left(\text{for } \mu_{\max} > D\right)$

Now from (12.1) & (12.4)

$$D\left(s_0 - \frac{DK_s}{\left(\mu_{s\max} - D\right)}\right) = \frac{D}{\gamma_s} n_{1s}$$

Therefore

$$n_{1s} = \gamma_{\mathrm{s}}\left(s_0 - \frac{DK_s}{\left(\mu_{s\max} - D\right)} \right)$$

For $D = \mu_p\left(n_{1s}\right)$

$$D = \frac{\mu_{p\max} n_{1s}}{K_p + n_{1s}} \Rightarrow n_{1s} = \frac{K_p D}{\left(\mu_{p\max} - D\right)}$$

$$\left(\text{for } \mu_{p\max} > D\right)$$

Putting in eqn.(12.1) we get

$$D\left(s_0 - s_s\right) - \frac{\mu_{s\max} s_s}{\gamma_s \left(K_s + s_s\right)} \frac{K_p D}{\left(\mu_{p\max} - D\right)} = 0$$

Solving for s_s

$$s_s = \frac{-B + \sqrt{B^2 + 4 s_0 K_s}}{2} \qquad (12.5)$$

where

$$B = \left[\frac{\mu_{s\max} n_{1s}}{D \gamma_s} - K_s + s_0 \right]$$

Also from eqn. (12.2)

$$-Dn_{1s} + \gamma_{\mathrm{s}} D\left(s_0 - s\right) - \frac{D}{\gamma_{\mathrm{p}}} n_{2s} = 0$$

$$\therefore \ n_{2s} = \gamma_{\mathrm{p}}\left[-n_{1s} + \gamma_{\mathrm{s}}\left(s_0 - s_s\right)\right] \qquad (12.6)$$

So steady states are as follows:

Steady State 1:

$$\mathrm{s_s} = s_0$$

$$n_{1s} = 0$$

$$n_{2s} = 0$$

Steady State 2:

$$s_s = \frac{K_s D}{\left(\mu_{s\max} - D\right)}$$

$$n_{1s} = \gamma_s \left(s_0 - \frac{D K_s}{\left(\mu_{s\max} - D\right)} \right)$$

$$n_{2s} = 0$$

and

Steady State 3:

$$s_s = \frac{-B + \sqrt{B^2 + 4 s_0 K_s}}{2}$$

$$n_{1s} = \frac{K_p D}{\left(\mu_{p\max} - D\right)}$$

$$n_{2s} = \gamma_{\mathrm{p}}\left[\frac{-K_p D}{\left(\mu_{p\max} - D\right)} + \gamma_{\mathrm{s}}\left[s_0 - \left(\frac{-B + \sqrt{B^2 - 4 s_0 K_s}}{2}\right)\right]\right]$$

Where

$$\mathrm{B} = \left[\frac{\mu_{s\max}}{D\gamma_{\mathrm{s}}}\frac{K_p D}{\left(\mu_{p\max} - D\right)} - K_s + s_0\right]$$

Linear Stability Analysis:

Jacobian matrix can be formed as

$$J = \begin{pmatrix} -D - \frac{n_1}{\gamma_s}\frac{\partial \mu_s(s)}{\partial s} & \frac{-\mu_s}{Y_s} & 0 \\ n_1 \frac{\partial \mu_s(s)}{\partial s} & \left(-D + \mu_s(s) - \frac{n_2}{\gamma_p}\frac{\partial \mu_p(n_1)}{\partial n_1}\right) & \frac{-\mu_p(n_1)}{\gamma_p} \\ 0 & n_2 \frac{\partial \mu_p(n_1)}{\partial n_1} & -D + \mu_p(n_1) \end{pmatrix} \tag{12.7}$$

$$\frac{\partial \mu_s}{\partial s} = \frac{\mu_{s\max} K_s}{\left(K_s + s\right)^2}$$

$$\frac{\partial \mu_p}{\partial n_1} = \frac{\mu_{p\max} K_p}{\left(K_p + n_1\right)^2}$$

Thus for Steady State 1, (0,0,0), we have

$$A = \begin{pmatrix} -D & 0 & 0 \\ 0 & -D & 0 \\ 0 & 0 & -D \end{pmatrix}$$

$$\left| A - \lambda I \right| = 0$$

$$\left|A - \lambda I\right| = 0$$

$$\lambda_i = a_{33} \quad \text{and} \quad \left[\lambda_i^{\,2} - \lambda_i a_{11} - a_{21} a_{12}\right] = 0$$

Now $a_{33} < 0$ and

$-a_{11} > 0$ so $a_{11} < 0$

$-a_{21} a_{12} > 0$

Now

$$a_{11} = -\left(D + \frac{n_{1s}}{\gamma_s}\frac{\partial \mu_s}{\partial s}\right)$$

$$(D+\lambda)^3 = 0 \quad \Rightarrow \quad \lambda_i = -D$$

So as D is always >0, so $\lambda_i < 0$

So Stable Steady State.

Now, for steady state 2, we have

$$A = \begin{pmatrix} a_{11} & \dfrac{D}{\gamma_s} & 0 \\ a_{21} & 0 & \dfrac{-\mu_p(n_1)}{\gamma_p} \\ 0 & 0 & -D+\mu_p(n_1) \end{pmatrix}$$

Now $\left(D+\frac{n_{1s}}{\gamma_s}\frac{\partial\mu_s}{\partial s}\right)$ is always +ve

so $a_{11}<0$ is satisfied

$$a_{33} = -D + \mu_p\left(n_1\right)$$

$$= -D \frac{\mu_{p\max}\left[\gamma_s\left(s_0 - \frac{DK_s}{\left(\mu_{s\max} - D\right)}\right)\right]}{K_p + \gamma_s\left(s_0 - \frac{DK_s}{\left(\mu_{s\max} - D\right)}\right)}$$

$$\Rightarrow \quad -D\left(K_p + n_{1s}\right) + \mu_{p\max} n_{1s} < 0$$

$$\therefore \quad \frac{-DK_p}{\left(\mu_{p\max} - D\right)} < n_{1s}$$

For $D>\mu_{pmax}$

$$\frac{-DK_p}{\left(\mu_{p\max}-D\right)} > n_{1s}$$

So for $D>\mu_{pmax}$ and $D<\mu_{pmax}$, this condition should be satisfied.

For Stability

$$\frac{K_p}{\left(D-\mu_{p\max}\right)} > \frac{K_s}{\left(\mu_{s\max}-D\right)}$$

Now $-a_{21}.a_{12}>0$

$$a_{21} = n_{1s} \frac{\partial \mu_s}{\partial s} > 0$$

$$a_{12} = -\frac{\mu_s(s)}{\gamma_s} < 0$$

So condition $-a_{21}.a_{12}>0$ is always satisfied
so steady state exist only if $D<\mu_{smax}$ and stable for $D<\mu_{pmax}$.
and conditionally stable for $D>\mu_{pmax}$ only if

$$\frac{K_p}{\left(D-\mu_{p\max}\right)} > \frac{K_s}{\left(\mu_{s\max}-D\right)}$$