Equations for Plug Flow

Nutrient $S = S(x, y, z, t)$
cell density $u = u(x, y, z, t)$ satisfy:

$$S_t = d_x^S S_{xx} + d_r^S \nabla_{yz}^2 S - v(r) S_x - \gamma^{-1} u f_u(S)$$
$$u_t = d_x^u u_{xx} + d_r^u \nabla_{yz}^2 u - v(r) u_x + u[f_u(S) - k]$$

in the tubular reactor

$$\Omega = \{(x, y, z) : 0 < x < L,\ y^2 + z^2 < R^2\}$$

with velocity profile:

$$v(r) = V_{max}[1 - (\frac{r}{R})^2],$$

and Monod uptake kinetics:

$$f_u(S) = \frac{mS}{a + S}.$$

Useful notation:

$$L^u u = d_x^u u_{xx} + d_r^u \nabla_{yz}^2 u - v(r) u_x$$

Danckwerts' Boundary Conditions

at $x = 0$:

$$\begin{aligned} v(r)S^0 &= -d_x^S S_x + v(r)S \\ 0 &= -d_x^u u_x + v(r)u, \end{aligned}$$

at $x = L$:

$$\begin{aligned} d_x^S S_x - v(r)S &= -v(r)S, \text{ i.e., } S_x = 0 \\ u_x &= 0 \end{aligned}$$

See R. Aris, "Mathematical Modeling, a chemical engineers perspective", Academic Press, 1999.

No Wall Growth Single Species

in the fluid:

$$
\begin{aligned}
S_t &= L^S S - \gamma^{-1} u f_u(S) \\
u_t &= L^u u + u[f_u(S) - k]
\end{aligned}
$$

at $x = 0$:

$$
\begin{aligned}
v(r) S^0 &= -d_x^S S_x + v(r) S \\
0 &= -d_x^u u_x + v(r) u,
\end{aligned}
$$

at $x = L$:

$$
S_x = u_x = 0
$$

on the wall $r = R$

$$
\begin{aligned}
S_r &= 0 \\
u_r &= 0.
\end{aligned}
$$

Radial Boundary Conditions ($r = R$)

wall-attached bacterial fraction
$w = w(x, R\cos\theta, R\sin\theta, t) \in [0, w_{max}]$ satisfies:

$$w_t = w[f_w(S)G(W) - k_w - \beta] + \alpha u(1 - W),$$

where $W = w/w_{max}$.

radial boundary conditions for S:

$$-d_r^S S_r = \gamma^{-1} w f_w(S)$$

radial boundary conditions for u:

$$-d_r^u u_r = \alpha u(1 - W) - w f_w(S)[1 - G(W)] - \beta w.$$

With Wall Growth

wall-attached bacterial fraction on $r = R$
$w = w(x, R\cos\theta, R\sin\theta, t) \in [0, w_{max}]$ satisfies:

$$w_t = w[f_w(S)G(W) - k_w - \beta] + \alpha u(1 - W),$$

where $W = w/w_{max}$.

radial boundary conditions for S:

$$-d_r^S S_r = \gamma^{-1} w f_w(S)$$

radial boundary conditions for u:

$$-d_r^u u_r = \alpha u(1 - W) - w f_w(S)[1 - G(W)] - \beta w.$$

Summary of Single-Population Model

in the fluid:

$$\begin{aligned} S_t &= L^S S - \gamma^{-1} u f_u(S) \\ u_t &= L^u u + u[f_u(S) - k] \end{aligned}$$

on the wall $r = R$

$$w_t = w[f_w(S)G(W) - k_w - \beta] + \alpha u(1 - W).$$

at $x = 0$:

$$\begin{aligned} v(r)S^0 &= -d_x^S S_x + v(r)S \\ 0 &= -d_x^u u_x + v(r)u, \end{aligned}$$

at $x = L$:

$$S_x = u_x = 0$$

on the wall $r = R$

$$\begin{aligned} -d_r^S S_r &= \gamma^{-1} w f_w(S) \\ -d_r^u u_r &= \alpha u(1 - W) - w[f_w(S)(1 - G(W)) + \beta]. \end{aligned}$$

Many-Populations with Wall Growth

in the fluid

$$\begin{aligned} S_t &= L^S S - \sum_i \gamma_i^{-1} u^i f_{ui}(S) \\ u_t^i &= L^i u^i + u^i [f_{ui}(S) - k_i] \end{aligned}$$

on the wall $r = R$

$$\begin{aligned} -d_r^S S_r &= \sum_i \gamma_i^{-1} w^i f_{wi}(S) \\ -d_r^i u_r^i &= \alpha_i u^i (1 - W) \\ &\quad -w_i [f_{wi}(S)(1 - G_i(W)) + \beta_i] \\ w_t^i &= w^i [f_{wi}(S) G_i(W) - k_{wi} - \beta_i] \\ &\quad +\alpha_i u^i (1 - W). \end{aligned}$$

where $W = \sum_i w^i / w_{max}$. at $x = 0$

$$\begin{aligned} v(r) S^0 &= -d_x^S S_x + v(r) S \\ 0 &= -d_x^i u_x^i + v(r) u^i, \end{aligned}$$

at $x = L$

$$S_x = u_x^i = 0.$$

Linear Stability of Washout Steady State

$$S \equiv S^0, \quad u \equiv 0, \quad w \equiv 0.$$

Linear stability analysis:

$$\begin{aligned} S &= S^0 + \epsilon \exp(\lambda t)\bar{S} \\ u &= \epsilon \exp(\lambda t)\bar{u} \\ w &= \epsilon \exp(\lambda t)\bar{w} \end{aligned}$$

$0 < |\epsilon| << 1$, leads to the non-standard eigenvalue problem

$$\begin{aligned} \lambda\bar{S} &= L^S\bar{S} - \gamma^{-1}\bar{u}f_u(S^0) \\ \lambda\bar{u} &= L^u\bar{u} + \bar{u}[f_u(S^0) - k] \\ \lambda\bar{w} &= \bar{w}[f_w(S^0)G(0) - k_w - \beta] + \alpha\bar{u} \end{aligned}$$

with homogeneous Danckwerts' b.c. $(x = 0, L)$ and radial b.c. on $r = R$:

$$\begin{aligned} 0 &= d_r^S\bar{S}_r + \gamma^{-1}\bar{w}f_w(S^0) \\ 0 &= d_r^u\bar{u}_r + \alpha\bar{u} - \bar{w}[f_w(S^0)(1 - G(0)) + \beta]. \end{aligned}$$

Principal Eigenvalue

Theorem: There exists a real simple eigenvalue $\lambda^* > f_w(S^0)G(0) - k_w - \beta$ belonging to the interval with endpoints:

$$f_w(S^0) - k_w, \quad f_u(S^0) - k - \frac{L}{V_{max}}\lambda$$

where $-\lambda < 0$ is the principal eigenvalue of the (scaled $\bar{x} = x/L$, $\bar{r} = r/R$) eigenvalue problem:

$$\begin{aligned}
\lambda u &= \theta_x u_{\bar{x}\bar{x}} - (1 - \bar{r}^2)u_{\bar{x}} + \theta_r \bar{r}^{-1}(\bar{r}u_{\bar{r}})_{\bar{r}}, \\
0 &= -\theta_x u_{\bar{x}} + (1 - \bar{r}^2)u, \quad \bar{x} = 0 \\
0 &= u_{\bar{x}}, \quad \bar{x} = 1 \\
u_{\bar{r}} &= 0, \quad \bar{r} = 1,
\end{aligned}$$

$\theta_x = (d_x^u/L^2)(L/V_{max})$, $\theta_r = (d_r^u/R^2)(L/V_{max})$. Corresponding to λ^* is an eigenvector $(\bar{S}, \bar{u}, \bar{w})$ satisfying $\bar{S} < 0$, $\bar{u} > 0$ in $\overline{\Omega}$ and $\bar{w} > 0$ in $r = R$.

If $\lambda^* < 0$ then washout is stable in the linear approximation; if $\lambda^* > 0$ then it is unstable.

Global Stability of Washout

Theorem: If both

$$f_u(S^0) - k - \frac{L}{V_{max}}\lambda < 0, \;\; f_w(S^0) - k_w < 0,$$

then $\lambda^* < 0$ and

$$\lim_{t\to\infty}\left(\int_\Omega u dV + \int_{r=R} w dA\right) = 0.$$

Conjecture: The result remains valid if only $\lambda^* < 0$.

Population steady state

The equations for a steady state are

$$
\begin{aligned}
0 &= L^S S - \gamma^{-1} u f_u(S) \\
0 &= L^u u + u[f_u(S) - k], \quad \text{in } \Omega \\
0 &= w[f_w(S)G(W) - k_w - \beta] + \alpha u(1 - W), \ r = R.
\end{aligned}
$$

Danckwerts' boundary conditions at $x = 0, L$ and radial boundary conditions:

$$
\begin{aligned}
d_r^S S_r &= -\gamma^{-1} w f_w(S) \\
d_r^u u_r &= -\alpha u(1 - W) + w[f_w(S)(1 - G(W)) + \beta].
\end{aligned}
$$

Theorem: Let $\lambda^* > 0$ and $f_w(S^0)G(0) - k_w - \beta \neq 0$. Then there exists a radially symmetric steady state solution (S, u, w) satisfying (in cylindrical coordinates)

$0 < S(x, r) \leq S^0, u(x, r) > 0,$ and $0 < w(x) \leq w_{max}$.

Criterion for Survival

$\lambda^* > 0$ if **both**

$$f_w(S^0) - k_w > 0$$

and

$$f_u(S^0) - k - \frac{L}{V_{max}}\lambda > 0$$

hold, **or if**

$$f_w(S^0)G(0) - k_w - \beta > 0$$

holds.

In case of **no wall growth** ($\alpha = w = 0$),

$$\lambda^* = f_u(S^0) - k - \frac{L}{V_{max}}\lambda$$

so middle inequality suffices for survival.

Effects of Influx of Antibiotic

Concentration $A = A(x, y, z, t)$ satisfies:

$$\begin{aligned} A_t &= d_x^A A_{xx} + d_r^A \nabla_{yz}^2 A - v(r) A_x \\ 0 &= d_r^A A_r, \quad r = R \text{ (impenetrable biofilm)} \\ v(r) A^0 &= -d_x^A A_x + v(r) A, \quad x = 0 \text{ (influx of A)} \\ 0 &= A_x, \quad x = L. \end{aligned}$$

As for substrate in absence of bacteria,

$$A(x, y, z, t) \to A^0, \quad t \to \infty.$$

If planktonic cell death rate $k = k(A^0)$, $k' > 0$, then effect on λ^* is minimal since:

$$f_w(S^0) G(0) - k_w - \beta < \lambda^*$$

where we assume adherent cell death rate k_w independent of A. Contrast to case of no wall growth ($\alpha = w = 0$) where

$$\lambda^* = f_u(S^0) - k(A^0) - \frac{L}{V_{max}} \lambda.$$

A pair of eigenvalue problems

$$
\begin{aligned}
\lambda u &= L^i u + au, \quad \Omega \\
\lambda w &= bw + \alpha u, \quad r = R \\
0 &= d_r u_r + \alpha u - cw, \quad r = R \qquad (1)\\
0 &= -d_x u_x + v(r)u, \quad x = 0 \\
0 &= u_x, \quad x = L
\end{aligned}
$$

The corresponding adjoint problem is given by:

$$
\begin{aligned}
\lambda u &= L_i u + au, \quad \Omega \\
\lambda w &= bw + cu, \quad r = R \\
0 &= d_r u_r + \alpha u - \alpha w, \quad r = R \qquad (2)\\
0 &= d_x u_x + v(r)u, \quad x = L \\
0 &= u_x, \quad x = 0
\end{aligned}
$$

here, a, b, c, α are real constants.

In order to see in what sense (2) is adjoint to (1) we make the following observation.

Proposition
Let $u \in C^2(\Omega) \cap C^1(\overline{\Omega})$ satisfy the Danckwerts' boundary conditions at $x = 0, L$, $\hat{u} \in C^2(\Omega) \cap C^1(\overline{\Omega})$ satisfy the adjoint Danckwerts' boundary conditions at $x = 0, L$, u, w satisfy the inhomogeneous radial boundary condition

$$h = d_r u_r + \alpha u - cw, \quad r = R$$

and $\hat{u}, \hat{w}$ satisfy the homogeneous adjoint radial boundary condition in (2). Then we have

$$\begin{aligned} &\int_\Omega (L^i u)\hat{u} dV + \int_{r=R} (bw + \alpha u)\hat{w} dA \\ = &\int_\Omega (L_i \hat{u}) u dV + \int_{r=R} h\hat{u} + w(b\hat{w} + c\hat{u}) dA \end{aligned}$$

If $h \equiv 0$, then we obtain the adjoint relation of (2) and (1).

Principal Eigenvalue Theorem Let $\alpha, c > 0$. Then there exists a real simple eigenvalue $\lambda^* > b$ of (1) satisfying:

$$\begin{array}{ll} b+c < \lambda^* \leq a-\lambda_i, & \text{if } b+c < a-\lambda_i \\ b+c = \lambda^*, & \text{if } b+c = a-\lambda_i \\ a-\lambda_i < \lambda^* < b+c, & \text{if } b+c > a-\lambda_i \end{array}$$

Corresponding to eigenvalue λ^* is an eigenvector $(\bar{u}, \bar{w})$ satisfying $\bar{u} > 0$ in $\overline{\Omega}$ and $\bar{w} > 0$ in $r = R$. If λ is any other eigenvalue of (1) corresponding to an eigenvector $(u, w) \geq 0$, then $\lambda = \lambda^*$ and $(u, w) = c(\bar{u}, \bar{w})$ for some $c > 0$. $\bar{u}, \bar{w}$ are axially symmetric, i.e., in cylindrical coordinates (r, θ, x), $\bar{u} = \bar{u}(r, x), \bar{w} = \bar{w}(x)$.

λ^* is also an eigenvalue of (2) corresponding to an eigenvector $(u, w) = (\psi, \chi)$. Moreover, (ψ, χ) has the same uniqueness up to scalar multiple, positivity and symmetry properties as does $(\bar{u}, \bar{w})$.

bacterial growth is limited by supplied substrate

Let (ψ^i, χ^i) be the PEV corresponding to the eigenvalue $\overline{\lambda_i}$ of (2) in the case that $a = 0, b = -\beta_i, \alpha = \alpha_i, c = \beta_i, d_r = d_r^i, d_x = d_x^i$. Normalize (ψ^i, χ^i) by requiring $\psi^i, \chi^i \leq \phi \leq 1$. By PEV Theorem and the fact that $b + c = 0$, we have $\overline{\lambda_i} < 0$.

Theorem: A Priori Estimates

$$\limsup_{t\to\infty} S(t,x,y,z) \leq S^0,$$

uniformly in $(x,y,z) \in \Omega$ and

$$\limsup_{t\to\infty} \Big(\int_\Omega S\phi dV + \sum_i \gamma_i^{-1} [\int_\Omega u^i \psi^i dV + \int_{r=R} w^i \chi^i dA] \Big) \leq \frac{2\pi S^0 \int_0^R r v(r) dr}{\min_j\{\lambda^S, -\overline{\lambda_j} + k_j, -\overline{\lambda_j} + k_{wj}\}}$$