Equations for Plug Flow

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

\[
S_t = d_x^S S_{xx} + d_r^S \nabla^2_{yz} S - v(r) S_x - \gamma^{-1} u f_u(S)
\]
\[
u_t = d_x^u u_{xx} + d_r^u \nabla^2_{yz} u - v(r) u_x + u[f_u(S) - k]
\]
in the tubular reactor

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

with velocity profile:

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

and Monod uptake kinetics:

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

Useful notation:

\[
L^u u = d_x^u u_{xx} + d_r^u \nabla^2_{yz} u - v(r) u_x
\]
Danckwerts’ Boundary Conditions

at $x = 0$:

$$v(r)S^0 = -d_x^S S_x + v(r)S$$
$$0 = -d_x^u u_x + v(r)u,$$

at $x = L$:

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

No Wall Growth Single Species

in the fluid:

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

at \( x = 0 \):

\begin{align*}
0 &= -d^S_x S_x + v(r) S \\
0 &= -d^u_x u_x + v(r) u,
\end{align*}

at \( x = L \):

\begin{align*}
S_x &= u_x = 0
\end{align*}

on the wall \( r = R \)

\begin{align*}
S_r &= 0 \\
u_r &= 0.
\end{align*}
Radial Boundary Conditions ($r = R$)

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

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

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

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:

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

on the wall \( r = R \)

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

at \( x = 0 \):

\[ v(r) S^0 = -d_x^S S_x + v(r) S \]
\[ 0 = -d_x^u u_x + v(r) u, \]

at \( x = L \):

\[ S_x = u_x = 0 \]

on the wall \( r = R \)

\[ -d_r^S S_r = \gamma^{-1} w f_w(S) \]
\[ -d_r^u u_r = \alpha u (1 - W) - w[f_w(S)(1 - G(W)) + \beta]. \]
Many-Populations with Wall Growth

in the fluid

\[ S_t = L^S S - \sum_i \gamma_i^{-1} u^i f_{ui}(S) \]
\[ u^i_t = L^i u^i + u^i [f_{ui}(S) - k_i] \]

on the wall \( r = R \)

\[ -d^S_r S_r = \sum_i \gamma_i^{-1} w^i f_{wi}(S) \]
\[ -d^i_r u^i_r = \alpha_i u^i (1 - W) \]
\[ -w_i[f_{wi}(S)(1 - G_i(W)) + \beta_i] \]
\[ w^i_t = w^i [f_{wi}(S)G_i(W) - k_{wi} - \beta_i] + \alpha_i u^i (1 - W). \]

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

\[ v(r)S^0 = -d^S_x S_x + v(r)S \]
\[ 0 = -d^i_x u^i_x + v(r)u^i, \]

at \( x = L \)

\[ S_x = u^i_x = 0. \]
Linear Stability of Washout Steady State

\[ S \equiv S^0, \quad u \equiv 0, \quad w \equiv 0. \]

Linear stability analysis:

\[
\begin{align*}
S &= S^0 + \epsilon \exp(\lambda t) \bar{S} \\
u &= \epsilon \exp(\lambda t) \bar{u} \\
w &= \epsilon \exp(\lambda t) \bar{w}
\end{align*}
\]

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

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

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

\[
\begin{align*}
0 &= d^S_r \bar{S}_r + \gamma^{-1} \bar{w} f_w(S^0) \\
0 &= d^u_r \bar{u}_r + \alpha \bar{u} - \bar{w} [f_w(S^0)(1 - G(0)) + \beta].
\end{align*}
\]
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:

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

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

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

$$\theta_x = (d_{x}^{u}/L^2)(L/V_{\text{max}}), \quad \theta_r = (d_{r}^{u}/R^2)(L/V_{\text{max}}).$$

Corresponding to $\lambda^*$ is an eigenvector $(\bar{S}, \bar{u}, \bar{w})$ satisfying $\bar{S} < 0$, $\bar{u} > 0$ in $\bar{\Omega}$ and $\bar{w} > 0$ in $\bar{r} = R$.

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

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

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

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

Danckwerts’ boundary conditions at \( x = 0, L \) and radial boundary conditions:

\[ d^S_r S_r = -\gamma^{-1} w f_w(S) \]
\[ d^u_r u_r = -\alpha u(1 - W) + w[f_w(S)(1 - G(W)) + \beta]. \]

**Theorem:** Let \( \lambda^*_\beta > 0 \) 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)

\[ 0 < S(x, r) \leq S^0, \quad u(x, r) > 0, \quad \text{and } 0 < w(x) \leq w_{\text{max}}. \]
Criterion for Survival

\[ \lambda^* > 0 \text{ if both} \]

\[ f_w(S^0) - k_w > 0 \]

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:

$$A_t = d^A_{xx}A_{xx} + d^A_{rr}\nabla^2_{yz}A - v(r)A_x$$

$$0 = d^A_r A_r, \quad r = R \text{ (impenetrable biofilm)}$$

$$v(r)A^0 = -d^A_xA_x + v(r)A, \quad x = 0 \text{ (influx of A)}$$

$$0 = A_x, \quad x = L.$$ 

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 $\lambda^*$ 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

\[ \lambda u = L_i u + au, \quad \Omega \]
\[ \lambda w = bw + \alpha u, \quad r = R \]
\[ 0 = d_r u_r + \alpha u - cw, \quad r = R \]  
\[ 0 = -d_x u_x + v(r) u, \quad x = 0 \]
\[ 0 = u_x, \quad x = L \]

The corresponding adjoint problem is given by:

\[ \lambda u = L_i u + au, \quad \Omega \]
\[ \lambda w = bw + cu, \quad r = R \]
\[ 0 = d_r u_r + \alpha u - \alpha w, \quad r = R \]
\[ 0 = d_x u_x + v(r) u, \quad x = L \]
\[ 0 = u_x, \quad x = 0 \]

here, \( a, b, c, \alpha \) are real constants.
In order to see in what sense (2) is adjoint to (1) we make the following observation.

**Proposition**

Let \( u \in C^2(\Omega) \cap C^1(\Omega) \) satisfy the Danckwerts' boundary conditions at \( x = 0, L \), \( \hat{u} \in C^2(\Omega) \cap C^1(\Omega) \) 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

\[
\int_\Omega (L_i^i u) \hat{u} dV + \int_{r=R} (bw + \alpha u) \hat{w} dA \\
= \int_\Omega (L_i \hat{u}) u dV + \int_{r=R} h \hat{u} + w(b \hat{w} + c \hat{u}) dA
\]

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:

\[
\begin{align*}
    b + c &< \lambda^* \leq a - \lambda_i, & \text{if } b + c < a - \lambda_i \\
    b + c &= \lambda^*, & \text{if } b + c = a - \lambda_i \\
    a - \lambda_i &< \lambda^* < b + c, & \text{if } b + c > a - \lambda_i
\end{align*}
\]

Corresponding to eigenvalue $\lambda^*$ is an eigenvector $(\bar{u}, \bar{w})$ satisfying $\bar{u} > 0$ in $\overline{\Omega}$ and $\bar{w} > 0$ in $r = R$. If $\lambda$ 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 $(r, \theta, x)$, $\bar{u} = \bar{u}(r, x), \bar{w} = \bar{w}(x)$.

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

16
bacterial growth is limited by supplied substrate

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

**Theorem: A Priori Estimates**

\[
\limsup_{t \to \infty} S(t, x, y, z) \leq S^0,
\]
uniformly in \((x, y, z) \in \Omega\) and

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