Andrew's substrate inhibition model. Steady-states & stability.
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Consider Andrew's substrate inhibition model of specific growth rate.

$$\mu = \frac{\mu_m \cdot s}{K + s + K_i \cdot s^2}$$

Mark s and choose |Symbolic|Differentiate on Variable| followed by |Symbolic|Simplify| yields:

$$\frac{d}{ds}\mu = 0 = \mu_m \cdot \frac{K - K_i \cdot s^2}{\left(K + s + K_i \cdot s^2\right)^2}$$ ← condition for the maximum point in μ.

Mark s and choose |Symbolic|Solve for Variable| yields:

$$s_{max} = \begin{bmatrix} \frac{1}{\sqrt{K_i}} \cdot \sqrt{K} \\ \frac{-1}{\sqrt{K_i}} \cdot \sqrt{K} \end{bmatrix}$$

← o.k. $s_{max} = \sqrt{\frac{K}{K_i}}$

← Negative concentration; invalid

Copy s_{max}, mark s in the μ equation at the top of this page, choose |Symbolic|Substitute for Variable| followed by |Symbolic|Simplify| yields:

$$\mu_{max} = \frac{\mu_m}{2 \cdot \sqrt{K \cdot K_i} + 1}$$

Steady-States -- (Manually Derived) Analytical Solution.

Biomass: dx/dt=0 $\quad 0 = (\mu(s) - D) \cdot x$

Substrate: ds/dt=0 $\quad 0 = D \cdot \left(s_f - s\right) - \frac{1}{Y} \cdot \mu(s) \cdot x$

Depending on the value of the operating parameters D and s_f, we have either:

- one steady-state (Case 1),
- two steady-states (Case 2), or
- three steady-states (Case 3).

Case 1. For $\mu_{max} < D$ we have one steady-state, namely washout of biomass.

$$x = 0 \qquad s = s_f$$

Case 2. For $D < \mu_{sf} < \mu_{max}$ and $s_f \le s_{max}$ we have two possible steady-states.

$$\mu_{sf} = \mu\left(s_f\right) = \frac{\mu_m \cdot s_f}{K + s_f + K_i \cdot s_f^2}$$

1. washout steady-state: $x = 0 \qquad s = s_f$

2. non-washout steady-state

$$D = \mu \qquad D = \frac{\mu_m \cdot s}{K + s + K_i \cdot s^2}$$

Mark s and choose |Symbolic|Solve for Variable| yields two solutions:

$$s = \begin{bmatrix} \frac{1}{2 \cdot D \cdot K_i} \cdot \left[(\mu_m - D) + \sqrt{D^2 - 2 \cdot D \cdot \mu_m + \mu_m^{\ 2} - 4 \cdot D^2 \cdot K_i \cdot K} \right] \\ \frac{1}{2 \cdot D \cdot K_i} \cdot \left[(\mu_m - D) - \sqrt{D^2 - 2 \cdot D \cdot \mu_m + \mu_m^{\ 2} - 4 \cdot D^2 \cdot K_i \cdot K} \right] \end{bmatrix}$$

← Hi solution: $s_{max} < s$

← Lo solution: $s < s_{max}$

Of these two, only the lower solution is physically feasible because we must have $s \le s_f \le s_{max}$.

$$s = \frac{1}{2 \cdot D \cdot K_i} \cdot \left[(\mu_m - D) - \sqrt{(\mu_m - D)^2 - 4 \cdot D^2 \cdot K_i \cdot K} \right]$$

$$x = Y \cdot (s_f - s)$$

Case 3. For $D < \mu_{sf} < \mu_{max}$ and $s_{max} < s_f$ we have three possible steady-states.

1. washout steady-state: $x = 0 \qquad s = s_f$

2 & 3. non-washout steady-states (one on each side of s_{max})

$$s_1 = \frac{1}{2 \cdot D \cdot K_i} \cdot \left[(\mu_m - D) - \sqrt{(\mu_m - D)^2 - 4 \cdot D^2 \cdot K_i \cdot K} \right] \qquad x_1 = Y \cdot (s_f - s_1)$$

$$s_2 = \frac{1}{2 \cdot D \cdot K_i} \cdot \left[(\mu_m - D) + \sqrt{(\mu_m - D)^2 - 4 \cdot D^2 \cdot K_i \cdot K} \right] \qquad x_2 = Y \cdot (s_f - s_2)$$

Steady-States -- Brute-Force Mathcad Analytical Solution.

Given

Biomass: dx/dt=0 $\qquad 0 = (\mu - D) \cdot x$ $\qquad$ where $\qquad \mu = \frac{\mu_m \cdot s}{K + s + K_i \cdot s^2}$

Substrate: ds/dt=0 $\qquad 0 = D \cdot (s_f - s) - \frac{1}{Y} \cdot \mu \cdot x$

$$\text{Find}(x, s, \mu) \rightarrow \begin{bmatrix} 0 & \frac{1}{[2 \cdot (D \cdot K_i)]} \cdot \left(2 \cdot D \cdot K_i \cdot Y \cdot s_f + D \cdot Y - \mu_m \cdot Y + Y \cdot \sqrt{D^2 - 2 \cdot D \cdot \mu_m + \mu_m^{\ 2} - 4 \cdot D^2 \cdot K \right. \\ s_f & \frac{\left[\frac{-1}{[2 \cdot (D \cdot K_i)]} \cdot \left(2 \cdot D \cdot K_i \cdot Y \cdot s_f + D \cdot Y - \mu_m \cdot Y + Y \cdot \sqrt{D^2 - 2 \cdot D \cdot \mu_m + \mu_m^{\ 2} - 4 \cdot D^2 \cdot K_i \cdot K} \right. \right.}{Y} \\ \mu_m \cdot \frac{s_f}{(K + s_f + K_i \cdot s_f^{\ 2})} & D \end{bmatrix}$$

Each column in the above matrix represents a steady-state solution.

Numerical Steady-State Solution -- Useful for more complicated expressions.

Operating condition:

$s_f := 10$

Model parameters:

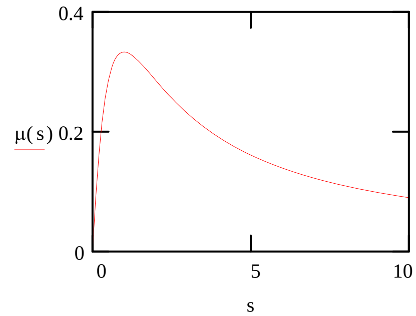
Specific growth rate: $\mu_m := 1$ $\quad K := 1$ $\quad K_i := 1$ $\quad \mu(s) := \dfrac{\mu_m \cdot s}{K + s + K_i \cdot s^2}$

Yield coefficient: $Y := 0.5$

$s := 0, 0.1 .. s_f$

s=0 as an initial guess is o.k. for v5 but not for v7.

Maximum specific growth rate μ: $s := 0.1$ ... initial guess



Given $\quad \dfrac{d}{ds}\mu(s) = 0 \qquad s_{max} := \text{Find}(s) \qquad s_{max} = 1$

$\mu_{max} := \mu(s_{max}) \qquad \mu_{max} = 0.333$

Initial guesses:

$x := 5 \qquad s := 0$

Given Steady-state equations:

dx/dt: $\quad 0 = (\mu(s) - D) \cdot x$

ds/dt: $\quad 0 = D \cdot (s_f - s) - \dfrac{1}{Y} \cdot \mu(s) \cdot x$

$ss(D) := \text{Find}(x, s) \qquad x_a(D) := ss(D)_0 \qquad s_a(D) := ss(D)_1$

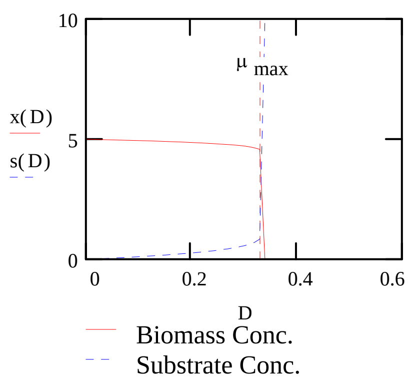
An example: $ss(0.1) = \begin{pmatrix} 4.944 \\ 0.113 \end{pmatrix}$

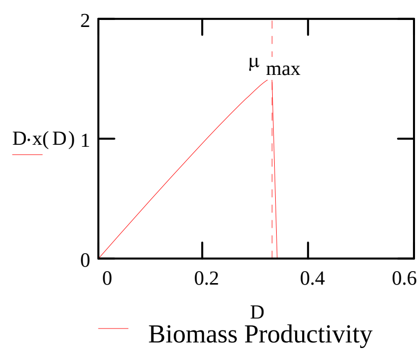
Combine washout steady-state and non-washout steady-state.

$x(D) := \text{if}(\mu_{max} < D, 0, x_a(D))$

$s(D) := \text{if}(\mu_{max} < D, s_f, s_a(D))$

Steady-state plot & dependence of D·x on D: $\qquad D := 0, 0.01 .. 0.4$





Note that cell productivity increases monotonically with D, right up to μ_{max}, beyond which point cell washout suddenly occurs. The maximum cell productivity occurs at: $D_{max} := \mu_{max}$

The maximum cell productivity is: $D_{max} \cdot x(D_{max}) = 1.5$

Localized Stability Analysis.

Jacobian matrix: (Evaluated by marking x or s in dynamic equations and choose |Symbolic|Differentiate on Variable|.)

$$A = \begin{bmatrix} \mu(s) - D & \frac{d}{ds}\mu(s)\cdot x \\ \frac{-1}{Y}\cdot\mu(s) & -D - \frac{1}{Y}\cdot\frac{d}{ds}\mu(s)\cdot x \end{bmatrix}$$

$$\text{eigenvalue}(A) = \det\cdot\left|\lambda\cdot I - A\right| = \left|\begin{bmatrix} \lambda - (\mu(s) - D) & -\frac{d}{ds}\mu(s)\cdot x \\ \frac{1}{Y}\cdot\mu(s) & \lambda + D + \frac{1}{Y}\cdot\frac{d}{ds}\mu(s)\cdot x \end{bmatrix}\right| = 0$$

$$0 = (\lambda - (\mu(s) - D))\cdot\left(\lambda + D + \frac{1}{Y}\cdot\frac{d}{ds}\mu(s)\cdot x\right) + \frac{1}{Y}\cdot\mu(s)\cdot\frac{d}{ds}\mu(s)\cdot x$$

For non-washout steady-state, μ=D

$$0 = \lambda\cdot\left(\lambda + D + \frac{1}{Y}\cdot\frac{d}{ds}\mu(s)\cdot x\right) + \frac{1}{Y}\cdot D\cdot\frac{d}{ds}\mu(s)\cdot x$$

$$0 = \lambda^2\cdot Y + \lambda\cdot D\cdot Y + \lambda\cdot\mu'\cdot x + D\cdot\mu'\cdot x$$

Mark λ and choose |Symbolic|Solve For Variable| yields the following eigenvalues:

$$\lambda = \begin{pmatrix} -D \\ \frac{-1}{Y}\cdot\mu'\cdot x \end{pmatrix}$$

← This eigenvalue is automatically negative.

← This eigenvalue is negative when μ' is positive. Thus, the high steady-state where the μ versus s curve is declining with s is unstable, while the lower steady-state is stable.

Condition for stability:

$\frac{d}{ds}\mu(s) > 0$ ... Stable.

$\frac{d}{ds}\mu(s) < 0$ ... Unstable.

$$\cdots{}_i\cdot K\Big)\qquad \frac{1}{\left[2\cdot\left(D\cdot K_i\right)\right]}\cdot\left(2\cdot D\cdot K_i\cdot Y\cdot s_f + D\cdot Y - \mu_m\cdot Y - Y\cdot\sqrt{D^2 - 2\cdot D\cdot\mu_m + \mu_m{}^2 - 4\cdot D^2\cdot K_i\cdot K}\right)$$

$$\Big) + Y\cdot s_f\Big] \quad \frac{\left[\frac{-1}{\left[2\cdot\left(D\cdot K_i\right)\right]}\cdot\left(2\cdot D\cdot K_i\cdot Y\cdot s_f + D\cdot Y - \mu_m\cdot Y - Y\cdot\sqrt{D^2 - 2\cdot D\cdot\mu_m + \mu_m{}^2 - 4\cdot D^2\cdot K_i\cdot K}\right) + Y\cdot s_f\right]}{Y}$$

$$D$$