Fed-Batch Bioreactor. Dynamic simulation and quasi-steady state calculations.
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Operation conditions:

$s_f := 10$ ... Feed substrate concentration

$F := 1.005$ ... Flow rate

$V := 10$ ... Fermentor volume (max)

Constitutive relations:

$\mu_m := 1$ ... maximum specific growth rate

$K := 1$ ... Michaelis-Menten constant

$A := 0.5$ ... constant part of yield coefficient

$B := 0$ ... linear part of yield coefficient

$\mu(s) := \frac{\mu_m \cdot s}{K + s}$ ... Monod specific growth rate

$Y(s) := A + B \cdot s$ ... yield coefficient

The following equation avoids overshoot:

$\mu(s) := \text{if}\left(s \le 0, 0, \frac{\mu_m \cdot s}{K + s}\right)$

Dynamic Equations:

$\text{dxdt}(x, s, v) := \left(\mu(s) - \frac{F}{v}\right) \cdot x$

$\text{dsdt}(x, s, v) := \frac{F}{v} \cdot \left(s_f - s\right) - \frac{\mu(s)}{Y(s)} \cdot x$

$\text{dvdt}(x, s, v) := F$

$$\text{ydot}(t, y) := \begin{bmatrix} \text{dxdt}\left(y_0, y_1, y_2\right) \\ \text{dsdt}\left(y_0, y_1, y_2\right) \\ \text{dvdt}\left(y_0, y_1, y_2\right) \end{bmatrix}$$

Initial conditions: $x_0 := 0.1$ $s_0 := s_f$ $v_0 := 0.1$

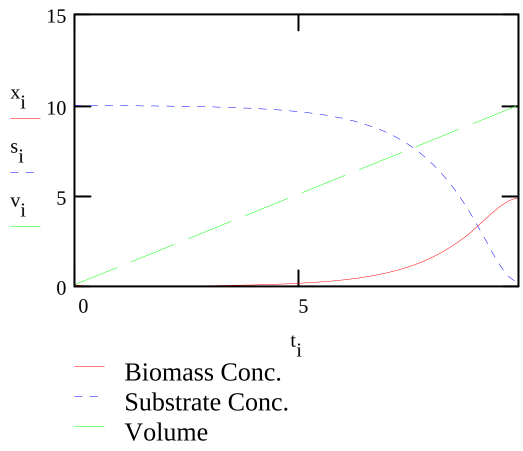
$$y_{initial} := \begin{bmatrix} x_0 \\ s_0 \\ v_0 \end{bmatrix} \begin{matrix} \text{... biomass} \\ \text{... substrate} \\ \text{... volume} \end{matrix}$$

Solve both sets of ODEs (integrate from $t_0 := 0$ to $t_f := \frac{V - v_0}{F}$ in $\text{nstep} := 100$

$\text{yout} := \text{rkfixed}\left(y_{initial}, t_0, t_f, \text{nstep}, \text{ydot}\right)$

$t := \text{yout}^{\langle 0 \rangle}$ $x := \text{yout}^{\langle 1 \rangle}$ $s := \text{yout}^{\langle 2 \rangle}$ $v := \text{yout}^{\langle 3 \rangle}$

Plots of state variables $i := 0 .. \text{last}(t)$



Conditions at $t_{nstep} = 9.851$

$x_{nstep} = 4.889$

$s_{nstep} = 0.225$

$v_{nstep} = 10$

Productivity of biomass:

$$\frac{v_{nstep} \cdot x_{nstep} - v_0 \cdot x_0}{t_f} = 4.962$$

Rule of Thumb in optimization: In general, maximum biomass productivity coincides with depletion of the substrate at the end of the run.

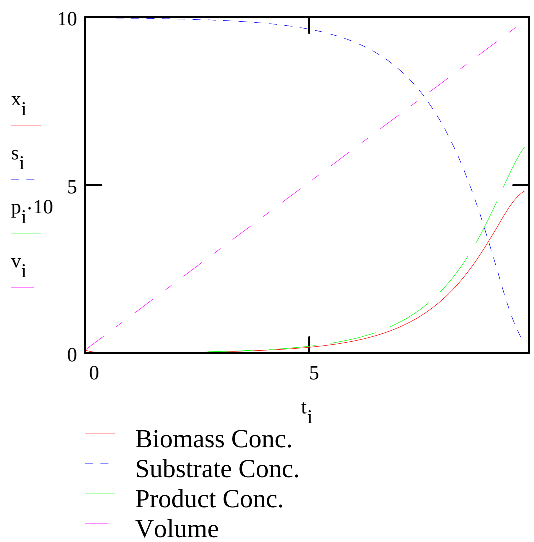
Consideration of product formation (as an after-thought). If a product production does *not* consume substrate -- penicillin fermentation comes close to this case, then the dynamic equation for the product is completely decoupled from the rest. We can either integrate it simultaneously with the other dynamic equations, or do so separately afterwards. A separate file (ferment4.mcd) demonstrates the first approach. Here, we demonstrate the latter approach.

$\alpha(s) := 0.1$ ... growth related product formation

$\beta(s) := 0.02$ ... maintenance-related product formation

$$\text{dpdt}(x, s, p, v) := \alpha(s) \cdot \mu(s) \cdot x + \beta(s) \cdot x - \frac{F}{v} \cdot p$$

Start with $p_0 := 0$ Integrate: $i := 0 .. \text{nstep} - 1$ $\delta t := \frac{t_f}{\text{nstep}}$ $p_{i+1} := p_i + \text{dpdt}(x_i, s_i, p_i, v_i) \cdot \delta t$



Quasi-steady state operation #1. Keep $x=x_0$=constant and implement **constant flow rate F**.

$$\frac{d}{dt}v=F \quad \Rightarrow \quad v=v_0+F\cdot t \quad \leftarrow \text{linearly increasing volume.}$$

Note that with a constant flow rate F, the biomass and substrate concentrations are changing with time, at least initially until the substrate is almost depleted. Once we decide to implement a constant flow rate, it is not in our power to desire how the biomass and substrate concentration should change with time, as this is governed by the dynamic equations. Only for certain initial conditions do we achieve quasi-steady state operation dx/dt=0. For the reason mentioned below, the initial condition should be $x_0=Y\cdot s_f$ and $s_0\approx 0$. Otherwise, we have to wait for the fermentor to settle to this condition before dx/dt=0 commences. If the initial condition does not satisfy $x_0=Y\cdot s_f$ and $s_0\approx 0$, it should at least closely satisfy $x_0\approx Y\cdot(s_f-s_0)$; otherwise, the biomass concentration will ontinue to drift for some time. When the initial concentrations satisfy $x_0\approx Y\cdot(s_f-s_0)$, after substrate concentration reaches a low, almost zero level ($s\approx 0$), biomass concentration stays constant ($x=Y\cdot s_f$).

This argument is based on the assumption that the flow rate is sufficiently low. When this is the case, F/V=D is also sufficiently low; thus, s is also low. Note that $s\approx 0$, i.e., almost complete conversion of the substrate; however, strictly $s\neq$constant.

From $$\frac{d}{dt}x=0=\left(\mu(s)-\frac{F}{v}\right)\cdot x \quad \Rightarrow \quad \mu(s)=\frac{F}{v}=D \quad \Rightarrow \quad s=\frac{D\cdot K}{\mu_m-D}$$

Because F is constant, reactor volume increase linearly with time. Consequently, $\mu(s)=D=F/V$ decreases with time, and substrate concentration, albeit low, also gradually decreases.

From $$\frac{d}{dt}s=D\cdot(s_f-s)-\frac{\mu}{Y}\cdot x \quad \Rightarrow \quad x=Y\cdot(s_f-s)-\frac{1}{D}\cdot\left(\frac{d}{dt}s\right)$$ With $s\approx 0$ and $ds/dt\approx 0$ ⇒ $x=Y\cdot s_f$

When quasi-steady state has been reached, the *total* biomass level X_t increases linearly with time.

$$X_t=x\cdot v=Y\cdot s_f\cdot(v_0+F\cdot t)=x_0\cdot v_0+Y\cdot s_f\cdot F\cdot t$$

Biomass productivity is approximately constant: $$\frac{X_t-x_0\cdot v_0}{t}=Y\cdot s_f\cdot F$$

If a product production does *not* consume substrate, the dynamic equation for the product is decoupled.

From $$\frac{d}{dt}p=\alpha\cdot\mu\cdot x+\beta\cdot x-D\cdot p \qquad P_{t0}=p_0\cdot v_0$$

$$\Rightarrow \quad \frac{d}{dt}P_t=(\alpha\cdot D+\beta)\cdot X_t=\left(\alpha\cdot\frac{F}{v_0+F\cdot t}+\beta\right)\cdot\left[Y\cdot s_f\cdot(v_0+F\cdot t)\right]=Y\cdot s_f\cdot(\alpha\cdot F+\beta\cdot v_0+\beta\cdot F\cdot t)$$

Integrate to yield total amount of product: $$P_t=P_{t0}+Y\cdot s_f\cdot\left(\alpha\cdot F\cdot t+\beta\cdot v_0\cdot t+\frac{1}{2}\cdot\beta\cdot F\cdot t^2\right)$$

Product concentration: $$p=\frac{P_t}{v}=\frac{p_0\cdot v_0}{v}+Y\cdot s_f\cdot\left(\alpha\cdot D+\beta\cdot\frac{v_0}{v}+\frac{1}{2}\cdot\beta\cdot D\cdot t\right)\cdot t$$

Note: these equations are valid only when quasi-steady state conditions prevail!

Example by simulation.

Initial conditions: $s_0 := 0$ $x_0 := Y(s_0)\cdot(s_f - s_0)$ $x_0 = 5$ $v_0 := 0.1$

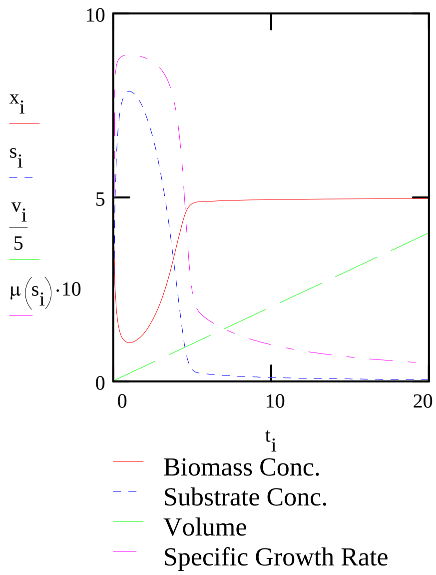
$$y_{initial} := \begin{bmatrix} x_0 \\ s_0 \\ v_0 \end{bmatrix} \begin{matrix} \text{... biomass} \\ \text{... substrate} \\ \text{... volume} \end{matrix}$$

Integrate ODEs from $t_0 := 0$ to $t_f := 20$ in $nstep := 200$

$yout := rkfixed(y_{initial}, t_0, t_f, nstep, ydot)$

$t := yout^{\langle 0 \rangle}$ $x := yout^{\langle 1 \rangle}$ $s := yout^{\langle 2 \rangle}$ $v := yout^{\langle 3 \rangle}$

Plots of state variables $i := 0 .. last(t)$



Conditions at $t_{nstep} = 20$

$x_{nstep} = 4.974$

$s_{nstep} = 0.053$

$v_{nstep} = 20.2$

Productivity of biomass:

$$\frac{v_{nstep}\cdot x_{nstep} - v_0\cdot x_0}{t_f} = 4.998$$

After the initial transient phase, the system settles down to a quasi-steady state operation with dx/dt≈0. Note that both s and μ(s) declines gradually after the initial transient.

Quasi-steady state operation #2. Keep **both** $x=x_0$=constant and $s=s_0$=constant or dx/dt=ds/dt=0.

Flow rate is **exponentially increasing**, unlike the first quasi-steady state mode.

From $\frac{d}{dt}x=0=\left(\mu(s)-\frac{F}{v}\right)\cdot x \Rightarrow \mu(s)=\frac{F}{v}=D \Rightarrow \frac{d}{dt}v=F=D\cdot v \Rightarrow v=v_0\cdot\exp(D\cdot t)$

$D=\mu(s)=\mu\left(s_0\right)=\text{constant} \qquad \Rightarrow F=\mu(s)\cdot v_0\cdot\exp(D\cdot t)$

Furthermore, the initial biomass and substrate levels have to satisfy:

From $\frac{d}{dt}s=0=\frac{F}{v}\cdot\left(s_f-s\right)-\frac{\mu(s)}{Y(s)}\cdot x \Rightarrow x=Y(s)\cdot\left(s_f-s\right)$ at t=0 and all subsequent t.

When quasi-steady state has been reached, the *total* biomass level X_t increases exponentially with time.

$$X_t=x\cdot v=x_0\cdot v_0\cdot\exp(D\cdot t)=X_{t0}\cdot\exp(D\cdot t)$$

If a product production does *not* consume substrate, the dynamic equation for the product is decoupled.

From $\frac{d}{dt}p=\alpha\cdot\mu\cdot x+\beta\cdot x-D\cdot p=\left[\left(\alpha+\frac{\beta}{D}\right)\cdot x-p\right]\cdot D$

Integrating the above equation with α, β, D, x all being constant yields:

$p=A\cdot\exp(-D\cdot t)+\left(\alpha\cdot x+\frac{\beta}{D}\cdot x\right)$ where A takes cares of the initial condition, whose effect dies out exponentially with time, and $p\rightarrow(\alpha+\beta/D)\cdot x$=constant with time.

At t=0, $p=p_0$, $x=x_0$ and $D=\mu(s_0)$, $p_0=A\cdot\exp(-D\cdot 0)+\left(\alpha\cdot x_0+\frac{\beta}{D}\cdot x_0\right) \Rightarrow A=p_0-\left(\alpha\cdot x_0+\frac{\beta}{D}\cdot x_0\right)$

$$p=p_0\cdot\exp(-D\cdot t)+\left(\alpha\cdot x+\frac{\beta}{D}\cdot x\right)\cdot(1-\exp(-D\cdot t))$$

When quasi-steady state has been reached, the *total* product level P_t increases exponentially with time.

$$P_t=p\cdot v=\left[p_0\cdot\exp(-D\cdot t)+\left(\alpha\cdot x+\frac{\beta}{D}\cdot x\right)\cdot(1-\exp(-D\cdot t))\right]\cdot\left(v_0\cdot\exp(D\cdot t)\right)$$

$$\Rightarrow P_t=\left[p_0+\left(\alpha\cdot x+\frac{\beta}{D}\cdot x\right)\cdot(\exp(D\cdot t)-1)\right]\cdot v_0$$

Integrate to yield total amount of product: $P_t=P_{t0}+Y\cdot s_f\cdot\left(\alpha\cdot F\cdot t+\beta\cdot v_0\cdot t+\frac{1}{2}\cdot\beta\cdot F\cdot t^2\right)$

Product concentration: $p=\frac{P_t}{v}=\frac{p_0\cdot v_0}{v}+Y\cdot s_f\cdot\left(\alpha\cdot D+\beta\cdot\frac{v_0}{v}+\frac{1}{2}\cdot\beta\cdot D\cdot t\right)\cdot t$

Thus, this second mode of quasi-steady state fed-batch operation is more restricted. The two quasi-steady state constraints dx/dt=0 and ds/dt=0 are translated into two equivalent restrictions on the operating parameters: F being exponential and the constant relationship between x_0 and s_0. In theory, we have to adjust the initial conditions of x and s just right, or we would not achieve quasi-steady state operation thereafter. In practice, we can tolerate some drifts in x and s but continue to implement the exponential feeding strategy.

In optimization, biomass productivity is related to $\mu \cdot x$. Thus, we want to maximize $D \cdot x = \mu(s) \cdot x = \mu(s) \cdot Y(s) \cdot (sf - s)$. The following calculation and dynamic simulation both yield the same result.

Approach #1. Find the maximum in the $\mu(s) \cdot Y(s) \cdot (sf-s)$.

$s := 1$ Given $0 = \frac{d}{ds}\mu(s) \cdot Y(s) \cdot \left(s_f - s\right)$ $\text{Find}(s) = 2.317$

Approach #2. Change s_0 below and see how the biomass productivity change.

Initial conditions: $s_0 := 2.317$ ← Change this number.

$x_0 := Y\left(s_0\right) \cdot \left(s_f - s_0\right)$ $x_0 = 3.841$ $v_0 := 0.1$

Exponential feed programming: $F_0 := \mu\left(s_0\right) \cdot v_0$ $k := \mu\left(s_0\right)$ $F(t) := F_0 \cdot \exp(k \cdot t)$

$F_0 = 0.07$ $k = 0.699$

Dynamic Equations:

$$\text{dxdt}(t,x,s,v) := \left(\mu(s) - \frac{F(t)}{v}\right) \cdot x$$

$$\text{dsdt}(t,x,s,v) := \frac{F(t)}{v} \cdot \left(s_f - s\right) - \frac{\mu(s)}{Y(s)} \cdot x$$

$$\text{dvdt}(t,x,s,v) := F(t)$$

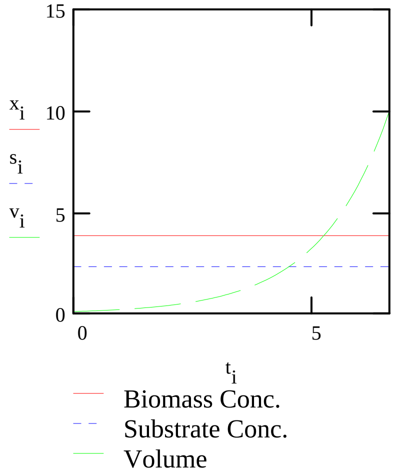
$$\text{ydot}(t,y) := \begin{bmatrix} \text{dxdt}\left(t,y_0,y_1,y_2\right) \\ \text{dsdt}\left(t,y_0,y_1,y_2\right) \\ \text{dvdt}\left(t,y_0,y_1,y_2\right) \end{bmatrix} \qquad \text{I.C.} \qquad y_{initial} := \begin{bmatrix} x_0 \\ s_0 \\ v_0 \end{bmatrix} \begin{matrix} \text{... biomass} \\ \text{... substrate} \\ \text{... volume} \end{matrix}$$

Integrate all three ODEs from $t_0 := 0$ to $t_f := \frac{1}{k} \cdot \ln\left(\frac{V}{v_0}\right)$ in $\text{nstep} := 100$

$\text{yout} := \text{rkfixed}\left(y_{initial}, t_0, t_f, \text{nstep}, \text{ydot}\right)$

$t := \text{yout}^{\langle 0 \rangle}$ $x := \text{yout}^{\langle 1 \rangle}$ $s := \text{yout}^{\langle 2 \rangle}$ $v := \text{yout}^{\langle 3 \rangle}$

Plots of state variables $i := 0 .. last(t)$



Conditions at $t_{nstep} = 6.593$

$x_{nstep} = 3.841$

$s_{nstep} = 2.317$

$v_{nstep} = 10$

Productivity of biomass:

$$\frac{v_{nstep} \cdot x_{nstep} - v_0 \cdot x_0}{t_f} = 5.769$$