Comments on Productivity of Batch & Continuous Bioreactors (Chapter 9)

Topics

Definition of productivity

Comparison of productivity of batch vs flowing systems

Updated: October 17, 2017
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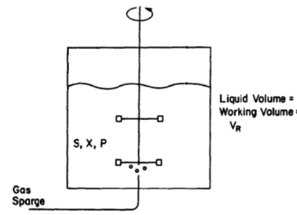
Review Batch Reactor



Cell Balances (constant volume):

$$\frac{dN_X}{dt} = V_R \frac{dX}{dt}$$

$$\frac{dX}{dt} = \mu_{net} X = \left(\mu_g - k_d\right) X \quad \Rightarrow \quad \mu_{net} = \frac{1}{X}\frac{dX}{dt}$$

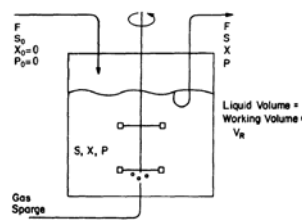
Cycle time for a batch system (lump non-productive time as "lost"):

$$t_c = t_{lag} + t_{growth} + t_{harvest} + t_{prep} = t_{growth} + t_{lost} = \frac{1}{\mu_m} \ln\left(\frac{X_m}{X_0}\right) + t_{lost}$$

Productivity (average rate of production):

$$r_b = \frac{1}{V_R}\frac{\Delta N_X}{\Delta t} = \frac{X_m - X_0}{t_c} = \frac{Y_{X/S} S_0}{\left(1/\mu_m\right)\ln\left(X_m/X_0\right) + t_{lost}}$$

Review Steady State Chemostat (CSTR)



Cell balance:

$$\mu_{net} = \mu_g - k_d = D$$

Substrate balance:

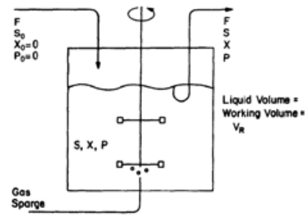
$$\frac{D\left(S_0 - S\right)}{X} = \frac{D}{Y_{X/S}^{app}} = \frac{\mu_g}{Y_{X/S}^{M}} + \frac{q_P}{Y_{P/S}} + m$$

Rate of cell production:

$$\dot{N}_X = FX = V_R\left(DX\right)$$

Productivity is the DX term

Chemostat Productivity with Monod Kinetics



From Monod expression:

$$\mu_g = \frac{\mu_m S}{K_S + S} \quad \Rightarrow \quad S = \frac{K_S \mu_g}{\mu_m - \mu_g}$$

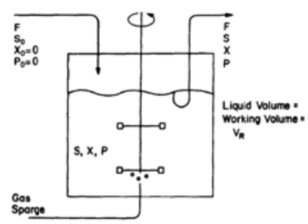
Substrate balance (net = growth):

$$\frac{D(S_0 - S)}{X} = \frac{\mu_g}{Y_{X/S}^M} \quad \Rightarrow \quad X = (S_0 - S) Y_{X/S}^M = \left(S_0 - \frac{K_S D}{\mu_m - D} \right) Y_{X/S}^M$$

Productivity:

$$r_C = DX = D(S_0 - S) Y_{X/S}^M = D\left(S_0 - \frac{K_S D}{\mu_m - D} \right) Y_{X/S}^M$$

Chemostat Productivity with Monod Kinetics



What happens with increasing D?

- At small D the cell mass concentration is at its maximum

$$X = \left(S_0 - \frac{K_S D}{\mu_m - D} \right) Y_{X/S}^M \to S_0 Y_{X/S}^M$$

- As D increases X always decreases, but…
- … the productivity will <u>increase</u> since the increase in D is faster than the decrease in X
- As D approaches μ_m the cell concentration goes to zero (cell mass washout) & the productivity DX will also go to zero

$$D_{max} = \frac{\mu_m S_0}{K_S + S_0}$$

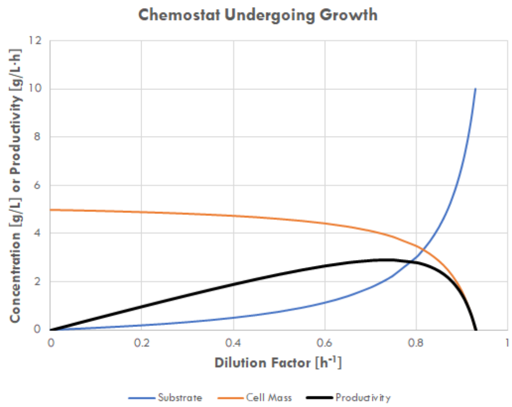
- There will be an optimum productivity in between

Chemostat Productivity with Monod Kinetics

Optimal productivity when d(DX)/dD = 0

$$D_{opt} = \mu_m\left(1-\sqrt{\frac{K_S}{K_S+S_0}}\right)$$

$$\frac{X_{opt}}{Y^M_{X/S}} = \left(K_S+S_0\right) - \sqrt{K_S\left(K_S+S_0\right)}$$



$$r_{C,opt} = Y^M_{X/S}\mu_m\left(1-\sqrt{\frac{K_S}{K_S+S_0}}\right)\left(K_S+S_0-\sqrt{K_S\left(K_S+S_0\right)}\right)$$

Chemostat Productivity with Monod Kinetics

Normally in chemostat $S_0 >> K_S$ so:

$$r_{C,opt} = Y^M_{X/S}\mu_m\left(1-\sqrt{1-\frac{K_S}{K_S+S_0}}\right)\left(K_S+S_0-\sqrt{K_S\left(K_S+S_0\right)}\right) \approx Y^M_{X/S}\mu_m S_0$$

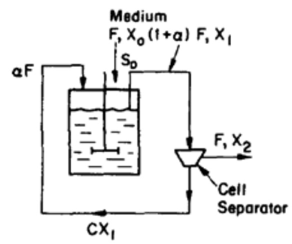
Usually greater productivity in chemostat than batch system

$$\frac{r_{C,opt}}{r_b} \approx \ln\left(\frac{X_m}{X_0}\right) + \mu_m t_{lost}$$

Typically X_m/X_0 10 to 20 & t_{lost} 3 to 10 hours

- Example in text, $X_m/X_0 = 20$, $t_{lost} = 5$ h, $\mu_m = 1\ h^{-1}$, then ratio is 8

Productivity – Chemostat with Recycle



Cell balance:

$$\mu_{net} = D\left[1+\alpha\left(1-C\right)\right]$$

Substrate balance in growth phase:

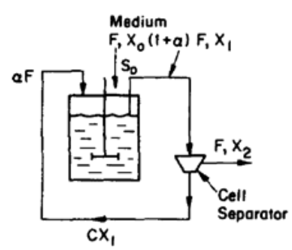
$$\frac{D\left(S_0 - S\right)}{X_1} = \frac{\mu_g}{Y^M_{X/S}} \quad\Rightarrow\quad X_1 = \frac{\left(S_0 - S\right)Y^M_{X/S}}{1+\alpha\left(1-C\right)}$$

$$X_2 = \left[1+\alpha\left(1-C\right)\right]X_1 = \left(S_0 - S\right)Y^M_{X/S}$$

Productivity is DX_2:

$$r_C = DX_2 = D\left(S_0 - S\right)Y^M_{X/S}$$

Productivity – Chemostat with Recycle



Monod growth kinetics:

$$S = \frac{K_S\mu_g}{\mu_m - \mu_g} = \frac{K_S D\left[1+\alpha\left(1-C\right)\right]}{\mu_m - D\left[1+\alpha\left(1-C\right)\right]}$$

$$r_C = D\left(S_0 - S\right)Y^M_{X/S}$$

$$= D\left(S_0 - \frac{K_S D\left[1+\alpha\left(1-C\right)\right]}{\mu_m - D\left[1+\alpha\left(1-C\right)\right]}\right)Y^M_{X/S}$$

Mathematically similar to non-recycle case

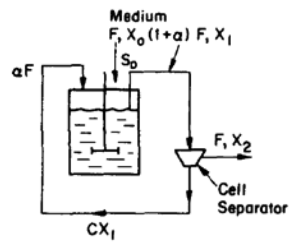
$$r_C = \frac{D'}{1+\alpha\left(1-C\right)}\left(S_0 - \frac{K_S D'}{\mu_m - D'}\right)Y^M_{X/S} \quad \text{where} \quad D' \equiv D\left[1+\alpha\left(1-C\right)\right]$$

Productivity – Chemostat with Recycle

Washout dilution rate

$$D'_{max} = D_{max}\left[1+\alpha\left(1-C\right)\right] = \frac{\mu_m S_0}{K_S + S_0}$$

Optimum at $dr_C/dD = 0$ also $dr_C/dD' = 0$

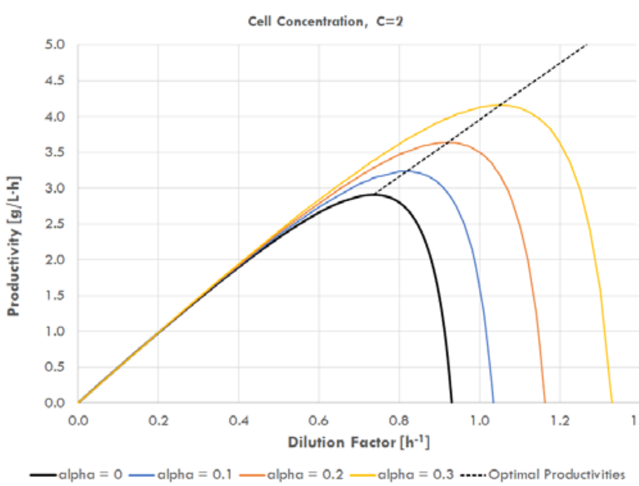


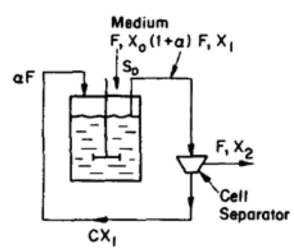
$$D'_{opt} = \mu_m\left(1-\sqrt{\frac{K_S}{K_S+S_0}}\right) \Rightarrow D_{opt} = \frac{\mu_m}{1+\alpha\left(1-C\right)}\left(1-\sqrt{\frac{K_S}{K_S+S_0}}\right)$$

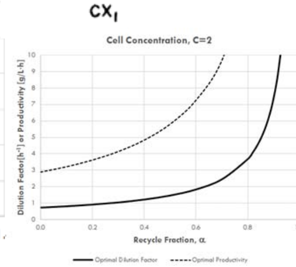
$$X_{2,opt} = Y^M_{X/S}\left[\left(K_S+S_0\right)-\sqrt{K_S\left(K_S+S_0\right)}\right]$$

$$r_{C,opt} = \frac{D}{1+\alpha\left(1-C\right)}\left(1-\sqrt{\frac{K_S}{K_S+S_0}}\right)\left[\left(K_S+S_0\right)-\sqrt{K_S\left(K_S+S_0\right)}\right]Y^M_{X/S}$$

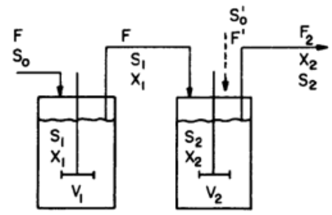
Productivity – Chemostat with Recycle







Productivity – Multi-Stage Chemostat



1st reactor looks like a single reactor.

Great deal of flexibility in operating the 2nd reactor

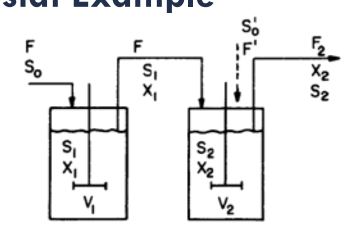
- Additional substrate added?
- Different concentration added?
- Different volumes?

Remember that the downstream material balances must incorporate the cell mass entering from the upstream reactors

Productivity must include the contribution of both volumes

$$\dot{N}_X = F_2 X_2 \quad \Rightarrow \quad r_{2-stage} = \left(\frac{F_2}{V_1 + V_2} \right) X_2$$

Productivity – Multi-Stage Chemostat Example



Does order make a difference?

- Sometimes

Example – two vessels, 800 L & 200 L
10 g/L substrate @ 100 L/h
Max yield 0.5 g cell mass/g substrate
Monod growth, μ_m = 1 h^{-1} & K_S = 0.75 g/L

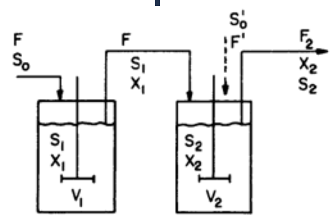
1st reactor, 800 L:

$$\mu_{g,1} = D_1 = 100 / 800 = 0.125$$

$$S_1 = \frac{K_S D_1}{\mu_m - D_1} = \frac{(0.75)(0.125)}{(1)-(0.125)} = 0.1071$$

$$X_1 = (S_0 - S_1) Y_{X/S} = (10 - 0.1071)(0.5) = 4.946$$

Productivity – Multi-Stage Chemostat Example



2^{nd} reactor, 200 L:

$$\mu_{g,2} = D_2\left(1-\frac{X_1}{X_2}\right) = (0.5)\left(1-\frac{4.9464}{X_2}\right)$$

$$\mu_{g,2} = \frac{\mu_m S_2}{K_S + S_2} = \frac{S_2}{0.75+S_2}$$

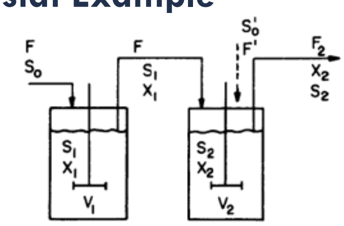
$$X_2 = Y_{X/S}(S_1 - S_2) + X_1 = 0.5(0.1071 - S_2) + 4.9464$$

Solving iteratively:

$$\mu_{g,2} = 0.00516,\ S_2 = 0.00389,\ X_2 = 4.9981$$

$$r_C = \frac{F}{V_1+V_2}X_2 = \frac{100}{800+200}(4.9981) = 0.49981$$

Productivity – Multi-Stage Chemostat Example



What if we change the order?

1^{st} reactor, 200 L:

$$\mu_{g,1} = D_1 = 100/200 = 0.500$$

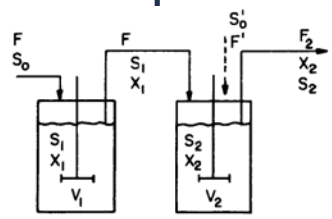
$$S_1 = \frac{K_S D_1}{\mu_m - D_1} = \frac{(0.75)(0.5)}{(1)-(0.5)} = 0.75$$

$$X_1 = (S_0 - S_1)Y_{X/S} = (10-0.75)(0.5) = 4.625$$

2^{nd} reactor, 800 L:

$$\left.\begin{aligned} \mu_{g,2} &= D_2\left(1-\frac{X_1}{X_2}\right) = (0.125)\left(1-\frac{4.625}{X_2}\right) \\ \mu_{g,2} &= \frac{\mu_m S_2}{K_S+S_2} = \frac{S_2}{0.75+S_2} \\ X_2 &= Y_{X/S}(S_1-S_2) + X_1 = 0.5(0.75-S_2) + 4.625 \end{aligned}\right\} \Rightarrow \begin{aligned} \mu_{g,2} &= 0.00929 \\ S_2 &= 0.00704 \\ X_2 &= 4.9965 \end{aligned}$$

Productivity – Multi-Stage Chemostat Example



What if we make the reactor sizes different?

1st reactor, 900 L:

$$\mu_{g,1} = D_1 = 100 / 900 = 0.1111$$

$$S_1 = \frac{K_S D_1}{\mu_m - D_1} = \frac{(0.75)(0.1111)}{(1)-(0.1111)} = 0.09375$$

$$X_1 = (S_0 - S_1) Y_{X/S} = (10 - 0.09375)(0.5) = 4.9531$$

2nd reactor, 100 L:

$$\left.\begin{aligned} \mu_{g,2} &= D_2 \left(1 - \frac{X_1}{X_2}\right) = (1.0000)\left(1 - \frac{4.9531}{X_2}\right) \\ \mu_{g,2} &= \frac{\mu_m S_2}{K_S + S_2} = \frac{S_2}{0.75 + S_2} \\ X_2 &= Y_{X/S}(S_1 - S_2) + X_1 = 0.5(0.09375 - S_2) + 4.9531 \end{aligned}\right\} \Rightarrow \begin{aligned} \mu_{g,2} &= 0.00872 \\ S_2 &= 0.0066 \\ X_2 &= 4.9967 \end{aligned}$$

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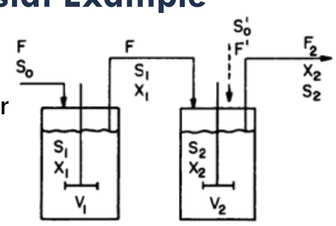
Productivity – Multi-Stage Chemostat Example



What if we switch the order of these reactor

1st reactor, 100 L:

$$\mu_{g,1} = D_1 = 100 / 100 = 1.0$$

$$S_1 = \frac{K_S D_1}{\mu_m - D_1} = \frac{(0.75)(1.0)}{(1)-(1.0)} \to \infty$$

This is a washout condition – this configuration will not work properly!

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Summary

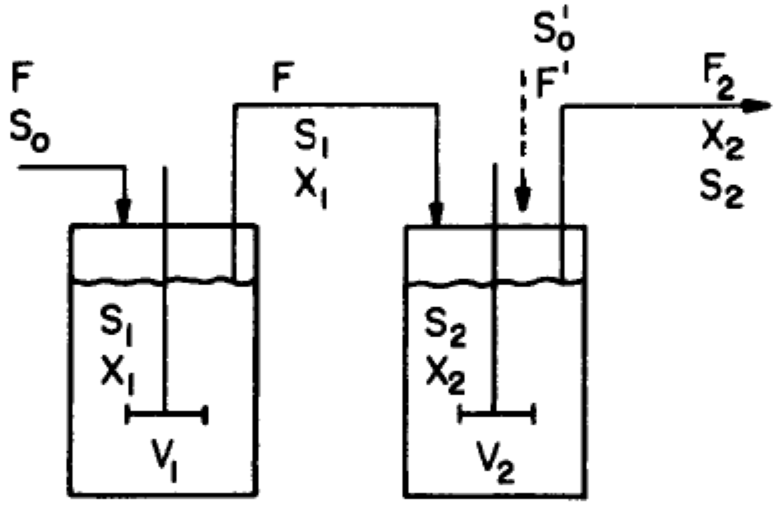
Definition of "productivity" gives us a quantitative means to decide how to size & operate a bioreactor

- Not just "what can be done" but also "what should be done"

Some of the simple configurations have simple relationships for optimal productivity – some are much more complicated

Supplemental Slides

Other Configurations – Multi-Stage Chemostat



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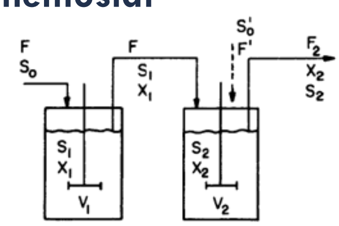
Material Balances – Multi-Stage Chemostat



Only growth & $X_0 = 0$

Cell balance – transient to steady state

$$V_1 \frac{dX_1}{dt} = -FX_1 + \mu_{net,1} X_1 V_1 \quad \Rightarrow \quad \mu_{g,1} = \frac{F}{V_1}$$

$$V_2 \frac{dX_2}{dt} = FX_1 - \left(F + F'\right) X_2 + \mu_{net,2} X_2 V_2 \quad \Rightarrow \quad \mu_{g,2} = \left(\frac{F + F'}{V_2}\right) - \left(\frac{F}{V_2}\right)\left(\frac{X_1}{X_2}\right)$$

Substrate balance – transient to steady state

$$V_1 \frac{dS_1}{dt} = FS_0 - FS_1 - \frac{\mu_{g,1} X_1}{Y_{X/S}^M} V_1 \quad \Rightarrow \quad \frac{\left(F/V\right)\left(S_0 - S_1\right)}{X_1} = \frac{\mu_{g,1} X_1}{Y_{X/S}^M}$$

$$V_2 \frac{dS_2}{dt} = FS_1 + F'S_0 - \left(F + F'\right) S_2 - \frac{\mu_{g,2} X_2}{Y_{X/S}^M} \quad \Rightarrow \quad \frac{\left(F/V_2\right)\left(S_1 - S_2\right)}{X_2} + \frac{\left(F'/V_2\right)\left(S_0 - S_2\right)}{X_2} = \frac{\mu_{g,2}}{Y_{X/S}^M}$$

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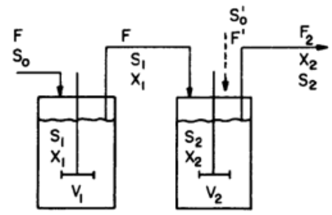
Material Balances – Multi-Stage Chemostat



For Monod growth

$$\mu_{g,1} = \frac{\mu_m S_1}{K_S + S_1} \quad \Rightarrow \quad S_1 = \frac{\mu_{g,1} K_S}{\mu_m - \mu_{g,1}}$$

$$\mu_{g,2} = \frac{\mu_m S_2}{K_S + S_2} \quad \Rightarrow \quad S_2 = \frac{\mu_{g,2} K_S}{\mu_m - \mu_{g,2}}$$

… where $\mu_{g,2}$ is more complicated than just the dilution factor