Comments Transient Material Balances

Description of cell mass growth

Qualitative

$$\text{Substrates} + \text{Cells} \rightarrow (\text{extracelluar Products}) + (\text{more Cells})$$

Quantitative

$$\sum S_i + X \rightarrow \sum P_i + nX$$

Stoichiometry (example, aerobic)

$$\underset{\text{subtrate}}{CH_mO_n} + a\ O_2 + b\ NH_3 \rightarrow c\ \underset{\text{biomass}}{CH_\alpha O_\beta N_\delta} + d\ H_2O + e\ CO_2$$

Material Balance – Batch Reactor

Cell Balances:

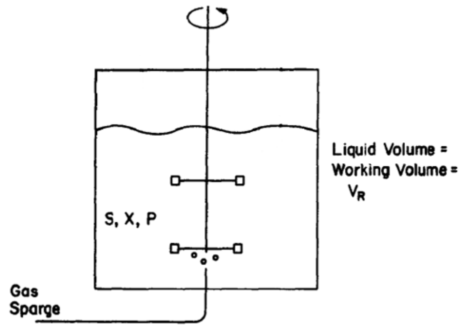
$$V_R \frac{dX}{dt} = V_R \mu_g X - V_R k_d X = V_R \mu_{net} X$$

$$\mu_{net} \equiv \frac{1}{X}\frac{dX}{dt}$$

Substrate Consumption & Product Growth:

$$q_S \equiv -\frac{1}{X}\frac{dS}{dt}$$

$$q_P \equiv +\frac{1}{X}\frac{dP}{dt}$$



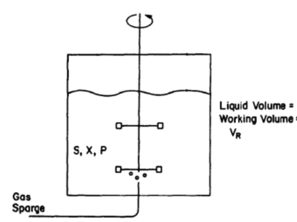
Material Balance – Batch Reactor

If μ_{net} is constant then get exponential growth phase

$$\frac{dX}{dt} = \mu_{net} X$$

$$\frac{dX}{X} = \mu_{net}\, dt$$

$$\ln\left(\frac{X}{X_0}\right) = \mu_{net}\, t \quad \Rightarrow \quad X = X_0 \exp\left(\mu_{net}\, t\right)$$



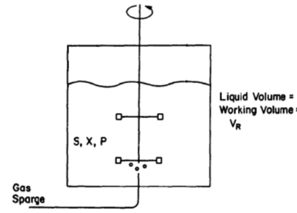
Followed by deceleration growth (unbalanced growth) & stationary (growth equal to death) phases

Material Balance – Batch Reactor

Death phase is 1st order in cell concentration & gives exponential decay

$$\frac{dX}{dt} = -k_d X$$

$$\ln\left(\frac{X}{X_{S0}}\right) = -k_d\, t \quad \Rightarrow \quad X = X_{S0}\exp\left(\mu_{net}\, t\right)$$



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Some Growth Models

Substrate-Limited Growth (*Moser* equation, *Monod* for n=1)

$$\mu_g = \frac{\mu_m S^n}{K_S + S^n}$$

Substrate-Limited Growth (*Contois* equation)

$$\mu_g = \frac{\mu_m S}{K_{SX} X + S}$$

Noncompetitive Substrate Inhibition

$$\mu_g = \frac{\mu_m}{\left(1+\frac{K_S}{S}\right)\left(1+\frac{S}{K_1}\right)}$$

Competitive Substrate Inhibition

$$\mu_g = \frac{\mu_m}{K_S\left(1+\frac{S}{K_1}\right)+S}$$

Noncompetitive Product Inhibition

$$\mu_g = \frac{\mu_m}{\left(1+\frac{K_S}{S}\right)\left(1+\frac{P}{K_p}\right)}$$

Competitive Product Inhibition

$$\mu_g = \frac{\mu_m}{K_S\left(1+\frac{P}{K_p}\right)+S}$$

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Monod Growth Model

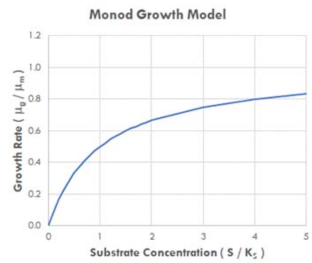
Substrate-Limited Growth

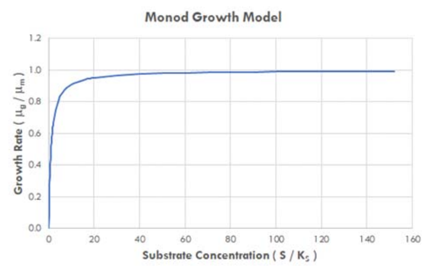
$$\mu_g = \frac{\mu_m S}{K_S + S} \quad \Rightarrow \quad \frac{\mu_g}{\mu_m} = \frac{(S / K_S)}{1 + (S / K_S)}$$

- Limits:
  - Constant growth rate at large substrate concentrations
  - Proportional to substrate concentration at low concentrations

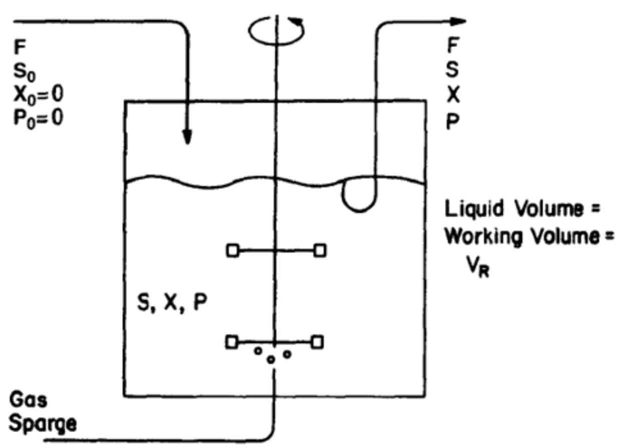
Also:

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

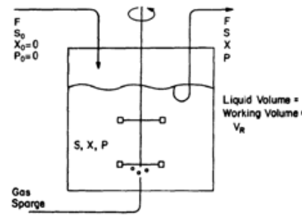




Material Balances – Ideal Chemostat (Section 6.3.2)



Material Balances – Ideal Chemostat (CSTR)



Cell balance:

$$V_R \frac{dX}{dt} = FX_0 - FX + \left(V_R \mu_g X - V_R k_d X\right)$$

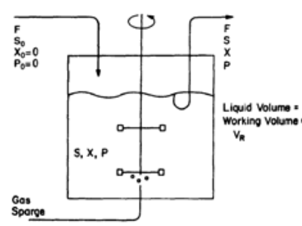
$$\frac{dX}{dt} = DX_0 + \left(\mu_g - k_d - D\right) X$$

where: $D \equiv F/V_R$

Usually feed is cell mass & product free

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

Material Balances – Ideal Chemostat (CSTR)



At steady state & negligible death rate

$$0 = \left(\mu_g - D\right) X \quad \Rightarrow \quad \mu_g = D$$

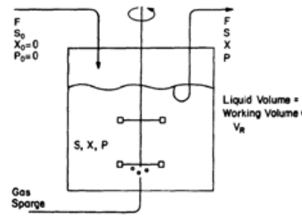
Growth rate can be controlled by changing the dilution rate!

- However, if the dilution rate is too large then the cell mass is "washed out" – the culture cannot reproduce fast enough to grow before it is removed

Material Balances – Ideal Chemostat (CSTR)

Substrate balance

$$V_R \frac{dS}{dt} = FS_0 - FS + V_R\left(-\frac{\mu_g X}{Y^M_{X/S}} - \frac{q_P X}{Y_{P/S}} - m_s X\right)$$



At steady state

$$0 = D(S_0 - S) - \left(\frac{\mu_g}{Y^M_{X/S}} + \frac{q_P}{Y_{P/S}} + m_s\right)X \quad \Rightarrow \quad \frac{D(S_0 - S)}{X} = \frac{\mu_g}{Y^M_{X/S}} + \frac{q_P}{Y_{P/S}} + m_s$$

- Linear equation of substrate consumption
  - Grow cell mass
  - Create product
  - Provide energy to the cell mass

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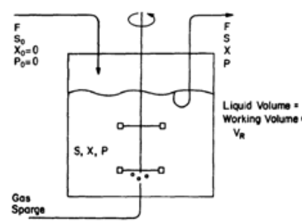
Material Balances – Ideal Chemostat (CSTR)

If negligible product formation & maintenance, then:



$$\frac{D(S_0 - S)}{X} = \frac{\mu_g}{Y^M_{X/S}} \quad \Rightarrow \quad X = Y^M_{X/S}\frac{D}{\mu_g}(S_0 - S)$$

$$= Y^M_{X/S}(S_0 - S)$$

Substrate (for *Monod* eqn):

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

$$X = Y^M_{X/S}\left(S_0 - \frac{K_S \mu_g}{\mu_m - \mu_g}\right) = Y^M_{X/S}\left(S_0 - \frac{K_S D}{\mu_m - D}\right)$$

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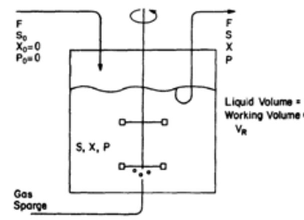
Material Balances – Ideal Chemostat (CSTR)



Product formation – steady state with introduction of cell mass (but no net growth):

- From cell balance:

$$0 = DX_0 + (\mu_{net} - D)X \quad \Rightarrow \quad X = X_0$$

- From substrate balance:

$$0 = D(S_0 - S) - \left(\frac{\mu_g}{Y^M_{X/S}} + \frac{q_P}{Y_{P/S}} + m_s \right) X \quad \Rightarrow \quad S = S_0 - \frac{1}{D} \frac{q_P X}{Y_{P/S}}$$

- From product yield definition:

$$P - P_0 = Y_{P/S}(S - S_0)$$

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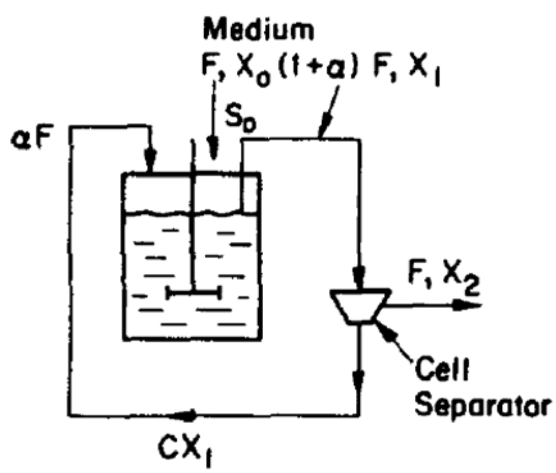
Other Configurations – Chemostat with Recycle



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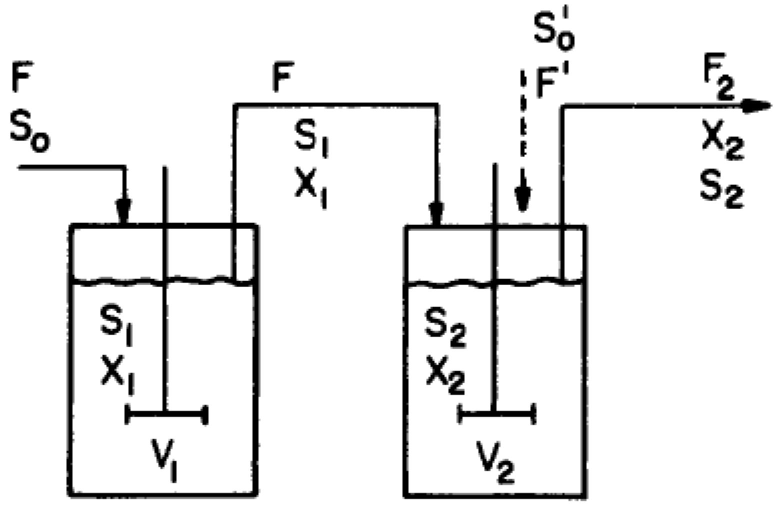
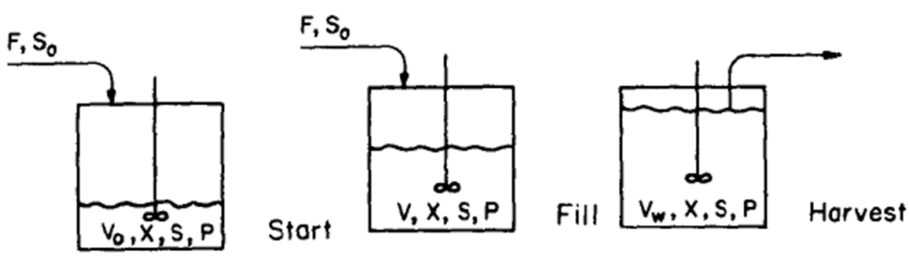
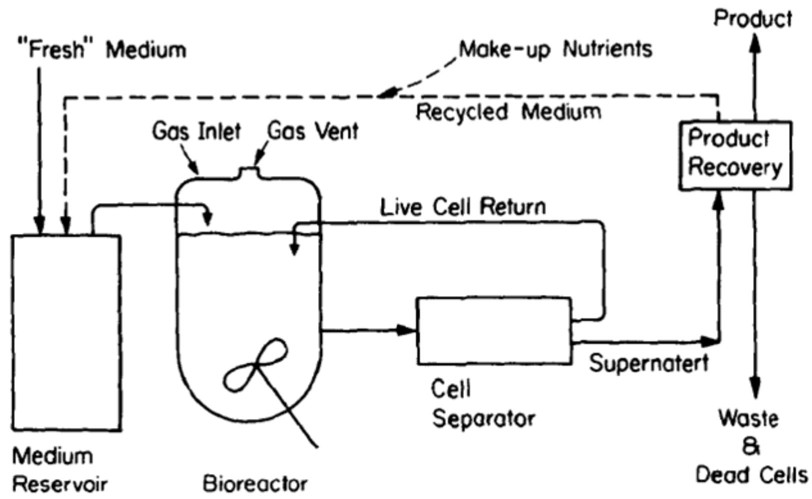
Other Configurations – Multi-Stage Chemostat



Other Configurations – Fed Batch



Other Configurations – Perfusion



Use of Batch Data in Flow Reactors

For a batch reactor

$$\frac{dX}{dt} = \mu_{net} X$$

For a CSTR it makes sense that the outlet concentration is related to the batch reactor's results such that:

$$\mu_{net}\left(X - X_0\right) = \left[\left(\frac{dX}{dt}\right)_{\text{batch}}\right]_{t=t_{extent}}$$

where t_{extent} is some characteristic batch time that represents the extent of reaction

Use of Batch Data in Flow Reactors

For a chemostat the dilution factor D controls the growth factor μ_{net}

You can relate the two systems & show performance by

- Plot dX/dt vs X for the batch data
- Plot a straight line through X_0 on the horizontal axis with a slope of D
- The intersection of the batch results curve & the chemostat performance line will give the value of X within the chemostat. The original batch X vs. t data will then give the corresponding t_{extent}.

Product composition can be determined either by:

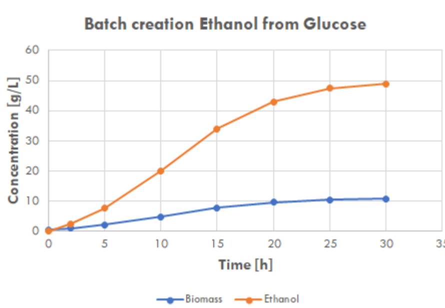
- Find the corresponding P at t_{extent}, or
- Do a similar DP/dt vs. P analysis

Use of Batch Data in Flow Reactors

Using data from Example 6.2, ethanol from glucose using *S. cerevisiae*

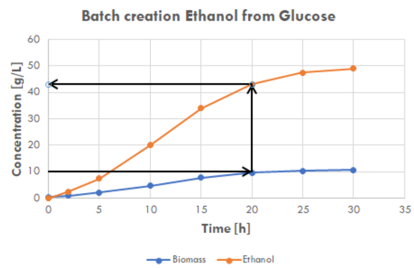
- Time derivatives estimated from central differences

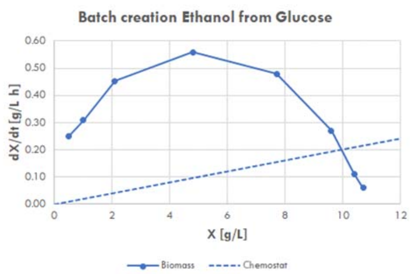
Time [h]	Glucose [g/L]	Biomass [g/L]	Ethanol [g/L]	dX/dt [g/L h]	dP/dt [g/L h]
0	100	0.5	0	0.25	1.25
2	95	1	2.5	0.31	1.46
5	85	2.1	7.5	0.45	2.08
10	58	4.8	20	0.56	2.65
15	30	7.7	34	0.48	2.30
20	12	9.6	43	0.27	1.35
25	5	10.4	47.5	0.11	0.60
30	2	10.7	49	0.06	0.30

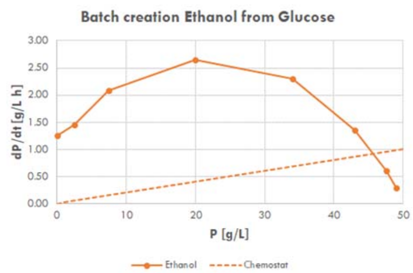


Use of Batch Data in Flow Reactors

For a chemostat, D=0.05 h^{-1}







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Use of Batch Data in Flow Reactors

For a batch reactor “productivity” is the time-derivative increase in concentration vs. time.

For a CSTR the analogous term is the dilution factor times the concentration, e.g., $D \times P$

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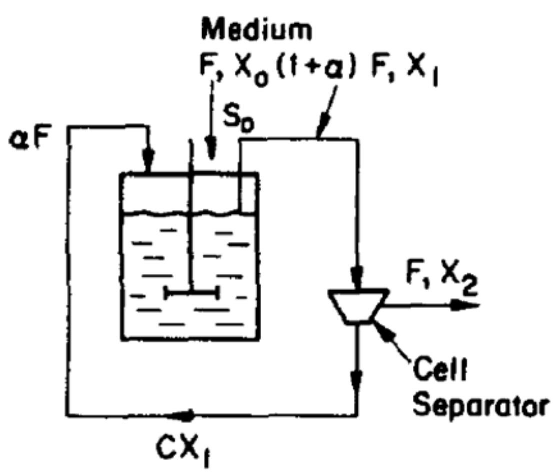
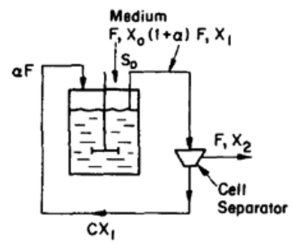
Details for Other Bioreactor Configurations

Other Configurations – Chemostat with Recycle



Material Balances – Chemostat with Recycle



Cell balance:

$$V\frac{dX_1}{dt} = FX_0 + \alpha F(CX_1) - (1+\alpha)FX_1 + V\mu_{net}X_1$$

$$\frac{dX_1}{dt} = D\left[X_0 + \alpha(CX_1)\right] - (1+\alpha)DX_1 + \mu_{net}X_1$$

α = Ratio recycle flowrate to fresh feed rate

C = Concentration factor in Cell Separation

At steady state with X_0=0

$$0 = D\left[\alpha(CX_1)\right] - (1+\alpha)DX_1 + \mu_{net}X_1$$

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

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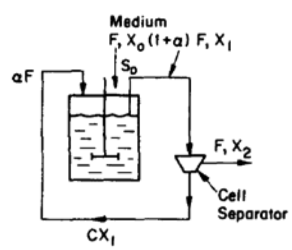
Material Balances – Chemostat with Recycle



Cell balance around Cell Separator @ steady state:

$$(1+\alpha)FX_1 = \alpha F(CX_1) + FX_2$$

$$X_2 = \left[1+\alpha(1-C)\right]X_1$$

Since C > 1 then $X_2 < X_1$

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Material Balances – Chemostat with Recycle

Substrate balance

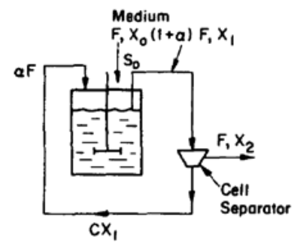
$$V_R \frac{dS}{dt} = FS_0 + \alpha FS - (1+\alpha) FS + V_R \left(-\frac{\mu_g X_1}{Y^M_{X/S}} - \frac{q_P X_1}{Y_{P/S}} - m_s X_1 \right)$$

$$\frac{dS}{dt} = D(S_0 - S) - \left(\frac{\mu_g X_1}{Y^M_{X/S}} + \frac{q_P X_1}{Y_{P/S}} + m_s X_1 \right)$$

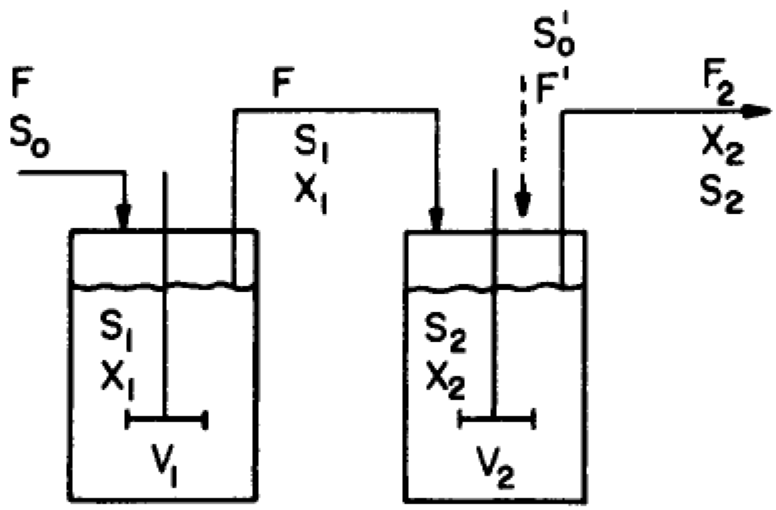
At steady state & growth limited

$$0 = D(S_0 - S) - \left(\frac{\mu_g X_1}{Y^M_{X/S}} + \frac{q_P X_1}{Y_{P/S}} + m_s X_1 \right) \Rightarrow$$

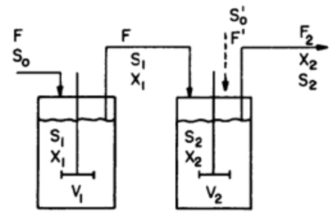
$$X_1 = \frac{D}{\mu_g} Y^M_{X/S} (S_0 - S) \Rightarrow X_1 = \frac{Y^M_{X/S}(S_0 - S)}{1+\alpha(1-C)}$$



Other Configurations – Multi-Stage Chemostat



Material Balances – Multi-Stage Chemostat



Cell balance – 2 reactors in series

$$V_1 \frac{dX_1}{dt} = FX_0 - FX_1 + \mu_{net,1} X_1 V_1$$

$$V_2 \frac{dX_2}{dt} = FX_1 + F'X_0 - (F + F')X_2 + \mu_{net,2} X_2 V_2$$

1st reactor looks like a single reactor. Focus on the downstream reactor(s)

At steady state with X_0=0

- Now growth rate dependent on cell mass compositions

$$0 = FX_1 - (F + F')X_2 + \mu_{net,2} X_2 V_2 \quad \Rightarrow \quad \mu_{net,2} = \frac{F + F'}{V_2} - \frac{F}{V_2}\frac{X_1}{X_2} = D_2 - \frac{F}{V_2}\frac{X_1}{X_2}$$

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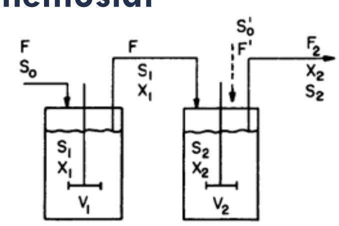
Material Balances – Multi-Stage Chemostat



Substrate balance – focus on 2nd reactor

$$V_2 \frac{dS_2}{dt} = FS_1 + F'S_0 - (F + F')S_2 + V_2\left(-\frac{\mu_{g,2}}{Y^M_{X/S}} - \frac{q_P}{Y_{P/S}} - m_s \right) X_2$$

At steady state with only cell mass growth:

$$0 = FS_1 + F'S_0 - (F + F')S_2 - \frac{\mu_{g,2} X_2}{Y^M_{X/S}} V_2 \quad \Rightarrow$$

$$S_2 = \frac{FS_1 + F'S_0}{F + F'} - \frac{\mu_{g,2} X_2}{Y^M_{X/S}} \frac{V_2}{F + F'} = \frac{FS_1 + F'S_0}{F + F'} - \frac{\mu_{g,2} X_2}{D_2 Y^M_{X/S}}$$

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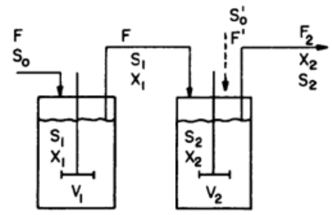
Material Balances – Multi-Stage Chemostat



Must simultaneously solve the 3 equations for cell mass & substrate concentrations as well as growth rate

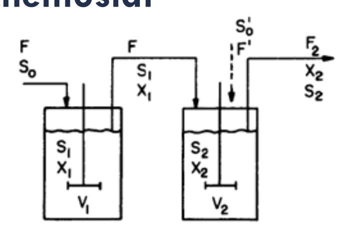
For Monod eqn:

$$\mu_{g,2} = D_2 - \frac{F}{V_2}\frac{X_1}{X_2}$$

$$S_2 = \frac{FS_1 + F'S_0}{F + F'} - \frac{\mu_{g,2} X_2}{D_2 Y_{X/S}^M}$$

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

Material Balances – Multi-Stage Chemostat



Care must be taken to specify an iteration technique to solve this set of non-linear equations

- Simplest technique would be direct substitution, but it is doubtful that this would be a robust way to solve