10.37 Chemical and Biological Reaction Engineering, Spring 2007
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Lecture 13: Biological Reactors- Chemostats

This lecture covers: theory of the chemostat, fed batch or semi-continuous fermentor operations

Biological Reactors (Chemostat)

Concentration/Combustion constant
Biological CSTR

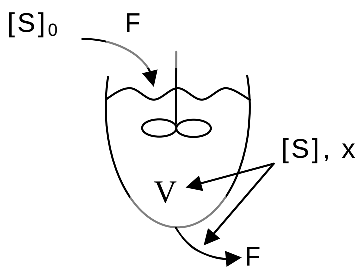

Figure 1. Diagram of a chemostat.

F = Volumetric flow rate

$$x = \frac{\text{biomass}}{\text{volume}}$$

$[S]_0$ = Concentration of growth limiting substrate. (for growing cells)

At steady-state, biomass balance

~~In~~ – Out + Prod = ~~Acc~~

Sterile feed: In=0
Steady state: Acc=0

$-Fx + r_x \mathrm{V} = 0$ at steady-state

Cell growth kinetics $r_x = \mu x$

$-Fx + \mu x \mathrm{V} = 0$

Solve $\mu = \frac{F}{\mathrm{V}}$

D=Dilution rate $\equiv \frac{F}{\mathrm{V}} = \frac{1}{\tau}$

$$\mu = D$$

Biological (μ) Mechanical (D)

When at steady-state, can control cell mass.

Allows precisely reproducible cell states.

Not easy to run at steady-state.

Material balance on [S] (sugar concentration)

In – Out + Prod = Acc (Acc → 0 at steady-state)

$$F[S]_0 - F[S] - \frac{1}{Y_{\frac{x}{s}}}\mu x \mathrm{V} = 0$$

Yield coefficient ($Y_{\frac{x}{s}}$) $= \dfrac{\text{mass biomass created}}{\text{mass substrate consumed}}$

Divide by V

$$D\underbrace{([S]_0 - [S])}_{\text{change in sugar concentration}} = \frac{\mu x}{Y_{\frac{x}{s}}}$$

At steady-state $\mu = D$

$$x = Y_{\frac{x}{s}}([S]_0 - [S])$$

What is the value of $[S]$? What more information do we need?

$\mu = f([S])$ ← must choose a growth model to connect μ and $[S]$

Monod growth model:

$$\mu = \frac{\mu_{\max}[S]}{K_s + [S]} \rightarrow \text{at steady-state} \rightarrow D = \frac{\mu_{\max}[S]}{K_s + [S]}$$

$$\boxed{[S] = \frac{K_s D}{\mu_{\max} - D}} \longleftarrow \text{substitute in x equation}$$

$$x = Y_{\frac{x}{s}}\left([S]_0 - \frac{K_s D}{\mu_{\max} - D}\right)$$

Specifying $\mu_{\max}$, K_s, $Y_{\frac{x}{s}}$, D, $[S]_0$, can predict x, $[S]$.

$x < 0$ is non-physical but formally in solution

$\mu_{\max} - D$ can go to 0. If you turn knobs incorrectly: if D is too high, the cells cannot grow fast enough to reach steady-state. Washout will occur.

so use $x = 0$ to find $D_{\max}$

$$D_{\max} = \frac{\mu_{\max}[S]_0}{K_s + [S]_0}$$

For $D > D_{\max}$ "washout", no steady-state.

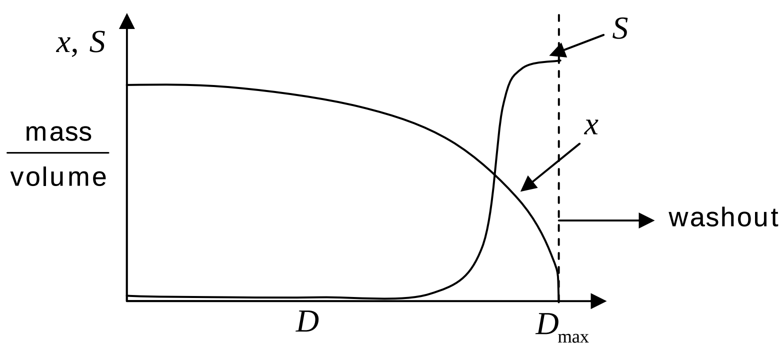

Figure 2. Biomass/volume versus dilution rate. Beyond the maximum dilution rate, washout occurs.

For real systems $K_s << [S]_0$. Most cell growth systems reach maximum at fairly low concentrations; hence x is flat, then drops off sharply.

If biomass is the product, is there a best operating condition?

What should we consider?

$\frac{dx}{dD}$ optimize x with respect to D? D=0 (no, because this would be batch reactor)

Define productivity as $\frac{\text{biomass}}{(\text{reactor volume})(\text{time})} = xD$

$\frac{d(xD)}{dD} = 0$ for optimum. (is a maximum)

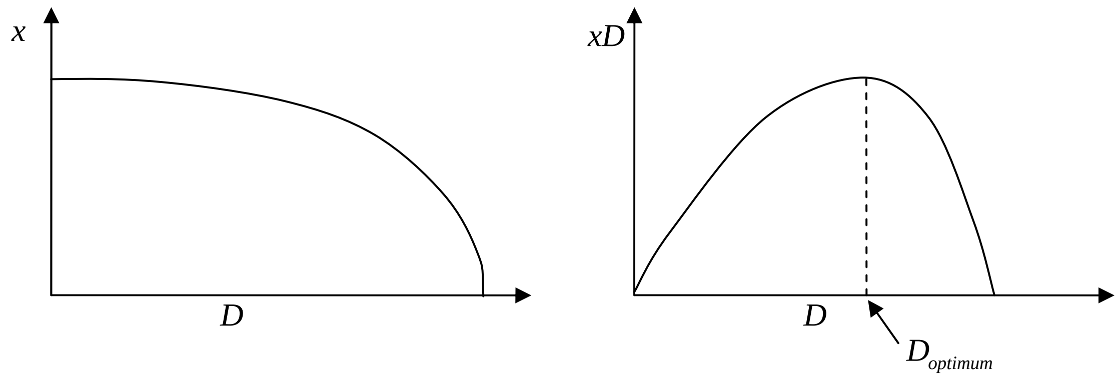

Figure 3. Left: Biomass/volume versus dilution rate. Right: Productivity versus dilution rate.

$$D_{optimum} = \mu_{\max}\left(1 - \sqrt{\frac{K_s}{K_s + [S]_0}}\right)$$

$$K_s << [S]_0$$

$$D_{optimum} \approx \mu_{\max}$$
$$\approx D_{\max}$$

Close to washout conditions.

Operability would be difficult. We would not want to run too close to washout conditions.

Fed-batch fermentor (microbes or mammalian cells)
-used to achieve very high cell densities (e.g. hundreds of grams cell dry weight (c.d.w)/liter)

If you want $x_{final} = \frac{100\ g}{L}$

If $Y_{\frac{x}{s}} \approx 0.5$, $[S]_0 = \frac{200\ g}{L} \approx 20\% \frac{wt}{volume}$ ← Toxic, sugar content cells will die

Why do we not feed all at once? Cells will die.

Calculate medium feed rate in order to hold μ constant.

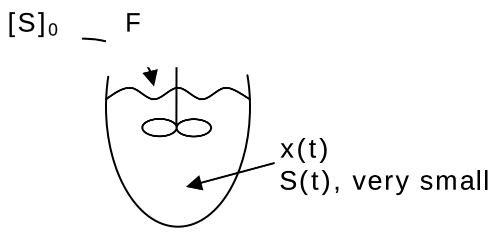

Figure 4. Diagram of a fed-batch fermentor.

If μ is constant, $\text{biomass} = \text{biomass}\big|_{t=0} e^{\mu t}$

There is a dilution term, because as we feed in fresh medium, volume will change. Volume often doubles.

$$x\,\mathrm{V} = x_0\,\mathrm{V}_0\,e^{\mu t}$$

$$\underbrace{\text{Feed } F[S]_0}_{\text{sugar feed}} = \underbrace{\frac{\mu x_0\,\mathrm{V}_0\,e^{\mu t}}{Y_{\frac{x}{s}}}}_{\text{sugar consumed}}$$

Assume <u>all</u> converted into biomass.

$$F = \frac{x_0\,\mathrm{V}_0}{[S]_0 Y_{\frac{x}{s}}}\mu e^{\mu t}$$

Exponential flow rate. Typically μ specified as "small."

Dilution:

$$\frac{d\,\mathrm{V}}{dt} = F$$

$$\mathrm{V}(t) = \mathrm{V}_0\left(1 + \frac{x_0}{[S]_0 Y_{\frac{x}{s}}}\left(e^{\mu t} - 1\right)\right)$$

$$x = \frac{\text{biomass}}{\mathrm{V}} = \frac{x_0 e^{\mu t}}{1 + \frac{x_0}{Y_{\frac{x}{s}}[S]_0}\left(e^{\mu t} - 1\right)}$$

$$= \frac{x_0\,\mathrm{V}_0\,e^{\mu t}}{\mathrm{V}}$$

"Logistic equation"

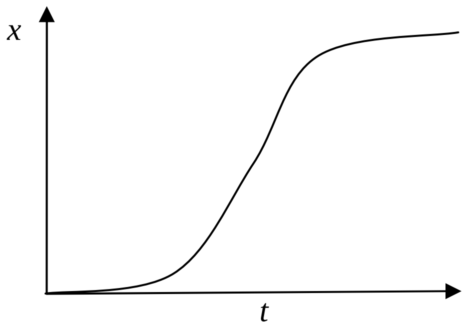

Figure 5. Graph of logistic growth.

If product is something cells are making:

Product synthesis kinetics

1) $\frac{1}{x}\frac{dP}{dt} = \alpha\mu$ growth associated (e.g. ethanol)

$P \equiv \frac{\text{product}}{\text{volume}}$

2) $\frac{1}{x}\frac{dP}{dt} = \beta$ not growth associated (e.g. antibiotics, proteins, antibodies)

$P = \beta\int_0^t x dt$ integrate for amount of product.