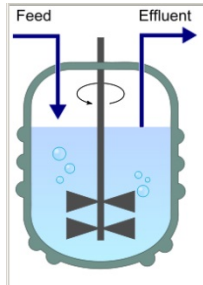# Biol 398/Math 388:

A simple chemostat model of nutrients and population growth

Background. The chemostat is an idealization of a reactor for growing populations of cells like yeast. Nutrients are fed continuously at a fixed flow rate and concentration, and effluent is extracted at a fixed flow rate. A slight subtlety in the extraction part is that what is extracted is at a fixed flow rate, to keep the volume constant, but the effluent has a concentration that depends on the reaction. An illustration of the chemostat is given below.

The basic assumption of the chemostat is that the contents are sufficiently well mixed that the concentration of the mixture is uniform throughout the container. Under this assumption, we do not need to consider spatial effects or non-uniformity of nutrients and cells: all cells have equal access to nutrient. If the volumetric inflow rate is Q (vol/time), then the **dilution rate** is $q = Q/V$ in units of (1/time), where the volume of the mixture in the tank is V (and that's constant: the effluent outflow rate is assumed the same as the inflow dilution rate). The **feed concentration** is u (in concentration units, mass or molar). Then the concentration of the nutrient $y(t)$ can be determined as follows:

Figure 1. Chemostat cartoon from Wikipedia.

Rate of change of nutrient = inflow rate – outflow rate – rate consumed in the tank.

Now, the inflow rate is $q*u$ (and this is assumed to be a constant, independent of time). The outflow rate is $q*y(t)$, because the effluent is extracted from the uniform, well-mixed tank contents. Thus, we have

$$\frac{dy}{dt} = qu - qy(t) - \text{consumption rate}$$

The model of consumption we consider is called Monod, Michaelis-Menten, or Briggs-Haldane, depending on the context, and it adds a third term to the mass balance equation due to cell population consumption of the nutrient.

$$\frac{dy}{dt} = qu - qy(t) - \frac{1}{\varepsilon}V_{max}\frac{y}{K+y}x(t)$$

to capture inflow, outflow, and metabolism of the nutrient. Here we introduce x, the concentration of yeast cells in the mixture, and the parameter e denotes a unit conversion rate between biomass (the units of x) and nutrient concentration.

We model the population of cells with its own differential equation, coupled with the nutrient by

$$\frac{dx}{dt} = -qx + V_{max}\frac{y}{K+y}x,$$

so that the net growth rate depends on the nutrient level. This model leads to a coupled pair of differential equations, because the consumption model depends on the size of the population:

$$\frac{dy}{dt} = qu - qy - \frac{1}{\varepsilon}V_{max}\frac{y}{K+y}x$$

$$\frac{dx}{dt} = -qx + V_{max}\frac{y}{K+y}x$$

Among the interesting things to consider is the equilibrium, or steady state. By equilibrium, we mean a state that would remain constant in time if we reached it. Since constant functions have 0 derivative, steady states can be found by setting the right hand side of the DE system to 0:

$$\frac{dy}{dt} = 0 = qu - qy - \frac{1}{\varepsilon}V_{max}\frac{y}{K+y}x$$

$$\frac{dx}{dt} = 0 = -qx + V_{max}\frac{y}{K+y}x$$

Looking at the second equation, we see that x=0 works (but that's not interesting, as the cell population would be extinct). If x is not 0, then we must have

$$q = V_{max}\frac{y}{K+y}, \quad or$$

$$y = \frac{qK}{V_{max} - q}$$

as part of the equilibrium condition. Plugging the first part of this into the first equation, we get that

$$qu - qy = \frac{1}{\varepsilon}qx$$

$$x = \varepsilon(u - y)$$

Two important things to note are that the steady state nutrient concentration is independent of the federate u, while the cell population depends linearly on u. That's not what we observed in the terSchure experiments.

Many organisms require and/or live off multiple nutrients. What happens in such a case? There are at least three possible structures for multiple nutrients, each of which can be written

$$\frac{dx}{dt} = -qx + f(y,z)x$$

$$\frac{dy}{dt} = qu - qy - \frac{1}{\varepsilon}f(y,z)x$$

$$\frac{dz}{dt} = qv - qz - \frac{1}{\delta}f(y,z)x$$

in which y and z denote the two nutrients, with x again denoting the cell population. All three of these state variable quantities are measured in concentration units. The numbers ε and δ denote conversion rates of biomass concentration/nutrient concentration. The choice of the function f is the tough bit of modeling, with the following three being popular:

$$f(y,z) = \begin{cases} \dfrac{Vy}{K+y} + \dfrac{Uz}{M+z}, & \text{when the cells use either y or z.} \\[2em] V\dfrac{y}{K+y}\dfrac{z}{M+z}, & \text{when the cells use both y and z} \\[2em] V\min\left\{\dfrac{y}{K+y}, \dfrac{z}{M+z}\right\}, & \text{when the cells use both y and z under limitation} \end{cases}$$

We will start with the last form, working out the steady state and data comparison in detail.
The system is then

$$\frac{dx}{dt} = -qx + V \min\left\{\frac{y}{K+y}, \frac{z}{M+z}\right\} x$$

$$\frac{dy}{dt} = qu - qy - \frac{1}{\varepsilon} V \min\left\{\frac{y}{K+y}, \frac{z}{M+z}\right\} x$$

$$\frac{dz}{dt} = qv - qz - \frac{1}{\delta} V \min\left\{\frac{y}{K+y}, \frac{z}{M+z}\right\} x$$

And when we seek a steady state of (x,y,z), the first equation tells us that

$$0 = \left(-q + V \min\left\{\frac{y}{K+y}, \frac{z}{M+z}\right\}\right) x$$

$$\frac{q}{V} = \min\left\{\frac{y}{K+y}, \frac{z}{M+z}\right\}$$

To explore this equation, we need to examine which ratio (the y one or the z one) gives the min.

$$\frac{y}{K+y} = \min\left\{\frac{y}{K+y}, \frac{z}{M+z}\right\}$$

$$\Leftrightarrow \frac{y}{K+y} \leq \frac{z}{M+z}$$

$$\Leftrightarrow y(M+z) \leq z(K+y)$$

$$\Leftrightarrow \frac{M}{K} y \leq z$$

Above the line z=My/K, we have the y ratio giving the min, while below the line the z ratio gives the min. Now, let's look at what happens when the min equals q/V.

Above the line, we have   Below the line we have

$$\frac{y}{K+y} = \min\left\{\frac{y}{K+y}, \frac{z}{M+z}\right\}$$

$$\Leftrightarrow \frac{M}{K} y \leq z$$

$$\frac{q}{V} = \frac{y}{K+y}$$
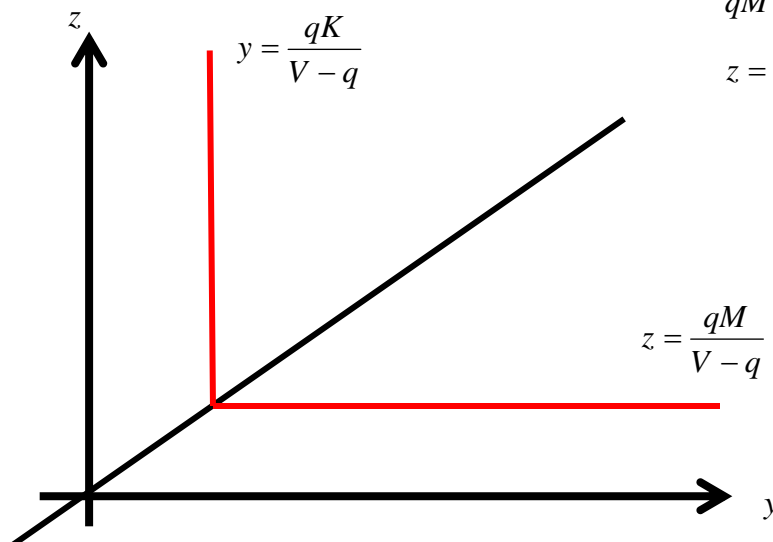
$$qK + qy = Vy$$

$$y = \frac{qK}{V-q}$$

$$\frac{z}{M+z} = \min\left\{\frac{y}{K+y}, \frac{z}{M+z}\right\}$$

$$z \Leftrightarrow \frac{M}{K} y \geq z$$

$$\frac{q}{V} = \frac{z}{M+z}$$

$$qM + qz = Vz$$

$$z = \frac{qM}{V-q}$$

$$y = \frac{qK}{V-q}$$

$$z = \frac{qM}{V-q}$$

So, at this point we know that any equilibrium value is a point on one of those two line segments. We need to use the next two differential equations to narrow it down some.

$$\frac{q}{V} = \min\left\{\frac{y}{K+y}, \frac{z}{M+z}\right\}, so$$

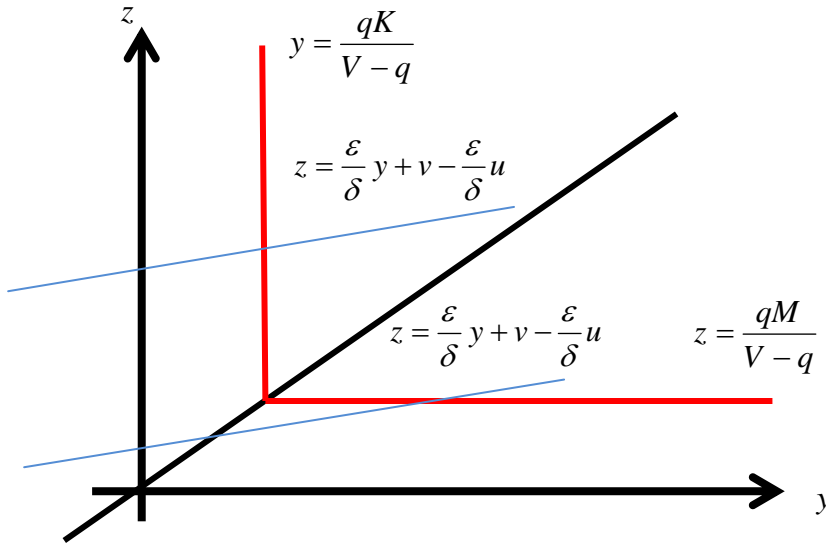$$0 = qu - qy - \frac{1}{\varepsilon}qx$$

$$0 = qv - qz - \frac{1}{\delta}qx$$

which simplifies the second and third by using the first (i.e, q/V in place of the complicated min expression). Noting that x is in both, we can eliminate x:

$$\varepsilon(u - y) = \delta(v - z)$$

$$z = \frac{\varepsilon}{\delta}y + v - \frac{\varepsilon}{\delta}u, or$$

$$y = \frac{\delta}{\varepsilon}z + u - \frac{\delta}{\varepsilon}v$$

Depending on whether we want *z* as a function of *y* or vice versa. If we plot this line formula onto the previous graph, we see the blue lines, whose intercepts depend on *u*.

The intersection of the blue line with the red "L" is the equilibrium. As we change the input value of the feed concentration, u, the blue line – and hence the equilibrium -- will change. The final piece of the puzzle is to determine the value of the steady states for x,y,z, as a function of u. To do this task, we note that the "cross over" point of the L corresponds to

$$z = \frac{\varepsilon}{\delta}y + v - \frac{\varepsilon}{\delta}u = \frac{M}{K}y,$$

$$\frac{\varepsilon}{\delta}u = -\frac{M}{K}y + \frac{\varepsilon}{\delta}y + v$$

$$u = \left(1 - \frac{M\delta}{K\varepsilon}\right)y + \frac{\delta}{\varepsilon}v$$

Using finally that the equilibrium value at that corner point is y=qK/(V-q), we obtain

$$u* = \left(1 - \frac{M\delta}{K\varepsilon}\right)\frac{qK}{V-q} + \frac{\delta}{\varepsilon}v$$

When u is less than u*, the equilibrium is on the vertical branch of the red L. When u is greater, the equilibrium is on the horizontal branch. To summarize, we have

$$u* = \left(1 - \frac{M\delta}{K\varepsilon}\right)\frac{qK}{V-q} + \frac{\delta}{\varepsilon}v$$

$$u \le u* \Rightarrow$$

$$y = \frac{qK}{V-q}$$

$$z = \frac{\varepsilon}{\delta}y + v - \frac{\varepsilon}{\delta}u$$

$$x = \varepsilon(u - y)$$

$$u \ge u* \Rightarrow$$

$$z = \frac{qM}{V-q}$$

$$y = \frac{\delta}{\varepsilon}z + u - \frac{\delta}{\varepsilon}v$$

$$x = \delta(v - z)$$