Computer Science 477/577

Chemostats 19 January, 2008

A Continuous Problem

We have selected the chemostat as starting point for investigation. This is because the chemostat has a number of attractive features for the student new to simulation; 1) it is continuous, 2) it written in terms of a pair of ordinary differential equations, and 3) it has a clear biological interpretation. To begin the study, consider unconstrained growth of a microorganism.

Growth of a Microorganism

Suppose we have some container that is filled with a *nutrient medium* (consisting of sugars and salts, sometimes amino acids and nitrogen). Second, imagine a drop, or *culture* of some microorganism is introduced to the media. This is called *inoculation.* Let

$$N(t) = \text{density of microorganism at time } t. \tag{1}$$

The time the microorganism require to reproduce can be measured with a growth constant

$$K = \text{rate of reproduction per unit time.} \tag{2}$$

The time evolution of the microorganism population can now be expressed

$$N(t + \Delta t) = N(t) + KN(t)\Delta t \tag{3}$$

Algebraically rearranging terms gives

$$\frac{N(t + \Delta t) - N(t)}{\Delta t} = KN(t) \tag{4}$$

The worth of this expression increases as Δt gets smaller, because there is no averaging of quantities over long intervals. The best form will be then correspond to the limit $\Delta t \to 0$, which defines the derivative.

$$\frac{dN}{dt} = KN \tag{5}$$

This expression can be solved analytically by integration, first rearranging

$$\frac{dN}{N} = Kdt, \tag{6}$$

and now integrating

$$\int_{N(0)}^{N(t)} \frac{dN}{N} = \int_0^t K dt, \tag{7}$$

$$\ln(N(t)) - \ln(N(0)) = Kt, \tag{8}$$

finally, giving the expression

$$N(t) = N(0)e^{Kt}. \tag{9}$$

This is the exponential growth of a population first noted by Malthus in 1798, with an alarmist reaction. It is easy to see that if the population is in constant decline (through emigration, predation, whatever) the relation would be,

$$N(t) = N(0)e^{-Kt}. \tag{10}$$

Another significant quantity for growth or decay is the doubling time (or half-life). It is found by simply writing

$$\frac{N(\tau)}{N(0)} = \frac{N(0)e^{K\tau}}{N(0)} = 2, \tag{11}$$

and solving for τ,

$$\tau = \frac{\ln 2}{K}. \tag{12}$$

With half-life found with the same method.

What is wrong with this model?

K is fixed. If we relax the modeling assumptions of a single growth rate, then $K \to K(t)$.

Making a better model

The time history of $K(t)$ is not something experimentalists can measure. So instead we often try to make the assumption that the reproductive rate depends upon the amount of resources (nutrient concentration), C. If we assume the relation between growth rate and nutrient level is linear, then

$$K(C) = \kappa C. \tag{13}$$

Further, we will need to assume that one unit of population is *yielded* by α units of nutrients. Now the growth equations can be rewritten

$$\frac{dN}{dt} = \kappa C N \tag{14}$$

$$\frac{dC}{dt} = -\alpha \frac{dN}{dt} = -\alpha \kappa C N. \tag{15}$$

Like before, the equations can be solved analytically. This time it is a little harder, because there are now a pair of equations. Begin with the second equation in the pair

$$\frac{dC}{dt} = -\alpha\frac{dN}{dt}, \tag{16}$$

and integrate to get

$$C(t) = -\alpha N(t) + C(0). \tag{17}$$

Which can then be plugged back into the first equation

$$\frac{dN}{dt} = \kappa CN = \kappa(C(0) - \alpha N))N \tag{18}$$

by comparing the form of this equation to the original growth equation we see that

$$K = \kappa(C(0) - \alpha N), \tag{19}$$

hence we have 'derived' *density dependent growth*. By integrating, we arrive at a the *logistic growth equation*

$$N(t) = \frac{N(0)B}{N(0) + (B - N(0))e^{-rt}} \tag{20}$$

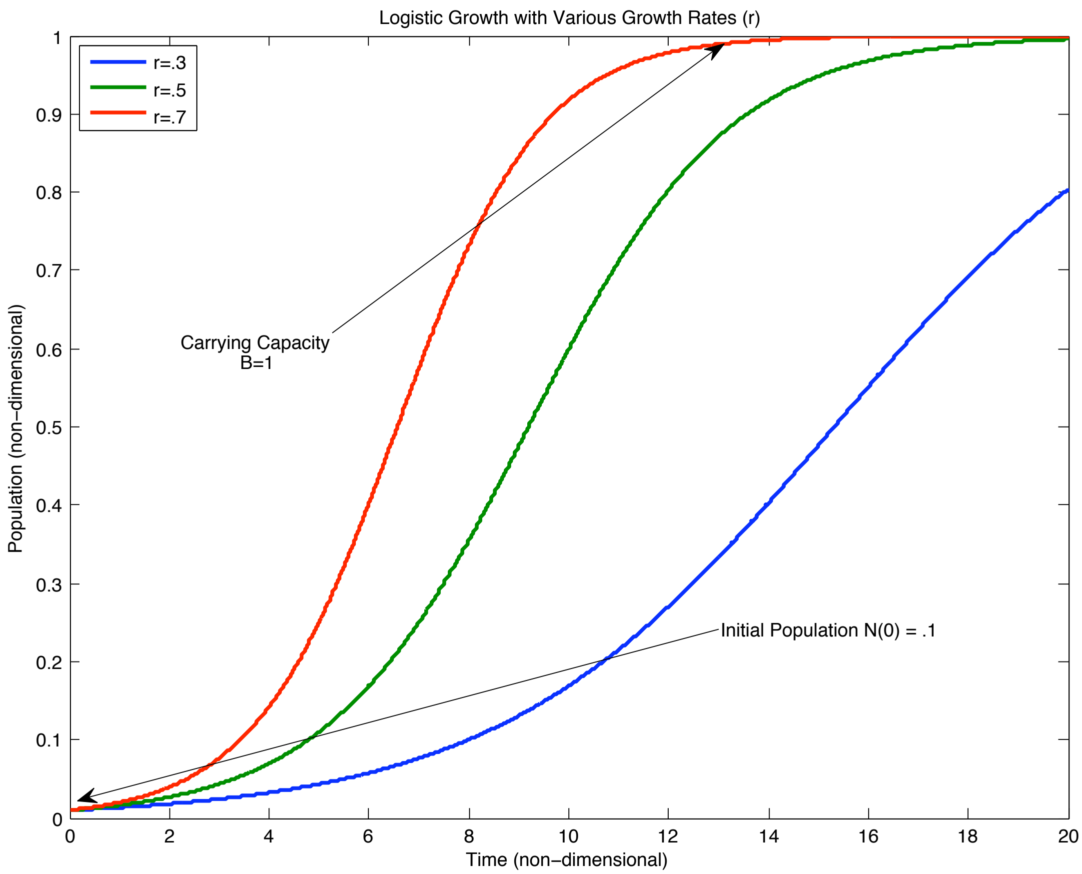
with $B = C(0)/\alpha$ and $r = \kappa C(0)$. These are more than convenient parameters, they define the behavior of the system because B is the *carrying capacity*, and r is the growth rate. The relationship between these parameters is plotted in figure 1.

Growth of Bacteria in a Chemostat

In order to keep a constant supply of some microogranism, or to create a bioreactor for production of microorganism metabolic byproducts, like ethanol, chemostats are used. The key is to provide a constant inflow and outflow of the nutrient broth. A balance must be found, between having sufficient flow to keep the microorganism community viable, but not so high that the community is simply washed out.

The goal of this section will be to use the techniques of the previous sections to write a model for the chemostat. Let us begin with a table to identify each variable.

Figure 1: Logistic growth for various growth rates.



Quantity	*Symbol*	*Dimensions*
Nutrient concentration in chamber	C	Mass/volume
Nutrient concentration in reservoir	C_o	Mass/volume
Bacterial population density	N	Number/volume
Yield constant	$Y = 1/\alpha$	
Volume of chamber	V	Volume
Flow rate	F	Volume/time

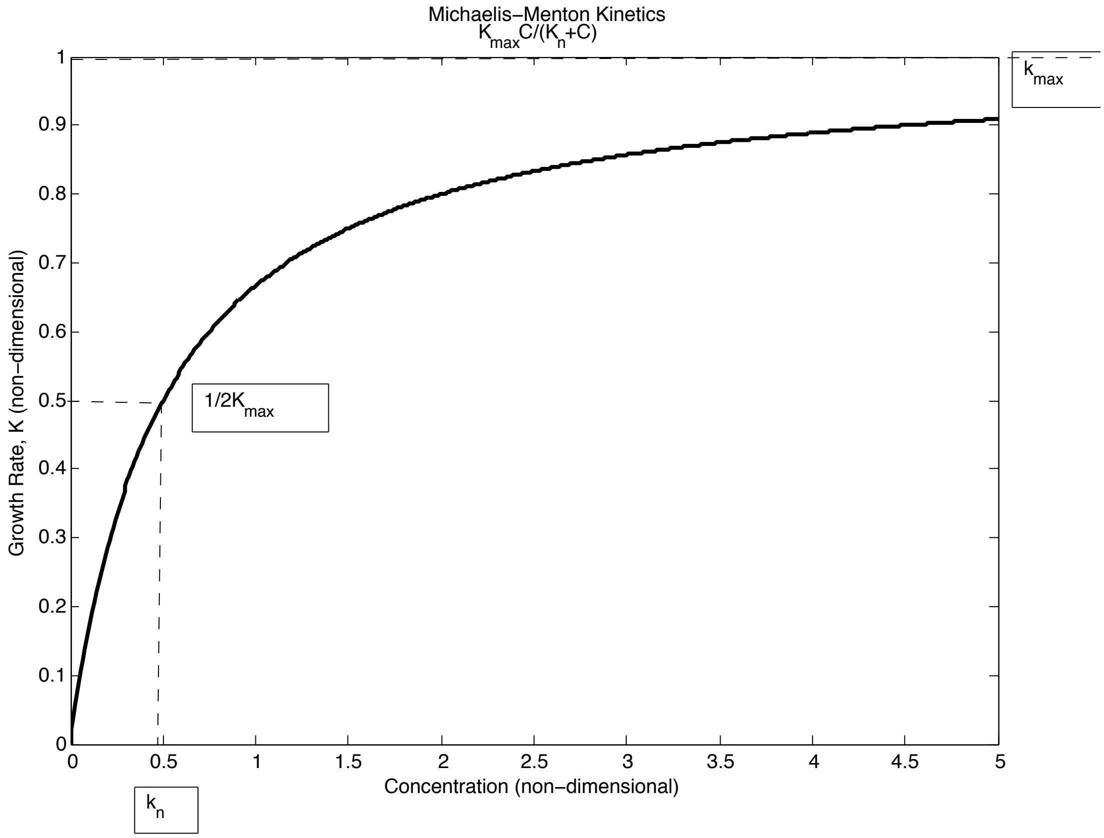
It is always best when modeling to begin by making assumptions explicit. Our will be:

1. The chamber is well stirred, and a single value of N and C are justified. That is, there is no spatial dependence of the variables.

2. While the nutrient medium has many components, there is a single limiting agent, such that we can track a single value, C, and not other nutrients.

3. Growth rate depends on concentration $K \to K(C)$. Previously we used a linear relation. This time, we will use the Michaelis-Menten assumption that there is increase up to a certain level of growth $(K_m ax)$, which seems more realistic,

$$K(C) = \frac{K_{max} C}{K_n + C}. \tag{21}$$



4. Nutrient consumption is proportionate to nutrient concentration. This is as it was before, when finding the logistic equation.

Applying the assumptions, and noting the dimensions in the table, we get

$$\frac{dN}{dt} = K(C)N - \frac{FN}{V}, \tag{22}$$

$$\frac{dC}{dt} = -\alpha\frac{dN}{dt} + \frac{FC_o}{V}. \tag{23}$$

using the Michaelis-Menten assumption, and the expression for $\frac{dN}{dt}$ gives

$$\frac{dN}{dt} = \frac{K_{max}C}{K_n + C}N - \frac{FN}{V}, \tag{24}$$

$$\frac{dC}{dt} = -\alpha\left(\frac{K_{max}C}{K_n + C}N - \frac{FN}{V}\right) + \frac{FC_o}{V}. \tag{25}$$

We are now beyond having a system that can be easily solved analytically. The above must be solved *numerically*, which is the focus for the remainder of the lectures.

Non-dimensional Form of the Equations

To simplify analysis, we shall use a non-dimensional form of the equations. These are derived by defining *characteristic* scales for each of the variables.

$$N \rightarrow \tilde{N}N^* \tag{26}$$

$$C \rightarrow \tilde{C}C^* \tag{27}$$

$$t \rightarrow \tilde{t}t^* \tag{28}$$

where the variable with the ~ is the dimensionless scale value. For instance a typical value of N might be 100,000 cells/liter, so $\tilde{N} = 1$. The * component is the portion carrying the units and the value. Applying our rescaling involves simply substituting the terms into equations 24

$$\frac{d\tilde{N}N^*}{d(\tilde{t}t^*)} = \frac{K_{max}\tilde{C}C^*}{K_n + \tilde{C}C^*}N - \frac{F\tilde{N}N^*}{V}, \tag{29}$$

$$\frac{d\tilde{C}C^*}{d(\tilde{t}t^*)} = -\alpha\left(\frac{K_{max}\tilde{C}C^*}{K_n + \tilde{C}C^*}\tilde{N}N^* - \frac{F\tilde{N}N^*}{V}\right) + \frac{FC_o}{V}. \tag{30}$$

Divide through by N^* and C^* respectively, manipulate algebraically

$$\frac{d\tilde{N}}{d\tilde{t}} = t^*\frac{K_{max}\tilde{C}}{K_n/C^* + \tilde{C}}\tilde{N} - t^*\frac{F\tilde{N}}{V}, \tag{31}$$

$$\frac{d\tilde{C}}{d\tilde{t}} = -\left(\frac{-\alpha K_{max}t^*N^*}{C^*}\right)\left(\frac{\tilde{C}}{K_n/C^* + \tilde{C}}\tilde{N}\right) - t^*\frac{F\tilde{C}}{V} + t^*\frac{FC_o}{VC^*}. \tag{32}$$

Observe that if

$$t^* = \frac{V}{F}, \quad C^* = K_n, \quad N^* = \frac{K_n}{\alpha t^* K_{max}} \tag{33}$$

The equations are free of all scale values, and we can drop the ~

$$\frac{dN}{dt} = \alpha_1\left(\frac{C}{1+C}\right)N - N \tag{34}$$

$$\frac{dC}{dt} = -\left(\frac{C}{1+C}\right)N - C + \alpha_2, \tag{35}$$

A dimensionless expression. Finally, note that the number of free parameters has been reduced from 6 to 2. The parameters are

$$\alpha_1 = \frac{VK_{max}}{F} \tag{36}$$

and

$$\alpha_2 = \frac{C_o}{K_n} \tag{37}$$

These equations are simpler, and more revealing.

Steady State Solutions

We expect that the long term behavior system will not change

$$\frac{dN}{dt} = 0 \quad (38)$$
$$\frac{dC}{dt} = 0 \quad (39)$$

or, in terms of equation **??**

$$\alpha_1 \left(\frac{C}{1+C}\right) N - N = 0 \quad (40)$$
$$-\left(\frac{C}{1+C}\right) N - C + \alpha_2 = 0, \quad (41)$$

which can be solved algebraically. The result is that there are two possible steady states. The first is trivial

$$N_{ss} = 0 \quad (42)$$
$$C_{ss} = \alpha_2, \quad (43)$$

no microorganism, no change. The second is more interesting

$$N_{ss} = \alpha_1 \left(\alpha_2 - \frac{1}{\alpha_1 - 1}\right) \quad (44)$$
$$C_{ss} = \frac{1}{\alpha_1 - 1}. \quad (45)$$

But we note that for it to exist $\alpha_1 > 1$, which limits the basic parameters that can yield a steady state.