

# The Chemostat-Part 2

H.T. Banks and Marie Davidian

MA-ST 810

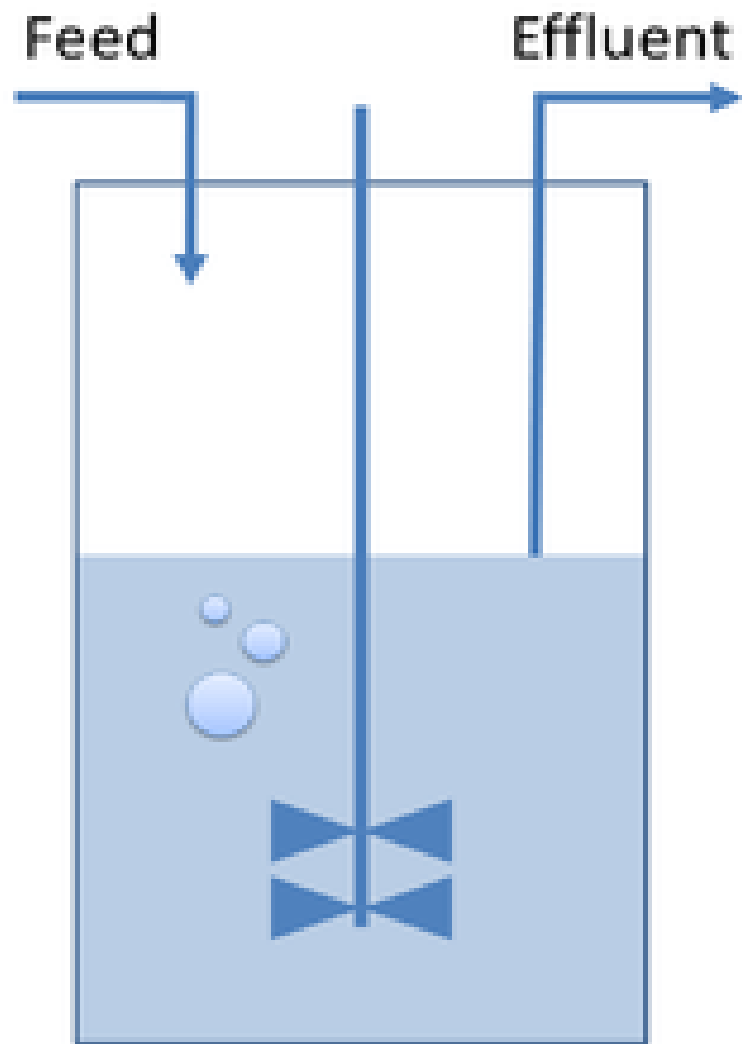
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North Carolina State University

Raleigh, NC 27695

*Center for Research  
in Scientific Computation*  
*North Carolina State University*

**Center for Quantitative Sciences  
in Biomedicine**  
**North Carolina State University**



# The Mathematical Model

Modeling is based on compartmental analysis, laws of mass action, and mass balance. We can describe the container with a coupled set of differential equations derived using mass balance and laws of mass action: ( $\frac{dm}{dt} \propto \rho(m)$ ) :

$$\begin{aligned}\frac{dN(t)}{dt} &= r(c(t))N(t) - qN(t) \\ \frac{dc(t)}{dt} &= qc_0 - qc(t) - \frac{1}{y}r(c(t))N(t).\end{aligned}$$

# Steady State of the System

For this system, we want to find the steady state, i.e., we want to find constants  $(\bar{N}, \bar{c})$  such that

$$\left. \frac{dN}{dt} \right|_{(\bar{N}, \bar{c})} = 0$$
$$\left. \frac{dc}{dt} \right|_{(\bar{N}, \bar{c})} = 0.$$

We found that a nontrivial steady state is given by

$$(\bar{N}, \bar{c}) = \left( y(c_0 - \bar{c}), \frac{K_m q}{R_{max} - q} \right).$$

Remark: There also exists a trivial solution to the equilibrium problem, specifically  $(\bar{N}, \bar{c}) = (0, c_0)$ , which is easily verified from the original system. However, this solution is not of interest to us, as it implies that  $N = 0$ , which implies that there is no action taking place (it also represents an unstable equilibrium).

We see from (4) that  $\bar{c}$  depends on  $c_0$ , which means for any  $c_0$ , we will arrive at a different equilibrium, but if we were to *start* at  $(\bar{N}, \bar{c})$ , we would stay there, and this is true if  $(\bar{N}, \bar{c})$  is  $(0, c_0)$  or that represented by (4). However, if we start at a point other than an equilibrium, for the (4) equilibria, it will converge to those equilibria, but, as we shall later establish, it will *never* converge to  $(0, c_0)$  because by definition  $y \neq 0$ , and since we started at a point *other than* equilibrium,  $c_0 \neq \bar{c}$  therefore,  $\bar{N} \neq 0$ . Thus we say that  $(0, c_0)$  is an *unstable equilibrium* while the nontrivial state  $(\bar{N}, \bar{c})$  of (4) is a *stable equilibrium*.

# A Brief Review of Phase Plane Analysis

- Summarize methodology and results pertaining to qualitative analysis for ordinary differential equations (see [BoyceDiPrima]).
- Ideas can often be used to evaluate (at least in part) the correctness of an assumed *mathematical model*
- Unfortunately, we do not have in mathematical modeling the analogue of statistical techniques such as residual plots to ascertain correctness of an assumed *statistical model*.

Recall that a steady state of a differential system is the point where the dynamics are equal to zero. That is, for a given differential equation

$$\frac{dx}{dt} = F(x), \quad (1)$$

the point  $x_e$  is called a *steady state* or *equilibrium* of the equation if  $F(x_e) = 0$ . Note that in general  $x$  and  $F$  are vectors.

We further define the concepts of *stable*, *asymptotically* and *unstable steady states*.

Given a differential equation (1), with  $x_e$  a steady state,

- we call  $x_e$  a *stable* steady state if for any  $\epsilon > 0$ , there exists a  $\delta > 0$  such that if  $x_0$  is any initial point satisfying  $|x_0 - x_e| < \delta$ , then  $|x(t; x_0) - x_e| < \epsilon$  for all  $t > 0$ .
- We say that a steady state is *asymptotically stable* if it is stable and in addition  $x(t; x_0) \rightarrow x_e$  as  $t \rightarrow \infty$ .

Examples of behavior of trajectories near an asymptotically stable steady state and a stable steady state are depicted in the first and last plots, respectively, of Figure 2, while typical behavior near an unstable steady is depicted in the middle plot of Figure 2.

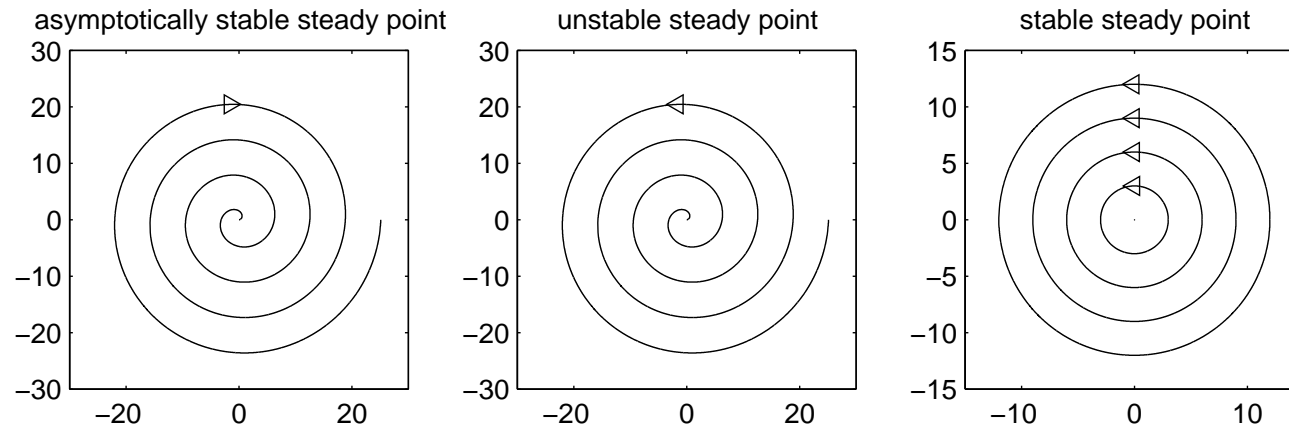


Figure 2: Three types of steady states

Intuitively: stable steady state only requires solutions  $x(t; x_0)$  remain near steady state for  $x_0$  in a small neighborhood near steady state— asymptotically stable guarantees  $x(t)$  will tend to  $x_e$ .

There are analytical tests to check for stability properties of steady states. We first consider linear differential equations. Given an  $n$  vector differential equation

$$\frac{dx}{dt} = Ax, \quad (2)$$

then  $x_e = 0$  is clearly a steady state point. The eigenvalues  $\lambda$  (which may be real, complex, or a combination thereof) of the matrix  $A$  are defined by solutions to

$$\det(A - \lambda I) = |A - \lambda I| = 0.$$

These eigenvalues can be used to completely characterize the qualitative behavior of solutions near a steady state of (2) as well as to partially characterize those of the general nonlinear system (1).

We find

- If the real parts of the eigenvalues of the matrix  $A$  are all negative, then  $x_e$  is an asymptotically stable steady state.
- If the real part of at least one of the eigenvalues of the matrix  $A$  is positive, then  $x_e$  is an unstable steady state.
- If the real parts of the eigenvalues of the matrix  $A$  are all zero, then  $x_e$  is a stable steady state, but not an asymptotically stable steady state.

Next we summarize the rather remarkable eigenvalue results for *general nonlinear differential equations* and their linearizations..

Observe that using a Taylor series we find

$$\begin{aligned} dx/dt &= F(x) = F(x_e) + \frac{dF}{dx}(x_e)(x - x_e) + o(x - x_e) \\ &= \frac{dF}{dx}(x_e)(x - x_e) + o(x - x_e) = A(x - x_e) + o(x - x_e), \end{aligned}$$

where  $A = \frac{dF}{dx}(x_e)$  and  $o(\epsilon)$  denotes a term that satisfies  $\frac{o(\epsilon)}{\epsilon} \rightarrow 0$  as  $\epsilon \rightarrow 0$ .

We can approximate to first order the nonlinear dynamical system above by a linear system

$$\frac{dx}{dt} \approx Ax - Ax_e$$

or for  $z = x - x_e$  we have

$$\frac{dz}{dt} = Az + H. O. T. \approx Az$$

where *H. O. T.* represents *higher order terms*. One can prove the fundamental result:

Given a differential equation

$$\frac{dx}{dt} = F(x),$$

with steady state  $x_e$ , let  $A = \frac{dF}{dx}(x_e)$ .

Then for this nonlinear system we have:

- If the real part of the eigenvalues of the matrix  $A$  are all negative, then  $x_e$  is an asymptotically stable steady state.
- If the real part of at least one of the eigenvalues of the matrix  $A$  is positive, then  $x_e$  is an unstable steady state.
- If the real part of the eigenvalues of the matrix  $A$  are all zero, then the stability properties of  $x_e$  cannot be determined by the linear part of the system alone and thus rely on the higher order terms.

Returning to the chemostat model

$$\dot{N}(t) = r(c)N - qN$$

$$\dot{c}(t) = q(c_0 - c) - \frac{1}{y}r(c)N$$

$$N(0) = N_0$$

$$c(0) = 0,$$

where

$$r(c) = \frac{R_{max}c}{K_m + c},$$

we determined for this system there were 2 steady states:

$$(0, c_0), \text{ and } (N_1, c_1),$$

where

$$N_1 = q(c_0 - c_1),$$

$$c_1 = \frac{K_m q}{R_{max} - q}.$$

We noted that while  $(N_1, c_1)$  is stable,  $(0, c_0)$  is either a stable node or a saddle point (unstable). To further investigate stability properties, one can consider the linearization matrix, which for  $\mathcal{X} = (N, c)$ , is given by

$$A = \frac{\partial \mathcal{F}}{\partial \mathcal{X}} = \begin{pmatrix} r(c_1) - q & r'(c_1)N_1 \\ -\frac{r(c_1)}{y} & -q - \frac{r'(c_1)}{y}N_1 \end{pmatrix}.$$

One can readily argue that the eigenvalues of this matrix do *not* satisfy  $\Re(\lambda_i) = 0$ , which means there could be *no sustained oscillations*. In the graph in Figure 3 below, the system would display attributes of the solid line, rather than that of the dotted line.

Recall that solutions of  $\dot{x} = Ax$  are of the form

$$x(t) = \kappa_1 \exp(\lambda_1 t) + \kappa_2 \exp(\lambda_2 t)$$

where the  $\lambda_k$  are roots of  $|A - \lambda I| = 0$ . Since for  $\lambda_k = \mu_k + i\delta_k$ , solutions are of the form

$$x_k(t) = \kappa_k \exp(\mu_k t) (\cos \delta_k t + i \sin \delta_k t),$$

and no sustained oscillations are possible unless  $\mu_k = \Re(\lambda_k) = 0$ .

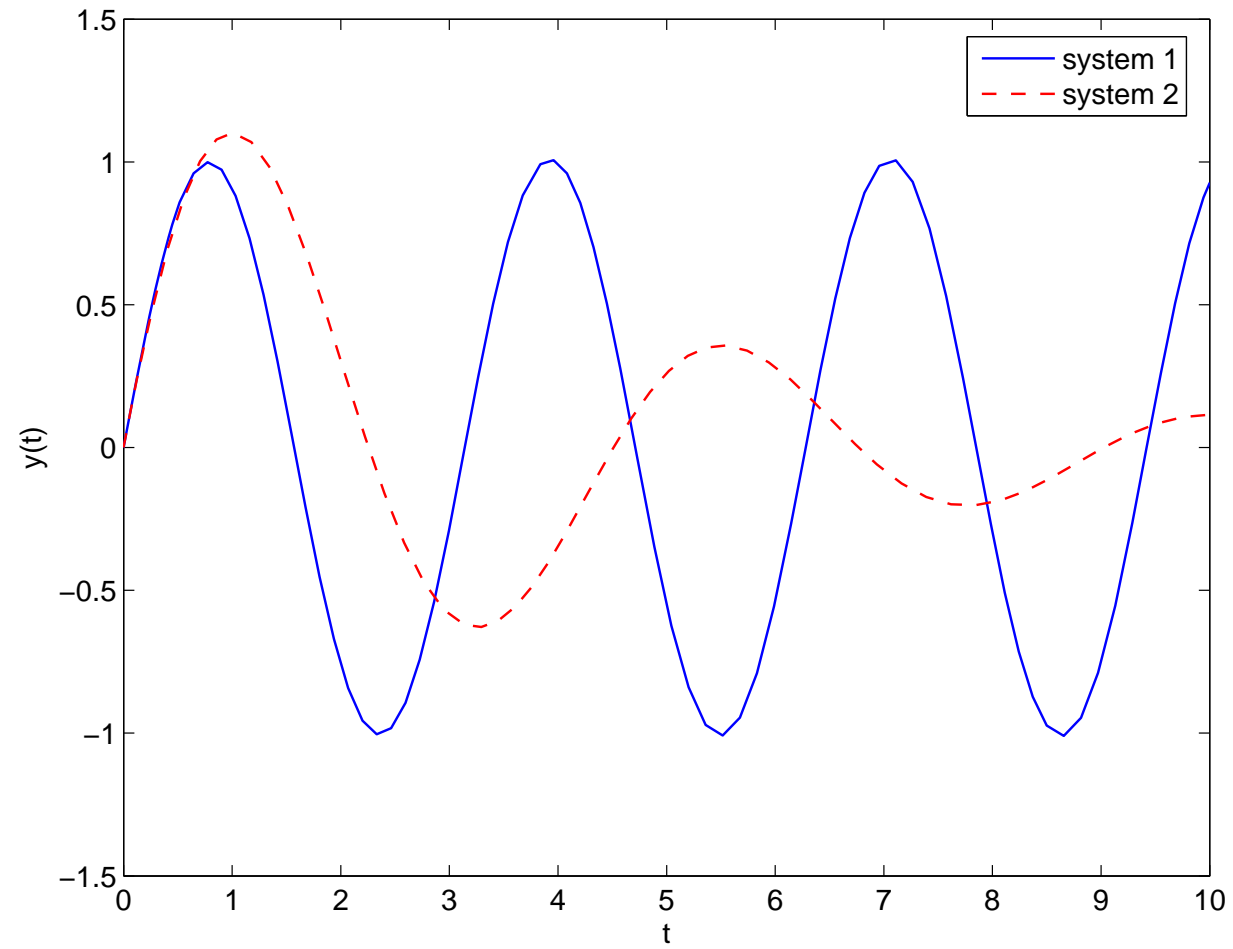


Figure 3: Asymptotically stable versus sustained oscillatory system

How can we use these results to further investigate the correctness of our model? Turning to the literature we find that *experimentally*, chemostats, under certain physical conditions, *will* exhibit *sustained oscillations!!!* This implies that our model is not adequate. Thus, we should endeavor to improve it, and as a first correction, one might perhaps question as in [Andrews], whether the nonlinearities are incorrect.

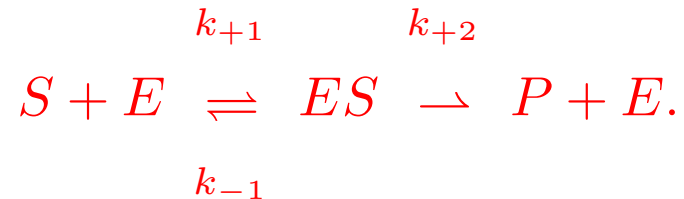
**Remark:** As we shall discuss below, the investigations of [BC, TL] suggest that the oscillations were produced by delays inherent in the system. We shall consider the series of studies leading to this conclusion.

We first ask, is the Monod (Michaelis-Menten) hypothesis for  $r(c)$  *incorrect*? As argued in [Andrews], the answer is yes. Andrews hypothesized that there exists an inhibitive effect for large concentrations of nutrient, and posited a new velocity term:

$$r_I(c) = \frac{R_{max}c}{K_m + c + \frac{c^2}{K_{IC}}},$$

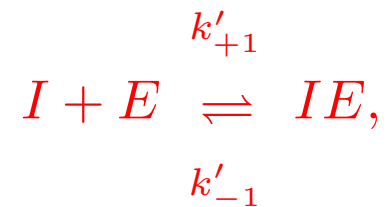
where  $c^2$  dominates for large  $c$ . This means that large  $c$  yields  $r_I(c) \approx 0$ .

We recall briefly the theory of inhibitors and velocity kinetics discussed earlier)–(see [BanksLN, Rub]. Recall the Michaelis-Menton system:



Note: Often one can infer from the velocity assumption what the assumptions the modelers are making about the inhibitor dynamics. For this type of system, there are several types of inhibitors  $[I]$  possible:

- Competitive Inhibitor - where  $[I]$  competes with  $[S]$  for the active site on  $E$ . This means that



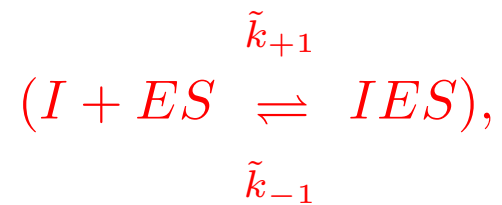
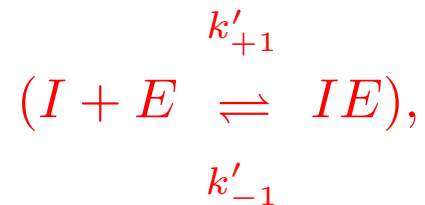
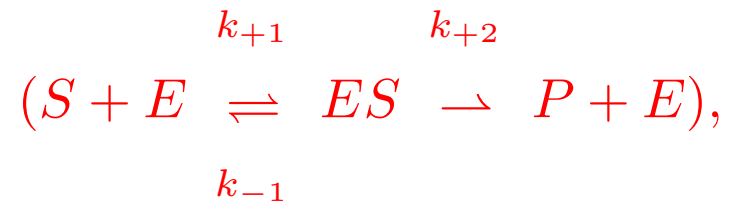
and we define

$$K_I \equiv \frac{k'_{-1}}{k'_{+1}}.$$

Thus, our velocity assumption is

$$v = \frac{V_{max}[S]}{K_m + \frac{K_m}{K_I}[I] + [S]}.$$

- Noncompetitive Inhibitor - where  $[I]$  binds with both  $E$  and  $ES$ .  
This means that



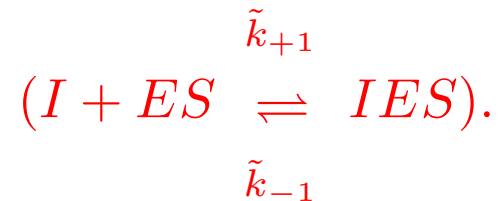
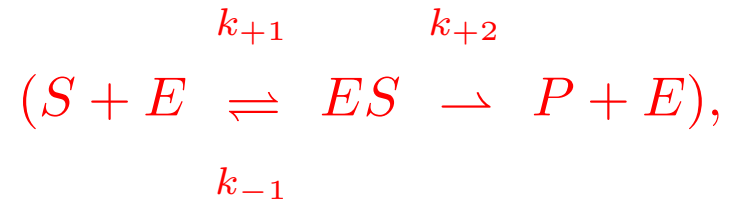
and we define, in this case,

$$K_{IE} \equiv \frac{k'_{-1}}{k'_{+1}}, \text{ and } K_{IC} \equiv \frac{\tilde{k}_{-1}}{\tilde{k}_{+1}},$$

with our velocity assumption defined as

$$v = \frac{V_{max}[S]}{K_m \left(1 + \frac{[I]}{K_{IE}}\right) + [S] \left(1 + \frac{[I]}{K_{IC}}\right)}.$$

- Uncompetitive Inhibitor - where  $[I]$  binds only with  $ES$ . Thus

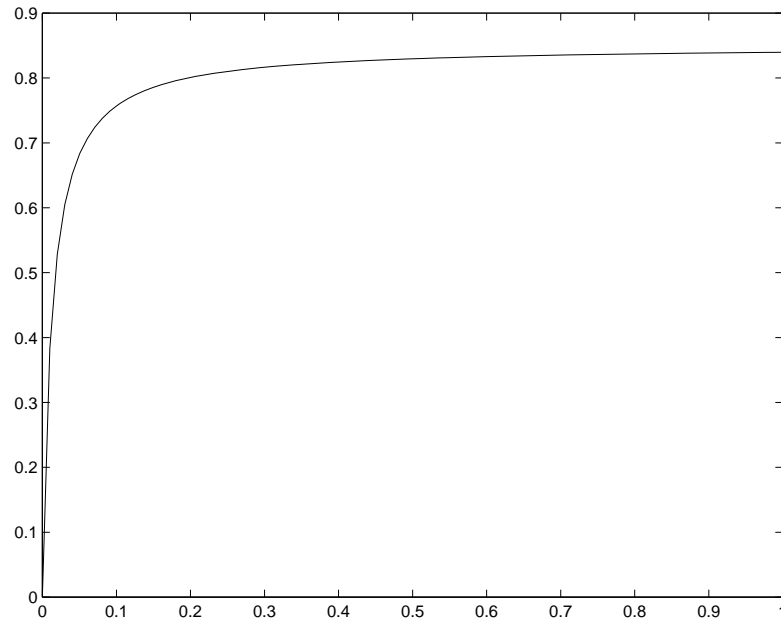


We define  $K_{IC}$  as above and our velocity assumption is defined as

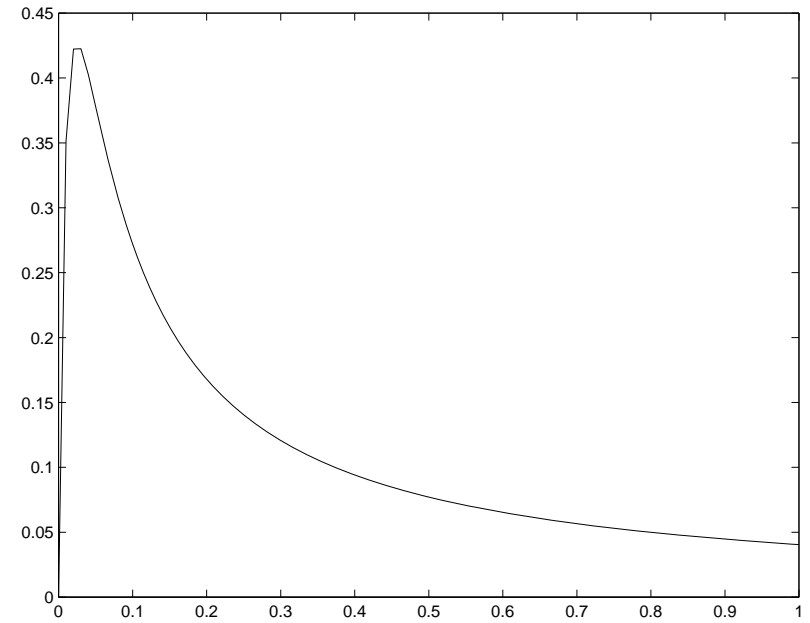
$$v = \frac{V_{max}[S]}{K_m + [S] \left(1 + \frac{[I]}{K_{IC}}\right)},$$

which is equivalent to the velocity term proposed by Andrews, when  $c = [S] = [I]$ .

Thus, we see that for the two proposed velocity terms, the Monod term tends to  $V_{max}$  as  $c$  tends to infinity. The Andrews' term, however, tends to 0 for increasing  $c$ . This is physically equivalent to inhibition of growth for an overabundance of nutrient.



$$r(c) = \frac{V_{max}c}{K_m + c}$$



$$r_I(c) = \frac{V_{max}c}{K_m + c + \frac{c^2}{K_{IC}}}$$

Figure 4: Monod's versus Andrews' Velocity Terms

So, using Andrews' velocity term, Bush and Cook [BC] proposed a new model

$$\begin{aligned}\dot{N}(t) &= \frac{V_{max}c(t)}{K_m + c(t) + \frac{c^2(t)}{K_{IC}}}N(t) - qN(t), \\ \dot{c}(t) &= q(c_0 - c(t)) - \frac{1}{y} \frac{V_{max}c(t)}{K_m + c(t) + \frac{c^2(t)}{K_{IC}}}N(t),\end{aligned}\tag{3}$$

but, we ask, can this new model account for the observed oscillations? As we shall see, the answer is no!. Below we will continue to explore the reason this oscillation exists, but for the moment we take a slight digression that is also revelent to our investigations and modeling methodology.

## **REMARKS ON ANOTHER METHODOLOGY:**

### **Dimensionless (Nondimensional) Analysis**

The purpose of dimensionless analysis is to reduce the number of dependent parameters. In the field of applied mathematics, when used for qualitative analysis, (determining trends of systems), this method can be very effective, but when used for inverse problems or parameter estimation, it can be a hindrance.

The method of dimensionless analysis is described below using our model as an example:

Introduce new variables in (3) (scale variables)

$$\begin{aligned}X(t) &= \frac{N(t)}{yK_m} \\Y(t) &= \frac{c(t)}{K_m} \\ \xi &= R_{max}t \\ \alpha &= \frac{Q}{R_{max}} \\ \beta &= \frac{K_m}{K_{IC}},\end{aligned}$$

and using these new variables, we claim that the system can be

rewritten as:

$$\begin{aligned}\frac{dX}{d\xi} &= \frac{XY}{1 + Y + \beta Y^2} - \alpha X \\ \frac{dY}{d\xi} &= \alpha(Y_0 - Y) - \frac{XY}{1 + Y + \beta Y^2} \\ X(0) &= \frac{N_0}{yK_m} \\ Y(0) &= 0,\end{aligned}$$

where  $Y_0 = \frac{c_0}{K_m}$ .

Thus, when we count the required parameters, the original system, given in (3), one needs  $q$ ,  $R_{max}$ ,  $K_m$ ,  $y$ ,  $K_{IC}$ ,  $c_0$ , for a total of 6 parameters. On the other hand, the new system model only requires

$\alpha, \beta, Y_0$  (3 parameters):

$$X(\xi; \alpha, \beta, Y_0)$$

$$Y(\xi; \alpha, \beta, Y_0),$$

which is fine for *qualitative analysis*, but for *inverse problems*, one would still need  $R_{max}, K_m, y, K_{IC}$  to scale the new system solutions to the old system (as well as the new system parameters,  $\alpha, \beta, Y_0$ ), so *little is gained by this method for inverse or parameter estimation problems!!!* Bush and Cook analyze stability properties for these and more general models by replacing the velocity terms by generic one in a non-dimensional formulation. Their results reveal shortcomings in the models.

# A General Result on Sustained Oscillations

Before going to the topic of sensitivity analysis, we summarize the result by Bush and Cook [BC]. An ODE system

$$\begin{aligned}x' &= g(y)x - \alpha x \\y' &= \alpha(y - y_0) - g(y)x,\end{aligned}$$

where function  $g$  satisfies:

$$\left\{ \begin{array}{l} \frac{\partial g}{\partial y} > 0 \text{ for } 0 < y < y^*, \\ \frac{\partial g}{\partial y} < 0 \text{ for } y^* \leq y < y^{**}, \\ g(0) = 0, \\ g(y) = \alpha \text{ has two roots } y_1, y_2 \text{ between } 0 \text{ and } y^{**}, \end{array} \right.$$

can not have sustained oscillations.

Note that the requirement imposed on the function  $g$  is quite natural. It captures the typical behavior one would expect in inhibitor kinetics, and is readily satisfied by all the examples we presented in our discussions. The above result *strongly suggests* that an incorrect nonlinearity is not the source of difficulty for lack of sustained oscillations in our models. So we still must ask what is the problem with our model for the chemostat?? More later!

# Sensitivity Analysis

Assume we have a dynamic model:

$$\begin{aligned}\frac{\partial x(t, \theta)}{\partial t} &= \mathcal{F}(x(t, \theta), \theta) \\ x(0) &= x_0(\theta).\end{aligned}$$

Here,  $x \in \mathbb{R}^N$ ,  $\theta \in \mathbb{R}^p$ . We denote the solution to the dynamic system  $x(t, \theta)$  and the observation of  $x(t, \theta)$   $f(t, \theta)$ , i.e.,  $f(t, \theta) = \mathcal{C}x(t, \theta)$  in our conventional notation. For example, consider the chemostat problem, where  $x(t, \theta)$  is a vector that contains two

components  $N(t, \theta)$  for bacteria and  $c(t, \theta)$  for nutrients. We have

$$\left\{ \begin{array}{l} \mathcal{C} = \begin{pmatrix} 1 & 0 \end{pmatrix}, \text{ hence } f(t, \theta) = N(t, \theta) \text{ when we only observe the bacteria} \\ \mathcal{C} = \begin{pmatrix} 0 & 1 \end{pmatrix}, \text{ hence } f(t, \theta) = c(t, \theta) \text{ when we only observe the nutrients} \\ \mathcal{C} = I_2, \text{ hence } f(t, \theta) = (N(t, \theta), c(t, \theta))^T \text{ when we observe both the} \\ \quad \text{bacteria and nutrients} \end{array} \right.$$

Here,  $I_2$  is an identity matrix with dimension 2.

Sensitivity analysis is used to analyze the sensitivity of the observation  $f$  to the change of the parameter  $\theta$ . If one observes a graph such as on the left side of Figure 5, we would expect that  $f$  is not sensitive to  $\theta_1$  and hence our ability to estimate  $\theta_1$  through  $f$  is very limited. But if we observe a graph such as on the right side of Figure 5, we would expect that  $f$  is sensitive to  $\theta_k$  and hence our possibility to estimate  $\theta_k$  through  $f$  is much better. We formalize this idea.

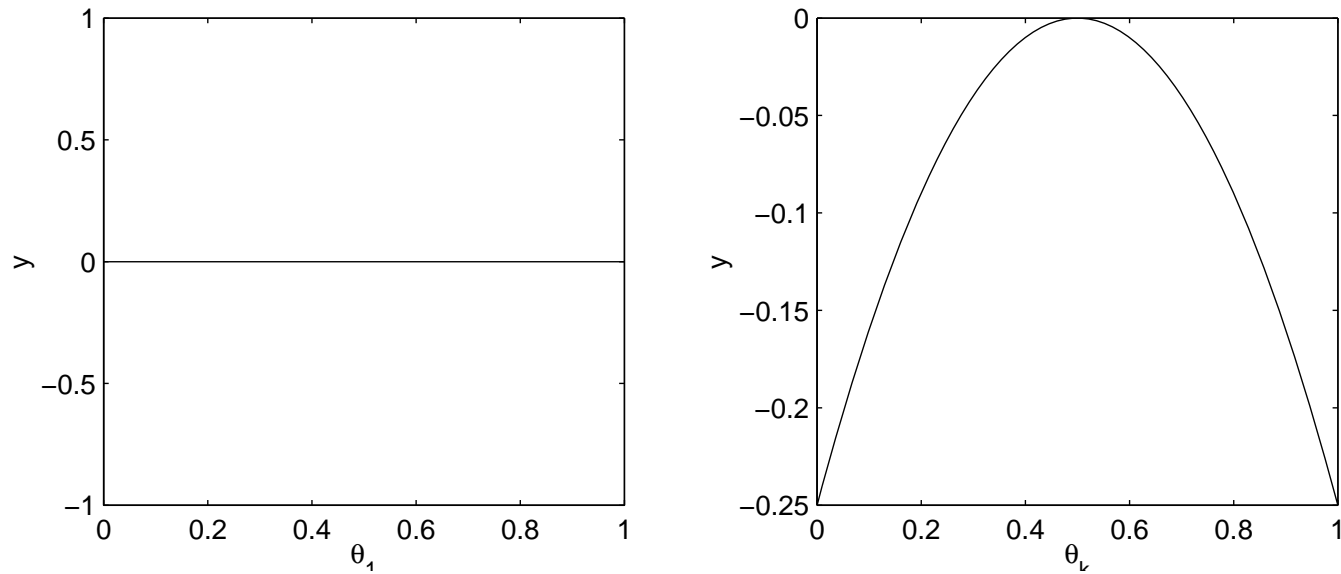


Figure 5: Sensitivity illustration

Under mild conditions that permits exchange of operators, we have  $\frac{\partial f}{\partial \theta} = \frac{\mathcal{C}x(t,\theta)}{\partial \theta} = \mathcal{C} \frac{\partial x(t,\theta)}{\partial \theta}$ . The quantity  $\frac{\partial x(t,\theta)}{\partial \theta}$  describes sensitivity of the solution of the dynamic system to the parameter  $\theta$ . This yields that the sensitivity of our observation is related to the sensitivity of the solution through the operator  $\mathcal{C}$ . Hence we only concentrate on understanding the sensitivity of the solution.

Assume our dynamic system is sufficiently smooth so that we can exchange the order of differentiation with respect to  $t$  and  $\theta$ . Taking derivative with respect to  $\theta$  on both sides of the system, we obtain

$$\frac{\partial(\frac{\partial x(t,\theta)}{\partial \theta})}{\partial t} = \frac{\partial(\mathcal{F}(x(t,\theta),\theta))}{\partial \theta} = \frac{\partial \mathcal{F}}{\partial x} \Big|_{(x(t,\theta),\theta)} \frac{\partial x(t,\theta)}{\partial \theta} \Big|_{(t,\theta)} + \frac{\partial \mathcal{F}}{\partial \theta} \Big|_{(x(t,\theta),\theta)}.$$

The initial condition will be

$$\frac{\partial x_0(\theta)}{\partial \theta} = \begin{cases} 0 & \text{if } x_0 \text{ does not depend on } \theta. \\ x'_0(\theta) & \text{if } x_0 \text{ does depend on } \theta. \end{cases}$$

Letting  $v_\theta(t) = \frac{\partial x(t, \theta)}{\partial \theta}$ , we can rewrite the above system as

$$\frac{dv_\theta(t)}{dt} = \mathcal{A}v_\theta(t) + \frac{\partial \mathcal{F}(x(t, \theta), \theta)}{\partial \theta}, \quad (4)$$

with initial condition

$$v_\theta(0) = \begin{cases} 0 & \text{if } x_0 \text{ does not depend on } \theta. \\ x'_0(\theta) & \text{if } x_0 \text{ does depend on } \theta. \end{cases}$$

Here,  $\mathcal{A} = \frac{\partial \mathcal{F}(x(t, \theta), \theta)}{\partial x}$ .

Equation 4 is called the *sensitivity equation* or *variational equation*.

It describes the sensitivity quantity  $v$ . It is worth noting that in statistical use,  $v$  is typically a matrix, where each row corresponds to a time point. The  $i$ th row of  $v$  would be

$$\left( \frac{\partial x(t_i, \theta)}{\partial \theta_1}, \frac{\partial x(t_i, \theta)}{\partial \theta_2}, \dots, \frac{\partial x(t_i, \theta)}{\partial \theta_p} \right).$$

We return to the chemostat model:

$$\dot{N}(t) = r(c(t))N(t) - qN(t)$$

$$\dot{c}(t) = q(c_0 - c(t)) - \frac{1}{y}r(c(t))N(t)$$

$$N(0) = N_0$$

$$c(0) = 0.$$

As noted in previous lectures, this model is unable to explain sustained oscillations, which have been observed in practical applications of the chemostat system.

As noted earlier, it was hypothesized by Andrews that the inadequacy of this model was due to inadequacies of the non-linearity term

$$r(c(t)) = \frac{R_{max}c(t)}{K_m + c(t)}.$$

However, upon examination of a whole new class of alternate

non-linearities, we saw that none of them was able to explain the observed sustained oscillations.

In a subsequent analysis by Thingstad and Langeland [TL], the authors posited that perhaps the *form* of the nonlinearity was not the difficulty; perhaps there were deeper underlying reasons:

1. An enzymatic controlled process
2. The cell cycle – it takes a certain amount of time for cells to divide.

In other words, a cell can immediately convert food, but more nutrient doesn't necessarily increase cell reproduction immediately.

This last point suggests that there exists a delay inherent to the system. A concept first explored by **Minorsky** [Min1, Min2, Min3] in the 1940's when he observed that the mechanism which would shift the ballast of a ship (in order to maintain stability afloat) would work well for relatively smooth waters, but for more turbulent waves, the mechanism would actually *cause* sustained oscillatory motion of the ship.

The system for this mechanism was at the time believed to be a simple harmonic oscillator,

$$m\ddot{x}(t) + c\dot{x}(t) + kx(t) = f(t),$$

which theoretically should have governed the mechanism, but Minorsky showed that there was a delay between the action of the mechanism and the reaction of the ship, during which time the mechanism would again attempt to correct, and so on. Thus,

Minorsky suggested a new system for the mechanism

$$m\ddot{x}(t) + c\dot{x}(t - \tau_1) + kx(t - \tau_2) = f(t),$$

which would still govern the system properly, but would account for the observed sustained oscillations. (Subsequent analysis for delay systems proved him correct!!)

Over the years, these ideas have been applied in many different instances, including the transportation of the NASA Space Shuttles. The shuttles are not designed for sustained stable flight, so after reentry from a mission, it is difficult to navigate them to a particular location. After the successful landing of a space shuttle at Edwards AFB in CA, the shuttle is must then be hoisted onto the back of a 747 jumbo jet, which transports it from the landing port in CA to the next launch port at Cape Kennedy in FL.

Engineers assumed that the “piggy-back” configuration was stable, but during one return route, the pilot of the 747 complained that the tail rudder was shaking wildly. This shaking was due to an unaccounted for delay between the disturbed air from the shuttle reaching the plane’s tail. Eventually the problem was solved by using a tail-fairing, which induced the air to bypass the 747’s tail.

Thingstad and Langland suggested that the growth rate of the bacteria was not instantaneously effected by  $c(t)$ , but rather by  $c(t - \tau)$  ( $c(t)$  with an incorporated delay). Thus, the underlying assumption is that increased nutrient does not result immediately in increased rate of growth perhaps because cell division is delayed.

This suggests that  $\left. \frac{dN}{dt} \right|_{growth} \propto r(c(t - \tau))$ , which results in the proposed new chemostat system

$$\begin{aligned}\dot{N}(t) &= r(c(t - \tau))N(t) - qN(t) \\ \dot{c}(t) &= q(c_0 - c(t)) - \frac{1}{y}r(c(t))N(t).\end{aligned}$$

It should be noted that while the first term is effected by the delay, the second term is not. This is because uptake of  $c(t)$  itself is not affected by the delay; the growth of bacteria,  $N(t)$ , is.

We note that this new system is no longer a differential equation. The reason is because if we were to consider the original initial conditions

$$N(0) = N_0, \quad c(0) = 0,$$

we would not be able to determine a present point for the system because it requires also  $c(-\tau)$ , which is outside the known range of values. Thus, we reclassify the system according to the *State of the System*, or the information needed to integrate forward, as a *Delay Differential Equation* (also called *Difference Differential Equation*, or *Functional Differential Equation*). We see that the *state* of this system is

$$(N(t), \{c(t - \xi)\}_{\xi \in [0, \tau]}),$$

the second part of which is actually a function on an interval, rather than a single value,  $c(0)$ , as in the original case. Thus, for all values of  $t \in [0, \tau]$ , we need values of  $c(t + \xi)$ , for all  $\xi \in [-\tau, 0]$ .

It turns out that this new model will produce the sustained oscillation as observed experimentally -see [TL]. In practice, how large does  $\tau$  need to be to break down stability? In actuality, *any* amount of  $\tau$  (for  $\tau > 0$ ) will produce the oscillations in these models (this is not true for all delay systems).

We consider briefly how this model might be simulated. We proceed using a tool called the *Method of Steps*, which will be explained by way of an example:

Example: Suppose we have a system defined as

$$\begin{aligned}\dot{x}(t) &= ax(t) + bx(t - \tau) \\ x(\xi) &= \varphi(\xi), \quad -\tau < \xi \leq 0.\end{aligned}$$

When we are solving this system on the interval  $[0, \tau]$ , the system is actually

$$\dot{x}(t) = ax(t) + b\varphi(t - \tau),$$

which we can solve by treating it as

$$\dot{x}(t) = ax + f,$$

which is routine to solve. Thus, we have a solution on the interval  $[0, \tau]$ . using this solution, we can “step” forward and continue solving.

Unfortunately, there are not always simple systems like this to solve. For example, if

$$\dot{x}(t) = ax(t) + \int_0^\tau P(\xi)x(t - \xi)d\xi,$$

then there is no way we can step forward as before. There are methods one may use to overcome this obstacle. One such method is like *Finite Elements*, which was developed for this problem by Banks and Kappel (see [BK]).

Finally we consider the new delay differential equation system for the chemostat:

$$\begin{aligned}\dot{N}(t) &= r(c(t - \tau))N(t) - qN(t) \\ \dot{c}(t) &= q(c_0 - c(t)) - \frac{1}{y}r(c(t))N(t).\end{aligned}$$

Upon close inspection, biologists in general are displeased with this system because it is based on the assumption that  $\tau$  is uniform for all cells present in the chemostat system. A modification of the model (to be discussed later) assumes a distribution of delays across the cells. That is, one posits that

$$P = \{p(\tau)\},$$

where the  $\tau$  are distributed according to some probability distribution, i.e.,  $\tau \sim P\{p(\tau)\}$ .

# References

- [Andrews] J. F. Andrews, A mathematical model for the continuous culture of microorganisms utilizing inhibitory substrates, *Biotechnology and Bioengineering*, **10** (1968), 707–723.
- [BanksLN] H. T. Banks, *Modeling and Control in the Biomedical Sciences*, Lecture Notes in Biomathematics, Vol. **6**, Springer-Verlag, Heidelberg, 1975.
- [BEG] H. T. Banks, S. L. Ernstberger and S. L. Grove, Standard errors and confidence intervals in inverse problems: sensitivity and associated pitfalls, *J. Inv. Ill-posed Problems*, **15** (2006), 1–18.
- [BK] H. T. Banks and F. Kappel, Spline approximations for functional differential equations, *J. Differential Equations*, **34**

(1979), 496–522.

- [BHMJA] L. Becks, F. M. Hilker, H. Malchow, K. Jrgens and H. Arndt, Experimental demonstration of chaos in a microbial food web, *Nature*, **435** (2005), 1226–1229.
- [BHWW] S. Bengtsson, J. Hallquist, A. Werker and T. Welander, Acidogenic fermentation of industrial wastewaters: Effects of chemostat retention time and pH on volatile fatty acids production, *Biochemical Engineering J.*, **40** (2008), 492–499.
- [BoyceDiPrima] W. E. Boyce and R. C. DiPrima, *Elementary Differential Equations and Boundary Value Problems*, J. Wiley & Sons, New York, 1965 (or one of the many later editions).
- [BH] G. E. Briggs and J. B. S. Haldane, A note on the kinetics of enzyme action, *Biochem. J.*, **19** (1925), 338–339.
- [BC] A. W. Bush and A. E. Cook, The effect of time delay and

growth rate inhibition in the bacterial treatment of wastewater, *J. Theoret. Biol.*, **63** (1976), 385–395.

[BW] G. J. Butler and G. S. K. Wolkowicz, A mathematical model of the chemostat with a general class of functions describing nutrient uptake, *SIAM J. Applied Mathematics*, **45** (1985), 137–151.

[Cap] J. Caperon, Time lag in population growth response of *isochrysis galbana* to a variable nitrate environment, *Ecology*, **50** (1969), 188–192.

[CN] A. Cunningham and R. M. Nisbet, Time lag and co-operativity in the transient growth dynamics of microalge, *J. Theoret. Biol.*, **84** (1980), 189–203.

[HHW] S. B. Hsu, S. Hubbell and P. Waltman, A mathematical theory for single-nutrient competition in continuous culture of

- micro-organisms, *SIAM J. Appl. Math.*, **32** (1977), 366–383.
- [JE] L. E. Jones and S. P. Ellner, Effects of rapid prey evolution on predator-prey cycles, *J. Math. Biol.*, **55** (2007), 541–573.
- [Mac] N. MacDonald, Time lag in simple chemostat models, *Biotechnol. Bioeng.*, **18** (1976), 805–812.
- [MM] L. Michaelis and M. Menten, Die kinetik der invertinwirkung, *Biochem. Z.*, **49** (1913), 333–369.
- [Min1] N. Minorsky, Experiments with activated tanks, *Trans. ASME*, **69** (1941), 735–747.
- [Min2] N. Minorsky, Self-excited oscillations in dynamical systems poessessing retarded actions, *J. Appl.Mechanics*, **9** (1942), A65–A71.
- [Min3] N. Minorsky, *Nonlinear Oscillations*, Van Nostrand, New York, 1962.

- [Monod] J. Monod, La technique de la culture continue: Theorie et applications, *Ann. Inst. Pasteur, Lille*, **79** (1950), 390–410.
- [NS] A. Novick and L. Szilard, Description of the Chemostat, *Science*, **112** (1950) 715–716.
- [PK] S. Pavlou and I. G. Kevrekidis, Microbial predation in a periodically operated chemostat: a global study of the interaction between natural and externally imposed frequencies, *Math Biosci.*, **108** (1992), 1–55.
- [Rub] S. I. Rubinow, *Introduction to Mathematical Biology*, John Wiley & Sons, New York, 1975.
- [SW] H. L. Smith and P. Waltman, *The Theory of the Chemostat*, Cambridge Univ. Press, Cambridge, 1994.
- [TL] T. F. Thingstad and T. I. Langeland, Dynamics of chemostat culture: The effect of a delay in cell response, *J. Theoret. Biol.*,

48 (1974), 149–159.

[WMB] H. A. Wichman, J. Millstein and J. J. Bull, Adaptive molecular evolution for 13,000 phage generations: a possible arms race, *Genetics*, **170** (2005), 19–31.

[DD] D. E. Dykhuizen and A. M. Dean, Evolution of specialists in an experimental microcosm, *Genetics*, **167** (2004), 2015–2026.

[WWE] L. M. Wick, H. Weilenmann and T. Egli, The apparent clock-like evolution of *Escherichia coli* in glucose-limited chemostats is reproducible at large but not at small population sizes and can be explained with Monod kinetics, *Microbiology*, **148** (2002), 2889–2902.