BIOMATHEMATICS

Q:1:- Describe the model Exponential Growth

From our approximation

$$KN(t)h = N(t+h) - N(t)$$

we have that

$$KN(t) = \frac{1}{h}(N(t+h) - N(t))$$

Taking the limit as $h \to 0$, and remembering the definition of derivative, we conclude that the right-hand side converges to $\frac{dN}{dt}(t)$. We conclude that N satisfies the following differential equation:

$$\boxed{\frac{dN}{dt} = KN}. \tag{2}$$

We may solve this equation by the method of *separation of variables*, as follows:

$$\frac{dN}{N} = K\,dt \;\Rightarrow\; \int \frac{dN}{N} = \int K\,dt \;\Rightarrow\; \ln N = Kt + c\,.$$

Evaluating at $t = 0$, we have $\ln N_0 = c$, so that $\ln(N(t)/N_0) = Kt$. Taking exponentials, we have:

$$\boxed{N(t) = N_0 e^{Kt}} \qquad \text{(exponential growth: Malthus, 1798)}$$

Bacterial populations tend to growth exponentially, so long as enough nutrients are available.

Q:2:- Describe the model Logistic Equation

We solve $\frac{dN}{dt} = rN\left(1 - \frac{N}{B}\right) = r\frac{N(B-N)}{B}$ using again the method of separation of variables:

$$\int \frac{B\,dN}{N(B-N)} = \int r\,dt\,.$$

We compute the integral using a partial fractions expansion:

$$\int \left(\frac{1}{N} + \frac{1}{B-N}\right) dN = \int r\,dt \;\Rightarrow\; \ln\left(\frac{N}{B-N}\right) = rt + c \;\Rightarrow\; \frac{N}{B-N} = \widetilde{c}e^{rt} \;\Rightarrow\; N(t) = \frac{\widetilde{c}B}{\widetilde{c} + e^{-rt}}$$

$$\Rightarrow\; \widetilde{c} = N_0/(B - N_0) \quad \Rightarrow \quad \boxed{N(t) = \frac{N_0 B}{N_0 + (B - N_0)e^{-rt}}}$$

We can see that there is a B asymptote as $t \to \infty$. Let's graph with Maple:

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with(plots):
f(t):=t->(0.2)/(0.2+0.8*exp(-t)):
p1:=plot(f(t),0..8,0..1.3,tickmarks=[0,2],thickness=3,color=black):
g:=t->1:
p2:=plot(g(t),0..8,tickmarks=[0,2],thickness=2,linestyle=2,color=black):
display(p1,p2);
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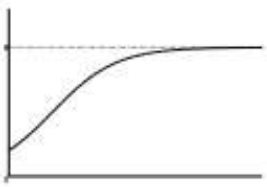


Q:3:-Describe the model Chemostat

total biomass: $N(t)\,V$ and total nutrient in culture chamber: $C(t)\,V$

biomass change in interval Δt due to growth:

$$N(t+\Delta t)V - N(t)V \;=\; [N(t+\Delta t) - N(t)]V \;=\; K(C(t))\,N(t)\,\Delta t\,V$$

so contribution to $d(NV)/dt$ is "$+K(C)NV$"

bacterial mass in effluent:
in a small interval Δt, the volume out is: $F \cdot \Delta t\ (\frac{m^3}{s}s =)m^3$
so, since the concentration is $N(t)\ g/m^3$, the mass out is: $N(t) \cdot F \cdot \Delta t\ g$
and so the contribution to $d(NV)/dt$ is "$-N(t)F$"

for $d(CV)/dt$ equation:
we have three terms: $-\alpha K(C)NV$ (depletion), $-C(t)F$ (outflow), and $+C_0F$ (inflow), $\rightsquigarrow$

$$\begin{aligned}\frac{d(NV)}{dt} &= K(C)NV - NF\\ \frac{d(CV)}{dt} &= -\alpha K(C)NV - CF + C_0F\,.\end{aligned}$$

Finally, divide by the constant V to get this system of equations on N, C:

$$\begin{aligned}\frac{dN}{dt} &= K(C)N - NF/V\\ \frac{dC}{dt} &= -\alpha K(C)N - CF/V + C_0F/V\end{aligned}$$

Q:4:- Describe the model Linearization

We wish to analyze the behavior of solutions of the ODE system $dX/dt = F(X)$ *near a given steady state* $\bar{X}$. For this purpose, it is convenient to introduce the displacement (translation) relative to $\bar{X}$:

$$\hat{X} = X - \bar{X}$$

and to write an equation for the variables $\hat{X}$. We have:

$$\frac{d\hat{X}}{dt} = \frac{dX}{dt} - \frac{d\bar{X}}{dt} = \frac{dX}{dt} - 0 = \frac{dX}{dt} = F(\hat{X} + \bar{X}) = \underbrace{F(\bar{X})}_{=0} + F'(\bar{X})\hat{X} + \underbrace{o(\hat{X})}_{\approx 0} \approx A\hat{X}$$

where $A = F'(\bar{X})$ is the *Jacobian* of F evaluated at $\bar{X}$.
We dropped higher-order-than-linear terms in $\hat{X}$ because we are only interested in $\hat{X} \approx 0$
(small displacements $X \approx \bar{X}$ from $\bar{X}$ are the same as small $\hat{X}$'s).

Recall that the Jacobian, or "derivative of a vector function," is defined as the $n \times n$ matrix whose (i, j)th entry is $\partial f_i/\partial x_j$, if f_i is the ith coordinate of F and x_j is the jth coordinate of x.

One often drops the "hats" and writes the above *linearization* simply as $dX/dt = AX$,
but it is extremely important to remember that what this equation represents:
it is an equation for the displacement from a particular equilibrium $\bar{X}$.
More precisely, it is an equation for *small* displacements from $\bar{X}$.
(And, for any other equilibrium $\bar{X}$, a different matrix A will, generally speaking, result).

For example, let us take the chemostat, after a reduction of the number of parameters:

$$\frac{d}{dt}\begin{pmatrix} N \\ C \end{pmatrix} = F(N, C) = \begin{pmatrix} \alpha_1 \frac{C}{1+C} N - N \\ -\frac{C}{1+C} N - C + \alpha_2 \end{pmatrix}$$

so that, at any point (N, C) the Jacobian $A = F'$ of F is:

$$\begin{pmatrix} \alpha_1 \frac{C}{1+C} - 1 & \frac{\alpha_1 N}{(1+C)^2} \\ -\frac{C}{1+C} & -\frac{N}{(1+C)^2} - 1 \end{pmatrix}.$$

In particular, at the point $\bar{X}_2$, where $\bar{C} = \frac{1}{\alpha_1 - 1}$, $\bar{N} = \frac{\alpha_1(\alpha_1\alpha_2 - \alpha_2 - 1)}{\alpha_1 - 1}$ we have:

$$\begin{bmatrix} 0 & \beta(\alpha_1 - 1) \\ -\dfrac{1}{\alpha_1} & -\dfrac{\beta(\alpha_1 - 1) + \alpha_1}{\alpha_1} \end{bmatrix}$$

where we used the shorthand: $\beta = \alpha_2(\alpha_1 - 1) - 1$. (Prove this as an exercise!)

Q:5:-Describe Interpreting.

Let us give an intuitive interpretation of σ.

We make the following "thought experiment":
suppose that we isolate a group of P infected individuals, and allow them to recover.

Since there are no susceptibles in our imagined experiment, $S(t) \equiv 0$, so $\frac{dI}{dt} = -\nu I$, so $I(t) = Pe^{-\nu t}$.

Suppose that the ith individual is infected for a total of d_i days, and look at the following table:

cal. days→ / Individuals	0	1	2		...	d_1	∞	
Ind. 1	X	X	X	X	X	X		$= d_1$ days
Ind. 2	X	X	X	X				$= d_2$ days
Ind. 3	X	X	X	X	X			$= d_3$ days
...								
Ind. P	X	X	X	X				$= d_P$ days
	$=I_0$	$=I_1$	$=I_2$	...				

It is clear that $d_1 + d_2 + \ldots = I_0 + I_1 + I_2 + \ldots$
(supposing that we count on integer days, or hours, or some other discrete time unit).

Therefore, the average number of days that individuals are infected is:

$$\frac{1}{P}\sum d_i \;=\; \frac{1}{P}\sum I_i \;\approx\; \frac{1}{P}\int_0^\infty I(t)\,dt \;=\; \frac{1}{P}\int_0^\infty e^{-\nu t}\,dt \;=\frac{1}{\nu}.$$

On the other hand, back to the original model, what is the meaning of the term "βSI" in dI/dt?

It means that $I(\Delta t) - I(0) \approx \beta S(0) I(0) \Delta t$.

Therefore, if we start with $I(0)$ infectives, and we look at an interval of time of length $\Delta t = 1/\nu$, which we agreed represents the average time of an infection, we end up with the following number of new infectives:

$$\beta(N - I(0))I(0)/\nu \;\approx\; \beta N I(0)/\nu$$

if $I(0) \ll N$, which means that each individual, on the average, infected $(\beta N I(0)/\nu)/I(0) = \sigma$ new individuals.

We conclude, from this admittedly hand-waving argument[19], that σ represents the *expected number infected by a single individual* (in epidemiology, the *intrinsic reproductive rate* of the disease).

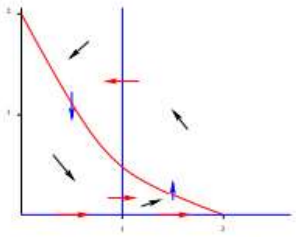
Q:6:-Describe Nucllcline Analysis.

For the previous example, $N = 2$, $\beta = 1$, $\nu = 1$, and $\gamma = 1$:

$$\begin{aligned} \frac{dS}{dt} &= -SI + 2 - S - I \\ \frac{dI}{dt} &= SI - I \end{aligned}$$

with equilibria at $(2, 0)$ and $(1, 1/2)$, the I-nullcline is the union of I=0 and S=1.

When $I = 0$, $dS/dt = 2 - S$,
and on $S = 1$, $dS/dt = 1 - 2I$,
so we can find if arrows are right or left pointing.

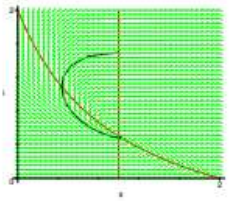


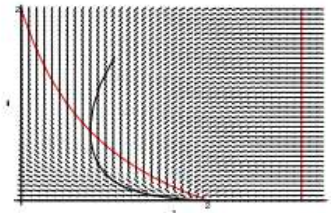
On the S-nullcline $I = \frac{(2-S)}{S+1}$ we have

$$\frac{dI}{dt} = \frac{(S-1)(2-S)}{S+1}$$

and therefore arrows point down if $S < 1$, and up if $S \in (1, 2)$. This in turn allows us to know the general orientation (NE, etc) of the vector field.

Here are computer-generated phase-planes[20] for this example as well as for a modification in which we took $\nu = 3$ (so $\sigma < 1$).





In the first case, the system settles to the positive steady state, no matter where started, as long as $I(0) > 0$.

In the second case, there is only one equilibrium, since the vertical component of the I-nullcline is at $S = 3/1 = 3$, which does not intersect the other nullcline. The disease will disappear in this case.

Q:7:-Describe a variation:STD's.

Suppose that we wish to study a virus that can only be passed on by heterosexual sex. Then we should consider two separate populations, male and female. We use $\bar{S}$ to indicate the susceptible males and S for the females, and similarly for I and R.

The equations analogous to the SIRS model are:

$$\begin{aligned}
\frac{d\bar{S}}{dt} &= -\bar{\beta}\bar{S}I + \bar{\gamma}\bar{R} \\
\frac{d\bar{I}}{dt} &= \bar{\beta}\bar{S}I - \bar{\nu}\bar{I} \\
\frac{d\bar{R}}{dt} &= \bar{\nu}\bar{I} - \bar{\gamma}\bar{R} \\
\frac{dS}{dt} &= -\beta S\bar{I} + \gamma R \\
\frac{dI}{dt} &= \beta S\bar{I} - \nu I \\
\frac{dR}{dt} &= \nu I - \gamma R .
\end{aligned}$$

This model is a little difficult to study, but in many STD's (especially asymptomatic), there is no "removed" class, but instead the infecteds get back into the susceptible population. This gives:

$$\begin{aligned}
\frac{d\bar{S}}{dt} &= -\bar{\beta}\bar{S}I + \bar{\nu}\bar{I} \\
\frac{d\bar{I}}{dt} &= \bar{\beta}\bar{S}I - \bar{\nu}\bar{I} \\
\frac{dS}{dt} &= -\beta S\bar{I} + \nu I \\
\frac{dI}{dt} &= \beta S\bar{I} - \nu I .
\end{aligned}$$

Writing $\bar{N} = \bar{S}(t) + \bar{I}(t)$ and $N = S(t) + I(t)$ for the total numbers of males and females, and using these two conservation laws, we can just study the following set of two ODE's:

$$\begin{aligned}
\frac{d\bar{I}}{dt} &= \bar{\beta}(\bar{N} - \bar{I})I - \bar{\nu}\bar{I} \\
\frac{dI}{dt} &= \beta(N - I)\bar{I} - \nu I .
\end{aligned}$$

Homework: Prove that there are two equilibria, $I = \bar{I} = 0$ and, provided that

$$\sigma\bar{\sigma} = \left(\frac{N\beta}{\nu}\right)\left(\frac{\bar{N}\bar{\beta}}{\bar{\nu}}\right) > 1$$

also $I = \frac{N\bar{N} - (\nu\bar{\nu})/(\beta\bar{\beta})}{\bar{\nu}/\bar{\beta} + N}$, $\bar{I} = \frac{N\bar{N} - (\nu\bar{\nu})/(\beta\bar{\beta})}{\nu/\beta + \bar{N}}$.

Furthermore, prove that the first equilibrium is unstable, and the second one stable.

Q:8:-

As an illustrative example, let us consider the following set of chemical reactions:

$$E + P \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} C \xrightarrow{k_2} E + Q, \qquad F + Q \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} D \xrightarrow{k_4} F + P, \tag{10}$$

which may be thought of as a model of the activation of a protein substrate P by an enzyme E; C is an intermediate complex, which dissociates either back into the original components or into a product (activated protein) Q and the enzyme. The second reaction transforms Q back into P, and is catalyzed by another enzyme (a phosphatase denoted by F). A system of reactions of this type is sometimes called a "futile cycle", and reactions of this type are ubiquitous in cell biology. The mass-action kinetics model is then obtained as follows. Denoting concentrations with the same letters (P, etc) as the species themselves, we have the following vector of species, stoichiometry matrix Γ and vector of reaction rates $R(S)$:

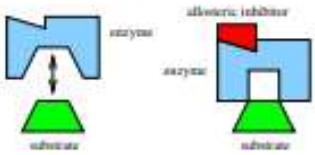
$$S = \begin{pmatrix} P \\ Q \\ E \\ F \\ C \\ D \end{pmatrix}, \quad \Gamma = \begin{pmatrix} -1 & 1 & 0 & 0 & 0 & 1 \\ 0 & 0 & 1 & -1 & 1 & 0 \\ -1 & 1 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & -1 & 1 & 1 \\ 1 & -1 & -1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & -1 & -1 \end{pmatrix} \quad R(S) = \begin{pmatrix} k_1 EP \\ k_{-1} C \\ k_2 C \\ k_3 FQ \\ k_{-3} D \\ k_4 D \end{pmatrix}.$$

From here, we can write the equations (9). For example,

$$\frac{dP}{dt} = (-1)(k_1 EP) + (1)(k_{-1} C) + (1)(k_4 D) = k_4 D - k_1 EP + k_{-1} C .$$

Q:9:-Describe Allosteric Inhibition.

In *allosteric inhibition*[28], an inhibitor does not bind in the same place where the catalytic activity occurs, but instead binds at a different *effector* site (other names are *regulatory* or *allosteric* site), with the result that the shape of the enzyme is modified. In the new shape, it is harder for the enzyme to bind to the substrate.



A slightly different situation is if binding of substrate can always occur, but product can only be formed (and released) if I is not bound. We model this last situation, which is a little simpler.
Also, for simplicity, we will assume that binding of S or I to E are independent of each other.
(If we don't assume this, the equations are still the same, but we need to introduce some more kinetic constants k's.)

A reasonable chemical model is, then:

$$E + S \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} ES \xrightarrow{k_2} P + E$$

$$EI + S \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} EIS$$

$$E + I \underset{k_{-4}}{\overset{k_4}{\rightleftharpoons}} EI$$

$$ES + I \underset{k_{-5}}{\overset{k_5}{\rightleftharpoons}} EIS$$

where "EI" denotes the complex of enzyme and inhibitor, etc.

It is possible to prove (see e.g. Keener-Sneyd's *Math Physiology*, exercise 1.5) that there results under quasi-steady state approximation a rate

$$\frac{dp}{dt} = \frac{V_{\max}}{1 + i/K_{\mathrm{i}}} \cdot \frac{s^2 + as + b}{s^2 + cs + d}$$

for some suitable numbers $a = a(i), \ldots$ and a suitably defined K_{i}.

Notice that the maximal possible rate, for large s, is lower than in the case of competitive inhibition.

One intuition is that, no matter what is the amount of substrate, the inhibitor can still bind, so maximal throughput is affected.

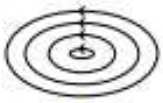
Q:10:-Describe Periodic Behaviour

Periodic behaviors (i.e, oscillations) are very important in biology, appearing in diverse areas such as neural signaling, circadian rythms, and heart beats.

You have seen examples of periodic behavior in the differential equations course, most probably the harmonic oscillator (mass spring system with no damping)

$$\begin{aligned} \frac{dx}{dt} &= y \\ \frac{dy}{dt} &= -x \end{aligned}$$

whose trajectories are circles, or, more generally, linear systems with eigenvalues that are purely imaginary, leading to ellipsoidal trajectories:



A serious limitation of such linear oscillators is that they are not *robust*:

Suppose that there is a small perturbation in the equations:

$$\begin{aligned} \frac{dx}{dt} &= y \\ \frac{dy}{dt} &= -x + \varepsilon y \end{aligned}$$

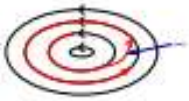
where $\varepsilon \neq 0$ is small. The trajectories are not periodic anymore!

Now dy/dt doesn't balance dx/dt just right, so the trajectory doesn't "close" on itself:

Depending on the sign of ε, we get a stable or an unstable spiral.

When dealing with electrical or mechanical systems, it is often possible to construct things with precise components and low error tolerance. In biology, in contrast, things are too "messy" and oscillators, if they are to be reliable, must be more "robust" than simple harmonic oscillators.

Another disadvantage of simple linear oscillations is that if, for some reason, the state "jumps" to another position[99] then the system will simply start oscillating along a different orbit and never come back to the original trajectory:



To put it in different terms, the particular oscillation depends on the initial conditions. Biological objects, in contrast, tend to reset themselves (e.g., your internal clock adjusting after jetlag).