INSA Lyon
Fall semester
2022-2023

BS-3-COMATH1-S1 - Biomathematics 1 :
Modelling biological dynamics
with ordinary differential equation

Introduction to modeling skills (2 h)
Part 1/2

Objectives :
The goal of this exercise sheet is to understand how mathematical models can be designed from biological observations and simplifying assumptions. Three applications : shark versus tuna, the Michaelis-Menten model, the Hill function.

Exercice 1. *Shark versus Tuna*
Consider a number S of sharks in a part of the observed zone. In the same zone, we consider a number T of tunas. Note that S and T depend on the time $t \geq 0$. At time $t = 0$, $S(0) = S_0 >$ and $T(0) = T_0 > 0$.
Shark and Tuna birth rates are respectively b_S and b_T, and their death rates are d_S and d_T.

1. Represent with a scheme (compartments) the fact that sharks by eating tuna increase their population but decrease the tuna one.
2. How would you write this in terms of mathematical modeling using ordinary differential equations.
3. How would you represent it on a graph with time on the $x-axis$ and population on the $y-axis$?
4. How would you represent it on a graph with tunas on the $x-axis$ and sharks on the $y-axis$?
5. What kind of behavior could you predict?

Assignment : I advise you to read the story of the Lotka-Volterra model

Exercice 2. *The Michaelis-Menten equation*
Leonor Michaelis (1875-1949, Germany) and Maud Menten (1879-1960, Canada) are at the origin of this work. The problem considered is the following : an enzyme E catalyses a substrate S to give a product P. In other words, E binds with S at a rate k_1 resulting in a complex named ES. This reaction is reversible and its inverse rate is k_2. The complex then gives the enzyme E and a product P at a rate k_3 (which could be reversible at rate k_4. They set up 2 main assumptions to simplify the problem :

(i) the product formation is not reversible.

(ii) the binding of E and S is much faster that the release of P which is called a pre-equilibrium assumption.

The objective of Michaelis and Menten was the to be able to measure estimate the rate at which P is formed (that is called the velocity of the reaction) in function of the concentration of the substrate S.

1. Write the chemical reaction and give a scheme to illustrate it with an without the assumptions.
2. Give an interpretation of assumptions (i) and (ii) in terms of the parameter values and reaction.
3. Let us focus first on the ES complex variation.
   (a) Determine the velocity of formation of the complex ES.
   (b) Determine the velocity of splitting of the complex ES.
   (c) Deduce from the two previous questions an equation for the variation of concentration of the complex ES with respect to time.
   (d) From assumption (ii), simplify this equation.
   (e) Find then a relationship between concentrations $[E]$, $[S]$ and $[ES]$. We denote the Michaelis constant as $K_M = (k_2 + k_3)/k_1$.
4. Because $[ES]$ is a transient event, it is quite difficult to get data from it. The goal here is to express it in terms of the substrate S.
   Denote $[E_T]$ the total concentration of enzyme in the experiment.
   (a) Give a relationship between $[E_T]$, $[E]$ and $[ES]$.
   (b) From previous result of questions 3.e. and the previous question, express $[ES]$ in terms of the substrate S.
   (c) Using the product P formation equation, express the velocity v of the P production in terms of $[ES]$ first, then in term of S.
   (d) Suppose that $[S]$ is very large (saturation of the substrate in the experiment). The velocity $v = \dfrac{dP}{dt}$ is then called v_{max}. Express v_{max} in function of $[E_T]$.
5. From the previous results, express v in terms of $[S]$, K_m and v_{max}.
6. Draw the graph of v with respect to $[S]$. What does happen if $S = k_m$?

Exercice 3. *Hill function*

Some enzymes (such as hemoglobin) do not follow the same saturating kinetics as the classic Michaelis-Menten's. One of them is called the Hill function and is the object of this exercise.

Let explain it with the example of cell division. Assume that the cell type we study has several receptors sensitive to division (mitosis) regulators. When a regulator binds a receptor this one becomes active. If all the dedicated receptors are turned on, mitosis can start.

We assume in the exercise that the cell response to the division signal is proportional to the number of activated receptors.

Denote

(a) $[G]$: the regulator concentration,

(b) $[R]$: free receptors concentration,

(c) $[L]$: activated receptor concentration,

(d) $[C]$: cell concentration,

as well as the total number of receptors :

$$[R]+[L]=m[C]$$

where m is the average number of receptors (specific to the regulators) by cell.
If n regulators are required to activate one receptor, then the relationship between receptors and regulators is given by

$$R+nG \rightleftharpoons L. \tag{1}$$

Remark : in general, $n=1,2,3$.

1. Draw figures to illustrate these mechanisms.
2. Use the law of mass action to write an equation dealing with relation (1).
3. We assume that the cell division rate, denoted F is proportional to the number activated receptor over the total number of receptors.
   (a) Write a formula for F.
   (b) From question 2., and formula (), deduce a formula of F in terms of $[G]$ and n.
   (c) Draw the graph of F with respect to $[G]$.
   (d) What should be the value of $[G]$ to get $F/2$?
   (e) What does happen when n goes to infinity? Represent it on a graph.