The synthesizing unit

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1 Introduction

All ecologists are familiar with Holling's disc equation, also called the type II functional response, which describes the intake rate of a forager as a hyperbolic function of food abundance. For ecologists, but not for mathematicians, a hyperbolic function means a function of the form $f(x) = x/(a+x)$. Hyperbolic functions have a horizontal asymptote when x goes to infinity, which in this case should be interpreted as the maximum intake rate that will be obtained when food is unlimited. The assumed mechanisms behind the disc equation are perhaps less widely known, but can easily be explained in terms of a service facility (in this case the forager) at which customers (here food items) arrive in some random manner. The terms servers and customers stem from an extensive theory of applied probability, known as queuing theory. In this chapter the idea is worked out that biological processes can be explained in terms of services facilities that produce or synthesise something. Such facilities are therefore named synthesising units.

2 Holling's disc equation

The synthesising unit underlying Holling's disc equation serves customers one at a time and each service takes some length of time and ends with the deliverance of a product (an ingestible piece of food). Customers that find the server busy at arrival depart. Under the assumption of very large but constant numbers of servers and customers in want of service, the rules of mass action can be applied. These rules imply that the rate at which customers arrive at an empty service unit is proportional to the product of the number of customers and the number of empty service units in the system. The rate at which servers finish their job and products are delivered is simply proportional to the number of busy servers. These assumptions are

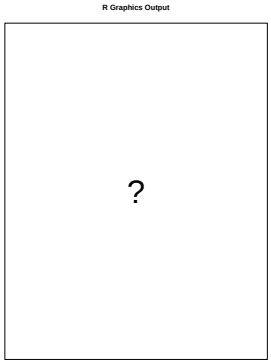

Figure 1: Customers arriving at an empty server are served one at a time. Each service takes some length of time and ends with the deliverance of a product, at which the server becomes empty again. Customers finding a busy server depart.

equivalent to the assumption that both the interarrival time and the service time are exponentially distributed.

The model can be written as a set of two differential equations that give the rate of change in the density of empty (S_0) and busy (S_1) servers:

$$\frac{\mathrm{d}S_0}{\mathrm{d}t} = -\frac{\mathrm{d}S_1}{\mathrm{d}t} = -\dot{b}XS_0 + \dot{k}S_1$$

where X is the density of customers that want to be served and $\dot{b}$ and $\dot{k}$ are constants (Fig. 1). These equations equal to zero at the (stable) equilibrium (sometimes called pseudo-equilibrium, because X is assumed constant), and this reveals $S_1^* = \frac{\dot{b}}{\dot{k}}XS_0$, where S_0^* and S_1^* refer to the equilibrium densities. It follows that the processing rate per server , which equals times the fraction of busy servers at equilibrium (this fraction is equivalent to the fraction of time a specific server is busy), is a hyperbolic function of the density of customers X

$$\dot{J} = \dot{k}\frac{S_1^*}{S_0^* + S_1^*} = \dot{k}\frac{\frac{\dot{b}}{\dot{k}}XS_0^*}{S_0^* + \frac{\dot{b}}{\dot{k}}XS_0^*} = \frac{\dot{b}X}{1 + \frac{\dot{b}}{\dot{k}}X} \tag{1}$$

Note that if the rate at which the customers arrive, which is given by $\dot{b}X$, is extremely large, then all servers will be busy all the time (if a customer has been served, a new customer immediately arrives) and the process rate reaches its maximum at $\dot{k}$, which can be interpreted as the 'servicing' rate.

Apparently, the approach is so obvious that it has popped up in biology under a variety of headings. Holling's disc equation dealing with animals and

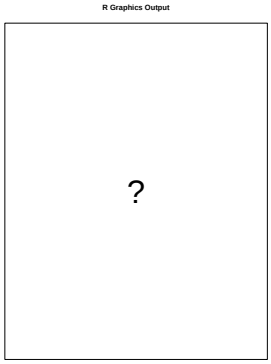

Figure 2: Holling's type II functional response equation, the Michaelis-Menten function and the Monod curve all describe the process rate as a hyperbolic function of the 'food' density. The maximum is given by the 'servicing' rate. The tangent at the origin equals the 'searching' rate. The food density at which the process rate equals half the maximum process rate is equivalent to the half-saturation constant, which equals the ratio of the servicing rate and the searching rate.

their food (where $\dot{b}$ is interpreted as the searching rate or area of discovery and $1/\dot{k}$ as the handling time), the Michaelis-Menten curve used in enzyme kinetics (with enzymes in the role of servers and substrates in the role of customers), or the Monod curve treating the growth of microbial populations, are all based on the same principle that being 'empty' and being 'busy' are events strictly separated in time. One might call it a conservation argument for time. In the latter two biological realms the resulting hyperbolic equation is often written in the form of

$$\dot{J} = \dot{k}\frac{X}{\frac{\dot{k}}{\dot{b}} + X} = \dot{J}_m\frac{X}{X_K + X}$$

where $\dot{J}_m$ is the maximum process rate (which equals the 'servicing' rate $\dot{k}$) and X_K, which is equal to $\dot{k}/\dot{b}$, is the so-called half-saturation constant, which can be interpreted as the density of X at which the process rate has a value half of the maximum (Fig. 2). Disadvantage of this representation compared to that of Holling is that it obscures the underlying idea of a server being either 'empty' or 'busy'.

The idea of considering biological processes in terms of facilities that serve customers plays a central role in DEB theory. The servers, which are often enzymes or complexes of enzymes, are called synthesising units. They bind substrate molecules (customers) to synthesise a product molecule. More

complex systems than the one described above can now be dealt with in a systematic way. Synthesising units may, for example, require one or more copies of one or more types of substrates in order to synthesise a product.

3 Parallel and sequential processing

Consider, for example, a synthesising unit that requires two molecules, one of substrate type A and one of substrate type B, to produce a product molecule C. Suppose further that the binding of one type of molecule does not interfere with that of the other, which may be called parallel processing. The density of empty units is given by S_{00}, the density of those with only A bound by S_{10}, with only B by S_{01} and if both A en B are bound by S_{11} (Fig. 3). The following differential equations apply:

$$\begin{aligned}
\frac{\mathrm{d}S_{00}}{\mathrm{d}t} &= -\left(\dot{b}_A X_A + \dot{b}_B X_B\right) S_{00} + \dot{k} S_{11} \\
\frac{\mathrm{d}S_{10}}{\mathrm{d}t} &= \dot{b}_A X_A S_{00} - \dot{b}_B X_B S_{10} \\
\frac{\mathrm{d}S_{01}}{\mathrm{d}t} &= \dot{b}_B X_B S_{00} - \dot{b}_A X_A S_{01} \\
\frac{\mathrm{d}S_{11}}{\mathrm{d}t} &= \dot{b}_B X_B S_{10} + \dot{b}_A X_A S_{01} - \dot{k} S_{11}
\end{aligned}$$

In equilibrium

$$\begin{aligned}
S^*_{00} &= \frac{1}{x_A + x_B} S^*_{11} \\
S^*_{01} &= \frac{x_A}{x_B} S^*_{00} = \frac{x_A}{x_B \left(x_A + x_B\right)} S^*_{11} \\
S^*_{10} &= \frac{x_B}{x_A} S^*_{00} = \frac{x_B}{x_A \left(x_A + x_B\right)} S^*_{11}
\end{aligned}$$

where x_A and x_B are scaled substrate densities, $x_A = \frac{\dot{b}_A}{\dot{k}} X_A = \frac{X_A}{X_{KA}}$ and $x_B = \frac{\dot{b}_B}{\dot{k}} X_B = \frac{X_B}{X_{KB}}$. As the equilibrium densities for all states of the server are expressed in terms of the density of the busy server, it is easy to arrive at the process rate per server (equivalent to the production rate of product C), which, as before, equals $\dot{k}$ times the fraction of busy servers

$$\begin{aligned}
\dot{J}_C &= \dot{k} \frac{S^*_{11}}{S^*_{00} + S^*_{01} + S^*_{10} + S^*_{11}} \\
&= \dot{k} \frac{1}{\left(x_A + x_B\right)^{-1} + x_A x_B^{-1} \left(x_A + x_B\right)^{-1} + x_B x_A^{-1} \left(x_A + x_B\right)^{-1} + 1}
\end{aligned}$$

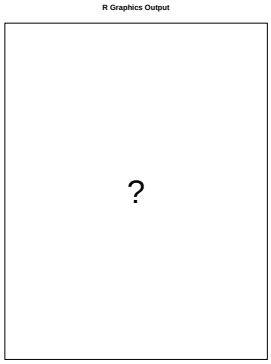

Figure 3: In parallel processing the binding of one type of molecule does not interfere with that of the other. A synthesising unit that requires two molecules, one of substrate type A and one of substrate type B, binds these two molecules in a random order. When both molecules are bound, the busy unit will produce a product molecule C after some length of time and then returns to the empty state.

This expression can (after some algebraic manipulation) be simplified to

$$\dot{J}_C = \dot{k}\frac{1}{1 + x_A^{-1} + x_B^{-1} - (x_A + x_B)^{-1}}$$

or

$$\dot{J}_C = \frac{1}{\dot{J}_{Cm}^{-1} + \dot{J}_A^{-1} + \dot{J}_B^{-1} - \left(\dot{J}_A + \dot{J}_B\right)^{-1}}$$

where $\dot{J}_{Cm} = \dot{k}$ is the maximum process rate, and $\dot{J}_A = \dot{b}_A X_A$ and $\dot{J}_B = \dot{b}_B X_A$ are the rates at which molecules of substrate A and B, respectively, arrive at each server. Thus, $\dot{J}_{Cm}^{-1}$ is the expected 'servicing' time, and $\dot{J}_A^{-1}$ and $\dot{J}_B^{-1}$ are the expected interarrival times of molecules of type A and B, respectively.

It can be shown (see also problem 4) that if both types of substrates can not be bound simultaneously (i.e. the binding of one can only start when the other is already bound) and when the order in which the molecules arrive is important, say first A and then B, (this is called sequential processing) that the process rate decreases to

$$\dot{J}_C = \frac{1}{\dot{J}_{Cm}^{-1} + \dot{J}_A^{-1} + \dot{J}_B^{-1}}$$

The expected processing time $\dot{J}_C^{-1}$ is then simply the sum of the expected 'servicing' time $\dot{J}_{Cm}^{-1}$ and the expected interarrival times of the molecules (here $\dot{J}_A^{-1}$ plus $\dot{J}_B^{-1}$).

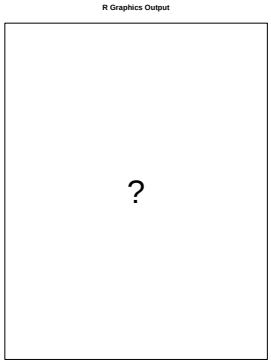

Figure 4: Contours of the production rate as a function of the rates at which molecules of substrate A and B, respectively, arrive, for a parallel processing SU that requires two molecules, one of substrate type A and one of substrate type B, to produce a molecule C (as in Fig. 3).

The parallel processing synthesising unit described above behaves very much like a minimum operator (Fig. 4), where it is assumed, following Liebig's law, that the processing rate is only limited by one type of substrate, the so-called limiting substrate

$$\dot{J}_C = \dot{J}_{Cm}^{-1} \max\left(\frac{X_A}{X_{KA}+X_A}, \frac{X_B}{X_{KB}+X_B}\right)$$

In ecology, use of the minimum operator in growth models has been popularised by Tilman[6]. The SU approach should, however, be preferred, not only for its elegance and greater realism, but also because it prevents numerical problems related to the stepwise change of the minimum operator, in further applications, for example in population models.

4 Handshaking protocols

In metabolic pathways intermediate products are formed by one unit (enzyme or set of enzymes), which another to produce a next product subsequently uses. The behaviour of the total complex, and thus the production rate of the end product, depends upon the way the exchange between the units is organised. What types of so-called 'handshaking' protocols are used for this organisation? Here two extremes are evaluated for the case of two units. The first unit is called the carrier (C), the second the synthesising unit (SU), and the complex the carrier-synthesising unit (CSU) complex (Fig. 5). The first

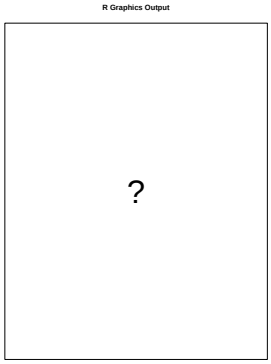

Figure 5: In a carrier-synthesising unit (CSU) complex, the carrier binds a substrate molecule X and produces an intermediate product Y. This product can get lost (if no empty synthesising units are available) or it can be bound by the synthesising unit which subsequently produces an end product Z. Various protocols by which the coupling between the deliverance and use of the intermediate product is organized are possible.

extreme is the 'closed' protocol, in which the carrier only passes its product to the SU if the SU is empty. In contrast, in the 'open' protocol the carrier releases its product irrespective of the state of the SU. The closed protocol thus requires an organisation (for example, a specific spatial configuration) that allows information exchange between the carriers and the synthesising units with respect to the state of the SUs. Such organisation is not needed in the open protocol. The production rate is, however, slightly higher in the closed protocol, as will be shown now.

The open protocol can be described by the following two differential equations

$$\begin{aligned} \frac{\mathrm{d}C_0}{\mathrm{d}t} = -\frac{\mathrm{d}C_1}{\mathrm{d}t} &= -\dot{b}XC_0 + \dot{k}_Y C_1 \left(S_0 + S_1\right) \\ \frac{\mathrm{d}S_0}{\mathrm{d}t} = -\frac{\mathrm{d}S_1}{\mathrm{d}t} &= -\dot{k}_Y C_1 S_0 + \dot{k}_Z S_1 \end{aligned}$$

where C_0 and C_1 are the number of carriers in the open and busy state, respectively, and S_0 and S_1 the number of SUs in the open and busy state, respectively. The total number of carriers is assumed constant and equals c and the constant number of SUs is equal to s. X is the substrate density and $\dot{b}$, $\dot{k}_Y$ and $\dot{k}_Z$ are constants. The term $\dot{b}XC_0$ gives the binding rate of the substrate, and $\dot{k}_Y C_1 \left(S_0 + S_1\right)$ indicates the rate at which the intermediate product Y is formed. Note that $\dot{k}_Y C_1$ would have been an alternative but entirely equivalent description, because the sum of S_0 and S_1 is constant. Only

the interpretation of the constant $\dot{k}_Y$ would have been slightly different. The intermediate product is utilised at a rate equal to $\dot{k}_Y C_1 S_0$, and finally the rate at which product Z is synthesised equals $\dot{k}_Z S_1$. The equations for the closed protocol are very similar, except that the rate at which the intermediate product Y is formed equals the rate at which it is utilised, i.e. $\dot{k}_Y C_1 S_0$. In equilibrium, the open protocol reveals

$$C_1^* = \frac{\dot{b}X}{s\dot{k}_Y}\left(c - C_1^*\right)$$

and

$$S_1^* = \frac{\dot{k}_Y C_1^*}{\dot{k}_Z}\left(s - S_1^*\right)$$

which gives

$$C_1^* = \frac{c\dot{b}X}{s\dot{k}_Y + \dot{b}X}$$

and

$$S_1^* = \frac{s\dot{k}_Y C_1^*}{\dot{k}_Z + \dot{k}_Y C_1^*}$$

Combining (the hyperbolic function of a hyperbolic function is again a hyperbolic function) gives

$$S_1^* = \frac{cs\dot{k}_Y\dot{b}X}{s\dot{k}_Y\dot{k}_Z + \left(\dot{k}_Z + c\dot{k}_Y\right)\dot{b}X}$$

and a rate of product synthesis of

$$\dot{J}_Z = \dot{k}_Z S_1^* = \left(\frac{1}{c}\frac{1}{\dot{b}X} + \frac{1}{cs}\frac{1}{\dot{k}_Y} + \frac{1}{s}\frac{1}{\dot{k}_Z}\right)^{-1}$$

For the closed protocol, the solution does not run as smoothly. Combining

$$C_1^* = \frac{c\dot{b}X}{\dot{k}_Y\left(s - S_1^*\right) + \dot{b}X}$$

and

$$S_1^* = \frac{s\dot{k}_Y C_1^*}{\dot{k}_Z + \dot{k}_Y C_1^*}$$

gives a quadratic equation of the form $aS_1^{*2} + bS_1^* - 1 = 0$, with the (relevant) solution $S_1^* = \left(-b + \sqrt{b^2 + 4ac}\right)/2a$, where $a = -\dot{k}_Z\left(sc\dot{b}X\right)^{-1}$ and $b =$

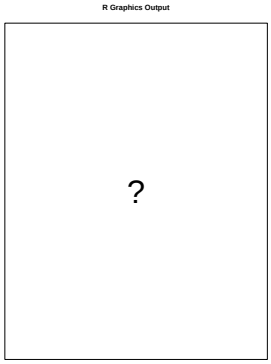

Figure 6: The production of a product Z as a function of the substrate X arrival rate, using the open (dotted line), and closed protocol (solid line). The approximated function for the closed protocol is given by a dashed line. Parameter values are ...

$-\dot{k}_Z \left(c\dot{b}X\right)^{-1} + \dot{k}_Z \left(sc\dot{k}_Y\right)^{-1} + s^{-1}$. This gives rise to a rather complicated function relating the synthesising rate of the end product Z to the substrate density X. Yet, under certain conditions an approximate solution is possible (using a Taylor expansion, see Appendix), giving a rate of product synthesis $\dot{J}_Z = \dot{k}_Z S_1^* \approx \dot{k}_Z \left(b + a/b\right)^{-1}$. Hence

$$\dot{J}_Z \approx \left(\frac{1}{c}\frac{1}{\dot{b}X} + \frac{1}{cs}\frac{1}{\dot{k}_Y} + \frac{1}{s}\frac{1}{\dot{k}_Z} - \left(cs\dot{k}_Z\dot{b}X\left(\frac{1}{c}\frac{1}{\dot{b}X} + \frac{1}{cs}\frac{1}{\dot{k}_Y} + \frac{1}{s}\frac{1}{\dot{k}_Z}\right)\right)^{-1}\right)^{-1}$$

which shows that the synthesising rate of the end product Z is larger (at least according to the approximation) under the closed protocol than under the open protocol (Fig. 6). The difference is, however, small, with the pleasant consequence that hyperbolic functions seem to be generally applicable.

5 Summary

Organisms use resources (substrates, food, light) to produce things (products, tissue, work). Here the synthesising unit is introduced as a unifying framework, enabling a systematic treatment of resource use by organisms.

6 Further reading

Kooijman [1] provides general solutions for more complex SUs. The treatment given above used the rules of mass action, assuming very large numbers of food items/substrate molecules and SUs. For small numbers a truly stochastic approach is required. The interested reader is referred to a general introduction to stochastic processes, for example Ross [4] or Syski [5]. Van der Meer and Smallegange [3] discuss the stochastic case for interfering foragers.

7 Problems

1 Holling's model can be extended by introducing a second type of 'food' item. Presume, however, that these items are inedible. It only costs time to 'handle' them. One might think of a filter-feeder whose feeding apparatus is temporarily clogged with inedible silt particles that have to be removed [2]. Write down the relevant differential equations and give the resulting functional response equation.

2 The resulting functional response equation from Problem 1 has been used as a descriptor of interference, with the inedible food items in the role of competitors that cost interference time at encountering them. Explain why this approach is invalid.

3 Consider two substitutable substrates, which both can be bound and processed (but not simultaneously), resulting in the synthesis of a product. The two substrates have different arrival rates and processing rates. Give the rate of product formation as a function of the arrival rates of the substrates.

4 Consider a synthesising unit that requires two molecules of substrate type A and two of type B, to produce a product molecule C. Consider further three alternative ways of processing: (a) sequential processing where the order is completely fixed, (b) sequential processing where the two molecules of each substrate type have to be bound directly after each other, but where the order of substrates is random (hence two sequences are possible AABB or BBAA), and (c) parallel processing. Which procedure yields the highest production rate, and which one the lowest? Give the production rate as a function of the substrate densities for all three alternatives.

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