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# A Consumer-Resource Description of Public-Goods Production in Microbes

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# Abstract

During the last century, microbes were studied as organisms that behave individually. However, over the recent years they have become an important system to study the evolution of collective behaviours in biological systems. The production of public goods, substances that are secreted to the external medium and provide benefit to cells in the vicinity, is one of these behaviours. The aim of this project is to propose a family of models that can describe the growth of microbial populations when they produce public goods. In particular, we will focus our description on those bacteria that use quorum sensing. Quorum sensing is a cell-to-cell communication mechanism that can regulate the expression of certain collective behaviours, like the production of public goods, in response to changes in population density. It is proposed a mean-field description based on consumer-resource ecological models. Therefore, as the simplest possible description, our formalism intends to be a first step to develop a more elaborated theory to study the production of public goods in microbes.

# Resumen

*Durante el siglo pasado, los microorganismos fueron estudiados como agentes que se comportan individualmente. Sin embargo, en estos últimos años se han convertido en un importante sistema para estudiar la evolución de los comportamientos colectivos en sistemas biológicos. La producción de bienes públicos, sustancias secretadas al medio externo y que proporcionan un beneficio a las células adyacentes, es uno de estos comportamientos. El objetivo de este trabajo es proponer una familia de modelos que pueda describir el crecimiento de poblaciones microbianas cuando producen bienes públicos. En particular, nos centraremos en aquellas bacterias que utilizan quorum sensing. El quorum sensing es un mecanismo de comunicación entre células que puede regular la expresión de ciertos comportamientos colectivos, como la producción de bienes públicos, en respuesta a cambios en la densidad de población. Se propone una descripción en campo medio, basada en modelos ecológicos consumidor-recurso. Por lo tanto, siendo esta la descripción más sencilla posible, nuestro formalismo pretende ser un primer paso para desarrollar una teoría más elaborada para el estudio de la producción de bienes públicos en microorganismos.*

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# Chapter 1

## Introduction

For decades, microbes were considered as organisms that behave individually, disregarding the possibility of more complex behaviours. However, in the last years their social behaviour has been recognized and increasingly studied [1]. Social behaviours are those which have fitness consequences for the actor and the recipient [2]. In particular, cooperation, as part of these social behaviours, is the one that provides a benefit to the recipient [2]. This situation opens the possibility for the existence of non-cooperators (also known as defectors, free-riders, non-producers or cheaters): individuals that do not pay the cost associated to the cooperation but get the benefit.

Among all the collective behaviours present in microbes, we will focus on the production of public goods (PGs), a costly resource that is available to others. Due to the nature of this process, producers are often considered cooperators [3]. More specifically, we are interested in those microbes that use a quorum sensing (QS) mechanism, as several species of bacteria [4]. Quorum sensing is a cell-to-cell communication mechanism that can regulate the expression of certain collective behaviours, such as the secretion of enzymes, surfactants, antimicrobial, virulence factors and siderophores, or phenomena as bioluminescence and biofilm formation [5].

It has been experimentally shown that bacteria with a QS mechanism behave collectively once the population density reaches a threshold [6]. The way in which bacteria monitor the cell density is through the so called ‘autoinducers’ (AIs). These molecules are released to the environment and their presence induces the production of more molecules within the population. As the bacterial culture grows, AIs are accumulated and once a threshold concentration is reached, the expression begins [6].

In this thesis we aim to provide the first steps towards a better understanding of causes and consequences of PG production in microbes. The main questions that we address are: a) when and why is activated the production of PGs, b) which are the differences between microbes that use a QS mechanism to regulate the production and those that do not, and c) which are the conditions needed to have coexistence between cooperators and cheaters. To this end, in Chapter 2 we describe the growth of microbes at a population level including the presence of PGs as an additional resource. In particular, we focus on bacteria that use a QS mechanism to regulate this production. Then, within the established QS framework, we look for expressions for the population density threshold and the value of the AI density threshold. After that, in Section 2.2 we study the differences between microbes that use a QS mechanism and those that do not, describing a particular case. Finally, in Chapter 3 we incorporate non-producers into the model to understand the conditions under which coexistence occurs between cooperators and

cheaters.

To simplify the mathematical description, we propose a non spatial family of models in which microbes only interact through the resources. To this end, we use classic consumer-resource (CR) models [7]. We look for a macroscopic description because of the complexity of the QS mechanism in a biochemical sense. A detailed description of the interactions between all the molecules involved in this process requires several approximations [8, 9] that are beyond our goal. Instead, we will introduce the QS mechanism in an effective way, considering, as I will explain later, the PGs as a new resource. Furthermore, the time scale used in our formalism will be the ecological time, and evolutionary processes such as mutations are neglected. Ecological time scales are between hours and days while the evolutionary time scale oscillates between months and years for microbes, depending on the species [10]. The mutations could change the behaviour of the strains (from cooperator to cheater or vice versa) and complicate the description.

In order to introduce our formalism, we need to take an overview of the CR models, including the intraspecific competition (between the same species/strains) and interspecific competition (between different species/strains).

## 1.1 Ecological models of competition

For many years, the main equations of this area have been the logistic equation [11] and those proposed by Volterra [12] and Lotka [13]. The logistic model (LM) is a growth model of intraspecific competition where the population grows until it reaches its maximum possible size (carrying capacity). The Lotka-Volterra (LV) competition model also accounts for interspecific competition between several species.

The logistic equation is

$$\dot{X} = r \left( 1 - \frac{X}{K} \right) X \quad (1.1)$$

where  $X$  is the size of the population,  $r$  is the growth rate and  $K$  is the carrying capacity. The equations for the LV competition model for two species are

$$\begin{aligned} \dot{X}_1 &= r_1 X_1 \frac{K_1 - X_1 - \alpha_{12} X_2}{K_1} \\ \dot{X}_2 &= r_2 X_2 \frac{K_2 - X_2 - \alpha_{21} X_1}{K_2} \end{aligned} \quad (1.2)$$

where  $X_1$  and  $X_2$  are the population size of the two species,  $K_1$  and  $K_2$  the corresponding carrying capacities,  $r_1$  and  $r_2$  the corresponding growth rates, and  $\alpha_{12}$  and  $\alpha_{21}$  ( $\alpha_{12}, \alpha_{21} > 0$  for LV competition model) are the *per capita* decline (per individual of species 2 and 1 respectively).

However, these models encapsulate the interactions between individuals in parameters that do not show biological constraints from the resources. For this reason, CR models were developed during the second half of the last century. They allow a more detailed representation of the population growth depending on the availability of resources.

### 1.1.1 Intraspecific competition for resources and Herbert model

All organisms need resources to grow, and once they are taken by one individual, these resources are unavailable to other organisms. Therefore, competition for resources is

something common in nature. CR models represent population growth and the consumption of resources when the amount of nutrients is a variable of the system. A usual model for describing this process in the case of intraspecific competition is [14, 7]:

$$\begin{aligned}\dot{X} &= f(R)X \\ \dot{R} &= -\beta f(R)X\end{aligned}\tag{1.3}$$

where  $X$  is the population density (individuals/volume),  $R$  the density of resources (mass/volume),  $f(R)$  is the growth rate or consumption function ( $\text{time}^{-1}$ ) and  $\beta$  is the resource quota (units of  $R$  contained in one unit of  $X$ ). Alternatively, we can work with the yield coefficient  $\beta^{-1}$  (population density produced by a unit of  $R$ ).

Both equations from (1.3) are related as

$$\dot{X} = -\frac{1}{\beta}\dot{R}\tag{1.4}$$

what gives us the conserved quantity

$$R(t) + \beta X(t) = R_0 + \beta X_0 = \text{constant}\tag{1.5}$$

since we have a closed system. It is the biomass available in the system. Using Eq. (1.5) and a linearization of  $f(R)$  we can recover the LM equation [15]. We start from

$$\begin{aligned}\dot{X} &= \alpha' R X \\ \dot{R} &= -\beta \alpha' R X\end{aligned}\tag{1.6}$$

where  $\alpha'$  is the growth rate per unit of density of resources. Substituting  $R(t)$  from (1.5) in the equation of  $\dot{X}$  in (1.4), we get:

$$\dot{X} = \alpha' (R_0 + \beta X_0 - \beta X) X = \frac{\alpha'}{\beta} \left( \frac{R_0}{\beta} + X_0 \right) \left( 1 - \frac{X}{\frac{R_0}{\beta} + X_0} \right) X = r \left( 1 - \frac{X}{K} \right) X\tag{1.7}$$

where  $K = R_0/\beta + X_0$  is the carrying capacity and  $r = \alpha' K/\beta$ . In this way, we obtain the parameters of the reduced system  $r$  and  $K$  as functions of the parameters related to the consumption of resources.

CR models provide a general framework where we can study a more realistic dynamics in which resources are relevant. In the LM case, we have not introduced more parameters respect to the original logistic equation. There are two,  $r$  and  $K$ , that are now defined by the new parameters  $\alpha'$  and  $\beta$ , although it is true we need an extra initial condition ( $R_0$ ). However, we have to consider a couple of points. In a more complicated system, as we will see later, the integration of the conserved quantity is not always easy. And on the other hand, we will need to fit the parameters of  $f(R)$  and  $\beta$  in experiments.

Equations (1.6) do not incorporate any process leading to population decays. The Herbert model introduces the maintenance rate (endogenous metabolism), that accounts for the effects of non-growth energy consumption processes, such as metabolism, production of extracellular molecules or cell motility [16, 17]. The model is as follows:

$$\begin{aligned}\dot{X} &= [f(R) - m] X = \left[ \frac{\alpha R}{K_R + R} - m \right] X \\ \dot{R} &= -\beta f(R) X = -\beta \frac{\alpha R}{K_R + R} X\end{aligned}\tag{1.8}$$

where  $f(R)$  is fixed as a Monod function [18],  $\alpha$  is the maximum growth rate,  $K_R$  is the half-saturation constant (when  $f(R = K_R) = \alpha/2$ ) and  $m$  is the maintenance rate that encapsulates all the costs. A detailed study of the dynamics of the Herbert model can be found in the Appendix B, where we also propose a general LM equation for the case of having non-growth costs.

The Herbert model is often described accompanied by the Pirt and Compromise models. The maintenance costs are in the biomass equation ( $\dot{X}$ ) in the Herbert model, while Pirt's model includes them in the resource equation ( $\dot{R}$ ). We will use Herbert model, first, because Pirt's model is not convenient. It predicts a negative value of resources in the stationary state, what it is not reasonable. And second, because if one considers that the maintenance term is consumed through resources when there are plenty of them, and through the biomass when resources are scarce, this model, known as Compromise model [17], turns out to be a rescaled version of the Herbert model.

### 1.1.2 Interspecific competition for resources

In interspecific competition, the abundance of one species inhibits the growth of other species. The main interest in this kind of competition is to study under which conditions we can find coexistence between some them.

The LV competition model introduced in the previous section is one of the simplest cases where we can find coexistence between two species. Mathematically, this property is shown by the existence of a non-trivial fixed point (non-zero population). I show below (Figure 1.1) an example of this situation for the LV equations.

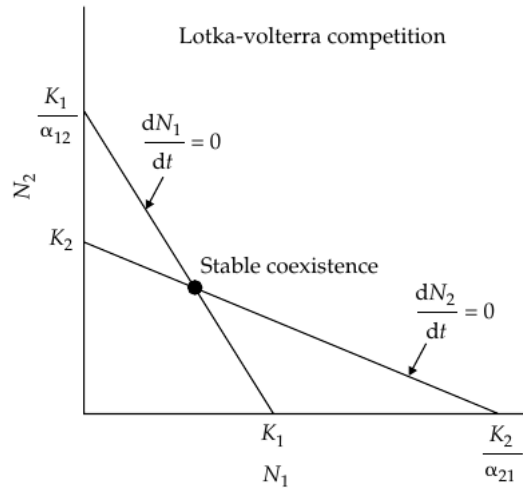


Figure 1.1: Nullclines in phase space of the Lotka-Volterra competition model for two species.  $N_1$  and  $N_2$  are the population of species 1 and 2 respectively. Figure obtained from [19].

From Figure 1.1 we can see that coexistence occurs when  $K_1 < K_2/\alpha_{21}$  and  $K_2 < K_1/\alpha_{12}$ , where the meaning of these parameters was defined in the previous section. With this result, it can be conclude that coexistence occurs if each species inhibits itself (with the intraspecific competition) more than it inhibits the other species.

But, as I said before, we want to focus on CR models, where parameters are directly related to observable traits of species and, therefore, are more easily measured. An



increase in the density of one species leads to an increase in the consumption of the limiting resources, lowering the levels of the resources and influencing the growth rates of other species. The simplest case is the interspecific competition with a single limiting resource [7, 15, 19]. In this situation we have  $n$  species sharing a single resource. The dynamical system is as follows:

$$\begin{aligned}\dot{X}_i &= [f_i(R) - m_i] X_i \\ \dot{R} &= h(R) - \sum_i^n \beta_i f_i(R) X_i\end{aligned}\tag{1.9}$$

where  $h(R)$  defines the habitat's rate of supply of the resources, and, in general,  $f_i(R)$  is a Monod function. It can be noticed that this set of equations is a generalization of the Herbert model.

Working with this description has a price: it is very complicated to obtain coexistence. This is called the competitive exclusion principle or  $R^*$  rule [20] and it reads: ' $n$  consumer species cannot coexist in a stable equilibrium state with fewer than  $n$  resources'.

In order to visualize this statement, we can study the case of two species with one resource:

$$\begin{aligned}\dot{X}_1 &= [f_1(R) - m_1] X_1 \\ \dot{X}_2 &= [f_2(R) - m_2] X_2 \\ \dot{R} &= h(R) - \beta_1 f_1(R) X_1 - \beta_2 f_2(R) X_2\end{aligned}\tag{1.10}$$

Independently of the number of terms in equation  $\dot{R}$ , the fixed points of the system only allow two possibilities. For both  $X_1$  and  $X_2$ , the two possible cases are either  $X_i^* = 0$  or  $f_i(R^*) = m_i$ . Since we are interested in the coexistence, we will not take  $X_i^* = 0$ . Hence,  $f_i(R^*) = m_i$  gives us two values of  $R^*$ , that we will call  $R_1^*$  and  $R_2^*$ . In general, one of the two  $R^*$ -values will be smaller, having  $R_1^* < R_2^*$  or  $R_2^* < R_1^*$ . In the first case, species 1 can sustain a stable population at a resource level that is too low for species 2, that goes extinct. In the second case, we have the opposite situation. Therefore, the species with the lowest value of  $R^*$  outcompetes the other, driving it to extinction.

Generalizing for  $n$  species, the two possible situations for fixed points are identical: either  $X_i^* = 0$  or  $f_i(R^*) = m_i$ . Now the  $R^*$  values can be ordered as  $R_1^* < R_2^* < \dots < R_n^*$ , surviving only the species with the lowest  $R^*$ -value. The only case in which we can find coexistence is when any of the  $R^*$ -values are equal, but this condition is a very specific case. It would mean that these species have the same parameters, so either they are the same species or they sustain the population in the same way with the same costs.

From this point, the literature includes a wide variety of possible solutions to the coexistence problem. One obvious case is to introduce more resources in the model [19]. However one can condense all the resources in only one as the total available resources, unless they follow different dynamics and each one needs a different differential equation. Other possibilities contemplate population density dependence in the growth rates [21] or heterogeneity in the limiting environmental factors such as temperature, salinity or soil pH in addition to a single resource [19]. This heterogeneity can be spatial [7] or temporal [22] or both [23]. In our description, we try to solve the problem of the coexistence between the cheater and the cooperator strains including a second resource derived from public good production, in such a way that we can obtain coexistence under some conditions for the parameters.

# Chapter 2

## A family of models for PG production regulated by QS

The aim of our formalism is to describe the growth of microbial populations when they produce public goods, in the context of consumer-resources models. Now we will focus on the case that PG production is regulated by QS. We leave aside the situation where the production is unconditional (no QS mechanism), that will be explained in section 2.2.

We start presenting the formalism for a single strain of cooperative bacteria, that is the wild type strain. The dynamical system is as follows:

$$\begin{aligned}\dot{X} &= f(R)X - m_1X + (g(Q)X - m_2X)\theta(R_{cr} - R) \\ \dot{Q} &= [km_2X - qg(Q)X]\theta(R_{cr} - R) \\ \dot{R} &= -\beta f(R)X\end{aligned}\tag{2.1}$$

Let's explain all the terms one by one.

- The variables:  $X$  is the population density of cooperators,  $R$  the density of resources from the medium (the initial food for bacteria) and  $Q$  the density of resources from PGs. The first resource  $R$  is a limiting resource, while we will consider that  $Q$  could be obtained by bacteria *ad infinitum*. This means that for the time scales that we study (ecological time), the concentration of substances degraded by the PGs is much higher than the initial available resources from the media.
- The functions:  $f(R)$  and  $g(Q)$  are the growth rates or consumption functions of  $R$  and  $Q$  respectively.  $\theta(R_{cr} - R)$  is the step function that introduces the dynamics of the PG production.
- The parameters:  $\beta$  and  $q$  are the corresponding resource quotas, and  $m_1$  is the initial metabolic cost before the activation of PG production, including the production of AIs.  $m_2$  would be the additional cost that appears due to the new production of PGs and AIs after the activation, so  $m_2 > m_1$ .  $k$  is the resource quota of production from the PGs by bacteria. It shows us the fraction of energy from the cost  $m_2$  that was invested and ended as resource  $Q$  after the whole process of generation.

The set of equations (2.1) is a piecewise smooth dynamical system. We begin from the Herbert model (Eq. (1.8)), reproducing the growth of populations with a maintenance cost. Then we introduce the PGs as an effective resource using a new differential equation, where the PGs are not the elements that bacteria consume. We will work with those PGs

that are enzymes, released to the environment by cells to degrade complex molecules into smaller ones that can be used by them. For instance, carbon sources as disaccharide are degraded into monosaccharides, used as nutrient to promote growth.

The second part of the dynamical system is included in the dynamics by a step function. This approximation is known as the logic approximation in system biology, where it is used to simplify calculations for the activation of gene transcription [24] and the step function approximates an abrupt behaviour. There are biochemical and theoretical evidences that indicate that the QS activation function is abrupt, like a pulse [25]. The activation comes from the change of state of bacteria from down-regulated to up-regulated [8, 6], that is, before and after the activation of the cooperative behaviour respectively. These names (up- and down-regulated) come from the fact that before the threshold, the individuals produce fewer signalling molecules than after the threshold.

The threshold that will appear in the step function is the critical value of the resources  $R_{cr}$ . However, the variable that should be used as a threshold parameter is the population density  $X$ . We have to remember that the regulation of cooperative behaviours with a QS mechanism is activated with a cell density threshold. Using the  $R_{cr}$  as the threshold is just a matter of facilitating the work. Besides, we will be able to relate both variables in the cases that we study, so we will obtain the expression of the critical value of the population. However, it is also important to remark that there are some evidences that relate starvation with the QS response [26].

In order to study the dynamical systems of our family of models, we will follow the next steps:

1. Find the fixed points that produce non-zero values of population (and coexistence in the last section).
2. Study the stability of the fixed points.
3. Obtain conserved quantities (for those systems that allow us to do it) in order to relate the critical values.
4. Reduce the dimension of the dynamical system using the conserved quantity.

The last step has an explanation. We have observed that the fixed points we look for appear as a line of marginal fixed points, characterized by a zero eigenvalue. The marginality of these fixed points makes them to depend on the initial conditions. This is necessary, since the final population density in an experiment will depend on the initial density of resources and bacteria. Using the conserved quantity, we will see that we can obtain a reduced dynamical system where the marginal fixed points shrinks to a single fixed points. These single fixed points of the reduced system keep the information from the original fixed points, eliminating the eigenvalue equal to zero.

To make it clearer, we recall the case of the LM system (Eq. (1.6)) described in the introduction. Studying the nullclines, we can obtain a line of marginal stable fixed points when  $R^* = 0$  (with eigenvalues  $\lambda_1 = 0$  and  $\lambda_2 = -\alpha'\beta X^*$ ), avoiding the case  $X^* = 0$ . Integrating the conserved quantity, we found a relation between  $R$  and  $X$ , used in Eq. (1.7) to reduce the system. In this way, we obtained the well-known logistic equation, and the marginal stable fixed points change to a stable fixed point for  $X^* = K = X_0 + R_0/\beta$  ( $r > 0$  in our case). Therefore, we can obtain a reduced dynamical systems where the information of the resources is encapsulated in the parameters of the new system, and

the fixed points that we want are totally stable. We will be able to apply this last step in a couple of situations, obtaining for example, a generalization of the logistic equation with a maintenance rate from the Herbert model.

The conditions needed to reduce a general dynamical system in 2D are shown in Appendix A.

## 2.1 Results

We begin the analysis of the dynamical system in the down-regulated phase, that is, when  $R > R_{cr}$  (or  $X < X_{cr}$ ). This phase is described by the Herbert model:

$$\begin{aligned}\dot{X} &= [f(R) - m_1] X \\ \dot{R} &= -\beta f(R) X\end{aligned}\tag{2.2}$$

The complete study of this model is done in the Appendix B and we only show some of the results here.

The simplest case is when  $f(R)$  is linear. The way in which we can explain this kind of function is through the Monod function  $f(R) = \alpha R / (K_R + R)$ , where  $\alpha$  is the maximum growth rate and  $K_R$  is the half-saturation constant. Taking  $K_R \gg R$ , the function can be approximated as  $f(R) \simeq \alpha R / K_R = \alpha' R$ . This approximation is consistent with the fact that  $R$  is the limiting resource and it could be very small from the beginning. Therefore, the system (2.2) becomes

$$\begin{aligned}\dot{X} &= [\alpha' R - m_1] X \\ \dot{R} &= -\beta \alpha' R X\end{aligned}\tag{2.3}$$

This is very similar to the LM dynamical system explained before, but introducing  $m_1$  seems that can give us a more realistic behaviour. We find a line of marginal fixed points for  $X^* = 0$ , so our population always disappears at the end of the dynamics. However,  $X$  presents a maximum, appearing when  $R = R_M = m_1 / \alpha'$  ( $d^2 X / dt^2 < 0$  for  $R = R_M$ ). The initial condition  $R_0 > R_M$  has to be fulfilled to see this behaviour (Figure 2.1(a)). Otherwise, we will not have a maximum and population will decay directly until zero (Figure 2.1(b)). In addition, we find the first constraint. The fact that  $R \ll K_R$  implies  $m_1 < \alpha$  to avoid contradictions, because  $m_1 > \alpha$  would yield  $R_M > K_R$ .

Henceforth, this maximum will be interpreted as the critical value of the population,  $R_M = R_{cr}$ . This election is supported by the results from [26, 27]. The authors from these references state that the regulation of PGs production by QS generally occurs in the transition from the exponential to the stationary phase. Actually, the threshold of our description could be before or after the maximum, but taking this point, we simplify the problem a lot. However, it may be thought that the initial model should be like the LM equations in order to have an exponential phase and a stationary phase. But that is why we use the step function. We separate the stationary phase from the exponential growth including the second resource only for the last part. And using the Herbert model at the beginning, we include a reason to activate the production. It is a matter of starvation: once the population reaches the threshold, the population will decrease, so if bacteria do not activate the production of PGs at this point, they will die.

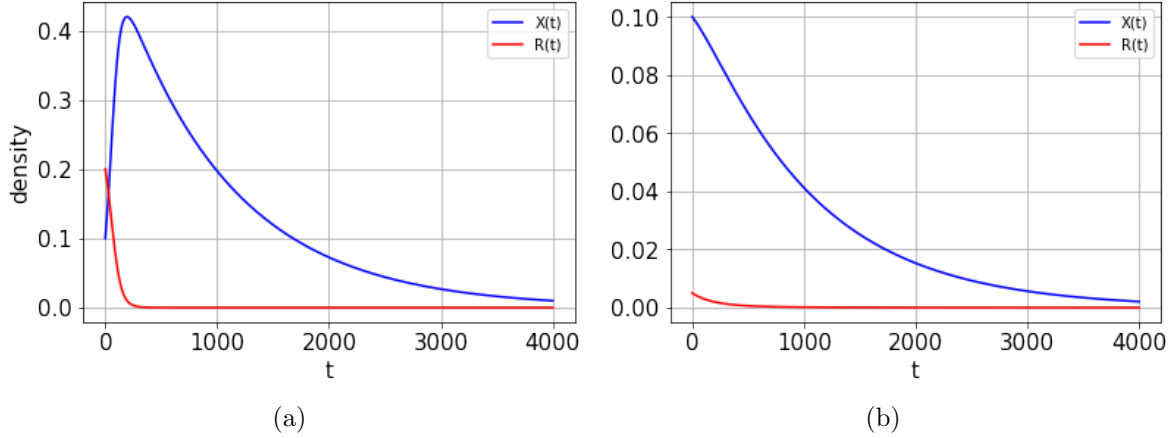


Figure 2.1: Dynamics of  $X$  and  $R$  in Eq. (2.3) when: (a)  $R_0 > R_M$  and (b)  $R_0 < R_M$ . The parameters and initial conditions used in arbitrary units are:  $\alpha = 0.1$ ,  $\beta = 0.5$ ,  $m_1 = 0.001$ ,  $K_R = 1$ ,  $R_M = m_1/\alpha' = 0.01$ ,  $X_0 = 0.1$ ,  $R_0 = 0.2$  in (a) and  $R_0 = 0.005$  in (b).

Returning to Eq. (2.3), we can obtain a relation between  $X$  and  $R$  through a conserved quantity. Dividing and integrating the equations, we find that:

$$X(t) + \frac{R(t)}{\beta} - \frac{m_1}{\beta\alpha'} \ln(R(t)) = X_0 + \frac{R_0}{\beta} - \frac{m_1}{\beta\alpha'} \ln(R_0) \quad (2.4)$$

The conserved quantity itself does not have a clear biological interpretation because the dynamical system is not complete. The biomass invested in those processes represented by the maintenance rate disappears and we do not have any equation to see where. We have to introduce a third equation to understand the role of the conserved quantity.

This third equation needs to be related to the maintenance rate  $m_1$  and we know that only part of this cost is expended in the production of AIs. We can introduce the dynamics of the AIs just using a parameter that gives the part of  $m_1$  invested in these molecules. The whole dynamical system would be

$$\begin{aligned} \dot{X} &= [\alpha'R - m_1]X \\ \dot{R} &= -\beta\alpha'RX \\ \dot{A} &= \delta m_1 X \end{aligned} \quad (2.5)$$

where  $A$  is the density of AIs and  $\delta$  is the quota of the maintenance rate invested in the production of AIs. In our formalism, we are going to consider the mean lifetime of the molecules much longer than the ecological time of the experiments. Hence, the lifetime can be approximated as infinite, and we neglect any possible ‘death rate’ for AIs. Our description is thought for laboratory experiments. These laboratory experiments are prepared to enable the growth of bacteria, so the AIs are necessarily accumulated [8].

This dynamical system is equivalent to the SIR mean-field model [28], where the susceptible population ( $S$ ) would be the resources rescaled by  $\beta$ , the infected ( $I$ ) would be the microbes and the recovered ( $R$ ) would be the AIs rescaled by  $\delta$ . For example, the SIR mean-field model has a conserved quantity that is the total size of the population,

$S + I + R = \text{constant}$ . In our case, we can obtain the corresponding quantity multiplying the differential equations by some factors:

$$\delta\beta\dot{X} + \delta\dot{R} + \beta\dot{A} = 0 \Rightarrow X + \frac{R}{\beta} + \frac{A}{\delta} = B = \text{constant} \quad (2.6)$$

This conserved quantity,  $B$ , is a constant with a real biological meaning: it is the total biomass available in the system, composed out of biomass from individuals, resources and biomass expended in maintenance, with the corresponding quotas. This result does not depend on the form of  $f(R)$ , so although we are studying the linear case, the total available biomass is always conserved.

Now, we can understand the role of the conserved quantity of Eq. (2.4). Dividing  $\dot{X}/\dot{R}$  and integrating we obtain a part of  $B$ , while the other part is obtained dividing  $\dot{R}/\dot{A}$ . This last operation leads to the following relation:

$$\frac{A(t)}{\delta} + \frac{m_1}{\beta\alpha'} \ln(R(t)) = \frac{A_0}{\delta} + \frac{m_1}{\beta\alpha'} \ln(R_0) \quad (2.7)$$

Adding Eq. (2.4) and (2.7), we recover  $B$ . In addition, we can use Eq. ((2.7)) at the critical value of the resources to obtain the threshold of the AIs:

$$A^* = A_0 + \frac{\delta m_1}{\beta\alpha'} \ln\left(\frac{R_0\alpha'}{m_1}\right) \quad (2.8)$$

This threshold appears when the velocity of production of AIs ( $\dot{A}$ ) is maximum:  $d^2A/dt^2|_{X_{cr}} = \delta m_1 dX/dt|_{X_{cr}} = 0$ , where  $A$  pass from convex to concave. In this sense, bacteria would activate the production of PGs when they perceive that the rate at which AIs are produced decreases. Using the conserved quantities, we can even obtain a dynamical system of a single equation for the dynamics of the AIs:

$$\dot{A} = \frac{\delta m_1}{\beta} \left[ \beta X_0 + R_0 \left( 1 - e^{-\frac{\beta\alpha'}{\delta m_1}(A-A_0)} \right) \right] - m_1(A - A_0) \quad (2.9)$$

All the previous results can be generalized to the case of the Monod function  $f(R) = \alpha R/(K_R + R)$ , obtaining the following relations:

$$\begin{aligned} X &= X_0 + \frac{1}{\beta} \left( 1 - \frac{m_1}{\alpha} \right) (R_0 - R) - \frac{m_1 K_R}{\alpha\beta} \ln\left(\frac{R_0}{R}\right) \\ A &= A_0 + \frac{\beta\alpha K_R}{\delta m_1} \ln\left(\frac{R_0}{R}\right) + \frac{\beta\alpha}{\delta m_1} (R_0 - R) \end{aligned} \quad (2.10)$$

and the critical values are obtained substituting the critical value of the resource that makes  $\dot{X} = 0$ :  $R_{cr} = K_R m_1 / (\alpha - m_1)$ . Here we see the constraint  $\alpha > m_1$  in a clearer way. It is needed in order to have  $R_{cr} > 0$ .

Coming back to the system (2.3), we can employ the first conserved quantity of Eq. (2.4) to reduce the number of equations to only one, as in the case of the LM equations. We have been able to do it using the Lambert  $W$  function  $W(x)$  [29], where it is the inverse of the expression  $W(x)e^{W(x)} = x$ , allowing to solve a number of transcendental

equations related to that expression. The derivation is explained in Appendix B. The reduced dynamical system is:

$$\begin{cases} \dot{X} = -m_1 \left[ W_{-1} \left( \left( -\frac{R_0}{R_{cr}} \right) e^{-\frac{R_0}{R_{cr}}} e^{\frac{\alpha'\beta}{m_1}(X-X_0)} \right) + 1 \right] X & R > R_{cr} \\ \dot{X} = -m_1 \left[ W_0 \left( \left( -\frac{R_0}{R_{cr}} \right) e^{-\frac{R_0}{R_{cr}}} e^{\frac{\alpha'\beta}{m_1}(X-X_0)} \right) + 1 \right] X & R < R_{cr} \end{cases} \quad (2.11)$$

where the subscripts of the Lambert  $W$  function indicate the branch in which it is acting. We have considered this set of equations as a generalization of the logistic equation. It reproduces exactly the dynamics of the 2D dynamical system changing the line of marginal fixed points into a single fixed point, as in the logistic case, and it allows us to recover the logistic equation in the limit of  $m_1 \rightarrow 0$ .

### 2.1.1 Production of public goods

Once the population density has reached the threshold ( $R < R_{cr}$ ), bacteria start producing PGs, introducing a new equation for resources  $Q$  in the dynamical system. The equations are:

$$\begin{aligned} \dot{X} &= [f(R) - m_1 + g(Q) - m_2] X \\ \dot{Q} &= km_2 X - qg(Q)X \\ \dot{R} &= -\beta f(R)X \end{aligned} \quad (2.12)$$

where we incorporate the new costs due to the production of PGs and AIs in the up-regulated state through  $m_2$ , and the second resource available due to PG production through  $km_2$ .

When we seek the fixed points  $(X^*, Q^*, R^*)$ , we find two possibilities to get  $\dot{R} = 0$ :  $X^* = 0$  or  $R^* = 0$ . The later comes from the fact that  $f(R^*) = 0$  only when  $R^* = 0$  because there cannot be a growth rate when there is no resource (like linear or Monod functions). For  $X^* = 0$ , the population become extinct. As we are interested in a state where  $X^* \neq 0$ , we take  $R^* = 0$ . It is reasonable to take  $R^* = 0$  since it is easier for microbes to consume this resource. Besides, having passed the threshold of  $R = R_{cr}$  our system will remain in the PG production state because  $R$  will not increase.

Taking  $R^* = 0$ , the fixed points that do not imply  $X^* \neq 0$  are given by

$$\begin{aligned} \dot{X} = 0 &\Rightarrow g(Q^*) = m_1 + m_2 \\ \dot{Q} = 0 &\Rightarrow g(Q^*) = \frac{km_2}{q} \end{aligned} \quad (2.13)$$

In order to have fixed points,  $g(Q^*)$  must be equal to both expressions in (2.13). Therefore, we need a relation between the parameters:

$$q = k \frac{m_2}{m_1 + m_2} \quad (2.14)$$

This relation is interpreted as a balance between the production and the consumption of PGs in the stationary regime. The amount of resource  $Q$  needed to increase in one unit the population density,  $q$ , is the amount of density of resources  $Q$  produced by bacterium,  $k$ , weighted by the fraction of the cost that corresponds to  $m_2$ .

Under this condition, these fixed points are a line of marginal stable ones, as we can see from their eigenvalues:

$$\lambda_1 = 0 \quad \lambda_2 = -q(g')^* X^* \quad \lambda_3 = -\beta(f')^* X^* \quad (2.15)$$

where  $(f')^* = \left. \frac{\partial f(R)}{\partial R} \right|_{R^*} > 0$  and  $(g')^* = \left. \frac{\partial g(Q)}{\partial Q} \right|_{Q^*} > 0$  for any monotonically increasing function. Any growth rate that depends on the resources will fulfill these conditions, since the more amount of resources, the higher possibilities of growing.

One of the goals of this project is to reproduce, at least qualitatively, some experimental figures for the growth of bacteria. The main experimental reference has been the one from Diggle [27] where they studied the fitness and coexistence of different strains of *Pseudomonas aeruginosa*. This bacterium is an opportunist pathogen responsible of a large number of infections.

We are going to focus on the figure shown below (Figure 2.2). It shows the dynamics of the population density of the different strains. It was carried out in a LB medium, where bacteria initially have available resources before the activation of the QS mechanism.

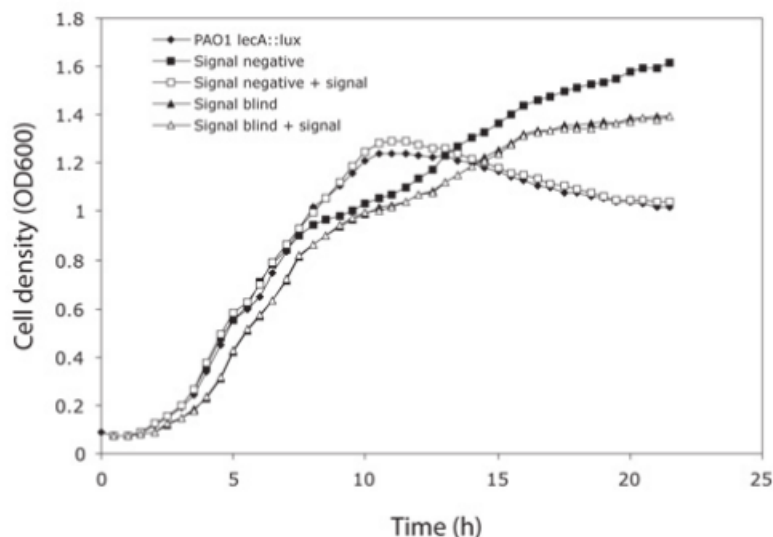


Figure 2.2: Plot of the dynamics of the different strains for *Pseudomonas aeruginosa* in a LB medium. From reference [27].

There is a clear difference between those strains that activate the PG production and those that do not. For instance, the dynamics of the wild type strain (black diamonds in Figure 2.2) is an exponential growth followed by a decrease to a stationary value, smaller than the maximum of the population. This maximum gave us the idea of using the maximum of the population as the threshold for the PG production. On the other hand, the signal blind strains (triangles in Figure 2.2), mutants that do not produce PGs, show a logistic growth. This means that the dynamics starts with an exponential growth followed by a stationary phase where the population reaches its maximum value.

Since we are treating the case of a wild type strain in this section, we want to obtain the conditions for reproducing its qualitative dynamics from Figure 2.2. We are interested in finding an expression for the stationary value of the population in order to compare it with the experimental results. It may be possible to find this value since we know we have



conserved quantities for this closed system. Again, these conserved quantities only would make sense if we take a larger dynamical system incorporating the dynamics of the AIs to complete the system. The simplest case is when both  $f(R)$  and  $g(Q)$  are linear. A way of deriving the corresponding dynamical system is starting from the Monod functions and using the following approximations:

$$\begin{aligned} f(R) &= \frac{\alpha R}{K_R + R} \simeq \frac{\alpha}{K_R} R = \alpha' R \\ g(Q) &= \frac{\gamma Q}{K_Q + Q} \simeq \frac{\gamma}{K_Q} Q = \gamma' Q \end{aligned} \quad (2.16)$$

This approximation is justified when there are few available resources, taking  $K_R \gg R$  and  $K_Q \gg Q$ . In principle this approximation is suitable for  $f(R)$  since  $R$  is the limiting resource. If  $R_0 \ll K_R$ ,  $f(R)$  will fulfill always the approximation because  $R$  always decreases. However,  $Q$  can vary in a wide range of values depending on the parameters, so we cannot ensure that  $K_Q \gg Q$  at any time. We will study the case of nonlinear  $g(Q)$  later.

To get the first relation between variables, we need to obtain a conserved quantity. Dividing  $\dot{Q}/\dot{R}$  from Eq. (2.12) and integrating, we find the following equation:

$$Q(R) = \frac{km_2}{q\gamma'} \left[ 1 - \left( \frac{R}{R_{cr}} \right)^{\frac{q\gamma'}{\beta\alpha'}} \right] \quad (2.17)$$

where the initial conditions are  $Q(t_{cr}) = Q_{cr} = 0$  and  $R(t_{cr}) = R_{cr}$  because the PG production starts when we reach the critical population. The stationary value of  $Q$ , because  $R^* = 0$ , is  $Q^* = \frac{km_2}{q\gamma'}$ , which agrees with the  $Q^*$  that we obtain in Eq. (2.13).

Again, diving  $\dot{X}/\dot{R}$  from Eq. (2.12) and integrating (and also using Eq. (2.14)):

$$X(R) = X_{cr} + \frac{R_{cr} - R}{\beta} - \frac{km_2\gamma'}{(\beta\alpha')^2} \left[ 1 - \left( \frac{R}{R_{cr}} \right)^{\frac{q\gamma'}{\beta\alpha'}} \right] \quad (2.18)$$

where  $X(t_{cr}) = X_{cr}$  is the initial condition for the population density. The stationary value of the population would be:

$$X^* = X_{cr} + \frac{R_{cr}}{\beta} - \frac{km_2\gamma'}{(\beta\alpha')^2} \quad (2.19)$$

In order to work with this value, we write it in function of the original initial coordinates  $X_0$  and  $R_0$  before the activation of the production. Substituting  $X_{cr}$  and  $R_{cr}$  by its respective expressions (remember that we are in the linear case):

$$X^* = X_0 + \frac{R_0}{\beta} - \frac{m_1}{\alpha'\beta} \ln \left( \frac{R_0\alpha'}{m_1} \right) - \frac{km_2\gamma'}{(\beta\alpha')^2} \quad (2.20)$$

Written in this way, we can see that this stationary value is smaller than the corresponding stationary value of LM equation ( $X^* = X_0 + R_0/\beta$ ) with the same initial conditions. This prediction is reasonable since the maintenance rates will produce a smaller stationary value than in the case in which we do not have these costs. In addition, this stationary value has to be smaller than the maximum of the population (following the dynamics of

the wild type strain in Figure 2.2). The later requires a couple of conditions derived from Eq. (2.19):

$$\begin{aligned} \frac{R_{cr}}{\beta} &< \frac{km_2\gamma'}{(\beta\alpha')^2} \\ X_{cr} &> \frac{km_2\gamma'}{(\beta\alpha')^2} - \frac{R_{cr}}{\beta} \end{aligned} \quad (2.21)$$

The first condition implies

$$\frac{m_1 \beta\alpha'}{m_2 k\gamma'} < 1 \quad (2.22)$$

where  $m_1/m_2 < 1$  so the condition is reduced to  $\beta\alpha' < k\gamma'$ . From the second inequality we can obtain a sufficient condition:

$$X_{cr} > \frac{km_2\gamma'}{(\beta\alpha')^2} \quad (2.23)$$

Now, we show in Figure 2.3 the dynamics of bacteria and resources in the linear case. The used parameters are in an arbitrary scale, but they have been selected to fulfill the previous conditions.

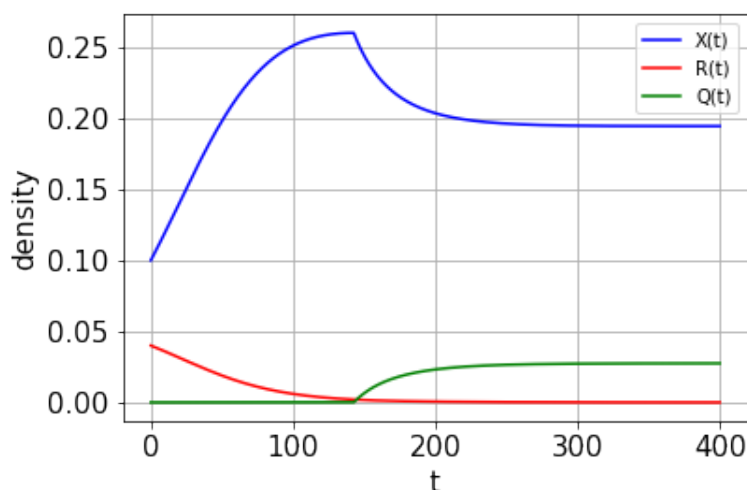


Figure 2.3: Dynamics of  $X$ ,  $R$  and  $Q$  during the whole process. The parameters and initial conditions used in arbitrary units are:  $\alpha = 0.5$ ,  $\beta = 0.2$ ,  $\delta = 0.5$ ,  $m_1 = 0.001$ ,  $m_2 = 0.01$ ,  $K_R = 1$ ,  $K_Q = 1$ ,  $k = 0.4$ ,  $\gamma = 0.4$ ,  $X_0 = 0.1$ ,  $R_0 = 0.04$ ,  $Q_0 = 0$ .

For  $X$ , We obtain something similar to the behaviour of wild type strain, but there is an important difference. In Figure 2.3, the shape of the exponential growth of  $X$  can be modified, but the shape of its maximum (sharp top) cannot, at least with linear functions. It is possible to see this analysing the curvature of the  $X$  line. The second derivative of the variable  $X$  is:

$$\ddot{X} = (-\beta f' f - qg'g + g'km_2)X^2 + [f + g - (m_1 + m_2)]^2 X \quad (2.24)$$

where  $f'$  and  $g'$  are the derivatives respect to the corresponding resources. Using linear functions,  $R$  and  $Q$  are always very low, so we can approximate  $f(R) \sim 0$  and  $g(Q) \sim 0$ .

With this approximation, the second derivative is

$$\ddot{X} \simeq g'km_2X^2 + (m_1 + m_2)^2X > 0 \quad (2.25)$$

So  $X$  is always convex. Besides, using the previous approximation in  $\dot{X}$  ( $\dot{X} \simeq -(m_1 + m_2)X$ ), we see that the value of  $X$  always decreases. That is why we see this characteristic shape of  $X$  in Figure 2.3.

Following the idea of reducing the dynamical system using conserved quantities, we want to see whether the marginal stable fixed points change to stable fixed points. We can plug  $R(X, Q)$  (with  $m_1 + m_2 = km_2/q$ ) in  $\dot{X}$ , reducing the dimension of the system. Now we have a stable fixed point (instead of a line of marginal stable points) with the following eigenvalues:

$$\lambda_1 = -\beta\alpha'X^* \quad \lambda_2 = -q\gamma'X^* \quad (2.26)$$

These eigenvalues are the same as the non-zero eigenvalues of the complete dynamical system. Therefore, it is reasonable to think that the assumption made in Appendix A (equality between the non-zero eigenvalues from the marginal fixed points and the eigenvalues of the reduced dynamical system) can be extended to any dimension.

Apart from the linear case, there are not many possibilities to find conserved quantities in the system. The next step is to consider  $f(R) \simeq \alpha'R$  and  $g(Q) = \gamma Q/(K_Q + Q)$ , as we said before, taking into account that  $R$  is the limiting resource and  $Q$  should saturate if there is an excess. Dividing  $\dot{Q}/\dot{R}$  and integrating we find the relation

$$R(Q) = R_{cr}e^{-\frac{\beta\alpha'}{km_2-q\gamma}Q} \left[ 1 + \left( 1 - \frac{q\gamma}{km_2} \right) \frac{Q}{K_Q} \right]^{\frac{K_Q q \gamma \beta \alpha'}{(km_2 - q\gamma)^2}} \quad (2.27)$$

Dividing  $\dot{X}/\dot{Q}$  and integrating, we can obtain the following equation:

$$X(Q) = X_{cr} + \int_0^Q \frac{\alpha'R(\tilde{Q}) + g(\tilde{Q}) - m_1 - m_2}{km_2 - g(\tilde{Q})} d\tilde{Q} \quad (2.28)$$

which is not a trivial integral, although it is still a good result. However, if we take both  $f(R)$  and  $g(Q)$  as Monod functions, we will not be able to obtain an analytical expression for  $X(R)$ . Dividing  $\dot{Q}/\dot{R}$  and integrating we would obtain

$$e^{\frac{Q}{km_2-q\gamma}} \left[ 1 + \left( 1 - \frac{q\gamma}{km_2} \right) \frac{Q}{K_Q} \right]^{-\frac{K_Q q \gamma}{(km_2 - q\gamma)^2}} = e^{\frac{R_{cr}-R}{\alpha\beta}} \left( \frac{R}{R_{cr}} \right)^{-\frac{K_R}{\beta\alpha}} \quad (2.29)$$

which is a transcendental equation. For this case, we show again the dynamics of bacteria and resources (Figure 2.4).

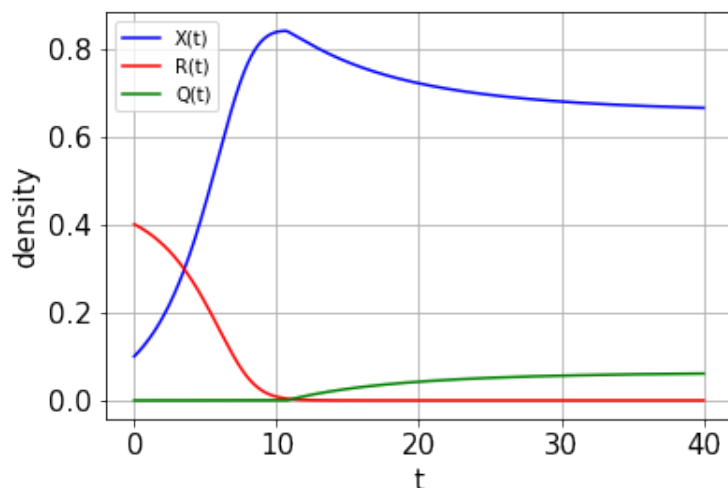


Figure 2.4: Dynamics of  $X$ ,  $R$  and  $Q$  during the whole process. The parameters and initial conditions used in arbitrary units are:  $\alpha = 0.5$ ,  $\beta = 0.5$ ,  $\delta = 0.5$ ,  $m_1 = 0.01$ ,  $m_2 = 0.02$ ,  $K_R = 0.2$ ,  $K_Q = 1$ ,  $k = 0.5$ ,  $\gamma = 0.5$ ,  $X_0 = 0.1$ ,  $R_0 = 0.4$ ,  $Q_0 = 0$ .

Now,  $X$  is closer to the real behaviour, having the possibility of a concave shape at the maximum. The change of time scale is significant when we use the Monod functions. The order of magnitude of growth rates that we use can be compared with other works in this line as [30]. The rates of this reference (obtained from Figure 2.2) are between zero and one in units of  $\text{hours}^{-1}$ . Our parameters are also in this interval so they are in the same scale, in hours. This would fit to the time scale observed in Figure 2.2. Gathering this result with the shape of the maximum, we can conclude that the Monod functions provide a better description than the linear functions.

## 2.2 QS vs no QS

So far, we have focused on the growth of bacteria when they use a QS mechanism to regulate the production of PGs. However, there are cases where the production of PGs is not density-dependent. One of these cases can be seen in the experiment from Gore with yeast [31].

The question is: can we distinguish between the two situations, having or not a QS mechanism, within the formalism? Recalling the Herbert model, the critical value of the resources (when we do not apply any approximation) is  $R_{cr} = K_R m_1 / (\alpha - m_1)$ . Now, we define a new parameter  $R' = R_0 / R_{cr}$ . If  $R' > 1$ , the population will pass through a maximum, and then it will decay until zero. On the other hand, if  $R' < 1$ , the population decays until zero directly. Therefore, if the production is activated when  $R = R_{cr}$ , the only way of avoiding the activation mechanism of QS is having always the condition  $R' < 1$ . It implies that the strain has to activate the production of PGs from the beginning to survive, since they will never reach  $R = R_{cr}$ .

It is important to remark that the threshold of the QS mechanism is in the population, not in the resources. We use  $R_{cr}$  as an indicator of the level population, since high cell population density will be accompanied by low density of resources. See, however, the reference [26]. Our hypothesis is that the microbes without QS mechanism are always described by the dynamical system of one consumer-two resources. Those that have a QS

mechanism begin from the Herbert model (one consumer-one resource), and once they reach  $R = R_{cr}$ , they are described by the system of one consumer-two resources. Our explanation for this behaviour is the following: the denominator of  $R_{cr}$  is  $\alpha - m_1$ . If  $\alpha \gg m_1$ ,  $R_{cr}$  would be small and it is likely to fulfill always  $R' > 1$ . However, if  $\alpha \sim m_1$ ,  $R_{cr}$  tends to a very large number, making very hard to fulfill  $R' > 1$ . All this arguments can be repeated for the linear approximation. When  $K_R \gg R$ , the critical value is  $R_{cr} = m_1 K_R / \alpha$ . If  $\alpha \gg m_1$ , it is possible to obtain  $R' > 1$ . If  $\alpha \sim m_1$ ,  $R_{cr} \sim K_R \gg R$  so  $R' < 1$  is always fulfilled.

As an example, we are going to study the differences between yeast and bacteria. In particular, we want to compare the budding yeast *Saccharomyces cerevisiae* and the bacterium *Pseudomonas aeruginosa*. They represent the cases of activation without threshold and QS mechanism respectively. For the maintenance rates, we know that  $m_1$  is much larger for yeast than for bacteria. Yeast are eukaryotes, having specialized organelles such as mitochondria, while bacteria are prokaryotes and they do not have. These organelles imply an additional energetic maintenance cost. Furthermore, the eukaryotes are bigger than the prokaryotes. The volume of yeast before cell division is around the hundreds of  $\mu m^3$  [32], while bacteria are around the units of  $\mu m^3$  or less [33]. This volume requires also a higher maintenance cost because of the growth of the cell and the maintenance itself. The only point where bacteria could add a higher cost respect to yeast is the production of AIs. However, these molecules do not imply a significant cost. The mutant strain that do not produce the AI signal molecule (signal-negative strain, black squares in Figure 2.2) have practically the same growth as the wild type strain in the exponential phase.

For the maximum growth rate  $\alpha$  we do not have a lot to say. Taking the measurement of the doubling time (time needed to pass from  $N$  individuals to  $2N$ ) as a reference, we find that *Pseudomonas aeruginosa* has a doubling time between 30 and 60 minutes depending on the medium [34], and yeast is around 90 minutes [35]. The experimental growth rate is frequently measured as the inverse of the doubling time. Therefore, we can say that the maximum growth rates of both species are, under the same experimental conditions, in the same order of magnitude. Even we could consider that yeast has a smaller  $\alpha$  than bacteria (the doubling time is larger).

Under these assumptions, it is reasonable to suppose that  $(\alpha - m_1)_{Pseudomonas} \gg (\alpha - m_1)_{yeast}$ . This does not ensure that  $\alpha \sim m_1$  for yeast, but at least we can see that  $R_{cr, yeast} \gg R_{cr, Pseudomonas}$ , making harder the access to the activation mechanism by yeast. Hence, comparing with *Pseudomonas aeruginosa*, it is a good approximation to consider that yeast is described by the dynamical system of one consumer-two resources from the beginning.

The set of equations that governs the dynamics of producers when there is no QS mechanism is the following:

$$\begin{aligned} \dot{X} &= [f(R) - m_1 + g(Q) - m_2] X \\ \dot{Q} &= km_2 X - qg(Q)X \\ \dot{R} &= -\beta f(R)X \end{aligned} \tag{2.30}$$

The analysis of the previous section is still valid, but changing  $R_{cr} \rightarrow R_0$  and  $X_{cr} \rightarrow X_0$ . For example, in the linear case, the stationary value of the population density is

$$X^* = X_0 + \frac{R_0}{\beta} - \frac{km_2\gamma'}{(\beta\alpha')^2} \tag{2.31}$$

This value is smaller than the predicted by the logistic equation, but larger than the value of the strain with the QS mechanism from Eq. (2.20) (the difference between QS and no QS mechanism is in  $m_1$ , not in  $m_2$ , so in principle it will be larger).

The hypothesis shown in this section could be used to explain why some microbes use a QS mechanism. The idea is that organisms with high maintenance rates need an early activation of the production of PGs, being more efficient. On the other hand, organisms with low maintenance rates can use a communication mechanism to optimize the production of PGs, waiting until having a sufficiently high cell density. This reasoning seems a good approach but there is a counterexample. The yeast *Cryptococcus neoformans* uses a signalling mechanism, very similar to the QS bacterial mechanism [36]. This mechanism is used for the production of virulence factors, so it is not directly related with the PG production. Therefore, we cannot ensure that being an eukaryote and high maintenance rates (larger size and organelles) imply the absence of QS mechanisms.

## Chapter 3

# The effect of non-producers

So far, we have studied the case of a single strain with intraspecific competition. Now, we will introduce another strain in the dynamical system, but with the difference that this strain is of a non-producer type. These microbes, in general, are mutants of the original wild type strain, and need to be differentiated from the producers through all the possible parameters. In principle, we do not know if they share any of these rates.

We want to obtain under which conditions both strains can coexist. Following the scheme of the previous section, we start from the Herbert model. And again, we focus on those bacteria with a QS mechanism. Encompassing the whole dynamics of the populations, the system is:

$$\begin{aligned}\dot{X} &= [f_X(R) - m_{1X} + (g_X(Q) - m_{2X})\theta(R_{cr} - R)] X \\ \dot{C} &= [f_C(R) - m_C + g_C(Q)\theta(R_{cr} - R)] C \\ \dot{Q} &= [km_2X - q_Xg_X(Q)X - q_Cg_C(Q)C]\theta(R_{cr} - R) \\ \dot{R} &= -\beta_Xf_X(R)X - \beta_Cf_C(R)C\end{aligned}\tag{3.1}$$

where we have introduced the corresponding terms of  $C$  (cheaters) in  $\dot{Q}$  and  $\dot{R}$ . We have not put a new metabolic cost for  $C$  after  $R < R_{cr}$  because this would be the main characteristic of the cheater: non-producing the product but getting the benefit through  $g_C(Q)$ .

Before activating the production of PGs, the dynamical system is similar to the single strain case:

$$\begin{aligned}\dot{X} &= (f_X(R) - m_{1X}) X \\ \dot{C} &= (f_C(R) - m_C) C \\ \dot{R} &= -\beta_Xf_X(R)X - \beta_Cf_C(R)\end{aligned}\tag{3.2}$$

The first thing that we must say about this set of equations is that, equalling all the parameters, we can add both populations and use a reduced system of the variable  $X + C$ , recovering the single strain problem. As we will see later, this situation does not change the conditions for coexistence, so it could be a nice approximation to reduce the number of parameters of the problem. The approximation itself is just to consider that both mutant and wild type are differentiated only in the regulation of PGs and its assimilation. However, we have to be careful once we are working on a particular circumstance. For example, there are mutants that do not produce the signalling molecule

before the activation of production [27], although it is true that this strain produces PGs, so the problem would be only in this stage. To avoid the lack of generality, we will always use different parameters between the strains in this section.

Coming back to the problem, we begin looking for the fixed points  $(X^*, C^*, R^*)$ . We soon realize that there is only a line of marginal fixed points in the  $R$  axis: if we started having  $X^* = 0$  (from  $\dot{X}$ ) or  $C^* = 0$  (from  $\dot{C}$ ), it would imply the equations  $f_C(R^*)C^* = 0$  or  $f_X(R^*)X^* = 0$  respectively (from  $\dot{R}$ ), where  $R^*$  would be the lowest possible one (remember the competitive exclusion principle from the point 1.1.2). In both cases the final situation is  $X^* = C^* = 0$  because either the two populations are zero using the previous conditions (having the line of marginal fixed points) or  $R^* = 0$ . The last equality would also lead to  $X^* = C^* = 0$  using the third equation of the dynamical system, so it belongs to the line of marginal fixed points.

The behaviour is similar to the case of one strain, but now we have two values of  $R$  which maximize the populations:  $R_{MX}$  for  $X$  and  $R_{MC}$  for  $C$ , that are defined as in the previous section for the different functions  $f(R)$ . The dynamics of the populations depends on the parameters and the initial value of the resource, as in the single strain case, but we find more possible situations:

- $R_{MX} > R_{MC} > R_0$  or  $R_{MC} > R_{MX} > R_0$ : both populations decrease exponentially to zero from the initial condition.

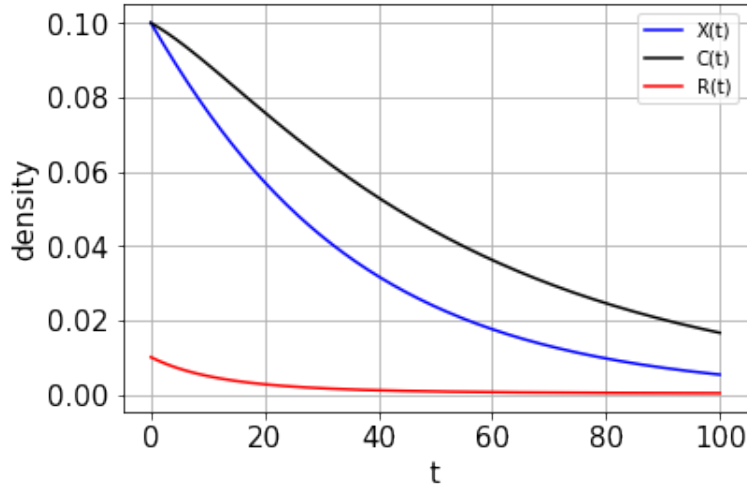


Figure 3.1: Dynamics of  $X$ ,  $C$  and  $R$  in the Herbert model with Monod functions. The parameters and initial conditions used in arbitrary units are:  $\alpha_X = 0.3$ ,  $\alpha_C = 0.7$ ,  $\beta_X = 0.5$ ,  $\beta_C = 0.5$ ,  $m_{1X} = 0.03$ ,  $m_C = 0.02$ ,  $K_{RX} = 0.8$ ,  $K_{RC} = 0.6$ ,  $X_0 = 0.1$ ,  $C_0 = 0.1$ ,  $R_0 = 0.01$  ( $R_{MX} \simeq 0.09$  and  $R_{MC} \simeq 0.02$ ).

- $R_0 > R_{MX} > R_{MC}$  or  $R_0 > R_{MC} > R_{MX}$ : both populations reach their respective maximum as in the single strain case, but the strain with the lowest critical value reaches it later.



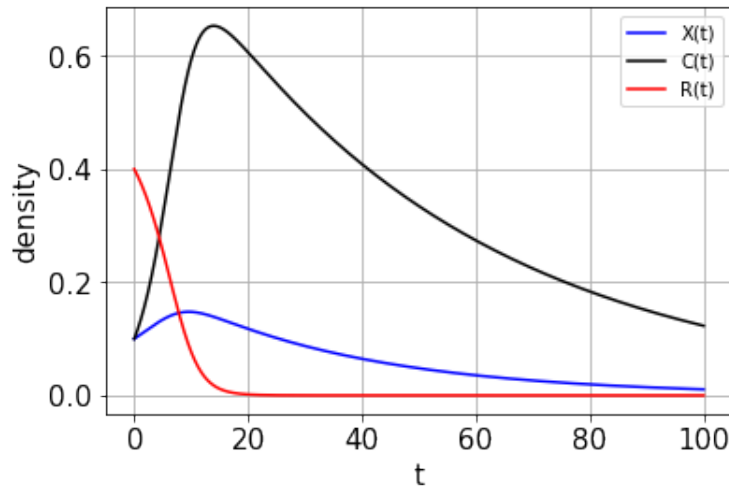


Figure 3.2: Dynamics of  $X$ ,  $C$  and  $R$  in the Herbert model with Monod functions. The parameters and initial conditions used in arbitrary units are:  $\alpha_X = 0.3$ ,  $\alpha_C = 0.7$ ,  $\beta_X = 0.5$ ,  $\beta_C = 0.5$ ,  $m_{1X} = 0.03$ ,  $m_C = 0.02$ ,  $K_{RX} = 0.8$ ,  $K_{RC} = 0.6$ ,  $X_0 = 0.1$ ,  $C_0 = 0.1$ ,  $R_0 = 0.4$  ( $R_{MX} \simeq 0.09$  and  $R_{MC} \simeq 0.02$ ).

- $R_{MX} > R_0 > R_{MC}$  or  $R_{MC} > R_0 > R_{MX}$ : only the population with the lowest critical value will reach a maximum, while the population of the other strain decreases exponentially.

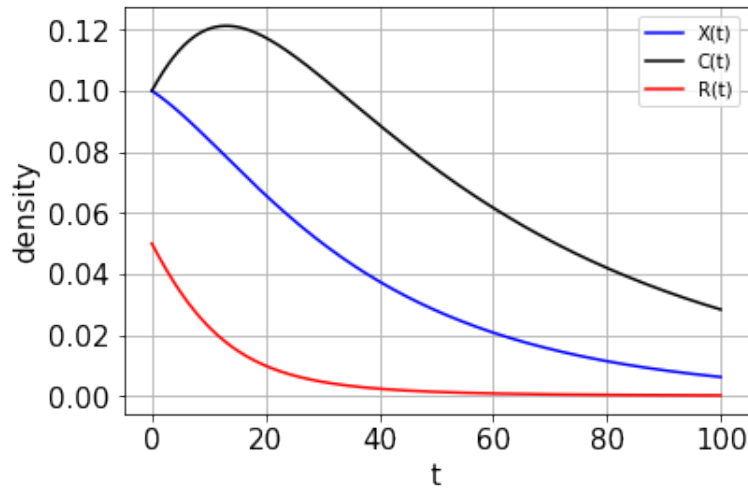


Figure 3.3: Dynamics  $X$ ,  $C$  and  $R$  in the Herbert model with Monod functions. The parameters and initial conditions used in arbitrary units are:  $\alpha_X = 0.3$ ,  $\alpha_C = 0.7$ ,  $\beta_X = 0.5$ ,  $\beta_C = 0.5$ ,  $m_{1X} = 0.03$ ,  $m_C = 0.02$ ,  $K_{RX} = 0.8$ ,  $K_{RC} = 0.6$ ,  $X_0 = 0.1$ ,  $C_0 = 0.1$ ,  $R_0 = 0.05$  ( $R_{MX} \simeq 0.09$  and  $R_{MC} \simeq 0.02$ ).

The maximum that can be used as the critical value for activating the production of PGs cannot be  $R_{MC}$  because the cheater does not produce them. Therefore, the critical value is  $R_{cr} = R_{MX}$ . However, we do not have a relation as  $X_{cr} = X_{cr}(R_{cr})$ , since now we cannot integrate as straightforward as before.

### 3.1 Production of public goods

After the critical value, the system is:

$$\begin{aligned}
 \dot{X} &= [f_X(R) - m_{1X} + g_X(Q) - m_{2X}] X \\
 \dot{C} &= [f_C(R) - m_C + g_C(Q)] C \\
 \dot{Q} &= km_{2X}X - q_X g_X(Q)X - q_C g_C(Q)C \\
 \dot{R} &= -\beta_X f_X(R)X - \beta_C f_C(R)C
 \end{aligned} \tag{3.3}$$

Studying the fixed points  $(X^*, C^*, Q^*, R^*)$ , we start again looking at  $\dot{R}$  and there are two possibilities:

- $R^* \neq 0$ : in this situation both populations have to be zero, since the only case that they do not vanish implies that one of them has to be negative (due to the equation of  $\dot{R}$ ).
- $R^* = 0$ : there are three possibilities.
  1. Both populations are zero again.
  2. A fixed value for the population of the cooperator  $X^* \neq 0$  while the population of the cheater is zero ( $C^* = 0$ ). It happens when  $g_X(Q^*) = m_{1X} + m_{2X} = km_{2X}/q_X$ , where the condition  $q_X = km_{2X}/(m_{1X} + m_{2X})$  has to be fulfilled. This condition is the same as Eq. (2.14), obtained for a single wild type strain.
  3. Coexistence between the two strains.

The fact that Eq. (2.14) precludes coexistence agrees with experimental evidences. Microbes that show coexistence between cooperators and cheaters usually have some mechanisms to promote it. For example, cooperative strains of the bacterium *Pseudomonas aeruginosa* and the yeast *Cryptococcus neoformans* use the privatization of some specific PGs [37, 31]. These kind of mechanisms could increase the yield coefficient of the cooperator  $(q_X)^{-1}$ , since they need to produce more cells with the same amount of resource  $Q$  than where they were alone (without cheaters). Otherwise, cooperators will not be able to sustain their population since they are feeding the cheaters as well. An increase of  $(q_X)^{-1}$  is equivalent to a decrease of  $q_X$  changing Eq. (2.14) to this inequality:

$$q_X < k \frac{m_{2X}}{m_{1X} + m_{2X}} \tag{3.4}$$

Now, we focus on the case of coexistence for  $R^* = 0$ , where the value of the fixed points is given by

$$R^* = 0 \quad g_X(Q^*) = m_{1X} + m_{2X} \quad g_C(Q^*) = m_C \quad X^* = \frac{q_C m_C}{km_{2X} - q_X(m_{1X} + m_{2X})} C^* \tag{3.5}$$

that is, again, a line of marginal fixed points. Implicitly, we are avoiding the competitive exclusion principle (although there are two resources, we are in the case of  $R^* = 0$  so basically there is only one resource). We use the same  $Q^*$  for both strains, obtaining a relation between the maintenance costs and the parameters of  $g(Q)$ . That is why we cannot take the same parameters for wild type and mutant. Otherwise  $g_C(Q^*) = g_X(Q^*) = m_C = m_{1X} + m_{2X}$  and the cheater would have the same cost as the producer,

not being a real cheater. But as I said at the beginning of this section, we are free to take  $m_{1X} = m_C$ . The last equation of (3.5) indicates that  $km_{2X} > q_X(m_{1X} + m_{2X})$  in order to have  $X^*, C^* > 0$ . In this way, we obtain the inequality from Eq. (3.4).

The Jacobian of the fixed points of Eq. (3.5) has the following eigenvalues:

$$\begin{aligned} \lambda_1 &= -\beta_X f'_X X^* - \beta_C f'_C C^* & \lambda_2 &= 0 \\ \lambda_3, \lambda_4 &= \frac{-q_X g'_X X^* - q_C g'_C C^* \pm \sqrt{(q_X g'_X X^* + q_C g'_C C^*)^2 + 4q_C m_C C^* (g'_X - g'_C)}}{2} \end{aligned} \quad (3.6)$$

where  $f'_X = \left. \frac{\partial f_X(R)}{\partial R} \right|_{R^*=0}$ ,  $f'_C = \left. \frac{\partial f_C(R)}{\partial R} \right|_{R^*=0}$ ,  $g'_X = \left. \frac{\partial g_X(Q)}{\partial Q} \right|_{Q^*}$ ,  $g'_C = \left. \frac{\partial g_C(Q)}{\partial Q} \right|_{Q^*} > 0$ , and we have used the relation between  $X^*$  and  $C^*$  in the second member of the square root.

The only way of obtaining negative eigenvalues is when  $g'_X < g'_C$ . This condition means that the rate of the consumption function at the stationary state must be smaller for the cooperator than for the cheater. A direct biological interpretation would be that the cooperator receives fewer resources than the cheater. This result is connected with the mechanisms that promote coexistence. If the cooperators receive fewer resources than the cheaters, they need to increase the yield coefficient to avoid the extinction.

Now, we have to make sure to have real eigenvalues. The condition would be just to impose a positive value inside the square root of the eigenvalues  $\lambda_3$  and  $\lambda_4$  (substituting  $X^*$  by its relation with  $C^*$ ):

$$\left( \frac{q_X^2 (g'_X)^2 q_C m_C}{[km_{2X} - q_X(m_{1X} + m_{2X})]^2} + \frac{q_C (g'_C)^2}{m_C} + \frac{2q_X g'_X q_C g'_C}{km_{2X} - q_X(m_{1X} + m_{2X})} \right) C^* - 4(g'_C - g'_X) > 0 \quad (3.7)$$

where the only negative term is  $-4(g'_C - g'_X)$ , so this inequality seems to be fulfilled in a large region of the parameter space.

Until here, it could seem that we have found all the conditions for coexistence. However, the problem depends on the functions  $g_X(Q)$  and  $g_C(Q)$  as well. I will show the two cases studied over this report, that is the linear and Monod functions.

- $g_X(Q) \simeq \frac{\gamma_X}{K_{QX}} Q$  and  $g_C(Q) \simeq \frac{\gamma_C}{K_{QC}} Q$ .

Using the conditions from Eq. (3.5), we find the following relation between the parameters:

$$\begin{aligned} Q^* &= \frac{(m_{1X} + m_{2X})K_{QX}}{\gamma_X} = \frac{m_C K_{QC}}{\gamma_C} \Rightarrow \\ \gamma_X &= \frac{m_{1X} + m_{2X}}{m_C} \frac{K_{QX}}{K_{QC}} \gamma_C \end{aligned} \quad (3.8)$$

Moreover, the condition  $g'_X < g'_C$  implies

$$\gamma_X < \frac{K_{QX}}{K_{QC}} \gamma_C \quad (3.9)$$

Gathering both things we reach the inequality  $m_{1X} + m_{2X} < m_C$ , which contradicts one of our first statements. Therefore, we cannot have coexistence with linear functions for  $g_X(Q)$  and  $g_C(Q)$ .

- $g_X(Q) \simeq \frac{\gamma_X Q}{K_{QX} + Q}$  and  $g_C(Q) \simeq \frac{\gamma_C Q}{K_{QC} + Q}$ .

Using the conditions from Eq. (3.5), we find the following relation between the parameters:

$$Q^* = \frac{(m_{1X} + m_{2X})K_{QX}}{\gamma_X - (m_{1X} + m_{2X})} = \frac{m_C K_{QC}}{\gamma_C - m_C} \Rightarrow \quad (3.10)$$

$$\frac{K_{QX}}{K_{QC}} = \frac{m_C}{(m_{1X} + m_{2X})} \frac{\gamma_X - (m_{1X} + m_{2X})}{\gamma_C - m_C}$$

where we get two conditions more,  $\gamma_X > m_{1X} + m_{2X}$  and  $\gamma_C > m_C$ . The condition  $g'_X < g'_C$  implies

$$\frac{K_{QX}}{K_{QC}} < \frac{\gamma_X}{\gamma_C} \frac{m_C^2}{(m_{1X} + m_{2X})^2} \quad (3.11)$$

Gathering both things we get another condition for coexistence:

$$\gamma_X - (m_{1X} + m_{2X}) < \frac{m_C}{(m_{1X} + m_{2X})} (\gamma_C - m_C) \quad (3.12)$$

The final list of conditions for coexistence (and for Monod functions) is:

$$\left\{ \begin{array}{l} q_X < k \frac{m_{2X}}{m_{1X} + m_{2X}} \\ \gamma_X > m_{1X} + m_{2X} > m_C \\ \gamma_C > m_C \\ \gamma_X - (m_{1X} + m_{2X}) < \frac{m_C}{(m_{1X} + m_{2X})} (\gamma_C - m_C) \\ K_{QX} = K_{QC} \frac{m_C}{(m_{1X} + m_{2X})} \frac{\gamma_X - (m_{1X} + m_{2X})}{\gamma_C - m_C} < K_{QC} \end{array} \right. \quad (3.13)$$

We show the dynamics of bacteria and resources (Figure 3.4), where all the parameters fulfill the previous conditions.

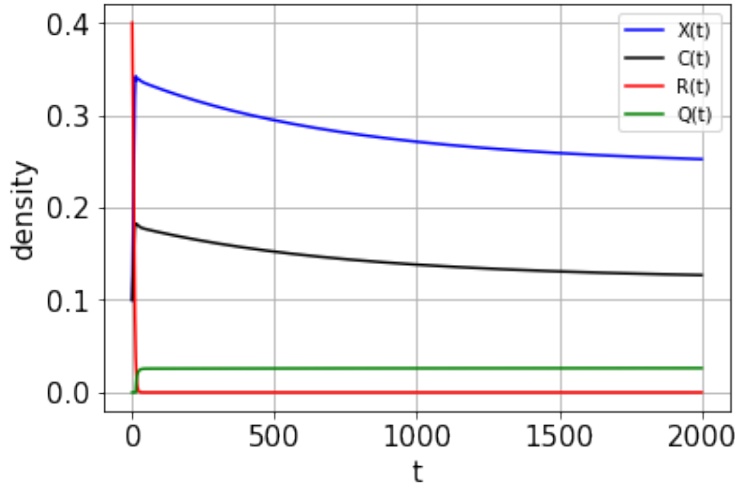


Figure 3.4: Dynamics of  $X$ ,  $C$ ,  $R$  and  $Q$  during the whole process. The parameters and initial conditions used in arbitrary units are:  $\alpha_X = 0.7$ ,  $\alpha_C = 0.3$ ,  $\beta_X = 0.8$ ,  $\beta_C = 0.8$ ,  $m_{1X} = 0.03$ ,  $m_{2X} = 0.05$ ,  $m_C = 0.02$ ,  $K_{RX} = 0.8$ ,  $K_{RC} = 0.6$ ,  $K_{QC} = 0.5$ ,  $k = 0.9$ ,  $q_X = 0.5$ ,  $q_C = 0.5$ ,  $\gamma_X = 0.1$ ,  $\gamma_C = 0.4$ ,  $X_0 = 0.1$ ,  $C_0 = 0.1$ ,  $R_0 = 0.4$ ,  $Q_0 = 0$ .

In this case, the system presents coexistence, but the relaxation time until the stationary phase is much longer than for one strain alone.

Once we have defined the competition between strains with a QS mechanism, we can propose, following the previous section again, the model for the case when there is no QS mechanism. Repeating the argument used with a single strain, we know that microbes that do not use QS always produce PGs, so the model can be applied forgetting the part of the critical resource from the beginning:

$$\begin{aligned}\dot{X} &= [f_X(R) - m_{1X} + g_X(Q) - m_{2X}] X \\ \dot{C} &= [f_C(R) - m_C + g_C(Q)] C \\ \dot{Q} &= km_{2X}X - q_Xg_X(Q)X - q_Cg_C(Q)C \\ \dot{R} &= -\beta_Xf_X(R)X - \beta_Cf_C(R)C\end{aligned}\tag{3.14}$$

where the initial conditions that we would use here are not any critical value but the real initial conditions of the strains.

# Chapter 4

## Conclusions

In this Master's thesis, we have proposed and analysed a family of models to study the growth of microbial populations when they produce public goods. In particular, we have focused on those bacteria that present a QS mechanism. Our formalism is based on a mean-field description of consumer-resource ecological models and it constitutes the first step to develop a more elaborated formalism. We have studied three cases: a single strain of producers with QS mechanism, a single strain of producers without QS mechanism and both cases including the presence of cheaters. Besides, we have obtained numerical results to compare them with the analytical treatment.

The formalism contributes with some predictions. We have obtained equations for the population density threshold and the AIs threshold that depend on the parameters and the initial conditions. To my knowledge, this is the first time that expressions for these values are derived. Another prediction of our description is discriminating the cases where the production of PGs is activated through a threshold. We are not very sure that it can be generalized for any microbe, but it seems to work for the cases studied, bacteria vs yeast. We have also demonstrated that the linearization of the growth rates  $g_X(Q)$  and  $g_C(Q)$  does not allow coexistence between cooperator and cheater. In the case of Monod functions for these growth rates, we obtain several conditions for observing coexistence.

Leaving the biological interpretation on a side, we have also obtained new results from a more theoretical perspective. We have defined a generalized logistic equation with a maintenance rate. It was derived from the Herbert model, and in its linear version ( $f(R)$  linear), it can be applied to the SIR mean-field model as well.

This result is connected with a common rule between the studied dynamical systems. Finding a conserved quantity and using it to write one of the variables as a function of the other variables, we can eliminate one equation of the system. If the system has marginal fixed points (only for a single eigenvalue equal to zero), it is possible to reduce the dynamical system keeping all the information about the marginal fixed points. The new reduced system will have a single fixed point that has the same stability than the original fixed points, eliminating the eigenvalue equal to zero. We have found the conditions that a 2D dynamical system has to fulfill to exhibit this property. It would be interesting to find the needed conditions for a  $n$ -dimensional dynamical system.

There are several directions for future work that depart from our results. The first part would be theoretical. We did not have enough time to study the parameter space of the dynamical systems to see all the possible behaviours that this formalism can offer. Besides, we want to go beyond the mean-field approach and to use a spatial one. Including the spatial structure, we will obtain a more complete description of the problem. It

is important to remark that we have not introduced any local effect experimentally observed. Mechanisms such as privatization [37], policing [38], or generalized reciprocity [39] have been observed in *Pseudomonas aeruginosa* for PGs production. These mechanisms participate in the coexistence between cooperators and cheaters.

Experimentally, we propose ideas to prove some of the results. One could measure the thresholds of the population density and density of AIs varying the initial values of the resource and bacteria in order to see whether it fits with our theoretical expressions. Furthermore, it is known that the level of resources affects the activation of PGs production, as in *Pseudomonas aeruginosa* [26]. It would be interesting to check if the critical value of the resources is a real threshold for the activation. A possible experiment is to use a chemostat (see chapter 4 of [15] for the details of the dynamical system). Using this approach and for a maximum possible concentration of resources of the medium sufficiently large, the critical value of the resources  $R_{cr}$  becomes a stable stationary value  $R^*$ . We can wait until obtaining the stationary value and to see if the production is activated. The stationary value of the population density  $X^*$  depends on the maximum possible concentration of resources of the medium, while  $R^* = R_{cr}$  does not. Therefore,  $X^*$  can be varied maintaining  $R_{cr}$  to see whether the production is activated. If there is dependence respect to the limiting resources, the values of  $X^*$  and  $A^*$  (AIs accumulated in the medium) should fit with the critical values obtained in our formalism,  $X_{cr}$  and  $A_{cr}$  respectively. In the opposite case, the AIs will activate the production of PGs without dependence in the resource concentration, and it would be necessary to review our description to change these dependencies.

# Appendix A

## Demonstration of dynamical system reduction in 2D

We want to show that it is possible to describe marginal fixed points (with only one eigenvalue equal to zero) as a single fixed point in a reduced dynamical system. This property has been observed in conservative dynamical systems, so we will explore only this kind of systems. The single fixed point (in the reduced dynamical system) will have the same non-zero eigenvalue as the marginal fixed points in the complete dynamical system. In this way, we preserve the stability of the original fixed points, eliminating the eigenvalue equal to zero.

The utility of this process consists in reducing the number of equations of the dynamical system, preserving all the information about the marginal fixed points. This information is, for instance, the initial conditions that lead the system to the possible final fixed points (if they are attractive).

In order to accomplish this task, we not only need a conserved quantity, but also a non-transcendental relation between the variables. This means that we have to be able to write one of the variables as a function of the others. Otherwise, we cannot eliminate one of the equations from the dynamical system.

We present the demonstration for a 2D dynamical system. We start from:

$$\begin{aligned} \dot{x}_1 &= f(x_1, x_2) \\ \dot{x}_2 &= g(x_1, x_2) \end{aligned} \tag{A.1}$$

For any fixed point of the system ( $f(x_1^*, x_2^*) = 0$  and  $g(x_1^*, x_2^*) = 0$ ), the Jacobian is the following:

$$J|_{x_1^*, x_2^*} = \begin{pmatrix} \left. \frac{\partial f}{\partial x_1} \right|_{x_1^*, x_2^*} & \left. \frac{\partial f}{\partial x_2} \right|_{x_1^*, x_2^*} \\ \left. \frac{\partial g}{\partial x_1} \right|_{x_1^*, x_2^*} & \left. \frac{\partial g}{\partial x_2} \right|_{x_1^*, x_2^*} \end{pmatrix} \tag{A.2}$$

The eigenvalues of this Jacobian are:

$$\lambda^{2D} = \frac{1}{2} \left[ \left. \frac{\partial f}{\partial x_1} \right|_{x_1^*, x_2^*} + \left. \frac{\partial g}{\partial x_2} \right|_{x_1^*, x_2^*} \pm \sqrt{\left( \left. \frac{\partial f}{\partial x_1} \right|_{x_1^*, x_2^*} + \left. \frac{\partial g}{\partial x_2} \right|_{x_1^*, x_2^*} \right)^2 + 4 \left. \frac{\partial f}{\partial x_2} \right|_{x_1^*, x_2^*} \left. \frac{\partial g}{\partial x_1} \right|_{x_1^*, x_2^*}} \right] \tag{A.3}$$



We want to have marginal fixed points. A sufficient condition would be  $\partial f/\partial x_2|_{x_1^*, x_2^*} = 0$  or  $\partial g/\partial x_1|_{x_1^*, x_2^*} = 0$ , obtaining

$$\lambda_z^{2D} = 0 \quad \lambda_{nz}^{2D} = \left. \frac{\partial f}{\partial x_1} \right|_{x_1^*, x_2^*} + \left. \frac{\partial g}{\partial x_2} \right|_{x_1^*, x_2^*} \quad (\text{A.4})$$

where the subscript ‘ $z$ ’ means zero and ‘ $nz$ ’ means non-zero. Once we have the eigenvalues, we want to see if we can keep the non-zero eigenvalue in a reduced dynamical system (with only one equation). The reduction is accomplished by using a conserved quantity that relates both variables  $x_1$  and  $x_2$ . Without loss of generality, we will take the expression  $x_1 = x_1(x_2)$ . Our reduced dynamical system is

$$\dot{x}_2 = g[x_1(x_2), x_2] \quad (\text{A.5})$$

where the fixed points taken for the 2D system are also fixed points of this equation ( $g[x_1(x_2^*), x_2^*] = g(x_1^*, x_2^*) = 0$ ). The eigenvalue of these fixed points in the one dimensional system is

$$\lambda^{1D} = \left. \frac{dg}{dx_2} \right|_{x_2^*} \quad (\text{A.6})$$

In order to develop this expression, we need to know the dependency of  $g$  on  $x_1$ . Something common in the models studied in this thesis is the form  $g(x_1, x_2) = h(x_1)l(x_2)$ , so we will assume that  $g$  is separable. Now, the eigenvalue can be written as

$$\lambda^{1D} = \left. \frac{d[h(x_1)l(x_2)]}{dx_2} \right|_{x_2^*} = l(x_2^*) \left[ \left. \frac{dh(x_1)}{dx_1} \frac{dx_1(x_2)}{dx_2} \right] \right|_{x_2^*} + h(x_1^*) \left. \frac{dl(x_2)}{dx_2} \right|_{x_2^*} \quad (\text{A.7})$$

The second term of Eq. (A.7) is related with the non-zero eigenvalue of the complete dynamical system:

$$h(x_1^*) \left. \frac{dl(x_2)}{dx_2} \right|_{x_2^*} = \left. \frac{\partial g}{\partial x_2} \right|_{x_1^*, x_2^*} = \lambda_{nz}^{2D} - \left. \frac{\partial f}{\partial x_1} \right|_{x_1^*, x_2^*} \quad (\text{A.8})$$

Introducing this equation in (A.7), the eigenvalues are related as

$$\lambda^{1D} = \left. \frac{d[h(x_1)l(x_2)]}{dx_2} \right|_{x_2^*} = l(x_2^*) \left[ \left. \frac{dh(x_1)}{dx_1} \frac{dx_1(x_2)}{dx_2} \right] \right|_{x_2^*} - \left. \frac{\partial f}{\partial x_1} \right|_{x_1^*, x_2^*} + \lambda_{nz}^{2D} \quad (\text{A.9})$$

Finally, for obtaining the relation  $\lambda^{1D} = \lambda_{nz}^{2D}$ , we need the following equality:

$$\left. \frac{\partial f}{\partial x_1} \right|_{x_1^*, x_2^*} = l(x_2^*) \left[ \left. \frac{dh(x_1)}{dx_1} \frac{dx_1(x_2)}{dx_2} \right] \right|_{x_2^*} \quad (\text{A.10})$$

relating  $f$  and  $g$ .

Knowing that  $g(x_1^*, x_2^*) = h(x_1^*)l(x_2^*) = 0$ , we have two possibilities, either  $h(x_1^*) = 0$  or  $l(x_2^*) = 0$ . The eigenvalues would be:

$$\begin{cases} \text{If } h(x_1^*) = 0 \Rightarrow \lambda^{1D} = \lambda_{nz}^{2D} = \left. \frac{\partial g}{\partial x_2} \right|_{x_1^*, x_2^*} \\ \text{If } l(x_2^*) = 0 \Rightarrow \lambda^{1D} = \lambda_{nz}^{2D} = \left. \frac{\partial f}{\partial x_1} \right|_{x_1^*, x_2^*} \end{cases} \quad (\text{A.11})$$

These two possible cases are reflected in the logistic model and Herbert model equations (Eq. 1.6 and 1.8 respectively). For the logistic model we have that  $h(x_1^*) = 0 \Rightarrow \alpha R^* = 0$ , so  $\lambda^{1D} = \lambda_{nz}^{2D} = -\alpha\beta X^*$ . In the Herbert model we find the other case, where  $l(x_2^*) = 0 \Rightarrow X^* = 0$ , so  $\lambda^{1D} = \lambda_{nz}^{2D} = \alpha R^*/(K_R + R^*) - m$ . And these models fulfill all the required conditions exposed in this Appendix.

# Appendix B

## Dynamics of the Herbert model

In this appendix we are going to study the 2D dimensional system of one consumer and one resource with a maintenance rate for the consumer, in a closed environment without adding resource. Then, we will reduce the system using the conserved quantity resulting from dividing both equations and integrating.

The dynamical system is the following:

$$\begin{aligned}\dot{X} &= [f(R) - m] X \\ \dot{R} &= -\beta f(R) X\end{aligned}\tag{B.1}$$

where  $X$  is the population density (individuals/volume),  $R$  the density of resources (mass/volume),  $f(R)$  is the growth rate or consumption function ( $\text{time}^{-1}$ ) and  $\beta$  is the resource quota (units of  $R$  contained in one unit of  $X$ ). We can work with the yield coefficient  $\beta^{-1}$  (population density produced by a unit of  $R$ ), and  $m$  is the maintenance rate which encapsulates all the non-growth costs. The Herbert model is always associated with the Monod function  $f(R) = \alpha R / (K_R + R)$ , where  $\alpha$  is the maximum growth rate, and  $K_R$  is the half-saturation constant. However, we will start studying the case of a general function  $f(R)$ .

Computing the nullclines, we can quickly see that we only have one possibility for finding fixed points:  $X^* = 0$  for both equations. Taking these nullclines, we have a line of marginal fixed points with the eigenvalues

$$\lambda_1 = 0 \quad \lambda_2 = f(R^*) - m\tag{B.2}$$

where  $f(R^*)$  is evaluated depending on the initial conditions. Now we see an interesting property of the system.  $X$  has a maximum if  $f(R_M) = m$  where  $R_M = R_{cr}$  is named as the critical value in the main text. Something that we have to request is that  $f(R_{cr}) = m$  has only one root  $R_{cr}$ , and this is fulfilled by a monotonically increasing function  $f(R)$ . The consumption function must show this characteristic because it is a biological property: the more amount of resource, the more capability of increasing the population, and vice versa. Keeping this condition, it is also mandatory that  $f(R = 0) = 0$  (no resource, no growth), so  $f(R) = R \cdot h(R)$ . The functions that are used in these kind of models are the Monod function or the linear function, both monotonically increasing functions with zero value at  $R = 0$ .

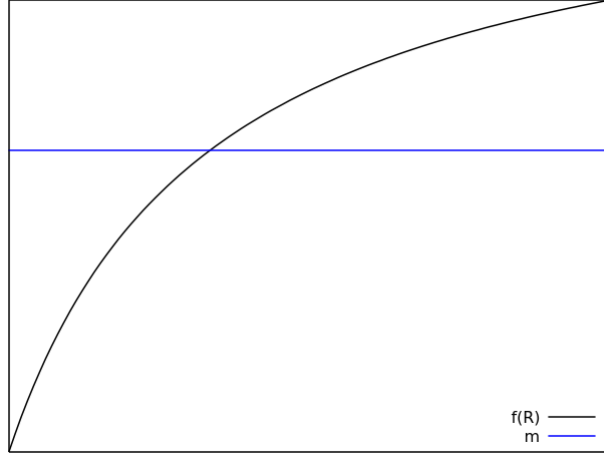


Figure B.1: Representation of a monotonically increasing function  $f(R)$ . The blue line represents the maintenance rate, so the intersection between the two lines defines the critical value  $R_{cr}$ .

Something important to remark is that this critical value only appears in the dynamics if  $f(R_0) > m$ , or due to the characteristic of increasing function,  $R_0 > R_{cr}$ , because  $R$  decreases always ( $\dot{R} < 0$ ), so does  $f(R)$ .

Once we have clarified this, it is easy to see that this point is a maximum:

$$\left. \frac{d^2 X}{dt^2} \right|_{R_{cr}, X_{cr}} = - \left. \frac{df(R)}{dR} \right|_{R_{cr}} \beta m (X_{cr})^2 < 0 \quad (\text{B.3})$$

where  $\frac{df(R)}{dR} > 0$  for an increasing function.

Let us start with the reduction to one dimension. We obtain the conserved quantity dividing both equations and integrating. The general result is

$$X(t) = X_0 + \frac{R_0 - R}{\beta} + \frac{m}{\beta} \int_{R_0}^R \frac{dR'}{f(R')} \quad (\text{B.4})$$

To continue, we must specify a form for  $f(R)$ . Let's see different cases:

- $f(R) = \frac{\alpha R}{N+R} \simeq \frac{\alpha R}{N} = \alpha' R$ , when  $N \gg R$ . For this case, the integral yields:

$$X(t) = X_0 + \frac{R_0}{\beta} - \frac{R(t)}{\beta} + \frac{m}{\beta \alpha'} \ln \left( \frac{R(t)}{R_0} \right) \quad (\text{B.5})$$

The Lambert  $W$  function [29], which fulfills  $W(x)e^{W(x)} = x$ , allows us to express  $R$  as a function of  $X$ . Doing some algebra, we can get this formula:

$$R(X) = -R_{cr} W \left( \left( -\frac{R_0}{R_{cr}} \right) e^{-\frac{R_0}{R_{cr}}} e^{\frac{\alpha' \beta}{m} (X - X_0)} \right) \quad (\text{B.6})$$

We substitute  $R(X)$  in  $\dot{X}$ , obtaining the new equation for the system:

$$\dot{X} = -m \left[ W \left( \left( -\frac{R_0}{R_{cr}} \right) e^{-\frac{R_0}{R_{cr}}} e^{\frac{\alpha' \beta}{m} (X - X_0)} \right) + 1 \right] X \quad (\text{B.7})$$

This equation has two fixed points:  $X^* = 0$  and  $X^* = X_{cr}$ . This last point is special because it is found when  $W(A|_{X^*=X_{cr}}) = -1$  where  $A$  is the argument of our Lambert  $W$  function. Therefore,  $A(X^* = X_{cr}) = -1/e$  at that point, which is the one that separates the two branches of real solutions (fig. (B.2)).

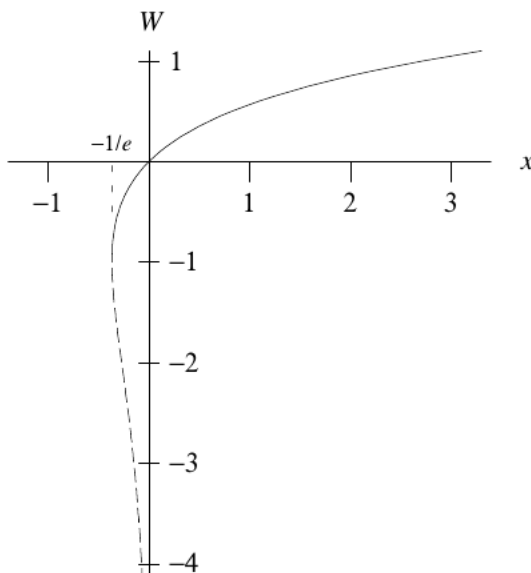


Figure B.2: Plot of the real branches of the Lambert  $W$  function.  $W_0(x)$  is the dashed line and  $W_{-1}(x)$  is the continuous line. Figure from [29].

We can demonstrate that  $A(X^* = X_{cr}) < A(X^* = 0)$ , so  $-1/e < A(0) < 0$ . This means that our system can be evaluated in the two real branches of the Lambert  $W$  function, having  $-1 < W_0(A) < 0$  and  $-\infty < W_{-1}(A) < -1$ .

The eigenvalue is:

$$\lambda = -m - mW(A(X^*)) - \alpha'\beta X^* \frac{W(A(X^*))}{1 + W(A(X^*))} \quad (\text{B.8})$$

Depending on the branch that we choose, the stability of the fixed points changes: taking  $W_{-1}(A)$ , the fixed point  $X^* = 0$ , is unstable ( $\lambda > 0$ , because  $-\infty < W_{-1}(A) < -1$ ), and  $X^* = X_{cr}$  is superstable ( $\lambda = -\infty$ , since  $W_{-1}(A) \rightarrow 1^-$ ). Taking  $W_0(A)$ , the fixed point  $X^* = 0$ , is stable ( $\lambda < 0$ , because  $-1 < W_0(A) < 0$ ), and  $X^* = X_{cr}$  is superunstable ( $\lambda = +\infty$ , since  $W_{-1}(A) \rightarrow 1^+$ ). And these results does not depend neither the initial conditions nor the parameters. How do we decide in which branch we are? It depends on the initial condition:  $W(A(X_0)) = -\frac{R_0}{R_{cr}}$ . So, if  $R_0 > R_{cr}$  then  $W(A(X_0)) = W_{-1}(A(X_0)) < -1$  and if  $R_0 < R_{cr}$  then  $W(A(X_0)) = W_0(A(X_0)) > -1$ .

Summing up, if  $R_0 > R_{cr}$ , the dynamics of  $X$  starts from the branch  $W_{-1}(A)$ , passes through the maximum  $X_{cr}$  (changing to the branch  $W_0(A)$ ), and finishes at  $X^* = 0$ . If  $R_0 < R_{cr}$ ,  $X$  remains always in the branch  $W_0(A)$  and tends directly to  $X^* = 0$ . This is exactly the behaviour of the 2D system. Due to the change of

branches, we can divide the system as follows:

$$\begin{cases} \dot{X} = -m \left[ W_{-1} \left( \left( -\frac{R_0}{R_{cr}} \right) e^{-\frac{R_0}{R_{cr}}} e^{\frac{\alpha' \beta}{m}(X-X_0)} \right) + 1 \right] X & R > R_{cr} \\ \dot{X} = -m \left[ W_0 \left( \left( -\frac{R_0}{R_{cr}} \right) e^{-\frac{R_0}{R_{cr}}} e^{\frac{\alpha' \beta}{m}(X-X_0)} \right) + 1 \right] X & R < R_{cr} \end{cases} \quad (\text{B.9})$$

This result is a generalization of the logistic equation in one dimension, introducing a maintenance rate. From this system, we can recover the logistic case doing the limit of  $m \rightarrow 0$ . Using the iterative formula of the  $W$  function,

$$\begin{aligned} W_{0,-1}(A) &= \ln(-A) - \ln(-W_{0,-1}(A)) \\ &= \ln(-A) - \ln(-\ln(-A) + \ln(-\ln(-A) + \dots)) \quad A < 0 \end{aligned} \quad (\text{B.10})$$

we can perform the limit of the dynamical system:

$$\begin{aligned} \lim_{m \rightarrow 0} \dot{X} &= \lim_{m \rightarrow 0} [-m W_{0,-1}(A)] X - \lim_{m \rightarrow 0} m X = \lim_{m \rightarrow 0} [-m W_{0,-1}(A)] X \\ &= \lim_{m \rightarrow 0} [-m \ln(-A)] X + \lim_{m \rightarrow 0} X m \ln(-\ln(-A) + \ln(-\ln(-A) + \dots)) \\ &= - \lim_{m \rightarrow 0} [m \ln(-A)] X \end{aligned} \quad (\text{B.11})$$

The last equality is due to the fact that  $\ln(-A)$  is of order  $\mathcal{O}(m^{-1})$ , so  $m$  will dominate over  $\ln(-\ln(-A) + \ln(-\ln(-A) + \dots))$ . Continuing with the limit:

$$\begin{aligned} - \lim_{m \rightarrow 0} [m \ln(-A)] X &= - \lim_{m \rightarrow 0} \frac{\alpha' m}{m} [\beta(X - X_0) - R_0] X - \lim_{m \rightarrow 0} X m \ln \left( \frac{R_0 \alpha'}{m} \right) \\ &= -\alpha' [\beta(X - X_0) - R_0] X \end{aligned} \quad (\text{B.12})$$

Finally, gathering terms:

$$\begin{aligned} \lim_{m \rightarrow 0} \dot{X} &= -\alpha' [\beta(X - X_0) - R_0] X = \frac{\alpha'}{\beta} (X_0 + R_0/\beta) \left( 1 - \frac{X}{X_0 + R_0/\beta} \right) X \\ &= r \left( 1 - \frac{X}{K} \right) X \end{aligned} \quad (\text{B.13})$$

- All the results from this section can be generalized for a general  $f(R)$  of the form  $f(R) = \alpha R^n / (K_R^n + R^n)$  (Monod). The study of the fixed points is the same. The main difference is that the maximum of the population happens when  $R_{cr}^n = m K_R^n / (\alpha - m)$ . In this context, the relation between  $X$  and  $R$  is the following:

$$\begin{cases} X(t) = X_0 + \frac{1}{\beta} \left( \frac{m}{\alpha} - 1 \right) [R(t) - R_0] + \frac{m K_R}{\alpha \beta} \ln \left( \frac{R(t)}{R_0} \right) & n = 1 \\ X(t) = X_0 + \frac{1}{\beta} \left( \frac{m}{\alpha} - 1 \right) [R(t) - R_0] + \frac{m K_R^n}{\alpha \beta (1-n)} [R^{1-n}(t) - R_0^{1-n}] & n > 1 \end{cases} \quad (\text{B.14})$$

For  $n = 1$ , that is the Monod function, we can also apply the  $W$  function, and the results are the same as in the case of  $f(R) = \alpha' R$ , changing some parameters in the equations:

$$\begin{cases} \dot{X} = - \left[ \frac{\alpha R_{cr} W_{-1}(A)}{K_R - R_{cr} W_{-1}(A)} + m \right] X & R > R_{cr} \\ \dot{X} = - \left[ \frac{\alpha R_{cr} W_0(A)}{K_R - R_{cr} W_0(A)} + m \right] X & R < R_{cr} \end{cases} \quad (\text{B.15})$$

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where  $R_{cr} = K_R m / (\alpha - m)$  and  $W(A)$  has the same equation as in the linear case (changing  $R_{cr}$ ):

$$W(A) = W \left( \left( -\frac{R_0}{R_{cr}} \right) e^{-\frac{R_0}{R_{cr}} e^{\frac{\alpha\beta}{K_R m} (X - X_0)}} \right) = W \left( \left( -\frac{R_0}{R_{cr}} \right) e^{-\frac{R_0}{R_{cr}} e^{\frac{\alpha'\beta}{m} (X - X_0)}} \right) \quad (\text{B.16})$$

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