A realistic and mechanistic model for the population interaction of bacteria and their bacteriophage viruses

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Abstract

After an analysis of some actual models for bacteria-phage interaction we present a new differential equations system where the susceptible cell population is physiologically structured by the number of viral receptors on which an attach-detach mechanism is regarded. The interaction takes place in a limited resources environment, modeled via the logistic equation, and in company of a phage resistant bacterial strain. In a first formulation we consider finite attach and detach rates over bacterial phage receptors. A second and simpler model is obtained when neglecting viral detachments. Both formulations are first presented in a discrete manner and converted to their corresponding continuous fashions.

1 Introduction

Bacteriophage viruses, frequently referred as phages, where discovered in 1915 by the English bacteriologist Frederick William Twort (1877-1950) and the French-Canadian microbiologist Félix d'Herelle (1873-1949).

As in [7] the class of phages that we will regard in this paper are the lytic ones that, contrary to the lisogenic kind, definitively kill the host cell at the end of their replication process. We can think of lytic phages as bacteria predators.

As a reference on the history and general information on phages we recommend the work of S. Matsukazi, et. al. [13], and as a critic point of view of phage therapy the article by B. Levin and J. Bull [12].

In the following section we explain the biological aspects of bacteria-phage interaction that must be regarded in any model for such dynamics. In §3 we recall and discuss some actual mathematical models related to this paper in three subsections. The first deals with the asumption of an average mass action law adsorption constant for susceptible cells, while the next subsection focuses the attention on physiologically structured bacterial populations. In the last subsection of §3 we discuss models where the viral attach-detach mechanism is included. In §4 we briefly explain some key modeling considerations. Section 5 is where we explain the main assumptions in our approach. In §6 and §7 we present our models in a discrete and in a continuos version, respectively. In §8 we include some concluding remarks.

2 Description of the biological process

The phages we study carry out a Lytic Cycle, that for our purposes in this paper will be decomposed in the following steps:

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Step 1. **Approach.** It refers to the way in which the phage and its future host, the bacteria, come close enough to make contact.

Step 2. **Contact or adsorption.** The moment when the virus touches the bacterial surface and remains close to it.

Step 3. **Attachment.** It is the moment when the phage docks onto a target cell receptor. We may refer to this step also as "phage adsorption".

Step 4. **Penetration or DNA-RNA absorption.** Consists of the injection of the viral DNA or RNA to the interior of the bacteria.

Step 5. **Replication.** It is the process by which the virions[1] are assembled inside the prokaryote.

Step 6. **Lysis.** It refers to the rupture of the cell envelope and liberation of virions to the outside environment.

It is important to notice that there are various theories regarding the approach and contact steps. It may be possible that some kind of attraction force of an electrostatic kind is what brings the virus near their host surface and makes it stay nearby [17]. In this line, the chemical composition of the surrounding environment and its physical conditions, in particular the temperature, play a crucial role. In [17] is concluded that "The rate of interaction of several viruses and their host cells in chemically defined media can be adjusted to any desired value between zero and the maximum theoretically possible rate, by control of the ionic constitution of the medium alone."

Regarding the contact step, it is also believed that after approaching its target, phages remain on the surface performing a "random walk" until the receptor where to bind is found [15].

Another belief regarding the way in which the phage finds a docking point, that is somehow natural when modeling, is pure chance, i.e. to consider that all virus move freely in the environment and occasionally find and touch a receptor [20]. In this sense it is clear that all conditions that are external to the prokaryotes and the viruses, aside of their respective concentrations, will impact the speed at which the contact step is completed and so its frequency.

For our purposes it is not very important if the virus is attracted or if it finds its way to the bacterial cell by chance, nor is if it 'walks' over the surface or bounces among many cells. What is essential is to determine and measure the speed at which the bacteriophages get attached to receptors in a given medium as a function of the phage and bacteria concentrations as we will discuss later on.

The attachment step presents an issue of great relevance and decisive importance in choosing the modeling approach. What happens when a virus binds to a receptor, in our case a particular bond of a lipopolysaccharide molecule located on the cell surface, is that the process can end in an irreversible binding, yielding to penetration, or it can be reversible, liberating the phage from the lipopolysaccharide protein back to the environment [9]. Although it is possible that the environmental circumstances allow to suppose that all phage attachments result irreversible, and so the penetration is a direct consequence of the attachment, in other words: adsorption implies DNA-RNA absorption. In this work we study both possible attachment mechanisms[2].

In order to grasp this attach detach phenomenon we can think of a typical key-lock opening operation [15] or equivalently from a consequence point of view, we can imagine that the virus travels through a small but long tube going forward and backwards randomly before getting

[1] Complete and infective virus particles.

[2] In [17] it is mentioned that it is also possible that the bacterial cell have receptors of the 'second kind', i.e. receptors that hold the virus while they really are not channels for the DNA-RNA absorption. In this work such possibility is not considered.

irreversibly attached. The probabilities for a forward and backward movement are not necessarily equal.

Once the phage is irreversibly attached its DNA is injected into the bacteria quickly reaching its cytoplasm.

This DNA-RNA absorption automatically triggers a radical change in the metabolic functions of the prokaryote [18], in fact, it ceases to be a bacteria and becomes a virus replication facility, whose only purpose is to assemble virions using all available resources from the interior of the cell. Notice that the cell envelope is essentially unaffected in this process even when the cell stops feeding itself among all other usual metabolic functions. Related to this phenomenon are the papers by Abedon *et. al.* [1] and Weld *et. al.* [23] where it is mentioned that phage infected bacterial cells do not grow.

The cycle ends with the expulsion of all existent virions to the outside by breaking the cell envelope. The number of liberated virus particles is known as the "burst size" and it can range from 1 or 2 up to one hundred, or even more.

Besides all things related with this Lytic Cycle there are many other factors that may impact the life or death of a bacteria and a phage. For the sake of clarity we consider a phage dead when it has completely and irreversibly lost its capacity to carry out the Lytic Cycle, i.e. when it is not capable of entering a cell to get offspring anymore.

Regarding the phages, some of the following things can happen at any time:

- In what we shall call Super Infections, phages can attach themselves, reversibly or irreversibly, to lipopolysaccharide receptors of an infected bacteria and also inject their genetic information. Nevertheless this extra DNA-RNA injection will not increase nor decrease the burst size, the virus is simply lost.

- Lipopolysaccharide attachments, reversible or irreversible followed by expulsion of the DNA-RNA outside of the virus, can occur even if the host cell is dead. It doesn't matter if the prokaryotic cell remains entire or the cell envelope is broken after the lysis explosion, the lipopolysaccharide molecules can adsorb phages at any time, as long as the bond of attachment is present on the lipopolysaccharide protein. These cell envelope fragments together with the membranes from cells that remain entire, is what we shall refer as "bacterial debris" or simply "debris". We give this debris a very important role and impact in our models. In [18] we find arguments that support this great impact of bacterial debris, even conceiving it as the mechanism for bacteria-phage coexistence.

- Bacteriophages may also attach to inorganic particles [17]. The attachment can be of the two kinds we are considering.

- Viral DNA-RNA can not penetrate a bacteria by itself in normal conditions, the only possible way for this to occur is by completing its corresponding step of the Lytic Cycle. So, if occasionally the DNA-RNA is expelled from the virus to the environment, it will not penetrate a bacterium in a successful manner.

3 Some actual models related to this paper

3.1 Models based on average mass action law adsorption constants

A common and well intended strategy to model bacteria-phage dynamics it to consider that the viral attachment on bacteria is irreversible and the interaction between these two biological entities occurs according to the mass action law, being proportional to the product of their count

numbers, such as the total population count or the concentration by volume unit. It seems realistic to think that the number of interactions per time unit is the same for p phages and q bacteria that for q phages and p bacteria.

This assumption, that always holds for the initial instant, will be completely valid along time if one of the following two things happens:

1. Each bacterium has only one phage receptor, then the interaction becomes one to one as in a chemical reaction.

2. The number of receptors on each cell is infinite and we consider that infected cells continue adsorbing phages as susceptible cells do, i.e. if we consider super infections that do not diminish the bacterial count once an adsorption takes place and that all cells preserve their adsorption potential unaltered.

Being none of these assumptions completely correct we may use the mass action law carefully.

In the same line of ideas, associated to the bacteria-phage interaction we may find the concept of MOI (Multiplicity of Infection) ratio, defined as the number of free phages per susceptible bacterium. So, as long as the MOI is low, of order 10^{-2} or 10^{-1}, the mass action law will give us good approximations to the real phenomena because super infections will rarely occur.

As a departure point we shall consider the work by D. Bascompte [3] that stands as the first mathematical model done specifically for the microbiology experiments by M. Llagostera [20] where the following $m+n$ delay ODE system is proposed.

$$\begin{aligned}
\dot{S}_j(t) &= \left(\alpha_j - \sum_{i=1}^{n} k_{ij} P_i(t)\right) S_j(t), \\
\dot{P}_i(t) &= d_i - m_i P_i(t) - \left(\sum_{j=1}^{m} k_{ij} S_j(t)\right) P_i(t) + \sum_{j=1}^{m} k_{ij} b_{ij} e^{-\mu_j T_{ij}} S_j(t - T_{ij}) P_i(t - T_{ij}),
\end{aligned} \tag{1}$$

for $j = 1, 2, \ldots, m$ and $i = 1, 2, \ldots, n$.

System (1) considers m bacterial strain concentrations S_j that increase in time with Malthusian growth rates $\alpha_j \geq 0$ and interact with n concentrations of phages of kind P_i. The irreversible adsorption of phages into bacterial cells occurs according to the mass action law with adsorption constants $k_{ij} \geq 0$. Once adsorptions occur, a fixed average delay time T is elapsed and then an average burst size $b \geq 0$ number of new virions are released from each infected cell. The initial condition involved due to the delay is considered to be an arbitrary time parametrized $m+n$-dimensional curve whose components belong to the Banach space $C([-T, 0], \mathbf{R})$ of real continuous functions defined over the real interval $[-T, 0]$ with the supreme norm. However, in this model the viral adsorption on infected cells or over bacterial debris is not considered.

The article by E. Beretta and Y. Kuang [2] that models a marine bacteriophage infection with latency period, happens to share the same hypothesis and similar conditions that [3] but considering $m = n = 1$. Nevertheless, a new state variable $I(t)$, standing for the concentration of infected cells, is added to the system together with a logistic growth rate depending on a medium or carrying capacity C to produce system (1.11) in [2] as follows.

$$\begin{aligned}
\dot{S}(t) &= \alpha S(t) \left(1 - \frac{S(t) + I(t)}{C}\right) - K S(t) P(t), \\
\dot{I}(t) &= -\mu_i I(t) + K S(t) P(t) - e^{-\mu_i T} K S(t - T) P(t - T), \\
\dot{P}(t) &= \beta - \mu_p P(t) - K S(t) P(t) + b e^{-\mu_i T} K S(t - T) P(t - T).
\end{aligned} \tag{2}$$

where all the sub indexes from (1) disappear since $m = n = 1$ and β, μ_p, K replace d, m, k in (1). We notice that the logistic growth rate term includes the fraction $(S(t) + I(t))/C$, thus the infected bacteria are assumed to feed from the available resources. In fact, not as we could wish, the infected bacteria play a part only as resource consumers but they do not adsorb phages.

System (2) looked for an improvement of the following equations that were proposed in [8],

$$\begin{aligned} \dot{S}(t) &= \alpha S(t)\left(1 - \frac{S(t)}{C}\right) - KS(t)P(t), \\ \dot{P}(t) &= bKS(t-T)P(t-T) - \mu_p P(t) - KS(t)P(t), \\ \text{with} \quad I(t) &= \int_{t-T}^{t} KS(\theta)P(\theta)d\theta, \end{aligned} \tag{3}$$

but also of the following more simple ones[3] in [4],

$$\begin{aligned} \dot{S}(t) &= \alpha S(t)\left(1 - \frac{S(t)}{C}\right) - KS(t)P(t), \\ \dot{I}(t) &= KS(t)P(t) - \lambda I(t), \\ \dot{P}(t) &= b\lambda I(t) - \mu P(t). \end{aligned} \tag{4}$$

In [11], a later work by one of the authors of [2], the resource consumption by infected cells is neglected and a phage density dependent mortality term is added obtaining the following system.

$$\begin{aligned} \dot{S}(t) &= \alpha S(t)\left(1 - \frac{S(t)}{\gamma}\right) - KS(t)P(t), \\ \dot{P}(t) &= -\mu_p P(t) - mP^2(t) - KS(t)P(t) + bKe^{-\mu_i T}S(t-T)P(t-T), \end{aligned} \tag{5}$$

Neglecting the resource consumption by infected cells seems to be a good idea, because we believe, as we mentioned before, that once infected, a bacterium is no other thing that a virus replication machine that stops all its normal metabolic functions. Regarding the inclusion of a density dependent mortality term on phages, we think that it may be more convenient to allow super infections and/or phage adsorption on debris. The impact of such measure will be similar because as a consequence of the dynamics we may expect large concentration of phages to be close to large concentration of bacterial cells and debris.

Although, being (4) a somewhat simple system, it contains an interesting ingredient regarding the existence of a degradation rate for the infected bacteria. Even when we do not relate the infected cells with the phage reproduction, as it is done by adding the $b\lambda I(t)$ term to $\dot{P}(t)$ in (4), because we think it is not a good idea to eliminate the latency period, we consider that the receptors on infected cells and debris do degrade at a constant rate over time and that during their active life they may adsorb phages, all this in the line of [18] and also as a conclusion of the interdisciplinary work in [19].

In this line is that the authors of [10] present as a start of their mathematical modeling the following system.

$$\begin{aligned} \dot{S}(t) &= (\Lambda - \gamma P(t))\, S(t), \\ \dot{I}(t) &= \gamma P(t)S(t) - \varepsilon I(t), \\ \dot{P}(t) &= m\gamma P(t-\tau)S(t-\tau) - \gamma P(t)\left(S(t) + I(t)\right), \end{aligned} \tag{6}$$

[3]Mainly because there is no time delay.

where Λ, γ, τ, m stand for $\alpha, k, T, be^{-\mu T}$ in (1) with $m = n = 1$ and without indexes, i.e. in a one bacterial strain versus one phage dynamics these four parameters represent the bacterial Malthusian growth rate, the mass action law adsorption constant, the latency period and the burst size once affected by the mortality rate of bacteria[4], respectively. The infected cells degradation rate is denoted by ε.

We notice that in system (6) it is considered that infected cells degrade at a constant rate but that they also adsorb phages with the same average constant that susceptible cells do.

Another interesting work that applies the mass action law, is the one by R. Payne and V. Jansen [16], that presents a phage therapy model including a host for the bacteria, given by the following equations.

$$\begin{aligned} \dot{x} &= ax - bvx - H(t)x, \\ \dot{y} &= ay + bvx - ky - H(t)y, \\ \dot{v} &= kLy - bvx - mv - h(t)v, \end{aligned} \tag{7}$$

where x and y stand for the susceptible and phage infected bacteria concentrations over time, while v represents the free phage concentration, depending also on the time variable. Here a, b, L, m stand for α, k, b, m in (1), for $m = n = 1$ and without indexes. All lysis occur at a constant rate k over infected cells, similarly to (4). The main addition of this system, is that the host responses against the bacteria or against the phage are incorporated via the time dependent functions $H(t)$ and $h(t)$.

3.2 Physiologically structured population dynamics

Given that the mass action law with a fixed adsorption constant is really appropriate only for small MOI values and that the real bacteria-phage interaction that we are interested in is characterized by having, in general, burst size values with at least two figures, that rapidly produce high phage concentration levels, thus big MOI values too, it is important to look for some other alternatives to model the manner in which the actual interaction occurs.

H. Smith [22], with whom we completely agree in this point, sustains that the mass action kinetics, i.e. the one determined by a mass action law constant multiplied by the product of the bacterial and viral concentrations, used to estimate the phage attack, but also considering it to be equal to the phage loss, is not correct. He mentions an experimentally based recent work where a wide variation of these values is found. In [22], in order to calculate the number of phage adsorptions on bacterial cells the mass action law adsorption constant is divided by an increasing function that depends on the phage concentration. For low concentration values the adsorption occurs according to the mass action law but it diminishes as the viral count increases.

Another alternative is, for example, to characterize the problem via the study of an average adsorption function that changes over time similarly to what is done in [10]. Other options are to physiologically structure the bacterial populations or concentrations. In this line we recall the works by Calsina and Saldaña [6] together with the book edited by Metz and Dieckmann [14].

In [7] we regard a bacterial structure by the cell size assuming that the receptor density per cell surface unit is constant, while the burst size is proportional to the cell volume. The assumption we made about a uniform distribution of phage receptors on the cells membrane happens to be a bit unrealistic, in order to improve this approach is that we move on and profit from more realistic and elaborated considerations that are discussed in the remaining of this subsection and the following one.

[4] Actually this is our interpretation because the authors of [10] assume it to be the burst size itself.

In [9] and [10] the regarded key aspect is the natural division of bacterial populations into sub populations according to the number of receptors on the surface of each individual. In this way, in [10] system (6) is modified into the following $2N_{\mathrm{MAX}}+3$ system of equations

$$\begin{aligned}
\dot{S}_n(t) &= (\Lambda - \gamma_n P(t))\, S_n(t) + \sum_{m=0}^{N_{\mathrm{MAX}}}{}' \, \alpha_{nm} S_m - \left(\sum_{m=0}^{N_{\mathrm{MAX}}}{}' \, \alpha_{mn} \right) S_n, \\
\dot{I}_n(t) &= \gamma_{n+1}(S_{n+1}(t) + I_{n+1}(t))P(t) - \gamma_n I_n(t) P(t) - \varepsilon I_n(t), \\
\dot{P}(t) &= mP(t-\tau) \sum_{n=0}^{N_{\mathrm{MAX}}} \gamma_n S_n(t-\tau) - P(t) \sum_{n=0}^{N_{\mathrm{MAX}}} \gamma_n (S_n(t) + I_n(t)),
\end{aligned} \tag{8}$$

where N_{MAX} is the maximum number of receptors on a single bacterium, $n = 0, \ldots, N_{\mathrm{MAX}}$. The $'$ sign indicates that when $m = n$ the corresponding term is not added. The coefficients α_{nm} measure the rate at which the individuals from sub population m shift to sub population n, i.e. the rate at which individuals gain or lose receptors. In [10] is also said that Λ can be replaced by Λ_n in order to allow different growth rates for each sub population.

An essential ingredient of (8) is the term $\gamma_{n+1}(S_{n+1}(t)+I_{n+1}(t))P(t)$ in the equation for the infected cells derivative $\dot{I}_n(t)$, because it implies that there is a receptor loss when an adsorption takes place, modeling super infections in an appropriate way.

In [9] and [10] it is considered that the number of active receptors on each cell is a phenotype (i.e. the actual expression or instance of the bacterial genes that is influenced by environmental and interaction factors), and so it is related to the structure or division into bacterial sub populations, each one grouping cells with the same number of receptors on its membrane. The authors point that they "would like to show based on several lines of evidence that phenotype switching between sub populations must exist, and that it plays a subtle but important role for bacterium/phage population dynamics".

3.3 Reversible bindings

In [15] R. Moldovan, et. al., revisit the phage rate of adsorption on E. Coli by conducting experiments along with theoretical analysis that show that the population of unbound λ phages decreases with time and, in general, obeys a double-exponential function characterized by a fast and a slow decay times. They present a kinetic model that describes the interaction between the phage and the receptor as an on-and-off process followed by an irreversible binding and claim that their model successfully predicts the double exponential behavior seen in the experiment for small MOI values and allows the corresponding rate constants to be extracted from single measurements.

The proposed equations of the kinetic model in [15] are the following:

$$\begin{aligned}
\frac{dN_{\mathrm{BP}}}{dt} &= kN_{\mathrm{B}}N_{\mathrm{P}} - (k' + k'')N_{\mathrm{BP}}, \\
\frac{dN_{\mathrm{P}}}{dt} &= k'N_{\mathrm{BP}} - kN_{\mathrm{B}}N_{\mathrm{P}}, \\
\frac{dN_{\mathrm{B}}}{dt} &= k'N_{\mathrm{BP}} - kN_{\mathrm{B}}N_{\mathrm{P}}, \\
\frac{dN^*_{\mathrm{BP}}}{dt} &= k''N_{\mathrm{BP}},
\end{aligned} \tag{9}$$

where N_{B}, N_{P}, N_{BP} and N^*_{BP}, respectively, represent the susceptible bacteria, the free phages, the transient bacteria-phage complexes and the infected bacteria populations depending on the

time variable. In our usual notation:

$$N_{\mathrm{BP}}(t) = C(t), \quad N_{\mathrm{B}}(t) = S(t), \quad N_{\mathrm{P}}(t) = P(t), \quad N^*_{\mathrm{BP}}(t) = I(t).$$

The non negative constant k measures the speed at which free phages bind to susceptible bacteria obeying the mass action law and creating the so called transient bacteria-phage complexes. The susceptible bacteria and free phages count is decreased in kPS units per time unit while the transient complexes count increases in the same amount.

Nevertheless, this phage adsorption over susceptible bacteria is considered to be non permanent but reversible instead, and, from it, detachments will occur at a non negative constant rate k' over the complexes count, i.e. the susceptible bacteria and free phages count will increase in $k'C$ units per time unit while this quantity will be instantaneously subtracted from the transient bacteria-phage complexes.

Finally a non negative constant k'' measures the rate at which a temporary attachment on bacterium-phage complex becomes a permanent binding, i.e. an infected cell. There may be more than one attached virus on a bacterium, so complexes are not necessarily one to one.

As the authors point, the double exponential function that results from solving this model is a good approximation only for small MOI and will not be valid in general. Despite this last inconvenient, we believe that the main assumption, namely the described attach-detach mechanism, is an excellent idea that may be applied to construct realistic bacteria-phage interaction models.

4 Key aspects to consider

In this paper we take special care of the following points and try to include them in the best way.

1. **Delay**. Due to the existence of a latency period that is comparable to the duplication time for a Malthusian growing bacterial population, the delay must be considered in any modeling attempt. Experimental evidence in [20] together with the work of Calsina, Palmada and Ripoll [5] show that the average latency period of a bacterial population that interacts with one phage kind is highly representative and thus can be regarded as a good approximation to the real phenomena.

2. **Resistant bacteria**. The experimental evidence pointing the existence of the so called "mutant" or resistant bacteria that will be found in any culture, even if it is seeded only with a single susceptible cell, calls for the inclusion of a state variable to represent this kind of bacteria itself. We mention here, because we consider it to be a key aspect, that, in the case of physiologically structured bacterial models, the resistant bacteria and the bacteria with zero adsorption potential (i.e. with zero phage free receptors) are not the same nor are comparable. This is because they have genetic differences that cause the formers and their descendants to lack the physiological component that allow us to structure the others.

3. **Super infections and phage adsorption on debris**. It is well known that phages do not detect if a cell is susceptible or already infected and super infections occur whenever there are phages surrounding an infected cell. In the same way, as mentioned in [18] these viruses may also bind to the free receptors on dead bacteria corpses or membrane fragments known as debris. They are even adsorbed by inorganic particles such as glass filters according to [17]. It is very important to consider that viruses get adsorbed on susceptible and infected cells, but also on debris. It may be that the adsorption rates over receptors that do not

belong to a healthy living organism are not as high as usual (see the conclusion of the interdisciplinary work in [19]), but the number of receptors on infected cells and debris can be some orders of magnitude above the bacterial count and they can not be ignored.

4. **Average adsorption constant and low adsorption on bacteria**. As we already mentioned, the mass action law with a fixed average adsorption constant is really appropriate only for small MOI values, but in actual bacteria-phage interactions the high phage concentration levels are rapidly reached. The main reason why the use of an average adsorption constant can fail has to do with the fact that the heterogeneity of the individual phage adsorption potential in a bacterial population will cause different infection and thus death rates. In a few words, the groups of cells that adsorb phages faster will die sooner. There is undeniable evidence that this heterogeneity exists, in fact, in [9] this heterogeneity is experimentally demonstrated by means of a fluorescent tagging method used on phages.

5. **Limited resources**. In a closed *in vitro* culture or in a natural environment we will always deal with limited resources that impact in a considerable way the dynamics of the species that feed from them. It is also true that regarding an unlimited resource scenario helps to simplify the modeling and calculation work in a significant manner, but again, it is a good approximation only for small concentration or population count values.

5 Main assumptions in our approach

The outer membrane's outer leaflet of the cell envelope in Gram-Negative bacteria, such as *Salmonella enterica*, is formed mainly by lipopolysaccharide molecules (LPS). These LPS are synthesized on the interior membrane's interior leaflet of the cell, as part of the metabolic normal functions, and then flipped to their final location[21].

The LPS synthesis process can produce molecules that contain a particular phage receptor, if the specific bond that is recognized by the virus is present, otherwise, if the synthesized LPS piece lacks this specific bond, it will not be a receptor but a simple cell envelope building block. It is important to point that the LPS conformation or molecule length is genetically determined and so by the LPS synthesis process the bacterial cell will intend to produce LPS molecules of the length that its DNA determines. Nevertheless it can happen that a LPS molecule result shorter than that genetically determined and so it can lack the specific phage recognition bond. As a consequence of this a bacterial population can present individuals with different number of phage receptors or, in other words, as stated in [9], a stochastic gene expression or stochastic phenotype having impact on a particular phage receptor. In [9] it is experimentally concluded that within an Escherichia Coli population under a high concentration attack of λ-phage it is possible to find individual cells that absorb viral DNA in a very smaller proportion than other bacteria of similar size in the same medium. This article presents an estimated maximum bound for the number of receptors on a single cell envelope and also a receptor distribution graphic of an experimental population sample.

In [10], as we already mentioned, a heterogeneous population dynamics model based on bacterial sub populations of individuals of the same number of receptors is proposed (see (8)). The corresponding equations include phenotype switching coefficients α_{mn}. Based on [9, 10] we now assume that phenotype switching is not stochastic but strongly influenced and guided by two factors:

- Bacterial division.
- Cell growth.

The bacterial division, also called binary fission, will produce that the cell envelope or at least its outer membrane gets divided into two remaining pieces that will stand for the cell envelopes of the daughter cells. Some building blocks may be lost, but in essence the two new cells will inherit the mother's envelope. In this way the mother cell's receptors will be divided between the daughters. For this we make two assumptions:

- The quantity of receptors of each sister is not necessarily the same, one can have more than the other.
- There may be some small receptors loss due to the fission, i.e. the sum of the number of receptors on the daughter cells will be equal or less than the mother's.

In the other hand, during the cell growth and before the next fission, each individual bacterium will develop new receptors at some speed that will be different depending on the environment conditions but mainly on the number of receptors that the cell itself already has.

As mentioned before, but not considered up to this point, the attach detach mechanism related to reversible bindings (see subsection 3.3) may be assumed to occur. We will suppose that any virus can complete step 3 of the lythic cycle over any available receptor it is able to find, after that the phage can be absorbed or return back to the environment. In this sense, we will assume that it is possible that the receptors of susceptible bacteria adsorb phages faster or easier than those of infected, dead or lysed cells. Although the probabilities for a virus to be irreversibly attached or released will not vary depending on the status of the receptor's cell.

6 Discrete model

In order to construct the equations that model the above assumptions and considerations, we will assume that there are only two kinds of bacteria, namely susceptible and resistant (often called 'mutants'), sharing the environment with one phage strain. An individual susceptible bacterium can have in principle any number of phage receptors on its membrane varying from zero up to a maximum possible value. We will define the following state variables, regarding $m \in \mathbf{N}$ as the maximum number of possible receptors on a single bacterium.

- $S_j(t)$ that will represent the susceptible bacterial sub population concentration at time t characterized by having j receptors, all of them phage free.
- $C_{j,f}(t)$ standing for the count per volume unit at time t of transient or temporary susceptible bacteria and phage complexes. Each complex will have one bacterial cell with a total of j receptors of which f will be phage free, thus it will have $j - f$ attached virus, all of them at step 3 of the lythic cycle, i.e. before injecting their DNA and having still the possibility to leave the cell. Notice that $S_j(t) \equiv C_{j,j}(t)$.
- $M(t)$, the virus resistant or 'mutant' bacteria concentration that will vary depending on time.
- $P(t)$, the phage concentration at time t.
- $R(t)$ that will represent the bulk concentration, at a given time t, of free phage receptors that remain after the DNA absorption step of the lythic cycle. This will be the sum of all the receptors of infected, dead and lysed bacteria. We may refer to this state variable as the free docking points concentration.

- $V(t)$ that will stand for the one to one transient virus-receptor complexes concentration at time t. Here we refer only to the case when a single virus is attached to one individual receptor that belonged to the concentration represented by $R(t)$.

Related to the attach detach mechanism we will consider the following non negative constants:

- k_1, the average adsorption constant according to the mass action law between free phages and free receptors of susceptible bacteria. This will imply that the adsorption rate for a phage concentration $P(t)$ that interacts with a bacterial sub population of those cells that have f free receptors out of j at time t, that is $C_{j,f}(t)$, will be $k_1 f P(t) C_{j,f}(t)$.
- k_2, the average mass action law adsorption constant for the interaction of free phages and free receptors on debris and infected cells. This will imply that the adsorption rate for a phage concentration $P(t)$ that interacts with a bulk receptors concentration $R(t)$ will be given by $k_2 P(t) R(t)$.
- k', the average rate at which the adsorbed phages are released from the receptors, being the same aside from the receptor nature.
- k'', the average rate at which the adsorbed phages are permanently attached to their receptors and inject their DNA, also being the same aside from the receptor status.

In principle we restrict $k_1 \geq k_2$, which allows the susceptible bacteria receptors adsorption to be faster than the rest of receptors, but not the contrary.

We let T be the latency period corresponding to the mean time between infection and lysis.

We assume that in the absence of phages the total bacterial concentration count will exhibit a logistic growth based on a growth factor $\alpha = \beta - \mu$, where β represents the increase due to cell division and μ the mortality. A real constant $U \in (0, \infty]$ will stand for the medium capacity or the quantity of available resources that are shared among susceptible and resistant bacteria all together. We assume that bacteria, once infected, do not feed anymore.

For this purpose we define the logistic birth rate functions

$$\begin{aligned} \beta_1(t) &= \alpha_1 - \alpha_1 \frac{M(t) + \sum_{i=0}^{m} \left[S_i(t) + \sum_{g=0}^{i-1} C_{i,g}(t) \right]}{U} + \mu, \\ \beta_2(t) &= \alpha_2 - \alpha_1 \frac{M(t) + \sum_{i=0}^{m} \left[S_i(t) + \sum_{g=0}^{i-1} C_{i,g}(t) \right]}{U} + \mu, \end{aligned} \tag{10}$$

related to the susceptible and mutant bacteria respectively, with $0 < \alpha_2 \leq \alpha_1$.

In (10) the constants α_1, α_2 correspond to the Malthusian rates at which the susceptible and mutant populations could grow with no resources restriction of any kind, being this possible if $U = \infty$, i.e. considering an infinite medium capacity. Thus for a finite medium capacity $U > 0$ we assume that the growth rate diminishes in

$$\alpha_1 \frac{M(t) + \sum_{i=0}^{m} \left[S_i(t) + \sum_{g=0}^{i-1} C_{i,g}(t) \right]}{U}$$

for both kinds of bacteria. We add the mortality rate μ because we are interested, not in the growth rate, but in the birth rate[5].

[5]Bacteria are not actually born from a mother cell, they divide into two sister cells. For our purposes, to think of a birth rate, it will be necessary to consider that one of the cells is the mother and the other is the daughter, but who is who is not important at all.

Notice that for a given $t \in \mathbf{R}$ if $\alpha_1 > \alpha_2$ then $\beta_1(t) - \beta_2(t) = \alpha_1 - \alpha_2 > 0$, meaning that the susceptible bacteria will posses at any time a competitive advantage over the mutant strain.

As we referred in the previous section, we assume a "phenotype switching" between sub populations [10], modeling the receptor development and the change of receptors count due to the cell division by means of constant coefficients ρ_{ij} that measure the conversion rate from sub population number i to subpopulation number j. We consider that a susceptible cell that gains a new receptor will switch at a constant rate $\rho_{j,j+1} \geq 0$ from sub population S_j to S_{j+1} or from $C_{j,f}$ to $C_{j+1,f+1}$, whenever $j < m$. Also, a cell of the S_j sub population that divides produces two sister cells that will belong to some sub populations S_i and S_k where $i + k \leq j$. Similarly, if the susceptible cell has some phages already attached, it belongs to a sub population $C_{j,f}$ and the binary fission will produce two daughter cells that will belong to some sub populations $C_{i,g}$ and $C_{k,h}$ where $i + k \leq j$ but also $\frac{g}{i} \approxeq \frac{f}{j} \approxeq \frac{h}{k}$, i.e. the attached phages will place each sister cell in the sub population that keeps a similar proportion of total-free receptors to that of the mother. This proportion has to be similar instead of sharp because we use natural numbers as indexes. We associate constants $\rho_{j,i}$, for $i = 1, 2, \ldots, j$, to measure the rates at which a mother cells with j receptors produces a daughter cell with i receptors.

We accomplish to include these two "phenotype switching" phenomena by means of a non negative ρ coefficients matrix of the form

$$\begin{pmatrix} \rho_{0,0} & \rho_{0,1} & 0 & 0 & & \cdots & 0 \\ \rho_{1,0} & \rho_{1,1} & \rho_{1,2} & 0 & & \cdots & 0 \\ \vdots & \vdots & \ddots & \ddots & \ddots & & \vdots \\ \rho_{j,0} & \rho_{j,1} & \cdots & \rho_{j,j} & \rho_{j,j+1} & \cdots & 0 \\ \vdots & \vdots & & & \ddots & \ddots & \vdots \\ \rho_{m-1,0} & \rho_{m-1,1} & & & \cdots & \rho_{m-1,m-1} & \rho_{m-1,m} \\ \rho_{m,0} & \rho_{m,1} & & \cdots & & \rho_{m,m-1} & \rho_{m,m} \end{pmatrix} \tag{11}$$

where $\sum_{i=0}^{j} \rho_{j,i} = 1$ and $\rho_{j,i} = 0$ whenever $i > j + 1$ for $j = 1, 2, \ldots, m$.

Each row of this matrix must fulfill another requirement related to the assumption that when a cell division takes place, the envelope of the mother is broken and used by the sister-daughters with a small or null waste of receptors. So we will ask that the coefficients $\rho_{j,i}$ for a fixed j be such that $\rho_{j,0} \approxeq \rho_{j,j}, \rho_{j,1} \approxeq \rho_{j,j-1}, \cdots$.

Using all the elements mentioned in this subsection we write our proposed model, which will be fully explained in the following pages.

$$
\begin{aligned}
\dot{S}_j(t) &= 2\beta_1(t)\sum_{i=j}^{m}\rho_{i,j}S_i(t) +' \rho_{j-1,j}S_{j-1}(t)\\
&\quad -\left[\beta_1(t)+\mu+jk_1P(t) +' \rho_{j,j+1}\right]S_j(t)+k'C_{j,j-1},\\
\dot{C}_{j,f}(t) &= 2\beta_1(t)\sum_{i=j}^{m}\rho_{i,j}\left[\sum_{g>\max\{(\mathrm{f}-\frac{1}{2})\frac{\mathrm{i}}{\mathrm{j}},-1\}}^{g\le\min\{(\mathrm{f}+\frac{1}{2})\frac{\mathrm{i}}{\mathrm{j}},\mathrm{i}\}} C_{i,g}(t)\right] +' \rho_{j-1,j}C_{j-1,f-1}(t)\\
&\quad -\left[\beta_1(t)+\mu+fk_1P(t) +' \rho_{j,j+1}\right]C_{j,f}(t)+(j-f+1)k'C_{j,f-1}(t)\\
&\quad -(j-f)(k'+k'')C_{j,f}(t) +' (f+1)k_1P(t)C_{j,f+1}(t),\\
\dot{V}(t) &= -(m+\delta+k')V(t)+k_2R(t)P(t)\\
&\quad +\sum_{i=0}^{m}\left[\sum_{g=0}^{i}(i-g)[(i-g-\iota)k''+\mu]C_{i,g}(t)\right],\\
\dot{R}(t) &= -\left(\delta+k_2P(t)\right)R(t)+k'V(t)\\
&\quad +\sum_{i=0}^{m}\left[\sum_{g=0}^{i}g((i-g)k''+\mu)C_{i,g}(t)\right],\\
\dot{P}(t) &= d-mP(t)-\left(k_1\sum_{i=0}^{m}\left[\sum_{g=0}^{i}gC_{i,g}(t)\right]+k_2R(t)\right)P(t)\\
&\quad +k'\left(V(t)+\sum_{i=0}^{m}\left[\sum_{g=0}^{i}(i-g)C_{i,g}(t)\right]\right)\\
&\quad +be^{-\mu T}k''\chi_{[T,\infty)}(t)\sum_{i=0}^{m}\left[\sum_{g=0}^{i}(i-g)C_{i,g}(t-T)\right],\\
\dot{M}(t) &= (\beta_2(t)-\mu)M(t).
\end{aligned}
\tag{12}
$$

We use the symbol $+'$ to indicate an addition that is performed whenever it makes sense.

The initial conditions of (12) are $S_j(0)\equiv C_{j,j}(0)=S_{j,0}\geq 0$, $P(0)=P_0\geq 0$, $R(0)=R_0\geq 0$, $C_{j,f}(0)=V(0)=V_0=0$, $0\leq j\leq m$, $0\leq f<j$.

Important note: The Greek letter ι in (12) represents one unit and corresponds exactly to one receptor. In order to reduce the number of equations, it is possible to change the measure units by grouping the sub populations into conglomerates of receptor ranges. This can be easily accomplished only by adjusting the actual value of ι.

To follow, we explain as clearly as possible, all the equations in (12).

The simplest equation is the last one which trivially sets the mutant bacteria population concentration derivative $\dot{M}(t)$ to be the product of the concentration and the difference of the 'birth' minus the mortality rates over time. In this way the resistant bacteria concentration will grow at a time depending rate

$$
\alpha_2-\alpha_1\frac{M(t)+\sum_{i=0}^{m}\left[\sum_{g=0}^{i}C_{i,g}(t)\right]}{U}.
$$

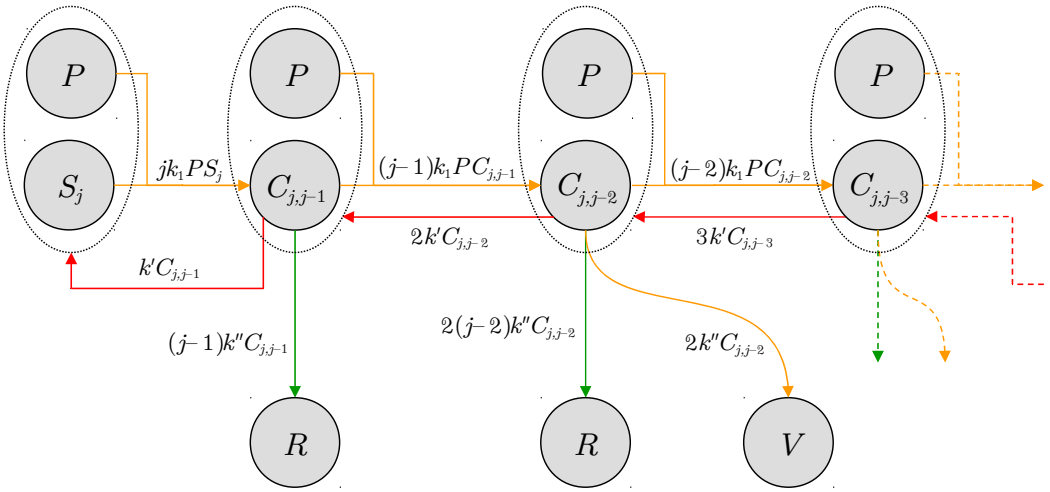

Figure 1: Interaction diagram for the first adsorptions.

Notice that if $\alpha_1 > \alpha_2$ then, for high population concentrations near to the medium capacity U we can have $\dot{M}(t) < 0$.

Given that this state variable $M(t)$ only interacts with the rest via the resource consumption we will explain the remaining equations separately based on the previous discussion and the interaction diagrams on figures 1 and 2.

Beginning with the susceptible bacteria carrying j receptors, all of them phage free, represented by S_j, we notice that its concentration will be instantaneously:

S.a) Increased in

$$2\beta_1(t)\sum_{i=j}^{m}\rho_{i,j}S_i(t)$$

that is the sum of the new born individuals proceeding from all sub populations with more or equal number of receptors that are born with j receptors. In each sub population S_i there will be $2\beta_1(t)S_i(t)$ new born cells per time unit that will be distributed among the sub populations S_k at constant rates $\rho_{i,k}$, $k = 0, 1, 2, \ldots, i$. All new born cells participate in this distribution because $\sum_{k=0}^{i}\rho_{i,k} = 1$.

S.b) Increased in $\rho_{j-1,j}S_{j-1}$ units because the individuals S_{j-1} gain one receptor at a constant rate $\rho_{j-1,j}$. This will not apply when $j = 0$, so the $+'$ sign is included.

S.c) Decreased at a variable birth rate $\beta_1(t)$, because the just divided cells will not belong to S_j, unless they are added on item S.a).

S.d) Decreased at a constant mortality rate μ.

S.e) Decreased by jk_1PS_j due to its interaction with the free phages concentration P and because each cell has j free receptors that adsorb phages according to the mass action law with constant k_1 (see figure 1).

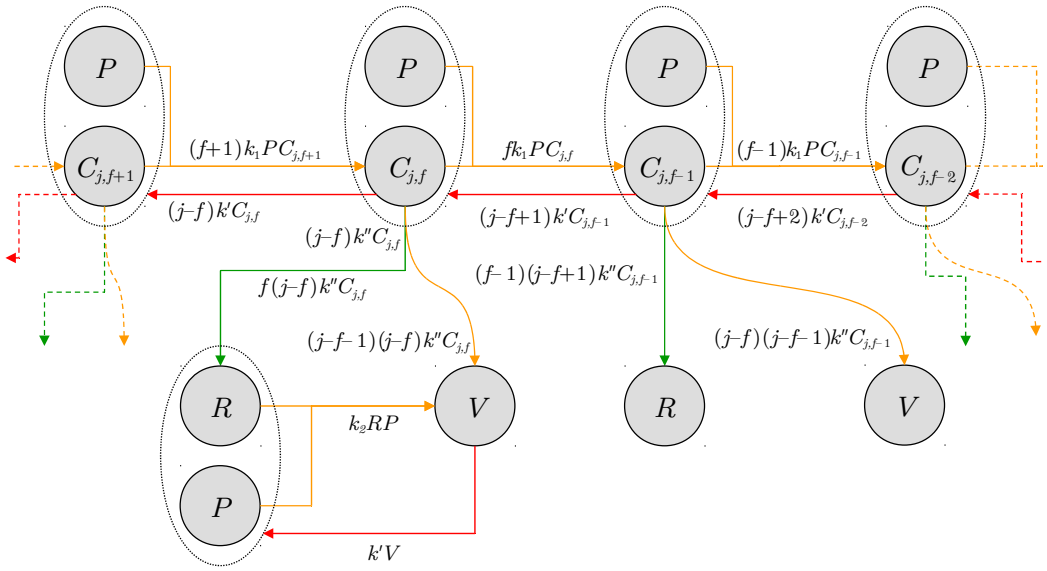

Figure 2: Interaction diagram around the $(j-f)^{\text{th}}$ adsorption.

S.f) Decreased at a constant rate $\rho_{j,j+1}$ because the cells that gain a receptor will abandon the sub population. This will not apply when $j = m$, so the $+'$ sign is included.

S.g) Increased when the process of item S.e) is reverted, that is when a transient complex of one virus and a cell $C_{j,j-1}$ is separated. This separation occurs at a constant rate k', so it increases S_j in $k'C_{j,j-1}$ per time unit.

Regarding the transient complex of j-receptors bacteria with f free receptors denoted by $C_{j,f}$, its concentration will be instantaneously:

C.a) Increased in

$$2\beta_1(t)\sum_{i=j}^{m}\rho_{i,j}\left[\sum_{g>\max\{(\mathrm{f}-\frac{1}{2})\frac{\mathrm{i}}{\mathrm{j}},-1\}}^{g\leq\min\{(\mathrm{f}+\frac{1}{2})\frac{\mathrm{i}}{\mathrm{j}},\mathrm{i}\}} C_{i,g}(t)\right]$$

offspring from all sub populations with more or equal number of receptors. Being this item similar to S.a), this time, as we already said, it is also necessary that $\frac{g}{i}\approxeq\frac{f}{j}$. For this last condition we group the sub populations $C_{i,g}$ for a fixed i by means of a round function that joins all values of $g\in\left((f-\frac{1}{2})\frac{i}{j},(f+\frac{1}{2})\frac{i}{j}\right]\cap\mathbf{N}$, if $j>0$, or $g\in\{0,1,\ldots,i\}$, if $j=0$, and relates them to f. One easy way to interpret this grouping is to think that the population of a complex $C_{j,f}$ (j total receptors and f free receptors) will incorporate the offspring of a complex $C_{i,g}$ with $i\geq j>0$ whenever $\left|\frac{g}{i}-\frac{f}{j}\right|$ is small as possible, this is when $f-\frac{1}{2}<\frac{gj}{i}\leq f+\frac{1}{2}$. For $j=0$ as a special case, $C_{0,0}$ will accept new born cells of a complex $C_{i,g}$ for any g.

C.b) Increased in $\rho_{j-1,j}C_{j-1,f-1}$ units because the individuals $C_{j-1,f-1}$ gain one (phage free) receptor at a constant rate $\rho_{j-1,j}$. This will not apply when $j=0$, so the $+'$ sign is present.

C.c) Decreased at a variable birth rate $\beta_1(t)$, because the just divided cells will not belong to $C_{j,f}$, unless they are added on item C.a).

C.d) Decreased at a constant mortality rate μ.

C.e) Decreased by $fk_1PC_{j,f}$ due to its interaction with the free phages concentration P and because each cell has f free receptors that adsorb phages according to the mass action law with constant k_1.

C.f) Decreased at a constant rate $\rho_{j,j+1}$ because of the cells that gain a (free phage) receptor. This will not apply when $j = m$, so we include the sign $+'$.

C.g) Increased when the process of item C.e) is reverted for $C_{j,f-1}$, that is when a virus gets separated from a transient complex $C_{j,f-1}$. This separation (see figure 2) occurs at a constant rate k' over each of the $j - f + 1$ occupied receptors, so it increases $C_{j,f}$ in $(j - f + 1)k'C_{j,f-1}$ per time unit.

C.h) Increased by $(f + 1)k_1PC_{j,f+1}$, as the counterpart of C.e), due to the cells with one more free receptor $C_{j,f+1}$ that acquire another phage from the concentration P and because each cell has $f + 1$ free receptors that adsorb phages according to the mass action law with constant k_1 (see figure 2). The sign $+'$ is present because of the case when $j = m$.

C.i) Decreased when the process of item C.e) is reverted for this same class, that is when a virus gets separated from a transient complex $C_{j,f}$. This separation (see figure 2) occurs at a constant rate k' over each of the $j - f$ occupied receptors, so it decreases $C_{j,f}$ in $(j - f)k'C_{j,f-1}$ per time unit.

C.j) Decreased by $(j - f)k''C_{j,f}$ (see figure 2) because of a viral DNA adsorption that occurs at a fixed rate k'' over $j - f$ receptors over each cell.

The concentration in time of the one to one transient virus-receptor complex represented by $V(t)$ will be instantaneously:

V.a) Decreased at a constant rate $m + \delta$ because the phages degrade at a rate m while the receptors do so at rate δ.

V.b) Decreased because of the released virus at a constant rate k' (see figure 2).

V.c) Increased as a consequence of the interaction between the bulk receptors concentration R and the free phages concentration P according to the mass action law with adsorption constant k_2 (see figure 2).

V.d) Increased in $(j - f - \iota)(j - f)k''C_{j,f}$ when the event described in item C.j) takes place and for all possible values of j and f. This number is obtained because a cell with f free receptors out of j will end with $j - f - \iota$ one to one transient complexes after one of the viruses inject its DNA (see figure 2).

V.e) Increased in the sum of $(j - f)\mu C_{j,f}$ over all bacterial concentration indexes because of the natural death of all bacteria, where each class $C_{j,f}$ contributes with its $j - f$ occupied receptors.

The bulk concentration in time of the receptors on debris and on infected bacteria $R(t)$ will be instantaneously:

R.a) Decreased at a constant degradation rate δ.

R.b) Decreased as a consequence of its interaction with the free phages concentration P according to the mass action law with adsorption constant k_2 (see figure 2).

R.c) Increased in $k'V$ units because of the receptors that become free when the detachments over the one to one transient complexes V take place at a constant rate k'.

R.d) Increased in $f(j-f)k''C_{j,f}$ when the event described in item C.j) takes place and for all possible values of j and f. This number is obtained because the cells have f free receptors (see figure 2).

R.e) Increased in the sum of $f\mu C_{j,f}$ over all bacterial concentration indexes because of the natural death of all bacteria, where each class $C_{j,f}$ contributes with its f phage free receptors.

Finally, the phage concentration $P(t)$ will be instantaneously:

P.a) Increased by a fixed dose supply d.

P.b) Decreased at a constant degradation rate m.

P.c) Decreased as a consequence of its interaction with the total count of free receptors over the susceptible cell membranes given by

$$\sum_{i=0}^{m}\sum_{g=0}^{i} gC_{i,g}$$

that occurs according to the mass action law with adsorption constant k_1.

P.d) Decreased as a consequence of its interaction with the bulk concentration of docking points R, according to the mass action law with adsorption constant k_2 (see figure 2). This is the counterpart of item R.b).

P.e) Increased in $k'V$ units because of the phages that become free when the detachments over the one to one transient complexes V take place at a constant rate k'.

P.f) Increased when the events of items S.e) and C.e) are reverted in a fraction k' of the total count of occupied receptors over the total bacterial population that can be computed as

$$\sum_{i=0}^{m}\sum_{g=0}^{i}(i-g)C_{i,g}.$$

P.g) Increased as a consequence of the lysis that produces $be^{-\mu T}$ virions for each cell that was infected at time $t-T$. The count of these cells correspond to the product of the constant k'' multiplied by the total count of occupied receptors over susceptible cells given by

$$\sum_{i=0}^{m}\sum_{g=0}^{i}(i-g)C_{i,g}(t-T).$$

Once a virus is permanently attached we only consider the bulk concentrations of free receptors $R(t)$ and the one to one transient receptor-phage complexes $V(t)$ at time t, the bacterial cells themselves abandon the system.

In (12), the equation for $\dot{S}_j$ is included for the sake of clarity, because $S_j(t) \equiv C_{j,j}(t)$, but it can be omitted if we redefine the logistic growth rate functions of (10) as

$$\begin{aligned} \beta_1(t) &= \alpha_1 - \alpha_1 \frac{M(t) + \sum_{i=0}^{m} \left[\sum_{g=0}^{i} C_{i,g}(t)\right]}{U} + \mu, \\ \beta_2(t) &= \alpha_2 - \alpha_1 \frac{M(t) + \sum_{i=0}^{m} \left[\sum_{g=0}^{i} C_{i,g}(t)\right]}{U} + \mu. \end{aligned} \tag{13}$$

Direct viral attach with no detach

In this case the viruses will bind to the bacteria receptors directly and inject their DNA with no detach possibility, so every viral adsorption will be followed by an absorption. We consider this process to occur according to the mass action law with constants k_1 and k_2 for susceptible bacteria and for the bulk concentration of receptors respectively. The transient complexes are no longer regarded and so the logistic growth rate functions change to

$$\begin{aligned} \beta_1(t) &= \alpha_1 - \alpha_1 \frac{M(t) + \sum_{i=0}^{m} S_i(t)}{U} + \mu, \\ \beta_2(t) &= \alpha_2 - \alpha_1 \frac{M(t) + \sum_{i=0}^{m} S_i(t)}{U} + \mu, \end{aligned} \tag{14}$$

with $0 < \alpha_2 \leq \alpha_1$, producing the following system

$$\begin{aligned} \dot{S}_j(t) &= 2\beta_1(t) \sum_{i=j}^{m} \rho_{i,j} S_i(t) +' \rho_{j-1,j} S_{j-1}(t) - \left[\beta_1(t) + \mu + jk_1 P(t) +' \rho_{j,j+1}\right] S_j(t), \\ \dot{P}(t) &= d - \left(m + k_1 \sum_{i=0}^{m} i S_i(t) + k_2 R(t)\right) P(t) \\ &\quad + be^{-\mu T} k_1 P(t-T) \chi_{[T,\infty)}(t) \sum_{i=0}^{m} i S_i(t-T), \\ \dot{R}(t) &= -\left(\delta + k_2 P(t)\right) R(t) + k_1 P(t) \sum_{i=0}^{m} i(i-\iota) S_i(t) + \mu \sum_{i=0}^{m} i S_i(t), \\ \dot{M}(t) &= (\beta_2(t) - \mu) M(t). \end{aligned} \tag{15}$$

As in (12) we use the symbol $+'$ to indicate an addition that is performed whenever it makes sense and ι stands for one unit and corresponds exactly to one receptor.

The initial conditions of (15) are $S_j(0) = S_{j,0} \geq 0$, $P(0) = P_0 \geq 0$, $R(0) = R_0 \geq 0$, $0 \leq j \leq m$.

Also as in (12) the simplest equation is the last one which sets $\dot{M}(t)$ to be the product of the concentration and the difference of the increase minus the mortality rates over time. In this way the resistant bacteria concentration will grow at a time depending rate

$$\alpha_2 - \alpha_1 \frac{M(t) + \sum_{i=0}^{m} S_i(t)}{U}.$$

As before we explain the remaining equations of (15) separately. Beginning with the susceptible bacteria carrying j phage free receptors, we notice that its concentration will be instantaneously:

S'.a) Increased in

$$2\beta_1(t)\sum_{i=j}^{m}\rho_{i,j}S_i(t)$$

that is the sum of the new born individuals proceeding from all sub populations with more or equal number of receptors that are born with j receptors (see item S.a)).

S'.b) Increased in $\rho_{j-1,j}S_{j-1}$ units because the individuals S_{j-1} gain one receptor at a constant rate $\rho_{j-1,j}$. This will not apply when $j=0$, so the $+'$ sign is included.

S'.c) Decreased at a variable birth rate $\beta_1(t)$, because the just divided cells will not belong to S_j, unless they are added on item S'.a).

S'.d) Decreased at a constant mortality rate μ.

S'.e) Decreased by jk_1PS_j due to its interaction with the free phage concentration P and because each cell has j free receptors that adsorb phages according to the mass action law with constant k_1.

S'.f) Decreased at a constant rate $\rho_{j,j+1}$ because the cells that gain a receptor will shift to sub population S_{j+1}. This will not apply when $j=m$, so the $+'$ sign is included.

The phage concentration $P(t)$ will be instantaneously:

P'.a) Increased by a fixed dose supply d.

P'.b) Decreased at a constant degradation rate m.

P'.c) Decreased as a consequence of its interaction with the total count of free receptors over the susceptible cell membranes given by

$$\sum_{i=0}^{m} iS_i,$$

that occurs according to the mass action law with adsorption constant k_1.

P'.d) Decreased as a consequence of its interaction with the bulk concentration of free receptors R according to the mass action law with adsorption constant k_2.

P'.e) Increased as a consequence of the lysis that produces $be^{-\mu T}$ virions for each cell that was infected at time $t-T$. The count of these cells correspond to the product of constant rate k_1, $P(t-t)$ and the total count of free receptors over susceptible cells given by

$$\sum_{i=0}^{m} iS_i(t-T).$$

Since the lysis takes place only after T time units we multiply by $\chi_{[T,\infty)}(t)$.

Finally, the bulk concentration in time of the receptors on debris and on infected bacteria $R(t)$ will be instantaneously:

R'.a) Decreased at a constant degradation rate δ.

R'.b) Decreased as a consequence of its interaction with the free phages concentration P according to the mass action law with adsorption constant k_2.

R'.c) Increased as a consequence of the adsorption event referred in items S'.e) and P'.c) that involve

$$k_1 P \sum_{i=0}^{m} iS_i$$

cells that end with one less free receptor, so each cells of a sub population S_i will contribute to add $(i - \iota)$ receptors to the bulk concentration R.

R'.d) Increased as a consequence of the natural death event in items S'.d) that involve

$$\mu \sum_{i=0}^{m} iS_i$$

receptors, because each sub population S_i contributes to add i phage free receptors per cell to the bulk concentration R.

7 Continuous model

In order to get a continuous version for system (12) we may assume that the receptor synthesis process is related to the receptor's adsorption capability in the sense that a completely finished and properly placed receptor will present its maximum and final adsorption potential and during the previous moments the receptor will possess a fraction of this final adsorption capability proportional to the advance in its placement process. In this way for all practical matters a receptor that is a fraction placed will be a fraction of a receptor.

Under the above consideration we will replace the discrete number of receptors $j \in \mathbf{N}$ by a continuous real variable $x \in \mathbf{R}$. In the same manner the free receptors number $f \in \mathbf{N}$ will change to the real number $y \in \mathbf{R}$. In this way $C_{j,f}(t)$ becomes the density function $C(x, y, t)$ for $(x, y) \in \{(x, y) \in \mathbf{R}^2 | 0 \leq x \leq m, 0 \leq y \leq x\}$.

Since the total susceptible bacterial population is now given by

$$S(t) = \int_0^m \int_0^x C(x, y, t) dy dx$$

we redefine the logistic birth functions to

$$\beta_1(t) = \alpha_1 - \alpha_1 \frac{M(t) + S(t)}{U} + \mu,$$
$$\beta_2(t) = \alpha_2 - \alpha_1 \frac{M(t) + S(t)}{U} + \mu,$$

and let $\rho = \rho(u, v)$ be the division transition function from a bacteria that has u receptors to a one having v receptors. The condition $\sum_{i=0}^{j} \rho_{j,i} = 1$, for all $j = 1, 2, \ldots, m$, imposed on the coefficients matrix (11) for the discrete system has to be modified into

$$\int_0^u \rho(u, v) dv = 1, \tag{16}$$

for all $u \in [0, m]$.

The elements $\rho_{j,j+1}$ of the coefficients matrix (11) are transformed into a continuous function $\nu(x) : [0, m] \to \mathbf{R}$, that represent the velocity at which a bacteria with x receptors develops or gains a new receptor. Due to its biological nature, this function must satisfy $\nu(x) > 0$, whenever $x \in [0, m)$, and $\nu(m) = 0$ in order to allow all cells to eventually reach the maximum number of receptors m and to avoid that cells with m receptors to develop new ones.

Considering all this elements we introduce the following system

$$
\begin{aligned}
C_t(x,y,t) &= 2\beta_1(t)\int_x^m \rho(u,x)C\left(u,\frac{uy}{x},t\right)du - \left[\beta_1(t)+\mu+k''(x-y)\right]C(x,y,t)\\
&\quad -\nu(x)\left(C_x(x,y,t)+C_y(x,y,t)\right)-\nu'(x)C(x,y,t)\\
&\quad +k_1P(t)\left[C(x,y,t)+yC_y(x,y,t)\right]\\
&\quad +k'\left[(y-x)C_y(x,y,t)+C(x,y,t)\right]\\
\dot{V}(t) &= -(m+\delta+k'+k'')V(t)+k_2R(t)P(t)\\
&\quad +\int_0^m\int_0^u (u-v)[(u-v-\iota)k''+\mu]C(u,v,t)dvdu\\
\dot{R}(t) &= -\left(\delta+P(t)\right)R(t)+k'V(t)+\int_0^m\int_0^u v((u-v)k''+\mu)C(u,v,t)\\
\dot{P}(t) &= d-mP(t)-\left(\int_0^m\int_0^u vk_1C(u,v,t)dvdu+k_2R(t)\right)P(t)\\
&\quad +k'\left[V(t)+\int_0^m\int_0^u (u-v)vC(u,v,t)dvdu\right]\\
&\quad +be^{-\mu T}k''\chi_{[T,\infty)}(t)\int_0^m\int_0^u (u-v)C(u,v,t-T)dvdu\\
\dot{M}(t) &= (\beta_2(t)-\mu)M(t)
\end{aligned}
\tag{17}
$$

where $\nu'(x) = \frac{d}{dx}\nu(x)$ and, as in system (12), ι stands for one unit and corresponds exactly to one receptor.

What follows is an explanation, intended to be as clear as possible, of how system (17) is obtained from (12) by means of a limit process, and/or, in the opposite direction, why is that the latter is a discretization or a discrete approximation of the former.

For the first equation in (17), we notice that after grouping some terms we can rewrite the equation for $\dot{C}_{j,f}(t)$ in (12) as

$$
\begin{aligned}
\dot{C}_{j,f}(t) &= 2\beta_1(t)\sum_{i=j}^{m}\rho_{i,j}\left[\sum_{g>\max\{(\mathrm{f}-\frac{1}{2})\frac{\mathrm{i}}{\mathrm{j}},-1\}}^{g\le\min\{(\mathrm{f}+\frac{1}{2})\frac{\mathrm{i}}{\mathrm{j}},\mathrm{i}\}} C_{i,g}(t)\right]\\
&\quad -\left(\beta_1(t)+\mu+k''(j-f)\right)C_{j,f}(t)\\
&\quad +'\,\rho_{j-1,j}C_{j-1,f-1}(t)-'\,\rho_{j,j+1}C_{j,f}(t)\\
&\quad +'\,k_1P(t)\left((f+1)C_{j,f+1}(t)-fC_{j,f}(t)\right)\\
&\quad +k'\left((j-(f-1))C_{j,f-1}(t)-(j-f)C_{j,f}(t)\right).
\end{aligned}
\tag{18}
$$

The term

$$2\beta_1(t)\sum_{i=j}^{m}\rho_{i,j}\left[\sum_{g>\max\{(\mathrm{f}-\frac{1}{2})\frac{\mathrm{i}}{\mathrm{j}},-1\}}^{g\leq\min\{(\mathrm{f}+\frac{1}{2})\frac{\mathrm{i}}{\mathrm{j}},\mathrm{i}\}} C_{i,g}(t)\right], \tag{19}$$

as we pointed out in item C.a, represents the increment of the bacteria-phage complexes, with j receptors of which f are phage free, due to the division of all complexes with greater or equal number of total receptors, but such that the total/free receptors proportion of the divided cell is similar (as near as possible) to $\frac{j}{f}$. We have to do this because in the discrete version we can not consider fractions of receptor and we have to place the divided cells somewhere, but in the continuum version we do not have restrictions of this kind. Instead of (19) we can write

$$2\beta_1(t)\int_x^m \rho(u,x)C\left(u,\frac{uy}{x},t\right)du \tag{20}$$

in the equation for $C_t(x,y,t)$, and this time

$$\frac{u}{\frac{uy}{x}} \equiv \frac{x}{y},$$

which means that a just divided cell of a transient complex will increase the density of complexes possessing exactly the same proportion of total and free receptors that it actually has. The rounding process of the inner sum in (19) is no longer necessary.

The next line in (18) explains itself.

We notice that if $\vec{u}=(1,1,0)$ then the directional derivative

$$\begin{aligned}\nabla_{\vec{u}}\left(\nu(x)C(x,y,t)\right) &= \lim_{\Delta\to 0}\frac{\nu(x)C(x,y,t)-\nu(x-\Delta)C(x-\Delta,y-\Delta,t)}{\Delta}\\ &\approx\ -\ \frac{\nu(x-\Delta)C(x-\Delta,y-\Delta,t)-\nu(x)C(x,y,t)}{\Delta}\\ &\approx -\nu(x-1)C(x-1,y-1,t)-\nu(x)C(x,y,t)\\ &= \rho_{j-1,j}C_{j-1,f-1}(t)-\rho_{j,j+1}C_{j,f}(t).\end{aligned} \tag{21}$$

Similarly, the partial derivative

$$\begin{aligned}\frac{\partial}{\partial y}\left(k_1P(t)yC(x,y,t)\right) &= k_1P(t)\lim_{\Delta\to 0}\frac{(y+\Delta)C(x,y+\Delta,t)-yC(x,y,t)}{\Delta}\\ &\approx k_1P(t)\frac{(y+\Delta)C(x,y+\Delta,t)-yC(x,y,t)}{\Delta}\\ &\approx k_1P(t)\left((y+1)C(x,y+1,t)-yC(x,y,t)\right)\\ &= k_1P(t)\left((f+1)C_{j,f+1}(t)-fC_{j,f}(t)\right),\end{aligned} \tag{22}$$

and also

$$\begin{aligned}\frac{\partial}{\partial y}\left(k'(y-x)C(x,y,t)\right) &= k'\lim_{\Delta\to 0}\frac{(y-x)C(x,y,t)-(y-x-\Delta)C(x,y-\Delta,t)}{\Delta}\\ &\approx k'\frac{(y-x)C(x,y,t)-(y-x-\Delta)C(x,y-\Delta,t)}{\Delta}\\ &\approx k'\left((y-x)C(x,y,t)-(y-x-1)C(x,y-1,t)\right)\\ &= k'\left((j-(f-1))C_{j,f-1}(t)-(j-f)C_{j,f}(t)\right).\end{aligned} \tag{23}$$

Notice that in (21) and (23) we are taking the left hand derivative and in (22) the right hand derivative.

The equations of the remaining state variables in (17) are direct translations to the continuous case of (12) that do not involve any complicated details.

The corresponding continuous version for an attach with no detach process would be the following

$$
\begin{aligned}
S_t(x,t) + \frac{\partial}{\partial x}\left(\nu(x)S(x,t)\right) &= 2\beta_1(t)\int_x^m \rho(u,x)S\left(u,t\right)du - \left[\beta_1(t) + \mu + k_1 x P(t)\right]S(x,t) \\
\dot{P}(t) &= d - \left(m + k_1\int_0^m uS(u,t)du + k_2 R(t)\right)P(t) \\
&\quad + be^{-\mu T}k_1 P(t-T)\chi\left[T,\infty\right)(t)\int_0^m uS(u,t-T)du \\
\dot{R}(t) &= -\left(\delta + P(t)\right)R(t) + k_1 P(t)\int_x^m u(u-\iota+\mu)S\left(u,t\right)du \\
\dot{M}(t) &= (\beta_2(t) - \mu)M(t)
\end{aligned}
$$

where $\nu'(x) = \frac{d}{dx}\nu(x)$ and, as in system (12), ι stands for one unit and corresponds exactly to one receptor.

8 Concluding remarks

We have introduced realistic models for the bacteria-phage population interaction which takes into account in a mechanistic manner all the relevant facts that, as far as we know, impact the growth and decay rates of both populations: presence of phage resistant bacteria, latency period, phage adsorption on each individual phage receptor on dead or alive bacterial membranes, attach-detach phenomena and limited resources.

Although in an actual biological situation the discrete versions of our models could have several thousands of equations becoming unbearable in its complexity, either analytically or numerically, we can choose one of the following alternatives:

- Work on the PDE continuous versions.
- Change the measure units and adjust the actual value of an individual receptor ι by grouping the sub populations into conglomerates of receptor ranges.

Moreover, system (12) by itself should improve our understanding of a complex dynamics and all involved mechanisms of actual bacteria-phage interaction and could serve as a departure point for further work.

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