



Bacterial debris—an ecological mechanism for coexistence of bacteria and their viruses

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Abstract

A model of bacteria and phage survival is developed based on the idea of shielding by bacterial debris in the system. This model is mathematically formulated by a set of four nonlinear difference equations for susceptible bacteria, contaminated bacteria, bacterial debris and phages. Simulation results show the possibility of survival, and domains of existence of stable and unstable solutions
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1. Introduction

Multiplication of virulent bacteriophages (bacterial viruses) consists of three steps (Adams, 1959; Hayes, 1968). In the first, a phage attaches itself to a receptor on the bacterial envelope and injects its DNA into the cell, thus stopping its autonomous functioning. The second step consists of a so-called latent period, during which the phage multiplies inside the infected bacterium. Finally, cell lysis releases into the system newly created phages, leaving behind a dead bacterium, or debris (Kutter et al., 1994). The burst size (number of phages released from each cell) is usually of the order of 10–100, depending on the physiological conditions of the host bacterium (Hadas et al., 1997; Rabinovitch et al., 1999a). This process recurs along a sequence of “generations”. Following a finite number of generations, all bacteria would be extinct, and having no sustenance, the phages too would die out after some additional time. In nature however, this does not occur: both bacteria and phages do survive. The problem of how they coexist thus arises; this has interested the biological community for quite a long time now.

Experimental work and model calculations of this process are abundant, starting with Campbell (1961), and the seminal work by Levin et al. (1977). But before discussing their results, let us consider a possible general solution to the survival problem, namely that of resistant bacteria (Abedon, 2003). According to this hypothesis, a phage-resistant mutant, which preexists in the system (Luria and Delbruck, 1943), takes over under phage multiplication, while the susceptible bacteria die. The phages then develop new means to infect the resistant strain, and so on. This hypothesis however is unable to explain results, both experimentally and theoretically (e.g., Bohannan and Lenski, 2000). Resistant bacteria do occur in reality, but (a) the sensitive, wild-type strains do not disappear, and (b) the “arms race” between phages and bacteria is too slow to account for the long term behaviour of both species.

Existing mathematical models are usually based on Levin et al. (1977) and treat evolution in chemostat cultures. They consist of several coupled nonlinear ordinary differential equations describing the time evolution of the different species: phages, bacteria, and sometimes nutrients.

The article by Schrag and Mittler (1996) is an excellent review of the developments achieved until 1995, as well as a source of relevant references. It gives a systematic discussion of all existing hypotheses to resolve the problem, namely numerical refuge, arms

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race, transitory immuneness and spatial refuge, and concludes that spatial refuge is the preferred survival mechanism. This contention however was opposed in a recent comprehensive review by Bohannan and Lenski (2000) describing numerous experiments and calculations on several bacterium/bacteriophage interacting systems. Observing that several bacterial mutations occur in the system, and maybe long-term phage mutations as well, they conducted an in-depth investigation of how these mutations influence the behaviour of the system and its adaptation to environmental changes, and showed that in the long run, original susceptible bacteria still exist, albeit in small quantities, together with a group of original, non-modified phages.

We propose here yet another solution to the question of co-existence, based on the idea of *shielding* by *bacterial debris*: when an active phage adsorbs into fragments of lysed cells, so-called debris (Kutter et al., 1994), its DNA is injected into it in a suicidal manner; having no living organism to thrive on, it cannot multiply and is discounted from the system as a phage. After some elapsed time, in either a standing culture or a serial experiment, the amount of debris can be large enough so as to effectively shield the remaining bacteria, depending of course on the natural dissolution rate of the debris.

2. The model

Unlike previous calculations (e.g. Levin et al., 1977; Schrag and Mittler, 1996; Bohannan and Lenski, 2000), a rather simple model is considered here, which assumes that resources are abundant and practically inexhaustible, hence they do not appear in the equations. Phage multiplication starts by penetration of its DNA into a bacterium, where it spends a latent period τ , after which the infected bacterium bursts, releasing a number β of new phages into the system. We consider here a “generation” model whereby all bursts and new infections occur at discrete points in time separated by τ , and the time evolution of the concentrations of all species in the system is monitored only at these time points. Resistant bacteria as well as statistical changes and spreads, usually accounted for in other models, are ignored here. The system consists of four species with the following concentrations at time step g : sensitive bacteria N_g , infected bacteria M_g , debris D_g , and phages V_g . Uninfected bacteria multiply at a rate ψ' , so that at time step $g+1$, and without the presence of phages, their concentration would increase by ψN_g , where

$$\psi = \exp(\psi'\tau) - 1 \approx \psi'\tau \quad \text{for } \psi'\tau \ll 1 \quad (1)$$

is, in the absence of phages, the self-multiplication rate per phage generation. We follow the customary assumption that phages are adsorbed onto bacteria at a rate

proportional to the product of their concentrations and an adsorption time constant δ' , such that the concentration of uninfected bacteria at time step $g+1$ is reduced by the amount $\delta N_g V_g$, where $\delta \approx \delta'\tau$. The balance equation for susceptible bacteria is therefore

$$N_{g+1} = (1 + \psi)N_g - \delta N_g V_g. \quad (2)$$

Next we consider the balance equation for the transition of infected bacteria to step $g+1$: to the M_g already present, $\delta N_g V_g$ are added through infection of N_g , and $\delta N_{g-1} V_{g-1}$ are subtracted by burst after a generation period of one step from $g-1$ to g and their transformation into debris. This gives: $M_{g+1} = M_g + \delta N_g V_g - \delta N_{g-1} V_{g-1}$, and a simple argument allows this balance equation to be readily simplified by setting $M_0 = 0$, and $M_1 = \delta N_0 V_0$, to give

$$M_{g+1} = \delta N_g V_g. \quad (3)$$

Note that at this instant, all previously infected bacteria till step $g-1$ have already burst, and are absent from the balance equation.

We further assume that the dissolution of debris is proportional to q per generation, and the decrease of phage concentration per generation, by all mechanisms except the adsorption, is proportional to d_v . (These quantities are obtained from a similar argument to that leading to ψ : for example, if q' is the dissolution rate, then $q \approx q'\tau$, provided that $q'\tau \ll 1$.) The changes of concentrations of species D and V in one generation are thus given by the following equations:

$$D_{g+1} = (1 - q)D_g + \delta N_{g-1} V_{g-1}, \quad (4)$$

$$V_{g+1} = (1 - d_v)V_g + \beta \delta N_{g-1} V_{g-1} - \delta V_g \Sigma_g, \quad (5)$$

where β is the burst size. In the last term of Eq. (5), $\Sigma_g = N_g + M_g + D_g$ incorporates the possibility of a secondary infection of M . Assuming that the adsorption rate δ is the same on all infectable species N , M , D , allows rescaling all concentrations as follows: by multiplying Eqs. (2)–(5) by δ , redefining $\delta N \rightarrow N$, $\delta M \rightarrow M$, etc., and replacing $\delta N_{g-1} V_{g-1}$ with M_g by Eq. (3), the following set of difference equations is obtained:

$$N_{g+1} = (1 + \psi)N_g - N_g V_g, \quad (6)$$

$$M_{g+1} = N_g V_g, \quad (7)$$

$$D_{g+1} = (1 - q)D_g + M_g, \quad (8)$$

$$V_{g+1} = (1 - d_v)V_g + \beta M_g - V_g \Sigma_g. \quad (9)$$

In this set of Eqs. (6)–(9) (subsequently denoted by (S)), the concentrations are measured in units of δ^{-1} . To solve (S) one must impose a set of initial values N_0 , M_0 , D_0 , V_0 . If no phages are introduced in the system ($V_0 = 0$), then $M_g = D_g = V_g = 0$ for all g , and N increases indefinitely. This solution, of course, is quite uninteresting.

It is easily seen that (S) has two fixed point (steady-state) solutions (subscript p), obtained by inserting $N_{g+1} = N_g = N_p$, $M_{g+1} = M_g = M_p$, etc. The trivial solution $N_p = M_p = D_p = V_p = 0$ is an unstable saddle point F_1 since an arbitrarily small positive change in N would cause an increase away from F_1 . The interesting fixed point solution F_2 is

$$V_p = \psi, \tag{10}$$

$$N_p = d_v / [\beta - 1 - \psi(1 + 1/q)], \tag{11}$$

$$M_p = N_p \psi, \tag{12}$$

$$D_p = N_p \psi / q, \tag{13}$$

which must all be positive. This is possible as long as $\beta > 1 + \psi(1 + 1/q)$, a seemingly strange result, since one would intuitively expect to get a solution only when the debris dissolution rate is *small*. However, a small q , along with a reasonable value of β would make N_p negative in Eq. (11). It will be shown below that too small a dissolution rate causes large population oscillations, ultimately leading to the null solution.

3. Stability analysis of F_2

In order to analyse the stability of the fixed point F_2 in the four-dimensional space of the physical parameters β, ψ, q, d_v we linearize system (S) in the vicinity of F_2 , and calculate the eigenvalues of the Jacobian matrix. This is done, as usual, by setting $N_g = N_p + n_g$, $M_g = M_p + m_g$, $D_g = D_p + d_g$, $V_g = V_p + v_g$, where n_g, m_g, d_g, v_g are small increments, and neglecting second-order terms. The linearized system is given in matrix form by

$$\begin{bmatrix} n_{g+1} \\ m_{g+1} \\ d_{g+1} \\ v_{g+1} \end{bmatrix} = \begin{bmatrix} 1 & 0 & 0 & -N_p \\ \psi & 0 & 0 & N_p \\ 0 & 1 & 1 - q & 0 \\ -\psi & \beta - \psi & -\psi & 1 - N_p \beta \end{bmatrix} \begin{bmatrix} n_g \\ m_g \\ d_g \\ v_g \end{bmatrix}. \tag{14}$$

The fourth degree characteristic equation for the eigenvalues is constructed by subtracting λ from the diagonal terms of the matrix, and equating the determinant to zero. Its roots are functions of the physical parameters, and can be all real, or pairwise complex conjugate. The necessary condition for F_2 to be a stable fixed point is that the absolute values of *all* eigenvalues be < 1 . While it is hard to visualize the entire four-dimensional space of all parameters, we have chosen to represent some of the stability properties in the subspace of (β, ψ) for several discrete values of q and d_v . For the T4-*Escherichia coli* system (Hadas et al., 1997; Rabinovitch et al., 1999a, b), β varies roughly between 2 and 200, while $5 \times 10^{-3} < \psi' < 3.5 \times 10^{-2}$, and $10 < \tau < 35$, which yields $0.05 < \psi < 1.2$. Due to their

strong viability, the dissolution time constant d_v of the phages is typically rather small, on the order of 10^{-3} per generation, or less. Being almost undocumented, the values of q on the other hand, were chosen rather arbitrarily in these calculations. The composite Fig. 1 consists of three frames corresponding to different values of $d_v = 10^{-6}, 10^{-4}$, and 1.5×10^{-3} , where the curves of the stable/unstable transition limit (solid lines) are shown for a set of three values of $q = 8 \times 10^{-4}, 1.5 \times 10^{-3}$, and 3×10^{-3} . The dashed lines represent the locus where the denominator in Eq. (11) changes sign for the corresponding q . Below these lines the fixed point has negative coordinates, and is certainly non-physical, although instability also occurs between solid and dashed lines for the same q . Notice that the solid and dashed lines become indistinguishable in the lower frame.

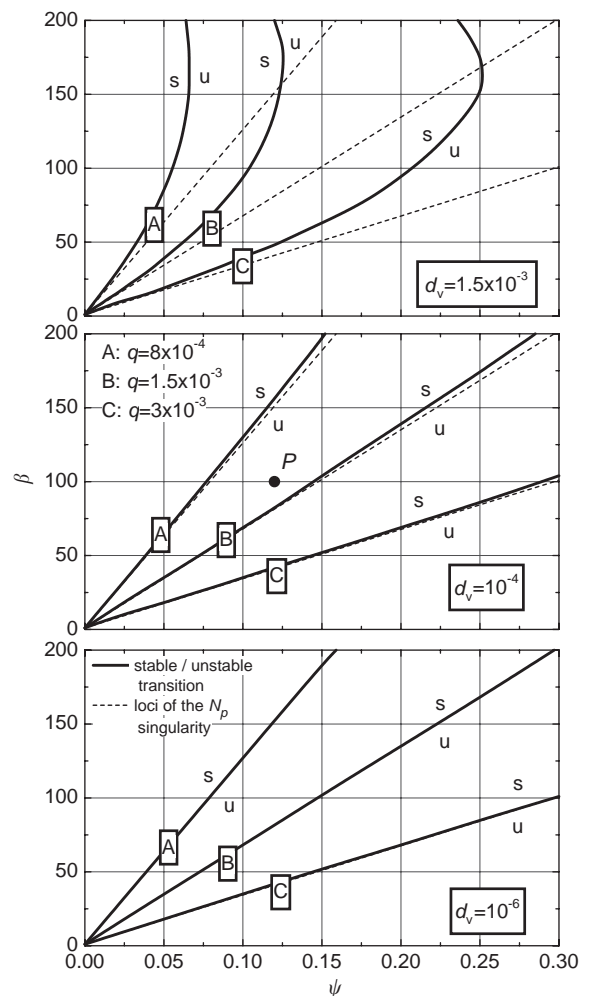


Fig. 1. The (ψ, β) parameters' subspace showing the loci curves (solid lines) across which a transition occurs between regions (s/u) of stable and unstable fixed points of system (S), for different values of q , and three "layers" of $d_v = 10^{-6}, 10^{-4}$, and 1.5×10^{-3} . Also shown (dash lines) are the loci of singularity of N_p , according to Eq. (11). The legends apply to all frames. For the meaning of the point $\bullet P$, see text, Section 4.

The numerical mapping of eigenvalues for all three q values in the displayed section of the (β, ψ) plane shows in fact that they are either all four real, or two real and a pair of complex conjugate. The last case always occurs on both sides of the vicinity of the stability curves, making the F_2 points stable/unstable *foci*, with all $|\lambda| < 1$, or at least one $|\lambda| > 1$, respectively; the dynamical solution of (S) will therefore *spiral* either into, or away from F_2 , provided that the starting point was inside/outside the basin of attraction (BA) of F_2 , respectively.

4. Time series simulations

In order to understand the qualitative features of this model, we subsequently present the time evolution of the component species, by direct simulation of the time series of system (S) for a few typical conditions. Only the species N , D , and V will be addressed and displayed since M remains very small at all times, and its evolution is rather inconsequential. All simulations were carried out with $d_v = 10^{-4}$, at the point P in the (β, ψ) plane, i.e. $\psi = 0.12$, $\beta = 100$, Fig. 1, middle frame.

4.1. An unstable system

We begin with a typical evolution of an unstable system with $q = 8 \times 10^{-4}$, shown in Fig. 2. The coordinates in the three-species subspace (N, D, V) of the corresponding unstable fixed point F_2 are, by Eqs. (10)–(13): $N_p = -1.9 \times 10^{-6}$, $D_p = -2.9 \times 10^{-4}$

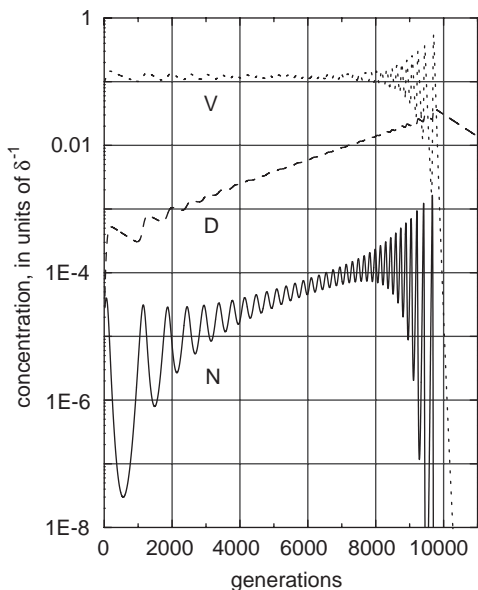


Fig. 2. A diverging oscillatory time series, corresponding to the point P in Fig. 1 and $q = 8 \times 10^{-4}$. The fixed point F_2 is unstable. Initial conditions are $N_0 = 2 \times 10^{-5}$, $V_0 = 0.1$, $D_0 = 0$. Species N and V eventually die out abruptly, while D decays exponentially.

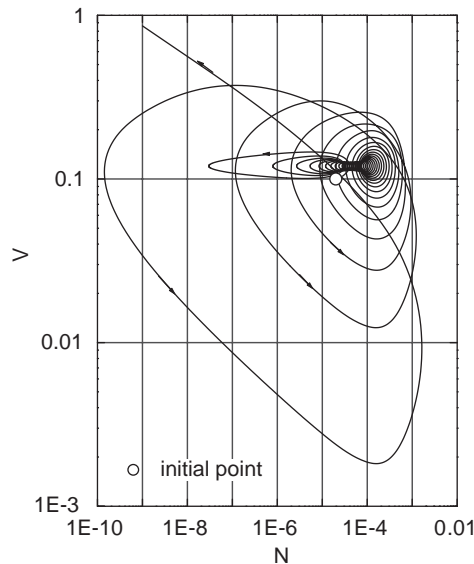


Fig. 3. The trajectory in the (V, N) phase plane of the time series of Fig. 2.

(both negative), and $V_p = 0.12$. Initiated at $N_0 = 2 \times 10^{-5}$, $V_0 = 0.1$, $D_0 = M_0 = 0$, this simulation illustrates the progress of oscillations during three stages, typified by the amplitude of N : the first starts with a relatively large amplitude oscillations which decrease until, in the second stage, the oscillations become again progressively larger. Stage three is marked by a complete, and very rapid collapse of both bacteria and phages, and slow exponential decay of D . Under varying initial conditions the species populations may oscillate more or less widely, and the duration of the series may be more or less extended. However, F_2 being an unstable fixed point, all species eventually become extinct. Fig. 3 illustrates the time evolution of the same example in the (V, N) phase plane, where the three stages can easily be identified.

4.2. A stable system

Next, we consider a stable system corresponding to $q = 1.5 \times 10^{-3}$, which situates P above the stable/unstable locus. The stable fixed point F_2 is a focus at: $N_p = 5.3 \times 10^{-6}$, $D_p = 4.24 \times 10^{-4}$, $V_p = 0.12$. The “co-existence ratio” defined here as V_p/N_p is about 2.3×10^4 , in good agreement with experimental results, e.g. Chao et al. (1977). Note that the approach of the dynamical solution towards a stable focus always presents a damped (convergent) oscillatory behaviour. Initiated at $N_0 = 10^{-6}$, $V_0 = 0.1$, $D_0 = M_0 = 0$, the time evolution in this case is represented in Fig. 4. The first minimum of any convergent oscillatory N -series, indicated by a little arrow in this figure, is always the deepest of all. The solid line spiral trajectory in the (V, N) phase plane illustrates this behaviour in Fig. 5,

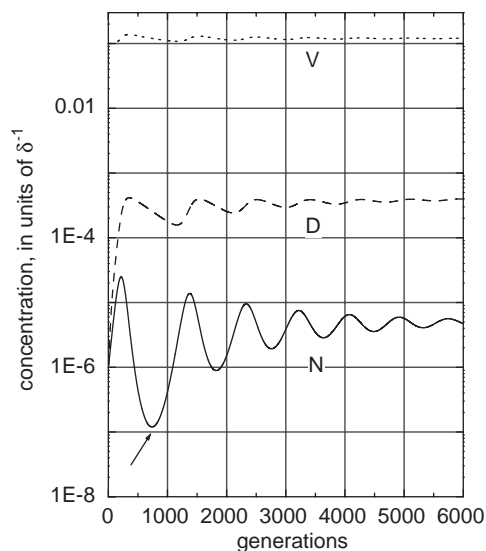


Fig. 4. A stable focus time series, corresponding to the point P in Fig. 1 and $q = 1.5 \times 10^{-3}$. The coordinates of F_2 are: $N_p = 5.3 \times 10^{-6}$, $D_p = 4.24 \times 10^{-4}$, $V_p = 0.12$. Initial conditions: $N_0 = 10^{-6}$, $V_0 = 0.1$, are situated inside the BA. The series converges towards F_2 , and the little arrow indicates the first (deepest) down swing of the N population.

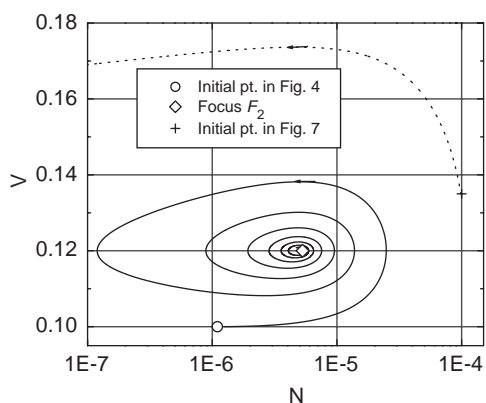


Fig. 5. The phase plane (V, N) trajectories corresponding to the time series represented in Fig. 4 (solid line), and in Fig. 7 (dashed line), respectively.

indicating that the initial state point is situated within the BA of F_2 . Indeed it will subsequently be shown that stability is obtained only within some of initial combinations of bacteria and phage populations.

The precise boundaries of the “mathematical” BA of a given fixed point F_2 are very hard to determine, even partially in the two-dimensional subspace (N, V) . It may be infinite, or have a finite extent, with a very complicated shape. However, since we are dealing here with the model of a real “biological” system, inherently unable to capture all its details, it is reasonable therefore to impose some additional constraints on the size of the BA, inferred from an understanding of the real system. For example, we may assume that if, during its evolution in time, the population of bacteria N falls

below a certain lower level, it should be regarded as practically extinct. As a matter of illustration we choose a lower limit of $N \approx 10^{-10}$, which, due to the scaling by δ^{-1} , corresponds to about 3 individuals/ml in the sample. Thus, when the value of N drops below this limit during its first, deepest, down swing, the species becomes “extinct”, thereby drastically reducing the extent of the corresponding BA.

Fig. 6 represents the map of such a biological BA of F_2 (diamond) in the (N, V) plane. It was constructed by simulating a large number of time series initiated at various points (N_0, V_0) in the plane. All series initiated *inside* the contour stayed above the lower limit of 10^{-10} , while those starting *outside* dropped below this value. A sample of such initial points (crosses) is shown around the contour, the adjacent negative numbers $-s$ indicating the values 10^{-s} below which drop the first minima of the corresponding N -series. It is seen that the boundaries of the BA extend over more than three orders of magnitude of N , while the V range is extremely narrow. The system becomes unstable for initial N populations above 10^{-4} .

Fig. 7 represents the simulation of the same physical system, except that it was initiated from a state outside the BA, namely at $N_0 = 10^{-4}$, $V_0 = 0.135$, $D_0 = M_0 = 0$, indicated by the cross marked A on the BA map of Fig. 6. The results show a relatively rapid extinction of N , followed by the usual exponential decay of D and V , occurring in the absence of live bacteria. This behaviour is also illustrated in the (V, N) phase plane of Fig. 5 by the dashed line monotonous trajectory.

4.3. Shielding by debris

Finally, we wish to demonstrate the main idea announced in the Introduction, namely *shielding* by *debris*, whereby active phages are “wasted” by sterile

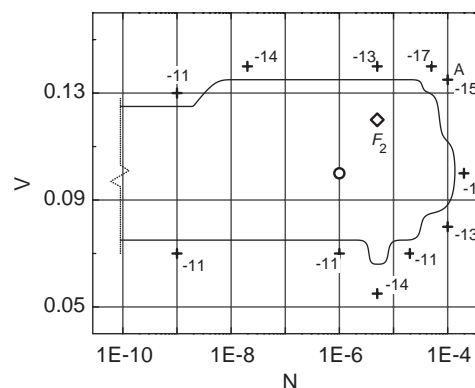


Fig. 6. The BA — of the stable focus F_2 \diamond . See text for definition. The circle \circ indicates the initial point corresponding to the time series of Fig. 4. Crosses $+$ indicate initial points outside the BA, while the adjacent negative numbers $-s$ indicate that the first down swing of the correspondingly initiated time series drops below 10^{-s} . The cross marked A corresponds to the time series of Fig. 7.

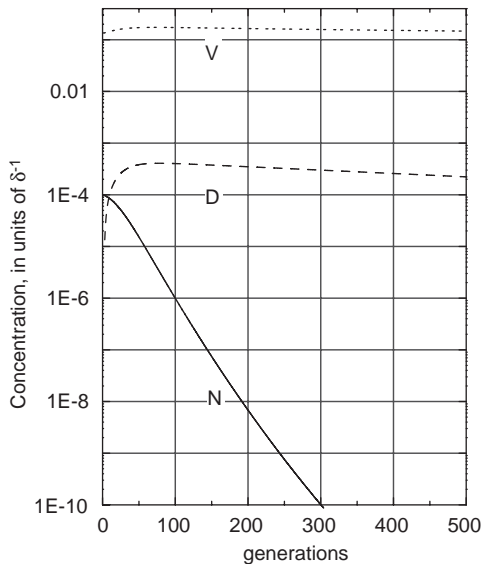


Fig. 7. Same system as in Fig. 4, except that the initial conditions $N_0 = 10^{-4}$, $V_0 = 0.135$, $D_0 = 0$, are situated outside the BA.

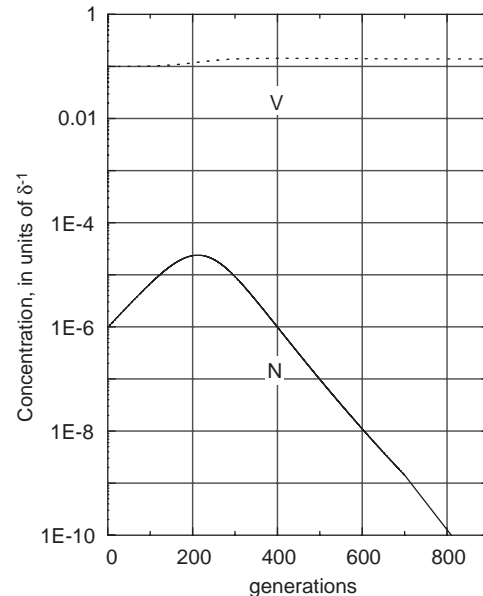


Fig. 8. The time series for a physical system identical to the one in Fig. 4, with debris discarded. The focus F_2 with coordinates $N_p = 1.01 \times 10^{-6}$, $V_p = 0.12$ is unstable. Initial conditions as in Fig. 4.

infection of a relatively large population of remnants of dead bacteria (debris) in the culture, thus being discounted from the system, without further consequences.

Reasoning backwards for this purpose, we solve instead of (S), a system of equations with only three components N , M , and V , where debris D are completely ignored

$$N_{g+1} = (1 + \psi)N_g - N_g V_g, \tag{15}$$

$$M_{g+1} = N_g V_g, \tag{16}$$

$$V_{g+1} = (1 - d_v)V_g + \beta M_g - V_g(N_g + M_g). \tag{17}$$

An analysis of stability for the fixed points similar to that in Section 3 leads, instead of Eq. (14), to the following linearized system:

$$\begin{bmatrix} n_{g+1} \\ m_{g+1} \\ v_{g+1} \end{bmatrix} = \begin{bmatrix} 1 & 0 & -N_p \\ \psi & 0 & N_p \\ -\psi & \beta - \psi & 1 - \beta N_p \end{bmatrix} \begin{bmatrix} n_g \\ m_g \\ v_g \end{bmatrix}, \tag{18}$$

where, instead of Eq. (11), we now have $N_p = d_v / (\beta - 1 - \psi)$.

The characteristic equation for the eigenvalues λ of the linearized system is now of degree three, for the roots of which, there exist explicit, albeit not particularly interesting, algebraic formulae. Instead, we conducted a thorough mapping of the section of the (β, ψ) plane shown in Fig. 1, middle frame (ignoring of course, the now irrelevant q -loci), and solved the eigenvalue problem of system (18) numerically on a sufficiently dense grid of points. It is well known that the roots of such a problem can be either all three real, or one real

and a pair of complex conjugates. The mapping results were quite revealing: over the whole examined grid of points we *invariably* found *at least one* eigenvalue for which $|\lambda| > 1$, making the corresponding fixed point *unstable*. It can therefore safely be concluded that the system becomes unstable in the absence of debris.

For the chosen set of physical parameters (i.e. point P , and $d_v = 10^{-4}$), the fixed point F_2 in the (V, N) phase plane is at $N_p = 1.01 \times 10^{-6}$, $V_p = 0.12$. Initiated at the same initial point as in Fig. 4 (i.e. $N_0 = 10^{-6}$, $V_0 = 0.1$, $M_0 = D_0 = 0$), the time evolution is illustrated in Fig. 8, where N , after increasing for some time, collapses eventually, followed by a slow exponential decay of the phages.

5. Analysis

In a recent publication (Rabinovitch et al., 2002), empirical relations were obtained between the latent period τ and the burst size β of T4 phage on the one hand, and the bacterium *E. coli* doubling time T on the other, as follows:

$$\tau = 1.14 - 0.0068T^2, \tag{19}$$

$$\beta = (0.254T - 0.00166T^2)\exp(92.1/T). \tag{20}$$

Given the defining relationship between the growth rate ψ' and the doubling time T , as $\psi'/T = \ln 2$, Eq. (1) can be rewritten as

$$\psi = \exp(0.693\tau/T) - 1 = 2.203\exp(-0.0047T) - 1, \tag{21}$$

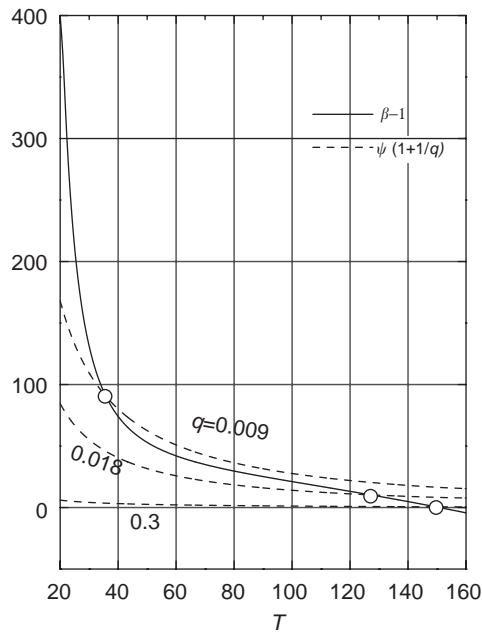


Fig. 9. Analysis of Eq. (11) determining the range of possible steady-state solutions.

where the second equality results from the substitution of Eq. (19) for τ .

As already mentioned in Section 2, Eq. (11), a steady-state solution is possible only if $\beta - 1 > \psi(1 + 1/q)$. Fig. 9 shows both $\beta - 1$ and $\psi(1 + 1/q)$ as functions of T for several typical values of q . The range of existence of stable solutions in the corresponding cases resides to the left of the points of intersection, marked by open circles. For example, the smallest shown $q = 0.009$ allows for steady-state solutions only below $T \approx 34$, while for larger values of T , diverging concentration oscillations are expected, leading to extinction of all species. The higher the value of q however, the broader will be the range of T , permitting steady-state solutions. This rather unexpected result could possibly be explained by *excess shielding* for small q values, i.e. the shielding is so efficient as to encourage an excess of bacteria in the system, which in turn, induces a larger population of phages, and so on, leading to extensive oscillations and eventual extinction.

6. Discussion

The relatively simple mathematical model developed in this work has shown that the presence of bacterial debris in the bacteria–bacteriophage system alters its asymptotic solution from an unstable focus to a possibly stable one, thus becoming a haven of survival and coexistence of both species. A number of remarks seem to be in order:

1. If the value of δ' is of the order of $10^{-12} \text{ min}^{-1} \text{ ml}^{-1}$ (Abedon, pers. Comm.), concentrations below $10^{-10} \delta^{-1}$ may be considered extinct, as explained above (part 4.2). Extinction levels under other values (e.g. Bohannan and Lenski, 2000) would be estimated correspondingly.
2. Asymptotic levels of concentration are reached only after a very long time.
3. The properties of the debris are of paramount importance for the system survival. This includes the “suicidal” penetration of phages to bacterial debris, and its decay rate. For example: is the phage adsorption rate δ the same for N and for D , as we somewhat arbitrarily assumed in the calculations? The answer may be crucial for the assessment of the model. These properties are hitherto unknown, and it would be quite advantageous to measure them.
4. Persistence of bacterial cells in the environment is conditioned by existence of viral decay, as implied by Eq. (11).

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