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Evolution of virulence driven by predator–prey interaction: Possible consequences for population dynamics

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ABSTRACT

The evolution of pathogen virulence in natural populations has conventionally been considered as a result of selection caused by the interactions of the host with its pathogen(s). The host population, however, is generally embedded in complex trophic interactions with other populations in the community, in particular, intensive predation on the infected host can increase its mortality, and this can affect the course of virulence evolution. Reciprocally, in the long run, the evolution of virulence within an infected host can affect the patterns of population dynamics of a predator consuming the host (e.g. resulting in large amplitude oscillations, causing a severe drop in the population size, etc.). Surprisingly, neither the effect of predation on the evolution of virulence within a host, nor the influence of the evolution of virulence upon the consumer's dynamics has been addressed in the literature yet. In this paper, we consider a classical *S–I* ecoepidemiological model in which the infected host is consumed by a predator. We are particularly interested in the evolutionarily stable virulence of the pathogen in the model and its dependence upon ecologically relevant parameters. We show that predation can prominently shift the evolutionarily stable virulence towards more severe strains as compared to the same system without predation. We demonstrate that the evolution of virulence can result in a succession of dynamical regimes and can even lead to the extinction of the predator in the long run. The presence of a predator can indirectly affect the evolution within its prey since the evolutionarily stable virulence becomes a function of the prey growth rate, which would not be the case in a predator-free system. We find that the evolutionarily stable virulence largely depends on the carrying capacity K of the prey in a non-monotonous way. The model also predicts that in an eutrophic environment the shift of virulence towards evolutionarily stable benign strains can cause demographically stochastic evolutionary suicide, resulting in the extinction of both species, thus artificially maintaining severe strains of pathogen can enhance the persistence of both species.

1. Introduction

The evolution of virulence in natural populations has always been an important field of both theoretical and experimental studies (Anderson and May, 1982; Bull, 1994; Taylor et al., 1998; Day, 2001, 2002; Friman et al., 2009). In previous works, the major focus has been on interactions between the pathogen and its host. It is obvious, however, that populations are generally involved in complex trophic interactions with other populations and that this should be taken into account when one is modelling the evolution of virulence in real ecosystems. It has been shown that predation of infected populations can both increase and decrease the infection prevalence (Packer et al., 2003; Holt and Roy, 2007), and that predation can also affect the transmission rate of a pathogen by triggering anti-predator defence behaviour in prey populations (Rigby and Jokela, 2000; Matz and Kjelleberg, 2005; Friman et al., 2009). An additional important role of predation consists in increasing the mortality of the prey, and theoretical studies predict that such an increase can affect the course of evolution of virulence (Anderson and May, 1982; Lenski and May, 1994; Elbert and Weisser, 1997; Williams and Day, 2001; Dieckmann, 2002). Note that the increase in mortality caused by predation depends, in turn, on the virulence of the consumed prey via a complex feedback: indeed, the predator density – which determines the intensity of the prey mortality – largely depends on the density of the prey, which is a function of pathogen virulence.

On the other hand, in the case where an important part of the predator's diet consists of infected prey, the effects of the evolution of virulence upon the ecological dynamics may take place over a large timescale, and shifting towards milder (or more severe) forms of disease can cause succession of regimes of

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dynamics of predator–prey interaction (e.g. transition from high amplitude oscillations to a stable equilibrium). Such possibilities should be taken into account when anticipating the long-term implications of predator-control programs for infectious disease in prey populations (Johnson et al., 1965; Hawlena et al., 2010; Greenman and Hoyle, 2010). As an example, a recent hypothesis (known as 'keeping herds healthy') suggests that the total population size of prey subjected to infection will rise in the presence of predator, thus a high level of predation ought to be beneficial for conservation purposes (Hudson et al., 1998; Packer et al., 2003; Stiling and Moon, 2005). This prediction, however, is based on considering only short-term dynamics and does not include the possible effects over a long-term evolutionary time-scale (e.g. an evolution-mediated extinction of the predator or both populations (see Section 3).

To the best of our knowledge, the effect of predation on virulence evolution is almost entirely unaddressed in the literature (but see Choo et al., 2003). The same goes for the influence of virulence evolution in a prey population upon the dynamics of its predator. In this paper, we shall attempt to make a contribution towards filling in these gaps. We consider a classical predator–prey model where the prey population is subjected to an infectious disease, and the predator consumes infected prey individuals. We are mainly interested in the evolutionarily stable virulence in this model and its dependence on ecologically relevant parameters (e.g. prey growth rate, predator attack rate, carrying capacity of the environment). In this paper, we assume the existence of a trade-off relationship between the transmission rate and the virulence (see Alizon et al., 2009 for a review). The evolutionarily stable virulence is defined as the virulence for which the pathogen can persist in the system and is stable with respect to invasion of other mutant strains (Maynard Smith, 1976; Lenski and May, 1994; Dieckmann, 2002).

Based on the derived analytical expressions as well as on numerical simulations, we found that predation can shift the evolutionarily stable virulence towards more severe strains compared to the same system without predation. We show that evolution of virulence can result in the extinction of the predator in the model. The presence of a predator in the system can indirectly affect the shift of pathogen evolution in the prey when the properties of environment are changed (this is not observed in a predator-free system). For example, we found that the evolutionarily stable virulence would largely depend on the carrying capacity of prey K, such dependence being non-monotonous. For both small and large K (eutrophic and oligotrophic ecosystems) the evolutionarily stable virulence is close to the one that would be observed in the same system without predator, the maximal virulence is attained for *intermediate* values of K. The drop in the evolutionarily stable virulence for large K occurs because of the appearance of an interesting dynamical regime implying oscillations of species densities with maximal and minimal values situated well below the equilibrium densities. The model also predicts that in an eutrophic environment the shift of virulence towards evolutionarily stable benign strains would lead to extinction of both species (this is known as evolutionary suicide, see Parvinen, 2005). Thus, the presence of severe strains can be also more beneficial for both prey and predator than milder strains.

2. Model equations

We consider an SI model combined with a Rosenzweig–MacArthur predator–prey model. This model is rather standard, and was first suggested by Chattopadhyay and Bairagi (2001). The prey population is divided into healthy (S) and infected (I) subpopulations. For the sake of simplicity we suggest that the predator (P) consumes infected prey individuals. Note that such a scenario is fairly usual and has been reported in several different ecosystems (Kabata, 1985; Hudson et al., 1992, 1998; Lafferty, 1992; Lafferty and Morris, 1996; Friend, 2002; Packer et al., 2003; Johnson et al., 2006; Duffy and Sivars-Becker, 2007; Liao et al., 2008; Venturino, 2010). The system's dynamics are described by the following set of differential equations:

$$\frac{dS}{dt} = r\left(1-\frac{S+I}{K}\right)S-\lambda SI, \tag{1}$$

$$\frac{dI}{dt} = \lambda SI-(D_0+D)I-f(I)P, \tag{2}$$

$$\frac{dP}{dt} = \theta f(I)P-Pd, \tag{3}$$

where r is the maximum *per capita* growth rate of the healthy prey, and K is its carrying capacity. We assume that only healthy individuals can reproduce; however, the infected subpopulation still influences the growth by competing for resources and thus contributing to the carrying capacity. We parameterize transmission of the disease via the mass action term $\lambda S I$, the coefficient λ being called the transmission coefficient. The disease is only transmitted horizontally, i.e. there is no transmission of disease from parents to offspring. The predator-independent part of the mortality of infected prey is the sum of the background mortality, D_0 and the disease-induced mortality D, which we shall henceforth refer to as the virulence of the disease.

The consumption of infected prey by the predator is described by a term of the form $f(I)P$, where f is the functional response which we consider to be of Holling type II:

$$f(I) = m\frac{I}{I+a}. \tag{4}$$

Here the parameters m and a represent the maximal consumption rate (per predator) and the half-saturation constant, respectively. The other parameters describing predator dynamics are the trophic efficiency coefficient θ and the natural mortality d. We consider only the case where the infection is specific to the prey, and so the predator can consume infected prey without becoming infected itself.

In order to investigate the evolution of the pathogen, we assume the existence of a trade-off relationship between its transmission rate and its virulence, i.e. $\lambda=\lambda(D)$. This assumption is implemented in a large number of theoretical investigations, and moreover, a number of experiments report evidence of the existence of such a trade-off in natural systems (see Alizon et al., 2009 for a critical review). Following previous theoretical works we shall consider $\lambda(D)$ to be an increasing function, which becomes saturated for large D. The specific parameterisation of $\lambda(D)$ which we shall use is given by (cf. Dieckmann, 2002; Alizon et al., 2009):

$$\lambda(D) = \alpha\frac{D}{D+C}. \tag{5}$$

Note that (5) is not the only possible choice of parameterisation for a saturating trade-off relationship. In the section Discussion, we shall address the way the parameterisation of $\lambda(D)$ influences the results obtained.

In order to obtain the evolutionarily stable virulence, we shall implement the criterion based upon the theory of adaptive dynamics developed in Dieckmann (2002) which, in turn, is based on the concept of invasion fitness (Metz et al., 1992). We assume that a mutant strain of pathogen (denoted by I_1) is introduced into the system where the resident population of infected prey, I, is at its equilibrium. Letting the invading strain be characterised

by virulence D_1, the invasion of the mutant strain is described by

$$\frac{dI_1}{dt} = \left(\lambda(D_1)S^* - (D_0+D_1) - \frac{f_1(I^*,I_1)}{I_1}P\right)I_1, \quad (6)$$

where $f_1(I^*, I_1)P$ represents consumption of the infected prey I_1 by the predator in the presence of resident strain at $I=I^*$. Eq. (6) can be re-written as

$$\frac{dI_1}{dt} = g(D,D_1)I_1, \quad (7)$$

where $g(D,D_1)$ is the invasion fitness of the mutant. A successful invasion is possible in the case where $g(D,D_1)>0$. An evolutionarily stable virulence D^* is defined as a virulence which characterises a viral strain which can persist in the system, and for which invasion by other mutant strains becomes impossible (Maynard Smith, 1976; Lenski and May, 1994). The necessary conditions for this (see Dieckmann, 2002; Parvinen, 2005) are

$$\left.\frac{\partial g(D,D_1)}{\partial D_1}\right|_{D=D*} = 0 \text{ and } g(D*,D*) = 0. \quad (8)$$

In the case of the evolutionarily *stable* virulence, the invasion fitness should have its local maximum equal to zero at $D=D^*$. This would happen when the second derivative of the invasion fitness is negative:

$$\left.\frac{\partial^2 g(D,D_1)}{\partial D_1^2}\right|_{D=D*} < 0. \quad (9)$$

Note that condition (9) always holds in case the trade-off function is given by (5). Note that (8) gives us analytical expressions for evaluating D^*; however, derivation of (8) is based on the assumption that the equilibrium (S^*,I^*,P^*) is stable and thus this criterion is not applicable to the case where the dynamics show sustained oscillations. To determine the evolutionarily stable virulence D^* when the population densities are oscillatory we proceed by introducing a small amount of a mutant strain into the system and by integrating the resultant equations numerically. The value D^* will be defined as the one for which invasion of any mutant (when initially rare) becomes impossible. This can be verified by directly checking 'all' D in the vicinity of D^*. We consider that the evolution process acts on a much larger timescale than that of any population oscillations, i.e. variation in D is much slower than that of species densities through a cycle. In other words, mutations are assumed to occur so rarely that the model trajectories have always settled on the attractor before another mutation occurs.

To describe the consumption of prey infected by strain I_j in the presence of another strain I_i we use the following parameterisation of the functional response of the predator:

$$f_i(I_i,I_j) = m\frac{I_i}{I_i+I_j+a}. \quad (10)$$

Such an extension of the functional response (4) is justified since both infected strains have close values of D, and their symptoms should be so similar that the predator is incapable of distinguishing between infected subpopulations of either type I_j or I_i.

3. Modelling results

Analytical treatment of the model along with numerical simulations show that the coexistence of S, I and P is possible either as a stationary stable state or through oscillations around this state. The coordinates of the unique nontrivial stationary state (S^*,I^*,P^*) are given in Appendix (A2–A4) together with the corresponding stability conditions. Since we are interested here in the evolution of the virulence and transmission rate, it is natural to consider bifurcation diagrams on the λ–D plane, which represents the evolutionary space. The structure of the diagrams largely depends on the magnitude of the carrying capacity K. For small K, the nontrivial stationary state is stable throughout its entire domain of existence (the white region in Fig. 1a). With an increase of K, the domain of existence of the nontrivial stationary state becomes larger (see Fig. 1b); however, regions corresponding to oscillatory dynamics begin to appear on the diagram (grey regions). The stationary state becomes unstable via a Hopf bifurcation when crossing the boundary between regions of stable and unstable coexistence. With an increase in K, the regions corresponding to oscillatory dynamics grow in size, and for large values of K only a small part of the domain of full coexistence remains stable (Fig. 1c). Note that this transition from stable equilibrium to oscillatory dynamics with an increase in carrying capacity is similar to the 'paradox of enrichment' as displayed by the classical Rosenzweig–MacArthur predator–prey model (Rosenzweig, 1971).

Numerical simulations show that the species densities oscillations in the model exhibit two different patterns of dynamics. For small values of λ and K one can observe 'classical' oscillations, when the maximal and minimal species densities through the cycle are located close to(S^*,I^*,P^*). An example of such behaviour is shown in Fig. 2a, where the unstable stationary densities are depicted by dashed lines. For large values of λ and K, however, another pattern of dynamics appears. Such a situation is represented in Fig. 2b. The densities of all species still oscillate periodically, but now the oscillations of P are characterised by rather small amplitude, i.e. for the maximal and minimal densities through the period we have $(P_{\max}-P_{\min})/P_{\max} \ll 1$, and, interestingly, by increasing λ and K one can make the amplitude of those oscillations as small as possible. More surprisingly, the oscillations of P take place far away from the equilibrium P^*. For instance, for parameters given in Fig. 2b the stationary density of the predator, $P^*=15.01$, i.e. it is larger than $P_{\max}$ or $P_{\min}$ by an order of magnitude (depending on model parameters the ratio between P^* and $P_{\max}$ can even be of 2–3 orders of magnitude). Note that the maximal value of S through the cycle is also smaller than its stationary value. As such, one can consider that oscillations in the system occur in the vicinity of a certain 'virtual' equilibrium $(\tilde{S},\tilde{I},\tilde{P})$ which is located far away from the actual equilibrium (S^*,I^*,P^*). Fig. 2c shows a typical trajectory of such oscillations in 3-D phase space, starting from the vicinity of (S^*,I^*,P^*).

The joint evolution of the virulence and transmission rate in the model takes place on the λ–D space along the evolutionary curves $\lambda(D)$ given by (5). Three possible outcomes are represented in Fig. 1d (constructed for the same parameters as Fig. 1b). The evolutionary curve can lie completely outside the domain of full coexistence (curve 1); the curve can cross the domain of coexistence but the evolutionarily stable virulence D^* occurs outside the domain (curve 3). Finally, in the most interesting case, D^* belongs to the domain of coexistence (curve 2).

It is convenient to investigate the outcome of virulence evolution by considering all possible realisations of the trade-off function (5) for a given set of ecological (i.e. non disease-related) parameters for the system. To do this, we plotted the evolutionarily stable virulence D^* in the parametric space of α and C, thus covering all possible forms of $\lambda(D)$. This is represented in Fig. 3, which is constructed for the same parameters as the diagrams in Fig. 1a–c. We show the relative increase Δ in the stable virulence over that obtained in the system without predator (S–I model), which is defined by

$$\Delta = \frac{D^*}{\sqrt{CD_0}}, \quad (11)$$

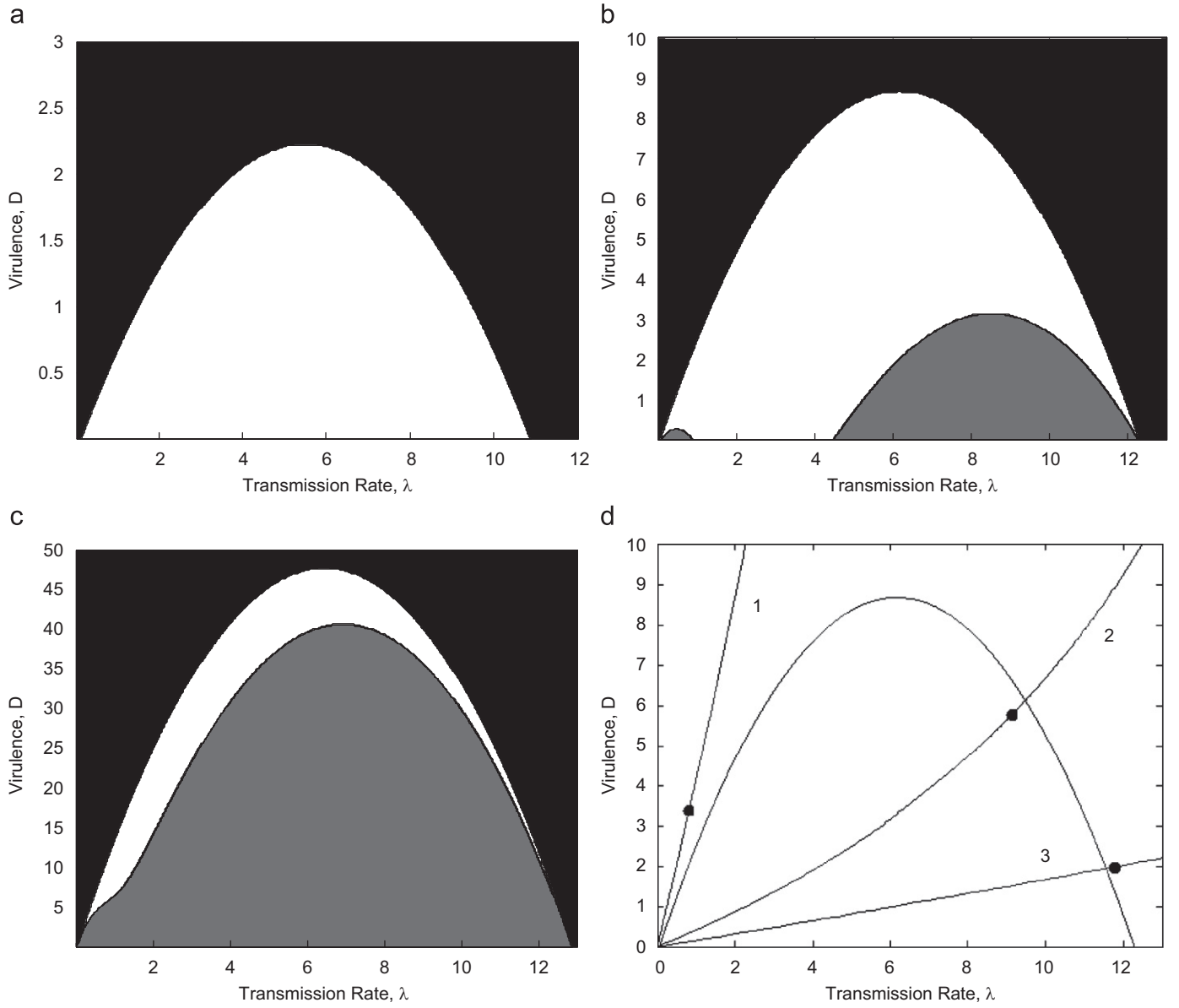

Fig. 1. The bifurcation diagrams for existence and stability of the nontrivial steady state of model (1–3) in λ–D evolutionary space for $\theta=0.5$; $a=1$; $d=0.1$; $m=1.5$; $r=2$; $D_0=0.1$ and varying values of the carrying capacity K: (a) $K=1$; (b) $K=3$; and (c) $K=15$. White regions indicate existence and stability of the nontrivial steady state, grey regions indicate existence only, and black regions indicate that the nontrivial steady state does not exist. (d) The joint evolution of the virulence and the transmission rate, which are related by the trade-off function (5). The blips on the curves represent the evolutionarily stable values $\lambda(D^*)$, D^*. The curves 1–3 are constructed for parameters $C=100$, $\alpha=25$; $C=10$, $\alpha=25$; $C=40$, $\alpha=250$, respectively; the other parameters are the same as in (b). The regions of existence, stability and nonexistence are the same for (b).

where $\sqrt{CD_0}$ gives the stable virulence in the S–I model (see Dieckmann, 2002). The right-hand side diagrams (1a–c) are the zoom of the left-hand diagrams for small α and C.

Fig. 3a shows the evolutionarily stable virulence D^* for small K when the coexistence of the three populations occurs at a stationary stable mode (corresponding to the λ–D diagram in Fig. 1a). To compute the evolutionarily stable virulence D^* we used the condition (8). The analytical expression for D^* is given in Appendix B. Note that (B2) gives only implicit expression for D^* since it is a cubic equation. We found that D^* is unique in the given model (see Appendix B). Analysis of the diagram in Fig. 3a shows that an evolutionarily stable virulence implying the coexistence of all three species is only possible within a limited domain of the α–C space of the trade-off function. In the black domain, the evolutionarily stable virulence implies persistence of the prey population only (i.e. a reversion to an S–I system). In such regions, the establishment of a predator in the ecosystem becomes impossible when the virulence of the infection is already evolutionarily stable ($D=D^*$). In the case where the virulence is still evolving towards the stable D^*, the predator can initially establish itself for some transient values of D and λ, but later on the evolutionary increase in D will eventually drive the system out of the domain of persistence, resulting in the predator's extinction. The boundary of the domain of existence of D, which allows for the establishment of the predator can be computed analytically based on (B3) derived in Appendix B. Enrichment of the environment (by increasing K) results in an enlargement of the domain where D^* is obtained in the predator–prey system. Fig. 3b and c show the evolutionarily stable virulence $D^*$for $K=3$ and 15, respectively.

By comparing all of the diagrams in Fig. 3, one can conclude that the presence of a predator can prominently shift the disease

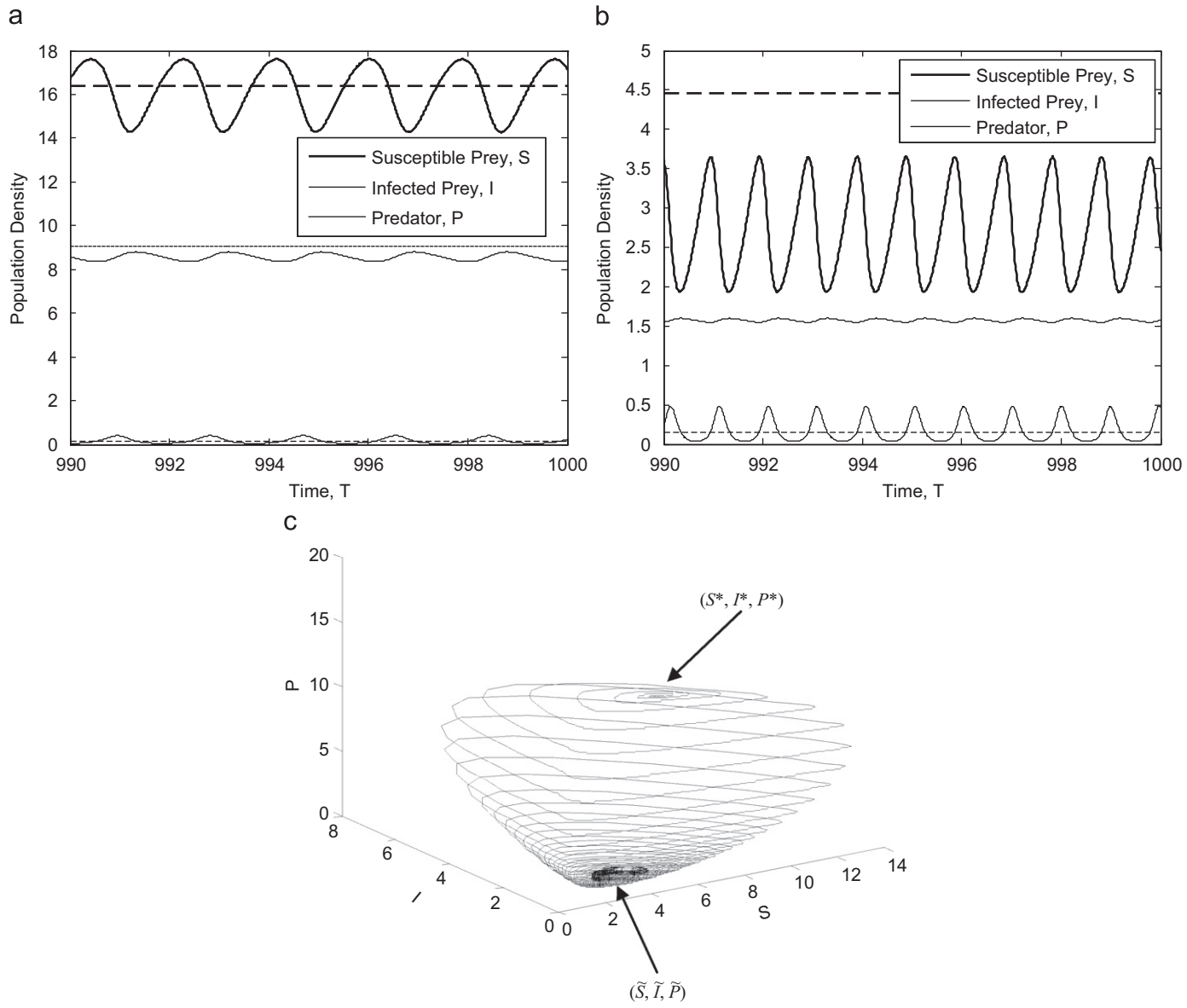

Fig. 2. Two main types of temporal oscillations in the model (1–3). (a) Oscillations take place around their stationary state(S^*,I^*,P^*), constructed for $\lambda=2.5$, $D=25$, $K=20$; the other parameters are the same as in Fig. 1. (b) Oscillations (plotted for $\lambda=10$, $D=25$, $K=20$) occur in the vicinity of a certain 'virtual' equilibrium $(\tilde{S},\tilde{I},\tilde{P})$ which is located far away from the actual equilibrium(S^*,I^*,P^*), $S^*=4.46$, $I^*=0.15$, $P^*=15.01$. The unstable stationary densities are depicted by dashed lines (P^* is not shown in (b)). (c) The same oscillations as in (b) shown in the 3-D phase space. The trajectory starts near(S^*,I^*,P^*)and spirals down to a limit cycle about $(\tilde{S},\tilde{I},\tilde{P})$.

towards more virulent strains when compared with the analogous S–I system. Such an increase can be even more pronounced with smaller values of background mortality D_0. For instance, for $D_0=0.02$ (other model parameters being kept the same) the relative increase Δ can be as large as 100. Note also that for smaller D_0 the domain of existence of D^* becomes larger (for the sake of brevity we do not show the corresponding diagrams). Finally, it ought to be emphasised that the successful establishment of a predator always results in an increase of D^* when compared to the initial predator-free system, i.e. $D^*>\sqrt{CD_0}$.

Analysis of all the diagrams in Fig. 3 also shows that for successful coexistence of all species S, I and P, the parameter α should be neither too small nor too large, when the value of C is fixed. Indeed, a small α signifies a small transmission rate of the disease (see (5)), and, as a result, the evolutionary curve on D–λ plane lies completely outside of the domain of species coexistence is this case (curve 1 in Fig. 1d). On the other hand, large values of α cause the evolutionary curve in the D–λ plane to leave the domain of species coexistence at $D<\sqrt{CD_0}$, which is the minimal possible value for D^* (curve 3 in Fig. 1d), and the evolutionarily stable virulence cannot be achieved inside the coexistence domain. Finally, a case where we have large values of both α and C is not suitable for an evolutionarily stable coexistence of species either; in this case $\lambda\approx\alpha D/C$ so we have a linear trade-off between the virulence and the transmission rate. The nonexistence of a stable D^* in the case where λ is proportional to D can easily be proved analytically in the given model. This is in accordance with earlier papers considering pure epidemiological models, which also display nonexistence of any evolutionarily stable virulence for a linear trade-off (Lenski and May, 1994; Dieckmann, 2002).

The next important step consists in an investigation of the dependence of the evolutionarily stable virulence on the ecological parameters of the model. Since the system contains a large number of parameters, we shall only consider the influence of some of them on D^*. We shall mostly focus on the role of the

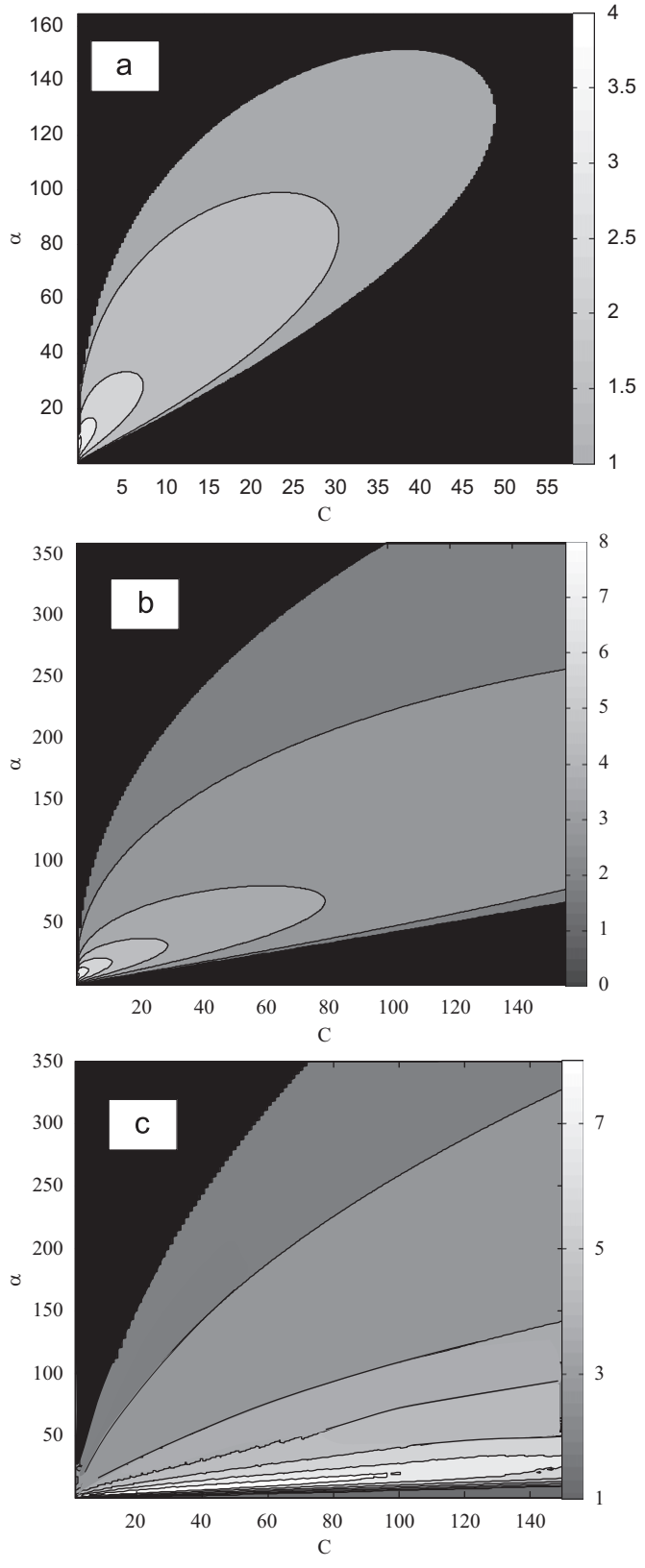

Fig. 3. The evolutionarily stable virulence D^* in system (1–3) as a function of parameters α and C of the trade-off function (5) constructed for the same parameters as the diagrams in Fig.1a–c. We show the relative increase Δ in the evolutionarily stable virulence over that obtained in the system without predator. The coexistence of the three species S, I, P at the evolutionarily stable virulence is impossible in the black domain. Diagrams (b) and (c) show only part of the domain of coexistence. For more details see the text.

carrying capacity, K, on the evolution of virulence in the prey. Fig. 4 shows the evolutionarily stable virulence for different degrees of enrichment of the environment (obtained by gradually increasing the prey's carrying capacity K). In Fig. 4a we have plotted $D^*(K)$ for different values of predator attack rate m, and in Fig. 4b we have plotted $D^*(K)$ for different values of the maximum *per capita* growth rate r, of the prey.

All the curves exhibit rather counter-intuitive behaviour. For small carrying capacity K (which can be interpreted as an oligotrophic environment), the evolutionarily stable virulence increases dramatically with an increase in K. Further, D^* attains its maximum for an intermediate value of K, and further enrichment of the system results in a decrease of D^*. Note that for large K (eutrophic ecosystems) the value of D^* tends to $\sqrt{CD_0}$, i.e. the evolutionarily stable virulence in the absence of a predator. Variation of other model parameters does not affect the qualitative behaviour of $D^*(K)$. An important conclusion that can be drawn is that predation can only pronouncedly shift the evolution of virulence in ecosystems with intermediate values of enrichment. In particular, in highly eutrophic systems the presence of a predator will have almost no effect on the virulence of a pathogen of its prey. Also, from Fig. 4a one can conclude that increasing the attack rate of predator (parameter m) results in an increase in D^*. The same concerns the increase in the *per capita* growth rate of prey r, see Fig. 4b.

It is possible to come up with a simple (but not mathematically strict) explanation for the observed drop of D^* for large K. When the predator density P is fixed (and so can be included into the mortality of prey), the evolutionarily stable virulence can be estimated as (cf. Dieckmann, 2002)

$$D^* \approx \sqrt{C(D_0 + mP/(a + s\langle I\rangle))}, \tag{12}$$

where $\langle I\rangle$ is the time average density of infected prey. As such, a large value of P will signify a large value of D^*. In the case where P is not stationary, expression (12) can still provide us with some estimation of D^* when we understand P as the time average density. With an increase in K, the stable coexistence of species in the full model (1–3) is replaced by oscillatory dynamics (see Fig. 1), the average density $\langle P\rangle$ is seen to decrease with increases in K. In Fig. 4 the parts of the curves shown by dashed line correspond to oscillatory dynamics. This phenomena is shown in Fig. 5a constructed for $m=1.5$; $r=2$, the other parameters are the same as in Fig. 1. This resulting decrease in $\langle P\rangle$ for larger values of K predicts the drop in D^* which is observed in the diagram. The values of $\langle P\rangle$ as well as those of $\langle I\rangle$ and $\langle S\rangle$ are rather different from their equilibrium values, in particular, we have $\langle P\rangle \ll P^*$ (see Fig. 5b showing the equilibrium densities).

The observed drop in P for large K is related to the emergence of oscillations of the type shown in Fig. 2b and c and cannot be explained in a simple way, it is a result of complex non-linear interactions of species including both qualitative and quantitative aspects, which can be revealed by direct numerical simulations. Interestingly, implementation of analytical expression (B2) for the situation where the equilibrium (S^*,I^*,P^*) is unstable, will always predict a monotone increase of D^* with K. This is related to the fact that the stationary density P^* increases monotonically with K and, since we have $\langle P\rangle \ll P^*$, the analytical prediction gives us erroneous results (cf. Fig. 5a and b). In Fig. 5a we also show the time average density of S and I as well as the time average density of total prey population $S+I$ obtained for the evolutionarily stable virulence. One can see that a pronounced enrichment of the ecosystem will finally result in a decrease in the densities of all species.

Finally, an interesting conclusion can be drawn when comparing the patterns of system dynamics in the case of the evolutionarily stable D^* with those corresponding to large values of D

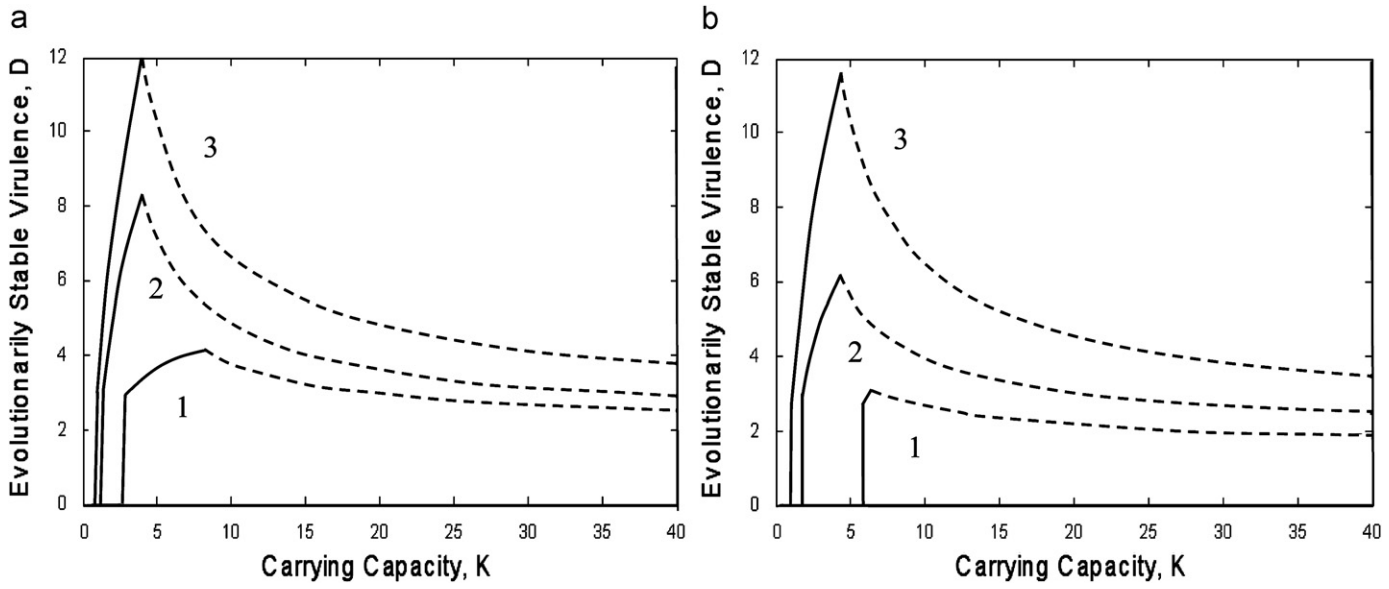

Fig. 4. Dependence of the evolutionarily stable virulence D^* on ecologically relevant parameters of the model. The evolutionarily stable virulence D^* is plotted as a function of the carrying capacity K of the prey for different values of predator attack rate m (a: $r=2$; 1, 2 and 3 are plotted for $m=1$, $m=2$ and $m=3$, respectively) and for different values of the per capita prey growth rate r (b: $m=1.5$; 1, 2 and 3 are plotted for $r=1$, $r=2$ and $r=4$, respectively). The other parameters are the same as in Fig. 1. The maximal value of D^* is obtained for intermediate values of K. The dashed parts of the curves correspond to oscillation of species densities.

(severe strains). The model predicts that in eutrophic systems, larger virulence will be beneficial to species persistence compared to lower virulences (benign strains). An example of such a situation is represented in Fig. 6, which is constructed for the evolutionarily stable D^* (Fig. 6a, $D^*=3.3$) and for a larger virulence, D, which is evolutionarily unstable (Fig. 6b, $D=8$). In both figures, the oscillations of total prey density ($S+I$) are plotted along with those of predator P. One can see from the graph that the evolutionarily stable virulence corresponds to oscillations with prey densities extremely close to zero. This signifies the eventual extinction of the prey population due to stochastic variation and, as a result, a further extinction of the predator. Interestingly, for large D the oscillations in prey density become dumped and extinction of species is less probable.

Fig. 7 shows two bifurcation diagrams in the λ–D evolutionary space indicating the domains (grey regions) for which an extinction of species will take place due to populations reaching dangerously low densities (i.e. the total prey population falls below the threshold density N_0 in the course of oscillations). In both diagrams, constructed for $K=15$ and 40, we show the trade-off curve used to construct Fig. 6. One can see that large values of D and λ (white regions) can guarantee the persistence of all species (either via a stable or an oscillatory mode); however, they are not generally evolutionarily stable for large K. As a result, evolution of virulence towards the low evolutionarily stable value of D will lead to the extinction of both the species. This phenomenon is an example of the demographically stochastic 'evolutionary suicide' reported earlier in other models (Parvinen, 2005). Comparison of both diagrams in Fig. 7 shows that the enrichment of the ecosystem will result in enlargement of the domain of 'evolutionary suicide'.

4. Discussion

It has been well recognised that the evolution of virulence of a pathogen largely depends on the mortality of its host (Lenski and May, 1994; Elbert and Weisser 1997; Williams and Day, 2001; Dieckmann, 2002). Although the predation can be an important source of host mortality, surprisingly, its effect on virulence evolution has not been sufficiently addressed in the literature. In this paper, we emphasise the importance of trophic interactions between species in the evolution of virulence in natural populations. Another important part of our work is to demonstrate the necessity of taking into account evolutionary processes when one is modelling predator–prey interactions, i.e. population dynamics. A particularly significant conclusion is that these two processes impart an influence upon each other, and due to the complex nature of their interplay, neither variations in the ecological aspects nor the evolutionary aspects of the ecoepidemiological models can be discounted in future investigations.

Our model indicates that adding a dynamical predator (with the density depending on that of prey) into an initial host–pathogen system can result in a substantial increase in the evolutionarily stable virulence of the host, by shifting it towards more severe strains. We derived a semi-analytical expression for the evolutionarily stable virulence as a function of biologically relevant parameters (see Appendix B). In particular, we found that an increase in the attack rate of the predator should result in a shift towards more severe strains. More interestingly, we saw that in the presence of a predator (consumer), the evolutionarily stable virulence of the prey's pathogen becomes a function of life traits of the prey (e.g. the *per capita* growth rate, the carrying capacity, etc.), which would not be the case in a predator-free system. The dependence of the evolutionarily stable virulence on the carrying capacity K of the environment becomes of particular interest.

The significant point here is that in the model, the highest evolutionarily stable virulence D^* is attained for intermediate levels of environmental enrichment, in other words, the dependence of D^*on K is non-monotonic (see Fig. 4), the maximal virulence is attained for *intermediate* values of K. Interestingly, the shift of the evolutionarily stable virulence towards more benign strategies for large K is caused by a reduction in the predator's impact upon the infected prey, which, in turn, is due to the appearance of a counter-intuitive dynamical regime shown in Fig. 2b and c. Such patterns are characterised by low-amplitude oscillations of predator density around a certain value of P, which can be considered a 'virtual' stationary density and is located far away from the actual unstable equilibrium of the system – in particular, the increase in K results into a decrease in the average

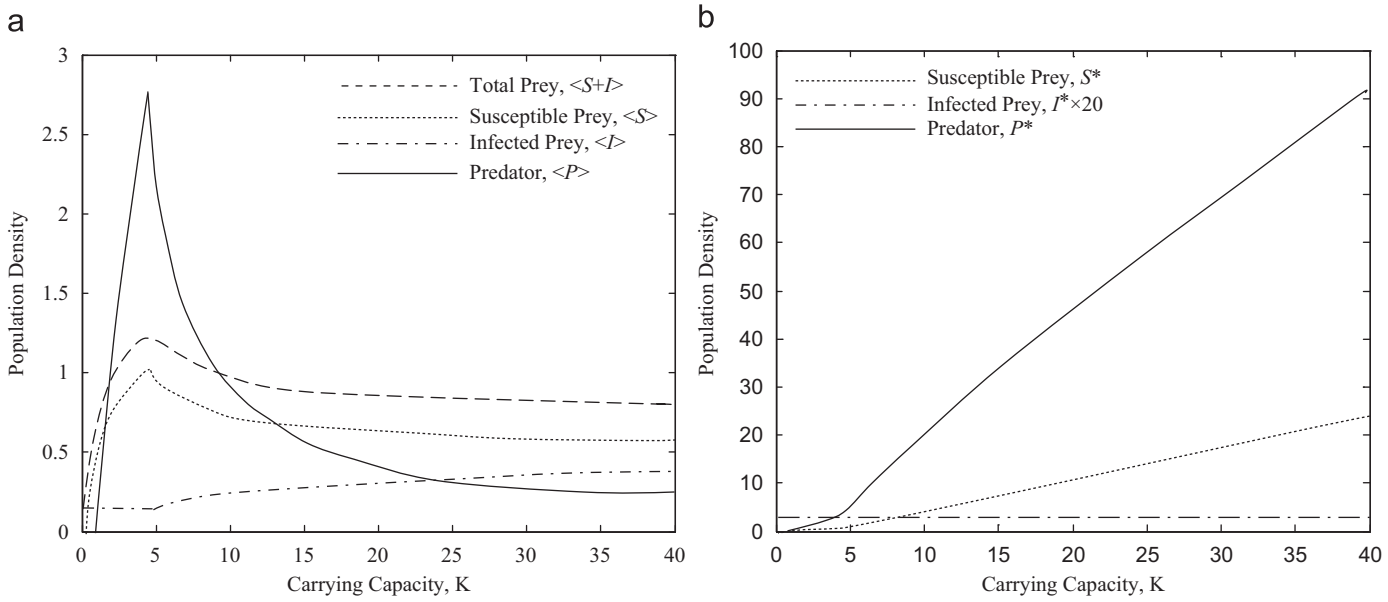

Fig. 5. Non-monotonous dependence of time average species densities $<S>$, $<I>$, $<S+I>$, $<P>$ and steady state densities (b) on the degree of enrichment K in the system. Here $m=1.5$, $r=2$, $\alpha=25$ and $C=10$; the other parameters are the same as in Fig. 1. One can see a tremendous difference between the stationary density of predator P^* and the average density $<P>$ for large K due to the fact that oscillations takes place far away from the equilibrium (e.g. Fig. 2c).

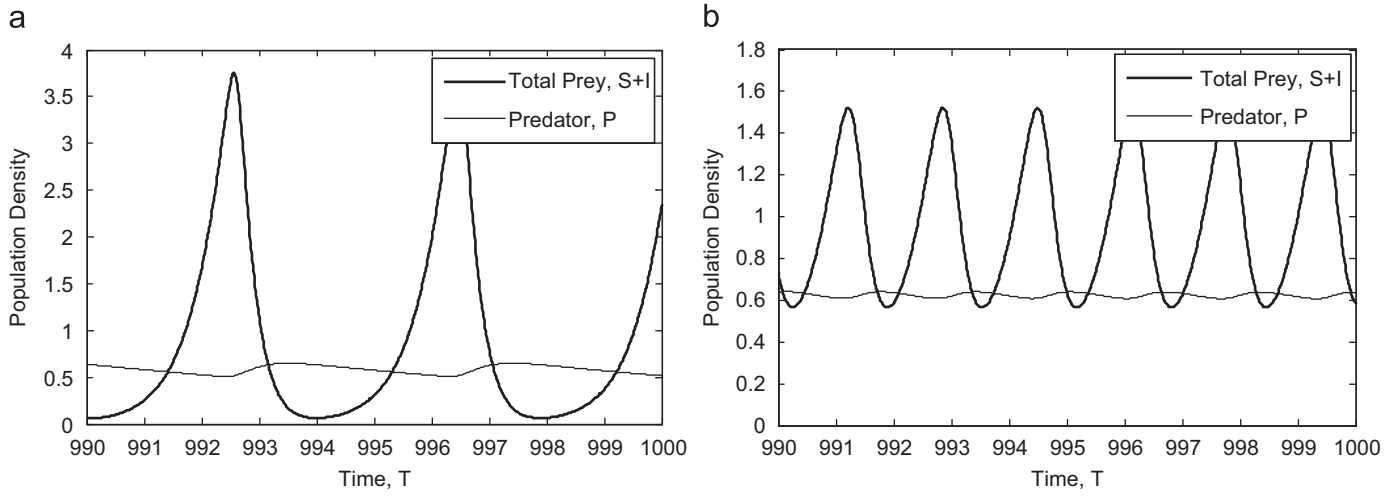

Fig. 6. Large values of pathogen virulence could be beneficial compared to low virulence (benign strains) for parameters $K=40$; $\alpha=25$; $C=10$, and all other parameters the same as in Fig. 1. (a) Temporal dynamics of total prey ($S+I$) and P predator densities is shown for the evolutionarily stable virulence, $D^*=3.3$; (b) Temporal variation of ($S+I$) and P are plotted for the larger, but evolutionarily unstable, $D=8$. For the evolutionarily stable virulence the oscillations with prey densities comes extremely close to zero. This signifies an eventual extinction of the prey population due to stochastic processes, and hence the consequent extinction of the predator. On the contrary, for larger D the oscillations of prey density become dumped and extinction of species is less probable.

value of P (reducing the predator pressure), thus causing a decrease in D^*. Note that it has been demonstrated in a number of models that long-term averages of species densities can show different behaviour compared to the behaviour of equilibrium densities, when a control parameter is being varied (e.g. Armstrong and McGehee, 1980; Abrams, 2009). However, an important particularity of our model is that *both* the minimal and the maximal species densities (S, P) through a population cycle are located well below the equilibrium densities (see Fig. 5). Such pattern of dynamics, to the best of our knowledge, has not been shown in ecological modelling yet.

Another ecological application of the above oscillations could be the well-know paradox of enrichment, which predicts the emergence of oscillations in a predator–prey system with increasing amplitude as a response to enlarging of the carrying capacity of the environment, such behaviour being rarely observed in nature (Rosenzweig, 1971; Scheffer and de Boer, 1995; McCauley et al., 1999). Our model shows that in the case where the consumed host is contaminated by a disease/pathogen, one should expect a drop (and not an increase!) in the amplitude of the oscillations of predator density. Moreover, contrary to some earlier works (e.g. plankton studies, see Walters et al., 1987; McCauley et al., 1988; Leibold, 1989; Mazumder, 1994), the enrichment of the ecosystem will provoke a *decrease* of the time average of population sizes of all species. Interestingly, a similar stabilisation effect of infection has been reported in eco-epidemic models with infected predators (Hilker and Schmitz, 2008; Oliveira and Hilker, 2010).

The model indicates that evolutionary processes can result in extinction of the predator in a predator–prey system. This can occur through two different scenarios. In the first case, the current virulence of the pathogen in the prey population is still evolving towards its evolutionarily stable value given by $\sqrt{cD_0}$, which is

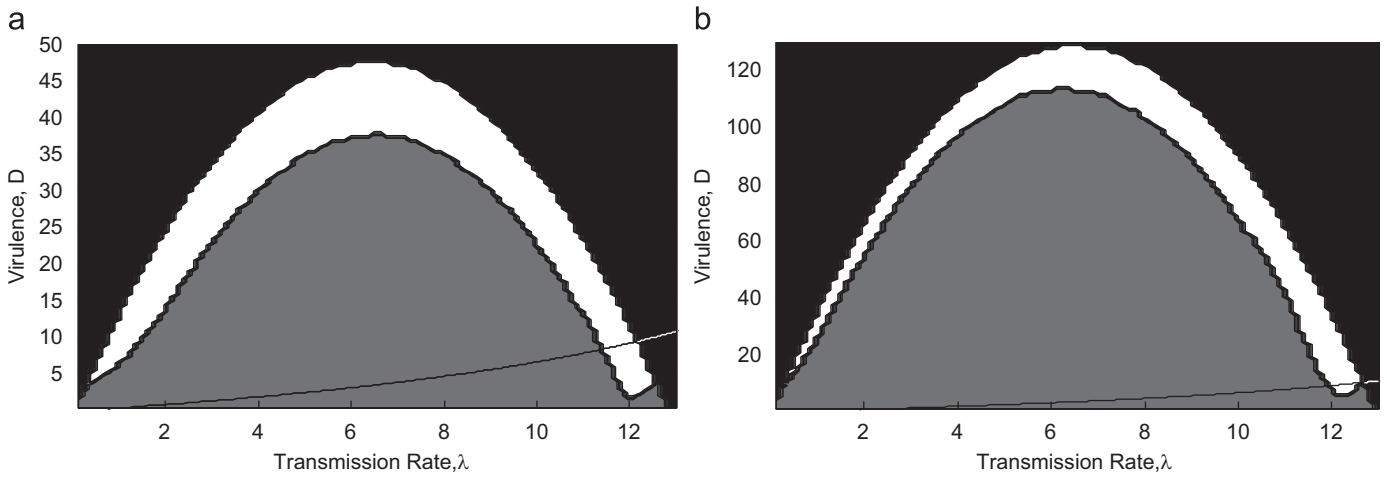

Fig. 7. λ–D bifurcation diagram showing the domain of expected extinction of species (grey domain) in which the total prey density $S+I$ falls below the threshold value $N_0=0.05$ during the course of oscillations for (a) $K=15$, and (b) $K=40$, together with the trade-off curve (solid line) with $\alpha=25$; $C=10$. The white region represents the area in which healthy levels of prey population are maintained (i.e. they stay above N_0). The black regions indicate that the nontrivial steady state does not exist. The other model parameters are kept the same as in Fig.1a.

achieved outside the domain of predator–prey coexistence in the evolutionary space (e.g. curve 3 in Fig. 1d). In this case, the initial establishment of predator is only a transient regime and the system will be eventually driven out of the domain of prey–predator coexistence. Eventual predator extinction in this case will be a *deterministic* extinction. In the second scenario, the virulence evolves to values, which allow deterministic coexistence of populations via oscillations of species density, but the total prey population reaches dangerously low densities that in real-life situations would allow natural perturbations to cause extinction of the prey, so inducing an eventual extinction of the predator. Interestingly, this extinction does not hold for all virulences – safe population densities can be maintained for higher virulences than the evolutionarily stable one. As a result, the disease's evolution effectively causes its own extinction, so this type of behaviour is known in the literature as evolutionary suicide (Parvinen, 2005 and the references therein). This is a demographically *stochastic* evolutionary suicide since the extinction is caused by natural fluctuations in population density rather than being inherent in the model.

Note that the potential influence of predation on the evolution of virulence was first studied theoretically by Choo et al. (2003), where it was found that a predator could increase the evolutionarily stable virulence of its prey. Another surprising scenario reported in the cited work was that an increase in the background mortality D_0 of prey could result in a *decrease* in the virulence. However, the above results were obtained for the case where the functional response of the predator was linear and, thus the equilibrium in the system was always stable. Another important particularity of the system investigated by Choo et al. (2003) was a constant prey growth rate, i.e. $rS=$const. Our study shows that moving to the oscillatory dynamics from the stable equilibrium can alter the behaviour of the evolutionarily stable virulence (see Fig. 4). Moreover, we found that considering a more realistic situation where the total prey growth rate is not constant and is described by the logistic equation can affect the conclusions made by Choo et al. (2003): we found that in model (1)–(3) an increase of background mortality does not result in a decrease of the evolutionarily stable virulence.

Our theoretical results offer several important implementations regarding the efficacy of predator-based control programmes for the spread of infectious diseases/pathogens. In particular, the modelling predictions bring into question the hypothesis of 'keeping herds healthy' suggesting that predation ought to be beneficial for the preservation of natural populations which are subject to infectious disease (Hudson et al., 1998; Packer et al., 2003; Stiling and Moon, 2005). We show that in the presence of a predator, large amplitude oscillations driven by trophic interactions may result in a demographically stochastic evolutionary suicide of both species. Analysis of model (1–3) also reveals (we do not show the corresponding graphs for the sake of brevity) that the introduction of a predator into an S–I model may both increase and decrease the disease prevalence (cf. Holt and Roy, 2007). Note that one should also be careful when choosing the 'right' predator with the aim to control infected prey individuals. The initial successful establishment of the predator can turn out to be only a transient regime until the predator's final extinction due to the evolution of disease virulence.

In our study, we considered a specific parameterisation of the trade-off between the virulence and the transmission rate given by the hyperbolic function (5). Our investigation showed that the implementation of another parameterisation with similar properties (e.g. exponential or trigonometric functions given by $D=\alpha(1-\exp(-D/\beta))$ and $D=\alpha\, a\tan(-D/\beta)$, respectively) does not change the qualitative results obtained. Note that parameterization (5) has a certain advantage over the above functions since it makes analytical expressions for D^* to be more tractable.

A more important concern is about possible restrictions of the paper's results regarding the choice of predation in the model. Throughout the paper, we have considered a predator consuming only infected prey. Are our results robust? We should say that based on numerical studies of an extended model, the previous qualitative findings remain the same in the case when we allow the predator to consume small amounts of healthy prey. In particular, the dependence of the evolutionarily stable virulence D^* on the key model parameters (K, r, m) is similar to the one shown in Fig. 4. Overall, small perturbations of model (1–3), by allowing small predation of healthy prey, result in a slight reshaping of the coexistence domain in the evolutionary space. However, the size of the domain of predator–prey coexistence in the evolutionary space becomes larger in the case where the predator's diet includes an additional source of food, the healthy prey S. Note that the opposite scenario (most of the predator's diet includes the healthy prey) implies a different bifurcation structure of the model (e.g. three nontrivial coexistence stationary states become possible in the system) and should be analysed elsewhere.

In this paper we considered the evolution of virulence in predator–prey system with infected prey. A number of ecologically important cases, however, include predator–prey interactions where the predator (e.g. a top predator) is infected by a disease/pathogen (Venturino, 2002; Hilker and Schmitz, 2008; Venturino, 2010). Evolution of virulence in such systems should be considered in a separate paper. Our preliminary investigations show, however, that the influence of predator–prey interactions on the course of virulence evolution would be smaller compared to systems with infected prey, at least, in the case of stable equilibria in the corresponding systems. Indeed, in simple models, the death rate of predators is not affected by prey density. Computation of evolutionarily stable virulence in such case is rather straightforward and it results in a 'prey-independent' expression $D^*=\sqrt{CD_0}$, where D_0 is the background mortality of predator; C has the same meaning as in (5). We should admit that such trivial situation can change in case of oscillatory dynamics and thus the trophic interactions would play an important part in the evolution of the infection within the predator.

To complete the paper, we would like to point out possible future directions. Firstly, it would be interesting to implement some other approaches in the modelling of virulence evolution, that are different to the approach based on adaptive dynamics. In particular, one can implement the quantitative genetics framework allowing one to study short-term evolution in ecoepidemiological models (e.g. Abrams, 2001; Day and Proulx, 2004; Duffy and Sivars-Becker, 2007). Secondly, it would be interesting to investigate more complex scenarios of evolution in predator–prey systems. For instance, a typical situation is when both prey and predator can be contaminated by a common disease (Fuhrman and Suttle, 1993), and a particularly interesting scenario includes the case where the prey is the intermediate host and the predator plays the role of the definite host (Fenton and Rands, 2006; Lefèvre et al., 2008). Thirdly, more detailed field observations, intended to provide experimental/field evidence for changes in virulence driven by trophic interactions, would be extremely helpful. Unfortunately, most of the current field observations are limited by only reporting the disease prevalence in predator–prey systems. For example, it would be important to reveal as well variations in the mortality rate of infected species (to be able to estimate changes in virulence) as well its correlation with the predation load. Finally, it will be important to extend the current research to some more complicated scenarios of disease transmission including vector-borne diseases, multi-infection contamination and vertically transmitted pathogens. In particular, the presence of multiple infections in a single host should lead to increased competition among pathogens since the host can only survive as long as it resists the most virulent strains of the disease (Frank, 1992; Alizon and van Baalen, 2008).

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Appendix A

Here we list the stationary states of model (1–3) and discuss briefly their stability properties.

(i) The trivial stationary state (0,0,0). It is always unstable.

(ii) The disease-free stationary state (K,0,0). Analysis of the Jacobian at this stationary state indicates its stability for$D>\lambda K+D_0$.

(iii) The predator-free stationary state (S^1,I^1,0) with $S^1=(D+D_0)/\lambda$, $I^1=r(K\lambda-D-D_0)/[\lambda(K\lambda+r)]$. Analysis of Jacobian tells that this state is stable for

$$D>\frac{kmr(K\lambda-D-D_0)}{\lambda a(K\lambda+r)+r(K\lambda-D-D_0)}-D_0, \tag{A1}$$

(iv) The coexistence state (S^*,I^*,P^*), where the stationary values are determined by

$$S^*=\frac{rK(km-d)-K\lambda da-rda}{r(km-d)}, \tag{A2}$$

$$I^*=\frac{da}{km-d}, \tag{A3}$$

$$P^*=\frac{r\lambda kKa(km-d)-\lambda^2 kKda^2-r\lambda kda^2-r(D+D_0)ka(km-d)}{r(km-d)^2}. \tag{A4}$$

The state exists if $km-d>0$ and the following two conditions are satisfied

$$\lambda<[rK(km-d)-rda]/(Kda), \tag{A5}$$

$$\lambda^2 Kda+[-rK(km-d)^2+rda]\lambda+r(D+D_0)(km-d)<0. \tag{A6}$$

The stability of the state is determined by the Jacobian J at this state which reads

$$J(S^*,I^*,P^*)=\begin{pmatrix} -\frac{rS^*}{K} & -S^*\left(\frac{r}{K}+\lambda\right) & 0 \\ \lambda I^* & \frac{mI^*P^*}{(a+I^*)^2} & -\frac{mI^*}{(a+I^*)} \\ 0 & \frac{kmaP^*}{(a+I^*)^2} & 0 \end{pmatrix}.$$

The eigen values of J are given by the following characteristic equation:

$$-\mu^3+\eta_1\mu^2+\eta_2\mu+\eta_3=0, \tag{A7}$$

where the coefficients η_i are given by

$$\eta_1=-\frac{rS*}{K}+\frac{KmI*P*}{(a+I)^2K},$$

$$\eta_2=-\lambda I^*S^*\left(\lambda+\frac{r}{K}\right)-m\frac{(Kda-rI^*S^*)}{(a+I)^2K}P^*,$$

$$\eta_3=-\frac{rdmaS^*P^*}{(a+I^*)^2K}.$$

According to the Routh–Hurwitz stability criterion, stability of (S^*,I^*,P^*) takes place if and only if the following conditions hold

$$\eta_i<0,\quad \eta_2\eta_1>\eta_3. \tag{A8}$$

In this paper, we used numerical simulations to evaluate the stability conditions (A8).

Appendix B

Here we derive analytically the equation for the evolutionarily stable virulence D^*.

The invasion fitness of mutant strain I_1 (when I_1 is small) is given by

$$g(D,D_1)=\lambda(D_1)S^*(D)-\frac{m}{I^*+a}P^*(D)-(D_0+D_1), \tag{B1}$$

where the stationary densities S^*, I^* and P^* are determined by (A2), (A3) and (A4), respectively. By applying conditions (8) we obtain after some simplification the following cubic equation for the evolutionarily stable virulence D^*:

$$D^3\beta_1+D^2\beta_2+D\beta_3+\beta_4=0 \tag{B2}$$

with the coefficients: $\beta_1=r(km-d)$, $\beta_2=3C\beta_1$, $\beta_3=C\beta_2-\alpha KC\beta_1+C\alpha d(\alpha K+r)a$,

$\beta_4=C^2r(-\alpha Kkm+kmC+\alpha da-Cd+\alpha Kd)$. The polynomial (B2) may have at most one root for which $D^*>0$. This can be seen from the following.

The second and the third derivatives of the polynomial are positive for $D>0$, since $km-d>0$. In case $\beta_4<0$, (B2) should have one positive root since $\beta_1>0$ (to provide the stable virulence, this solution should also satisfy $P^*>0$). The existence of two or three positive roots in this case would signify the existence of a local maximum with a negative second derivative, which is impossible. In case $\beta_4>0$, there exist no positive roots of (B2). This follows from the fact that for $\beta_4>0$ we have $\beta_3>0$. Indeed, the opposite statement (i.e. $\beta_4>0$, $\beta_3<0$) would signify (C is almost positive)

$$C>\alpha K-da\alpha/(km-d);\quad C>0;$$
$$C<\alpha K/(3r)-\alpha d(\alpha K+r)a/(3r(km-d)),$$

which is equivalent to:

$$0<K-da/(km-d)<K/(3r)-d(\alpha K+r)a/(3r(km-d)).$$

It is easy to show that the above inequality has no solutions, thus $\beta_i>0$, $i=1,2,3,4$ and (B2) has no positive roots in this case.

The boundary of the domain of existence of stable virulence $D^*>0$ implying S^*, I^*, $P^*>0$ is given by the condition $P^*=0$ at the boundary, which signifies $D^*=\sqrt{D_0C}$. By substituting $\sqrt{D_0C}$ for D in (B2) we obtain the following implicit quadratic equation relating C and α.

$$\sigma_1\alpha^2+\sigma_2\alpha+\sigma_3=0 \tag{B3}$$

where $\sigma_1=CdaK\sqrt{D_0C}$, $\sigma_2=C^2rd(a+K)+Cr(Kd-Kmk+da)\sqrt{D_0C}-C^2rKmk$,

$$\sigma_3=r(mk-d)\sqrt{(D_0C)^3}+3rC(mk-d)(D_0C+C\sqrt{D_0C})+C^3r(mk-d).$$

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