Optimal killing for obligate killers: the evolution of life histories and virulence of semelparous parasites

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SUMMARY

Many viral, bacterial and protozoan parasites of invertebrates first propagate inside their host without releasing any transmission stages and then kill their host to release all transmission stages at once. Life history and the evolution of virulence of these obligately killing parasites are modelled, assuming that within-host growth is density dependent. We find that the parasite should kill the host when its per capita growth rate falls to the level of the host mortality rate. The parasite should kill its host later when the carrying capacity, K , is higher, but should kill it earlier when the parasite-independent host mortality increases or when the parasite has a higher birth rate. When $K(t)$, for parasite growth, is not constant over the duration of an infection, but increases with time, the parasite should kill the host around the stage when the growth rate of the carrying capacity decelerates strongly. In case that $K(t)$ relates to host body size, this deceleration in growth is around host maturation.

1. INTRODUCTION

Research on the evolution of virulence attempts to explain the damage inflicted by a parasite on its hosts as the result of an evolutionary process which maximizes the parasite's fitness (Anderson & May 1982; May & Anderson 1983; Herre 1993; Bull 1994; Ewald 1994; Read 1994; Ebert & Herre 1996; Levin 1996). The majority of studies on this subject are based on parasites which release transmission stages throughout the period of infection, i.e. transmission occurs from the living host. In these parasites the death of the host imposes a cost on the parasite. However, many microparasites *must kill* their host to achieve transmission, since no transmission occurs before the death of the host. These obligately killing parasites grow inside their host and convert host biomass into parasite transmission stages. When the host breaks open, millions of, usually long-lived, transmission stages are released into the environment (Anderson & May 1981; Miller *et al.* 1983). Obligately killing parasites are found among many groups of organisms, including bacteriophages (Lenski & Levin 1985), nuclear polyhedrosis viruses, granulosis viruses (Miller *et al.* 1983), bacteria (Sayre & Wergin 1977; Ebert *et al.* 1996), nematodes (Poinar 1975), fungi (Evans 1982; Samson *et al.* 1988) and microsporidia (Green 1974; Ruttner-Kolisko 1977; Anderson & May 1981).

The fitness of such 'first grow then kill' parasites has two components: the within- and the between-host component. While the latter is mainly determined by the transmission efficiency per infective

propagule and their longevity, the former depends on within-host growth, host survival and the time until the parasite kills the host (Anderson & May 1981, 1982). In this paper we propose a model for the evolution of virulence of obligately killing parasites, which rests on two main assumptions. First, a host is a limited resource and within-host growth of parasites is therefore density dependent. Second, within-host growth and between-host transmission are independent from each other, which allows one to model the within-host dynamics without considering the between-host dynamics. This is justified if the average time a transmission stage rests in the environment before being taken up by the next host is much longer than the average time of infection, an assumption supported for many obligately killing microparasites (Anderson & May 1981) (although this assumption is certainly not valid for all host-parasite systems). We concentrate on two questions. First, when is the optimal time to kill the host? Second, what is the optimal parasite birth rate (within-host growth)?

2. THE MODEL

We use the number of transmission stages a parasite is expected to produce as a measure of parasite fitness. This definition is related, but not equal to, the number of secondary infections a parasite can produce when introduced into a novel population (compare Anderson & May 1991; Ebert & Herre 1996). To avoid confusion, and because our model is not an epidemiological model, we restrict ourselves to the standard life history fitness definition for semelparous organisms (Stearns 1992). The fitness of an

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obligately killing semelparous parasite, R , can then be estimated as

$$R(t_{\text{kill}}) = S(t_{\text{kill}})e^{-mt_{\text{kill}}}, \quad (1)$$

where $S(t_{\text{kill}})$ is the number of transmission stages produced at the time, t_{kill} , the parasite kills the host and m is the host mortality rate independent of the parasite. At this stage we exclude parasite-induced mortality besides the intentional killing of the host at t_{kill} . We assume that no transmission stages are released when the host dies for reasons other than being killed by the parasite (e.g. predation) and that there is no immune response.

Under these conditions, and in the absence of constraints, the parasite should kill the host instantaneously. However, since production of transmission stages takes time and resources, and a host represents a limited resource for a growing parasite, we introduce a density-dependent form for parasite growth, the logistic equation

$$\frac{dN(t)}{dt} = bN(t) \left(1 - \frac{N(t)}{K}\right), \quad (2)$$

where b is the parasite birth rate (equal to the maximal within-host growth rate of the parasite). $N(t)$ can be seen as the number of cells of a unicellular parasite, or more generally as parasite biomass, and K is the carrying capacity. We assume that $N(t)$ at the start of an infection is 1, but larger values can be used in case dose effects are investigated (Ebert 1997). For the moment we assume that K is a constant and that $N(t_{\text{kill}})$ is proportional to the number of transmission stages a parasite produces, i.e. $S(t_{\text{kill}}) = cN(t_{\text{kill}})$, where c is the conversion efficiency, which can be scaled out of the model. To find the optimal time to kill the host we substitute expression (2) into equation (1) and differentiate it with respect to t_{kill} . This yields the expression

$$\frac{dN}{dt} \frac{1}{N} = m. \quad (3)$$

Equation (3) shows that fitness is maximized in terms of killing time when the per capita growth rate of the parasite is equal to m . For $b > m$, $R(t_{\text{kill}})$ is hump shaped when plotted against t_{kill} (figure 1).

If K is constant, parasite biomass inside the host at any time after infection is given by

$$N(t) = \frac{N_0 K e^{bt}}{K + N_0(e^{bt} - 1)}. \quad (4)$$

$N(t)$ asymptotically approaches K (figure 1a). Using equation (3) we arrive at the following equation for the optimal killing time:

$$t_{\text{kill}} = \frac{1}{b} \ln \left((K - 1) \left(\frac{b}{m} - 1 \right) \right). \quad (5)$$

Equation (5) shows that the optimal time to kill the host decreases when host mortality increases (figures 1, 2). The number of transmission stages produced at the optimal moment to kill the host is

$$N(t_{\text{kill}}) = K \left(1 - \frac{m}{b}\right) \quad (6)$$

Figure 1. Density limited growth of the parasite inside the host (a) and the expected parasite fitness for two different host background mortality rate, m . (b) t_{kill} indicates the optimal time since infection to kill the host. $K = 10^6$, $b = 0.4$, $c = 1$.

and decreases with increasing mortality rate (figures 1, 2). As can be seen in figures 1 and 2, a large change in mortality is required to produce a large change in the optimal time to kill the host. In contrast, $R(t_{\text{kill}})$ decreases strongly when m increases.

A higher carrying capacity, K , increases the optimal time to kill the host and increases $N(t_{\text{kill}})$ (figure 2). For a given time after infection, $N(t)$ will be greater for a higher K , because density-dependent reduction in growth becomes effective at higher K . An increase in the parasite birth rate, b , decreases the optimal time to kill the host and increases the parasite fitness, $R(t)$.

(a) *The resource carrying capacity grows over time*

Next we consider the case that K changes over time. This could be, for example, when K is a function of host size or something related to host size. We model K growing monotonically over time, i.e. $K = K(t)$, but reaching an asymptote, just as it is typical for a growing host. Independent of the exact form for $K(t)$, the optimal killing time can still be derived from equation (3). Rearranging equation (3) results in the following condition:

$$\frac{N(t)}{K(t)} = 1 - \frac{m}{b}. \quad (7)$$

Figure 2. The dependence of the optimal time to kill the host, the parasite biomass inside the host, $N(t = t_{kill})$, and the expected parasite biomass when the parasite kills the host, $R(t_{kill})$ as a function of the parasite birth rate, b , (upper graphs) and the carrying capacity K (lower graphs). K is assumed to be constant over time. The two curves in each graph represent two levels of parasite independent host mortality rate, m . Solid line: $m = 0.01$; stippled line: $m = 0.2$. In the upper three graphs $K = 10^9$, in the lower three graphs $b = 0.4$. $c = 1$ in all graphs.

The parasite should kill the host when $N(t)$ reaches a certain fraction of the carrying capacity $K(t)$, determined by the ratio of host mortality and parasite growth rate.

We ask now what influences the optimal time to kill the host? With respect to host mortality rate, m , there are two possibilities. First, if the per capita growth rate of the carrying capacity, $dK/dt K$, is always smaller than m , the parasite does not benefit from the extra increase in K because it is offset by m . Second, if $dK/dt K$ is initially higher than m , a net growth of resource for the parasite is possible. Because $N(t)/K(t)$ increases monotonically with t , the optimal time to kill the host decreases when m increases. With respect to b , there are also two cases. If the parasite grows at a rate equal to or slower than $K(t)$, $N(t)$ will only approach $K(t)$ when $K(t)$ is already close to or equal to the maximum size of K . This situation is therefore similar to the case of a parasite growing in a host with a constant K (see above). In contrast, if the parasite is growing much faster than $K(t)$, its growth will eventually become limited by the growth of $K(t)$. Depending on the details of a host-parasite system, different functions of host growth, and therefore of $K(t)$, are conceivable. Young hosts might increase their body mass exponentially, but have deterministic growth, as is the case for many insect hosts. In other cases, hosts have indeterminate growth, as, for example, many crustaceans do. A linear increase in $K(t)$ is conceptually not different from a constant K . The effect of a

higher growth rate (slope) of $K(t)$ is similar to increasing the constant carrying capacity. We chose a sigmoidal function for $K(t)$, because it is the most general form. Other growth functions (e.g. the van Bertalanffy growth curve) lead to the same conclusions. Sigmoidal growth of $K(t)$ is modelled as

$$K(t) = \frac{K_{ini} K_c e^{kt}}{K_c + K_{ini}(e^{kt} - 1)}, \quad (8)$$

where K_{ini} is host size at the time of infection, k is the maximum per capita growth rate of the host and K_c is the 'carrying capacity of the carrying capacity'. Figure 3 shows that for small values of b , the parasite reaches $K(t)$ at the time when it is already close to K_c . For larger b , parasite biomass comes close to $K(t)$ before K_c is reached and parasite growth is limited by the growth of $K(t)$ (figure 3). It turns out that the parasite should kill the host about the time when the growth of $K(t)$ decelerates strongly, which in growing hosts corresponds to maturation. Since $K(t)$ is independent of b , the time at which $dK/dt K = m$ is independent of b . Even if b is very high, it is not beneficial for the parasite to kill the host earlier. Thus, there exists a minimum time, t_{min} , before which the parasite should not kill the host. Using equation (8), t_{min} is given by

$$t_{min} = \frac{1}{k} \ln \left(\left(\frac{K_c}{K_{ini}} - 1 \right) \left(\frac{k}{m} - 1 \right) \right). \quad (9)$$

Hence, the optimal time to kill the host will not approach zero, as was the case for a constant K , when b

Figure 3. Growth trajectories for $K(t)$ and for the parasite for four different values of parasite birth rate, b ($m = 0.1$, $K_{\text{ini}} = 10^6$, $K_c = 10^9$, $k = 0.4$). Time of infection in all cases is $t = 0$.

becomes very high. Equation (9) further shows that, as K_c increases, t_{min} increases as well, but when K_{ini} , k or m increase, the minimum time to kill the host decreases.

(b) *Introducing a cost of virulence*

It is possible that diseased hosts suffer additional mortality independent of the intentional killing of the host, because the infected host might be less responsive to predator attack, or less tolerant of stress. We include an additional host mortality rate, $v(t)$, that depends on the parasite biomass relative to the current carrying capacity, such that $v(t)$ is highest when the parasite has reached the host's carrying capacity. We chose the function

$$v(t) = g \frac{N(t)}{K(t)}. \quad (10)$$

Here g is a constant indicating the strength of the cost of virulence. There are two possible scenarios. First, death of the host due to the cost of virulence leads to zero fitness of the parasite. Second, parasites which die with their hosts because of the general mortality rate, m , have a fitness of zero, but parasites in hosts which die from the cost of virulence, $v(t)$, produce transmission stages equivalent to their biomass, $N(t)$, at the time the host dies. For both scenarios, the optimal time to kill the host decreases when g increases and it is nearly the same for both scenarios. Host fitness is higher for the second scenario, but the additional fitness the parasite gains from producing transmission stages in 'too early killed' hosts is small (less than 2% for the parameter values simulated). For scenario 1, the fitness of the parasite when it kills the host is given by

$$R(t_{\text{kill}}) = S(t_{\text{kill}}) e^{-m t_{\text{kill}}} \exp \left(\int_0^{t_{\text{kill}}} -v(x) dx \right). \quad (11)$$

Figure 4 shows for scenario 1 how parasite fitness depends on b , for different values of g . The equivalent

Figure 4. Dependence of parasite fitness, R , on the parasite birth rate, b , for different levels of cost of virulence. $m = 0.2$, $k = 0.6$, $K_{\text{ini}} = 10^6$, $K_c = 10^9$, $c = 1$.

graph for scenario 2 would be so similar that the lines are indistinguishable. When g is high, a pronounced fitness peak appears at intermediate levels of b . The decrease in fitness with increasing b is best explained by considering figure 3. When b is high, $N(t)$ quickly reaches $K(t)$, which causes additional mortality, because $N(t)/K(t)$ is high. Fitness is highest when b is such that $N(t)$ comes close to $K(t)$ shortly before the host is killed.

3. DISCUSSION

Obligately killing parasites release transmission stages only after the death of the host. Thus, killing the host is an obligate part of the parasites life cycle. Therefore, in the absence of functional constraints, an obligately killing parasite maximizes its fitness when it kills the host immediately (this model, see also Levin & Lenski (1983)). In models for parasites with continuous transmission from the living host the optimal virulence in the absence of functional constraints and trade-offs is zero (Anderson & May 1982; May & Anderson 1983; Lenski & May 1994). In other, more realistic aspects, our model and models of continuously infective parasites reach comparable conclusions. The higher the host background mortality, the earlier the parasite should kill its host (figures 1, 2; see also Anderson & May 1982; May & Anderson 1983; Kakehashi & Yoshinaga 1992; Lenski & May 1994). This finding seems universal to all models on the evolution of virulence (Ebert & Herre 1996) and has its equivalent in life history theory (Promislow & Harvey 1990; Stearns 1992). Further, both types of models predict that when a cost of virulence exists, intermediate levels of within-host growth can be optimal, corresponding with intermediate levels of virulence (for reviews, see Bull 1994; Read 1994; Ebert & Herre 1996; Levin 1996). In a model of a bacteriophage system, Levin & Lenski (1983) derived some of the conclusions we presented here for the case of a constant K .

(a) *The effect of limited resources for the parasite*

Since a host is a limited resource for a parasite, within-host growth must be limited, i.e. growth must

Table 1. *Examples of experimental host-parasite systems suitable to test assumptions and predictions of the model*

(Note that the references given do not address the questions raised in the here presented model, but rather serve to indicate examples where these host-parasite systems have been used successfully to address other evolutionary or ecological questions.)

host/parasite	system	reference
<i>Escherichia coli</i> /Phage T4	bacterium-phage	Lenski & Levin 1985
<i>Meloidogyne</i> sp./ <i>Pasteuria penetrans</i>	nematode-bacterium	Sayre & Wergin 1977
<i>Daphnia magna</i> / <i>Pasteuria ramosa</i>	crustacean-bacterium	Ebert <i>et al.</i> 1996
<i>Daphnia magna</i> / <i>Tuzetia</i> sp.	crustacean-microsporidium	Mangin <i>et al.</i> 1995
<i>Daphnia magna</i> / <i>Metschnikoviella bicuspidata</i>	crustacean-fungus	Green 1974
<i>Plodia interpunctella</i> /Granulosis virus	insect-virus	Sait <i>et al.</i> 1994
<i>Lymantria dispar</i> /Nuclear polyhedrosis virus	insect-virus	Slavicek <i>et al.</i> 1992
<i>Pieris brassicae</i> /Granulosis virus	insect-virus	Hochberg 1991
<i>Lymantria dispar</i> / <i>Entomophaga maimaiga</i>	insect-fungus	Hajek & Shimazu 1996

be density dependent. Biologically, the carrying capacity, K , may be proportional to the host's biomass and/or the host's energy intake and is therefore experimentally accessible, e.g. as host weight or body size. We predict that the parasite should kill the host later and produce more transmission stages per host when K is higher. For any time t , $N(t)$ will be higher when K is higher. Thus, parasites in larger hosts will produce more biomass than parasites in smaller or poorly fed hosts.

Table 1 lists host-microparasite systems which can be studied under controlled laboratory conditions and which appear suitable for experimental tests. Ideally it should be possible to measure parasite biomass in relation to the time since infection and to count the transmission stages at the host's death, which is an important parasite fitness component. Further, one might measure body size and resource uptake of the host, which are estimates of the carrying capacity (K or $K(t)$) of the parasite and relate it to $N(t)$, $N(t_{\text{kill}})$ and t_{kill} . Monitoring parasite growth inside the host would allow an estimate of the parasite growth parameters and test the assumption that growth is density dependent.

Many hosts grow during an infection, which is likely to lead to a change in the carrying capacity for parasite growth. We used in our model a sigmoidal growth function, but other growth functions characterized by a rapid juvenile host growth phase and a deceleration of growth when maturity is reached would lead to the same conclusion. The higher the resource growth rate, k , (steepness of juvenile growth) and the higher the maximum size of the carrying capacity, K_c , the later the parasite should kill the host. In contrast, the higher the initial level of the carrying capacity, K_{ini} , the earlier the parasite should kill the host, because when K_{ini} is high, density limitation is weaker during the early growth phase of the parasite. In experimental host-parasite systems, where $K(t)$ relates to host size, the parameters k , K_c and K_{ini} can be manipulated experimentally, for example by altering feeding conditions, age at initial infection, or using host strains selected for different body sizes or growth rates.

A strong deceleration of growth of $K(t)$ corresponds approximately to the age at maturity of a host. Rapidly growing parasites which infect their hosts early in life should kill them around the age of maturation. This is because an infection which grows rapidly comes close to $K(t)$ before $dK/dt K = m$ and it will kill the host approximately at the same time, disregarding when the infection started. Consistent with this prediction is that for some parasites of holometabolic insects it has been reported that they kill the host in the last larval stage, shortly before the host pupates (Kellen *et al.* 1965).

The cost of virulence is a crucial assumption in many virulence models. It states that unintentional, premature host killing is detrimental to the parasite when this loss in fitness is not compensated by a fitness gain in some other variable, e.g. production of transmission stages. Since the lifetime fitness of an obligately killing parasite is relatively easy to estimate (number of transmission stages at t_{kill}), the 'cost of virulence' hypothesis can be tested. We suggest to do this by using parasite strains with different virulence and to quantify parasite fitness under controlled conditions. Such strains can be produced by serial passage experiments in the same host (this leads to increased virulence) or in different hosts (this leads to attenuation of virulence) (e.g. Pavan *et al.* 1981). If a cost of virulence exists, the relationship between parasite fitness and virulence should be hump shaped. Testing the cost of virulence in a parasite with continuous transmission is technically much more demanding, since the release of transmission stages over the entire infectious period has to be monitored to estimate parasite fitness.

(b) *Parasitic castration and host fecundity compensation*

By manipulating the host life history, the parasite might be able to influence its carrying capacity and thus influence the optimal time to kill the host and increase its fitness. For example, many parasites castrate their host before they kill them (Baudoin 1975). Castration can lead to more resources available for the parasite (i.e. a higher K) and we would predict

that the parasite should kill the host later. Castration is sometimes found in combination with gigantism, in which the hosts grow to abnormally large size (Minchella 1985). Whether this benefits the parasites is not clear in all cases, but if it does, then it might do so via an increased carrying capacity for parasite growth, which would allow the parasite to grow more rapidly and produce more transmission stages.

In contrast to this, hosts can have some influence on resource allocation as well. For example, parasitized hosts might shift resources toward early fecundity (Minchella & Loverde 1981; Minchella 1985; Michalakakis & Hochberg 1994), attempting to reproduce before the parasite monopolizes the resources. This shift in resource allocation would reduce the available resources for the parasite and would therefore lead to an earlier optimal time to kill the host and to a reduced parasite fitness. Thus, the evolution of fecundity compensation in the host would cause an increase in the virulence of the parasite.

(c) Outlook

Obligately killing parasites are particularly common among invertebrate hosts and are often used as biocontrol agents, since transmission stages can be produced on a commercial scale and survival of transmission stages in the field is good (Miller *et al.* 1983). Our model is only a first step into the understanding of the life history and the evolution of virulence of these microparasites. We have highlighted the importance of density-dependent within-host growth and the costs of virulence and have derived testable predictions for a set of models with varying assumptions. We believe that most of our assumptions are reasonable and reflect, at least qualitatively, the biology of many obligately killing parasites and their hosts.

We did not consider multiple infections. Without having formalized it, we expect to find that higher parasite birth rates are favoured and that the time to kill the host will decrease (Bonhoeffer & Nowak 1994; Nowak & May 1994; van Baalen & Sabelis 1995; Frank 1996). The evolution of virulence of obligately killing parasite under conditions of frequent multiple infections will be considered at a later stage.

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