Note

When to Reproduce? A New Answer to an Old Question

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abstract: We present a life-history model based on the assumptions that juvenile survival follows a negative exponential function and that fecundity gain increases linearly with time to maturity. This model predicts that the optimal fitness is achieved when survival at maturity is 0.368 (e^{-1}). Survival at the time of maturity is therefore an invariant. We tested this prediction by using published data from infection experiments with mammalian nematodes, where both the initial number of juveniles colonizing a habitat (host) and the numbers surviving at the time of maturation were known. We found that the mean survival at maturity, both across and within species, was remarkably close to our predicted mean. As a control, we also looked at studies where the parasite species was adapted to a host species other than the one used in the reported experiment. In these experiments the mean survival at maturity differed from what our model predicted. Maturation at a fixed survival probability therefore appears as an adaptive trait evolved in a predictable environment, in this case, a host species. Our result further suggests that measures designed to increase juvenile parasite mortality, such as drugs or vaccines, will select for faster developmental rates.

Keywords: age at maturity, parasitic nematodes, drugs, developmental time, invariant.

Introduction

The age at which first reproduction takes place can have a huge impact on fitness (Roff 1992). Reproducing as soon as possible includes obvious benefits, such as an increased chance of surviving the juvenile phase and a shorter generation time. However, reproducing too early will also involve fitness costs. Spending a short period in the juvenile phase means little time to grow, so postponing maturity would lead to reproduction at a bigger body size (Skorping et al. 1991; Morand and Sorci 1998; Gemmill et al. 1999). For most poikilothermic organisms, fecundity usually increases with body size, and delayed maturity will therefore lead to more offspring. Moreover, postponing age at maturity has also been shown to increase adult life span (Skorping et al. 1991; Charnov 1993).

So how should the life history of an organism be molded between these trade-offs to achieve optimal fitness? It has long been realized that the mortality rate during the juvenile phase must be an important determinant of age at maturity. If mortality during the prereproductive period is high, delaying maturity in order to grow bigger could be a disastrous strategy, because an individual dying before reproduction will leave no offspring. It is therefore generally accepted that when mortality is age dependent, organisms should reproduce earlier when juvenile mortality rates are increased. A number of different models based on these assumptions have been proposed (see Roff 1992), most of them designed for and adapted to restricted taxonomical groups.

Here we take a more general approach. We present a model that is based on the proposed trade-off between the fitness gain of having a longer prereproductive growth period and the fitness cost of decreasing survival with time. By making some simple assumptions about the shape of these two fitness functions, we arrive at a surprising conclusion. If survival through time follows a negative exponential function while fitness gain from postponing maturity increases linearly with time, the optimal time at maturation will be reached when the chance of survival has reached e^{-1}, or 0.368. We also show that this result is independent of the shape of the survival curve and the slope of the fitness gain function. Survival at the time of maturation therefore appears to be an invariant.

This general model is applicable to any organism where the two simple assumptions of survival and fitness gain with time are fulfilled. One prediction from the model is that when a cohort of newborn individuals colonizes a patch (e.g.,

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tadpole larvae in a pond or parasite infective stages in a host), they will, on average, start reproducing when 36.8% of the original cohort remains.

Infection experiments routinely performed by parasitologists provide an ideal context in which our model can be tested. In such studies a known dose of infective, juvenile stages is initially given to a host, which is subsequently examined for surviving parasites at the time of patency (i.e., when parasite reproduction starts). Nematodes infecting mammalian hosts have been frequently studied with this approach, so there are ample data available in the literature, covering a broad range of host and parasite species. Nematodes, furthermore, fit the assumptions of our model quite closely because of a well-established positive relationship between age at maturity and fecundity (Skorping et al. 1991) and a juvenile survival likely to show an exponential decrease with time (Krebs 2001). We therefore tested our model in nematodes of mammals by establishing the proportion of parasites surviving until patency in a host across a range of both host and parasite species and under varying experimental conditions.

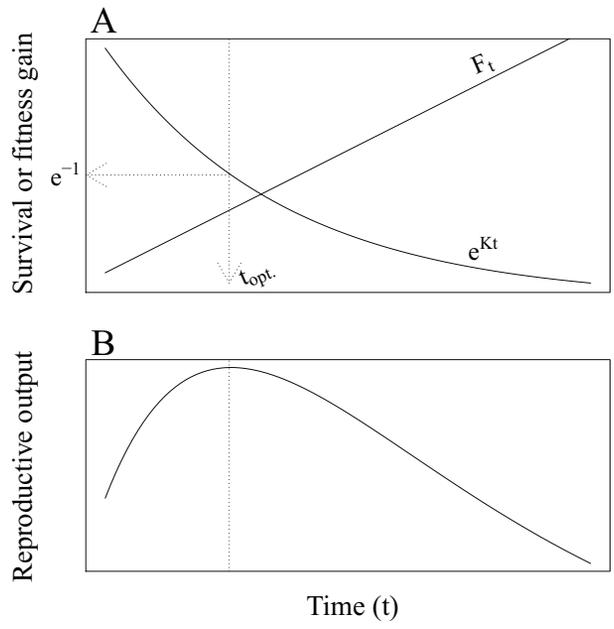

Figure 1: *A*, For a juvenile individual in a new habitat, reproductive output equals the product of fitness gain with time (F_t) and survival probability to maturity (e^{Kt}). *B*, Optimal time at reproduction (t_{opt}) is associated with a survival rate of e^{-1}. Neither the slope of the fitness gain curve nor the shape of the survival curve is critical to this result.

Methods

Model

Our model is based on the following reasoning and assumptions. When a newborn organism is introduced into a new habitat, it will encounter several mortality factors. Survival rates from these follow a negative exponential form (fig. 1*A*) and can be described as

$$S_{\text{total}}(t) = e^{-k_1 t} \times e^{-k_2 t} \times \ldots \times e^{-k_n t},$$

where $k_1 \ldots k_n$ is exposure to mortality factors $1 \ldots n$. This equation can be rearranged to

$$S_{\text{total}}(t) = e^{Kt},$$

where $K = -(k_1 + k_2 + \ldots + k_n)$.

Fitness gain ($F(t)$), here defined as lifetime fecundity, increases linearly with developmental time t (fig. 1), so that individuals maturing at a higher age are more fecund:

$$F(t) = at,$$

where a is a constant and represents the rate at which fecundity increases with age. Overall fitness ($R(t)$) is the product of fitness gain (fecundity $F(t)$) and fitness loss (survival; i.e., $t \times S_{\text{total}}(t)$). Thus,

$$R(t) = F(t) \times S_{\text{total}}(t),$$

that is,

$$R(t) = ate^{Kt}.$$

In relation to developmental time, this function increases initially, reaches a peak, and then falls steeply. The derivative of $R(t)$ is

$$\frac{dR}{dt} = ae^{Kt}(Kt + 1).$$

Reproductive output is at its maximum where the derivative is 0. It follows that the optimal developmental time T_{opt} is

$$T_{\text{opt}} = \frac{-1}{K},$$

for which the optimal reproductive output is then

$$R_{\max} = -\frac{a}{K}e^{-1}.$$

Survival at T_{opt} is therefore

$$S_{\text{opt}} = e^{(-(1/K)K)},$$

that is,

$$S_{\text{opt}} = e^{-1}.$$

Our model was inspired by and is, in all essence, similar to the model published by Alerstam and Högstedt (1983). When published, this model received some criticism (summarized in Roff 1992, pp. 114–117), but since we have adapted

the model to deal with another problem this criticism is not relevant in our case. The model predicts that the optimal time at maturation will be when survival probability has reached e^{-1}. Prematurational survival is therefore an invariant.

Data Collection

To test our prediction, we needed data on a group of organisms with a large number of controlled infection experiments and where both the infective dose and the number of surviving individuals at the age of reproduction could be quantified. We would also prefer to have a data set consisting of species from several different hosts and with a wide range in age at maturity. Nematodes from the intestinal system of mammals fulfilled all these criteria.

We made up a list of all known intestinal nematode species observed in experimental mammalian hosts, using Anderson (2000) as a source. We then used the ISI database to search for these species by typing the species name in the "title" field. We restricted the search to the 20-year period from 1987 to 2006, assuming that all relevant data from this period would give us a representative and unbiased sample. All nematode species that produced 30 hits or more in such a search were selected for further analysis. We included the information from a paper in our data set if it complied with the following criteria: (1) Experimental infections must have been given in a single dose. (2) Hosts must have been slaughtered and worms counted at the start of reproduction for the nematode species studied. In order to get a sufficient number of data points, we allowed the time of observation to deviate +25% from the prepatency times found in Taylor et al. (2007). (3) In studies where parasite mortality or developmental rates were manipulated, for example, by anthelmintics, diet, or immune suppressants, only the control animals were used. (4) Parasites must have been naturally adapted to the hosts used in the experiments; that is, only nematodes that are naturally occurring in these hosts were included.

These search criteria produced data from 77 different published papers including 202 independent observations (experiments) on 10 different species of nematodes (see the appendix, available online). Most of the experiments in this data set were what we call "homologous infections," that is, infections where the parasite infective stages were isolated from the same host species as the one used in the experiment. In these experiments, we assume that the parasite was adapted to the experimental host, which is a basic assumption for any optimality model. However, there were also data where the parasite strain was obtained from a host species other than the one used in the experiment—these we refer to as "heterologous infections." In these experiments, we cannot expect the parasite to be optimally adapted to its experimental host. Heterologous infections therefore provide a control for our prediction that, in a habitat an organism is adapted to, it should scale its development toward a survival at maturity of 0.368. Data are deposited in the Dryad Digital Repository, http://dx.doi.org/10.5061/dryad.2362q (Skorping et al. 2016).

Statistical Analysis

To evaluate whether the observed survival rate at maturity was different from our predicted mean and/or equal between the two types of parasite-host combinations, we performed a generalized linear mixed model (GLMM) by using the MASS library of R (Venables and Ripley 2002) with the following R syntax: glmmPQL(Survival.rate~Adaptation, random = ~+1 | Class/Order/Family/Genus/Species, family = quasibinomial), where the predictor Adaptation contains two levels representing homologous and heterologous parasite-host combinations. A binary GLMM was used because the response variable represents proportions and because we wanted to account for phylogeny by including it as a random effect factor. Significance from our predicted survival rate (0.368) was evaluated by using the confidence intervals from the GLMM. These intervals were calculated by using the Bradley-Terry2 library of R (Turner and Firth 2012). We also calculated the significance without accounting for phylogeny by using Wilcoxon signed-rank tests with continuity correction. When testing the two parasite-host combinations against each other and when testing each of them against the predicted survival rate, we used two-sample and one-sample tests, respectively. The significance level in all tests was set to $\alpha = 0.05$ with two-tailed testing.

Results

The mean survival rate for most nematode species in homologous infections had a narrow range (median = 0.390, range = 0.319–0.410; table 1*A*). Survival rates in heterologous infections had a much broader range (median = 0.278, range = 0.090–0.346; table 1*B*). The variations around the mean were quite large for both the homologous and heterologous groups of parasites (fig. 2*A*, 2*B*). However, for the homologous group the highest frequency of observations appeared around the arithmetic mean at 0.386 (fig. 2*A*, 2*C*). This is not different from the predicted mean of our theoretical model (fig. 2*C*).

For the heterologous group, no pattern of increased frequency of observations around the mean value was observed (fig. 2*B*, 2*C*), and the mean from the data set deviated from the predicted mean of our theoretical model (fig. 2*C*). Despite the variation at the level of individual observations, variation at the species level was narrow for the homologous group of parasites but much larger for the heterologous group (fig. 2*C*; table 1). All species with homologous infections showed mean survival rates higher than those of their

Table 1: Prepatent periods, range of infective doses and mean juvenile survival times of different species of nematodes recorded from 77 papers in the period 1987–2006

Species	Host	Parasite adapted to	Parasite infected in	Prepatency from literature	Prepatency range from studies	Range of infective dose	No. studies	No. experiments	Mean survival rate (%)
A, Homologous infections:									
Trichinella spiralis	Mice/rats			6	4–6	50–3,000	17	32	39.9
Haemonchus contortus	Sheep			20	21–28	5,000–30,000	9	21	37.8
Ancylostoma caninum	Dogs			17–27	26–30	500–1,000	3	8	40.6
Nippostrongylus brasiliensis	Mice/rats			6–15	5–9	400–6,000	13	28	39.9
Oesophagostomum dentatum	Pigs			19–49	21–35	2,000–20,000	3	18	35.0
Ostertagia ostertagi	Calves			21	25–31	25,000–130,000	5	12	41.0
Strongyloides ratti	Rats			4–8	6–9	10–3,000	4	7	38.0
Trichuris muris	Mice			36–43	34–35	50–400	5	16	40.4
Trichostrongylus colubriformis	Sheep			18–21	17–24	30,000	4	8	37.2
Trichuris suis	Pigs			41–45	49–56	2,000–5,000	3	7	31.9
B, Heterologous infections:									
Trichinella spiralis		Rats	Mice	6	6–8	50–500	2	5	34.1
Haemonchus contortus		Sheep	Goats	20	18–28	5,000–30,000	3	9	20.1
Nippostrongylus brasiliensis		Rats	Mice	6–15	5–6	400–600	4	8	34.6
Strongyloides ratti		Rats	Mice	4–8	6	1,000	1	1	9.0
Trichostrongylus colubriformis		Sheep	Goats	18–21	17–24	30,000	2	9	27.8

Note: An experiment is defined as the survival rate in an individual host, or the mean survival rate in a group of hosts when only that measurement was recorded.

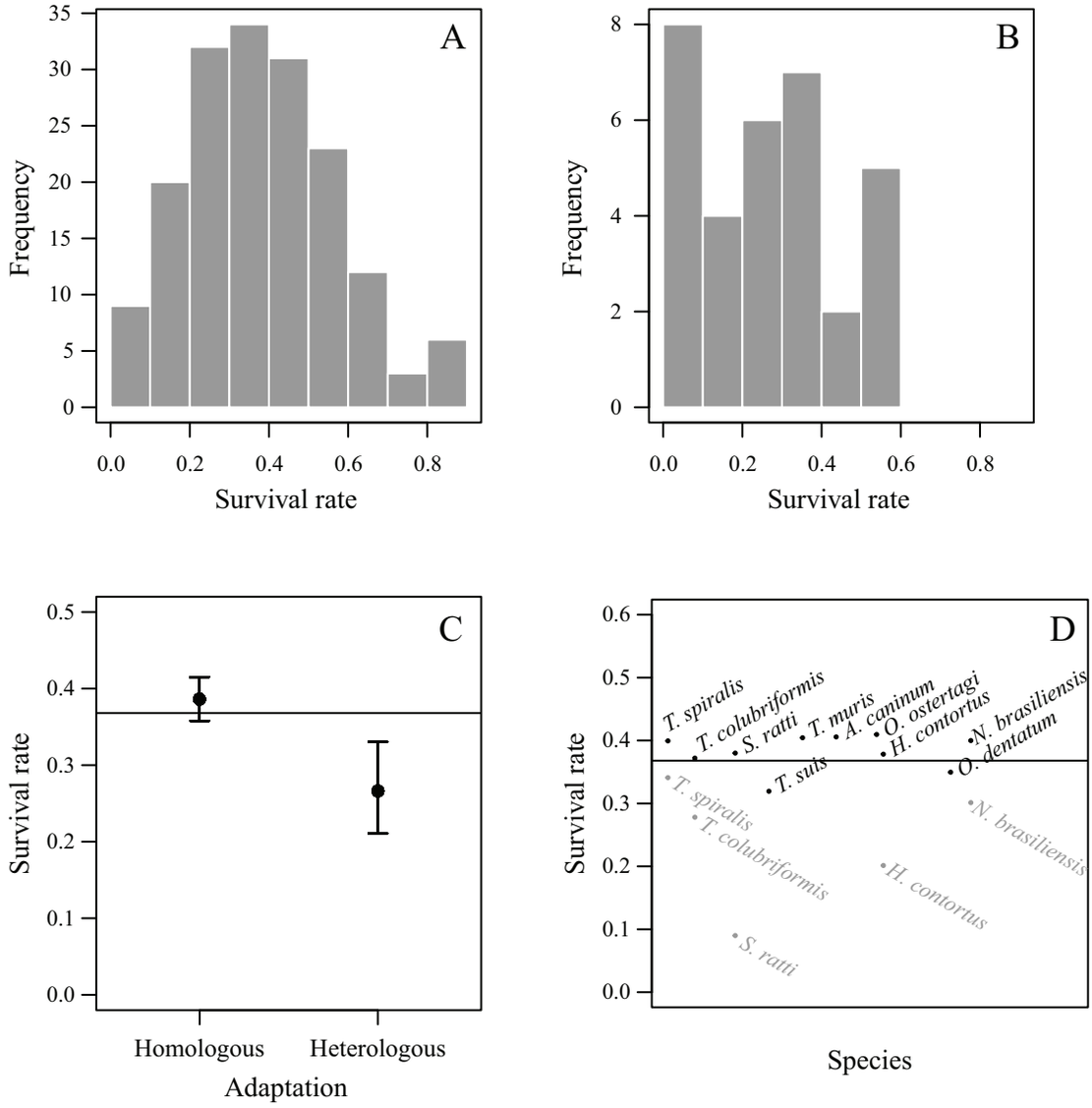

Figure 2: *A–C*, Frequency distribution of survival rates for homologous (*A*, $n = 175$) and heterologous (*B*, $n = 32$) parasite-host combinations and mean survival rates for the two parasite-host combinations with corresponding 95% confidence intervals estimated from the generalized linear mixed model (GLMM; *C*). The homologous group has a higher survival rate than the heterologous group (GLMM: $t = 3.271$, df $= 191$, $P = .001$; Wilcoxon test: $P = .003$). *D* shows the rates at the species level (see table 1 for full species names), with parasites from homologous and heterologous groups in black and gray, respectively. The horizontal lines in *C* and *D* represent the predicted mean from our theoretical model ($e^{-1} = 0.368$). The homologous group does not differ from e^{-1} (confidence interval from GLMM in *C* and one-sample Wilcoxon test: $P = .453$), while the heterologous group does (confidence interval from GLMM in *C* and one-sample Wilcoxon test: $P = .006$).

heterologous counterparts, suggesting a higher degree of adaptation in the former group.

Discussion

The species used in this study comprise nematodes from two classes and four orders. They come from many different hosts, their body length varies from 3 to 40 mm, and their prematurational developmental time ranges from about 5 to 50 days. Yet from the time when they infect the host until the onset of reproduction they all experience a mean survival rate close to our predicted invariant.

Such a close fit suggests that our model assumptions are realistic. Nematodes in mammals tend to show endemic population densities (May and Anderson 1979); hence, lifetime reproduction should be an appropriate measure for fitness. A negative exponential survival curve for the juvenile stage has been described for a wide range of invertebrates, includ-

ing parasites (Krebs 2001). Although cross-species analyses of nematodes indicate that fecundity increases exponentially with maturation time (Skorping et al. 1991), the data are insufficient to assume that such a relationship occurs within a species. Moreover, the fitness effect of this fecundity gain must be devalued by the increase in generation time, and in our model we therefore made the simple assumption of a linear relationship between fitness gain and maturation time.

A prediction from our model is that a juvenile nematode, when entering a host, is able to detect cues that will be indicative of future survival rate. A major source of juvenile mortality among nematodes is the host's immune response (Anthony et al. 2007), and several studies suggest that helminth parasites have the capacity to monitor host immune status and adjust their developmental rate accordingly (Babayan et al. 2010; Lamb et al. 2010; Allen and Maizels 2011). If juvenile survival is a tightly constrained invariant, as our results suggest, this would explain a range of other, apparently counterintuitive observations. For example, although many parasite life-history traits can readily be changed through selection, no such effect was observed on prematurational survivorship (Paterson and Barber 2007). Genetic variation in host resistance is reported to have no effect on the numbers of sexually immature nematodes, although it strongly affects worm size and fecundity (Stear et al. 1997), which is in accordance with our model. Moreover, juvenile mortality is not reduced in immune-deficient hosts (Guinnee et al. 2003), and the immune response can enhance, rather than impair, parasite developmental rate (Davies et al. 2001; Babayan et al. 2010). Such a plasticity in developmental rate to counteract perceived mortality rates would also explain why widely different infective doses apparently had no effect on survival rate, although immunity to nematodes tends to be density dependent (Anthony et al. 2007; Bleay et al. 2007).

Obviously, there must be limits to how flexible a life-history strategy can be, and nematodes appear to be better at reaching their optimal developmental rate when they are adapted to one host species. In heterologous infections, they seem to be unable to adjust their survival toward the optimum, probably because there are qualitative differences between host immune systems. All five heterological species showed a survival below the theoretical optimum. This suggests that parasites adapted to one host will generally have a reduced fitness in a new host species, confirming earlier studies on local adaptation (Ebert 1994; Greischar and Koskella 2007).

Our results are highly relevant for disease control. Parasites are a major cause of disease and mortality, among both humans and animals (Taylor et al. 2007; Hall et al. 2008; Brooker 2010), and most current control methods are based on antiparasitic drugs. Evolutionary biologists have for decades argued that since both drugs and vaccines increase parasite mortality but are not 100% efficient, they could act as strong selective factors on parasite life histories (Skorping and Read 1998; Gandon et al. 2001; Lynch et al. 2008). In our study, juvenile survival appears to be an invariant, suggesting that drugs primarily affecting adult mortality should have no selective effect on juvenile developmental rate in nematodes, contrary to earlier predictions, which have assumed that such a selective pressure could lead to a delay of the juvenile phase and therefore bigger and more fecund worms (Morand and Sorci 1998; Skorping and Read 1998; Morand and Poulin 2000; Lynch et al. 2008). However, many of the current drugs are also affecting the immature developmental stages of parasites, as are some of the new drug candidates being developed (see, e.g., Kaminsky et al. 2008). Since many nematodes show the highest pathogenicity in their juvenile phase (Taylor et al. 2007), designing drugs that target immature stages is of high priority. Our results suggest that such drugs will have no long-term effect on parasite survival but will lead only to selection for faster development. Given the extensive application of antihelminthic drugs over the past decades, one might speculate whether such an evolutionary change has already happened. A systematic survey of changes in developmental time throughout the past century has yet to be accomplished, but for some species the results are interesting. For example, the pig nematode *Oesophagostomum dentatum* was reported to have a developmental time of 60 days in 1948 (Anderson 2000), but in 1995 the shortest time to maturity was 19 days (Christensen et al. 1995).

Integrating evolutionary and ecological dynamics has been seen as the next major step toward a better understanding of biological consequences of environmental changes (Schoener 2011). Our results suggest that current control strategies can lead to rapid alterations in juvenile developmental rate. Such a directional change in one life-history trait is also likely to affect other biological characters, such as worm body size, longevity, and virulence. We would also expect this to have direct ecological consequences, for example, by shifting parasite populations from an endemic to a more epidemic state and by increasing their resilience to human intervention.

Finally, we believe the assumptions of this model to be simple and general enough to help understand variations in age at maturity in a range of organisms, including free-living ones. A negative exponential survival rate is common in many fish species and invertebrates (Krebs 2001), and in most poikilothermic species there is a positive relationship between body size and fecundity. Implications from this study might therefore reach out of the field of parasitology.

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