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Understanding parasite strategies: a state-dependent approach?

Frédéric Thomas, Sam P. Brown, Michael Sukhdeo and François Renaud

Understanding and predicting parasite strategies is of interest not only for parasitologists, but also for anyone interested in epidemiology, control strategies and evolutionary medicine. From an ecological and evolutionary perspective, parasites are an important feature of their hosts' selective environment, and may have diverse roles, ranging from the evolution of host sex to host-sexual selection behavior. Generally, it is the hosts and their biology that have been the focus of these evolutionary investigations, but we approach the subject from the parasites' perspective, illustrating the sophistication of parasite strategies in dealing with contrasting and unpredictable environments.

Studies on the evolution of life history strategies in parasites have reported significant trait variability at all levels: between species, between populations and between individuals of the same population [1–6]. Although several variables that are associated with the expression of life history traits have been identified [4], it remains difficult to explain all of the variability observed, especially at the intraspecific level. This situation is particularly problematic in investigations on virulence or on parasite reproduction at the expense of host well-being [7].

Our thesis is that an important weakness in current analyses is related to the extent to which parasites perceive their immediate and external environment, and respond appropriately through adaptive phenotypic plasticity. A potentially important part of intraspecific variation in parasitic life history traits may result from the parasites' abilities to perceive a much larger set of environmental variables than is traditionally accepted, and to respond in a state-dependent manner to maximize their lifetime reproductive success (i.e. the number of fertile offspring that an individual produces during its lifetime and the number of offspring that survive to breed themselves). Exploring the potential for strategic plasticity in parasites and identifying the mechanisms used to gain information from their external environment would be a novel approach with prospective for improving control strategies and medical treatments. Although ectoparasites could

also be considered in this article, we restrict our discussion to endoparasites.

Parasites and state-dependent models

Among free-living organisms, life history decisions are often state dependent. That is, they depend on the organism's physiological state and also on conditions related to external circumstances [8,9]. For several reasons, the ability to recognize fitness-related environmental cues to adjust strategic decisions is likely to be of great adaptive value to many free-living species. Similar arguments can be made for parasites. However, whereas state-dependent models have considered parasites as a potential state impacting on the optimal strategies of their free-living hosts [10–13], parasites have not been considered as state-dependent players in their own right.

On first reflection, it might appear that parasites have little need of state-dependent strategies (with their attendant costs of sensory and computational apparatus, i.e. the neural mechanisms that coordinate sensory input with the appropriate motor outputs) because they inhabit predictable, homeostatically maintained internal environments within their hosts [14]. In parasitic worms (e.g. cestodes, nematodes and trematodes), many of the specific behaviors involved in migration through the host, habitat selection and mate selection occur as fixed-action patterns (genetically programmed stereotyped behaviors) [15,16]. Fixed-action patterns evolve under stable or predictable environmental conditions. In stochastic free-living environments, homeostatic hosts represent predictable physico-chemical and topological substrates to their parasites. Thus, for many situations, parasites may perceive their hosts as extremely predictable environments in which fixed responses are appropriate [16]. Nevertheless, these same parasitic worms have sophisticated nervous systems and sensory structures that are as complex or more complex than their free-living counterparts [14,17–19]. These elaborate neurosensory arsenals may be required because parasite environments also contain many levels of heterogeneity.

The environment of parasites is made up of at least two dimensions, which are ecologically different: the host (i.e. the immediate environment) and the habitat of the host (i.e. the ecosystem). A first source of environmental heterogeneity for parasites is the host itself because the host can be old or young, male or female, sensitive or resistant, full of competitors or a virgin territory. Furthermore, parasites are, in a sense, prisoners of their hosts and have little option of changing host, and thus must make the best of whatever host they may find themselves within. A second level of environmental heterogeneity is due to the variability of the ecosystem in which the infected host and the host population live. For example, the ecosystem can be more or less rich in resources, in predators or in parasitic species, it can be more or

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less permanent due to disturbance, or the host population density can be variable. These sources of heterogeneity and their interactions contribute to build variable selective landscapes, in which parasites live and have to maximize their lifetime reproductive success. In such a context, it would not be surprising if selection favored the ability to perceive a diversity of signals that indicate or correlate with specific environmental parameters (immediate and/or external), thus affecting their immediate and future fitness.

Variability in the internal host environment

Parasites may recognize the physiological and biochemical conditions of their hosts that are of selective importance. A good example would be the age of the host. Host longevity following infections can strongly influence the success of a fixed-parasite strategy, and this should exert strong selective pressure on parasites to adapt their developmental program to the age of their hosts. Despite these theoretical expectations for host-age-specific strategies [4,20], there is currently no evidence of parasites altering their reproductive effort (and virulence) when infecting an old host with short life expectancy (few days or few weeks). However, parasites are known to respond to a wide variety of host-generated cues that signal changes in their host biology.

It is probably impossible to understand fully the sensory perception of parasites, but their behavioral responses to environmental signals provide a small window into their perceptual worlds. The well-studied phenomenon of 'spring rise' in domestic animals is a good example from parasitology textbooks. Nematode infections acquired during late autumn and winter will arrest their development within the host, but will resume development in response to hormones secreted during lactation, and begin shedding infective stages just when the susceptible lambs and calves begin weaning. There are several other examples of parasites adapting their development to their hosts' endocrine signals. One of the more exotic adaptations is seen in the bladder-inhabiting monogeneans that coordinate their transmission to a single day when their frog hosts emerge from the ground to mate [21].

Adaptive responses by parasites to host environmental conditions can be even more closely coordinated. The adult liver fluke *Fasciola hepatica* lives in the bile duct and feeds on blood of the human host. These worms respond to the gastrointestinal hormones in the blood that regulate host gut function. At the beginning of a meal, the hormone cholecystokinin (CCK) is secreted and this triggers contractions of the bile ducts that can expel the worms along with the bile. The worms respond to CCK by attaching to the mucosa with their powerful ventral suckers [22]. Motilin, secreted at the end of a meal, stops bile duct contraction and the worms

respond to this hormone by releasing their sucker attachment and resuming their locomotory activity. This behavior is clearly adaptive and supports the idea that parasites have the capability to detect and respond to subtle changes in the immediate environment of the host.

Another state that parasites may *a priori* perceive in their immediate environment is the presence of other parasites within the host, and there is an abundance of literature that confirms the density-dependent nature of parasites responding to intraspecific and interspecific competition. Competitors may be sensed directly or through the intermediary of the host immune system. Taylor *et al.* [23] investigated facultative virulence in *Plasmodium chabaudi* infections of mice to test whether competition among co-infecting genotypes led to a facultative increase in replication rate and consequently virulence. Hosts infected with more than one parasite genotype experienced raised virulence relative to hosts infected with a single genotype, supporting theoretical models demonstrating that within-host competition drives increases in virulence [24–27]. However, these results did not exclude an alternate host-centered hypothesis that the presence of multiple genotypes places a higher demand on the host immune system, thus leading to an elevated loss of host condition and subsequent increase in virulence [23]. Also, the relationship between virulence and reproduction could be decoupled in some parasite strategies [28].

In other situations, parasites may benefit from the presence of other parasites (of the same species or not) when, for example, cooperation among parasites allows a better exploitation of the host [29]. In such a case, fitness benefits may be gained by parasites that are able to detect the presence and/or numbers of other parasite individuals before adopting a particular strategy. The phenomenon of 'hitchhiking parasites' provides a good example (e.g. the trematode *Maritrema subdolum* [30]). Some parasites (manipulators) are able to alter their hosts' behavior to increase their susceptibility to predators (the next host). Hitchhiking species preferentially infect those hosts that are already infected with manipulators and get the benefits of increased transmission, without the costs associated with manipulating host behavior [30]. A different example is quorum-sensing bacteria which coordinate gene-expression with cell density. By monitoring a constitutively produced signal molecule, individual bacteria can limit their expression of group-beneficial phenotypes to cell densities that guarantee an effective group outcome [31]. For bacterial pathogens, this flexibility has important consequences for the expression of virulence genes. Quorum signaling offers an important advantage of surprise to a bacterial invader, aiding the coordination of a rapid and overwhelming attack through the synchronized production of virulence factors [32,33].

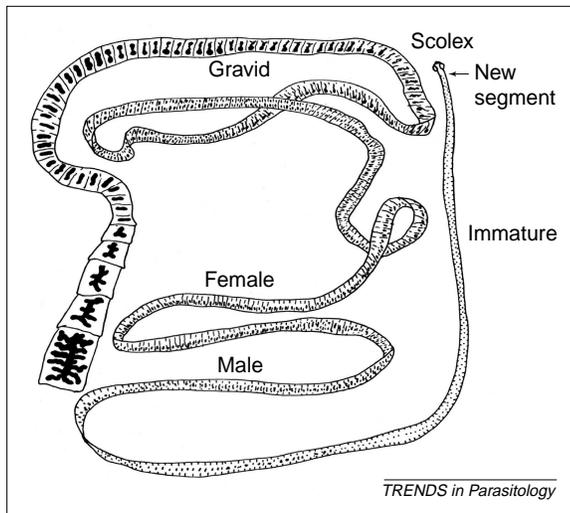


Fig. 1. Egg production strategy in the common rat tapeworm *Hymenolepis diminuta*. New segments are produced in the neck region just below the scolex, and they mature as they move down the strobila (body); terminal gravid segments (full of eggs) are shed into the fecal stream. Reproduced, with permission, from Ref. [39].

Variability in the host external environment

It may be possible for parasites to perceive the external environment of their hosts, such as the predation risk of their hosts, and adjust their strategy accordingly. Free-living crustaceans can evaluate the abundance of fish predators, without the need to see them directly, by detecting components of the fish mucus in the water [34]. Parasites within the crustaceans could enjoy selective advantages if they gain access to this information. This could be done directly (i.e. similar to the host) or indirectly by detecting chemicals produced by the host when the host detects predators. In the case of parasites having no interest in finishing their life cycle in the gut of a fish, an adaptive answer, when detecting a high abundance of fish, would be to increase virulence to exploit the host before it becomes a prey. Conversely, for parasites finishing their life cycle in a fish, detecting the abundance of their definitive hosts in the environment could be useful information to adjust traits such as the length of prepatency and/or the optimal manipulative effort required for the crustacean to be eaten by a fish predator.

More generally, parasites perceiving the imminent death of their host (for whatever reason) are expected to adjust their strategy. It is frequently observed that parasite virulence is higher when the host is in poor condition or experiencing stressful conditions [35]. Traditionally, this observation is interpreted as evidence that a poor body condition is associated with a lower ability to resist parasitic infections. However, being in poor condition is also a classical state before dying; hence, a higher virulence of parasites could also be the result of a sudden change in their host exploitation strategy.

For gut-inhabiting parasites, the host food-stream provides an accurate account of the host's ability to

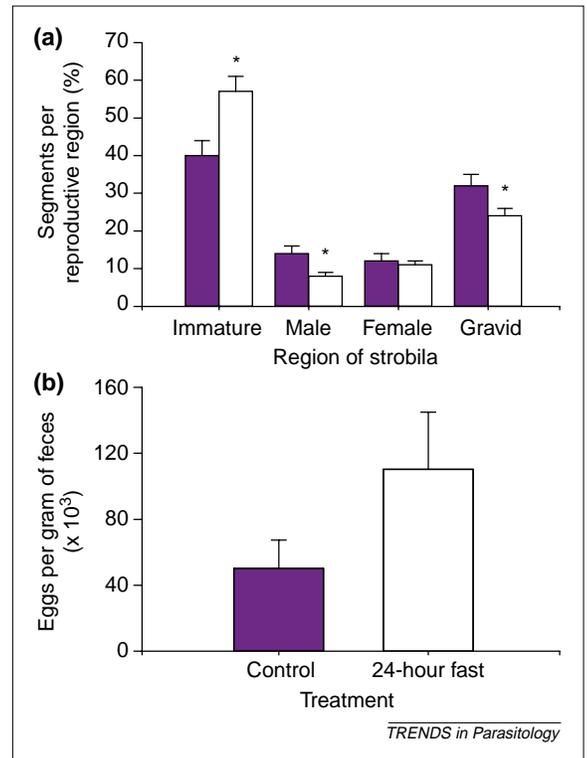


Fig. 2. Reproductive differentiation of segments in the tapeworm strobila in fed rats (solid bars) and rats starved for 24 h (open bars). All rats were infected with 10 infective cysticerci of *Hymenolepis diminuta* recovered from infected flour beetles (*Tribolium confusum*). The rats were fed normally until the experimental treatments (starve or feed) began on Day 15 post-infection. Means represent 10 adult worms recovered from each treatment group (two worms per rat); lines represent standard error, * indicates $P \leq 0.05$. (a) Starved worms respond by decreasing the maturation rate of immature segments (the proportion of immature segments increase) and increasing development of sexual segments (male segments decrease). High production of parasite eggs (b) is maintained by the continued maturation and shedding of gravid segments (gravid segments decrease in a).

gather resources. Prolonged starvation of the host (famine) signals a significant reduction in food availability and an increase in host mortality, and it should be advantageous for parasites to divert their resources towards increased egg production. The rat tapeworm *Hymenolepis diminuta* has a segmented strobila (body) that comprises distinct immature, male, female and gravid segments, which occur in stable proportions (Fig. 1). The immature segments become mature as they move down the strobila until they become gravid, containing viable eggs, and are shed into the lumen and passed out with the feces. This egg assembly-line strategy is coordinated via several large nerve cords from the worm's brain that connect all of the segments [36]. When the rat host undergoes prolonged fasting (24 h), the worms respond by decreasing the maturation of the sexual segments and diverting resources towards the gravid segments to increase or maintain high levels of egg production (Fig. 2). One interpretation of these data is that the worms are responding to host starvation by trading off future egg production for current egg production.

In theory, other kinds of environmental information could be obtained indirectly by parasites. Parasites could, for instance, have a reliable indicator of their host population density by detecting internal changes that occur inside their hosts when they meet conspecifics (sexual partners or competitors). The frequency of these signals is expected to have some correlation with the host population density or at least with the probability of intraspecific contacts between hosts. Given that the host population density might greatly influence the success of high versus low virulence strategy, as well as vertical versus horizontal transmission strategy, parasites may be able to evaluate host population density before adopting a strategy. Similarly, manipulative parasites that rely on predation for their transmission could benefit from perceiving these signals in that their optimal manipulative effort is likely to be influenced by the density of manipulated hosts [20].

Concluding remarks

We suggest that the environmental perception of parasites could be much more sophisticated than traditionally imagined. In addition to signals from their immediate environment, there may be a large number of direct and indirect cues that provide reliable

information on the host external environment. Detecting these signals and responding appropriately in a state-dependent manner could greatly enhance the fitness of parasites, and there is no *a priori* reason to believe that this phenomenon has not been selected during the course of evolution. To understand how parasites perceive the world, more research is needed to determine the range of information-seeking mechanisms used and to identify the ecological significance of their behavioral responses. In addition, the identification of the costs of acquiring the relevant information (e.g. development and maintenance of sensory apparatus) and the resulting cost and/or benefit trade-offs must be an important consideration in these analyses [37,38]. Generalizations must be considered with caution because information that is relevant for one parasite species is not necessarily relevant for another parasite species. It would be interesting to determine whether different parasite species experiencing similar ecological pressures evolve perception of similar signals (i.e. evolutionary convergence). From a medical viewpoint, we might be able to send artificially altered information to a parasite that would change its strategic decisions in a way that reduces the parasite's pathological consequences. Even if we are far from this at the moment, this research area is promising.

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