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INFLUENCING RANDOM TRANSMISSION IS A NEUTRAL CHARACTER IN HOSTS

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ABSTRACT: This study introduces an individual-based model on a host–parasite assemblage to investigate whether hosts are necessarily selected for obstructing the transmission of virulent parasites to conspecifics. Contrary to the widespread notion, a host's ability to influence parasite transmission within the host population is a neutral character provided that parasite transmission routes are random, with no reference to genetic relatedness. Due to a lack of selection pressure under such circumstances, hosts may fail to evolve counteradaptations against manipulations by parasites to enhance transmission. However, vertically biased transmission (biased toward kin) selects hosts for a decrease of parasite transmission, while it is also known to select parasites to decrease virulence. Horizontally biased transmission routes (biased toward nonrelated conspecifics) select hosts to increase parasite transmission. In this case, their interests coincide with that of their virulent parasites in enhancing transmission to conspecifics. This finding yields the predictions that hosts infected by virulent pathogens, but unable to recover from disease, should be prone to emigrate from their natal territories and also to enhance transmission at a distance from their natal ranges. These results may considerably improve our understanding of the epidemiology of contagious pathogens and the evolution of social and sexual behavior in host species.

A host–parasite interaction can be divided into 3 periods, i.e., infection, growth, and multiplication within the host, followed by transmission to a new host. Animal species have developed a wide variety of characteristics that function to avoid infection by microparasites and macroparasites. Aspects of sexual selection, foraging strategies, social behavior, and habitat selection may often serve to avoid contacts with infective stages of parasites. Once infected, however, hosts exhibit a wide variety of physiological, immunological, and behavioral defenses either to expel parasites or to stop their multiplication (Barnard and Behnke, 1990; Clayton and Moore, 1997; Poulin, 1998). Despite these costly evasive and defensive efforts, most vertebrates living in nature are chronically infected with several species of parasites. In the third period of host–parasite interactions, theoretically, an obstruction of parasite transmission by the infected hosts could be an effective defense measure, yielding benefits to the host population as a whole.

Can selection act on hosts to influence transmission probabilities of their parasites? Aspects of host behavior such as degree of sociality, mating patterns (monogamy/promiscuity), timing and location of defecation, contacts with potential vectors, etc., are, arguably, characters with variable genetic components. Apart from other costs and benefits of these behavioral characters, they can potentially change the infected hosts' capability to distribute parasites (Apanius and Shad, 1994).

Although some animals have been observed to participate in parasite transmission actively, this behavior is typically interpreted either as a manipulation of the host by its parasites or as a nonadaptive coincidental side-effect of infection (Moore and Gotelli, 1990; Poulin, 1995). Contrary to this view, one could argue that selection maximizes the relative reproductive success of hosts; hence, infected animals could gain some relative advantage by increasing parasite transmission and thus decreasing the absolute reproductive output of conspecifics. To investigate this possibility, an individual-based model was developed to test the adaptive value of host-induced parasite transmission within the framework of a host–parasite system.

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METHODS

Individual-based models illustrate variability at the individual level (Judson, 1994) and treat extinction of alleles and species in a more realistic manner than traditional population-based models (Uchmanski and Grimm, 1996); therefore, they are particularly suitable for modeling host–parasite coadaptation (Reiczigel and Rózsa, 1998).

A diagram of the model is presented in Figure 1. It mimics a host population of discrete generations (n = 50). Hosts have diploid genomes harboring 10 loci occupied by either resistance or susceptibility alleles. The phenotype of host resistance is determined by these loci, and no environmental variance is assumed. At the outset, resistance or susceptibility alleles are allocated randomly to these loci with a probability of 50–50%. An allele called host-induced parasite transmission (HPT) and its inactive allelic counterpart compete for positions on the 11th locus. Simulation experiments are designed to study the changes of allele frequency at this single locus, whereas the 10 loci for resistance or susceptibility alleles serve only to provide a host–parasite model system as an environment.

For the sake of simplicity, the HPT allele frequency starts at 0.5 at each run. In the first generation of each run, hosts are infected by parasite burdens of random size, equally distributed within a range of 0–10. A host life cycle starts with 2 subcycles of host defense and parasite reproduction. On average, hosts halve their parasite burden, but the actual efficacy of this decimation depends on their genotype. Surviving parasites then duplicate themselves.

In the host breeding phase, 2 parents are chosen randomly for each offspring (n = 100). Parental alleles are inherited by simple Mendelian rules, whereas no mutation occurs. To illustrate vertical transmission from parent to offspring, the size of an offspring parasite burden is random, exhibiting normal distribution with an expected value equalling the mean of the parental burdens.

Parasite burdens are potentially increased by individuals harboring allele(s) of HPT, who transmit parasites to conspecifics actively. HPT homozygotes increase the parasite burdens of 10 conspecifics chosen randomly, whereas heterozygotes do the same with 5 conspecifics. They add 5 parasites, i.e., mean parasite burden at the start, to the parasite burdens of conspecifics contacted, without achieving any decrease in their own parasite burdens; thus, no dilution effect occurs (see below). Hosts homozygous for the inactive allele do not transmit parasites to members of the same generation.

Half of the offspring are selectively eliminated in the next phase. The probability of death for an individual host is proportional to the number of resistance alleles and the number of parasites, weighted equally. The surviving half of the offspring generation is then redefined as parent generation to start a new life cycle.

Apart from the host-induced transmission of parasites among members of the same generation, the main idea of this model is that both host resistance and parasite burden size are selected against, i.e., resistance is costly and parasites are virulent. Such simple models can mimic some aspects of host–parasite systems quite reliably; e.g., host resistance is normally distributed, whereas parasite distribution is aggregated

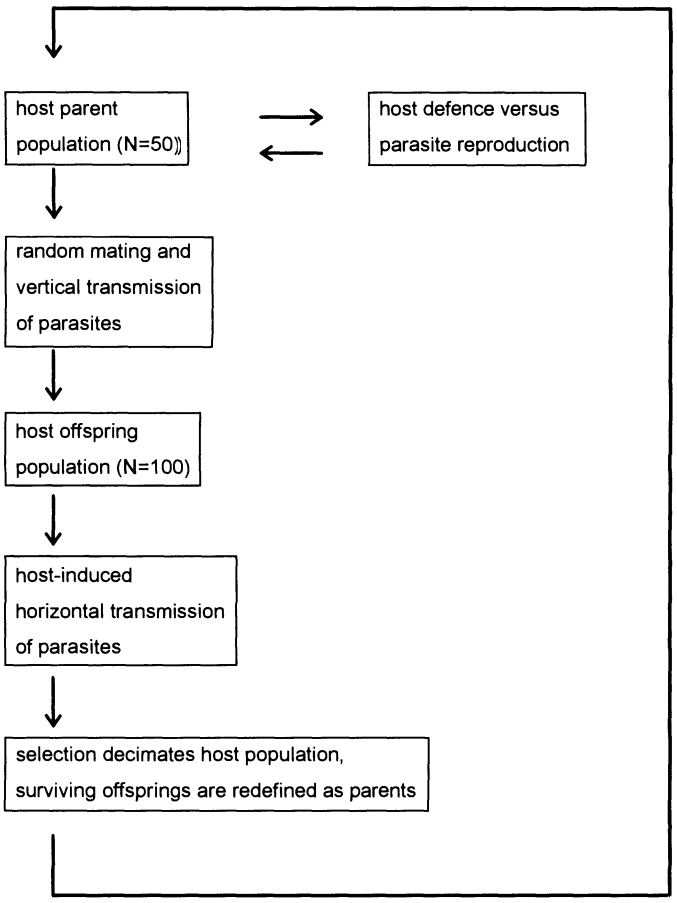

FIGURE 1. Life cycles of hosts and parasites in the model.

due to selection pressure. The population mean of resistance levels and that of parasite burdens interact in a somewhat oscillating pattern (Fig. 2). The model was implemented by a computer program written in QBASIC of about 100 lines in length, which is available upon request.

Simulation 1 mimics a scenario of random infection routes with no reference to kinship among members of the same generation. Active parasite transmission can be oriented toward any member of the population including the parasite transmitter itself. In simulation 2, there is a precedence of vertical transmission routes among individuals more closely related to each other than the population average. Kin recognition is based on the presence of HPT allele and it is defined to be rather ineffective; individuals lacking the HPT allele have a 20% lower probability of becoming infected due to active parasite transmission as compared to HPT homozygotes (10% for heterozygotes). Transmission is horizontally biased in simulation 3; host-induced parasite transmission is biased in favor of transmission routes among individuals less related to each other than the population average. Again, kin recognition is based on the presence of HPT and it is inefficient; homozygous HPT genotypes have a 20% lower probability of becoming infected due to active parasite transmission as compared to individuals homozygous for the inactive allele (10% for heterozygotes). Note that enhancing parasite transmission increases the parasite burdens of all members of the population. However, this disadvantage is not equally shared by the different genotypes in simulations 2 and 3.

Sensitivity analyses were carried out to check for the potential influences of host population size (changed to 25 and 100), the number of host defense/parasite reproduction subcycles per host generation (changed to 1 and 4), and the number of transmissive contacts initialized by active parasite transmitters (changed to 5 and 20 for homozygotes, and to 2 and 10 for heterozygotes).

Each simulation experiment contained 200 simulation runs, and each run mimicked 100 host generations. Wilcoxon signed-rank tests (2-

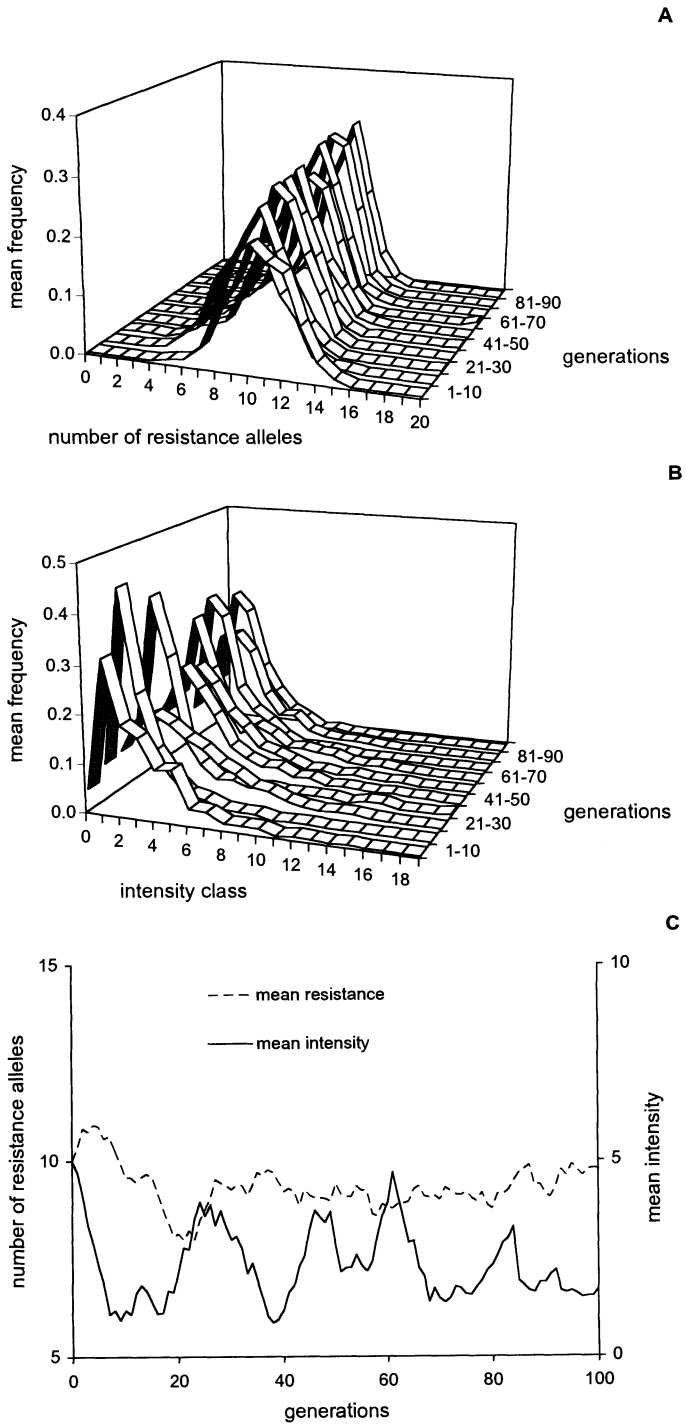

FIGURE 2. Selection against both high host resistance and high parasite burden in a model system provides some features characteristic of natural host–parasite assemblages. The distribution of host resistance is approximately normal (A), while the distribution of parasites among hosts is aggregated (B). Each line represents the mean of 10 generations. The population mean of resistance levels and that of parasite burdens apparently interact in an oscillating pattern (C). Data were obtained from a single simulation run with no host-induced parasite transmission present.

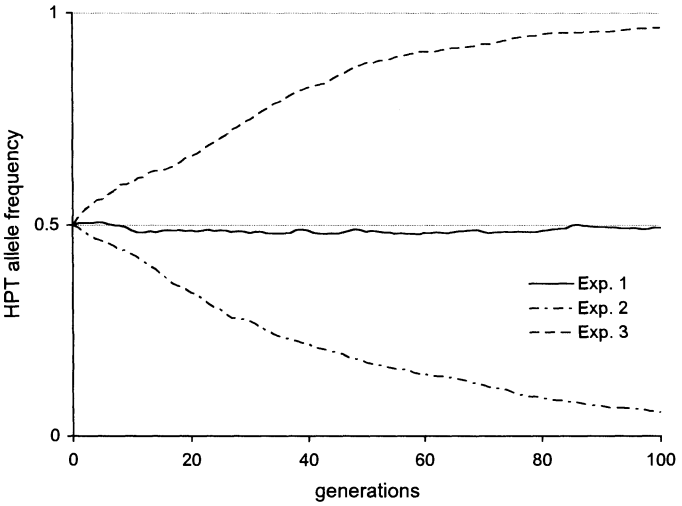

FIGURE 3. Changes in the relative frequency of a hypothetical host allele responsible for host-induced parasite transmission in different simulations. Each line represents the mean of 200 simulation runs. Transmission routes are random in simulation 1, biased toward kin in simulation 2, and biased toward nonrelated individuals in simulation 3.

tailed) were used to analyze the results of simulations, i.e., to examine whether HPT allele frequencies (0.5 at the start) were significantly increasing or decreasing during the runs. Calculations were carried out by using Instat 2.04.

RESULTS

The results of simulation 1 could not be differentiated from the expected outcome of random genetic drift exhibited by a neutral pair of alleles. HPT allele frequencies at the end of the runs were not significantly higher or lower than the starting values ($P = 0.7507$). Simulation 2 indicated a selective advantage of the inactive allele. HPT allele frequencies were lower at the end of the runs than the starting values ($P < 0.0001$). Simulation 3 resulted in a selective advantage of the HPT allele; its frequencies were higher at the end of the runs than the starting values ($P < 0.0001$). Figure 3 summarizes these results.

Finally, the sensitivity analyses showed that the above results were robust enough not to be affected by the major variables. HPT remained a neutral allele in simulation 1, was selected against in simulation 2, and selected for in simulation 3, in the case of all the different variables tested in the sensitivity analyses.

DISCUSSION

Previous studies have shown that host species may benefit from distributing parasites to another species in the context of interspecific competition for resources (Freeland, 1983; Hudson and Greenman, 1998). A new interpretation of the history of human diseases suggests that a similar process might have occurred among human races. The Caucasian race acquired resources from other races partially by distributing its more species-rich parasite assemblage. This process relies on a difference of resistance; the host species or race that benefits from parasite distribution is less susceptible to infection as compared to the competing species or race. Once the introduced pathogens cycle more rapidly within the new population, they also tend to acquire higher virulence (Ewald, 1994). On the contrary, the present model illustrates processes within a single host population and does not imply a difference in resistance or a difference in virulence exhibited in different hosts. Another way of profiting from the distribution of parasites is to decrease parasite burdens by transferring parasites to conspecifics (dilution effect, reviewed by Hart [1992]). In the present model, however, transmitting parasites is defined as not yielding the benefit of decreasing individual parasite burdens, e.g., parasitic and infectious life stages of the parasite species are differentiated. Thus, a helminth infrapopulation inhabiting the host gut cannot be decreased by enhancing transmission of helminth eggs to conspecifics.

Simulation 1 demonstrates random pathogen transmission with no reference to genetic relatedness among host individuals. Random transmission (often equalled to horizontal transmission by different authors) is close to realistic in pathogens characterized either by a sit-and-wait transmission strategy or by high spatial mobility during transmission. The latter feature may be due to an inherently high ability of pathogens to disperse or a consequence of water-borne, predator-borne, or vector-borne transmission (Ewald 1994, 1995). Provided that infection routes often involve transmission through great distances or long periods of time, transmission is rather unpredictable, with no reference to genetic kinship among hosts. Therefore selection is neutral toward alleles that influence parasite transmission apparently because the disadvantages caused by host-induced transmission affect all possible genotypes equally. In this context, it is worth noting that host manipulation by parasites to increase parasite transmission have often been documented in parasite species of indirect life cycles such as in larvae of trematodes and acanthocephalans (Moore, 1984; Poulin, 1994a). Unlike the typical arms race of host–parasite evolutionary conflicts, this is a unilateral action: parasites are selected to manipulate hosts to facilitate transmission, while being manipulated or not is a neutral character in the gene pool of the host population.

A classic example, i.e., the lancet fluke (*Dicrocoelium dendriticum*), may help to interpret this argument. Fluke larvae kill the ant intermediate host. When dying, ants are manipulated by the parasites to fix themselves onto the top of grass blades to enhance the flukes' transmission into the definitive host, a ruminant (Poulin, 1995). Imagine a hypothetical mutant allele in a colony of ants that enables infected ants to die underground. The ant-to-ant transmission route is interrupted by long developmental phases in ruminants and snails (vectors, from the ants' point of view); thus, transmission is inherently random with no reference to kinship among ants. Consequently, the benefits of not transmitting flukes would be equally shared by all ant colonies within the area, with no reference to the presence or absence of the mutant allele. This allele cannot ensure a selective advantage to the ant colony that harbors it as compared to those colonies that do not and, thus, it would not be selected for. An active participation in the distribution of a lethal pathogen, the lancet fluke, is, therefore, a neutral character in the evolution of ants. They simply let themselves be manipulated without a chance for counteradaptation.

Simulation 2 introduces vertically biased transmission into the model. Hosts are effectively selected to decrease parasite transmission provided that infection is biased toward their rel-

atives. This situation enables hosts to decrease their contribution to parasite distribution and to develop counteradaptations to oppose parasite manipulation as hypothesized previously by Poulin (1994b). On the other hand, vertically biased transmission also exerts selection pressure on parasites to decrease their virulence (Ewald, 1994, 1995).

Simulation 3 mimics horizontally biased transmission of pathogens within the host population. In this case, the relative reproductive success of an allele can be increased by enhancing the spread of parasites to nonrelated conspecifics, thus decreasing their absolute reproductive success. This phenomenon appears to be identical with the evolution of spiteful behavior that is defined as a behavior that harms others without benefit to the self (Hamilton, 1970; Gadagkar, 1993). Within the context of social behavior of animals, however, there are a few if any examples known for spite, perhaps due to 2 causes. First, spite is typically costly; an animal attacking a conspecific will immediately face a counterattack by similar means. However, the situation is different when actively transmitting pathogens. Diseases can often be transmitted anonymously, and, even if the identity of the spiteful individual is known, it cannot be revenged simply by a similar action. Secondly, harming nonrelatives is just an indirect way of helping those who are more related than the population average. Considering the social behavior of animals, searching for nonrelatives and harming them is probably not a cost-effective way of helping relatives as compared to a direct help of the few closely related kin. However, there may be no such choice for animals chronically infected by virulent pathogens. They have a reduced ability to help relatives directly, whereas their ability to harm many individuals simultaneously is greatly improved. It may well be adaptive for them to profit from this increased ability by focusing spite on nonrelatives.

Possible predictions are that an infected host unable to recover from disease should be prone to emigrate from the natal territory and to become more social and promiscuous than uninfected conspecifics living in their natal ranges. Cliff swallows (*Hirundo pyrrhonota*) are known to increase natal dispersal due to ectoparasitism, although the authors' interpretation of this phenomenon was different (Brown and Brown, 1992). An increase of spatial movement activity due to parasite infection was often interpreted as a manipulation by the parasite to increase transmission probability (Moore and Gotelli, 1990; Poulin, 1994a, 1995). An alternative, nonexclusive interpretation offered here is that this phenomenon is a host adaptation to bias transmission toward nonrelated conspecifics. Previous studies suggested that animals may be selected to exclude immigrants from social groups (Peck, 1990) perhaps to reduce the inflow of parasites (Freeland, 1976). The evolution of outsider exclusion may be viewed as an intraspecific counteradaptation against this emigrate-when-diseased strategy.

To summarize, hosts are not selected for influencing the transmission of randomly transmitted, thus predictably virulent, parasites to conspecifics. Moreover, horizontally biased transmission may even exert selection pressure on hosts to facilitate the spread of virulent pathogens within certain parts of the host population. The discovery of the neutral nature of random pathogen transfer may considerably improve our understanding of the epidemiology of contagious pathogens and the evolution of social and sexual behavior in animals. It is also an intriguing possibility that the evolutionary mechanisms described above may have influenced the evolution of human behavior and the history of mankind.

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