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Superinfection reconciles host–parasite association and cross-species transmission

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HIGHLIGHTS

- Many parasites appear to exhibit host specificity.
- Many parasites are also efficient in cross-species transmissions.
- The above two phenomenon are largely incompatible without adaptive mutations.
- Superinfection facilitates apparent host specificity and cross-species transmission.

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ABSTRACT

Parasites are either dedicated to a narrow host range, or capable of exploiting a wide host range. Understanding how host ranges are determined is very important for public health, as well as wildlife, plant, livestock and agricultural diseases. Our current understanding of host–parasite associations hinges on co-evolution, which assumes evolved host preferences (host specialization) of the parasite. Despite the explanatory power of this framework, we have only a vague understanding of why many parasites routinely cross the host species' barrier. Here we introduce a simple model demonstrating how superinfection (in a heterogeneous community) can promote host–parasite association. Strikingly, the model illustrates that strong host–parasite association occurs in the absence of host specialization, while still permitting cross-species transmission. For decades, host specialization has been foundational in explaining the maintenance of distinct parasites/strains in host species. We argue that host specializations may be exaggerated, and can occur as a byproduct (not necessarily the cause) of host–parasite associations.

1. Introduction

Many parasites in nature are associated with a host species, or a group of related species. Examples of host–parasite association can be found in a range of disease systems including HIV/SIV, rabies, malaria, and Lyme borreliosis (Garamszegi, 2006; Hahn et al., 2000; Kurtenbach et al., 2002; Streicker et al., 2010). In certain cases there are natural barriers to the exploitation of multiple host species, e.g. sexually transmitted diseases. Yet other disease systems relying on direct, vectored, or environmental transmission allow for a potentially wide host range. In these systems, the factors that determine whether parasites focus on a narrow range of species or adopt a more generalist strategy are typically not known, yet the mechanisms at play have important consequences for public health and beyond. For instance, zoonotic parasites cause significant human disease burden worldwide (Jones et al., 2008), and any practical disease intervention strategy requires some knowledge of the associated host species. Further, these parasites may transmit through multiple wildlife species. Such complex transmission cycles are robust in the sense that blocking transmission from one host species may only partially control human disease risk—as demonstrated in North American Lyme disease (Tsao et al., 2004). Recently, an urgent hunt for the reservoir host(s) of Ebola virus, Henipavirus, and SARS-coronavirus has implicated bats (Dobson, 2005). Given our limited understanding of the transmission competency of alternative hosts, and of bat-virus dynamics in general, it is unclear if targeting any number of bat species would be effective in reducing human disease risk.

Arguably, one of the worst-case scenarios for public health is a host shifting event, defined as a parasite/strain that was previously zoonotic and now circulates exclusively among humans; HIV/AIDS is a prime example (Hahn et al., 2000). Additional examples are drawn from studies on primate malarias, which have identified multiple host shifts from non-human primates to humans (Krief et al., 2010; Mu et al., 2005), which include the malaria parasites *Plasmodium falciparum* and *P. vivax*. All of these examples illustrate

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that understanding parasite host ranges is crucial for global disease management.

The prevailing data on host–parasite systems suggest there are at least two influential factors in determining a parasite's host range (Woolhouse et al., 2001): (1) the community-level contact structure, which determines opportunities for cross-species transmission; and (2) the standing genetic diversity of the parasite. Essentially, the combination of host species availability and the potential for adaptive evolution is thought to be the dominant force in shaping a parasite's host range. A realized host range that is less than all contactable hosts (few infections in some species, despite them being accessible to the parasite) reflects a degree of host association by the parasite or strain. A central concept is that host–parasite association results from host specialization; the adaptive evolution of the parasite, leading to a specific host preference (Levene, 1953). The difficulty with host specialization is that it does not easily explain how many parasites routinely cross the species' barrier, unless we invoke recurrent adaptation by the parasite. For example, a parasite that evolves a preference towards one host species is unlikely to cause an outbreak in an alternate species, unless a mutation occurs that either enhances cross-species transmission, or improves within-species transmission in the alternative host population. While this condition is plausible for rapidly-mutating viruses, it is cumbersome for relatively slow-evolving bacteria and protist parasites, and, we argue, not the only mechanism that can explain variable patterns of host–parasite association in nature.

In this study we use mathematical modeling to examine whether general parasite transmission processes can lead to variability in host association patterns (along a spectrum of restricted to unrestricted host ranges) while still allowing for frequent cases of cross-species transmission. Notably, we explore this in the absence of recurrent adaptation to isolate the potential effects of ecology and transmission. Specifically, we focus on the role of superinfection in driving host associations and cross-species transmissions—two common, empirical phenomena that appear to be at odds with each other. Although earlier studies have investigated parasite transmission in heterogeneous populations (Gandon, 2004; Woolhouse et al., 2001), the effects of superinfection in such populations are rarely invoked.

2. System of equations

$$\begin{aligned}
\frac{dS_1}{dt} &= b_0\left(S_1+I_{1A}+I_{1B}\right)-b_1\left[\left(S_1+I_{1A}+I_{1B}\right)^2\right] \\
&\quad -\mu S_1-\left[\beta S_1\left(I_{1A}+I_{1B}\right)+\beta r S_1\left(I_{2A}+I_{2B}\right)\right] \\
\frac{dS_2}{dt} &= b_0\left(S_2+I_{2A}+I_{2B}\right)-b_1\left[\left(S_2+I_{2A}+I_{2B}\right)^2\right] \\
&\quad -\mu S_2-\left[\beta S_2\left(I_{2A}+I_{2B}\right)+\beta r S_2\left(I_{1A}+I_{1B}\right)\right] \\
\frac{dI_{1A}}{dt} &= \beta S_1 I_{1A}+q\beta I_{1B}I_{1A}+q\beta r I_{1B}I_{2A}+\beta r S_1 I_{2A}-(\mu+v)\,I_{1A} \\
\frac{dI_{1B}}{dt} &= \beta S_1 I_{1B}+\beta r S_1 I_{2B}-\left[q\beta I_{1B}I_{1A}+q\beta r I_{1B}I_{2A}+(\mu+fv)\,I_{1B}\right] \\
\frac{dI_{2A}}{dt} &= \beta S_2 I_{2A}+\beta r S_2 I_{1A}+\varepsilon q\beta I_{2B}I_{2A}+\varepsilon q\beta r I_{2B}I_{1A}-(\mu+v)\,I_{2A} \\
\frac{dI_{2B}}{dt} &= \beta S_2 I_{2B}+\beta r S_2 I_{1B} \\
&\quad -\left[\varepsilon q\beta I_{2B}I_{2A}+\varepsilon q\beta r I_{2B}I_{1A}+(\mu+fv)\,I_{2B}\right].
\end{aligned}$$

2.1. The deterministic model

The model depicted in Fig. 1 and the system of equations in Section 2 represents a host–parasite system of two host species (S), denoted by subscripts 1 and 2, and two parasites: A and B. Infected hosts are classified as either I_{1A}, I_{1B}, I_{2A}, I_{2B}. Host populations recover from losses (natural mortality and disease-induced mortality, also called virulence) via a density-dependent birth rate, $bN = (b_0 - b_1N)N$, where b_0 is the density-independent birth rate and b_1 is a density-dependent factor. Both strains have a higher transmission rate between hosts of the same species compared to cross-species transmission, reflecting a degree of ecological separation between host types, controlled by parameter r. Parasite B transmits within each host species at rate βSI, where β is the transmission rate. Parasite A transmits at rate βSI in both host species, and additionally is capable of superinfection (infecting an individual currently infected by parasite B). The superinfection rates are $q\beta SI$ for I_1 and $\varepsilon q\beta SI$ for I_2. This assumption articulates that we regard A as an aggressive mutant, which superinfects I_{1B} preferentially (that is, parameter $\varepsilon < 1$ ensures the superinfection rate of type 2 hosts is lower than that of type 1 hosts). The reasoning for this assumption is that the ability to superinfect a host is jointly dependent on the aggression of the superinfecting strain (to outcompete the inhost resident strain) and host–specific immunity (to permit secondary infection), i.e. a combination of host and parasite effects. It is therefore conservative to assume that distinct host species differ in their degree to permit superinfection ($[I_{1B} \rightarrow I_{1A}] \neq [I_{2B} \rightarrow I_{2A}]$). Potential specific mechanisms include differences in the cost or quality of immune activation, which may be initiated (or exacerbated) from immune priming by an unrelated parasite (Telfer et al., 2010), or by species-specific energy expenditures, such as migration (Altizer et al., 2011; Weber and Stilianakis, 2007). The parameter ε allows a range of superinfection disparity to be explored. The outcome of superinfection is immediate takeover of the I_B individual by strain A, yielding an I_A individual. Rates of primary infections of both hosts by both strains are equal; there is no intrinsic host preference. As a consequence of its aggression, strain A carries a greater virulence cost (reflected by v) in I_1 and I_2 subpopulations than strain B (where virulence is modeled by $-fvI$ with $f < 1$). We examine a range of differences in virulence costs between strains. We set equal population sizes and growth dynamics of S_1 and S_2 in order to distinguish the effects of superinfection in isolation, otherwise a larger (or more fecund) host group may confound the advantage or cost of superinfection; we show in Supplementary materials that relaxing these assumptions does not change the general outcome of our model. Initial conditions and parameters are listed in Table 1. All deterministic simulations began with strain B at equilibrium followed by an introduction of strain A and an evolutionary period of 500 years. We arbitrarily define a host-associated parasite as having 80% of its infections in one host species.

2.2. The stochastic model

We extended our analysis with stochastic simulations of the superinfection model and compared these with results from a stochastic host-specialization model, both implemented by the adaptive tau-leap method (Cao et al., 2007) in a Gillespie framework (Gillespie, 1977). Our chief aim was to examine whether appreciable cross-species transmission occurred in the absence of adaptive evolution. Modeling host specializations typically includes some form of explicit tradeoff in parasite transmission (Anderson and May, 1979; Gudelj et al., 2004; Regoes et al., 2000). The essential idea is that a parasite that increases its transmission to one host species does so at the cost of transmission to alternative host types. The cost to the specialist parasite is that by increasing its exploitation of one host, it consequently reduces its exploitation and transmission in alternative hosts (Frank, 1996; Regoes et al., 2000). We model this phenomenon by having two β values, β_L and β_H, which represent a low and high transmission rate, respectively. We then compare this asymmetrical transmission model with the