Inverse-Gene-for-Gene Infection Genetics and Coevolutionary Dynamics

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Abstract: The genetic basis of infection in host-parasite interactions has traditionally been considered within the framework of either gene-for-gene (GFG) or matching-allele models. We present an alternative model, termed inverse-gene-for-gene (IGFG), where pathogen infectiousness is determined by parasite recognition of host signals and/or receptors or where there is active host searching by parasites. We show that coevolutionary dynamics under IGFG are both qualitatively and quantitatively different from those of the GFG model, and we suggest that this new approach may be applicable to a range of important host-parasite systems that are not currently catered for by the existing frameworks.

Keywords: antagonistic coevolution, infectivity, resistance, host-parasite, gene-for-gene, matching allele.

Introduction

Whether successful infection occurs in a host-pathogen system often depends on the specific combination of host and parasite genotypes. Two major models of infection genetics have been proposed—the gene-for-gene (GFG) model and the matching-allele (MA) model—and there has been much debate as to which model best represents the genetic basis of infection in host-parasite interactions (Frank 1993b, 1996a, 1996b; Parker 1994, 1996). However, another possibility, which we call the inverse-gene-for-gene (IGFG) model, has received much less attention. In this article, we describe the possible biological mechanisms that may give rise to this form of interaction, and we compare the resulting coevolutionary dynamics with those from a typical GFG framework.

GFG infection genetics are well studied, both theoretically and empirically (Flor 1956; Thompson and Burdon 1992; Frank 1993a; Sasaki 2000). The simplest case of GFG is represented by the situation where host and parasite each have a single locus with two alleles: the host has an allele for either resistance or susceptibility, and the parasite has an allele for either virulence or avirulence. (Throughout this article, we use the term "virulence" in the plant pathology sense, referring to the ability of a parasite to cause infection rather than the parasite’s impact on host fitness.) The underlying mechanistic basis of GFG-like interactions is that resistance is inducible and requires recognition of the pathogen by the host. Hence, resistance requires that hosts have a receptor that recognizes an elicitor produced by the parasite, whereas loss of the elicitor by the pathogen or absence of a matching resistance allele results in infection. In a two-locus–two-allele haploid model, infection—and therefore disease—occurs in the combinations shown in figure 1.

Alternatively, however, infection may require recognition of the host by the pathogen and, in this case, the host gains resistance by losing the receptors targeted by the pathogen. Bacteria-bacteriophage interactions provide an example of this type of pattern despite traditionally having been assumed to be GFG-like: infection requires the bacteriophage to bind to specific bacterial cell surface receptors, and resistance requires modification or loss of these receptors (Lenski and Levin 1985; Lenski 1988). Similar infection genetics may play a role wherever plant or animal parasites actively seek out their hosts (Haas et al. 1995; Pierce et al. 2003). Clearly, the underlying infection genetics of these host-pathogen systems will be fundamentally different from those assumed by the standard GFG model, as they are more appropriately modeled using the alternative IGFG framework (fig. 1). However, despite this clear and potentially important distinction, we are unaware of any studies that have attempted to assess the implications of IGFG infection genetics for host-parasite coevolution. Here we modify an established multilocus GFG model (Sasaki 2000; Fenton and Brockhurst 2007) to incorporate IGFG infection genetics and compare the consequences of the two types of infection genetics on coevolutionary dynamics.
Figure 1: Probability of infection under each host and parasite genotype combination for haploid gene-for-gene (GFG; A) and inverse-gene-for-gene (IGFG; B) models for (i) a single locus and (ii) a two-locus scenario (separate loci have identical symbols). A $\sigma$ indicates the degree of resistance (the reduction in the probability of infection) conferred by a single effective resistance gene ($\sigma = 0$ implies complete resistance). A $r_i$ denotes an allele for parasite virulence, $v_i$ denotes avirulence, $r_i$ denotes host resistance, and $v_i$ denotes susceptibility. Hence, these subscripts reflect the binary values used to define host and parasite genotypes in the model (see “Model Structure” and appendix). Note that, in diploids with GFG, virulence is usually recessive while resistance is dominant; with IGFG, virulence is expected to be dominant and resistance is recessive.

Model Structure

Our IGFG model is based on the haploid multilocus GFG model of Sasaki (2000); we outline the general structure of the model in the main article and leave a detailed description to the appendix. The model assumes there are $n$ loci, each with two alleles in the host, that contribute to resistance to the parasite, and $n$ corresponding virulence loci in the parasite that contribute to successful infection. Hence, the host genotype for resistance is denoted by a string of binary numbers $s = s_1, s_2, \ldots, s_n$ and, correspondingly, the parasite genotype is denoted by $t = t_1, t_2, \ldots, t_n$, where the value of each is either 1 or 0, denoting resistance or susceptibility, respectively, in the host or virulence or avirulence, respectively, in the parasite. As described above, the outcome of contact between a given host and a given parasite is determined by the combination of alleles at their respective resistance and virulence loci. In the standard GFG model, (partial) resistance occurs if there is at least one allele $i$ where $s_i = 1$ and $t_i = 0$ (i.e., a parasite avirulence gene is matched by a host resistance gene at a given locus; fig. 1A). Note that, mechanistically, $t_i = 0$ (parasite avirulence) implies the presence of elicitor $i$ in the pathogen. However, for the IGFG model, (partial) resistance occurs either if there is at least one allele $i$ where $s_i = 1$ (i.e., the host has a resistance allele) or if $s_i = 0$ and $t_i = 0$ (i.e., a host susceptible gene is matched by a parasite avirulence gene at a given locus; fig. 1B). Note that, mechanistically, $s_i = 1$ (host resistance) implies the absence of a host factor recognized by the pathogen. We assume that each effective resistance allele confers partial
resistance to infection, reducing the probability of successful infection by a specified amount $\sigma$ (only for values of $\sigma = 0$ is there complete resistance). Following Sasaki (2000), we assume that $\sigma > 0$, so that typically the pathogen can persist even when the host is fixed at all resistance loci.

The outcomes of infection for all possible host and parasite genotype combinations determine the relative fitness of each genotype, and these are modified by intrinsic per-gene costs to the host and parasite of harboring resistance or virulence genes, respectively (Sasaki 2000; Fenton and Brockhurst 2007). The resulting relative fitnesses determine the contribution of each genotype to the next generation. The populations are assumed to be asexual (there is no recombination), but random mutations occur at a low rate between genotypes and complete the gene frequency dynamics between generations. Population size is held constant, and all interactions are determined by host and pathogen relative abundances and allele frequencies. The model is completely deterministic and the case illustrated is for five loci, each with two alleles, in both the host and the pathogen (see appendix for details).

**Results**

Analysis of the GFG model shows that combinations of both low host and low parasite per-allele costs ($c_H$ and $c_P$, respectively) result in sustained coevolutionary cycles among alleles at all five loci (CYC region, fig. 2A; see also Sasaki 2000; Fenton and Brockhurst 2007). However, high parasite per-allele costs of virulence in the pathogen results in the absence of alleles for parasite virulence and stable levels of host resistance consisting of polymorphism at either a single resistance locus or two resistance loci (the regions labeled SR/NV and DR/NV, respectively, in fig. 2A). On the other hand, high per-allele resistance costs in the host ($c_H$) result in the absence of both host resistance and parasite virulence alleles (labeled NR/NV in fig. 2A). In all of these situations, there is a small amount of added variation that is maintained by recurrent mutation at all loci; however, switching off mutation in the simulations results in the loss of this variation, confirming the evolutionary trend to monomorphism or dimorphism in the SR, DR, and NV cases.

Analysis of the IGFG model, however, reveals very different coevolutionary dynamics for the same parameter values (fig. 2B). As before, low host and parasite costs result in coevolutionary cycles. However, low costs to virulence in the parasite produce three qualitatively new outcomes of coevolution not observed with the GFG model. First, both the host and parasite populations may be monomorphic, with the hosts becoming fixed for one of the several single resistance alleles (i.e., absence of a single
receptor) but all parasites being maximally virulent and fixed for all five possible virulence genes (labeled SR/5V in fig. 2B). Second, the host population may be fixed for any two resistance alleles but the parasite population exhibits extreme stable polymorphism, such that some parasites have no virulence alleles but the remainder have the maximal number (labeled DR/N,5V in fig. 2B). Third, for high per-allele costs of resistance, the host population can be completely susceptible but the parasite population is fixed for virulence at all loci (labeled NR/5V in fig. 2B).

Finally, even when the predicted qualitative outcomes are the same, the two models predict different dynamics. In particular, the nature of coevolutionary cycles differs considerably for the two models (fig. 3; see appendix). As described by Sasaki (2000), the GFG model produces either regular, frequent fluctuations in host and parasite genotypes, formed by consecutive cycles in frequency of alternating loci, or irregular, nonrepeating cycles (see appendix). Both of these dynamics show constant coevolutionary change in both the host and the parasite. However, for the IGFG model, although regular fluctuations can occur for intermediate per-allele costs of resistance, relatively high or low costs of resistance can result in punctuated coevolutionary dynamics, with long periods of stasis periodically interrupted by sudden bursts of coevolution. Broadly, two types of punctuated coevolution occur. The first, coevolutionary "spikes," occur at low values of $c_i$ (see appendix) and are characterized by rapid escalation of parasite virulence (in both the number of virulence alleles and their frequency) followed by a crash (fig. 3A). This pattern occurs because parasites are at a strong disadvantage under the IGFG model and the presence of even low numbers of resistance alleles greatly restricts their ability to infect; it is only because each effective resistance allele confers partial resistance that any infection can occur at all. Hence, the greatest determinant of parasite fitness becomes the cost of harboring virulence alleles, and so virulence drops, followed by a gradual decline in host resistance. Eventually, resistance of the host population approaches 0, allowing virulence alleles to quickly spread throughout the population. This is followed by a rapid increase in the number and frequency of resistance alleles within the host population due to the low costs of resistance, which drives virulence back down to 0, where it remains until resistance has waned sufficiently to favor another burst of virulence. The second form of punctuated coevolution, coevolutionary "collapse," is characterized by parasite virulence occurring at maximal levels, interrupted by occasional crashes in virulence, followed by rapid recovery to maximal virulence (fig. 3B). This occurs at high per-allele costs of resistance, which slows the buildup of resistance in the host population, allowing parasite virulence to remain maximal. Eventually, resistance increases to a point where the likelihood of infection is very low, regardless of the number of virulence alleles. At this point, the cost of carrying virulence alleles becomes too great and they are quickly selected out of the parasite population. This is followed by a rapid drop in costly resistance alleles that, in turn, favors parasite virulence.

Discussion

Our results emphasize that host-pathogen systems characterized by IGFG interactions form a third and distinct class of genetic interactions in addition to the classic GFG and MA systems. Very different types of coevolutionary dynamics emerge from IGFG interactions relative to those from classical GFG models. In our model, all parameters except the determination of the host-pathogen genetics (based on the underlying recognition mechanisms) were kept constant, yet this resulted in contrasting coevolutionary outcomes, both in terms of levels of polymorphism and in the quantitative form of coevolutionary cycles (where they occurred). In particular, under IGFG, potentially very high virulence levels may occur, even when the host shows very low levels of resistance (regions marked SR/5V and NR/5V in fig. 2B). These differences between the two models arise because under GFG it is possible for one pathogen genotype to infect all host genotypes, and every pathogen can infect at least one host genotype (see fig. 1). However, under IGFG, it is not possible for any pathogen genotype to infect all hosts, and there is no host that is universally susceptible.

Therefore, there is a difference in the balance of power between host and parasite for the two systems: GFG is inherently parasite biased, whereas IGFG is host biased. Mechanistically, the difference between the GFG and IGFG systems arises from which partner (host or parasite) has the responsibility for determining the outcome of host-parasite contact (in terms of successful infection, or not). Under GFG, resistance is inducible and requires the host to recognize the pathogen. Conversely, under IGFG, the onus of infection lies with the pathogen, which needs to recognize the host in order to infect. As with any coevolutionary situation, the evolutionary outcomes are influenced by the different phenotypic consequences of the mutational effects, and these are different for GFG and IGFG.

There are likely to be further important evolutionary differences between IGFG and GFG that are not accounted for in the current model. In particular, to facilitate direct comparison of GFG and IGFG in the current analysis, mutation rates of hosts and pathogens were assumed to be the same. However, given the mechanistic differences that underlie the resistance/virulence mechanisms in GFG and IGFG, it is likely that mutation rates will be asym-
Figure 3: Coevolutionary host and parasite trajectories for the inverse gene-for-gene model showing (A) spiking punctuated coevolutionary dynamics (host per-allele cost $c_h = 0.05$, parasite per-allele cost $c_p = 0.13$) and (B) collapsing punctuated coevolutionary dynamics ($c_h = 0.73$, $c_p = 0.13$). The two top panels show the frequency distributions over time of the number of resistance and virulence alleles in the host and parasite populations, respectively; the darker colors represent higher frequencies. The bottom two panels show the change in frequency of the host resistance and parasite virulence alleles at each locus, where different line styles represent different loci. Parameter values are the same as for figure 1.
metrical between hosts and parasites and the relative magnitudes will differ between the GFG and IGFG models. Specifically, the evolution of a novel recognition genotype is likely to require a gain of function mutation, whereas evasion of recognition would likely require a loss of function mutation. Therefore, because mutation rate would be expected to be greater in loss of function mutations, differences in evolutionary potential between the antagonists may arise through differences in mutational supply.

Additionally, it is likely that there will be consistent differences between IGFG and GFG in terms of the costs of resistance and virulence (resulting in populations with IGFG vs. GFG falling in different regions of figs. 2 and 3). In GFG, a pathogen would be expected to gain virulence by loss of function mutations, while in IGFG this would be achieved by gain of function (recognition). Therefore, in GFG, increased virulence of the pathogen might be readily achieved, but it may also be very costly, while in IGFG this would apply to resistance in the host. It is interesting that in one of the best-studied naturally occurring plant-pathogen GFG systems, there has been a demonstration of a cost to multiple virulences (Thrall and Burdon 2003) but little evidence of a cost to multiple resistances. More generally, costs of resistance have been difficult to demonstrate in induced defenses, and they may in many cases be negligible in the undiseased state (Bergelson and Purrington 1996; Purrington 2000).

The goal of this article has been largely heuristic, pointing out that IGFG is an important alternative to classical GFG. In this context, it is important to note that the Sasaki (2000) model that we have used is oversimplified. For example, it assumes that both host and pathogen populations are haploid and asexual, gene effects are equal, and costs are multiplicative. It also ignores numerical dynamics, and it assumes the pathogen has no impact on the host density; it is well established that inclusion of numerical dynamics can change the conditions for maintenance of resistance polymorphisms (Bowers et al. 1994; Thrall and Antonovics 1994) and coevolutionary outcomes (Bowers et al. 2003). Under IGFG, a universally resistant host can eliminate the pathogen (if there is complete resistance, such that $\sigma = 0$). The model may therefore only be applicable to situations where the genetic effects give partial resistance or where the pathogen has alternative hosts and/or alternative mechanisms of persistence, such as saprophytism or long-lived resting stages.

Given these reservations, it is difficult to extrapolate from our theoretical model directly to empirical data without considerable more information. However, coevolutionary dynamics in bacteria-bacteriophage systems do resemble those predicted by several aspects of this IGFG model. Specifically, bacteria typically dominate coevolutionary interactions with phage, such that resistance traits are often more readily evolvable than infectivity traits (effectively, the host has an evolutionary advantage over the phage; Lenski and Levin 1985; Bohannan and Lenski 2000; Brockhurst et al. 2007). Furthermore, periods of stasis interspersed with bouts of rapid coevolution have been observed in experiments with *Pseudomonas fluorescens* and phage $\Phi_2$ (Buckling and Hodgson 2007), which more closely matches the dynamics of our IGFG model. It remains to be seen whether other host-parasite systems that are traditionally modeled using a GFG framework are more accurately described as being IGFG.

Sasaki (2000) showed that coevolutionary outcomes sometimes maintain, and sometimes obliterate, standing genetic variation in resistance and/or virulence, even when the underlying mechanisms are genetically highly specific. We have shown that the conditions under which this happens also depend on the underlying assumptions about the mechanistic nature of host-pathogen interaction, and the IGFG model represents a broad but neglected class of interactions, often with unique consequences for coevolutionary outcomes. We suggest that a range of important host-parasite systems such as those involving bacteriophage and any system where parasites actively seek out their hosts may be more appropriately modeled using the IGFG framework presented here. Clearly there are other ways, such as mutational propensity, in which IGFG systems may have evolutionarily distinct outcomes from GFG systems, but these remain to be investigated.

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**APPENDIX**

Outline of Model Structure and Classification of Coevolutionary Cycles

**Model Structure**

Our model is based on the multilocus gene-for-gene (GFG) model of Sasaki (2000). Here we outline the basic structure of the model, which is common to both our model and that of Sasaki, leaving the details of our modifications for
the main article. The model assumes there are $n$ loci in the host that confer partial resistance to the parasite and $n$ corresponding virulence loci in the parasite that contribute toward successful infection. Each locus has one of two alleles: resistant or susceptible in the host and virulent or avirulent in the parasite. Hence, the host genotype for resistance is denoted by a string of binary numbers $s = s_1, s_2, \ldots, s_n$ and the parasite genotype is denoted by $t = t_1, t_2, \ldots, t_n$, where each digit is either a 1 or a 0, denoting resistance or susceptibility, respectively, in the host or virulence or avirulence, respectively, in the parasite. The outcome of contact between a given host and a given parasite is determined by the combination of alleles at their respective resistance and virulence loci and whether the underlying genetics are assumed to be GFG or inverse-gene-for-gene (IGFG; see fig. 1 and the main text for details).

To incorporate partial resistance, it is assumed that each effective resistance gene (as determined by the genotype infection matrix shown in fig. 1) reduces the probability of successful infection to $\sigma$. Hence, if $r(s, t)$ is the number of effective resistance genes of host genotype $s$ when attacked by parasite genotype $t$, then the probability of successful infection is

$$Q(s, t) = \sigma^{r(s, t)}.$$ 

The mean parasite load for host genotype $s$ and the mean host availability for parasite genotype $t$ are then $\bar{w}_t = \sum_s \sigma^{r(s, t)} p(t)$ and $\bar{w}_s = \sum_s \sigma^{r(s, t)} q(s)$, respectively.

Finally, the model assumes that the fitness of host $s$ decreases on the basis of its number of resistance genes due to a cost per gene, $c_s$, of maintaining resistance, and also because of the cost of being infected, at a per parasite rate $\beta_s$. Hence, the fitness of host genotype $s$ is

$$w(s) = \exp\left(-|s| c_s - \beta_s \sum_t \sigma^{r(s, t)} p(t)\right),$$

where $|s|$ is the number of resistance genes harbored by the host. Similar arguments show the fitness of parasite genotype $t$ to be

$$w(t) = \exp\left(-|t| c_t + \beta_t \sum_s \sigma^{r(s, t)} q(s)\right),$$

where $|t|$ is the number of virulence genes harbored by the host, $c_t$ is the cost to the parasite per virulence gene, $\beta_t$ is the fitness gain to the parasite of successful infection, and $q(s)$ is the frequency of hosts with genotype $s$ in the population.

Genotype frequencies change between generations due to selection according to

$$q(s) = \frac{w(s) q(s)}{\bar{w}_s},$$

$$p(t) = \frac{w(t) p(t)}{\bar{w}_t},$$

where $\bar{w}_s = \sum_s w(s) q(s)$ and $\bar{w}_t = \sum_t w(t) p(t)$ are the mean fitnesses of hosts and parasites, respectively, in the population. In addition, there are assumed to be rare mutations, at rate $\mu$, in each generation between alleles at each locus.

**Classification of Coevolutionary Cycles**

As described in the main text, the GFG and IGFG models tend to exhibit very different coevolutionary dynamics within the “cycling” region of parameter space. Here we explore in more detail these different behaviors, and we classify their dynamics within the $c_s-c_t$ parameter space on the basis of the frequency and regularity of the observed allele frequency cycles from model simulations. In all cases, the observed cycles were sustained for more than 20,000 generations, which was long enough to exclude transient dynamics and allow the system to settle into its natural, long-term behavior.
It should be noted that these classifications are, by necessity, subjective, and there may not be clear boundaries delimiting the occurrence of these cycle types. Furthermore, this analysis is not exhaustive, and there may be small regions of parameter space for both models where alternative cycling dynamics occur. However, the parameter values used for the simulations were chosen to be representative of the whole of the cycling region of parameter space for each model, and it is unlikely that any important dynamical behaviors were missed. Therefore, we believe that this classification is useful in giving an overview of how the two models differ in their predicted coevolutionary dynamics.

Broadly speaking, observed coevolutionary cycles could be placed into one of three categories:

1. Regular cycles: Cycles with a constant amplitude. In some cases, these cycles were asynchronous, such that the frequencies of the different alleles rose and fell at different times (fig. A1). In other cases, the cycles were synchronous, in that the frequencies of different alleles rose and fell together (fig. A2).

2. Irregular cycles: Cycles with an irregular amplitude (fig. A3). These cycles appear to be chaotic, but the occurrence of chaos is not crucial to our argument, and so we did not calculate Lyapunov exponents.

3. Punctuated coevolution: Defined as infrequent but repeating patterns, in which there was a clear period of stasis between the end of one cycle and the beginning of the next (see fig. 3). These could be further subdivided into two categories: (a) “spiking” dynamics, in which parasite virulence was typically very low but was undergoing periodic rapid escalation in virulence before crashing back down (fig. 3A); and (b) “collapsing” dynamics, in which parasite virulence was typically maximal but was undergoing periodic crashes in virulence before climbing rapidly back to maximal levels (fig. 3B).

Both models produced regular cycles, although they tended to be synchronized in the IGFG model, whereas the GFG model tended to show desynchronized cycles (fig. A4). Furthermore, the other two types of cycling were each unique to one of the models; irregular cycles were observed only for the GFG model, whereas the long-period cycles characteristic of punctuated coevolution were observed only for the IGFG model (fig. A4). Once again, we emphasize that the location of the boundaries plotted in figure A4 are somewhat subjective. In particular, for a given value of $c_p$, the model tends to show a smooth transition from spiking dynamics, through regular cycles, to collapsing dynamics as $c_h$ is increased. For the purposes of this analysis, we defined punctuated dynamics as being characterized by the presence of prolonged periods of apparent stasis in parasite allele frequencies and coupled with an asymmetric cycle in host allele frequencies (e.g., fig. 3), compared with the uninterrupted and symmetrical fluctuations in allele frequencies characteristic of regular cycles (e.g., fig. A2).
Figure A1: Coevolutionary host and parasite trajectories. The two top panels show the frequency distributions over time of the number of resistance and virulence alleles in the host and parasite populations, respectively; the darker colors represent higher frequencies. The bottom two panels show the change in frequency of the host resistance and parasite virulence alleles at each locus, where different line styles represent different loci. Desynchronized regular cycles generated from the gene-for-gene model (host per-allele cost $c_h = 0.13$, parasite per-allele cost $c_p = 0.05$).
Figure A2: Coevolutionary host and parasite trajectories. The two top panels show the frequency distributions over time of the number of resistance and virulence alleles in the host and parasite populations, respectively; the darker colors represent higher frequencies. The bottom two panels show the change in frequency of the host resistance and parasite virulence alleles at each locus, where different line styles represent different loci. Synchronized regular cycles generated from the inverse-gene-for-gene model (host per-allele cost $c_h = 0.31$, parasite per-allele cost $c_p = 0.15$).
Figure A3: Coevolutionary host and parasite trajectories. The two top panels show the frequency distributions over time of the number of resistance and virulence alleles in the host and parasite populations, respectively; the darker colors represent higher frequencies. The bottom two panels show the change in frequency of the host resistance and parasite virulence alleles at each locus, where different line styles represent different loci. Irregular cycles generated from the gene-for-gene model (host per-allele cost $c_h = 0.13$, parasite per-allele cost $c_p = 0.13$). Other parameter values are the same as for figures 1 and 2.
Figure A4: Phase diagram from the main article, with the addition of approximate boundaries (dashed lines) between the qualitatively different cycling behaviors. See figure 2 for definitions of region labels. $c_p =$ parasite per-allele cost; $c_H =$ host per-allele cost.

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