

LETTER

Neutral drift and polymorphism in gene-for-gene systems

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Abstract

Pathogens are a main driving force of the evolution of plants and animals. Being resistant to diseases confers a high selective advantage to hosts, yet many host–pathogen systems show a remarkable degree of polymorphism of host resistance and pathogen virulence. The most common explanation of this phenomenon is that both resistance and virulence genes are costly and that there is selection against those genes when they are unnecessary. Here, we use stochastic multi-locus simulations to show that the origin and the maintenance of genetic polymorphism in plant–pathogen systems can be explained without costs. In multi-locus gene-for-gene systems, temporal domination of a super pathogen can cause polymorphism in resistance through neutral drift. With an increasing number of susceptible alleles in the host population, pathogen types other than the super race are able to cause infections and invade the population, leading to higher pathogen diversity and in turn to higher host diversity.

Keywords

Co-evolution, gene-for-gene, host pathogen interactions, neutral drift, pathogen evolution, polymorphism.

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INTRODUCTION

Understanding the dynamics of host–pathogen interactions and their consequences on genetic diversity is a central goal in a wide range of areas such as epidemiology, agriculture and conservation biology. Plant–pathogen systems are a good model to study co-evolution since the genetic system that controls interaction with many parasites is comparatively simple. A widely used model to illustrate the genetic interactions between hosts and pathogens is the gene-for-gene hypothesis (Flor 1955). It states that a pathogen is able to infect a host unless the host carries a specific resistance gene (R-gene) that matches a specific pathogen avirulence gene (Av-gene). Since its introduction by Harold Flor in the 1950s, gene-for-gene interactions have been found in many plant–pathogen systems (Burdon 1987; Thompson & Burdon 1992). A lot of theoretical and practical effort has been put into understanding and predicting the evolutionary dynamics of these systems. A series of mathematical deterministic models has investigated how the frequencies of R- and Av-genes change in the course of pathogen–host co-evolution, mainly focusing on the stability of equilibrium points for host and pathogen gene frequencies (Leonard & Czocho 1980). All of these

models concluded that polymorphism is not possible unless virulence and resistance impose a fitness cost, and that in the absence of selection against unnecessary genes, only the super races would persist: the super pathogen that has lost all Av-genes, and the super host that possesses all R-genes (Jayakar 1970; Leonard & Czocho 1980; Sasaki 2001). Hosts possessing as many R-genes as possible and pathogens possessing as few Av-genes as possible would always be selected for in a co-evolutionary arms race, since more R-genes provide more resistance to the host and fewer Av-genes turn the pathogen more virulent. Plant pathologists use the term virulence to denote pathogen infectivity rather than parasite-induced host mortality, and we follow their convention.

Many experimental studies on plant–pathogen systems show high polymorphisms in both pathogen virulence and host resistance (Jarosz & Burdon 1991; Thrall & Burdon 2003). However, it has been very difficult to measure costs in plant–pathogen systems (Bergelson & Purrington 1996), and estimates about the cost of virulence differ by more than an order of magnitude (Leonard & Czocho 1980; Burdon 1987; Jarosz & Burdon 1991). Almost all studies investigating costs of virulence were not carried out in the field, and many of them could not show clear evidence for a

fitness cost of virulence at all (Bergelson *et al.* 2001; Leach *et al.* 2001). A recent review on plant–pathogen co-evolution concluded that there is too little data to make qualitative assumptions about virulence costs (Bergelson *et al.* 2001). On the resistance side, thus far only a single study provided evidence for a cost of a typical gene-for-gene resistance (Rigby *et al.* 2002; Tian *et al.* 2003), and the authors point out that the results obtained for one specific R-gene are probably not representative. In a review of published studies, Bergelson & Purrington (1996) found that half of the investigated systems did not reveal any resistance costs. If fitness costs of resistance and virulence are often so small or even absent, then how could polymorphism evolve and be maintained?

Recently, a metapopulation model incorporating limited host and pathogen dispersal showed that genetic variation can be maintained without assuming any cost of virulence or resistance (Thrall & Burdon 2000), supporting the notion that spatial structure helps maintain polymorphism in systems of genetic interactions (Nuismer *et al.* 1999; Sasaki *et al.* 2002). To what extent the spatial structure influences the quantity of genetic variability remains unclear. In a wild plant–pathogen metapopulation, resistance and virulence varied markedly among local subpopulation, but spatial isolation could not explain why super pathogens did not dominate the system (Thrall & Burdon 2003).

In the model described here, considerably high levels of polymorphism can be maintained even in the absence of fitness costs or any metapopulation structures. In contrast to most of the earlier models on gene-for-gene interactions, the population size of our model is finite. In finite populations, mechanisms such as genetic drift can greatly influence the population dynamics (Kimura 1983). We show that in gene-for-gene systems, periods of selective neutrality imposed by super-races are a common phenomenon, giving rise to increased genetic variability. Once a super-pathogen dominates the population, selection on R-genes becomes neutral, since no combination of R-genes can prevent an infection by the super-pathogen. As a consequence, drift will lead to increased polymorphism in the host population. Eventually, this polymorphism will allow other pathotypes than the super-pathogen to infect hosts, since many hosts are not fully resistant anymore. We show here that such processes, paired with stochasticity, can readily shape the genetic dynamics of finite populations in gene-for-gene interactions.

THE MODEL

To investigate host–pathogen dynamics, we created an individual-based program simulating stochastic multi-locus gene-for-gene interactions in a finite host population (program code available on request). Our model assumes haploid asexual inheritance of host resistance and pathogen

virulence. Although plant hosts are usually diploid, the assumption of haploidy makes the model even more conservative because the resistance allele is usually dominant (Hulbert *et al.* 2001), allowing susceptible alleles in heterozygotes to escape the effects of selection. Both host and pathogen genetics are modelled by assuming L loci with possible alleles 0 and 1, defined as susceptibility/resistance in the host and virulence/avirulence in the pathogen, respectively (having a virulence allele is functionally equivalent with not having an Av-gene). As in a true gene-for-gene interaction, resistance occurs only when there is at least one matching pair of 1-alleles at the same locus. L , the number of loci, is the same for hosts and for pathogens and kept constant throughout an entire simulation run, allowing for 2^L possible genotypes.

The initial host population consists of n fully susceptible hosts (where all alleles are 0) and 1% of the hosts are infected by a completely avirulent pathotype (where all alleles are 1). For simplicity, multiple infections are not allowed, and a susceptible host can be infected only by one pathotype at a time. After this initialization, a simulation run consists of 100 000 time steps. In each time step, three consecutive processes simulate the population dynamics: (1) infection; (2) natural host mortality; and (3) host birth.

To model an individual infection, two host individuals are picked randomly from the population. Only if the first picked host is infected, and the second picked host is uninfected, then the pathogen of the first host attempts to transmit itself to the second host. Otherwise, no infection will occur. If the uninfected host is susceptible according to the gene-for-gene relationship, infection occurs with probability $1 - (nv \times cv)$, where nv is the number of virulence alleles of the pathogen, and cv is the cost per virulence allele. To ensure that each host is picked on average once per time step, the random selection of host pairs is repeated $n/2$ times.

After infection, hosts die at a rate of 0.1 per time step because of natural mortality, resulting in an average host life span of 10 time steps. Dead hosts are replaced in the population by selecting a random host to produce offspring with the probability of $1 - (a + nr \times cr)$, where a is the aggressiveness of an infecting pathogen, nr is the number of resistance alleles of the host, and cr is the cost per resistance allele. This procedure is repeated until all dead hosts are replaced. If a host is uninfected, a equals 0, otherwise a equals 0.1. Note that the aggressiveness of a pathotype is independent of its genotype. Regardless of the infection status of the parent, offspring hosts are born uninfected, i.e. no vertical transmission takes place. Host mutation can occur with rate mb whenever a host produces an offspring, while pathogen mutation can occur with rate mp whenever a pathogen attempts to infect an uninfected host. Both host and pathogen mutation induces the same effect of switching

the state of a randomly picked allele either from 0 to 1 or from 1 to 0.

To understand the effect of fitness costs on polymorphism, we ran simulations with four different cost situations: (1) no costs; (2) virulence costs only; (3) resistance costs only; and (4) both virulence and resistance costs. Costs were chosen to be $cv = 0.05$ and $cr = 0.005$, and each cost situation was simulated with five different population sizes ($n = 500, 1000, 2000, 5000$ or $10\ 000$) and with 2, 3, 4 or 5 loci, resulting in 80 different parameter sets. Each set consisted of 10 simulations, each simulation running for 100 000 time steps. To investigate the effect of the magnitude of costs, we ran an additional 25 sets with 5 loci, $n = 10\ 000$ and all possible combinations of $cv = 0, 0.025, 0.05, 0.075, 0.1$ and $cr = 0, 0.0025, 0.005, 0.0075, 0.01$. In all simulations, we set $mp = 10^{-3}$ and $mb = 10^{-4}$.

RESULTS

Genetic polymorphism, both of virulence and resistance, occurred in all simulations, even in the absence of fitness costs (Fig. 1). Increasing the population size and increasing the number of loci generally resulted in higher polymorphism. We used the average number of different genotypes as a measure of genetic polymorphism. To avoid stochastic noise because of mutation events, only the genotypes whose abundance was higher than 1% of the corresponding population size were included in the census.

Virulence polymorphism

In the absence of fitness costs, the average number of distinct pathogen genotypes at each time step was between 1.92 ($n = 10\ 000, 2$ loci) and 4.76 ($n = 5000, 5$ loci), clearly rejecting the notion of a single pathotype dominating the population. Adding fitness costs for virulence reduced pathogen diversity: average virulence polymorphism was always lower when only virulence costs were added, and it was virtually insensitive to changes in population size or number of loci. Resistance costs, on the other hand, had a strong effect on virulence polymorphism, increasing to a maximum of 6.89 average genotypes ($n = 10\ 000, 5$ loci). At large population sizes, the average genetic variation of the pathogen population often more than doubled when resistance costs were assumed, and this increase was stronger when virulence costs were present (Fig. 1a).

Resistance polymorphism

Resistance polymorphism was generally lower than virulence polymorphism, and the differences of the results between the four cost situations were less pronounced, especially in small population sizes. With no fitness costs in

the system, resistance polymorphism averaged in the range of 1.2 ($n = 500, 2$ loci) to 3.54 ($n = 10\ 000, 5$ loci). When resistance costs were added, the average genetic variation of the host population was always lower and highly insensitive to changes in population size or number of loci. Simulations with virulence costs resulted in a markedly higher average resistance polymorphism compared with the no-cost situation, and it did so in all tested parameter combinations. When both types of costs were included, the results ranged slightly below the values of the corresponding simulations where only virulence costs were assumed (Fig. 1b).

The dynamics of the super races

By definition, the super pathogen is able to infect any host genotype and does not depend on the abundance of a specifically susceptible host. Therefore, it is expected to play an important role on the population genetic dynamics. We measured how long the super pathogen dominated a completely monomorphic pathogen population where no other pathotype has a frequency higher than 1% of the pathogen population size. Figure 2 shows that even in the absence of costs, monomorphic dominance occurs only with moderate frequency in most cases, and specifically the addition of resistance costs strongly reduces its occurrence.

To illustrate how the super pathogen influences the dynamics, we show a typical simulation run ($n = 1000, 2$ loci) where no fitness costs were applied (Fig. 3a). For better visibility, we have taken as an example a simulation run where mutation rates were one magnitude higher in order to accelerate the population dynamics (with lower mutation rates, the dynamics were not fundamentally different but occurred on a different time-scale). Overall, the infection prevalence raises quickly to about 80% and does not fluctuate strongly over the course of a simulation run. Looking at the dynamics of each genotype, we see a long phase between time step 0 and 65 000 with high pathogen polymorphism, and another phase between time steps 65 000 and 95 000 where only the super pathogen is abundant and no pathogen polymorphism occurs. In the first phase, the super pathogen is the most frequent but not the only pathotype. In the latter phase, we observe a strong increase of the super host. Also, average resistance – the probability of any given host to be resistant against a random pathogen from the population – is highest in this phase. On the host side, phases of polymorphism and dominance of a single host type alternate. In the final phase after time step 95 000, pathogen polymorphism takes over again.

Our interpretation of these dynamics is as follows. Initially, the super pathogen increases quickly in frequency,

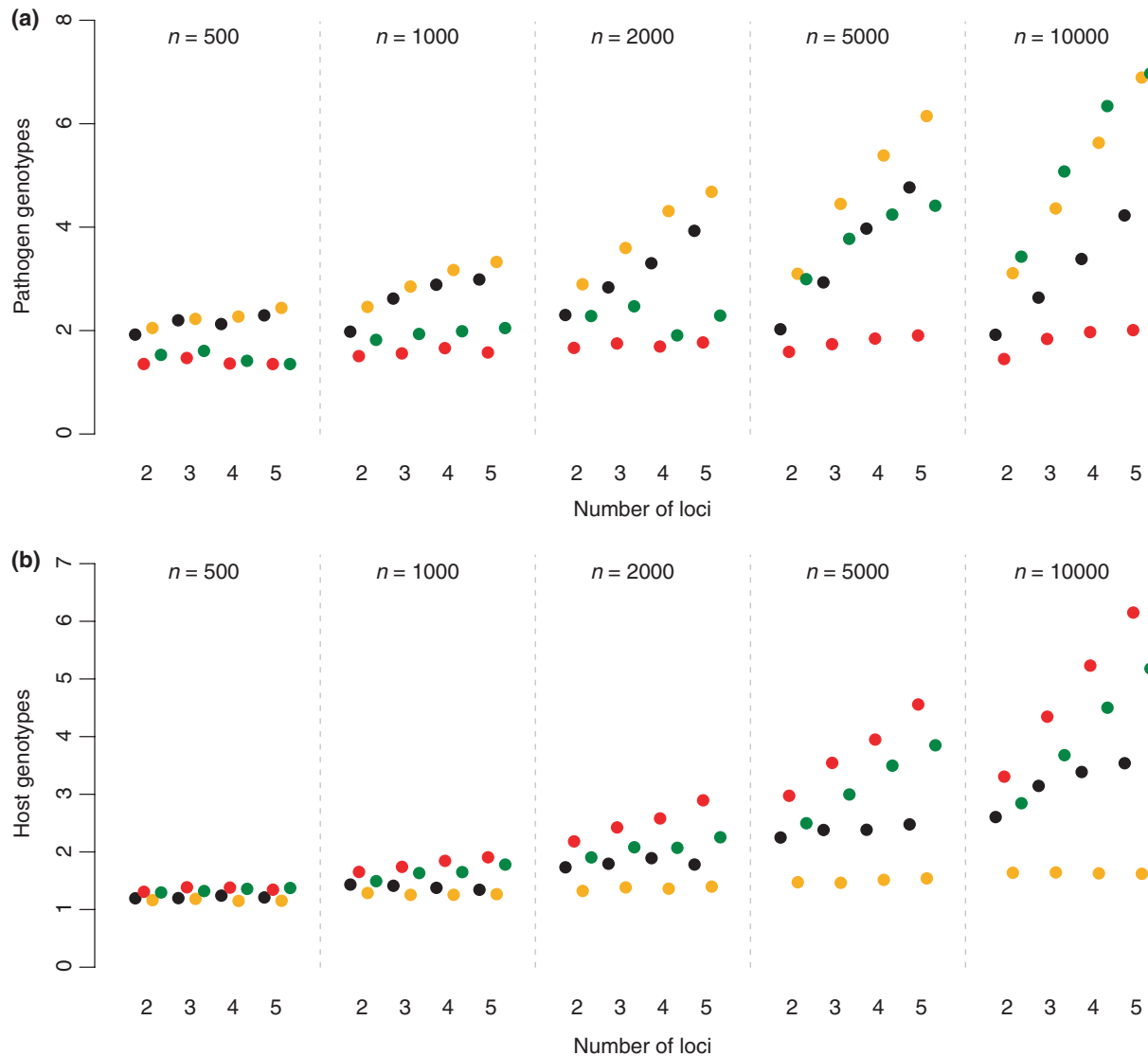


Figure 1 The number of pathogen (a) and host (b) genotypes, averaged over 10 simulation runs. The following colour scheme was applied: black ($cv = cr = 0$), red ($cv = 0.05, cr = 0$), orange ($cv = 0, cr = 0.005$) and green ($cv = 0.05, cr = 0.005$). The figure shows the results for different number of loci and different population sizes n .

and although it dominates the populations, other pathotypes are also abundant since the frequency of the super host has not yet increased significantly. During the phases when the super host does not dominate the system, pathogen polymorphism may be high since in a multi-locus system, there are always multiple pathotypes that can infect any given non-super host. However, at about time step 65 000, a co-evolutionary arms race between super host and super pathogen sets in, increasing the frequencies of both. Once the super pathogen has entirely taken over the pathogen population, selection in the host population becomes neutral, and the gene frequencies of the hosts start drifting. Eventually, the super host decreases to low frequencies, and

pathotypes other than the super pathogen can increase in abundance. The super host may increase again in frequency if the abundance of the super pathogen is low, since this is the only pathotype capable of infecting the super host. At this point, an arms race may take off again.

The three phases that we have just described – arms race, host drift and pathogen drift – occur irregularly and with an unpredictable length of time, because of the stochastic nature of the model. The results of our simulations indicate that the absence of the super host, e.g. by drifting away, is the decisive factor for pathogen polymorphism to emerge. Figure 2 shows that phases of elevated pathogen polymorphism occur less frequently in large populations, as is

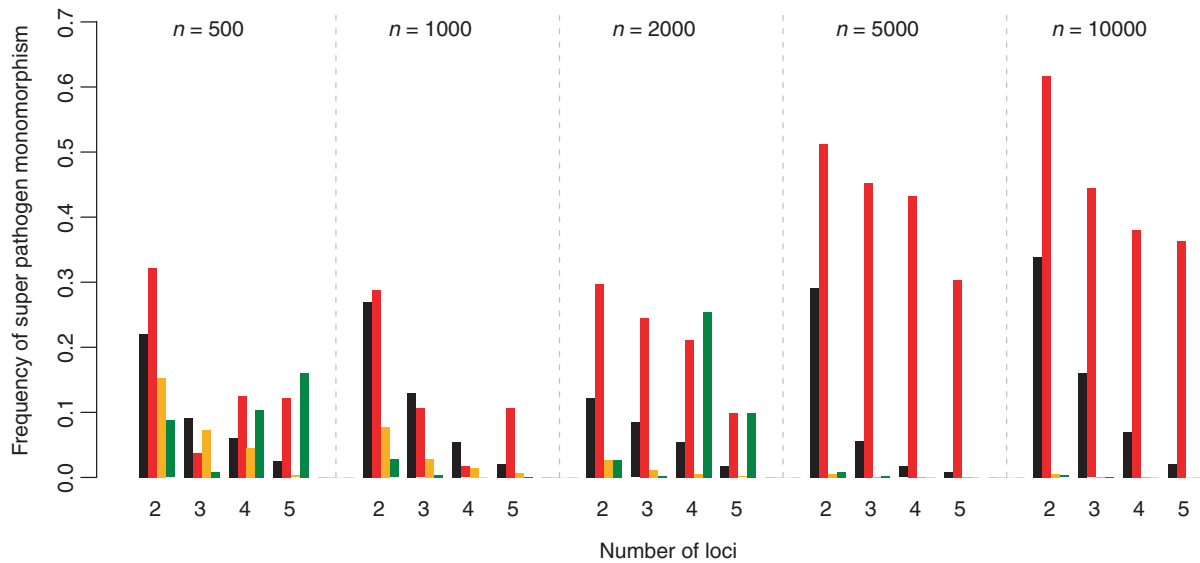


Figure 2 The percentage of time where only the super pathogen was abundant, i.e. no other pathotype had a frequency higher than 1% of the pathogen population size, averaged over 10 simulation runs. Colour scheme is the same as in Fig. 1. The figure shows the results for different number of loci and different population sizes n .

predicted by classical population genetic theory. The effect of genetic drift is also influenced by the rate of mutation, and the rates we have chosen here are moderate. However, repeating the simulations with mutation rates a magnitude times smaller or bigger than the original rates confirmed that the results are not qualitatively different (data not shown). Furthermore, the assumption of a higher mutation rate of the pathogens compared with the hosts is justified since we assume equal generation times for both hosts and pathogens, whereas in natural systems, pathogens have usually shorter generation times.

The role of virulence and resistance costs

The results presented in Figs 1 and 2 show that the simulations can be broadly classified in two groups: those with resistance costs and those without. When resistance is costly, pathogen polymorphism increases remarkably while host polymorphism decreases. Both effects are strongest for larger population sizes. The same is true for virulence costs: when virulence is costly, host polymorphism increases while pathogen polymorphism decreases.

To understand the differences between the effects caused by these two types of costs, we compare the dynamics of genotype frequencies in simulations with $n = 1000$ and 2 loci for three scenarios: (i) no cost of resistance or virulence (Fig. 3a); (ii) virulence costs only (Fig. 3b); and (iii) resistance costs only (Fig. 3c). When comparing the no-cost scenario with that assuming virulence costs, two differences become apparent during the course of the simulation: on the one

hand, the super pathogen is comparatively rare in phases of pathogen polymorphism. This is intuitively plausible since virulence is costly. On the other hand, phases of total dominance of the super pathogen occur more frequently (Fig. 3b). The reasons leading to more monomorphic phases of the super pathogen are more intricate. As we have argued above, the super host must decrease in frequency to allow for the emergence of pathogen polymorphism. Since virulence is costly, there is a selection pressure on the super pathogen to get rid of the unnecessary virulence genes, and that in turn selects again for the super host and may prevent it from drifting away. These co-evolutionary interactions can prolong the monomorphic phases of the super pathogen.

When looking at the temporal dynamics of genotype frequencies when only resistance costs were applied, we find that the super pathogen is almost always the most frequent pathotype, and hosts are therefore selected for reduced resistance since resistance is costly but in most cases useless because of the predominance of the super pathogen. As a consequence, pathogen polymorphism increases, and monomorphic phases of the super pathogen are very rare. In the co-evolutionary arms race between pathogen virulence and host resistance, pathogens are generally more flexible in their evolutionary response since they have a higher mutation rate, as in our model, and because they have much shorter generation times. It is therefore not surprising that costs on the host side have a stronger impact on the evolutionary dynamics than costs on the pathogen side (Fig. 3c).

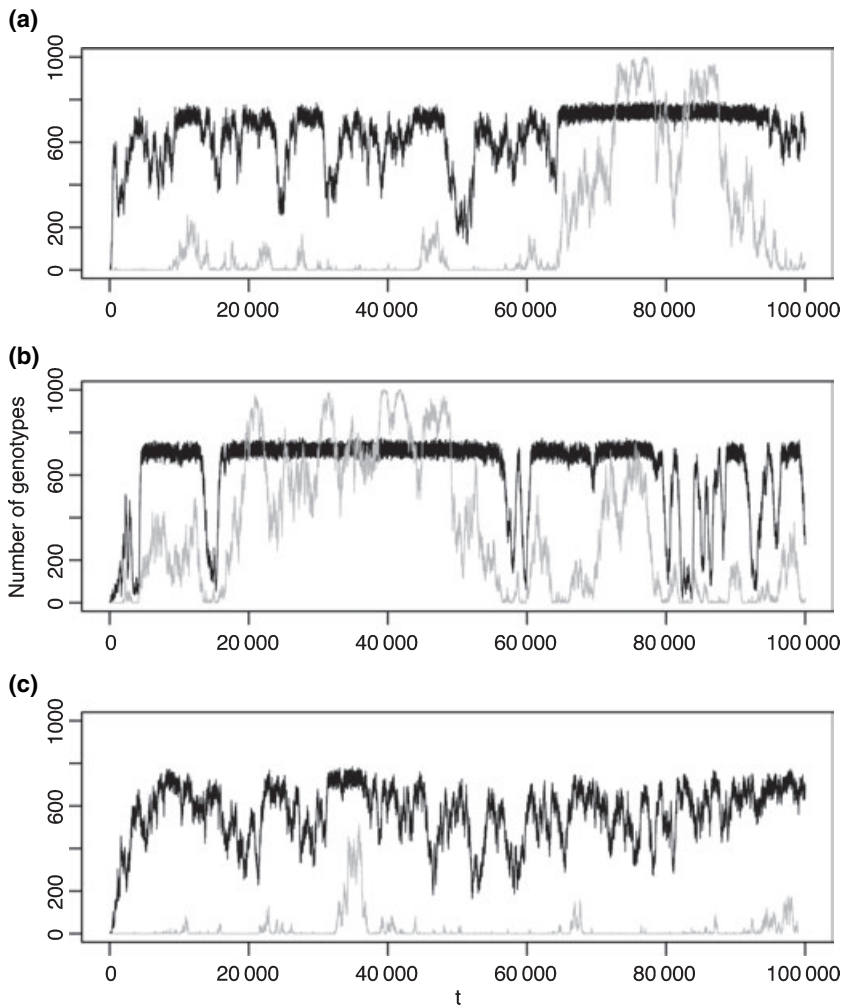


Figure 3 Genotype dynamics of a typical simulation run with 2 loci and $n = 1000$. (a) No cost ($c_v = c_r = 0$); (b) virulence cost only ($c_v = 0.05$, $c_r = 0$); (c) resistance cost only ($c_v = 0$, $c_r = 0.005$). Black line: super pathogen, grey line: super host.

The magnitude of fitness costs

The investigation of the effect of the magnitude of fitness costs on pathogen and host polymorphism revealed that with increasing virulence costs, pathogen polymorphism generally decreases while host polymorphism increases. On the other hand, increasing resistance costs mostly leads to lower host polymorphism and higher pathogen polymorphism (Table 1). Furthermore, the results show that when virulence and resistance costs are present, both polymorphisms are often higher as compared with the no cost situation. The sensitivity of pathogen polymorphism with respect to changes in resistance costs is remarkable. For instance, increasing the costs of resistance from 0 to 0.01 leads to an increase in pathogen polymorphism of about 200–450%. Host polymorphism appears to be less sensitive to the magnitude of both virulence and resistance costs. However, it should be noted that host polymorphism decreases with increasing resistance costs and is usually highest when resistance costs are absent.

Table 1 The number of pathogen (a) and host (b) genotypes, averaged over 10 simulation runs

c_v	c_r				
	0	0.0025	0.005	0.0075	0.01
(a) Pathogen genotypes					
0	4.66	6.21	6.99	7.59	8.21
0.025	2.77	5.46	6.03	5.99	5.37
0.05	1.91	5.45	7.08	7.60	7.81
0.075	1.82	4.41	6.44	7.50	8.26
0.1	1.70	3.77	5.26	6.57	7.41
(b) Host genotypes					
0	3.23	2.00	1.63	1.39	1.27
0.025	5.05	3.71	2.95	2.55	2.20
0.05	6.01	5.46	5.27	4.81	4.62
0.075	6.34	6.33	6.54	6.44	6.23
0.1	6.49	7.20	7.55	7.48	7.15

All values were obtained with 5 loci and $n = 10\,000$.

DISCUSSION

The gene-for-gene system, and particularly its evolutionary dynamics, has been of strong interest since its introduction more than 50 years ago. Thus far, population genetic models failed to explain the maintenance of polymorphism in the absence of fitness costs imposed by virulence and resistance alleles because they did not take into account the stochastic nature of finite systems subjected to forces of mutation and drift. Also, the majority of these deterministic models were based on one locus only. A recent multi-locus model however, taking into account the metapopulation structure of many plant pathogen systems, was able to show that spatial explicitness could be sufficient to get high levels of polymorphism without the assumption of costs (Damgaard 1999; Thrall & Burdon 2000).

To our knowledge, the model presented here is the first to show that high levels of polymorphism can evolve and be maintained in a non-spatial gene-for-gene system. It is clear that natural plant pathogen interactions happen in a spatial setting, but the details of spatial structures in ecological interactions and their consequences are often subtle and not always fully understood (Ruckelshaus *et al.* 1997; Hauert & Doebeli 2004). Spatially explicit individual-based models almost always assume finite population sizes implicitly. We have excluded spatial structure in our model to investigate the effects of finite population sizes and drift in isolation. Since non-spatial models are essentially an extreme case where populations are totally mixed, it will be interesting to understand how the various factors of spatial explicitness influence the evolutionary dynamics of finite gene-for-gene systems.

The results of our model are strongly influenced by neutral drift processes. Genetic bottlenecks (e.g. caused by fluctuating parasite prevalence), transmission probabilities, aggressiveness and natural host death rates all have an effect on drift and the population dynamics, and may thus influence the levels of polymorphism observed. Although the parameter values chosen for the simulations reflect realistic scenarios, it would be interesting to investigate the sensitivity of the population dynamics to these parameters. Furthermore, the model presented here does not include multiple infections, although it may play an important role, for instance in the evolution of parasite aggressiveness (Gandon *et al.* 2002). Simulation runs where multiple infections were allowed did show even higher levels of polymorphism (data not shown). However, implementing multiple infections in an individual-based model is inherently complex and requires further attention.

The definition of the gene-for-gene system implies the existence of a super pathogen able to infect all host types. This super pathogen takes away all selection pressure on the

host towards higher resistance, and when resistance alleles are costly, it even reverses the selection pressure towards lower resistance. The same logic applies to fully susceptible hosts that can be infected by any pathotype. It is the co-evolutionary interactions within these two regimes of selective neutrality that are responsible for the polymorphism reported here.

As an alternative to the gene-for-gene model, a matching allele model (Frank 1996) has been proposed to explain genetic plant-pathogen interactions, and it has been shown that it does not require costs of resistance and virulence to explain polymorphism. There has been a debate about which model reflects realistic plant pathogen interactions more appropriately, and although a lot of available evidence supports the gene-for-gene perspective, it is probably too early to come to a final conclusion about the applicability of the matching allele model.

Finally, costs have been a major argument for the maintenance of polymorphism (Brown 2003; Tian *et al.* 2003). Contrary to the common belief, we have shown that resistance costs affect host polymorphism adversely, and that it is indeed virulence costs that promote host polymorphism. This observation is along the line with results from deterministic models which showed that the distribution of resistance alleles depends on virulence costs, and the distribution of virulence alleles depends on resistance costs (Frank 1993). Only very few studies could demonstrate a clear cost of resistance, and we hope to have showed that such a cost is not necessary for the maintenance of polymorphism.

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