Stability of Equilibria in a Gene-for-Gene Coevolution Model of Host-Parasite Interactions

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ABSTRACT

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Stability of resistance/susceptibility and virulence/avirulence polymorphisms in a gene-for-gene host-parasite coevolution model was tested by numerical analysis. Computer simulations were run for 752 different combinations of parameter values in the model. Repeated simulations with different initial frequencies of resistance and virulence alleles revealed the presence of an unstable limit cycle for each combination of parameter values. Represented in a phase plane, unstable limit cycles repel gene frequencies (i.e., gene frequencies starting inside the limit cycle spiral inward toward an internal equilibrium point; those starting outside the limit cycle spiral outward toward fixation or extinction). Depending on their initial frequencies in the model, alleles for virulence and susceptibility either spiraled toward equilibrium or they became fixed. Likewise, alleles for avirulence and resistance moved either toward equilibrium or extinction. Thus, the position of the unstable limit cycle and the initial gene frequencies determined whether the system went toward a stable equilibrium or fixation of virulence and susceptibility. The position of the unstable limit cycle depended on the values of key parameters in the model. For some combinations of parameter values, the unstable limit cycles extended so far from the equilibrium point that new genes for virulence could not possibly enter the parasite population at frequencies outside the limit cycle. In those cases, the polymorphisms were regarded as stable in biological terms. Two versions of the coevolution model were compared. In the hard-selection version, virulence alleles carry an associated fitness cost of reduced inherent rate of reproduction on either susceptible or resistant hosts. In the competition version, only unnecessary virulence carries a fitness cost, because the cost of virulence is expressed as reduced competitive ability on susceptible hosts. Polymorphisms were stable for moderate costs of unnecessary virulence in the competition version of the model but usually were not stable for the hard-selection version. In the competition version, polymorphisms were stable even when there was no cost of resistance, provided that the cost of unnecessary virulence was moderately high.

Gene-for-gene interactions between host resistance and parasite virulence commonly occur in plant diseases caused by biotrophic pathogens as well as in some diseases caused by necrotrophic pathogens. Often they are manifested as complex polymorphisms with large numbers of resistance genes and corresponding virulence genes in host and parasite populations (1). In diseases of cultivated crops, such as the rusts and powdery mildews of cereals, we characterize these polymorphisms in terms of pathogenic races and race-specific resistance.

It is important to understand how such polymorphisms are maintained in natural pathosystems, because the genes for race-specific resistance in cultivated crops arose in wild ancestors of those crops. Understanding why genes for resistance and virulence persist at intermediate frequencies in natural pathosystems (1) should help us enhance the durability of resistance in cultivated crops. For example, with such understanding, we may find better ways to identify durable resistance, or we may develop novel ways of exploiting interactions that stabilize parasite populations or minimize their damage to hosts.

In 1977, Leonard (10) proposed a model of selection pressures in host-parasite interactions to account for polymorphisms of resistance and virulence in natural pathosystems. In the model, host and parasite fitness are interrelated. The frequency of resistance in the host population determines whether selection will favor genes for virulence or avirulence in the parasite. Likewise, the frequency of virulence in the parasite population determines whether selection will favor genes for resistance or susceptibility in the host.

The model has a single nontrivial, internal equilibrium point at which selection pressures are balanced and there is no change in the frequency of either resistance or virulence. This equilibrium point is called internal, because it occurs at frequencies of resistance and virulence greater than 0 and less than 1. The position of the internal equilibrium point, in terms of frequencies of resistance and virulence, depends on values assigned to key parameters in the model.

The fact that the model has an equilibrium point, however, does not necessarily mean that it is stable. Stable equilibrium points are those for which any perturbation of gene frequencies away from equilibrium will result in a return to the equilibrium point. Return to a stable equilibrium may occur either directly or through a series of damped oscillations of gene frequencies. For unstable equilibrium points, gene frequencies will not return to equilibrium after they have been displaced from it. They may go toward fixation or extinction, or in the case of limit cycles, other possibilities exist. Given reasonable estimates of likely ranges for parameter values, it is easy to calculate the position of the equilibrium point in Leonard's model, but determining the stability of equilibria in the model has proven more challenging.

The question of stability is significant, because Leonard's model may contain clues to the causes of stable polymorphisms in natural pathosystems. The first test of this is to determine whether the polymorphisms in the model are stable and similar to those observed in natural pathosystems. Leonard's model predicts equilibrium frequencies of resistance (low frequency) and virulence (high frequency) similar to those found in natural host-parasite systems (2,5,10,11,14,19), but Sedcole (17) and Fleming (4) questioned the stability of equilibria in the model.

Sedcole (17) and Fleming's (4) mathematical analyses of Leonard's model were either inconclusive or indicated that the equilibrium is unstable. However, these analyses are based on

linearized approximations of a nonlinear system, so they describe only the behavior (i.e., patterns of gene frequency changes) near the equilibrium point. As described below, it is possible for stable polymorphisms to exist in a model even if the equilibrium point is locally unstable.

Sedcole (17), Fleming (4), and Leonard and Czochor (14) tested the model's behavior away from the equilibrium point through numerical analysis by way of computer simulations. Their analyses, however, were too superficial to clarify the true behavior of the model. They used only a few sets of parameter values and did not test a wide range of gene frequency oscillations about the equilibrium point. Therefore, the specific tracks of gene frequency oscillations that they observed either converging toward the equilibrium point or diverging from it cannot be regarded as representative of all possible outcomes from different sets of parameter values or initial gene frequencies.

Czochor (3) developed a new mathematical method for difference equations to analyze behavior of the model beyond the immediate vicinity of the equilibrium point. His method is so computationally complex that he was limited in the number of combinations of parameter values that he could test. Therefore, he could not make general conclusions about the behavior of the model.

Although Fleming (4) and Leonard and Czochor (13) mentioned the possibility that limit cycles may occur in Leonard's model, they did not identify any specific limit cycles. Limit cycles for a model such as Leonard's are defined in terms of a phase plane in which the frequency of virulence is plotted on one axis and

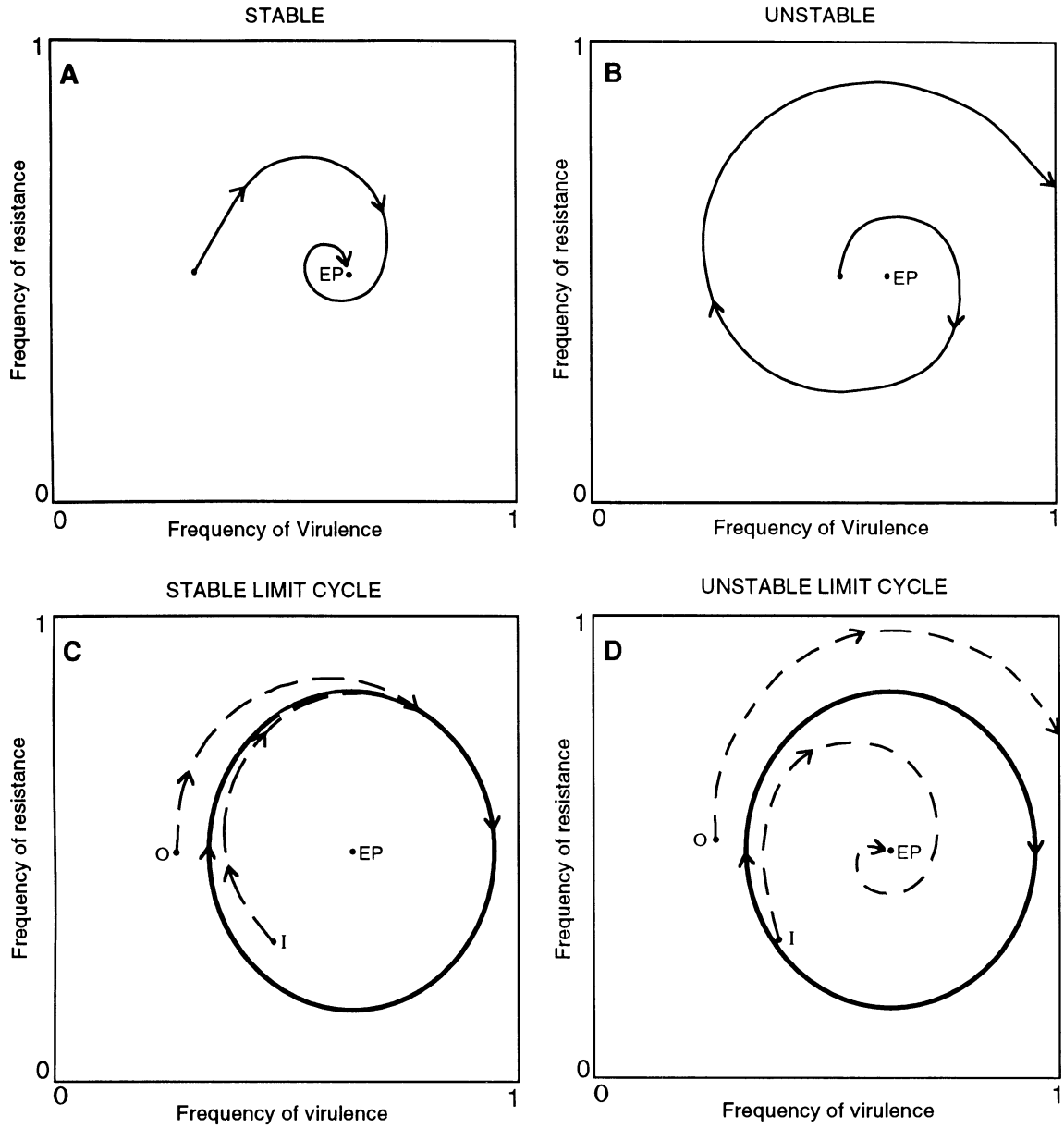

Fig. 1. Diagrammatic representations of four patterns of gene frequency changes in hypothetical host-parasite models. **A,** Stable equilibrium: frequencies of the resistance and virulence genes, plotted in a phase plane, spiral inward toward a stable, internal equilibrium point (EP). **B,** Unstable equilibrium: gene frequencies spiral outward away from an unstable equilibrium point (EP) until virulence becomes fixed in the parasite population and resistance is lost in the host population. **C,** Stable limit cycle: if gene frequencies start anywhere on the closed trajectory represented by the circle with the solid line, they remain in that trajectory as they cycle around the internal equilibrium point (EP). Gene frequencies starting outside the limit cycle (for example at point O), spiral inward toward the limit cycle. Gene frequencies starting inside the limit cycle (e.g., point I) spiral outward toward the limit cycle. **D,** Unstable limit cycle: gene frequencies starting on an unstable limit cycle continue in its closed trajectory, but gene frequencies that start outside the unstable limit cycle (e.g., point O) spiral outward toward fixation of virulence and loss of resistance. Gene frequencies that start inside the unstable limit cycle (e.g., point I) spiral inward toward the internal equilibrium point (EP). For a very large unstable limit cycle whose trajectory essentially follows the boundaries of the phase plane, nearly any initial frequencies of resistance and virulence genes lead to an inward spiral toward the internal EP.

the frequency of resistance is plotted on the other (Fig. 1). Each combination of resistance and virulence frequencies can be represented by a point in the phase plane. Selection pressures defined in Leonard's model cause the combined frequency values for successive host and parasite generations to follow a trajectory around the internal equilibrium point in the phase plane. A limit cycle is a trajectory that forms a closed loop around the internal equilibrium point. That is, if a limit cycle exists and if the frequencies of resistance and virulence start on that limit cycle, they will always stay on the cycle as they move around the equilibrium point with successive generations.

Limit cycles may be either stable or unstable. The limit cycle is said to be stable if gene frequencies are attracted to it (Fig. 1C). That is, for stable limit cycles, frequencies that start either inside (nearer the equilibrium point) or outside the limit cycle will follow trajectories that bring them into the limit cycle. The opposite occurs with unstable limit cycles (Fig. 1D). Gene frequencies only slightly inside an unstable limit cycle will spiral away from the limit cycle and toward the equilibrium point as if repelled by the limit cycle. Gene frequencies that start slightly outside an unstable limit cycle will spiral outward toward the edges of the phase plane where the frequencies become either 0 or 1.

Because Leonard's model combines two nonlinear equations, it is not obvious from simple inspection whether the trajectories of gene frequencies will spiral inward or outward from any given point that is not at equilibrium. Furthermore, no mathematical methods have been developed to detect limit cycles in models like Leonard's. This is because Leonard's model employs difference equations rather than differential equations, which are biologically less realistic but mathematically more tractable.

In the research described here, the behavior of Leonard's model was analyzed through multiple simulation runs with each of 752 different sets of parameter values using a range of different starting points for resistance and virulence gene frequencies. The results of these simulations demonstrated that the model has an unstable limit cycle. This has implications not previously encountered in analyses of host-parasite coevolution models. As described below, equilibria in the model may be stable in biological terms even though they do not fit mathematical criteria of stability.

THE MODEL

The model is for a gene-for-gene interaction between a foliar parasite causing localized infections in an annual plant species in an environment with a discrete growing season in which there is one host generation per year (10,11,13,14). For simplicity, only one host locus and one parasite locus are considered. There are two alleles at the host locus, one for resistance and one for susceptibility, and there are two alleles at the parasite locus, one for virulence and one for avirulence. As in typical gene-for-gene interactions, the avirulent parasite phenotype attacks the susceptible host phenotype that is also susceptible to the virulent phenotype. The allele for resistance confers complete or partial resistance to the avirulent phenotype of the parasite but is ineffective against the virulent phenotype.

The relative fitnesses of parasite phenotypes are determined by the nature of the host population, and the relative fitnesses of the host phenotypes are determined by the nature of the parasite population (10,11,13,14). The parasite reproduces only on the host plant, so relative fitnesses of the two parasite phenotypes are determined only by the nature of the specific interaction between the host and parasite phenotypes. Infection by the parasite does not kill the host outright. Instead, the degree to which the relative fitness of the host is reduced is determined by the severity of disease (i.e., numbers of infections per plant) and by the effectiveness of the host plant's resistance to the parasite phenotypes attacking it. The reduction in host fitness is manifested in the succeeding generation. In the model, plants with fitness severely impaired by disease produce fewer seeds than those with less severe infection. This means that genetic feedback between host and parasite populations is delayed instead of immediate (13,14). The composition of the parasite population may change in response to selection during the current growing season, but the impact of the changed parasite population on the relative fitness of the host population is not seen until the next growing season when the new generation of seedlings emerges.

In its simplest form, which will be considered here, the model assumes the parasite to be haploid and resistance to be fully dominant. This eliminates the possibility of heterozygote selection as a mechanism to stabilize the polymorphisms. Obviously, stable polymorphisms in self-pollinated hosts and asexual or haploid parasites do not depend on heterozygote selection.

In the model, relative fitness of the avirulent parasite on the susceptible host, W_{AS}, is 1. Relative fitness of the avirulent parasite on the resistant host, W_{AR}, is $1 - t$, in which t represents the effectiveness of the resistance. Relative fitness of the virulent parasite on the susceptible host, W_{VS}, is $1 - k$, in which k is the cost of virulence. On the resistant host, the relative fitness of the virulent parasite, W_{VR}, is $1 - k + a$, in which a is a parameter that determines the type of selection in the parasite population. When $a = 0$, there is a cost of virulence even when it is necessary to parasitize the resistant host. This can be thought of as hard selection (20), in which the presence of the virulence gene causes a reduction in the intrinsic rate of reproduction by the parasite. Thus, the virulent parasite reproduces at the same rate on both the susceptible and the resistant hosts, but its reproductive rate is less than that of the avirulent parasite on the susceptible host. On the other hand, when $a = k$, virulence has a fitness cost only when it is unnecessary, as it is when the virulent parasite infects a susceptible host. This can be thought of as soft selection (20), in which the virulent parasite's relative fitness is reduced in competition with the avirulent parasite on a susceptible host but not on a resistant host, which does not support the avirulent parasite (10,11,14). Competition among multiple infections on single host leaves has been shown to reduce the number of spores produced per infection by rust or powdery mildew fungi (7–9,16, 18,21). The competition model assumes that on susceptible plants infected with both virulent and avirulent parasite phenotypes, the avirulent phenotypes can outcompete virulent phenotypes for nutrients to support sporulation. This competition model with a fitness cost only for unnecessary virulence is equivalent to the model used by Groth and Person (6) and Person et al (15). If there is no cost of unnecessary virulence (i.e., if $k = 0$), there can be no internal equilibrium point and no stable polymorphism in the model (10,11,13,14).

Relative fitness of the susceptible host in the model is $1 - sW_{AS}$ when it is attacked by the avirulent parasite and $1 - sW_{VS}$ when it is attacked by the virulent parasite (10,11,13,14). Parameter s reflects the severity of disease and takes into account environmental factors, such as climate and host density, that affect disease development. The fitness of the resistant host is $1 - c - sW_{AR}$ or $1 - c - sW_{VR}$ when attacked by the avirulent or the virulent parasite. Parameter c represents the fitness cost of resistance either when it is unnecessary or when it is ineffective, as it is if the parasite population is made up entirely of the virulent phenotype.

Frequencies of genes for virulence and avirulence in the parasite population at the start of the ith host generation are n_i and m_i, respectively; frequencies of genes for resistance and susceptibility in the host population in the model are p_i and q_i, respectively. For a haploid parasite, virulence and avirulence gene frequencies are the same as the phenotype frequencies. For dominant resistance genes, the frequency of the resistant host phenotype is $1 - q_i^2$. Fitnesses of virulent and avirulent parasite phenotypes are calculated by multiplying the proportions of resistant and susceptible plants in the host population by the relative fitness of virulent or avirulent phenotypes on each host phenotype (10,11, 13,14). During the growing season, selection changes the composition of the parasite population from n_i to n_{i+1}, in which

$$n_{i+1} = \frac{n_i[1 - k + (1 - q_i^2)\,a]}{1 - (1 - q_i^2)\,t + n_i[(1 - q_i^2)\,(a + t) - k]}. \quad \text{(eq. 1)}$$

The impact of the parasite on seed production by resistant and susceptible host phenotypes determines the composition of the host population in the next growing season. Fitnesses of resistant and suscetible host phenotypes are determined by multiplying the proportions of virulent and avirulent parasites by the relative fitness of resistant or susceptible phenotypes when infected by each parasite phenotype (10,11,13,14). The frequency of the gene for resistance in the next growing season is

$$p_{i+1} = \frac{p_i[1 - c - s(1 - t) + n_{i+1}\, s(k - a - t)]}{1 - s + n_{i+1}\, ks + (1 - q_i^2)[ts - c - n_{i+1}\, s(a + t)]}. \quad \text{(eq. 2)}$$

At equilibrium, $n_{i+1} - n_i = 0$, so the frequency of resistant plants at equilibrium (10) is

$$(1 - \hat{q}^2) = k/(a + t). \quad \text{(eq. 3)}$$

Also, at equilibrium, $p_{i+1} - p_i = 0$, so the frequency of virulence in the parasite population at equilibrium (10) is

$$\hat{n} = (ts - c)/(ts + as). \quad \text{(eq. 4)}$$

In addition to the internal equilibrium point, there are four trivial equilibrium points at $n = 0$, $p = 0$; $n = 0$, $p = 1$; $n = 1$, $p = 0$; and $n = 1$, $p = 1$ (4).

From mathematical analysis as well as simulation runs, Sedcole (17) concluded that the model's internal equilibrium point is unstable. In his simulation, the gene frequencies spiraled outward in the phase plane (away from the equilibrium point) until the virulence gene became fixed in the parasite population (17). However, Sedcole misinterpreted Leonard's model. His simulation had an immediate, reciprocal genetic feedback between host and parasite populations such that $n_{i+1} = g(p_i,n_i)$ and $p_{i+1} = f(p_i,n_i)$, in which $g(p_i,n_i)$ and $f(p_i,n_i)$ are functions of p_i and n_i, the frequencies of genes for resistance and virulence in the ith generation. Leonard, however, intended the model to represent a delayed feedback, so that $n_{i+1} = g(p_i,n_i)$ but $p_{i+1} = f(p_i,n_{i+1})$. The change in virulence frequency during the growing season is determined by the frequency of resistance and susceptibility in the host population at the beginning of the growing season. These frequencies are assumed to remain constant through the season. With delayed feedback, however, the change in frequency of resistance from one growing season to the next depends not on the composition of the parasite population at the beginning of the first growing season but rather on its composition at the end when host plant seeds are produced. Leonard and Czochor's (14) simulations using delayed feedback showed two apparently different behaviors of the model. When Leonard and Czochor started gene frequencies near the internal equilibrium point, the frequencies cycled around the equilibrium point in what appeared to be a closed trajectory. When they started gene frequencies further from equilibrium, there was a distinct inward spiral of the gene frequencies toward the internal equilibrium point. Leonard and Czochor analyzed the four trivial equilibrium points in the model mathematically and found that they are unstable. They concluded that with no stable equilibrium point in the model there must be one or more stable limit cycles. This was the only way they could account for an inward spiral of gene frequencies toward what they regarded as an unstable internal equilibrium point.

Fleming (4) considered three variations of the model. The first two are the versions used by Leonard (10,11) and Leonard and Czochor (13,14) and Sedcole (17). The third version is for continuous reciprocal feedback between host and parasite populations. In Fleming's third version, there are no discontinuities of host generations such as occur in temperate regions or in warm regions where the climate alternates between wet and dry seasons.

Fleming (4) confirmed that with Sedcole's version of the model, the internal equilibrium is locally unstable. However, his mathematical analysis showed that Leonard and Czochor (13) were incorrect in assuming that the internal equilibrium point in Leonard's version of the model is necessarily unstable. For some parameter values in the model, particularly with low disease severity (low s), his analysis was inconclusive. For high values of s, the equilibrium in Leonard's model was locally unstable. Local instability means only that local perturbations of gene frequencies to very small distances from the equilibrium point will not result in a return to equilibrium. Fleming's mathematical analysis cannot determine what the trajectories would be for gene frequencies that start further from the equilibrium point. Fleming's simulation run with Leonard's model yielded an inward spiral of gene frequencies toward the equilibrium point. Consequently, he agreed with Leonard and Czochor (14) that there must be a stable limit cycle, at least for the set of parameter values used in his simulation run.

Fleming's analysis of his continuous reciprocal feedback version of the model showed neutral stability of the internal equilibrium point. Neutral stability differs from limit cycles in allowing an unlimited number of closed trajectories of gene frequencies around the equilibrium point. With neutral stability there is no attraction to or repulsion from any of the trajectories. In other words, wherever the gene frequencies start in the phase plane, they will repeatedly pass through that starting point in each cycle around the equilibrium point. They will not deviate from the initial cycle either toward or away from equilibrium.

Fleming (4) concluded that Leonard's model lacks robustness, because three different versions of the model all have different stability properties. Therefore, Fleming suggested that other factors not included in the model are necessary to explain the observed stability of polymorphisms in natural host-parasite systems. It can be argued, however, that understanding which versions of the model will allow stable polymorphisms for the greatest variety of parameter values should provide useful information about which types of host-parasite interactions are more likely to coevolve with stable gene-for-gene polymorphisms. For example, Fleming's analysis suggests that, other things being equal, diverse polymorphisms of resistance/susceptibility and virulence/avirulence are more likely to accumulate for diseases of annual plants with discrete generations than for diseases of perennial plants in the humid tropics.

Czochor (3) developed a new mathematical method to analyze stability of internal equilibrium points in models that employ difference equations rather than differential equations. The method is analogous to but more complex than Fleming's (4). Application of Czochor's method to Leonard's model removes the uncertainty over local stability of equilibria for certain sets of parameter values that Fleming's analysis cannot resolve. Czochor's method is extremely cumbersome, but he was able to test 26 combinations of parameter values. He showed that the internal equilibrium was stable for most combinations that he tested, but the equilibrium was unstable for some sets of parameter values with $a = 0$ and $s > 0.6$.

Sedcole's (17), Fleming's (4), Leonard and Czochor's (13), and Czochor's (3) analyses all provide partial views of the behavior of Leonard's model, but none of them provides a complete picture. The results of extensive simulations reported here show features of the model's behavior that neither Sedcole, Fleming, Leonard, nor Czochor anticipated. Briefly, the approach in these simulations was to determine how far from the equilibrium point the gene frequencies could start and still produce an inward spiral toward the internal equilibrium point.

SIMULATIONS

A computer program was written in BASIC to run simulations with Leonard's model at double precision (i.e., gene frequencies calculated to 17 significant digits in the range from 10^{-39} to 1.0) on a personal computer. Although the program allows multiple parasite generations per host generation, the simulation runs described here were done with one parasite generation per host generation. Results from a few preliminary simulation runs with multiple pathogen generations per host generation yielded results qualitatively similar to those described below for runs with single pathogen generations per host generation.

Examples of typical simulation runs are shown in Figure 2. These two simulations were run with $t = 1.0$ (reproduction by the avirulent parasite was completely suppressed on the resistant host), $c = 0.03$ (low cost of resistance), $s = 0.8$ (high disease severity), $k = 0.3$ (moderately high cost of virulence), and $a = 0$ (fitness cost of virulence expressed as reduction in inherent reproductive rate by the virulent parasite [i.e., hard selection]). The first simulation (Fig. 2A) was started with virulence frequency $n_0 = 0.2$ and frequency of the dominant resistance gene $p_0 = 0.163$, which is its equilibrium frequency; $p = 1 - q$, and at equilibrium $1 - q^2 = k/(a + t)$. The simulation was run for 165 host generations (165 years for an annual plant). In the phase plane, gene frequencies spiraled inward toward the equilibrium point. This kind of inward spiral led Leonard and Czochor (13) and Fleming (4) to believe that there must be a stable limit cycle in the model if the internal equilibrium point is not locally stable. The simulation shown in Figure 2A was continued through 2,000 host generations (data not shown) without encountering a stable limit cycle, although the inward spiral became progressively less pronounced as gene frequencies approached the equilibrium point.

The second simulation (Fig. 2B) was run with exactly the same set of parameter values. Only the starting frequency of virulence was changed, so that $n_0 = 0.18$ instead of 0.20. This time the gene frequencies spiraled outward. In fact, in the next cycle around the equilibrium point, the allele for virulence became fixed in the parasite population, and the allele for susceptibility became fixed in the host population. This behavior indicates an unstable limit cycle passing through the phase plane to the left of the equilibrium point at a position approximately equivalent to $n = 0.19$. If the initial gene frequencies for virulence and resistance start within the limit cycle, they spiral inward toward the equilibrium point, but if they start outside the limit cycle, they spiral outward until virulence and susceptibility become fixed in the parasite and host populations.

The internal equilibrium point illustrated in Figure 2 is not globally stable. In a globally stable system, any initial combination of resistance and virulence gene frequencies would lead to a stable equilibrium or, at least, a stable polymorphism. This is not the case in Figure 2, because the polymorphism is quickly lost if the gene frequencies start outside the unstable limit cycle. New virulence genes introduced into the parasite population by mutations or rare migrations certainly would enter that population at frequencies less than 0.19. Therefore, they would be destined for fixation in the population rather than coexistence with alleles for avirulence in stable polymorphisms. For this reason, we may regard the system represented in Figure 2 as unstable in biological terms.

It is conceivable, however, that a system with an unstable limit cycle could be stable in biological terms. If the unstable limit cycle were larger than that shown in Figure 2 (i.e., if it extended closer to the boundaries of the phase plane), new resistance and virulence genes would be more likely to enter the populations at initial frequencies within the unstable limit cycle. If the unstable limit cycle was so large that it essentially followed the boundaries of the phase plane, it would be virtually impossible for new genes for resistance and virulence to enter the host and parasite populations at frequencies that were not within the limit cycle. In that case, we would regard the system as highly stable in biological terms, because it would inevitably lead to stable polymorphisms. Thus, in biological terms, the degree of stability of the system is proportional to the size of the unstable limit cycle.

As described in a preliminary report (12), there is an unstable limit cycle for every set of parameter values that might be reasonably considered in this model. The position of the limit cycle, however, varies with different parameter values. As described above, we can use the position of the limit cycle to assess the stability of equilibria for the different parameter values. For example, with some sets of parameter values, the unstable limit cycle passes to the left of the equilibrium point at $n < 10^{-30}$. Obviously, virulence could never occur at a frequency so low, because the parasite population would never include as many as 10^{30} individuals. Therefore, we may regard the internal equi-

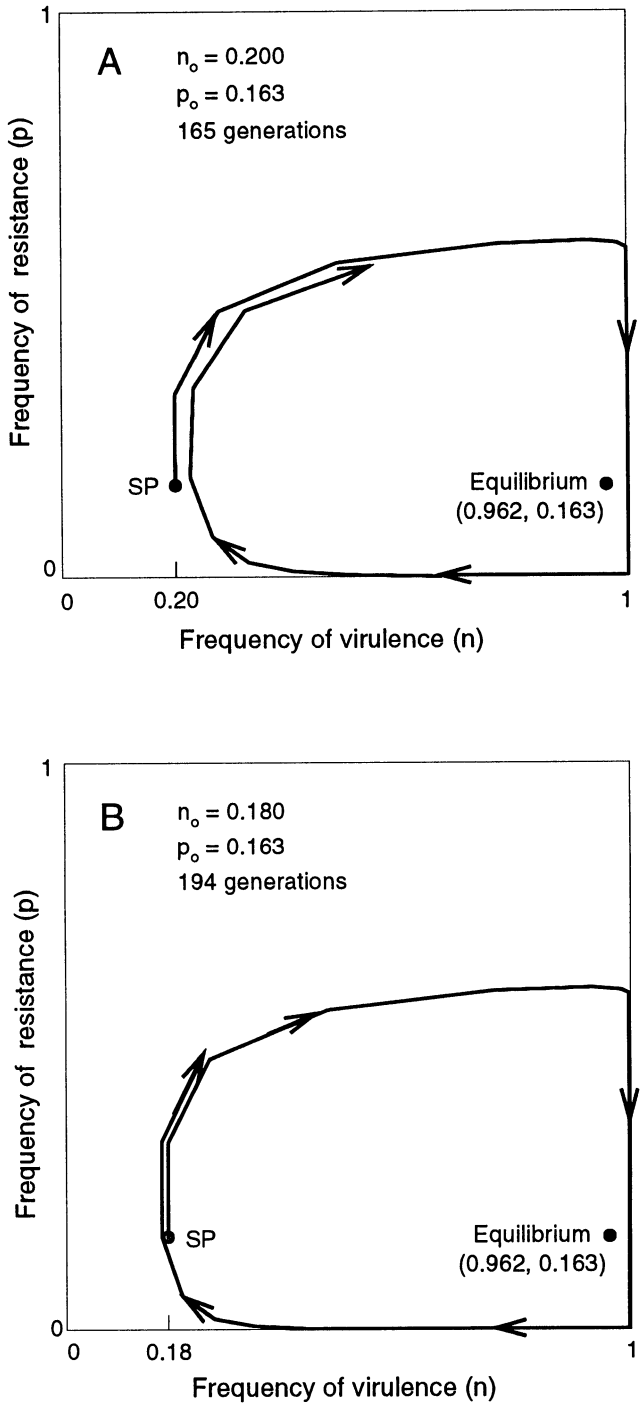

Fig. 2. Phase planes from simulations with a host-parasite coevolution model in which p is the frequency of a dominant allele for resistance in the host and n is the frequency of virulence in a haploid parasite. Simulations were run for the hard-selection version of the model ($a = 0$) with high disease severity ($s = 0.8$), complete resistance ($t = 1.0$), low fitness cost of resistance ($c = 0.03$), and moderately high fitness cost of virulence ($k = 0.3$). With these parameter values, the equilibrium frequencies of alleles for virulence and resistance are $n_{eq} = 0.962$ and $p_{eq} = 0.163$. **A,** Initial frequencies (SP) started at $n_0 = 0.200$ for virulence and $p_0 = 0.163$ for resistance. The simulation was run for 165 generations. The allele frequencies spiral inward. **B,** Parameter values are the same as in **A**, but initial allele frequencies are $n_0 = 0.180$ for virulence and $p_0 = 0.163$ for resistance. The simulation was run for 194 generations. The outward spiral of allele frequencies in **B**, in contrast to the inward spiral in **A**, indicates an unstable limit cycle that passes to the left of the equilibrium point at approximately $n = 0.190$. Allele frequencies starting anywhere inside the limit cycle spiral inward, and allele frequencies starting outside the limit cycle spiral outward until the alleles for virulence and susceptibility become fixed in the parasite and host populations.

librium point as stable under those conditions, regardless of what a mathematical analysis may tell us.

NUMERICAL ANALYSIS OF STABILITY

Simulations were run for combinations of parameter values over the following ranges: $s = 0.2$, 0.5, or 0.8; $t = 0.5$, 0.8, or 1.0; $c = 0.00$, 0.01, 0.02, 0.03, 0.05, 0.07, 0.10, 0.20, or 0.30; $k = 0.01$, 0.02, 0.05, 0.10, 0.20, 0.30, 0.40, or 0.50; and $a = 0.0$ or k. It was not necessary to test every combination of parameter values, because some did not yield an internal equilibrium point. For each set of parameter values tested, the position of the unstable limit cycle was determined. The initial frequency of the resistance gene, p_0, in the test simulation runs was set equal to its equilibrium frequency, and the initial frequency of virulence, n_0, was varied. Typically, the first run yielded an inward spiral. Then the value of n_0 was increased in each successive run with the same set of parameter values until the gene frequencies spiraled outward instead of inward.

For both the hard-selection version of Leonard's model ($a = 0$) and the competition version ($a = k$), higher values of c, the cost of resistance, lead to larger unstable limit cycles (i.e., greater stability of equilibria in biological terms) (Fig. 3). In Figures 3 and 4, stability is represented in terms of $-\log n$ at the lowest

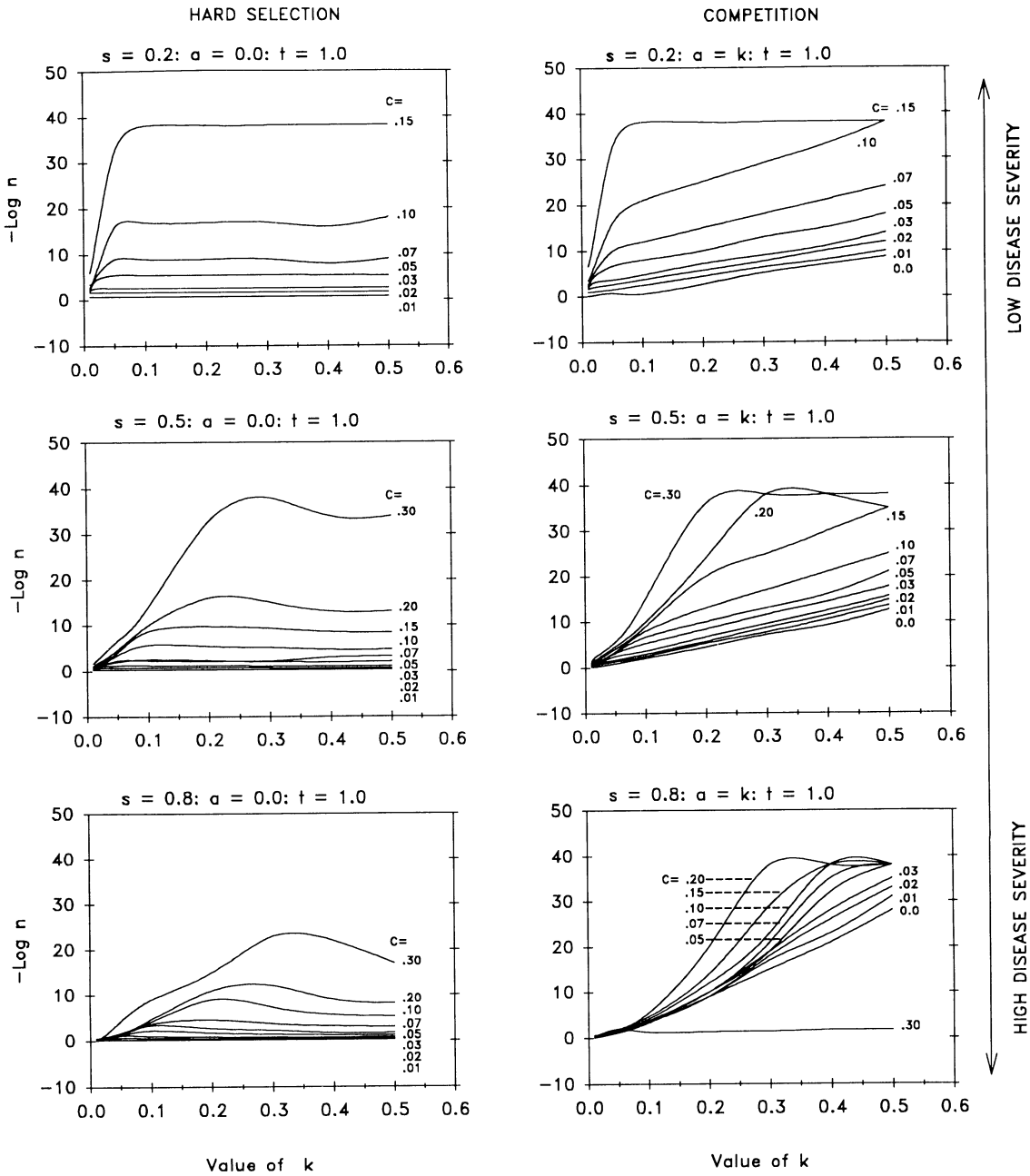

Fig. 3. Effect of parameter values on stability of polymorphisms in a host-parasite coevolution model: s represents disease severity, t effectiveness of resistance (completely effective at $t = 1$), c cost of resistance, and k cost of virulence. Simulations were run for the hard-selection (graphs on the left with $a = 0$) and competition (graphs on the right with $a = k$) versions of the model. The position of the unstable limit cycle for each combination of parameter values is indicated by $-\log n$, in which n is the frequency of virulence at its lowest point on the limit cycle. In general terms, the higher the position of a curve for values of $-\log n$ in each graph, the more stable the system is for that set of parameter values. Combinations of parameters represented by points on the curves with $-\log n > 10$ indicate stable equilibria, because new genes for virulence would enter the system at $n > 10^{-10}$, causing gene frequencies to spiral toward the equilibrium point (Fig. 1D). Equilibria are more stable for the competition version than for the hard-selection version of the model. Also, stability increases with increasing disease severity in the competition version but decreases in the hard-selection version of the model.

point (i.e., nearest to 0) for n in the unstable limit cycle. If n_0 occurs outside the limit cycle (nearer to 0), a stable polymorphism will not arise. For $c < 0.05$ in the hard-selection version, an initial virulence frequency of $n_0 < 10^{-5}$ leads to fixation of virulence and susceptibility rather than to a stable polymorphism. Parasite populations are likely to contain more than 10^5 individuals, and mutations to virulence are likely to occur at frequencies less than 10^{-5} per generation. Therefore, the hard-selection version of the model does not allow stable polymorphisms with resistance genes with fitness costs lower than 5%. Furthermore, in the hard-selection version of the model, increasing disease severity (greater values of s) reduces the stability of the equilibria (Fig. 3) and, thus, reduces the probability that stable polymorphisms could accumulate during coevolution.

The behavior of the competition version of Leonard's model ($a = k$) differs from that of the hard-selection version. First, the unstable limit cycle occurs further from the equilibrium point. For low values of c, a stable polymorphism can be maintained if the cost of the corresponding virulence, k, is great enough, particularly for high values of s, the disease severity parameter (Fig. 3). For example, at $s = 0.8$ and $c = 0.01$, the unstable limit cycle occurs at a position equivalent to $n \leq 10^{-20}$ when $k \geq 0.35$. If the parasite population contains less than 10^{20} individuals, any virulence must occur at a frequency within the limit cycle. Notice that in the competition version of the model, the equilibria become more stable with increasing disease severity. In fact, with $s = 0.8$, it is possible to have stable polymorphisms even when there is no cost of resistance (i.e., $c = 0.0$). This can occur for $k > 0.2$. One exception to the trend of increasing stability of equilibria with higher values of c is shown in the breakdown

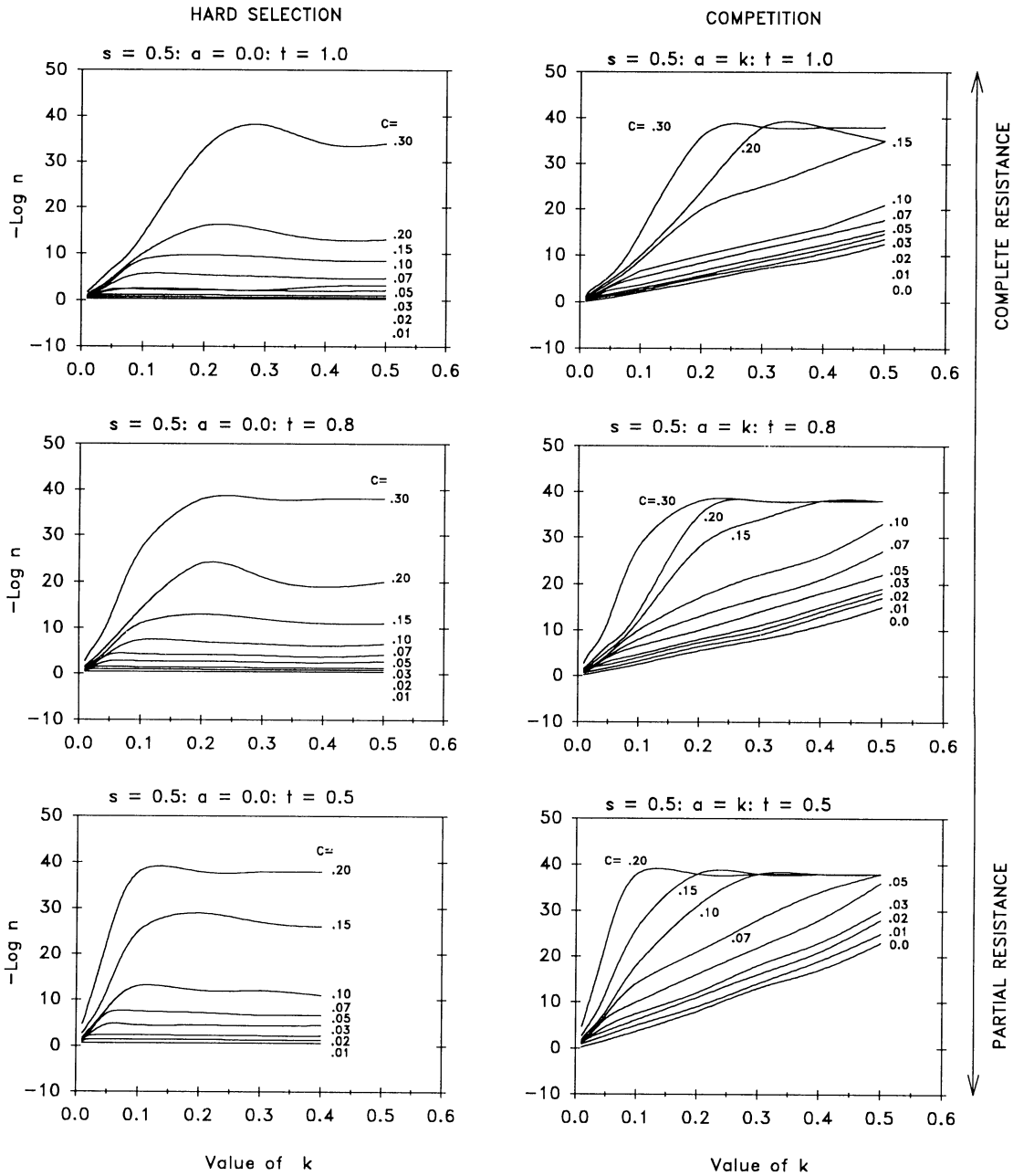

Fig. 4. Effect of partial resistance on stability of equilibria in the hard-selection (graphs on the left with $a = 0$) and competition (graphs on the right with $a = k$) versions of the host-parasite coevolution model. Figure 3 provides parameter details. The position of the unstable limit cycle for each combination of parameter values is indicated by $-\log n$, in which n is the frequency of virulence at its lowest point on the limit cycle. In general terms, the higher the position of a curve for values of $-\log n$ in each graph, the more stable the system is for that set of parameter values. Combinations of parameters represented by points on the curves with $-\log n > 10$ indicate stable equilibria, because under those conditions new genes for virulence would enter the system inside the limit cycle, causing gene frequencies to spiral toward the equilibrium point (Fig. 1D). Equilibria are more stable for partial resistance ($t < 1.0$) than for complete resistance ($t = 1.0$). This effect is more pronounced for the competition version of the model ($a = k$) than for the hard-selection version ($a = 0$).

of stability when $c = 0.3$ and $s = 0.8$. In environments of high disease severity, resistance genes with too great a cost in fitness would not be maintained in stable polymorphisms in the competition model. Of course, high-cost resistance genes also would be lost from the host population at very low disease severities, because their benefits would not outweigh their costs.

For both the hard-selection and competition versions of Leonard's model, the equilibria are more stable for partial resistance ($t \leq 0.8$) than for immunity ($t = 1.0$) (Fig. 4). This effect is more pronounced with the competition version than with the hard-selection version of the model. With the competition version, stable polymorphisms are possible for partial resistance genes that have gene-for-gene specificity, even when they have no fitness cost and when $s \leq 0.5$. These results suggest that genes for partial resistance (i.e., resistance that allows some sporulation by avirulent parasite genotypes in infections on resistant plants) should be common in gene-for-gene relationships.

For both versions of Leonard's model and for both high and low values of either s or t, no stable polymorphisms are possible with very low values of k. In Leonard's model, there is nothing to prevent new virulence genes with little or no fitness cost from becoming fixed in parasite populations within a few hundred years after they arise. Such genes would go undetected not only for lack of avirulence alleles to compare with them, but also because the corresponding resistance genes eventually would be lost from the host population as well. Without the resistance genes, there would be no way to distinguish virulence and avirulence alleles.

DISCUSSION

The salient features of Leonard's model uncovered by these simulations are the unstable limit cycle and its variable position depending on values of key parameters in the model. The position of the unstable limit cycle can be used as a measure of the relative stability of polymorphisms for resistance and virulence in the model. The further the limit cycle is from the equilibrium point, the more stable the polymorphism is.

Results of the simulations in this study emphasize the importance of parameter a in determining the stability of equilibria. The value of a can be used to change Leonard's model from one of hard selection in the parasite population to a soft-selection model of fitness determined by direct competition between parasite phenotypes. This change in the model has profound implications for the stability of its polymorphisms.

Simulations with the hard-selection version of Leonard's model produced results consistent with the limited, earlier conclusions from mathematical analyses. For example, both Fleming (4) and Czochor (3) concluded that high disease severity destabilizes the system when $a = 0$. This also was demonstrated in this study in simulations with $a = 0$, $s = 0.8$, and $c \leq 0.1$. These combinations produced unstable limit cycles near the equilibrium point, which means that any introduction of new resistance and virulence at low frequencies leads to fixation of virulence rather than to a stable polymorphism.

The hard-selection model is not consistent with observations of natural host-parasite systems, because it indicates that stable polymorphisms could not develop in environments highly conducive to disease except for resistance genes with fitness costs greater than 10%. There is little or no evidence of such high-cost resistance genes in cultivated crops in which the effects of resistance genes on yield is critically important. Use of race-specific resistance in cultivated crops is not generally associated with detectable yield decline, so we may assume $c \leq 0.05$ (10,11). In a study designed to measure cost of resistance, H. G. Welz, T. Miedaner, and H. H. Geiger (*unpublished data*) found no detectable change in frequency of resistance to powdery mildew in rye over six generations in the absence of disease. The lack of stability of polymorphisms in the hard-selection version of Leonard's model except at low disease severity or high cost of resistance makes it unacceptable as an explanation of coevolution in natural host-parasite systems.

The competition version of Leonard's model, however, behaves quite differently from the hard-selection model. It seems surprising now that Sedcole (17), Fleming (4), and Leonard and Czochor (13,14) paid so little attention to the situation of $a = k$. In its simplest sense, this situation makes the model equivalent to Groth and Person's (6) and Person et al's (15) earlier parasite selection model in which virulence has a fitness cost only when it is unnecessary, as it is on plants with no resistance. When $a = k$, stable polymorphisms are possible in Leonard's model, because for most combinations of parameter values the unstable limit cycle is so far from the equilibrium point that genes for virulence and resistance will always enter the populations at frequencies within the limit cycle.

The simulations reported in this study considered only the special situation of a single parasite generation per host generation. Thus, the possibility of variable costs of virulence over multiple parasite generations in the growing season did not arise. Obviously, this possibility will need to be considered in future work with the model. This realization is an important outcome of the study. With emphasis on soft selection based on competition, the impact of changes in parasite population density assumes greater significance for investigations of polymorphisms and their stability in host-parasite systems.

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