Kin selection and virulence in the evolution of protocells and parasites

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SUMMARY

The evolution of parasite virulence and the origin of cooperative genomes in primitive cells are both problems that balance cooperative and competitive interactions among symbionts. I analyse the trade-off among three correlated traits: competitiveness against other genotypes for resources within hosts (protocells), damage to the host (virulence), and rate of horizontal transmission from one host to another. All three life-history components are strongly influenced by kin selection. For example, when genetic relatedness within hosts is high, each genotype is competing for resources with closely related genotypes. This competition among relatives favours increased horizontal transmission to colonize new hosts and compete against non-relatives. My analysis shows that many aspects of parasite and protocell evolution must be studied with the theoretical tools of social evolution. I discuss extensions that are required for a general theory of symbiosis.

1. INTRODUCTION

I show how the interactions among competitiveness, virulence and genetic relatedness influence the evolution of parasite life histories. I analyse three correlated traits that are properties of each genotype: competitiveness against other genotypes for resources within hosts, damage to the host (virulence), and rate of horizontal transmission from one host to another. I also show that many problems in host–parasite coevolution occur in the origin of cooperative genomes.

Eigen & Schuster (1979) initiated recent work on the evolution of early genomes. Their hypercycle model suggested that mutually complementary genes could evolve by coupling in a cyclic replicative system. Maynard Smith (1979) pointed out that a member of the cycle could become parasitic by receiving the benefits from its predecessor in the cycle but not contributing anything to its successor (Bresch *et al.* 1980). Parasitism appears inevitable in hypercycles unless cycle members are bound together spatially, forcing interactions among close genetic relatives. Spatial structure can occur by the membrane boundaries of protocells or by a variety of forces that restrict movement (Boerlijst & Hogeweg 1991; May 1991). However, even strictly isolated groups that never exchange members can suffer parasitism within groups (Szathmáry & Demeter 1987; Szathmáry 1989*a*, *b*). One of my aims is to quantify the forces that favour cooperation or virulence in simple models of protocells.

A separate line of research has focused on the evolution of parasite virulence. Parasites face a trade-off between damaging their hosts (virulence), which destroys their food supply, and the benefits of rapid growth and transmission (Levin & Pimental 1981; Anderson & May 1982, 1991; Ewald 1983; May & Anderson 1983). Competition among parasites within a host is another factor that causes, as a side effect, the evolution of increased virulence (Bremermann & Pickering 1983; Knolle 1989). When parasites within a host all have the same genotype, competitive traits provide no advantage because the coefficient of relatedness among parasites is one. The fitness advantage of increased competitive ability rises as the coefficient of relatedness among parasites declines. Thus low relatedness among parasites can favour increased virulence (Bremermann & Pickering 1983; Frank 1992; Herre 1993; Ewald 1994; Nowak & May 1994).

The selective forces acting on transmission are particularly interesting. When genetic relatedness within hosts is high, each genotype is competing for resources with closely related genotypes. This competition among relatives favours increased transmission to colonize new hosts and compete against non-relatives. The role of kin selection in the evolution of dispersal is well known (Hamilton & May 1977), but has not been applied to the evolution of parasite transmission rates and the correlated effects on virulence.

2. LIFE CYCLE

My analysis of kin selection and the virulence of parasites applies to a variety of life cycles. I describe two examples to introduce the models that follow. I consider the generality and limitations of the particular assumptions in the Discussion.

The first example is the simple membrane-bound groups of genes that formed protocells in early evolution. I assume that a protocell is a bag that starts with k copies of genetic material. I refer to each copy

as a 'chromosome' or a 'parasite', depending on the context. I often refer to a protocell as a 'host'. The 'copies' are either identical strands of genetic material or strands that have recently diverged from a common ancestor.

The chromosomes compete within the host for resources. Success at acquiring resources influences that rate at which chromosomes can replicate themselves within the host. More competitive chromosomes (parasites) use up local resources more quickly and reduce the overall success of the host and its group of chromosomes. This reduction in host success is called 'virulence'.

The host competes with other protocells for resources from the environment. The host produces a progeny cell after it has acquired sufficient resources and the chromosomes have replicated. The fitness of the host and its chromosomes depend on the rate of progeny production. Segregation of chromosomes occurs when progeny are formed: k chromosomes are chosen randomly from the pool of copies in the host.

The protocell example describes the basic life cycle of vertically transmitted parasites, and also captures the essence of conflict and cooperation in the early evolution of cellular genomes. Horizontal transmission between hosts is another important process in the evolution of virulence. Horizontal transmission occurs 'passively' when parasites move between hosts independently of the characters encoded by their chromosomes. For example, chromosomes may leak out through membrane boundaries and then be picked up by other hosts from the environment. Or other organisms may act as vectors that move chromosomes between hosts. Horizontal transmission is 'active' when chromosomes encode specific traits that influence their rate of movement between cells.

The second example shows that the mechanisms of horizontal transmission can also bind together groups of parasite chromosomes in ways that are similar to the protocell model. For example, suppose parasites require a vector for transmission between hosts. If each host encounters at most one vector during infection and one during transmission, then all parasites in a host have been bound together by their common history of transmission. If each new transmission samples k copies of the parasite chromosomes, then this model matches the no-mixing protocell model above. In this case, the success of the group is the probability of vector-borne transmission before the host dies.

Passive mixing occurs when there is transmission between vector-bound lineages which is not influenced by parasite genotype. For example, a host may be infected by several vectors, mixing vector-bound lineages during the sampling phase when k chromosomes ride out on a transmitting vector.

Active mixing occurs when parasite traits influence their rate of transmission between vector-bound lineages. For example, a parasite chromosome may influence the number of vectors attracted to a host, it may increase its own probability of getting a ride on particular vectors relative to locally competing chromosomes, or it may create alternative transmission pathways through soil, wind and water.

These examples show the generic features of protocell and parasite life cycles which are addressed by the following models.

3. NO MIXING

Imagine a host with several copies of the same chromosome. Two opposing selection pressures act on the characters of the chromosomes. First, the chromosomes compete for resources within the host to replicate themselves. Success in this competition is measured by the competitiveness of each chromosome, z_{ij}, where z is a quantitative character for the jth chromosome in the ith host. The relative success of each chromosome in a host is z_{ij}/z_i, where z_i is the average value of chromosomes in the ith host. Selection on competitiveness favours an increase in z.

The second force is competition among hosts for resources from the environment. I assume that chromosomes with high competitiveness within hosts contribute less to the upkeep of the host or reduce the host's vigour. Thus the average success of the host and of the chromosomes in the host is proportional to $1-z_i$. Combining the two forces yields the fitness function

$$w_{ij} = (z_{ij}/z_i)\,(1-z_i).$$

An increase in an individual chromosome's character z_{ij} has two correlated effects: increased competitiveness within the host, and increased virulence that reduces the group's and the host's success.

The evolution of z is a typical problem for the theory of kin selection: a trade-off between individual and group fitness. The equilibrium value of z can be obtained by the standard application of the Price equation (Price 1970, 1972), as described in Appendix 1. The form of the Price equation required is

$$\bar{w}\Delta\bar{z} = \mathrm{cov}_i(w_i, z_i) + E_i[\mathrm{cov}_{j\cdot i}(w_{ij}, z_{ij})], \qquad (1)$$

where I use redundant notation to emphasize that the first covariance, selection among groups, is taken over groups subscripted by i, and the second covariance, selection within groups, is taken over individuals within groups $j\cdot i$.

The equilibrium, z^*, is obtained by finding a local maximum for equation (1) with respect to small variants in z (see Appendix 1), which yields $z^* = 1-R$, where R, the coefficient of relatedness from kin selection theory (Hamilton 1964, 1970), measures the variance in the character among hosts relative to the total variance over all chromosomes in the population. When chromosomes within hosts are closely related, selection favours low competitiveness among chromosomes and low virulence.

If chromosomes never mix between hosts, then three forces affect the evolution and R and z^*.

1. Selection favours R and z to be related by the equilibrium equation, $z^* = 1-R$.

2. Mutations reduce the similarity among chromosomes within hosts, thus reducing R. This force is controlled by two parameters, the mutation rate, μ, and the change in character values caused by each

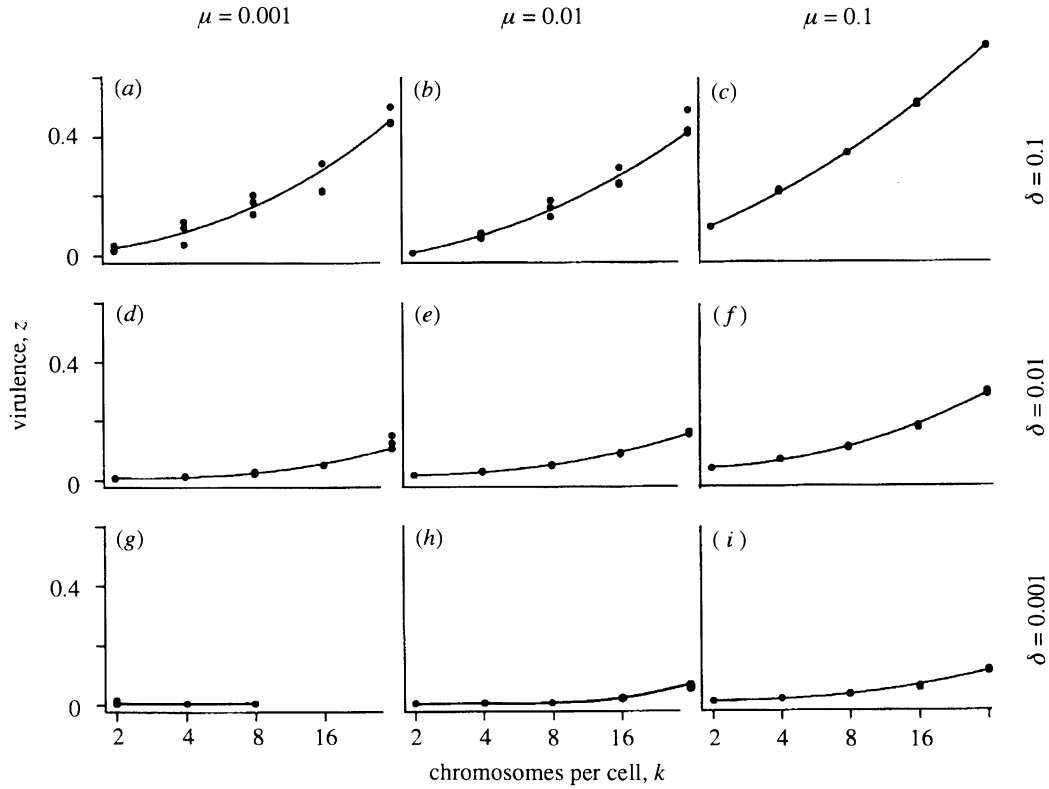

Figure 1. The equilibrium level of virulence in a model with no mixing. Virulence, z, is determined by the number of chromosomes per host, k, the mutation rate, μ, and the effect per mutation, δ. The equilibrium virulence closely matches the prediction $z^* = 1-R$, as discussed in the text, where relatedness, R, is determined by a balance among mutation, selection and segregation. The plots show data from a simulation. In each run a population of 1000 protocells was initialized with k chromosomes, each with a trait value that was chosen according to a uniform random number between 0 and 1. In each generation 1000 cells were selected stochastically for reproduction with probabilities proportional to cellular fitness $1-z_i$, where z_i is the average trait value of chromosomes in the ith cell. For each cell chosen, k replicates of chromosomes were chosen stochastically from the chromosome pool. A replicate of a chromosome was chosen with probability proportional to relative fitness within the cell, z_{ij}/z_i. A particular parent chromosome may be chosen repeatedly. Replicates of chromosomes mutate at rate μ, with each mutation causing a change in trait values by an amount $\pm\delta$. The simulation was run for 15000 generations to initialize the system, and then the average trait value in the population, $\bar{z}$, and the coefficient of relatedness between pairs of chromosomes within cells, R, were measured in the following 15000 generations. The plots show the median value of $\bar{z}$ over 15000 generations for each of three replicate runs and for each combination of parameters k, μ and δ. Fluctuations over time were moderate as measured by the difference between the 95th and 5th percentiles for $\bar{z}$ in each run divided by the median value. The measure is 29% when averaged over all 135 runs, which is not very large considering that for many runs the median of $\bar{z}$ is close to zero. In (*g*) and (*h*) I used a population size of 10000 and 45000 generations of initialization because drift is stronger and convergence is slower for weak mutational effects. In (*g*), close convergence to equilibrium (of the order of 10^{-3}) required 150000 generations of initialization for the case of $k = 8$. Constraints on computer time prevented runs for $k = 16, 32$.

mutation, δ. I assume that, for each mutational event, z_{ij} is changed by $\pm\delta$, where the directions of change occur with equal probability, subject to the constraint that $0 \leqslant z_{ij} \leqslant 1$.

3. Segregation samples from the local chromosomes when the host reproduces. I assume that each host starts with k copies of the chromosome of interest. When the host reproduces, replicates of the local chromosomes are chose stochastically according to relative fitness within the host, z_{ij}/z_i. This sampling reduces the variance within hosts and increases relatedness.

Relatedness, R, and equilibrium trait values, z^*, are held in balance by a delicate interaction among mutation, selection and segregation. I used stochastic computer simulations to study this balance, as described in the legend for figure 1. This figure shows the evolution of character values, z, as a function of the number of chromosomes per host, k, the mutation rate, μ, and the effect per mutation, δ. For all cases shown, $z \approx 1-R$ as predicted by the theory, with the error generally of the order of 10^{-2} or less. Relatedness declines and trait values rise as the mutation rate, μ, and mutation step, δ, increase. An increase in the number of chromosomes per cell, k, causes an increase in virulence because more copies reduce the variation among cells caused by sampling during segregation.

4. PASSIVE MIGRATION

The frequency and magnitude of mutations play an important role in the dynamics of relatedness and the evolution of virulence when there is no mixing of parasites (chromosomes) between hosts. In this section,

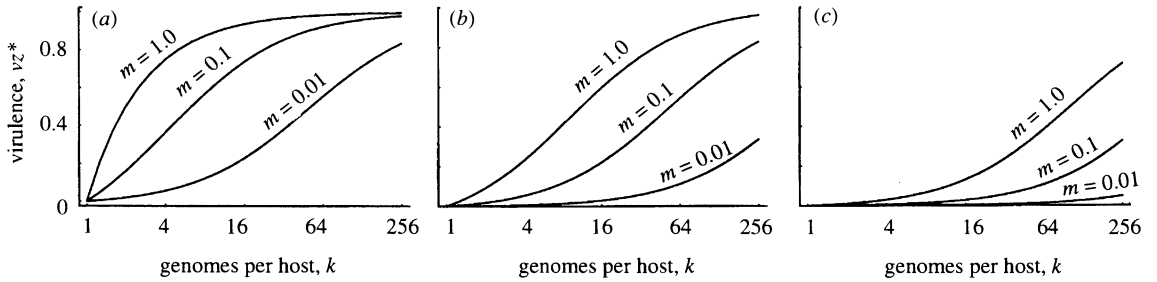

Figure 2. Evolution of virulence controlled by the number of parasites per host, k, and the rate of passive migration, m. The parameter a controls the strength of the association between virulence and competitiveness: (*a*) $a = 1.0$, (*b*) $a = 0.1$, (*c*) $a = 0.01$.

I examine the role of mixing (migration) between hosts. The migration in this case is passive because it is a fixed attribute of the system that is not influenced by genotype.

The equilibrium result is the same, $z^* = 1-R$, but typically migration will be a more potent force than mutation in setting the distribution of genetic variance that determines relatedness. The individual chromosomes are haploid, thus R is equivalent to the standard inbreeding coefficient of population genetics, F. The equilibrium value of F can be obtained from the recursion

$$F' = (1/k)+F[(k-1)/k](1-m)^2,$$

by setting $F' = F$, where F' is the value of F after one round of segregation and migration at rate m (see Appendix 1). The equilibrium is

$$R = F = 1/[k-(k-1)(1-m)^2], \tag{2}$$

which allows the equilibrium virulence, z^*, to be expressed in terms of the number of parasites per host, k, and the amount of mixing between groups of parasites, m. The prediction is shown in figure 2*a*.

Computer simulations were used as described in the legend for figure 1 to test the quality of this prediction. As in the previous model, $z^* \approx 1-R$, except when the mutational effects are of greater magnitude than the migration rate. In that case virulence evolves according to the results shown in figure 1 under the assumption of no mixing. A second type of departure from the prediction occurs when the size of mutational effects is small ($\delta = 0.001$), and the mutation rate is 0.001 or 0.01. In this case sufficiently frequent migration can overcome weak mutation, so that with $m \geqslant 0.01$ the theory based on migration holds.

In this model both competitiveness and virulence are determined by the underlying trait z. This can be generalized to linear trade-offs between competitiveness and virulence in which the fitness function is

$$w_{ij} = [(1-a)+az_{ij}/z_i](1-vz_{ij}), \tag{3}$$

where vz is the virulence caused by the underlying trait z, and az is the competitiveness caused by z, so that the ratio of virulence to competitiveness is v/a. The equilibrium level of virulence is

$$vz^* = a(1-R)/[a(1-R)+R], \tag{4}$$

where relatedness, R, is given by equation (2). The effect of varying a is shown in figure 2*b*, *c*.

5. ACTIVE MIGRATION

I now extend the model by allowing the rate of migration to be under genotypic control. There are three characters. Competitiveness for resources within the host determines each parasite's success relative to its neighbours. Damage to the host's reproductive success (virulence) determines the average success of the group of parasites within the host, because the parasites live within the host and their total success is tied to the vigour of the group. In the first two sections I examined the evolution of competitiveness and virulence as correlated characters determined by a single underlying trait, z. I now add the third key characteristic of a parasite, the transmission (migration) from one host to another.

I introduce active migration by reviewing a standard model for the evolution of dispersal when relatives compete for local resources (Hamilton & May 1977; Motro 1982; Frank 1986; Taylor 1988). The particular model and the results that I summarize are explained in Frank (1986).

The fitness function for a trait z_{ij} that determines the dispersal rate for the jth chromosome in the ith host is

$$w_{ij} = (1-z_{ij})/[1-z_i+(1-c)\bar{z}] + (1-c)z_{ij}/[1-\bar{z}+(1-c)\bar{z}]. \tag{5}$$

The first term is the success of an individual that stays at home with probability $1-z_{ij}$ relative to the intensity of competition at home: the frequency of non-migrants, $1-z_i$, plus the frequency of immigrants, $(1-c)\bar{z}$, where $\bar{z}$ is the average rate of dispersal and c is the mortality (cost) incurred during dispersal. The second term is the success of an individual that migrates with probability z_{ij} and survives the journey with probability $1-c$. Upon arrival it faces competition from non-migrants, with frequency $1-\bar{z}$, and from other immigrants that arrive at a frequency of $(1-c)\bar{z}$.

The Price equation method outlined above (see Frank 1986) can be used to obtain the equilibrium dispersal rate

$$z^* = (R-c)/(R-c^2), \tag{6}$$

where R is the coefficient of relatedness among chromosomes within hosts, and c is the cost of dispersal. We can use equation (2) for the equilibrium value of R, but now the migration rate m in that equation depends on z. The rate of successful migration is $m = (1-c)\bar{z}/(1-c\bar{z})$. Substituting this value of m into equation

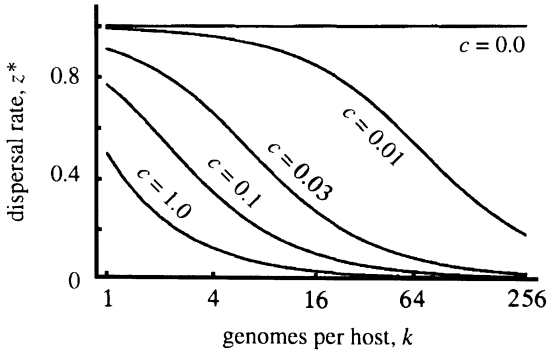

Figure 3. Evolution of dispersal rate controlled by the number of parasites per host and the cost of dispersal, c.

(2) to obtain R, and then using that value of R in equation (6), we obtain a nonlinear equation in z^* that can be solved numerically for the equilibrium in terms of the cost of migration, c, and the number of parasites per host, k (Taylor 1988). The result is plotted in figure 3. This result holds unless mutational effects are of greater magnitude than the rate of successful migration, m. When mutation is sufficiently strong relative to migration, relatedness is reduced and the rate of dispersal declines.

In summary, competition among relatives within hosts favours the evolution of increased horizontal transmission. This increased 'dispersal' may occur by enhanced mixing among sets of parasites during transmission or by additional release of propagules from a stable host.

6. THE FULL MODEL

I now incorporate the evolution of migration (parasite transmission) as a correlated trait of competitiveness and virulence. There are several ways in which correlations can arise among these traits. For example, dispersal may require more resources, such as a protein coat. This increased requirement for resources raises the dispersing parasite's competitiveness and reduces the vigour of the group. Lower group success is synonymous with virulence in these models.

Competitiveness, virulence and dispersal are combined into a fitness function by merging equations (3) and (5) to yield

$$w_{ij} = [(1-a)+a(z_{ij}/z_i)]\,(1-vz_i)\{(1-dz_{ij})/[1-dz_i+(1-c)\,d\bar{z}] + (1-c)\,dz_{ij}/[1-d\bar{z}+(1-c)\,d\bar{z}]\},$$

where the dispersal probability is determined by dz. This model emphasizes the extent to which selection on each character affects the evolution of the other characters.

This equation contains the previous models as special cases. For example, if $d = 0$, then one obtains equation (3) and the equilibrium result in equation (4). If $a = v = 0$, the equilibrium dispersal probability dz is given by the result for z^* in equation (6).

The equilibrium for the full model is obtained in the usual way with the Price equation, yielding a single polynomial in z^*:

$$0 = [d\alpha(1-dz^*)-v\beta^2-\gamma]\,R-cd\alpha\beta+\gamma,$$
$$\alpha = 1-vz^*,$$
$$\beta = 1-dcz^*,$$
$$\gamma = a\alpha\beta^2/z^*,$$
$$R = 1/[k-(k-1)\,(1-m)^2],$$
$$m = (1-c)\,dz^*/\beta,$$
$$0 \leqslant z^* \leqslant 1/\max(v,d).$$

The equilibrium trait value, z^*, depends on five parameters. The parameters a, v and d determine the relation between the trait and competitiveness, virulence and dispersal, respectively. The parameters k and c are the number of parasites per host and the cost of dispersal. Results for various parameter combinations are shown in figure 4 and discussed below.

7. DISCUSSION

Kin selection plays a central role in the evolution of protocells and parasites. I summarize my main conclusions with respect to parasite evolution and then describe analogies with protocell evolution.

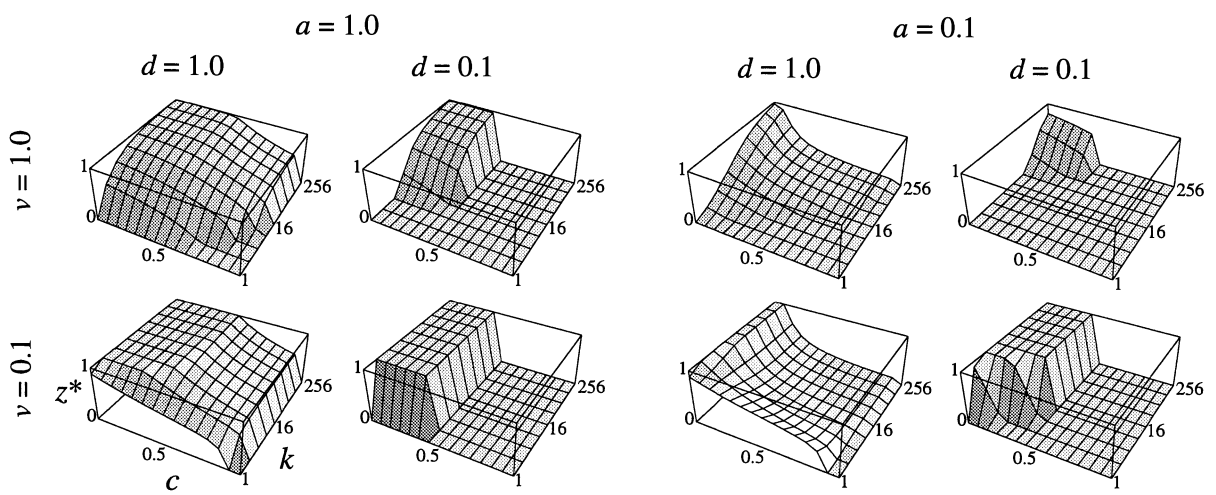

Figure 4. Equilibrium trait values z^*. Trait value z affects three correlated characters: virulence is vz, competitiveness within hosts is az, and the active dispersal rate is dz. Each plot shows z^* as a function of the number of parasites per host, k, and the cost of dispersal, c.

The first model analysed a simple trade-off between competitiveness within the host and virulence. The formal result for this model is $z^* = 1 - R$, the virulence depends on one minus the relatedness among parasites within hosts. This result isolates an important process that occurs in a variety of more complex models (Bremermann & Pickering 1983; Frank 1992; Nowak & May 1994). This model also matches the intuitive notion that increased relatedness within hosts tends to decrease competition, thus reducing harm to the host, and increasing the success of the local group of parasites.

The analysis showed an interesting distinction between life cycles in which relatedness is dominated by mutational processes and those in which migration dominates. When mutation is more potent than migration, relatedness and virulence are held in a delicate balance among mutation, selection and segregation (figure 1). For example, mutation would dominate in a vertical, uniparentally inherited parasite. In this case, the number of parasites k that are sampled (segregate) in each generation can greatly influence relatedness and virulence. Small k increases the sampling variance among hosts and thus increases relatedness, which enhances cooperation and reduces virulence. Virulence increases rapidly with increasing k. This may explain why metazoans typically have a life cycle that passes through a single-celled stage, which samples (transmits) a small number of chromosomes from one cell rather than a large number of chromosomes from the whole organism (Maynard Smith 1988).

The second model applied a theory of dispersal based on kin selection to the evolution of parasite transmission rates. Previous theory showed that dispersal rates increase as the relatedness rises among competitors within a natal patch (Hamilton & May 1977). The surprising outcome is that dispersal rates can rise to high levels even when the probability of successful migration is low (high cost, c, in figure 3). The reason is that an individual competing with close relatives gains little net inclusive fitness by winning locally against its relatives. Even a small chance of successful migration and competition against non-relatives can be favored.

In terms of parasite life history, increased relatedness within the host favours traits that enhance horizontal transmission. Selection favouring enhanced transmission can occur even if the rate of successful transmission is low. There is a subtle feedback in this process. If successful transmission is rare (high cost, c) then relatedness within hosts is likely to be high, which in turn favours traits that enhance transmission. However, to complete this analysis it is necessary to consider another type of cost for parasite dispersal: the mechanisms of horizontal transmission often have virulence effects on the host (e.g. diarrhoea).

The final model ties together the traits of competitiveness, virulence and dispersal. I assumed that each of these three traits changed linearly with a single underlying cause, z. I varied the rate of change for each trait to study how correlations among these traits influence the evolution of parasite life histories. The results are shown in figure 4. The equilibrium levels of competitiveness, virulence and dispersal are az^*, vz^* and dz^*, respectively. The probability of successful migration is $1-c$, where c is the cost of dispersal. The number of parasites infecting each host is k.

Reducing the virulence effects, v, causes an increase in both competitiveness within the host and dispersal rate (compare the top and bottom rows in figure 4). The change in v for the case $a = 0.1$ and $d = 1.0$ is particularly interesting. With strong virulence effects ($v = 1.0$), high dispersal and competitiveness occur only when the costs of dispersal are low and the number of parasites per host is high. In this case relatedness among parasites in each host is low and, as expected, competition among parasites drives the evolution of trait values. The drop with increasing cost of dispersal at high k appears to be a more complex effect. The most likely explanation is that high costs of dispersal cause low rates of successful migration and high levels of relatedness in hosts. This in turn reduces the strength of selection on competitiveness, thus lowering the equilibrium trait values.

With low virulence effects, $v = 0.1$, for $a = 0.1$ and $d = 1.0$, competitiveness and dispersal are nearly unchanged or rise as k declines and the relatedness in hosts increases. In this case selection on transmission rates appears to be driving the evolution of parasite life histories because competitiveness within a host increases despite the rise in relatedness among competitors. Interactions among the five parameters and the dynamics of relatedness determine the parasite life histories shown in figure 4.

These interpretations for parasites also apply to the evolution of protocells or vertically transmitted symbionts. From an abstract point of view, the models apply whenever there are trade-offs among competitive success in a group, damage to the average success of group members (virulence), and dispersal. For vertically transmitted symbionts, the key is how replicates compete within local groups and are sampled for transmission. Orderly mendelian segregation is a mechanism that prevents internal competition and promotes cooperative traits; linkage on chromosomes also prevents competition. The transition from the earliest protocells, in which the molecules of genetic material probably competed for resources and transmission, to mendelian genetics is an important puzzle in evolutionary history (Maynard Smith 1988). Although autosomes are relatively orderly, no mechanism is known by which eukaryotic cells prevent competition among mitochondria and other symbionts.

The models also suggest one mechanism for the origin of parasites among protocells. The strong selective pressures that favour reduced competition with relatives promote horizontal transmission.

These models have three important limitations: (i) the mechanism of correlation among traits; (ii) the lack of emphasis on ecological dynamics and epidemiology; and (iii) the absence of coevolution among the genes of symbiotic partners.

I assumed that the three traits, competitiveness, virulence and dispersal, were all controlled by a single

underlying cause. In reality there may be several causes for the correlations among traits. My simple model describes the main trade-offs, but cannot provide a complete analysis without adding many more parameters. It is reasonable to assume that such trade-offs may occur, but it is difficult to envisage the specific mechanisms. My simple model emphasizes the general processes that must always be present whenever trade-offs occur.

My models do not address the effects of parasitism on the abundance of hosts. High virulence may reduce the number of hosts if parasites regulate host populations. Fewer hosts will reduce the probability of successful transmission and bind parasite success more closely to that of its host (Lenski & May 1994). Less migration also increases the relatedness among parasites in hosts, reducing competitiveness and virulence. In a recent paper, Nowak & May (1994) combined epidemiological and genetic processes and showed the potential for complex dynamics and polymorphisms in the evolution of virulence.

The role of coevolution among symbiotic partners is particularly interesting. In my models there is a single kind of chromosome or strand of genetic material, with a common, optimal type and a range of 'nearby' mutants with slightly altered phenotypic effects. Eigen & Schuster (1979) refer to this sort of population, held in mutation–selection balance, as a 'quasi-species', which I shorten to 'species' here.

Models for the origin of genetic systems have focused on cooperation among different species and the evolution of a stable genome. Different species, each on a physically separate strand, were probably required in early evolution because the mutation rate per molecule for a single, long strand would have been too great for progressive evolution. Eigen & Schuster (1979) call this small limit for replicative molecules in early evolution the 'error threshold'.

Multispecies models for the origin of cooperative genomes search for conditions under which mutualistic communities can evolve (Eigen & Schuster 1979; Szathmáry & Demeter 1987; Szathmáry 1989*a*, *b*). Parasites form the greatest barrier to cooperative, stable communities, as in the single-species models that I presented (Maynard Smith 1979; Bresch *et al.* 1980; Szathmáry 1989*a*, *b*). What conditions favour cooperative coevolution of different species?

Kin selection, or group selection, is one process that favours cooperative evolution of communities (Wilson 1980). An individual tends to be cooperative to the extent that its actions affect the fitness of relatives within its local group. Relatives are genetically similar members of the same species. The process of kin selection is widely known, and has been applied by several authors to the problem of protocells (Szathmáry & Demeter 1987; Szathmáry 1989*a*, *b*). The models presented here formalize and extend that theory.

A second process that promotes cooperation among species is physical binding (Wilson 1992). Parasites that are vertically transmitted with their hosts have a component of their fitness bound to the success of their host (Yamamura 1993; Ewald 1994). Different species of genetic material may be physically bound on a single chromosome, preventing competition for resources between bound members and promoting cooperative synergism in their phenotypic effects (Maynard Smith & Szathmáry 1993). One of the central questions in the evolution of cooperative communities concerns traits that prevent asymmetric transmission of species, such as the origin of chromosomes and of fair meiosis in mendelian segregation (Maynard Smith 1988). It is easy to see that completely bound species form a higher-level unit, but how does complete binding evolve without cheating by a component?

The third process of cooperative evolution arises through genetic similarities between different species. The fact that genetic similarities within species promote cooperative behaviour through kin selection is well understood and universally accepted. I recently showed that genetic correlations between species have similar effects to kin selection in promoting cooperation (Frank 1994). Kin selection is not driven by identity by descent, but rather, there is a more general process that promotes cooperation whenever there are genetic correlations within or between species. Kin tend to be similar because they share a common ancestor, and it is easy to see how such similarities lead to relatedness and cooperation in local groups. I showed that selection among aggregates of species (communities) creates spatial correlations between species. These genetic correlations between species enhance cooperative evolution in the same way as kin selection.

In summary, the trends for competitiveness, virulence and dispersal described here should hold in more realistic and complex models. My analyses establish a formal link between problems of protocells and parasites and the study of conflict and cooperation in social evolution. This is a first step towards a general theory of symbiosis. A general theory must also explain the evolution of reduced competition within communities and incorporate the role of genetic correlations between species.

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APPENDIX 1

Here I provide a derivation of the Price equation (Price 1970, 1972) and describe the methods used in §3 to illustrate my approach. At the end of Appendix 1 I provide more details on the recursion for F' used in §4.

Here is the derivation of the Price equation. Let there be a population (set) where each element is labelled by an index i. The frequency of elements with index i is q_i, and each element with index i has some character, z_i. One can think of elements with a common index as forming a subpopulation that makes up a fraction q_i of the total population. No restrictions are placed on how elements may be grouped.

A second (descendant) population has frequencies q_i' and characters z_i'. The change in the average character value, $\bar{z}$, between the two populations is

$$\Delta\bar{z} = \Sigma q_i' z_i' - \Sigma q_i z_i. \qquad (A\ 1)$$

Note that this equation applies to anything that evolves, since z may be defined in any way. For example, z_i may be the gene frequency in entities i, and thus $\bar{z}$ is the average gene

frequency in the population; or z_i may be the square of a quantitative character, so that one can study the evolution of variances of traits. Applications are not limited to population genetics. For example, z_i may be the abundance of a particular compound in galaxy i.

The strange characteristics of the Price equation come from the way it associates entities from two populations. The value of q_i' is not obtained from the frequency of elements with index i in the descendant population, but from the proportion of the descendant population that is derived from the elements with index i in the parent population. If we define the fitness of element i as w_i, the contribution to the descendant population from type i in the parent population, then $q_i' = q_i w_i/\bar{w}$, where $\bar{w}$ is the mean fitness of the parent population.

The assignment of character values z_i' also uses indices of the parent population. The value of z_i' is the average character value of the descendants of index i. Specifically, for an index i in the parent population, z_i' is obtained by weighting the character value of each entity in the descendant population by the fraction of the total fitness of i that it represents. The change in character value for descendants of i is defined as $\Delta z_i = z_i' - z_i$.

Equation (A 1) is true with these definitions for q_i' and z_i'. We can proceed with the derivation by a few substitutions and rearrangements:

$$\begin{aligned}\Delta\bar{z} &= \Sigma\, q_i(w_i/\bar{w})\,(z_i+\Delta z_i) - \Sigma\, q_i z_i \\ &= \Sigma\, q_i(w_i/\bar{w}-1)\, z_i + \Sigma\, q_i(w_i/\bar{w})\,\Delta z_i,\end{aligned}$$

which, using standard definitions from statistics for covariance (cov) and expectation (E), yields the Price equation

$$\bar{w}\,\Delta\bar{z} = \mathrm{cov}(w_i, z_i) + E(w_i \Delta z_i). \qquad \text{(A 2)}$$

The two terms may be thought of as changes due to selection and transmission, respectively. The covariance between fitness and character value gives the change in the character caused by differential reproductive success. The expectation term is a fitness-weighted measure of the change in character values between ancestor and descendant. The full equation describes both selective changes within a generation and the response to selection.

The covariance term in equation (A 2) would normally be written without subscripted variables as $\mathrm{cov}(w, z)$. The subscripts provide additional clarity when the equation is used to expand itself:

$$\bar{w}\,\Delta\bar{z} = \mathrm{cov}_i(w_i, z_i) + E_i[\mathrm{cov}_{j\cdot i}(w_{ij}, z_{ij}) + E_{j\cdot i}(w_{ij}\Delta z_{ij})], \qquad \text{(A 3)}$$

where E and cov are taken over their subscripts when there is ambiguity, and $j\cdot i$ are the individuals (subgroups), j, for a fixed group, i. The partition of i into subgroups j is arbitrary. This recursive expansion of the E term in equation (A 2) shows that transmission is itself an evolutionary event that can be partitioned into selection among subgroups and transmission of those subgroups. The expansion of the trailing expectation term can continue until no change occurs during transmission.

Note that no biological assumptions are involved in the derivation. The Price equation is simply manipulation of notation to describe arbitrary changes in population composition.

The next step is to apply equation (A 3) to the problem in §3. First, note that chromosomes are transmitted as units, so $\Delta z_{ij} = 0$ and equation (A 3) reduces to the shorter form of equation (1) given in the text. The fitness of the jth chromosome in the ith group (host) is $w_{ij} = (z_{ij}/z_i)\,(1-z_i)$, as given in the text, and thus the fitness of the ith group is $w_i = (1-z_i)$. The next step is to fill in the terms of equation (1) in a way that can be solved for a local maximum.

First, let $z_{ij} = z + \epsilon g_{ij}$, where g is the additive genetic variability of the trait values, and $\epsilon < 1$ is a scaling for the genetic component. For groups, $z_i = z + \epsilon g_i$, where g_i is the average of g_{ij} within group i. Secondly, $\mathrm{cov}(w_i, z_i) = -\epsilon^2 V_a$, where V_a is the genetic variance in trait values among groups, i.e. the variance in g_i. Thirdly, $E_i[\mathrm{cov}_{j\cdot i}(w_{ij}, z_{ij})] = \epsilon^2[(1-z)/z]V_w$ to second order in ϵ, where V_w is the component of the genetic variance in the population within groups, and $V_t = V_a + V_w$ is the total genetic variance in the population. Combining these terms yields

$$\bar{w}\,\Delta\bar{z} = \epsilon^2[-V_a + (1/z-1)\,V_w].$$

Our goal is to find a trait value, z^*, such that any small deviants from this value suffer reduced fitness. Thus the local maximum can be obtained by setting to zero the derivative of $\bar{w}\,\Delta\bar{z}$ with respect to ϵ evaluated at $\epsilon \to 0$. This yields $z^* = 1-R$, with $R = V_a/V_t$, the coefficient of relatedness from kin selection theory.

I conclude Appendix 1 by explaining how the recursion

$$F' = (1/k) + F[(k-1)/k]\,(1-m)^2$$

was derived in §4. The inbreeding coefficient, F, has many interpretations (Wright 1969), but the easiest way to build a recursion is by focusing on the probability of identity by descent, thus for my application F is the probability that two chromosomes chosen from the same individual are identical by descent. All chromosomes are equally likely to be chosen, and sampling is done with replacement. Other definitions are: F' is the value of F after one generation, k is the number of chromosomes per individual, m is the migration rate, the fraction of the chromosomes in an individual derived from randomly chosen members of the population, and $1-m$ is the fraction of chromosomes that come from the single, asexual parent. The probability of identity by descent for pairs of chromosomes, F', can be derived by assuming that the first chromosome is chosen, and then considering the possible relations of that chromosome to a second chromosome. There are two components. First, the second chromosome chosen may be the same one as the first, with probability $1/k$, because sampling is with replacement. Second, the other chromosome may be different from the first, with probability $(k-1)/k$. In this case, the pair of chromosomes is identical by descent if neither were immigrants, with probability $(1-m)^2$, multiplied by the probability that pairs of chromosomes in the parent are identical by descent, F.

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