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MODELS OF SYMBIOSIS

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Abstract.—A tentative outline of concepts is proposed for the evolutionary genetics of symbiosis. There are three main topics. The first concerns the tension between the integrative and disruptive forces of kin selection. Kin selection can be disruptive because competition among close relatives favors dispersal and a reduction in relatedness among neighbors. Kin selection acts independently within each species of a symbiotic community but has important consequences for the integration of the community into a cooperative unit. The second topic describes the evolution of beneficial, synergistic effects between species. The evolution of mutual effects depends on various correlations between species. Genetic correlations are analogous to linkage disequilibrium in standard Mendelian genetics. Correlations in reproductive success between symbiotic partners arise from codispersal and reproductive synchrony. The third topic concerns the evolution of asymmetrical symbioses in which one species can dominate its partner. Dominance may explain the evolution of uniparental inheritance among cytoplasmic symbionts and a peculiar form of germ-soma separation in the symbionts of insects.

The evolution of cooperative groups has played a major role in the history of life. The first primitive genomes probably formed by symbiotic association of separate replicators. The great transition to eukaryotic cells followed domestication of a community of symbiotic bacteria. Various degrees of sociality have evolved in nearly every taxa, from the reproductive aggregations of slime molds to complex insect societies (Maynard Smith and Szathmáry 1995).

Several well-known processes influence cooperation and conflict within groups. Kin selection favors similar replicators to cooperate according to their shared traits (Hamilton 1964). Reciprocity favors cooperation when a helpful individual obtains benefits returned from its partner (Trivers 1971). Reproductive interests overlap when symbionts are transmitted together vertically down a lineage (Fine 1975).

As with any theoretical system that has grown haphazardly over time, a variety of conceptual gaps and incompatible notions about cooperation and symbiosis have crept into the literature. For example, vertical transmission of replicators down a lineage is generally believed to guarantee full cooperation within the lineage because each replicator's success is tied to the success of the group. But competition within groups can influence cohesion even in purely asexual, nonmixing lineages (Szathmáry and Demeter 1987). Vertical transmission is rel-

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evant, but it must be analyzed in a proper framework of reproductive interests (Frank 1996*c*). A similar haziness exists in concepts such as kin selection and reciprocity when applied to symbiotic groups.

Enough progress has been made on disparate puzzles—the origin of early genomes, the mixing of symbiotic lineages, the domestication of vertically transmitted symbionts—that many insights and difficulties recur. The separate problems, when viewed together, suggest a tentative outline for the evolutionary genetics of symbiosis. This article is an expanded outline.

There are three main topics. The first concerns the interaction between kin selection and patterns of transmission. Although kin selection is a familiar process, recent work has demonstrated surprising dynamics when relatives interact. For example, kin selection is recognized as an integrating force in cooperative groups. But close interaction among relatives also leads to competition among kin, favoring high rates of dispersal that disrupt group integration (Hamilton and May 1977; Frank 1994*b*).

Kin selection concerns symbiosis, or living together, among members of the same species. The word *symbiosis* is usually reserved for interactions between species. But logical development of the subject, outlined below, suggests a natural flow of ideas from one species to two.

The second main topic concerns the origin and subsequent evolution of interactions between two species. I consider symmetrical interactions in which neither species can dominate the other. The problem is how two independent species can be changed into a pair with positively correlated reproductive interests. If the correlation becomes perfect, then two species have evolved into a higher-order unit of organization.

The third topic addresses asymmetrical interaction between species, in which one partner can dominate the other. The dominant species may, for example, restrict migration of its partner. This increases relatedness within the local population of the partners, which causes kin selection to favor coherence and orderly integration within the partner groups. Or the dominant partner may prevent competition among its symbionts, imposing a form of reproductive fairness in the probability of transmission. With opportunities for local gain denied, the symbionts can increase their fitness only by increasing the joint success of the host-symbiont group.

ONE SPECIES: INTEGRATING AND DISRUPTIVE FORCES OF KIN SELECTION

The simplest evolutionary problem consists of a symbiont in relation to a nonevolving partner species. The partner may be a host that provides resources, with symbionts (parasites) forming a population within each host. Or the partner and symbiont may be free-living species of approximately the same size, sharing a common resource. The group, in this case, is composed of a two-species community in which the symbiont is evolving and the partner is evolutionarily fixed.

The evolutionary problem of how the symbiont evolves in each case is the same as the problem of sustainable yield in a group-structured population (Frank

1996*c*). The resource may be a host, in which case resource exploitation by the symbiont (parasite) damages the host. Thus, the problem of parasite virulence within an evolutionarily fixed host is a good model for the one-species problem.

Kin Selection and Virulence in a Protocell Model

A useful formulation of this one-species problem follows the protocell model (Szathmáry and Demeter 1987; Frank 1994*b*, 1996*c;* Maynard Smith and Szathmáry 1995). Protocells are simple membrane-bound groups of genes that formed in early evolution. Each protocell can be thought of as a bag that starts with k copies of genetic material. I refer to the protocell as the host because it is a passive resource that contains symbionts. I refer to each copy of genetic material as a chromosome, parasite or symbiont, depending on the context. In these one-species models, the copies are identical strands of genetic material or strands that have recently diverged from a common ancestor. Later, I develop multispecies protocell models, in which different kinds (species) of genetic material interact.

The chromosomes compete within the host for resources. Success at acquiring resources influences the 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 cell 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. Sampling of chromosomes occurs when progeny are formed—k chromosomes are chosen randomly from the pool of copies in the host. I refer to this sampling process as segregation.

This 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. In the simplest model, all symbionts are transmitted vertically, down a lineage of protocells, and there is no horizontal transmission between protocells.

The level of cooperation within cells depends on the kin selection coefficient of relatedness among members of each cell (Szathmáry and Demeter 1987). When relatedness is high, cooperation is favored, and the group behaves as an integrated unit maximizing the replication rate of the cell. When relatedness is low, competition within the group is intense, and the sustainable yield of the group is low. Indeed, in the model outlined here, the success of cells increases linearly with the coefficient of relatedness within cells, r (Frank 1994*b*). This shows that kin selection is the primary integrating force, and cooperative behavior of the group is a continuous phenomenon that culminates in a completely integrated unit when $r = 1$.

The coefficient of relatedness, r, is a statistical measure of correlation that can be described in several equivalent ways. It is the slope (regression) of group genotypic value on individual genotypic value (Hamilton 1970). The slope is one

if all members of the group are genetically identical; the slope is low when the correlation between individual and group is small. The coefficient r is also the genetic variance among groups divided by the total variance in the population (Hamilton 1975; Wilson 1980). Thus, as variance among groups increases, the groups become increasingly integrated, cooperative units.

How can r be less than one if there is no horizontal transmission and mixing among cells? The distribution of genetic variance depends on the balance between mutation and segregation (Szathmáry and Demeter 1987; Frank 1994*b*). Mutation causes differences among members of the same group, increasing variance within groups and decreasing variance among groups. This lowers r. Segregation is a sampling process that chooses k replicators to be transmitted to offspring from the pool in each cell. When $k = 1$, each new cell begins with no variance within the group; when k is large, each new cell begins with the same within-group variance as its parent. Thus, strong segregation (low k) reduces within-group variance and increases relatedness.

Transmission Patterns and Cooperative Groups

The protocell model with no horizontal mixing is a model with purely vertical transmission. But vertical transmission, by itself, has no influence on cooperative evolution in this model. Horizontal transmission can also bind together groups of parasites in ways that are similar to the protocell model (Frank 1994*b*). 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 chromosome, 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 multiplied by the average number of hosts infected by each vector.

Mixing of lineages occurs in the protocell model when horizontal transmission moves parasites between cells. Mixing of lineages occurs in the second, vector-bound model, when a host is infected by several vectors. The vector-bound lineages mix during the sampling phase when k chromosomes ride out on a transmitting vector.

The evolution of group behavior is simple when the rate of mixing among lineages is not directly influenced by parasite genotype (Frank 1994*b*). Groups are cooperatively integrated in proportion to r, the coefficient of relatedness in groups, as before. Without mixing, r is determined by a balance between mutation and segregation. When mixing has a stronger influence on the distribution of genetic variance within and among groups, then r is determined by the balance between the rate at which mixing reduces genetic variance among groups, and sampling k symbionts during segregation increases variance among groups.

The problem is more interesting when parasites influence their own rate of mixing. Kin selection can then act as a disruptive rather than integrating force. I discuss this surprising aspect of kin selection in the next section.

Kin Selection as a Disruptive Force

Kin selection is an integrative force in groups. As relatedness rises, the degree of shared reproductive interests increases among group members. But close relatedness in groups also implies that relatives are competing with each other for limited resources. Hamilton and May (1977) pointed out that competition among relatives favors some individuals to disperse from their group. The surprising outcome is that dispersal rates can rise to high levels even when the probability of successful migration is low. The reason is that an individual competing with close relatives gains little net inclusive fitness by winning locally against its relatives (Frank 1986; Taylor 1988). Even a small chance of successful migration and competition against nonrelatives can be favored.

In terms of symbiont life history, increased relatedness within the host favors traits that enhance horizontal transmission and ''infection'' of other groups (Frank 1994*b*). Selection favors enhanced horizontal transmission even if the rate of successful transmission is low. There is a subtle feedback in this process. If successful transmission is rare, then relatedness within hosts is likely to be high, which in turn favors traits that enhance horizontal transmission. But increased horizontal transmission enhances mixing of lineages and reduces relatedness, which favors local competition and disrupts group integration.

This duality of kin selection as an integrative and disruptive force has interesting implications for early evolution and the origin of parasitism. Imagine, in a protocell model, a primitive membrane-bound population of replicating molecules. With no horizontal transfer of replicators between lineages of protocells, relatedness remains high within protocells, and the protocell integrates into a functional unit. But this close relatedness within cells favors horizontal transfer of some replicators to avoid competition with relatives, causing infection of other cells and competition against nonrelatives. Thus, from the earliest phases of cooperative evolution, kin selection favored the origin of horizontal transmission and parasitism. The consequent mixing of lineages would have broken up the close relatedness that favors cooperation. Kin selection was both an integrating and destructive force in early evolution and was probably not sufficient to create higher-level units of organization.

Multidimensional Nature of Symbiotic Evolution

I have discussed models in which symbionts evolve to harm their host (virulence) even when transmission is purely vertical. This conclusion contradicts the commonly repeated belief that vertical transmission binds the reproductive interests of the symbiont to its host. By the standard argument, increased vertical transmission necessarily favors reduced virulence. In the extreme, with purely vertical transmission, a symbiont that harms its host harms itself; thus, purely vertically transmitted symbionts must be either neutral or beneficial. This standard argument contains some truth but requires important qualifications (Frank 1996*c*).

The first qualification can be summed up as follows: traits evolve and individuals reproduce. Consider, for example, a vertically transmitted symbiont with

two traits. One trait aids host metabolism and increases host fitness. The second trait affects competition among symbionts for transmission to the next generation. Greater success in competition is associated with damage to the host. The metabolism and competitive traits are uncorrelated.

If the net effect of the symbiont is detrimental to the host, the symbiont will be lost from the population of hosts (Fine 1975). This occurs because hosts without the symbiont will outreproduce infected hosts, driving infected host lineages to extinction. Because the symbiont is vertically transmitted, loss of infected hosts implies extinction of the symbiont.

The symbiont is maintained if the net effect on the host is beneficial. In spite of this demographic constraint required for maintenance, the competitive trait of the symbiont will evolve according to the theory outlined earlier. The degree of harm to the host will evolve according to the coefficient of relatedness among symbionts within hosts. Relatedness depends on the balance between mutation and segregation. Harm is measured relative to the maximum benefit provided when the beneficial metabolic trait is fully expressed and the competitive trait evolves to be harmless because of high relatedness. Thus, traits can evolve to be harmful or beneficial as long as the individual succeeds in reproducing. This suggests a multidimensional theory of symbiont trait evolution analogous to the Lande and Arnold (1983) theory for quantitative traits.

A small amount of horizontal transmission alleviates the demographic requirement that symbionts have a net beneficial effect on their hosts. Lipsitch et al. (1995) have shown, by theoretical argument, that many symbionts classified as vertically transmitted are likely to be maintained in the host by occasional horizontal transmission. They suggest that purely vertical transmission may be less common than appears at first glance.

TWO SPECIES

The examples in the previous section emphasize how a single character of one species evolves without evolutionary modification of characters in its symbiotic partner. I now turn to the joint evolution of characters in symbiotic pairs. This can be expressed as the joint evolution of two loci: one locus in the symbiont and one locus in the partner.

My focus is on cooperative evolution. I divide aspects of cooperative evolution into two parts. The first occurs when symbiont and partner have mutually beneficial effects on each other—a positive synergism between loci. The use of *locus* to describe partner and symbiont may seem a bit strange; it would seem more natural to say ''a positive synergism between species.'' I use *locus* to emphasize that the symbiont and partner could be two different replicating molecules (genes or chromosomes) in a primitive genome or an insect and its bacterial symbiont. The emphasis is, once again, on traits rather than on individuals or species (Dawkins 1982).

The second part of cooperative evolution concerns various processes that bind together the reproductive interests of the two loci. The most obvious form of binding is physical, in which two separate replicators are joined together chemi-

cally to form a longer chromosome. The joined pair of loci may always be transmitted together, in which case their reproductive interests are completely aligned and they form a single evolutionary unit, as if they were a single locus. Or the loci may be shuffled occasionally by recombination, in which case they ''codisperse'' with a probability of $1 - \rho$, where ρ is the recombination fraction. I have used standard genetic language, but physical binding might just as well cause a host locus and a symbiotic bacterial locus to codisperse, with shuffling defined by a parameter analogous to recombination.

Physical binding is easy to understand, but other types of association between pairs of loci have similar evolutionary consequences. Reproductive synchrony prevents competition and binds reproductive interests via the common timing of replication. Reproductive entrainment among chromosomes is certainly one of the outstanding features of mitosis and meiosis. These orderly cellular processes are derived conditions from the primitive state of scramble competition among a pool of unconstrained replicators.

Loci that have a positive synergism on reproductive success can develop statistical correlations between genetic variation at the loci (Frank 1994*a*). These correlations can arise even when there is limited codispersal. Such conclusions are well known in standard Mendelian population genetics. A pair of loci on separate chromosomes, recombining freely, will develop a statistical association when there is a positive or negative interaction between loci. This statistical association is called linkage disequilibrium. Thus, synergism creates associations between loci, and statistical association may have consequences similar to physical linkage.

This discussion emphasizes that symbiotic genetics shares many similar properties with standard, Mendelian genetics. But a generalization is required, removing the standard assumptions of meiotic reproductive synchrony and rigid patterns of codispersal.

Synergism between Symbionts

Many models of cooperative symbiosis start with the assumption that each individual donates a fraction of its energy to aid partners. For example, hypercycle models assume mutual enhancement of replication by separate species of replicators and then study the conditions under which complex genomes can evolve (Eigen and Schuster 1979; Maynard Smith and Szathmáry 1995). Models for the origin of chromosomes start with the assumption of positive synergism between separate replicators and then ask when selection favors those separate replicators to become biochemically linked on chromosomes (Maynard Smith and Szathmáry 1993).

I studied the prior step in the evolution of cooperative symbiosis (Frank 1994*a*, 1995*b*): how do different loci first evolve to aid partner loci? This step must be passed before one can invoke synergism to study hypercycles, genomic integration, and the evolution of chromosomes. I emphasized the early evolution of genetic systems, but the models apply to any kind of cooperative mutualism with behaviorally inflexible traits (e.g., biochemical mutualism).

Two processes influence the origin of synergistic traits. First, both partners

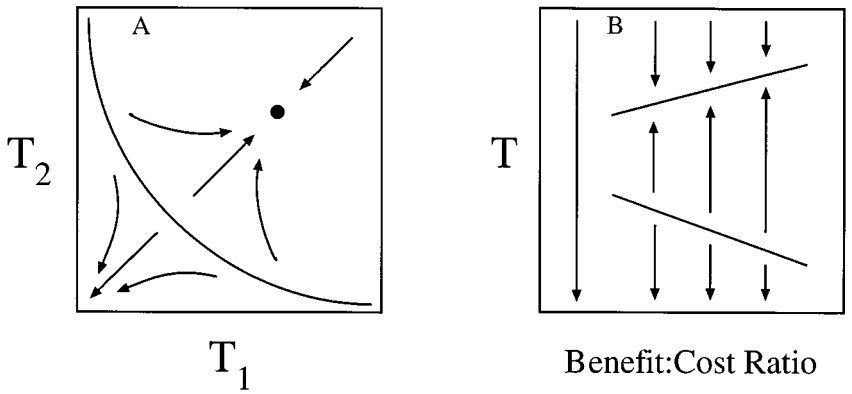

FIG. 1.—The threshold model for the evolution of cooperative symbiosis. Connor (1995) calls this type of synergism, in which traits are costly to the actor but have return benefits, ''investing in mutualism.''

must have a minimal level of expression for their mutualistic trait. Second, pairs that develop positive synergism must be associated in space so that benefits conferred to a partner are returned to the initial donor. These spatial associations have two components: selection creates spatial association (linkage disequilibrium) in trait values among symbiotic partners (Frank 1994*a*), and the benefits of cooperation, returned from partners, must be provided to relatives of the original donor (Hamilton 1972; Wilson 1980).

The initial level of trait expression and the spatial associations determine threshold trait values that are required for the origin and evolution of synergistic symbiosis (fig. 1*A*). Locus 1 has a trait, T_1, that enhances the reproductive rate of species 2 but reduces its own fitness. Likewise, locus 2 has a trait, T_2, that enhances the reproduction of locus 1 at a cost to itself. Larger values of T provide more benefit to the partner at a higher cost to the donor. When both loci have low trait values, as would be expected when the partners first meet, selection pressure continually pushes the traits to lower values. If, however, the pair of traits is above a threshold upon first meeting, then cooperation can increase because of synergistic feedback. Statistical association between loci increases the probability that a particular group will have a pair of symbionts above the threshold.

An example of how the benefit-cost ratio affects cooperative evolution is shown in figure 1*B*. The benefit-cost ratio defines a scaling for the positive effect an individual has on its partner relative to its own cost. In this example, both partners start with the same trait value, T. If the benefit-cost ratio is low, then selection reduces trait values from any starting point. As benefits increase relative to costs, the potential for positive feedback increases: lower trait values are needed to get over the initial threshold, and the traits evolve to higher equilibrium values.

This threshold is a key step in the origin of synergistic traits and cooperative

symbiosis. Once the threshold is passed, symbionts may evolve through an irreversible stage, which leads to an obligate relationship in which neither partner can live alone (Frank 1995*b;* Maynard Smith and Szathmáry 1995).

Two Loci into One Unit: Codispersal

Mutually beneficial interactions between symbionts occur in many systems. For example, fig trees require specialized wasps for pollination; these wasps complete their life cycle within figs. Leeches have bacterial symbionts that they require to supplement their blood diet; the symbionts depend on leeches for resources and transmission. These symbioses have evolved into highly interdependent systems, yet the partners remain clearly distinct.

Important transitions in the history of life occurred when distinct symbiotic partners melded into a new, higher-level unit (Maynard Smith and Szathmáry 1995). The origin and early evolution of genetic systems has become a model for the formation of new units. In this section, I describe the problem and discuss two alternative pathways for the evolution of symbiotic replicators into complex, well-integrated genomes.

The mutation rate per replicating molecule was probably quite high in early evolution because complex repair enzymes had not yet evolved (Eigen 1971, 1992). The number of mutations per generation in each replicating molecule increases with the size of the molecule. Adaptive evolution can occur only when the rate of increase in fitness caused by selection is greater than the rate of decay in information caused by mutation. Thus, mutation rate sets an upper limit, or ''error threshold,'' on the size of replicating molecules. This creates a paradox because the size limit of early replicators without repair enzymes is too small to code for complex repair enzymes. Complex genomes cannot evolve without repair to lower mutation, and repair cannot evolve without complex genomes.

One solution is a ''multispecies genome,'' with different replicators cooperating to catalyze the reproduction of genomic partners. With cooperative symbiosis, molecule size can remain small while genome size increases. Repair enzymes could be produced cooperatively, allowing genome complexity to increase. Thus, the puzzle is how symbioses among early replicators formed well-integrated communities. Eigen and Schuster's (1979) hypercycle model was the first effort to address this problem.

In a hypercycle with two physically separated loci, *A* and *B,* each locus produces gene products that catalyze the replication of the other locus. The pair of loci, with *A* enhancing *B*'s replication rate and *B* enhancing *A*'s replication, is more efficient and competitive than either replicator reproducing alone. Thus, a cooperative hypercycle can outcompete any individual replicators that do not take part in a cycle. After hypercycles form, the cycles may be packaged into cells to enhance efficiency.

Eigen and Schuster (1979) assumed a positive synergism between *A* and *B* as a preexisting condition for hypercycles. A realistic model must consider how synergism first evolves. The full chain of events in hypercycle evolution is: weak synergism → weak spatial association and correlation → strong synergism → strong spatial binding into cells.

Two different kinds of spatial association influence symbiotic evolution. May-

nard Smith (1979) pointed out the critical role of spatial association within populations of each type of replicator, for example, *B* with *B.* Suppose, for instance, that there is a population of *A*'s and *B*'s mixed together. Initially, there is strong synergism, with all of the *A*'s aiding *B*'s reproduction and, in return, all of the *B*'s catalyzing *A*'s reproduction. Imagine a mutant of *B* that does not reciprocate and, by reducing time or energy devoted to reciprocating, can reproduce faster than other *B*'s. This parasitic mutant can outcompete the cooperative *B*'s because it gains the benefits of *A*'s cooperation but does not bear any cost of returning benefits to *A.*

The tendency for parasitism (virulence) increases as the coefficient of relatedness among the *B*'s declines, as discussed above in the one-locus models. Close spatial association increases relatedness; loose spatial association decreases relatedness. Thus, without the assumption of moderate or strong spatial binding *within* each replicator species, selection favors deterioration to weak synergism from the initial state of strong synergism assumed by Eigen and Schuster.

The associations *between A* and *B* also influence transitions between strong and weak synergism, as discussed above. Statistical associations (linkage disequilibrium) in traits of *A* and *B* make it easier to pass the threshold in figure 1*A.* Once the threshold is passed, the synergistic traits tend to be enhanced. Thus, maintenance of strong synergism does not require continued spatial association between *A* and *B,* and it is self-perpetuating as long as relatedness within replicator populations does not fall too low.

Maynard Smith (1979), Bresch et al. (1980), and Szathmáry (1989) suggested that spatial binding preceded strong synergism, as in the following chain: weak synergism → strong spatial binding into cells → strong synergism. Spatial binding increases the coefficient of relatedness within replicator species and the linkage disequilibrium between species, both favorable for synergism. But close association forces the different kinds of replicator, *A* and *B,* to compete for the same resources. If one assumes that spatial association precedes synergism, then what maintains a mixture of *A* and *B* within cells before synergistic effects? Spatial association does solve the kin selection problem within replicator groups, but must all cooperative symbioses depend on such close spatial association between species?

In summary, two models were proposed for solution to the Eigen paradox of how complex genomes first arose. The original hypercycle model assumed that synergism preceded packaging into cells. Later models, concerned about low relatedness among replicators of the same kind, assumed that packaging preceded synergism. The outcome, in either case, is a cell with two or more kinds of replicator (multiple loci) in which the replicators have biochemically synergistic interactions. This community of replicators formed an early, complex genome. The replicators are physically unlinked and transmitted vertically in each generation.

Distinguishing Vertical Transmission, Reproductive Synchrony, and Codispersal

At first glance, it may seem that protocells, with populations of synergistic replicators, are fully integrated units. Each replicator's success is tied to the suc-

cess of the cell because of the purely vertical transmission. It is necessary, however, to distinguish among several processes.

Codispersal is a measure of the frequency at which two particular replicator molecules are transmitted together. This measure is similar to $1 - \rho$, where ρ is the recombination fraction of population genetics, but it is not necessary for entities to be physically linked. Selection can also create statistical associations (linkage disequilibrium) between pairs of loci that are not physically linked. Linkage disequilibrium occurs when pairs of loci have positive or negative synergistic effects on the reproduction of their groups.

Reproductive synchrony is the temporal binding of replication. Synchronous pairs of replicators cannot compete because, by definition, their reproductive success is correlated. Physical linkage causes reproductive synchrony. But physically linked replicators may recombine, so they do not necessarily codisperse.

These processes describe why vertical transmission does not, by itself, integrate replicators into a single unit. Consider, for example, the single-species models described earlier. There is no reproductive synchrony in the population of replicators within the cell; thus, competition is possible. Indeed, if there is a limited number of copies transmitted to daughter cells, then dispersal of one particular copy is negatively correlated with dispersal of neighboring copies. Codispersal is therefore not guaranteed among individuals within the population because segregation limits transmission to daughter cells. The two-species model is similar, but one must account for synchrony and codispersal both within and between species.

Physical Binding and the Origin of Chromosomes

Physical linkage of two species into one molecule forms a complex chromosome that, to some extent, integrates replicators into higher units. Maynard Smith and Szathmáry (1993) studied the evolution of physical linkage with a simple model. They began with positive synergism between a pair of unlinked species in a protocell. Pairs that became physically linked suffered a cost because, being larger, they replicated more slowly than their independent neighbors. The new chromosome had an advantage because the chance that a daughter cell lacks either species is zero for the large chromosome but can occur when the species are physically separate. A daughter cell that is missing one species may be significantly less fit because it lacks the positive synergistic effect between species. This model illustrates what were probably the key processes in chromosome evolution, but it is limited because the degree of synergism is fixed by assumption rather than being a labile property of two coevolving species.

Physical linkage changes protocells from a community with two distinct species to a population of a single species. With no recombination, the problem reverts to the one-species model with no reproductive synchrony among replicators. Recombination creates a variation on the two-species model, with reproductive synchrony between species but not between chromosomes and partial codispersal between species.

Without physical linkage or some orderly way of guaranteeing codispersal of species, a cell must transmit a pool of replicators so that both species will, with

high probability, be present in daughter cells. Physical linkage allows the number of replicator copies transmitted to progeny to be reduced to one. Cell division can then be tied to the cycle of chromosome replication. This is a model of bacterial genetics. With respect to the main chromosome, the cell is a fully integrated unit. But evolutionary history did not stop there. More species were added to the cell. Originally, species may have been added because of parasitism or because of positive synergistic benefits. In either case, the multispecies problem arose again.

Reproductive Fairness

One pathway to the formation of integrated units is physical linkage and low copy number. An alternative is enforced reproductive synchrony or fairness. The cell cycle of eukaryotes locks the different chromosomes into a rigid pattern of reproductive synchrony and codispersal. Mitosis replicates all chromosomes and transmits them to daughter cells with the same copy number as the parental cell. Meiosis reduces the copy number of each chromosome in half, typically from two to one. This process of segregation reduces the level of codispersal among loci. The probability of codispersal is typically 0.5 for loci on different chromosomes and $1 - \rho$ for loci on the same chromosome, where ρ is the recombination factor.

The segregation process that reduces copy number during meiosis is usually rigidly controlled. Each daughter cell has an equal chance of receiving any particular copy of a chromosome. Thus, the potential conflicts that can arise because of reduced codispersal are mitigated by enforced reproductive fairness. Randomized segregation prevents reproductive bias within the group. The only way for a copy to increase overall success is to enhance the productivity of the group. Reproductive fairness is an integrating force that acts independently from kin selection and codispersal.

The ubiquitous and apparently simple unity of meiotic genetics obscures the fact that we really do not understand how such complex order first originated and is now maintained. Exceptions to reproductive fairness do occur when a chromosome manages to bias success within the genome in its own favor (Lyttle 1991). Segregation bias, or meiotic drive, happens when a particular copy of a chromosome is in more than one-half of the successful gametes, circumventing randomization and reproductive fairness. Such drive occurs in many different organisms but appears to be relatively rare.

Two observations from meiotic drive systems point to interesting features of reproductive fairness. First, certain chromosomes acquire blocks of loci that rarely recombine and therefore codisperse with a very high probability (Lyttle 1991). Meiotic drive is frequently associated with these large blocks of codispersing loci. The mechanisms of drive appear to require cooperation between two or more loci, and large blocks of codispersing loci provide greater opportunity for the creation of internal, physically linked units that compete against other parts of the genome. In genetic language, strong linkage disequilibrium is required to favor synergism between drive loci (Prout et al. 1973; Charlesworth and Hartl 1978).

Haig and Grafen (1991) suggested that recombination is favored because it breaks up blocks of integrated, internal units, preventing potential subversion of reproductive fairness. This is an interesting idea, but it is difficult to know how it can be compared with the many other theories for the evolution of recombination (Maynard Smith 1978). Whether true or not, their idea is intriguing because it calls attention to the unsolved problem of how reproductive fairness is enforced uniformly across all chromosomes.

The second interesting set of observations on drive systems addresses the problem of enforcement, although these observations are not specifically related to recombination. When a chromosome that causes drive is observed, other loci throughout the genome are typically found that repress the drive (Lyttle 1991). The best example is an experiment conducted by Lyttle (1979). He attached a piece of a chromosome that causes meiotic drive to the *Y* chromosome of *Drosophila melanogaster*. He then introduced the attached *Y* drive system into population cages that did not contain major suppressors of drive. Each population accumulated suppressors scattered over much of the genome, each of small effect, which suggests that modifiers evolve rapidly.

Repression of competition by fair meiosis has been widely recognized as an integrating force of eukaryotic genomes. The idea that policing of competition can reduce internal conflict and favor complex, cooperative groupings has been developed in particular for social insects (Ratnieks and Visscher 1989) and more generally by several authors (Leigh 1977; Alexander and Borgia 1978; Dawkins 1982; Alexander 1987; Wilson and Sober 1994).

I developed a formal model for the evolution of policing traits (Frank 1995*a*). This model analyzes an interesting interaction between kin selection and repression of competition. When relatedness is high, kin selection is a strong integrating force, and costly traits that repress competition are generally not favored. As relatedness declines, internal competition increases. Low relatedness is particularly likely when the interaction is between different species, as in symbioses and the evolution of genomes. Under low relatedness situations, there are potentially large benefits for integrating symbionts into a unit. Thus, low relatedness is more conducive than high relatedness to the spread of policing traits and the integration of units via repression of internal competition.

CONTROL OF SYMBIOTIC PARTNERS

The interactions described in the previous sections are all symmetrical; that is, one symbiotic partner cannot dominate the other. The model with repression of competition does assume interference among symbionts, but the policing is a mutual interaction among equals. Many symbioses are asymmetrical, consisting of a large, multicellular host and symbiotic microorganisms. A similar asymmetry occurs between cellular hosts and intracellular symbionts.

I discuss two aspects of asymmetrical symbioses. The first concerns types of control imposed by the host on the mixing patterns of its symbiont. Reduced mixing increases the coefficient of relatedness among symbionts and may, in some cases, increase the codispersal between host and symbiont. These pro-

cesses tend to align the reproductive interests of host and symbiont and integrate them into a single unit. Working against this integration is the Hamilton and May (1977) effect, which favors the symbionts to disperse away from their close relatives within lineages and mix with other lineages. This mixing, favored by symbionts, disrupts the integration of the host-symbiont pair.

Reduced mixing between lineages is, however, not enough for full integration. Processes by which the host manipulates symbiont reproduction and transmission are the second aspect of asymmetrical control. The host can potentially ''domesticate'' the symbionts by aligning reproductive interests and unifying the group. For example, the host may influence the number of symbionts transmitted (segregation) or impose reproductive fairness among the symbionts.

Symbiont Mixing

Control of symbiont mixing has been widely discussed in the context of genomic conflict and the evolution of uniparental inheritance of cytoplasmic elements (Eberhard 1980; Cosmides and Tooby 1981; Hurst 1994). When cytoplasmic lineages mix during syngamy, the relatedness among cytoplasmic elements is reduced. If the host can prevent mixing by imposing uniparental inheritance, then relatedness increases within hosts and lower virulence is favored.

The hosts gain from low mixing and high relatedness of their symbionts. However, Hoekstra (1987) pointed out a complication with the evolution of host control over cytoplasmic mixing. Although reduced mixing would eventually cause symbionts to evolve lower virulence in response to higher relatedness, that evolutionary response would occur over time and would not provide an immediate benefit to an individual host that restricted mixing of its cytoplasmic elements. The benefit of restricted mixing is a delayed benefit to the mean fitness of the host population rather than to an individual host. Thus, a host modifier allele that restricted mixing would not necessarily increase in frequency.

Individual hosts that restricted cytoplasmic mixing would gain an immediate advantage if they could avoid harmful parasites that invade during syngamy (Hoekstra 1990; Hastings 1992). Restricted cytoplasmic mixing is also advantageous when cytoplasmic elements increase expression of their competitive and virulent traits in direct response to local diversity (Hurst 1990; Law and Hutson 1992).

This reasoning about cytoplasmic symbionts applies to a wide range of interactions (Frank 1996*b*). For example, fig trees appear to control the number of wasps that colonize each fig. When the number of colonists is low and relatedness is high within figs, the wasps produce a highly female-biased sex ratio. The female wasps disperse pollen and benefit the fig—males destroy host resources but do not provide any benefit. When more wasps colonize a fig, relatedness drops and the wasps produce more male offspring. Sons are a mother's way to compete against cofounding, unrelated females (Hamilton 1967). The rise in males associated with mixing of wasp lineages reduces the fitness of the host tree (see Frank 1996*b* for further discussion of this example in terms of symbiosis theory).

Hoekstra's (1987) argument for the cytoplasmic example shows that only spe-

cial conditions favor host control of symbiont mixing, in spite of the fact that the hosts would typically gain from restricted mixing. In general, a modifier allele in the host must gain an immediate fitness advantage for controlling symbiont mixing. This occurs if the effects of symbionts within a particular host are directly influenced by the genetic variation among symbionts within that host (Frank 1996*b*).

Domestication

The eukaryotic genome contains genetic elements of diverse phylogenetic origin (Margulis 1981). Those elements were probably infectious symbionts at first but have been domesticated into the host life cycle (Bell 1993). Integration depends on the degree of codispersal, reproductive synchrony, and reproductive fairness. Elements vary in the extent to which they are fully integrated. For example, the mitochondria of some hermaphroditic plants cause abortion of pollen development, which leads to a male-sterile phenotype (Hanson 1991). These male-sterile plants produce more seeds than hermaphrodites (reviewed in Frank 1989).

Mitochondria are usually transmitted to future generations only through ovules and not through pollen, whereas nuclear genes are transmitted equally through pollen and ovules. Thus, a mitochondrion causing male sterility increases its transmission rate to future generations but often decreases the fitness of nuclear genes by reducing the sum of ovule and pollen success. The conflict between mitochondria and nuclear genes occurs because there is only partial codispersal, with opportunity for the mitochondria to increase dispersal at the expense of nuclear genes. Many other examples of conflict between genomic elements are known (Werren et al. 1988; Charlesworth et al. 1994). In spite of these conflicts, the eukaryotic genome is a fairly well-integrated unit, and the history of eukaryotes is a story of intracellular domestication (Bell 1993).

Buss (1987) emphasized a similar tension between conflict and cooperation in the evolution of multicellular organisms. In the cellular models discussed earlier, replicator molecules compete within cells for transmission to future generations. In multicellular organisms, cells may compete for transmission to offspring.

Most multicellular organisms are differentiated into tissues that predominantly contribute to reproduction and tissues that are primarily nonreproductive. This germ-soma distinction creates the potential for reproductive conflict when cells are not genetically identical. Genetically distinct cellular lineages can increase their fitness by gaining preferential access to the germ line. This biasing can increase in frequency even if it partly reduces the overall success of the group.

One way to control renegade cell lineages is with policing traits that enforce a germ-soma split early in development (Buss 1987). This split prevents reproductive bias among lineages during subsequent development. Once the potential for bias has been restricted, a cell lineage can improve its own fitness only by increasing the fitness of the individual. This is another example of how reproductive fairness acts as an integrating force in the formation of units.

Maynard Smith (1988) agreed with Buss's logic about the potential for cell lineage competition, but he argued that metazoans solved their problems of cell

lineage competition by passing through a single-celled stage in each generation. When an individual develops from a single cell, all variation among subsequent cell lineages must arise by de novo mutation. In Maynard Smith's view, such mutations must be sufficiently rare that the genetic relatedness among cells is essentially perfect. Thus, the soma sacrifice reproduction as a natural, altruistic act in favor of their genetically identical germ-line neighbors. Buss recognized the importance of de novo mutations within an individual but argued that these would be sufficiently common to favor significant cell lineage competition and policing. Michod (1997) recently developed mathematical models that support Buss's point of view in this debate.

The mechanisms by which hosts transmit their symbionts are influenced by the same problems as germ-soma differentiation (Frank 1996*a*). The most common pathway of transmission for beneficial symbionts is from mother to offspring via the eggs (Buchner 1965). This pathway of vertical transmission inevitably limits the number of symbionts that succeed in passage to the next generation. This limitation can potentially separate symbionts into distinct germ and soma in much the same way as metazoans separate cellular lineages into reproductive and nonreproductive tissues.

Two additional factors influence symbiont transmission when compared with cellular differentiation in metazoans. First, when symbionts are transmitted vertically, from parent to offspring of the host, hundreds or thousands of symbiont cells typically infect each offspring. This large founding population contrasts with the single-celled bottleneck typical of a newborn metazoan. Thus, a host develops with a potentially diverse set of symbionts. Second, symbionts may infect a host horizontally—from another host individual or from the environment. Such mixing of symbiont lineages greatly decreases relatedness within hosts and favors within-host competition. Selection will always favor the symbionts to transmit partly by horizontal routes to enhance their reproductive rate and to avoid competition against relatives within the host (Hamilton and May 1977; Frank 1994*b*).

Hosts can control symbionts by imposing a germ-soma split among the population of symbionts that develop within the host. Somatic symbionts, denied access to the germ line, can only increase their fitness by enhancing the success of the host and thereby increasing the reproductive rate of their kin in the germ line. Reproductive fairness is imposed among symbionts if, early in host development, a random subset of symbionts is sequestered for the germ line. Buchner's (1965) review of transmission of insect symbionts provides considerable anecdotal evidence to evaluate this theory. Buchner was not concerned with the theoretical ideas discussed here, yet he concluded his overview by noting a common progression within host lineages of limiting the transmissible symbionts to narrower subsets from spatially confined locations.

I reviewed these concepts and related observations elsewhere (Frank 1996*a*). Here I briefly summarize one example in which there is a clear separation of germ and soma.

The sucking louse *Haematopinus* divides its symbionts into transmissible and somatic forms during early development. In the female embryos, the cells that

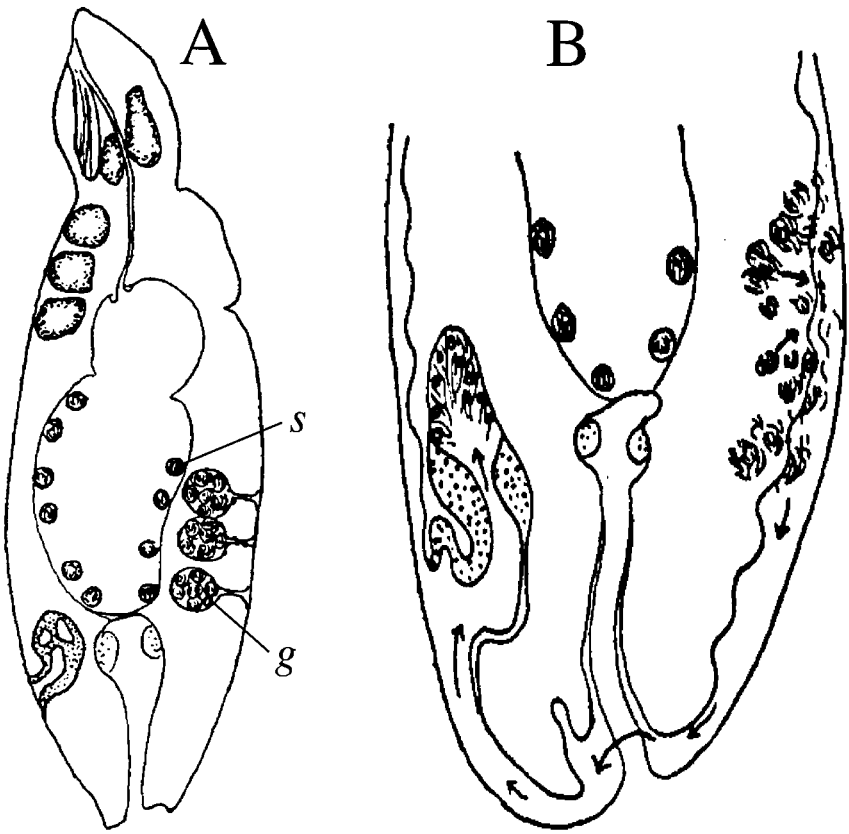

FIG. 2.—The separation of symbionts into germ and soma in the sucking louse, *Haematopinus suis* (from Buchner 1953). In *A*, the symbionts are separated early in development into the somatic (*s*) population contained in storage organs lining the gut and the germ-line (*g*) population temporarily stored in special organs hanging from dorsal side of the larva. In *B*, germ-line storage organs deteriorate. The symbionts are released and flow toward the developing ovaries. The direction of movement is shown by the arrows.

contain symbionts separate into two groups (fig. 2*A*). One set migrates to the midgut. This group is eventually contained in specialized gut organs, from which the symbionts apparently contribute essential vitamins to the host. The other set moves under the upper surface and forms storage aggregations that hang down into the body cavity.

The storage organs degenerate as the third larval molt begins, releasing symbionts into the molting fluid between the old and new cuticle (fig. 2*B*). The symbionts move with the molting fluid to an opening that leads to the developing ovaries. Each of the ovarioles differentiates a group of prehensile cells that extend toward the incoming symbionts. The symbionts are captured and then moved into a cushion of cells that is pushed between the ovarioles and the ovi-

duct. Each egg is then infected as it develops. The somatic symbionts stored near the gut are apparently never transmitted.

This clear separation of germ and soma does not occur in all cases of symbiont transmission. Indeed, the subject is fascinating because of the great diversity of transmission patterns. Yet, from Buchner's conclusion, localization of transmission forms does appear to be common, and perhaps, also as suggested by Buchner, there is an evolutionary trend toward increasing localization for particular host-symbiont associations.

In summary, host-symbiont interactions provide a rich subject for empirical study. There is great diversity in transmission patterns and wide variation in the evolutionary age and degree of integration among extant host-symbiont relationships.

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