

Chapter 24

Modelling the Evolution of Mutualistic Symbioses

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Abstract

Mutualistic microbial symbioses are one of the key innovations in the evolution of biological diversity, enabling the expansion of species' niches and the production of sophisticated structures such as the eukaryotic cell. For some of the best-studied cases, we are beginning to have network models of symbiotic metabolism, but this work is in its infancy and has not been developed with an evolutionary perspective. However, theoreticians have long been interested in how these symbioses arise and persist and have applied modelling approaches from economics, evolution, ecology, and sociobiology to a number of fundamental questions. We provide an overview of these questions, followed by specific modelling examples. We cover economic game theory, including the Prisoner's Dilemma, the Snowdrift game, and biological markets. We also describe the eco-evolutionary framework of adaptive dynamics, inclusive fitness, and population genetic models. We aim to provide insight into the strengths and weaknesses of each approach and into how current evolutionary methods can benefit an understanding of the mechanistic basis of host–symbiont interactions elucidated by molecular network models.

Key words: Symbiosis, Mutualism, Game theory, Adaptive dynamics, Inclusive fitness, Biological markets, Population genetics, Cooperative bargaining

1. Introduction

Mutualistic microbial symbioses have played a fundamental role in the evolution and diversification of life. These widespread interactions range from the ancient symbiotic merger of prokaryotic lineages in eukaryotes, to plant colonization of land assisted by fungi, to bacteria that extend the metabolic capabilities of their animal and plant hosts (1–7). The advantage of mutualistic symbiosis is that each species cooperates by contributing commodities that the partner species cannot (cheaply) produce itself, resulting in mutual benefit. We define cooperation broadly as any action that increases the fitness of the recipient (8). Some authors require that cooperation be selected for because of the fitness benefits provided to others (9); we feel that this condition is overly restrictive, not to mention extremely difficult to demonstrate empirically

Table 1
Definitions of terms

Term	Definition
Cooperation	Action by one individual that increases the fitness of a recipient individual (8)
Altruism	Cooperation with a fitness cost to the actor
By-product cooperation	Cooperation without a fitness cost to the actor (8, 71)
Mutualism	Reciprocal cooperation between individuals of different species
Symbiosis	An interaction in which an individual spends a significant portion of its lifecycle within or in close association with an individual of another species
Obligate/facultative symbiosis	Partners must associate with one another/do not have to associate to survive or reproduce
Vertical/horizontal transmission	Symbionts are transmitted from parent to offspring/through the environment between non-relatives
Partner choice	Individuals distinguish between potential partners and interact with those that will provide higher benefits (22)
Partner fidelity feedback	Partners engage in repeated interactions, such that improving the fitness of the partner increases its ability to provide rewards (8)
Sanctions	Inferior partners are not rewarded, or the interaction with inferior partners is terminated (23)

(definitions for this chapter are summarized in Table 1). When cooperation entails a fitness cost to the actor, there is an intrinsic conflict of interest between partners, as each could increase its fitness by giving less or taking more. Indeed, studies of natural symbioses have found that symbiont behaviour varies continuously from mutualistic to parasitic (10) and that hosts can cheat their symbionts through enslavement (11). The conflict of interest can also take the form of a “tragedy of the commons” when multiple symbionts interact with the host, as each symbiont could exploit the cooperation of the others (12).

1.1. Overview of Mutualistic Bacterial Symbioses

Mutualistic symbioses are typically comprised of a multicellular “host” and a microbial “symbiont.” We focus here on bacterial symbionts that provide some metabolic capability that their host lacks. A prominent example is nitrogen-fixation by alpha-proteobacteria and cyanobacteria that associate with leguminous plants, lichens, and insects (5, 13). Bacterial symbionts that associate with insects are known to synthesize essential amino acids or B vitamins, to recycle nitrogen, and to expand the host’s diet by

degrading cellulose or detoxifying plant toxins (14). Photosynthesis by cyanobacteria is used as a nutritional strategy by some fungi, forming holobionts called lichens (15). Symbionts can also help protect their hosts, for example *Vibrio fischeri*, which are housed in a light organ of their host squids and provide chemiluminescence as camouflage (16), and a number of facultative bacteria that protect aphids from attack by fungi and parasitoids as well as heat stress (17). It is common for hosts to harbour multiple symbiont species, such as the case of the sharpshooter and its two symbionts, *Baumannia* and *Sulcia*, that serve complementary metabolic functions (18).

1.2. Network Models of Symbiosis

While metabolic models have been constructed only for the best-studied symbioses, it is already clear that these models can give considerable insight into the interaction between hosts and symbionts (for related modelling approaches, see Chapter 6 by Arita, and Chapter 20 by Behre et al.). Though metabolic network models have not been used to test evolutionary hypotheses, these models can provide estimates of the costs of cooperating with the host, identify potential conflicts of interest between host and symbionts, and suggest previously unidentified benefits to the host. We are aware only of network models constructed for *Buchnera aphidicola*, an aphid symbiont, and two species of rhizobia. A constraint based flux-balance analysis (FBA) model was developed for *B. aphidicola* containing 196 gene products with 240 metabolic compounds and 263 reactions that was parameterized with empirical data on export rates of essential amino acids (19). This model predicts that 94% of *B. aphidicola* genes are essential for growth and shows that amino acid export to the host is costly in terms of biomass production, suggesting that indirect selection for increased host fitness via vertical transmission has shaped this microbe's metabolism. *Rhizobium etli*, a symbiont of pea, has a metabolic network constructed of 363 genes with 371 metabolic compounds and 387 reactions (20). The objective function used to optimize fluxes across this network included amino acid cycling, ammonium export, and the accumulation of poly-beta-hydroxybutyrate (PHB) and glycogen as energy stores. FBA of *in silico* gene deletions gave several predictions consistent with experimental data; one intriguing result that suggests fitness conflict between host and symbiont is that removing the ability to store PHB and/or glycogen increases nitrogen fixation rates. A symbiosis interactome model including 440 proteins with 1,041 interactions was constructed for the *Medicago* symbiont *Sinorhizobium meliloti* (21). This model was used to predict novel symbiotic proteins, of which three out of four were validated experimentally. These models represent an important first step in understanding the mechanistic basis of costs and benefits in mutualistic symbioses.

1.3. Models of Mutualistic Symbiosis

Models attempting to explain the origin and maintenance of mutualistic symbioses typically investigate the question of how hosts and symbionts resist the “temptation to defect,” i.e. to exploit a cooperative partner. Cooperation within and between species can be favoured by several mechanisms: (1) partner choice, the selection of one or multiple individuals to associate with on the basis of signals that reflect future cooperative investment (22); (2) partner fidelity, the association of individuals over repeated interactions, such that investment in the partner increases the cooperative benefits received in future iterations of the interaction (8); (3) sanctions, a form of punishment for poorly performing partners in which benefits are withheld or the interaction is terminated (23); and (4) vertical transmission of symbionts or spatially structured interactions, which can align fitness interests through multilevel selection (24). We introduce the modelling approaches that have been used to study mutualistic symbioses, summarized in Table 2. We discuss the context in which each model type is used and illustrate the methods with examples from the literature in Subheading 2; models are presented from the most simple to the most biologically realistic. In Subheading 3 we briefly summarize software used in this research and we conclude in Subheading 4 with future perspectives, including connecting evolutionary models to molecular network models, and guidelines for how to select a modelling approach.

2. Modelling Approaches

2.1. Game Theory

Game theory was originally developed by economists to explain how rational actors should behave in social interactions (25). The central concept is the “unbeatable strategy” that maximizes personal benefit against all potential partner strategies, also known as the “evolutionarily stable strategy” (ESS). In models of mutualistic symbioses, players may either “cooperate” or “cheat,” depending on the amount of commodity they contribute to their partners. Game theoretic models are the simplest type of phenotypic model: the genetic basis of traits is not specified and population dynamics are typically assumed to be constant. Nevertheless, these simplifications allow for analysis of otherwise intractably complex games and strategies.

2.1.1. The Prisoner’s Dilemma

The classic game used to ask how intra- and interspecific cooperation can evolve is the Prisoner’s Dilemma (26, 27). As demonstrated in Fig. 1, the ESS of this game is mutual cheating, but two modifications allow cooperators to persist. First, iterated games between pairs of players can favour cooperation by allowing current investment to depend on the partner’s past behaviour.

Table 2
A comparison of modelling approaches

Type	Model	Pros	Cons	References
Economic	Game Theory Biological Markets	Simple models with many extensions (e.g., spatial structure; repeated, flexible interactions) Focus is on partner choice and negotiation	Typically no ecological dynamics and no genetics Typically no ecological dynamics and no genetics	(27, 72, 73) (22, 37)
Eco-evolutionary	Adaptive Dynamics	Fitness depends on population dynamics; Analytic characterization of equilibria	No genetic basis; assumes separation of ecological and evolutionary time scales	(74)
Genetic	Inclusive Fitness Population Genetics	Considers intraspecific interactions within the symbiosis Tracks allele frequencies; explicit genetic architecture	Typically no ecological dynamics Typically no ecological dynamics	(24, 75) (55, 76)

	Cooperator $S (I_S > 0)$	Cheater $S (I_S = 0)$
Cooperator $H (I_H > 0)$	$b(I_S) - c(I_H), b(I_H) - c(I_S)$	$-c(I_H), -b(I_H)$
Cheater $H (I_H = 0)$	$b(I_S), -c(I_S)$	0,0

Fig. 1. Payoff matrix for the Prisoner's Dilemma game. The payoffs for the host (H) and the symbiont (S) depend on the amounts each player invests in the interaction (I). Investment by each player gives a benefit ($b(I)$) to the partner at a cost ($c(I)$) to itself. In this game, mutual cooperation yields a higher payoff than mutual cheating. If its partner cooperates, a player could gain more by investing nothing, but cooperating with a cheater is costly.

Second, spatial structure can favour cooperation by causing repeated interactions with the same partner, or its close relatives, who are likely to share the same strategy. An example that combines these conceptual mechanisms is the model of Doebeli and Knowlton (28). The benefits ($b(I)$) and costs ($c(I)$) of the amount invested (I) are:

$$b(I) = b_0(1 - e^{-b_1 I})$$

$$c(I) = c_0 I$$

where coefficients b_0 , b_1 , and c_0 determine the shape of the benefit and cost curves. These benefits and costs yield the initial payoffs for the host ($P_H[1]$) and symbiont ($P_S[1]$) with strategies consisting of the initial investment amounts ($I_H[1]$ and $I_S[1]$):

$$P_H[1] = b_0(1 - e^{-b_1 I_S[1]}) - c_0 I_H[1]$$

$$P_S[1] = b_0(1 - e^{-b_1 I_H[1]}) - c_0 I_S[1]$$

The reward rates (b_H and b_S) determine the effect of the previous payoff on investment in the next iteration, so that investment by one partner is rewarded by investment by the other partner:

$$I_H[2] = I_H[1] + b_H P_H[1]$$

$$I_S[2] = I_S[1] + b_S P_S[1].$$

This type of flexible strategy is further discussed in Note 1. The evolution of cooperation can then be modelled by replacing resident trait values with mutant trait values whenever individuals with a mutated trait perform better than the resident. In non-spatial simulations, investment by both species evolves to zero. However, if hosts and symbionts interact only with neighbours, investment and reward rate increase through coevolution, maintaining the mutualism.

2.1.2. Summary and Extensions

While iterated interactions between the same individuals are unlikely to be a realistic model of bacterial symbionts, which

typically associate for multiple bacterial generations within their hosts, these simplified models provide valuable intuition for the processes that enable mutualism to evolve. In this case, the key ingredients are prolonged interactions and spatial structure that act to couple host and symbiont fitness. Another two-player cooperation game is the Hawk–Dove or Snowdrift game, which is the same as the Prisoner’s Dilemma except that the payoff from mutual cheating is worse than that from being cheated; thus, even when the partner defects, the best strategy is to cooperate. This game may more accurately describe interactions in which players cooperate by producing a public good (29), making it relevant for cases with a potential “tragedy of the commons.” Frequency-dependent selection is generated even in single-round games, such that cooperators and cheaters coexist in the absence of spatial structure (30). Spatial structure has the opposite effect on cooperation in the Snowdrift game as in the Prisoner’s Dilemma, with lower frequencies of cooperation than in non-structured populations (29).

2.2. Biological Markets

The games described above assume that individuals are constrained to interact with a given partner. However, individuals often have control over whether they interact and which partners, if any, are chosen. In these cases, commodity exchange resembles a market where many potential partners contribute to the supply of and demand for commodities. In an idealized economic model of resource trade, the divergent capacities of hosts and symbionts for resource acquisition can result in “comparative advantage”, i.e. trading the resource that each species can obtain cheaply to enable net benefit for both (31). However, the game theoretic considerations above suggest that additional mechanisms are required to ensure fair trade.

2.2.1. Cooperative Bargaining in the *Rhizobia–Legume Symbiosis*

Negotiation is a way for partners to reach a mutually satisfactory solution and can be modelled through cooperative bargaining games. In these games, individuals do not exchange commodities until the partner makes an acceptable offer (32, 33). Akçay and Roughgarden (34) take a cooperative bargaining approach to address the evolution of resource exchange in the rhizobia–legume symbiosis. In their model, host-plant growth (g_H) depends on the simultaneous amino acid flux (A_H) and carbon flux (C_H), while rhizobia growth (g_S) depends on the allocation of carbon to the nodules (C_S) minus the amount of energy used to fix nitrogen that is exported to the plant (A_S):

$$g_H = A_H C_H,$$

$$g_S = C_S - A_S.$$

A given set of growth rates, $G = (g_H, g_S)$, is termed a “contract”; altered nutrient fluxes cause different growth rates and are considered “offers”, $G' = (g'_H, g'_S)$. Offers that increase both partners’ growth are accepted immediately. If an offer decreases one partner’s growth, the host and symbiont play a “war of attrition”. The length of time each partner stays in the game is relative to (1) the cost of not receiving mutualistic benefits and (2) the benefit received under its preferred contract. This leads to the condition that G' will be accepted if $g'_H g'_S > g_H g_S$. Thus, the host and symbiont reach a “Nash Bargaining Solution” defined as the investment level that maximizes their joint payoff.

2.2.2. Summary and Extensions

Cooperative bargaining is an attractive model for symbiosis as it provides a mechanism for the resolution of conflicts over fair trading that arise in biological markets. Resource exchange fluxes between host and symbiont represent a candidate mechanism for this type of interaction (35). Other models incorporate aspects of negotiation through the formation and/or termination of the interaction. This “partner choice” enables hosts and symbionts to preferentially interact with cooperators (22). Partner choice requires that there be an abundance of partners to choose among and that individuals be able to recognize which partners will be cooperators. The rhizobia–legume symbiosis meets these conditions (36), and while the mechanism is unknown it may involve variation in host–symbiont signalling during the formation of symbiosis. To advertise their cooperativeness, players may “bid” for the commodity offered by the partner species (37). Alternatively, individuals may simply terminate poor interactions and acquire new partners (38, 39). Hosts may have an advantage here, since bacterial symbionts are likely to be killed by the host’s defence responses if the interaction goes poorly and the bacteria may not be able to disperse from their hosts if they are being exploited.

2.3. Adaptive Dynamics

Whether a mutant can successfully invade a population is likely to depend on the population densities and traits of both the focal and interacting species. As the population dynamics themselves depend on the phenotypes present, trait evolution can feed-back into the ecological dynamics of a species, producing the coupled ecological and evolutionary dynamics that are the basis of the “Adaptive Dynamics” framework (40, 41). To manage the increased complexity of eco-evolutionary feedbacks, these models simplify evolution by ignoring the genetic basis of traits and assuming that ecological dynamics reach equilibrium in between mutation events. Note 2 further discusses modelling phenotypes rather than genotypes and Note 3 discusses the potential importance of population dynamics. Adaptive dynamics models differ from most other approaches in that they explicitly test for disruptive selection leading populations to become polymorphic

through “evolutionary branching.” This outcome occurs when fitness is nonlinear and frequency-dependent, such that rare phenotypes have an advantage. In other cases, the adaptive dynamics approach demonstrates that species evolve to ESS trait values identical to those attained in other phenotypic models.

2.3.1. Adaptive Dynamics of Obligate Mutualisms

Ferrière et al. (42) use adaptive dynamics to investigate the evolution of commodity exchange between two obligate mutualist species. The ecological dynamics of two mutualists with population densities H and S are given by per-capita growth rates:

$$\begin{aligned} \frac{1}{H} \left(\frac{dH}{dt} \right) &= -g_H(I_H) - d_H H + S I_S (1 - \alpha H), \\ \frac{1}{S} \left(\frac{dS}{dt} \right) &= -g_S(I_S) - d_S S + H I_H (1 - \beta S), \end{aligned}$$

where I_H and I_S are the amount of commodities traded between species. The per-capita growth rates are decreased by investment in these commodities ($-g_H(I_H)$ and $-g_S(I_S)$) and by intraspecific competition ($-d_H H$ and $-d_S S$). Meanwhile, the population growth rates are increased by receiving commodities from the partner species ($S I_S$ and $H I_H$), modified by intraspecific competition ($(1 - \alpha H)$ and $(1 - \beta S)$). For given trait values, both partners reach ecological equilibrium densities H^* and S^* .

The evolution of commodity investment proceeds by considering the fate of rare mutations in the investment traits of each species. The growth rate of a rare mutant is given by the invasion fitnesses (w_H and w_S) of mutants with phenotypes I_{Hmut} and I_{Smut} at the ecological equilibrium:

$$\begin{aligned} w_H(I_{Hmut}, I_H, I_S) &= -g_H(I_{Hmut}) - d_H H^* + I_S [1 - \alpha(I_{Hmut} - I_H) H^*] S^*, \\ w_S(I_{Smut}, I_H, I_S) &= -g_S(I_{Smut}) - d_S S^* + I_H [1 - \beta(I_{Smut} - I_H) S^*] H^*. \end{aligned}$$

In addition to affecting each species’ intrinsic growth rate, the amount invested into mutualism affects intraspecific competition for partners, described by the functions α and β . Competition is symmetric when α and β are constants and asymmetric when they are functions of the mutation size and direction. The direction of coevolution is found by calculating how invasion fitness changes as a function of the mutant trait; setting these fitness gradients to zero gives the coevolutionary outcome:

$$\begin{aligned} \left. \frac{\partial w_H}{\partial I_{Hmut}} \right|_{I_{Hmut}=I_H} &= -g'_H(I_H) + \alpha' I_S H^* S^* = 0, \\ \left. \frac{\partial w_S}{\partial I_{Smut}} \right|_{I_{Smut}=I_S} &= -g'_S(I_S) + \beta' I_H H^* S^* = 0. \end{aligned}$$

The points that satisfy each equality are the trait values that the species evolves towards and can be visualized as evolutionary

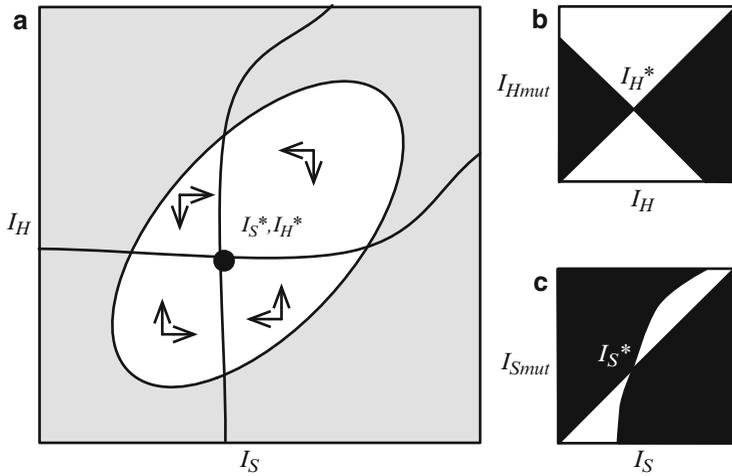


Fig. 2. The adaptive dynamics approach. (a) Diagram of the ecological and evolutionary space with respect to host and symbiont levels of investment (I_H and I_S). The species coexist at intermediate investment levels (*white*), but go extinct when investment is too high or too low (*grey*). Evolutionary isoclines (*solid lines*) are the set of trait values that each species evolves towards. The intersection of these isoclines (I_H^* , I_S^*) is the coevolutionary singularity; in this case, it is an attractor, as shown by the vectors of the selection gradient. The evolutionary process can be further visualized using “pairwise invasibility plots” for the host (b) and the symbiont (c). These plots show the sign of the invasion fitness of a rare mutant in a resident population, given that the trait of the partner species is fixed at the coevolutionary singular point. Combinations of mutant and resident trait values at which the mutant can invade the population are *black*; those at which it cannot invade are *white*. In (b), when resident investment (I_H) is above I_H^* , mutants with lower investment can invade (points below the diagonal are *black*); conversely, if I_H is below I_H^* , mutants with higher values can invade (points above the diagonal are *black*). At the intersection of these regions, no strategy can invade (the areas above and below the diagonal are *white*), i.e. this is an ESS. However, in (c), the symbiont exhibits different dynamics; at the convergent point I_S^* , mutants with any other investment level can invade (the areas above and below the diagonal are *black*). Consequently, the population experiences disruptive selection that leads to the emergence of polymorphism through “evolutionary branching”.

isoclines (Fig. 2a). Where these evolutionary isoclines intersect, there is a coevolutionary singularity (43) (Fig. 2) that the species will evolve to if it is ecologically feasible. If competition is symmetric, α' and β' are zero, therefore investment in mutualism evolves to zero and both obligate mutualists go extinct. When competition is asymmetric and gives better partners a moderate competitive advantage, the trait values in each species evolve to the evolutionary singular point. This point can either be (1) an ESS (Fig. 2b) and evolution will halt or (2) an “evolutionary branching point” (Fig. 2c) and the species will become polymorphic. In this model, the type of singular point depends on whether investment increases or decreases the competitive advantage and whether the costs of investment increase or decrease with investment level. Measuring the average level of investment after evolutionary branching shows that polymorphism is beneficial for the mutualism overall, as highly cooperative partners more than compensate for cheaters.

2.3.2. Summary and Extensions

This model makes the intriguing prediction that diversification of hosts and/or symbionts increases the total amount of resources invested in mutualism, and supports the idea that asymmetric investment into partners based on their cooperativeness (e.g. through partner choice) is important in order for obligate mutualisms to evolve. While most symbiosis models examine how the level of cooperation evolves, other important questions are how vertical transmission and obligate symbioses can evolve from interactions that presumably began as horizontally acquired and facultative. Adaptive dynamics models predict that if avoiding infection is costly to the host, then vertical transmission of symbionts is favoured, and, furthermore, that vertical transmission favours the evolution of dependency (44).

2.4. Inclusive Fitness

Even if cooperation is not reciprocated, cooperative genes can receive indirect benefits by helping relatives. This concept is termed “inclusive fitness” and dates back to Hamilton (45), who showed that for costly helping behaviour to be selected, the costs (c) must be less than the benefits (b) weighted by the average relatedness between actor and recipient (r), i.e. $br - c > 0$. Inclusive fitness models use this relationship to determine whether selection can favour cooperative traits that do not directly aid the actor. These models typically do not specify the genetic basis for cooperative traits, but rather use Hamilton’s relatedness parameter (r), which can be understood as the proportion of shared genes between actor and recipient and is defined more formally as a phenotypic or genotypic regression (46). This general formulation of inclusive fitness theory has been widely applied to study cooperation and conflict in bacteria (47).

2.4.1. Inclusive Fitness of Symbiont–Symbiont Conflict

West et al. (23) take an inclusive fitness approach to determine the role of intraspecific interactions when multiple related symbionts interact with a single host, such as nitrogen-fixing rhizobium bacteria interacting with a legume host-plant. Without allowing the plant strategy to evolve, they consider how host sanctions influence the evolution of symbiont investment. Rhizobium fitness is a function of nitrogen-fixation strategy, I_S : $w_S = I_H(1 - I_S)f(I_S)$, where host investment is a linear function of symbiont strategy ($I_H = a + I_S$) and $f(I_S)$ is the effect of host sanctions on symbiont fitness. The parameter a controls the importance of symbiotically fixed nitrogen to plant fitness.

Differentiating fitness (w_S) with respect to nitrogen-fixation rate (I_S) and using the regression definition of relatedness (r) between rhizobia that infect different nodules on the same plant allows the ESS level of nitrogen-fixation to be calculated as

$$I_S^* = 1 - 2a + r + \sqrt{(4a - 4a^2 + (1 + r)^2)/2(2 + r)},$$

which is an increasing function of r . Comparing models with sanctions on individual nodules versus the case where plant resources are distributed evenly across the nodules of a plant demonstrates that nodule sanctions dramatically increase the level of N-fixation.

2.4.2. Summary and Extensions

This model demonstrates that sanctions can maintain much higher levels of symbiont cooperation than kin selection alone, providing a mechanism to avert the “tragedy of the commons” when multiple symbionts infect a host. This approach can also be used to model host and symbiont coevolution if relatedness is interpreted as genetic covariance (24). The regression between mutualist genotypes across partner species, r , can be positive due to spatial structure (28) or partner choice (22). In the extended formulation of Frank (24), the condition for host investment I_H to increase is: $b_1 r_{I_H, I_H} + b_2 r_{I_S, I_H} - c > 0$, where r_{I_H, I_H} is the regression of sub-population host investment on individual host investment, r_{I_S, I_H} is the regression of sub-population symbiont investment on individual symbiont investment, c is the cost to the individual host, and the b_1 and b_2 are the respective benefits. Frank’s model (24) demonstrates that spatial structure allows positive correlations between mutualist species to evolve through positive fitness feedbacks acting in local populations. This is similar to multilevel selection models, but explicit models incorporating within- and between-host selection on symbiont traits have only been explored thus far in pathogenic systems (48).

2.5. Population Genetics

Population genetic models differ from the phenotypic modelling approaches described above in that the genetic basis of mutualistic behaviour is specified (see Note 2). The dynamics of genetic models can give insight into the consequences of epistatic selection, which captures how alleles in the two species interact with one another to give non-additive fitness effects. Many population genetic models, however, assume simple single-gene haploid or diploid inheritance, making them similar to models where the genetics are unspecified (49–52). Furthermore, these models typically do not incorporate population dynamics, focusing instead on aspects of the evolutionary process such as rates of adaptation, fixation probabilities of beneficial alleles, and the existence of balanced polymorphisms. However, they do allow evolutionary processes to occur on the same time scale as ecological dynamics and might be better suited to cases of high mutation frequency.

2.5.1. Population Genetics of Coral Symbioses

Day et al. (53) develop a population genetic model to describe how coevolution between corals and zooxanthellae may influence coral bleaching. Although zooxanthellae are photosynthetic dinoflagellates, this model is readily applicable to any facultative symbiosis involving a host and a bacterial partner. Their model

demonstrates how ecological and genetic models can be combined. Coral hosts (H) and zooxanthellae symbionts (S) can reproduce both in free-living form and in their associated “holobiont” form (M). One way that bleaching of the holobiont, i.e. failure of the symbiosis, occurs is through dissociation at rate ξ . Hosts and symbionts associate to form new holobionts at rate γ . The population dynamics are thus:

$$\begin{aligned}dM/dt &= g_M M - \xi M + \gamma HS, \\dH/dt &= \xi M + g_H H - \gamma HS, \\dS/dt &= \xi M + g_S S - \gamma HS.\end{aligned}$$

The growth rate of hosts (g_H) is assumed to be negative, while the growth rates of holobionts (g_M) and symbionts (g_S) include logistic density dependence. Both host and symbiont are assumed to be haploid, with a single di-allelic locus that influences the holobiont dissociation threshold through ξ . The holobiont population dynamics can depend on host and symbiont genotypes through the growth parameter (g_M) and the rate of dissociation (ξ). There can be both an additive effect of the genotypes as well as an epistatic interaction term.

The model can be simplified by assuming that the alleles that determine the tolerance of the symbiosis do not affect free-living growth rates. Selection on host and symbiont alleles is described by the parameters w_H and w_S . Under a purely additive model, the host and symbiont allele frequencies (p_{HM} and p_{SM}) in the holobiont are given by:

$$\begin{aligned}dp_{HM}/dt &= p_{HM}(1 - p_{HM})w_H + Dw_S, \\dp_{SM}/dt &= p_{SM}(1 - p_{SM})w_S + Dw_H,\end{aligned}$$

where D is the interspecific linkage disequilibrium, whose dynamics are given by

$$dD/dt = D[(1 - 2p_{HM})w_H + (1 - 2p_{SM})w_S].$$

Thus, resistance alleles experience not only direct selection, but also indirect selection due to associations with the resistance allele in the other species. The type of genetic effect is important to the evolutionary outcome. With additive genetic effects, interspecific linkage disequilibrium decays and the partners evolve independently. Alternatively, positive epistasis can occur, with the strongest bleaching tolerance when both resistance alleles are present. Increasing linkage between partners’ genotypes causes indirect selection to accelerate the evolution of bleaching tolerance. On the other hand, negative epistasis occurs when only a single resistance allele in either host or symbiont is sufficient for bleaching tolerance. In this case, negative genetic correlations between host and symbiont evolve and indirect selection slows the evolution of tolerance.

2.5.2. Summary and Extensions

This example shows that even simplified genetic systems can lead to complex models when multiple species are interacting in an ecological framework. In particular, it demonstrates that epistasis between species can impact the resilience of the symbiosis. More genetically complex models have been developed, such as the class of multi-locus population genetic models (e.g. 54). Analysis of such models based on different types of ecological interactions conclude that only a single polymorphic locus can be maintained with competitive or mutualistic interactions, while host–pathogen interactions yield a variety of outcomes including limit cycles and chaotic allele dynamics (55). Another type of population genetic model considers the combined action of genetic drift and selection; an application of this technique to the aphid-*Buchnera* symbiosis demonstrates that host population size and the number of symbionts transmitted determines the rate of fixation of deleterious, beneficial, and selfish mutations (56).

3. Available Software

While there are no dedicated software packages for evolutionary models of symbiosis, Mathematica (57) is widely used for its ability to perform symbolic mathematics. Simulations can be run in any programming language, but Matlab (58) has user-friendly debugging routines, R (59) has a wide array of built-in statistical distributions, and C (60)/C++ (61) are unmatched for their speed and usability. Meanwhile, an extensive range of programs have been developed for individual- or agent-based simulations, which track the behaviour and status of individuals following programmed rules (reviewed in ref. 62).

4. Perspectives

Thus far, models of the evolution of mutualistic symbioses have focused on broad and relatively general questions: (1) how do species overcome the temptation to defect? (2) how is the tragedy of the commons averted when multiple symbionts interact with a host? and (3) how do symbioses become vertically transmitted and/or obligate? We look forward to the integration of different modelling approaches and a more complete synthesis of how different mechanisms shape these interactions (e.g. 63).

Meanwhile, the applicability of these evolutionary models to biological systems can be dramatically improved by understanding the mechanisms underlying cooperation. For example, our growing understanding of the genetic basis of symbioses makes it

possible to develop evolutionary models with parameterizations based on molecular and functional data (64–66). An area ripe for integration is the use of metabolic and protein–protein networks to establish costs and benefits of different strategies and identify the molecular trade-offs that shape symbiosis evolution. Combining network models with existing evolutionary approaches will enable us to make coevolutionary predictions for real-world symbioses, including under global change, and to design novel symbioses. Understanding the structure of these networks may also enable predictions about the speed and feasibility of evolutionary change to the interaction, such as the conditions that would lead mutualistic symbionts to transition into organelles or pathogens. Empirically parameterized models will provide insight into studies of experimental evolution, where the effects of perturbations in the structure of interactions can be tested, molecular coevolution, in order to detect cross-genome epistatic selection, and even comparative phylogenetics, to test hypotheses of diversification and extinction rates with respect to patterns of symbioses (e.g. 67).

5. Notes

When modelling the evolution of a symbiosis, it is important to combine simple analytical equations with more complex simulations as a means of cross-validating the robustness of assumptions and conclusions. In addition, several key decisions must be made, including:

1. Phenotype or Genotype? Phenotypic models that assume quantitative traits are simpler and are likely to give the same results as a single-locus haploid genetic model. Thus, they may be sufficient in many cases. However, genetic models can provide important insight if there is a non-additive interaction between alleles of host and symbiont. They can also model situations where evolution occurs on the same time-scale as ecological dynamics.
2. Constant or Dynamic Populations? When symbioses involve non-linear cost and benefit functions, the interactions can be strongly dependent on population densities. Furthermore, interactions that are sometimes or always pathogenic tend to have non-equilibrium population dynamics. In these cases, models that explicitly consider population dynamics will likely give the most insight. Exceptions might be facultative symbioses, wherein population densities are largely determined by other factors.

3. Fixed or Flexible Strategies? Species may have very different options for how they interact. At the most basic level, all models assume that evolving species either invest in the interaction or not. The investment level may be constant or updated over repeated interactions. Additionally, species may have the potential to choose whether to interact at all, what partner(s) to interact with, and how long to interact for. Partners may also communicate to advertise their cooperativeness or to negotiate. Finally, hosts may be able to impose sanctions against cheaters and to control symbiont transmission mode.

In the course of modelling, a number of problems can be encountered. These include the classification of an evolutionary equilibrium (just because it exists does not mean it can be reached, or that it will be stable), double counting of individuals when considering inclusive fitness, and different consequences of synchronous and asynchronous updating in (spatial) simulations. Therefore, we recommend consultation of more in depth resources, including the guides by Otto and Day (68), Edelman-Keshet (69), and Hastings (70), as well as those listed in Table 2.

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