PERSPECTIVES

Strategic analysis in evolutionary genetics and the theory of games

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This paper is written in memory of John Maynard Smith. In a brief survey it discusses essential aspects of how game theory in biology relates to its counterpart in economics, the major transition in game theory initiated by Maynard Smith, the discrepancies between genetic and phenotypic models in evolutionary biology, and a balanced way of reconciling these models. In addition, the paper discusses modern problems in understanding games at the genetic level using the examples of conflict between endosymbionts and their hosts, and the molecular interactions between parasites and the mammalian immune system.

Introduction and historical remarks

The former editor of this journal, J. B. S. Haldane, inspired John Maynard Smith to apply rigorous evolutionary reasoning to phenomena that at first sight seem puzzling in light of the Darwinian theory, but could be explained with the aid of innovative mathematical modelling. One such puzzle involved restrained aggression, which seemed to undermine the notion of a struggle for fitness-enhancing resources. Restraints on aggression had been documented across a wide range of animal taxa, and attempts to understand the evolutionary logic of aggression and restraints on aggression prompted Maynard Smith and Price (1973) to introduce the field of evolutionary game theory. Maynard Smith developed the conceptual framework of this field and impressively demonstrated its numerous applications for biology (Maynard Smith 1982). His analyses of animal strategies were typically based on phenotypic models of evolution, but he was among the first to acknowledge the discrepancies between phenotypic and genetic models of evolutionary games (Maynard Smith 1981). Indeed, many geneticists have critiqued the validity of phenotypic models and, thus, Maynard Smith's framework. Here I will discuss this critique, possibilities for reconciling phenotypic and genetic models of evolution, and examples of how problems at the genetic level can be illuminated by strategic analysis.

Game theory was originally designed as a mathematical tool for economics and other social sciences. The first mathematical foundation of game theory was laid by John von Neumann (1928), but it was largely through the book he wrote with Oskar Morgenstern that economists became aware of this new branch of mathematics (von Neumann and Morgenstern 1944). Only a few years later, John Nash (1951) created the method of game analysis that has been most frequently applied in economics. This method is to search for 'Nash equilibria'. A Nash equilibrium is a profile of strategies, one for each player, such that no player can improve his payoff by changing his strategy as long as all others act according to this profile. For a two-person game, a Nash equilibrium is a pair of strategies (p, q) with the property that p is a best response to q and q a best response to p. The term 'best response' means that the expected payoff is maximised. Economic applications of the Nash equilibrium deal, for example, with markets, bargaining, auctions, education, communication, and public goods.

Before the origin of evolutionary game theory, economists typically justified applications of the Nash equilibrium by invoking the notion of a rational player who is capable of solving all problems in zero time, at no cost, and without ever being hampered by computational limits. Further, it was assumed that all players in a game know that all players know that all players are rational. With such an extreme idealisation, it would seem quite unrealistic to apply the Nash equilibrium to economic problems encountered by

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Keywords. John Maynard Smith; game theory; evolutionarily stable strategy; population genetics; genetic constraint; phenotypic evolution.

humans in the real world. For many decades, however, economic theory was largely based on strong rationality assumptions. Therefore, it came as a complete surprise to most economists when Maynard Smith and Price (1973) introduced the field of evolutionary game theory, a field that quickly became one of the most successful tools for understanding the evolution of interactions among animals, plants, and other organisms. In developing this field, Maynard Smith disentangled game theory from its rationality assumptions, and established its role in population biology. With some delay, economists adopted his approach so that evolutionary game theory became part of their field as well, invoking social learning and imitation instead of natural selection as the process that changes the population frequencies of alternative strategies.

The simplest model of evolutionary game theory uses a 'mass action' approach with random pairwise interactions among individuals in an infinite population. Strategies are traits with a pattern of exact inheritance that resembles a haploid genetic model without sex and recombination. When two individuals meet, they play a two-person game in strategic form, described by a payoff matrix. Payoff is interpreted as the change in an individual's expected fitness. The key idea for analysing the evolutionary game is to search for strategies that would be maintained by selection once they are established in a population. For a context broader than that of binary interactions, Maynard Smith (1982) defined an evolutionarily stable strategy (ESS) by the property that a population of animals playing this strategy cannot be invaded by any initially rare mutant strategy. He also characterized the evolutionary stability of a strategy p for symmetric two-person games. Let us use the notation $E(p, q)$ for the expected payoff to an individual playing strategy p against strategy q. Maynard Smith's famous characterisation of an ESS p can be stated as follows:

(i) $E(p, p) \geq E(q, p)$ for all strategies q, and (ii) if another strategy q exists with $q \neq p$ and $E(q, p) = E(p, p)$, then $E(p, q) > E(q, q)$.

The first condition (i) for an ESS means that p is a best response to p. One could also say that the pair (p, p) of strategies is a Nash equilibrium (this equilibrium is symmetric, but asymmetric equilibria also occur in the evolutionary study of asymmetric games). The interesting message from this reformulation is that in a simple evolutionary game, the evolutionarily stable strategies correspond to a subset of the Nash equilibria of that game. An ESS thus satisfies the central requirement for a rational strategic decision. This reflects the adaptive forces exerted by natural selection – the decision process of the evolutionary game.

Economists (e.g. Weibull 1995) and mathematicians (e.g. Hofbauer and Sigmund 1998) have enthusiastically adopted the main ideas expressed in Maynard Smith's (1982) book on evolution and the theory of games. Interestingly, these ideas had been foreshadowed by Nash in his doctoral thesis at Princeton University (Nash 1950), where he already discussed a mass action interpretation of his equilibrium concept. However, in contrast to Maynard Smith's work, Nash's mass action approach was largely unknown and had not left any trace in the history of economics before he received the Nobel Prize in 1994. It seems that at the time the mathematical reviewers did not allow him to express this insight which was conceptual rather than mathematical. What a mistake!

Reconciling genetic and phenotypic models of evolution

From a population geneticist's point of view, the concept of an ESS is problematic because it overemphasizes the adaptive power of natural selection in real diploid populations where phenotypic optimisation can be impeded, for example, by pleiotropic gene effects, recombination, epistasis, and selfish genetic elements. On the other hand, biologists have studied so many phenomena that turned out to be highly adaptive that population geneticists may sometimes underestimate the adaptive power of natural selection. Birds have wings with superb aerodynamic properties. These wings are not cast into quadratic shapes by genetic constraints, as Maynard Smith would have put it. Karlin (1975) expressed the contrasting view that selection models with more than one locus and recombination do not support the idea of fitness optimisation even in the simplest possible case where genotypes have constant fitness independent of genotype frequencies and population densities. In the same spirit Moran (1964) had advocated the "non-existence of adaptive topographies". But if the theory does not permit the bird to have its wings, there must be a problem with the theory. Mathematically the statements of Karlin and Moran were undisputable. The problem, therefore, must lie in the concepts used.

In extending work by Eshel and others (Eshel and Feldman 1984, see also Hammerstein 1996b for more details about the history of the ideas involved), I tried to clarify the conceptual confusion that made it so difficult for many geneticists and many students of phenotypic evolution to appreciate each others evolutionary insights (Hammerstein 1996a). This clarification is based on the idea that evolution will change the genetic system itself when genetic constraints become a strong impediment to phenotypic adaptation. The simplest of all possible cases is that of a model with one locus, two alleles, and a heterozygote fitness advantage like in sickle cell anaemia. Ignoring genetics, a naive believer in adaptive phenotypic evolution would have to think that the phenotype associated with the heterozygote should increase in frequency from generation to generation until it finally covers the entire population. Of course, we know that Mendelian segregation will not allow the population to consist entirely of the optimal

phenotype. However, the model in which we derive this trivial conclusion is quite narrow in scope. If our model included, for example, the possibility for gene duplication followed by a crossing over event, this process could combine the two alleles of the heterozygote on the same chromosome. Once the genetic rearrangement has taken place, the population would lose the less adaptive phenotypes associated with the homozygotes of the original gene. Another way of overcoming something like sickle cell anaemia by genetic rearrangement is to think of a new mutation at some locus in the genome that has not yet been included in the mathematical model. Suppose that this new mutation has a dominant phenotypic effect that is equivalent to that of the heterozygote. Such a gene would spread and the sickle cell allele would decrease in frequency.

The message is that if genetic constraints cause strong maladaptations, one can at least imagine ways of how these constraints could be resolved by evolutionary mechanisms. To summarize this I invoke a journey on a streetcar (Hammerstein 1996a). The streetcar stands for an evolving population. Its passengers are meant to be the genes in this population. At least two loci that can undergo recombination are considered. Attention is drawn to the stops (equilibrium states of the evolving population). At each stop passengers (new alleles or duplicate genes) enter or leave the streetcar and within the streetcar recombination takes place. Imagine now the streetcar stops and the phenotypes are not adapted to the environment. If one takes into account a particularly wide range of potential mutations, or of appropriate duplication and crossing over events, then the streetcar will not remain in this maladaptive equilibrium. The streetcar starts moving again after an appropriate new passenger enters it that undermines the genetic constraint responsible for this particular maladaptive equilibrium.

Of course, the idea that a new mutation can destabilize an equilibrium state is not one that would surprise any population geneticist. In order to see why the streetcar argument is more subtle, however, consider a modeller working with a two-locus model with 97 potential alleles for one locus and 51 for the other. Suppose further that the modeller knows which phenotypes are associated with every possible genotype. Using some starting condition the modeller uses a computer to determine the course of evolution in this population, and he finds that evolution stops at an equilibrium containing some of these alleles. Now the modeller challenges the population with another allele as a mutation drawn from the repertoire of 97 and 51 alleles. None manage to successfully invade and pull the population away from the maladaptive state. What does this tell us? It means that within the limited range of the modeller's hypothetical population, evolution is stuck. But the limitation of the model is one that the modeller imposed. He only gave it certain mutants to work with. What if we now extended the number of potential alleles for one locus from 97 to 98? Depending on its phenotypic effects, the new allele might invade and get a new round of evolution started – putting the streetcar back in motion. Starting with our maladaptive equilibrium, if one considers enough of these potential extensions, one will eventually hit a mutant that does put the streetcar back in motion in phenotype space. In this sense, phenotypically maladaptive equilibria are 'temporary stops' of the streetcar.

Suppose now that the streetcar has reached a 'final stop' where the extension procedure just discussed will not cause a phenotypic change. A number of mathematical results, starting with a seminal paper by Eshel and Feldman (1984), suggest that a final stop is necessarily a phenotypically adaptive state (see also Hammerstein and Selten 1994; Eshel 1996; Hammerstein 1996a,b; Weissing 1996). Eshel (1996) prefers to talk of the theory of long-term evolution. The reason why I have been using the term 'streetcar theory' is that it draws more attention to fundamental differences between stops than to the time scale.

It is important to point out that in the thought experiment just illustrated we excluded alleles that would selfishly affect the mechanics of reproduction. The reason is that every phenotypic population state, no matter how adaptive or maladaptive, can be altered by selfish genetic elements. It is also important to note that the environment is kept constant, the population is infinite, and there are no stochastic perturbations in the mathematical streetcar journey.

Why does the streetcar paradigm reconcile genetic and phenotypic approaches to evolution? Temporary stops depend on genetic detail and this is the domain of population genetics theory. Final stops depend on phenotypic adaptation because genetic rearrangements have removed all genetic constraints. It is an empirical question whether the human observer of natural phenomena would see more streetcars at final than at temporary stops. Sickle cell anaemia, for example, is a clear case of a temporary stop. A philosophical comment is that one cannot hold the argument of genetic constraints against a theoretical research programme where the search is for final stops. Conversely, one cannot criticise the emphasis on maladaptive properties if the research programme is directed toward temporary stops. Neither genetic nor phenotypic modellers of evolution will be losing face if they subscribe to the streetcar philosophy.

A word must now be said about evolutionary game theory. In the simple framework described in the introduction, a final stop must satisfy the first condition (i) for an ESS, and this implies that the population stops at a Nash equilibrium. If one assumes that the final stop is phenotypically monomorphic (but there might be genetic polymorphism), then the second condition (ii) must be satisfied. However, conditions (i) and (ii) are not sufficient for the 'final stop property' (Hammerstein 1996a). At a temporary stop, no general statement can be made because genetic detail matters.

Conflict between endosymbionts and their hosts

Maynard Smith (1982) stated that his method of thinking in game-theoretic terms was foreshadowed by Fisher's ideas about the evolution of the sex ratio. This means that it was already foreshadowed by Karl Düsing (1883) who developed the central argument about sex ratios shortly after Darwin had raised the issue. While the first task of sex ratio theory was to identify the selective forces responsible for an offspring male:female ratio near 1 : 1, subsequent work dealt with a plethora of exceptions to the even ratio. A particularly exciting idea was put forward by Cosmides and Tooby (1981), who suggested that a sex ratio conflict exists between nuclear and cytoplasmic DNA. According to their argument, cytoplasmic DNA with maternal inheritance would be under selection to favour a bias towards female offspring. The argument is simple but compelling. Evolutionarily speaking, to be located in a male organism is a dead end for cytoplasmic DNA.

Unless one makes very specific assumptions, cytoplasmic inheritance not only implies the sex ratio conflict, but also the absence of selection for cooperation of cytoplasmic DNA with male organisms. Here we see a dramatic game-like situation at the genetic level. Of course, genes have no interests, but incompatible selective forces acting on different parts of the genome are the analogue of a conflict of interest. The difficulty is to figure out by what means nuclear and cytoplasmic genes can interact, and how much strategic power there is on both sides; this power relationship should predict the strength of the female bias. Perhaps this exact quantitative problem cannot be resolved for any of the known intragenomic conflicts unless one has enough insights into the chemical pathways that both sides can modulate. However, the identification of intragenomic conflict alone can be extremely fruitful, as demonstrated by the following example.

Wolbachia are intracellular bacteria with cytoplasmic inheritance. They are known for a number of radical effects on the reproduction of their hosts (O'Neill *et al*. 1997). In arthropods, and depending on the bacterial strain and host, they feminise genetic males (FEM), induce parthenogenesis (PI), kill male offspring (MK), or modify sperm in such a way that development stops more or less with the first mitotic division unless the egg is infected as well. The latter phenomenon is referred to as cytoplasmic incompatibility (CI). There can be different mutually incompatible CI-types of *Wolbachia* (bidirectional CI).

With the 'dead end' argument in mind it is relatively easy to understand why selection can favour all these strong modifications of host physiology. It is much less clear what stops the host from suppressing these modifications. Given that cell division must be protected against malfunctions that would induce unrestrained cell proliferation, it could be the case that checkpoints designed to keep cell division under control are suitable targets for parasites such as CI-inducing *Wolbachia* that benefit from undermining host development. From the female host's point of view there would be a robustness trade-off, namely to be safe from problems like cancer, or from loss of potential offspring in cytoplasmically incompatible matings. At present it is an open problem whether such a trade-off really exists, and whether *Wolbachia* are targeting check points with their modification of sperm.

The CI phenomenon is very interesting in relation to population genetics. Suppose that a host population is divided into two compartments that are connected via migration at a symmetric rate m. Suppose, further, that in a haploid one-locus model weak selection favours allele A in compartment 1 and B in compartment 2. Of course, such a situation can easily lead to a genetic polymorphism with almost no genetic divergence between the compartments due to the stirring effect of migration (Nagylaki 1992). If we now introduce two strains of *Wolbachia*, one into each compartment, there can be a separating equilibrium that largely keeps the different strains in the different compartments, leading to more genetic divergence (figure 1). One could ask how small would the migration rate have to be to induce the same divergence without the presence of *Wolbachia*? Telschow *et al*. (2002) called this the 'effective migration rate'. With the help of this concept they showed for CI that *Wolbachia* can severely distort the genetic demography of host populations, with the effective migration being substantially smaller, and inducing demographic sinks and sources. From demonstrating the effective reduction of migration it seems like a small step

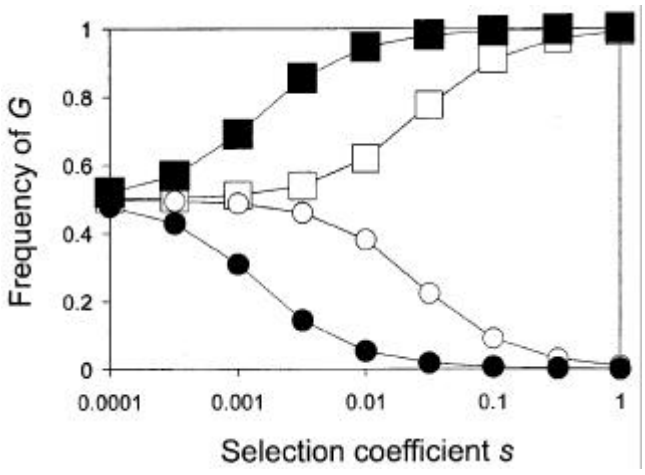

Figure 1. Genetic divergence with and without *Wolbachia* (after Telschow *et al*. 2002). Squares and circles represent the equilibrium frequencies of an allele G at a nuclear locus in two subpopulations with symmetric migration at rate $m = 0.01$. G is selectively favoured in one subpopulation and selected against in the other. Black indicates a *Wolbachia* infected population (bidirectional cytoplasmic incompatibility, with CI level of 0.9), and white an uninfected population. Note that with infection, the same divergence occurs at much lower levels of selection.

to conceive of a role these bacteria might play in insect speciation. Our work in progress supports this idea and indicates that *Wolbachia* can have an effect substantially stronger than the recessive nuclear incompatibilities invoked in typical scenarios that consider reinforcement of postzygotic isolation by the emergence of prezygotic isolation.

Evolutionary games involving the immune system

While endosymbionts are not primarily known as sources of intraorganismic conflict, pathogens with at least partially horizontal transmission are obvious candidates for participation in battles that take place in or on the host organism. The other obvious participant is the host immune system. Given the intriguing complexity of this system it seems daring to think that simple models might shed some light on strategic interactions among hosts and parasites. John Maynard Smith would have given it a try, had he found an interesting piece of information on which such a model could be grounded. One of the general lessons he taught his students is that simple models often tell us more about complicated biological systems than do complicated models. As a theoretician, and in real life, he was a gifted caricaturist. Had he been exposed to the following facts about the interactions among filarial nematodes and the mammalian immune system, he undoubtedly would have sketched out an insightful caricature.

A high proportion of the known species of nematodes have adopted a parasitic life style. They are continuously exposed to an array of effector mechanisms of their host's immune system but their life span can be on the order of years (Plaisier *et al*. 1991). Recently, some of the ways in which nematodes cope with the immune response have been revealed (Hartmann and Lucius 2003). Nematodes secrete cystatins that inhibit, for example, proteases involved in antigen processing and presentation, leading to a reduction of T cell responses in the host. Cystatins of parasitic nematodes also modulate cytokine responses in a way that inhibits the Th1 response, thereby creating an anti-inflammatory environment. In contrast, cystatins of the non-parasitic nematode *Caenorhabditis elegans* induce the production of the pro-inflammatory Th1 cytokine IL-12 (Hartmann and Lucius 2003), and have no major inhibitory effect on cell proliferation. These findings indicate that cystatins of parasitic nematodes are evolutionarily designed to alter the host's immune response in favour of the parasite. How, then, can one study this game? In an ongoing study with Susanne Hartmann and Richard Lucius, I theoretically examine evolutionary steps where the parasite can induce or inhibit one of the host's cytokines. This means that a mutant parasite strategy can only alter one more signal of the cytokine network, compared to the strategy from which it mutated. The host, on the other hand, can establish or remove a signal as a mutational step.

The immune system is usually challenged by many pathogens and the nematode under consideration is only one of them. Therefore, any rearrangement of the cytokine network needs to be judged by how it affects the immune system's overall performance in the evolutionary game with many different opponents. The network thus needs to be robust against a variety of possible attempts by pathogens to modulate the system to their advantage. To a large extent, this robustness can be achieved by installing redundant activation signalling paths. If one of two redundant paths suffices to trigger an effector mechanism, parasite strategies cannot easily evolve the means to efficiently disturb the cytokine network in their favour unless they manage to disturb two activation pathways in a single evolutionary step.

The immune system not only activates its own responses with cytokine signals, it also inhibits its responses with cytokine signals. One such inhibitory signal is IL-10 and it plays a role in the regulation of Th1 versus Th2 responses. If Th2 is upregulated, this induces (among other signals) the cytokine IL-10, which inhibits the inflammatory Th1 response. Nematodes and other helminths can suppress this inflammatory response (which is probably dangerous to them) by exploiting the inhibitory IL-10 pathway. Our theoretical work so far shows that the evolution of the immune system cannot easily protect organisms from the adverse effects of parasitic modulation of inhibitory cross-regulatory signals if the cross-regulation as such is strongly needed. This is why IL-10 seems to be a 'weak spot' of the immune system that is targeted by many pathogens.

I wish to conclude with the remark that in order to analyse games played by the immune system, methods of analysis are needed that differ substantially from those originally used in evolutionary game theory. The nematode example was given here to illustrate this point. Similarly, the study of conflict between endosymbionts and their hosts requires some methodological caution because the reproductive value of an offspring depends in a complicated way on its nuclear and cytoplasmic genotype. However, despite all methodological issues, these studies should be conducted in the spirit of game-theory if one aims to capture the essence of the conflicts involved, and it was Maynard Smith who first opened our eyes to this approach.

Acknowledgements

I am very grateful to Nicole Hess, Edward Hagen and Susanne Hartmann for many helpful comments and suggestions. This work was supported by the Deutsche Forschungsgemeinschaft (SFB 618).

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