The sociobiology of molecular systems

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Abstract | It is often assumed that molecular systems are designed to maximize the competitive ability of the organism that carries them. In reality, natural selection acts on both cooperative and competitive phenotypes, across multiple scales of biological organization. Here I ask how the potential for social effects in evolution has influenced molecular systems. I discuss a range of phenotypes, from the selfish genetic elements that disrupt genomes, through metabolism, multicellularity and cancer, to behaviour and the organization of animal societies. I argue that the balance between cooperative and competitive evolution has shaped both form and function at the molecular scale.

Modern synthesis
The evolutionary synthesis in the early twentieth century that brought together Mendelian genetics with natural selection theory, giving birth to population genetics theory.

Sociobiology
The study of social phenotypes, including both competitive and cooperative phenotypes.

Sociogenomics
The study of the genomics and genetics of social behaviour. Key premises are that social behaviours have some genetic basis and that genes are functionally conserved across species.

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Although Darwin searched long and hard for a workable theory of inheritance, it was some 70 years before natural selection was fused with Mendelism in the modern synthesis[1]. A similar, if altogether more deliberate, separation between evolutionary and mechanistic disciplines has occurred over the past 50 years. The current healing of this rift — between sociobiology and molecular biology — is the subject of this Review.

In the 1950s, the nascent field of molecular biology was crystallized by the solution of the structure of DNA. In the wake of this discovery was the seminal paper by Hamilton, 'The genetical evolution of social behaviour'[2], which offered the first formal extension of Darwinism to social traits. Hamilton explained how seemingly paradoxical traits, in which one individual reduces its lifetime reproduction to help others, can evolve by natural selection. In addition, Hamilton helped to found a field that shows how natural selection can act at any level of biological organization, from genes to species[3,4]. Given its title, one might expect that Hamilton's work would be combined with the insights of Watson, Crick and others. Instead, the two new disciplines took decades to meet.

Why did it take so long for genetics-oriented fields such as molecular biology and microbiology to consider social evolution? One explanation lies in the fact that classical examples of social behaviours, such as animal cooperation, were traditionally difficult phenotypes for genetic analysis[5]. This is now changing, and there are serious efforts underway to understand the genetics and genomics of social animals in the field of sociogenomics[5–9]. Perhaps the most crucial issue, however, is that the core theories of sociobiology — inclusive fitness theory, multilevel selection theory and evolutionary game theory — tend to ignore genetic details[8,10]. Adaptation is the process by which phenotypes, not genotypes, fit to their environment. As a result, theoreticians of social evolution often define genes only by their link to a particular phenotype. A gene can be any functional unit of inheritance, encoding anything from a regulatory microRNA to multiple proteins.

It is becoming clear that these theories of adaptation have a role in the molecular sciences. With many molecular networks well described, there is an increasing emphasis on functional understanding and the discovery of the 'design principles' that underlie molecular networks[11,12]. Despite the engineering terminology, these design principles are the result of the adaptive process[13] (something that is reflected in the emergence of evolutionary systems biology[14,15]). Sociobiology teaches us that a major component of adaptation comes from the potential for phenotypes in one individual to affect others, and to do so across multiple scales of biological organization (FIG. 1).

Here I ask how social evolution affects molecular systems. I use the metaphor of biological networks — in which nodes can be any interacting set of molecules, individuals, cells or species — and I focus on networks that are either molecular or have effects at the molecular level. Sometimes, this requires me to cross organizational levels, such as asking how natural selection on a network of organisms influences the evolution of metabolic networks. The main sections reflect four potential network properties that can be affected by social evolution: their functional scale, the number and nature of connections among nodes, the diversity of nodes, and how networks change over short and long time scales (FIG. 2). However, at no time do I intend to suggest that sociobiology is the only explanatory framework. The reader should always be mindful of complementary, or sometimes competing, explanations[16].

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Inclusive fitness theory
Theory in which natural selection is analysed in terms of the effects of an actor on its own reproduction as well as its effects on other individuals; the latter effects are weighted by the genetic similarity (relatedness) between the actor and others.

Multilevel selection theory
Theory in which natural selection is analysed in terms of the effects of an actor on its own reproduction as well as on members of its social group; the latter effects are weighted by the genetic similarity (relatedness) between the actor and the group.

Functional scale of biological networks

The existence of adaptation implies that agents of natural selection, be they single genes or groups of organisms, will tend to be optimized to perform the functions that improve their fitness[17–19] (BOX 1). The existence of an optimizing process, however, does not mean that a hypothesized optimal solution will always be reached, as optimization is constrained both by the nature of biology[20] and the stochastic nature of the evolutionary process[16,21]. Nevertheless, molecular biology is seeing a surge of interest in optimization techniques that is associated with the introduction of engineering principles to understand biological networks[11,20].

The functional scale at which optimization occurs is defined by the level at which natural selection acts[22,23] (BOX 1; FIG. 1). Phenotypes can operate at the scale of the few genes of a transposable element up to the many genes, across many individuals, of something like a honeybee colony. This section discusses how the potential for evolutionary competition among the agents acting at different functional levels — genes, organisms and species — can influence the functional scale, and form, of genetic and metabolic networks.

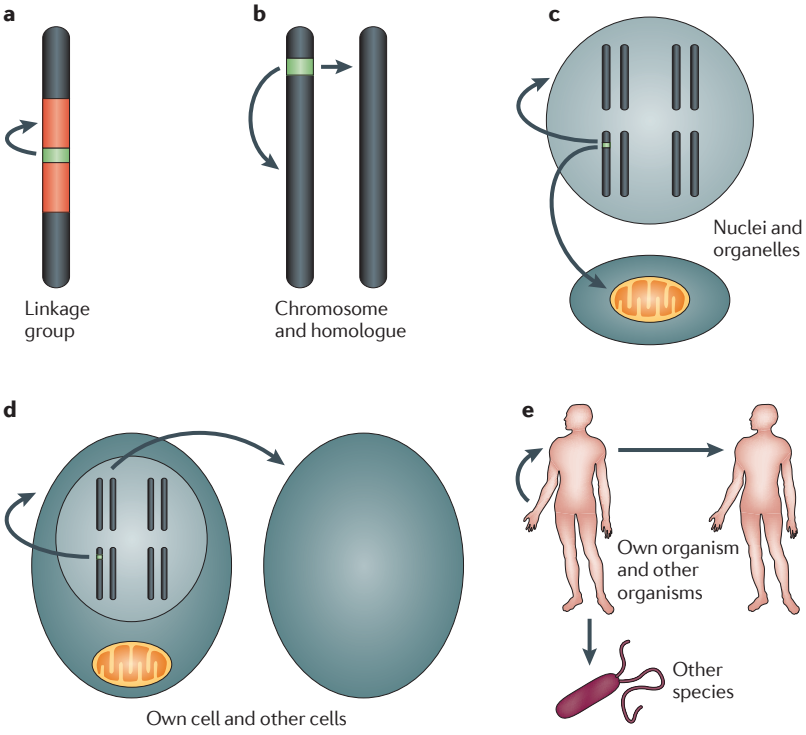

Figure 1 | **Multilevel selection.** A summary of the potential social consequences of a gene across different levels of biological organization is shown (see also BOX 1). The gene can affect many potential groups of common evolutionary interest. Consider a gene that promotes the transmission of itself and its linkage group (**a**). This might help or harm other levels, including unlinked sites on its and other chromosomes (**b**). It can also have differential fitness effects on the nucleus versus organelles (**c**) and on its carrier cell, as well as other interacting cells (**d**). Finally, it can affect the fitness of the organism that carries it and other organisms of the same or different species (**e**). These multiple layers of fitness effects may all feed back on the fitness of the focal gene. For example, if the promotion of an element's own transmission within a host reduces the host's ability to reproduce, this may mean that the element is not favoured by natural selection.

Genetic networks. Systems biologists assume that a particular genetic or biochemical network is optimized to perform a particular function as a way to constrain complex models[12]. For example, one can understand the complex feedback loops that are seen in the heat shock response of bacteria in terms of optimization for criteria such as robustness and speed of response[24]. This exercise rests on two key assumptions. The first, which is often discussed[25], is that regulatory networks are inherently modular, such that one can analyse only a small piece of them (such as the heat shock response) and gain understanding[12]. The second, which is less discussed, is that one knows the level at which natural selection is operating. As the examples below show, correctly identifying the level at which selection acts is not always trivial, but is essential for gaining further understanding of a molecular system.

Genomes often seem to function as a coherent unit (FIG. 3), but there are many examples in which this assumption is violated[26]. The most obvious cause of violation is the transposable element. Unlike the heat shock response, a typical transposition event makes little sense from the perspective of the whole genome, as it is likely to impose a fitness cost to the organism. It is only when one realizes that these small groups of genes act as selfish agents that we see the level at which the appearance of design occurs. Transposons adapt to spread within genomes, even though this can harm the organisms that carry them. And sometimes one has to think at an even smaller scale to find adaptation. Transposable elements are themselves threatened by the evolution of shorter 'parasitic' sequences that encode the recognition sequence that is required for replication without encoding the replication proteins[26,27]. The importance of these forms of adaptation is well illustrated by the human genome. About half of our DNA comes from the action of transposable elements[27]. Evolutionary competition within organisms means that major features of molecular biology are not understandable by considering the optimization of organism-level phenotypes alone[11].

The potential for evolutionary competition to affect genetic networks is even more acute when interacting genes can be in different organisms. Just as genes in a genome can be viewed as tightly associated species living together (FIG. 3), multi-species communities can be viewed as a large genome in which the component parts are in different organisms[28]. This perspective has naturally emerged with the study of metagenomics, which uses DNA sequencing to indentify the genes — but not necessarily the species — of microorganisms in a given environmental sample[29].

Unlike genomes, however, most multi-species groups do not exist in tight physical association. This means that species are freer to evolve selfish phenotypes that harm other members of the community, without the negative consequences feeding back on the genotypes that caused them. At the species level, a herbivorous insect can eat one plant and then find another, but at the genome level, a highly active transposable element is likely to harm itself if it prevents

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genome duplication[30] (BOX 2). Accordingly, the scale and extent of functional organization in networks involving multiple species, including those of the human microbiome[31,32], will generally be much more limited than the networks within a cell. At most, one expects members of only a few species to work towards a common evolutionary goal. By contrast, it is clear that hundreds or thousands of different genes can work together towards common organismal functions.

Metabolic networks. Understanding the form and function of metabolic networks also rests on identifying the scale at which natural selection operates. This is illustrated by another use of optimization principles in systems biology, flux balance analysis. Flux balance analysis is a modelling technique that is designed to remove the need to know the precise rates of flux through a metabolic network. Instead, one simply assumes that all rates in the biochemical network are optimized to maximize growth. This has proven powerful in predicting a number of features of metabolic networks, including the behaviour of mutants[33] and rates of substrate usage[34]. Social evolution, however, again teaches us the importance of applying the logic of optimization at the appropriate level of social organization.

Caution is most acutely required when studying the metabolism of multi-species groups[35], which may not optimize anything as a collective. Even at the single-species level, it can be difficult to identify the functional scale of metabolism. A systematic analysis of the possible goals that bacteria evolve to optimize suggested that they typically pursue one of two key objectives: maximize growth rate or maximize growth yield[36]. Cells sometimes use short molecular pathways that maximize growth rate, and at other times they use longer, more efficient pathways that maximize total yield (that is, they maximize the total cell number irrespective of the time it takes). Why do metabolic pathways differ so greatly in their design? Part of the answer lies in the need to respond to different environmental conditions. For example, it may be beneficial to use the longer, more efficient pathways under nutrient stress[37]. Another factor, however, is social evolution.

As an example, take ATP production from sugars[38]. Glucose is first broken down to pyruvate, which then can be put through the citric acid cycle to yield around 32 ATPs per glucose molecule by aerobic respiration. However, many microbes will simultaneously ferment pyruvate to lactic acid or ethanol, with a yield of only two ATPs. Although wasteful, simultaneous fermentation provides a way to increase the rate of ATP production on top of that achieved by the citric acid cycle alone. When competing with other strains and species, therefore, natural selection can favour cells that wastefully use resources just to ensure that competitors do not get them first. By contrast, when cells are surrounded by clone mates, natural selection can act on them as a group and favour pure respiration to maximize group efficiency. Support for this hypothesis comes from a study on budding yeast, *Saccharomyces cerevisiae*[39], in which wild-type cells outcompeted cells with a modified sugar transporter that prevents fermentation in the presence of oxygen. However, on their own the engineered cells seemed to achieve a higher yield than did the wild type, revealing the potential benefits of cooperatively slowing down growth to improve yield. Understanding whether organisms are cooperating or competing can help to explain the architecture of metabolic networks.

Interestingly, a similar phenomenon is seen in tumours. In the eyes of social evolution, the emergence of a tumour marks a change in the level at which natural selection acts (BOX 1; FIG. 3). Compared to their non-cancerous counterparts, tumour cells no longer evolve to promote the survival and reproduction of the whole organism, but rather are naturally selected to promote the survival and reproduction of their cell lineage within the organism. Cancer cells commonly display something called the 'Warburg effect' after its discoverer, which is an increase in glucose uptake associated

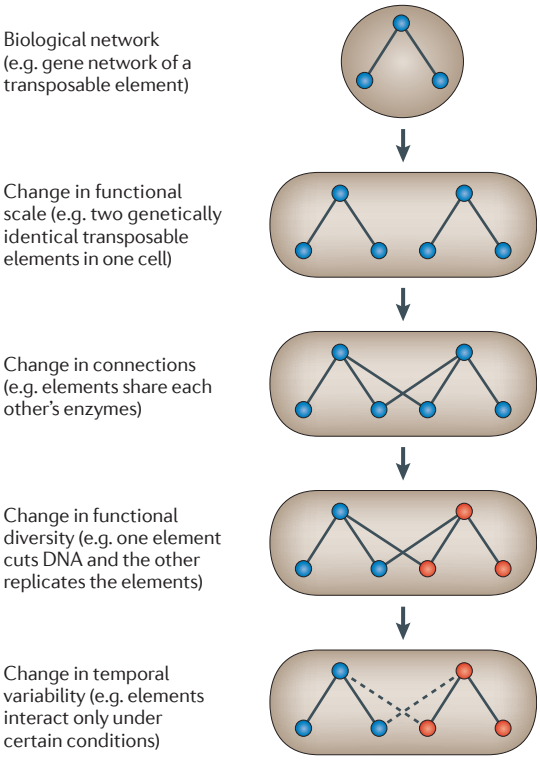

Figure 2 | **Properties of biological networks.** A network can represent multiple scales of organization, with nodes representing interacting set of molecules, individuals, cells or species. The focus here is on networks that are either molecular, or have effects at the molecular level. The figure shows simple cartoon networks along with the properties discussed in the main text that can be altered as a result of social evolution. Functional scale is the number of nodes that operate towards a common evolutionary goal. Connections define the way that the nodes in the network interact. Functional diversity is the degree to which nodes in the network differ in form and function. Temporal variability is the tendency of networks to change in real and evolutionary time.

Evolutionary game theory
A theory designed to recognize frequency-dependent fitness effects in evolution, which occur because the strategies of one individual affect the fitness of another individual. Game theory logic is used in both inclusive fitness and multilevel selection.

Functional scale
The number of genes, cells or organisms that operate towards a common evolutionary goal (the scale of agency). For example, the genes of a transposable element typically operate at a much lower functional scale than the genetic networks underlying cellular growth and division.

Agent
A gene, cell, organism or any group of these that has the same evolutionary interests. Natural selection on agents leads to them to behave as though they are striving to maximize their genetic representation in later generations.

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Box 1 | **The logic of social evolution theory**

Most of the theory discussed in this article comes from the extensive literature on social evolution, including Hamilton's inclusive fitness (also known as kin selection), multilevel selection and evolutionary game theory (reviewed in REFS 4,121–124). To give an idea of the underlying logic, this box reduces social evolution theory to a two-step heuristic that can, in principle, be applied by any biologist to any trait of interest. This approach is implicit in many studies, particularly in animal behaviour[125] and a growing number that consider molecular details[9,26,126].

Step 1: identify the fundamental agent of evolutionary interest

Life has a nested structure. Genes have formed genomes, haploids have become diploids, multiple genomes are combined in cells that have nuclear DNA plus a mitochondria or plasmid, cells have combined to make multicellular organisms, and organisms have formed societies or multi-species coalitions (FIG. 1). Understanding the adaptive function of a particular phenotype requires one to first identify the fundamental agent of evolutionary interest. A first assessment can be made by starting at the lowest level of biological organization, the gene, and working up through each level until one reaches a level at which the different units can benefit, in an evolutionary sense, from a difference in the phenotype. For example, if we consider two polar bears fighting on an ice sheet, then fighting serves the whole organism and all hierarchies below. The fighting of one bear will not, however, benefit the other, so in this example an individual bear is the agent.

Natural selection can operate at multiple levels simultaneously, but identifying the level at which agents exist typically provides a good first intuition on adaptive function[4]. That is, it would probably be incorrect to try to interpret our polar bear fighting as serving the interests of one of its liver cells against other bear cells, or indeed the common interests of both bears as an adaptive unit. However, if the focal phenotype were cancer, or the growth rate of a bacterial cell in the bear's intestine, it would probably be unwise to consider the bear as an indivisible agent of natural selection. In this vein, a recurring theme in the literature is to assume that large populations of animals or microbes form indivisible agents of natural selection. This position has been called 'naive group selection' because, although group-level natural selection certainly can occur, it is naive to assume it without first considering the possibility for evolutionary competition at lower levels[4,23,127].

Step 2: classify the phenotype on the basis of its fitness effects on agents

Hamilton's analysis of social behaviours classifies phenotypes on the basis of their effects on the lifetime reproductive fitness of a focal agent that shows the phenotype (actor) and any other agents that are affected by the phenotype (recipients). For two parties, this gives four classes of social behaviour, whose distinct requirements for evolution can be crucial for understanding their adaptive function (BOX 2). The fighting bear is displaying selfish (+/–) behaviour; the other classes are mutual benefit (+/+), altruism (–/+) and spite (–/–) (the symbols indicate the effects on the personal reproductive fitness (direct fitness) of the actor and recipient, respectively) (FIG. 3).

Applying these two steps to the study of a molecular network helps one to identify the level of functional organization that is associated with the resulting phenotype, and understand the evolutionary conditions that have shaped the network.

with a shift from aerobic respiration to fermentation[40] and the ability to selfishly outgrow normal cells. The evolutionary link between the evolution of cancer and microbial metabolism was not lost on Warburg: "Oxygen gas, the donor of energy in plants and animals is dethroned in the cancer cells and replaced by an energy yielding reaction of the lowest living forms, namely, a fermentation of glucose."[41] The change in the level of selection from organism to the cell — or, as in the case of yeast, from the group to individual — seems to commonly shift metabolism to shorter pathways that improve short-term competition.

Connections within biological networks

A second key feature of biological networks is the way in which nodes interact and are connected with one another. Understanding who interacts with whom is clearly a social evolution problem in the case of animal or human groups, but does social evolution also influence molecular interactions? This section discusses three properties of the way that genetic and metabolic networks are connected: modularity, robustness and specificity. There is evidence that each property can be influenced by the relative importance of competitive and cooperative phenotypes.

Modularity. Biological networks tend to show modularity, in the sense that they can be separated into units that work semi-independently. A related observation is that many biological networks seem to be scale-free networks[42,43]. When and why modularity should evolve in biological networks is a subject of much discussion, with some authors focusing on the possible adaptive function of modularity and others focusing on modularity as a by-product of other evolutionary processes[12,16,44,45].

The general effects of social evolution on modularity, if any, are not clear. However, the nested layers of competition in biological systems (FIG. 1) certainly have the potential to generate modules of common evolutionary and functional interest, such as the sets of genes found in transposable elements[26]. A second potential influence on modularity comes from the link between cooperative phenotypes and pleiotropy, which has been identified in microbes[9]. Microbial groups commonly suffer from selfish phenotypes, as exemplified by the occurrence of cheater mutants. For example, some loss-of-function mutants in bacteria gain a competitive advantage by using the growth-promoting secretions of wild-type strains without themselves contributing[46]. The prospects for maintaining cooperation are improved if cheater mutations carry pleiotropic effects

Scale-free network
A network in which the distribution of the number of connections from each node follows a power law. This means that some nodes are highly connected (hubs), and paths through the network are shorter than those in highly ordered networks.

Cheater mutant
A mutant that does not invest in a public good but benefits from the investment of others, such as a bacterial mutant that does not produce a secreted enzyme but uses the enzyme of wild-type cells.

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that reduce their carrier's fitness. An example of this is seen in the slime mould or social amoeba, *Dictyostelium discoideum*. Cells of this species aggregate to form a fruiting body in which around 20% of cells die in a stalk to hold the others aloft as reproductive spores. A single gene, *dimA*, links the altruistic act of stalk formation with spore formation, thereby limiting the range of possible cheating strategies[47].

Such pleiotropic links between costly cooperative traits (for example, stalk production) and personal benefits (for example, spore production) may be a frequent property in the genetics underlying cooperative traits, which helps to stabilize them over evolutionary time[9,47]. Increasing pleiotropy will tend to reduce modularity when it links modules that underlie cooperative phenotypes with modules that underlie competitive phenotypes[43]. The prediction, then, is that the emergence of cooperative phenotypes at one level of biological organization will be relatively more disruptive to modular structure than are competitive phenotypes at the same level.

Robustness. Another property that can arise from the number and nature of the connections in biological networks is their robustness to perturbations. The potential for links between social evolution and robustness is seen in the ability of multicellular organisms to limit the emergence of cancers, which are an example of selfish phenotype evolution[48].

Cancer is almost never caused by a single mutation[49]. Instead, multiple mutations are required for cancer cells to divide, move and even cooperate with each other against the host[48,50]. This mutational complexity is partly explained by the need to protect the cell from apoptosis or immune system attack, which can be triggered by single mutations[51]. These links between cancer mutations and cell death is another example of the pleiotropic constraints discussed above, which is also sometimes known as 'antirobustness'[52]. But the main explanation for the mutational complexity of cancer is probably the robustness of cell phenotypes to many single mutations. Theory suggests that natural selection will favour mutational robustness whenever mutation rates are sufficiently high to threaten the stability of a phenotype[53]. Cancer is a socially mediated selection for robustness, because multicellular organisms are long-lived enough to be threatened by *de novo* mutations that disrupt their functioning. The hypothesis is that natural selection for cooperation among somatic cells has led to them to be highly robust to potentially cancer-causing mutations. Similar predictions can be made for transposable elements and pathogens that, in their attempts to spread in hosts, may promote robustness in host molecular systems[54].

Of course, robustness can arise in genetic networks for reasons that are unrelated to social competition. Indeed, mutational robustness can often arise as a by-product of natural selection on other phenotypes[55], such as the need to tolerate variable environments[56]. Nevertheless, it seems inevitable that selection for robustness from the challenges of cancer, parasites and selfish genetic elements has altered the genetic networks of mammals and other groups. But how are these effects manifested? This is a more complicated question than might at first be assumed. One way to achieve robustness is to evolve distinct modules with similar functions: if a system loses one module, another can take its place. However, this form of redundancy does not seem to be common. Theory and experiments suggest that genetic networks may more often display a phenomenon called 'distributed robustness'; in such

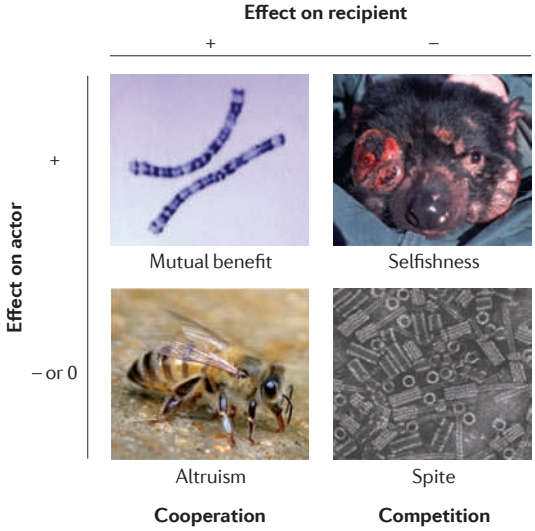

Figure 3 | **Hamilton's classes of social phenotype.** Hamilton's classes of social phenotype are based on their effects on the direct fitness of their carrier (actor) and any other agents that are affected by the phenotype (recipients). Direct fitness is roughly equivalent to lifetime total reproduction in whole organisms or, more precisely, the long-term contribution of an agent's alleles to the gene pool from its own reproduction. The images depict the mutual benefit among genes in a human chromosome; a selfish tumour on a Tasmanian devil; an altruistic honeybee worker carrying water back to the colony; and an electron micrograph of the headless phages (R-pyocins) that suicidal bacteria use to kill others (see main text). A key binary distinction is made between competitive and cooperative phenotypes, because it is cooperative phenotypes that underlie the spectacular transitions to higher levels of organization, such as the emergence of genomes via mutual benefit, or multicellularity via altruism (BOXES 1,2). A criticism of the classification is that terms such as 'cooperation' and 'altruism' carry hermeneutic baggage, which can be confusing when people first encounter the terms in a biological context[23]. However, the meaning of these fitness-based definitions is formally rooted in theory[2,123] and, once this is understood, they offer an intuitive shorthand. The use of such definitions is also older than most realize: the first fitness-based definition of altruism dates close to the origin of the word in the nineteenth century[140]. The top left image is from Getty images. The top right image is courtesy of M. Jones, University of Tasmania, Australia. The bottom left image is courtesy of F. Ratnieks, University of Sussex, UK. The bottom right image is reproduced, with permission, from REF. 141 © (1965) Elsevier.

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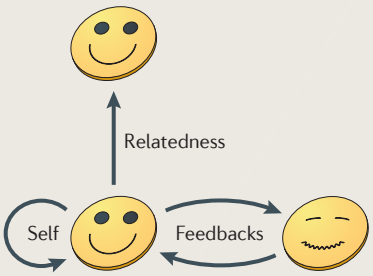
Box 2 | **Explaining cooperative phenotypes**

Selfish phenotypes, whether directed at members of the same species or another species, often make immediate sense in terms of basic Darwinian principles. However, understanding the evolution of many molecular systems requires one to also consider how and why cooperation can evolve. This box highlights some of the key factors that shape the balance between cooperation and competition.



Relatedness

Natural selection can favour altruistic phenotypes (FIG. 3) when more copies of the alleles underlying the phenotype are transmitted via others than are lost through the decrease in personal reproduction. This is possible with genetic relatedness or, more formally, when individuals have an above-average chance of sharing alleles at the loci that define the social phenotype. The key corollary is that increased genetic relatedness among interacting agents will tend to favour cooperation over competition, one of the key factors that leads to increased natural selection at higher levels of biological organization[22,128] (FIG. 1). Another consequence is that altruism is expected only in interactions that involve genetically related agents, restricting it to interactions that involve conspecifics (or the paired alleles at a diploid locus)[78].

Feedback benefits

Mutual benefit is possible both within and between species (and within and between loci). To evolve, this requires that helping carries no energetic cost, or that there are feedback benefits to helping for the actor or its relatives. Strong phenotypic feedbacks among unrelated mutualistic agents — among different loci in genomes and among species in a community — have a similar role to relatedness among altruistic agents of the same species[30].

Ecology and power

Explaining social phenotypes also requires one to consider the relative costs and benefits for all parties involved. These, in turn, are affected by ecological conditions[129] and the relative power of parties to obtain their interests[130]. For example, the ability of a bacterial cell to reject a costly plasmid from another cell may be constrained by both its physical ability to resist conjugation and a lack of information about whether a plasmid is beneficial or costly[131].

Pre-adaptation

Understanding modern phenotypes requires one to consider past, as well as present, function. The multiple origins of altruistic workers in bees, ants and wasps are associated with ancestral monogamy[132] and maternal care[133,134], which may both have been important in the subsequent evolution of worker sterility. In addition, the tendency of selfish elements to transfer genes between organisms and species can be beneficial to organismal adaptations in the long term[135]. However, this benefit should typically not be invoked to explain why the elements move the genes, which is more likely to be due to short-term selection on elements to reproduce, as well as the inability of genomes to stop them[26].

cases, the exact cause of robustness can be difficult to identify but seems to arise from the connections in a genetic network[57–59].

Specificity. Many molecular networks rely on highly specific interactions among their component parts that both reduce network complexity and limit unwanted crosstalk. Specific molecular interactions can also arise as a result of natural selection for cooperation. As discussed above, agents that invest in costly cooperation are susceptible to others that use the cooperative investment without contributing (BOX 2). One way to limit interactions with exploitative genotypes is to form permanent physical associations, as occurs among genes in a genome[60]. Another way is to discriminate between cooperative and competitive genotypes by using molecular interactions. This has led to the widespread evolution of molecular recognition systems that, unusually, can occur across different organisms. The evolution of specificity in these systems is strongly shaped by social evolution.

A simple example of a molecular recognition system is seen in *S. cerevisiae*, which recognizes other cooperators using a single glycoprotein[61]. The glycoprotein, produced by the gene *FLO1*, allows cells to flocculate together in clumps that protect the cells from stresses. The exclusion of cells that do not invest in the costly glycoprotein occurs simply because expressing cells stick more to one another than to cells that do not express *FLO1*. More complex recognition systems are seen in bacteria. One of the most striking is the clustered regularly interspaced short palindromic repeats (CRISPR) system. It has emerged that bacteria insert short sequences of foreign DNA into the CRISPR loci of their chromosome[62,63]. These generate small RNAs that target foreign DNA for destruction, enabling bacteria to acquire immunity against viruses, plasmids and probably transposable elements.

Bacteria also use molecular recognition to kill off competitors, by using bacteriocins[64]. The simplest bacteriocin systems are expressed from short operons encoding a toxic protein, which damages nucleic acids or membrane function, and an immunity protein that recognizes and inhibits the action of its cognate toxin[65]. Releasing the toxin harms cells that do not carry the immunity protein, and the process seems to be spiteful (FIG. 3) because toxin release coincides with the expression of proteins that lyse the releasing cell. Some species also release large protein machines that attach to the cells of conspecifics and physically puncture holes in them. These draconian contraptions are 'tamed' bacteriophages that have become permanently integrated into the chromosome and decapitated (the genes for the head capsule and replication have been lost[66]). What determines the specificity of these phage derivatives? For one class, R-pyocins (FIG. 3), specificity is determined by a variable locus that affects binding to the lipopolysaccharide (LPS) that coats cells. This locus ensures that the phage tails released by one bacteria will not bind to the LPS of its clonemates[67].

In multicellular organisms, the decision of colonial marine invertebrates to fuse with neighbouring animals, or to reject them, has been tracked in two species, to a different highly polymorphic locus in each. Both systems require one allele to be shared between individuals for fusion to occur[68,69]. The systems, in common with the major histocompatibility complex (MHC) of vertebrate adaptive immunity[70], possess immunoglobulin-like domains. However, the homology among the three systems — two from marine invertebrates and MHC in vertebrates — seems to end there. This suggests that there are multiple evolutionary origins to such self- or non-self discrimination in animals[68]. The effectiveness of self- or non-self discrimination rests on most individuals having different genotypes at the recognition

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loci. And losing the ability to reject conspecific tissue can have important consequences. In Tasmanian devils, reduced MHC variability is associated with the spread of a transmissible cancer that has killed half of their population[71] (FIG. 3). However, theory suggests that the evolution of diversity at recognition loci is not explained by intraspecific competition[72]. This makes particular sense for vertebrate immunity, which has a central role in distinguishing self-epitopes from those of pathogenic microbes, and may even help to select the most beneficial microbial flora in the gut[73,74].

Strong natural selection to protect cooperative investments has generated some of the most sophisticated examples of molecular specificity in nature. In particular, the hypervariable loci of bacterial[62] and vertebrate[70] adaptive immunity represent cooperative loci that protect the organism against assaults from the competitive loci of parasitic agents.

Diversity in biological networks

The efficiency benefits of individual specialization and the division of labour apply to biological systems as they do to human society[75]. This section discusses how competition and cooperation affect the functional diversity that is seen among genes, cells and organisms and the impact of this diversity at the molecular level.

Diversity among genes. Internal competition can increase the overlap in function in biological systems. This is seen in the multiple copies, and numerous classes, of transposable elements that have spread in human genomes[15,21]. Analogously, one also sees considerable overlap in biological function among species in many communities[76], despite the fact that competitive exclusion will tend to weed out similar species from any given community[77]. By contrast, highly cooperative genomes are expected to only retain the number of functionally similar loci that are beneficial for the propagation of that genome, which appears to be a relatively modest number of overlapping loci[58].

Diversity among cells and organisms. The evolution of diversity within single-species groups of cells or organisms is mechanistically different to that within a group of genes or species. The reason for this lies in the differing nature of social coalitions. Genes and species form 'egalitarian' coalitions of functionally distinct agents, such as a histidine kinase and a response regulator, or a plant and a pollinator. Cells and organisms of one species form 'fraternal' coalitions of similar agents[78], which start out with much less functional diversity than would an equivalent coalition of genes or species. And there is an additional factor that reduces diversity in fraternal coalitions: the exchangeability of agents in fraternal coalitions also allows for more extreme forms of cooperation than are possible in egalitarian coalitions. Honeybees sacrifice themselves to help their genetic relatives, but they do not do it to save other species (FIG. 3). This is because the benefactors of self-sacrifice must include individuals that share alleles with the dying bees for the bee's genotype to increase in frequency through the action (BOX 2). The corollary is that the most cooperative forms of fraternal coalitions are also the most genetically similar[2,23].

The challenge of generating diversity within groups of genetically similar cells and organisms has strongly shaped molecular systems. One solution that is seen in bacteria is to make use of stochasticity, whereby cells that happen to have a few more copies of a particular molecule have one phenotype, whereas other cells have another phenotype[79]. However, the most impressive system for generating diversity is that of eukaryotic development, in which stochasticity is used alongside positional signalling and cellular interactions to generate the sophistication that is seen in multicellular organisms. A full review of developmental biology is beyond the scope of this article, but there are relevant parallels between the molecular interactions that take place during the development of a multicellular organism and the development of castes (for example, queen versus worker) in eusocial insects. As for multicellular development, the field of sociogenomics is finding evidence that DNA methylation and microRNA expression help insects to diversify into different castes[80–82]. There is also a potential role for the production of a range of transcripts from a single locus through alternative splicing of exons[83,84]. Therefore, whereas intron evolution is often linked to the spread of selfish transposable elements[85], the evolution of diversity in exons is more likely to be driven by selection for altruistic multicellular, and possibly societal, organization.

There are important differences in the way that cells of multicellular organisms generate functional diversity as compared to the individuals of insect societies. With the exception of cells of the immune system[86], the cells that make up multicellular organisms are basically clonal, whereas the individuals of most insect societies are not clonal. The existence of genetic differences among individuals opens up the possibility of using not only epigenetics but also genetics to generate functional diversity and determine caste fate[6]. This has led to a wide variety of fascinating, and sometimes bizarre, caste-determination systems that use mixed sexual and asexual reproduction, or the cross-hybridization of genetically distinct lineages[6]. The genetic diversity among individuals in social insect colonies also generates reproductive competition that has strongly shaped their biology in ways not seen in multicellular organisms[87,88].

Change in biological networks

Biological networks are not static. This section discusses how social evolution influences the way that molecular systems change in real time and over evolutionary time.

Real-time change. Evolutionary models highlight the potential for conditional responses to promote cooperation, such as the behavioural rule 'only cooperate if cooperated with'[30,89]. In many animals, conditionality can be imposed by using the nervous system and, ultimately, cognition. At the cellular level, however, conditionality will often be mediated by real-time alterations

Eusocial insects
Social insects that display a division between work and reproduction among individuals. The clearest examples have morphologically distinct workers, as seen in many ants, bees, wasps and termites.

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Box 3 | **Storms in a teacup: contemporary debates in social evolution**

Sociobiology is prone to high-profile claims that one set of theory is wrong or useless. There are numerous examples of such claims, but that with the highest profile is the ongoing series of papers that attack one of the key frameworks, inclusive fitness[136–138]. Some of these attacks are so spirited that they can give the impression that sociobiology is in disarray. In reality, the issues raised in such papers have been discussed long before in a more measured and systematic fashion (reviewed in REFS 87,121,123).

The attacks on any one framework also miss the fundamental need for pluralism in the study of biology (as in the famous quote, "All models are wrong but some are useful", from George Box). Social evolution has seen important contributions from several theoretical frameworks. Inclusive fitness theory is certainly one of these, but there is also multilevel selection theory, neighbour-modulated fitness theory and population genetics, to name a few. Of course, there is the legitimate question of which framework is most useful for which class of problems[139], although, for many biological problems, one can directly translate between the frameworks[87,121,123]. This reveals that genetic relatedness is indeed an important factor in social evolution, but it is certainly not the only one (BOX 2). One can read more about the debates in dedicated articles[23,122], but this Review hopefully illustrates the utility in applying multiple frameworks. Indeed, although I have defended inclusive fitness in this box, I make more use of multilevel selection theory in the main text (see also BOX 1 and FIG. 1).

to the strength of connections in molecular networks[90]. This is well illustrated by quorum sensing in microbes, whereby cells secrete and detect small molecules that are known as autoinducers[91,92]. A high autoinducer concentration is probably normally associated with high cell density, low diffusion of molecules and high genetic relatedness among cells. These are good conditions for cooperation, and many microbial species use quorum sensing to activate a host of cooperative products, including digestive enzymes, scavenging molecules and even light in the case of the bacteria that live in bioluminescent animals[93]. Related to this, a recent study showed that bacteria transcriptionally regulate cooperative secretions so that they are made only when the required nutrients are in abundance[94]. Such prudent regulation makes secretions 'cheap' and helps to protect against cheater mutants by making cooperation effectively cost free.

Evolutionary change: cooption. Evolution is about genetic change over time and, in addition to real-time dynamics, the social component of natural selection affects how molecular systems change over time, as described below.

One recurring pattern of evolutionary change is cooption of non-cooperative traits for new cooperative functions. For example, although cellular differentiation may explain much of the functional purpose of DNA methylation, microRNAs and splicing, the genetic origin of all of these mechanisms can be traced back to competition between transposable elements and their repressors[26,95]. Furthermore, the most impressive diversity generator of all, the adaptive immune system, relies on enzymes that, again, originated as selfish elements[86]. The ability of selfish elements to recognize and manipulate DNA appears to have been invaluable for the development of modern multicellular organisms.

Other examples of cooption are more species specific. An RNAi study showed that termite queens signal their presence — and prevent workers from becoming reproductive — by using a glycosyl hydrolase[96]. Members of this class of enzyme are used by termites to digest cellulose but, when applied to smaller substrates, they have the potential to release volatile signals. An enzyme central to the basic ecology of the termites — eating wood — seems to have found a new function in the social context.

Evolutionary change: protein evolution. Social effects have the potential to both decrease and increase the rates of molecular change. The evolution of cooperative phenotypes may constrain molecular change when pleiotropic constraints are important for their persistence[47]. In the honeybee (FIG. 3), proteins that are more strongly expressed in queens show higher variability than do worker-biased proteins[97], which might suggest functional constraints on the proteins of altruistic individuals. However, pleiotropic constraints will rarely prevent cheating entirely. Some natural strains of *D. discoideum*, for example, successfully cheat other strains[98]. And laboratory selection experiments have generated cheater mutants in *D. discoideum*[99] as well as in the socially similar bacterium *Myxoccus xanthus*[100]. One can then use these mutants to select for a second set of mutants that resist cheating[100,101], suggesting that cycles of cheater and resistance evolution are possible[102]. Such co-evolutionary processes not only cause change in molecular systems, they can also increase the standing genetic variation in the population. As discussed above, the spectacular variability in MHC loci is thought to arise because parasites adapt to the most common MHC genotypes[103]. The result is negative frequency-dependent selection, whereby the benefit of a particular MHC allele decreases as it becomes more frequent in a population. This can drive the continual turnover of genotypes and maintain diversity, because no one genotype can dominate.

Another way to evaluate the effects of social evolution on rates of molecular change is to correlate sociality with changes in DNA sequence across genes and species. Recent natural selection for a new function is expected to cause more changes at sites that cause amino acid changes (non-synonymous changes) than at sites that do not (synonymous change). There is evidence that social evolution can affect this pattern. An excess of non-synonymous changes has been associated with

Neighbour-modulated fitness theory
Closely aligned to inclusive fitness theory, this framework analyses natural selection in terms of the effects on the actor of its social trait, combined with the effects of the social trait in other individuals on the actor, where the latter effects are weighted by the genetic similarity (relatedness) between the actor and others.

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Social phenotype
A phenotype in one individual that affects the fitness of other individuals. 'Individual' here could mean a gene, cell, organism or even a group — whatever is appropriate for the analysis of the phenotype.

social phenotypes in diverse systems, including selfish genetic elements and their repressors[26,104], sperm membrane genes[105] and bacterial secretion[106]. There are confounding effects, however, because rates of genetic change are additionally influenced by the effectiveness with which deleterious alleles are removed from a population (purifying selection). Evolutionary rates are also affected by fundamental factors such as protein abundance[107] and localization[108], and social phenotypes might generally experience weaker selection because they are often only expressed some of the time. When this weakens purifying selection, it will tend to increase the genetic diversity associated with social traits relative to the diversity associated with non-social traits[109]. Finally, mutation rate is another important factor. For example, high mutation rate may explain the extreme variability that is seen at centromeres as opposed to a hypothesis of selfish element evolution[110,111]. Only by carefully dissecting the potential effects of all such factors can one hope to see the true effect of social evolution on evolutionary rates.

Evolutionary change: gene expression evolution. Little is understood of the link between social evolution and the rates at which gene expression levels change over evolutionary time. However, recent work with yeast suggests that genes with high responsiveness in expression in short timescales also show a high evolutionary variability in gene expression[112]. These responsive genes tend to encode proteins that interact with the environment and mediate the response to environmental changes[112], and many cooperative traits are conditionally expressed[94]. There is a hint, then, that social phenotypes may drive high rates of gene expression evolution.

Conclusion

As the process of adaptation causes genetic change at a locus, there are nearly always consequences for the propagation of other loci, be they in the same or a different organism, or in the same or a different species (FIG. 1). Sometimes these fitness effects will map cleanly onto the typical view of evolution by natural selection, such as a mutation that makes a bacterium divide more rapidly. However, I hope to have illustrated that social effects can be counter-intuitive for the typical view of evolution. These effects influence not only social phenotypes but also the underlying networks of molecular interactions. Sociobiology offers a framework to make sense of this complexity. Much of this framework, however, was not developed with molecular biology in mind. There is the potential for development and refinement, as well as synthesizing with associated ideas (BOX 3).

This synthesis is underway. My argument that sociobiology is important for molecular biology is mirrored in a number of contemporary themes in the literature. The growing field of sociogenomics[5–9] is revealing how complex social behaviours can be dissected at the molecular level. Related to this, evolutionary biologists are putting increasing emphasis on developmental biology as the central process that converts genotype to phenotype in multicellular species[113,114]. On the theoretical side, models of collective behaviour are revealing how interactions among groups of cells or organisms can produce impressive, and robust, higher-level structure[115–117]. And at the subcellular level, the use of network theory has similar goals for understanding the structure to be found in gene regulation and metabolism[36,118].

A goal for the future is to combine such systems-level analyses of genetics, development and social organization with an appreciation that any given system is strongly affected by the scale of natural selection and the importance of cooperation[119,120]. Indeed, whereas sociobiology tends to focus on altruism, its main lesson for molecular biology is perhaps that there are nested layers of competition, both ancient and modern, that affect every genotype.

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Competing interests statement
The author declares no competing financial interests.

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