Inclusive Fitness and the Sociobiology of the Genome

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September 9, 2013

Abstract

Hamilton's Rule provides conditions for the evolutionary success of a gene. These conditions ensure that the gene is *selfish* in the sense described by Richard Dawkins (1976). By this very fact, inclusive fitness does not explain why the genome of a successful species consists of genes that predominantly cooperate in promoting the fitness of their carriers.

Hamilton's rule shows that prosocial altruistic genes, antisocial predatory genes, and antisocial spiteful genes can all enjoy evolutionary success, and gives no reason why or how the prosocial altruistic genes come to predominate in successful organisms.

The genome evolves when it suppresses alleles that detract from, and promotes alleles that enhance, the fitness of the reproductive population. This implies first that genes do not maximize inclusive fitness but rather interact strategically in complex ways involving collaboration, promotion, and suppression across loci and across individual carriers. It also implies that for any species there is a *core genome* that specifies the common phenotypic characteristics of the species, including biochemical interactions among loci and social interactions among individuals. The core genome, not the gene, is the central replicator in species evolution.

Hamilton's Rule provides conditions for the evolutionary success of a gene. These conditions ensure that the gene is *selfish* in the sense described by Richard Dawkins (1976). In particular, as Hamilton's rule makes clear, the conditions for the evolutionary success of a gene are distinct from the conditions under which the gene enhances the fitness of its carrier. However, it is equally true that the evolutionary success of a gene does not ensure that it enhances the mean fitness of members of the reproductive population. Therefore inclusive fitness does not explain why the genome of a successful species consists of genes that predominantly

*I would like to thank Samuel Bowles, David Haig, Steven Frank, Peter Godfrey-Smith, David Queller, Laurent Lehmann, Samir Okasha, Peter Richerson,Joan Roughgarden, Elliot Sober, and Mattijs van Veelen for advice in preparing this paper.

cooperate in promoting the fitness of the reproductive population. Indeed, Hamilton's rule equally predicts the evolutionary success of prosocial altruistic genes, antisocial predatory genes, and antisocial spiteful genes (these terms are formally defined below).

The genome evolves when it suppresses alleles that detract from and promotes alleles that enhance the fitness of reproductive population. This bears two implications that are developed in this paper. First, genes do not maximize inclusive fitness, but rather interact strategically in a biochemically, and socially complex manner involving collaboration, promotion, and suppression across loci and across carriers. Second, for any species there is a *core genome* that specifies the common phenotypic characteristics of the species, including biochemical interactions among loci and social interactions among individuals. The core genome is a *replicator* in sense of remaining intact across many generations, despite meiosis and crossover. The core genome, not the gene is the central replicator in species evolution.

1 Hamilton's Rule

Classical genetics did not model cases in which individuals sacrifice on behalf of non-offspring, such as sterile workers in an insect colony (Wheeler 1928), cooperative breeding in birds (Skutch 1961), and altruistic behavior in humans (Darwin 1871). This problem was addressed by William Hamilton (1963, 1964ab, 1970), who noted that if a gene favorable to helping others is likely to be present in the recipient of an altruistic act, then the gene could evolve even if it reduces the fitness of the carrier. Hamilton called this *inclusive fitness* theory.

Hamilton developed a simple inequality, operating at the level of the gene, determining the conditions for the evolutionary success of an allele. The contemporary formulation of this rule (we will return to Hamilton's original formulation later) says that if an allele in individual A increases the fitness of individual B whose degree of relatedness to A is r, and if the cost to A is c, while the fitness benefit to B is b, then the allele will evolve if

$$br > c. \tag{1}$$

We call $br - c$ the *inclusive fitness* of the focal allele. Subsequent research supported some of Hamilton's major predictions (Maynard Smith and Ridpath 1972; Brown, 1974; West-Eberard 1975; Krackauer, 2005).

To derive Hamilton's Rule in the case of a haploid species, suppose there is an allele at a locus of the genome that induces carrier A to incur a fitness change c that leads to a fitness change b to individual B. If $b > 0$, A bestows a gain upon

B, and if $c > 0$, A experiences a fitness loss. However, in general we make no presumption concerning the signs or magnitudes of b and c, except that selection is not so strong that the population becomes extinct in a single period. Suppose the frequency of this allele in the population is q, where $0 < q < 1$, and the probability that B has a copy of the allele is p. Then if the size of the population is n, there are qn individuals with the focal allele, they change the number of members of the population from n to $n + qn(b - c)$, and they change the number of focal alleles from qn to $qn + qn(pb - c)$. Thus the frequency of the allele from one period to the next will increase if

$$\Delta q = \frac{qn + qn(pb - c)}{n + qn(b - c)} - q = \frac{q(1 - q)}{1 + q(b - c)} \left(b \frac{p - q}{1 - q} - c \right) > 0. \quad (2)$$

The condition for an increase in the focal allele thus is

$$b \left(\frac{p - q}{1 - q} \right) > c. \quad (3)$$

Note that when carriers interact only with other carriers, $p = 1$, so Hamilton's rule is satisfied whenever $b > c$, while if interaction is random, so $p = q$, then Hamilton's rule can never be satisfied when the cost c is positive.

The equivalence of (3) with Hamilton's rule (1) requires

$$p = r + (1 - r)q. \quad (4)$$

In this equation, r is commonly interpreted as the probability that an agent A with focal allele a will encounter another agent B who also has the allele, through some biophysical or social regularity specific to the species. With probability $1 - r$, it is assumed that the recipient B is a random member of the population, so B has the focal allele with a probability equal to the frequency q of the allele in the population. Because r is a probability under this interpretation, $0 \leq r \leq 1$, so if $c > 0$, then from (1) it follows that $b > 0$ as well, so $b - c = br - c + b(1 - r) > 0$. But then the population change $qn(b - c)$ is also strictly positive.

Often (4) is explained using the concept of identity by descent (Malécot 1948, Crow 1954), where r is the probability that both donor A and recipient B have inherited the same focal allele from a common ancestor. For instance, if A and B are full siblings, then $r = 1/2$ because this is the probability that both have inherited the focal allele from the same parent. Moreover, if the siblings have inherited the focal allele from different parents, then they will still be the same allele with a probability equal to the frequency of the allele in the population, assuming no assortative mating. In general, r will then be the expected degree of identity by descent of recipients.

The rather stunning conclusion from this exercise in elementary algebra and gene-counting is what we may call Hamilton's Harmony Principle. To state this principle succinctly, we say the allele a is *helpful* if its carriers enhance the fitness of other individuals that it encounters ($b > 0$), *altruistic* if it incurs a fitness cost in so doing ($c > 0$), and *prosocial* if increases mean population fitness. We then have:

Hamilton's Harmony Principle: A helpful gene is evolutionarily successful only if it satisfies Hamilton's rule (1), in which case it is necessarily prosocial.
Note that it is possible but not necessary that such a gene be altruistic, although the altruistic case is the one that is not handled by classical genetics.

The importance of this principle for sociobiology is inestimable, and mirrors similar assertions concerning the social value of selfishness in humans offered by Bernard Mandeville in his famous *Fable of the Bees* (1705), in which "private vices" give rise to "public virtues," and Adam Smith's (1776) equally famous dictum, "It is not from the benevolence of the butcher, the brewer, or the baker that we expect our dinner, but from their regard to their own interest." While economists have determined the precise conditions—they are far from universal–under which Mandeville and Smith are correct (Mas-Colell et al. 1995), Hamilton's Harmony Principle is true in general.

However, the assumption in this principle that the gene is helpful leaves open the question as to the evolutionary status of genes that are not helpful. An alternative to Hamilton's Harmony Principle is, indeed, *prima facie* equally possible. Suppose the focal allele is *predatory* in the sense that its carriers benefit ($c < 0$), and is *harmful* in that it imposes costs on other individuals ($b < 0$). Then Hamilton's rule becomes $(-b)r < (-c)$, which can be satisfied even though the focal allele is *antisocial* in the sense that $b - c < 0$. For instance, suppose $b = -4$, $c = -3$ and $r = 1/2$. Then $br - c = 1 > 0$, so Hamilton's rule is satisfied, but $b - c = -1$, so the allele is antisocial. In fact, the focal allele in this case is evolutionarily successful yet antisocial for any $r < 3/4$.

It is common for sociobiologists to invoke what I have termed Hamilton's Harmony Principle to explain the appearance of design in nature (Dawkins 1996), and the tendency for species exhibiting a high level of social cooperation to exhibit a high degree of relatedness as well. For instance, in a letter to the journal *Nature* protesting a critique of Hamilton's rule by Nowak et al. (2010), signed by 153 biological researchers, Abbot et al. (2011) assert:

> Natural selection explains the appearance of design in the living world, and inclusive fitness theory explains what this design is for. Specifically, natural selection leads organisms to become adapted as if to

maximize their inclusive fitness.

In fact, inclusive fitness theory does nothing of the sort, because we have an equally possible scenario:

Hamilton's Disharmony Principle: A predatory gene that is harmful may satisfy Hamilton's rule despite being antisocial.
where we say an allele is *antisocial* if it is evolutionarily successful at the expense of mean population fitness.

Moreover, in our basic equation (3) for Hamilton's rule, $p < q$ is *prima facie* as likely as $p > q$. In the case $p < q$, we see that r in (4) must be negative, so r cannot be interpreted as a probability at all. In particular, r cannot then be interpreted as a degree of relatedness in the usual sense of the term. Indeed, it is a common occurrence that helping is costly ($c > 0$), but helping involves reducing the fitness of others, so $b < 0$, and (4) can hold with $r < 0$, while the focal allele is still altruistic ($c > 0$). Examples are warfare in ants (Hölldobler and Wilson 1990) and humans (Bowles and Gintis 2011), as well as generally spiteful behavior in many species (Hamilton 1970, Foster et al. 2001, Gardner et al. 2004).

Hamilton's Rule can be extended to deal with heterogeneous relatedness, diploidy, dominance, coordinated cooperation, local resource competition, inbreeding, as well as other complications (Uyenoyama and Feldman 1980, Michod and Hamilton 1980, Queller 1992, Wilson et al. 1992, Taylor 1992, Rousset and Billard 2007), with an equation closely resembling (1) continuing to hold. In general, however, the frequency q will appear in (1), and if selection is strong, b and c may be functions of q as well, so the interpretation of r as relatedness becomes accordingly more complex (Michod and Hamilton 1980).

Of course, in general b and c will also depend on the frequency of alleles at other loci of the genome, and since the change in frequency q of the focal allele in the population will affect the relative fitnesses of alleles at other loci, inducing changes in frequency at these loci, which in turn will affect the values of b, c, and even r. For this reason, Hamilton's rule presupposes *weak selection*, in the sense that gene frequencies do not change appreciably in a single reproduction period. Therefore Hamilton's rule does not imply that a successful allele will move to fixation in the genome. Moreover, alleles at other loci that are enhanced in inclusive fitness by the focal allele's expansion may undergo mutations that enhance the inclusive fitness of the focal allele, while alleles at other loci that are harmed by the expansion of the focal allele may develop mutations that suppress the focal allele.

2 What Hamilton's Rule Does and Does Not Say

Hamilton's inclusive fitness criterion provides an analytically rigorous condition for the evolutionary success of an allele. Because this condition can be satisfied in the case of genes that sacrifice on behalf of relatives ($b, c, r > 0$). Hamilton (1964b) provided a plausible explanation of social cooperation. However, inclusive fitness theory renders equally plausible biochemical and social behaviors that are comparatively rarely observed. This is because, as is clear from (3) and (4), Hamilton's Rule does not place any limitations on the signs of the three variables that occur therein. For instance, assuming random mutations, spiteful behavior, where $r, b < 0$ and $c > 0$, is *prima facie* equally as likely as $r, b, c > 0$, in the sense that to every pair (r, b) satisfying Hamilton's rule, there is another pair $(-r, -b)$ that does so as well. Moreover, the condition for the focal allele to enhance the fitness of the population is $n + qn(b - c) > n$, or $b > c$, as we see from (2). If Hamilton's Rule is satisfied by (b, r, c) with $b, r, c > 0$, then the rule is equally satisfied by $(-b, -r, c)$, in which case $b - c < 0$. Inclusive fitness theory therefore makes no prediction concerning the effect of a successful gene on the fitness of its carrier when $c > 0$.

It might be thought that in fact the case $r < 0$ is relatively rarely encountered, and therefore this problem with Hamilton's rule can be safely ignored. The problem, however, is that Hamilton's rule does not explain *why* this case is rarely encountered. Of course, we can simply say that natural selection is unfavorable to such cases, which is true. However, this brings us back to the state of population biology in 1963, before the appearance of Hamilton's rule, when there was no genome-level analysis of social interaction among individuals.

A new set of problems arise if $c < 0$, which is *prima facie* as plausible as $c > 0$. These problems are suggested by the Hamilton Disharmony Principle. Indeed, a mutant allele with $c < 0$ has no relatives, so $r = 0$ and Hamilton's Rule is necessarily satisfied. Moreover, when the focal allele increases in frequency and $r > 0$, then for $b < 0$ and $|b| > |c|$, the focal allele, which we call *predatory*, is necessarily both harmful ($b < 0$) and antisocial ($b - c < 0$). Evolutionary dynamics of course generally suppress such "outlaw" mutants (Leigh 1977). The dynamics of outlaw suppression, however, are not and cannot be represented in inclusive fitness theory, which does not model the interaction among genetic loci.

In principle there are twelve possibilities for the signs of b, r, and c, ignoring cases where b or c is zero, but four of these cannot satisfy Hamilton's rule. As stressed by Hamilton (1964a), Bourke (2011) and van Veelen (2009), Hamilton's Rule allows us to study the other eight categories of social interaction in terms of the concepts *altruistic*, *cooperative*, *predatory*, and *spiteful*. These possibilities are depicted in Table 1. We call the allele *altruistic* if $b, c > 0$, so when Hamilton's

b	c	$r > 0$	$r = 0$	$r < 0$
> 0	> 0	Altruistic	—	
> 0	< 0	Cooperative		
< 0	> 0	—		Spiteful
< 0	< 0	Predatory		

Table 1: Variety of Behaviors that can Satisfy Hamilton's Rule

rule is satisfied we have $r > 0$ and the focal allele sacrifices an amount of fitness c in order to add an amount b of fitness to the recipient. If $b > 0 > c$, then the allele is *cooperative*, and since $b - c > 0$, the allele contributes unambiguously to the fitness of its carrier. A cooperative allele will always be selected, as in this case Hamilton's Rule is always satisfied. If $r < 0$ in this case, the helping allele is conferring benefits preferentially on non-relatives, and so long as these benefits are not too large, i.e., as long as $b|r| < |c|$, the focal allele will increase in frequency. If $c < 0$ and $b < 0$, we call the allele *predatory*. When $r > 0$ in this case, if Hamilton's rule is satisfied provided relatives are not too greatly harmed; i.e., provided $|b|r < |c|$. When $r < 0$ in the selfish case, Hamilton's Rule is necessarily satisfied and the gene will evolve, although it enhances the fitness of the genome only if the harm b is sufficiently small ($|b| < |c|$). Finally, if $c > 0 > b$, we call the allele *spiteful* because the focal individuals pays a fitness cost to hurt the recipient. According to Hamilton's Rule, a spiteful allele will evolve if $r < 0$ and $|b||r| > c$, although it is uniformly destructive to carriers of the genome. (Hamilton 1970, Gardner et al. 2004). For example, a worker in an insect colony who cares for larvae may have a gene that leads it to kill larvae that are not full siblings, or in a diploid species, a germline allele may disable the other allele when the carrier is heterozygous at the focal locus.

3 Inclusive Fitness and Kin Selection

William Hamilton's early work in inclusive fitness focused on the role of genealogical kinship in promoting prosocial behavior. Hamilton writes, in his first full presentation of inclusive fitness theory (Hamilton 1964a, p. 19):

> In the hope that it may provide a useful summary, we therefore hazard the following generalized unrigorous statement of the main principle that has emerged from the model. The social behaviour of a species evolves in such a way that in each distinct behaviour-evoking situation the individual will seem to value his neighbours' fitness against his

> own according to the coefficients of relationship appropriate to that situation.

Because of this close association between inclusive fitness and the social relations among genealogical relatives, John **?** called Hamilton's theory *kin selection*, by which he meant that individuals are predisposed to sacrifice on behalf of highly related family members.

A decade after Hamilton's seminal inclusive fitness papers, motivated by new empirical evidence and Price's equation (Price 1970), **?** revised his views, writing:

> Kinship should be considered just one way of getting positive regression of genotype... the inclusive fitness concept is more general than kin selection.

Nevertheless the two are often equated, even in the technical literature. For instance, throughout his authoritative presentation of sexual allocation theory, Stuart **?**, identifies inclusive fitness with kin selection in several places and never distinguishes between the two terms at any point in the book.

This idiosyncratic identification is a source of confusion, because for most sociobiologists, kin selection remains, as conceived by **?**, a social dynamic based on close genealogical association:

> By kin selection I mean the evolution of characteristics which favour the survival of close relatives of the affected individual.

The Wikipedia definition is similar:

> Kin selection is the evolutionary strategy that favours the reproductive success of an organism's relatives, even at a cost to the organism's own survival and reproduction.... Kin selection is an instance of inclusive fitness.

Moreover, while kin selection is a special case of inclusive fitness in the sense that Hamilton's rule applies generally, not just to situations where organisms favor their close genealogical kin, in another sense kin selection is far more general than inclusive fitness. This is because in all but the simplest organisms, kin selection does not describe the behavior at a single locus, but rather an inherently social behavior in which individuals recognize their close relatives through complex phenotypic associations that require higher-level cognitive functioning. Indeed, in general these phenotypic associations arise precisely to permit cooperation among close genealogical kin. Moreover, if a mutant gene induces its carriers to interact preferentially with others who have copies of the gene, as recognized by phenotypic characteristics that produced by genes that are linked with the mutant gene,

then such a mutant will be evolutionarily successful only if the association is helpful rather than harmful. Then Hamilton's Harmony principle proves that this gene will be prosocial. We can thus expect kin selection to arise spontaneously in many situations. This of course is observed in many species.

This example shows that, despite the fact that inclusive fitness theory has nothing to say about interactions among loci, it can be a powerful analytical tool when deployed in models of interaction among loci.

4 A Generalized Hamilton's Rule

The focal allele in Hamilton's rule does not confer benefits randomly across the population, but rather targets carriers of the allele (or non-carriers if $r < 0$); i.e., when Hamilton's rule holds, we have $p \neq q$ in (3). But in general the focal allele could be pleiotropic and have more than one targeting pattern. We explore two additional such patterns. First, the focal allele may additionally impose a cost β uniformly on all members of the population. The case $\beta > 0$ occurs in "tragedy of the commons" cases (Hardin 1968, Wenseleers and Ratnieks 2004), such as when the focal allele bestows benefits preferentially on copies of itself in other carriers through an action that depletes a protein used in chemical processes by somatic cells (Noble 2011). The case $\beta < 0$ occurs in a parasite when the focal allele induces its carriers to suppress members of a rapidly growing strain that kills its host prematurely (Frank 1996).

We will also consider the case where the focal allele imposes a cost α on carriers who do not have a copy of the focal allele (Keller and Ross 1998). For example, $\alpha > 0$ can occur if A redirects brooding care from non-relative to relative larvae in an insect colony, and $\alpha < 0$ can occur if the focal allele helps other alleles at the focal locus that benefits carriers by avoiding possibly deleterious homozygosity at the focal locus. If $\alpha f(q)$ is the fitness reduction of non-relatives when the fraction of focal alleles in the population is q, we must have $f(0) = f(1) = 0$, and we can assume $f'(0) = 1$ and $f'(1)$=0. We assume the simplest function with these properties is $f(q) = q(1-q)^2$, although the exact shape of the function is not important.

If the population size is n in the current period, population size n' in the next period will include $n + qn(b-c)$ individuals because of the helping behavior, but this will be reduced by $n\beta q$ and $n\alpha f(q)$. The number of relatives of the helping allele in the current period is qn, which is increased by the helping behavior by $qn(pr-c)$, and decreased through lower efficiency by $qn\beta q$. Thus the new population size is

$$n' = n(1 - \alpha q(1-q)^2 - \beta q) + qn(b-c), \tag{5}$$

and (2) becomes

$$\Delta q = \frac{qn(1-\beta q) + qn(pb-c)}{n(1-\alpha q(1-q)^2 - \beta q) + qn(b-c)} - q > 0, \tag{6}$$

which simplifies to

$$b(p-q) + \alpha q(1-q)^2 > c(1-q). \tag{7}$$

Substituting $p = r + (1-p)q$, we get the Generalized Hamilton's Rule

$$br > c - \alpha q(1-q). \tag{8}$$

An alternative derivation of the Generalized Hamilton's Rule using the regression approach is presented in Appendix A1.

The effect of an increase in the focal allele on population fitness is the sign of dn'/dq, which is given by

$$\frac{dn'}{dq} = n(b - c - \alpha(1 - 4q + 3q^2) - \beta). \tag{9}$$

Note that in the case of Hamilton's Rule, which is the above with $\alpha = \beta = 0$, population fitness increases with the frequency of the helping allele in the case of altruism or cooperation, where $b > c$, and decreases in the case of spite ($b - c < 0$). In the case of the Generalized Hamilton's Rule, the fitness effect is indeterminate. As we explain below, Hamilton (1964a) included the $\beta \neq 0$ affect in his calculations, but he did not consider the case where the generalized fitness effects are unevenly distributed among the alleles at the focal locus ($\alpha \neq 0$).

It is useful to give descriptive names to the social interactions when α and/or β is nonzero. We may call the case $\alpha > 0$ *theft*, the case $\beta > 0$ *pollution*, and the case $\beta < 0$ and $\alpha < 0$ as *social generosity* and *non-kin generosity*, respectively. In the socially generous case, we also say that the allele is producing a *public good* (West et al. 2007, p. 57). This follows the common use of the term in economic theory (Olson 1965). Equation (8) shows *the degree of pollution or social generosity has no bearing on whether the allele can evolve*. Moreover, a thieving altruist ($b, c, \alpha > 0$) will evolve, as will a thieving cooperative allele ($b, \alpha > 0 > c$). Finally, the producer of a public good will evolve only if it gains in inclusive fitness from so doing ($br > c$).

The most critical implication of the Generalized Hamilton's Rule is that neither social generosity nor pollution has any bearing on whether an allele will evolve, as

seen in equation (8), despite the fact that a socially generous allele unambiguously enhances the fitness its host, and a polluting allele unambiguously has the opposite effect, as seen in equation (9).

It is interesting to note that Hamilton's seminal paper (1964a) explicitly includes the pollution and public goods aspect of inclusive fitness, an aspect of his analysis that later writers have ignored. Hamilton called the public good/pollution effect of Generalized Hamilton's rule a *dilution effect* because it affect the rate but not direction of change in the frequency of the focal allele. Hamilton also notes that the dilution effect can lead a successful allele to reduce population fitness. A streamlined presentation of Hamilton's argument, which is quite opaque in the original, is presented in Appendix A3.

5 Genes Do Not Maximization Inclusive Fitness

If the genome's success is based on a pattern of cooperation, promotion, and suppression across loci, which will occur, for instance, if the production of a protein, RNA sequence, or social behavior requires the collaborative activity of many genes (Noble 2011), or if there are frequency dependent social interactions among individuals in a social species (Maynard Smith 1982), then neither genes nor individuals can be characterized as maximizing inclusive fitness. The conditions under which a population genetics model of gene flow implies fitness maximization at the gene or individual level has been carefully explored (Grafen 1999, 2002, 2006; Metz et al. 2008; Gardner and Wild 2011; Gardner West and Wild 2011). With frequency independence, they affirm the maximization hypothesis. With frequency dependence, the hypothesis it is in general false, and no careful researcher has ever claimed otherwise.

For a simple example, consider two loci, with alleles a_1, b_1 at the first locus and alleles a_2, b_2 at the second. Suppose b_2 is favored over a_2 by an amount γ_2, but suppose a_1 produces a substance that favors a_2. Suppose a_1 is favored over b_1 by an amount γ_1, but a_2 produces a substance that favors b_1. Let q_1 and q_2 be the frequency of a_1 and a_2 in the population, respectively. Assuming the interactions are linear, we can write

$$\frac{dq_1}{dt} = q_1(\gamma_1 - \beta_1 q_2) \tag{10}$$

$$\frac{dq_2}{dt} = q_2(\beta_2 q_1 - \gamma_2), \tag{11}$$

where $\alpha_1, \alpha_2, \beta_1, \beta_2 > 0$ and $\alpha_1/\beta_1, \alpha_2/\beta_2 < 1$. The unique equilibrium of this system is $(q_1^*, q_2^*) = (\alpha_1/\beta_1, \alpha_2/\beta_2)$. This is a neutrally stable focus known as the *Lotka-Voltera* model (Takeuchi 1996). Because paths through time in this model

are closed loops, all alleles eventually return to an earlier level of inclusive fitness, which means that the fitness of individual alleles oscillate in time. This precludes fitness maximization (Moran 1964, Akin 1982). Moreover, it is likely that only one of the four combinations (a_i, b_j) for $i, j \in \{1, 2\}$ maximizes the fitness of carriers of the genome. Therefore, a mutant regulator gene that suppresses the unfavorable combinations may well arise, in which case it will grow to fixation, as will the favorable alleles at the two loci.

The general point is that if there is a conflict among loci concerning fitness maximization, and if the frequency of alleles at one locus affect the fitness costs and payoffs at other loci, then it is logically impossible that the allele at each locus maximize its inclusive fitness. Rather, the proper setting is *evolutionary game theory*, in which players (i.e., loci) respond strategically to the behavior of other players (i.e., change allele frequency at a locus), and equilibrium, if it is attained, is likely to be a Nash equilibrium in the genome in which each gene plays a best response to the strategy choice of other genes; that is, inclusive fitness cannot be increased at any locus without inducing inclusive fitness-reducing costly countermoves at other loci (Maynard Smith 1982, Hammerstein and Reichert 1988, Taylor 1989, Weibull 1995, Nowak 2006, Traulsen and Nowak 2006, Gintis 2009). In a dynamic context, standard game theory must be supplemented by additional analytical tools that deal with the fact that the rules of the game themselves, as inscribed in the genomes of the players, will evolve according to the dynamics of natural selection (Levin 2009, Akçay and Roughgarden 2011, Akçay and van Cleve 2012). For instance, the rate of recombination in the genome can evolve to counteract collusion among mutant alleles.

6 The Core Genome as Replicator

Many biologists have recognized that a gene promotes the fitness of its host only if it is complemented by a well-orchestrated configuration of genes with which it interacts (Sober and Lewontin 1982, Hammerstein and Leimar 2006, Noble 2011). Some theorists rely on Hamilton's Rule to maintain the contrary position that the gene is the only, or the most important, replicator (Dawkins 1976). Because in species that reproduce using meiosis and recombination, the genome dies with the body it inhabits, and is torn apart and reassembled in its offspring, Dawkins (1982b, p. 47) argues, the individual is but a vehicle for the transportation of genes across metazoan bodies. Dawkins writes that a replicator must have a

> low rate of spontaneous, endogenous change, if the selective advantage of its phenotypic effects is to have any significant evolutionary effect.... too long a piece of chromosome will quantitatively disqual-

> ify itself as a potential unit of selection, since it will run too high a risk of being split by crossing over in any generation.

Dawkins is correct in maintaining that the individual is a vehicle and not a replicator. However, the results of gene sequencing show that all but a small fraction of genes in a metazoan species, abstracting from rare mutations, are shared by all individuals in the reproductive population, or fall into a few categories that are preserved across generations. Among these categories are *synonymous*, *neutral*, and *mixed strategy* gene sets. A *synonymous gene set* consists of alleles at a single locus whose differences are base substitutions that entail identical protein, enzyme, and regulatory products, and hence do not have distinct phenotypic effects. Non-synonymous alleles that have fitness neutral, or near-neutral, phenotypic effects (e.g., tail length or eye color), form *neutral gene sets* that are highly stable across generations despite their somewhat labile internal composition. For instance, body size may be fitness independent over some range, and many genes interact to produce a phenotypic body size that is generally in the fitness-neutral range. The frequency distribution of these genes in the core genome is determined by natural selection and unchanged by meiosis and crossover.

In addition, if a set of alleles at a particular locus have equal fitness but distinct phenotypic effects, and if this set is preserved across generations, the alleles are likely to be equally fit alternative strategies in a Nash equilibrium among loci, each being a fitness enhancing best response to the probability distribution of the other loci in the genome. We call such alleles *mixed strategy sets*. For example, a population equilibrium can sustain a positive fraction of altruistic and selfish alleles, or alleles promoting aggressive *vs*. docile behavior, under certain conditions. Similarly, loci that protect carriers against frequency-dependent variations in environmental conditions, including that of bacterial and viral enemies, can be maintained in a polyallelic state as a means of species-level risk reduction. These include the *immune system gene sets* that maintain considerable heterogeneity to deal with a variety of possible infectious agents.

Another example of a mixed strategy gene set is the interaction of suppressor genes and their targets, where the fitness of the suppressor depends on a positive frequency of target genes. Leffler (2013) document such a set stabilized by balancing selection at least since the primate-hominin split. Finally, heterozygote advantage involves a pair of alleles that maintain positive frequency despite the fitness cost to homozygous carriers. We may call this an *overdominance set*. Additional features arise in dealing with sex-linked genes, including maternal-paternal conflict, but these also can be identified as characteristics of the species that are conserved across many generations.

In species that recognize individuals, including many birds and mammals, such recognition is based wholly on genes outside the core genome, which are shuffled and redistributed through meiosis and recombination. Species that recognize group differences, such as humans, succeed because of linkage disequilibrium among non-core loci that is maintained by assortative mating.

In sum, the typical phenotypic characteristics of the species, including biochemistry, physiology, and social behavior, are conserved despite crossover and meiosis. We call the genes that support this phenotypic commonality the species' *core genome* and the loci that are more or less intraspecifically heterogeneous the *variant genome*—see Riley and Lizotte-Waniewski (2009) for an application to bacterial species. The core genome is a replicator and hence subject to the laws of natural selection. Individuals, social groups, as well as their extended phenotypes and constructed niches, simply vehicles for the expression and evolution of the core genome.

The sociobiological point is that the core genome of social species codes not only for the general phenotypic character of the individual, but also for the species' extended phenotype and characteristic social behaviors. If the species is commonly partitioned into groups, such as insect colonies, schools of fish, herds of elephants, primate communities, and hunter-gatherer groups, then these groupings are the phenotypic expressions of the core genome of the species, as modulated by its characteristic environment, and are subject to selection on that basis.

Another way of expressing this point is to note that sociality in a species is an extension of multicellular cooperation within the genome, and indeed there is a common population model which subsumes both as special and virtually isomorphic cases (Gardner et al. 2007). Because cooperation among loci within the genome is limited to a single instance of a genetic locus, even the simplest of fitness-enhancing processes, such as the sharing of genetic material in microbes and sexual reproduction in metazoans, requires the interaction of two or more copies of key genetic loci, and this can occur only through interactions between carriers. This interaction of loci is precisely the subject matter of sociobiology, and the processes involved are characteristic of social species. Just as the genome codes for the patterns of interaction among loci in the genome, so it codes for the characteristic patterns of interactions of loci in two or more carriers; i.e., the genome codes for the social structure of the organisms it creates. In particular, social species live in groups precisely when the conditions for such groups are coded in the core genome.

Just as a computer program includes different functional subprograms, some of which work alone and others of which operate with many copies functioning in parallel, with an overarching set of signaling and behavior protocols that facilitate communication and collaboration across subprograms, so the core genome endows

its carriers with the protocols for fitness-enhancing interaction among genetic loci located in a plurality of individuals. If the carriers of the core genome form social groups of characteristic size, composition, and behavior, this is because the core genome provides its carriers with instructions as to which environments to seek, and within these environments, how to interact with conspecifics. Social groups are thus genetic rather than epigenetic, although in advanced social species epigenetic cultural forces may be integrally involved in the constitution of social groups. Because social groups are expressions of the core genome, and groups with particular characteristics will evolve only if they enhance the fitness of the reproductive population supported by the core genome, we conclude that if we are to use the term "group selection" at all, it must be understood as section *for the network of genes that underlie the constitution of the social group*. In this context, the idea of group selection as competition among groups with the reproduction of the successful groups is misleading because social groups are not units of selection, but rather vehicles that are generally reconstituted anew in each generation.

7 Conclusion

William Hamilton's inclusive fitness theory is the analytical starting point of modern sociobiology. Inclusive fitness theory justifies the stress by Richard Dawkins and his followers on the selfish nature of the gene, as well as on the status of the individual as vehicle rather than replicator. But neither inclusive fitness theory, nor any other plausible theory, supports the notion that the gene is the most important replicator, or that genes maximize inclusive fitness. We have argued that the core genome is the critical replicator in the evolution of complex multicellular species, and that the success of the core genome depends on its solving coordination problems among its genetic loci.

The evolutionary process, from the first RNA molecules to advanced metazoans and complex social species, involves solving the problem of promoting cooperation among selfish genes (Maynard Smith and Szathmáry 1995). That genes generally contribute to the fitness of the individuals in which they reside is the result, not of inclusive fitness maximization, but of a complex evolutionary and intragenomic dynamic involving the suppression of antisocial and promotion of prosocial alleles (Leigh 1971, Buss 1987, Michod 1997, Noble 2011).

The evolutionary forces that determine the complex interactions among loci in metazoans and among individuals in social species must be studied using, in addition to inclusive fitness theory, the phenotypic gambit (Grafen 1984), evolutionary game theory (Wilson 1977, Taylor 1992, Taylor 1996), agent-based modeling (Gintis 2009), the physiology of suppressor and promoter genes (Leigh 1977,

Noble 2011), as well as species-level systematics and ecology.

In their famous critique of inclusive fitness theory as an explanation of cooperation in general, and eusociality in particular, Nowak et al. (2010) correctly observe:

> Advocates of inclusive fitness theory claim that many empirical studies support their theory. But often the connection that is made between data and theory is superficial. For testing the usefulness of inclusive fitness theory it is not enough to obtain data on genetic relatedness and then look for correlations with social behaviour. Instead one has to perform an inclusive fitness type calculation for the scenario that is being considered and then measure each quantity that appears in the inclusive fitness formula. Such a test has never been performed.

The error of these advocates is to argue that inclusive fitness theory, in the form of Hamilton's Rule, shows that costly cooperation can evolve, then to observe costly cooperation, and finally to claim that their data support inclusive fitness theory. In fact, inclusive fitness theory does not favor cooperation over conflict, so the assertion that it explains cooperation in complex multicellular species and social groups is simply false. Cooperation is the product of evolution at the level of the core genome, a notion not available to inclusive fitness theory as currently formulated.

A1 Regression Approach to the Generalized Hamilton's Rule

Hamilton (1970) developed a more general notion of relatedness based on the Price equation (Price 1970), an approach developed by Queller (1992), Frank (1998), and many others. We can show that this approach can also be used to derive the Generalized Hamilton's Rule (suggested by Laurent Lehmann, personal communication).

Suppose in each period each individual is called upon once to help and once potentially to receive help. Only the individual with the helping allele actually helps. Let w_{ij} be the fitness of an individual where $i = 1$ if the individual has the helping allele, $i = 0$ otherwise, and $j = 1$ if the individual is helped, and $j = 0$ if not helped. Then we can write

$$w_{ij} = 1 - ci + bj - (1 - i)\alpha - \beta q, \tag{A1}$$

where all parameters are as defined in the previous section. The frequency p_{ij} of

type ij is given by

$$\begin{aligned} p_{00} &= (1-q)(r+(1-r)(1-q)) \\ p_{01} &= p_{10} = (1-q)q(1-r) \\ p_{11} &= q(r+(1-r)q). \end{aligned}$$

We can write the regression equations for w_{ij} as

$$\begin{aligned} w_{ij} &= \hat{w}_{ij} + \epsilon_{ij} \\ &= \gamma_0 + \gamma_1 i + \gamma_2 j + \epsilon_{ij}, \end{aligned}$$

where $\hat{w}_{ij}$ is the additive fitness and ϵ_{ij} is an error term. For least squares estimation we minimize

$$\sum_{i=0}^{1}\sum_{j=0}^{1} p_{ij}(w_{ij}-\hat{w}_{ij})^2 = \sum_{i=0}^{1}\sum_{j=0}^{1} p_{ij}\epsilon_{ij}^2$$

with respect to γ_0, γ_1, and γ_2. We find that

$$\begin{aligned} \gamma_0 &= 1-\alpha-q\beta \\ \gamma_1 &= \alpha - c \\ \gamma_2 &= b. \end{aligned}$$

The additive portion of fitness f_1 for the helping allele and f_0 for the non-helping allele are then given by

$$\begin{aligned} f_0 &= (p_{01}\hat{w}_{01} + p_{00}\hat{w}_{00})/(1-q) \\ f_1 &= (p_{11}\hat{w}_{11} + p_{10}\hat{w}_{10})/q \end{aligned}$$

The condition $f_1 > f_0$ then becomes, after some simplification,

$$br + \alpha > c,$$

which is the correct Generalized Hamilton's Rule expression. Note that $br + \alpha - c = \gamma_2 r + \gamma_1$, which means that the reasoning leading to the Generalized Hamilton's Rule is the same as for the traditional Hamilton's rule, only the parameters being altered.

A2 A Model of Outlaw Suppression

We can model outlaw suppression formally in terms of the Generalized Hamilton's Rule. Suppose a polluting allele x satisfies (8), so the GHR is simply Hamilton's Rule:

$$b_x r_x + \alpha_x > c_x. \tag{A2}$$

Suppose further that an allele at locus y imposes a punishment $p_y = -\alpha_y > 0$ on each carrier of the x allele at a cost c_b to itself. The gain to copies of y from suppression of x is

$$b_y = \nu\alpha_x + q_x\beta_x,$$

where ν is the probability that the host of allele y does not contain a copy of the x allele. Allele y also receives the gain b_y so y's net fitness sacrifice is $c_y - b_y$. We assume the cost of punishing p_y is $c_y = \kappa p_y$, for some $\kappa > 0$. The punishment p_y is dissipated, so it does not appear as a transfer of fitness to the y allele. Thus the GHR for the y allele becomes

$$(\nu\alpha_x + q_x\beta_x)(1 + r_y) > \kappa p_y. \tag{A3}$$

The effect of suppression on allele x is to increase the cost of x's action from c_x to $c_x + q_y p_y$. Thus the revised GHR for allele x becomes

$$b_x r_x + \alpha_x > c_x + q_y p_y. \tag{A4}$$

If there is an interior equilibrium to this two-equation system, it is easy to check that the equilibrium values q_x^* and q_y^* satisfy

$$q_x^* = \frac{p_y q_x \kappa}{(1 + r_y)(\nu\alpha_x + q_x\beta_x)} \tag{A5}$$

$$q_y^* = \frac{b_x r_x - c_x + \alpha_x^*}{p_y}. \tag{A6}$$

Clearly if p_y is sufficiently large, the x allele will have a low but non-zero frequency in the population. Thus the GHR shows that an equilibrium level of an outlaw gene can be maintained, and the suppression is more complete the larger is the punishment p_y, the smaller the cost of punishing κp_y, the higher the relatedness r_y at the suppressor gene, the stronger the pollution effect β_x, the stronger the thieving effect α_x, and the lower the probability ν that the suppressor locus contains a copy of the thieving allele. The GHR also shows that suppression will occur where there are no relatedness effect is the outlaw gene; i.e., when $b_x = 0$ or $r_x = 0$ but $c_x < 0$, so the outlaw gene's gain is purely in personal fitness.

A3 Hamilton's Seminal Analysis

The original derivation of the inclusive fitness criterion in Hamilton (1964a) is more general than Hamilton's Rule as commonly expressed, and by modifying one of his assumptions, his derivation gives our Generalized Hamilton's Rule. Following Hamilton (but with simplified notation), suppose the population is diploid, and the alleles at the focal locus are numbered $k = 1, \ldots, m$. Let R_{ij} be the fitness increment (positive or negative) over baseline fitness unity conferred by an individual of genotype ij at the focal locus on members of the population who carry the i allele, and let T_{ij} be the total fitness increment conferred by an individual with genotype ij on the population. Let the frequency of genotype ij be p_{ij}, and let p_i be the frequency of allele i in the population. With random mating, we have $p_{ij} = p_i\, p_j$. Hamilton (1964a) assumes this, but this plays no role in the analysis. The total fitness effect of one individual carrying allele i at the focal locus is then given by

$$T_i = \sum_j p_{ij}\, T_{ij}\,, \tag{A7}$$

and the total fitness effect on allele i due to one carrier of allele i is given by

$$R_i = \sum_j p_{ij}\, R_{ij}\,. \tag{A8}$$

We then define

$$S_i = T_i - R_i \tag{A9}$$

for $i = 1, \ldots, m$, which Hamilton (1964a) calls the *dilution effect* for reasons discussed below. Note that the signs of R_i, S_i, and T_i are indeterminate, but if we assume sufficiently weak selection at this locus, which we do, and if $\overline{T}$ is the total increment in population fitness in one period, then

$$\overline{T} = \sum_i p_i\, T_i > -1, \tag{A10}$$

so population fitness $1 + \overline{T}$ is strictly positive.

Following Hamilton, let us assume that the dilution effect S_i is uniformly distributed over the alleles at the focal locus, and let

$$\overline{S} = \sum_i p_i\, S_i \tag{A11}$$

$$\overline{R} = \sum_i p_i\, R_i\,, \tag{A12}$$

so $\overline{T} = \overline{R} + \overline{S}$. Then the expression for an increase in the frequency of allele i is given by

$$\Delta p_i = \frac{p_i + p_i R_i + p_i \overline{S}}{1 + \overline{T}} - p_i \tag{A13}$$

$$= p_i \frac{1 + R_i + \overline{S}}{1 + \overline{R} + \overline{S}} - p_i \tag{A14}$$

$$= p_i \frac{R_i - \overline{R}}{1 + \overline{T}}. \tag{A15}$$

From this we get Hamilton's Rule, in the form that allele i will increase through natural selection exactly when

$$R_i > \overline{R}. \tag{A16}$$

We can thus *define* the inclusive fitness of allele i as R_i. Because the rate growth of allele i is $g_i = \Delta p_i / p_i$, we observe that $R_i > R_j$ exactly when $g_i > g_j$, so alleles at the focal locus are relatively successful in proportion to their inclusive fitness. If the R_i are frequency independent, we can then say that genes "maximize their inclusive fitness."

As Hamilton stresses, the sign and magnitude of $\overline{S}$ do not affect (A16), but only the rate at which the frequency of allele i changes in the population. It is for this reason that Hamilton calls $\overline{S}$ a 'dilution' effect.

Hamilton assumes without comment that $R_i > 0$, but this need not be the case. For instance, suppose $m = 2$, $R_{22} = 0$, and $R_{21} = -\alpha < 0$; i.e., there are two alleles, and the heterozygote imposes a fitness loss α on the second allele. Then $R_2 = -\alpha p_{12}$, $\overline{R} = -\alpha p_2 p_{12}$, and $R_i - \overline{R} = R_i + \alpha p_2 p_{12}$, which can be positive even if $R_i < 0$. This of course is the case of the "outlaw" allele.

In general, the assumption that $\overline{S}$ is uniformly distributed among alleles at the focal locus is overly restrictive. In biochemical terms it prevents using inclusive fitness theory to analyze segregation distortion and other allele actions that disfavor other alleles at the focal locus (Ratnieks 1988, Ratnieks and Reeves 1992, Burt and Trivers 2006), or to analyze social helping behaviors ($b, r, c > 0$) that involve imposing costs on non-relatives. So let us assume that allele i at the focal locus receives fraction $\gamma_i \overline{S}$, where $\gamma_i \geq 0$ and $\sum_i \gamma_i = 1$. Then (A13) becomes

$$\Delta p_i = \frac{p_i + p_i R_i + p_i \gamma_i \overline{S}}{1 + \overline{T}} - p_i \tag{A17}$$

$$= p_i \frac{1 + R_i + \gamma_i \overline{S}}{1 + \overline{R} + \overline{S}} - p_i \tag{A18}$$

$$= p_i \frac{R_i - \overline{R} - (1 - \gamma_i)\overline{S}}{1 + \overline{T}} \tag{A19}$$

It is clear that the revised condition for allele i to proliferate,

$$R_i - (1 - \gamma_i)\overline{S} > \overline{R}, \tag{A20}$$

is the appropriate generalization of our GHR. Note that this inequality can be satisfied even if $R_i < 0$, so the successful allele is uniformly harmful to carriers of the genome.

Note that this analysis does not depend on any particular notion of relatedness. However, (A16) reduces to our expression for Hamilton's Rule (1) if we assume there are two alleles at the focal locus one of which is the wild type with zero fitness contribution and the other conferring fitness b on all individuals other than itself, with self-fitness increment $-c$. In this case $R_i = br - c$, $\overline{R} = p_i(br - c)$, so (A16) reduces to (1). In addition $T = b - c$ and $S = (1 - r)b$, which are both positive when $b > 0$. This gives the standard contemporary interpretation of Hamilton's Rule. In particular, if the gene is indeed a helping gene ($b > 0$), some of the benefits to the recipient will be directed to non-carriers of the allele, so all members of the population gain from the helping behavior. Moreover, we get the GHR expression (8) with $\gamma_i = 0$ and $\overline{S} = -\alpha$.

The dilution effect is important not because it affects the rate of change in the frequency of the focal allele, but because when $\overline{S} < 0$, the success of the focal allele can come at the expense of a lower mean population fitness $1 + \overline{T}$ even when $\overline{R} > 0$. Indeed, the above analysis shows that the conditions for allele success and the conditions for contributing to the success of the reproductive population are distinct.

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