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Hamilton's Rule in finite populations with synergistic interactions

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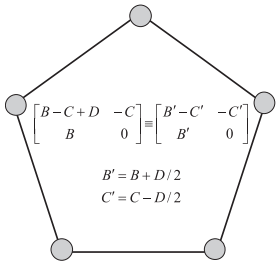
HIGHLIGHTS

- I review recent results from synergistic games on evolutionary graphs.
- The synergistic fitness effects require higher-order relatedness coefficients.
- But when genetic renewal is rare, linear relatedness coefficients will suffice.
- In this case, a synergistic game has an equivalent additive game.

GRAPHICAL ABSTRACT



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ABSTRACT

Much debate has appeared in the literature over the generality of the inclusive fitness approach in the modeling of evolutionary behavior. Here I focus on the capacity of the inclusive fitness approach to effectively handle non-additive or synergistic interactions. I work with a binary interaction with the matrix game $\begin{bmatrix} a & b \\ c & d \end{bmatrix}$ and I restrict attention to transitive (homogeneous) populations with weak selective effects. First of all I observe that the construction of "higher-order" relatedness coefficients permits these synergistic interactions to be analyzed with an inclusive fitness analysis. These coefficients are an immediate generalization of Hamilton's original coefficient and can be calculated with exactly the same type of recursive equations. Secondly I observe that for models in which the population is not too large and local genetic renewal is rare (e,g, rare mutation), these higher order coefficients are not needed even with non-additive interactions; in fact the synergistic interaction is entirely equivalent to a closely-related additive one. The overall conclusion is that in the study of synergistic binary social interactions (2-player games) in a finite homogeneous population with weak selection and rare genetic renewal, a standard inclusive-fitness analysis is able to predict the direction of allele-frequency change. I apply this result to analyze a recent model of Allen and Nowak (2015).

1. Introduction

The study of the evolution of social behavior has been hugely enriched by Hamilton's (1964) construction of inclusive fitness and the wealth of literature which has developed and extended its ideas over the past half century. Much recent controversy (Nowak et al., 2010; Abbot et al., 2011; Bourke, 2011; Herre and Wcislo, 2011; Nowak et al., 2011; Allen et al., 2013; Liao et al., 2015; Queller et al., 2015) has arisen over the significance and centrality of the inclusive-fitness approach. The resulting debate, which typically identifies apparent misunderstandings, has certainly led to a clarification and sharpening of our understanding of the inclusive fitness method. One of the most significant issues in this debate concerns the capacity of the inclusive-fitness approach to handle non-additive or "synergistic" fitness effects and this question is close to my own recent interests. I believe that a synergistic inclusive fitness theory is now firmly in place and that has

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prompted me to reply to a recent paper of Allen and Nowak (2015) where it is asserted that "inclusive fitness can only be formulated if each individual's genotype contributes a separate, well-defined amount to each other individual's fitness." In my response below I first observe that a natural generalization of the standard notion of relatedness can give us an inclusive-fitness analysis of non-linear (quadratic) fitness effects. Secondly I point out that there are some quite standard population models for which the classical "additive" inclusive-fitness analysis is already able to handle synergistic fitness effects. Those are the ones in which the process through which new genetic material enters a neighborhood, for example, mutation, is rare.

At the core of an inclusive-fitness analysis is the inclusive-fitness effect

$$W_{\mathrm{IF}} = \sum\nolimits_k a_{ik} R_{i-k} \tag{1.1}$$

of a single focal actor i whose behavior generates a fitness change a_{ik} in a number of recipients k (Hamilton, 1964). Here W_{IF} is a linear combination of the effects a_{ik} each weighted by the focal relatedness R_{i-k} to the individual k, this being a measure of the extent of common genetic ancestry between i and k (Michod and Hamilton, 1980). It has been shown many times in different ways (Hamilton, 1964; Charlesworth, 1980; Queller, 1992a; Taylor 1996, and many more recent papers cited below) that under a suite of simple assumptions, particularly weak selection and additive gene action, the sign of W_{IF} will tell us whether the selective effects of the action of an allele will cause its frequency to increase or decrease.

To be more precise about the assumption of additivity, it requires that the fitness effect a_{ik} of the action of i on individual k depends only on the genotype of i and is independent of all other genotypes, particularly that of k. This is, I believe, the condition that Allen and Nowak (2015) had in mind with the stipulation that "each individual's genotype contributes a separate, well-defined amount to each other individual's fitness."

An enormous body of work generated over the past 50 years has produced many versions and extensions of the fundamental Eq. (1.1). Much of the recent work in social evolution looks at binary matrix games in which the selective effects of the behavior are directly coded by genetic alleles, and in that domain it appears to be the case that a linear combination of fitness effects such as is found in Eq. (1.1) will do the job only under particular "additive" conditions, often referred to as "equal gains from switching." Queller (1985, 1992b) was the first to discuss these non-additive or "synergistic" effects and he observed that they would require an extension of the standard approach.

One such extension is based on the use of a multilinear regression analysis (Queller, 1992a, 1992b; Gardner et al., 2011). This approach retains the mathematical form of the inclusive fitness effect (1.1) but the fitness effects a_{ik} are no longer constructed mechanistically directly from the entries of the payoff matrix (e.g. by following the effects of a fecundity benefit through the pattern of offspring dispersal), rather they are replaced by more general coefficients of linear regression. Effectively this approach says that for the purpose of measuring allele frequency change, the fitness-determining interactions behave as if they combine additively. However in forming this linear combination, the biologically meaningful parameters such as the entries of the payoff matrix and offspring dispersal probabilities are often replaced by more abstract entities and one loses the direct intuition of the formulation.

Here I will work with another type of extension, one that preserves the meaning of the fitness effects a_{ik}, but extends the summation found in (1.1) to incorporate quadratic fitness effects a_{ijk} and corresponding relatedness coefficients R_{ij-k}. In this extension, individuals i and j are in a sense joint actors in that the fitness effect a_{ijk} on k depends not simply on the genotype of the focal actor i, but on the product $x_i x_j$ of the genotypes of i and j, and the coefficients of relatedness R_{ij-k} depend on the various probabilities of genetic identity among all three individuals.

Finally and unexpectedly, I will observe that in the case in which local genetic renewal (mutation or migration) is rare, and the population size is not too large, these generalized relatedness coefficients R_{ij-k} are not actually needed; rather the quadratic synergistic effects referred to above can be handled with the standard coefficients R_{i-k}. To be more explicit, I will show (Eq. (2.6) below) that in this case, the inclusive-fitness effect can be given an "additive" formulation in which every individual's genotype does indeed contribute a separate, well-defined amount to each other individual's fitness. In the Appendix I provide a simple worked example of this. I end with an inclusive fitness analysis of the two examples discussed by Allen and Nowak (2015).

2. Inclusive fitness with pairwise interactions

2.1. Population structure

I begin with a finite population represented as an evolutionary graph, a set of nodes, indexed by i and j, etc., each occupied by a single asexual haploid breeder. The structure of the population is a specification of fitness interactions among the nodes as well as node succession, the probability that in each time step, breeder i is replaced by breeder j or by its offspring. An evolutionary graph has a homogeneous or *transitive* structure (Taylor et al., 2007b) if for any given pair i, j of nodes there is an *isomorphism* of the node set mapping i to j, that is, a bijection which preserves all components of the structure: interaction and node replacement. Roughly speaking, the structure "looks the same" from every node, that is, if an inhabitant of any node was blindfolded and removed and then put back on a node at random, it would be unable to tell whether it had been moved. When transitivity fails, the orbits of the set of all isomorphisms partition the node set into reproductive classes and individuals in different classes might have different reproductive values which typically need to be accounted for. To keep the analysis simple I will assume the population has a transitive structure.

There are many ways to model birth and death and here I allow either a Moran process in which in any time-step there is a single birth and death, or a Wright-Fisher process in which generations are non-overlapping and in each time-step all individuals bear offspring and die and the offspring repopulate the nodes.

I suppose that there are two alternative alleles A and B in the population determining behavior and I let the genotypic value x_i of the breeder on node i be the frequency of A in its genotype. To maintain local genetic variability, we need a source of new genetic material and I assume that this comes through "long-range" migration or mutation or both.

2.2. Matrix games

In each generation an individual has a number of pairwise interactions, each playing the game with payoff matrix $\begin{bmatrix} a & b \\ c & d \end{bmatrix}$ (Maynard Smith, 1982; Queller, 1985; Nowak and May, 1992; Nowak et al., 2004) where the first row gives the payoffs to an A-player (with an A or B partner) and the second row belongs similarly to B. I assume that the payoffs represent small increments in fitness, small enough that we can ignore second-order effects. For each offspring, the average payoff is added to the baseline fitness of 1. Here we take individual fitness to measure genetic contribution to the next generation.

In inclusive-fitness studies, a normalized version of the matrix is often used. If we subtract d from each entry so that the payoff

from a B–B interaction is zero, the matrix can be written in the form

$$\begin{bmatrix} B-C+D & -C \\ B & 0 \end{bmatrix} \tag{2.1}$$

where

$$\begin{aligned} B &= c-d, \\ C &= d-b \\ D &= a-b-c+d \end{aligned} \tag{2.2}$$

The matrix (2.1) has the "cost-benefit" form found in Hamilton's Rule, that is, each A-individual, as actor, gives benefit B to its partner at cost C, but if the partner is also A, it gives a "synergistic" bonus D (Queller 1985, 1992b). The advantage of the form (2.1) is that it situates the quadratic fitness effect entirely in the parameter D; when a focal actor i interacts with j, the gift D is received by j only if the product $x_i x_j$ is 1.

2.3. An inclusive-fitness analysis

Tarnita et al. (2009) provide an elegant general analysis of the matrix game $\begin{bmatrix} a & b \\ c & d \end{bmatrix}$ in a finite population with weak selection and rare symmetric mutation between A and B. They show that the condition for the allele A to have a selective advantage over B has the form.

$$\sigma(a-d) > (c-b) \tag{2.3}$$

for a coefficient σ that depends on the population structure but not on the payoffs a, b, c and d. Taylor and Maciejewski (2012) extend this analysis to "infinite"-population models in which the mechanism that maintains genetic diversity need not be rare, whether it is mutation or a process of migration "from afar." Using the matrix form (2.1), they show that the inclusive-fitness effect has the following simple form:

$$W_{\mathrm{IF}} = \beta B - \gamma C + \left[\frac{\beta+\gamma}{2} + \left(q-\frac{1}{2}\right)\alpha\right] D \tag{2.4}$$

Here the coefficients α, β and γ are independent of both the matrix payoffs and the average allele frequency q. Since β and γ are independent of D, they will be unchanged if we set D equal to zero. But in this case we have a standard "additive" benefit-cost interaction and thus β and γ must depend only on the standard relatedness coefficients R_{i-k}. However the coefficient α typically requires the calculation of higher-order coefficients R_{ij-k}. Such coefficients are defined in terms of quadratic genotypic covariances of the form $\mathrm{cov}(x_i x_j, x_k)$ first identified by Queller (1985, 1992b, Eq. 2.8) and further analyzed and developed by Ohtsuki (2010), Taylor and Maciejewski (2012) and Taylor (2013). A simple worked example of these R-coefficients in action is found in the Appendix.

Taylor and Maciejewski (2012) show that, in comparison to β and γ, the coefficient α in Eq. (2.4) has the same order as the rate of genetic renewal. When this is generated by rare mutation, its effect is small compared to the effect of β and γ and Eq. (2.4) simplifies to:

$$W_{\mathrm{IF}} = \beta B - \gamma C + \left(\frac{\beta+\gamma}{2}\right) D \tag{2.5}$$

Eq. (2.5) delivers two striking conclusions. First, relative allelic fitness is independent of allele frequency q, and secondly, synergistic interactions (captured by the effect D) can be handled with standard coefficients of relatedness such that the higher-order coefficients R_{ij-k} need not be calculated. Of course they are still present hidden inside the coefficient $(\beta+\gamma)/2$ of D, but Eq. (2.5) gives us a general formulation of the inclusive fitness effect in a finite population with rare mutation in terms of the standard relatedness coefficients R_{i-k}.

To emphasize this, we can rewrite Eq. (2.5) in the form

$$W_{\mathrm{IF}} = \beta\left(B+\frac{D}{2}\right) - \gamma\left(C-\frac{D}{2}\right) \tag{2.6}$$

which tells us that a non-additive interaction with benefit B, cost C and synergistic bonus D, can be modeled as an additive interaction with benefit $B' = B + D/2$ and cost $C' = C - D/2$. Effectively Eq. (2.6) asserts that the synergistic behavior can be captured with a standard benefit-cost interaction in which the benefit is given to all interactants regardless of their genotype provided that we add $D/2$ to the benefit and subtract $D/2$ from the cost. In terms of the matrix formulation, what Eq. (2.6) tells us is that in case genetic renewal is rare (through rare mutation or migration) the synergistic matrix game $\begin{bmatrix} B-C+D & -C \\ B & 0 \end{bmatrix}$ is equivalent to the additive game

$$\begin{bmatrix} B-C+D & -C+D/2 \\ B+D/2 & 0 \end{bmatrix} \tag{2.7}$$

If the transformation Eqs. (2.2) are applied to Eq. (2.5), the condition that $W_{\mathrm{IF}} > 0$ can be written:

$$(\beta+\gamma)(a-d) > (\beta-\gamma)(b-c) \tag{2.8}$$

and this is the condition (2.3) of Tarnita et al. (2009) with $\sigma = \frac{\beta+\gamma}{\beta-\gamma}$.

2.4. Relatedness

Finally we recall the definition of relatedness. We say that two individuals i and k are *identical by descent* (IBD) if they have a common ancestor without any intervening mutation. Given that, the *relatedness* R of an actor i to a recipient k can be expressed as

$$R_{i-k} = \frac{G_{ik} - \overline{G}}{G_0 - \overline{G}} \tag{2.9}$$

where G_{ik} is the probability that the two are IBD, $G_0 = 1$ is the probability that an individual is IBD to itself, and $\overline{G}$ is the average IBD of an individual to all individuals in the population (Rousset and Billiard, 2000; Taylor et al., 2007a). Then the relatedness of an individual to itself ($G = G_0$) is $R_0 = 1$ and the average relatedness to the population ($G = \overline{G}$) is $\overline{R} = 0$. I point out that the normalization in Eq. (2.9) (subtracting $\overline{G}$ and then dividing by $1-\overline{G}$) is conventional when working with transitive populations but is optional in that the G-coefficients can serve on their own as relatedness. An advantage of the normalization is that it gives us negative coefficients of relatedness (whereas G_{ik} is always ≥ 0). However in non-transitive populations for which there are different reproductive classes, the normalization can be problematic as $\overline{G}$ can vary among different classes (Taylor, 2009).

The standard R-coefficient in Eq. (2.9) will serve my needs in the analysis of the next section, but in the Appendix I provide the analogous formula for the higher-order coefficients R_{ij-k}.

3. An inclusive-fitness analysis of the example of Allen and Nowak

Allen and Nowak (2015) consider a finite population with non-overlapping generations and N haploid breeders each of which has a large number n of asexual offspring. They use a two-allele model with bi-allelic mutation and general matrix game $\begin{bmatrix} a & b \\ c & d \end{bmatrix}$ as described above. The offspring engage in many binary interactions, a proportion r of which are with sibs while the remaining $1-r$ are random in the population at large. The total game payoff for each offspring provides a small fitness increment and then to form the next generation of adults, N offspring are chosen from the

population at large, with probability weighted by fitness. This is a transitive population structure with non-overlapping generations which updates through what is generally called a Wright-Fisher process.

Allen and Nowak (2015) use fixation probability to compare the fitness of A and B, but under weak selection in a transitive population, the inclusive-fitness effect will provide an equivalent condition (Taylor et al., 2007a; Tarnita and Taylor, 2014) and I now obtain their results with a general inclusive-fitness analysis.

3.1. A general analysis

I begin with a comment about the general inclusive-fitness Eq. (1.1). The fitness effects a_{ik} must capture *all* effects of the matrix interaction, not only the immediate effects B, C and D on future fecundity but also the later derived effects, often called "secondary" (West and Gardner, 2010). For example in a population of constant size an extra offspring given to one individual must reduce the fitness of another. For that matter, even if the population is growing, such effects can still be felt in terms of the total RV of the population gene pool. In the model of Allen and Nowak, these secondary effects are all felt at random in the population and focal relatedness to these is $\overline{R}=0$ (Eq. 2.9). Thus in the following analysis I can restrict attention to the immediate fecundity effects of B, C and D.

To calculate β and γ in Eq. (2.5), we can set $D=0$ (see discussion after Eq. 2.4) so that each offspring interaction consists of a single B-gift at cost C. Since the interaction is between sibs with probability r and is otherwise at random, the inclusive-fitness effect has the form:

$$W_{IF} = B(rR_S + (1-r)\overline{R}) - CR_0 = BrR_S - C \tag{3.1}$$

where R_S is the relatedness between offspring sibs.

Allen and Nowak (2015) make two alternative assumptions about the action of mutation. In the first, mutation effectively occurs in the adult so that all offspring of a mutant adult are mutant (and therefore all IBD). In the second case, the mutation occurs and takes effect in the offspring such that a mutant offspring is not IBD to its sibs.

3.2. The first mutation scenario

Here the entire focal sibship is effectively (phenotypically) clonal and $R_S=1$, giving

$$W_{IF} = Br - C \tag{3.2}$$

From the coefficients of B and C we get $\beta=r$ and $\gamma=1$, and the condition (2.8) that $W_{IF}>0$ becomes:

$$(r+1)(a-d) > (r-1)(b-c) \tag{3.3}$$

as obtained by Allen and Nowak (2015), Eq. (10) for their equivalent condition $\rho_A > \rho_B$.

3.3. The second mutation scenario

In this case effective mutation occurs independently among the offspring. To calculate the relatedness between sibs we first note that two sibs are IBD if neither is mutant and the probability of that is:

$$G_S = (1-u)^2 \approx 1-2u \tag{3.4}$$

We calculate $\overline{G}$ from the recursive equation:

$$\overline{G}' = (1-u)^2\left(\frac{1}{N} + \frac{N-1}{N}\overline{G}\right) \tag{3.5}$$

where the prime means "next generation." To be IBD, two random next-generation offspring must first both be non-mutant. Given that, they are sibs with probability $1/N$ (since the number of offspring is large) and in that case are IBD; otherwise their parents are two random offspring from the current generation and in that case are IBD with probability $\overline{G}$. At equilibrium, $\overline{G}'=\overline{G}$, and this solves to give $\overline{G}=1-2Nu$ (see the note at the end of the Appendix for the best way to obtain the solution). Then from Eq. (2.9) the relatedness between sibs is:

$$R_S = \frac{G_S-\overline{G}}{1-\overline{G}} = \frac{1-2u-(1-2Nu)}{1-(1-2Nu)} = \frac{N-1}{N} \tag{3.6}$$

and from Eq. (3.1):

$$W_{IF} = BrR_S - C = Br\frac{N-1}{N} - C \tag{3.7}$$

From the coefficients of B and C, we get $\beta = r\frac{N-1}{N}$ and $\gamma=1$ and the condition (2.8) that W_{IF} is positive can be written:

$$(rN+N-r)(a-d) > (rN-N-r)(b-c) \tag{3.8}$$

as obtained by Allen and Nowak (2015; Section 6) for their equivalent condition $\rho_A > \rho_B$.

4. Discussion

4.1. Additive and non-additive games

Matrix-game models have a significant venerable history (Maynard-Smith and Price, 1973; Maynard-Smith, 1982; Queller, 1985; Nowak and Sigmund, 2004) and receive much theoretical attention today. The game matrix $\begin{bmatrix} a & b \\ c & d \end{bmatrix}$ provides the fitness effects of the interaction in terms of the strategies (in our case, genotypes) of both players. Hamilton (1964) framed his inclusive-fitness analysis in terms of the fitness effects of the actions of a focal individual i on all whose fitness is affected by that behavior. For example he talks about the fractions of the harm and benefit which the individual itself causes to the fitness of its neighbors k, where these fractions are in fact the coefficients of relatedness R_{i-k}. But his discussion assumes that these fitness effects are independent of the genotypes of these neighbors; these genotypes enter only into the calculation of relatedness. A game can be modeled in this way only when it satisfies the condition $a+d=b+c$. By subtracting the constant d from all payoffs, such "additive" games can be written in the form $\begin{bmatrix} B-C & -C \\ B & 0 \end{bmatrix}$ and can be interpreted in the Hamiltonian framework; each A-individual gives benefit B to its partner at cost C, regardless of the partner genotype.

Queller (1985, 1992b) was the first to observe that, again by subtracting d, the same general game could be written in the form $\begin{bmatrix} B-C+D & -C \\ B & 0 \end{bmatrix}$ which allows the effects to be described in a Hamiltonian inclusive-fitness framework--D is an extra benefit an A-individual bestows if its partner also carries the A-allele. Queller pointed out that the D-term requires a modification of the standard inclusive-fitness formulation, and that is what has led to the introduction of the higher-order relatedness coefficients R_{ij-k}. These can be calculated following the same recursive approach that works for the standard coefficients (e.g see the Appendix) and thus this gives us a natural generalization of the inclusive-fitness method.

That story is interesting enough but now it takes a rather unexpected turn. These generalized relatedness coefficients R_{ij-k} appear in the general formulation (2.4) only in the α-term, while the terms β and γ involve only the standard coefficients R_{i-k}. Furthermore the order of α is the same as the order of the mechanisms of local genetic renewal, be they mutation or migration from afar (Taylor and Maciejewski, 2012). In the case in which the only such force is provided by mutation and this is assumed to be rare, the contribution of these generalized

relatedness coefficients is negligible and can be ignored. That gives us Eq. (2.5) which involves only the standard coefficients R_{i-k}. What this tells us is that *we can treat the synergistic interaction as if it were an additive benefit-cost interaction*.

Just to highlight this a bit more, the system of recursive equations for the various IBD coefficients G generally allows us to see that the higher order coefficients G_{ijk} can be written as linear combinations of the standard coefficients G_{ijk}. As an example of this, study the system (A1) in the Appendix––the equations for G_3 and G_4 can be solved together giving us expressions for G_3 and G_4 in terms of G_1 and G_2. Because of the nature of the recursive system, this will generally be the case, and what that tells us is that we can expect the coefficient of D in the inclusive fitness formula (2.5) to be a linear combination of the coefficients β and γ of B and C. But we would expect this linear combination to depend on the population structure, so that it is quite unexpected that, in the case in which genetic renewal is rare, the coefficient of D is $(\beta+\gamma)/2$ for *all* populations regardless of their structure.

4.2. Mutation and migration

In formulating a mathematical model we need a source of new genes; otherwise, even given the effects of selection, the population will eventually be genetically uniform. Two standard mathematical ways to provide this are found in genetic mutation and migration "from afar"; this final requirement is needed as in a structured population, migrants from near-by are apt to find relatives where they settle. In fact, to be quite formal, we often assume that the population is "infinite," so that migrants are certain to be unrelated to those they encounter. Furthermore this allows us to assume that they carry the allele A with a fixed probability q, and that is needed in the model formulation. A similar assumption is made in the mutation process.

I observe that in models, such as Wright's (1943) island model with large population size, we often assume that migration is the sole force for local genetic renewal and that it is not rare. As a consequence, the simple form for W_{IF} given by Eq. (2.5) no longer holds and we need the α term of Eq. (2.4), and as I have observed, this generally requires the calculation of the higher-order relatedness coefficients (Ohtsuki, 2010; Taylor and Maciejewski, 2012). As a consolation for this additional complexity, we get a form of frequency dependence through the long-term allele frequency q, and with that comes the possibility of a stable polymorphism of pure strategies (Taylor and Maciejewski, 2012).

Finally, I remark that I assumed throughout that the population structure is transitive, but Eqs. (2.4–2.8) hold in heterogeneous (non-transitive) structures provided the inclusive-fitness effect is formulated using reproductive values (Taylor, In preparation).

4.3. Additivity and the strength of selection

Almost no fitness interactions have strictly linear effects and one should not talk of linear approximations without introducing the strength of selection. Hamilton, in his original 1964 analysis, felt it reasonable to assume linear effects on fitness only because most benign mutations are of small effect. I should point out that the scenario Hamilton seems to have had in mind was that genotype affects behavior (phenotype) which in turn affects the fitness of one or more individuals. In our haploid model if an individual's fitness is a function $w=f(z_1,z_2,\ldots,z_n)$ of the phenotypes of n individuals, and if genotype x has a small effect on phenotype, $z=z_0+\delta x$, then a first-order Taylor expansion will give us a fitness effect that is linear in the genotypic values: $w=w_0+\delta\sum(\partial f/\partial z_i)x_i$ (Grafen, 1985). In the matrix game model I work with here there is an assumption of weak selection, but this does not give us a first-order Taylor expansion in genotype because fitness connects directly with genotype without going through a continuous intermediate z.

4.4. Some remarks on the effects of population structure

Right from the beginning (Wilson, 1975), questions about the effects of the population structure were raised. Over the past decade, considerable attention has been paid to the spatial assortment of individuals (Hauert and Doebeli 2004; Traulsen and Nowak, 2006; Ohtsuki and Nowak, 2006; Ohtsuki, 2010) and it has increasingly been made clear that we should have a wide range of modeling approaches in our evolutionary toolbox and be prepared to choose the one (or ones!) that give us the technical capacity and/or the insights that we want. A particularly interesting (and longstanding) debate of this type is one that compares the theoretical and technical advantages of approaches using inclusive fitness and multilevel selection (Lehmann et al., 2007; Damore and Gore, 2012; Frank, 2013; Okasha, 2015).

Considerable work particularly at the microbial level over the past decade has revealed a surprisingly rich variety of behaviors, particularly cooperative behaviors that exhibit marked frequency dependence in that the frequency of the competing types affects the very structure of the population and can even alter the payoffs in the matrix (Smith et al., 2010; Damore and Gore, 2012). In this case, under weak selection, Hamilton's Rule can perhaps give us a *short-term* account of allele frequency change, but more special-purpose models are needed to understand long-term behavior.

One significant aspect of working with microbes is that, perhaps due to their simple structure and short generation time, it is often much easier to measure the fitness effects of the behavior––the benefits and costs––than it is with larger slower more complex organisms. Chuang et al. (2010) study an interesting "synthetic" microbial system in which they are able to chemically modify the benefit of a public good interaction and measure the effect on Hamilton's Rule. I find this work particularly interesting as it employs what might be called a "natural" agent-based simulation and such approaches significantly enhance our understanding of the working of our mathematical models. In one case the effective benefit changed in a non-linear way across treatments (with different cooperator frequencies) and that led to some counter-intuitive findings. Such results alert us to the simplicity of the assumptions we generally make in our mathematical models and this is most certainly true of Hamilton's Rule. Having made that point, it works the other way around as well. Mathematical models can give us valuable indications of what to look for in setting up our simulations.

5. Conclusions

Evolutionary models of binary interaction with the general game matrix $\begin{bmatrix} a & b \\ c & d \end{bmatrix}$ can be handled with an inclusive fitness approach provided "higher-order" relatedness coefficients are employed. These coefficients are an immediate generalization of Hamilton's original concept of relatedness and can be calculated with exactly the same type of recursive equations. However, models that rely upon rare mutation as the source of genetic renewal provide an interesting special case in which the general game matrix is equivalent to an "additive" matrix ($a+d=b+c$) such that the higher-order coefficients are not needed and a standard inclusive-fitness analysis will correctly measure allelic fitness.

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Appendix

The purpose of the appendix is to use a simple finite population to illustrate the inclusive-fitness calculation using the higher-order relatedness coefficients and then demonstrate that the same answer is obtained using the additive matrix form (2.7).

Population structure. I consider the 5-cycle (Fig. 1). In each time step each A-individual gives a fecundity benefit B to each of its two neighbors at cost C. In addition, when the neighbor also carries the allele A, an extra benefit D is bestowed. I assume that these fitness effects are small and augment the base fecundity 1. An offspring is a clone of its parent with probability $1-u$ and otherwise it is A or B with probabilities q or $1-q$.

Relatedness calculation. I begin by noting that the symmetry of the structure (Fig. 1) allows us to get by with only five IBD coefficients, and to simplify the analysis I call them G_i $(0\le i\le 4)$:

- $G_0=G_{11}=1$: to self
- $G_1=G_{12}$: to neighbor
- $G_2=G_{13}$: to non-neighbor
- $G_3=G_{123}$: three in a row
- $G_4=G_{124}$: three not in a row

In addition we let $\overline{G}=\frac{G_0+2G_1+2G_2}{5}$ be the average G of an individual to the population. The one-step recursive equations for the G_i are

$$G_1=\frac{1-u}{2}(G_2+G_0),\quad G_3=\frac{1-u}{3}(G_1+G_2+G_4) \tag{A1}$$

$$G_2=\frac{1-u}{2}(G_2+G_1),\quad G_4=\frac{1-u}{3}(G_2+G_3+G_4)$$

For example, to obtain the G_1 equation, calculate the probability that nodes 1 and 2 are IBD. Choose the node of the pair that was most recently replaced, say node 2 (by symmetry), and ask where the offspring came from. With probability u it was a mutant (giving $G=0$) and otherwise (probability $1-u$) it came from nodes 1 or 3 with equal probability ½.

To solve these equations to first order in u the most elegant approach is to set $G_i=1-g_iu$ and simplify the equations to get

$$g_1=1+\frac{g_2+g_0}{2},\quad g_3=1+\frac{g_1+g_2+g_4}{3} \tag{A2}$$

$$g_2=1+\frac{g_2+g_1}{2},\quad g_4=1+\frac{g_2+g_3+g_4}{3}$$

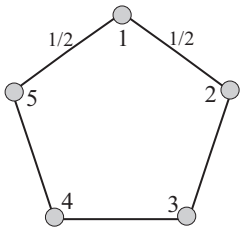

Fig. 1. The 5-cycle. There are 5 nodes each with 2 neighbors and each occupied by a single haploid breeder. I use Moran updating so that there is one birth in each time step with the offspring displacing each neighbor with probability ½. This is a transitive population structure.

And, noting that $g_0=0$, these solve to give:

$$g_1=4,\ \ g_2=6,\ \ g_3=7\ \ and\ \ g_4=8 \tag{A3}$$

This gives us $\overline{G}=1-\overline{g}u=1-4u$ since $\overline{g}=\frac{g_0+2g_1+2g_2}{5}=4$. Finally, again using the symmetry, we need only five relatedness coefficients and Taylor (2013) provides the formulae for these in a transitive population, although in that presentation the R-coefficients are not normalized.

$$\text{self}: R_0=R_{1-1}=\frac{G_0-\overline{G}}{G_0-\overline{G}}=1$$

$$\text{neighbour}: R_1=R_{1-2}=\frac{G_1-\overline{G}}{G_0-\overline{G}}=\frac{\overline{g}-g_1}{\overline{g}}=\frac{4-4}{4}=0$$

$$\text{non}-\text{neighbour}: R_2=R_{1-3}=\frac{G_2-\overline{G}}{G_0-\overline{G}}=\frac{\overline{g}-g_2}{\overline{g}}=\frac{4-6}{4}=-\frac{1}{2} \tag{A4}$$

$$\text{synergistic inside}: R_3=R_{12-2}=\frac{G_2-\overline{G}+(G_0-G_1)q}{G_0-\overline{G}}=\frac{\overline{g}-g_1+g_1q}{\overline{g}}=q$$

$$\text{synergistic outside}: R_4=R_{12-3}=\frac{G_3-\overline{G}+(G_1+G_2-2G_3)q}{G_0-\overline{G}}=$$

$$=\frac{\overline{g}-g_3+(2g_3-g_1-g_2)q}{\overline{g}}=q-\frac{3}{4}$$

The final two formulae in (A4) follow from the general equations:

$$R_{ij-j}=R_{ij-i}=\frac{(G_{ij}-\overline{G})+(G_0-G_{ij})q}{G_0-\overline{G}}$$

$$R_{ij-k}=\frac{(G_{ijk}-\overline{G})+(G_{ik}-G_{ijk})q+(G_{jk}-G_{ijk})q}{G_0-\overline{G}} \tag{A5}$$

found in unnormalized form in (Taylor 2013). Note that the first of these equations is a special case of the second. To give some intuition for the second equation, note that it modifies the effect of D when the gift is given by i to j and affects the fitness of k. And since we are keeping track of the change in A-frequency, the coefficient R_{ij-k} essentially counts the instances where k has the allele A. Now the actor i is assumed to already carry A, so for the gift to be given we need j to carry A, so that means we want the cases in which j and k both carry A. First this will occur when all three are IBD and that's covered by the first bracket on the right. Secondly this will happen when i and k are IBD but not IBD to j (and the probability of that is $G_{ik}-G_{ijk}$) but j independently carries A, and the probability of that is q. That's covered by the second bracket on the right. Analogously, we might have that j and k are IBD but not IBD to i (and the probability of that is $G_{jk}-G_{ijk}$) but both j and k independently carry A, and the probability of that is q, as they are IBD. That's covered by the third bracket.

Inclusive-fitness analysis. I begin with the full analysis that makes use of the synergistic relatedness coefficients R_{ij-k}. The inclusive-fitness effect turns out to be:

$$W_{\mathrm{IF}}=B\left(R_{1-2}-\frac{R_{1-1}+R_{1-3}}{2}\right)-C\left(R_{1-1}-\frac{R_{1-5}+R_{1-2}}{2}\right)$$
$$+D\left(R_{12-2}-\frac{R_{12-1}+R_{12-3}}{2}\right) \tag{A6}$$

derived as follows. Take node 1 as a focal A-actor $(x_1=1)$ and consider its interaction with node 2. First it gives node 2 a fecundity benefit B and the potential extra offspring increase the mortality of nodes 1 and 3. The initial gift is weighted by the relatedness coefficients R_{1-2}, and the secondary mortality effects are weighted by R_{1-1} and R_{1-3}. Then it pays the cost C of the gift and the potential reduction in offspring decreases the mortality of

nodes 5 and 2. The initial effect is weighted by the relatedness coefficient R_{1-1}, and the secondary mortality effects are weighted by R_{1-5} and R_{1-2}. Finally its synergistic gift of D to node 2 is dependent upon having $x_2=1$, and in this case as for B, the potential extra offspring increase the mortality of nodes 1 and 3. The initial effect is weighted by the relatedness coefficient R_{12-2}, and the secondary mortality effects are weighted by R_{12-1} and R_{12-3}. When we substitute the expressions from the Eq. (A4), we get:

$$\begin{aligned} W_{\mathrm{IF}} &= B\left(R_1-\frac{R_0+R_2}{2}\right)-C\left(R_0-\frac{R_1+R_1}{2}\right)+D\left(R_3-\frac{R_3+R_4}{2}\right), \\ &= B\left(0-\frac{1-1/2}{2}\right)-C\left(1-\frac{0}{2}\right)+D\left(q-\frac{q+q-3/4}{2}\right) \\ &= -\frac{1}{4}B-C+\frac{3}{8}D \end{aligned} \tag{A7}$$

Now I do the "additive" analysis provided by Eq. (2.6) with benefit $B+D/2$ replacing B and cost $C-D/2$ replacing C. According to the result of (A7) we will get:

$$\begin{aligned} W_{\mathrm{IF}} &= \left(B+\frac{D}{2}\right)\left(R_1-\frac{R_0+R_2}{2}\right)-\left(C-\frac{D}{2}\right)\left(R_0-\frac{R_1+R_1}{2}\right) \\ &= -\frac{1}{4}\left(B+\frac{D}{2}\right)-\left(C-\frac{D}{2}\right)=-\frac{1}{4}B-C+\frac{3}{8}D \end{aligned} \tag{A8}$$

as before. Note that these equations both give us $\beta=-1/4$ and $\gamma=1$, so that $\frac{\beta+\gamma}{2}=\frac{3}{8}$, and as expected from Eq. (2.5), this is the coefficient of D.

I remark that the 5-cycle analyzed above is a transitive population, and in this case, under many updating rules, W_{IF} depends only on the size of the population. This surprisingly simple result is an effect of a cancelation between primary and secondary effects (Taylor, 1992). For example, for a Moran process with BD updating, $\beta=-\gamma/(N-1)$ where N is population size (Taylor et al., 2007b; Grafen and Archetti, 2008) and thus by Eq. (2.5) the inclusive-fitness effect always has the form $W_{\mathrm{IF}}=-\frac{1}{N-1}B-C+\frac{N-1}{2N}D$. We could have written the final answer in Eq. (A8) without having done any work at all.

Note: the method we used above to solve the Eq. (A1) can be used to easily solve Eq. (3.5) with $\overline{G}'=\overline{G}$. The equation is $\overline{G}=(1-u)^2\left(\frac{1}{N}+\frac{N-1}{N}\overline{G}\right)$ and to work to first order in u, we set $\overline{G}=1-\overline{g}u$ and $(1-u)^2=1-2u$. Multiplying through by N gives us
$N(1-\overline{g}u)=(1-2u)(1+(N-1)(1-\overline{g}u)$
and to first order in u, this solves to give $\overline{g}=2N$.

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