Polyandry, Life-History Trade-Offs and the Evolution of Imprinting at Mendelian Loci

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Manuscript received April 16, 2004
Accepted for publication August 19, 2004

ABSTRACT

Genomic imprinting causes parental origin-dependent differential expression of a small number of genes in mammalian and angiosperm plant embryos, resulting in non-Mendelian inheritance of phenotypic traits. The “conflict” theory of the evolution of imprinting proposes that reduced genetic relatedness of paternally, relative to maternally, derived alleles in offspring of polygamous females supports parental sex-specific selection at gene loci that influence maternal investment. While the theory’s physiological predictions are well supported by observation, the requirement of polyandry in the evolution of imprinting from an ancestral Mendelian state has not been comprehensively analyzed. Here, we use diallelic models to examine the influence of various degrees of polyandry on the evolution of both Mendelian and imprinted autosomal gene loci that influence trade-offs between maternal fecundity and offspring viability. We show that, given a plausible assumption on the physiological relationship between maternal fecundity and offspring viability, low levels of polyandry are sufficient to reinforce exclusively the fixation of “greedy” paternally imprinted alleles that increase offspring viability at the expense of maternal fecundity and “thrifty” maternally imprinted alleles of opposite effect. We also show that, for all levels of polyandry, Mendelian alleles at genetic loci that influence the trade-off between maternal fecundity and offspring viability reach an evolutionary stable state, whereas pairs of reciprocally imprinted alleles do not.

Genomic imprinting is the parental germline-specific epigenetic modification and subsequent differential expression of genes during embryonic and postnatal mammalian development and during plant endosperm development (John and Surani 1996; Baroux et al. 2002). In mammals, a large proportion of imprinted genes affect fetal and placental growth, with expressed paternal alleles generally increasing growth and expressed maternal alleles decreasing growth (Beechey 1999; Moore 2001; Reik et al. 2001; Wilkins and Haig 2003).

The “conflict” theory of evolution of imprinting provides an explanation for the parental origin-dependent gene expression levels in terms of relatedness asymmetries between the parental alleles at loci that, when expressed in embryonic tissues, influence the amount of resources received from the mother by her offspring (Haig and Westoby 1989; Moore and Haig 1991; Haig 1992). Such alleles therefore have two significant evolutionary consequences: they alter both maternal fecundity and offspring viability.

Different aspects of the evolution of imprinting have been modeled by a variety of methods. Much of this work has been extensively reviewed elsewhere (Haig 2000; Spencer 2000; Wilkins and Haig 2003). In relation to models that provide explicit tests of the conflict theory of imprinting, two approaches have predominated. Haig and colleagues (Haig 1992, 1997; Wilkins and Haig 2001, 2002) used game theoretical models, which seek to define an unbeatable, evolutionary stable state (ESS) at equilibrium. These models found that imprinting evolves exclusively under polyandry, with paternally inherited alleles favoring increased maternal investment in offspring, and maternally inherited alleles favoring reduced investment, consistent with the predictions of the theory. Mochizuki et al. (1996) reached similar conclusions using multivariate quantitative genetic models, which defined, at equilibrium, stable values of mean population gene expression levels at zygotic loci that influence maternal investment in offspring. In addition, Mochizuki et al. (1996) attempted to explain other aspects of imprinted gene biology in their models; for example, the perceived paucity of imprinted genes was explained in terms of selection against recessive deleterious mutations in their coding regions. However, deleterious mutations are unlikely to provide a sufficiently strong selective force to prevent the evolution of imprinting (Haig 2000; Spencer 2000), and other more plausible explanations have been proposed (Haig 2000).

Adopting a different approach, Spencer and colleagues constructed a series of population genetic models to examine the evolution of imprinting in a variety of contexts, including autosomal and X chromosome linkage
(Spencer et al. 1998, 2004). Their single-locus, diallelic models examined the evolutionary dynamics of imprinted alleles under either monogamy or polyandry (in which a female mates with two males). Consistent with the conflict theory, they found that polyandry increases the amount of parameter space available to paternally inherited alleles that favor greater maternal investment in offspring compared to maternally inherited alleles. However, an important point of disagreement with earlier models emerged in their finding that, with their assumptions, imprinting evolves under monogamy and the direction of imprinting is sometimes opposite to that predicted by the conflict theory (Spencer et al. 1998).

In seeking to resolve the disagreement between the two types of models, Haig (1999a) questioned the suitability of diallelic models for examining long-term trends in evolution. However, Hurst (1999) subsequently argued that the disagreement between the models relates not to a general unsuitability of diallelic models for analyzing long-term evolutionary change but, rather, to the manner in which Spencer et al. (1998) applied their diallelic models to the problem. Specifically, he contended that Spencer et al. (1998) do not distinguish between alleles that evolve because they are imprinted, rather than in spite of being imprinted. In effect, the models of Spencer et al. (1998) are uncontrolled because they do not consider a comparison of imprinted and biallelically expressed genes with identical effects on viability and fecundity. However, Spencer (2000; Spencer et al. 2004) is agnostic about the resolution proposed by Hurst (1999) and points to the difficulty in applying constraints to parameter space in genetic models.

The single-locus, diallelic models of Parker and MacNair (1978; MacNair and Parker 1978) are relevant to the evolution of alleles influencing parent-offspring conflict, but are restricted to Mendelian dominant and recessive alleles, concepts that lose their utility in the context of mutations producing changes in allele expression level at loci encoding gene dosage-sensitive effects on phenotype. For imprinted loci, the relevant analysis is of alleles whose phenotypic effects depend on their level of expression in progeny and that therefore inhabit the region between the two extremes of full dominance and full recessivity.

A subset of genetic loci encoding gene dosage-sensitive effects on phenotype influence the amount of maternal investment in offspring expressing the genes, e.g., genetic loci encoding placental growth factors. If the magnitude of the effect on maternal investment depends on the concentration of the gene product (RNA or protein), it follows that alleles with different transcription rates at such a locus, which alter gene product concentration, will influence the trade-off between maternal fecundity and offspring viability. In this study, we deal exclusively with such mutant alleles, but we make few assumptions about the relationship between allele expression levels and fecundity or viability, other than to assume that such a relationship exists, is smooth, and that offspring viability increases with increasing amounts of maternal investment. We also assume a “law of diminishing returns” such that progressively larger costs to maternal fecundity are associated with progressively smaller increases in offspring viability. If the difference from wild type in expression level (and, therefore, phenotypic effects) of a new mutant allele depends on its parental origin, the allele is said to be “imprinted”; new alleles whose effects are independent of parental origin are referred to as “Mendelian.”

Here, we describe a series of diallelic models of the evolution of Mendelian and imprinted alleles and compare their behavior in monogamous and polyandrous populations. We analyze the effects of different levels of polyandry on their evolution and on interactions between the two systems of inheritance. Since we are primarily interested in relating the short-term behavior of individual alleles to the long-term predictions of kin selection models, we do not analyze in detail the stability of internal polymorphisms, but rather focus on the allele invasion and fixation boundaries. We resolve the major point of disagreement between game theoretical and diallelic models, and we provide for the first time an explicit analysis of the influence of arbitrary levels of polyandry on the evolution of Mendelian and imprinted alleles that influence the trade-off between maternal fecundity and offspring viability.

MODEL FORMULATION AND ANALYSIS

Darwinian fitness is the product of two variables: viability, defined as the probability of survival to reproduce, and fecundity, defined as the number of offspring produced. In our model, as we show, new mutant alleles that enhance either or both of these factors increase in frequency, whereas alleles that decrease either factor are eliminated. Here, we are predominantly interested in alleles that increase one of the components of Darwinian fitness, while decreasing the other, and we analyze the conditions that allow such alleles to spread. We consider exclusively alleles that are expressed in offspring and affect maternal fecundity and offspring viability by influencing the level of maternal investment in offspring. As noted above, a mutant imprinted allele alters phenotype relative to wild type only when inherited from the imprinting parent. A mutant Mendelian allele alters the phenotype relative to wild type regardless of its parental origin.

Imprinted expression at loci governing trade-offs between maternal fecundity and offspring viability: Dealing first with paternally imprinted alleles, we designate a reduction or increase in relative fecundity experienced by a female mating exclusively with males homozygous for a new mutant paternally imprinted allele as c. For example, if matings between homozygous wild-
type individuals produce $N$ offspring, and matings between females and males homozygous for a mutant allele produce $N \pm \delta$, then we have

$$e = \frac{N - (N \pm \delta)}{N}.$$  (1)

The fecundity of such a female, mating exclusively with homozygous mutant males, relative to one mating exclusively with wild-type males, is then $F = 1 - e$.

The viability of offspring inheriting the mutant allele from the imprinting (male) parent is $w$. Note that $F$, $w$, and $e$ are always measured relative to the corresponding parameters in the population whose invasion is being considered, which we refer to as the wild-type population. We can derive the invasion conditions for new paternally imprinted alleles by considering that, for the new mutant to invade, it is necessary that the fraction of offspring that carry the mutant allele must do better than the same fraction of the offspring of a homozygous wild-type male. In a polyandrous mating system, where a female accepts $m$ randomly chosen mates during her reproductive life, the change in relative fecundity resulting from the presence of a single heterozygous male among her partners will be, on average, $\frac{e}{2m}$.

We therefore require that

$$\left(1 - \frac{e}{2m}\right) w > 1,$$

which leads to

$$e < \frac{2m(w - 1)}{w}.$$  (2)

The boundary separating alleles that can invade from those that are excluded is therefore delineated by the function

$$F_1 = 1 - \frac{2m(w - 1)}{w}.$$  (3)

This is the invasion boundary for paternally imprinted alleles. The fixation boundary for the imprinted allele is identical to the invasion boundary for the wild-type allele. The appropriate inequality is then

$$\left(1 - \frac{(2m - 1)e}{2m}\right) > (1 - e)w,$$

which leads to

$$F_2 = 1 - \frac{2m(w - 1)}{2m(w - 1) + 1} = \frac{1}{2m(w - 1) + 1}$$

as the fixation condition for a paternally imprinted allele. Corresponding boundary conditions for monogamous populations are found by setting $m = 1$. The invasion and fixation conditions for paternally imprinted alleles under monogamy are also the conditions for maternally imprinted alleles under any degree of polyandry. This follows because, while the fecundity costs or benefits associated with paternally imprinted alleles can be shared among several females if there is polyandry, those associated with maternal alleles cannot. The viability advantage or disadvantage imparted to offspring then remains unaltered by polyandry.

**Mendelian expression at loci governing trade-offs between maternal fecundity and offspring viability:** If $c$ is the fecundity cost imposed on matings between a homozygous mutant female and $m$ homozygous mutant males, then the cost imposed on a wild-type female by a single heterozygous male and $m - 1$ homozygous wild-type males is, on average,

$$\frac{c}{2(m + 1)}$$

and the invasion condition for mutant Mendelian alleles (assuming a linear relationship between $c$ and offspring viability) is

$$\left(1 - \frac{c}{2(m + 1)}\right) \left(1 + \frac{w}{2}\right) > 1,$$

which leads to

$$F_3 = 1 - \frac{2(m + 1)(w - 1)}{w + 1}$$

as the invasion boundary. Given that each homozygous parent now contributes a cost of $\frac{c}{2}$ independently, the requirement for fixation is

$$\left(1 - \frac{(2m - 1)c}{2m}\right) \left(\frac{1 + w}{2}\right)^2 > (1 - e)w,$$

leading to

$$F_4 = 1 - \frac{4m(w - 1)}{4m(w - 1) + w + 1}$$

as the fixation boundary for Mendelian alleles. As before, the boundaries for a monogamous population are found by setting $m = 1$. With these functions, we can predict whether hypothetical mutant alleles conferring values of $F$ and $w$ different from the wild-type allele will be eliminated, reach a polymorphic equilibrium, or go to fixation.

To confirm that the dynamics of such genetic systems allow the predicted outcomes to be attained for alleles conferring any pair of values for $F$ and $w$, we constructed and iterated recurrence equations to model the evolution of all three types of allele: maternally imprinted, paternally imprinted, and Mendelian, for arbitrary degrees of polyandry (see Appendix). The evolutionary outcomes for a large number of hypothetical values of $F$ and $w$ can be plotted over limited ranges as fate maps (Figure 1A).

**The trade-off between maternal fecundity and offspring viability:** Quantitative data describing the relationship between gene expression levels in offspring, level of maternal investment in offspring, and offspring viability
First, we observe that, by assumption, all changes in these variables are produced by changes in the concentration of some substance in progeny. Therefore, we expect the relationship between $F$ and $w$ to be a smooth one. We would not, for example, expect changes in growth factor concentration to produce pairs of values $(F, w)$ scattered throughout parameter space. Rather, these values will be constrained to lie on a curve within parameter space by the dose-response relationship between, for example, growth factor concentration in embryonic tissues and the amount of maternal investment.

Second, we can rule out a strictly linear relationship if we assume that imprinted alleles are derived from ancestral Mendelian systems with optimal expression levels. This is because a linear relationship would lead to maximal or minimal expression in the Mendelian context if it has negative slope (except in one special case) and would not involve a trade-off if it had positive slope. The special case is that of a linear function whose slope is equal to that of the invasion boundary at the point $(F, w) = (1, 1)$. Then, paradoxically, all possible values are stable in the sense that no alternative allele can invade.

Finally, we exclude functions that have local or global maxima within the ranges of the parameters we investigate. Some of these are biologically plausible (see Mochizuki et al. 1996), but all of them imply that the concentrations of the factors involved become toxic at some level in the sense that both fecundity and viability are reduced. Since we do not rely on such toxic effects to explain the evolution of imprinting we do not discuss the properties of such functions here. The function we choose is $W = f(C)$, where

$$f(C) = K(1 - e^{-(b + C)})$$

where $W$ is the viability of offspring inheriting a mutant imprinted allele from the imprinting parent, or two copies of a Mendelian allele, relative to the viability of wild-type offspring; $C$ is the change in relative fecundity experienced by females homozygous for a maternally imprinted allele, females mating exclusively with males homozygous for a paternally imprinted allele, or females homozygous for a Mendelian allele mating exclusively with males homozygous for the same Mendelian allele; and $K$ is the value of $W$ that is approached as $C$ takes very large positive values. $C > 1$ makes no biological sense and is therefore irrelevant to our model. Substituting

$$b = \ln\left(\frac{K}{K - 1}\right)$$

ensures that the curve passes through the point $(0, 1)$.

Maternal fecundity and offspring viability in the wild-type population are set at unity and $W$ and $C$ are measured relative to this. In fact, $W$ and $C$ are identical to the variables $w$ and $c$ used to determine invasion and fixation conditions above. We use the uppercase symbols only to distinguish the subset of values determined by Equation 6.
The exact values taken by this function are not critical, but it must pass through coordinates \( \{C, W\} = \{0, 1\} \) (Figure 1B). A useful feature of the function is that its slope is different at every point so that, if an evolutionary stable value of \( C \) exists, it will be unique. We now consider that all possible alleles that can be generated by changes in expression level at the locus studied produce phenotypes [values of \( C \) and \( f(C) \)] determined by this function.

By inverting \( f(C) \) (Equation 6; that is, by expressing \( C \) as a function of \( W \) rather than \( W \) as a function of \( C \)) and substituting \( F = 1 - C \), we obtain the viability/fecundity function

\[
g(W) = 1 + \ln \left( \frac{K - W}{K - 1} \right),
\]

which can be plotted on the same coordinates as the invasion and fixation boundaries (Figure 1A). Note that, to describe a trade-off, any viability/fecundity function must lie entirely in the top left and bottom right quadrants of the parameter space described in Figures 1B and 2, A and B. By mathematically shifting the function relative to the invasion boundary, we can model a population with any of the continuum of alleles that it represents at fixation. In what follows, for convenience, we set \( K = 1.5 \), where the function represents an allele that is inviable in a monogamous system, as we shall show. Other values involve more mathematical manipulation without advancing the argument.

**Recurrence equations for imprinted and Mendelian alleles under arbitrary degrees of polyandry:** In the preceding sections we derived invasion and fixation conditions for Mendelian and imprinted alleles that influence the trade-off between maternal fecundity and offspring viability. We now supply recurrence equations that allow the dynamics of such alleles to be investigated, and we discuss some of their properties. These equations can be used to investigate the behavior of alleles in populations with any level of polyandry and can accept any function relating offspring viability and maternal fecundity. (The derivations are given in the appendix.)

We consider a population that is large enough for the effects of drift to be ignored. Mating is random and females can mate with more than one male during their reproductive lives. Generations do not overlap. First, we model the invasion of a paternally imprinted allele \( A^I \) into a population where some alternative allele \( A \) is fixed. The recurrence is then

\[
p' = \frac{2p^2T(p)w + pqT(p)w + pqT(q)}{2\bar{W}}
\]

where \( p \) is the relative frequency of \( A^I \); \( q = 1 - p \) is the relative frequency of \( A \); \( T(p) \) is the transmission function associated with \( A^I \) (see appendix); \( T(q) \) is the transmission function associated with \( A \); \( w \) is the relative viability of offspring that inherit a copy of \( A^I \) from the imprinting parent compared to offspring inheriting a wild-type allele; and \( \bar{W} \) is the population fitness. In the present case

\[
T(p) = 1 - e \left( p \left( \frac{1 - \frac{1}{2m}}{2} \right) + \frac{1}{2m} \right)
\]

\[
T(q) = 1 - e \left( 1 - \frac{1}{2m} \right)
\]

where \( e \) and \( m \) are as defined previously:

\[
\bar{W} = p^2T(p)w + pqT(p)w + pqT(q) + q^2T(q).
\]

The change in frequency of \( A^I \) between generations can be approximated (see appendix for justification) as

\[
\Delta p = \frac{2p^2T(p)w + pqT(p)w + pqT(q)}{2\bar{W}} - p.
\]

Setting \( \Delta p = 0 \) and solving for \( p \) to find the stable points produces three solutions, the boundary solutions \( p = 0 \) and \( p = 1 \), and one internal equilibrium,

\[
\hat{p} = \frac{cw + 2m(1 - w)}{e(1 - w)(2m - 1)}
\]

Therefore, for any set of the variables \( c, w, \) and \( m \), internal equilibria, when they exist, are unique. They are also stable since \( \Delta p > 0 \) for all \( p < \hat{p} \), and \( \Delta p < 0 \) for all \( p > \hat{p} \). Polymorphic states are stable in the sense that the system tends to return to them when it is perturbed. They must also be transient in the face of continued mutation because it is known that, for the form of \( f(C) \) under consideration (Equation 6), there is only one evolutionarily stable point for each imprinted allele, whether maternal or paternal. The location of the stable internal equilibrium for paternally imprinted alleles depends upon \( m \) whereas the internal equilibria for maternally imprinted alleles are independent of \( m \) (Figure 2, C and D). When there is any degree of polyandry in the population the evolutionarily stable points for maternal and paternal imprints do not coincide and so the population can never be invadable by new maternally and paternally imprinted alleles simultaneously.

Note that setting \( \hat{p} = 0 \) or 1 and solving for \( e \) immediately recovers the invasion and fixation conditions deduced previously by different means. Further, iterating this recurrence using a suitable range of values for \( c, w, \) and \( m \) reproduces the fate maps derived from the invasion and fixation conditions (Figure 2, A–D). Therefore the deterministic one-locus, two-allele model of imprinted alleles is entirely consistent with the conclusions derived from consideration of the invasion and fixation conditions alone.

**New mutant imprinted alleles cannot invade under monogamy:** Equation 6 can be written

\[
f(e) = \frac{3}{2} - \frac{e^c}{2}.
\]

To investigate the behavior of the system when phenotypic fitnesses are constrained by \( f(e) \) and when the mating
system is monogamous, we substitute the right-hand side into the expression for $\hat{p}$ (Equation 14) obtained for imprinted alleles and set $m = 1$ to obtain

$$\hat{p} = \frac{\epsilon'(3\epsilon - 2) - \epsilon + 2}{\epsilon(1 - \epsilon)}.$$  \hspace{1cm} (15)

We then ask whether there are any values of $\epsilon$ for which $\hat{p} > 0$ by solving

$$\frac{\epsilon'(3\epsilon - 2) - \epsilon + 2}{\epsilon(1 - \epsilon)} > 0.$$  \hspace{1cm} (16)

This leads to

$$\epsilon'(3\epsilon - 2) - \epsilon < -2$$

for which there are no solutions. We therefore conclude that no alternative imprinted alleles can invade the population as currently constituted. We defer discussion of polyandrous populations until after we have introduced the recurrences for the Mendelian case.

**New mutant Mendelian alleles cannot invade under monogamy:** Mendelian alleles alter the relationship between maternal fecundity and offspring viability in a manner that is independent of parental origin. We must therefore calculate $\epsilon$ in a manner slightly different from the case of imprinted alleles (see **APPENDIX**). Also, there is now only one class of heterozygote, whereas in the imprinted case there are two.

The recurrence we obtain is

$$p' = \frac{p^2 T(p) w + pq T(pq) ((1 + w)/2)}{W}$$  \hspace{1cm} (17)

$$W = p^2 T(p) w + 2pq T(pq) ((1 + w)/2) + q^2 T(q)$$  \hspace{1cm} (18)

$$\Delta p = \frac{p^2 T(p) w + pq T(pq) ((1 + w)/2) - p}{W}$$  \hspace{1cm} (19)

where

$$T(p) = 1 - \frac{cm(3p + 1) - p + 1}{4m}$$  \hspace{1cm} (20)

$$T(pq) = 1 - \frac{cm(6p + 1) - 2p + 1}{8m}$$  \hspace{1cm} (21)

$$T(q) = 1 - \frac{cp(3m - 1)}{4m}.$$  \hspace{1cm} (22)
Apart from the different calculation of $c$, the other variables are as described above.

Setting $\Delta p = 0$ and solving for $p$, we obtain an expression for $p$ as before. In addition to the two boundary conditions, we obtain
\[
\hat{p} = \frac{c(m + 1)(w + 1) + 8m(1 - w)}{8cw(1 - w)}.
\]
(23)

Setting $\hat{p} = 0$ or 1 again recovers the invasion and fixation conditions, respectively, demonstrating that our allele frequency model is consistent with arguments based on the conditions necessary for invasion and fixation to occur.

To model the constraint imposed by $f(c)$ we substitute
\[
w = \frac{3}{2} - \frac{e^{-c}}{2}
\]
and
\[
\frac{1 + w}{2} = \frac{3}{2} - \frac{e^{-c/2}}{2}.
\]
Then, to determine whether new alleles can invade a monogamous population, we set $m = 1$ and solve
\[
\lim_{c \to 0} \frac{1}{p} \left( \frac{d\Delta p}{dp} \right) > 1.
\]
This leads to
\[
e^{c/2}(3e - 4) - c < -4
\]
(24)
for which there are again no solutions. Thus, as in the case of imprinted alleles, we conclude that no alternative Mendelian alleles can invade a monogamous population. In summary, we find that with an allele determining $c = 0$ and $w = 1$ at fixation, no alternative allele can invade a monogamous population. An allele that renders the population uninvadable in an imprinting system also makes it uninvadable in a Mendelian system while monogamy prevails. This is so because, for invasion to occur, the slope of $g(W)$ must differ from that of the invasion boundary at the point $[F, w] = \{1, 1\}$.

For example, the invasion boundary in a Mendelian system under monogamy is (as already established by two independent arguments) determined by
\[
F_0 = 1 - \frac{4(w - 1)}{1 + w}.
\]
The derivative of the function with respect to $w$, when evaluated at $w = 1$ is
\[
-2.
\]
The version of $g(W)$ we use is
\[
g(W) = 1 + \ln(3 - W)
\]
whose derivative evaluated at $W = 1$ is again
\[-2.
\]
Now the invasion boundary for an imprinted allele in a monogamous population is determined by substituting $m = 1$ in Equation 2,
\[
F_i = 1 - \frac{2(w - 1)}{w},
\]
whose derivative evaluated at $w = 1$ is, unsurprisingly,
\[-2.
\]
This point regarding the derivatives of the invasion condition and $g(W)$ function is quite general and will apply to any such function, not just the one we have chosen to illustrate our argument. We therefore conclude that imprinted alleles are unable to evolve in a monogamous Mendelian population in which the uninvadable allele has reached fixation.

**Polyandry and the evolution of imprinting:** To analyze the interaction between various levels of polyandry and the invasion of imprinted alleles, we first model a polyandrous Mendelian population at equilibrium. To depict this Mendelian population, we modify $g(w)$ to
\[
g(w) = \ln\left(\frac{2 - w - m(w - 1)}{m + 1}\right) - \ln\left(\frac{1}{m + 1}\right) + 1.
\]
(25)

Although this alteration looks quite radical, we are merely shifting the original function so that, for any $m$, its derivative, evaluated at $w = 1$, is equal to that of the invasion boundary. It then represents a polyandrous population that is uninvadable by other Mendelian alleles. We omit the derivation, which is straightforward. Allied to this modified function is a correspondingly modified version of $f(c)$,
\[
f(c) = \frac{m + 2}{m + 1} - \frac{e^{-c}}{m + 1}.
\]
(26)

These two modified functions determine a population in which no new Mendelian alleles can evolve. We now examine whether imprinted alleles can evolve in such a population.

First, we consider paternally imprinted alleles. Substituting the right-hand side of Equation 26 for $w$ in the recurrence for imprinted alleles (Equation 9) gives
\[
\hat{p} = \frac{e^{c}(e(m + 2) - c + 2m)}{e(1 - 2m)(e^{c} - 1)}.
\]
(27)

For $\hat{p} > 0$ we require
\[
e^{c}(m + 2) - c < -2m.
\]
(28)
Setting $m = 1$ produces no solutions, which is in agreement with our finding that imprinting does not evolve under monogamy. However, for all higher values of $m$ (polyandry), there are some values of $c$ that satisfy the inequality. That is to say, some paternally imprinted alleles can invade. To determine whether any of these alleles can reach fixation we set $\hat{p} \geq 1$ and obtain
Again we find that for all values of \( m > 1 \) this expression has solutions indicating that some paternally imprinted trading alleles reach fixation.

We next consider whether maternally imprinted alleles can evolve in a polyandrous Mendelian population at equilibrium. First, we substitute into the recurrence equation for imprinted alleles (Equation 9) the transmission functions for maternally imprinted genes, which are unaffected by the number of mates a female accepts and are therefore obtained by setting \( m = 1 \) in the versions used for paternally imprinted alleles:

\[
T(p) = 1 - \frac{cp}{2} - \frac{c}{2} \tag{30}
\]

\[
T(q) = 1 - \frac{cp}{2} \tag{31}
\]

Proceeding as for paternal imprints above, we replace \( w \) in the recurrence with the right-hand side of Equation 26, obtain an expression for \( \hat{p} \), and solve for \( \hat{p} > 0 \) and \( \hat{p} \geq 1 \) to determine whether invasion and fixation, respectively, can occur. For the invasion condition, we get

\[
e^{c(m + 2/2) - 2c} \hat{c} < -2 \tag{32}
\]

Again, there are no solutions for \( m = 1 \), confirming that maternally imprinted alleles cannot evolve in a Mendelian population under monogamy, but there are solutions for \( m > 1 \), indicating that maternally imprinted alleles can invade a polyandrous population.

For fixation, we get

\[
e^{c(m + 3/2) - 2c} \leq -2 \tag{33}
\]

which again has solutions only when \( m > 1 \). We therefore conclude that for any Mendelian population at equilibrium, in which an uninvadable allele has become fixed, invasion by maternally or paternally imprinted alleles can occur under polyandry but not under monogamy.

**DISCUSSION**

We present a diallelic model of the evolution of imprinting that has several novel features. The model that results from these innovations resolves the contradictions that existed between previous diallelic models (Spencer et al. 1998, 2004; Haig 1999a; Hurst 1999; Spencer 2000) and verbal and game theoretical treatments of the conflict theory (Moore and Haig 1991; Haig 1992, 1997; Mochizuki et al. 1996; Burt and Trivers 1998; Wilkins and Haig 2001, 2002).

First, following Burt and Trivers (1998) we attribute all of the costs or benefits of altered resource demand by imprinted alleles in progeny directly to maternal fecundity, which consequently becomes a frequency-dependent selection coefficient. We model this by employing transmission functions to quantify the average effect of fecundity changes on the transmission of alleles of all kinds to the next generation. This strategy allows us to examine the effects of arbitrary degrees of polyandry on the evolution of imprinted alleles, which has not been achieved previously.

Second, and similar to the diallelic models of Parker and McNair (1978), we incorporate a function relating maternal fecundity costs to offspring viability, which is analogous to the resource allocation/survivorship functions used in previous models of imprinting (Haig 1992; Mochizuki et al. 1996). Implicit in the rationale for using this function is that imprinting is a parental origin-specific change in allele expression level. Different allele expression levels will affect the relationship between mother and offspring in a predictable way and produce a dose-response curve in parameter space that contains information about all of the alleles that can be produced by changing the expression level of the gene in question. The restricted parameter values provided by the trade-off function facilitate the discussion of long-term evolution by identifying, for all three classes of allelic expression (Mendelian, maternally imprinted, paternally imprinted), alleles that are optimal in the sense that they cannot be displaced by another allele of the same class. We can therefore draw conclusions about the long-term stability of particular alleles. In contrast, the diallelic models of Spencer et al. (1998, 2004) do not incorporate this condition and are therefore unsuitable for analyzing the long-term outcome of populations experiencing recurring invasions of imprinted and Mendelian alleles. This point can be illustrated by considering that, in a population fixed for an allele not precisely coincident with the Mendelian optimum, a new allele closer to the optimum, which happens to be imprinted, could invade the population under monogamy. As noted by Hurst (1999), such alleles (which might usefully be termed “opportunistic”) invade in spite of, rather than because of, imprinting.

Although our trade-off function, in the absence of relevant experimental data, undoubtedly has some arbitrary features, we contend that it is more realistic to include such functions than to analyze unconstrained parameter values, which assume that physiological constraints do not apply. We contend that this omission is one of the reasons why Spencer’s models produce conclusions that disagree with other models of imprinting (Haig 1999a; Hurst 1999), particularly, in predicting the evolution of imprinting under monogamy. In contrast, our analysis supports kin selection and quantitative genetic models that show that imprinted alleles cannot invade under monogamy (Haig 1992; Mochizuki et al. 1996).

In the light of our findings, we can reappraise the disagreement between the diallelic and game theoretical models of the conflict theory. Hurst (1999) is correct to point out that the models of Spencer et al. (1998) do not compare the behavior of Mendelian alleles with
those of imprinted alleles of similar phenotypic effect and are therefore uncontrolled. However, Spencer (2000) argued that the restricted parameter space analyzed under an assumption of zero net fitness effects of mutants underpinning game theory models cannot be translated into workable population genetic models of imprinting, and he appears to remain agnostic about the resolution proposed by Hurst (1999; see also Spencer et al. 2004). However, as we show herein, the root of the disagreement lies with Spencer et al.’s models: first, because they lack an explicitly defined trade-off between the costs and benefits to an individual inheriting an imprinted allele and, second, because they ignore the effects of selection on Mendelian alleles. We suggest that Haig’s (1999a) view that diallelic models are generally unsuitable for studying long-term evolutionary change is, strictly speaking, undeniable because many more than two alleles can exist at a locus over evolutionary time. It is the inclusion, in our diallelic models, of a trade-off function and a Mendelian population at equilibrium that allows us to model long-term change in the context of conflict theory of imprinting. In this context, it is debatable to what extent Hurst’s (1999) modification of Spencer et al. (1998) actually addresses the central issue of long-term evolution under the conflict theory. His analysis defines areas of parameter space occupied exclusively by imprinted alleles under polyandry, but stops short of analyzing whether such alleles will actually evolve. Also, the analysis relies on the occurrence of deleterious recessive mutations to mediate between the evolution of imprinted vs. Mendelian expression. However, weak selection due to recessive mutations probably has an insignificant role in the evolution of imprinting (Haig 1999b). In contrast, our models unambiguously specify the types of alleles that can invade and establish precisely the conditions that allow imprinting to replace Mendelism, for arbitrary degrees of polyandry.

We modeled polyandry over a wide range of the parameter values to determine whether any biologically relevant trends could be discerned. We note that increasing the degree of polyandry has a proportionately smaller effect than lower levels of polyandry in enhancing the invasion of imprinted alleles, with the intensity of this effect tailing off rapidly for higher values. Significantly, therefore, we conclude that the strongest influence of polyandry occurs at the lower, biologically plausible, values.

We also address comprehensively, for the first time, the effect of different levels of polyandry on the evolution of Mendelian alleles. We show that, similar to imprinted alleles, increasing levels of polyandry promote the invasion and fixation of Mendelian alleles that are relatively more demanding of maternal resources, resulting in reduced fecundity and increased offspring viability. In addition, we show that, for a particular level of polyandry and a specific viability/fecundity trade-off function, an ESS is possible. In contrast, an ESS is not possible for both maternally and paternally imprinted alleles simultaneously, and oppositely imprinted alleles are predicted to continue to coevolve until a mechanistic constraint, such as complete allelic silencing (zero transcription), or maximum transcriptional flux is achieved.

Our model, and most previous models of imprinting, implicitly treats alleles as mechanistically self-contained units with all of the information necessary to specify imprinted expression available in cis. However, in reality, imprinted expression probably relies on complex interactions between both cis- and trans-acting factors, some of which operate in the parental germline and others postfertilization (Moore and Reik 1996). Two models of such interactions have been attempted, using kin selection approaches. Burt and Trivers (1998) explored how the different relatednesses of parental germline and offspring, cis- and trans-acting factors encoding components of the imprinting machinery result in conflicts between imprinter genes and imprinted genes. In a somewhat similar study, Wilkins and Haig (2002) analyzed the stability of imprinting in the context of conflicts between such trans-acting modifier genes in an attempt to account for apparently different mechanisms operating at maternally and paternally silenced imprinted loci (Reik and Walter 2001). In a genetic model, Hurst (1999) considered the evolution of a modifier locus that converts imprinted to Mendelian expression at a target locus, but did not analyze the implications of different patterns of expression or inheritance of the modifier and target loci. Genetic analysis of such interactions will require the development of more sophisticated multilocus, diallelic models.

We thank D. Brown, L. D. Hurst, P. Fitzpatrick, H. N. Lim, Y. Mills, J. Wilkins, and anonymous referees for helpful comments. T.M. is supported by a Wellcome Trust/Irish Health Research Board “New Blood” Research Fellowship.

LITERATURE CITED


Communicating editor: J. B. Walsh

APPENDIX

New mutant alleles that are costly, relative to wild-type alleles, to maternal fecundity are transmitted to future generations less efficiently than wild-type alleles. Recurrence equations that model the evolution of such alleles must incorporate the reduced efficiency in allele transmission. We derive functions for the mean cost of each type of allele and then associate these functions with the frequency of the appropriate allele. We begin by deriving transmission functions for paternally imprinted alleles.

In a polyandrous population, females mate with some collection of m mates drawn randomly and independently from the total population of males. If we assume that two alleles are segregating in the population, one imprinted, A1, and the other unimprinted, A, there are three male genotypes. Let their frequencies be

\[ X_1 = A^1A^1 \]
\[ X_2 = A^1A \]
\[ X_3 = AA. \]

Each collection of m mates accepted by each female will consist of some combination of these three genotypes. The expected frequencies and compositions of these collections are given by the multinomial expansion of

\[ (X_1 + X_2 + X_3)^m, \]

which can be written as

\[ \sum_{a_1,a_2,a_3} m! \prod_{i=1}^{3} X_i^{a_i}, \]

where \( a_i \) is the number of males of genotype \( X_i \) in the combination, and the sum is taken over all \( a_i \) such that \( \sum_{i=1}^{3} a_i = m \), and similarly for the product, \( \prod_{i=1}^{3} a_i \). If the relative frequency of individuals homozygous for \( A^1 \) in the population is \( X_1 \) and that of heterozygous individuals is \( X_2 \), it is evident that the expected frequency of \( A^1 \) in the combination of males accepted by a female (\( p_x \)) is given by

\[ p_x = \sum_{a_1,a_2,a_3} m! \prod_{i=1}^{3} X_i^{a_i} \left( \frac{2a_1 + a_2}{2m} \right), \]

which is its frequency in the adult population. That is, \( p_x = X_1 + (X_2/2) \). We now derive an expression for the frequency of the imprinted allele in males, which is weighted by the effects of altered fecundity, \( p_e \). We find that for any combination of male genotypes

\[ p_e = \sum_{a_1,a_2,a_3} m! \prod_{i=1}^{3} X_i^{a_i} \left( \frac{2a_1 + a_2}{2m} \right) \times \left( 1 - \sum_{a_1,a_2,a_3} m! \prod_{i=1}^{3} X_i^{a_i} \left( \frac{2a_1 + a_2}{2m} \right)^c \right) \]

\[ = \sum_{a_1,a_2,a_3} m! \prod_{i=1}^{3} X_i^{a_i} \left( \frac{2a_1 + a_2}{2m} \right) - \sum_{a_1,a_2,a_3} m! \prod_{i=1}^{3} X_i^{a_i} \left( \frac{2a_1 + a_2}{2m} \right)^2 \]

\[ = p - \frac{c}{2m} \sum_{a_1,a_2,a_3} m! \prod_{i=1}^{3} X_i^{a_i} \left( 2a_1 + a_2 \right)^2 \]

\[ = p - \frac{c}{2m} \sum_{a_1,a_2,a_3} m! \prod_{i=1}^{3} X_i^{a_i} \left( 4a_1^2 + 4a_1a_2 + a_2^2 \right). \]

Since the expectation of \( 4a_1^2 \), \( E[4a_1^2] \), is given by

\[ 4E[a_1^2] = 4E[a_1]^2 + 4 \text{Var}[a_1] \]

\[ = 4mX_1 + 4X_1^2m(m-1) \]

and

\[ E[4a_1a_2] = 4 \text{Cov}[a_1, a_2] + 4E[a_1]E[a_2] \]

\[ = 4m(m - 1)X_1X_2 \]

while

\[ E[a_2^2] = E[a_2]^2 + \text{Var}[a_2] \]

\[ = mX_2 + X_2^2m(m-1), \]

it follows that

\[ p_e = p - \frac{c}{4m} \left[ 4mX_1 + X_2^2m(m-1) + 4X_1X_2m(m-1) + mX_2 + X_2^2m(m-1) \right] \]

\[ = p - \frac{c}{4m} \left[ 4X_1 + X_2 + (m - 1)(2X_1 + X_2)^2 \right]. \]

Substituting \( p = X_1 + (X_2/2) \) gives
\[ p_e = p - \frac{c}{4m} \left[ 2p + 2X_i + 4(m - 1)p^2 \right]. \]

We now make the substitution \( X_i = p^2 \), which is equivalent to assuming that adult genotypes are at Hardy-Weinberg frequencies. Naturally, this introduces a small error into our calculations. However, we can justify the substitution by noting that the size of the error approaches zero as \( p \to 0 \) or 1, which are the points of major interest. We can then write

\[ p_e = p - \frac{c}{4m} \left( 2p + 2p^2 + 4(m - 1)p^2 \right) \]
\[ = p - \frac{c}{2m}(1 + p + 2(m - 1)p) \]
\[ = p \left( 1 - cp \left( 1 - \frac{1}{2m} \right) - \frac{c}{2m} \right). \]

The function

\[ T(p) = 1 - cp \left( 1 - \frac{1}{2m} \right) + \frac{1}{2m} \] (A1)

is a frequency-dependent coefficient of fecundity that can be associated with the frequency of the imprinted allele in males to construct a recurrence equation. First, however, we need to derive an equivalent function \( T(q) \) to determine the effects of the imprinted allele on the relative frequency of the nonimprinted allele. The derivation is similar to that for \( T(p) \) and gives

\[ T(q) = 1 - cp \left( 1 - \frac{1}{2m} \right). \] (A2)

We now consider the transmission functions to be associated with Mendelian alleles. The effects of new mutant alleles on fecundity and viability are independent of parental origin, but it is still true that the cost associated with paternally inherited alleles can be shared among several females. The maximum cost occurs when females homozygous for the new mutant allele mate with some combination of similarly homozygous males. We designate this cost \( c \), as before, and consider that half of this total is associated with maternally inherited, and half with paternally inherited, alleles. This allows us to find the costs associated with the new Mendelian alleles in homozygous offspring as the mean of the costs determined for maternally and paternally imprinted alleles, and so

\[ T(p^2) = 1 - \frac{1}{2} \left[ \frac{c(p + 1)}{2} + cp \left( 1 - \frac{1}{2m} \right) + \frac{1}{2m} \right] \]
\[ = 1 - \frac{c(m(3p + 1) - p + 1)}{4m}. \] (A3)

Similarly the costs associated with the alleles of the wild-type homozygotes will be such that

\[ T(q^2) = 1 - \frac{1}{2} \left( \frac{cp}{2} + cp \left( 1 - \frac{1}{2m} \right) \right) \]
\[ = 1 - \frac{cp(3m - 1)}{4m}. \] (A4)

The heterozygotes have two different cost functions depending upon which parent contributed the mutant allele. We therefore take the mean of these functions since there will be equal numbers of each kind, as follows:

\[ T(2pq) = 1 - \frac{1}{4} \left[ \frac{cp}{2} + cp \left( 1 - \frac{1}{2m} \right) + \frac{1}{2m} \right] \]
\[ + \left( \frac{c(p + 1)}{2} + cp \left( 1 - \frac{1}{2m} \right) \right) \]
\[ = 1 - \frac{c(m(6p + 1) - 2p + 1)}{8m}. \] (A5)

These functions are used to construct the recurrences given in the main text. Equations A1 and A2 are used in recurrences for imprinted alleles. Equations A3, A4, and A5 are used to model Mendelian alleles.