

Genetic Conflicts, Multiple Paternity and the Evolution of Genomic Imprinting

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ABSTRACT

We present nine diallelic models of genetic conflict in which one allele is imprintable and the other is not to examine how genomic imprinting may have evolved. Imprinting is presumed to be either maternal (*i.e.*, the maternally derived gene is inactivated) or paternal. Females are assumed to be either completely monogamous or always bigamous, so that we may see any effect of multiple paternity. In contrast to previous verbal and quantitative genetic models, we find that genetic conflicts need not lead to paternal imprinting of growth inhibitors and maternal imprinting of growth enhancers. Indeed, in some of our models—those with strict monogamy—the dynamics of maternal and paternal imprinting are identical. Multiple paternity is not necessary for the evolution of imprinting, and in our models of maternal imprinting, multiple paternity has no effect at all. Nevertheless, multiple paternity favors the evolution of paternal imprinting of growth inhibitors and hinders that of growth enhancers. Hence, any degree of multiple paternity means that growth inhibitors are more likely to be paternally imprinted, and growth enhancers maternally so. In all of our models, stable polymorphism of imprinting status is possible and mean fitness can decrease over time. Neither of these behaviors have been predicted by previous models.

GENOMIC imprinting is the differential expression of genes, depending on the sex of the parent from which they were inherited (Barlow 1995; John and Surani 1996; Franklin *et al.* 1996). In its typical form, imprinting is the nonexpression in at least some tissues for some period of development of a paternally or maternally derived gene. The best known example is that of insulin-like growth factor II (*Igf-2*) in humans and mice: in most tissues, only the paternally derived allele is expressed and the maternally derived allele is silent (Giannoukakis *et al.* 1993; DeChiara *et al.* 1991). This form of non-Mendelian expression thus renders the individual functionally haploid at the imprinted locus. Theoretical arguments suggest that diploidy is strongly favored in organisms with high levels of recombination, such as mammals (Otto and Goldstein 1992), leading to the question of how an imprinted system might arise. Spencer and Williams (1997) showed that without some direct advantage to imprinting, the frequency of a modifier gene that caused its target locus to be imprinted would change at a rate only of the order of the mutation rate at the target locus. Hence, they argued, imprinting is unlikely to spread unless there is some direct selective advantage to being imprinted.

Such an advantage has been hypothesized by Haig and his colleagues in terms of genetic conflicts among fathers, mothers and their offspring: “an embryo’s paternal genome is selected to take more resources from maternal tissues than is the embryo’s maternal genome” (Haig 1992). In brief, taking eutherian mammals as the model organisms, all the offspring in one (or more) pregnancies have the same mother, and so it is in her best genetic interest to share the resources she passes on equally among them. A father, however, has no such assurance, and so it is in his genetic interest to arrange for his offspring to get more of the resources than others with different fathers. This is a form of parental genetic conflict that depends on the existence of multiple paternity. There is, however, a second possible form of genetic conflict: a form of mother–offspring conflict. All offspring do better if they obtain more of the mother’s resources, but she may improve her reproductive success by holding some back for future pregnancies. In mammals in particular, a mother may have birthing problems if the offspring are too large. There is also a third possible source of genetic conflict between sibs only: it is in each sib’s interest to obtain more resources at the expense of other siblings.

As a result of the first of these conflicts, it was predicted that growth enhancers acting early in development will be maternally inactivated, whereas growth inhibitors will be paternally inactivated (Haig 1992; Haig and Graham 1991). This prediction appears to be well supported. For example, *Igf-2* is a growth en-

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hancer that in most tissues is normally maternally imprinted (*i.e.*, only the paternal copy is active) in both mice and humans. *Igf-2* receptor (*Igf2-r*) is a growth inhibitor that in mice is only maternally expressed. In humans, however, *Igf2-r* appears to be polymorphically imprinted: some small number of individuals have monoallelic expression, but most are biallelic (Xu *et al.* 1993). One explanation for this difference between mice and humans invokes different levels of multiple paternity in the two species (Xu *et al.* 1993). After studying some quantitative models, Mochizuki *et al.* (1996) claimed that multiple paternity was essential for the evolution of imprinting.

In this paper, we develop a series of explicitly genetic models that incorporate some of the genetic conflicts described above, and we allow females to be either monogamous or bigamous so that we can assess the role of multiple paternity. (A classification of the models is shown in Table 1.) We particularly examine the dynamics and stability of a single-locus diallelic system in which allele *A* is never inactivated, but allele *a* is inactivated when passed on by an individual of the imprinting sex (thus permitting either maternal or paternal imprinting). The assumption that an imprinted gene is completely inactivated is not crucial, as we note below. Whereas Haig's models are mostly verbal and often describe the genetic conflicts in terms of game theory, we have chosen to start with explicitly genetic models that allow the evolutionary consequences of conflicts to be reflected in changes in genotype frequencies. These different approaches lead to different conclusions (in an analogous way to the optimality and modifier theory approaches for analysis of the evolution of recombination; see Feldman *et al.* 1997). Our models also address the criticism of Franklin *et al.* (1996) that Haig's treatment of the genetic conflict hypothesis does not adequately consider the effects over more than one generation.

MODELS

SM1: Sibling conflict, maternal imprinting, monogamous females: We assume each female has two offspring by the same father, but mating occurs at random. Imprinting is assumed to be maternal: the *a* allele is inactivated if passed on by the mother. If both offspring are imprinted (by which we mean that they carry

an inactivated *a* allele), they each have viability $1 + u$, relative to 1 for offspring in families without imprinting. If one sib is imprinted and the other not, then the relative viabilities are $1 - s$ and $1 + t$. In the case of a growth-enhancing gene like *Igf2*, *s* and *t* are both positive, since an imprinted offspring is smaller than its unimprinted sib. If, as a result of both offspring being imprinted, the mother has more resources postpartum to aid the offspring, the value of *u* would also be positive. It might be argued, however, that $u = 0$, since any reduction in the production of growth factor could have been selected previously for the same reason, without the evolution of imprinting. Since the algebra does not preclude negative values for any of these parameters, however, we put no restrictions on their signs. Indeed, for a growth inhibitor like *Igf2-r*, *s* and *t* are negative, because imprinting makes the offspring larger. Nevertheless, we must have $s \leq 1$ and $t, u \geq -1$.

Let *x* be the frequency of *AA* genotypes, *y* that of *Aa* heterozygotes, and *z* ($= 1 - x - y$) that of *aa* genotypes. With the aid of Table 2, in which the paternal allele is written first and an imprinted allele is in parentheses, we derive the following recursions

$$Tx' = x^2 + xy\left[\frac{3}{4} + \frac{1}{4}(1+t)\right] + y^2\left[\frac{1}{8} + \frac{1}{8}(1+t)\right] \quad (1a)$$

$$Ty' = xy\left[\frac{1}{2} + \frac{1}{4}(1-s) + \frac{1}{4}(1+u)\right] + xz(2+u) + y^2\frac{1}{8}(4-s+t+u) + yz\left[\frac{1}{4} + \frac{1}{4}(1+t) + \frac{1}{2}(1+u)\right] \quad (1b)$$

$$Tz' = y^2\left[\frac{1}{8}(1-s) + \frac{1}{8}(1+u)\right] + yz\left[\frac{1}{4}(1-s) + \frac{3}{4}(1+u)\right] + z^2(1+u) \quad (1c)$$

where *T* is the mean viability, namely the sum of the right sides of Equations 1a, 1b and 1c. After the algebra,

$$T = 1 + (1-x)u - \frac{1}{4}(s-t+3u)y. \quad (1d)$$

The substitutions and $p = x + \frac{1}{2}y$ and $q = 1 - p$ lead to

$$x' = pB, \quad (2a)$$

$$y' = p(1-B) + qB, \quad (2b)$$

TABLE 1

Classification of models by form of genetic conflict, which sex imprints, and mating system

	Sibling conflict		Parent-offspring conflict	
	Maternal imprinting	Paternal imprinting	Maternal imprinting	Paternal imprinting
Females monogamous	SM1	SP1	P-OM1	P-OP1
Females bigamous	SM2	SP2	P-OM2	P-OP2

$$z' = q(1 - B), \quad (2c)$$

$$t = 1 + qu + y\frac{1}{4}(t - s - u), \quad (2d)$$

where $B = (p + yt/4)/T$. Since $p' = \frac{1}{2}(p + B)$ at equilibrium $\hat{p} = \hat{B}$, all equilibria have the quasi-Hardy-Weinberg form $(\hat{x}, \hat{y}, \hat{z}) = (\hat{p}^2, 2\hat{p}\hat{q}, \hat{q}^2)$. This simple form of recursion is not surprising in retrospect, since the model is one in which inheritance via the father follows Hardy-Weinberg assumptions (hence the p and q terms in Equations 2, a-d) with selective differences arising only through the effect of maternally inherited genes (hence the terms with B). For example, in constructing the equation for x' , an A allele must be inherited from the father, which occurs at frequency p , and similarly one must be inherited from the mother. This also occurs at a frequency p , but there is also a selective advantage, t , to those with an imprinted sib, namely one quarter of those with a heterozygous mother.

There are three equilibria of this system: two trivial ones at which A and a , respectively, are fixed, and the third is given by

$$\hat{x} = \frac{(2u-t)^2}{(s-t+u)^2}, \hat{y} = \frac{2(2u-t)(s-u)}{(s-t+u)^2}, \hat{z} = \frac{(s-u)^2}{(s-t+u)^2}, \quad (3)$$

which is feasible (*i.e.*, $0 \leq \hat{x}, \hat{y}, \hat{z} \leq 1$) if and only if $2s < 2u < t$ or both inequalities are reversed. We can determine the (local) stability of any one of these equilibria by examining the leading eigenvalue of the system linearized around that equilibrium. Near fixation of A [*i.e.*, $(x, y, z) = (1, 0, 0)$], the leading eigenvalue is $1 - \frac{1}{4}(s - u)$. Thus, a population fixed for A is stable to invasion by a alleles if $u < s$. (If $u = s$, a consideration of the quadratic terms of the expansion shows that the re-

quirement for stability is $t > 2u$.) If the inequality is reversed, a will invade at a rate proportional to the difference $u - s$. Similarly, near fixation of a , the leading eigenvalue is

$$1 + \frac{t - 2u}{4(1 + u)},$$

and A will invade if $t > 2u$. (If $t = 2u$, the quadratic terms of the expansion show that the requirement for stability is $u > s$. Note that this condition is simply the invasibility condition at the other fixation.)

The stability of the internal equilibrium depends on the leading eigenvalue

$$\lambda_i = 1 + \frac{(2u-t)(s-u)}{4(s-t+u) + 2t(s-u)}. \quad (4)$$

Feasibility of the equilibrium implies that either the denominator of the right-hand term is negative and the numerator is positive (when $2s < 2u < \eta$), or both are positive (when the inequalities are reversed). Thus, the polymorphic equilibrium is stable and feasible only when both fixation equilibria are unstable.

This analysis proves local stability, but in fact, as we now show following the method of Karlin (1972), the internal equilibrium is globally stable whenever it is locally stable. We first require that the transformation $F(p, B) = (p', B')$ be bimonotonic, by which we mean that if both $p \leq \tilde{p}$ and $B \leq \tilde{B}$, then we have that both $p' \leq \tilde{p}'$ and $B' \leq \tilde{B}'$ with strict inequality unless both $p = \tilde{p}$ and $B = \tilde{B}$. Since it can be shown that all four partial derivatives $\partial p' / \partial p$, $\partial p' / \partial B$, $\partial B' / \partial B$ and $\partial B' / \partial p$ are positive, F is indeed bimonotonic. Second, we require just one internal equilibrium. Third, we require that both fixation equilibria are locally unstable if the internal equilibrium is locally stable. Thus, all populations that

TABLE 2
Mating table when females are monogamous

			Proportions of offspring pairs and their viabilities under sibling conflict and maternal imprinting									
Parents		Frequency of mating	$AA,A(a)$		$AA,a(a)$		$A(a),A(a)$	$A(a),aA$	$A(a),a(a)$		$aA,a(a)$	$a(a),a(a)$
Mother	Father		AA,AA	$1+t$	AA,aA	$1+t$	$1+u$	$1-s$	$1+u$	aA,aA	$1+t$	$1+u$
			1,1	$1-s$	1,1	$1-s$	$1+u$	$1+t$	$1+u$	1,1	$1-s$	$1+u$
AA	AA	x^2	1	0	0	0	0	0	0	0	0	0
AA	Aa	xy	1/4	0	1/2	0	0	0	0	1/4	0	0
AA	aa	xz	0	0	0	0	0	0	0	1	0	0
Aa	AA	yx	1/4	1/2	0	0	1/4	0	0	0	0	0
Aa	Aa	y^2	1/16	1/8	1/8	1/8	1/16	1/8	1/8	1/16	1/8	1/16
Aa	aa	yz	0	0	0	0	0	0	0	1/4	1/2	1/4
aa	AA	zx	0	0	0	0	1	0	0	0	0	0
aa	Aa	zy	0	0	0	0	1/4	0	1/2	0	0	1/4
aa	aa	z^2	0	0	0	0	0	0	0	0	0	1
			AA,AA	AA,Aa	$AA,(a)A$	$AA,(a)a$	Aa,Aa	$Aa,(a)A$	$Aa,(a)a$	$(a)A,(a)A$	$(a)A,(a)a$	$(a)a,(a)a$
			1,1	1,1	$1+t$	$1+t$	1,1	$1+t$	$1+t$	$1+u$	$1+u$	$1+u$
					$1-s$	$1-s$		$1-s$	$1-s$	$1+u$	$1+u$	$1+u$
Proportions of offspring pairs and their viabilities under sibling conflict and paternal imprinting												

are not fixed for one allele move away from the fixations (because they are locally unstable) without cycling (because of the bimonotonicity) all the way (because of the uniqueness of the internal equilibrium and bimonotonicity) to the polymorphic equilibrium (because it is locally stable). In other words, the internal equilibrium is globally stable.

We can easily show, however, that the mean viability, T , need not increase or be maximized at equilibrium (see Figure 1 for some numerical examples), even when the internal equilibrium is feasible and stable. Moreover, even though all equilibria have a quasi-Hardy-Weinberg form, the value of T restricted to such points is not maximized at equilibrium. To show this property, we substitute $y = 2pq$ into Equation 2d, differentiate T with respect to q , equate the result to zero and solve for q , giving $\tilde{q} = (t - s + u)/2(t - s - u) \neq \tilde{q}$.

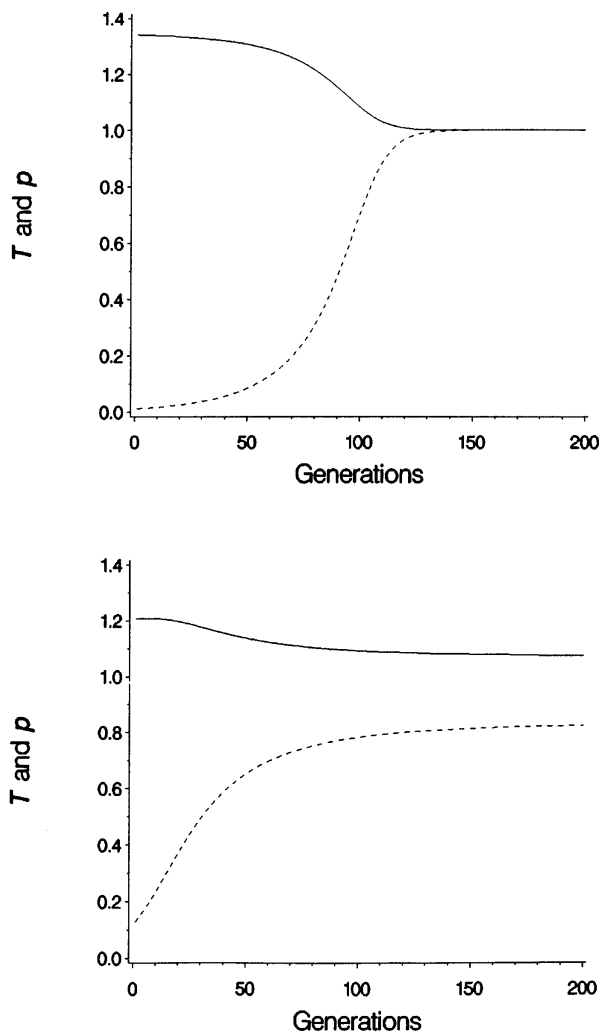


Figure 1.—Mean viability, T (solid line), and frequency of allele A , p (dashed line), as a function of time for Model SM1. If both offspring are imprinted, their viabilities are $1 + u$ relative to unimprinted families. If one sib is imprinted and the other is not, viabilities are $1 - s$ and $1 + t$, respectively. For the upper graph $s = 0.893$, $t = 0.909$, and $u = 0.347$, and for the lower graph $s = 0.1$, $t = 0.9$, and $u = 0.2$.

(Since $\partial^2 T / \partial q^2 = u + s - t < 0$ when the internal equilibrium exists, we are sure of a maximum rather than a minimum. Of course, if \tilde{q} is not between 0 and 1, T will be maximized at either $q = 0$ or 1.)

In summary, a population will be stably nonimprinting if the advantage of two imprinted sibs is less than the disadvantage of an unimprinted individual with an imprinted sib (*i.e.*, $u < s$). If this advantage is greater, then an imprintable allele will invade, but it will only move to fixation if this advantage is more than half that of an imprinted individual with an unimprinted sib (*i.e.*, $2u > t$). It is particularly worth noting that (1) multiple paternity is not necessary for the evolution of imprinting and (2) imprinted sibs may have greater viabilities than unimprinted sibs (*i.e.*, $u > 0$) and yet imprinting may still not evolve.

A growth-enhancing gene is likely to be maternally imprinted if $(0 <) s < u$ and $(0 <) t < 2u$. But a growth inhibitor may also be maternally imprinted, provided that $s < u$ and $t < 2u$. Since a growth inhibitor would likely have negative values for s and t , if u is positive (which will be true if larger offspring have little effect on the mother), these conditions will always be fulfilled. In other words, if imprinting is beneficial both for a single sib and for two sibs, it is likely to be fixed. Thus, sibling conflict does not predict the paternal and maternal imprinting of, respectively, growth inhibitors and enhancers.

SM2: sibling conflict, maternal imprinting, bigamous females: We now assume that each female has two offspring by different fathers, leaving all other assumptions unchanged. With the aid of Table 3 and a little algebra, we find that the recursions are identical to those above. The reason for this identity is simply that all possible sibships occur in the same proportions. Thus, not only is multiple paternity unnecessary for the evolution of maternal imprinting if pure sibling conflict is the driving mechanism, but its presence would not help the process.

SP1: sibling conflict, paternal imprinting, monogamous females: This model is identical to SM1, except that imprinting is assumed to be paternal, as is the case for *Igf2-r* in mice. The same mating table (Table 2) applies, except that the offspring are imprinted differently (the bottom lines of the table). This change in the offspring's imprinting pattern cancels out, however, and again we are left with the recursions shown above (Equation 1). Thus, the conditions for the evolution of paternal imprinting (given sibling conflict as the driving force) are the same as those for maternal imprinting. In particular, conditions exist for invasion of both growth enhancers and growth inhibitors that are paternally imprinted.

SP2: sibling conflict, paternal imprinting, bigamous females: This model is the obvious parallel to SM2. The recursions, however, are different from the previous three models because the sibships arise from two

TABLE 3
Mating table when females have two offspring by different fathers

			Proportions of offspring pairs and their viabilities under sibling conflict and maternal imprinting									
Parents		Frequency of mating	<i>AA,AA</i>	<i>AA,A(a)</i>	<i>AA,aA</i>	<i>AA,a(a)</i>	<i>A(a),A(a)</i>	<i>A(a),aA</i>	<i>A(a),a(a)</i>	<i>aA,aA</i>	<i>aA,a(a)</i>	<i>a(a),a(a)</i>
Mother	Father		1,1	1 + <i>t</i> , 1 - <i>s</i>	1,1	1 + <i>t</i> , 1 - <i>s</i>	1 + <i>u</i> , 1 + <i>u</i>	1 - <i>s</i> , 1 + <i>t</i>	1 + <i>u</i> , 1 + <i>u</i>	1,1	1 + <i>t</i> , 1 - <i>s</i>	1 + <i>u</i> , 1 + <i>u</i>
<i>AA</i>	<i>AA,AA</i>	x^3	1	0	0	0	0	0	0	0	0	0
<i>AA</i>	<i>AA,Aa</i>	$2x^2y$	1/2	0	1/2	0	0	0	0	0	0	0
<i>AA</i>	<i>AA,aa</i>	$2x^2z$	0	0	1	0	0	0	0	0	0	0
<i>AA</i>	<i>Aa,Aa</i>	xy^2	1/4	0	1/2	0	0	0	0	1/4	0	0
<i>AA</i>	<i>Aa,aa</i>	$2xyz$	0	0	1/2	0	0	0	0	1/2	0	0
<i>AA</i>	<i>aa,aa</i>	xz^2	0	0	0	0	0	0	0	1	0	0
<i>Aa</i>	<i>AA,AA</i>	yx^2	1/4	1/2	0	0	1/4	0	0	0	0	0
<i>Aa</i>	<i>AA,Aa</i>	$2xy^2$	1/8	1/4	1/8	1/8	1/8	1/8	1/8	0	0	0
<i>Aa</i>	<i>AA,aa</i>	$2xyz$	0	0	1/4	1/4	0	1/4	1/4	0	0	0
<i>Aa</i>	<i>Aa,Aa</i>	y^3	1/16	1/8	1/8	1/8	1/16	1/8	1/8	1/16	1/8	1/16
<i>Aa</i>	<i>Aa,aa</i>	$2y^2z$	0	0	1/8	1/8	0	1/8	1/8	1/8	1/4	1/8
<i>Aa</i>	<i>aa,aa</i>	yz^2	0	0	0	0	0	0	0	1/4	1/2	1/4
<i>aa</i>	<i>AA,AA</i>	zx^2	0	0	0	0	1	0	0	0	0	0
<i>aa</i>	<i>AA,Aa</i>	$2zxy$	0	0	0	0	1/2	0	1/2	0	0	0
<i>aa</i>	<i>AA,aa</i>	$2z^2x$	0	0	0	0	0	0	1	0	0	0
<i>aa</i>	<i>Aa,Aa</i>	zy^2	0	0	0	0	1/4	0	1/2	0	0	1/4
<i>aa</i>	<i>Aa,aa</i>	$2zy^2$	0	0	0	0	0	0	1/2	0	0	1/2
<i>aa</i>	<i>aa,aa</i>	z^3	0	0	0	0	0	0	0	0	0	1
			<i>AA,AA</i>	<i>AA,Aa</i>	<i>AA,(a)A</i>	<i>AA,(a)a</i>	<i>Aa,Aa</i>	<i>Aa,(a)A</i>	<i>Aa,(a)a</i>	<i>(a)A,(a)A</i>	<i>(a)A,(a)a</i>	<i>(a)a,(a)a</i>
			1,1	1,1	1 + <i>t</i> , 1 - <i>s</i>	1 + <i>t</i> , 1 - <i>s</i>	1,1	1 + <i>t</i> , 1 - <i>s</i>	1 + <i>t</i> , 1 - <i>s</i>	1 + <i>u</i> , 1 + <i>u</i>	1 + <i>u</i> , 1 + <i>u</i>	1 + <i>u</i> , 1 + <i>u</i>
Proportions of offspring pairs and their viabilities under sibling conflict and paternal imprinting												

fathers who pass on differently imprinted genes (unlike the situation under maternal imprinting). Table 3 and a little algebra give the following recursions

$$\begin{aligned}
 TX' &= x^3 + x^2y \left[\frac{3}{2} + \frac{1}{2}(1+t) \right] + x^2z(1+t) \\
 &+ y^3 \left[\frac{1}{8} + \frac{1}{8}(1+t) \right] + xy^2 \left[\frac{3}{4} + \frac{1}{2}(1+t) \right] \\
 &+ y^2z \frac{1}{4}(1+t) + xyz(1+t)
 \end{aligned} \quad (5a)$$

$$\begin{aligned}
 TY' &= x^2y \frac{1}{2}(2-s) + x^2z(2-s) + y^3 \frac{1}{8}(4-s+t+u) \\
 &+ xy^2 \frac{1}{4}(6-2s+t+u) + y^2z \frac{1}{4}(6-s+2t+2u) \\
 &+ xz^2(2+t+u) + yz^2 \frac{1}{2}(2+t+u) + xyz(4-s+t+u)
 \end{aligned} \quad (5b)$$

$$\begin{aligned}
 TZ' &= y^3 \frac{1}{8}(2-s+u) + xy^2 \frac{1}{4}(1-s) + y^2z \frac{1}{4}(5-2s+3u) \\
 &+ z^3(1+u) + xz^2(1-s) + yz^2 \frac{1}{2}(4-s+3u) \\
 &+ xyz(1-s),
 \end{aligned} \quad (5c)$$

where

$$T = 1 + u - (s - t + 2u) \left(x + \frac{1}{2}y \right) + (s - t + u) \left(x + \frac{1}{2}y \right)^2. \quad (5d)$$

Again, the substitutions $p = x + \frac{1}{2}y$ and $q = 1 - p$ lead to a simpler recursion

$$x' = pC \quad (6a)$$

$$y' = p(1 - C) + qC \quad (6b)$$

$$z' = q(1 - C) \quad (6c)$$

$$T = 1 + (t - s)pq + uq^2, \quad (6d)$$

where $C = p(1 + tq)/T$. Because $p' = \frac{1}{2}(p + C)$ we again have that at equilibrium, the genotype frequencies are quasi-Hardy-Weinberg. There are again three equilibria, two of which are the fixations, but the third is given by quasi-Hardy-Weinberg equations that differ from Equation 3

$$\hat{x} = \frac{(u-t)^2}{(s-t+u)^2}, \hat{y} = \frac{2s(u-t)}{(s-t+u)^2}, \hat{z} = \frac{4s^2}{(s-t+u)^2}. \quad (7)$$

Near fixation of A (i.e., $x = 1$), the leading eigenvalue of the linearized system is $1 - \frac{1}{2}s$, and so the requirement for the invasion of an imprintable allele is simply that there is an advantage to the imprinted sib of an unimprinted offspring. The cost to the unimprinted offspring is immaterial to the initial invasion of the imprintable allele. (If $s = 0$, the quadratic terms of the expansion show that the fixation is stable if $t > u$, in which case this cost does matter.) Similarly, near fixation of a , the leading eigenvalue is

$$1 + \frac{t-u}{2(1+u)},$$

so A does not increase if $t < u$. (If $t = u$, the requirement is $s < 0$.)

The third equilibrium is feasible if and only if $u < t$ and $s < 0$, which are also the conditions for it to be a protected equilibrium, or both inequalities are reversed. Its leading eigenvalue turns out to be

$$\lambda_i = 1 + \frac{s(u-t)}{2[s(1+t) + u-t]}, \quad (8)$$

which is < 1 , and the equilibrium is therefore (locally) stable whenever it is protected.

Because the equation for T can be written in terms of allele frequencies rather than genotype frequencies [*i.e.*, Equation (6d)], this system is simpler than that of SM1. This simplicity arises because the bigamous mating system we use is essentially one of random mating. One consequence of this relative simplicity is that we can prove that any equilibrium is globally stable whenever it is locally stable by showing that the recursion for p is monotonic because monotonicity excludes any cycling. Now, it suffices to show that C is monotonic, which follows from the positivity of $\partial C / \partial p$. The conditions $0 \leq p \leq 1$, $s \leq 1$, and $t, u \geq -1$ ensure that this quantity is strictly positive, except possibly in biologically uninteresting cases when $u = -1$ and either (or both) $p = 0$ or $s = 1$.

Again, the mean fitness, T , may decrease and need not be maximized at equilibrium. Solving $\partial T / \partial p = 0$ gives the value of p that maximizes T , namely $\tilde{p} = (2u + s - t) / 2(u + s - t) \neq \hat{p}$. (We can rule out a minimum, since $\partial^2 T / \partial p^2 = 2(u + s - t) < 0$ whenever the internal equilibrium is stable. If the internal equilibrium does not exist, the system iterates to one of the boundaries.) It is extremely unusual for one-variable, random-mating, viability-selection schemes to neither minimize nor maximize mean fitness.

Comparing the results of SP1 and SP2 allows us to see the effects of multiple paternity. Let us first consider a growth inhibitor (*i.e.*, $s, t < 0$). The invasion of an imprinting allele (a) is clearly more likely under multiple paternity, since the requirement $s < 0$ is always true if imprinting is advantageous in a mixed sibship, whereas under monogamy, the requirement $s < u$ may not be. Multiple paternity means that the advantage to a solitary imprinted offspring need not be greater than the advantage to each of a pair of imprinted sibs, this difference arising because each member of the pair has a different father. Similarly, near fixation of a , an unimprintable allele (A) will find it harder to invade under multiple paternity even if $u < 0$, since the condition $t > u$ is more restrictive than that under monogamy, $t > 2u$. Thus, multiple paternity favors the evolution and fixation of the paternal imprinting of a growth inhibitor when sibling conflict is the driving force.

For a growth enhancer (*i.e.*, $s, t > 0$), however, multiple paternity retards the evolution of imprinting. The condition for the invasion of a ($s < 0$) is now contradicted, and that for the stability of the fixation of a ($t < u$) is less likely than under monogamy ($t < 2u$).

P-OM1: parent-offspring conflict, maternal imprinting, monogamous females: We now develop a model in which the genetic conflict is between the mother and her offspring, and imprinting is maternal. (An alternative formulation is derived in appendix A.) In the case of a growth enhancer, bearing unimprinted offspring, which requires more maternal resources, has a direct cost to a mother, whereas an imprinted offspring confers an advantage on the mother's viability. For a growth inhibitor, however, imprinting is beneficial to the offspring but (probably) detrimental to the mother. We will assume that there is no sibling conflict (*i.e.*, no cost to an imprinted individual with an unimprinted sib). We also assume that the A allele is never imprinted, but the a allele always is imprinted when passed on maternally.

Suppose that an imprinted offspring has viability $1 - s$ relative to an unimprinted sibling. Again, we will assume that each female has exactly two offspring by the same father. Further suppose that the increase in a female's fertility per imprinted offspring is $t/2$, which we model by assuming that the whole sibship's viability increases by this amount. (In the model of appendix A, this selection pressure acts solely on females.) Thus, for growth enhancers $s, t > 0$ (and $s \leq 1$), while these values are negative for growth inhibitors (although $t \geq -1$). Using Table 2 as the mating table (but with different selection parameters), we derive the following

$$Tx' = x^2 + xy\left(1 + \frac{1}{8}t\right) + y^2\left(\frac{1}{4} + \frac{1}{16}t\right), \quad (9a)$$

$$Ty' = xy\left(1 - \frac{1}{2}s + \frac{3}{8}t - \frac{3}{8}st\right) + xz(2 - s + t - st) + y^2\left(\frac{1}{2} - \frac{1}{4}s + \frac{1}{4}t - \frac{3}{16}st\right) + yz\left(1 - \frac{1}{2}s + \frac{5}{8}t - \frac{1}{2}st\right) \quad (9b)$$

$$Tz' = y^2\left(\frac{1}{4} - \frac{1}{4}s + \frac{3}{16}t - \frac{3}{16}st\right) + yz\left(1 - s + \frac{7}{8}t - \frac{7}{8}st\right) + z^2(1 - s + t - st), \quad (9c)$$

where

$$T = 1 + (t - s - st)\left(1 - x - \frac{1}{2}y\right) + \frac{1}{8}sty. \quad (9d)$$

Again, the substitutions $p = x + \frac{1}{2}y$ and $q = 1 - p$ lead to a simpler recursion

$$x' = pD \quad (10a)$$

$$y' = p(1 - D) + qD \quad (10b)$$

$$z' = q(1 - D) \quad (10c)$$

$$T = 1 + (t - s - st)q + \frac{1}{8}sty, \quad (10d)$$

where $D = (p + \frac{1}{8}t)/T$. Hence, all equilibria are quasi-Hardy-Weinberg. There are two fixation equilibria, as before, and the third possible internal equilibrium is given by $(\hat{x}, \hat{y}, \hat{z}) = (\hat{p}^2, 2\hat{p}\hat{q}, \hat{q}^2)$, where $\hat{p} = (4s - 3t + 4st)/st$ and $\hat{q} = (-4s + 3t - 3st)/st (= 1 - \hat{p})$, which is feasible whenever

$$\frac{4s}{3-3s} < t < \frac{4s}{3-4s}, \quad (11)$$

with the right inequality ignored if $s > \frac{3}{4}$. Near fixation of A (i.e., $x = p = 1$), the leading eigenvalue of the linearized system is $1 + (-4s + 3t - 3st)/8 = 1 + \hat{q}st/8$. Thus, whenever the internal equilibrium is feasible, fixation of A is unstable. Similarly, the other fixation ($x = p = 0$) is also unstable whenever the internal equilibrium is feasible, because the leading eigenvalue is

$$\lambda_0 = 1 + \frac{\hat{p}st}{8(1-s)(1+t)}. \quad (12)$$

The leading eigenvalue for the internal equilibrium is $\lambda_i = 1 - \hat{p}\hat{q}s^2/6(1-s)$, and so feasibility implies (local) stability. The stability conditions are summarized in Figure 2. In short, both growth enhancers and growth inhibitors may evolve to be maternally imprinted under this process, but it is not enough for the parameters s and t to be of the appropriate sign; imprinting only evolves in a subset of the parameter space. Global stability can be shown in the same manner as for model SM1.

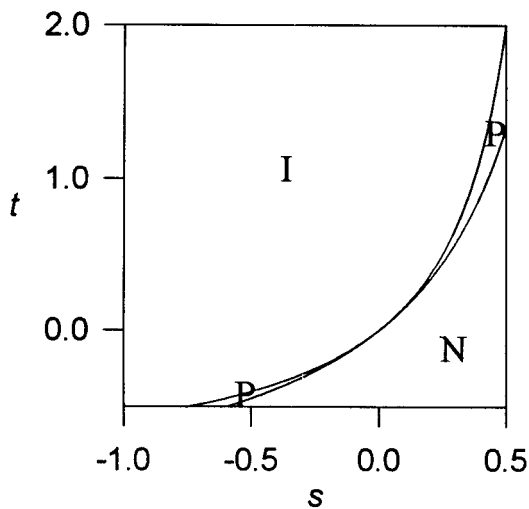


Figure 2.—Regions of parameter space determining stability of the three equilibria in Model P-OM1. Imprinted offspring have viability $1 - s$ relative to unimprinted offspring, and the increase in a female's fertility per imprinted offspring is $t/2$. Region I (Imprinting) has the a fixation stable to invasion by A , a successfully invades the A fixation, and the internal equilibrium does not exist (in the biologically relevant simplex). Region P (Polymorphism) has a stable internal equilibrium, i.e., both A and a are present, A successfully invades a fixation, and vice versa. Region N (Non-imprinting) has the A fixation stable to invasion by a , A successfully invades the a fixation, and the internal equilibrium does not exist (in the biologically relevant simplex).

P-OM2: parent-offspring conflict, maternal imprinting, bigamous females: We now assume that each female has two offspring by different fathers, leaving all other assumptions unchanged. Table 3 is the appropriate mating table. Again, because all possible sibships occur in the same proportions, model P-OM2 is identical to model P-OM1. Multiple paternity has no effect on the ability of parent-offspring conflict to lead to maternal imprinting.

P-OP1: parent-offspring conflict, paternal imprinting, monogamous females: This model is identical to P-OM1, except that imprinting is assumed to be paternal. This difference, however, has no effect on the genotype frequency recursions. Thus, as is the case in our model with sibling conflict, the conditions for the evolution of paternal imprinting given parent-offspring conflict as the driving force are the same as those for maternal imprinting. In particular, conditions exist for the invasion of both growth enhancers and growth inhibitors that are paternally imprinted.

P-OP2: parent-offspring conflict, paternal imprinting, bigamous females: This model is the natural extension of P-OP1 to the case in which each pair of offspring of a female have different fathers. This time, however, as with sibling conflict, multiple paternity does affect the recursions. Using Table 3 as the mating table, we derive the following equations

$$TX' = x^3 + x^2y\left(2 + \frac{1}{4}t\right) + x^2z\left(1 + \frac{1}{2}t\right) + xy^2\left(\frac{5}{4} + \frac{1}{4}t\right) + xyz\left(1 + \frac{1}{2}t\right) + y^3\left(\frac{1}{4} + \frac{1}{16}t\right) + y^2z\left(\frac{1}{4} + \frac{1}{8}t\right) \quad (13a)$$

$$TY' = x^2y\left(1 - \frac{1}{2}s + \frac{1}{4}t - \frac{1}{4}st\right) + x^2z\left(2 - s + \frac{1}{2}t - \frac{1}{2}st\right) + xy^2\left(\frac{3}{2} - \frac{3}{4}s + \frac{5}{8}t - \frac{1}{2}st\right) + xz^2\left(2 - s + \frac{3}{2}t - st\right) + xyz\left(4 - 2s + 2t - \frac{3}{2}st\right) + y^3\left(\frac{1}{2} - \frac{1}{4}s + \frac{1}{4}t - \frac{3}{16}st\right) + y^2z\left(\frac{3}{2} - \frac{3}{4}s + \frac{7}{8}t - \frac{5}{8}st\right) + yz^2\left(1 - \frac{1}{2}s + \frac{3}{4}t - \frac{1}{2}st\right) \quad (13b)$$

$$TZ' = xy^2\left(\frac{1}{4} - \frac{1}{4}s + \frac{1}{8}t - \frac{1}{8}st\right) + xz^2\left(1 - s + \frac{1}{2}t - \frac{1}{2}st\right) + xyz\left(1 - s + \frac{1}{2}t - \frac{1}{2}st\right) + y^3\left(\frac{1}{4} - \frac{1}{4}s + \frac{3}{16}t - \frac{3}{16}st\right) + y^2z\left(\frac{5}{4} - \frac{5}{4}s + t - st\right) + yz^2\left(2 - 2s + \frac{7}{4}t - \frac{7}{4}st\right) + z^3(1 - s + t - st), \quad (13c)$$

where

$$T = (1-s)(1+t) + \left(s - t + \frac{3}{2}st\right)\left(x + \frac{1}{2}y\right) - \frac{1}{2}st\left(x + \frac{1}{2}y\right)^2. \quad (13d)$$

The substitutions $p = x + \frac{1}{2}y$ and $q = 1 - p$ lead to a simpler recursion

$$x' = pE \quad (14a)$$

$$y' = p(1 - E) + qE \quad (14b)$$

$$z' = q(1 - E) \quad (14c)$$

$$T = (1 - s)(1 + t) + \left(s - t + \frac{3}{2}st\right)p - \frac{1}{2}stp^2, \quad (14d)$$

where $E = p(1 + \frac{1}{2}tq)/T$. Hence, as before, all equilibria are quasi-Hardy-Weinberg. There are two fixation equilibria, as before, and the third possible internal equilibrium is given by $(\hat{x}, \hat{y}, \hat{z}) = (\hat{p}^2, 2\hat{p}\hat{q}, \hat{q}^2)$, where $\hat{p} = (2s - t + 2st)/st$ and $\hat{q} = (-2s + t - st)/st$, which is feasible whenever

$$\frac{2s}{1-s} < t < \frac{2s}{1-2s}. \quad (15)$$

Near fixation of A (i.e., $x = p = 1$), the leading eigenvalue of the linearized system is $1 + (-2s + t - st)/4 = 1 + \hat{q}st/4$. Thus, whenever the internal equilibrium is feasible, the fixation of A is unstable. Similarly, the other fixation (i.e., $x = p = 0$) is also unstable whenever the internal equilibrium is feasible, because the leading eigenvalue is

$$\lambda_0 = 1 + \frac{\hat{p}st}{4(1-s)(1+t)}. \quad (16)$$

The leading eigenvalue for the internal equilibrium is $\lambda_i = 1 - \hat{p}\hat{q}s^2/2(1-s)$, so feasibility implies (local) stability. Notice the similarity in form between these eigenvalues and those for P-OM1. The stability conditions are summarized in Figure 3.

A comparison of Figures 2 and 3 (or Inequalities 11 and 15) shows that for growth inhibitors ($s, t < 0$), the likelihood of paternal imprinting is increased by multi-

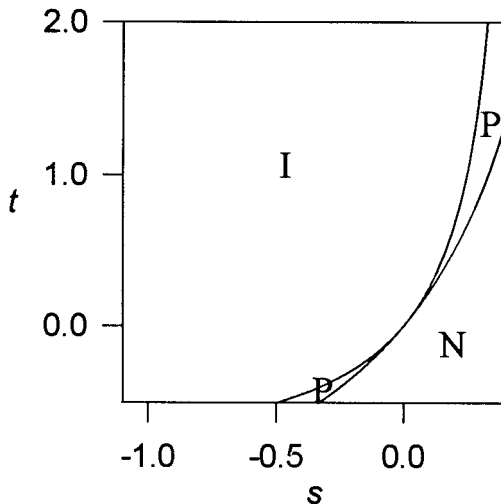


Figure 3.—Regions of parameter space determining stability of the three equilibria in Model P-OP2. Regions I, P, and N as for Figure 2.

ple paternity, because the region of parameter space affording imprinting under monogamy is a subset of that under bigamy. Similarly, multiple paternity does not favor the evolution of nonimprinting alleles. We cannot, however, deduce the relative likelihood of polymorphism. The mere size of regions of parameter space does not permit us to make such a deduction, since different regions of parameter space need not all have the same prior probability of being encountered. See Spencer and Marks (1993) for a fuller explanation. Analogously, for growth enhancers, multiple paternity favors nonimprinting over paternal imprinting.

As in SP2, the bigamous mating system allows us to write the mean fitness, T , and the allelic recursions in terms of allele frequencies. Again, we can prove that any equilibrium is globally stable whenever it is locally stable by showing the monotonicity of the recursion for p . It suffices to show that E is monotonic, which follows from the positivity of $\partial E/\partial p$. The conditions $0 \leq q \leq 1$, $s \leq 1$ and $t \geq -1$ ensure that this quantity is strictly positive, except when $s = 1$, or both $t = -1$ and $q = 1$, which are not biologically relevant.

Again, the mean fitness, T , may decrease and need not be maximized at equilibrium. Solving $\partial T/\partial p = 0$ gives the value of p that maximizes T , namely $\hat{p} = (s - t + \frac{3}{2}st)/st \neq \hat{p}$. (We can rule out a minimum, since $\partial^2 T/\partial p^2 = -st < 0$ whenever the internal equilibrium is stable. If the internal equilibrium does not exist, the system iterates to one of the boundaries.)

DISCUSSION

The results of our explicitly genetic modeling contradict those of previous verbal and quantitative genetic models for the evolution of imprinting of growth enhancers and inhibitors. First, our models (including that in Appendix A) imply that genetic conflicts need not lead to growth enhancers being maternally imprinted and growth inhibitors being paternally imprinted, as has been suggested (Haig 1992; Haig and Graham 1991). In fact, under sibling conflict with monogamous females, the dynamics of our paternal and maternal imprinting models were identical. Moreover, in all of our models, some range of parameter values permits the evolution of imprinting of growth enhancers and, for some different range, imprinted growth inhibitors can increase when rare.

Second, our models suggest that multiple paternity need not play a role in the evolution of imprinting, *contra* Mochizuki *et al.* (1996). Two pairs of our models that differed in just this aspect—maternal imprinting driven by sibling or parent-offspring conflict with monogamous and bigamous females—were dynamically equivalent. Multiple paternity can, however, make a difference in some circumstances, particularly with paternal imprinting. In our models of sibling and parent-offspring conflict, multiple paternity favors the pater-

nal imprinting of growth inhibitors, but it retards paternal imprinting of growth enhancers.

Nevertheless, in spite of our first result, our models do predict that mammalian growth enhancers are more likely to be maternally imprinted, and mammalian growth inhibitors paternally so (rather than vice versa), a sort of qualified Haig prediction. Thus, the objection of Franklin *et al.* (1996) that the genetic conflict hypothesis fails to adequately consider what happens over more than one generation appears unimportant. Because paternal imprinting of growth inhibitors is more likely with bigamous females (SP2 and P-OP2) than monogamous females (SP1 and P-OP1), the equivalence of models SP1, SM1 and SM2, as well as P-OP1, P-OM1 and P-OM2, means that it is also more likely than maternal imprinting of growth inhibitors (whatever the mating system). The prediction that growth inhibitors are more likely to be paternally imprinted follows because no mammals are likely to be strictly monogamous. A similar argument holds for why growth enhancers are more likely to be maternally rather than paternally imprinted. This asymmetry emerges from the interaction between multiple paternity and genetic conflict.

Exceptions to Haig's prediction are likely to occur in species with either (or both) low levels of multiple paternity or the parts of parameter space where both maternal and paternal imprinting are favored. In the parent-offspring conflict models, for instance, these overlapping parts of parameter space are where there are larger values of t for a given s . In other words, paternal imprinting of growth enhancers and maternal imprinting of growth inhibitors is possible if the fertility benefit to a mother is large (or the cost small) compared to the disadvantage to the offspring. Of course, even in these circumstances, as well as under strict monogamy, Haig's prediction is as likely to hold as not.

Third, our models (including that in appendix A) consistently suggest that some genes can be polymorphically imprinted, and that this polymorphism can be at least locally stable. Again, our findings contradict those of Mochizuki *et al.* (1996), who found no equilibria in which both parental alleles could be expressed (except in the unlikely circumstance of complete monogamy). Our polymorphisms may exist for either paternal or maternal imprinting, with monogamous and bigamous females and under sibling and parent-offspring conflict. In all models (except that in appendix A), the form of the internal equilibrium mimicked a standard Hardy-Weinberg equilibrium. This parallel arises because the gamete passed on by one sex is never imprinted and is irrelevant to selection. The only selective differences occur because of the imprinting status of the other gene. As a result, the genotype frequency iterations take a special form (*e.g.*, Equations 2a-d), which ensures that all equilibria have this quasi-Hardy-Weinberg form. This property has also been observed

in some apparently unrelated models of sexual selection (Karlin 1978). The polymorphic imprinting of the Wilm's tumor suppressor gene (*WT1*) and the *Igf2-r* gene in humans (Jinno *et al.* 1994; Xu *et al.* 1993) could be mediated by these mechanisms. It is worth noting that a stable, viability-maintained polymorphism of imprinting alleles is not possible because of the haploid nature of imprinting systems (Pearce and Spencer 1992).

Fourth, our models suggest that imprinting need not always evolve, even under conditions that in verbal treatments would seem to favor it. For example, in model P-OP2, $s = 0.1$ and $t = 0.2$ keep the nonimprinting allele (A) fixed even though imprinting is favored ($s > 0$) and the familial fertility decrease per imprinted offspring ($t/2$) is equal in size. The genetic conflict hypothesis can, therefore, explain why some genes involved in the development of the placenta (*e.g.*, mouse platelet-derived growth factor-B, *PDGF-B*, Levéen *et al.* 1994; Franklin *et al.* 1996) are not imprinted. The failure of Haig's verbal explanations to explain either polymorphism in imprinting status or the nonimprinting of genes like *PDGF-B* was seen as a significant problem for the hypothesis by Franklin *et al.* (1996).

This last result does not agree with Mochizuki *et al.* (1996), who found that whenever imprinting was favored, any degree of multiple paternity would lead to the evolution of imprinting. To explain why some genes affecting embryonic growth are not inactivated, they were forced to invoke a negative selective effect of deleterious mutations. Even then, it appears from their paper that some degree of asymmetry in expression of paternally and maternally derived genes always evolved; true Mendelian expression was not possible. This incomplete inactivation can be thought of as a generalized form of imprinting (Hall 1990). We should point out that although we motivate our modeling by considering an imprinted gene to be completely inactivated, our treatment applies equally well to this generalized imprinting. An $A(a)$ individual, for instance, is one in which the paternal A gene is expressed at a greater level than the maternal a gene.

The contrast between our results and those of Mochizuki *et al.* (1996) warrants closer inspection. They considered a quantitative genetic model that is formally equivalent to one-locus haploid transmission with a continuum of alleles affecting the degree of expression when passed from the father (x) or the mother (y). If one imagines x and y to control the expression of a growth factor, $z = x + y$ is the amount of resource the offspring demands from its mother *in utero*. The trait pair (x, y) is assumed to have a constant genetic covariance matrix, and it evolves according to the standard multivariate selection formula, which states that the change in trait means is given by the product of the genetic covariance matrix times the vector of selection differentials (Lande 1979). Selection is considered to

operate through a viability effect, $W(z)$, and a fertility effect. In females, the number of offspring produced is the total resource available (which is independent of genotype) divided by the resource demand per offspring. The precise parameterization of selection differs somewhat from our models, but the essential elements are the same. The difference in the models lies in the way the genes are transmitted. Mochizuki *et al.* (1996) have no genes in their model, but instead, they consider the competition between a continuous series of clones. We explicitly examine the transmission of the imprintable gene, which means there are two classes of heterozygotes having opposite phenotypes. The essential feature of imprinting is this dependence of phenotype on the sex that transmits the allele, and it is only by having heterozygotes that the unexpressed allele gets transmitted with selection parameters that depend on the expressed homolog. The model of Mochizuki *et al.* (1996), by ignoring heterozygotes, overlooks an essential attribute of genomic imprinting, so it is not surprising that polymorphism is nearly nonexistent, and their model requires polygamy to set up the competition between alleles.

Fifth, in all our models, certain reasonable parameter values led the mean fitness, T , to decline, sometimes for many generations. This unintuitive property implies that purely verbal models of imprinting may give an incomplete and inaccurate picture of its evolution. In evolutionary genetic models where the dynamical system involves two genotypic frequencies, it is rare that the mean fitness increases under all selection regimes. Even in our models that could be described in terms of allele frequencies, the mean fitness did not necessarily increase.

A further reason for the differences between Haig's (1992) game theoretic results and our genetic ones lies in the different way that families are treated. For example, if a female is heterozygous and mates with homozygous males, half the offspring are heterozygotes and half are homozygotes, and Haig's models have just two parameters (a_2 and a_3) describing their relative resource allocations from the mother. But there are three types of two-offspring families in our models, those with two homozygotes, those with one homozygote and one heterozygote, and those with both heterozygotes. In our models of sibling conflict, we have three parameters to describe the fitnesses (s , t and u), and the fitnesses are also different in our parent-offspring conflict models. In short, Haig (1992) does not have a sibship effect.

One shortcoming of our models is that they do not explain why imprinting should be fixed for long periods of evolutionary time. Why is *Igf-2*, for example, imprinted the same way in humans and mice when these species have had separate evolutionary lineages for more than 60 million years (Penny and Hasegawa 1997)? An imprintable allele could easily be replaced in this time by an unimprintable one (with appropriate selection parameters). The conservation of imprinting

status may be telling us something about the distribution of selection coefficients of newly arising mutations.

Although our models include features missing from previous analyses, they are clearly simplistic in a number of respects. For instance, the assumption that all females have exactly two offspring and the strict monogamy/bigamy rule are both made for mathematical tractability, and do not hold for real populations. Nevertheless, it seems unlikely that relaxing these assumptions would have any substantive effect on our deterministic models. Indeed, the assumption of two offspring is not critical; what matters is that families have the same mean size. The alternative formulation of parent-offspring conflict and maternal imprinting in the model of appendix A does not lead to qualitatively different results. More important is our assumption that the imprinting status is determined solely by the allele at the target imprintable locus. It is also plausible that whether or not a gene is imprinted depends on alleles at a second modifier locus (as in Spencer and Williams 1995, 1997). In the case of *Igf-2*, for instance, reduced expression of the downstream *H19* gene region (arising from either the deletion or abnormal methylation of *H19*) leads to loss of maternal imprinting and resultant overexpression of *Igf-2* (Leighton *et al.* 1995; Steenman *et al.* 1995). Finally, we have assumed that only imprinting status causes different selective pressures. It is quite possible, of course, that alleles that differ in their ability to be imprinted also differ in their direct viability effects.

All well-studied examples of imprinting in animals come from placental mammals (Barlow 1995; John and Surani 1996). Moore and Haig (1991) have argued that this restriction to live bearers is to be expected from the theory of genetic conflicts in pregnancy. A recent instance of parent-of-origin effect on the methylation of a transgene in the externally fertilizing and developing zebrafish *Danio rerio* (Martin and McGowan 1995) suggests, however, that imprinting may yet be discovered in other vertebrate groups. We note that the genetic conflicts (especially sibling conflict) analogous to those occurring in our models may be found in many nonmammalian species.

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APPENDIX A: AN ALTERNATIVE MODEL OF PARENT-OFFSPRING CONFLICT WITH MATERNAL IMPRINTING

In this appendix, we present an alternative formulation of parent-offspring conflict and maternal imprinting. This model has interesting mathematical properties, and it has the novel feature of selection acting differently on males and females because of the effect of offspring size on female fertility, but it cannot be compared directly to P-OP1 and P-OP2. The biological conclusions from this model and P-OM1 and P-OM2 are not significantly different.

As in P-OM1, we assume that there is no sibling conflict (*i.e.*, no cost to an imprinted individual with an unimprinted sib) and that the *A* allele is never imprinted, but the *a* allele always is imprinted when passed on maternally. It is clear that there are four types of zygotes produced—*AA*, *A(a)*, *aA*, and *a(a)*—with respective frequencies in males and females of m_{11} , m_{12} , m_{21} , m_{22} , f_{11} , f_{12} , f_{21} , and f_{22} . Viability selection arising from body size is identical in both sexes. Hence, the respective viabilities of the four types are 1, $1 - s$, 1, and $1 - s$, where $0 < s < 1$ for a growth enhancer and $s < 0$ for a growth inhibitor. The four types of females have, respectively, none, half, half, and all their offspring imprinted; thus, sex-dependent selection acts on females (only) with respective viabilities of $1 - t$, $1 - t/2$, $1 - t/2$, and 1, with $0 < t < 1$ for a growth enhancer and $t < 0$ for a growth inhibitor. For the same reasons that P-OM1 and P-OM2 are equivalent, we need not concern ourselves about multiple paternity.

If p_m is the frequency of the *A* allele in sperm and p_f is the frequency in eggs, then after selection the genotypic proportions are shown in Table A1. The recursion equations in p_m and p_f are as follows

$$p'_m = \frac{p_m(1 - s) + p_f + p_m p_f s}{2[1 - (1 - p_f)s]} \quad (\text{A1a})$$

$$p'_f = \frac{p_m p_f (1 - t) + \frac{1}{2}[p_m(1 - s) + p_f - p_m p_f (2 - s)]\left(1 - \frac{1}{2}t\right)}{1 - \frac{1}{2}(p_m + p_f)t - (1 - p_f)s + \frac{1}{2}p_m(1 - p_f)st} \quad (\text{A1b})$$

TABLE A1

Offspring genotype frequencies for an alternative model of parent-offspring conflict and maternal imprinting

Genotype	Male	Female
<i>AA</i>	$p_m p_f$	$p_m p_f (1 - t)$
<i>A(a)</i>	$p_m (1 - p_f) (1 - s)$	$p_m (1 - p_f) (1 - s) (1 - t/2)$
<i>aA</i>	$(1 - p_m) p_f$	$(1 - p_m) p_f (1 - t/2)$
<i>a(a)</i>	$(1 - p_m) (1 - p_f) (1 - s)$	$(1 - p_m) (1 - p_f) (1 - s)$

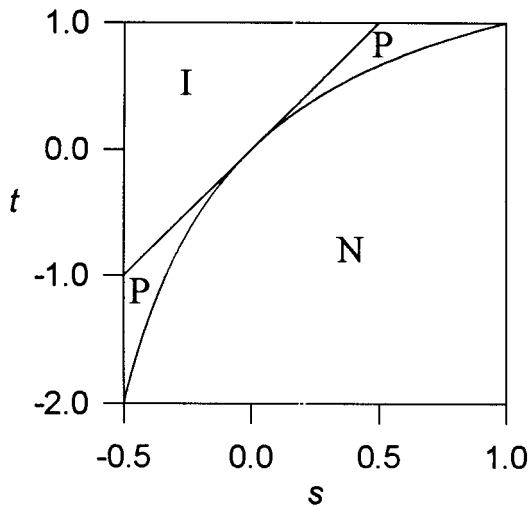


Figure A1.—Regions of parameter space determining stability of the three equilibria in the alternative model of parent-offspring conflict and maternal imprinting. Regions I, P, and N as for Figure 2.

Equilibria occur where $p'_m = p_m$ and $p'_f = p_f$. Solving this system gives three equilibria, the first of which corresponds to the fixation of the imprintable allele, $x: p_m = p_f = 0$, near which the Jacobian's leading eigenvalue is

$$\lambda_0 = 1 - \frac{t-2s}{4(1-s)}. \quad (\text{A2})$$

Hence, imprinting is stable when $t > 2s$ (because we always have $s < 1$). For a growth enhancer, therefore, imprinting is stably fixed when the benefit to mothers from having two smaller (imprinted) children is more than twice the viability advantage of larger (unimprinted) offspring. For a growth inhibitor, the condition is that the benefit to a mother with two smaller

(imprinted) offspring is less than twice the viability disadvantage of smaller (imprinted) offspring.

The second equilibrium corresponds to the fixation of the unimprintable allele, $A: p_m = p_f = 1$, near which the leading eigenvalue is

$$\lambda_1 = 1 - \frac{2s-t(1+s)}{4(1-t)}. \quad (\text{A3})$$

Thus the nonimprinting equilibrium is stable when $t < 2s/(1+s)$, provided $s > -1$; $t > 2s/(1+s)$ when $s < -1$. For a growth enhancer, this condition occurs when the disadvantage of having larger offspring is sufficiently small (certainly $< 2s$).

There may also be a third internal equilibrium,

$$\hat{p}_m = \frac{2s-t}{st}, \quad (\text{A4a})$$

$$\hat{p}_f = \frac{(1-s)(2s-t)}{2s(t-s)}, \quad (\text{A4b})$$

which requires that $0 < s < t < 2s$ or $t < 2s < 0$ for biological feasibility (*i.e.*, $0 < \hat{p}_m, \hat{p}_f < 1$). This internal equilibrium is stable when the leading eigenvalue

$$\lambda_i = 1 - \frac{(t-2s)[2s-t(1+s)]}{2(1-s)t^2} \quad (\text{A5})$$

is < 1 . Combining this stability requirement with that for feasibility gives $t > 2s/(1+s)$ when $s > -1$, the reverse of the stability condition for the second equilibrium. The existence and stability conditions are summarized in Figure A1.

This analysis proves local stability, but Karlin's (1972) method (as outlined for model SM1 above applied to the function $F(p_m, p_f) = p'_m, p'_f$) shows that the internal equilibrium is actually globally stable whenever it is locally stable.