The Effect of Genetic Conflict on Genomic Imprinting and Modification of Expression at a Sex-Linked Locus

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ABSTRACT

We examine how genomic imprinting may have evolved at an X-linked locus, using six diallelic models of selection in which one allele is imprintable and the other is not. Selection pressures are generated by genetic conflict between mothers and their offspring. The various models describe cases of maternal and paternal inactivation, in which females may be monogamous or bigamous. When inactivation is maternal, we examine the situations in which only female offspring exhibit imprinting as well as when both sexes do. We compare our results to those previously obtained for an autosomal locus and to four models in which a dominant modifier of biallelic expression is subjected to the same selection pressures. We find that, in accord with verbal predictions, maternal inactivation of growth enhancers and paternal inactivation of growth inhibitors are more likely than imprinting in the respective opposite directions, although these latter outcomes are possible for certain parameter combinations. The expected outcomes are easier to evolve than the same outcomes for autosomal loci, contradicting the available evidence concerning the direction of imprinting on mammalian sex chromosomes. In most of our models stable polymorphism of imprinting status is possible, a behavior not predicted by verbal accounts.

THE differential expression of mammalian genes depending on the sex of the parent from which they are inherited is known as genomic imprinting (Barlow 1995; Franklin *et al.* 1996; John and Surani 1996; Bartolomei and Tilghman 1997). 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 of an imprinted gene is that of insulin-like growth factor II (*Igf-2*): in most tissues of all mammals studied to date (*e.g.*, humans, mice, rats, deer mice, pigs, sheep, and opossum) only the paternally derived gene is expressed and the maternally derived gene is silent (Dechiara *et al.* 1991; Giannoukakis *et al.* 1993; Pedone *et al.* 1994; Vrana *et al.* 1998; Nezer *et al.* 1999; McLaren and Montgomery 1999; O'Neill *et al.* 2000). 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.

The most prominent suggestion for the evolutionary origin of genomic imprinting, the "genetic-conflict hypothesis," was proposed by Haig and co-workers (Haig and Graham 1991; Moore and Haig 1991; Haig 1992). It argues that multiple paternity within or among a female mammal's pregnancies gives rise to a genetic conflict between parents. All offspring are equally related to their mother, whereas they may have different fathers. Fetal growth-promoting genes such as *Igf-2* should be inactivated by the mother, according to the genetic-conflict hypothesis, because she can maximize their survival (and hence her own fitness) by controlling the rate at which she nourishes her offspring. It is in the father's interest, however, to ensure that his children survive, possibly at the expense of half-sibs not his, and so he makes sure their growth-enhancing genes are transcribed. This conflict can also be viewed as being between mothers and their offspring (Spencer *et al.* 1998). The prediction for growth-inhibiting loci, such as murine insulin-like growth factor 2 receptor (*Igf2-r*), follows from the same logic: they should be maternally active only. And, indeed, these predictions seem to be largely upheld, although there are intriguing exceptions (Hurst and McVean 1998; Spencer *et al.* 1999; Spencer 2000).

A number of these exceptions concern loci on the mammalian X chromosome, inferred from the effects of uniparental disomy in humans, as well as XO mice and humans, which develop as females. For instance, XO mice that inherit their single X chromosome from their father are developmentally retarded compared to both XO mice with a maternal X and normal XX females

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TABLE 1

Model and case names developed in this article

Case	Biology modeled
IP1	Imprinting, paternal inactivation, monogamous females
IP2	Imprinting, paternal inactivation, bigamous females
IMF1	Imprinting, maternal inactivation in females only, monogamous females
IMF2	Imprinting, maternal inactivation in females only, bigamous females
IMA1	Imprinting, maternal inactivation in all, monogamous females
IMA2	Imprinting, maternal inactivation in all, bigamous females
BF1	Biallelic modifier, female expression only, monogamous females
BF2	Biallelic modifier, female expression only, bigamous females
BA1	Biallelic modifier, expression in all, monogamous females
BA2	Biallelic modifier, expression in all, bigamous females

(Jamieson *et al.* 1998). This observation suggests that a fetal growth enhancer on the X is paternally inactivated or downregulated, the opposite prediction from the original verbal version of the genetic-conflict hypothesis. Nevertheless, mathematical modeling of this hypothesis as it applies to autosomal genes has revealed that the purely verbal descriptions are misleading and such nonstandard outcomes are possible (Spencer *et al.* 1998; Iwasa *et al.* 1999). In this article, therefore, we examine mathematically the effect of genetic conflict on potential imprinting at a sex-linked locus.

MODELS

Following Spencer *et al.* (1998), we assume that mating is random and each female has exactly two offspring in a sibship. When females are monogamous, clearly both offspring have the same father; when females are bigamous, we assume two randomly selected fathers have one offspring each. The various cases we develop are listed in Table 1.

Imprinting models: We adapt the autosomal parent-offspring conflict model of Spencer *et al.* (1998) to apply to a sex-linked locus. Suppose that there are two alleles, A and a, at the X-linked locus, with the A allele having standard expression and a being imprintable. In the terms of this model, deciding whether or not imprinting evolves entails finding the conditions under which a can invade a population fixed for A and when a can fix, driving A to extinction. Let x be the frequency of AA females, y be that of Aa females and z ($= 1 - x - y$) be that of aa females. The frequency of A males is denoted by p and that of a males by q ($= 1 - p$). As in Spencer *et al.* (1998), the parent-offspring conflict is implemented by assuming that the effect of imprinting reduces the viability of the imprinted individual by an amount s ($s \leq 1$), but increases the viability of the sibship as a whole by an amount $t/2$ ($t \geq -1$) per imprinted sib. For growth enhancers, therefore, s and t are positive; for growth inhibitors, they are negative.

Case IP1: We first treat the case of paternal inactivation and monogamous females. With the help of Table 2, we derive the following iterations for the values of x, y, z, p, and q after a single generation of selection, x', y', z', p', and q', respectively,

$$\begin{aligned} T_f x' &= p\left(x + \frac{y}{2}\right) \\ T_f y' &= p\left(1 - \left(x + \frac{y}{2}\right)\right) + q\left(x + \frac{y}{2}\right)(1 - s)\left(1 + \frac{3t}{4}\right) \\ T_f z' &= q\left(1 - \left(x + \frac{y}{2}\right)\right)(1 - s)\left(1 + \frac{3t}{4}\right), \end{aligned} \tag{1}$$

in which the mean fitness of females, T_f, is the sum of the right-hand sides of Equations 1 so that $x' + y' + z' = 1$, and

$$p' = x + \frac{y}{2} \quad \text{and} \quad q' = \frac{y}{2} + z. \tag{2}$$

These equations afford just two equilibria (*i.e.*, values of x, y, z, p, and q such that $x' = x$, $y' = y$, $z' = z$, $p' = p$, and $q' = q$), both of which are trivial: fixation of A (*i.e.*, $x = 1$, $y = 0$, $z = 0$, $p = 1$, and $q = 0$) and fixation of a (*i.e.*, $x = 0$, $y = 0$, $z = 1$, $p = 0$, and $q = 1$). Local stability analysis (Edelstein-Keshet 1988; see appendix a) shows that just one of these equilibria is stable for given values of s and t: fixation of A when $t < 4s/(3 - 3s)$ and fixation of a when $t > 4s/(3 - 3s)$. Indeed, the stability can be shown (see appendix a) to be global.

Case IP2: If each female mates at random with two different males, Table 3 allows us to show that Equations 1 become

$$\begin{aligned} T_f x' &= p\left(x + \frac{y}{2}\right)\left(1 + \frac{tq}{4}\right) \\ T_f y' &= xq(1 - s)\left(1 + \frac{t}{2}\left(1 + \frac{q}{2}\right)\right) \\ &\quad + \frac{y}{2}\left(1 - sq\left(1 + \frac{t}{2}\left(1 + \frac{q}{2}\right)\right) + \frac{3tq}{4}\right) + zp\left(1 + \frac{tq}{4}\right) \\ T_f z' &= q\left(\frac{y}{2} + z\right)(1 - s)\left(1 + \frac{t}{2}\left(1 + \frac{q}{2}\right)\right), \end{aligned} \tag{3}$$

whereas Equations 2 are unchanged. Local stability analysis (see appendix a) shows that case IP2 affords the same two fixation equilibria as for case IP1, as well as a potential third internal equilibrium, at which the female genotype frequencies are given by the quasi-Hardy-Weinberg formula $(\hat{x}, \hat{y}, \hat{z}) = (\hat{p}^2, 2\hat{p}\hat{q}, \hat{q}^2)$, where

TABLE 2

Mating table for imprinting models with monogamous females

Brood	Mother: *AA* Father: *A* Frequency: *xp*	*AA* *a* *xq*	*Aa* *A* *yp*	*Aa* *a* *yq*	*aa* *A* *zp*	*aa* *a* *zq*	Viabilities under paternal inactivation (case IP1)		Viabilities under maternal inactivation if just females affected (case IMF1)		Viabilities under maternal inactivation if all individuals affected (case IMA1)	
AA, AA	¼	0	1/16	0	0	0	1	1	1	1	1	1
AA, A	½	0	⅛	0	0	0	1	1	1	1	1	1
A, A	¼	¼	1/16	1/16	0	0	1	1	1	1	1	1
Aa, Aa	0	¼	0	1/16	0	0	$(1-s)(1+t)$	$(1-s)(1+t)$	1	1	1	1
aA, aA	0	0	1/16	0	¼	0	1	1	$(1-s)(1+t)$	$(1-s)(1+t)$	$(1-s)(1+t)$	$(1-s)(1+t)$
Aa, A	0	½	0	⅛	0	0	$(1-s)(1+t/2)$	$1+t/2$	1	1	1	1
aA, A	0	0	⅛	0	0	0	1	1	$(1-s)(1+t/2)$	$1+t/2$	$(1-s)(1+t/2)$	$1+t/2$
Aa, a	0	0	0	⅛	0	0	$(1-s)(1+t/2)$	$1+t/2$	1	1	$1+t/2$	$(1-s)(1+t/2)$
aA, a	0	0	⅛	0	½	0	1	1	$(1-s)(1+t/2)$	$1+t/2$	$(1-s)(1+t)$	$(1-s)(1+t)$
a, a	0	0	1/16	1/16	¼	¼	1	1	1	1	$(1-s)(1+t)$	$(1-s)(1+t)$
AA, a	0	0	⅛	0	0	0	1	1	1	1	1	1
AA, aA	0	0	⅛	0	0	0	1	1	$1+t/2$	$(1-s)(1+t/2)$	$1+t/2$	$(1-s)(1+t/2)$
aa, A	0	0	0	⅛	0	0	$(1-s)(1+t/2)$	$1+t/2$	$(1-s)(1+t/2)$	$1+t/2$	$(1-s)(1+t/2)$	$1+t/2$
aa, aa	0	0	0	1/16	0	¼	$(1-s)(1+t)$	$(1-s)(1+t)$	$(1-s)(1+t)$	$(1-s)(1+t)$	$(1-s)(1+t)$	$(1-s)(1+t)$
aa, a	0	0	0	⅛	0	½	$(1-s)(1+t/2)$	$1+t/2$	$(1-s)(1+t/2)$	$1+t/2$	$(1-s)(1+t)$	$(1-s)(1+t)$
Aa, aa	0	0	0	⅛	0	0	$(1-s)(1+t)$	$(1-s)(1+t)$	$1+t/2$	$(1-s)(1+t/2)$	$1+t/2$	$(1-s)(1+t/2)$
A, a	0	0	⅛	⅛	0	0	1	1	1	1	$1+t/2$	$(1-s)(1+t/2)$

Maternally derived alleles are written first. All broods are of fixed size 2.

TABLE 3

Mating table for imprinting models with bigamous females

Brood	Mother: *AA* Fathers: *A, A* Frequency: xp^2	*AA* *A, a* $2xpq$	*AA* *a, a* xq^2	*Aa* *A, A* yp^2	*Aa* *A, a* $2ypq$	*Aa* *a, a* yq^2	*aa* *A, A* zp^2	*aa* *A, a* $2zpq$	*aa* *a, a* zq^2	Viabilities under paternal inactivation (case IP2)	Viabilities under maternal inactivation if just females affected (case IMF2)	Viabilities under maternal inactivation if all individuals affected (case IMA2)
AA, AA	¼	0	0	1/16	0	0	0	0	0	1, 1	1, 1	1, 1
AA, A	½	¼	0	⅛	1/16	0	0	0	0	1, 1	1, 1	1, 1
A, A	¼	¼	¼	1/16	1/16	1/16	0	0	0	1, 1	1, 1	1, 1
Aa, aA	0	0	0	0	1/16	0	0	0	0	$(1 - s)(1 + t/2), 1 + t/2$	$1 + t/2, (1 - s)(1 + t/2)$	$1 + t/2, (1 - s)(1 + t/2)$
Aa, Aa	0	0	¼	0	0	1/16	0	0	0	$(1 - s)(1 + t), (1 - s)(1 + t)$	1, 1	1, 1
aA, aA	0	0	0	1/16	0	0	¼	0	0	1, 1	$(1 - s)(1 + t), (1 - s)(1 + t)$	$(1 - s)(1 + t), (1 - s)(1 + t)$
Aa, A	0	¼	½	0	1/16	⅛	0	0	0	$(1 - s)(1 + t/2), 1 + t/2$	1, 1	1, 1
aA, A	0	0	0	⅛	1/16	0	0	0	0	1, 1	$(1 - s)(1 + t/2), 1 + t/2$	$(1 - s)(1 + t/2), 1 + t/2$
Aa, a	0	0	0	0	1/16	⅛	0	0	0	$(1 - s)(1 + t/2), 1 + t/2$	1, 1	$1 + t/2, (1 - s)(1 + t/2)$
aA, a	0	0	0	⅛	1/16	0	½	¼	0	1, 1	$(1 - s)(1 + t/2), 1 + t/2$	$(1 - s)(1 + t), (1 - s)(1 + t)$
a, a	0	0	0	1/16	1/16	1/16	¼	¼	¼	1, 1	1, 1	$(1 - s)(1 + t), (1 - s)(1 + t)$
AA, a	0	0	0	⅛	1/16	0	0	0	0	1, 1	1, 1	$1 + t/2, (1 - s)(1 + t/2)$
AA, aA	0	0	0	⅛	0	0	0	0	0	1, 1	$1 + t/2, (1 - s)(1 + t/2)$	$1 + t/2, (1 - s)(1 + t/2)$
AA, Aa	0	¼	0	0	1/16	0	0	0	0	$1 + t/2, (1 - s)(1 + t/2)$	1, 1	1, 1
AA, aa	0	0	0	0	1/16	0	0	0	0	$1 + t/2, (1 - s)(1 + t/2)$	$1 + t/2, (1 - s)(1 + t/2)$	$1 + t/2, (1 - s)(1 + t/2)$
aa, A	0	0	0	0	1/16	⅛	0	0	0	$(1 - s)(1 + t/2), 1 + t/2$	$(1 - s)(1 + t/2), 1 + t/2$	$(1 - s)(1 + t/2), 1 + t/2$
aa, aa	0	0	0	0	0	1/16	0	0	¼	$(1 - s)(1 + t), (1 - s)(1 + t)$	$(1 - s)(1 + t), (1 - s)(1 + t)$	$(1 - s)(1 + t), (1 - s)(1 + t)$
aa, a	0	0	0	0	1/16	⅛	0	¼	½	$(1 - s)(1 + t/2), 1 + t/2$	$(1 - s)(1 + t/2), 1 + t/2$	$(1 - s)(1 + t), (1 - s)(1 + t)$
aA, aa	0	0	0	0	1/16	0	0	¼	0	$1 + t/2, (1 - s)(1 + t/2)$	$(1 - s)(1 + t), (1 - s)(1 + t)$	$(1 - s)(1 + t), (1 - s)(1 + t)$
Aa, aa	0	0	0	0	0	⅛	0	0	0	$(1 - s)(1 + t), (1 - s)(1 + t)$	$1 + t/2, (1 - s)(1 + t/2)$	$1 + t/2, (1 - s)(1 + t/2)$
A, a	0	0	0	⅛	⅛	⅛	0	0	0	1, 1	1, 1	$1 + t/2, (1 - s)(1 + t/2)$

Maternally derived alleles are written first. All broods are of fixed size 2.

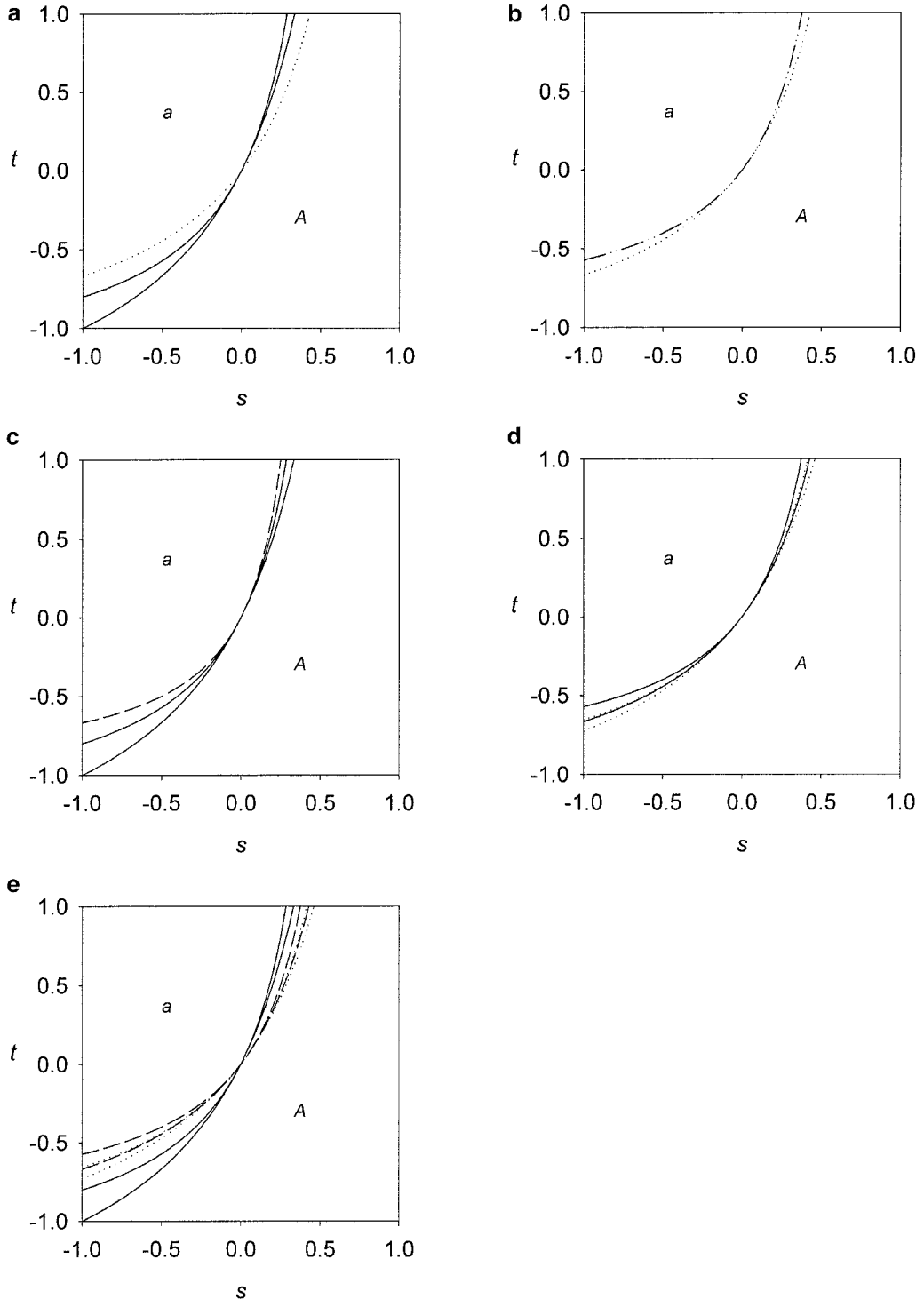

FIGURE 1.—Regions of *s-t* parameter space determining the stability of equilibria for various cases. The region to the right and below pairs of curves for each case has nonimprinting (*A* fixation); the region above and to the left has imprinting (*a* fixation); the region between each pair (not applicable for case IP1) has a stable polymorphism (*A* and *a*). (a) Cases IP1 (dotted line) and IP2 (solid lines). (b) Case IP1 (dotted line) and the corresponding autosomal model of SPENCER *et al.* (1998), P-OP1 (both lines). (c) Case IP2 (solid line) and the corresponding autosomal model of SPENCER *et al.* (1998), P-OP2 (dashed line and lower solid line). (d) Cases IMF1 and IMF2 (dotted lines) and IMA1, IMA2, P-OM1, and P-OM2 (solid lines). The lower solid line also applies to IP1. (e) Cases IP2 (solid lines), IMF2 (dotted lines), and IMA2 (dashed lines).

$$\hat{p} = \frac{s(4 + 3t) - 2t}{st} \tag{4}$$

is the equilibrium value for p. This third equilibrium is feasible (*i.e.*, all genotype frequencies are between zero and one) and locally stable provided

$$\frac{2s}{1 - s} < t < \frac{4s}{2 - 3s}, \tag{5}$$

which occurs if and only if both fixation equilibria are locally unstable. This tripartite division of parameter space into two regions of fixation and one region in between admitting polymorphism (see Figure 1) is typical of our results and mimics the autosomal model results of SPENCER *et al.* (1998).

Case IMF1: We now turn to maternal inactivation, starting with the case in which females are strictly monogamous. We assume that genes found in hemizygous males are not imprinted, even though they are maternally inherited; this assumption is reversed below in case

IMA1. With the help of Table 2, we derive the following iterations in which T_f and T_m are the normalizing mean female and male fitnesses, respectively,

$$T_f x' = p\left(x + \frac{y}{2}\left(1 + \frac{t}{8}\right)\right)$$

$$T_f y' = p(1 - s)\left(\frac{y}{2}\left(1 + \frac{5t}{8}\right) + z\left(1 + \frac{3t}{4}\right)\right) + q\left(x + \frac{y}{2}\left(1 + \frac{t}{8}\right)\right)$$

$$T_f z' = q(1 - s)\left(\frac{y}{2}\left(1 + \frac{5t}{8}\right) + z\left(1 + \frac{3t}{4}\right)\right) \quad (6)$$

and

$$T_m p' = x + \frac{y}{2}\left(1 + \frac{t}{8}\right) \quad \text{and} \quad T_m q' = \frac{y}{2}\left(1 + \frac{t}{8}\right) + z\left(1 + \frac{t}{4}\right). \quad (7)$$

As for case IP2, there are three possible equilibria, two trivial fixations and an internal, polymorphic equilibrium, the expression for which is extremely long and so not given here. (It is available on request from H. G. Spencer and at http://www.otago.ac.nz/zoology/research/spencer.) Again, parameter space divides into three parts: for low values of t ($t < 8s/(6 - 5s)$), nonimprinting evolves, whereas for high values ($t > 2(6 - 9s - \sqrt{36 - 44s + 9s^2})/(-8 + 9s)$), imprinting evolves. In between these t values, numerical work indicates that the internal equilibrium is stable.

Case IMF2: We now use Table 3 to derive the iterations for maternal inactivation with bigamous females, obtaining Equations 6 and 7 again. Hence, the analysis of equilibria is the same as for case IMF1.

Case IMA1: We now assume that *a* alleles found in hemizygous males are imprinted, first confining our attentions to the case when females are strictly monogamous. With the help of Table 2, we derive the following iterations,

$$T_f x' = p\left(x + \frac{y}{2}\left(1 + \frac{t}{4}\right)\right)$$

$$T_f y' = p(1 - s)\left(\frac{y}{2}\left(1 + \frac{3t}{4}\right) + z(1 + t)\right) + q\left(x + \frac{y}{2}\left(1 + \frac{t}{4}\right)\right)$$

$$T_f z' = q(1 - s)\left(\frac{y}{2}\left(1 + \frac{3t}{4}\right) + z(1 + t)\right) \quad (8)$$

and

$$T_m p' = x + \frac{y}{2}\left(1 + \frac{t}{4}\right)$$

$$T_m q' = (1 - s)\left(\frac{y}{2}\left(1 + \frac{3t}{4}\right) + z(1 + t)\right), \quad (9)$$

in which

$$T_f = T_m = 1 + (t - s - st)\left(1 - x - \frac{y}{2}\right) + \frac{1}{8}sty. \quad (10)$$

The condition for *a* to invade is that $t > 4s/(3 - 3s)$; to fix it is $t > 4s/(3 - 4s)$. In between these values a stable equilibrium exists, at which the female genotype frequencies are given by the quasi-Hardy-Weinberg formula $(\hat{x}, \hat{y}, \hat{z}) = (\hat{p}^2, 2\hat{p}\hat{q}, \hat{q}^2)$, where

$$\hat{p} = \frac{4s(1 + t) - 3t}{st} \quad (11)$$

is the equilibrium value for p.

Case IMA2: When females are bigamous Equations 8 and 9 are unchanged, paralleling the identity between cases IMF1 and IMF2.

Modification of expression models: Hurst (1999) argued that the models of autosomal imprinting developed in Spencer *et al.* (1999) should be compared with models for a dominant modifier of biallelic expression that had the same effects on the fitnesses within sibships. (The dominance of the modifier allows its effect on the population to be felt as soon as it arises, as is the case for the imprintable mutant *a*.) He constructed a model of a dominant modifier of expression and showed that if females were strictly monogamous, the invasion conditions for this modifier were the same as those for the imprintable allele. Because such modifiers would retain the benefits of diploidy (such as masking of deleterious recessive mutations), he reasoned that modification of expression was more likely to evolve than imprinting. With multiple paternity, however, the conditions for an imprintable allele to invade were less restrictive than those for the modifier of expression. Thus Hurst (1999) concluded that multiple paternity was indeed necessary for autosomal imprinting to evolve (although it should be noted that he did not examine the fixation conditions for such modifiers).

We can derive comparable models of expression modification here. Suppose that a dominant, sex-linked modifier allele, *M*, confers on its bearers the same viabilities as imprinted individuals. We are interested in the conditions under which *M* can invade and replace the wild-type *m* allele. Table 4 shows these fitnesses (as well as offspring frequencies) for the sibships arising when females are strictly monogamous, for two sets of assumptions: that the expression of *M* is limited to females (case BF1) and that it is expressed in both sexes (case BA1). Table 5 shows the case when females are strictly bigamous.

In all these models, let x_1 be the frequency of *mm* females, x_2 be that of *Mm* females, and x_3 ($= 1 - x_1 - x_2$) be that of *MM* females. The frequency of *m* males is denoted by p_1 and that of *M* males by p_2 ($= 1 - p_1$).

Case BF1: Table 4 enables us to derive the following recursion for these frequencies,

$$T_f x_1' = p_1\left(x_1 + \frac{x_2}{2}\left(1 + \frac{t}{8}\right)\right)$$

$$T_f x_2' = p_1(1 - s)\left(\left(\frac{x_2}{2} + x_3\right)\left(1 + \frac{3t}{4}\right) - x_2\frac{t}{16}\right)$$

$$+ p_2(1 - s)\left(x_1 + \frac{x_2}{2}\right)\left(1 + \frac{3t}{4}\right)$$

$$T_f x_3' = p_2(1 - s)\left(\frac{x_2}{2} + x_3\right)\left(1 + \frac{3t}{4}\right), \quad (12)$$

in which T_f is the sum of the right-hand sides of Equations 12 so that $x_1' + x_2' + x_3' = 1$ and

$$T_m p_1' = \left(x_1 + \frac{x_2}{2}\right)\left(1 + p_2\frac{t}{4}\right) + \frac{x_2 p_1 t}{16}$$

$$T_m p_2' = \left(\frac{x_2}{2} + x_3\right)\left(1 + \frac{t}{4}\right) - \frac{x_2 p_1 t}{16}, \quad (13)$$

in which T_m is the sum of the right-hand sides of Equations 13 so that $p_1' + p_2' = 1$.

Local stability analysis shows that the modifying allele, *M*, can invade a population fixed for *m* if $t > t_M = 8(\sqrt{(3 - 2s)/(3 - 3s)} - 1)$. The condition for the fixation of *M* cannot be obtained using the usual methods (since the leading eigenvalue is exactly one; see APPENDIX B) and we have instead obtained it numerically (see APPENDIX B) and plotted it in Figure 2a. In between the dotted lines of Figure 2a, numerical work indicates that there is a stable polymorphism of *m* and *M*, mirroring the results for the imprinting models (except IP1), although we have not been able to find an analytical expression for its value.

Case BF2: Table 5 enables us to derive the following recursion for allele frequencies for the case when females are strictly bigamous,

$$T_f x_1' = p_1\left(\left(x_1 + \frac{x_2}{2}\right)\left(1 + \frac{p_2 t}{4}\right) + \frac{p_1 x_2 t}{16}\right)$$

$$T_f x_2' = p_1(1 - s)\left(\left(\frac{x_2}{2} + x_3\right)\left(1 + \frac{3t}{4}\right) - \frac{x_2 t}{16}\right)$$

$$+ p_2(1 - s)\left(\left(x_1 + \frac{x_2}{2}\right)\left(1 + \frac{3t}{4}\right) - \frac{p_1 x_1 t}{4}\right)$$

$$T_f x_3' = p_2(1 - s)\left(\left(\frac{x_2}{2} + x_3\right)\left(1 + \frac{3t}{4}\right) - \frac{p_1 x_2 t}{16}\right), \quad (14)$$

in which T_f is the sum of the right-hand sides of Equations 14 so that $x_1' + x_2' + x_3' = 1$ and Equations 13 for the iterations in males are unchanged.

The condition for *M* to invade is now less stringent: $t > t_M = 2(\sqrt{(25 - 17s)/(1 - s)} - 5)$; we have again used numerical methods to estimate the condition for its fixation (see Figure 2a).

Case BA1: If we now assume that the modifier *M* affects expression of *A* in both sexes, Equations 12 and 13 become

$$T_f x_1' = p_1\left(x_1 + \frac{x_2}{2}\left(1 + \frac{t}{4}\right)\right)$$

$$T_f x_2' = (1 - s)\left(p_1\left(\left(\frac{x_2}{2} + x_3\right)\left(1 + \frac{3t}{4}\right) + x_3\frac{t}{4}\right)\right.$$

TABLE 4

Mating table for monogamous females under dominant modifier of expression models

	Mother:	*mm*	*mm*	*Mm*	*Mm*	*MM*	*MM*	Viabilities assuming expression in females only (case BF1)	Viabilities assuming expression in both sexes (case BA1)
Brood	Father:	*m*	*M*	*m*	*M*	*m*	*M*		
	Frequency:	$x_1 p_1$	$x_1 p_2$	$x_2 p_1$	$x_2 p_2$	$x_3 p_1$	$x_3 p_2$		
mm, mm		¼	0	⅛	0	0	0	1, 1	1, 1
mm, m		½	0	¼	0	0	0	1, 1	1, 1
m, m		¼	¼	⅛	1/16	0	0	1, 1	1, 1
Mm, Mm		0	¼	⅛	1/16	¼	0	$(1 - s)(1 + t)$, $(1 - s)(1 + t)$	$(1 - s)(1 + t)$, $(1 - s)(1 + t)$
Mm, m		0	½	¼	⅛	0	0	$(1 - s)(1 + t/2)$, $1 + t/2$	$(1 - s)(1 + t/2)$, $1 + t/2$
Mm, M		0	0	¼	⅛	½	0	$(1 - s)(1 + t/2)$, $1 + t/2$	$(1 - s)(1 + t)$, $(1 - s)(1 + t)$
M, M		0	0	⅛	1/16	¼	¼	1, 1	$(1 - s)(1 + t)$, $(1 - s)(1 + t)$
mm, M		0	0	¼	0	0	0	1, 1	$1 + t/2$, $(1 - s)(1 + t/2)$
mm, Mm		0	0	¼	0	0	0	$1 + t/2$, $(1 - s)(1 + t/2)$	$1 + t/2$, $(1 - s)(1 + t/2)$
MM, m		0	0	0	⅛	0	0	$(1 - s)(1 + t/2)$, $1 + t/2$	$(1 - s)(1 + t/2)$, $1 + t/2$
MM, MM		0	0	0	1/16	0	¼	$(1 - s)(1 + t)$, $(1 - s)(1 + t)$	$(1 - s)(1 + t)$, $(1 - s)(1 + t)$
MM, M		0	0	0	⅛	0	½	$(1 - s)(1 + t/2)$, $1 + t/2$	$(1 - s)(1 + t)$, $(1 - s)(1 + t)$
Mm, MM		0	0	0	⅛	0	0	$(1 - s)(1 + t)$, $(1 - s)(1 + t)$	$(1 - s)(1 + t)$, $(1 - s)(1 + t)$
m, M		0	0	⅛	⅛	0	0	1, 1	$1 + t/2$, $(1 - s)(1 + t/2)$

All broods are of fixed size 2.

TABLE 5

Mating table for bigamous females under dominant modifier of expression models

Brood	Mother: / Fathers: / Frequency:	*mm* / *m, m* / $x_1p_1^2$	*mm* / *m, M* / $2x_1p_1p_2$	*mm* / *M, M* / $x_1p_2^2$	*Mm* / *m, m* / $x_2p_1^2$	*Mm* / *m, M* / $2x_2p_1p_2$	*Mm* / *M, M* / $x_2p_2^2$	*MM* / *m, m* / $x_3p_1^2$	*MM* / *m, M* / $2x_3p_1p_2$	*MM* / *M, M* / $x_3p_2^2$	Viabilities if just females affected (case BF2)	Viabilities if all individuals affected (case BA2)
mm, mm		$\frac{1}{4}$	0	0	$\frac{1}{16}$	0	0	0	0	0	1, 1	1, 1
mm, Mm		0	$\frac{1}{4}$	0	$\frac{1}{8}$	$\frac{1}{16}$	0	0	0	0	$1 + t/2$, $(1 - s)(1 + t/2)$	$1 + t/2$, $(1 - s)(1 + t/2)$
mm, MM		0	0	0	0	$\frac{1}{16}$	0	0	0	0	$1 + t/2$, $(1 - s)(1 + t/2)$	$1 + t/2$, $(1 - s)(1 + t/2)$
Mm, Mm		0	0	$\frac{1}{4}$	$\frac{1}{16}$	$\frac{1}{16}$	$\frac{1}{16}$	$\frac{1}{4}$	0	0	$(1 - s)(1 + t)$, $(1 - s)(1 + t)$	$(1 - s)(1 + t)$, $(1 - s)(1 + t)$
Mm, MM		0	0	0	0	$\frac{1}{16}$	$\frac{1}{8}$	0	$\frac{1}{4}$	0	$(1 - s)(1 + t)$, $(1 - s)(1 + t)$	$(1 - s)(1 + t)$, $(1 - s)(1 + t)$
MM, MM		0	0	0	0	0	$\frac{1}{16}$	0	0	$\frac{1}{4}$	$(1 - s)(1 + t)$, $(1 - s)(1 + t)$	$(1 - s)(1 + t)$, $(1 - s)(1 + t)$
mm, m		$\frac{1}{2}$	$\frac{1}{4}$	0	$\frac{1}{8}$	$\frac{1}{16}$	0	0	0	0	1, 1	1, 1
mm, M		0	0	0	$\frac{1}{8}$	$\frac{1}{16}$	0	0	0	0	1, 1	$1 + t/2$, $(1 - s)(1 + t/2)$
Mm, m		0	$\frac{1}{4}$	$\frac{1}{2}$	$\frac{1}{8}$	$\frac{1}{8}$	$\frac{1}{8}$	0	0	0	$(1 - s)(1 + t/2)$, $1 + t/2$	$(1 - s)(1 + t/2)$, $1 + t/2$
Mm, M		0	0	0	$\frac{1}{8}$	$\frac{1}{8}$	$\frac{1}{8}$	$\frac{1}{2}$	$\frac{1}{4}$	0	$(1 - s)(1 + t/2)$, $1 + t/2$	$(1 - s)(1 + t)$, $(1 - s)(1 + t)$
MM, m		0	0	0	0	$\frac{1}{16}$	$\frac{1}{8}$	0	0	0	$(1 - s)(1 + t/2)$, $1 + t/2$	$(1 - s)(1 + t/2)$, $1 + t/2$
MM, M		0	0	0	0	$\frac{1}{16}$	$\frac{1}{8}$	0	$\frac{1}{4}$	$\frac{1}{2}$	$(1 - s)(1 + t/2)$, $1 + t/2$	$(1 - s)(1 + t)$, $(1 - s)(1 + t)$
m, m		$\frac{1}{4}$	$\frac{1}{4}$	$\frac{1}{4}$	$\frac{1}{16}$	$\frac{1}{16}$	$\frac{1}{16}$	0	0	0	1, 1	1, 1
m, M		0	0	0	$\frac{1}{8}$	$\frac{1}{8}$	$\frac{1}{8}$	0	0	0	1, 1	$1 + t/2$, $(1 - s)(1 + t/2)$
M, M		0	0	0	$\frac{1}{16}$	$\frac{1}{16}$	$\frac{1}{16}$	$\frac{1}{4}$	$\frac{1}{4}$	$\frac{1}{4}$	1, 1	$(1 - s)(1 + t)$, $(1 - s)(1 + t)$

All broods are of fixed size 2.

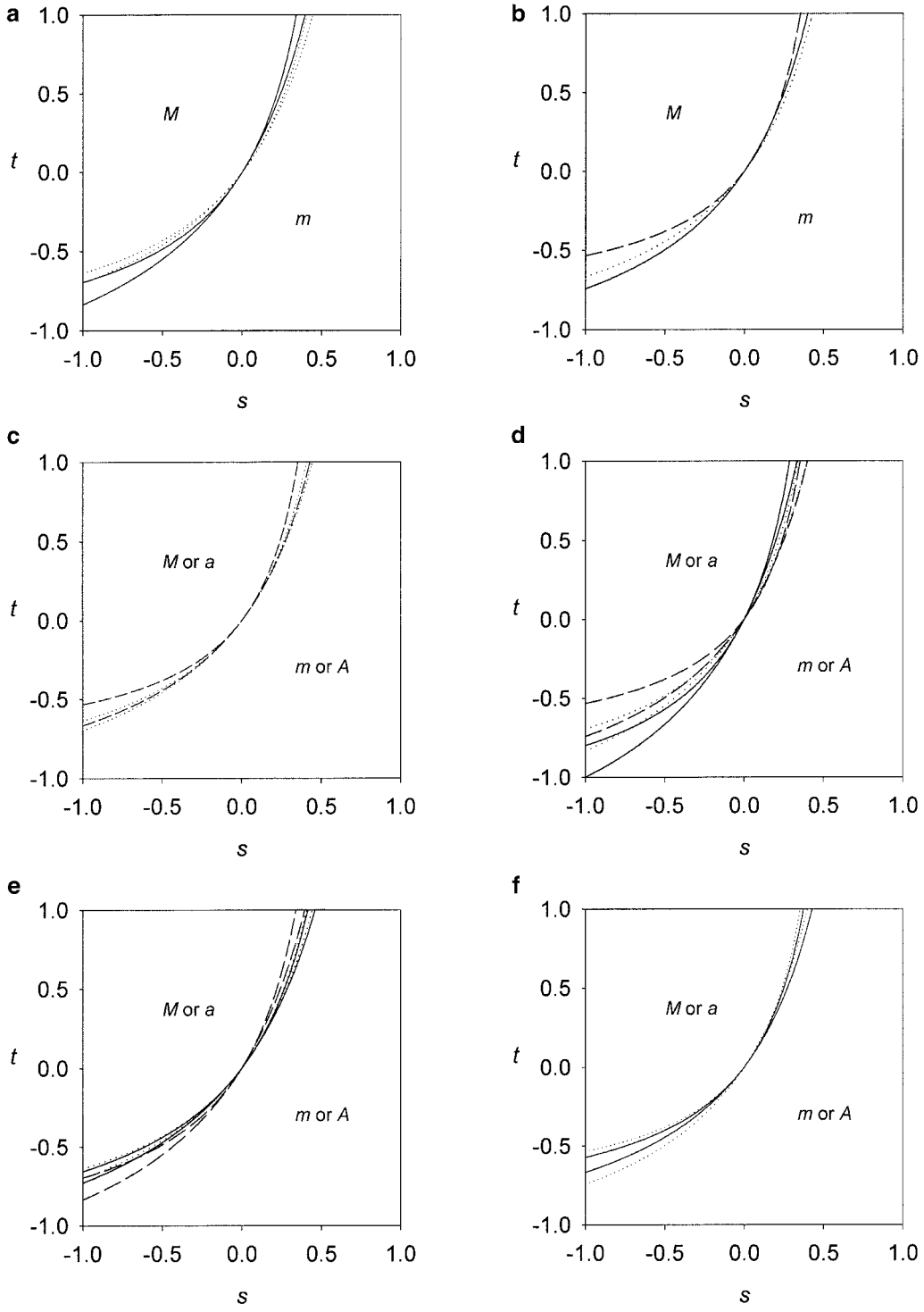

FIGURE 2.—Regions of *s*-*t* parameter space determining the stability of equilibria for various cases. Depending on the case being modeled, the region to the right and below pairs of curves for each case has nonimprinting (*A* fixation) or unmodified expression (*m* fixed); the region above and to the left has imprinting (*a* fixation) or modified expression (*M* fixed); the region between each pair has a stable polymorphism (*A* and *a* or *m* and *M*). (a) Cases BF1 (dotted lines) and BF2 (solid lines). (b) Cases BA1 (dotted and dashed lines) and BA2 (solid and dashed lines). (c) Cases BF1 (dotted lines) and BA1 (dashed lines). The lower dashed line also applies to IP1. (d) Cases BF2 (dotted lines), BA2 (dashed lines), and IP2 (solid lines). (e) Cases IMF1 and IMF2 (solid lines), BF1 (dotted lines), and BF2 (dashed lines). (f) Cases IMA1 and IMA2 (solid lines) and BA2 (dotted lines). The lower solid line and the upper dotted line also apply to BA1.

$$+ p_2\left(\left(x_1 + \frac{x_2}{2}\right)\left(1 + \frac{3t}{4}\right) + x_2\frac{t}{16}\right)$$

$$T_f x_3' = p_2(1 - s)\left(\left(\frac{x_2}{2} + x_3\right)\left(1 + \frac{7t}{8}\right) + x_3\frac{t}{8}\right), \quad (15)$$

and

$$T_m p_1' = \left(x_1 + \frac{x_2}{2}\right)\left(1 + p_2\frac{t}{4}\right) + \frac{x_2 t}{8}\left(p_1 + \frac{p_2}{2}\right)$$

$$T_m p_2' = (1 - s)\left(\left(\frac{x_2}{2} + x_3\right)(1 + t) - \frac{x_2 t}{8}\left(p_1 + \frac{p_2}{2}\right)\right). \quad (16)$$

Local stability analysis shows that the *M* allele will invade a population fixed for *m* if $t > 4s/(3 - 3s)$, the same condition as for the invasion of a paternally inactivated *a* into a population fixed for *A*. Stable fixation of *M*, however, requires larger values of *t* for a given *s*: $t > 8s/(6 - 9s)$.

Case BA2: If we now assume that the modifier *M* affects expression of *A* in both sexes, Equations 15 and 16 become

$$T_f x_1' = p_1\left(\left(x_1 + \frac{x_2}{2}\right)\left(1 + \frac{p_2 t}{4}\right) + \frac{x_2 t}{8}\left(1 - \frac{p_2}{2}\right)\right)$$

$$T_f x_2' = (1 - s)\left(p_1\left(\left(\frac{x_2}{2} + x_3\right)\left(1 + \frac{3t}{4}\right) + \frac{x_3 t}{4}\right) + p_2\left(\left(x_1 + \frac{x_2}{2}\right)\left(1 + \frac{7t}{8}\right) - \frac{x_1 t}{8}(1 + 2p_1)\right)\right)$$

$$T_f x_3' = (1 - s)p_2\left(\left(\frac{x_2}{2} + x_3\right)(1 + t) - \frac{x_2 t}{4}\left(1 - \frac{p_2}{2}\right)\right) \quad (17)$$

and

$$T_m p_1' = \left(x_1 + \frac{x_2}{2}\right)\left(1 + p_2\frac{t}{4}\right) + \frac{x_2 t}{8}\left(p_1 + \frac{p_2}{2}\right)$$

$$T_m p_2' = (1 - s)\left(\left(\frac{x_2}{2} + x_3\right)(1 + t) - \frac{x_2 t}{8}\left(p_1 + \frac{p_2}{2}\right)\right). \quad (18)$$

The successful invasion of *M* now requires $t > (\sqrt{64 - 8s + s^2} - 8 + 5s)/(3 - 3s)$, although the condition for fixation is identical to that for case BA2.

ANALYSIS

Local stability analysis results are summarized for all cases in Table 6.

Paternal inactivation: Case IP1 is notable as the only one of our models that fails to divide *s-t* parameter space in three, because no polymorphic equilibrium (either stable or unstable) exists. In contrast, case IP2 produces the same pattern as seen in all Spencer *et al.*'s (1998) models of autosomal imprinting due to genetic conflict: a region of parameter space between the two stable fixations in which a polymorphic equilibrium is locally (and indeed, globally) stable (see Figure 1a). Hence, one effect of multiple paternity on paternal X-locus inactivation is the possibility of polymorphism in imprinting status.

A second effect of multiple paternity can also be seen in Figure 1a: it reduces the proportion of parameter space leading to paternal inactivation for growth enhancers (s and $t > 0$) and increases it for growth inhibitors (s and $t < 0$). This result is the same as in the autosomal models (Spencer *et al.* 1998) and fits with the verbal prediction of the genetic-conflict hypothesis.

We can also make comparisons between these X chromosome models and the corresponding autosomal models of Spencer *et al.* (1998) as to how they partition parameter space. For example, Spencer *et al.*'s (1998) P-OP1 is directly comparable to IP1, differing only in that the former models an autosomal locus rather than an X-linked one. It turns out that the condition for the invasion of the imprintable *a* allele is the same in both cases: $t > 4s/(3 - 3s)$. Under the IP1 model, this inequality is also the condition for fixation of *a*; under P-OP1, however, fixation of imprinting is not stable unless t is somewhat larger, $t > 4s/(3 - 4s)$ (see Figure 1b). In between these values a stable internal equilibrium exists. Hence, for a paternally inactivated locus in a monogamous population, the effect of being sex linked (as opposed to autosomal) is to (i) eliminate the possibility of a polymorphism in imprinting status and (ii) increase the proportion of parameter space favoring the evolution of pure imprinting. This second conclusion also applies to a bigamous population as Figure 1c shows: the t threshold for the successful invasion of *a* is the same in both IP2 and P-OP2, but the threshold for its fixation is higher in the latter: $t > 2s/(1 - 2s)$ in P-OP2 *vs.* $4s/(2 - 3s)$ in IP2.

Maternal inactivation: As in the autosomal models of Spencer *et al.* (1998), there is no effect of multiple paternity on the likelihood of maternal inactivation, whether this inactivation applied to all offspring (cases IMA1 and IMA2) or female offspring only (cases IMF1 and IMF2). Both these cases permitted polymorphism in imprinting status for certain parameter combinations. Comparing these pairs of cases (see Figure 1d) shows that imprinting is more likely to evolve if the inactivation affects female offspring only.

Cases IMA1 and IMA2 have stability conditions, equilibrium values, and mean fitnesses identical to those for the corresponding autosomal P-OM1 model of Spencer *et al.* (1998), even though the iterations are necessarily different (since IMA1 and IMA2 have separate equations for males and females). Thus, there is no effect of autosomal *vs.* sex-chromosome inactivation if all offspring are imprinted. But if only female offspring are imprinted, cases IMF1 and IMF2 (Figure 1d) show that X chromosome inactivation can invade for all parameter values for which autosomal inactivation can invade, as well as at other values for which autosomal inactivation fails to evolve. X chromosome inactivation is thus more likely than autosomal inactivation.

Direction of imprinting: Since the invasion and fixation condition for *a* in case IP1 is the same as that for invasion in IMA1, Figure 1d also allows us to predict the direction of imprinting under strict monogamy. If maternal inactivation affects both sexes, fixation of a paternally inactivated allele is more likely than that of one that is maternally inactivated, whether the gene inhibits or enhances growth. This increased likelihood comes completely at the expense of the likelihood of polymorphism in imprinting; the regions of parameter space favoring fixation of the unimprintable *A* are identical.

If maternal inactivation affects just female offspring, again, under strict monogamy, fixation of a paternally inactivated allele is more likely than that of an allele that is maternally inactive (Figure 1d). Nevertheless, a maternally inactivated allele can successfully invade over a greater part of parameter space than a paternally inactivated allele and reach a stable polymorphism not possi-

TABLE 6

Fixation-equilibria stability conditions and polymorphic equilibria

Case	Condition for a or M to Invade	Condition for a or M to Fix	Polymorphic equilibrium
IP1	$t > \frac{4s}{3-3s}$	$t > \frac{4s}{3-3s}$	No
IP2	$t > \frac{2s}{1-s}$	$t > \frac{4s}{2-3s}$	$\hat{p} = \frac{s(4+3t)-2t}{st}$
IMF1	$t > \frac{8s}{6-5s}$	$t > \frac{2(6-9s-\sqrt{36-44s+9s^2})}{-8+9s}$	Complicated
IMF2	$t > \frac{8s}{6-5s}$	$t > \frac{2(6-9s-\sqrt{36-44s+9s^2})}{-8+9s}$	Complicated
IMA1	$t > \frac{4s}{3-3s}$	$t > \frac{4s}{3-4s}$	$\hat{p} = \frac{4s(1+t)-3t}{st}$
IMA2	$t > \frac{4s}{3-3s}$	$t > \frac{4s}{3-4s}$	$\hat{p} = \frac{4s(1+t)-3t}{st}$
BF1	$t > 8\left(\sqrt{\frac{3-2s}{3(1-s)}} - 1\right)$	Numerical solution (Figure 2a)	Not found analytically
BF2	$t > 2\left(\sqrt{\frac{25-17s}{1-s}} - 5\right)$	Numerical solution (Figure 2a)	Not found analytically
BA1	$t > \frac{4s}{3-3s}$	$t > \frac{8s}{3(2-3s)}$	Not found analytically
BA2	$t > \frac{\sqrt{64-s(8-s)}-8+5s}{3(1-s)}$	$t > \frac{8s}{3(2-3s)}$	Not found analytically

ble for the latter. Again, these conclusions apply to both growth enhancers and inhibitors.

When females are strictly bigamous, however, we obtain results more in accord with the genetic conflict's verbal predictions. Figure 1e shows that for growth enhancers ($s, t > 0$), both the curves for IP2 are above all those for IMF2 and IMA2, so inactivation is likely to be maternal rather than paternal, regardless of whether maternal inactivation occurs in all offspring or only in females. For growth inhibitors, the situation is reversed, and so they are more likely to be maternally active.

Biallelic modification: Figure 2a shows that multiple paternity has the same effect in the biallelic modifier-of-female-offspring models that it has in the models of autosomal and paternal X chromosome inactivation: it becomes easier for biallelic modifiers of growth inhibitors to invade and fix but more difficult for biallelic modifiers of growth enhancers to do so. If the modifier allele is expressed in both male and female offspring, however, multiple paternity has no effect on the likelihood of fixation; it only makes polymorphism more likely for growth inhibitors and less likely for growth enhancers (Figure 2b).

We can also predict which sort of modifiers—those affecting just female offspring or those affecting all offspring—is more likely to invade by considering Figure 2c for the monogamous and Figure 2d for the bigamous case. Under monogamy, modifiers that affect only female offspring are clearly more likely to succeed, and that is also true under bigamy for modifiers of growth inhibitors. For modifiers of growth enhancers, however, female bigamy causes modifiers affecting offspring of both sexes to invade and fix over a greater part of parameter space.

Imprinting or modification? Figure 2c reveals that, under strict monogamy, biallelic modifiers of female offspring are more likely to invade than paternally inactivated alleles, which (except for the effects of masking) are as likely to invade as modifiers of both sexes. But fixation of paternally inactivated alleles is more likely than fixation of either sort of modifier. Under strict bigamy, however, we find that for growth enhancers, modifiers are more likely to invade and fix, whereas growth inhibitors are more likely to be imprinted (Figure 2d). This deduction implies that growth inhibitors rather than growth enhancers are likely to be paternally inactivated.

The corresponding comparisons are made for mater-

nal inactivation in Figure 2, e and f. Comparing alleles that are imprintable only in female offspring with biallelic modifiers of female offspring (Figure 2e), we see that, for growth enhancers, imprinting is more likely than modification, whatever the mating system. For growth inhibitors, however, multiple paternity is needed to make imprinting less likely than modification. Figure 2f allows us to compare the regions of parameter space for the cases in which alleles are imprinted in all offspring with those in which modification occurs in all offspring. For growth enhancers, imprinting is more likely only under multiple paternity; conversely, for growth inhibitors, multiple paternity favors invasion of modification (but fixation of imprinting). With monogamy, modification and imprinting of both growth enhancers and inhibitors are equally likely to invade (ignoring masking again), although the latter are more likely to fix. Given that most if not all mammals show some degree of multiple paternity, we are left with the conclusion that growth enhancers rather than growth inhibitors are likely to be maternally inactivated.

Note also that Figure 2, e and f, shows that polymorphism in imprinting status is more likely to evolve than modification, for both growth enhancers (which will likely be maternally inactivated) and growth inhibitors (which will likely be paternally inactivated). This finding mirrors that of Spencer *et al.* (1998) for autosomes, but it is not evident from verbal versions of the genetic-conflict hypothesis.

DISCUSSION

The models developed and analyzed above show that most of the findings of Spencer *et al.* (1998) about the consequences of genetic conflict at autosomal loci are replicated for X-linked genes. Given some degree of multiple paternity, growth enhancers are more likely to be maternally inactivated and growth inhibitors paternally so, confirming the primary verbal prediction of the genetic-conflict hypothesis (Haig and Graham 1991; Haig 1992). Moreover, both of these effects are more likely than biallelic modification that has the same fitness consequences.

Multiple paternity is not necessary for imprinting to evolve, but it makes the above directional outcomes more likely. For example, with strict monogamy, the fixation of a paternally inactivated growth enhancer is more likely than that of one that is maternally inactivated in offspring of both sexes. Even with multiple paternity, imprinting can occur in the opposite direction from that predicted by the genetic-conflict hypothesis in suitable parts of parameter space.

Another point of agreement with the results of the autosomal modeling of Spencer *et al.* (1998) is that imprinting need not evolve, even under conditions that would seem to favor it under verbal versions of genetic conflict. For instance, in none of the cases of maternal inactivation (IMA1, IMA2, IMF1, and IMF2) would an imprintable growth enhancer with $s = 0.42$ and $t = 0.84$ invade, let alone fix, even though the cost of imprinting to an individual (s) matches the family-level benefit to that individual ($t/2$). This finding is important because in the autosomal model of Mochizuki *et al.* (1996), which used a hybrid quantitative genetic-game theory approach, any degree of multiple paternity led to the evolution of imprinting. For a more detailed critique of the game-theoretic approach to modeling the evolution of imprinting see Weisstein *et al.* (2002).

Polymorphism in imprinting status—the presence in a population of both imprintable and unimprintable alleles at a stable internal equilibrium—is another finding matching that derived from autosomal models (Spencer *et al.* 1998). Importantly, such outcomes can occur in parts of parameter space where biallelic modification cannot and so may be an expected consequence of genetic conflict. Admittedly, we know of no examples of such loci, although we note that few X chromosome loci are known to be imprinted in any way (Morison *et al.* 2001; but see Davis *et al.* 2001). At least two autosomal examples of polymorphism in imprinting status are known: the Wilm's tumor suppressor gene, *WT1*, on human chromosome 11 (Jinno *et al.* 1994) and the serotonin-2A (5-HT_{2A}) receptor gene, *HTR2A*, on human chromosome 13 (Bunzel *et al.* 1998). [Polymorphism in X-inactivation status is also known for at least two genes (Anderson and Brown 1999; Carrel and Willard 1999).] Moreover, because such polymorphism may be difficult to detect, careful analysis of known cases of imprinting may well reveal more examples of polymorphic imprinting status.

Several important contrasts can be made between the results of the above sex-chromosome models and those of the autosomal models of Spencer *et al.* (1998). The model of paternal inactivation at a sex-linked locus under strict monogamy is the only case that does not afford polymorphism in imprinting status for any part of parameter space. More importantly, however, genetic conflict leads to imprinting on sex chromosomes more easily than it does for autosomes, no matter what level of multiple paternity applies. Given that the meager evidence concerning the direction of imprinting in actual cases of X chromosome imprinting contradicts both the verbal and model-derived predictions of genetic conflict, we agree with Iwasa and Pomiankowski (1999) that it is an unlikely explanation for X chromosome imprinting in general.

It is important to understand just what we mean when we argue that certain outcomes are more likely than others. We are not saying simply that these outcomes occur over large parts of parameter space; there are two reasons for denying this link. First, the way in which parameter space is measured—*e.g.*, an arithmetic or a log scale—affects the size of different portions. Second, parts of parameter space that are small no matter how

they are measured can easily be reached by natural processes. Indeed, selection may be adept at finding such places, as in the case of the regions of parameter space of the standard viability selection model that maintain many alleles (Spencer and Marks 1988; Marks and Spencer 1991). In short, likely outcomes need not correspond to large parts of parameter space. Nevertheless, if a part of parameter space corresponding to one event is a subset of another, then we can make the qualitative deduction that the first event is less likely than the second, even if we cannot quantify this difference. In all cases above, our conclusions about the relative likelihoods of certain outcomes are based on the relevant parts of parameter space being subsets of others.

The failure of the genetic-conflict hypothesis to account for the apparent direction of imprinting of sex-linked genes led Iwasa and Pomiankowski (1999, 2001) to propose an alternative hypothesis that imprinting evolved under differential selection on males and females to enhance sex-linked expression. Because eutherian females are a mosaic of cells with paternally and maternally inactivated X chromosomes, expression of X-linked genes in females is expected to be the average of expression levels on each chromosome, whereas in males it is simply that from the sole, maternal, X. Down-regulating a paternal gene and upregulating the maternal copy thus allows greater expression in males than in females, whereas imprinting in the opposite direction permits preferential expression in females. Hence, the imprinting of genes that underlie characters subject to differing selection pressures in males and females will also be favored by selection. Clearly, this hypothesis should be examined in a way similar to that above; in particular, we would like to know whether imprinting or biallelic modification is favored.

Iwasa and Pomiankowski's (1999) hypothesis can, in fact, be generalized to autosomal loci. Imprinting at any locus causes offspring to resemble one parent—the one transmitting the active copy of the gene—more than the other (Spencer 2002). Hence, selection pressures that favor offspring being more like one parent than another will also favor the imprinting of the relevant genes. For X-linked loci, the different ploidy levels in males and females allow this parental resemblance to be limited to or enhanced in offspring of just one sex, but for autosomal genes offspring of both sexes are affected equally. Nevertheless, there are numerous potential characters that fit this scenario. For example, in many mammal species, males disperse much farther from their birthplace than do females. Hence, any predispersal juveniles that exhibit locally adapted features more like their mothers will have a selective advantage. An example that could be well worth examining in more detail (since we know its genetic basis) is coat color in the rock pocket mouse, *Chaeotodipus intermedius* (Hoekstra and Nachman 2003). Intriguingly, this scenario may also apply to angiosperm plants, the only group in addition to mammals in which genomic imprinting has been unambiguously recognized (Alleman and Doctor 2000), since pollen can often travel great distances.

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APPENDIX A: ANALYSES FOR IMPRINTING CASES

Case IP1: We use case IP1 as an example; the other cases are similar, except where noted below. To carry out local stability analysis we first find the leading eigenvalue for the system (1) and (2) linearized around the first equilibrium ($x = 1$, $y = 0$, $z = 0$, $p = 1$, and $q = 0$), which is given by

$$\lambda_1 = \frac{1}{4}\left(1 + \sqrt{9 + 6t - 2s(4 + 3t)}\right). \tag{A1}$$

Fixation of the unimprintable allele is locally stable whenever $\lambda_1 < 1$, which requires

$$t < \frac{4s}{3(1 - s)}. \tag{A2}$$

Similarly, the leading eigenvalue for the iterations around the second equilibrium (*i.e.*, $x = 0$, $y = 0$, $z = 1$, $p = 0$, and $q = 1$) is given by

$$\lambda_0 = \frac{1}{4}\left(1 + \sqrt{\frac{3(12 + t) - s(4 + 3t)}{(1 - s)(4 + 3t)}}\right), \tag{A3}$$

and so local stability, requiring $\lambda_0 < 1$, implies

$$t > \frac{4s}{3(1 - s)}. \tag{A4}$$

Hence, the imprinting fixation is locally stable if and only if the nonimprinting fixation is not and vice versa.

The equilibria for case IP1 also have the quasi-Hardy-Weinberg property found in the autosomal models of Spencer *et al.* (1998). If we write P for $x + y/2$, $Q = 1 - P$, and $B = p/T_f$, Equations 1 and 2 give

$$\begin{aligned} x' &= PB \\ y' &= P(1 - B) + QB \\ z' &= Q(1 - B) \\ p' &= P \\ q' &= Q. \end{aligned} \tag{A5}$$

Since $P' = (P + B)/2$, at equilibrium $\hat{p} = \hat{P} = \hat{B}$ and so $(\hat{x}, \hat{y}, \hat{z}) = (\hat{p}^2, 2\hat{p}\hat{q}, \hat{q}^2)$. Global stability can be demonstrated using the method of Karlin (1972; see also Spencer *et al.* 1998), by first noting that

$$\begin{aligned} T_f P' &= pP + \frac{1}{2}pQ + \frac{1}{2}qP\alpha \\ T_f Q' &= qQ\alpha + \frac{1}{2}pQ + \frac{1}{2}qP\alpha \end{aligned} \tag{A6}$$

in which $\alpha = (1 - s)(1 + 3t/4)$. Then writing $u = p/q$ and $v = P/Q$ we have $u' = v$ and

$$v' = \frac{uv + u/2 + \alpha v/2}{\alpha + u/2 + \alpha v/2}. \tag{A7}$$

Consideration of the partial derivatives $\partial u'/\partial u$, $\partial u'/\partial v$, $\partial v'/\partial u$, and $\partial v'/\partial v$ shows that the transformation (u', v') is bimonotonic, which completes the proof.

Case IP2: Deriving the conditions for local stability at all three equilibria is straightforward. The equilibria also have the quasi-Hardy-Weinberg property if we instead write

$$B = \frac{p(1 + tq/4)}{T_f}. \tag{A8}$$

We have been unable to prove the global stability result, however, although we suspect, from extensive simulations as well as the structure of the model, that it does hold.

Case IMF1: Deriving the conditions for local stability at the two fixation equilibria is straightforward. The expression for the allele frequency at internal equilibrium is extremely long and so is not given here, but may be obtained from H. G. Spencer or http://www.otago.ac.nz/zoology/research/spencer. Moreover, we have not been able to prove the conditions under which it is feasible or stable. Nevertheless, 10^5 simulations of Equations 6 and 7 with values of s and t independently and randomly sampled from the uniform distribution over $[-1, 1]$ and random initial genotype frequencies confirm the intuitively appealing suggestion that, for values of t violating the conditions for local stability of the fixations, the internal equilibrium is feasible and stable. No cases of cycling were detected: indeed, apart from some fluctuations in the first few generations, all simulations approached one of the three equilibria monotonically.

Case IMA1: This case is straightforward, being very similar to case IP2.

APPENDIX B: LOCAL STABILITY ANALYSES FOR BIALLELIC MODIFIER CASES

Case BF1: Standard local stability analysis provides the condition for the local stability of the fixation of m shown in Table 6. Unfortunately, at the fixation of M (*i.e.*, $x_1 = x_2 = p_1 = 0$, $x_3 = p_2 = 1$), the leading eigenvalue for the linearized system of iterations is identically one, which provides no information about the local stability (Edelstein-Keshet 1988). This property is a direct consequence of the dominance of M, which causes the rate of approach to fixation to be very slow. Moreover, we have not been able to discover an analytical solution for the polymorphic equilibrium that extensive simulation shows is always present. Hence, we used a numerical approach.

For a fixed value of s, we took an initial estimate of the value of t on the border between the regions of parameter space leading to fixation of M and stable polymorphism of M and m. Starting near the fixation of M ($x_1 = 0.001$, $x_2 = 0.02$, and $p_1 = 0.01$), we then iterated Equations 12 and 13 until the sum of the changes in the absolute values of these three variables was $<10^{-10}$ or else 10^6 iterations had been made. The slow approach to fixation indicated by the leading eigenvalue being 1 necessitated such high values. If the sum of the final values for these three variables was $<10^{-3}$, the system was considered to have reached fixation; otherwise the system was held to have iterated to the polymorphic equilibrium. This threshold might seem rather high, but was again necessitated by the slow approach to equilibrium. If fixation occurred, a smaller value of t was then tested; conversely, if polymorphism was reached, a larger value of t was chosen. Some 15 values of t were eventually tested, the last retained as the estimate of the critical value. Several values were then checked by substituting both s and t into Equations 12 and 13, which were then solved analytically. This check revealed that this procedure slightly overestimated t's true value, by $\sim$0.0058, and so this number was subtracted from all estimates. These corrected values are plotted in Figure 2a.

Case BF2: Standard local stability analysis again failed at the fixation of M and so we used the numerical process described above to estimate the critical value. It again slightly overestimated the true value and we corrected by subtracting 0.0070 from all values.