

# Population Models of Genomic Imprinting. I. Differential Viability in the Sexes and the Analogy With Genetic Dominance

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## ABSTRACT

Many single-locus, two-allele selection models of genomic imprinting have been shown to reduce formally to one-locus Mendelian models with a modified parameter for genetic dominance. One exception is the model where selection at the imprinted locus affects the sexes differently. We present two models of maternal inactivation with differential viability in the sexes, one with complete inactivation, and the other with a partial penetrance for inactivation. We show that, provided dominance relations at the imprintable locus are the same in both sexes, a globally stable polymorphism exists for a range of viabilities that is independent of the penetrance of imprinting. The conditions for a polymorphism are the same as in previous models with differential viability in the sexes but without imprinting and in a model of the paternal X-inactivation system in marsupials. The model with incomplete inactivation is used to illustrate the analogy between imprinting and dominance by comparing equilibrium bifurcation plots for fixed values of dominance and penetrance. We also derive a single expression for the dominance parameter that leaves the frequency and stability of equilibria unchanged for all levels of inactivation. Although an imprinting model with sex differences does not formally reduce to a nonimprinting scheme, close theoretical parallels clearly exist.

GENOMIC imprinting is the differential expression of genes according to parental origin (Solter 1988) and is characterized by an allele-specific epigenetic modification of paternally or maternally inherited genes. The expression of imprinted genes is consequently non-Mendelian: reciprocal heterozygotes lack functional equivalence. The best-known example of an imprinted gene is insulin-like growth factor II (*IGF2*) in mice and humans, for which in most tissues only the paternally derived copy is expressed (DeChiara *et al.* 1991; Giannoukakis *et al.* 1993). Estimates indicate that up to 200 functional human genes may be subject to imprinting (Barlow 1995), although currently only 20 definitive cases have been isolated (Morison and Reeve 1998). The mechanisms by which these genes are imprinted have not been fully elucidated. Although the methylation of cytosine has been repeatedly implicated as an important mechanistic feature (Jaenisch 1997; Reik and Walter 1998), recent work indicates that methylation is not the definitive "mark" of imprinting for *IGF2* (Jones *et al.* 1998).

The majority of theoretical work on imprinting has focused on its evolutionary origins and subsequent persistence (Mochizuki *et al.* 1996; Haig 1997; Iwasa 1998; Spencer *et al.* 1998). In contrast, less research has been conducted on the population genetic consequences of

imprinting. Pearce and Spencer (1992) introduced a range of models with viability selection at a single imprinted locus. They found that many of their models formally reduced to schemes with standard Mendelian inheritance and a modified parameter for genetic dominance. However, when selection affected the sexes differently, no equivalence between an imprinting scheme and the classic two-sex Mendelian schemes of Owen (1953) and Bodmer (1965) was apparent (as shown in model 6, Pearce and Spencer 1992).

Our purpose here is to further analyze this anomalous case with differential viability in the sexes. We focus on the maternal inactivation of autosomal genes, although all conclusions are equally applicable to a consideration of paternal silencing. We first construct a model with complete inactivation, then consider a more generalized model with incomplete silencing. In both cases, we look at the existence conditions for an internal equilibrium and the conditions for the stability of both internal and fixation equilibria.

As already mentioned, an imprinting model with differential viability in the sexes does not reduce to a Mendelian scheme with a modified parameter for genetic dominance. It is of interest to study the relationship between imprinting and dominance in the absence of such a formal equivalence. We use the model with incomplete inactivation to examine how changes in (1) the penetrance of imprinting and (2) dominance relations at the imprintable locus affect the number of equilibria and their stability, and compare the equilibrium bifurcation patterns produced in each instance.

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**TABLE 1**  
**Genotype viabilities and frequencies of genotypes for model 1**

Genotype A <sub>M</sub> A <sub>P</sub>	Female viability	Male viability	Frequency before selection
(A)A	1	1	$p_t p_m$
(A)a	1 - s	1 - t	$p_t(1 - p_m)$
(a)A	1	1	$(1 - p_t)p_m$
(a)a	1 - s	1 - t	$(1 - p_t)(1 - p_m)$

A<sub>M</sub> and A<sub>P</sub> are the maternally and paternally derived loci, respectively, and parentheses indicate the inactivation of the maternal allele.

Differential viability in the sexes has been the focus of a number of population genetic models (e.g., Owen 1953; Bodmer 1965; Kidwell *et al.* 1977; Babcock and Asmussen 1996). We suggest that imprinted genes may be especially prone to the effects of such selection, and that the models presented here therefore are not of purely abstract interest. A number of imprinted genes (e.g., *IGF2* and *IGF2r*) mediate the maternal resourcing of the fetus during pregnancy. We might reasonably expect that genes influencing the growth of offspring are liable to viability differences in the sexes, as males and females may have a different “optimal” size. Human male newborns are significantly larger than females (Penrose 1951; Nance *et al.* 1983). In the mouse a size difference in the sexes becomes apparent soon after birth (Bergmann *et al.* 1995).

AN IMPRINTING SYSTEM WITH DIFFERENTIAL VIABILITY IN THE SEXES

We consider a single diploid autosomal locus A with two alleles, A and a. The locus is subject to imprinting: when imprinting occurs, the maternally derived allele in an individual is not expressed. The viability of alleles at the A locus is different in the two sexes. We make the standard Hardy-Weinberg assumptions of no mutation, no genetic drift, no migration, and separate generations.

**Model 1—Full imprinting:** We first model the situation in which the maternally derived allele at the A locus is always inactive. All individuals in the population are therefore functionally haploid with respect to the imprinted locus. The viability of a phenotypically a female is 1 - s and the corresponding viability in males is 1 - t, relative to 1 for the A phenotype in both sexes. Table 1 gives the parameters for the model. Parentheses indicate the silencing of the allele on the maternally derived chromosome (A<sub>M</sub>). The A allele occurs at frequency p<sub>t</sub> in females and p<sub>m</sub> in males. The model is equivalent to model 6 in Pearce and Spencer (1992) with, in their nomenclature, w<sub>1f</sub> = w<sub>1m</sub> = 1, w<sub>2f</sub> = 1 - s, and w<sub>2m</sub> = 1 - t. Here we expand their analysis by looking at the

stability conditions for the internal and fixation equilibria.

The recursion equations for the sex-specific allele frequencies in the next generation (p<sub>t</sub>' and p<sub>m</sub>') are

$$\bar{w}_f p_t' = p_t p_m + \frac{1}{2} p_t (1 - p_m) (1 - s) + \frac{1}{2} (1 - p_t) p_m \quad (1a)$$

$$\bar{w}_m p_m' = p_t p_m + \frac{1}{2} p_t (1 - p_m) (1 - t) + \frac{1}{2} (1 - p_t) p_m, \quad (1b)$$

where

$$\begin{aligned} \bar{w}_f &= p_t p_m + p_t (1 - p_m) (1 - s) \\ &\quad + (1 - p_t) p_m + (1 - p_t) (1 - p_m) (1 - s) \\ &= 1 - s(1 - p_m) \end{aligned} \quad (1c)$$

$$\begin{aligned} \bar{w}_m &= p_t p_m + p_t (1 - p_m) (1 - t) \\ &\quad + (1 - p_t) p_m + (1 - p_t) (1 - p_m) (1 - t) \\ &= 1 - t(1 - p_m) \end{aligned} \quad (1d)$$

are the mean viabilities in females and males, respectively.

*Existence of an internal equilibrium:* Pearce and Spencer (1992) showed that there is a possible internal equilibrium p<sub>t</sub> = p<sub>t</sub>^, p<sub>m</sub> = p<sub>m</sub>^, where

$$\hat{p}_t = \frac{2st - s - t}{s(t - s)} \quad (2a)$$

and

$$\hat{p}_m = \frac{2st - s - t}{2st} = 1 - \frac{1}{2} \left( \frac{1}{s} + \frac{1}{t} \right). \quad (2b)$$

An admissible internal equilibrium with 0 < p<sub>t</sub>^, p<sub>m</sub>^ < 1 therefore exists if and only if

$$s > 0, t < 0, \text{ and } |t| > s > \frac{t}{2t - 1} > 0 \quad (3a)$$

or

$$s < 0, t > 0, \text{ and } |s| > t > \frac{s}{2s - 1} > 0. \quad (3b)$$

The existence conditions are symmetrical and require that s and t be of opposite sign.

*Local stability of internal equilibrium:* The local stability of an equilibrium depends on the eigenvalues, λ<sub>1</sub> and λ<sub>2</sub>, of the system linearized at that point (Hal dane and Jayakar 1964). The Jacobian matrix of partial derivatives of the model is

$$\begin{bmatrix} \frac{1 - t}{2(p_m t - t + 1)^2} & \frac{1}{2} \\ \frac{1 - s}{2(p_m s - s + 1)^2} & \frac{1}{2} \end{bmatrix} \quad (4)$$

and the eigenvalues are the roots of the characteristic equation evaluated at p<sub>t</sub> = p<sub>t</sub>^, p<sub>m</sub> = p<sub>m</sub>^, which is

$$\lambda^2 - \left( \frac{1}{2} - \frac{2s^2(t - 1)}{(s - t)^2} \right) \lambda + \frac{t + s(1 - t)}{s - t} = 0. \quad (5)$$

The equilibrium is locally stable when both roots are less than unity in magnitude. For the quadratic  $\lambda^2 - A\lambda + B$ , this is true if and only if (I)  $B < 1$  and (II)  $|A| + B \leq 1$  (Edelstein-Keshet 1988).

Looking at the quadratic (5),  $A > 0$  for all  $s, t < 1$  ( $s \neq t$ ), and the conditions for stability are (I)  $(t + s(1 - t))/(s - t) < 1$  and (II)  $(s + t)(t - s(2t - 1)) < 0$ . Condition I is met whenever  $s$  and  $t$  are of opposite sign. As condition II reduces to the existence conditions (3), an internal equilibrium is locally stable whenever it is feasible (i.e., when  $0 < \hat{p}_m, \hat{p}_t < 1$ ).

**Global stability of the internal and fixation equilibria:** Karlin (1972) showed that an equilibrium is globally stable when (A) it is locally stable; (B) all other equilibria are locally unstable; and (C) the system is bimonotonic (all elements in the Jacobian matrix are positive for  $0 \leq p_t, p_m \leq 1$ ). From our Jacobian matrix (4) it can be seen immediately that condition C is met. Condition A has already been demonstrated. Therefore, to infer the global stability of the polymorphic equilibrium, we need only prove the instability of the fixation equilibria for  $s$  and  $t$  values meeting the conditions (3). The characteristic equations for the fixation equilibria are

$$\lambda^2 - \frac{(t - 2)}{2(t - 1)}\lambda + \frac{t - s}{4(s - 1)(t - 1)} = 0 \quad (6a)$$

at  $p_t, p_m = 0$ , and

$$\lambda^2 - \frac{2 - t}{2}\lambda + \frac{s - t}{4} = 0 \quad (6b)$$

at  $p_t, p_m = 1$ . The conditions for local stability of the fixation equilibria are therefore

$$\begin{aligned} s < 0, t > 0, \text{ and } t < \frac{s}{2s - 1} \\ \text{or } s > 0, t < 0, \text{ and } s < \frac{t}{2t - 1} \\ \text{or } s < 0, t < 0 \end{aligned} \quad (7)$$

at  $p_t, p_m = 0$ , and

$$\begin{aligned} s > 0, t < 0, \text{ and } s > |t| \\ \text{or } s < 0, t > 0, \text{ and } t > |s| \\ \text{or } s > 0, t > 0 \end{aligned} \quad (8)$$

at  $p_t, p_m = 1$ .

Conditions (7) and (8) are satisfied only when the existence conditions (3) for a polymorphism are not met. Thus the fixation equilibria are stable if and only if a polymorphism is not present. As the system is bimonotonic, the two fixation equilibria and the polymorphism are globally stable for the regions of viability parameter space shown in Figure 1.

We show in the appendix that the existence conditions (3) for a stable polymorphism are identical to

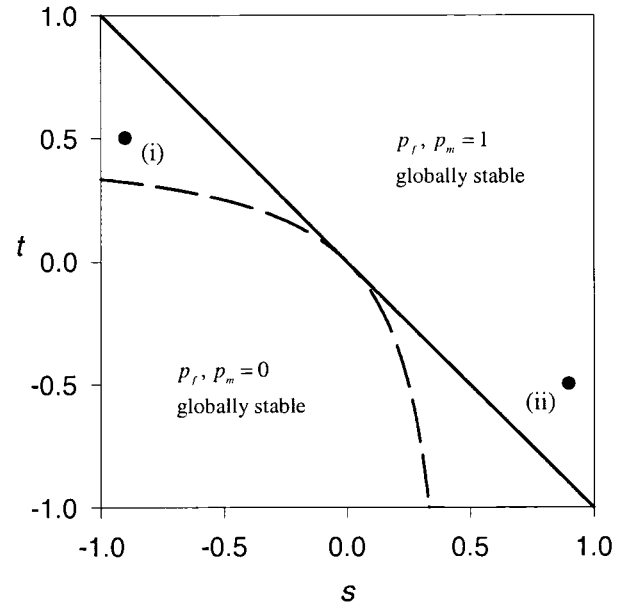


Figure 1.—Diagram of viability space ( $s, t$ ) for models 1 and 2, showing areas of global stability for the two fixation equilibria and a polymorphism. The dashed line is  $s = t/(2t - 1)$ ; the solid line  $s = -t$ . When  $s, t$  values lie in the region between the lines, a single globally stable polymorphism exists and both fixation equilibria are unstable. Points (i)  $s = -0.9, t = 0.5$  and (ii)  $s = 0.9, t = -0.5$  are the viability values used in the equilibrium bifurcation plots (Figures 2–4).

those in a nonimprinting model without heterozygote superiority or inferiority (Bodmer 1965, model 5). We might reasonably anticipate that the same conditions hold at intermediate levels of imprinting. The following model shows this expectation to be correct.

**Model 2—Imprinting with partial penetrance,  $\theta$ :** Model 1 assumes that the maternal allele at an imprinted locus is always completely silenced. It is likely, however, that inactivation is incomplete at the majority of imprinted loci; not all gametes or cell lineages within an individual necessarily contain an imprinted allele. Even the maternal inactivation of the *IGF2* locus in mice and humans is incomplete; full diploid expression is present in the choroid plexus, brain, and the adult human liver (DeChiara *et al.* 1991).

**Construction of model:** To model the situation with incomplete silencing we introduce two further parameters. Because some cells now have two active genes, we need to quantify the degree of dominance of  $A$  over  $a$ . We thus introduce a dominance parameter  $k$ . We assume for mathematical tractability that  $k$  is identical in the two sexes (as in Bodmer 1965). The viability of a nonimprinted heterozygote is therefore  $1 - ks$  and  $1 - kt$  in females and males, respectively. At this stage of the article we also limit  $k$  such that  $0 \leq k \leq 1$ , specifically excluding the possibility of heterozygote superiority or heterozygote inferiority at the imprintable locus (as in Bodmer 1965, Model 5). This assumption is relaxed later.

**TABLE 2**  
Genotype viabilities and frequencies for model 2

Genotype $A_M A_P$	Female viability	Male viability	Frequency before selection
(A)A	1	1	$p_t p_m$
(A)a	$1 - \theta s - (1 - \theta) ks$	$1 - \theta t - (1 - \theta) kt$	$p_t(1 - p_m)$
(a)A	$1 - (1 - \theta) ks$	$1 - (1 - \theta) kt$	$(1 - p_t)p_m$
(a)a	$1 - s$	$1 - t$	$(1 - p_t)(1 - p_m)$

$\theta$  is the penetrance of imprinting.

We quantify the effect of the partial inactivation of the maternal gene using the penetrance parameter  $\theta$  ( $0 \leq \theta \leq 1$ ). When  $\theta = 1$ , all maternal genes at the imprintable locus are effectively silent as in the model above.  $\theta = 0$  corresponds to standard Mendelian expression. If the phenotype is directly related to the proportion of active genes in an individual,  $\theta$  is simply that proportion. The parameter  $\theta$ , however, may be used to describe more complex situations if the ratio of the difference in viabilities of the reciprocal heterozygotes to the difference in viabilities of homozygotes is equal in the sexes. This requirement means that

$$\frac{f_{12} - f_{21}}{f_{11} - f_{22}} = \frac{m_{12} - m_{21}}{m_{11} - m_{22}},$$

where the genotypes  $\{(A)A, (A)a, (a)A, (a)a\}$  have a fitness of  $\{f_{11}, f_{12}, f_{21}, f_{22}\}$  in females and  $\{m_{11}, m_{12}, m_{21}, m_{22}\}$  in males. (Parentheses indicate the imprinted maternal allele.) In effect we are using  $\theta$  as a measure of the weighting of active and inactive alleles used to derive the fitness of a chimeric individual. Genotype viabilities and frequencies are as given in Table 2. An (A)a female, for example, has viability  $(1 - \theta)(1 - ks) + \theta(1 - s) = 1 - \theta s - (1 - \theta)ks$ .

An alternative scenario considers a population in which some proportion,  $\theta$ , of eggs has an inactive gene at the A locus and  $1 - \theta$  has an active gene, as in Table 3. Then the class of Aa females has two possible

**TABLE 3**

Genotype viabilities and frequencies for model 2

Genotype $A_M A_P$	Female viability	Male viability	Frequency before selection
AA	1	1	$(1 - \theta)p_t p_m$
Aa	$1 - ks$	$1 - kt$	$(1 - \theta)p_t(1 - p_m)$
aA	$1 - ks$	$1 - kt$	$(1 - \theta)(1 - p_t)p_m$
aa	$1 - s$	$1 - t$	$(1 - \theta)(1 - p_t)(1 - p_m)$
(A)A	1	1	$\theta p_t p_m$
(A)a	$1 - s$	$1 - t$	$\theta p_t(1 - p_m)$
(a)A	1	1	$\theta(1 - p_t)p_m$
(a)a	$1 - s$	$1 - t$	$\theta(1 - p_t)(1 - p_m)$

$\theta$  is the proportion of eggs containing an inactive allele.

phenotypes, Aa heterozygotes and a hemizygotes, at respective frequencies  $1 - \theta$  and  $\theta$ . The average fitness of an Aa female is then  $(1 - \theta)(1 - ks) + \theta(1 - s) = 1 - \theta s - (1 - \theta)ks$ . For both scenarios the recursion equations are

$$\begin{aligned} \bar{w}_f p_t' &= (1 - \theta) \\ &\times [p_t p_m + \frac{1}{2}(1 - ks)(p_t(1 - p_m) + (1 - p_t)p_m)] \\ &+ \theta [p_t p_m + \frac{1}{2}((1 - p_t)p_m + p_t(1 - p_m)(1 - s))] \end{aligned} \tag{9a}$$

$$\begin{aligned} \bar{w}_m p_m' &= (1 - \theta) \\ &\times [p_t p_m + \frac{1}{2}(1 - kt)(p_t(1 - p_m) + (1 - p_t)p_m)] \\ &+ \theta [p_t p_m + \frac{1}{2}((1 - p_t)p_m + p_t(1 - p_m)(1 - t))] \end{aligned} \tag{9b}$$

where

$$\begin{aligned} \bar{w}_f &= p_t p_m s(2k - 1)(1 - \theta) \\ &+ p_t(s(1 - \theta) - ks(1 - \theta)) \\ &+ p_m(s - ks(1 - \theta)) + 1 - s \end{aligned} \tag{9c}$$

$$\begin{aligned} \bar{w}_m &= p_t p_m t(2k - 1)(1 - \theta) \\ &+ p_t(t(1 - \theta) - kt(1 - \theta)) \\ &+ p_m(t - kt(1 - \theta)) + 1 - t \end{aligned} \tag{9d}$$

give the mean viability in females and males, respectively.

*Existence of internal equilibria:* The model has three potential internal equilibrium solutions: a symmetrical solution, where

$$p_t = p_m = \frac{2k(\theta - 1) - \theta + 2}{4k(\theta - 1) - 2(\theta + 1)} \tag{10a}$$

and two reciprocal solutions,

$$\begin{aligned} p_t &= \frac{s^2(4k(t - 1)(\theta - 1) + \theta - 2) - st(\theta - 2) - C}{4s^2(k(t - 2) + 1)(\theta - 1)} \\ p_m &= \frac{s^2(4kt(\theta - 1) - 4t\theta + \theta + 2) + st(3\theta - 2 - 4k(\theta - 1)) + C}{4st(k(s - 2)(\theta - 1) - \theta(s - 1) - 1)} \end{aligned} \tag{10b}$$

and

$$p_t = \frac{s^2(4k(t-1)(\theta-1) + \theta - 2) - st(\theta - 2) + C}{4s^2(k(t-2) + 1)(\theta - 1)}$$

$$p_m = \frac{s^2(4kt(\theta - 1) - 4\theta + \theta + 2) + st(3\theta - 2 - 4k(\theta - 1)) - C}{4st(k(s-2)(\theta - 1) - \theta(s-1) - 1)} \quad (10c)$$

in which

$$C = |s|[(t(\theta - 2) - s(4k(t-1)(\theta - 1) + \theta - 2))^2 - 8(k(t-2) + 1)(s(2t-1) - \hat{t}) \times (ks(\theta - 1) + 1)(\theta - 1)]^{1/2}.$$

A combined analytical and numerical analysis shows that only solution (10c) can give an internal equilibrium ( $0 < p_m, p_t < 1$ ) when  $0 \leq k \leq 1$ . This result is in agreement with the observation of Bodmer (1965) and Mandel (1971) that without heterozygote superiority there is at most one internal equilibrium in a deterministic single-locus, two-allele system. Such a concurrence is unsurprising; there is no reason to suppose that functional haploidy (in the form of imprinting) permits additional internal equilibria. We designate solution (10c) as  $p_t = \hat{p}_t, p_m = \hat{p}_m$ .

The conditions for a feasible internal equilibrium  $0 < \hat{p}_m, \hat{p}_t < 1$  turn out to be identical to the conditions (3) from model 1. The penetrance of imprinting thus has no effect upon the existence of an internal equilibrium.

**Stability of equilibria:** The Jacobian matrix for the system is

$$\begin{bmatrix} \frac{1 + (p_m - 1)^2(\theta - k(\theta - 1))s^2 + Xs}{2(Zs - 1)^2} & \frac{1 - ks^2(p_t - 1)^2(\theta - 1) + Ys}{2(Zs - 1)^2} \\ \frac{1 + (p_m - 1)^2(\theta - k(\theta - 1))\ell + Xt}{2(Zt - 1)^2} & \frac{1 - k\ell(p_t - 1)^2(\theta - 1) + Yt}{2(Zt - 1)^2} \end{bmatrix} \quad (11)$$

in which

$$X = k(2p_m(p_m - 1) + 1)(\theta - 1) - (p_m - 1)(p_m(\theta - 1) - \theta - 1)$$

$$Y = \hat{p}_t^2(1 - \theta) + k(2p_t(p_t - 1) + 1)(\theta - 1) - 1$$

$$Z = kp_m(1 - \theta) - p_m + p_t(2p_mk - k - p_m + 1)(\theta - 1) + 1.$$

An algebraic and graphical consideration of the maxima and minima of each element in the matrix (11) shows that all are positive for all  $s, t < 1, 0 \leq k \leq 1, 0 < p_t, p_m < 1$ . The system thus meets the conditions of Karl (1972) for bimonotonicity.

The elements of the Jacobian matrix (11) evaluated at the internal equilibrium  $p_t = \hat{p}_t, p_m = \hat{p}_m$  are too complex to handle efficiently, but it can be shown by substituting for the existence conditions [*i.e.*, at  $s = |t|$  and  $s = t/(2t - 1)$ ] and by numerically evaluating the eigenvalues for a range of  $s$  and  $t$  values, that the conditions (3) for the existence of the internal equilibrium also guarantee local stability.

The characteristic equations at the two fixation equilibria are

TABLE 4

Combinations of  $s, t$ , and  $k$  values corresponding to heterozygote superiority (+) and heterozygote inferiority (-)

	$k < 0$		$k > 1$	
	Males	Females	Males	Females
$s > 0, t > 0$	-	-	+	+
$s < 0, t < 0$	+	+	-	-
$s > 0, t < 0$	-	+	+	-
$s < 0, t > 0$	+	-	-	+

$$\lambda^2 - \frac{t(k(\theta - 1) - 1) - s(k(2t - 1)(\theta - 1) - \theta + \theta + 1) + 2\lambda}{2(s - 1)(t - 1)} + \frac{(t - s)\theta}{4(s - 1)(t - 1)} = 0 \quad (12a)$$

at  $p_t = 0, p_m = 0$  and

$$\lambda^2 - \frac{1}{2}(k(s + \hat{t})(\theta - 1) - \theta + 2)\lambda + \frac{1}{2}(s - \hat{t})\theta = 0 \quad (12b)$$

at  $p_t = 1, p_m = 1$ . The conditions for local stability of the fixation equilibria reduce to

$$s((2t - 1)(\theta - 2) + 2k(2t + 1)(\theta - 1)) + t(2k(\theta - 1) - \theta + 2) < 0$$

at  $p_t, p_m = 0$ , which gives the stability conditions (7) for  $p_t, p_m = 0$  in model 1, and

$$(s + \hat{t})(2k(\theta - 1) - \theta) < 0$$

at  $p_t, p_m = 1$ , which gives the stability conditions (8) for  $p_t, p_m = 1$  in model 1.

The fixation equilibria are therefore stable only for values of  $s$  and  $t$  where a locally stable polymorphism does not exist (as in model 1). As the system is bimonotonic the three equilibria are globally stable for the  $s, t$  values shown in Figure 1. Thus, the penetrance of imprinting (from  $\theta = 0$  to  $\theta = 1$ ) does not affect either the conditions for a stable polymorphism or the stability of fixation equilibria when  $0 \leq k \leq 1$ .

**Heterozygote superiority and inferiority at the imprinted locus:** We now consider the possibility of heterozygote superiority or inferiority (*i.e.*,  $k < 0, k > 1$ ) at the A locus in the nonimprinted portions of the population. It is worth noting first that whether  $k < 0$  or  $k > 1$  correspond to heterozygote superiority or inferiority in a particular sex depends on the signs of  $s$  and  $t$  (Table 4). Although this complicates matters somewhat, and excludes some parameter values from consideration (as  $k$  is equal in the two sexes), our formulation has the advantage of allowing us to vary a single parameter of dominance. The properties of Mendelian (nonimprinting) schemes with differential viability in the sexes and heterozygote superiority or inferiority have been exam-

ined in detail elsewhere (Bodmer 1965; Mandel 1971, following Owen 1953). It is not our intention to provide a comprehensive equivalent analysis of imprinting systems. Rather we aim here to illustrate one of the properties of imprinting systems: that imprinting essentially acts to moderate dominance relations at the imprinted locus.

*Imprinting as a moderator of dominance:* We concentrate on two representative points in the parameter space, (i)  $s = -0.9$ ,  $t = 0.5$  and (ii)  $s = 0.9$ ,  $t = -0.5$ , as shown in Figure 1. Point (i) lies in the region for  $s$ ,  $t$  where only a single stable polymorphism can exist when  $0 \leq k \leq 1$ . Point (ii) is of interest because for some values of  $k$ , there are three internal equilibria, a possibility first demonstrated mathematically by Owen (1953).

The equilibrium bifurcation plots (Figures 2–4) show the local stability and male allele frequency ( $p_m$ ) at the equilibria (10a–c) and the fixation equilibria for combinations of  $s$ ,  $t$ ,  $\theta$ , and  $k$ . Locally stable equilibria are shown by solid lines and unstable equilibria by dashed lines. The plots show equilibrium properties for specific parameter values and not gene frequency changes. Thus, when we describe these plots in terms of the “merging” of equilibria, or of equilibria “becoming” unfeasible, we are describing the pattern that equilibria produce, not any genetic process of change. We describe the plots as if “reading” them from left to right. The inclusion of allele “frequencies” outside (0, 1) in the bifurcation plots shows that feasible equilibria do not appear from “nowhere” (see Lewontin and Feldman 1988). Many equilibria have origins at biologically meaningless allele frequencies and become feasible only for certain parameter values. Equilibria with allele frequencies outside the range (0, 1) can also be locally stable in mathematical terms.

Let us first look at the case where  $\theta = 0$  (no imprinting). Figures 2a and 3a show the allele frequency and stability at equilibrium for, respectively, viability values (i) and (ii).

In Figure 2a it can be seen that a locally stable polymorphism exists for all  $k$ . When  $k < 0$  another, unstable, internal equilibrium exists and the fixation equilibrium at  $p_r$ ,  $p_m = 1$  is locally stable. When  $k \in (0, 1)$  only a single stable internal equilibrium exists. When  $k > 1$ , the fixation equilibrium at  $p_r$ ,  $p_m = 0$  is also locally stable.

In Figure 3a, when  $k \in (-2, \sim -1.24)$  there are two locally stable polymorphic equilibria with an unstable equilibrium at a frequency between, as shown by Owen (1953). Both fixation equilibria are unstable. At  $k \cong -1.24$ , the three internal equilibria merge to leave just one stable polymorphism. Thus, for  $k \in (\sim -1.24, 0)$  only a single stable polymorphism is feasible, with both fixation equilibria remaining unstable. At  $k = 0$ , the polymorphic equilibrium becomes unfeasible ( $p_m > 1$ ), and for  $k \in (0, 1.1)$ , the only stable equilibrium is  $p_r$ ,  $p_m = 1$ .

Note that in some instances one equilibrium seems

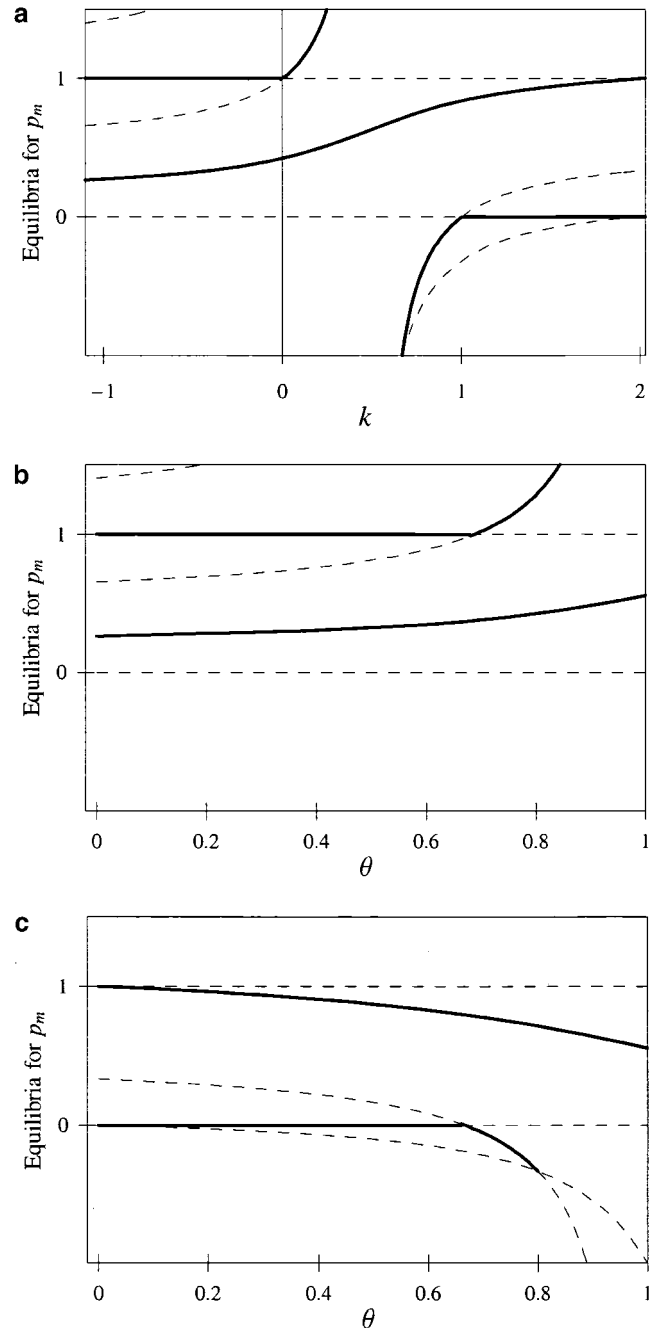


Figure 2.—Allele frequency and local stability for equilibria in model 2 for viability values (i)  $s = -0.9$ ,  $t = 0.5$ . (a) As a function of  $k$  with no imprinting ( $\theta = 0$ ). (b) As a function of  $\theta$  with  $k = -1.11$ . (c) As a function of  $\theta$  with  $k = 2$ . Solid lines, locally stable equilibrium; dashed lines, unstable equilibrium.

to exchange stability with another. As an example, in Figure 2a at  $k = 0$  the fixation equilibrium at  $p_r$ ,  $p_m = 1$  becomes unstable and transfers its stability to an equilibrium outside the feasible range (0, 1).

We now incorporate imprinting into our consideration. Figure 2b shows the equilibria for viability parameter values (i) when  $k = -1.11$  (for which  $1 - ks = 0$ ) as  $\theta$  varies from 0 to 1. Note the similarity in pattern

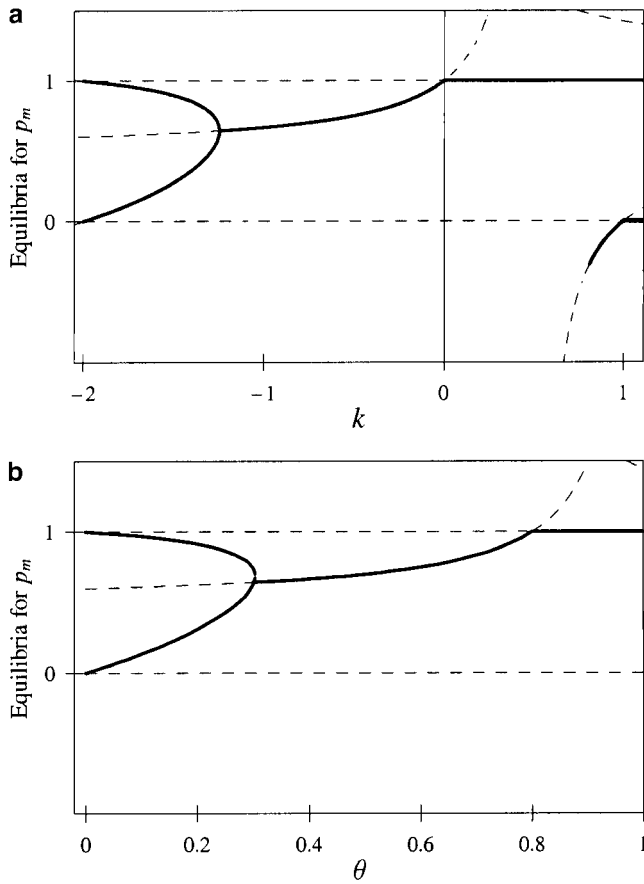


Figure 3.—Allele frequency and stability for equilibria in model 2 for viability values (ii)  $s = 0.9$ ,  $t = -0.5$ . (a) As a function of  $k$  with no imprinting ( $\theta = 0$ ). (b) As a function of  $\theta$  with  $k = -2$ . Solid lines, locally stable equilibrium; dashed lines, unstable equilibrium.

with Figure 2a as  $k$  ranges from  $-1.11$  to  $\sim 0.33$  there. As the penetrance of imprinting increases from 0 to 1, the gene frequency and stability at equilibrium behave as if  $k$  were increasing in the nonimprinted model (Figure 2a). Figure 2c shows the situation when  $k = 2$  and  $\theta$  increases from 0 to 1. Here imprinting acts to effectively decrease  $k$  (from 2 to  $\sim 0.33$  in Figure 2a). Similar observations are apparent for viability values (ii) and  $k = -2$  in Figure 3b, where the pattern as  $\theta$  increases from 0 to 1 closely mirrors that in Figure 3a as  $k$  increases from  $-2$  to  $\sim 0.9$ . The similarities in these bifurcation patterns occur because an increase in the penetrance of imprinting acts to moderate the value of the dominance parameter by reducing the number of functional heterozygotes in the population.

When  $\theta = 1$  (complete inactivation) there are no functional heterozygotes and the parameter  $k$  is eliminated from consideration. Therefore, the allele frequency at the internal equilibrium for  $\theta = 1$  must be the same in both Figures 2b and 2c. This fact is suggestive of another property of the model. Does the situation at  $\theta = 1$  correspond to a particular value for  $k$  in the partial penetrance model? At such a value for  $k$ , changes in

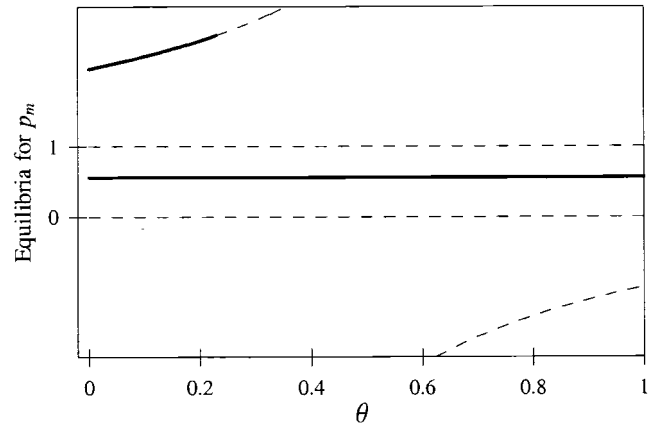


Figure 4.—Allele frequency and stability for equilibria in model 2 as a function of  $\theta$  with  $k = 10/29$  and viability values (i)  $s = -0.9$ ,  $t = 0.5$ . The allele frequency and local stability at all feasible equilibria are independent of  $\theta$ .

the penetrance of imprinting would not alter the allele frequency at equilibrium or the local stability of the equilibrium, because the moderation of dominance through imprinting has nothing to moderate. Equating the full imprinting recursions (1) with the incomplete penetrance recursions (9) gives no single solution for  $k$  in terms of  $\theta$ ,  $s$ , and  $t$ , thus confirming the finding of Pearce and Spencer (1992) that an imprinting model with differential viability in the sexes is not formally equivalent to a nonimprinting two-sex scheme. However, if we equate the expression for the feasible internal equilibrium in model 1 with that in model 2 when  $0 \leq k \leq 1$ , *i.e.*, equate (2) with (10c), we obtain a single solution that is independent of  $\theta$ , and, more surprisingly, also independent of  $t$

$$k = \frac{1}{2 - s}. \tag{13}$$

This value for  $k$  always lies in the range  $0 \leq k \leq 1$  (as  $s, t \leq 1$ ). This ensures that only one internal equilibrium can be present. Changes in  $\theta$  for this value of  $k$  can also never affect the stability of fixation equilibria, because, as shown earlier, the conditions for stability of all equilibria are independent of  $\theta$  when  $0 \leq k \leq 1$ .

As a confirmation that this special value for  $k$  is also independent of  $t$ , if the exercise is repeated for a model of paternal imprinting (with  $s$  again as the selection coefficient in females and  $t$  the coefficient in males), it can be shown that  $k = 1/(2 - t)$  creates the same relation. Full imprinting is therefore equivalent, with respect to all equilibria with allele frequencies in the range (0, 1) inclusive, to a nonimprinting or variable penetrance system with

$$k = \frac{1}{2 - (\text{selection coefficient in imprinting sex})}. \tag{14}$$

Figure 4 shows this equivalence graphically for viability values (i). For  $k = 1/(2 - s)$  [in this instance,  $k = 1/(2 - (-0.9)) = 10/29$ ], a change in the penetrance of imprinting affects neither the allele frequency nor stability at equilibrium, although the allele frequencies for unfeasible equilibria and dynamics are different.

#### DISCUSSION

A model of a one-locus, two-allele imprinting system with differential viability in the sexes does not formally reduce to the otherwise similar Mendelian schemes of Owen (1953) or Bodmer (1965), as shown by Pearce and Spencer (1992). However, we show here that while allele frequency dynamics and allele frequency at equilibrium are different in an imprinting system, other important features of the system are conserved.

The chief finding described here, and the main illustration of a sustained link between our two-sex imprinting model and previous Mendelian schemes, is the inconsequence of the penetrance of imprinting,  $\theta$ , to the existence conditions for a globally stable polymorphism when heterozygote superiority and heterozygote inferiority are not present at the imprintable locus. As shown in the appendix, the conditions are identical to those in Bodmer's (1965) nonimprinting scheme with differential viability in the sexes, Bodmer's model being the case with  $\theta = 0$ .

The existence conditions for a polymorphism are also the same as in Cooper's (1976) model of the X-inactivation system in marsupials, where the paternally derived X chromosome is inactivated in all somatic cells (Graves 1996). (X-inactivation in placental mammals is random with respect to parental origin in all embryonic cell lineages.) A model of the system in marsupials is mathematically equivalent to a model of the paternal inactivation of an X-linked locus (R. J. E. Anderson and H. G. Spencer, unpublished results). Cooper (1976) did not note the equivalence of the conditions he derived to those of Bodmer (1965), and the commonality of the motif was also missed by Pearce and Spencer (1992). Interestingly, when Cooper's (1976) model is modified to include an incomplete penetrance for X-inactivation, the polymorphism conditions are different (R. J. E. Anderson and H. G. Spencer, unpublished results). Complete functional haploidy is thus the essential factor in giving Cooper's X-linked model the polymorphism conditions identical to those in the models of autosomal genes here and in Bodmer (1965).

As Cooper (1976) pointed out, the probability of a stable polymorphism occurring in practice is minimal for realistically small values of  $s$  and  $t$ . For a value for  $s$  of, say,  $+0.001$ , we see from the conditions (3) that for a polymorphism to exist,  $t$  must lie in the range  $-0.00102 < t < -0.001$ . Thus, even when selection acts in opposite directions in the sexes, an unlikely align-

ment in the magnitude of selection coefficients is still required for a stable polymorphism to exist.

Sapienza (1989) originally pointed out an analogy between imprinting and dominance modification, and Spencer and Williams (1997) exploited structural similarities in models of these phenomena to investigate the invasion of imprinting modifiers into a nonimprinting population. Pearce and Spencer (1992) showed that the majority of imprinting models reduce to Mendelian schemes with modified dominance relations at the imprintable locus. The similarities in the equilibrium bifurcation diagrams (Figures 2 and 3) show that a relationship between imprinting and dominance is still apparent even in the absence of formal equivalence between imprinting and Mendelian models with differential viability in the sexes. This relationship is further emphasized by the fact that when

$$k = \frac{1}{2 - s}$$

(where  $k$  is the dominance parameter for the imprintable locus in both sexes) feasible equilibrium allele frequencies and the stability of feasible equilibria are independent of the penetrance of imprinting ( $\theta$ ) and the selection coefficient in males ( $t$ ). Imprinting effectively moderates dominance relations at a locus by reducing the number of functional heterozygotes in the population.

Sapienza (1989) went on to propose that genes modifying dominance may also inactivate imprinted genes as a side effect. However, as Haig and Trivers (1995) point out, this idea implicitly assumes that mutation in imprinted or modifier genes has been incapable of uncoupling an unwanted inactivation process. This assumption is impossible to substantiate empirically, and no good reason has been presented for accepting its validity.

The models described here naturally have limitations, being idealized in several respects. In addition to the usual assumptions of infinite population, no mutation, no drift, and so on, we make potentially unrealistic assumptions about the nature of dominance and imprinting. We assume in model 2, for instance, that dominance relations are the same in both sexes. Whether this assumption is fair depends on the underlying causes of dominance in real organisms. Dominance may simply be a characteristic of the interactions of genes themselves, an argument first championed by Wright (see, for example, Wright 1934) and reformulated in terms of metabolic pathways by Kacser and Burns (1981). If this is the case, dominance relations are likely to be similar in the sexes—an allele dominant in females through some intrinsic biochemical property it possesses is likely to also be dominant in males. If, however, dominance is mediated by genes at other loci (as proposed by Fisher 1928) then we might reasonably expect



modifier genes (especially sex-linked genes) that increase the viability of heterozygotes in one sex to arise. Note that these genes could be modifiers of imprinting. The evolution of both dominance and imprinting in circumstances with different viability in the sexes is, as far as we are aware, an unexplored area.

The construction of model 2 also depends on an assumption regarding the viability parameters, namely, that the ratio of the difference in viability between reciprocal heterozygotes to the difference in viability of homozygotes is equal in the sexes. This assumption is met if  $\theta$  is considered to be the proportion of inactive genes in each organism and if fitness is linearly related to this proportion, as in Table 2, or if  $\theta$  is the proportion of eggs containing an imprinted locus, as in Table 3.

Much of the research on the evolutionary origins of imprinting has focused on the potential battle between parents over resource allocation to the fetus in the "genetic conflict" hypothesis (as in Haig 1992). We might reasonably expect that genes governing fetal growth (such as the imprinted loci *IGF2* and *IGF2R*) are also particularly prone to viability differences in the sexes if males and females have a different "optimal" size at birth. This expectation is especially relevant in species with polygamous (particularly polygynous) mating systems, where sexual dimorphism in body size is the norm (Andersson 1994). Polygamy is naturally allied with the evolution of imprinting in the genetic conflict hypothesis (Mochizuki *et al.* 1996; Haig 1997), although a recent population genetic model fails to support a necessary relationship between the two (Spencer *et al.* 1998).

A further indication of a role for differential viability in the sexes at imprinted loci comes from the work of Skuse *et al.* (1997), who describe a putative imprinted gene for "social cognition" on the human X chromosome. The imprinting of this gene is probably an evolutionary consequence of selection for sex differences in social behavior. It has been suggested that the selective influence of sex differentiation and dosage compensation on sex-linked loci may predispose them to the evolution of imprinting (Iwasa 1998). We suggest, nevertheless, that viability differences in the sexes may also contribute to the evolution of imprinting for some autosomal genes. There has been a recent tendency in the literature toward a more pluralist approach in evolutionary hypotheses for imprinting, with a recognition that no single adaptive framework may effectively explain the occurrence of imprinting for all affected genes (Hurst and McVean 1997; Iwasa 1998). The influence of the Haigian genetic conflict in the evolution of imprinting at some loci may be supplemented or surpassed by other forms of conflict; both parent-offspring conflict (as in Spencer *et al.* 1998) and viability differences in the sexes (a form of intrapopulation conflict) may also contribute. We are currently working on evolutionary two-locus modifier models with differential viability in

the sexes, but the results are beyond the scope of this article.

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APPENDIX: BOUNDARY CONDITIONS  
IN Bodmer (1965)

Model 5 in Bodmer (1965), where there is no heterosis or heterozygote inferiority, has the same polymorphism conditions as model 1 and model 2. We demonstrate the equivalence of the conditions here.

After normalizing by the viability of AA, the relative viabilities in Bodmer (1965) are

	AA	Aa	aa
Males	1	$\frac{1}{1 - \mu_1}$	$\frac{1 - f\mu_1}{1 - \mu_1}$
Females	1	$\frac{1}{1 - \mu_2}$	$\frac{1 - f\mu_2}{1 - \mu_2}$

where to avoid confusion we have used  $f$  (with  $f < 0$ ) to denote Bodmer's parameter  $k$ . Equating this with our nomenclature (as in the nonimprinted portion of the population in model 2) gives

$$f = \frac{k - 1}{k}, \quad \mu_1 = \frac{kt}{kt - 1}, \quad \mu_2 = \frac{ks}{ks - 1}. \quad (A1)$$

For model 5 in Bodmer (1965), when  $\mu_1 > 0$ ,  $f < 0$ , a stable polymorphism is present when the following conditions are met:

$$|\mu_2| > \frac{\mu_1}{1 + 2\mu_1|f|} \quad \text{and} \quad |\mu_2| < \frac{\mu_1}{1 - 2\mu_1}. \quad (A2)$$

When  $\mu_1 > 0$ ,  $s > 0$ , so substituting for the solutions in A2 gives (with  $t < 0$ ,  $0 \leq k \leq 1$ )

$$\frac{ks}{1 - ks} > \frac{kt}{(2 - k)t - 1} \quad \text{and} \quad \frac{ks}{1 - ks} < \frac{kt}{1 - kt}, \quad (A3)$$

which, on simplification is

$$|t| > s > \frac{t}{2t - 1} > 0, \quad (A4)$$

which are the existence conditions for a polymorphism (3a).