Population Genetic Models of Genomic Imprinting

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ABSTRACT

The phenomenon of genomic imprinting has recently excited much interest among experimental biologists. The population genetic consequences of imprinting, however, have remained largely unexplored. Several population genetic models are presented and the following conclusions drawn: (i) systems with genomic imprinting need not behave similarly to otherwise identical systems without imprinting; (ii) nevertheless, many of the models investigated can be shown to be formally equivalent to models without imprinting; (iii) consequently, imprinting often cannot be discovered by following allele frequency changes or examining equilibrium values; (iv) the formal equivalences fail to preserve some well known properties. For example, for populations incorporating genomic imprinting, parameter values exist that cause these populations to behave like populations without imprinting, but with heterozygote advantage, even though no such advantage is present in these imprinting populations. We call this last phenomenon "pseudoheterosis." The imprinting systems that fail to be formally equivalent to nonimprinting systems are those in which males and females are not equivalent, *i.e.*, two-sex viability systems and sex-chromosome inactivation.

MANY observations have been made of the complementary roles of maternally and paternally derived alleles in the life and development of organisms. As early as the 1920s, while working with the dipteran Sciara, METZ (1938) discovered that during development a chromosome from the paternal parent may function quite differently from its maternal homolog in contrast to the usual Mendelian equivalent action. In 1971 SHARMAN concluded from his experiments with kangaroos that the mode of dosage compensation of the *X*-linked genes seemed to be paternal *X* inactivation, in contrast to the random *X*-inactivation seen in eutherian mammals (SHARMAN 1971). By the mid-1980s genomic imprinting became the subject of many more experiments and scientific interest. Experiments conducted with mice in which transgenes had been inserted revealed that the expression of the transgene depended on the sex of the parent from which it was inherited (HADCHOUEL *et al.* 1987; REIK *et al.* 1987; SAPIENZA *et al.* 1987; SWAIN, STEWART and LEDER 1987). Paternally derived alleles were expressed in appropriate tissues, whereas maternally derived alleles were not. Nevertheless, males who inherited the transgene from their mothers (and who thus did not express it), passed on the transgene into offspring in which it was expressed. The pattern of inactivation of the transgene was thus readjusted at each generation. The inactivation of the maternally derived transgenes appeared to correspond to its level of methylation (HADCHOUEL *et al.* 1987; REIK *et al.* 1987; SAPIENZA *et al.* 1987; SWAIN, STEWART and LEDER 1987) (reviews in MONK 1987; MARX 1988; SOLTER 1988; HALL 1990). The maternally inherited transgene was inactivated by the attachment of an increased number of methyl groups. Paternally derived transgenes, in contrast, were found to have a low level of methylation. The state of methylation thus depends on the sex of the parent from which the gene came and most importantly this state is reconstituted in each generation, depending on the sex of the individual passing on the allele. More recently, genomic imprinting has been used to describe the differential expression of genetic material where both alleles are expressed, but at different times, in different tissues, or at different levels, depending on their parental origin [see SOLTER (1988) and HALL (1990) for reviews]. Again there is evidence that the imprinting occurs by methylation at the molecular level (MARX 1988; SOLTER 1988; HALL 1990).

Genomic imprinting thus conflicts with normal Mendelian genetics in that although all alleles are passed on to the next generation, their parental origin affects their expression. Thus in contrast to other violations of the tenets of Mendelian genetics such as meiotic drive, it is the expression not the inheritance that is altered. Below we investigate some of the consequences of these deviations in some standard population genetic models. In particular, we examine the effects of the inactivation of an allele (or chromosome) on the dynamics of allele frequencies in various standard models. Last, we study models of differential gene expression in which the phenotype of the individual depends on the quantity of expression of alleles of maternal and paternal origin. This

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TABLE 1

Viability parameters used in the models

Model	Phenotype				
	A_1A_1	A_1-	A_1A_2	A_2A_2	A_2-
0	w_{11}^*		w_{12}^*	w_{22}^*	
1		w_1			w_2
2, 4	w_{11}	w_{11}	w_{12}	w_{22}	w_{22}
3, 5	w_{11}	w_{10}	w_{12}	w_{22}	w_{20}
6		w_{1m}, w_{1f}			w_{2m}, w_{2f}
8	w_{11}		w_{12}, w_{21}	w_{22}	

form of genomic imprinting is more complicated, but in its simplest forms is identical to the inactivation we model below.

MODELS

Model 0. Standard Mendelian inheritance: In order to facilitate comparisons between our models and to introduce our terminology, we first review the standard one-locus two-allele viability selection model [see, *e.g.*, CROW and KIMURA (1970) or HARTL (1980)]. We label the two alleles A_1 and A_2 and suppose they are at frequencies p and q, respectively (and so $p + q = 1$). Unless there are viability differences between males and females (as in model 2, below), p (and q) will be the same in both sexes after one generation, regardless of any initial differences. Let the three genotypes A_1A_1, A_1A_2 and A_2A_2 have viabilities w_{11}^*, w_{12}^* and w_{22}^*, respectively. (Table 1 shows the viabilities of the various genotypes in the models we construct.) The frequency of A_1 in the next generation is then given by

$$p' = (p^2w_{11}^* + pqw_{12}^*)/\bar{w}, \tag{1}$$

where $\bar{w}$ is the population mean fitness given by

$$\bar{w} = p^2w_{11}^* + 2pqw_{12}^* + q^2w_{22}^*. \tag{2}$$

Such a dynamic affords up to three equilibria where $\Delta p = p' - p = 0$. The equilibrium $p = 1$ always exists, is locally stable if $w_{11}^* > w_{12}^*$ and is globally stable if $w_{12}^* > w_{22}^*$ as well. Similarly the $p = 0$ equilibrium always exists, is locally stable if $w_{22}^* > w_{12}^*$ and is globally stable if $w_{12}^* > w_{11}^*$ as well. An internal equilibrium

$$\hat{p} = \frac{w_{12}^* - w_{22}^*}{2w_{12}^* - w_{11}^* - w_{22}^*} \tag{3}$$

also exists when either $w_{12}^* > w_{11}^*$ and w_{22}^* (in which case it is globally stable) or $w_{12}^* < w_{11}^*$ and w_{22}^* (when it is unstable). By globally stable we mean the system iterates to the equilibrium for all initial $p \in (0,1)$ and by locally stable, for all p sufficiently close to the equilibrium value. When $w_{12}^* > w_{11}^*$ and w_{22}^*, we say there is heterozygote advantage or heterosis and the system maintains both alleles in the population.

Model 1. Complete autosomal inactivation: We now introduce autosomal inactivation into model 0 by supposing that the maternally derived alleles are not expressed in an individual at all. The fitness of an individual receiving an A_1 allele from its father (an A_1- individual) is w_1 and the fitness of an individual receiving an A_2 allele from its father (an A_2- individual) is w_2. With random mating, the (preselection) zygotes in the next generation have the following phenotypic frequencies:

$$\begin{aligned}[A_1-] &= p^2 + pq = p \\ [A_2-] &= q^2 + pq = q.\end{aligned} \tag{4}$$

We may assume that p is the same for both males and females because an individual's sex does not affect its own viability but that of its offspring (of both sexes).

Following selection, the genotypic frequencies are

$$\begin{aligned}[A_1A_1] &= p^2w_1/\bar{w} \\ [A_1A_2] &= (pqw_1 + qpw_2)/\bar{w} \\ [A_2A_2] &= q^2w_2/\bar{w},\end{aligned} \tag{5}$$

where

$$\bar{w} = pw_1 + qw_2.$$

Thus

$$p' = \frac{p^2w_1 + \frac{1}{2}pq(w_1 + w_2)}{p^2w_1 + pq(w_1 + w_2) + q^2w_2}, \tag{6}$$

which is the same formula as for a nonimprinting system where the fitnesses of A_1A_1, A_1A_2 and A_2A_2 are respectively $w_{11}^* = w_1$, $w_{12}^* = (w_1 + w_2)/2$ and $w_{22}^* = w_2$. (We use w^*'s to denote viabilities of nonimprinting systems, throughout.) By applying the well-known results of model 0, we find that the only solutions to the equilibrium equation $p' = p$ are trivially $p = 0$ and $p = 1$. The internal equilibrium, $\hat{p}$, does not exist in this case. The stability of the $p = 0$ equilibrium may also be derived from model 0. The conditions for global stability, $w_{22}^* > w_{12}^* > w_{11}^*$ give $w_2 > w_1$. Similarly, the $p = 1$ equilibrium is globally stable if and only if $w_1 > w_2$.

The behavior of this model can also be deduced from the observation that, since viabilities depend solely on the paternal gamete, selection can be viewed as acting on the gametes, and so the model is formally equivalent to a haploid one of gametic selection. As is well known, deterministic constant viability haploid models cannot maintain polymorphism without mutation or structured populations, and so the system will iterate to fix the fitter of the two gametes: A_1 if $w_1 > w_2$, A_2 if $w_2 > w_1$.

One way this model can be generalized is to remove the restriction that only the maternal alleles are inactivated. We therefore introduce a parameter, α, the probability that the paternal allele is inactivated, requiring, therefore, that the maternal allele is im-

printed with probability 1-α. Thus $\alpha = 0$ in model 1.

As before, we can assume that the allele frequencies are equal in both sexes. Eight different zygotic phenotypes are possible and their frequencies are

$[A_1^-] = p^2(1 - \alpha)$

where the unexpressed allele is a maternal A_1

$[-A_1] = p^2\alpha$

where the unexpressed allele is a paternal A_1

$[A_1^-] = pq(1 - \alpha)$

where the unexpressed allele is a maternal A_2

$[-A_2] = pq\alpha$

where the unexpressed allele is a paternal A_1

$[A_2^-] = qp(1 - \alpha)$

where the unexpressed allele is a maternal A_1

$[-A_1] = qp\alpha$

where the unexpressed allele is a paternal A_2

$[A_2^-] = q^2(1 - \alpha)$

where the unexpressed allele is a maternal A_2 and

$[-A_2] = q^2\alpha$

where the unexpressed allele is a paternal A_2.

After viability selection we obtain

$$p' = [p^2((1-\alpha)w_1 + \alpha w_1) + \tfrac{1}{2}pq((1-\alpha)w_1 + \alpha w_2) + \tfrac{1}{2}qp((1-\alpha)w_2 + \alpha w_1)]/\bar{w} = \frac{p^2w_1 + \frac{1}{2}pq(w_1 + w_2)}{p^2w_1 + pq(w_1 + w_2) + q^2w_2}, \quad (6)$$

which is the same equation as before. In other words, provided one allele is always imprinted, the dynamics of the system are unaffected by which sex's alleles are imprinted.

Model 2. Partial autosomal inactivation: Let us now consider the case where inactivation occurs in only some individuals. That is, we introduce viability selection into CHAKRABORTY's (1989) model. CHAKRABORTY assumed a Hardy-Weinberg population (with no selection), but with a constant parameter, θ, equal to the probability that the maternally derived allele is unexpressed ($0 \leq \theta \leq 1$). The same θ value applied to both A_1 and A_2 alleles, and the paternally derived alleles were assumed to always be expressed (although these assumptions were shown to be easily modified). Model 1 thus has an implicit θ value of 1; model 0 one of 0. There are several possible interpretations of θ. For example, θ may be envisaged as the proportion of females in the population who pass on imprinted alleles (*e.g.*, if inactivation were temperature sensitive), the rest having standard inheritance patterns; it can be regarded as the proportion of imprinted eggs that (all) females pass on (*e.g.*, if the phenomenon were dependent on the age of the female); or it may be some combination of these two possibilities. Nevertheless, we are not yet aware of any reports which have demonstrated such intermediate values of θ in living organisms. For a particular allele we consider θ to be fixed (but see model 4, below).

If both alleles are expressed then in the next generation, the zygotes have the following phenotypic frequencies (CHAKRABORTY 1989):

$$[A_1A_1] = p^2(1 - \theta)$$
$$[A_1A_2] = 2pq(1 - \theta) \quad (7)$$
$$[A_2A_2] = q^2(1 - \theta).$$

If the maternally inherited allele is unexpressed then in the next generation, the zygotes have the following phenotypic frequencies (CHAKRABORTY 1989):

$$[A_1^-] = p^2\theta \text{ where the unexpressed allele is } A_1$$
$$[A_1^-] = pq\theta \text{ where the unexpressed allele is } A_2 \quad (8)$$
$$[A_2^-] = pq\theta \text{ where the unexpressed allele is } A_1$$
$$[A_2^-] = q^2\theta \text{ where the unexpressed allele is } A_2.$$

If we let w_{11} be the viability of an A_1A_1 or A_1^- individual, w_{12} that of an A_1A_2 individual and w_{22} that of an A_2A_2 or A_2^- individual, we obtain the postselection frequencies

$$[A_1A_1] = p^2w_{11}/\bar{w}$$
$$[A_1A_2] = [2pqw_{12} + \theta pq(w_{11} + w_{22} - 2w_{12})]/\bar{w} \quad (9)$$
$$[A_2A_2] = q^2w_{22}/\bar{w},$$

where the standardized mean fitness is

$$\bar{w} = p^2w_{11} + 2pqw_{12} + q^2w_{22} + \theta pq(w_{11} + w_{22} - 2w_{12}). \quad (10)$$

Therefore

$$p' = \frac{p^2w_{11} + pq[w_{12} + \frac{1}{2}\theta(w_{11} + w_{22} - 2w_{12})]}{p^2w_{11} + 2pq[w_{12} + \frac{1}{2}\theta(w_{11} + w_{22} - 2w_{12})] + q^2w_{22}}. \quad (11)$$

This shows the same formula as for a non-imprinting system in which $w_{11}^* = w_{11}$, $w_{22}^* = w_{22}$ and $w_{12}^* = w_{12} + \frac{1}{2}\theta(w_{11} + w_{22} - 2w_{12})$.

If the fitness of a heterozygote in which both alleles are expressed is less than the average homozygote fitness (in the imprinting system), then in the equivalent nonimprinting system the heterozygote fitness will be greater by the amount of $\frac{1}{2}\theta(w_{11} + w_{22} - 2w_{12})$. There is a limit to this increase, however: if w_{12} is less than w_{11} or w_{22}, then w_{12}^* can not be simultaneously larger than w_{11}^* and w_{22}^*. So if heterozygote advantage is not present in the imprinting system then it will not be exhibited in the equivalent nonimprinting system.

To see this, suppose that $w_{11} > w_{12}$ and, without loss of generality, that $w_{11} \geq w_{22}$. Then

$$\begin{aligned} w_{12}^* &= w_{12}(1-\theta) + \tfrac{1}{2}\theta(w_{11} + w_{22}) \\ &\leq w_{12}(1-\theta) + \theta w_{11} \\ &< w_{11}(1-\theta) + \theta w_{11} \\ &= w_{11} \\ &= w_{11}^*, \end{aligned} \tag{12}$$

i.e.,

$$w_{12}^* < w_{11}^*.$$

If heterozygote advantage exists in the imprinting system, however, it can be absent in the equivalent nonimprinting system. That is, if $w_{12} > w_{11}$ and w_{22} then $w_{12} > (w_{11} + w_{22})/2$ and $w_{12}^* < w_{12}$, and with certain parameter values we have $w_{12}^* < w_{11}^*$ or w_{22}^* so that the equivalent nonimprinting system exhibits no heterozygote advantage. Consequently no stable polymorphic equilibrium will be present in either system. An example is: $\theta = 0.9$, $w_{11} = 0.95$, $w_{12} = 1.0$ and $w_{22} = 0.85$, giving $w_{11}^* = 0.95$, $w_{22}^* = 0.85$, and $w_{12}^* = 0.91 < w_{11}^*$.

The only solutions to $p' = p$ are (from model 0), $p = 0$, $p = 1$ and (if it exists)

$$\hat{p} = \frac{(1-\theta)w_{12} + \tfrac{1}{2}\theta(w_{11} + w_{22}) - w_{22}}{(1-\theta)(2w_{12} - w_{11} - w_{22})}. \tag{13}$$

In order that $0 < \hat{p} < 1$ we require $\theta \neq 1$ and either (a) $w_{12}^* > w_{11}^*$ and w_{22}^*, which gives

$$w_{12} > \frac{(2-\theta)w_{11} - \theta w_{22}}{2(1-\theta)}$$

and

$$w_{12} > \frac{(2-\theta)w_{22} - \theta w_{11}}{2(1-\theta)}, \tag{14}$$

or (b) $w_{12}^* < w_{11}^*$ and w_{22}^*, which reverses these last two inequalities. In the first case $\hat{p}$ is stable, in the second unstable.

To see the effect of the level of imprinting on the internal equilibrium, we examine $\partial\hat{p}/\partial\theta$, which (when $\hat{p}$ is stable) has the same sign as $w_{11} - w_{22}$. Thus increasing the level of imprinting increases the equilibrium frequency of the allele of the fitter homozygote.

Model 3: Generalized autosomal inactivation: We now generalize model 2 so that the fitnesses of individuals with an unexpressed allele are not necessarily equal to the fitnesses of the homozygotes for the expressed allele. As before, let w_{11}, w_{12} and w_{22} be the viabilities of A_1A_1, A_1A_2 and A_2A_2 individuals respectively, but suppose imprinted individuals A_1^- and A_2^- have respective viabilities w_{10} and w_{20}. Proceeding as before, we obtain

$$p' = \frac{\begin{array}{c} p^2[(1-\theta)w_{11} + \theta w_{10}] \\ + pq[(1-\theta)w_{12} + \tfrac{1}{2}\theta(w_{10} + w_{20})] \end{array}}{\begin{array}{c} p^2[(1-\theta)w_{11} + \theta w_{10}] + 2pq[(1-\theta)w_{12} \\ + \tfrac{1}{2}\theta(w_{10} + w_{20})] + q^2[(1-\theta)w_{22} + \theta w_{20}] \end{array}} \tag{15}$$

This equation for p' shows equivalence to a nonimprinting system where

$$\begin{aligned} w_{11}^* &= (1-\theta)w_{11} + \theta w_{10} \\ w_{12}^* &= (1-\theta)w_{12} + \tfrac{1}{2}\theta(w_{10} + w_{20}) \\ w_{22}^* &= (1-\theta)w_{22} + \theta w_{20}. \end{aligned} \tag{16}$$

It is easily seen that when $(w_{10} + w_{20})/2 > w_{12}$, w_{12}^* is larger than w_{12}. Thus, it is possible for an imprinting system to exhibit the dynamics of a nonimprinting system with heterozygote advantage, even though no heterozygote advantage actually exists. To construct such an example, let us assume, without loss of generality, that $w_{11} > w_{12} > w_{22}$. We require that $w_{12}^* > w_{11}^*$, *i.e.*,

$$(1-\theta)w_{12} + \tfrac{1}{2}\theta(w_{10} + w_{20}) > (1-\theta)w_{11} + \theta w_{10} \tag{17}$$

which gives

$$w_{20} > 2\,\frac{(1-\theta)}{\theta}\,(w_{11} - w_{12}) + w_{10} \tag{18}$$

and also that $w_{12}^* > w_{22}^*$, *i.e.*,

$$(1-\theta)w_{12} + \tfrac{1}{2}\theta(w_{10} + w_{20}) > (1-\theta)w_{22} + \theta w_{20} \tag{19}$$

which gives

$$w_{20} < 2\,\frac{(1-\theta)}{\theta}\,(w_{12} - w_{22}) + w_{10}. \tag{20}$$

Thus,

$$\begin{aligned} 2\,\frac{(1-\theta)}{\theta}\,(w_{11} - w_{12}) + w_{10} &< w_{20} \\ &< 2\,\frac{(1-\theta)}{\theta}\,(w_{12} - w_{22}) + w_{10} \end{aligned} \tag{21}$$

and so

$$\tfrac{1}{2}(w_{11} + w_{22}) < w_{12}. \tag{22}$$

If $w_{22} > w_{12} > w_{11}$ then similar expressions can be found which must be met for heterozygote advantage to be mimicked. Thus if (21) holds and $w_{11} > w_{12} > w_{22}$ then apparent heterozygote advantage will be shown in the dynamically equivalent nonimprinting system. We call this property pseudoheterosis. As a numerical example consider the following: let $w_{11} = 0.9$, $w_{22} = 0.1$ and $\theta = 0.3$, and therefore, by (22), we require $w_{12} > 0.5$, say $w_{12} = 0.6$. Let $w_{10} = 0.01$

therefore, by (21), we require $1.41 < w_{20} < 2.34$ and so let $w_{20} = 1.5$. This gives $w_{11}^* = 0.6330$, $w_{12}^* = 0.64665$, and $w_{22}^* = 0.5200$. Thus we have $w_{11} > w_{12} > w_{22}$, whereas $w_{12}^* > w_{11}^* > w_{22}^*$ so that there is heterozygote advantage in the nonimprinting system but clearly none exists in the imprinting system. (Of course, the viabilities in this example may not be particularly realistic: $w_{11} > w_{22}$, but $w_{10} < w_{20}$, but see model 5, below.)

The stability analysis of the polymorphic equilibrium in this model is constructed in a similar manner to that of model 2. The polymorphic equilibrium is feasible and stable if and only if $w_{22}^*, w_{11}^* < w_{12}^*$ which gives (21) and hence (22).

The effect of θ on $\hat{p}$ is similar to the effect in model 2: $\partial\hat{p}/\partial\theta$ has the same sign as $w_{10} - w_{20}$. That is, greater penetrance of imprinting increases the equilibrium frequency of the allele of the fitter hemizygote.

Model 4. Imprinting *vs.* Mendelizing alleles: A natural question to ask about genomic imprinting is how the phenomenon originated. Our next model, therefore, looks at how imprinting affects an allele's ability to enter a non-imprinting population. Suppose we have one allele A_1 that is never imprinted and another A_2 that is imprintable, with probability θ. As in model 2, suppose that A_i-'s have the same viabilities as A_iA_i's, w_{ii} ($i = 1$ and 2).

The interative equation for p is thus

$$\begin{aligned} p' &= [p^2w_{11} + \tfrac{1}{2}\theta pqw_{11} + \tfrac{1}{2}pqw_{12} \\ &\quad + \tfrac{1}{2}(1-\theta)pqw_{12}]/\bar{w} \\ &= [p^2w_{11} + pq(w_{12} + \tfrac{1}{2}\theta(w_{11} - w_{12}))]/\bar{w} \end{aligned} \tag{23}$$

where

$$\bar{w} = p^2w_{11} + 2pq[w_{12} + \tfrac{1}{2}\theta(w_{11} - w_{12})] + q^2w_{22}. \tag{24}$$

This behaves as model 0 where $w_{11}^* = w_{11}$, $w_{22}^* = w_{22}$ and $w_{12}^* = w_{12} + \frac{1}{2}\theta(w_{11} - w_{12})$. Like model 2, this system cannot display pseudoheterosis, for if $w_{11} > w_{12}$, $w_{11}^* - w_{12}^* = (1 - \frac{1}{2}\theta)(w_{11} - w_{12}) > 0$ and so $w_{11}^* > w_{12}^*$. Alternatively, if $w_{11} < w_{12} < w_{22}$, then $w_{12}^* < w_{12} < w_{22} = w_{22}^*$

The internal equilibrium, $\hat{p}$, exists and is stable provided $w_{12}^* > w_{11}^*$ and w_{22}^*, *i.e.*, $w_{12} > w_{11}$ and $(2w_{22} - \theta w_{11})/(2 - \theta)$. Putting $\theta = 0$ recovers model 0 (as expected). Examining $\partial\hat{p}/\partial\theta$ reveals that just as in model 2 the level of imprinting increases the equilibrium frequency of the allele of the fitter homozygote.

The $p = 1$ equilibrium where A_1 is fixed will be stable if $w_{11}^* > w_{12}^*$, *i.e.*, if $w_{11} > w_{12}$, the same condition as without imprinting (model 0). In a finite population, however, deviations from deterministic behavior mean that the A_2 allele may still not invade even if $w_{12} > w_{11}$, the probability of success being an increasing function of $w_{12}^* - w_{11}^* = (1 - \frac{1}{2}\theta)(w_{12} - w_{11})$. Thus increasing the probability of imprinting decreases the chances that an imprintable allele will invade a finite population of nonimprintable alleles.

The invadability of a population of imprintable alleles by an nonimprintable allele (A_1) depends on the stability of the $p = 0$ equilibrium. Such an invasion will be successful if and only if $w_{22}^* < w_{12}^*$, *i.e.*, if $w_{22} < w_{12} + \frac{1}{2}\theta(w_{11} - w_{12})$. Thus for fixed viabilities, a larger value of θ increases the chance of success only if imprinting of the A_2 allele in an A_1A_2 heterozygote increases the viability.

Model 5. Generalized imprinting *vs.* Mendelizing alleles: Model 4 can be generalized in the same way model 3 generalizes model 2, introducing parameters w_{10} and w_{20}. We obtain a system for which

$$p' = \frac{p^2w_{11} + pq[\frac{1}{2}\theta w_{10} + (1 - \frac{1}{2}\theta)w_{12}]}{\begin{aligned} &p^2w_{11} + 2pq[w_{12} + \tfrac{1}{2}\theta(w_{10} - w_{12})] \\ &\quad + q^2[w_{22} + \theta(w_{20} - w_{22})] \end{aligned}} \tag{25}$$

and so

$$\begin{aligned} w_{11}^* &= w_{11} \\ w_{12}^* &= w_{12} + \tfrac{1}{2}\theta(w_{10} - w_{12}) \\ w_{22}^* &= w_{22} + \theta(w_{20} - w_{22}). \end{aligned} \tag{26}$$

The value of $\hat{p}$ and the conditions for its existence and stability may be calculated as previously. We can see from equations (26) that pseudoheterosis is possible, *e.g.*, with $\theta = 0.8$, $w_{11} = w_{10} = w_{20} = 1$, $w_{12} = 1.1$, $w_{22} = 1.2$. (This example certainly appears more realistic than that in model 2.)

The condition for the imprinting allele A_2 to invade becomes

$$2(w_{12} - w_{11}) > \theta(w_{12} - w_{10}) \tag{27}$$

which means that a greater level of imprinting favors invasion when A_1- individuals are fitter than A_1A_2's. Since

$$w_{12}^* - w_{11}^* = w_{12} - w_{11} - \tfrac{1}{2}\theta(w_{12} - w_{10}), \tag{28}$$

if w_{10} is close to w_{11}, we preserve our model 4 result that larger θ's reduce the probability of A_2 successfully invading a finite population (for given w's). If w_{10} is rather larger than w_{11}, however, then this result is reversed. (The deterministic model may no longer admit such an invasion, however, if w_{10} is very large.)

Model 6. Autosomal inactivation with two-sex viabilities: The next system we consider differs from model 1 in only one feature: viability selection affects the sexes differently. The following set of viability fitnesses are assumed: the fitness of male A_1-'s is w_{1m}, that of female A_1-'s w_{1f}, that of male A_2-'s w_{2m} and that of female A_2-'s w_{2f}. The first model is thus the special case in which $w_{1m} = w_{1f} (= w_1)$ and $w_{2m} = w_{2f} (= w_2)$. Following our previous procedure, we obtain, in

the female population after selection, the genotypic frequencies:

$$[A_1A_1]_f = p_m p_f w_{1f}/\bar{w}_f,$$
$$[A_1A_2]_f = (p_m q_f w_{1f} + q_m p_f w_{2f})/\bar{w}_f \quad (29)$$

and

$$[A_2A_2]_f = q_m q_f w_{2f}/\bar{w}_f,$$

where

$$\bar{w}_f = p_m w_{1f} + q_m w_{2f}. \quad (30)$$

Similarly, in the male population following selection the genotypic frequencies are:

$$[A_1A_1]_m = p_m p_f w_{1m}/\bar{w}_m$$

and (31)

$$[A_1A_2]_m = (p_m q_f w_{1m} + q_m p_f w_{2m})/\bar{w}_m$$
$$[A_2A_2]_m = q_m q_f w_{2m}/\bar{w}_m$$

where

$$\bar{w}_m = p_m w_{1m} + q_m w_{2m}. \quad (32)$$

Now, the frequencies of the A_1 allele in the female and male populations of this generation (denoted by p_f' and p_m' respectively) are:

$$p_f' = [A_1A_1]_f + \tfrac{1}{2}[A_1A_2]_f = [p_m p_f w_{1f} + \tfrac{1}{2}(p_m q_f w_{1f} + q_m p_f w_{2f})]/\bar{w}_f \quad (33)$$

and

$$p_m' = [p_m p_f w_{1m} + \tfrac{1}{2}(p_m q_f w_{1m} + q_m p_f w_{2m})]/\bar{w}_m. \quad (34)$$

Unfortunately this system is not formally equivalent to the well-known two-sex viability scheme of OWEN (1953), nor to a fertility selection scheme (BODMER 1965). The difference is a consequence of the different viabilities of the reciprocal heterozygotes. We therefore analyze the system in more detail.

Let us first suppose that neither w_{1m} nor w_{1f} is zero, so that we may divide (33) by w_{1f} and (34) by w_{1m} and write $w_f = w_{2f}/w_{1f}$ and $w_m = w_{2m}/w_{1m}$. We can see from (33) and (34) that if $w_m = w_f$ then $p_f' = p_m'$, otherwise $p_f' \neq p_m'$. Thus the previous result that allele frequencies are equal in males and females does not hold when there are viability differences between the two sexes. Now

$$\Delta p_f = p_f' - p_f = \frac{p_m q_f - q_m p_f w_f}{2(p_m + q_m w_f)} \quad (35)$$

and

$$\Delta p_m = p_m' - p_m = \frac{p_m(2q_m - q_f) + q_m(p_f - 2p_m)w_m}{2(p_m + q_m w_m)}. \quad (36)$$

At equilibrium $\Delta p_f = \Delta p_m = 0$. Thus, the numerators of (35) and (36) will equal zero. Adding the numerators gives:

$$2p_m q_m(1 - w_m) + p_f q_m(w_m - w_f) = 0. \quad (37)$$

This equality holds if either: (a) $q_m = 0$ (*i.e.*, $p_m = 1$) which on substituting into $\Delta p_m = 0$ gives $q_f = 0$ (*i.e.*, $p_f = 1$) and so the population is fixed for the A_1 allele in both sexes; or (b) $q_m \neq 0$ which gives

$$p_f = \frac{2p_m(1 - w_m)}{w_f - w_m}. \quad (38)$$

If $p_m = 0$ then p_f must also be equal to zero and so the A_2 allele is fixed in both sex systems. If $p_m \neq 0$ then:

$$\hat{q}_f = \frac{w_f - 2p_m - w_m(1 - 2p_m)}{w_f - w_m}. \quad (39)$$

Substituting (38) and (39) into $\Delta p_f = 0$ gives:

$$\hat{p}_m = \frac{w_f + w_m - 2w_f w_m}{2(w_m + w_f - w_f w_m - 1)}. \quad (40)$$

As $\hat{p}_m$ is an allele frequency it must lie between zero and one, and so by enforcing this range on (40) we see that for $0 < \hat{p}_m$ either

$$w_m + w_f > w_f w_m + 1 \quad \text{and} \quad w_m + w_f > 2w_f w_m \quad (41)$$

or

$$w_m + w_f < w_f w_m + 1 \quad \text{and} \quad w_m + w_f < 2w_f w_m \quad (42)$$

and for $\hat{p}_m < 1$ either $w_m + w_f > 2$ when (41) holds or $w_m + w_f < 2$ when (42) holds. So for $0 < \hat{p}_m < 1$ we have that either

$$w_m + w_f > \max(2, w_f w_m + 1, 2w_f w_m) \quad (43)$$

or

$$w_m + w_f < \min(2, w_f w_m + 1, 2w_f w_m). \quad (44)$$

Let us now consider the cases when w_{1m} or w_{1f} is zero. If they are both zero then clearly p_f and p_m halve every generation and the sole equilibrium is $p_f = p_m = 0$. Now, if $w_{1m} = 0$, but $w_{1f} \neq 0$ then (34) reduces to

$$p_m' = \tfrac{1}{2}p_m. \quad (45)$$

Now the only equilibrium value for (45) is $p_m = 0$, which on substitution into (33) gives $p_f = \frac{1}{2}p_f$ and so the equilibrium value is $p_f = 0$. Similar arguments show that when $w_{1f} = 0$, the only equilibrium is $p_m = p_f = 0$.

Figure 1 illustrates the changes in the A_1 allele frequency over time within a system constructed on the assumptions of model 6. In this system we have that $2w_m w_f = 2.0 < w_m + w_f = 2.5$ and $2 \leq w_m + w_f = 2.5$ (refer to Equation 43). Thus the necessary inequalities for a polymorphism hold and we see that the internal equilibrium is reached in both sexes. For the male population:

$$\hat{p}_m = \frac{w_f + w_m - 2w_f w_m}{2(w_m + w_f - w_f w_m - 1)} = 0.500 \quad (40)$$

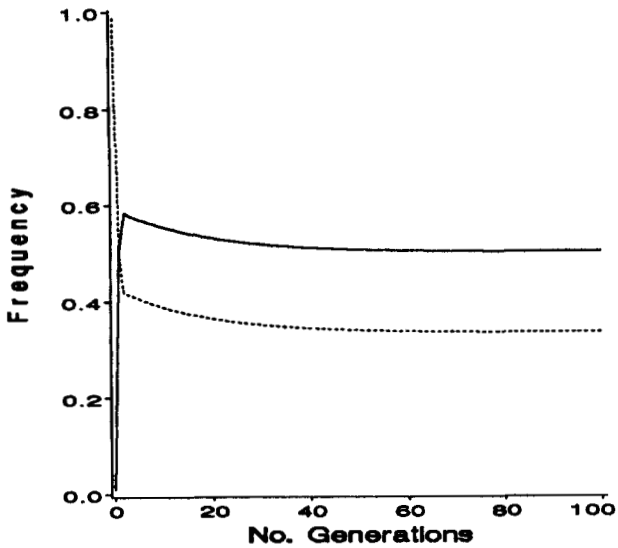

FIGURE 1.—The frequency of the A_1 allele over successive generations in model 6. $w_m = 0.5$ and $w_f = 2.0$. Initially $p_m = 0.01$ and $p_f = 0.99$. Males = solid line. Females = dotted line.

and for the female population:

$$\hat{p}_f = \frac{2\hat{p}_m(1 - w_m)}{w_f - w_m} = 0.333. \tag{46}$$

Note that, if the sex ratio is even, the total population has more A_2 alleles than A_1's, even though $w_m w_f = 1.0$, because the maternally derived alleles (more likely to be A_2's) are hidden from selection in the following generation's males.

Model 7. *X* chromosome imprinting: So far we have considered only imprinting involving the inactivation of autosomal alleles. Consider now the case in which the paternal X chromosome (or parts of it) are inactivated in female offspring. That is, only the maternal chromosome is expressed throughout an individual's soma [see MONK (1987) for a review of this phenomenon]. This situation differs from the classical X-inactivation in eutherian mammals which occurs after the zygote has undergone several cell divisions. Within each cell of the zygote, inactivation is random with respect to the parental origin of the chromosome. In the classical case, therefore, cell lineages express only one X chromosome but the organism generally has both X chromosomes expressed.

Continuing our formulation, assuming that males are the heterogametic sex, let A_1 males and $-A_1$ females have viability w_1, and A_2 males and $-A_2$ females have viability w_2. If the frequency of A_1 in the male population is p_m and that in the female population is p_f we obtain

$$p_f' = [p_m p_f w_1 + \tfrac{1}{2}(p_m q_f w_2 + q_m p_f w_1)]/\bar{w}_f \tag{47}$$

where

$$\begin{aligned}\bar{w}_f &= p_m p_f w_1 + p_m q_f w_2 + q_m p_f w_1 + q_m q_f w_2 \\ &= p_f w_1 + q_f w_2\end{aligned} \tag{48}$$

and

$$p_m' = p_f w_1/\bar{w}_m \tag{49}$$

where

$$\bar{w}_m = p_f w_1 + q_f w_2 = \bar{w}_f. \tag{50}$$

Again our system is different from standard Mendelian models; in particular, its dynamics are different from those of a sex-linked locus with viability selection (MANDEL 1959).

Clearly $p_f = p_m = 0$ and $p_f = p_m = 1$ are equilibria. To discover whether any internal equilibria, $(\hat{p}_f, \hat{p}_m)$, are possible, we can follow MANDEL's (1959) treatment, defining $R_f = p_f/q_f$ and $R_m = p_m/q_m$. From (49) and (50) we immediately get that at equilibrium,

$$R_m = R_f w_1/w_2 \tag{51}$$

which yields (excluding irrelevant cases, *e.g.*, $R_f = 0$ and $w_1 = w_2$)

$$R_f = -w_2/w_1 < 0. \tag{52}$$

Obviously we have a nonsensical value for R_f and so we can conclude there are no polymorphic equilibria possible.

We can also explore the consequences of random X-inactivation by introducing β, the probability that the paternal X chromosome is imprinted. Thus the maternal X chromosome is imprinted with probability $1 - \beta$ and we have so far considered $\beta = 1$. Following our procedure in model 1 we obtain

$$\begin{aligned}p_f' = &[p_m p_f w_1(\beta w_1 + (1-\beta)w_1) \\ &+ \tfrac{1}{2}p_m q_f(\beta w_2 + (1-\beta)w_1) \\ &+ \tfrac{1}{2}q_m p_f(\beta w_1 + (1-\beta)w_2)]/\bar{w}_f \\ = &\frac{p_m p_f w_1 + \tfrac{1}{2}[p_m q_f(\beta w_2 + (1-\beta)w_1) + q_m p_f(\beta w_1 + (1-\beta)w_2)]}{p_m p_f w_1 + p_m q_f(\beta w_2 + (1-\beta)w_1) + q_m p_f(\beta w_1 + (1-\beta)w_2) + q_m q_f w_2}\end{aligned} \tag{53}$$

and

$$p_m' = \frac{p_f w_1}{p_f w_1 + q_f w_2}. \tag{49}$$

In contrast to random autosomal inactivation, random sex-chromosome activation does affect the allelic dynamics, but only those in the females. Using MANDEL's technique again, we can show that for an internal equilibrium we obtain the contradiction $R_f < 0$ and so no polymorphic equilibria exist. Thus, although the dynamics are altered by random inactivation, the equilibria are not.

Model 8. Differential gene expression: Most recently, genomic imprinting has been used to describe the differential expression of alleles (or chromosomes) depending on whether the allele (or chromosome) was paternally or maternally inherited (HALL 1990). In its

most general form such differential gene expression means that reciprocal heterozygotes have distinguishable phenotypes and hence possibly different viabilities. We can modify the Mendelian model 0 to this situation by simply requiring that A_1A_2 individuals have viability w_{12} whereas A_2A_1 individuals have viability w_{21} (which is not necessarily equal to w_{12}). The recurrence equation for the frequency of the A_1 allele is thus

$$p' = \frac{p^2w_{11} + \frac{1}{2}pq(w_{12} + w_{21})}{p^2w_{11} + pq(w_{12} + w_{21}) + q^2w_{22}}, \qquad (54)$$

which is the same formula as a nonimprinting system in which

$$\begin{aligned} w_{11}^* &= w_{11} \\ w_{12}^* &= \tfrac{1}{2}(w_{12} + w_{21}) \\ w_{22}^* &= w_{22}. \end{aligned} \qquad (55)$$

and

That is, differential gene expression gives identical dynamics to a standard system in which heterozygotes have viability equal to the arithmetic mean of the reciprocal imprinted heterozygote viabilities. The destruction of the symmetry of the viability matrix W (with entry w_{ij} in row i column j) thus does not lead to novel behavior of the system. Indeed, this result is known in another context, that of the parallel between the game theoretic approach to ESS (evolutionarily stable strategy) theory and standard one-locus Mendelian genetics [see CANNINGS and VICKERS (1989) for a recent example]. The viability matrices of the latter are payoff matrices of the former. (All payoff matrices are not viability matrices—even asymmetric viability matrices—however.)

Returning to Equations 55 we see that in addition to the $p = 0$ and $p = 1$ equilibria, the internal equilibrium

$$\hat{p} = \frac{w_{12} + w_{21} - 2w_{22}}{2(w_{12} + w_{21} - w_{11} - w_{22})}$$

will exist provided $\frac{1}{2}(w_{12} + w_{21}) > w_{11}$ and w_{22}. Thus for the dynamics of Mendelian heterosis to be mimicked at least one of the heterozygotes must have the highest viability. Nevertheless, a kind of pseudoheterosis is possible where one heterozygote has low viability, *e.g.*, $w_{11} = w_{22} = 1.0$, $w_{12} = 0.95$, $w_{21} = 1.1$.

The above formulation allows the easy examination of special cases of interest. For example, suppose the paternal and maternal alleles contribute to the overall phenotype in the ratio ϕ:$(1 - \phi)$. Under allelic selection, letting the A_i allele contribute w_i to the viability, the viability of an A_iA_j individual is $w_{ij} = \phi w_i + (1 - \phi)w_j$ $(i, j = 1, 2)$. Thus $w_{11}^* = w_1$, $w_{12}^* = \frac{1}{2}(w_1 + w_2)$ and $w_{22}^* = w_2$ which, like model 1, is formally haploid selection, affording no polymorphic equilibria.

TABLE 2

Equivalences between nonimprinting and imprinting models

	Model 0 parameter		
Model	w_{11}^*	w_{12}^*	w_{22}^*
1	w_1	$\frac{1}{2}(w_1 + w_2)$	w_2
2	w_{11}	$(1 - \theta)w_{12} + \frac{1}{2}\theta(w_{11} + w_{22})$	w_{22}
3	$(1 - \theta)w_{11} + \theta w_{10}$	$(1 - \theta)w_{12} + \frac{1}{2}\theta(w_{10} + w_{20})$	$(1 - \theta)w_{22} + \theta w_{20}$
4	w_{11}	$(1 - \frac{1}{2}\theta)w_{12} + \frac{1}{2}\theta w_{11}$	w_{22}
5	w_{11}	$(1 - \frac{1}{2}\theta)w_{12} + \frac{1}{2}\theta w_{10}$	$(1 - \theta)w_{22} + \theta w_{20}$
8	w_{11}	$\frac{1}{2}(w_{12} + w_{21})$	w_{22}

DISCUSSION

The most important of our conclusions is that the majority of our models incorporating imprinting could be shown to be formally equivalent to models in which there was no imprinting. That is, the allele frequencies in a particular imprinting system changed in exactly the same manner as those in certain corresponding nonimprinting systems. (The equivalences are summarized in Table 2.) Consequently, the equilibria in the imprinting system also corresponded to those found in these certain nonimprinting systems. For example, a system in which all the maternally derived alleles were inactivated was shown to behave as a haploid selection model. Complete inactivation of an autosomal allele thus leads to monomorphism. This equivalence between imprinting and nonimprinting systems has the important consequence that imprinting can never be detected by simply following allele frequency changes. (Of course, imprinting of this sort can easily be detected by setting up appropriate crosses and examining offspring genotype proportions.) This result mirrors several other discoveries that show how little can be deduced about a genetic population from analyzing the changes in allele frequencies. These discoveries include the equivalence of viability selection models and some fertility selection models (FELDMAN, LIBERMAN and CHRISTIANSEN 1983), the equivalence of constant viability selection models and some frequency dependent selection models (DENNISTON and CROW 1990), and the equivalence of BODMER's multiplicative fertility selection system and OWEN's (1953) two-sex viability selection system (BODMER 1965).

The formal equivalences do not, unfortunately, preserve some of the properties of the viabilities in the respective models. For example, an imprinting system with heterozygote advantage could behave like a nonimprinting system without such advantage. Consequently, under genomic imprinting, heterozygote advantage is not a sufficient condition for the maintenance of a diallelic polymorphism. Conversely, heterozygote advantage is not a necessary condition: an imprinting system without it can be formally equiv-

alent to a non-imprinting system with it, a property we call pseudoheterosis.

When the internal equilibrium, $\hat{p}$, exists (as it will when the equivalent nonimprinting model exhibits heterosis) its value depends on the penetrance of imprinting, θ. The larger the value of θ the closer $\hat{p}$ moves to fixation of the fitter type (A_iA_i and/or A_i^-).

Model 4 examines diallelic systems in which only one of the alleles is imprinted. Again this model is formally equivalent to a nonimprinting model. The effect of imprinting on an allele attempting to invade a finite nonimprinting population is to reduce the invasion's chance of success. Imprinting reduces the advantage the heterozygote might have over the unimprinted homozygote since many of the heterozygotes are selectively undifferentiated from the homozygotes. In model 5 (in which imprinted heterozygotes and homozygotes are not necessarily identical) a similar result holds if A_iA_i and A_i^- individuals are phenotypically similar. In this latter model, however, the conditions for a successful invasion in the deterministic case depend on θ, unlike those in model 4.

The exceptions to the rule of equivalence between imprinting and non-imprinting systems arise when the sexes are different, either in their viabilities, or in their level of ploidy. In nonimprinting models, *e.g.*, OWEN's (1953) two-sex viability system, or BODMER's (1965) fertility selection scheme, reciprocal heterozygotes had the same fitnesses. Imprinting contravenes this principle and even the sex-symmetry property of many fertility selection schemes (FELDMAN, LIBERMAN and CHRISTIANSEN 1983) does not apply. Our two-sex viability model has a polymorphic equilibrium provided certain restrictions on the viabilities apply, whereas with *X*-inactivation no polymorphic equilibria exist, even when the inactivation is random with respect to parental origin. This nonequivalence between imprinting and nonimprinting systems reveals the importance of the synonymity of reciprocal heterozygotes to standard Mendelian models. When viabilities from these latter models are represented in a matrix, this synonymity is manifested in the symmetry of the matrix. Such a matrix also corresponds to a symmetric payoff matrix of ESS (evolutionarily stable strategy) theory [see HINES (1987) for a review]. ESS theory, however, does not require that the payoff matrix be symmetric and, in general, it is not. Thus, our imprinting models can also be expected to be more generally equivalent to various models in game theory.

Of course, the models we have constructed are idealized in many respects, *e.g.*, in having constant viabilities and in ignoring genetic drift. Moreover, some (but by no means all) of the peculiar behaviors require parameter values that might be considered unlikely. Nevertheless, the models do serve to illustrate that genomic imprinting systems need not act at all like otherwise identical non-imprinting ones.

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