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The Inclusive Fitness Dynamics of Genomic Imprinting

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We develop a general inclusive fitness model for genetic evolution at an imprinted locus – one at which selection is allowed to act conditionally upon parental origin of the gene. In many cases of interest, such genes affect the fitness of relatives, particularly sibs. We formulate a matrilineal and patrilineal inclusive fitness and show that these can be used to describe the dynamics of change in mean expression levels. We classify and analyze the stability of equilibrium points and apply our results to some examples that have appeared in the literature, multiple paternity of a female's offspring, the "ovarian time-bomb," and loss-of-function mutations.

Keywords: Genomic imprinting, matrilineal and patrilineal inclusive fitness, dynamics, evolutionary stability

1. Introduction

Phenotypic plasticity is the response of genotype, through phenotypic expression, to different environmental conditions or cues. The environmental cues that trigger response may be biotic or abiotic, and many traits, whether behavioural, morphological, physiological, etc., demonstrate some level of phenotypic plasticity. In fact, with the enormous environmental variation observed in nature, it seems obvious that selection must favour genotypes capable of response. In an ideal world, the response will produce an optimal match of trait to environment.

Genomic imprinting can be thought of as a special type of phenotypic plasticity, in which an allele adjusts its level of activity in response to whether it spent the previous generation in a male or female germ line. Here, we think of the level of activity as the phenotype determined by the gene's control region. This plasticity of an allele's phenotype may not be expressed as plasticity of its bearers' phenotypes because, at a diploid locus, each individual has both a maternally and paternally derived allele.

Genomic imprinting is thought to operate through erasable, but heritable, modifications of DNA (such as cytosine methylation). The importance of such modifications is that they can provide the environmental cues that enable an imprinted allele to respond to parent-of-origin-dependent selection. If selection favors different levels of expression when alleles are maternally and paternally derived, then it will favour alleles that use such cues to alter their level of expression in response to parental origin. Alleles capable of this type of phenotypic response are observed in nature, most exhibiting specific inactivation when either maternally or paternally derived (for reviews see Reik and Surani, 1997; Reik and Walter, 2001).

What causes asymmetric selection dependent on parental origin? Is such asymmetry necessary for the evolution of parent-specific gene expression, in particular monoallelic expression, or can this evolve in its absence? A number of theories have

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been proposed to explain why parent-specific gene expression might evolve (e.g. Solter, 1988; Hall, 1990; Moore and Haig, 1991; Haig and Westoby, 1991; Haig, 1992; Tycko, 1994; Varmuza and Mann, 1994; Thomas, 1995; for reviews see Haig and Trivers, 1995; Hurst, 1997). Our purpose here is to provide a general framework for the dynamic evolution of genomic imprinting of which these theories can be viewed as particular cases.

Haig (1997) demonstrated that the theory of inclusive fitness can be modified to consider the inclusive fitness effects of the maternally and paternally derived alleles separately and used this to describe the ESS conditions for systems in which alleles may adjust their level of activity in response to parent-of-origin selective pressures. However, the model presented considered only the ESS stability of equilibria, and did not address the evolutionary dynamics and importantly the convergence of a population to the given equilibrium (CSS stability, Eshel, 1983; Christiansen, 1991). In this paper, we formalize Haig's inclusive fitness model in a dynamic context, we provide a general analysis of the evolutionary dynamics, and examine a number of examples.

2. The inclusive fitness model

We adopt the direct fitness approach of Taylor and Frank (1996) and consider an imprinted locus at which a large number of alleles are segregating. Let y_m and y_p denote the level of expression of the maternally and paternally derived alleles at this locus, and $\hat{y}_m$ and $\hat{y}_p$ denote the population average values. Assume that the fitness W of a focal individual depends upon its own levels of expression and on that of a number of neighbouring individuals. We let y_{ij} denote the maternal ($j=m$) and the paternal ($j=p$) level of expression in individual i, where i runs over the focal neighbourhood of effect and we reserve $i=0$ for the focal individual. We suppose that the fitness of the focal individual depends upon the levels $\mathbf{y}_m = (y_{im})$ and $\mathbf{y}_p = (y_{ip})$: $W = W(\mathbf{y}_m, \mathbf{y}_p)$.

The *matrilineal* ($j=m$) and the *patrilineal* ($j=p$) inclusive fitness effects are defined to be:

$$\Delta\hat{W}_j = \Delta\hat{W}_j(\hat{y}_m, \hat{y}_p) = \sum_i \frac{\partial W}{\partial y_{ij}} R_{ij}\Big|_{\substack{y_{im}=\hat{y}_m \\ y_{ip}=\hat{y}_p}} \qquad (1)$$

where the sum is over the focal neighbourhood of effect. Here R_{ij} is the *matrilineal* ($j = m$) or the *patrilineal* ($j = p$) relatedness of individual i (as actor) to the focal individual (as recipient) defined in the Appendix (A6) as a quotient of covariances. R_{ij} can also be defined as the expected number of copies in the focal genotype of the maternal or paternal allele in individual i. It is important to note that coefficients of relatedness need not be symmetric. For example, the paternal relatedness of a mother (actor) to her child (recipient) is 1/2, whereas the paternal relatedness of the child (actor) to her mother (recipient) is 0 (in the absence of inbreeding).

3. The dynamic model

Several previous models have examined the evolutionary dynamics of genomic imprinting for particular dynamical systems (Mochizuki et al., 1996; Iwasa et al., 1999; Kondoh and Higashi, 2000; Iwasa and Pomiankowski, 2001). Our objective is to track the change in the population means $\hat{y}_m$ and y_p under the action of selection, with as much generality as possible. Following the approach of Abrams et al. (1993) we employ the evolutionary dynamic:

$$\begin{bmatrix} d\hat{y}_m/dt \\ d\hat{y}_p/dt \end{bmatrix} = \begin{bmatrix} v_m & c_{mp} \\ c_{mp} & v_p \end{bmatrix} \begin{bmatrix} \Delta\hat{W}_m \\ \Delta\hat{W}_p \end{bmatrix}, \qquad (2)$$

where c_{mp} is the additive genetic covariance between $\hat{y}_m$ and $\hat{y}_p$, and v_j the additive genetic variance in $\hat{y}_j$, both c_{mp} and the v_j assumed constant. In the Appendix (A10) we justify the use of the inclusive fitness effects $\Delta\hat{W}_j$ in (2). Our objective is to find the set of evolutionary attractors, vector strategies $\hat{\mathbf{y}} = (\hat{y}_m, \hat{y}_p)$, that are expected to persist over evolutionary time, and to describe the conditions under which there is asymmetric expression of maternally and paternally derived alleles, $\hat{y}_m \neq \hat{y}_p$, at evolutionary equilibrium.

The additive genetic covariance c_{mp} in (2) describes how allelic levels of expression are correlated when maternally and paternally derived, and this will depend upon the level of plasticity in the expression of alleles. Essentially, we treat $\hat{y}_m$ and

y_p as two genetically correlated traits (Roff, 1997). We assume $c_{mp} \geq 0$ and we present three scenarios. In the first scenario, alleles are capable of independently adjusting their levels of expression when maternally derived from when paternally derived, and in this case $c_{mp} = 0$. In the second scenario, much of this independence is absent; for example, alleles that tend to have high levels of expression when paternally derived might also be required to have high levels of expression when maternally derived. In this case there will be a positive correlation among the expression of maternally and paternally derived alleles, $c_{mp} > 0$. In the third scenario, alleles are completely constrained in that they cannot vary their levels of expression in response to parental history. In this case $v_m = v_p = c_{mp}$, and the two-dimensional dynamical system (2) reduces to a one dimensional system. This will occur in systems that lack imprinting.

Several previous works have examined the evolutionary dynamics of genomic imprinting for particular dynamical systems (Mochizuki et al., 1996; Iwasa et al., 1999; Kondoh and Higashi, 2000). Our goal is to examine the evolutionary dynamics of genomic imprinting with as much generality as possible.

To accomplish this we make some simplifying assumptions about inclusive fitness effects $\Delta\hat{W}_j$. These are assumed to be differentiable functions of the positive variables $\hat{y}_m$ and $\hat{y}_p$, and to decrease in each variable. That is, $\frac{\partial}{\partial \hat{y}_j}\Delta\hat{W}_j(\hat{y}_m,\hat{y}_p) < 0$ and $\frac{\partial}{\partial \hat{y}_k}\Delta\hat{W}_j(\hat{y}_m,\hat{y}_p) < 0$ for $k \neq j$. In addition, both $\Delta\hat{W}_j$ are assumed to be positive at the origin ($\hat{y}_m = \hat{y}_p = 0$), but to be negative when either $\hat{y}_m$ or $\hat{y}_p$ is sufficiently large. These assumptions simply characterize the family of fitness functions W, such that for a given level of expression of the parent-k derived allele, there exists an optimal level of expression for the parent-j derived allele, that is unique, non-negative, and for which the inclusive fitness effect $\Delta\hat{W}_j$ is zero. Moreover, this optimal level of expression decreases as the expression of the parent-k derived allele increases. These assumptions mean that the benefit to the parent-j derived allele, resulting from an increase in its own activity, will decrease, as the total level of gene expression increases (either through increased activity of the parent-k or parent-j derived allele).

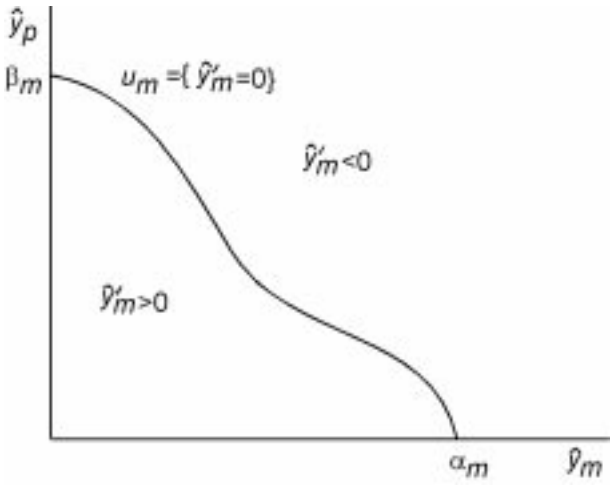

FIG. 1. A geometric representation of the maternal selection nullcline

We define the maternal ($j=m$) and paternal ($j=p$) selection nullclines to be the sets $u_j = \{\hat{y}'_j = 0\}$ on which the selection gradients are zero. Our analysis will require that these sets have a simple geometric structure in the phase-plane illustrated in Figure 1 for the case u_m, and described in the following proposition.

Proposition: Each selection nullcline, $u_j = \{\hat{y}'_j = 0\}$, is a differentiable curve with a strictly negative slope from a point α_j on the $\hat{y}_j$-axis to a point β_j on the $\hat{y}_k$-axis ($k \neq j$), such that $\hat{y}'_j < 0$ outside the curve and $\hat{y}'_j > 0$ inside the curve.

We present the proof for the case $u_m = \{\hat{y}'_m = 0\}$; the analogous result for the set u_p follows by simply interchanging the subscripts m and p. It follows from our assumptions on the $\Delta\hat{W}_j$ that $\hat{y}'_m = v_m\Delta\hat{W}_m + c_{mp}\Delta\hat{W}_p$ is a differentiable function of $\hat{y}_m$ and $\hat{y}_p$, decreasing in each variable, positive at the origin, and negative for sufficiently large $\hat{y}_m$ or $\hat{y}_p$. It follows that there are unique points α_m and β_m on the $\hat{y}_m$- and $\hat{y}_p$-axes, respectively, at which $\hat{y}'_m = 0$, with $\hat{y}'_m > 0$

on each axis between these points and the origin. If we take any point on the $\hat{y}_p$-axis between the origin and β_m (Fig. 1) and draw a horizontal line to the right from this point, then $\hat{y}'_m$ will decrease along this line and thus there will be a unique point at which it is zero. This defines the curve, and it clearly has α_m and β_m as its intersections with the axes. According to the implicit function theorem it is differentiable and has slope $-\frac{\partial \hat{y}'_m / \partial \hat{y}_m}{\partial \hat{y}'_m / \partial \hat{y}_p}$ which is negative by our assumptions above.

Note that α_m is the stationary level of expression for a maternally derived gene when the paternally derived gene is inactive, and a similar interpretation applies to α_p.

4. Parental antagonism

The kinship (or conflict) theory of genomic imprinting postulates that parent-specific gene expression is the result of parental antagonism. This arises when relations within an interaction group are asymmetric with respect to matrilineal and patrilineal kin. The simplest case is provided by multiple paternity of a mother's offspring (see Spencer et al., 1998, 1999; Haig, 1999; Hurst, 1999), but parental antagonism may also arise in other situations, for example, in populations with sex-biased dispersal (Haig, 2000b). Haig (1997) defined a gene to have parentally antagonistic effects if its expression is associated with an inclusive fitness benefit when the gene is inherited from one parent but an inclusive fitness cost when the gene is inherited from the other parent, more generally, if $\Delta\hat{W}_m$ and $\Delta\hat{W}_p$ do not share a common sign. We will see below, when we consider the ovarian time bomb (example 2) and loss of function mutations (example 3), that this definition is unsatisfactory, and we attempt a better definition below.

Fasten attention on an imprinted locus in a diploid population. In equation 1 we have defined the matrilineal inclusive fitness effect to be:

$$\Delta\hat{W}_m = \sum_i \frac{\partial W}{\partial y_{im}} R_{im} .$$

We now define the matrilineal excluded fitness effect (Haig, 2000a) to be:

$$\Delta\hat{W}_{m\times p} = \sum_i \frac{\partial W}{\partial y_{im}} R_{ip} . \qquad (3)$$

Here we have simply replaced matrilineal relatedness by patrilineal relatedness. Similary, we have defined the patrilineal inclusive fitness effect to be:

$$\Delta\hat{W}_p = \sum_i \frac{\partial W}{\partial y_{ip}} R_{ip}$$

and we now define the patrilineal excluded fitness effect (Haig, 2000a) to be:

$$\Delta\hat{W}_{p\times m} = \sum_i \frac{\partial W}{\partial y_{ip}} R_{im} . \qquad (4)$$

To see the significance of these definitions, we should start by allowing the possibility that the maternal and paternal allele might control somewhat different aspects of behaviour, which for convenience we will call the maternal and paternal phenotypes. An example of this will be found below in the ovarian time bomb (Example 2). Then the matrilineal inclusive fitness effect is the overall effect on the fitness of the focal individual of an increase in the activity of the focal matrilineal allele and of all its IBD copies. Now imagine that the matrilineal and patrilineal allele interchange phenotypic effects, so that the patrilineal allele controls the maternal phenotype. Then the matrilineal excluded fitness effect is the overall effect on the fitness of the focal individual of an increase in the activity of the focal patrilineal allele and of all its IBD copies, *when these control the maternal phenotype.* Similarly the patrilineal excluded fitness effect (4) is the overall effect on the fitness of the focal individual of an increase in the activity of the focal matrilineal allele and of all its IBD copies, *when these control the paternal phenotype.*

If the matrilineal inclusive and excluded fitness effects do not share common sign, that signals a disagreement between the matrilineal and patrilineal allele in the focal individual over control of the maternal phenotype and we say that there is *maternal parental antagonism.* This holds if $\Delta\hat{W}_m$ and $\Delta\hat{W}_{m\times p}$ do not share common sign (that is, they have opposite signs or if one is zero and the other non-zero). Similarly if the patrilineal inclusive and excluded fitness effects do not share common sign, we say that there is *paternal parental antagonism.*

At an unimprinted locus, the maternal and paternal phenotypes must be the same and the matrilineal excluded fitness effect will equal the patrilineal inclusive fitness effect, and the patrilineal excluded fitness effect will equal the matrilineal inclusive fitness effect. In this special case, parental antagonism is present whenever patrilineal and matrilineal inclusive fitness effects do not share common sign. And at an imprinted locus, if matrilineal and patrilineal coefficients of relatedness are identical, $R_{im} = R_{ip}$, for all i and there can be no parental antagonism.

5. The dynamics of genomic imprinting

The system (2) is considered a competitive dynamic system and a general treatment of such systems is given in Hirsch and Smale (1974). For this reason, we will omit much of the formalism in the proofs of the results that follow. A given flow, or evolutionary trajectory, of the phase-plane diagram of (2) traces the evolutionary history of a population, that is, it describes how the average level of expression of the maternally and paternally derived alleles, y_m and y_p, change within a population over time. The above Proposition allows us to analyze these dynamics in terms of the interaction between the selection nullclines u_m and u_p. There are three cases to examine. In the first case the selection nullclines contain the same points; in the second case they are distinct and do not intersect, and in the third case they are distinct but intersect at a finite number of points.

Case 1

We begin by examining the dynamics of (2) under the conditions that u_m and u_p contain the same points. Under these conditions the phase plane diagram will have the form of Figure 2. Here $u_m = u_p = u$ forms a continuous set of equilibrium points that divide the phase plane into two distinct regions. In Region I, which is the open set of all points inside u, we have $y_j > 0$ for both j and in Region II, which is the open set of all points outside u, we have $y_j < 0$ for both j. We can conclude that all evolutionary trajectories approach the set u of equilibrium points as depicted in Figure 2.

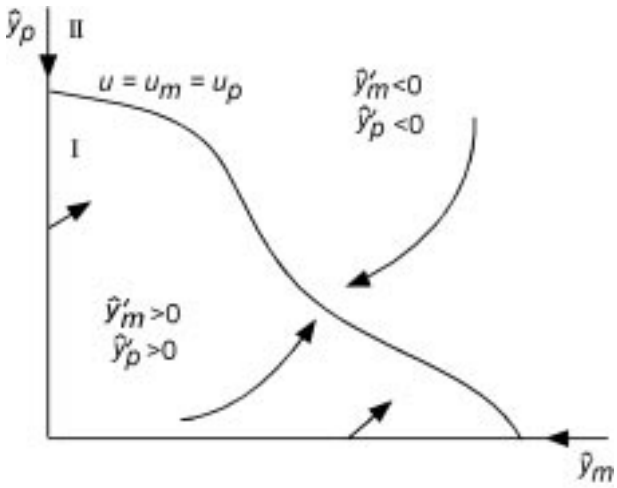

FIG. 2. The maternal and paternal selection nullclines form a continuous set of equilibrium points that divide the phase plane into two distinct regions. All evolutionary trajectories approach the set u of equilibrium points

We now turn our attention to evolutionary stability. Suppose the population is at the equilibrium point p on u but that the population mean is perturbed to a point q close to p. Will the population evolve back to the equilibrium point p?

Draw a small rectangle containing both p and q with sides parallel to the axes and the left upper corner and right lower corner lying on u (Fig. 3A). Taking all points lying on the boundary and the interior of such a rectangle yields a positively invariant closed set P. Thus the flow that begins at q must remain inside this rectangle for all time, and it follows that a flow that begins near p must stay near p. However, it need not return to p – there are points q arbitrarily near p about which an invariant set can be drawn which does not contain

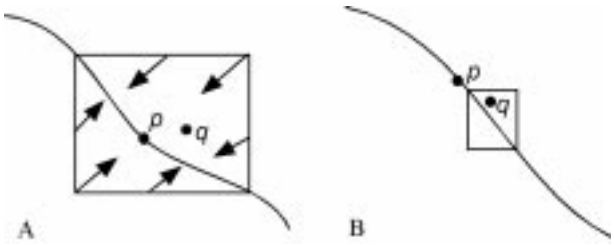

FIG. 3. The set u of equilibrium points is neutrally stable. A) A flow that begins at q must remain inside the rectangle for all time, and it follows that a flow that begins near p must stay near p. B) However, it need not return to p – there are points q arbitrarily near p about which an invariant set can be drawn which does not contain p

p (Fig. 3B). We conclude that the set u of equilibrium points is only neutrally stable and that there can be evolutionary drift along this line.

In the above case, the direction of selection is identical for maternal and paternal expression. Unequal expression of the two alleles, including complete inactivation of one allele, is a theoretical possibility. This might arise as a result of genetic drift along the line of neutral equilibrium. A more plausible scenario would invoke a change of selective regime, from one in which the nullclines were non-identical to one in which they coincide. If previously, there had been monoallelic expression as a result of differential selection, this qualitative pattern of expression might be maintained after the change of selective regime (Moore and Mills, 1999).

Case 2

Suppose now that the selection nullclines u_m and u_p do not intersect, so that one is outside the other. Under these conditions there exists no point (y_m, y_p) that is stationary for both a maternally and a paternally derived allele. We show that under these general conditions Haig's (1997) "loudest voice prevails" principle obtains – one of the two genes remains completely inactive while the other operates at its optimal level. The gene that remains active is the one whose nullcline is farthest from the origin. For example, suppose u_p lies outside u_m (Fig. 4). We show below that under these conditions there exists a unique equilibrium at $(0,\alpha_p)$. Moreover, this equilibrium is asymptotically stable and is a global attractor. Over evolutionary time, all populations will evolve to the equilibrium point $(0, \alpha_p)$.

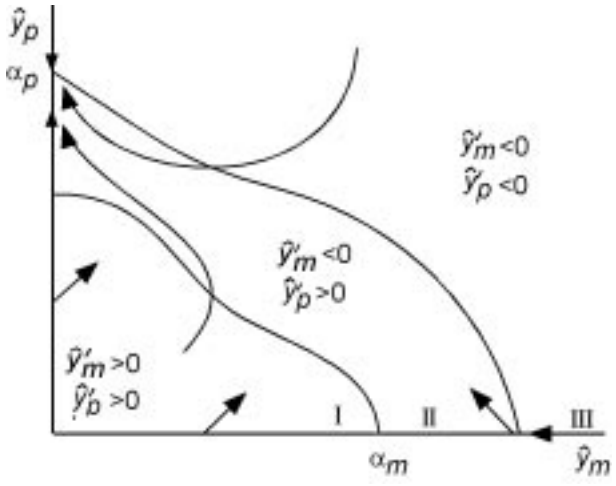

FIG. 4. The paternal selection nullcline lies outside the maternal selection nullcline. There exists a unique equilibrium at $(0,\alpha_p)$. This equilibrium is asymptotically stable and is a global attractor

The set of points (y_m, y_p) in the phase plane where neither $y'_m = 0$ nor $y_p = 0$ is divided into three basic regions by the selection nullclines (Fig. 4). Region I is the set lying below u_m, Region II is the set lying between u_m and u_p and Region III is the set lying above u_p.

We begin by observing that all evolutionary trajectories of Regions I and III must eventually enter Region II. Simply, we have that $y'_m \geq 0$ and $y_p > 0$ for all points (y_m, y_p) in Region I and its boundary, with equality iff $(y_m, y_p) \in u_m$. Similarly, for all points (y_m, y_p) in Region III and its boundary, $y'_m < 0$ and $y_p \leq 0$, with equality iff $(y_m, y_p) \in u_p$.

Now, once an evolutionary trajectory has entered Region II it will converge to the equilibrium point $(0, \alpha_p)$. This is a result of parental antagonism – $y'_m < 0$ and $y_p > 0$ at all points in the interior of Region II, and this drives the system to the equilibrium point.

In a similar way, we observe that if u_m lies outside u_p, then there exists a unique equilibrium at $(\alpha_m, 0)$. This equilibrium is asymptotically stable with all evolutionary trajectories converging to it. In this case, unlike *Case 1*, parent-specific monoallelic expression is a necessary outcome of the model.

An important general class of models are those in which fitness is given by a function $W(Y_0,Y_1,\ldots,Y_n)$, where $Y_i = y_{im} + y_{ip}$ is the total level of gene expression in the ith individual. The models of Mochizuki et al. (1996), Haig (1997), Iwasa et al. (1999), Kondoh and Higashi (2000), and multiple paternity model of Example 1 (see below), belong to this class. In such models, the conditions for $\Delta W_j = 0$ involve only the sum $\hat{y}_m + y_p$, hence all level curves of the ΔW_j and therefore of the y_j must be straight lines of slope –1. Thus the selection nullclines will have slope –1 and will be given by the equations:

$$u_p : \hat{y}_p = \alpha_m - \hat{y}_m$$
$$u_m : \hat{y}_p = \alpha_p - \hat{y}_m \,.$$

It follows that the nullclines are either identical throughout their length (Case 1), or contain no common points (Case 2). If they are identical, and if also the covariance matrix in (2) is non-singular, the inclusive fitness effects are both zero on the common nullcline and there is no parental antagonism. If they are disjoint, there will be a region where the signs of the Δw_j differ, there will be parental antagonism, and the "loudest voice prevails."

Case 3

Now suppose that the selection nullclines u_m and u_p are distinct and intersect. This implies that fitness is a function of both y_{im} and y_{ip}, and not merely of their sum. For simplicity, we assume that the two nullclines cross transversely at a finite number of points. Under these assumptions, the dynamics of (2) may be much more complicated than the previous cases, with the level of complexity depending on the number of intersections between the nullclines. However, in realistic cases the dynamics are likely to be fairly simple, with the nullclines intersecting only once. Here, we present a number of general results. In the discussion that follows we turn our attention to the more simple cases of a single intersection.

We begin by dividing the phase plane into four kinds of regions (Fig. 5):

$$\begin{aligned} &\text{I:} && y'_m > 0,\ y_p > 0,\\ &\text{II:} && y'_m < 0,\ y_p > 0,\\ &\text{III:} && y'_m < 0,\ y_p < 0,\\ &\text{IV:} && \hat{y}'_m > 0,\ y_p < 0. \end{aligned}$$

Selection is 'opposed' when y'_m, and y_p have opposite sign, and 'congruent' when y'_m, and y_p have same sign. Equilibria occur at all points where the nullclines intersect, as well as at the point $(0, \alpha_p)$, when u_p intersects the y_p-axis lies above u_m, and the point $(\alpha_m, 0)$, when u_m intersects the y_m-axis to the left of u_p. We now turn our attention to the stability of these equilibria.

Let **J** be the Jacobian matrix of the system of equations (2) evaluated at an equilibrium p. Then, p is asymptotically stable if all eigenvalues of **J** have negative real parts.

The eigenvalues of **J**, are:

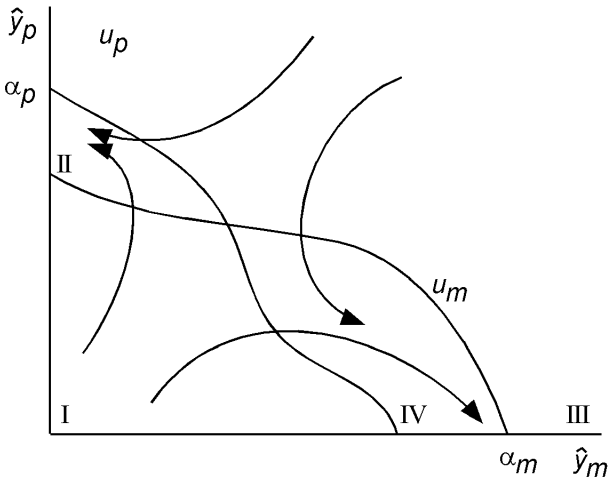

FIG. 5. The maternal and paternal selection nullclines are distinct, but intersect. The phase plane is divided into four kinds of regions:

$$\begin{aligned} &\text{I:} && y'_m > 0,\ y'_p > 0,\\ &\text{II:} && y'_m < 0,\ y'_p > 0,\\ &\text{III:} && y'_m < 0,\ y'_p < 0,\\ &\text{IV:} && y'_m > 0,\ y'_p < 0. \end{aligned}$$

$$\lambda = \frac{-\mathrm{Tr}\mathbf{J} \pm \sqrt{(\mathrm{Tr}\mathbf{J})^2 - 4\mathrm{Det}\mathbf{J}}}{2}, \quad \text{where}$$

$$\mathrm{Tr}\mathbf{J} = v_m \frac{\partial \Delta \hat{W}_m}{\partial \hat{y}_m} + c_{mp}\left(\frac{\partial \Delta \hat{W}_p}{\partial \hat{y}_m} + \frac{\partial \Delta \hat{W}_m}{\partial \hat{y}_p}\right) + v_p \frac{\partial \Delta \hat{W}_p}{\partial \hat{y}_p}.$$

$$\mathrm{Det}\mathbf{J} = \left(v_m v_p - c_{mp}^2\right)\left(\frac{\partial \Delta \hat{W}_m}{\partial \hat{y}_m}\frac{\partial \Delta \hat{W}_p}{\partial \hat{y}_p} - \frac{\partial \Delta \hat{W}_p}{\partial \hat{y}_m}\frac{\partial \Delta \hat{W}_m}{\partial \hat{y}_p}\right)$$

An interior equilibrium is asymptotically stable if $\mathrm{Tr}\mathbf{J} < 0$, and $\mathrm{Det}\mathbf{J} > 0$. These are the standard CSS conditions presented in Abrams et al. (1993). Since $\partial \Delta W_k / \partial y_j < 0$ for $j, k = m, p$, it follows that Tr**J** is always less than zero.

An analysis of our nullclines reveals that a vertex where the slope of u_m is steeper than that of u_p is asymptotically stable (Fig. 6). That is:

$$\text{slope of } u_m = -\frac{\partial \hat{y}'_m}{\partial \hat{y}_p} \Big/ \frac{\partial \hat{y}'_m}{\partial \hat{y}_m} < \text{slope of}$$

$$u_p = -\frac{\partial \hat{y}'_p}{\partial \hat{y}_p} \Big/ \frac{\partial \hat{y}'_p}{\partial \hat{y}_m}.$$

Thus, we have that $\dfrac{\partial \hat{y}'_p}{\partial \hat{y}_p}\dfrac{\partial \hat{y}'_m}{\partial \hat{y}_m} - \dfrac{\partial \hat{y}'_m}{\partial \hat{y}_p}\dfrac{\partial \hat{y}'_p}{\partial \hat{y}_m} > 0$ but

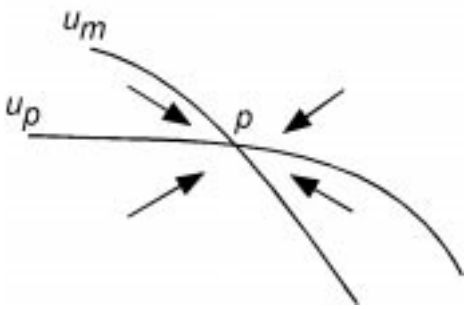

FIG. 6. An interior equilibrium is asymptotically stable if the slope of u_m is steeper than that of u_p.

this is exactly the condition Det**J** > 0. In this case, there is stabilizing selection for biallelic expression (see Example 3 below).

On the other hand, if at a vertex, p, the slope of u_p is steeper than that of u_m, then Det**J** < 0. In this case **J** has an eigenvalue with positive real part and an eigenvalue with negative real part, and thus p is a saddle (Fig. 7). The only other asymptotically stable equilibrium is $(0, \alpha_p)$ when $(0, \alpha_p)$ is above u_m, or $(\alpha_m, 0)$ when $(\alpha_m, 0)$ is to the right of u_p. In this case, there is disruptive selection on parent-specific expression levels that would favor monoallelic expression if the nullclines cross only once.

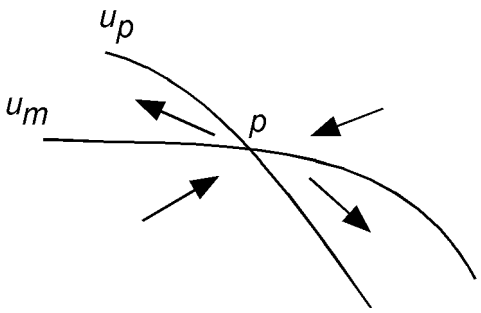

FIG. 7. An interior equilibrium is a saddle and thus unstable if the slope of u_p is steeper than that of u_m

We finish our presentation of the general dynamics with the assertion that every evolutionary trajectory approaches an equilibrium point. However, the evolutionary outcome may depend on initial conditions because multiple evolutionary attractors may exist (for proof of these assertions see Hirsch and Smale, 1974).

6. The relationship between the selection nullclines and the sets $\Delta\hat{W}_j = 0$

This relationship is dependent upon the observed level of genetic covariance, c_{mp}. Suppose that the graphs of the functions $\Delta\hat{W}_j = 0$ are distinct, though they may intersect. Then there are three possibilities. The first is that the maternal and paternal expression levels can evolve independently and $c_{mp} = 0$. In such cases, the selection nullclines and the graphs $\Delta\hat{W}_j = 0$ coincide and thus represent optimal levels of expression for maternally ($j = m$) and paternally ($j = p$) derived alleles. The second possibility is that the maternal and paternal levels are positively correlated, $c_{mp} > 0$ and the covariance matrix is non-singular. In this case, the selection nullclines are located between the graphs of the functions $\Delta\hat{W}_j = 0$, and the nullclines no longer represent optimal levels of expression for maternally and paternally derived alleles. For example, consider a region determined by the graphs $\Delta\hat{W}_j = 0$, for which the curve $\Delta\hat{W}_m = 0$ lies outside the curve $\Delta\hat{W}_p = 0$. At such a point an increase in maternal expression will increase matrilineal inclusive fitness but decrease patrilineal inclusive fitness. Both selection nullclines will run through this region and each one represents a set of strategies that "perfectly balances" the maternally and paternally derived selective pressures from the point of view of that allele. The nullclines, however, will be distinct: this balance is not the same from the perspective of the maternally and paternally derived alleles. The third possibility is that the covariance matrix in (2) is singular, and the nullclines must coincide – there will be no regions in the phase plane where selection is opposed. This will occur, for example, when $\Delta y_m = k\Delta y_p$ for some constant $k>0$.

Non-zero covariances are a constraint on perfect adaptation. An allele that broke these constraints could achieve higher relative fitness than a constrained allele. Therefore, long-term selection at loci subject to parental antagonism might be expected to reduce the genetic covariance term. Whether selection on the rest of the genome might sometimes oppose this process is a question deserving further study.

7. Examples

We now turn our attention to three biological scenarios with different dynamics. For simplicity, we assume for the remainder of the paper that the additive genetic covariance between $\hat{y}_m$ and y_p is zero ($c_{mp} = 0$) . In this case the nullclines u_j are simply the sets $\Delta w_j = 0$. We look at three examples. In Examples 1 and 2, the nullclines have no interior crossing, and the stable equilibrium is on the boundary. In Example 3 there is a single dynamically-stable interior crossing.

Example 1. Multiple paternity

We construct a simple competition model following Taylor and Frank (1996) in which each female mates with exactly n males. During development, littermates compete for maternal resources and an individual's fitness depends upon its relative competitive ability. In the simplest case, an individual's demand for resources is proportional to the total amount of growth factor produced, $Y = y_m + y_p$, such that an individual employing strategy Y in a sib-group with average strategy Z takes a proportion Y/Z of the resources available for development. More precisely, if $G(Z)$ denotes the average fitness within a Z-group, then

$$W = W(Y,Z) = \frac{Y}{Z} \cdot G(Z) \qquad (5)$$

We assume that $G(Z)$ is a concave-down function in Z, so that marginal group fitness decreases with high levels of competition within the group. For example, as competition intensifies, a larger proportion of resources might be wasted in the maintenance of the competition, and fewer resources are actually available for development. This fitness function W has been used previously to model virulence in the evolution of protocells and parasites (Frank, 1994).

The inclusive fitness effects are

$$\Delta \hat{W}_j = (1 - R_j)\frac{G(\hat{Y})}{\hat{Y}} + R_j G'(\hat{Y}) \qquad (6)$$

where $Y = y_m + y_p$ and R_j is the average j-relatedness of the sib group to the focal individual.

A simple model for group fitness with decreasing marginal return is $G(Z) = Z(2–bZ)$. In this case, the optimal level of expression ($\Delta w_j = 0$) from the perspective of the maternally ($j=m$) and paternally ($j=p$) derived genes is given by $Z = 2/b(1+R_j)$. Under this simple mating structure the coefficients of relatedness are $R_m = 1/2$ and $R_p = 1/2n$. Since fitness is a function of total amount of growth factor, we have an example of case A above. With strict monogamy ($n=1$), the relatedness coefficients are identical, $R_m = R_p$, the nullclines coincide, and there is no parental antagonism. For $n > 1$, the nullclines are disjoint and the system is parentally antagonistic. In such cases, paternally derived alleles prefer higher levels of demand than maternally derived alleles (Fig. 8) and we observe that the "loudest voice prevails"—the maternally derived allele becomes inactive and the paternally derived allele operates at its preferred level of expression. The opposite pattern of imprinting is predicted for demand inhibitors (Haig and Wilkins, 2000).

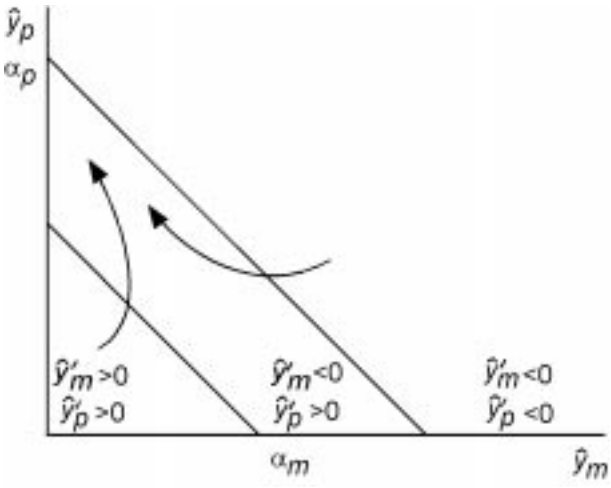

FIG. 8. In case of multiple paternity, the nullclines are disjoint and the system is parentally antagonistic. In this case, paternally derived alleles prefer higher levels of demand than maternally derived alleles and we observe that the "loudest voice prevails"– the maternally derived allele becomes inactive and the paternally derived allele operates at its preferred level of expression

When fitness is a function of the form $W(Y_0,Y_1,\ldots,Y_n)$, the nullclines are straight lines of slope –1 and cannot cross. However, nullclines can cross if fitness is a function of both y_{im} and y_{ip}, and not simply a function of their sum. For example,

sometimes an allele may be expressed on its own without a partner. If so, identical increments of maternal or paternal expression may not have identical effects on fitness, $\partial W/\partial y_{im} \neq \partial W/\partial y_{ip}$. Such might be the case if loss-of-function mutations occur in an allele's partner or if the allele is expressed in post-meiotic germ cells. Such will also often be the case for X-linked alleles subject to random X inactivation because maternal and paternal alleles are then expressed in different cells.

Example 2. The ovarian time bomb

Varmuza and Mann (1994) proposed that the inactivation of maternally-derived alleles at growth-factor loci has evolved as a defence against ovarian trophoblast disease (formally modelled by Iwasa et al., 1999). Maternal silencing is predicted because, for a given level of growth factor, female germ cells are more vulnerable to malignant transformation than are male germ cells. Varmuza and Mann's hypothesis, and the model of Iwasa et al. (1999), both assume a strict dependence between an allele's level of expression in a parent's germ line (i.e. after imprints are reset) and its parent-specific level of expression in subsequent offspring.

As in Example 1, the focal individual is an offspring within a litter. We modify our competition model to include an additional factor that describes the reduction in fitness of the focal individual from the development of ovarian trophoblast disease. The neighborhood of effect includes post-meiotic germ cell tumors that act to reduce the focal individual's probability of survival (ovarian teratomas are derived from oocytes that have already undergone meiosis I: Linder et al., 1975). Half of these tumors will have expression level y_m, and the other half will carry the mother's other allele; and will have an expected expression level $\hat{y}_m$. We assume that the reduction in survival due to ovarian trophoblast disease increases as maternal germ cell expression increases. For simplicity, we will represent this effect on survival by a factor. $\exp\left[-\alpha\left(y_m^2+\hat{y}_m^2\right)\right]$. Similarly, reduced survival from testicular germ cell tumors could be represented by a factor $\exp\left[-\beta\left(y_p^2+\hat{y}_p^2\right)\right]$, but we will follow Varmuza and Mann in assuming β is negligible and effectively zero. Thus, the fitness of the focal individual becomes:

$$W = e^{-\alpha\left(y_m^2+\hat{y}_m^2\right)} \cdot \frac{Y}{Z} \cdot G(Z) \tag{7}$$

and the inclusive fitness effects are

$$\Delta\hat{W}_m = e^{-2\alpha\hat{y}_m^2}\left\{\left(1-R_m\right)\frac{G\left(\hat{Y}\right)}{\hat{Y}} + R_m G'\left(\hat{Y}\right) - 2\alpha\hat{y}_m^2 G\left(\hat{Y}\right)\right\},$$

$$\Delta\hat{W}_p = e^{-2\alpha\hat{y}_m^2}\left\{\left(1-R_p\right)\frac{G\left(\hat{Y}\right)}{\hat{Y}} + R_p G'\left(\hat{Y}\right)\right\} \tag{8}$$

where the R_j are the relatednesses between sibs, as above, and the last term in ΔW_m is multiplied by the relatedness of the focal individual to itself which is 1. In the case of single paternity (n = 1), $R_m = R_p$, and the selection nullclines intersect at (0, α_p) (Fig. 9). This is the only equilibrium point and is evolutionarily stable. In region II of the phase plane (Fig. 9), decreased expression of maternally inherited alleles increases matrilineal inclusive fitness but decreases patrilineal excluded fitness, because of the asymmetric relatedness of germ cell tumors to the focal individual. Thus, in this region, matrilineal and patrilineal inclusive fitness effects have opposite sign, but since matrilineal and patrilineal relatednesses are always equal, there is no parental antagonism.

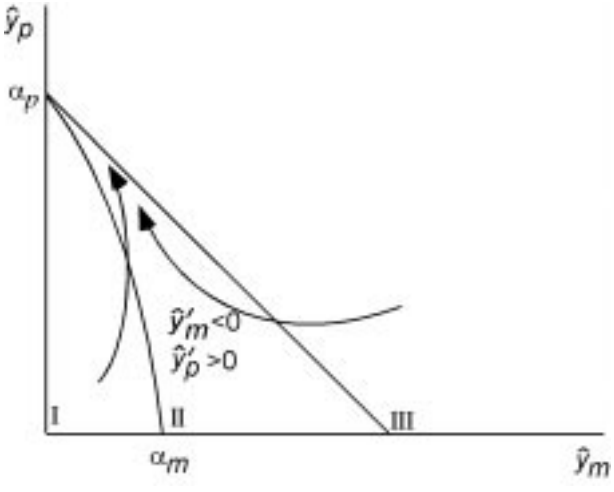

FIG. 9. In the ovarian time bomb, with single paternity, the selection nullclines intersect at the point (0,α_p). This is the only evolutionary equilibrium and it is dynamically stable

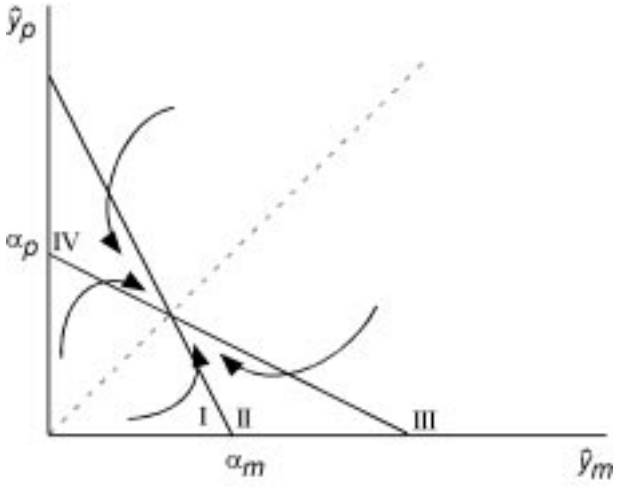

FIG. 10. In case of loss-of-function mutations the maternally and paternally derived alleles are under the same selective pressures and as a result the phase-plane diagram is symmetric through the line $y_m = y_p$. In such cases, there is a single stable interior equilibrium point to which all evolutionary trajectories converge

In the presence of multiple paternity ($n > 1$), $R_m \neq R_p$, the selection nullclines do not intersect and the dynamics conform to case 2 (Fig. 4) and parental antagonism is present as in Example 1.

In the previous two examples the selection nullclines either did not cross or intersected at the boundary of the phase plane. Suppose on the other hand that there is a single interior crossing of the nullclines. This will be an interior equilibrium of the dynamical system that might be stable (Fig. 10) or unstable (Fig. 5). We have had difficulty finding a mathematically simple example of the unstable case. One possibility would be to model allelic exclusion, say for immunoglobulin κ-chains (Mostoslavsky et al., 1998). In this case, there is a selective advantage for an individual B cell to express only one of the (rearranged) alleles at a locus, and one could imagine the choice of which allele to inactivate being based on parental origin. However, in fact, there is an effectively random choice of which allele to inactivate in each clonal lineage. Another possibility would be to model the effects of deleterious mutation under either strict or partial dominance (Hurst, 1997). If the reduction in fitness resulting from deleterious mutation is severe, then there will be a selective advantage for an individual to express only one of the alleles at the locus of interest. This occurs because when only one of the two alleles is active, then half of the time the mutation will occur at the silent allele, and the deleterious effects will not be felt. However, there is no greater advantage for having a maternally silent or paternally silent allele. Again, the choice of which allele to inactivate is effectively random. Example 3, below, provides a case of a stable interior equilibrium.

Example 3. Loss-of-function mutations

We finish by presenting an example in which there is a stable interior equilibrium point to which all evolutionary trajectories converge. Mochizuki et al. (1996) demonstrated that loss-of-function mutations might act to discourage parent-specific allele inactivation. The idea here is that the cost of a loss-of-function mutation will, on average, be less to individuals in which both alleles are expressed equally, than to those in which one of the alleles is expressed at a higher level than the other. We now incorporate this scenario into our model.

Let q be the frequency of loss-of-function mutations within the population of gametes. Realistically, q will change as parent-specific expression levels at the locus evolve, but for simplicity we assume that it is constant. We will assume that females are monogamous, with each mating producing a single zygote so that competition among siblings is absent. In this case, the inclusive fitness function W is

$$W = (1-q)^2 G(y_{0m} + y_{0p}) + \\ + (1-q)q\left[G(y_{0m}) + G(y_{0p})\right] \qquad (9)$$

The matrilineal ($j=m$) and patrilineal ($j=p$) inclusive fitness effects are:

$$\Delta\hat{W}_j = (1-q)^2 G'(\hat{Y}) + (1-q)qG'(\hat{y}_j) \qquad (10)$$

where $Y = y_m + y_p$. The maternally and paternally derived alleles are under the same selective pressures and as a result the phase-plane diagram is symmetric through the line $y_m = y_p$. The maternal ($j=m$, $k=p$) and paternal ($j=p$, $k=m$) selection nullclines are:

$$\hat{y}_j = \frac{1}{b} - (1-q)\hat{y}_k . \qquad (11)$$

The phase-plane diagram is shown in Figure 11. There is a single stable interior equilibrium point to which all evolutionary trajectories converge. The stability of this equilibrium point follows from the fact that the slope of the maternal nullcline u_m is steeper than that of the paternal nullcline u_p.

Mochizuki et al. (1996) modelled the effects of multiple paternity (polyandry) and loss-of-function mutations simultaneously to examine whether loss of function mutation could act to prevent loss of maternal expression in parentally antagonistic systems. They found that in the absence of polyandry the selective pressures on maternally and paternally derived alleles are symmetric and the ESS is found along the line $y_m = y_p$. However, as the frequency of polyandry increases, the paternal selection nullcline moves away from the origin. As a result the equilibrium point shifts from the line $y_m = y_p$, moving away from the y_m–axis and towards the y_p–axis. If polyandry is sufficiently rare (relative to the rate of loss-of-function mutation), then, at evolutionary equilibrium, both the maternally and paternally derived alleles will remain active, with the maternally derived allele expressed to a lesser degree than the paternally derived allele. However, if polyandry is sufficiently common, the selection nullclines will not cross and a maternally silent ESS will be observed.

Loss-of-function mutations provide a selective force that favours biallelic expression. However, the level expression need not be symmetric and it is possible that either a maternally or paternally silent ESS is observed despite the costs of functional hemizygosity. The observed outcome depends upon the relative strength of the disruptive selective force (e.g. parental antagonism) when compared to the observed rate of mutations. Spencer and Williams (1997; also see Spencer, 2000) noted that this selective force was very weak, of the same order as the mutation rate, and would usually be insignificant when there is positive selection for imprinting. It should be noted, however, that the models of Mochizuki et al. (1996) and Spencer and Williams (1997) consider germ line mutations only. Fitness costs of monoallelic expression associated with somatic mutations (e.g., increased predisposition to cancer) is likely to provide a stronger selective force against monoallelic expression, but this is yet to be formally modelled.

8. Discussion

How "special" is the phenomenon of genomic imprinting? At least from a mathematical point of view, does it require a special theory or is it simply an interesting variant of standard models? In genetic terms, we have an allele that finds itself in two different contexts or modes and is able to condition its behaviour accordingly. Similar examples come to mind: genes that find themselves in two types of individuals (male or female), or the same individual at different times (young and old), or different phases (surviving and breeding), or different environmental conditions (forest and field). In each case, the optimal pattern of expression in one mode may differ from the optimal pattern in the other. If these patterns are constrained to be identical in the two modes, natural selection will arrive at some compromise between the two modes, a pattern of expression that is the "best" on average. If the patterns are free to evolve independently, natural selection will favour genes with contingent patterns of expression that employ the optimal pattern in each mode.

In our evolutionary model we were interested in the effect of an allele on its own change in frequency $\Delta\hat{g}$, The analysis of the Appendix (A5 and A6) decomposed this effect into two components: dx_j, an allele's effect on expression level in mode j; and Δw_j, the effect of dx_j on inclusive fitness in mode j. The latter is, itself, the sum of the products of $\partial W/\partial y_{ij}$, the mode-$j$ effect of gene expression in individual i on the fitness of the focal individual, and R_{ij}, the mode-j relatedness of individual i to the focal individual. Evolutionary models sometimes restrict attention to only one mode, implicitly assuming that the allele is expressed only in that mode and the dx_j in the other is zero (e.g. sex-limited characters). Sometimes the models assume a tradeoff between the two modes (antagonistic pleiotropy), so that the $\partial W/\partial y_{ij}$ may be of different sign. For example, one's relatedness to neighbours might differ in the two modes (when young you are more likely to be with sibs, etc.) so that different relatednesses would be used for different j, and we would need a general expression such as (1) for inclusive fitness.

Haig (1997, 2000a) reformulated the concept of inclusive fitness using coefficients of parent-specific relatedness. Above we provide a general

mathematical framework for his "matrilineal" and "patrilineal" inclusive fitnesses using the direct fitness formulation of Taylor and Frank (1996) and a dynamic model of continuous-trait evolution. The difference between the inclusive fitness and direct fitness formulations is really just one of accounting: whether the focal individual is regarded as the recipient (the direct fitness approach) being affected by the behaviour of others, or the actor (the inclusive fitness approach) affecting the fitness of others. In models of genomic imprinting it is crucial to keep in mind which approach is being used as the relatedness coefficients are seldom symmetric (Haig, 2000a). In the direct fitness approach, relatedness is determined by taking a random maternal or paternal allele in individual *i* and then calculating its frequency in the focal individual. From a mathematical standpoint, the direct fitness formulation has advantages, because the inclusive fitness effect is easily obtained from the "fitness function" that relates the fitness of the focal individual to the behaviour of others. However, we often find the inclusive fitness approach more intuitive, with its emphasis on the fitness of a focal gene rather than a focal individual, especially when the population contains different classes of individuals.

The authors are not in total agreement about the efficacy of the continuous-trait model for understanding the evolution of genomic imprinting. This model assumes that a large number of alleles are segregating at a locus and tracks selective changes in the mean level of expression of a population. This approach, in its application to the evolution of genomic imprinting, was pioneered by Mochizuki et al. (1996). If one views the evolution of genomic imprinting as taking place by a series of selective sweeps in which better adapted alleles arise as new mutations and successively replace less adapted alleles (Haig, 1999), then the use of variances and covariances is somewhat problematic. The constraints on perfect adaptation become the non-occurrence over evolutionary of mutations time that uncouple antagonistic pleiotropic effects, not the covariance between the expression in different modes of the alleles currently present in a population. Complete unanimity and consistency would somehow be inappropriate in a collective work on internal conflicts, and all of us have found the process useful in clarifying our own ideas.

Acknowledgements

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APPENDIX

A)

Fasten attention on a rare mutant allele at the imprinted locus. Let its frequency at the maternal and paternal locus in a random individual i be g_{im} and g_{ip} (these will take values either 0 or 1). We use ^ to denote population-wide average. Hence $\hat{g}_m$ and $\hat{g}_p$ are the population frequencies of the mutant allele at the two loci. For simplicity, we will assume that the allele has no sex specific effects, then the frequency in mature males and females should be the same and $\hat{g}_m = \hat{g}_p = \hat{g}$. Let the maternal ($j=m$) and paternal ($j=p$) level of gene expression (the phenotype) in individual i be y_{ij} and let these have population average $\hat{y}_j$. Let the *maternal* and *paternal effects* dx_m and dx_p of the mutant allele be defined as the slope of the regression of y_{im} and y_{ip} on mutant allele frequency:

$$dy_{ij} = g_{ij} dx_j + \varepsilon_{ij} \qquad \text{(A1)}$$

where $dy_{ij} = y_{ij} - \hat{y}_j$ is the phenotypic deviation of individual i due to the mutant allele, and ε_{ij} has mean zero and is uncorrelated with g_{ij}. We assume that the dx_j are small – this is the reason for using differential notation. This "weak selection" assumption is standard in inclusive fitness arguments and we will use it to show that if selection changes the population wide allele frequency by an amount $\Delta\hat{g}$, then the change in the population mean $\hat{y}_j$ is given by:

$$\Delta \hat{y}_j = \Delta\hat{g}\ dx_j \qquad \text{(A2)}$$

Here are the details of this argument.

The slope dx_j of the regression in (A1) will, in general, depend on the population mean $\hat{g}$:

$$dy_{ij} = g_{ij} dx_j(\hat{g}) + \varepsilon_{ij}$$

If we use a "bar" to denote population mean after selection, then the mean phenotype deviations before and after selection are $dy_j = g dx_j(g)$, and $dy_j = g dx_j(g)$. Thus, the change in mean phenotype is

$$\Delta\hat{y}_j = d\bar{y}_j - d\hat{y}_j = \bar{g}dx_j(\bar{g}) - \hat{g}dx_j(\hat{g}) =$$

$$= (\bar{g} - \hat{g})dx_j(\hat{g}) + \bar{g}\left(dx_j(\bar{g}) - dx_j(\hat{g})\right)$$

$$= \Delta\hat{g}dx_j(\hat{g}) + \bar{g}\left(dx_j'(\hat{g})\Delta\hat{g} + o(\Delta\hat{g})\right) \qquad \text{(A3)}$$

where the "prime" denotes derivative of the dx_j. Now the second term is second order in the dx_j. Indeed the derivative of dx_j is certainly first order in dx_j and we will show below (A5) that $\Delta\hat{g}$ is also first order in the dx_j. It then follows that (A2) is valid to first order in the dx_j .

To model the population wide change in frequency of our mutant allele, $\Delta\hat{g}$, we use the direct fitness approach of Taylor and Frank (1996) which adds up the fitness effects of neighbours on a randomly chosen "focal" individual. Let i run over the interaction neighbourhood of the focal individual (with i=0 for the focal individual).

Assuming differentiability of the fitness function W, the fitness of the focal individual can then be written

$$W_0 = \hat{W} + \sum_i \left[\frac{\partial W}{\partial y_{im}} dy_{im} + \frac{\partial W}{\partial y_{ip}} dy_{ip} \right]$$

$$= \hat{W} + \sum_i \left[\frac{\partial W}{\partial y_{im}} g_{im} dx_m + \frac{\partial W}{\partial y_{ip}} g_{ip} dx_p \right] \qquad \text{(A4)}$$

where the sum is over the focal neighbourhood and the partial derivatives of W are evaluated at the population mean $y_{ij} = y_j$. Let g_0 be the mutant frequency among the gametes of the focal individual. We make an assumption of fair meiosis which gives us $g_0 = (g_{0m} + g_{0p})/2$. According to Price's (1972) covariance theorem the change $\Delta\hat{g}$ in population-wide mutant frequency $\hat{g}$ due to the differential effects of fitness is given by the equation:

$$\Delta\hat{g} = \frac{\mathrm{cov}(g_0, W_0)}{\hat{W}} =$$

$$= \frac{1}{\hat{W}} \sum_i \left[\frac{\partial W}{\partial y_{im}} \mathrm{cov}(g_0, g_{im}) dx_m + \frac{\partial W}{\partial y_{ip}} \mathrm{cov}(g_0, g_{ip}) dx_p \right]$$

$$= \frac{\mathrm{var}(g_0)}{\hat{W}} \sum_i \left[\frac{\partial W}{\partial y_{im}} R_{im} dx_m + \frac{\partial W}{\partial y_{ip}} R_{ip} dx_p \right]. \qquad \text{(A5)}$$

where the matrilineal (j=m) and the patrilineal (j=p) relatedness of individual i (as actor) to the focal individual (as recipient) is

$$R_{ij} = \frac{\mathrm{cov}(g_0, g_{ij})}{\mathrm{cov}(g_0, g_{0j})}. \qquad \text{(A6)}$$

(Michod and Hamilton, 1980). To obtain (A5) we have used the fact that $\mathrm{cov}(g_0, g_{0j}) = \mathrm{cov}(g_0, g_0)$ for $j = m, p$. This follows from the fact that $g_0 = (g_{0m} + g_{0p})/2$ and our assumption (above) that there are no sex-specific effects.

A word is needed about notation in (A6). For example, why have we chosen to write the denominator as $\mathrm{cov}(g_0, g_{0j})$ rather than $\mathrm{cov}(g_0, g_0)$? Relatedness is a quotient of covariances – covariances between transmission effectiveness and effect on behaviour. That is, from the point of view of an allele trying to propagate itself through its effect, two individuals are genetically similar if a behavioural change in one is correlated with a change in transmission frequency of the relevant allele in the other. In the above analysis, g_0 works as a transmission variable whereas the $g_{\bullet j}$ determine behaviour.

With the maternal and the paternal inclusive fitness effects defined by equation (1), equation (A5) tells us that the change in population-wide frequency of the mutant allele has the form

$$\Delta\hat{g} = \frac{\mathrm{var}(g_0)}{\hat{W}} \left(\Delta\hat{W}_m dx_m + \Delta\hat{W}_p dx_p \right). \qquad \text{(A7)}$$

Note that the effect of the allele on its frequency is expressed in (A7) as the sum of two terms, one for each parent j, each of which is the product of two factors – the effect dx_j of the allele on the level of expression, and the effect ΔW_j of this expression on inclusive fitness.

Putting (A2) and (A7) together, we get

$$\Delta\hat{y}_j = \frac{\mathrm{var}(g)}{\hat{W}} \left(\Delta\hat{W}_m dx_m dx_j + \Delta\hat{W}_p dx_p dx_j \right). \qquad \text{(A8)}$$

Finally, we are interested in the relationship between dx_m and dx_p . The point is that these might not be independent and that there might be some correlation among the pairs that are physically attainable. To model this we suppose that there are a large number of possible forms of the mutant

allele each with its own (dx_m, dx_p) pair and population frequency $\hat{g}$ and we suppose that the average mutant maternal and paternal effect is zero: $\mathrm{E}(\hat{g}\,dx_j) = 0$ for $j = m, p$ where E denotes the expectation over all mutant alleles. Then the overall change in the population mean y_j is the average of (A8) over all mutant alleles. To take this average, we use the fact that for each mutant allele,

$$\mathrm{var}(g) = \hat{g}(1-\hat{g})\frac{1+F}{2} = \hat{g}\,\frac{1+F}{2} + \mathrm{o}(\hat{g}) \qquad \text{(A9)}$$

where F is the inbreeding coefficient. Henceforth we will use the assumption that all mutant alleles are rare to ignore terms in $\mathrm{o}(\hat{g})$. Then

$$\begin{aligned}\Delta\mathrm{E}(\hat{y}_j) &= \frac{1+F}{2\hat{W}}\,[\,\Delta\hat{W}_m\,\mathrm{E}(\hat{g}\,dx_m\,dx_j) + \\ &\quad + \Delta\hat{W}_p\,\mathrm{E}(\hat{g}\,dx_p\,dx_j)] \\ &= \frac{1+F}{2\hat{W}}\,[\,\Delta\hat{W}_m\,\mathrm{cov}(dx_m\,,\,dx_j) + \\ &\quad + \Delta\hat{W}_p\,\mathrm{cov}(dx_p\,,\,dx_j)] \qquad \text{(A10)}\end{aligned}$$

and this (discrete-time) equation forms the basis of our dynamical system (2). To do this we note that the time step for the above equation is one generation and this is very small in terms of evolution, so we call it dt and then $\Delta\mathrm{E}(y_j)$ becomes $d\mathrm{E}(y_j)$ and we divide by dt to get the differential equation.

In a number of cases of interest, fitness W is a function of individual phenotype Y and sib-group average phenotype Z : $W = W(Y, Z)$ and these in turn are simply the sum of maternal and paternal levels of expression $Y = y_{0m} + y_{0p}$ and $Z = z_m + z_p = \mathrm{E}_i(y_{im} + y_{ip})$ where the expectation E_i is over the sib group. In this case the inclusive fitness effect (1) is:

$$\Delta\hat{W}_j = \frac{\partial W}{\partial Y} + \frac{\partial W}{\partial Z}R_j \qquad \text{(A11)}$$

where $R_j = \mathrm{E}_i(R_{ij})$ is average relatedness between two sibs (with replacement).