A Gene's-Eye View of Symbiont Transmission

Jeff Smith*

Department of Biology, Emory University, Atlanta, Georgia 30322

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ABSTRACT: Symbiotic associations between species are ubiquitous, but we only poorly understand why some symbioses evolve to be mutualistic and others to be parasitic. One prominent hypothesis holds that vertical transmission of symbionts from host parents to their offspring selects for symbionts that are benign or beneficial, while horizontal transmission of symbionts among unrelated hosts selects for symbionts that are less beneficial or outright harmful. A long-standing challenge to this hypothesis, however, is the existence of selfish genetic elements (SGEs). SGEs are passed exclusively from parent to offspring and are able to spread and persist in populations despite reducing the fitness of their hosts. Here I show that SGEs are in fact consistent with the transmission mode hypothesis if one measures transmission from the perspective of host genes instead of host organisms. Both meiotic drive genes and cytoplasmic sex ratio distorters require horizontal transmission, in the form of outbred sex, to spread as parasites. Transmission from parent to offpsring does not constrain SGEs to evolve toward mutualism. The gene-centered perspective I present here is applicable to symbioses at all levels of selection and brings closer together our understandings of cooperation within and between species.

Keywords: mutualism, selfish genetic elements, social evolution, symbiosis, vertical transmission, virulence.

Symbioses—intimate associations between species that can be mutualistic or parasitic—are ecologically abundant and phylogenetically diverse (de Bary 1879; Paracer and Ahmadjian 2000). They play an important role in evolution and are responsible for some of the major transitions in biological organization (Maynard Smith and Szathmáry 1995). Symbiosis can be thought of as cooperation and conflict between species—or more generally, between genetically dissimilar units. But unlike cooperation within species, where kin selection provides a unifying evolutionary principle (Queller 2000), there is no broadly supported theory with which to understand the evolution of symbiosis. When do symbionts evolve to increase or decrease the fitness of their hosts?

Much of our current conceptual framework for this question comes from work on the evolution of pathogen virulence, which seeks to understand when infectious diseases evolve to inflict more or less harm on their hosts (Dieckmann et al. 2005). Theoretical work in this field often models virulence as an increase in host mortality caused by infection (Anderson and May 1982; Lipsitch et al. 1995, 1996). Empirical studies, on the other hand, intepret virulence more broadly to include nonlethal damage and reductions in host fitness (Herre 1993; Ebert 1994; Mackinnon and Read 1999). This last meaning is most relevant to symbiosis. By definition, a symbiont's effect on the fitness of its host determines whether it is a parasite or a mutualist. In this article, I use the word "virulence" to mean the amount that infection reduces a host's fitness.

Virulence evolution is an active area of study, with many hypotheses competing for favor (Dieckmann et al. 2005). The most prominent of these proposes that virulence is largely determined by how symbionts are transmitted. In this view, horizontal transmission of symbionts among unrelated hosts favors increased virulence as a by-product of selection for increased infectiousness (Anderson and May 1982). Vertical transmission of symbionts from host parents to their offspring selects for decreased virulence by aligning the reproductive interests of both symbiotic partners. At the extreme, symbionts that have only vertical transmission can persist only if they increase their host's fitness (Fine 1975; Lipsitch et al. 1995, 1996). This transmission mode hypothesis has some empirical support, and its application to vertically transmitted symbionts in particular has been hailed as "an unmatched series of successes" (Ebert and Bull 2003, p. 19).

There is concern, however, over the scope of its applicability. Trade-offs between transmission mode and virulence may not be universal (Ebert and Bull 2003). Even when they are present, they sometimes explain little or

* Present address: Department of Biology, Indiana University, Bloomington, Indiana 47405; e-mail: smith74@indiana.edu.

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none of the response to selection (Turner et al. 1998; Messenger et al. 1999). Moreover, much of the empirical support for the hypothesis comes from extreme situations unlikely to reflect natural conditions (Fenner and Ratcliffe 1965; Bull et al. 1991) or has trouble distinguishing between the direct effects of transmission and confounding factors such as interactions among pathogens within hosts (Herre 1993).

Another problem with the transmission mode hypothesis is the existence of selfish genetic elements (SGEs). SGEs are genomic parasites that manipulate the genetic system of their hosts to favor their own transmission (Leigh 1991; Hurst and Werren 2001; Burt and Trivers 2006). Examples include segregation distorters, transposable elements, B chromosomes, homing endonucleases, and cytoplasmically inherited microorganisms. These elements often reduce host fitness, either by directly reducing survival and fecundity or by shifting sex ratios away from the host's optimum (Hurst et al. 1996; Mouton et al. 2004). They can invade and persist in host populations even while being transmitted exclusively from parent to offspring. Theoretical treatments of virulence evolution have recognized the problem posed by SGEs but have so far simply excluded them from analysis (Fine 1975; Lipsitch et al. 1995, 1996). Some authors cite SGEs as a limitation or failure of the transmission mode hypothesis (Herre et al. 1999) while others claim that SGEs should evolve toward mutualism (Camacho et al. 2000; Weeks et al. 2007).

Here I show that SGEs are entirely consistent with the transmission mode hypothesis if one measures transmission from the perspective of host genes instead of host organisms. It takes a gene-centered view of fitness to understand the evolution of SGEs (Hurst et al. 1996; Hurst and Werren 2001), so why not take a gene-centered view of transmission as well? Vertical transmission would then be host and symbiont genes sharing host bodies across generations, while horizontal transmission would be the movement of symbionts such that they share bodies with new host gene lineages. Virulent SGEs can thus persist because they exploit the horizontal transmission inherent in sexual reproduction.

That SGEs depend on outbred sex is well known (Hickey 1982; Bestor 1999; Hurst and Werren 2001) and has some empirical support (Futcher et al. 1988; Zeyl et al. 1996; Burt and Trivers 1998; Goddard et al. 2001; but see Zeyl et al. 1994; Shoemaker et al. 2002). The idea that SGEs are genomic parasites, however, has not progressed much further than metaphor. All comparisons with conventional pathogens have so far been qualitative. Here I present a theoretical treatment of symbiont transmission that quantifies the gene-centered transmission argument, makes explicit the similarities and differences between genomic and conventional parasites, and is applicable to symbioses at all levels of selection.

Model and Results

General Formulation

My approach is based on the Price equation (Price 1970, 1972), which partitions evolutionary change into two components: change due to selection and change due to heredity. If each individual in a population has some Malthusian fitness m and some value z for a character of interest (see table 1 for a list of terms and their definitions), then the Price equation states that the change over time of the mean character value of a population is equal to the covariance of that character with fitness plus the expected character change between parent and offspring:

$$\frac{d\bar{z}}{dt} = \mathrm{Cov}(m, z) + \mathrm{E}\left(\frac{dz}{dt}\right) \quad (1)$$

(for derivation, see the appendix in the online edition of the *American Naturalist*). To make the Price equation relevant to symbiosis, we can take our character of interest to be carriage of the symbiont, so that $z = 1$ if a host is infected and $z = 0$ if it is not. The fraction of the host population infected is thus $\bar{z}$, and equation (1) describes the population dynamics of infection.

The first term on the right-hand side of equation (1) describes how infection frequency changes due to the symbiont's effect on host fitness. This term can be rewritten $\mathrm{Cov}(m, z) = \alpha \mathrm{Var}(z)$, where α is the regression coefficient of symbiont carriage on fitness and $\mathrm{Var}(z)$ is the population variance for symbiont carriage. If infected individuals have fitness m_1 and character z_1 and uninfected individuals have m_0 and z_0, then $\alpha = (m_1 - m_0)/(z_1 - z_0) = (m_1 - m_0)/(1 - 0) = m_1 - m_0$. The value of α is thus the difference in fitness between infected and uninfected hosts. If α is positive, then the symbiont increases host fitness and is by definition a mutualist. If α is negative, then the symbiont decreases host fitness and is a parasite. Parasites are more virulent when they have larger negative values of α.

The second term on the right-hand side of equation (1) describes how infection frequency changes due to inheritance of the symbiont. The mean character value of an infected host lineage can change due to imperfect inheritance (incomplete vertical transmission), while the mean character value of an uninfected host lineage can change due to inheritance of the symbiont from unrelated infected individuals (horizontal transmission). These possibilities are diagrammed in figure 1.

Let total number of infected and uninfected hosts be

Table 1: Notation used

Symbol	Model	Explanation
n	All	Numerical abundance
q	All	Population frequency
z	All	Character value
m	All	Malthusian fitness in continuous-time models
w	All	Fitness in discrete-time models
α	All	Effect of symbionts on the fitness of infected hosts
H	All	Horizontal transmission
L	All	Symbiont loss
S	Conventional pathogen	No. susceptible hosts
I	Conventional pathogen	No. infected hosts
N	Conventional pathogen	Host population size
K	Conventional pathogen	Host carrying capacity
b	Conventional pathogen	Rate at which hosts give birth to offspring of the same type
ϵ	Conventional pathogen	Rate at which infected hosts give birth to uninfected hosts
u	Conventional pathogen	Death rate
β	Conventional pathogen	Mass-action infection constant
δ	Meiotic drive, sex ratio distorter	Distortion constant
f	Meiotic drive, sex ratio distorter	Inbreeding coefficient
μ	Sex ratio distorter	Investment in male gametes
ϕ	Sex ratio distorter	Investment in female gametes
G	Sex ratio distorter	Total gamete production
S	Sex ratio distorter	Sex ratio, measured as fraction of males in gamete pool

n_1 and n_0, respectively; let them be fraction q_1 and q_0 of the host population. We then write $\mathrm{E}(dz/dt) = q_0\dot{z}_0 + q_1\dot{z}_1 = q_1(q_0\dot{z}_0/q_1 + \dot{z}_1) = \bar{z}(n_0\dot{z}_0/n_1 + \dot{z}_1) = (H - L)\bar{z}$, where $H = n_0\dot{z}_0/n_1$, $L = -\dot{z}_1$, and the dot indicates differentiation with respect to time. The value of H is equal to the rate at which uninfected hosts become infected, per infected host. I define H as horizontal transmission. The value of L is equal to the rate at which infected host lineages become uninfected. I define L as symbiont loss. It includes the production of uninfected offspring (incomplete vertical transmission) as well as loss of infection due to, for example, immune clearance.

Substituting the above terms into equation (1), the dynamics of symbiont infection are

$$\frac{d\bar{z}}{dt} = \alpha\,\mathrm{Var}\,(z) + (H - L)\bar{z}. \qquad (2)$$

Because $\mathrm{Var}\,(z)$, L, and $\bar{z}$ are always positive, any symbiont that is parasitic, with $\alpha < 0$, must have horizontal transmission to become more frequent.

So far, this notation could easily be interpreted in the standard organismal view of symbiont transmission. The key to understanding SGE transmission, however, is to take a gene-centered interpretation of equation (2). In this interpretation, the Price equation refers not to a population of host individuals but to a population of host genes. "Infection" then means that symbionts and host genes share an individual host body. With a gene-centered interpretation of equation (2), we can compare the transmission rates of conventional and genomic symbionts on equivalent terms. Below, I apply this terminology to models of the three different symbionts: a conventional microbial pathogen, a meiotic drive gene, and a cytoplasmic sex ratio distorter.

Conventional Pathogen

The theoretical expectation that vertical transmission selects for avirulent or beneficial symbionts was developed

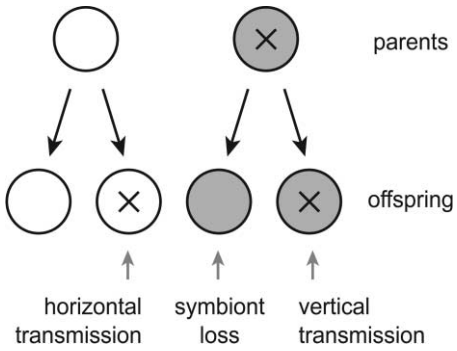

Figure 1: Diagrams of symbiont transmission from the perspective of host genes. Circles represent host individuals. X indicates symbiont infection ($z = 1$). Gray indicates host gene lineages infected in the parental generation ($i = 1$). White indicates host gene lineages uninfected in the parental generation ($i = 0$).

in an epidemiological model of an infectious agent, such as a virus or a bacterium that can be passed from parent to offspring. Using the model of Lipsitch et al. (1995) as a theoretical control, I now show that the measures of symbiont transmission derived above are identical to the conventional measures of horizontal and vertical transmission. In the model, the density of individuals susceptible to infection by the pathogen is S, while the density of those already infected is I. The total population density is N. Population growth is logistic with carrying capacity K. Each class of individuals i has a birth rate b_i and death rate u_i. The infection process follows mass action dynamics with an infection rate β. Vertical transmission of the pathogen to an individual's offspring is imperfect, so that infecteds give birth to new infecteds at a rate b_I and to new susceptibles at a rate ϵ. The dynamics of susceptible and infected densities are thus

$$\frac{dS}{dt} = b_S S\left(1 - \frac{N}{K}\right) - u_S S - \beta SI + \epsilon I\left(1 - \frac{N}{K}\right),$$

$$\frac{dI}{dt} = b_I I\left(1 - \frac{N}{K}\right) - u_I I + \beta SI.$$

Using the above measures, horizontal transmission is

$$H = \beta N q_0 \tag{3}$$

(see appendix). Equation (3) shows that horizontal transmission is proportional to the infection constant, population density, and the frequency of susceptible individuals. This is the conventional view of horizontal transmission for a pathogen with density-dependent dynamics (Lipsitch et al. 1995).

Symbiont loss is

$$L = \epsilon\left(1 - \frac{N}{K}\right) \tag{4}$$

(see appendix). Equation (4) shows that symbiont loss is the rate at which infected hosts produce uninfected offspring. This is the conventional view of vertical transmission (Lipsitch et al. 1995). In one sense, these results are unsurprising: epidemiological models like this one effectively assume that the host is haploid and asexual. Gene-level and organism-level measures of transmission would thus be identical.

Meiotic Drive

Gene-based measures of transmission give less trivial results when applied to germline parasites like SGEs. Consider the case of meiotic drive, in which a driving allele is inherited by more than half of a heterozygote's gametes. The terminology is somewhat arbitrary, but it is convenient to measure the transmission of a driving allele (which we label the "symbiont") from the perspective of some other locus in the genome (which we label the "host").

I use a simple, idealized model of meiotic drive in which organisms are isogamous, obligately sexual, and diploid. There is one driving allele at an autosomal locus. The host, or reference, locus is autosomal, selectively neutral, and unlinked to the drive locus. It is possible to measure transmission from the perspective of linked or cytoplasmic loci, but my goal here is only to illustrate how gene-based measures of transmission can be applied to SGEs, not to provide an exhaustive treatment. The model is shown schematically in figure 2.

Let a fraction $(1 + \delta)/2$ of a heterozygote's gametes contain the drive allele. This means a fair meiosis would have $\delta = 0$, while an allele that completely excludes its counterpart would have $\delta = 1$. At the drive locus, the driving and nondriving alleles are present in the population at frequencies q_1 and q_0, respectively. Let the frequencies of individuals with zero, one, or two copies of the driving allele be Q_0, Q_1, and Q_2, respectively, with absolute fitnesses W_0, W_1, and W_2. Under inbreeding, the frequency of heterozygotes is $Q_1 = 2q_1q_0(1 - f)$, where f is Wright's inbreeding coefficient (Crow and Kimura 1970) at the drive locus.

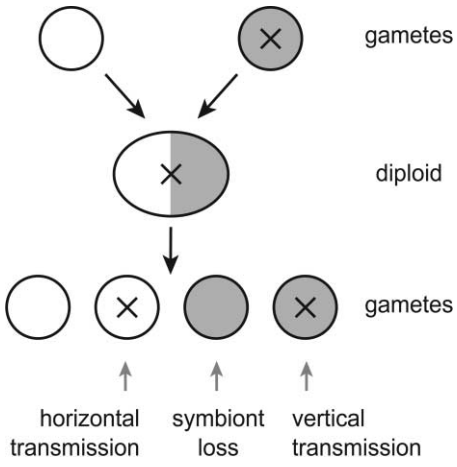

Figure 2: Transmission of a meiotic drive allele from the perspective of genes at an unlinked locus. Circles represent gametes, and ovals represent the diploids formed by these gametes. *X* indicates carriage of the meiotic drive allele. Gray indicates gene lineages at an unlinked locus that share gametes with the drive allele in the parental generation. White indicates gene lineages at an unlinked locus that do not share gametes with the drive allele in the parental generation. For simplicity, only the heterozygote is shown.

Applying our gene-based measure of horizontal transmission to this model, we find

$$H = W_1 q_0 \left(\frac{1+\delta}{2}\right)(1-f) \tag{5}$$

(see appendix). In general, this term is not equal to zero. Meiotic drive elements may thus be passed exclusively from parent to offspring, but from a gene's point of view, they are transmitted to some extent horizontally.

Comparing equations (5) and (3) shows that horizontal transmission is similar in many ways for both meiotic drive genes and conventional pathogens. The drive term $(1 + \delta)/2$ is analogous to the infection parameter β. Both are proportional to the frequency of uninfected lineages q_0. But whereas potential infectious contacts for directly transmitted pathogens occur at a rate proportional to total population density N, for germline pathogens they occur proportionally to the fitness of heterozygotes W_1 and to the outbreeding coefficient $(1 - f)$.

In effect, heterozygotes are where genetic lineages are allowed to mix and share their symbionts (alleles at other loci). Meiotic drive genes thus have horizontal transfer because of recombination and reassortment in heterozygotes. A decrease in the frequency of heterozygotes due to inbreeding or self-fertilization would constrain horizontal transmission. This inhibitory effect of inbreeding on the spread of driving elements is well known and empirically supported (Futcher et al. 1988; Goddard et al. 2001). We can now understand it as a constraint on horizontal transmission.

Symbiont loss in the meiotic drive model is

$$L = W_1 q_0 \left(\frac{1-\delta}{2}\right)(1-f) \tag{6}$$

(see appendix). This is very similar to equation (5) for H, except that it decreases with increasing δ. In other words, drive increases vertical as well as horizontal transmission. This happens because heterozygotes also contribute to symbiont loss. Because of the genetic shuffling that happens in heterozygotes, half of any heterozygote's gametes that do not have the driving element will have host alleles that used to share gametes with the element in the previous generation (in the gametes that formed that heterozygote). Increased drive reduces the number of gametes without the driving element and thus reduces symbiont loss. By the same argument, inbreeding decreases the number of organisms in which gene lineages are allowed to mix, thus increasing cotransmission of host and symbiont genes.

Notice that even if meiosis is fair at the drive locus, so that $\delta = 0$, H and L are still not equal to zero. This means that sexual recombination and reassortment create some level of horizontal transmission for all genes, not just selfish ones. For fair genes, horizontal transmission is exactly balanced by an equivalent amount of symbiont loss, so that $H = L$. The population genetics of such fair genes are then solely determined in this model by the genes' effects on their hosts' fitness. The equivalent dynamic in a pathogen context would be an infectious agent that does not reproduce within its host, so that every new host infected would be balanced by the previous host losing its infection. Horizontal transmission of fair genes is equal to zero, however, under complete selfing or inbreeding ($f = 1$). Gene-level horizontal transmission is thus not limited to selfish genetic elements—it is an inherent feature of sexual reproduction.

Cytoplasmic Sex Ratio Distorter

Now consider a different class of SGE: cytoplasmic elements that distort sex ratios to favor females and thus their own transmission. A simple case to model is one in which the host is hermaphroditic, capable of producing both male and female gametes. One example of such a system is cytoplasmic male sterility in plants, where mutant mitochondria shut down pollen production and thus reallocate resources to seed production (Schnable and Wise 1998). The model is shown schematically in figure 3. As in the meiotic drive model, we can measure transmission of the sex ratio distorter from the perspective of host genes at a nuclear autosomal locus. In this case, we take "infection" to mean that host genes share a zygote with distorters.

In the model, hosts produce a total gametic output G_i, which is divided into male output μ_i and female output ϕ_i. Uninfected hosts invest in male and female gamete production equally, so that $\phi_0 = \mu_0 = G_0/2$. Infected hosts have female-biased investment, so that $\phi_1 = G_1(1 + \delta)/2$, where δ measures the degree of sex ratio distortion ($\delta = 0$ for no bias, $\delta = 1$ for complete female bias). The next generation of hosts is produced from mating within the gamete pool, with an inbreeding or selfing rate f.

Horizontal transmission of the distorter is then

$$H = G_1 \left(q_0 \frac{G_0}{2\bar{\mu}}\right)\left(\frac{1+\delta}{2}\right)(1-f) \tag{7}$$

(see appendix). Because outbred sexual recombination shuffles nuclear genes among cytoplasms, sex ratio distorters are also transmitted horizontally to some extent. Maternal transmission does not by itself constrain SGEs to evolve toward mutualism. Equation (7) is very similar

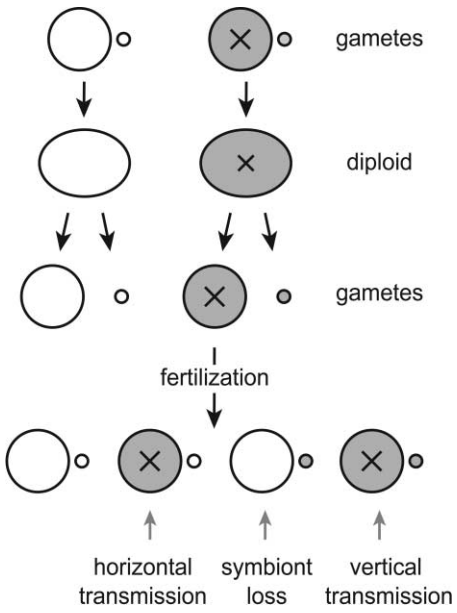

Figure 3: Transmission of a cytoplasmic sex ratio distorter from the perspective of genes at a nuclear autosomal locus. Large circles represent female gametes that transmit the distorter, and small circles represent male gametes that do not. Gray indicates gene lineages at a nuclear autosomal locus that share a zygote with the sex ratio distorter in the parental generation. White indicates nuclear gene lineages that do not share a zygote with the sex ratio distorter in the parental generation.

to equation (5) for horizontal transmission of meiotic drive genes. One difference is that the frequency of uninfected hosts q_0 is now scaled by a factor inversely proportional to $\bar{\mu}$, the mean investment in male gametes. Because every fertilization requires a male gamete, this scaling puts a lower limit on horizontal transmission when distortion is very strong. In these situations, most male gametes will come from uninfected hosts and thus contribute to horizontal transmission, even when uninfected hosts are very rare.

Symbiont loss in this model is

$$L = G_1\left(q_0\frac{G_0}{2\bar{\mu}}\right)\left(\frac{1-\delta}{2}\right)(1-f) \tag{8}$$

(see appendix). This again is similar to the meiotic drive case with the scaling mentioned above. Sex ratio distortion, like meiotic drive, decreases symbiont loss and increases vertical transmission of the distorting element. For both SGEs, inbreeding increases vertical transmission and decreases horizontal transmission.

The biggest difference between the meiotic drive and sex ratio distorter models is in their effect on the fitness of host genes. Host fitness in both models depends on total gametic output, but in the sex ratio distorter model, it also depends on fertilization success. Since male gametes compete for fertilization, the ultimate reproductive success of a host will depend on the sex ratio of its own gametes compared to the sex ratio of the total gamete population. In particular, hosts in female-biased populations can gain greater fitness by producing a male-biased sex ratio (Fisher 1930; Charnov 1982).

The fitness effect of the distorter is

$$\alpha = W_0\left(\frac{G_1}{G_0} - 1\right) - \delta G_1\left(\frac{S^*}{S} - 1\right) \tag{9}$$

(see appendix). Here, S is the population sex ratio, measured as the fraction of male gametes in the gamete pool, and S^* is the evolutionarily stable sex ratio (ESSR) for an uninfected population, given the inbreeding rate. The first term on the right-hand side of equation (9) describes the distorter's effect on host fitness through its effect on total gametic output. If the distorter reduces total gametic output such that $G_1 < G_0$, this fitness term will be negative. The second term in equation (9) describes the distorter's effect on host gene fitness through its effect on sex ratio. This term is proportional to the degree of sex ratio distortion and is negative if the ESSR is less female-biased than that of the gamete pool. If the ESSR is more female biased than the gamete pool, this term is positive.

Figure 4 plots the fitness effect of a sex ratio distorter for one set of parameters. Depending on conditions, a sex ratio distorter can be mutualistic or parasitic, or it can invade as a mutualist and then become a parasite as it spreads through the host population. Because inbreeding favors a female-biased sex allocation among nuclear genes, with an ESSR of $S^* = (1 - f)/2$ (Charlesworth and Charlesworth 1981; Nee et al. 2002), sex ratio distorters can increase the fitness of host genes under high levels of inbreeding if they bias sex ratios in the direction of the ESSR. High levels of selfing among plants, for example, can favor the spread of cytoplasmic male sterility even in the absence of inbreeding depression. This result holds even if hosts are allowed to have female-biased sex allocation in the absence of distorters (appendix).

The fitness effects of distorters become more negative as distorters become more common because infected hosts lose out on fitness through male gametes in a female-biased population. Interestingly, though, sex ratio distorters do not select for male-biased sex ratios among uninfected hosts unless transmission to female gametes is low (Werren 1987). Under all conditions, sex ratio distorters require some outbreeding and thus some horizontal transmission to invade as parasites.

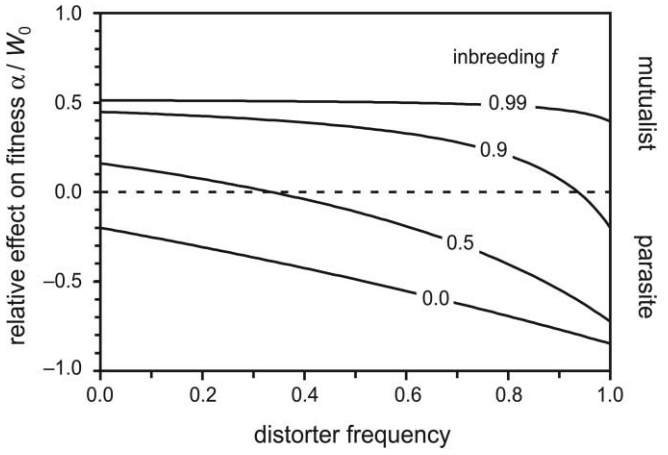

Figure 4: Effect of a sex ratio distorter on the fitness of its host as a function of inbreeding and frequency. Parameters: $G_0 = 1.0$, $G_1 = 0.8$, and $\delta = 0.95$. Dotted line indicates zero fitness effect. Above this line, the distorter increases fitness and is a mutualist. Below this line, the distorter decreases fitness and is a parasite.

Counterintuitively, inbreeding has zero net effect on the population dynamics of sex ratio distorters (appendix). Any loss of horizontal transmission caused by inbreeding is exactly balanced by an increase in vertical transmission and an increasingly positive effect on host fitness. The primary effect of inbreeding is to determine how sex ratio distorters affect the fitness of host genes.

Discussion

These results show that, from the perspective of other genes in the genome, selfish genetic elements have both vertical and horizontal transmission. Horizontal transmission, moreover, is absolutely required for elements to spread through host populations as parasites. There appears to be no theoretical support for claims (Camacho et al. 2000; Weeks et al. 2007) that SGEs should evolve toward mutualism simply because they are transmitted from parent to offspring. The existence of SGEs is completely consistent with the transmission mode hypothesis for the evolution of symbiont virulence—provided one measures transmission from the perspective of host genes instead of host organisms.

Transmission mode does not appear to be the whole story, however. In populations with any degree of outbreeding, all genes will have some horizontal transmission—not just the selfish ones. Likewise, many species acquire their mutualistic symbionts only through horizontal transmission (Wilkinson and Sherratt 2001). Horizontal transmission is thus necessary for symbionts to spread as parasites, but it is not sufficient to explain why some symbioses become parasitic and others become mutualistic.

My goal here has been to formalize a gene's-eye view of transmission and illustrate it with a few examples. A comprehensive analysis of SGEs within this framework—covering things like transposons, sex-linked drivers, and supernumerary B chromosomes—would be worthwhile but beyond the scope of this article. The ability to directly compare patterns of transmission across very different systems could help us distinguish between general principles of SGE evolution and the idiosyncratic biological details of any particular SGE (Helanterä 2006). Results so far show that different SGEs can respond very differently to similar ecological variables. Inbreeding, for example, limits the spread of meiotic drive genes but not the spread of cytoplasmic sex ratio distorters. Instead, it determines how distorters affect host fitness.

Inbreeding's effect on cytoplasmic incompatibility (CI), in particular, seems to warrant more attention. Some kinds of population structure, characterized by local competition and local genetic similarity, can actually make it easier for CI elements to spread (Frank 1997). The spiteful effect of CI (Foster et al. 2001; Gardner and West 2004), then, might be more effective under conditions of reduced horizontal transmission. This could explain the results of Shoemaker et al. (2002), who found that the prevalence of *Wolbachia* among several species of fig wasp is uncorrelated with inbreeding rates. The authors suggest that high levels of inbreeding and the hosts' female-biased sex ratios might make the bacteria less detrimental. The results of the sex ratio distorter model above seem to support this possibility as well. Models tailored to the biology of the fig wasp system may be able to distinguish between the two hypotheses or identify ways to test them.

A gene's-eye view of transmission shows how SGEs can

be used to test the transmission mode hypothesis directly, rather than just being broadly consistent with it. The hypothesis is only one of several potential mechanisms for the evolution of cooperation between species (Sachs et al. 2004), and how much it actually explains virulence evolution in natural systems is not clear (Ebert and Bull 2003). It has been difficult to assess its generality, in part because most formal models of the hypothesis rely on epidemiological approaches (Anderson and May 1982; Lipsitch et al. 1995, 1996) that are inappropriate for many host/symbiont systems, including SGEs. The work presented here clarifies how the hypothesis applies to these other systems and provides the proper measures of transmission and virulence to use when testing its predictions.

One major class of alternatives to the transmission mode hypothesis is that virulence is determined by interactions among symbionts within hosts. These alternatives draw on social evolution theory, too. They propose that reproduction of symbionts within hosts is cooperative and requires prudent use of host resources to avoid a tragedy of the commons (Levin and Pimentel 1981; Frank 1996) or requires the production of public goods that can used by cheater strains (Brown 1999; Chao et al. 2000; Smith 2001; Brown et al. 2002). These processes are not totally independent of transmission mode. Because high rates of horizontal transmission cause more hosts to become infected with multiple symbiont strains, it can be difficult to distinguish between-host from within-host effects (Herre 1993, 1995; Frank 1996). It is possible for multiple SGE strains to infect a single host—different types of *Wolbachia*, for example (Clancey and Hoffman 1996; Mouton et al. 2004), or both autonomous and nonautonomous transposons (Brookfield 1991)—but how this might affect SGE virulence has not been fully explored.

It is pleasing that the approach presented here brings closer together our understandings of cooperation within and between species. It shares with contemporary models of kin selection the same theoretical framework—the Price equation—and the same focus on how social traits affect the spread of individual alleles. Hamilton (1964, pp. 16,17) took a "gene's point of view" and showed that aiding kin can be favored by natural selection "because relatives, on account of their common ancestry, tend to carry replicas of the same gene." I have tried to expand this way of thinking to include cooperation between species by measuring how symbionts are associated with and affect genes in their hosts. Such a perspective clarifies how different evolutionary mechanisms translate across levels of selection, showing, for example, that the partners in "fidelity feedback" (Sachs et al. 2004) are genes. The broad degree of applicability that this affords is necessary if any theory of symbiotic evolution is to achieve the generality and explanatory power that kin selection has in explaining cooperation and conflict among genetically similar units of selection (Queller 2000).

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Appendix from J. Smith, "A Gene's-Eye View of Symbiont Transmission"

(Am. Nat., vol. 170, no. 4, p. 542)

Derivation of Results

Continuous-Time Price Equation

Here I derive a continuous-time version of the Price equation appropriate for models of populations with substantial overlap between generations. In a population of reproducing elements (cells, individuals, groups, etc.), let each type of element lineage at some time t be indexed with a subscript i. Let the absolute abundance of each type be x_i. Let the total number of elements (the population size) be $n = \sum x_i$ and the frequency of each element be $q_i = x_i/n$. The instantaneous rate of change in the abundance of an element is $\dot{x}_i = x_i m_i$, where the dot indicates differentiation with respect to time and m_i is the Malthusian fitness of i evaluated at that instant. In general, m_i can depend on any number of factors (such as the abundance of other elements), but at any given time it has some specific value.

The rate of change in total population size is $\dot{n} = \sum \dot{x}_i = \sum x_i m_i = n \sum q_i m_i = n\bar{m}$. The rate of change in the frequency of an element lineage is

$$\dot{q}_i = \frac{\dot{x}_i}{n} - \frac{x_i}{n^2}\dot{n} = q_i\left(\frac{\dot{x}_i}{x_i} - \frac{\dot{n}}{n}\right) = q_i(m_i - \bar{m}).$$

Now let each type of element have a value for some character z_i, also evaluated at time t. Element lineages retain their type designation over time, but their character value can change (even if they are chosen so that at t they match). For example, infected individuals may have $i = 1$ and $z = 1$, but their uninfected offspring ($z = 0$) still belong to the type $i = 1$ lineage (fig. 1). The rate of change in the character of type i lineages is dz_i/dt. The rate of change in the average character of the population is

$$\frac{d\bar{z}}{dt} = \frac{d}{dt}\left(\sum q_i z_i\right) = \sum (\dot{q}_i z_i + q_i \dot{z}_i)$$

$$= \sum q_i(m_i - \bar{m})z_i + \sum q_i \dot{z}_i.$$

With the standard definitions of covariance and expectation,

$$\frac{d\bar{z}}{dt} = \mathrm{Cov}(m, z) + \mathrm{E}\left(\frac{dz}{dt}\right).$$

Note that the Price equation describes evolutionary change only at the instant in which x, m, and z are defined, not for future times. The equation is a tool for partitioning evolutionary change within a model, but it is not by itself a dynamically sufficient description of evolution (Frank 1995).

Conventional Pathogen

This epidemiological model is a compartment model that tracks the densities of individuals with certain characters (infection status in this case) but not the individuals themselves. If we want the model to match the notation of the Price equation, we need to separate reproductive dynamics from character dynamics (fig. 1). If a class of individuals is present in total number n_i, then the Malthusian fitness of that class is $m_i = \dot{n}_i/n_i$. Thus,

$m_0 = b_S(1 - N/K) - u_S$ and $m_1 = (b_I + \epsilon)(1 - N/K) - u_I$. The ϵ term appears in m_1 because uninfected offspring born to infected parents still count toward their parent's fitness. The rate at which uninfected individuals gain infection is $\dot{z}_0 = \beta I$. The rate at which infected lineages lose infection is $\dot{z}_1 = -\epsilon(1 - N/K)$. With these values, horizontal transmission is $H = n_0\dot{z}_0/n_1 = S\beta I/I = \beta S = \beta N q_0$. Symbiont loss is $L = -\dot{z}_1 = \epsilon(1 - N/K)$.

Meiotic Drive

Meiotic drive and other SGEs are considered prime examples of selection acting simultaneously at different levels of biological organization (Hurst et al. 1996; Hurst and Werren 2001). The Price equation handles multilevel selection quite easily (Price 1972). I use lowercase letters for variables when they apply to individual lower-level elements and capital letters for variables when they apply to higher-level groups of elements. When it helps improve clarity, I also index individuals with the subscript i and groups with the subscript j. For example, the frequency of individuals of type i in groups of type j is q_{ij}. We can then handle multilevel selection scenarios by nesting the Price equation for individuals within the equation for groups:

$$\overline{W}\Delta\overline{Z} = \mathrm{Cov}(W, Z) + \mathrm{E}_j[\mathrm{Cov}_i(w, z) + \mathrm{E}_i(w\Delta z)]. \tag{A1}$$

The i subscripts indicate that the covariance and expectation are to be taken among individuals in a given group, and E_j indicates the expectation across groups. I use the discrete-time version of the Price equation here so as to be consistent with most other models of SGEs. The main difference between continuous and discrete-time models is the presence of fitness-weighting terms (W_{ij} and $\overline{W}$) in the latter.

The application of gene-level measures of transmission to multiple levels of selection is straightforward. Assuming that host alleles are neutral and unlinked to symbiont carriage, $\mathrm{Cov}_i(w, z) = 0$ and $w_{ij} = W_j$ for all j. We can therefore rewrite equation (A1) so that

$$\begin{aligned}
\overline{W}\Delta\overline{Z} &= \mathrm{Cov}(W, Z) + \mathrm{E}_j[\mathrm{E}_i(w\Delta z)] \\
&= \mathrm{Cov}(W, Z) + \mathrm{E}_j(q_{0j}w_{0j}\Delta z_{0j} + q_{1j}w_{1j}\Delta z_{1j}) \\
&= \mathrm{Cov}(W, Z) + \mathrm{E}_j(q_{0j}W_j\Delta z_{0j}) + \mathrm{E}_j(q_{1j}W_j\Delta z_{1j}).
\end{aligned}$$

The dynamics of symbiont infection are thus

$$\Delta\overline{Z} = \frac{1}{\overline{W}}[\alpha\,\mathrm{Var}(Z) + (H - L)\overline{Z}],$$

where horizontal transmission is

$$H = \frac{\mathrm{E}_j(q_{0j}W_j\Delta z_{0j})}{q_1},$$

and symbiont loss is

$$L = \frac{-\mathrm{E}_j(q_{1j}W_j\Delta z_{1j})}{q_1}.$$

For the meiotic drive case, the lower-level units of the Price equation correspond to the gene content of haploid gametes counted at fertilization, and the higher-level units correspond to the diploids formed by these gametes. Group indexes j will count the number of drive alleles a diploid has: 0 or 2 for homozygotes, 1 for heterozygotes. The frequencies of alleles within diploids are then $q_{00} = q_{12} = 1$ and $q_{01} = q_{11} = 1/2$. Since the driving element is unlinked to alleles at the host locus, offspring character values are $z'_{01} = z'_{11} = (1 + \delta)/2$. The change in character between generations is thus $\Delta z_{01} = z'_{01} - z_{01} = (1 + \delta)/2 - 0 = (1 + \delta)/2$ and $\Delta z_{11} = (1 + \delta)/2 - 1 = (\delta - 1)/2$. There is no drive in either of the homozygotes, so $\Delta z_{00} = \Delta z_{12} = 0$. Putting these values into the above expressions for H and L,

$$H = \frac{Q_1 q_{01} W_1 \Delta z_{01}}{q_1}$$

$$= 2q_1 q_0 (1-f)\left(\frac{1}{2}\right) W_1 \left(\frac{1+\delta}{2}\right)\left(\frac{1}{q_1}\right)$$

$$= W_1 q_0 \left(\frac{1+\delta}{2}\right)(1-f),$$

and

$$L = \frac{-Q_1 q_{11} W_1 \Delta z_{11}}{q_1}$$

$$= -2q_1 q_0 (1-f)\left(\frac{1}{2}\right) W_1 \left(\frac{\delta-1}{2}\right)\left(\frac{1}{q_1}\right)$$

$$= W_1 q_0 \left(\frac{1-\delta}{2}\right)(1-f).$$

Cytoplasmic Sex Ratio Distorter

In this model, our character of interest is whether host genes share a zygote with distorters. Thus $q_{ij} = 1$, $q_i = Q_j$, $w_i = W_j$, $z_1 = Z_1 = 1$, and $z_0 = Z_0 = 0$ (fig. 3). Each class of host produces a total gametic output G_i, divided into male investment μ_i and female investment ϕ_i, such that $G_i = \mu_i + \phi_i$. Uninfected hosts produce an equal sex ratio, such that $\phi_0 = \mu_0 = G_0/2$. Infected hosts produce a female-biased sex ratio, such that $\phi_1 = G_1(1+\delta)/2$ and $\mu_1 = G_1(1-\delta)/2$. The population sex ratio, counted as fractional male investment among the offspring gamete pool, is $S = \sum Q_i \mu_i / \sum Q_i G_i = \bar{\mu}/\bar{G}$. We can also write the sex ratio of an individual's gametic output as $S_i = \mu_i / G_i$.

The Price equation, in order to be self-consistent, must be clarified when characters are inherited differently through different components of fitness. In these cases, it will be necessary to divide fitness into its separate components, so that $w_i = w_{i,1} + w_{i,2} + \ldots + w_{i,C} = \sum_c w_{i,c}$. We can write these components in vector form as $\mathbf{w}_i = (w_{i,1}, w_{i,2}, \ldots, w_{i,C})$. Similarly, the mean character value of offspring derived through each component of fitness is $z'_{i,c}$, and $\mathbf{z}'_i = (z'_{i,1}, z'_{i,2}, \ldots, z'_{i,C})$. The average character value among all of i's offspring will thus be $z'_i = \sum_c z'_{i,c} w_{i,c} / w_i = (\mathbf{z}'_i \cdot \mathbf{w}_i)/w_i$, where the dot indicates the dot product (or scalar product) of the two vectors. This simply says that the mean character value among all offspring will reflect the relative amount of offspring that come from each fitness component. With this notation, $w_i \Delta z_i = w_i(z'_i - z_i) = (\mathbf{z}'_i \cdot \mathbf{w}_i) - z_i w_i$.

For the sex ratio distorter, we must separate fitness into inbred male, inbred female, outbred male, and outbred female components. Inbreeding can be thought of as a fraction f of the population selfing and fraction $(1-f)$ mating randomly (Charlesworth and Charlesworth 1981). Fitness is proportional to female investment in both the male and female inbred components (making the standard assumption that there are always enough male gametes to fertilize female gametes). Essentially, a little bit of male investment is all that is needed. Fitness in the outbred male component is proportional to male investment but also depends on the sex ratio of the gamete pool. Male gametes compete for fertilization, so that mating success is proportional to the number of female gametes in the gamete pool and inversely proportional to the number of male gametes. The outbred male component of fitness is thus $\mu_i \sum Q_i \phi_i / \sum Q_i \mu_i = \mu_i \bar{\phi}/\bar{\mu} = \mu_i(1-S)/S$ (Charnov 1982). Fitness in the outbred female component is proportional to female investment. Summarizing the above in vector form,

$$\mathbf{W}_i = \left[f\phi_i, f\phi_i, (1-f)\mu_i \frac{1-S}{S}, (1-f)\phi_i \right].$$

The order of vector components is inbred male, inbred female, outbred male, and outbred female.

Since the sex ratio distorter is inherited through the cytoplasm, the outbred female and both inbred components of fitness will retain their parental infection status. In the outbred male component of fitness, the fraction of host genes that share gametes with the distorter in the offspring generation will be the fraction that fertilize an infected female gamete. Under random mating in the outbred fraction, this will be equal to the fraction of female gametes infected: $Q_1\phi_1/(Q_1\phi_1 + Q_0\phi_0) = Q_1\phi_1/\bar{\phi}$. In vector form, then,

$$\mathbf{Z}_1' = \left(1, 1, \frac{Q_1\phi_1}{\bar{\phi}}, 1\right) \quad \text{and} \quad \mathbf{Z}_0' = \left(0, 0, \frac{Q_1\phi_1}{\bar{\phi}}, 0\right).$$

Putting it together, horizontal transfer is

$$\begin{aligned} H &= \frac{\mathrm{E}_j(q_{0j}W_j\Delta Z_{0,j})}{q_1} \\ &= \frac{Q_0(1)(\mathbf{Z}_0' \cdot \mathbf{W}_0 - Z_0W_0)}{Q_1} \\ &= \frac{Q_0\{(Q_1\phi_1/\bar{\phi})(1-f)\mu_0[(1-S)/S]\}}{Q_1} \\ &= \mu_0\phi_1Q_0\frac{\bar{\phi}}{\bar{\mu}\bar{\phi}}(1-f) \\ &= G_1\left(q_0\frac{\mu_0}{\bar{\mu}}\right)\left(\frac{1+\delta}{2}\right)(1-f). \end{aligned}$$

Symbiont loss is

$$\begin{aligned} L &= \frac{-\mathrm{E}_j(q_{1j}W_j\Delta Z_{1,j})}{q_1} \\ &= \frac{-Q_1(1)(\mathbf{Z}_1' \cdot \mathbf{W}_1 - Z_1W_1)}{Q_1} \\ &= -\left[\phi_1(1+f) + \mu_1\frac{1-S}{S}(1-f)\frac{Q_1\phi_1}{\bar{\phi}} - \phi_1(1+f) - \mu_1\frac{1-S}{S}(1-f)\right] \\ &= -\mu_1\frac{1-S}{S}(1-f)\left(\frac{Q_1\phi_1}{\bar{\phi}} - 1\right) \\ &= \mu_1\frac{\bar{\phi}}{\bar{\mu}}(1-f)\frac{Q_0\phi_0}{\bar{\phi}} \\ &= G_1\left(q_0\frac{\mu_0}{\bar{\mu}}\right)\left(\frac{1-\delta}{2}\right)(1-f). \end{aligned}$$

To find the fitness effect of the sex ratio distorter, we can rewrite fitness in terms of the sex ratio of an individual's gametic output and the evolutionarily stable sex ratio $S^* = (1-f)/2$ (Charlesworth and Charlesworth 1981; Nee et al. 2002).

$$\begin{aligned}
W_i &= \phi_i(1+f) + \frac{\mu_i(1-f)(1-S)}{S} \\
&= G_i(1-S_i)(1+f) + \frac{G_iS_i(1-f)(1-S)}{S} \\
&= G_i\left\{(1+f) + S_i\left[\frac{(1-f)(1-S)}{S} - (1+f)\right]\right\} \\
&= G_i\left[(1+f) + \left(\frac{S_i}{S}\right)(1-f-2S)\right] \\
&= G_i\left[(1+f) + \left(\frac{2S_i}{S}\right)(S^*-S)\right] \\
&= G_i\left[(1+f) + 2S_i\left(\frac{S^*}{S}-1\right)\right].
\end{aligned}$$

The fitness effect of the sex ratio distorter is then

$$\begin{aligned}
\alpha &= W_1 - W_0 \\
&= (G_1-G_0)(1+f) + 2(G_1S_1 - G_0S_0)\left(\frac{S^*}{S}-1\right) \\
&= (G_1-G_0)(1+f) + 2\left(\frac{S^*}{S}-1\right)(G_1S_1 - G_0S_0 + G_1S_0 - G_1S_0) \\
&= (G_1-G_0)\left[(1+f) + 2S_0\left(\frac{S^*}{S}-1\right)\right] + 2\left(\frac{S^*}{S}-1\right)(G_1S_1 - G_1S_0) \\
&= W_0\left(\frac{G_1}{G_0}-1\right) + 2G_1\left(\frac{S^*}{S}-1\right)(S_1-S_0).
\end{aligned}$$

If $S_0 = 1/2$ and $S_1 = (1-\delta)/2$, then

$$\begin{aligned}
\alpha &= W_0\left(\frac{G_1}{G_0}-1\right) + \frac{2G_1[(S^*/S)-1](1-\delta-1)}{2} \\
&= W_0\left(\frac{G_1}{G_0}-1\right) - \delta G_1\left(\frac{S^*}{S}-1\right).
\end{aligned}$$

This can also be rewritten as

$$
\begin{aligned}
\alpha &= (\phi_1 - \phi_0)(1+f) + (\mu_1 - \mu_0)(1-f)\frac{1-S}{S} \\
&= 2(\phi_1 - \phi_0) - (1-f)(\phi_1 - \phi_0) + (1-f)(\mu_1 - \mu_0)\frac{\bar{\phi}}{\bar{\mu}} \\
&= 2(\phi_1 - \phi_0) - \frac{(1-f)[(\phi_1 - \phi_0)\bar{\mu} - (\mu_1 - \mu_0)\bar{\phi}]}{\bar{\mu}} \\
&= 2(\phi_1 - \phi_0) - \frac{(1-f)[(\phi_1 - \phi_0)(Q_0\mu_0 + Q_1\mu_1) - (\mu_1 - \mu_0)(Q_0\phi_0 + Q_1\phi_1)]}{\bar{\mu}} \\
&= 2(\phi_1 - \phi_0) - \frac{(1-f)(\phi_1\mu_0 - \phi_0\mu_1)}{\bar{\mu}} \\
&= 2(\phi_1 - \phi_0) - \frac{(1-f)(\phi_1 - \mu_1)\mu_0}{\bar{\mu}} \\
&= 2(\phi_1 - \phi_0) - \frac{\mu_0}{\bar{\mu}}\frac{1}{2}[(G_1 + \delta G_1) - (G_1 - \delta G_1)](1-f) \\
&= 2(\phi_1 - \phi_0) - G_1\frac{\mu_0}{\bar{\mu}}\delta(1-f).
\end{aligned}
$$

The population dynamics of the sex ratio distorter are then

$$
\begin{aligned}
\Delta\overline{Z} &= \frac{\alpha\,\mathrm{Var}(Z) + (H-L)\overline{Z}}{\overline{W}} \\
&= \frac{\mathrm{Var}(Z)[2(\phi_1 - \phi_0) - G_1(\mu_0/\bar{\mu})\delta(1-f)] + G_1Q_0(\mu_0/\bar{\mu})\delta(1-f)Q_1}{\overline{W}} \\
&= \frac{\mathrm{Var}(Z)2(\phi_1 - \phi_0)}{\overline{W}} \\
&= \frac{(G_1 - G_0 + \delta G_1)\,\mathrm{Var}(Z)}{\overline{W}},
\end{aligned}
$$

which does not depend on the inbreeding coefficient *f*.