Adaptation and the Parliament of Genes

Abstract

Our modern understanding of adaptation by natural selection rests on assumptions about genes working together to produce organisms. However, there is considerable evidence for selfish genetic elements that distort the behaviour of individuals to increase their own transmission. How can we reconcile these opposing notions? We use a combination of population genetics, agent-based simulation, and game theory to model the evolution of both selfish genetic elements and genes that could suppress their distortion. We found that: (1) suppressor genes are more likely to be favoured when selfish genetic elements cause greater distortion; (2) selection on selfish genetic elements favours the evolution of greater distortion, making them more likely to be suppressed. We found these same results when examining an abstract model designed to illuminate the general principles, and models for three specific scenarios: an X chromosome driver, an imprinted gene, and a bacterial plasmid. Our results suggest that selection on selfish genetic elements will often drive coevolution with suppressors in a way that removes the impact of genetic conflict at the level of the individual.

Introduction

One of the most striking features of the natural world is the extent to which organisms appear designed or adapted (Paley 1829). Darwin (1859) provided the solution to this problem with his theory of natural selection. Our modern understanding of this theory is that genes that raise fitness will increase in frequency, leading to organisms that appear *as if* they have been designed to maximise their fitness (Fisher 1930; Hamilton 1964; Grafen 2006; 2009; 2014; Gardner 2009). This assumption of fitness maximisation has proved incredibly useful for explaining many aspects of adaptation, including behaviour, life history, and morphology (Stephens and Krebs 1986; Stearns 1992; West 2009; Westneat and Fox 2010; Davies et al. 2012). This work has not assumed that natural selection leads to 'perfect' fitness maximisers. Instead, it has used simple models based on fitness maximisation as a basis for studying the selective forces that lead to adaptation (Parker and Maynard Smith 1990).

A problem is that there is also considerable evidence for selfish genetic elements, which increase their own contribution to future generations at the expense of other genes in the same organism (Werren et al. 1988; Burt and Trivers 2006; Gardner and Úbeda 2017; Ågren and Clark 2018). Selfish genetic elements manipulate traits away from the individual optima, in order to increase their own transmission to the next generation (Hamilton 1967; Haig 2002; 2014; Burt and Trivers 2006; Gardner and Welch 2011; Bourke 2014). For example, genes that are passed cytoplasmically, to only female offspring, can be selected to distort the sex ratio towards the production of more females (Burt and Trivers 2006). Given this potential for genetic conflict, why has the assumption of fitness maximisation at the individual level then been so empirically useful for explaining adaptation (West and Gardner 2013; Ågren 2016)? This problem is especially apparent with research on sex ratios, which has provided both phenomenal support for the individual fitness maximisation

approach, and many of the clearest examples of selfish genetic elements (Charnov 1982; Jaenike 2001; Burt and Trivers 2006; West 2009).

Leigh (1971) provided a potential solution to this problem of genetic conflict by suggesting that selfish genetic elements would be suppressed by the 'parliament of genes'. Leigh's argument was that, because selfish genetic elements reduce the fitness of the other genes in the organism, the rest of the genome will have a united interest in suppressing the selfish genetic element. Furthermore, that because those other genes are far more numerous, they will be likely to win the conflict. Consequently, even when there is considerable potential for conflict within individuals, we would still expect adaptation at the individual level (Leigh 1977; 1983; Alexander and Borgia 1978; Dawkins 1982; Strassmann and Queller 2010; Gardner and Ross 2014; Queller and Strassmann 2018). Leigh (1971) demonstrated the plausibility of his argument by showing theoretically how a suppressor of a meiotic drive gene could be favoured.

However, Leigh's argument, and more recent studies of suppressor dynamics, raise a number of potential issues. Even if the parliament of genes can easily generate suppressors, whether a suppressor spreads can depend upon biological details such as any cost associated with the suppressor, the extent to which a selfish genetic element is distorting a trait, and the prevalence of that selfish genetic element (Prout et al. 1973; Crow 1991; Carvalho et al. 1997; Ridley 2000; Caubet et al. 2000; Randerson 2000; Haig 2006; Burt and Trivers 2006). Furthermore, selfish genetic elements are themselves also under evolutionary pressure to reach a level of distortion that would maximise their transmission to the next generation – how will this influence the likelihood that they are suppressed? Finally, segregation at suppressor loci might expose previously suppressed selfish genetic elements (Ridley 2000).

We investigated the parliament of genes hypothesis theoretically. Our general aim was to investigate the extent to which genetic conflict distorts a trait away from the value that would maximise individual fitness. We first provide an illustrative model, to elucidate basic principles that could apply to multiple scenarios. We then tested the robustness of our conclusions, by modelling three specific examples: selfish distortion of the sex ratio by an X chromosome driver; an altruistic helping behaviour encoded by an imprinted gene; and, production of a cooperative public good encoded on a horizontally transmitted bacterial plasmid.

General Approach

A selfish genetic element may be able to gain a propagation advantage through trait distortion ('*distorter*'). Any part of the genome that does not gain the propagation advantage from the trait distortion will be selected to suppress the distorter. This collection of genes (coreplicon; Cosmides and Tooby 1981) will comprise most of the genome, and so will constitute the majority within the parliament of genes. We account for the large size of this collection of genes by assuming that it is highly likely that a potential suppressor of a distorter can arise by mutation (high mutational accessibility). Consequently, we focus our analyses on when a distorter can spread, and when its suppressor can spread.

Our overall aim is to assess, given the potential for suppression, the extent that a distorter can distort the organism trait away from the individual optimum. In order to elucidate the selective forces in operation, we ask four questions in a step-wise manner, with increasing complexity:

(1) In the absence of a suppressor, when can a distorter invade?
(2) When can a costly suppressor of the distorter invade?
(3) What are the overall consequences of the distorter and its potential suppression for trait values at the individual and population level?
(4) If the extent to which the distorter distorts the organism trait can evolve, how will this influence the likelihood that it is suppressed, and hence the individual and population trait values?

Illustrative Model

We assume an arbitrary trait that influences organism fitness. In the absence of distorters, all individuals have the value of the trait that maximises their individual fitness. The distorter pulls the trait to a value at which the distorter is propagated to offspring more efficiently. We assume a large population of diploid, randomly mating individuals. The aim of this model is to establish key aspects of the population genetics governing distorters and their suppressors, in an abstract setting. We will subsequently address analogous issues in three specific biological scenarios.

(1) Spread of a Distorter

We consider a distorter, which we denote by y_1, that is dominant and distorts an organism trait value by some positive amount, denoted by k (k>0). This distortion increases the transmission of the distorter to offspring. Specifically, the distorter (y_1) drives at meiosis, in heterozygotes, against a non-distorter (y_0), being passed into the proportion (1+$t(k)$)/2 of offspring. $t(k)$ denotes the transmission bias (0<t(k)≤1) and is a monotonically increasing function of trait distortion $\left(\frac{\partial t}{\partial k} \geq 0\right)$.

Trait distortion leads to a fitness (viability) cost ($c_{drive}(k)$) at the individual level, reducing an individual's number of offspring from 1 to 1-$c_{drive}(k)$ (0<$c_{drive}(k)$≤1). The fitness cost is a monotonically increasing function of trait distortion $\left(\frac{\partial c_{drive}}{\partial k} \geq 0\right)$. We assume that $t(k)$ and $c_{drive}(k)$ do not change with population allele frequencies, but relax this assumption in our specific models.

We first ask what frequency the distorter will reach in the population in the absence of suppression. If we take p and p' as the population frequency of the distorter in two consecutive generations, then the population frequency of the distorter in the latter generation is:

$$\overline{w}\, p' = (1 - c_{drive}(k))\,(p^2 + (1-p)\,p\,(t(k)+1)), \qquad (1)$$

where $\overline{w}$ is the average fitness of individuals in the population in the current generation, and can be written in full as: $\overline{w} = (1 - c_{drive}(k))\left(p^2 + 2p(1-p)\right) + (1-p)^2$. In Appendix 1 we show, with a population genetic analysis of equation (1),

that the distorter will spread from rarity and fixate when $c_{drive}(k)<t(k)(1-c_{drive}(k))$. This shows that distortion will evolve when the number of offspring that the distorter gains as a result of distortion ($t(k)(1-c_{drive}(k))$) is greater that the number of offspring bearing the distorter that are lost as a result of reduced individual fitness ($c_{drive}(k)$).

(2) Spread of an autosomal suppressor

We assume that the distorter (y_1) can be suppressed by an autosomal allele (suppressor), denoted by *sup*. This suppressor (*sup*) is dominant and only expressed in the presence of the distorter (facultative), and its expression may lead to a fitness cost to the individual, c_{sup} ($0 \leq c_{sup} \leq 1$). This cost can arise for multiple reasons, including energy expenditure, or errors relating to the use of gene silencing machinery, and is likely to be relatively low (Qiu 2005). Gene silencing generally precedes the translation of the targeted gene, and so we assume that the costs of suppression (c_{sup}) is independent of the amount of distortion caused by the distorter (k).

We can write recursion equations detailing the generational change in the frequencies of the four possible gametes, y_0/+, y_0/*sup*, y_1/+, y_1/*sup*, with the respective frequencies in the current generation denoted by x_1, x_2, x_3 and x_4, and the frequencies in the subsequent generation denoted by an appended dash (’):

$$\begin{aligned}
\bar{w}\, x_1' &= x_1^2+x_1x_2+(1-t)(1-c_{drive})x_1x_3+((1-c_{sup})/2)x_1x_4+((1-c_{sup})/2)x_2x_3 \\
\bar{w}\, x_2' &= x_1x_2+((1-c_{sup})/2)x_1x_4+x_2^2+((1-c_{sup})/2)x_2x_3+(1-c_{sup})x_2x_4 \\
\bar{w}\, x_3' &= (1+t)(1-c_{drive})x_1x_3+((1-c_{sup})/2)x_1x_4+((1-c_{sup})/2)x_2x_3+(1-c_{drive})x_3^2+(1-c_{sup})x_3x_4 \\
\bar{w}\, x_4' &= ((1-c_{sup})/2)x_1x_4+((1-c_{sup})/2)x_2x_3+(1-c_{sup})x_2x_4+(1-c_{sup})x_3x_4+(1-c_{sup})x_4^2.
\end{aligned} \tag{2}$$

$\bar{w}$ is the average fitness of individuals in the current generation, and equals the sum of the equations’ right-hand sides. In Appendix 2, we show, with a population genetic analysis of our system of equations (2), that a suppressor will spread from rarity above a threshold level of distortion, k, if the cost of suppression (c_{sup}) is less than the cost of being subjected to trait distortion, $c_{sup}<c_{drive}(k)$. A threshold with respect to the level of distortion (k) arises because the cost of trait distortion ($c_{drive}(k)$) increases with greater distortion, but the cost of suppression (c_{sup}) is constant.

(3) Consequences for organism trait values

The extent of trait distortion at the individual level shows a discontinuous relationship with the strength of the distorter. When distortion is low, a suppressor will not spread ($c_{sup}>c_{drive}(k)$) and so the level of trait distortion at the individual level will increase with the level of trait distortion induced by the distorter (k). However, once a threshold is reached ($c_{sup}<c_{drive}(k)$), the suppressor spreads. We show in Appendix 3 that this causes the distorter (y_1) to lose its selective advantage and be eliminated from the population, leading to an absence of distortion at the individual level.

Overall, these results suggest that, given a relatively low cost of suppression (c_{sup}), the level of distortion observed at the individual level will either be low or absent. When a distorter is weak (low k), it will not be suppressed, but it will only have a small influence at the level of the individual. When a distorter is strong (high k), it will

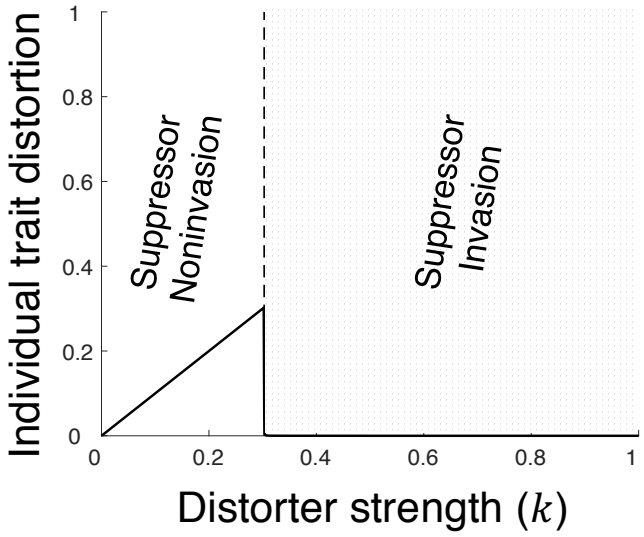

Figure 1. Distorter-suppressor dynamics and consequences for the organism. The trait distorter (y_1) and its suppressor (*sup*) are introduced from rarity. The resulting average trait distortion ($x_3\,k$) is plotted against the extent to which the distorter causes trait values to deviate from the individual optimum (k). Below a certain threshold strength ($c_{sup}>c_{drive}(k)$), to the left of the dashed line, the suppressor does not invade, and so the resulting trait distortion increases with the strength of the distorter (k). However, above this threshold, the suppressor invades, and the distorter is lost, restoring the trait to the individual optimum. The numerical solutions displayed graphically assume that the cost of suppression, the transmission benefit of distortion, and the individual fitness cost of distortion, are respectively given by: c_{sup}=0.15; t=0.87k and c_{drive}=0.9$k^{1.5}$.

be suppressed and so there will be no influence at the level of the individual (Fig. 1).

4) Evolution of trait distortion

We then considered the consequence of allowing the level of trait distortion (k) to evolve. We assume a distorter that distorts by k, and then introduce a rare mutant (y_2) that distorts by a different amount $\hat{k}$ ($\hat{k}\neq k$). This mutant (y_2) is propagated into the proportion (1+$t(\hat{k})$-$t(k)$)/2 of the offspring of y_2y_1 heterozygotes, and into the proportion (1+t($\hat{k}$))/2 of the offspring of y_2y_0 heterozygotes. We assume that the stronger of the two distorters is dominant, but found similar results when assuming additivity (Appendix 4). We assume that the similarity in coding sequence and regulatory control means that the original distorter and the mutant are both suppressed by the same suppressor allele, at the same cost (c_{sup}) (Qiu 2005). In Appendix 4, we write the recursion equations that detail the generational frequency changes in the different possible gametes (y_0/+, y_0/*sup*, y_1/+, y_1/*sup*, y_2/+, y_2/*sup*).

We show, with a population genetic analysis of our recursion equations in Appendix 4, that stronger mutant distorters ($\hat{k}>k$) will invade from rarity when the marginal increase in offspring they are propagated into exceeds the marginal increase in offspring they are lost from as a result of reduced fitness, which occurs when $\Delta t(1-c_{drive}(\hat{k}))>\Delta c_{drive}$, where Δ denotes marginal change ($\Delta t=t(\hat{k})-t(k)$; $\Delta c_{drive}=c_{drive}(\hat{k})-c_{drive}(k)$). Weaker mutant distorters ($\hat{k}<k$) are recessive so cannot invade from rarity.

It follows that, if distortion is initially low, and successive mutant distorters are introduced, each deviating only slightly from the distorters from which they are derived ("δ-weak selection"; Wild and Traulsen 2007), invading distorters will approach a 'target' strength, denoted by k_{target}, at which the marginal benefit of transmission is exactly counterbalanced by the marginal cost of reduced offspring fitness, which occurs when $\frac{\partial t}{\partial k}(1 - c_{drive}) = \frac{\partial c_{drive}}{\partial k}$. If mutations are larger (strong selection), invading distorters may overshoot this target ($\hat{k}$>k_{target}).

As evolution on the distorter increases the level of distortion, it makes it more likely that the distorter reaches the critical level of distortion where suppression will be favoured. If k_{target} is above this critical level (c_{sup}<$c_{drive}(k_{target})$), we show in Appendix 5, by sweeping across all parameter combinations, and numerically iterating our recursion equations to infer equilibria, that this will cause the distorter to spread to high frequency, which will then cause the suppressor to increase in frequency, reversing the direction of selection on the distorter, towards non-distortion (y_0), resulting in zero trait distortion at equilibrium (k^*=0) (Fig. 2a). Suppression only fails to evolve in cases where the distorter evolves towards low distortion, such that c_{sup}>$c_{drive}(k_{target})$ (Fig. 2b).

Selection on distorters will therefore tend to favour the suppression of these distorters. In Appendix 6, we tested the robustness of our results with an agent-based simulation, which also allowed continuous variation at the trait locus (not discrete variation: $\{0,k,\hat{k}\}$) as well as the suppressor locus (allowing partial suppression). The results of our simulation were in close agreement with our population genetic analysis (Supplementary Information 2, Fig. S1).

Specific Models

We tested the robustness of our above conclusions by developing models for three different biological scenarios where a gene could be selected to deviate a trait away from the individual level optimum: a sex ratio distorter on an X chromosome (X driver); an imprinted gene that is only expressed when maternally inherited; and a gene for the production of a public good by bacteria, which is encoded on a mobile genetic element. We examined these cases because they are different types of distortion, involving different selection pressures, in very different organisms.

In all of our specific models, we assume that the suppressor: is dominant; is only expressed in the presence of the distorter (facultative); completely suppresses the distorter; and may incur a fitness (viability) cost to the individual when it is expressed, independent of distorter strength, denoted by c_{sup} ($0 \leq c_{sup} \leq 1$) (Vaz and Carvalho 2004; Hall 2004; Hornett et al. 2014). These assumptions fit well to a molecularly characterised suppressor ("*nmy*") of a sex ratio distorter ("*Dox*") (Tao et al. 2001; 2007a,b; Ferree and Barbash 2007); and more generally to suppressors that act pre-translationally (Aravin et al. 2007; Doron et al. 2018). We also relax a simplifying assumption of our illustrative model, by allowing the transmission benefit and individual fitness cost of trait distortion to vary with the population frequency of the distorter.

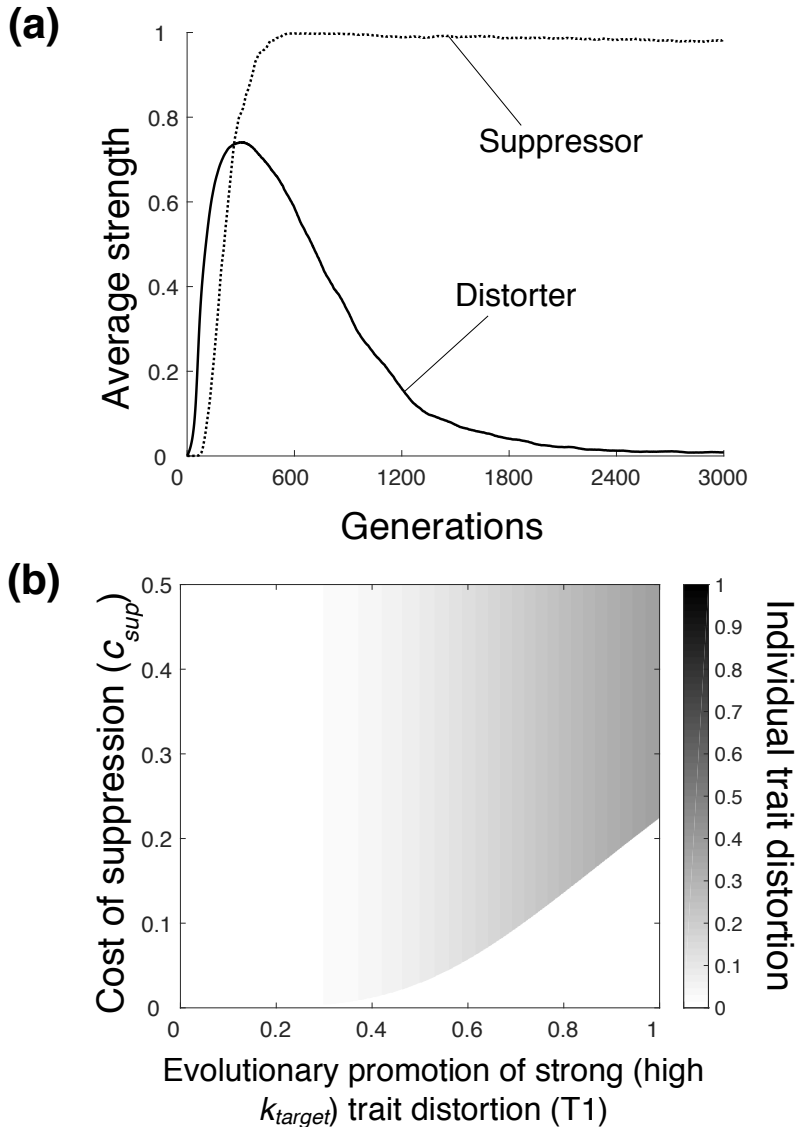

Figure 2. Evolution of trait distortion. Part (a) shows a specific example where a distorter and suppressor are introduced and, taking averages over 100 runs of the agent based simulation model (Appendix 6), the population average distorter (E[*k*]) and suppressor (E[*m*]) strengths are plotted over successive generations. Initially, both distorter (E[*k*]) and suppressor (E[*m*]) strength increases. Eventually, a threshold is passed, after which, distorters are lost from the population, meaning the trait is undistorted at equilibrium. Part (b) plots the equilibrium trait distortion for a range of scenarios in which suppression cost (c_{sup}) is varied alongside a model parameter, denoted by T1, that increases the target level of trait distortion (k_{target}), by decreasing the rate at which the marginal transmission advantage of trait distortion $\left(\frac{\partial t}{\partial k}\right)$ dissipates relative to the marginal individual cost of trait distortion $\left(\frac{\partial c_{drive}}{\partial k}\right)$ as the trait becomes increasingly distorted (k) (Supplementary Information 1). For high costs of suppression (c_{sup}), suppression cannot evolve, and so the evolutionary promotion of stronger trait distortion (T1) leads to increased trait distortion at equilibrium. For low costs of suppression (c_{sup}), the evolutionary promotion of stronger trait distortion (T1) leads initially to increased, but still low, trait distortion at equilibrium (bottom left quadrant), and then to no trait distortion at equilibrium, owing to suppressor spread (bottom right quadrant).

Sex Ratio Distortion

We examined sex ratio evolution in a diploid species, in a large outbreeding (panmictic) population, with non-overlapping generations, and where males and

females are equally costly to produce. Fisher (1930) and many others have shown that, in this scenario, individuals would be selected to invest equally in male and female offspring (Charnov 1982; West 2009). We assumed genetic sex determination with males as XY, and females as XX, and that females mate with λ mates per generation (Bull 1983). The distorter (y_1) that we considered is an X driving chromosome, which acts in males, killing Y-bearing sperm, and causing the male's mating partners to produce a higher proportion of female (XX) offspring. The proportion is given by (1+k)/2, where k denotes the proportion of Y-bearing sperm that are killed (0<k≤1). We assumed that the sex ratio distorter can be suppressed by a costly autosomal suppressor (*sup*). This biology corresponds to sex ratio distortion in flies (Jaenike 2001).

In Supplementary Information 3 we developed a population genetic model of this scenario. We found that, when distortion is weak (low k), suppressors are not favoured, but the distorter has very little impact at the individual level. When distortion is strong (high k), then suppression is favoured, and so there is no influence on the individual trait value. Consequently, the extent that the sex ratio deviates from the individual optimum of equal investment in the sexes: shows a domed relationship with the extent of distortion (k); and will often be negligible (Rood and Freedberg 2016) (Fig. 3ai). When we allowed the X chromosome driver to evolve, we found that higher levels of sex ratio distortion are favoured, increasing the likelihood that suppression will be favoured (Fig. 3aii).

Overall, our sex ratio model showed very similar results to our illustrative model. Furthermore, in our sex ratio model, we only obtained appreciable and detectable levels of sex ratio distortion (>60% females) if the cost of suppression exceeded a 15-35% viability reduction, which is a greater cost than what we would expect from natural gene suppression pathways (Fig. S6) (Unckless et al. 2015). We tested the robustness of our population genetic analysis with an agent-based simulation, permitting continuous variation at the distorter and suppressor loci, and a game theory model, analysing the optimal level of distortion for X chromosomes. In all cases, the different approaches were in close agreement (Fig. S4).

Our predictions are consistent with data on sex ratio distorters, especially X drivers in *Drosophila*. Across natural populations of *D. simulans*, there is a positive correlation between the extent of sex ratio distortion and the extent of suppression (Atlan et al. 1997). In both *D. mediopunctata*, and *D. simulans* the presence of an X linked driver led to the experimental evolution of suppression (Carvalho et al. 1998; Capillon and Atlan 1999). A field study on sex ratio distortion in the butterfly *Hypolimnas bolina* has shown that a suppressor can spread extremely fast, effectively reaching fixation in as little as ~5 generations (Hornett et al. 2006). In natural populations of *D. simulans* the prevalence of an X driver has been shown to sometimes decrease under complete suppression (Bastide et al. 2011; 2013). Finally, crossing different species of *Drosophila* has been shown to lead to appreciable sex ratio deviation, by unlinking distorters from their suppressors, and hence revealing previously hidden distorters (Blows et al. 1999).

Genomic Imprinting and Altruism

Genomic imprinting, as observed at a minority of genes in mammals and flowers, occurs when an allele has different epigenetic marks, and corresponding expression levels, when maternally and paternally inherited (Peters 2014). We examined the evolution of an altruistic helping behaviour in a population capable of genomic imprinting. A behaviour is altruistic if it incurs a cost (c) to perform, by the actor, and provides a benefit (b) to another individual, the recipient. Altruism is favoured if the genetic relatedness (R) between the actor and recipient is sufficiently high, such that $Rb>c$ (Hamilton 1964).

An individual may be more closely related to their social partners via their father than via their mother (asymmetric kin interactions), meaning relatedness is higher for genes that have been paternally inherited ($R_p>R_m$) (Haig 1997; 2000; Burt and Trivers 2006). An unimprinted altruism gene is expressed every generation, meaning its relatedness to social partners, averaged over successive generations, is $(R_p+R_m)/2$. However, a paternally expressed altruism gene is only expressed in half of all generations, because a given gene is only paternally inherited half of the time. A paternally expressed altruism gene is only expressed in generations in which relatedness is R_p. Altruism is simultaneously favoured at paternally expressed imprinted genes and disfavoured at unimprinted genes (selfish trait distortion) when $R_pb>c>((R_p+R_m)/2)b$ (Gardner and Úbeda 2017). Heightened relatedness via mothers ($R_p<R_m$) can likewise favour selfish maternally expressed altruism genes when $R_mb>c>((R_p+R_m)/2)b$, and we consider this case in our model (Haig 2002; 2013; Queller 2003; Úbeda and Gardner 2010; 2011; 2012).

We modelled the evolution of altruism in a large population of diploid, sexually reproducing individuals. The distorter (y_1) increases altruistic investment by some amount (k), at a fitness cost to the individual ($0<c(k)\leq 1$) and benefit to the social partner ($b(k)>c(k)$) that are both monotonically increasing functions of investment $\left(\frac{\partial\{b,c\}}{\partial k}\geq 0\right)$. The distorter ($y_1$) is only expressed when maternally inherited, whereas its potential suppressor (*sup*) is unimprinted (Wilkins and Haig 2001). Every generation, individuals associate in pairs with kin that they are maximally related to via their maternally inherited genes ($R_m=1$) but minimally related to via their paternally inherited genes ($R_p=0$). Individuals then have the opportunity to be altruistic to their partner, before mating at random in proportion to their fitness (fecundity), reproducing, then dying (non-overlapping generations).

In Supplementary Information 4, we showed with a population genetic analysis that our imprinting model produces very similar results to our illustrative model. When distortion is weak (low k), suppressors are not favoured, but the distorter has very little impact at the individual level. When distortion is strong (high k), then suppression is favoured, and so there is no influence on the individual trait value (Wilkins and Haig 2001; Wilkins 2010; 2011). Consequently, the extent that altruistic investment deviates from the individual optimum of zero investment: (a) shows a discontinuous relationship with the extent of distortion; and (b) will often be negligible (Fig. 3bi). Finally, when we allowed the imprinted gene to evolve, we found that

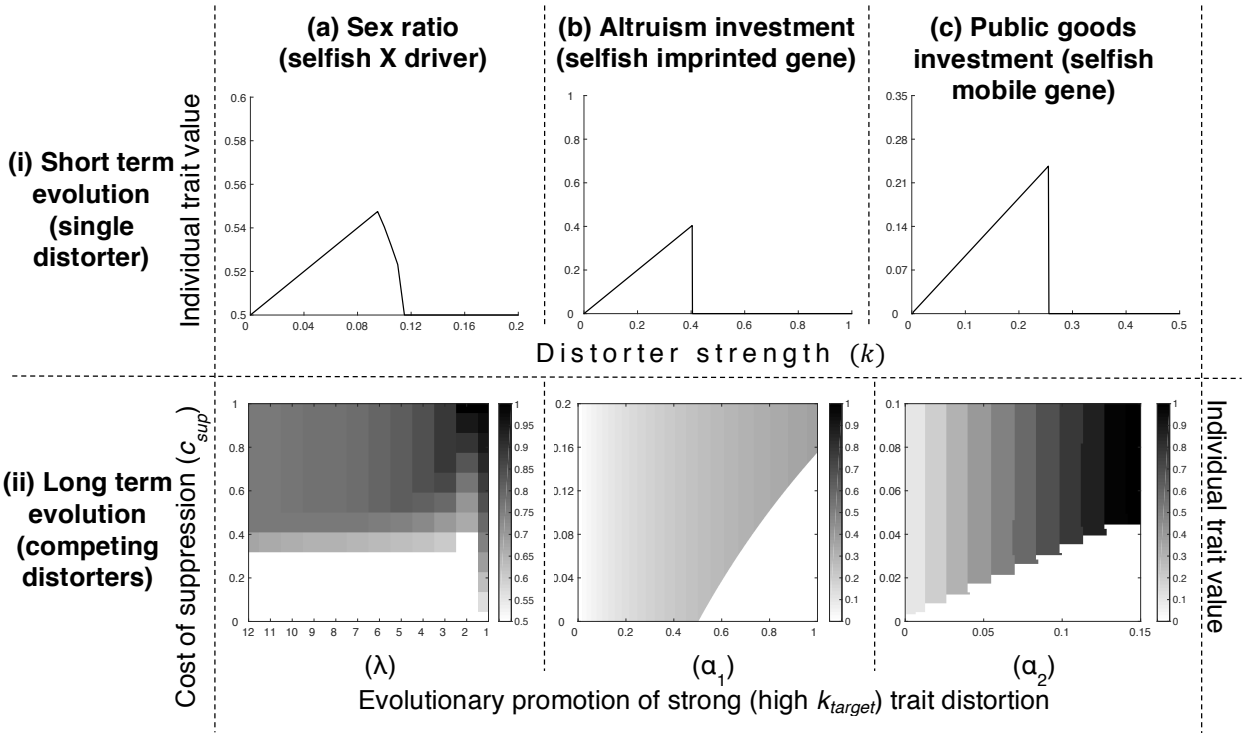

Figure 3. Specific Biological Scenarios. We examined three different biological scenarios: (a) selfish distortion of the sex ratio by an X chromosome (individual optimum at 0.5): (b) genomic imprinting for altruistic helping (individual optimum at 0); and (c) production of a public goods encoded on a horizontally transmitted bacterial plasmid (individual optimum at 0). For all three scenarios, equilibrium trait values at the individual level are plotted after both: (i) short term coevolution between a distorter and its potential suppressors; and (ii) long term co-evolution between an evolving distorter and its potential suppressors. Under short term evolution (i), a trait distorter (y_1) of fixed strength, and its suppressor (*sup*), are introduced from rarity, and the resulting average trait value is plotted against the extent to which the distorter (y_1) causes trait values to deviate from the individual optimum (k). For all three traits (ai,bi,ci), weak distorters (low k) can successfully distort trait values away from the individual optimum, but strong distorters cannot appreciably distort organism traits, as they are suppressed. Under long term evolution (ii), distorter strength can evolve, and the resulting trait value at equilibrium is plotted, for a range of parameter values, in which the cost of suppression (c_{sup}) is varied alongside a further model parameter ($\lambda/\alpha_1/\alpha_2$) that affects the target level of trait distortion (k_{target}) (Supplementary Information 1). For all three traits (aii,bii,cii), there is only appreciable trait distortion at equilibrium in the top right quadrant, when there is selection for strong trait distortion (high k_{target}) alongside a high suppression cost (c_{sup}). Furthermore, when the cost of suppression (c_{sup}) is low, there is either weak or no trait distortion at equilibrium.

higher levels of cooperative distortion were favoured, increasing the likelihood of suppression (Fig. 3bii).

Although there have been no direct tests, our predictions are consistent with data on imprinted genes. There is no evidence that traits influenced by imprinted genes deviate significantly from individual level optima (Burt and Trivers 2006). Significant deviation is only observed when imprinted genes are deleted, implying that imprinted trait distorters are either suppressed, or counterbalanced by oppositely imprinted genes pulling the trait in the opposite direction (Wilkins and Haig 2001; Wilkins 2010; 2011; Gardner and Ross 2014). Furthermore, although many different parties (coreplicons) have vested interests in genomic imprinting, our analysis suggests why the unimprinted majority could win control (Burt and Trivers 1998; Úbeda and Haig 2003). This could help explain both why, despite being favoured at every gene

subject to asymmetric social interactions, imprinting appears to be relatively rare within the genome (Gregg et al. 2010; Peters 2014; Galbraith et al. 2016), and why imprints are removed and re-added every generation in mice, handing control of genomic patterns of imprinting to unimprinted genes (Kafri et al. 1993; Haig 1997; Burt and Trivers 1998).

Horizontal Gene Transfer and Public Goods

We examined the evolution of public goods production in bacteria. Bacteria produce and excrete many extracellular factors that provide a benefit to the local population of cells and so can be thought of as public goods (West et al. 2007). Public goods production is associated with a fitness cost (c) to the individual and a benefit (b) to the group. In a well-mixed population, genetic relatedness at vertically inherited genes is zero ($R_{vertical}=0$), meaning cooperative traits such as public goods production are disfavoured at the individual level ($R_{vertical}b=0<c$) (Hamilton 1964; West and Buckling 2003; Frank 2010). However, if public goods genes are mobile, for example, because they reside on a plasmid, they can spread within groups, increasing genetic relatedness specifically at the mobile locus ($R_{horizontal}>0$), so that public goods production will be favoured at that locus ($R_{horizontal}b>c$) (Smith 2001; Nogueira et al. 2009; Mc Ginty et al. 2011; 2013; Dimitriu et al. 2014; 2016; 2018).

We modelled the evolution of public goods investment in a large, clonally reproducing population of microbes. The population is well-mixed ($R_{vertical}=0$), meaning the optimum public good production for individuals is zero (West and Buckling 2003). The distorter (y_1) increases public goods investment by some amount (k), at a fitness cost to the individual ($0<c(k)\leq 1$) and benefit shared within the group ($b(k)>c(k)$) that are both monotonically increasing functions of investment $\left(\frac{\partial\{b,c\}}{\partial k}\geq 0\right)$. The distorter ($y_1$) is mobile, and its potential suppressor (*sup*) is immobile (Johnson 2007; Mc Ginty and Rankin 2012; Doron et al. 2018). Each generation, individuals randomly aggregate into groups, and one allele at the mobile locus (y_0,y_1,y_2) spreads horizontally within each group, each with equal likelihood, increasing relatedness at the mobile locus (Niehus et al. 2015; Ghaly and Gillings 2018). Public goods may then be produced and shared within groups. Individuals then reproduce in proportion to their fitness before dying (non-overlapping generations).

In Supplementary Information 5, we showed with a population genetic analysis that our plasmid model produces very similar results to our illustrative model. When distortion is weak (low k), suppressors are not favoured, but the distorter has very little impact at the individual level. When distortion is strong (high k), then suppression is favoured, and so there is no influence on the individual trait value (Mc Ginty and Rankin 2012). Consequently, the extent that public goods investment deviates from the individual optimum of zero investment: (a) shows a discontinuous relationship with the extent of distortion; and (b) will often be negligible (Fig. 3ci). Finally, when we allowed the mobile distorter to evolve, we found that higher levels of public goods investment are favoured, increasing the likelihood of suppression (Fig. 3cii).

We lack empirical data that would allow us to test our model of mobile public goods genes. Genes associated with extracellular traits, which could represent cooperative public goods, appear to be overrepresented on mobile elements (Nogueira et al. 2009). However, this may be nothing to do with cooperation *per se* – genes involved with adaptation to new environments might be more likely to be horizontally acquired, and extracellular traits might be especially important in adaptation to new environments (Dimitriu et al. 2014; 2016; 2018; Niehus et al. 2015; Ghoul et al. 2016).

Discussion

We have found that the individual level consequences of selfish genetic elements ('*distorters*') will be either small or non-existent. If distorters lead to only small distortions of traits, then this will have a small effect on trait values at the individual level. If distorters lead to large distortions of traits then this selects for their suppression, and so there will be no effect on trait values at the individual level. Furthermore, selection on distorters favours higher levels of distortion, which will render them more likely to be suppressed. Consequently, the evolution of distorters will often drive their own demise (Fig. 4). These results suggest that even when there is substantial potential for genetic conflict, distorters will have relatively little influence at the individual level, in support of Leigh's (1971) parliament of the genes hypothesis.

Leigh's (1971) parliament of genes hypothesis assumes that suppression is likely because there will be a much greater number of genes where suppression is favoured. We have allowed for this, by assuming that it is relatively easy for suppression to evolve. Our emphasis here is to ask, if certain types of suppression can arise, then what will happen? Our model therefore describes the direction that we would expect natural selection to take on average. We are not claiming that appreciable trait distortion will never evolve, and there are cases where it has (Burt and Trivers 2006). Biological details will matter for different systems, which could influence factors such as the likelihood or rate at which suppressors arise. Certain types of suppression might be impossible, or incredibly hard to evolve. Furthermore, transient dynamics can lead to substantial distortion before suppressors spread, or when distorters outstrip suppressors in a coevolutionary arms race (Dyson and Hurst 2004; Hornett et al. 2006; Queller and Strassmann 2018).

Our analysis suggests solutions for several problems that have been levelled at individual level fitness maximisation and the parliament of genes. Ridley (2000) argued that adaptation may be limited if large portions of the genome are wasted by embroilment in "subversion and counter subversion", and that segregation at suppressor loci might expose previously suppressed distorters. Our analysis shows that distorters will generally be purged once their selective advantage is reversed by suppression, freeing up genomic space, and minimising their risk of becoming cross-generationally re-expressed. Crow (1991) and others have pointed out that the cost associated with some selfish genetic elements stems from linked deleterious genes, which is not recovered via suppression of the selfish genetic element, in which case suppressors will not spread in response to drivers that reach fixation (Feldman and Otto 1991). However, such drivers do not systematically bias trait values, and so

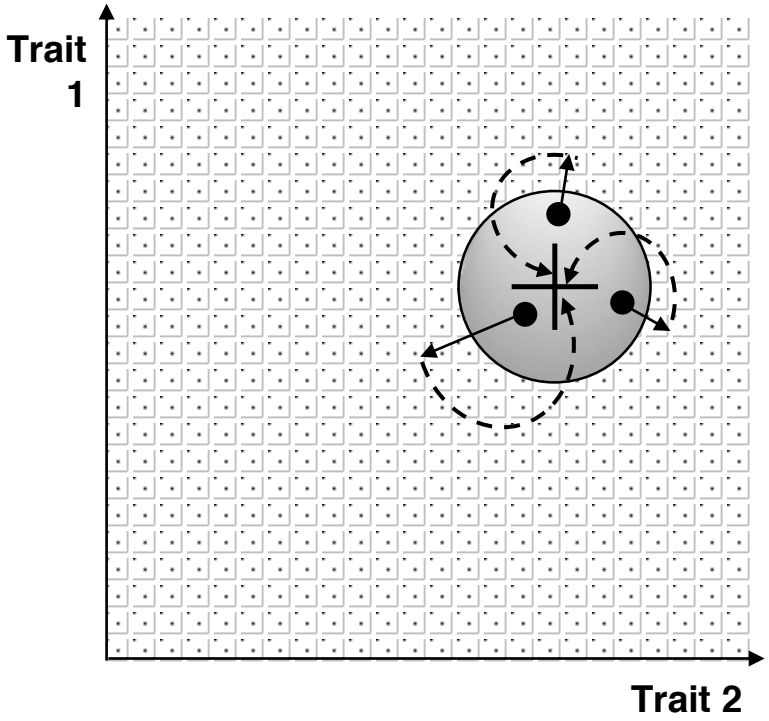

Figure 4: Selfish genetic elements evolve to be suppressed by the parliament of genes. The cross represents the position in phenotype space, here defined with respect to two traits, *1* and *2*, that maximises the fitness of an individual. The circle surrounding the cross represents the phenotype space where suppression of selfish genetic elements, that have distorted traits 1 or 2, would not be selected for. The surrounding area represents the phenotype space in which the parliament of genes is selected to suppress selfish genetic elements. The three dots represent three possible individuals, which, owing to weakly selfish genetic elements, are not maximising individual fitness (the dots do not lie exactly on the cross), although they are approximately (e.g. within the bounds of experimental error in measurement). Because these deviations from individual fitness maximisation are only slight, costly suppression of the weakly selfish genetic elements does not evolve. However, the selfish genetic elements will evolve to become more distorting (solid arrows), bringing individuals into the non-tolerated area of phenotype space, where they will be suppressed and individual fitness maximisation (the black cross) is regained (dashed arrows).

pose no problem to individual level fitness maximisation. We have shown that when traits are distorted, selection for suppressors is retained after driver fixation. Finally, some debate over the validity of assuming individual level fitness maximisation has revolved around whether selfish genetic elements are common or rare (Gardner and Grafen 2009; Grafen 2014; Haig 2014; Bourke 2014; Ågren 2016). We have shown that even if selfish genetic elements are common, they will tend to be either weak and negligible, or suppressed.

We emphasise that when the assumption of individual fitness maximisation is made in behavioural and evolutionary ecology, it is not being assumed that natural selection produces perfect fitness maximisers (Parker and Maynard Smith 1990). Many factors could constrain adaptation, such as genetic architecture, mutation and phylogenetic constraints (Williams 1966; Maynard Smith et al. 1985). Instead, the assumption of fitness maximisation is used as a basis to investigate the selective forces that have favoured particular traits (adaptations). The aim is not to test if organisms maximise fitness, or behave 'optimally', but rather to try to understand

particular traits or behaviours. The fitness maximisation approach has been extremely successful in explaining the life histories and behaviours of a wide range of organisms (Stephens and Krebs 1986; Stearns 1992; West 2009; Westneat and Fox 2010; Davies et al. 2012).

To conclude, to what extent should we expect selfish genetic elements to distort traits away from the values that maximise individual level fitness? Or to put it another way, how reasonable is the assumption of individual level fitness maximisation that forms the basis of modern behavioural and evolutionary ecology (Grafen 2006; 2009; 2014)? For many traits, such as foraging or predator avoidance, the only way that a gene can increase its own transmission to the next generation is by increasing the fitness of the individual carrying it. Consequently, for many traits, there will be no potential for genetic conflict, and individual level fitness maximisation is a reasonable assumption (West and Gardner 2013). However, for other traits, such as the sex ratio or altruistic cooperation, there can be the potential for genetic conflict. We have shown that in these cases, genetic elements will either have small and relatively negligible influences on individual level traits, or be suppressed. This suggests that even if there is the potential for appreciable genetic conflict, individual level fitness maximisation will still often be a reasonable assumption. This allows us to explain why certain traits, especially the sex ratio, have been able to provide such clear support for both individual level fitness maximisation and genetic conflict.

Appendix

Appendix 1: Distorter population frequency

We ask when a rare distorter (y_1) can invade a population fixed for the non-distorter (y_0). We take Equation (1), set $p'=p=p^*$, and solve to find two possible equilibria: $p^*=0$ (non-distorter fixation) and $p^*=1$ (distorter fixation). The distorter (y_1) can invade from rarity when the $p^*=0$ equilibrium is unstable, which occurs when the differential of p' with respect to p, at $p^*=0$, is greater than one. The distorter invasion criterion is therefore $c_{drive}(k)<t(k)(1-c_{drive}(k))$.

We now ask what frequency the distorter (y_1) will reach after invasion. The distorter (y_1) can spread to fixation if the $p^*=1$ equilibrium is stable, which requires that the differential of p' with respect to p, at $p^*=1$, is less than one. This requirement always holds true, demonstrating that there is no negative frequency dependence on the distorter, and that it will always spread to fixation after its initial invasion.

Appendix 2: Suppressor invasion condition

We ask when the suppressor (*sup*) can spread from rarity in a population in which the distorter (y_1) and non-suppressor (+) are fixed at equilibrium. We derive the Jacobian stability matrix for this equilibrium, which is a matrix of each genotype frequency (x_1', x_2', x_3', x_4') differentiated by each genotype frequency in the prior generation (x_1, x_2, x_3, x_4), at the equilibrium position given by $x_1^*=0$, $x_2^*=0$, $x_3^*=1$, $x_4^*=0$:

$$J = \begin{pmatrix} 1-t & \frac{1-c_{sup}}{2(1-c_{drive})} & 0 & 0 \\ 0 & \frac{1-c_{sup}}{2(1-c_{drive})} & 0 & 0 \\ t-1 & \frac{-3(1-c_{sup})}{2(1-c_{drive})} & 0 & \frac{-(1-c_{sup})}{1-c_{drive}} \\ 0 & \frac{1-c_{sup}}{2(1-c_{drive})} & 0 & \frac{1-c_{sup}}{1-c_{drive}} \end{pmatrix}. \quad \text{(A1)}$$

The suppressor can invade when the equilibrium is unstable, which occurs when the leading eigenvalue is greater than one. The leading eigenvalue is (1-c_{sup})/(1-c_{drive}), meaning the suppressor invasion criterion is $c_{drive}>c_{sup}$.

Appendix 3: Equilibrium distorter and suppressor frequencies

We ask what frequency the distorter (y_1) and suppressor (*sup*) will reach after initial suppressor (*sup*) invasion. We assume that the suppressor is introduced from rarity when the distorter has reached the population frequency given by *f* (x1→*f*, x3→1-*f*, {x2,x4}→0). We numerically iterate Equations (2), over successive generations, until equilibrium has been reached. At equilibrium, for all parameter combinations (f,t,c_{sup},c_{drive}), the suppressor reaches an internal equilibrium and the distorter is lost from the population ($x_1^*+x_2^*=1$, $x_3^*=0$, $x_4^*=0$). This equilibrium arises because distorter-presence gives the suppressor (*sup*) a selective advantage, leading to high suppressor frequency, which in turn reverses the selective advantage of the distorter (y_1), leading to distorter loss and suppressor equilibration.

Appendix 4: Invasion of a mutant distorter

We ask when a mutant distorter (y_2) will invade against a resident distorter (y_1) that is unsuppressed and at fixation ($k\neq\hat{k}$). We write recursion equations detailing the generational frequency changes in the six possible gametes, y_0/+, y_0/*sup*, y_1/+, y_1/*sup*, y_2/+, y_2/*sup*, with current generation frequencies denoted respectively by x_1, x_2, x_3, x_4, x_5, x_6, and next generation frequencies denoted with an appended dash (’):

$\bar{w}\ x_1' = x_1x_1+x_1x_2+(1-t(k))(1-c_{drive}(k))x_1x_3+((1-c_{sup})/2)x_1x_4+(1-t(\hat{k}))(1-c_{drive}(\hat{k}))$ (A2)
$x_1x_5+((1-c_{sup})/2)x_1x_6+((1-c_{sup})/2)x_2x_3+((1-c_{sup})/2)x_2x_5$

$\bar{w}\ x_2' = x_1x_2+((1-c_{sup})/2)x_1x_4+((1-c_{sup})/2)x_1x_6+x_2x_2+((1-c_{sup})/2)x_2x_3+(1-c_{sup})x_2x_4$
$+((1-c_{sup})/2)x_2x_5+(1-c_{sup})x_2x_6$

$\bar{w}\ x_3' = (1+t(k))(1-c_{drive}(k))x_1x_3+((1-c_{sup})/2)x_1x_4+((1-c_{sup})/2)x_2x_3+(1-c_{drive}(k))$
$x_3x_3+(1-c_{sup})x_3x_4+(1+t(k)-t(\hat{k}))(1-c_{drive}(\max(k,\hat{k})))x_3x_5+((1-c_{sup})/2)x_3x_6$
$+((1-c_{sup})/2)x_4x_5$

$\bar{w}\ x_4' = ((1-c_{sup})/2)x_1x_4+((1-c_{sup})/2)x_2x_3+(1-c_{sup})x_2x_4+(1-c_{sup})x_3x_4+((1-c_{sup})/2)x_3x_6$
$+(1-c_{sup})x_4x_4+((1-c_{sup})/2)x_4x_5+(1-c_{sup})x_4x_6$

$\bar{w}\ x_5' = (1+t(\hat{k}))(1-c_{drive}(\hat{k}))x_1x_5+((1-c_{sup})/2)x_1x_6+((1-c_{sup})/2)x_2x_5+(1-t(k)+t(\hat{k}))$
$(1-c_{drive}(\max(k,\hat{k})))x_3x_5+((1-c_{sup})/2)x_3x_6+((1-c_{sup})/2)x_4x_5+(1-c_{drive}(\hat{k}))$
$x_5x_5+(1-c_{sup})x_5x_6$

$\bar{w}\ x_6' = ((1-c_{sup})/2)x_1x_6+((1-c_{sup})/2)x_2x_5+(1-c_{sup})x_2x_6+((1-c_{sup})/2)x_3x_6+((1-c_{sup})/2)$
$x_4x_5+(1-c_{sup})x_4x_6+(1-c_{sup})x_5x_6+(1-c_{sup})x_6x_6.$

$\bar{w}$ is the average fitness of individuals in the current generation, and equals the sum of the right-hand side of the system of equations. The mutant distorter can invade

when the equilibrium given by $x_1^*=0$, $x_2^*=0$, $x_3^*=1$, $x_4^*=0$, $x_5^*=0$, $x_6^*=0$ is unstable, which occurs when the leading eigenvalue of the Jacobian stability matrix for this equilibrium is greater than one. Testing for stability in this way, we find that, if the mutant distorter is weaker than the resident, it can never invade. If the mutant distorter is stronger than the resident, it invades from rarity when $\Delta t(1-c_{drive}(\hat{k}))>\Delta c_{drive}$, where $\Delta t=t(\hat{k})-t(k)$, $\Delta c_{drive}=c_{drive}(\hat{k})-c_{drive}(k)$.

The implication is that, if trait distortion is initially low, and mutant distorters are successively introduced, each deviating only very slightly from the resident distorter from which they are derived, such that $\hat{k}=k\pm\delta$, where δ is very small ("δ-weak selection"; Wild & Traulson 2007), then distorters will approach a 'target' strength at which $\frac{\partial t}{\partial k}(1-c_{drive})=\frac{\partial c_{drive}}{\partial k}$. In the absence of suppression, this target (k_{target}) is the equilibrium level of distortion ($k^*=k_{target}$). However, if mutant distorters (y_2) are allowed to deviate appreciably from residents (y_1) (strong selection), then distorters may invade even if they overshoot the target ($\hat{k}>k_{target}$). In the absence of suppression, k_{target} is then not the equilibrium level of distortion, but rather, the minimum equilibrium level of distortion ($k^*>k_{target}$) (Supplementary Information 2, Fig. S1b).

We could alternatively have assumed that an individual's trait is distorted according to the average strength of its alleles (additive gene interactions), rather than according to the stronger (higher-k) allele (dominance). Such an assumption leads to a single invasion criterion for a mutant distorter, regardless of whether the mutant distorter is stronger or weaker than the resident distorter, given by: $\Delta t(2-c_{drive}(k)-c_{drive}(\hat{k}))>\Delta c_{drive}$. In the absence of suppression, this leads to an equilibrium level of distortion (k^*), that holds even under strong selection, that satisfies $2\frac{\partial t}{\partial k}(1-c_{drive})=\frac{\partial c_{drive}}{\partial k}$.

Appendix 5: Equilibrium distorter and suppressor frequencies (long term evolution)

We ask what equilibrium state will arise after the invasion of a mutant distorter. We assume that the mutant distorter (y_2) is introduced from rarity when the resident distorter (y_1) has reached the population frequency given by q. We numerically iterate Equations (A2), over successive generations, until equilibrium has been reached. At equilibrium, for all parameter combinations (q, $t(k)$, $t(\hat{k})$, c_{sup}, $c_{drive}(k)$, $c_{drive}(\hat{k})$), the resident distorter (y_1) is lost from the population (x_3,x_4=0), with either the mutant distorter (y_2) and non-suppressor (+) at fixation ($x_5^*=1$), or the non-distorter at fixation alongside the suppressor at an internal equilibrium ($x_1^*+x_2^*=1$). The latter scenario arises if the mutant distorter triggers suppressor invasion ($c_{sup}<c_{drive}(\hat{k})$). This equilibrium arises because mutant distorter-presence gives the suppressor (*sup*) a selective advantage, leading to high suppressor frequency, which in turn reverses the selective advantage of distortion, leading to distorter (y_1,y_2) loss and suppressor equilibration.

Appendix 6: Agent-based simulation

We construct an agent-based simulation to ask what level of trait distortion evolves when continuous variation is permitted at distorter and suppressor loci. We model a

population of N=2000 individuals and track evolution at two autosomal loci: a distorter locus (L1) and a suppressor locus (L2). Each individual has two alleles at the distorter locus, with strengths denoted by k_a and k_b, and two alleles at the suppressor locus, with strengths denoted by m_a and m_b (diploid). Strengths can take any continuous value between zero and one. We assume that, for both loci, the strongest (highest value) allele within an individual is dominant. The absolute fitness of an individual with at least one active meiotic driver ($\max(k_a,k_b)>0$) is: $1-c_{drive}(\max(k_a,k_b))(1-\max(m_a,m_b))-c_{sup}\max(m_a,m_b)$, and the absolute fitness of an individual lacking an active distorter ($\max(k_a,k_b)=0$) is 1. The function $c_{drive}(\max(k_a,k_b))$ is given an explicit form in simulations (Supplementary Information 1).

Each generation, there are N breeding pairs. To fill each position in each breeding pair, individuals are drawn from the population, with replacement, with probabilities given by their fitness (hermaphrodites). Breeding pairs then reproduce to produce one offspring, before dying (non-overlapping generations). Alleles at the suppressor locus (L2) are inherited in Mendelian fashion. Alleles at the distorter locus may drive, meaning the parental allele of strength k_a is inherited, rather than the allele of strength k_b, with the probability $(1+(t(k_a)-t(k_b))(1-\max(m_a,m_b)))/2$. The transmission bias function, t, is given an explicit form in simulations (Supplementary Information 1). Each generation, distorter and suppressor alleles have a 0.01 chance of mutating to a new value, which is drawn from a normal distribution centred around the pre-mutation value, with variance 0.2, and truncated between 0 and 1. We track the population average distorter strength, denoted by $E[k]$, and suppressor strength, denoted by $E[m]$, over 20,000 generations. We see that, allowing for continuous variation at the distorter and suppressor loci, if the cost of suppression (c_{sup}) is not excessively high, trait distortion at equilibrium is either low or nothing (Fig. 2a; Fig. S1b).

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