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Adaptation in the face of internal conflict: the paradox of the organism revisited

Manus M. Patten[1], Martijn A. Schenkel[1,2] and J. Arvid Ågren[3,4,*]

[1]*Department of Biology, Georgetown University, 37th and O St. NW, Washington, DC 20057, USA*
[2]*Groningen Institute of Evolutionary Life Sciences, University of Groningen, Nijenborgh 7, 9747 AG, Groningen, The Netherlands*
[3]*Department of Evolutionary Biology, Uppsala University, Norbyvägen 18D, Uppsala 752 36, Sweden*
[4]*Lerner Research Institute, Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195, USA*

ABSTRACT

The paradox of the organism refers to the observation that organisms appear to function as coherent purposeful entities, despite the potential for within-organismal components like selfish genetic elements and cancer cells to erode them from within. While it is commonly accepted that organisms may pursue fitness maximisation and can be thought to hold particular agendas, there is a growing recognition that genes and cells do so as well. This can lead to evolutionary conflicts between an organism and the parts that reside within it. Here, we revisit the paradox of the organism. We first outline its conception and relationship to debates about adaptation in evolutionary biology. Second, we review the ways selfish elements may exploit organisms, and the extent to which this threatens organismal integrity. To this end, we introduce a novel classification scheme that distinguishes between selfish elements that seek to distort transmission *versus* those that seek to distort phenotypic traits. Our classification scheme also highlights how some selfish elements elude a multi-level selection decomposition using the Price equation. Third, we discuss how the organism can retain its status as the primary fitness-maximising agent in the face of selfish elements. The success of selfish elements is often constrained by their strategy and further limited by a combination of fitness alignment and enforcement mechanisms controlled by the organism. Finally, we argue for the need for quantitative measures of both internal conflicts and organismality.

Key words: cancer, chimerism, genetic conflict, levels of selection, major transitions, organismality, selfish cells, selfish genetic elements, trait distortion, transmission distortion.

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* Author for correspondence (Tel.: +46 18 471 20 00; Email: arvid.agren@ebc.uu.se).

I. INTRODUCTION

Organisms are special. In contrast with non-living things, organisms appear to possess agency, an internal goal directedness not found in other material things (Wilson, 2005; Walsh, 2015; Ruse, 2018). In *Chance and Necessity*, Jacques Monod described it as 'essential to the very definition of living beings' (Monod, 1970, p. 9). How to characterise this purposefulness formally, however, is contentious (Pittendrigh, 1958; Williams, 1966; Mayr, 1988; Okasha, 2018, 2022).

One view maintains that agency and purpose is best understood as the product of natural selection. As such, it can be captured by the mathematics of an optimization program (see Section II), which finds that organisms should appear as agents trying to maximise their inclusive fitness (Grafen, 2014; see also Gardner, 2017; Huneman, 2019, 2021). This approach, which locates agency and adaptation in organisms, has a long and successful track record, especially in behavioural ecology (Davies, Krebs & West, 2012). Formally, evolutionary theorists have argued that for an entity to be able to evolve adaptations, all of its parts must work towards the same goal and there can be little to no selection within that entity (Gardner & Grafen, 2009; West & Gardner, 2013; Grafen, 2014). That is, the parts must demonstrate a unity of purpose, which in practice means no within-organism conflicts. A limitation of this traditional notion of organismal agency is therefore that it can struggle to account for conflicts within organisms, such as those stemming from selfish genetic elements and cancer cells. In the context of the major transitions in evolution, different types of organisms are thought to be formed when suborganismal particles form cooperative collectives (e.g. genes in genomes, cells in multicellular organisms), which similarly implies that conflict between suborganismal parts is absent (Okasha, 2006; West *et al.*, 2015).

Different parts of an organism's genome and body, however, may not always have the organism's interests at heart. From a theoretical perspective, this threatens the unity of purpose required for evolutionary agency to reside solely with organisms from within (Hurst, 1996; Clarke, 2016; Okasha, 2018; Howe *et al.*, 2022), although empirically organismal integrity appears to be maintained as these threats are kept in check (see also Section III). Nonetheless, agents like cancer cells and selfish genetic elements have the ability to promote their own propagation at the expense of other cells and genes (Burt & Trivers, 2006; Ågren & Clark, 2018). In the case of selfish genetic elements, these are not simply a curiosity; rather, they are the dominant component of animal and plant genomes. For example, transposable elements make up about half of the human genome, and more than 80% of some plant genomes (Wells & Feschotte, 2020). Similarly, cancer is not restricted to humans or even just mammals, but occurs in multicellular bodies across the tree of life (Aktipis, 2020). Rather than being cogs in the machinery that function to benefit the organism, genes and cells often act to benefit their own evolutionary interests at the expense of those of the organism.

Despite the opportunity for internal conflicts to erode the organism and shift agency to a lower level of organisation, they often do not, and organisms persist. This observation is what Richard Dawkins called 'the paradox of the organism' (Dawkins, 1990). In his words:

> '*The paradox of the organism is that it is not torn apart by its conflicting replicators but stays together and works as a purposeful entity, apparently on behalf of all of them. Not only is not torn apart; it functions as such a convincingly unified whole that biologists in general have not seen that there is a paradox at all! They have wrongly taken the organism for granted as the unit about which questions of adaptation should be asked.*' (Dawkins, 1990, p. S64)

Herein, we revisit the paradox of the organism. We review the biology of entities that may challenge organismal agency and fitness maximisation, and introduce a new way to classify such challengers. We then outline the various factors that may constrain conflicts and where this leaves the concept of organismality. In particular, we argue that the unity of purpose assumption of traditional accounts of organismal adaptation and agency ignores too much of within-organism dynamics. A full account of organismality requires such conflicts to be properly accounted for, and we end by arguing for the need for a quantitative measurement of such conflicts.

(1) Optimization theory – the algebra of agency

Evolution by natural selection explains the process and purpose of adaptation (Gardner, 2017). Inspired by economists, evolutionary biologists have found it helpful to formalize this insight in the language of optimization theory (Maynard Smith, 1978; Parker & Maynard Smith, 1990; Grafen, 2006). Here, purpose is captured by a maximisation problem of an agent pursuing the strategy that will maximise the value of an objective function. This usually takes the form of

$$\underset{s \in S}{s \max} \mathcal{H}(s), \tag{1}$$

where S is the set of strategies available and s is the one employed by the agent. $\mathcal{H}(s)$ is the real-valued objective function, defined for all strategies $s \in S$, that the agent seeks to maximise. The maximand, then, is the value of the

objective function, and the larger the value, the better the agent is at achieving its goal. This expression mathematically defines a goal in relation to an agent's strategy. It does not, however, imply that the goal is actually achieved; optimality models establish what the optimum is, not whether it is reached.

Optimization models have been used in many parts of biology. This approach has been especially popular in the study of social evolution, where individuals are treated as agents trying to maximise their (inclusive) fitness (Grafen, 1999, 2009; Gardner, 2013; West & Gardner, 2013; Paternotte, 2020). The individual-as-maximising-agent has been treated most extensively in Grafen's Formal Darwinism Project (Grafen, 2002, 2006, 2014). In this framework, the agent is the individual organism, the strategy set is made up of different phenotypes, and the maximand is inclusive fitness. By linking this optimization programme to the dynamics of allele frequency change (in the shape of the Price equation; Section II.2.*a*), Grafen provides an algebra of agency centred on the individual organism (Huneman, 2019, 2021), and this approach can be extended to capture tensions between different within-organism entities such as genes (Gardner & Welch, 2011; Gardner, 2014; Gardner & Úbeda, 2017).

II. A CLASSIFICATION OF SELFISH ELEMENTS

(1) Transmission *versus* trait distortion

Challenges to organismal agency come from a number of sources. In this section, we review the range of internal conflicts and introduce a new classification scheme for how they challenge organismal unity. This classification scheme also provides a starting point for a quantification of the paradox of the organism, in that it clarifies which internal conflicts are likely to be more harmful to organismality than others. Our focus is on 'selfish elements', which we use as a catch-all term to cover both selfish genetic elements and selfish cell lineages. Throughout we will use intentional words like 'selfish', 'goals', and 'strategy', as is common in evolutionary biology (Dawkins, 1995; Ågren & Patten, 2022; Ågren 2021; Howe *et al.*, 2022).

Selfish elements have been classified previously in different ways – for example, by their proximate mechanism (Burt & Trivers, 2006) or, in the case of selfish genetic elements alone, by the ultimate reason for their selfishness (Gardner & Úbeda, 2017). Given our interest in organismality, we organise selfish elements into a scheme that highlights the manner in which, and ultimately the extent to which, they prevent organisms from achieving a unity of purpose. To determine what makes a selfish element selfish, and to capture the variety of ways an element may be selfish, we ask: what is the element doing to maximise its evolutionary success that conflicts with the organism's attempt to do the same?

There are two fundamentally distinct answers to this question. First, some selfish elements achieve evolutionary success by interfering with the general rules of fair (i.e. Mendelian) *transmission*. In so doing they become over-transmitted relative to alternative versions of the gene or cell within the organism. Second, selfish elements may succeed evolutionarily by interfering with the development of *traits* of the organism, such that the element gains and the organism loses. Some selfish elements represent pure versions of trait or transmission distortion, while others show a mix of the two strategies (Fig. 1).

The difference between the two answers can be explained by an analogy to air travel and the things that airlines might prefer their passengers not to do. It is one thing to sneak on to a plane to Stockholm without paying for a ticket and then avail yourself of the complementary beverage service. The airline might wish these stowaways paid for their ticket to offset the extra fuel they burn, but other than that, they impose no further harm and the plane gets to where it intended to go. It is a different thing to grab control from the pilot and take the plane to Amsterdam. Stowaways confer no benefit on their carriers and may even exact an incidental cost on them, but for hijackers, who divert the plane from its desired destination, the cost inflicted is inseparable from their strategy for success.

A similar distinction applies to selfish elements. For *transmission* distorters, it is quite possible that their intermediate goals are orthogonal to those of the rest of the genome and the organism as a whole. To see why, note that selection within organisms and selection between organisms can be described as separate and independent processes, as captured by two terms of the Price equation [Price, 1970; Gardner, 2008; Frank, 2012; II.2.*a*; see also Okasha & Otsuka (2020) who are circumspect about the Price equation's ability to partition causes neatly]. Some transmission distorters might leave the between-organism component of selection effectively untouched, while prevailing owing to within-organism selection. This evolutionary pattern supports the argument that entities other than organisms may develop adaptations, but it does not threaten the unity of purpose required for organismal agency. With *trait* distorters, however, there seems little room for their selfish strategies to avoid impinging on the success of other genes in the genome and, therefore, on the fitness interests of the organism overall. In this case, adaptation is also occurring on the sub-organismal level, but not without disrupting the organism's unity of purpose.

Under our classification scheme, trait distorters are necessarily in conflict with the organisms in which they reside – the two levels of organisation disagree over some joint phenotype of the organism – but transmission distorters, at least in principle, can achieve their fitness-maximising goals without any harm done to the organism (Section II.2.*b*). In reality, however, many transmission distorters harm organismal fitness in the pursuit of their goals. Our survey of selfish elements (Sections II.3 and II.4) will show that virtually all of them are harmful to the organisms that host them, but our classification scheme paints trait distorters as the greater threat to organismality owing to their direct disruption of the unity of purpose.

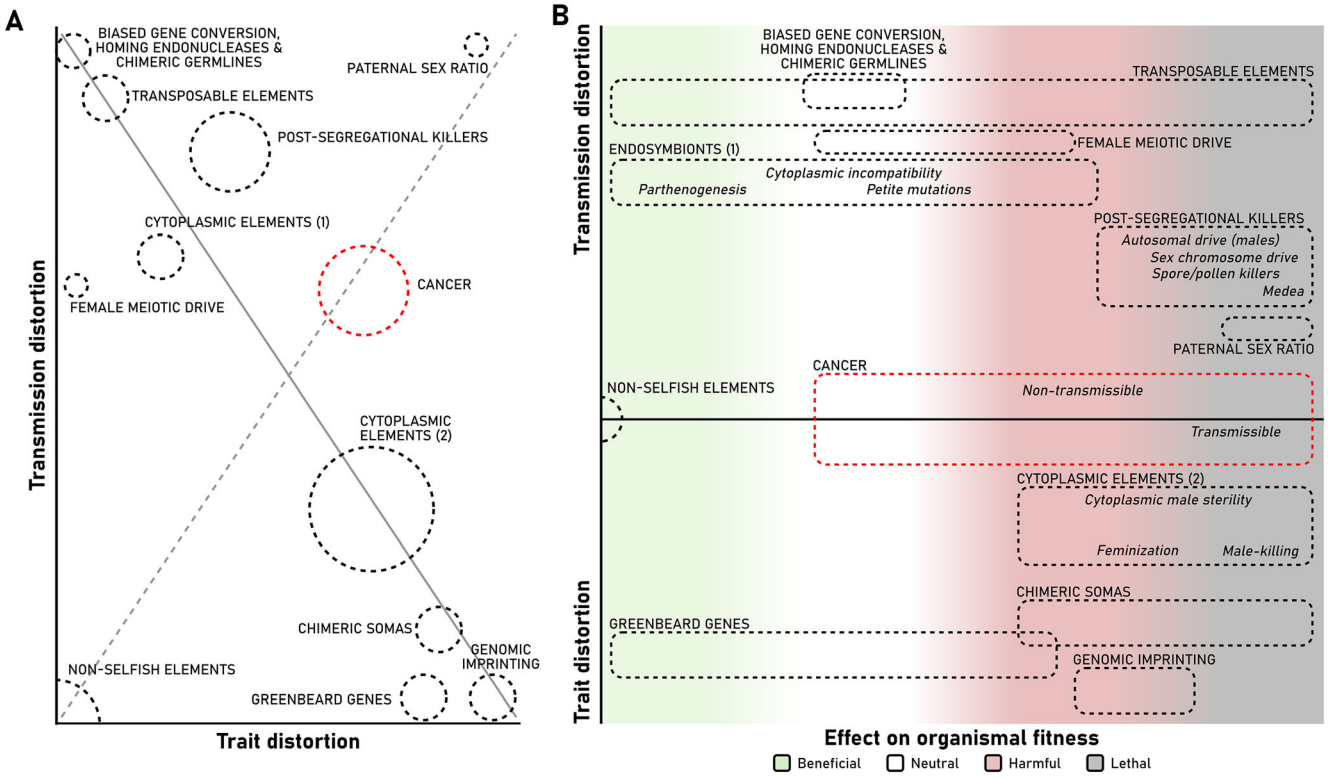

Fig. 1. A taxonomy of internal conflict. Selfish elements may undermine organismal integrity by distorting the transmission of genetic material or by distorting a specific trait of the organism. (A) Classification of selfish elements according to the extent to which they exhibit trait *versus* transmission distortion. The dashed grey diagonal indicates the isocline with selfish elements above this line exhibiting relatively more transmission distortion than trait distortion, and *vice versa* for those below the line. The solid grey diagonal indicates the primary axis of variation in selfish element strategies, and corresponds approximately to the vertical axis in B. Cancer is shown in red to underline that its selfish transmission gains are achieved within a generation and its evolutionary time horizon is not like the other elements depicted here. Non-selfish elements (e.g. Mendelian genes) exhibit negligible to no transmission or trait distortion and therefore would be positioned in the lower left corner of the graph. (B) Trait and transmission distortion are represented as the ends of a continuum, as indicated by the vertical axis. Strategies applied by selfish elements further vary in the magnitude of the harm inflicted on the organism, as indicated by the colour spectrum. Categories of selfish elements are indicated in capital letters and specific examples in italics. Cytoplasmic elements (1) and (2) refer, respectively, to endosymbionts and organelles that employ transmission- or trait-distorting strategies. Dashed boxes indicate the range of effects that a selfish element may cause.

Returning to our analogy, we admit that stowaways may drain the beverage cart, set off the fire alarm in the toilet, and cost extra fuel, all of which are harmful to the airline's bottom line. But none of these activities is necessary for them to achieve their goal. However, a hijacker that diverts a plane from London-Heathrow to London-Gatwick, despite displacing the plane just a few miles from its original destination, is unmistakably and intentionally causing the airline to miss its goal.

(2) Multi-level selection

(*a*) *The Price equation*

Price (1970) derived a general mathematical treatment of evolution that decomposes total evolutionary change into between-individual and within-individual components (see also Okasha, 2006; Gardner, 2008; Frank, 2012). In his derivation, Price indexed each individual in the population and recognised two ways that change may arise. First, 'selection', or the differential reproduction of individuals, is captured in Equation (2) by the covariance between individuals' phenotypes, z_i, and the number of their offspring, w_i. Second, 'transmission', or the inexact resemblance of ancestors and their descendants, is captured by the expected change in phenotype between an individual and its direct descendants (Δz_i), weighted by the number of offspring produced by these individuals (w_i). Combined, this gives

$$\overline{w}\Delta\overline{z} = \mathrm{Cov}(w_i, z_i) + \mathrm{E}(w_i \Delta z_i). \quad (2)$$

The second term of the Price equation permits yet another decomposition and shows that the expected change between

individuals and their descendants may be interpreted as a kind of selection itself. When there is the potential for variability within individuals – both variability for z and variability for the reproductive success of the component parts – the conditions for natural selection are met (Lewontin, 1970), and evolution can be captured thus:

$$\overline{w}\Delta\overline{z}=\mathrm{Cov}(w_i,z_i)+\mathrm{E}_i\left\{\mathrm{Cov}_j\left(w_{ji},z_{ji}\right)+\mathrm{E}_j\left(w_{ji}\Delta z_{ji}\right)\right\}, \quad (3)$$

where the final expectation term, $\mathrm{E}_j\left(w_{ji}\Delta z_{ji}\right)$, is typically assumed to be zero (Frank, 1995).

The application to certain selfish genetic elements is straightforward. If z is taken to represent the allele frequency of a meiotic driver, say, then diploid individuals take on one of three phenotypes ($z=\left\{0,\frac{1}{2},1\right\}$), and the average over the population of individuals, $\overline{z}$, returns the population allele frequency. Equation (3) uses the first term, $\mathrm{Cov}(w_i,z_i)$, to capture selection between different diploid genotypes and the first part of the second term, $\mathrm{Cov}_j\left(w_{ji},z_{ji}\right)$, to capture selection between the two alleles within an individual. In the latter covariance term, where selection is acting within individuals on the haploid genotypes, the z_{ji} may take one of two values ($z_{ji}=0$ or 1). In many cases of meiotic drive, the sign of these two terms is reversed, with selection between individuals favouring diploid genotypes with fewer driving alleles but selection within individuals (i.e. between alleles) favouring haploid genotypes with more. When the signs of the two terms of the Price equation are opposite, it is taken to represent an internal conflict, or a conflict between the levels of selection.

(*b*) *Internal conflict outside the Price equation*

Multi-level selection can be neatly captured within the Price equation, and this partitioning has been used previously to identify internal conflicts (Section II.2.*a*). Internal conflicts are recognised to occur when the two covariance terms of Equation (3) take different signs, as is the case, for example, for most known meiotic drivers. Our classification shows that this partition fails to capture all forms of internal conflict. This is not a failure of the Price equation, though, for the Price equation is merely a way of describing the evolutionary process – a thinking tool. For some internal conflicts we simply need to describe and think about things differently.

First, the Price equation, despite its incredible generality, may give the false impression that conflicts between organisms and their constituent parts always boil down to opposing selection between and within organisms. However, some internal conflicts do not involve any within-organism selection (i.e. the second term of Equation 2) and so lack opposing selection of this sort. We need look no further than imprinted genes or cytoplasmic male sterility factors to find selfish elements that do not drive during meiosis or at any point in the life cycle. And yet clearly a conflict exists between the fitness maximisation for the gene and for the organism in these cases.

Second, elements that show opposing directional selection between levels are typically not cases where the gene level and the organism level have different optima for a *single* phenotypic effect. This issue becomes clear when we appreciate that despite the fact that z is associated with fitness differences at both levels, the z measured at the higher level results from a different cause than the one measured at the level below (Okasha & Otsuka, 2020). In the meiotic drive example, the cause of fitness differences among individuals is a consequence of the differing fertilities or viabilities of the three genotypes that may occur at a driving locus. Within individuals, the cause of fitness differences has nothing to do with fertility or viability, but is instead a matter of the effective segregation ratio. If we were to ask what the optimum fertility and viability are, we would get the same answer from individuals and from the driving genes within them. If we were to ask what the optimum segregation ratio for the drive locus is, the individual would be indifferent, but the gene would not. Agreement and indifference are not hallmarks of conflict. For trait distorters, there appears to be no way to escape the conflict between the selfish element and the organism. By contrast, the harm to the organism caused by transmission distorters, as it is separate causally from the benefit they gain within organisms, would seem to be more easily ameliorated, and resolutions to such conflicts should be possible, at least theoretically. This is not to say that transmission distorters cannot be evolutionarily significant nor that they are inconsequential in development – just that it must be easier for organisms to achieve a unity of purpose in their presence than in the presence of trait distorters.

(3) Selfish genetic elements

(*a*) *Transmission-distorting genetic elements*

Examples from selfish genetic elements and selfish cell lineages demonstrate the usefulness of distinguishing between trait and transmission distortion. More exhaustive reviews of selfish elements can be found in Burt & Trivers (2006), Werren (2011), and Ågren & Clark (2018). We do not survey every possible example nor mechanism; instead, we highlight just a few to illustrate how our classification scheme works (Fig. 1).

First, some transmission-distorting selfish genetic elements may be neutral, or nearly so, with respect to their effects on organismal fitness. Among these we include homing endonuclease genes, transposable elements, some female segregation distorters, certain B chromosomes, and certain mitochondrial variants. We consider these 'neutral' because in principle all of them can promote their own transmission without any appreciable cost to the organism. For example, naturally occurring homing endonuclease genes will convert alternative alleles to homing alleles without any loss of fitness or fertility for their carriers and will readily spread to fixation (Burt & Koufopanou, 2004). These genes are only selfish in that they contribute nothing to organismal function and provide no benefit to other genes of the genome. The only harm

done is to the alternative allele at the locus, and it is only in this regard that the gene can truly be labelled 'selfish'. Likewise, transposable elements need not impose any harm and are therefore considered neutral in our classification. Their spread and stability depends on their copying themselves to other parts of the genome. While they may harm the organism, for example by inserting themselves into functional DNA, thereby rendering it non-functional or inducing large-scale chromosomal re-arrangements, this harm is not necessary for their success and in fact impedes it. Much like homing endonuclease genes (Burt & Koufopanou, 2004), there should be selection on transposable elements to lessen their harm on organisms (Haig, 2016). Finally, selfish elements that achieve drive by ensuring segregation to the functional oocyte rather than the polar bodies, e.g. female meiotic drivers (Clark & Akera, 2021) and B chromosomes that demonstrate gonotaxis (Camacho, 2022), also succeed without necessarily harming the organism. Any harm these elements incidentally cause is entirely separate from their selfish strategy.

In contrast to the selfish genetic elements above, there are others where harm is an inherent part of the strategy (Bravo Núñez, Nuckolls & Zanders, 2018; Fig. 1). In particular, various kinds of so-called male meiotic drivers act in diploid cells to sabotage descendant haploid gametes where they are absent; these are better described as post-segregational killers, as they do not cheat during but rather after meiosis (Fig. 2). For example, the autosomal *Segregation Distorter* (SD) system in *Drosophila* sees heterozygotes producing sperm that contain the SD complex nearly 100% of the time. For autosomal drivers, the loss of fertility they inflict on their carriers (theoretically as much as 50%) goes hand in hand with their mechanism for over-transmission: they win by killing the competition. Individuals with driving genotypes therefore experience selection against the driving gene at the between-organism level and selection for the driving gene at the within-organism level.

In principle, it is possible for these kinds of drivers to leave the organism no worse off (such as in Bates, Meade & Pomiankowski, 2022). For example, the effects of post-segregational killers may be neutral if the mating system is monandrous and if males that carry such killers continue to produce more gametes than can possibly achieve fertilisation. In such situations within-organism selection would leave selection at the between-organism level untouched. However, many drivers are located in inversions, which accumulate deleterious recessive alleles that impose a fitness cost on their bearers unrelated to the killing (Lyttle, 1991; Larracuente & Presgraves, 2012). This additional cost, although not a feature of the drive mechanism itself, can be taken as between-organism selection against the driver, setting up a situation in which selection at the different levels runs in opposite directions.

Sex-chromosome drivers also kill the competition to achieve their transmission advantage and come with an additional inescapable harm to the organism (Jaenike, 2001, 2008). Aside from their potential harm to fertility, they also change the sex ratio among the descendants of their carriers, and cause their bearers to overproduce offspring of one sex. As we have seen with several other selfish genetic elements thus far, this latter harm is not necessary to provide them their transmission advantage; it is simply a pleiotropic cost unrelated to the selfish strategy. One can think of it as though the harm to fertility is part of the driver's strategy, but the harm brought about by sex ratio skewing is not.

Cytoplasmic over-replicators provide another example of transmission distortion and fall somewhere between neutral and harmful (Fig. 1). For example, the *uadf5* mutant in

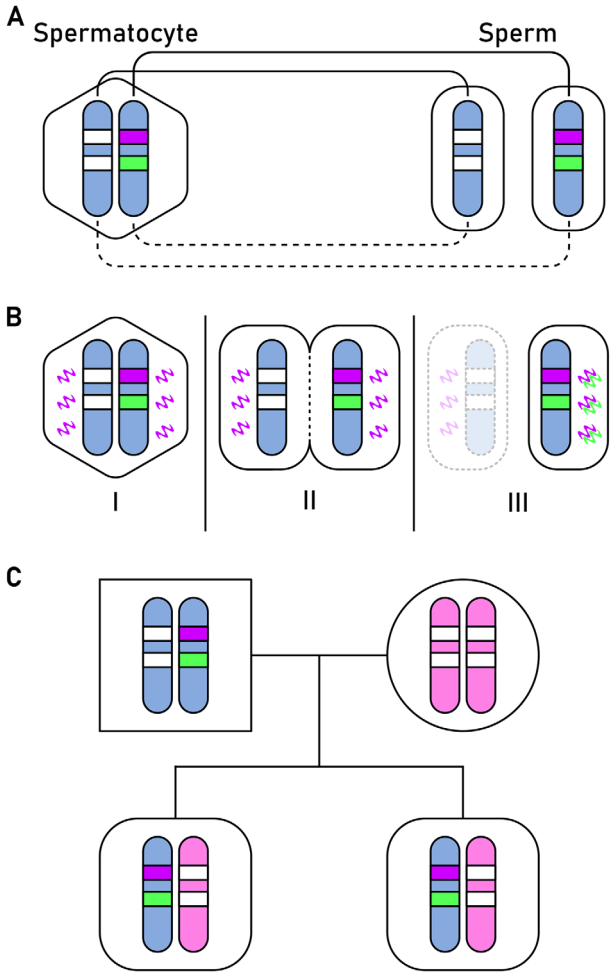

Fig. 2. Anatomy of conflict: post-segregational killers. (A) During meiosis, genetic variants at heterozygous loci find themselves represented in some gametes (solid lines) but not others (dashed lines). (B) Over-transmission can be achieved in different ways, such as when a genetic variant eliminates gametes that do not bear it. Here, such a variant is composed of two loci: one produces a poison (purple) that is put in all gametes during gametogenesis (I–II), whereas the other locus produces the antidote (green) in the gametic phase (III). Gametes that do not bear the antidote locus are eliminated. (C) Over-transmission as occurring in (B) causes heterozygous individuals to transmit only the selfish poison–antidote complex to their offspring.

C. elegans mitochondria (Gitschlag, Tate & Patel, 2020) and the *petite* mutations of yeast mitochondria (Chen & Clark-Walker, 1999) spread within a heteroplasmic cell lineage by replicating faster than wildtype mitochondria. Their replication advantage comes at a cost, as both involve the deletion of genes essential to metabolic function (Pereira, Gitschlag & Patel, 2021). While a fast-replicating metabolically competent mitochondrion may technically be possible, empirically it seems that replication and oxidative phosphorylation are subject to a trade-off, so that the best way for a mitochondrion to achieve over-replication is at the expense of oxidative phosphorylation. These mutants are therefore best thought of as bringing unintentional harm. The harm is separate from their strategy for over-transmission, but inescapable, given the constraints of their biology.

(*b*) *Trait-distorting genetic elements*

Trait distorters modify the traits of their host organisms in ways that enhance the fitness of the responsible genetic element but not the organism in which it resides. In contrast to transmission distortion, trait distortion does not entail selection within the organism, and so is not readily captured in a Price equation partition of multi-level selection (Section II.2.*a*). Owing to their effects on the phenotype of the organism, there is little room for neutral trait distorters. All of the elements discussed below cause harm to the organism by virtue of displacing it from its phenotypic optimum.

Genomic imprinting is a prime example of trait distortion. Imprinted genes, which are found in mammals and seed plants, are differentially expressed depending on their parent of origin, most typically with one allele remaining silent during development and the other expressed (Pires & Grossniklaus, 2014). Haig's kinship theory for the evolution of imprinted expression recognises that the two alleles of a gene may disagree over its optimal total expression level owing to how the gene's expression affects the fitness of kin, to whom the two alleles may be differentially related (Haig, 2000, 2013), and finds that imprinted expression – i.e. silencing of one allele; expression from the other – is an evolutionarily stable outcome of such disagreements. The kinship theory makes two key predictions: first, it predicts expression from the parental origin that favours higher total expression and silencing of the parental origin that favours lower expression; and, most important for our purposes, it predicts the total expression level of an imprinted locus will match that of the expressing parental origin's optimum. Therefore, the optimal phenotype from the perspective of an imprinted gene is different from that of either an unimprinted gene or from an imprinted gene with the reverse parental-origin-specific expression profile (Fig. 3).

We offer this simple heuristic example to make the logic and predictions more concrete. A paternally expressed imprinted gene in a mammal will favour the production of a relatively large, demanding placenta, owing to the likely possibility that it will not be present in future offspring born to the same mother and so gains no indirect fitness benefit from the mother's residual reproduction (Haig, 2002). By contrast, a maternally

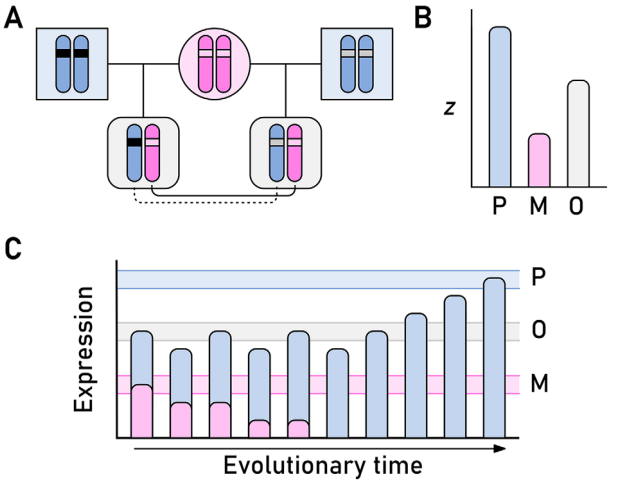

Fig. 3. Anatomy of conflict: selfish elements in social interactions. (A) In half-siblings, relatedness between patrigenic (P; blue) and matrigenic (M; pink) may be different; here, maternal half siblings are expected to exhibit higher relatedness for matrigenic than patrigenic genes. (B) Owing to these relatedness differences, patrigenes and matrigenes differ in their optimal value of a trait z (e.g. fetal growth rate); these optima may additionally deviate from those experienced by unimprinted genes of the offspring (O; grey). We assume here that the patrigene favours a higher expression level (similar to genes that extract resources from the mother, e.g. *IGF2*), although the pattern may be inverted (similar to genes with the opposite effect, e.g. *IGF2R*). (C) The different optima for z means that genes that affect z may have different optimal expression levels from the perspective of patrigenes (P; high), matrigenes (M; low), and unimprinted genes (O; medium). Over time, genomic imprinting may evolve to reduce the expression of matrigenes; inversely patrigenes will increase in expression. Eventually, matrigenes may be fully silenced and patrigenes will evolve unrestrictedly towards the patrigenic optimum value.

expressed imprinted gene will favour a relatively small placenta, owing to the fact that it is likely to be present in future offspring born to this mother and so can gain an indirect inclusive fitness benefit by tempering its demands on the mother. Finally, an unimprinted gene will favour a relatively medium-sized placenta, because, not knowing its parental origin, it must average over the first two possibilities. Each of these genes will influence organismal development with the aim of achieving their optimal phenotype. If we take the vast majority of genes, which are unimprinted, to be 'the parliament' (Leigh, 1971; Fromhage & Jennions, 2019), then the organismal optimum would be taken to be a medium-sized placenta. Any deviation from a medium-sized placenta would therefore be harmful to the organism. Note that regardless of the phenotype produced in the end, all genes of the offspring capable of affecting placental development experience the same direct fitness; there is no within-organism selection, no transmission distortion, at play. These genes may nonetheless differ in their inclusive fitness.

Another example of trait distortion is found in the sex-determination distorters (Fig. 1). Many cytoplasmic genomes are transmitted by just one of the sexes, most often females.

This is thought to have evolved to avoid the conflict that may ensue when cytoplasms contain a mix of different genotypes (Hurst & Hamilton, 1992). However, imposing uniparental inheritance also creates a different conflict, one between the cytoplasm and the nucleus. Because males are effectively an evolutionary dead end from the perspective of maternally inherited elements, cytoplasmic elements have evolved all manner of sex-distorting phenotypes (Engelstädter & Hurst, 2009; Perlman *et al.*, 2015). In plants, for example, cytoplasmic male sterility causes what would otherwise be hermaphroditic flowers to forgo reproduction through pollen, instead reallocating those resources to reproduction through ovules. If any of that lost male fertility is recouped as additional female fertility, then the selfish element gains and the organism loses. This forced reallocation of effort is part of the strategy of the selfish cytoplasm. Further, cytoplasmic male sterility, as it spreads leaves a population more and more female biased, and so forgoing male reproduction represents an increasing opportunity cost. This latter harm is not necessary for the element to spread, but is an inescapable harm to the organism nonetheless.

The Paternal Sex Ratio (PSR) chromosome of the parasitoid wasp *Nasonia vitripennis* is as harmful as it gets (Werren, Skinner & Charnov, 1981), reflecting both its roles as a transmission and trait distorter. In this species, sex is determined *via* haplodiploidy, where haploid (unfertilized) eggs develop into males and diploid (fertilised) eggs develop into females. PSR is a B chromosome that is transmitted by males only and, as such, it would prefer its carrier be male. It can achieve this by ensuring the destruction of all the other chromosomes that arrive with it in the sperm as it fertilises an egg. The paternally derived genome (except for PSR) is tagged for destruction, and all that remains after fertilisation and development is the maternally derived genome and the paternally inherited PSR chromosome. The result is a haploid organism with PSR, a male primed to engage in the exact same self-sabotage at the next bout of reproduction. Because PSR destroys all the genes that accompany it between the generations, it has been described as the most selfish genetic element of them all (Werren & Stouthamer, 2003). PSR thus displays characteristics of both strong trait distortion and transmission distortion (Fig. 1). Its trait-distorting effect is required for it to achieve transmission distortion.

These examples demonstrate that the success of trait-distorting genetic elements by necessity causes deviations from an organismal optimum. Hence, all trait-distorting genetic elements cause organisms to arrive at suboptimal phenotypes in their attempts to achieve their selfish aims. Unlike transmission-distorting genetic elements, trait distorters therefore always pose a threat to the integrity of the organism.

(4) Selfish cell lineages

(*a*) *Transmission-distorting cell lineages*

Internal conflicts require variation within organisms. For selfish genetic elements, sexual reproduction generates the requisite within-organism variation, allowing the conflicts they spur to arise generation after generation. For selfish cells, by contrast, the developmental program of many multicellular organisms ensures that any such internal variation is minimised or erased at the start of each generation by a single-cell bottleneck. Consequently, the variation required for internal conflict, which demands different identities among the various cells within an organism, must arise by mutation over the course of ontogeny. The evolutionary time horizon of such a selfish cell lineage is thus a single generation. Exceptions to these homogenising developmental programs exist, however, and provide a second source of within-organism variation that is regenerated reliably, leading to more durable internal conflicts that persist over evolutionary time. Only a few of the examples discussed below involve the kind of variation necessary for this latter, long-term evolutionary change to populations, which we consider to be genuine evolutionary conflict.

Transmission-distorting cell lineages simply make more copies of themselves, which in principle can be done without substantively changing the phenotype of the organism. In this regard, they have much in common with transposable elements and homing endonuclease genes, which similarly succeed without modifying the phenotypes of the organism in which they reside and may even be selected to minimise their harm. However, the mechanisms through which they gain their transmission distortion often come with an incidental cost, which can be considerable, to the fitness of the organism.

Cancer has long been portrayed as an example of selection within the organism (Frank, 2007; Fig. 4). In terms of the Price equation (Section II.2.*a*), we can index a cohort of individuals early in their ontogeny and then treat the same population of individuals later in ontogeny as their descendants. There can be viability selection on individuals for their cancer burden (individual-level selection, as captured by the covariance term in Equation 2) and also a change in the relative concentration of cancerous cells within them over that time interval (within-individual selection, the expectation term in Equation 2), giving rise to a total amount of change in the average cancer burden in the population. Within the lifespan of the organism, we may thus talk of cancer cells being selected for and causing change *within the developing body*. But these changes are wiped out in the next generation of organisms because, in general, all of the 'evolution' that cancer causes takes place in the ephemeral soma (Gardner, 2014; Bourrat *et al.*, 2022). This is not the sort of selection within organisms that could ever lead to the evolution of increased cancer over evolutionary time. Cancer's existence at a non-zero frequency – and any evolved defences against it – therefore relies on the repeated origin of selfish cancer cell lineages (Ågren, Davies & Foster, 2019). We therefore hesitate to lump together cancer with other forms of internal conflict that operate over evolutionary, as opposed to developmental, timescales.

Transmissible cancers, unlike traditional cancers, are exempt from this limited time horizon, because they may

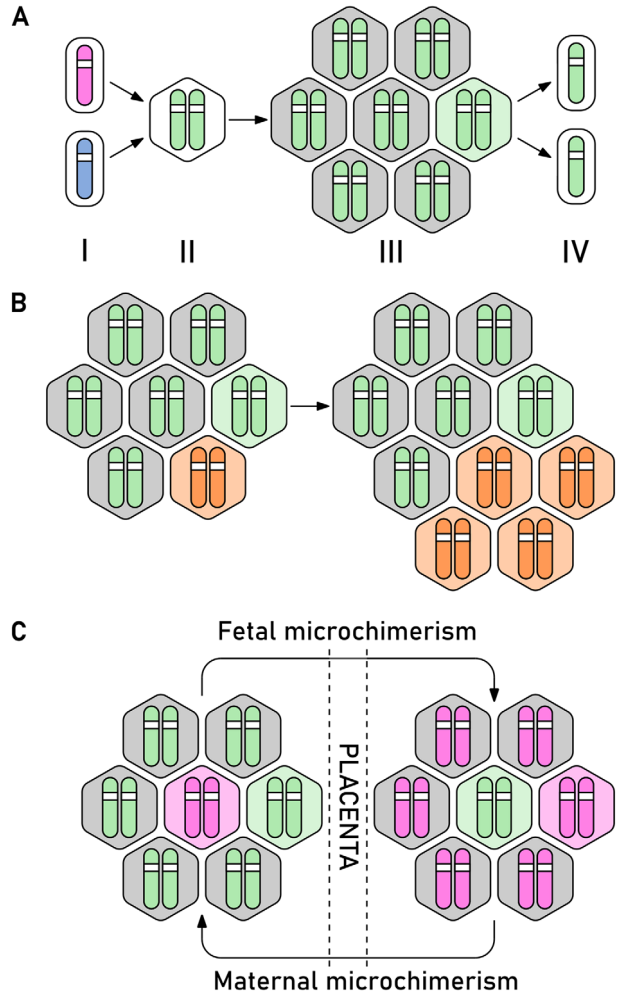

Fig. 4. Anatomy of conflict: selfish cell lineages. (A) Canonical multicellular organisms pass through a single-cell bottleneck, here depicted to occur *via* the fusion of two haploid gametes (I–II). From the single cell stage, multicellularity develops through mitotic growth (III). Conflict is minimised as all cells are genetically homogeneous, and somatic cells (depicted in grey) achieve evolutionary success by supporting the germ line (depicted in green), which transmits the shared genetic material by producing gametes (IV). (B) Cancerous cells (orange) may develop from cell lineages in which sufficient mutations have occurred as to confer an identity mismatch to the other cells in the organism. The cancerous cell lineage may then develop excessive growth at the expense of non-cancerous cells. (C) Microchimerism occurs when during fetal development, cells from the mother may be transferred across the placenta to the fetal tissue (maternal microchimerism; maternal cell depicted in pink) or, vice versa, fetal cells are transferred to the maternal tissue (fetal microchimerism; fetal cell depicted in green).

be transmitted to other individuals (similarly to selfish spermatogonial selection). Transmissible tumours are known from dogs, Tasmanian devils (*Sarcophilus harrisii*), and bivalves (Dujon *et al.*, 2020) and likely occur in other organisms as well (Ujvari, Gatenby & Thomas, 2016). The goal of a transmissible tumour, much like that of a transposable element, is to make more copies of itself within its host's body, making the tumour bigger and thus a more prolific source of propagules for its next host. This kind of within-individual selection may therefore lead to changes in the frequency of transmissible cancers across generations, in contrast to traditional tumours that die with their host. That said, we hesitate for a different reason to lump transmissible tumours in with other forms of internal conflicts. From a certain perspective transmissible tumours are simply another infectious agent (Metzger & Goff, 2016) and are, like a virus or a pathogenic bacterium, *external* to the organism.

Our attempt to classify cancer is further complicated by the recognition that many cancers manipulate host physiology to facilitate tumour growth. While their over-proliferation compels us to classify them as primarily transmission distorters, the fact they may, for example, remodel vasculature gives them some features of trait distorters. We are unaware of any cancers that over-proliferate without simultaneously exerting influence on the entire organism the way that homing endonucleases, for example, over-proliferate without affecting other genes in the genome.

A genuine, non-problematic transmission distorter would see the requisite internal variation arise regularly as a function of development. One notable example of this is found in the cottony cushion scale insects of the genus *Icerya*. In *Icerya*, hermaphrodites develop from fertilised eggs, some of which may result from self-fertilisation and some from outcrossing with rare haploid males (Mongue *et al.*, 2021). The sperm cells that fail to fertilise the egg may persist as a haploid tissue that becomes the haploid male germline of the hermaphrodite offspring. Any selfishness of sperm cells competing for representation in this potentially chimeric male germ line represents a case of transmission distortion and, much like other transmission distorters, need not bring any harm or modification otherwise to the hermaphrodite organism overall.

(*b*) *Trait-distorting cell lineages*

The separation between the germ line and the soma during development invites a form of internal conflict over a specific trait: the allocation of cells to germline *versus* somatic function (Buss, 1987). The time horizon over which this conflict plays out depends on the developmental mode of the organism.

In clonal organisms that develop from a single cell, cells can in principle jockey to be assigned to the germline rather than the evolutionary dead-end soma, and any variant that achieves this should be transmitted by the individual at higher than average rates (Buss, 1987). Here, within-individual variation can only come about by mutation, giving rise to some cells that tend to navigate towards or differentiate as germ cells. This can come at the expense of contributing to somatic function (e.g. Koufopanou, 1994), a classic case of underproviding a public good. The organism suffers from sub-optimal performance of its soma when cells compete for access to the germline. Owing to the single-cell

bottleneck between successive generations, though, the variation necessary for this form of within-individual selection is fleeting, and the threat to organismal unity of purpose is short-lived.

In aggregative or colonial organisms, however, where genetic heterogeneity is not dependent on mutation, there can be active competition to contribute to the germ line (e.g. Stoner, Rinkevich & Weissman, 1999; Strassmann, Zhu & Queller, 2000). This can leave organisms worse off. For example, some genetic variants in the slime mold *Dictyostelium discoideum* avoid differentiating into the somatic stalk, and the slug, which requires the somatic stalk for dispersing its spores, may end up lacking a stalk entirely (Buss, 1982). Variants that affect the allocation of cells to germline *versus* somatic fate under these developmental systems may experience selection both within and between organisms across many successive generations.

Another developmental system that regenerates within-organism heterogeneity every generation and lends itself to a variety of trait-distorting cells is chimerism, the coexistence of cells with different origins within a single body. For example, tamarins and marmosets (family Callitrichinae) regularly birth twins, and during pregnancy the twin placentae may fuse, leading to their circulations becoming attached and an exchanging of certain kinds of stem cells between co-twins (Sweeney *et al.*, 2012). An individual marmoset at birth is made up of its 'own' cells (as derived *via* mitotic division from the zygote), as well as those of its sibling. The two cell lineages within a marmoset, given their differing relatedness to the germline of their own body and that of other kin, can be selected to bring about different behaviours from one another (Haig, 1999; Patten, 2021). The resulting phenotype is likely to be an adaptive compromise between their differing interests. In particular, kin selection theory predicts that these conflicts among cell lineages should affect how the composite organisms behave towards relatives, both in terms of the demands they make on their mothers and other caregivers and in terms of the care they provide for younger siblings. The coexistence of multiple cell types within a single body may thus distort phenotypes relative to what would be optimal for a purely clonal organism.

In taxa with invasive placentation, such as many mammals, there is a possibility for a related form of selfish cell lineage: microchimerism (Fig. 4C). Here, the cells of the two parties in mammalian reproduction travel in both directions: fetal cells remain detectable in mothers decades after birth and maternal cells stay with their offspring for just as long. What these cells are up to is an area of active investigation (e.g. Sedov *et al.*, 2022). It is quite possible that the cells enter their new host with an aim of cooperating. Mothers and their offspring are genetic relatives, and so kin selection could favour the visiting cell line aiding its new host. On the other hand, they are not identical, which leaves room for parent–offspring conflict (Trivers, 1974). When we find fetal cells in maternal breast tissue, for example, the question arises whether those fetal cells are there to provide protection against breast cancer or whether they are there to force mothers to allocate more effort to lactation than would be optimal from the maternal inclusive-fitness perspective. If the latter, we have a trait distorter (the fetal cell line) that harms its carrier (the mother) by displacing her from her optimal phenotype. As cell lineages become selfish owing to a mismatch between the organismal identity and the cell's identity, it is to be expected that (micro-)chimeric cells too will exhibit phenotypes that are detrimental to organismal fitness.

III. ORGANISMALITY IN THE FACE OF INTERNAL CONFLICTS

As demonstrated above, the integrity of organismal agency is constantly challenged by a wide range of selfish elements. Yet, the persistence of organisms as apparent fitness-maximising agents suggests that internal conflicts do not overwhelm them, or, at least are managed in a way that prevents them from breaking down organismal functionality altogether.

Next, we discuss potential reasons why internal conflict does not subvert the organism as a fitness-maximising agent. The reasons can be grouped into three main categories: (*i*) factors that (re-)align the disparate agendas of sub-organismal units such as genes and cells; (*ii*) organism-level mechanisms that directly suppress internal conflicts and enforce cooperation; and (*iii*) intrinsic constraints on genes and cells that prevent them from exploiting the organism in which they reside. For each of these reasons, we discuss how they may affect internal conflict among both genes and among cells. We also discuss the need for a quantitative framework for the paradox of the organism, which would not only point out that these mechanisms can alleviate the impact of selfish elements and promote organismal *versus* sub-organismal adaptation but would also provide a way to measure the extent to which they do so.

(1) Alignment of sub-organismal and organismal agendas

Asexual reproduction leads to all genes being co-transmitted, resulting in offspring that are genetically uniform. As gene-level representation corresponds neatly to individual-level reproductive success, there is little scope for mutations to enhance gene-level fitness at the expense of individual-level fitness (Hickey, 1982; Bestor, 2000). In sexually reproducing organisms, the situation is markedly different. Meiosis reduces the per-individual contribution to offspring as well as per-gene representation, as fair meiosis means that a given allele ends up in only half of the gametes. Moreover, independent segregation of chromosomes means unlinked genes are no longer always co-transmitted (Mendel, 1865). Similarly, exchange of genetic material *via* e.g. horizontal gene transfer causes gene fitness (future representation) to diverge from individual fitness. Sex causes the divorce between gene-level and individual-level fitness and opens up the possibility for genes to evolve strategies that enhance their fitness at the individual's expense.

While sexual reproduction enables selfish genetic elements to escape their own deleterious effects, it may also help reduce the scope for selfish genetic elements to persist and spread. Meiotic recombination is sometimes costly as it may break up co-adapted gene combinations (Otto & Lenormand, 2002), but this equally applies to co-adaptation between selfish genetic elements (Haig & Grafen, 1991; Brandvain & Coop, 2012). Some selfish genetic elements, such as certain meiotic drivers, consist of two or more protein-coding genes, where one encodes a toxin and the other an antidote (Marshall & Hay, 2012; Fig. 2). Variations of this approach apply to, among others, *Medea* (Chen *et al.*, 2007), some meiotic drivers (Burga, Ben-David & Kruglyak, 2020), and some subtypes of greenbeards (Gardner & West, 2010). Tight linkage between the toxin and antidote genes enables their co-transmission, and thereby co-adaptation as a selfish genetic element. Recombination, however, reshuffles the toxin and antidote genes so that neither benefits from their alliance (Hartl, 1974). Toxin genes would be actively selected against as its bearers are purged from the population, and antidote genes are likely to be lost through genetic drift. Recombination therefore acts to realign genes to the organismal agenda by reducing the scope for genic alliances with otherwise co-segregating genes on a single chromosome.

The existence of selfish cell lineages is ultimately rooted in the disconnect between the organismal and cellular identities. In many multicellular organisms, the single-cell bottleneck at their origin followed by clonal cellular replication ensures that all cells in an individual have an identical genetic composition (barring novel mutations) (Fig. 4A). Cells of the same body are in principle fully related to each other (Queller, 2000; Howe *et al.*, 2022). Consequently, all gene copies residing within somatic cells have an equal chance of being represented in the germline, and so all benefit from furthering the fitness of the organism rather than trying to undermine it (Haig, 2021). Multicellular organisms of this kind can therefore also be considered as clonal groups experiencing group selection (Gardner & Grafen, 2009). Ultimately, this developmental program equates cellular identities with the organismal identity, effectively eliminating cell-to-cell conflict.

Other developmental programs do not by default result in homogenised groups of cells. This is the case when organismal reproduction occurs *via* budding or fission, such as in many fungi (Isaksson *et al.*, 2021) and in multicellular organisms that form through aggregations of unrelated cells, as in *D. discoideum* (Jahan *et al.*, 2022). Finally, even within organisms with the single-cell bottleneck, *de novo* mutation and subsequent chimerism can both lead to genetically dissimilar cells within an organism. Although on a smaller scale, the end product in all cases is fundamentally similar. In organisms that are mosaic or chimeric, cell-to-cell relatedness will be reduced and the strength of cellular kin selection is weakened accordingly. Other factors must act to prevent selfish cell lineages from breaking down the organism.

(2) Enforcement of cooperation

Different types of organisms have come into being *via* evolutionary transitions in individuality (Maynard Smith & Szathmáry, 1995; Bourke, 2011; West *et al.*, 2015). These are fundamental changes in the social organisation of biological entities, whereby lower-level units (particles) become organised into higher-level ones (collectives), typically associated with the transfer of fitness from particles to collectives (Michod, 1999, 2007; Clarke, 2014; but see Bourrat *et al.*, 2022). For example, eukaryotes represent collectives of genomes, multicellular organisms represent collectives of cells, and all organisms can be regarded as collectives of genes that have become organised into genomes. While each collective is a cooperative venture, the particles still retain opportunities for selfish behaviour to enhance their fitness. Suppressing selfishness *via* enforcement of cooperation is therefore essential to maintain the integrity of the organism (Ågren, Davies & Forster, 2019).

In the context of selfish genetic elements, collective-level enforcement has been conceptualised as the rule of the 'parliament of genes' (Leigh, 1971). Selfish genetic elements impose a cost on other genes in the genome, and the parliament of genes works by invoking the many-against-one principle. Here, the majority of genes experience a cost of the selfish gene, which is alone in experiencing a benefit of its selfishness. The cumulative action of selection acting on the afflicted majority of genes to suppress the selfish interest of the 'cabal of the few' outweighs the selection acting on the lone selfish genetic elements to exhibit selfishness. Over time, the interest of the genome as a whole will prevail.

Theoretical support for the parliament of genes hypothesis comes from modelling of trait distortion by selfish genetic elements (Scott & West, 2019; Veller, 2022). Trait distorters may persist over evolutionary time only when the distortion is weak. Higher levels of trait distortion inevitably induce selection for suppression, maintaining the status quo of organismal optimality. Other models have argued similarly that cooperative genes ought to be more prevalent than exploitative genes (Fromhage & Jennions, 2019; Garcia-Costoya & Fromhage, 2021). Consistent with theoretical predictions, genes suppressing selfish genetic elements have been described in numerous species (Hurst, Atlan & Bengtsson, 1996; Ågren & Clark, 2018). It is likely that many more selfish genetic elements persist cryptically in natural populations, as local suppression means their selfish effects only become apparent when diverged populations mix (Hurst & Werren, 2001; Ågren & Clark, 2018).

Enforcement of selfish cell lineages involves the regulation of cell proliferation and the detection and elimination of non-self-cells (Aktipis *et al.*, 2015). For example, the risk of harm from cancer may be reduced by the evolution of mechanisms that predispose proliferative cells towards apoptosis (e.g. Bartkova *et al.*, 2006), or programmed cell death may occur as a result of external cues provided by other cells, such as through the cell-mediated immune response (Grosberg & Strathmann, 2007). This is thought to be a key part of why

elephants do not experience higher rates of cancer than humans, despite their much bigger body size. Whereas humans have one copy of *TP53*, a key tumour suppressor gene, elephants have multiple (Abegglen *et al.*, 2016; Sulak *et al.*, 2016). Self–non-self-recognition systems also play an important role in detecting pre-cancerous cells (Corthay *et al.*, 2022), but may additionally be involved in the detection and elimination of microchimeric cells (Bonney & Matzinger, 1997). Enforcement is central to maintaining cellular cooperation, but the presence of suppression mechanisms has also caused an evolutionary arms race with selfish cells. For example, the loss of major histocompatibility complex (MHC) antigen presentation in some cancers might allow them to evade the immune system (Siddle *et al.*, 2013; Dhatchinamoorthy, Colbert & Rock, 2021).

(3) Constraints and higher-level processes

Another key to the maintenance of organismal integrity can be found in inherent constraints of selfish elements. Selfish elements are strikingly successful exploiters of organismal biology, and given the diversity of selfish elements it is unsurprising that many organismal features have been found to be open to exploitation. Nonetheless, as seen above, selfish elements are also subject to a variety of checks and balances that offset the benefits they reap from self-promotion, which may therefore prevent them from eroding the organism from within entirely.

In addition to the enforcement mechanisms described above, selfish elements may be unable to subvert the organism entirely because of limiting functional constraints imposed by the manner in which they exert their selfishness. One example is the toxin–antidote meiotic drive system where a single protein-coding gene is insufficient to form a functional selfish genetic element. Instead, two or more genes must form an alliance for a functional selfish genetic element to arise. Alternatively, ultimate constraints relate to the deleterious effects on the level of the organism, and hence are best considered from a multi-level selection perspective where selection between individuals opposes the spread of selfish elements (Okasha, 2006). Moreover, selfishness may be beneficial when rare and cooperators are abundant, but may become detrimental as it spreads and cooperators become rare, as has been found for cheaters in aggregative myxobacteria (Fiegna & Velicer, 2003).

While we have previously focused on the direct costs of selfish genetic elements, there may also be indirect costs. Selfish genetic elements are often located in regions with low recombination, such as inversions, or in genomic elements with clonal transmission, such as organellar genomes. This lack of recombination predisposes these elements to genetic decay *via* a variety of mechanisms (Bachtrog, 2013), most importantly Muller's ratchet, under which deleterious mutations accumulate through genetic drift (Muller, 1918). In diploids, a selfish genetic element that occurs at a low frequency in a population is likely to reside mostly in heterozygotes. At these low frequencies, recessive deleterious mutations linked to the element are sheltered from selection by being paired with functional copies on the alternative allele, so that negative selection against the selfish genetic element through linked deleterious mutations is relatively weak. As its frequency rises, the selfish genetic element will occur more and more frequently in homozygotes and so will encounter more negative selection. Hence, frequency-dependent selection acts to limit the spread of selfish genetic elements and prevent their fixation. As genetic variation for the selfish genetic element is maintained, the time frame available for suppressors to evolve among the parliament of genes remains open as well.

The effects of selfish genetic elements on their bearers may also have implications at the population level. For example, sex ratio distortion is a common consequence of the actions of selfish elements that bias sex determination, like sex chromosomal meiotic drivers (Jaenike, 2001) and cytoplasmic selfish genetic elements (including endosymbionts; Werren, Baldo & Clark, 2008). These population-level effects may act to limit their spread, as sex ratio selection will intensify with stronger sex ratio biases. A striking example of this effect is seen for the aforementioned PSR element in the parasitoid wasp *N. vitripennis* (Werren, Skinner & Charnov, 1981). Despite the ingenuity and power of its manipulation phenotype, PSR can normally only reach a population-level frequency among males of ∼3% as the demic population structure of *N. vitripennis* strongly modulates the spread of PSR *via* sex ratio selection and local extinction (Werren & Beukeboom, 1993).

Other population-level processes may also help restrict the spread of selfish genetic elements, but in more subtle ways. Male meiotic drivers are commonly associated with reduced sperm functionality (Price & Wedell, 2008), which is detrimental to male fitness when females mate with multiple males (Price *et al.*, 2008; Sutter & Lindholm, 2016; but see Bates, Meade & Pomiankowski, 2022). Between-individual selection exposes the reduced fitness of drive-bearing individuals, thereby acting as an individual-level selection pressure counterbalancing selfish within-organism adaptations.

Selfish cell lineages may run into all the foregoing constraints found for selfish genetic elements (i.e. mechanistic constraints, frequency dependence, higher level selection), but additionally may be uniquely constrained by two mechanisms that are not applicable to selfish genes. First, as mentioned previously, some selfish cell lineages such as non-transmissible cancers have to develop *de novo* within each individual organism. By contrast, suppression mechanisms for such selfish lineages may accumulate over evolutionary time. Selfish cell lineages that are able to move vertically or horizontally between organisms may however circumvent this constraint. Second, selfish cell lineages in chimaeras are often derived from relatives. In these cases, kin selection should temper their selfishness and prevent them from eroding the organism entirely from within. For example, in a chimeric marmoset's brain, the 'foreign' cell lineage derives from a sibling or perhaps a cousin (Haig, 1999; Patten, 2021), and these relatives retain an inclusive fitness stake in the host organism's fitness. We would not therefore

expect these foreign cells to harm the fitness of the host organism greatly. That said, as cellular identities are only partially aligned, chimeric cell lineages may experience some intragenomic conflict over the value of the organism in which they reside. Possibly, this may even explain the different phenotypes that chimeric cells have been found to exhibit (Boddy *et al.*, 2015).

IV. CONCLUSIONS

(1) Internal conflicts may disrupt the integrity, and upset the unity of purpose, of organisms. This led Dawkins (1990) to coin the term 'the paradox of the organism', to emphasise how the persistence of organisms as seemingly coherent, functional units is at odds with the possibility for selfish within-organism entities to pursue agendas that undermine the integrity of the organism. We have revisited this paradox, providing an overview of such selfish within-organism entities and the extent to which their pursuit of fitness maximisation interferes with organismal fitness and, by contrast, the mechanisms by which organismal adaptation may be upheld. In light of the paradox and the factors that may help resolve it, it becomes apparent that the prevailing organism concept is inadequate.

(2) A quantitative, rather than qualitative, depiction of the extent to which organisms may be undone by their internal conflicts is needed. Organisms have a special place in biology (Gould & Lewontin, 1979; Gould & Lloyd, 1999). They are traditionally defined as being devoid of internal conflict (Queller & Strassmann, 2009) and as exhibiting agency with a unity of purpose rooted in fitness optimization (Huneman, 2019, 2021). While these criteria are suitable for many questions related to adaptations, many organisms only partially meet these criteria, and the extent to which they do so may vary strongly between them. Rather than taking these definitions as qualitative requirements for organismality to occur, a quantitative approach is likely far more fruitful (Clarke, 2016). Such an approach can further be extended to encompass other levels of biological hierarchy, aiding our understanding of when adaptations arise and at what level of organisation they do so.

(3) Any account of organismality must recognise the fundamental differences between two sorts of internal conflicts. In this review, we distinguish between selfish elements that exploit organisms with the intent of distorting transmission and those that distort organismal traits. We conclude that, by and large, transmission distorters rarely seriously challenge organismal agency. Just because organisms have things associated with them that do them harm – whether viruses, barnacles, or homing endonucleases – it does not mean they are not appropriately thought of as cohesive agents. By contrast, trait distorters are a real threat to organismal agency and in particular the idea that phenotypes are organismal strategies shaped by adaptive evolution in response to selection on an organismal level (Section I.1). There are elements within organisms that influence those same phenotypes – at least to some extent – in ways that clearly do not maximise organismal (inclusive) fitness. Trait distorters therefore seem agential in a way that undermines the agency of their host organism. Transmission distorters appear agential too – in terms of pursuing evolutionary agendas – but not in a way that undermines their host, just in a way that might drain their host of resources. Whereas transmission distorters affect traits that the organism has no stake in (for example, segregation ratios at a specific locus), trait-distorting selfish elements are, by definition, unable to operate without affecting individual-level fitness.

(4) The threat that trait distorters pose to common notions of organismal agency and adaptation casts new light on past work on evolutionary transitions in individuality. Such transitions typically invoke the loss of fitness maximisation by particles at lower levels (genes and cells), and a transfer thereof to the higher-level collective [the individual organism (Michod, 1997, 2005; Michod & Roze, 1997)]. If such a transition is achieved, adaptation and agency are thought to reside solely at the higher level. However, given the multi-level selection framing of these ideas, a major transition appears to be nothing more than a triumph over transmission distortion. But this overlooks the lingering challenge from trait distorters, which we see as the greater threat to newly formed higher-level organisms.

(5) A more gradual approach to the concept of organismality is required; one that incorporates internal conflict, bridging the divide between individual-level and lower-level optimization, and one wherein agency may be feasible even without unity of purpose. A framework that quantifies the extent to which organisms are able to optimise their fitness in the context of internal conflict, and the extent to which sub-organismal elements may do so, will be a major contribution to our understanding of the paradox of the organism.

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