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Developmental origins of normal and anomalous random right-left asymmetry: lateral inhibition versus developmental error in a threshold trait

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Abstract

Dramatic examples of right-left asymmetry often inspire adaptive explanations, simply because it is hard to imagine how such forms could not be functionally significant. But are conspicuous morphological asymmetries necessarily adaptive? Surprisingly, in some species where direction of asymmetry is random, asymmetry in bilaterally paired traits may arise as a developmental error in a threshold trait. When cases of asymmetry are rare within a species, they are easily recognized as developmental errors. However, as asymmetrical individuals become more common, or if the asymmetry is in a signaling trait, the temptation to advance an adaptive explanation grows, particularly if the asymmetry is not clearly maladaptive. Several models of the ontogeny of asymmetry are described for both normal and anomalous random asymmetry of bilaterally paired traits. In the absence of selection, each model predicts different expected frequencies of symmetrical and asymmetrical individuals within a species, therefore such frequency distributions can effectively test for different models of development. In normal random asymmetries – where conspicuously asymmetrical individuals predominate – lateral inhibition of one side after the other has transformed appears to be an essential step in development. In anomalous random asymmetries – where conspicuously asymmetrical individuals are relatively rare – no lateral inhibition is required. Other potentially relevant variables include: purely stochastic variation in morphogen levels, use-induced asymmetry, and local (each side independent) versus central (*e.g.*, hormonal) signaling. Examples of normal and anomalous random asymmetries are reviewed for several animal groups. A closer examination of the spectacular forelimb asymmetry in empidid dance flies raises doubts about claims that the asymmetry – both its occurrence and its direction – is adaptive, even though enlargement of the forelimbs likely is. Additional studies are required to conclude that this asymmetry is truly adaptive, as opposed to the outcome of random developmental variation in a threshold trait. This dance-fly leg asymmetry illustrates nicely how alternative hypotheses need to be considered before interpreting such variation as adaptive, even in a signaling trait.

Contents

Introduction

Studies of conspicuous right-left morphological asymmetries have yielded valuable insights into how development evolves: are genes leaders or followers in evolution (Palmer, 2004, 2009; Schwander and Leimar, 2011)? Does behavior play a role in the generation of novel phenotypes (Kamimura, 2006; Palmer, 2006, 2012)? Do homologous traits in different taxa have homologous development (Palmer, 2004)? Do developmental pathways become more robust – less vulnerable to disruption (Masel and Siegal, 2009) – over evolutionary time (Palmer, 2004)?

Random morphological asymmetry – where conspicuous right (dextral) and left (sinistral) forms are equally common within a species (Fig. 1) – is a particularly intriguing class of right-left asymmetry (Palmer, 2005). Random right-left asymmetry is effectively a polyphenism (Nijhout, 2003) with two equally frequent categorical states: right (dextral) and left (sinistral). With few exceptions, the alternative phenotypes of this dimorphism are purely an outcome of development because genes that specify right and left are lacking (Palmer, 2004). Therefore, like other polyphenisms (Nijhout, 2003), studies of these two states (right and left) are fundamentally studies of developmental rather than genetic mechanisms. Significantly, during ontogeny, a developmental program in an individual must somehow be activated on one side or the other – but not both – even though the side that is activated varies *unpredictably* among individuals.

The developmental origin of asymmetry in two other classes of morphological asymmetry – fixed asymmetry and fluctuating asymmetry – differs in important ways from that of random morphological asymmetry and will not be considered in detail here. Briefly, in cases of fixed (directional) asymmetry, nearly all individuals within a species are conspicuously asymmetrical in the same direction (Palmer, 2009). During ontogeny, a developmental program must be turned on *predictably* on one side but not the other. How symmetry is broken in a predictable direction remains a great puzzle (Brown and Wolpert, 1990) and controversial (Vandenberg and Levin, 2010). In cases of fluctuating asymmetry, departures from symmetry are typically so small as to be detectable only with careful measurement (Palmer and Strobeck, 1986). During ontogeny, fluctuating asymmetries emerge as the cumulative consequence of numerous small errors during development (developmental noise) and are random in magnitude and direction (Graham *et al*., 2010).

Even among random morphological asymmetries, however, two qualitatively different types appear to exist: *normal* and *anomalous*. In some species, virtually all individuals are conspicuously asymmetrical (normal) whereas in others asymmetrical individuals are clearly the exception (anomalous). Among *normal* random asymmetries, the asymmetry is likely functionally significant (Palmer, 2009) whereas in cases of *anomalous* random asymmetries, asymmetrical individuals appear to be the outcome of errors during development (Socha *et al*., 1993; Radwan *et al*., 2002). But a genuine puzzle emerges when a species exhibits a mixture of symmetrical and asymmetrical individuals, and asymmetrical individuals are sufficiently numerous that they cannot easily be dismissed as developmental errors (Daugeron *et al*., 2011). In such cases, does a high incidence of asymmetrical individuals warrant an adaptive interpretation of the asymmetry – both its occurrence and direction – or might both the asymmetry and its direction simply be a non-adaptive outcome of independent development of paired structures?

Fig. 1. An example of a *normal* random asymmetry. Right-sided (upper) and left-sided (lower) individuals are equally common in males of the fiddler crab, *Uca deichmanni*, from the Pacific coast of Central America (original photo by A. Anker, used with permission).

Below I outline some possible models for the development of normal and anomalous random asymmetry and review examples from the literature. This review can hardly be considered exhaustive, but it does illustrate a range of examples of both types, for different taxa and traits, and it is sufficient a) to illustrate how different these two modes of development are, and b) to encourage caution before embracing adaptive hypotheses about morphological asymmetry.

Random right-left asymmetry as a threshold trait: developmental models

Threshold traits (polyphenisms) are traits that often occur as two categorical states within a species, and they are as fascinating as they are dramatic (Roff, 1996; West-Eberhard, 2003). They include defensive dimorphisms, feeding dimorphisms, life-cycle dimorphisms, dispersal dimorphisms, mating dimorphisms and caste polymorphism. Examples occur in many groups of animals. In these dimorphisms, each morph is thought to be adaptive and is induced to develop under different conditions (Roff, 1996; Nijhout, 1999, 2003).

The development of threshold traits differs from that of continuously varying traits (Fig. 2) (Nijhout, 1999; Moczek and Nijhout, 2003; West-Eberhard, 2003). For typical continuously varying traits, as signal level increases, degree of trait development increases more or less continuously. For threshold traits, however, as signal level increases, degree of trait development does not change much until some threshold is reached, at which point trait development changes dramatically but then no longer varies much with additional increase in signal level. Therefore, so long as the signal level is well below or well above the threshold (Fig. 2), limited variation in trait development occurs. Because other factors – like genetic differences among individuals, developmental noise, and other environmental effects – may influence the transition from one categorical state to the other as signal levels approach the threshold (Fig. 2), the actual shape of the threshold trait response curve for a sample of individuals may be more sigmoidal than stepped (*e.g.*, see Moczek and Nijhout, 2003; Tomkins and Moczek, 2008).

Conspicuous random right-left asymmetries in bilaterally paired traits (Palmer, 2005, 2009) (Fig. 1) are a special case of a threshold (polyphenic) trait where the same threshold exists on both sides of the body but the threshold is crossed on only one side during development. Therefore, the categorical difference developmentally is really between a wild-type or ‘untransformed’ state (O) and a developmental variant, or ‘transformed’ state (X), even though the transformed state may occur on either the left or right side. Therefore, this single categorical difference between untransformed and transformed on one side of the body can yield four phenotypic categories in a sample of individuals. If neither side transforms, or if both sides transform, then the outcome is a symmetrical individual (OO or XX, Fig. 3). However, if only one side transforms, some individuals in a population will be right-transformed (OX) whereas others will be left-transformed (XO, Fig. 3). In the models below, minor, continuous phenotypic variation about the categorical untransformed (X) and transformed (O) states is ignored.

In cases of random asymmetries in bilaterally paired traits, the expected frequency of the two categories of asymmetrical individuals (OX, XO) is always the same: both are equiprobable. However, the prevalence of asymmetrical forms (OX and XO combined), and the frequencies of each of the two symmetrical forms (OO and XX), depend on the model hypothesized to determine whether one side transforms or not (Fig. 3).

In the models below, I use the term morphogen rather broadly to refer to any internal, diffusible substance whose concentration determines a particular local developmental outcome (Gilbert, 2006), regardless of whether that outcome differs in space (as in morphogen gradients) or time (as happens during ontogeny). In this spirit a morphogen could be a nutrient, a hormone, a transcription factor, a growth factor, or some other diffusible substance. Inhibition of the transformation of one side from O to X by the other is imagined to be under central nervous system control, as suggested for both lobsters (Govind and Pearce, 1989) and snapping shrimp (Govind *et al*., 1988). Other forms of inhibition by diffusible substances are possible in theory, but seem unlikely given the physical distances between the right and left sides.

In cases of *normal* random asymmetry, some kind of lateral inhibition likely occurs during development: transformation of one side inhibits transformation of the other. Two possible models seem likely. They differ in how transformation is initiated (Fig. 3AB): chance differences in morphogen levels (intrinsic signal) versus chance differences in behavior (extrinsic signal) between sides.

Model A. Stochastic variation in morphogen levels plus lateral inhibition. During ontogeny morphogen levels increase, on average, at the same rate independently on each side (signal level, Fig. 2). By chance, morphogen levels cross the threshold that induces transformation on one side before the other. As soon as that side starts to transform, it inhibits transformation of the other, likely via the central nervous system. Inhibition of the contralateral side therefore only occurs after one side has begun to transform. Eventually, virtually all individuals become asymmetrical. Symmetrical untransformed or transformed individuals – OO and XX, respectively – are exceedingly rare (Fig. 3A) and only occur when either a) morphogen levels never reach the threshold on either side (OO) or b) morphogen levels cross the threshold on both sides nearly simultaneously such that both sides begin to transform before one can inhibit the other (XX). In this model, because asymmetry is induced by stochastic variation in morphogen levels it most likely cannot be biased in a particular direction by effects of the environment.

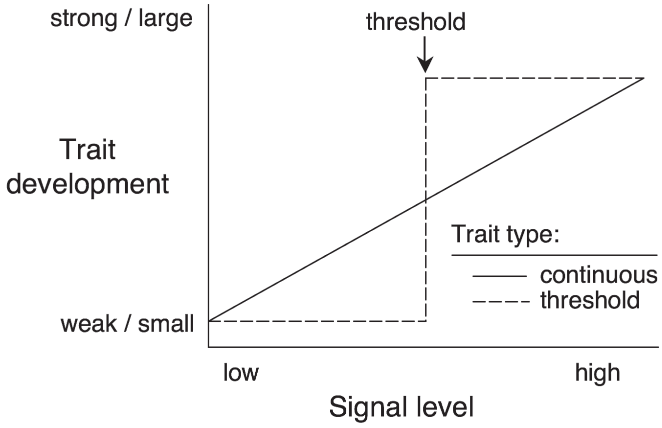

Fig. 2. Two idealized responses of trait development as a function of signal level for a continuously varying and a threshold trait. These two responses represent extreme examples that highlight the differences between them. In nature, however, many intermediate examples exist where trait responses for a sample of individuals are curvilinear or sigmoidal.

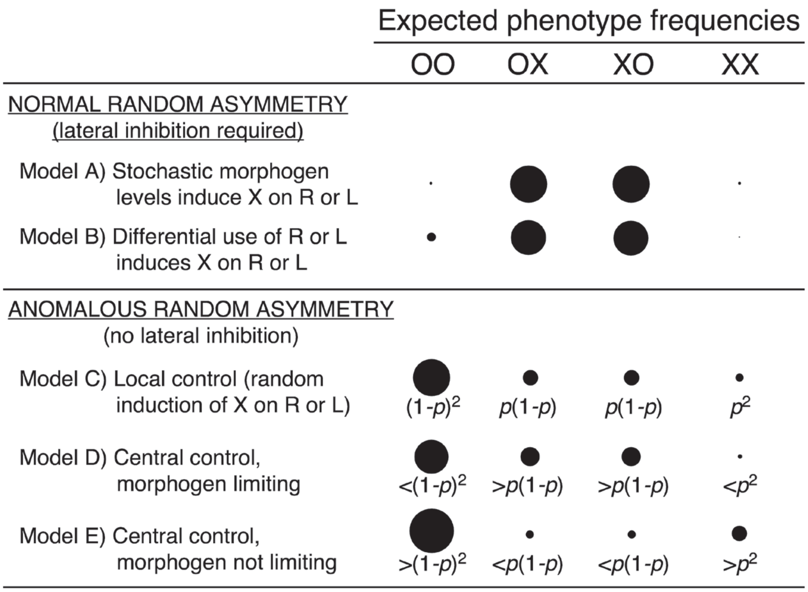

Fig. 3. Qualitative expected frequencies – in the absence of selection – of four possible phenotypes for a bilaterally paired trait in a sample of individuals. O may be thought of as the wild-type or unmodified state, X represents a developmental variant, or modified or derived state, and the position of the X in the letter-pair for each phenotype indicates the side of the transformed state: OX- right side modified, XO- left side modified. The four possible phenotypes are therefore: symmetrical individuals where neither side is modified (OO), individuals where only the right side is modified (OX), individuals where only the left side is modified (XO), and symmetrical individuals where both sides are modified (XX). Diameter of circle is roughly proportional to frequency of each phenotype for each of five models (see text for detailed description of each model). R- right side, L- left side, p- the probability that one side of the body transforms from O to X.

Model B. Behavioral variation plus lateral inhibition. During ontogeny, one side or the other – at random – may be used or stimulated more frequently. Whichever side is stimulated the most is induced to transform (Govind, 1989). Initiation of transformation on one side simultaneously inhibits transformation of the other, again, likely via the central nervous system. Should neither side receive sufficient use or stimulation neither transforms and an individual remains symmetrical (OO, Fig. 3B). Symmetrical transformation of both sides (XX, Fig. 3B) is exceedingly rare because the probability of both sides transforming simultaneously, before one side has a chance to inhibit the other, is so low. In this model, because asymmetry is induced by random differences in direction of behavior it most likely can be biased in a particular direction by manipulating the side that is used most frequently.

In cases of *anomalous* random asymmetry, where conspicuously asymmetrical individuals are rare or uncommon within a species, the frequencies of asymmetrical and symmetrical forms will also depend on how asymmetry develops. Here, three simple models

Table 1. Frequencies of occurrence of the large structure on the right and left sides of wild American lobsters, snapping shrimp, male fiddler crabs, and serpulid tube worms that exhibit *normal* random asymmetry.

	Side of larger structure					
	Neither	Right	Left	Both	Total	Source
A) American lobster (*Homarus americanus*) crusher claw						
Males	1	562	628	0	1191	
Females	2	602	638	0	1242	
Total	3	1164	1266*	0	2433	Herrick (1895, p. 144)
Percent of sample	0.1%	47.8%	52.0%	<0.001%†		
B) Snapping shrimp (*Synalpheus longicarpus*) snapper claw						
Total	11	2528	2459	2	5000	Darby (1934, p. 351)
Percent of sample	0.22%	50.6%	49.2%	0.04%		
C) Fiddler crab (*Uca lactea*) signaling claw in males						
Total	0	4071	4017	0	8088	Yamaguchi (1977, Table I)
Percent of sample	0%	50.3%	49.7%	0%		
D) Serpulid tube worm (*Hydroides* sp.) opercular plug						
H. dianthus	2	139	105	0	246	Zeleny (1905, Table III)
H. dianthus	0	528	531	153§	1212	Schochet (1973, Table I)
Total	2	667	636	153	1458	
Percent of sample	0.1%	45.7%	43.6%	10.5%		
H. ezoensus	0	4722	4460	743§	9925	Ichikawa & Takagaki (1942, Table I)
Percent of sample	0%	47.6%	44.9%	7.5%		

* The excess of left-sided lobsters is marginally significant statistically when both sexes are pooled (P = 0.039; *X*-square test), but not significant for either sex individually (P = 0.056 for males, P = 0.31 for females).

† Herrick (1895) reports a single case known to him out of an unknown total number of observations, and he later (Herrick, 1908) notes a single published example (Calman, 1906), again out of an unknown, but presumably quite large (*e.g.*, $>10^5$), total number of observations.

§ In both species, individuals bearing two opercular plugs appeared to be in transition from right- to left-sided or vice-versa as one plug was almost always 'more advanced' than the other and was eventually autotomized. The number of individuals with two opercular plugs can vary significantly over the year, from 1% in early summer to nearly 30% of the sample in early fall (Ichikawa and Takagaki, 1942).

seem likely (Fig. 3C-E), although others are possible. Significantly, in contrast to Models A and B, no lateral inhibition is involved.

Model C. Local control, stochastic initiation. As in Model A, during development, morphogen levels increase locally (*i.e.*, are released at specific sites on either side of the body) and independently on each side at the same rate, on average. By chance, morphogen levels cross the threshold that induces transformation on one side before the other. However, as no lateral inhibition occurs, if morphogen levels continue to increase on the lagging side, eventually, it will transform as well. The frequencies of symmetrical (OO, XX) and asymmetrical (OX, XO) individuals are therefore as expected for a binomial distribution, where p is the probability that one side of the body transforms from O to X (Fig. 3C). This model is the same as Model II of Whitten (1966).

Model D. Central control, morphogen is limiting. In contrast to Model C, morphogen levels rise centrally (*e.g.*, a hormone secreted by a localized gland and is distributed throughout the body), rather than locally on each side, but because morphogen levels are limiting a higher level of morphogen on one side is associated with a lower level on the other. As in Model C, no inhibition of the opposite side occurs when one side starts to transform, so eventually both sides transform if morphogen levels are high enough. Symmetrical individuals (OO, XX) are *less* frequent than expected for a binomial distribution whereas asymmetrical individuals (OX, XO) are more frequent (Fig 3D). This model is the same as Model I of Whitten (1966).

Model E. Central control, morphogen is not limiting. Like Model D, morphogen levels increase centrally such that both sides experience nearly identical levels. Unlike Model D, no morphogen competition occurs between sides. Symmetrical individuals (OO, XX) are *more* frequent than expected for a binomial distribution whereas asymmetrical individuals (OX, XO) are less frequent (Fig 3E) because the likelihood that morphogen levels differ between sides is lower.

Examples of normal random asymmetry of paired structures: threshold traits with lateral inhibition

Zoologists have suspected for well over a century that one side inhibits transformation of the other during the development of normal random asymmetries of paired traits (Zeleny, 1905). Detailed studies have been conducted with both crustaceans and polychaete worms. Field frequencies of symmetrical and asymmetrical forms (Table 1) are tricky to interpret, as they may have been influenced by selection, but they nonetheless provide a useful starting point for comparison with the models above.

Crustacea

Asymmetrical claws have evolved independently in a great many crustacean groups (Palmer, 1996, 2005, 2009). The claws of American lobsters, *Homarus americanus* H. Milne Edwards, 1837, illustrate a particularly clear example of how threshold-trait development combined with bilateral inhibition yields a conspicuous random asymmetry. The vast majority of wild lobsters have only one crusher claw, which occurs on the right or left effectively at random (Table 1A; the small but statistically significant excess of left-sided individuals remains puzzling). Surprisingly, a small percentage of individuals are symmetrical, but the frequencies of the two possible symmetrical states are quite different: 0.12% of individuals have no crusher claw at all (Herrick, 1895) whereas individuals with two crusher claws are so exceedingly rare that they draw special attention (*e.g.*, Calman, 1906). This pattern is more consistent with Model B (Fig. 3B), rather than Model A where the two symmetrical states are also rare but are equally common.

The large and, at first glance, puzzling disparity between the number of symmetrical lobsters with no or with two crusher claws (Table 1A) makes sense in light of what is known about crusher-claw development (Govind, 1989). When a juvenile lobster settles out of the plankton, it possesses two small cutter claws. This state persists through the 5th instar. Experimental manipulations reveal that whichever claw is exercised most during the 5th instar starts to transform into a crusher claw in the 6th. However, if activity is insufficient in both claws during the 5th instar, neither transforms into a crusher claw. Remarkably, that individual will retain two small cutter claws for the rest of its life because the temporal window of opportunity for transformation has passed. Significantly, despite dozens of different experimental manipulations involving hundreds of lobsters overall, Govind and colleagues never successfully induced a lobster to develop two crusher claws.

In lobsters, then, activity of one juvenile claw must cross some minimum threshold to induce transformation into a crusher claw. Once one claw begins to transform, it inhibits transformation of the other regardless of how much the other claw is used (Model B above). Even after autotomy of a transformed crusher claw, it regenerates on the same side (Govind, 1989). Such inhibition of one side by the other appears to be mediated by the central nervous system (Govind and Pearce, 1989).

Another pattern of control of asymmetry is evident in the stunningly asymmetrical chelae of snapping shrimp (Alpheidae). Chela asymmetry typically does not appear until later juvenile stages, like the 6th juvenile stage in *Alpheus heterochelis* Say, 1818 (Young *et al.*, 1994). Removal experiments suggest that, like lobsters, whichever claw is used the most by young juveniles is induced to become a snapper claw. However, after the initial asymmetry has been established, removal of the large snapper claw from one side induces the small claw on the other side to transform into a snapper and a small claw regenerates in place of the lost snapper (Darby, 1934; Mellon and Stephens, 1978). Therefore, unlike lobsters, direction of asymmetry is reversed when the large claw is lost. When both claws are removed simultaneously, though, the snapper regenerates on the same side, indicating that inhibition of the small claw can occur even without a snapper claw present (Read and Govind, 1997b). As in lobsters, the central nervous system appears to restrict what kind of claw regenerates following autotomy (Young and Govind, 1983; Govind *et al.*, 1988).

Several experimental manipulations of the snapping shrimp snapper claw can induce the small claw to transform into a snapper with variable success, including denervation (Mellon and Stephens, 1978), dactylotomy (Read and Govind, 1997a), closer muscle tenotomy (Govind *et al*., 1988) and gluing the dactyl into the closed position (Read and Govind, 1997b). Any of these experimental treatments can sometimes produce a shrimp with two snapper claws, a state that is only rarely observed in nature (Table 1B). This greater lability of the side on which the snapper claw develops in an individual is also associated with a higher incidence of double-snapper individuals, both in the field (Table 1B) and in the laboratory (Pearce and Govind, 1987). Inhibition of transformation of the pincer claw by the contralateral snapping claw does not appear to be as strict as in lobsters and fiddler crabs. However, symmetrical small-clawed shrimp appear to be five times more common in the field than symmetrical snapper-clawed shrimp, a pattern consistent with Model B (Fig. 3).

Curiously, lateral inhibition is not essential to the ontogeny of asymmetry in some crustacean examples. Male fiddler crabs (genus *Uca*), for example, possess a massive signaling claw that may exceed 40% of body weight (Crane, 1975). In all but one small clade of Australasian species, the signaling claw occurs on the right or left at random (Jones and George, 1982; Yamaguchi and Henmi, 2001). In contrast to lobsters and snapping shrimp, no symmetrical males of either type appear to occur as adults (Table 1C), a pattern more consistent with Model A. Fiddler crabs exhibit a rather odd mode of development of claw asymmetry (Vernberg and Kostlow, 1966; Yamaguchi, 1977; Yamaguchi and Henmi, 2001). Unlike lobsters, where only one claw transforms from small to large and inhibits transformation of the other side, both right and left claws start to transform into large signaling claws in very young crabs (4-5 mm carapace width). Eventually, one of the two large chelae is autotomized at random, and a small claw regenerates in its place. Once the side of the large claw has been determined, however, it remains fixed throughout all subsequent molts even when the large claw is lost and regenerated (Morgan, 1923; Vernberg and Kostlow, 1966; Yamaguchi, 1977; Ahmed, 1978). In fiddler crabs, therefore, lateral inhibition does not play a role in the *generation* of asymmetry, but it does play a crucial role in *maintaining* asymmetry in a particular direction in an individual once it is initiated. This is not true in all crabs, though. In other crab groups where right-sided individuals predominate, if the larger claw is lost the small claw transforms, at least to some degree, into a large one (Hamilton *et al*., 1976; Mellon and Stephens, 1978; Simonson, 1985; Norman and Jones, 1991).

Polychaete worms and other groups

Lateral inhibition appears to ensure asymmetrical development in polychaete worms as well, for example in the right or left position of the opercular plug in the serpulid polychaete *Hydroides dianthus* (Verrill, 1873) (Zeleny, 1905; Okada, 1933). In these tubeworms, one gill is modified as an opercular plug that closes off the opening of the calcareous tube when the worm withdraws. The plug normally occurs on either the right or left side in an adult worm, at random, although over 10% of individuals may possess two functional operculae in different states of maturity (Table 1D).

During ontogeny, post-settlement juveniles produce a calcareous tube and begin to develop gills on the head. Initially these gill pairs are symmetrical and no opercular plug is present. Later, one gill – typically the left one of the second most dorsal pair – begins to transform into an opercular plug, and its antimere drops off, leaving the young juvenile asymmetrical, with an opercular plug on one side and a rudimentary stub on the other. At any later stage during development, removal or loss of the fully developed opercular plug induces the stub on the other side to transform into a full-blown opercular plug, after which the base of the missing plug regenerates as a non-functional stub. Therefore, the direction of asymmetry is reversed following regeneration.

Curiously, individuals appear to autotomize and regenerate opercular plugs multiple times during their lives (Ichikawa and Takagaki, 1942; Schochet, 1973), which yields a high incidence of worms bearing two plugs, although one is almost always ‘more mature’ than the other and eventually drops off. Experiments by Okada (1933) seem to rule out inhibition of one side by the other via the central nervous system or by a diffusible substance. However, whatever inhibits the transformation of the opposite side appears to reside within the functional operculum (Model A above).

Finally, lateral inhibition presumably also ensures that the highly modified clasping priapium of male phallostethid fish (Parenti, 1996), or the single internal incisor (normally paired in all other mammals) of the São-Tomé island fruit bat (Juste and Ibanez, 1993), develops on only one side of the body. However, developmental mechanisms have not yet been tested in either of these groups.

Examples of anomalous random asymmetry of paired structures: threshold traits without lateral inhibition

In the preceding examples, asymmetrical bilateral structures are the normal state within a species and the asymmetry is presumably or demonstrably adaptive. However, small numbers of asymmetrical individuals sometimes occur in many normally symmetrical species, particularly where one or both sexes are dimorphic. These qualify as examples of anomalous random asymmetries, and their developmental appears to be quite different from normal random asymmetries, most notably in the lack of lateral inhibition (Models C-E, Fig. 3).

Some of the most spectacular anomalous random asymmetries are gynandromorphs, where most or all of one side of the body has the form of one sex whereas most or all of the other side is the opposite sex (for a recent overview see Yang and Abouheif, 2011). Although sample sizes are minute, the side that is predominantly male (or female) appears to be random. However, gynandromorphs typically arise due to sex-determination errors early in development (*e.g.*, anomalous chromosome-sorting) and affect most or all structures on one side of the body (Levin and Palmer, 2007), so they are not relevant to the present discussion of threshold traits.

Arthropods

Some less familiar but no less dramatic examples of anomalous random asymmetries occur in paired, bilaterally homologous structures like wings and legs. For example, wing dimorphisms within one or the other sex have evolved in many flying insect groups (Thayer, 1992). Among such wing-dimorphic insects occasional asymmetrical individuals – micropterous or brachyopterous on one side, macropterous on the other – have been reported in a wide range of taxa, including Hymenoptera (1 of 956 laboratory-reared individuals of an ichneumonid parasite, Salt, 1952), Diptera (1 of 201 field-collected individuals of a chloropid fly, Wheeler, 1994), and Hemiptera (up to 20% of males and 10% of females in a laboratory strain of red firebugs selected for microptery, Socha, 1995).

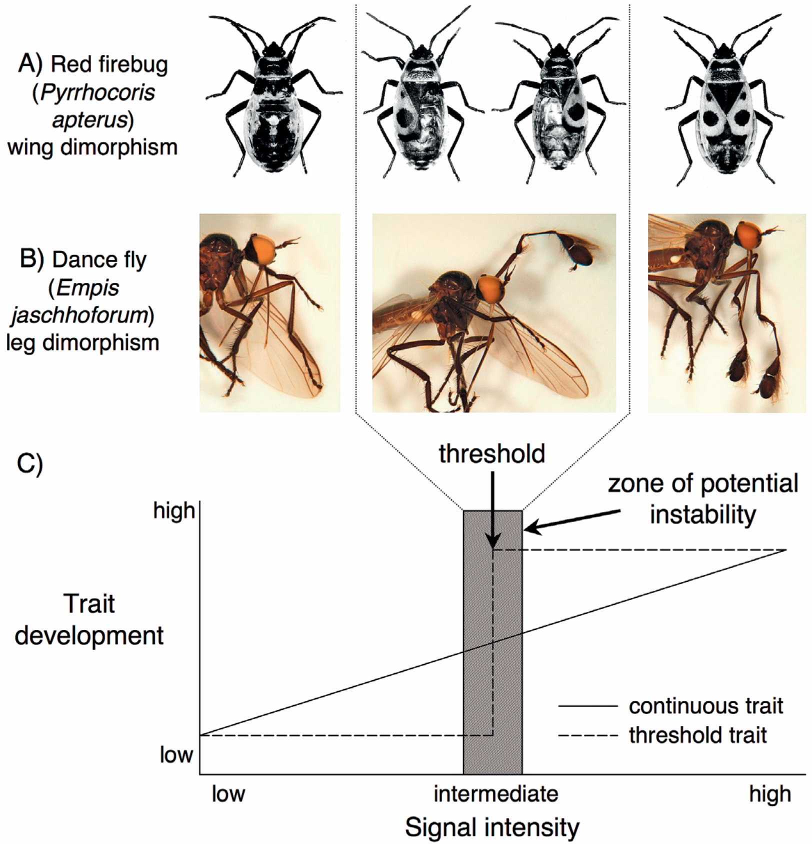

Fig. 4. An example of *anomalous* random asymmetry in (A) forewings of the red firebug, *Pyrrhocoris apterus* (Socha, 1995) and a possible example in (B) forelegs of the dance fly, *Empis jaschhoforum* (Daugeron *et al.*, 2011). (C) Hypothetical model for anomalous random asymmetries that arise due to small, random differences in signal level between the right and left sides in a threshold trait. Original photographs are from Socha (1995) and Daugeron *et al.* (2011), and used with permission.

The anomalous random asymmetries in red firebugs (*Pyrrhocoris apterus* (Linnaeus, 1758)) are particularly impressive (Fig. 4A) (Socha *et al*., 1993). They include macropterous forewings on one side of the body and micropterous on the other, with no lateral bias in occurrence. Although common in the *unstable micropterous* laboratory strain, Socha *et al*. (1993) recount examples of asymmetrical individuals in the field in both *P. apterus* and *P. marginatus* (Kolenati, 1845), including one given a name as an asymmetrical form, *P. apterus* f. *inaequalis*. Forewing asymmetry of an individual is not associated with any asymmetries of the legs or antennae, so it appears to arise via developmental processes specific to the transformed wing.

Anomalous random asymmetries are also known in leg-dimorphic chelicerates. In a male-dimorphic acarid mite, *Sancassania berlesei* (Michael, 1903), fighter males possess modified legs with which they may kill rival males, whereas scrambler males possess unmodified legs. Occasional intermorphs appear that have a scrambler leg on one side and a fighter leg on the other (7 of 127 experimental animals, Radwan *et al*., 2002). These latter two examples are both consistent with Model E (Fig. 3E).

In other arthropods with trait dimorphisms, however, few if any asymmetrical 'intermorph' individuals are known. Conspicuously asymmetrical forceps in dimorphic males of the earwig *Forficula auricularia* (Linnaeus, 1758) are 'fewer than 1 in 1000' (J. Tomkins, pers. comm. Oct. 2011). Among some wing-dimorphic thrips, hemimacropterae – adults with the wings about half the normal full length – do occur, but individuals that are micropterous on one side and macropterous on the other have never been reported (L. Mound, pers. comm. Oct. 2011).

Fish

Pelvic spines in stickleback fish occasionally show anomalous random asymmetry associated with a reduced pelvic girdle. A reduced pelvic girdle may reduce vulnerability of young sticklebacks to benthic insect predators (Reimchen, 1980). In ninespine sticklebacks (*Pungitius pungitius* (Linnaeus, 1758)), individuals with a fully-developed pelvic girdle almost always have paired, symmetrical spines (Blouw and Boyd, 1992). Even among hybrids between a fully-spined and a spineless population yielded offspring that were nearly all fully spined (*e.g*., only 3 of 870 individuals had a single spine and were therefore asymmetrical). Among fish that start to show a significantly reduced pelvic girdle, the incidence of individuals with asymmetrical spines is higher. In threespine stickleback, *Gasterosteus aculeatus* Linnaeus, 1758, pelvic girdle reduction is also associated with pelvic spine asymmetry. Contrary to what would be expected in anomalous random asymmetry, however, fish with asymmetrical pelvic spines most commonly posses the left spine (Bell *et al*., 1985), except in a few populations where right-spines are more common or where asymmetrical spines occur more or less equally on either side (Bell *et al*., 2007). This biased occurrence toward one side may arise as a byproduct of asymmetrical signaling in the *Nodal* cascade that specifies visceral asymmetry in vertebrates: *Pitx1* – a major candidate locus affecting pelvic reduction in sticklebacks (Shapiro *et al*., 2004) – is also involved in controlling visceral asymmetry and *Pitx1*-knockout mice also have relatively larger left limbs.

Tetrapods

Guinea pigs (*Cavia porcellus* (Linnaeus, 1758)) sometimes exhibit extra mammae, over and above the normal single pair. These range in degree of development from 'a mere bare circular skin-patch, lying in the mammary line, on one side only, to a pair of complete and functional mammary glands with their teats' and they may occur in either females or males (Sollas, 1909). Paired extra mammae are more common than expected (15 of 142 individuals, when only 3 are expected), but modest numbers of individuals present only a single extra mammary (14 of 142 when 37 are expected). A single extra mammary may occur on either the right or left side but extra left mammae appear to be more common ($P< 0.05$; Table 2). Regardless of this left bias, asymmetrical individuals are clearly much less common than expected due to binomial variation, a pattern consistent with Model E (Fig. 3).

Guinea pigs sometimes also exhibit extra toes on their hind feet (Castle, 1906; Wright, 1934). Guinea-pig fore feet typically have four toes, whereas hind feet have only three. In some strains, extra toes occur in over 30% of individuals, and they may appear on either the right, left or both sides (Table 3). Across two strains extra left toes were slightly but significantly more common (26% on the left vs. 22% on the right, Wright, 1934). Attempts to select for extra toes on only one side of the body, however, were completely unsuccessful (Castle, 1906). Therefore, although the capacity to produce an extra toe is heritable, the tendency for the extra toe to occur on the right or left is not, a result later confirmed by Wright (1934). As for mammae, however, asymmetrical individuals are less common than expected due to binomial variation, a pattern also consistent with Model E (Fig. 3).

Vestigial limbs or pelvic elements in otherwise legless tetrapods often show pronounced asymmetries. Either right or left may be present in legless skinks (Moch and Senter, 2011), whereas the right side is more likely reduced or absent in manatees (Shapiro *et al*., 2006).

Further evidence of a threshold trait with developmental error

Two other kinds of evidence suggest that anomalous random asymmetries are the outcome of developmental errors in a threshold trait (Models C-E, Fig. 3). First, in various lines of fruit flies mutant for eye-facet numbers (the *witty* mutation), asymmetrical individuals were almost always less common than expected due to binomial variation (Whitten, 1966). This result is consistent with Model E and clearly rejects Model D (morphogen limiting). *Eyeless* mutants in *Drosophila* may also manifest themselves as eyes that are asymmetrical to varying degrees (Grimaldi and Fenster, 1989). Attempts to select for left-sided ocelli in the *Drosophila subobscura* mutant line bearing the sex-linked recessive gene *ocelliless* were unsuccessful despite considerable phenotypic variation (Maynard Smith and Sondhi, 1960). These selection experiments provide direct evidence that there is no genetic basis to the tendency for a single ocellus of a bilateral pair to occur on one side of the body or the other, and provide further support for Model E (Fig. 3).

Table 2. Frequencies of occurrence of extra mammae on the right and left sides of laboratory crosses of domestic guinea pigs, *Cavia porcellus* (Sollas, 1909, p. 71-72), an example of an *anomalous* random asymmetry consistent with Model E.

		Side of extra mammae*			
Parental phenotypes	Crosses	Neither	Right	Left	Both
Extra mammae in both parents	7	26	1	5	11
Extra mammary on left†	8	25	1	3	2
Extra mammary on right†	4	29	0	0	0
Extra mammae on both sides†	8	33	0	4	2
Total		113	2	12	15
Expected if random§		101.4	18.6	18.6	3.4

* Counts are numbers of individual offspring pooled from all crosses; both offspring sexes pooled.

† Female parent only, the male parent was normal (*i.e*., no extra mammae).

§ Expected frequencies were computed using the overall proportion of extra mammaries at any mammary position (44 of 284) and assuming that the probability of occurrence in either the right or left position was random (Model C, Fig. 3); the observed frequencies are highly significantly different from expected ($P< 0.001$; asymmetrical individuals are less common than expected), also the number of individuals with extra left mammae is significantly greater than the number with extra right mammae expected if extra mammae occurred at random on the left or right sides ($P< 0.05$).

Table 3. Frequencies of occurrence of normal and extra toes on the right and left sides of the ‘Beltsville’ laboratory strain of domestic guinea pigs, *Cavia porcellus* (Wright, 1934, Table 8)*, an example of an *anomalous* random asymmetry consistent with Model E.

	Right side			
Left side	3-toed (normal)	‘poor’ 4-toed†	‘good’ 4-toed†	Total
3-toed (normal)	1362	96	33	1491
‘poor’ 4-toed†	149	101	34	284
‘good’ 4-toed†	50	55	96	201
Total	1561	252	163	1976

* Pooled frequencies regardless of toe quality (observed / expected): symmetrical 3-toed (1362 / 1177.7), asymmetrical (328 / 695.6), symmetrical 4-toed (286 / 102.8); $P <0.001$, contingency table analysis.

† Poor- extra toe poorly developed, good- extra toe well developed.

Second, another prediction of the threshold model for anomalous right-left asymmetries (Fig. 4C) is that asymmetry should be most common at intermediate signal levels, simply because at low levels neither side is likely to transform whereas at high levels both sides are likely to transform. Only when signal levels are close to the threshold do random differences in morphogen levels between sides yield asymmetric development. Some scattered observations support this view. For example, the one asymmetrical individual in the male-dimorphic ichneumonid parasite was intermediate in body size between the normal macropterous and micropterous males (Salt, 1952). In red firebugs, where forewings can be strikingly asymmetrical (Fig. 4A), a scatterplot of left versus right forwing length (Fig. 3 of Socha *et al*., 1993) reveals that asymmetrical individuals are most common at intermediate forewing lengths of 2 to 4.5 mm. Finally, asymmetrical forelegs in an empidid dance fly were more common among individuals with larger wings (Fig. 2 of Daugeron *et al*., 2011), although the sample size was too small to draw a robust statistical conclusion.

Discussion and conclusions

Random, conspicuous right-left asymmetries in bilaterally paired structures appear to fall into two broad categories: 1) *normal* (Fig. 1), where most individuals are asymmetrical and asymmetry is most likely adaptive (Palmer, 2005), and 2) *anomalous* (Fig. 4A), where asymmetrical individuals are rare or at least in the minority and where the asymmetry, per se, is not likely adaptive. Developmentally, however, the puzzle posed by each is the same: when one side starts to develop down a different path, why doesn't the other side do so as well? A closer examination of some possible developmental models (Figs. 3, 4C), and the examples of each outlined above, suggests that the mechanisms of developmental control differ between the two types. In *normal* random asymmetries, lateral inhibition is an essential component: transformation of one side inhibits transformation of the other (Models A-B, Fig. 3). In *anomalous* random asymmetries lateral inhibition appears to be absent: transformation of one side is largely independent of transformation of the other (Models C-E, Fig. 3).

So how should a case where asymmetrical individuals are common but not in the majority be interpreted? Is it an example of a normal or an anomalous random asymmetry? Is the asymmetry adaptive or simply a by-product of random developmental variation in a threshold trait? When the asymmetry is clearly maladaptive, as in the forewings of red firebugs (Fig. 4A), it is easy to accept that such asymmetries result from developmental error (Models C-E, Fig. 3). However, when the conspicuous asymmetry occurs in a signaling trait, as in the forelegs of a dance fly (Fig. 4B), plausible adaptive scenarios become tempting.

The case of the empidid dance fly, *Empis jaschhoforum* (Daugeron *et al*., 2011; Ritchie and Vahed, 2011), is therefore highly instructive. First, foreleg modification, when it occurs, is undeniably spectacular (Fig. 4B). Second, a strong case can be made that the hugely modified forelegs are a secondary sexual character: a) they occur only in males, which is consistent with the interpretation that they are used during courtship, b) they are likely used to deceive females into believing that the male is carrying a nuptial gift because deceptive nuptial gifts are employed by males of other empidid dance flies (Ritchie and Vahed, 2011). Third, adaptive explanations have been advanced both for the asymmetry itself and for the nearly equal occurrence of right- and left-sided forms.

But is this conspicuous asymmetry, and the nearly equal frequencies of right and left forms, adaptive? Unfortunately, because both phenomena are also consistent with an alternative hypothesis – that asymmetry emerges from developmental errors in a threshold trait (Models C-E, Figs 3, 4C) – neither hypothesis can be rejected without additional information.

The adaptive argument for the asymmetry itself has an appealing plausibility. First, asymmetrical forelegs may reflect an intermediate optimum: no forelimb enlargement may yield improved agility or flying duration (better short-range mating success) whereas two enlarged forelegs may yield better visibility (long-range attraction) but lower flying agility or greater flight costs (Daugeron *et al*., 2011). Asymmetrical individuals would therefore benefit from improved visibility but experience lower flight costs than doubly enlarged individuals. Second, a single foreleg may offer a more effective deceit because males typically only carry a single nuptial gift (Ritchie and Vahed, 2011). The relative rarity of symmetrical individuals with two modified forelegs (3%) is consistent with these interpretations, but the high incidence of individuals with symmetrical unmodified forelegs (55%) is not. Nonetheless, the prevalence of unmodified males might be evidence of a stable polymorphism maintained by frequency-dependent selection or by variable selection where males with unmodified forelegs are favored in some conditions, but males with singly-enlarged forelegs are favored in others (Daugeron *et al*., 2011).

A rather more fanciful adaptive argument has been advanced to explain the roughly equal frequencies of right- and left-sided forms: frequency-dependent selection might maintain a balance between right- and left-sided males within the species (Ritchie and Vahed, 2011). However, for frequency-dependent selection to maintain equal frequencies of right and left forms, the direction of asymmetry must be genetically determined, otherwise selection cannot operate. Unfortunately, in nearly all examples of random asymmetries, direction of asymmetry is not inherited (Palmer, 2004), which strongly suggests that the equal frequencies of enlarged right and left forelegs in *Empis jaschhoforum* is not maintained by selection. Furthermore, frequency-dependent selection further presumes that advantages accrue to the rarer morph, yet it is hard to imagine why females might prefer a right-sided male when left-sided males are more common.

However, before any conclusions about adaptive significance are drawn, an alternative, non-adaptive hypothesis must also be considered. Dance fly foreleg asymmetry may arise developmentally (Fig. 4B) the same way as asymmetry in the forewings of red firebugs (Fig. 4A): random developmental errors in a threshold trait (Fig. 4C and Model C of Fig. 3). Neither the asymmetry, nor the roughly equal frequencies of right- and left-sided individuals need be adaptive at all. One tantalizing observation is consistent with this hypothesis: asymmetrical (or doubly enlarged) forelimbs were almost exclusively restricted to individuals in the larger half of the wing-size spectrum (Fig. 2 of Daugeron *et al*., 2011). Unfortunately, sample sizes were too small to say whether this association of leg asymmetry with wing size is significant, so additional data are needed before an association with size can be tested robustly.

The dance fly foreleg asymmetry (Fig. 4B) is undeniably spectacular. It is also practically unique among insects, where conspicuous limb asymmetries are surprisingly rare (Palmer, 2005). This contrasts with crustaceans, where asymmetrical limbs have evolved multiple times (Palmer, 1996, 2005, 2009), particularly among limbs bearing chelae. Chela asymmetries appear to be overwhelmingly adaptive in crustaceans. Two different chelae on the same individual permit increased behavioral versatility. Often, they permit increased versatility in feeding (*e.g*., one robust claw for crushing and one more slender claw for probing, picking, tearing or rapid grasping, as in American lobsters (Herrick, 1895) or one large highly specialized claw for stunning prey and a smaller one for grasping prey, as in snapping shrimp (Anker *et al*., 2006)). They also permit significant division of labor (*e.g*., one large claw for signaling or agonistic interactions, but a small one that functions solely in feeding on sediment, as in fiddler crabs (Levinton *et al*., 1995)).

Just because the dance fly foreleg asymmetry is spectacular and occurs in a signaling trait is not, by itself, evidence that it is adaptive, particularly because both symmetrical forms also co-occur with the asymmetrical forms (Fig. 4B). To reject the non-adaptive hypothesis for dance fly foreleg asymmetry (Fig. 4), experiments are required to show that asymmetrical males have higher mating success (are more attractive, or are better able to mate) than symmetrical males with doubly enlarged forelegs. To conclude that the roughly equal frequencies of right- and left-sided forms is an outcome of frequency-dependent selection, breeding studies are required to determine whether direction of asymmetry is inherited. Finally, larger sample sizes of a wider range of body sizes are required to test whether the incidence of foreleg asymmetry depends on body size. A higher incidence of asymmetrical individuals of intermediate body sizes would be consistent developmental instability in a threshold trait (Fig. 4).

Until further studies are done, the jury is still out on whether the remarkable asymmetry in dance fly forelegs is adaptive or not. Anyone up for a trip to Mt. Fuji?

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