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Title	Fluctuating asymmetry in Drosophila
Author(s)	Vishalakshi, Chavali
Citation	, 69, 51-60
Issue Date	2011-03-31
Doc URL	http://hdl.handle.net/2115/45189
Type	bulletin (article)
File Information	LTS69_008.pdf

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Fluctuating asymmetry in *Drosophila*

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Fluctuating asymmetry (FA) or subtle differences between left and right sides of a trait has been considered as an indicator of an organism's ability to cope with genetic and environmental stresses during development. It is considered to play an important role in mate choice. However, over four decades of work on various organisms such as insects, reptiles, birds and mammals has left the field with no clear-cut relationship between increased fluctuating asymmetry and stress due to inconsistency in the results. Despite this, fluctuating asymmetry is still assumed to indicate developmental instability caused by various perturbations (either genetic and/or environmental in origin) during development. The present article provides a unified framework for the better understanding of fluctuating asymmetry and its association with stress in particular reference to *Drosophila*.

Introduction

The temptation to understand the patterns of asymmetries dates back to Aristotle, who observed the regular patterns of bilateral asymmetries in animals likes crabs, lobsters and crayfishes (Herrick, 1909). Earlier, it was thought that the asymmetries (i.e., deviations from symmetry) are unimportant, but recently researchers have begun to realize how important these asymmetries are (Palmer, 1996), as they play an important role in evolutionary patterns and processes (Wu et al., 2007). Bilateral symmetry (a pervasive feature of the body plans of most animals) gets disturbed in the presence of genetic and environmental stresses, and as a result, either developmental noise increases or developmental stability decreases (for definitions, see Table 1). Therefore, evolutionary biologists have started using asymmetry as a measure of developmental homeostasis (Table 1). The rationale behind this is that the same genetic and developmental programs control the development of the left and right sides of a bilaterally symmetrical organism and thus (any) departures from perfect bilateral symmetry can be used as a measure of genetic or environmental perturbations (Batterham et al., 1996).

The deviations from perfect symmetry can be conveniently grouped into three categories: directional asymmetry (DA), antisymmetry (AS) and fluctuating asymmetry (FA) (Van Valen, 1962). DA occurs when there is normally a greater development of a character on one side of the plane of symmetry than on the other (Van Valen, 1962), whereas AS occurs when most of the individuals in a population are asymmetric but it is unpredictable which side of an organism shows greater development (Timofeef-Ressovsky, 1934; Graham et al., 1993a). FA is defined as minor random deviations from perfect bilateral symmetry (Ludwig, 1932; Van Valen, 1962). The three different asymmetrical patterns are widespread throughout the natural populations (Polak, 2003). Nevertheless, under stressful conditions, there are many examples for the transitions in these three forms of asymmetry (i.e., from AS to DA, DA to FA, and also FA to AS) (Mather, 1953; McKenzie and Clarke, 1988; Graham et al., 1993a; Smith et al., 1997; Klingenberg et al., 1998; Lens and Van Dongen, 2000; Schneider et al., 2003; Leamy and Klingenberg, 2005). Out of three kinds of asymmetry, FA is used to measure developmental instability as it arises due to the random variations causing a structure to depart from its ideal symmetry during development, whereas antisymmetry and directional asymmetry are believed

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Table 1 : An overview of concepts used in the article

Terms	Explanations
Developmental noise	Any uncontrollable variation in phenotype due to random events during development
Developmental homeostasis	The property of an organism to adjust itself to variable conditions during development
Developmental stability (DS)	The ability to buffer development against random perturbations of environmental or genetic origin
Developmental instability (DI)	Random perturbations of environmental or genetic origin affecting development along developmental trajectory within particular environment
Fluctuating asymmetry (FA)	Small random deviations from perfect bilateral symmetry, i.e., normal distribution of right minus left differences (R-L) about a mean of zero
Directional asymmetry (DA)	When there is normally a greater development of a character on one side of the plane of symmetry than on the other, resulting in normal distribution of R-L differences about a mean which differs significantly from zero
Antisymmetry (AS)	When one side of the plane is consistently larger than the other, but the larger side may be either right or left at random, resulting in a bimodal distribution of R-L differences about a mean of zero
Positional fluctuating asymmetry (PFA)	Differences in the placement of bristles on an area, e.g., sternopleuron, between the two sides of the body, and thus as a measure of bristle positions or shape differences between the two sides

to have unknown genetic bases, and therefore are not commonly seen as reflective of developmental perturbations (Palmer, 1996).

The investigations on FA are burgeoning rapidly and are also attracting many *Drosophila* workers, and therefore, an extensive review is required to update the recent advances in this field. In view of this, an attempt has been made to include all the major investigations on fluctuating asymmetry in *Drosophila* as well as to discuss the role of FA as an indicator of stress and individual quality in sexual selection.

1. Fluctuating asymmetry

The term 'fluctuating asymmetry (FA)' is coined by Wilhelm Ludwig in his monumental monograph on biological asymmetry in 1932. FA is defined as 'small random deviations from a prior expectation of symmetric development in morphological traits' (Ludwig, 1932). Interest in FA stems from the notion that there is a target state of symmetry which all individuals aim to achieve, and those individuals who fail to develop symmetrically are, in some way, of poorer quality than those that do achieve symmetry. The core idea of FA studies is that the corresponding parts on the left and right sides of a bilaterally symmetrical organism are separate replicates of the same structure. The body sides of an individual share the same genome and constant environment, and also the external effects on development will be the same on both sides. Therefore, any deviation from symmetry is the consequence of an inability to cope with environ-

mental or genetic stress (Tomkins and Simmons, 2003). Therefore, fluctuating asymmetry has been considered to be a putative general biomarker of stress, as it responds to a wide range of stresses, and also has been correlated with many life history traits (Leung et al., 2003). Nevertheless, the literature has been plagued by controversy and heterogeneous results (e.g., Møller, 1997; Clarke, 1998; Palmer, 1999). Despite this, the most accepted view appears to be that FA is an indicator of stress and mate choice (Swaddle, 2003; Leamy and Klingenberg, 2005).

FA can be measured both at the population- and individual-levels. At the population level, it is usually measured as the variation of differences in the size, length and/or count of bilateral structures between the right and the left sides (R-L). At the individual level, it is most often assessed by mean of unsigned left- minus right-side differences (|R-L|). However, there are other indices of FA also (for details see Palmer, 1994). The analysis of FA is usually affected by measurement error, other types of asymmetry (DA or AS) and trait size. The appropriate statistical procedures for checking measurement error in the data and for adjusting DA, AS and size effects on FA and for testing significant differences in FA among two or more groups are discussed in detail by Palmer and Strobeck (1986, 2003).

2. Fluctuating asymmetry as an indicator of stress

Fluctuating asymmetry (FA) has been widely used

as an indicator of genetic (Table 2) and/or environmental stress (Table 3). The levels of FA are generally compared in populations that are subjected or not subjected to stress (Leamy and Klingenberg, 2005). The hypothesis in such comparisons is that FA will be higher in the more stressed populations compared to the control or unstressed populations (e.g., Pankakoski et al., 1992; Graham et al., 2000; Imasheva et al., 1997a, b; Rasmuson, 2002; Polak, 2003; Leamy and Klingenberg, 2005). In support of this approach, there are several studies that have detected FA responses to stress in different species of *Drosophila*. However, on the other hand, there are also many studies that have been unable to detect the expected relationship between stress and FA (see Tables 2 and 3). The inconsistency in the results depends on the degree of stress imposed, choice of trait and FA indices (Hoffmann and Woods, 2003; Leamy and Klingenberg, 2005). Moreover, in the studies dealing with the environmental stress, it is often assumed that FA has no genetic basis and the differences in FA levels of the stressed and unstressed populations are purely environmental in origin. But the levels of FA may also show some genotypic differences (unless isogenic lines or genetically identical lines are used) in response to stress. Similarly, for the studies dealing with genetic stress, the environmental conditions should be controlled enough so that the results of FA analysis should not be under the influence of internal and external components of the environment (Zhang and Hill, 2005). There is a report that the levels of FA for different morphological traits vary significantly among laboratory populations of *D. ananassae* (which were reared in controlled laboratory conditions, i.e., food, humidity and temperature, for several generations). The variation in the levels of FA among the laboratory populations is thought to be under the influence of internal component of the environment and genetic variability of populations as they were collected from different ecogeographical localities of India (for details, see Vishalakshi and Singh, 2006).

3. Role of fluctuating asymmetry in sexual selection

More than two decades have passed since Markow (1987) and Møller (1990) first suggested that FA, the morphological expression of developmental instability (DI), might play a role in sexual selection and/or communication (Uetz and Taylor, 2003). FA has been used as an empirical measure of the quality of individuals competing for reproductive success and particularly of a revealing aspect of an individual's phenotype (FA-sexual selection hypothesis; Uetz and Taylor, 2003). Field studies have shown that FA is higher in secondary sexual traits, which are often costly and extravagant in pattern, colouration and size. Also, FA is more pronounced in sexual traits than non-sexual traits (Møller and Pomiankowski, 1993; Rasmuson, 2002; Vishalakshi and Singh, 2006). But the connection between FA and sexual selection has not always been found (as reviewed in Simmons et al., 1999), and thus, the precise role of FA in the sexual selection process is often controversial (Tomkins and Simmons, 2003).

3.1 Studies in favor of FA-sexual selecion hypothesis

In *D. melanogaster*, FA in sternopleural bristle was associated with male mating success in laboratory (Markow, 1987). In *D. simulans,* mating males were larger than the single males and were characterized by reduced FA (Markow and Ricker, 1992). In *D. pseudoobscura*, the body size of mated and unmated males was similar, but the mated males exhibited less FA than the single males (Markow and Ricker, 1992). Further, in *D. buzzatii,* Santos (2001) found that FA in wing length was higher in non-mating males than in mating ones.

3.2 Studies against FA-sexual selection hypothesis

In *D. mojavensis,* mating males were larger than single males but showed a similar level of FA to that observed in single males (Markow and Ricker, 1992). In another study, Markow et al. (1996) found that the body size did not differ between mated and unmated males in either *D. simulans* or *D. pseudoobscura*. However, the mating males of *D. simulans* had significantly fewer sex comb teeth and the mating males of *D. pseudoobscura* had more sternopleural bristles than the single males, but no difference was found in the levels of FA in any bilateral traits between the mated and the unmated males in either species (Markow et al., 1996). In *D. buzzatii*, it was shown that body size was positively correlated with mating success and other fitness components (Santos et al., 1992; Norry et al., 1995), but Norry et al. (1998) found no phenotypic correlation between wing asymmetry and size, suggesting that wing asymmetry does not indicate male

Table 2 : Genetic stress and fluctuating asymmetry in *Drosophila*

Stressor	Species	Materials Focal	Materials Control	Traits*	Results	References
Inbreeding						
	D. melanogaster	Inbred lines	Their hybrids	SBN	FA increased	Robertson and Reeve (1952); Mather (1953); Beardmore (1960); Reeve (1960)
	D. melanogaster	Inbred lines	Outbred lines	SBN	No effect	Fowler and Whitlock (1994)
	D. ananassae	Inbred laboratory populations	Outbred lines	SBN, WL, W/T ratio, SCTN, ON	No effect	Vishalakshi and Singh (2008a)
	D. melanogaster	Inbred lines	Outbred lines	Wing vein	FA increased	Carter et al. (2009)
	D. subobscura	Inbred lines		ON	FA increased	Savić et al. (2008)
	D. subobscura	Isochromosomal lines (inbred)	Ditto (outbred)	Wing shape and size	FA increased	Santos et al. (2005)
Hybridization						
Interspecific crosses						
	D. melanogaster-simulans	Parental species	Their hybrids	SBN, WL, Fronto-orbital, frontal chaetae	FA increased	Markow and Ricker (1991)
	D. madeirensis-subobscura	Parental species	Their hybrids	Wing and centroid size	FA increased	Rego et al. (2006)
	D. buzzatii-koepferae	Parental species	Their hybrids	WL	No effect	Carreira et al. (2008)
	D. ananassae-pallidosa	Parental species	Their hybrids	SBN, WL, W/T ratio, SCTN, ON	No effect	Vishalakshi and Singh (2009a)
	D. mauritiana-melanogaster-simulans	Parental species	Their hybrids	WL, WD	FA increased	Stamenković-radak et al. (2009)
Intraspecific crosses						
	D. mercatorum	Parthenogenetic strain-sexually reproducing strain		SBN, WL, WD	FA increased	Andersen et al. (2002)
Mutations						
	D. melanogaster	32 lines with same genetic background with 5 visible mutations		SBN	FA increased	Bourguet (2000)
	D. melanogaster	*Notch (N)* mutants		6 different bristles	FA increased	Indrasamy et al. (2000)
	D. ananassae	Different mutants (single, double and triple mutations)		SBN, WL, W/T ratio, SCTN, ON	No effect	Vishalakshi and Singh (2008b)
	D. melanogaster	Heterozygous insertional mutation		Wing size and shape	FA increased	Debat et al. (2009)
	D. melanogaster			SBN, WL	No effect	Monedero et al. (1997)
	D. simulans	*Lethal hybrid rescue (Lhr)*		SCTN, VTN, WL, Tibia L	FA increased	Chatterjee et al. (2007)
Inversion polymorphism						
	D. subobscura	Isochromosomal lines		Wing size and shape	FA increased	Santos et al. (2005)
Directional selection						
	D. melanogaster	Faster developmental time		SBN	No effect	Shakarad et al. (2001)
	D. melanogaster	Index-based wing character		Wing traits	No effect	Pelabon et al. (2006)
	D. ananassae	Thorax length		SBN, WL W/T ratio SCTN, ON	No effect	Vishalakshi and Singh (2009b)
	D. melanogaster	Increased expression of *radius incompletus (ri)* mutation		Wing traits	FA increased	Imasheva et al. (1991)
Molecular chaperons						
Hsp90	D. melanogaster			Bristle and WL	No effect	Debat et al. (2006)
Hsp 83	D. melanogaster			Bristles	FA increased	Debat et al. (2006)

* SBN: sternopleural bristle number; WL: wing length; W/T ratio: wing to thorax ratio; SCTN: sex comb tooth number; ON: ovariole number; VTN: vaginal tooth number; Tibia L: tibia length; WD: wing width.

Table 3 : Environmental stress and fluctuating asymmetry in *Drosophila*

Stressor	Species	Conditions	Traits*	Results	References
Temperature					
	D. melanogaster	Increase of temperature from 25 to 30°C	SBN	FA increased	Parsons (1962); Imasheva et al. (1997a, b)
	D. buzzatii	Increase of temperature from 25 to 30°C	SBN, AB, WL	FA increased	Imasheva et al. (1997a)
	D. ananassae	Low and high temperature (20, 25 to 30°C)	SBN, WL, W/T ratio, SCTN, ON	FA increased	Vishalakshi and Singh (2008c)
	D. melanogaster	Range of temperature (18, 28 and 18–28°C)	Compartments of wing	FA increased	Trotta et al. (2005)
	D. subobscura	Warm adapted versus cold adapted populations	Wing shape asymmetry	FA increased	Santos et al. (2006)
	D. melanogaster	Extra Y chromosome	SBN	FA increased	Jokela and Portin (1991)
Nutrition					
	D. melanogaster		SBN, AB, ACN	FA increased	Imasheva et al. (1999)
	D. ananassae		SBN, WL, W/T ratio, SCTN, ON	No effect	Vishalakshi and Singh (2008d)
Larval crowding/density					
	D. ananassae		SBN, WL, W/T ratio, SCTN, ON	FA increased	Vishalakshi and Singh (2008d)
Multiple stress					
	D. melanogaster	Cold-ethanol-nutrition stress	OB, cross vein, WD, WL, SBN	FA increased for OB Other traits no effect	Woods et al. (1999)
Ectoparasite					
	D. nigrospiracula	Mites	SBN	FA increased	Polak (1993, 1997)
Parental age					
	D. melanogaster	Mother's age	SBN	No effect	Parsons (1962)
Heavy metals					
	D. melanogaster	Lead and benzene	SBN	FA increased	Graham et al. (1993b)
	D. melanogaster	Temperature and lead	SBN	No effect	Polak et al. (2004a)
Pesticide					
	D. melanogaster	Endosulphan	TL, WL, SBN, OB	No effect	Antipin and Imasheva (2001)
Chemical					
	D. melanogaster	Phenylthiourea	SBN	No effect	Parsons (1961)
	D. melanogaster	Arsenic	SBN	No effect	Polak et al. (2002)
Magentic fields					
	D. melanogaster	50 Hz of 1.5 and 80μ	SBN, WL	FA increased	Graham et al. (2000)
Host variation					
	D. pachea	Cactus host variation	Wing and leg size	No effect	Hurtado et al. (1997)
Seasonal change					
	D. melanogaster	Seasonal dynamics	TL, WL, SBN, OB	No effect	Antipin et al. (2001)
Habitat					
	D. serrata	Marginal versus central population	WL, WD, SBN, cross vein (wing)	No effect	Jenkins and Hoffmann (2000)

* AB: arista branches; ACN: abdominal chaetae number; SBN: sternopleural bristle number; WL: wing length; W/T ratio: wing to thorax ratio; SCTN: sex comb tooth number; ON: ovariole number; Tibia L: tibia length; WD: wing width; TL: thorax length; OB: orbital bristles.

quality in terms of phenotypic variation in body size. There is also evidence for the positive genetic correlation between sex comb size and FA in *D. bipectinata* (Polak et al., 2004b). However, in another study, Polak and Starmer (2005) found that males reared at 29℃ produced smaller and less symmetrical sex combs than males developed at 25℃. Also, they reported that there was a negative correlation between sex comb size and FA generated by means of heterogeneous exposure to thermal stress; i.e., both sex comb size and symmetry decreased with increasing temperature within the range experienced by the species in nature (Polak and Starmer, 2005). The relationship between genotype, developmental stability and mating performance has been investigated in *D. immigrans* (Polak and Stillabower, 2004). Among males, there was a significant positive relationship of positional fluctuating asymmetry (PFA, Polak, 1997, for definition see Table 1) with copulation latency (time elapsed between introduction of females and copulation) and copulation duration, but not with copulation frequency. Moreover, high developmental stability lines exhibited significantly shorter copulation latency and duration compared with low developmental stability lines. When these components of sexual performance were again contrasted between lines with among-individual differences in bristle asymmetry controlled statistically, significant line effects on copulation latency and duration disappeared (Polak and Stillabower, 2004). These results suggest that deficits in the developmental apparatus underlying one particular trait can compromise individual sexual performance, and thereby weakens the hypothesis that FA is a cue of overall 'genetic quality' (Polak and Stillabower, 2004). By using comprehensive multivariate analyses, Polak and Taylor (2007) have nicely shown that fluctuating asymmetry and minor morphological abnormalities (MMAs) in a condition-dependent sexual ornament (sex comb) in *D. bipectinata* are the significant targets of selection favouring their reduced expression in a natural population of New Caledonia *D. bipectinata*. Ornament size and developmental instability (DI measured as FA and MMAs) are positively correlated genetically and phenotypically, which is in contrast to the theoretical expectation of negative size-FA scaling under the assumption that FA reveals overall genetic quality. Furthermore, they have shown that there exists a significant additive genetic variance for MMAs,

demonstrating their evolutionary potential. Ornament DI in New Caledonian *D. bipectinata* is markedly elevated in comparison to the populations where such selection has not been detected, suggesting that the increased population-level DI is capacitating adaptive evolution (Polak and Taylor, 2007). In *D. ananassae*, Vishalakshi and Singh (2008e) found that the traits related to body size (thorax and wing length) of mated flies were larger than unmated ones, suggesting that sexual selection acts directly or indirectly on the body size. However, the levels of FA were similar in the mated and unmated flies for different morphological traits in both males and females, suggesting that FA cannot be used as an ideal phenotypic cue for choosy females and thereby weakens the FA-sexual selection hypothesis (Vishalakshi and Singh, 2008e).

3.3 Status of FA-sexual selection hypothesis

The inconsistency of results in the studies investigating the role of FA in sexual selection casts doubts on the existence of FA-sexual selection hypothesis. On the one side, there is evidence for the role that FA plays in sexual selection, e.g., in humans, insects, fishes and birds (for references see Polak and Taylor, 2007), but, on the other side, there are studies showing that FA cannot be considered as a reliable indicator of genetic quality (see section 3.2 for examples). So, the question arises why FA predicts sexual success in some species but not in others. The explanation for this may be that most species and populations do not have sufficient DI variation to sustain FA-mediated sexual selection (Polak and Taylor, 2007) due to the robust buffering mechanisms (Gibson and Wagner, 2000) that are maintained by canalizing selection (Polak and Taylor, 2007). As a result, the effectiveness of FA minimizes to reveal DI differences among individuals of a population, as FA is weakly correlated to the underlying DI (Houle, 2000; Polak and Taylor, 2007). Therefore, FA-sexual selection hypothesis may exist in populations with DI-enriched FA in a particular trait or in the whole genome due to genetic or environmental destabilizing factors (for references see Polak and Taylor, 2007). Otherwise, whatever FA we are getting reflects the compromised trait specific developmental buffering rather than overall genetic quality (as discussed by Polak and Taylor, 2007). But this explanation is based on the results of few studies, and therefore, in order to get in-depth knowledge of what role FA plays in sexual

selection, more investigations have to be carried out, which will definitely unveil the status of FA-sexual selection hypothesis, in general.

4. Does fluctuating asymmetry have any genetic basis?

Whether FA has any genetic basis or not is a subject for intense debate. FA is considered to be purely environmental in origin but it may also be under genetic control (Leamy 1997; Fuller and Houle, 2003). Empirical studies have shown that the heritability of FA is quite low (Mather, 1953; Thoday, 1958; Reeve, 1960), but significant heritability has also been found in some cases (Scheiner et al., 1991; Møller and Thornhill, 1997). Studies using QTL mapping and effect of single genes on FA have been used to disentangle the presence of dominance (intra-locus) and epistasis (inter-locus) interactions in the non-additive genetic architecture of FA in mice (Leamy and Klingenberg, 2005; Van Dongen, 2006).

5. Conclusions

Fluctuating asymmetry has been studied as an indicator of stress and individual quality in a wide variety of organisms ranging from viruses, animals to plants and also in fossil materials (see Graham et al., 2010, for references). FA is often considered as trait-, sex- and taxon-specific (Swaddle, 2003). However, due to inconsistency of results, we are unable to generalise any clear-cut relationships between FA and stress or individual quality, which compels us to think that FA is not a ubiquitous measure of individual quality. FA has considerable potential to assess stress and individual quality, provided the studies dealing with FA pay more attention to an appropriate methodology including sufficient statistical power and appropriate analysis (Knierim et al., 2007). This is also echoed from the statement "when studied with care, subtle deviations from symmetry (FA) offer a unique measure of developmental precision for many organisms and traits and may even yield insights into the evolution of conspicuous asymmetries" (Palmer, 1996).

Hence, it is essential to reconsider the association between FA and fitness and also the genetic architecture of FA under different stress conditions, which will help us in understanding the role of FA in macro-

and micro-evolutionary processes.

Acknowledgements

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