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The heritability of fluctuating asymmetry: a Bayesian hierarchical model

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The genetic architecture of fluctuating asymmetry (FA) as an estimate of developmental instability (DI) has received much attention in the recent literature. Although some studies report significant heritabilities of FA (h^2_{FA}) and DI, generally heritability estimates are low. Summarizing available estimates in a recently performed fixed effects meta-analysis has provoked a lot of discussion. One objection is that heritabilities in general are population and even trait specific, and that they are influenced by a number of stochastic processes. Summarizing available information by an average value has therefore only limited relevance. Meta-analyzes should in addition attempt to model the underlying stochasticity and mean values should be accompanied by a measure of variability (i.e., random effects model). In this paper, I explore and apply a Bayesian method, *hierarchical modeling*, to model between-population and between-trait heterogeneity in h^2_{FA}, taking estimation accuracy into account. The analysis confirms the low values of h^2_{FA}, with a 95% confidence interval ranging between 0.009 and 0.104. In addition, between-species and -population differences in heritabilities were much higher than between-trait heterogeneity, indicating that the weak genetic effects relative to environmental influences and sampling error affect different traits in a comparable way. Although at present it is difficult to analyze how different potential influential factors contribute to the variation in h^2_{FA}, Bayesian modeling can provide a valuable statistical tool to model the underlying stochasticity of genetic parameters in general.

1. Introduction

Recently, there has been a great interest in the heritability of fluctuating asymmetry (FA, i.e. small random deviations from perfect symmetry; Ludwig 1932, Van Valen 1962), an estimate of developmental instability (DI, i.e. the inability of an individual to buffer its development against random perturbations, Palmer & Strobeck 1992). Information on the importance of the genetic basis of FA and DI relative to other sources of variation is vital to understand morphological varia-

tion, the importance of FA and DI in evolutionary models of natural and sexual selection, and the suitability of FA as an estimator of genetic and/or environmental stress at both the individual and population level. Møller and Thornhill (1997) performed a meta-analysis and concluded after considering a number of potential biases that on average the heritability of FA equals 0.19. However, other researchers challenged this estimate for several reasons. Many studies concluded that the heritability of FA would rather range between 0 and 0.1 or even equal zero (Leamy 1997, Markow & Clarke 1997, Palmer & Strobeck 1997, Whitlock & Fowler 1997, Gangestad & Thornhill 1999), a range of values that is supported by many more recent empirical studies (e.g. Blanckenhorn *et al*. 1998, Windig 1998, Van Dongen *et al*. 1999, Woods *et al*. 1999). Furthermore, because individual single trait asymmetry is only a very crude estimate of individual DI, heritability estimates are expected to be low (Whitlock 1996, Houle 1997). In addition, heritabilities are population and trait specific and are affected by external factors that influence genetic variation like population history, breeding structure, intensity and direction of selection, mutation and genetic drift (e.g. Hoffmann & Parsons 1991, Houle 1998, Falconer & Mackay 1996, Pomiankowski 1997, Swaddle 1997). In addition, heritabilities estimate the relative importance of additive genetic variance against non-additive and environmental variance, all of which may vary between populations and traits (Falconer & Mackay 1996). As a consequence, it is very likely that heritabilities differ between species, populations and traits (*see* Møller & Thornhill 1997 for an explicit test). Therefore, a study aiming to summarize the available knowledge on the heritability of FA should attempt to model this between-population and between-trait heterogeneity and in addition estimate the distribution of hypothetical underlying parameters from which this heterogeneity originates. This comes down to a so-called random effects model (Normand 1999) in contrast to the fixed effects model applied by Møller and Thornhill (1997).

Bayesian hierarchical modeling is particularly suited for this purpose (Normand 1999). Bayesian statistics as opposed to more traditional techniques consider both the observations and the unobserved parameters as random variables. In other words, Bayesian techniques take the uncertainty of the parameter estimates into account, and a probability distribution is used as a fundamental measure of this uncertainty (Gelman *et al*. 1995). This aspect is especially useful for modeling heritabilities. A population-level heritability of a trait should be viewed as a realization of different evolutionary forces, many of which are stochastic. Therefore, if I hypothetically assume that this population would evolve a second time under exactly the same conditions (which is of course not possible), the realized heritability is likely to be different from the first value just by chance. Therefore, observed heritabilities (i.e. the parameters of interest) reflect a sample from a distribution, and are not fixed as is generally assumed by traditional statistical techniques. The result of a Bayesian analysis is a posterior distribution, which quantifies the uncertainty (i.e. 95% confidence interval) about the parameters after the observations have been made. Basically, both the data and a priori information (i.e. in the form of a prior distribution) are combined to obtain the posterior distributions. The choice of this prior distribution is the subjective part of a Bayesian analysis and has been the subject of many debates (e.g. Royall 1997). In a hierarchical model, heterogeneity in the parameter of interest can be modeled at different nested levels, taking estimation accuracy into account. These different levels may reflect some hypothetical evolutionary context. It is important to note that Bayesian analyses focus on estimating posterior distributions of parameters of interest. They do not aim at testing statistical significance in the traditional sense. Levels of significance or *p*-values can be defined as the probability that the outcome of an experiment or observation could have been more extreme than the observed outcome, assuming the null hypothesis is true (Neter *et al*. 1990). The underlying idea is that if one would repeat an experiment or sampling procedure many times under exactly the same conditions (which is often impossible from a practical point of view) and when the null-hypothesis is correct, that in a proportion, which equals the *p*-value of the test, the outcome will be at least as extreme as the observed one. Thus *p*-values take only sampling variation into account, whereas estimates of heritabilities (among many other biologically meaningful parameters) are sub-

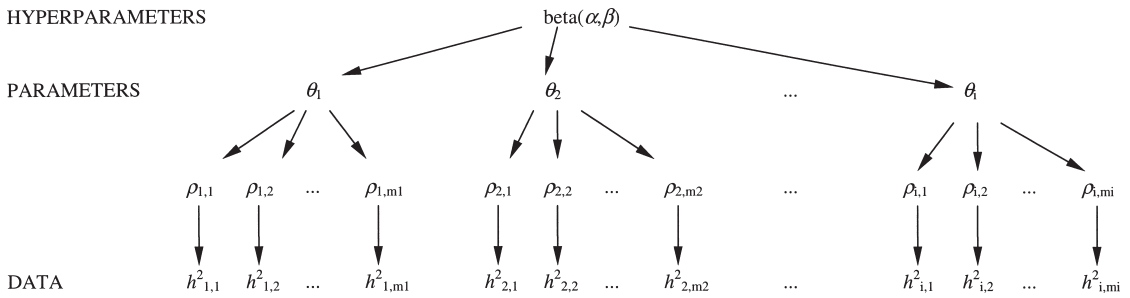

Fig. 1. Four-level hierarchical model describing heterogeneity in the heritability of fluctuating asymmetry. α and β represent the so-called parameters of the hyperdistribution reflecting between-species and -population heterogeneity in the heritability of FA. The θ values are the species or population specific underlying parameter values of the heritability of FA where the subscript i indicates the species (or population). The ρ values indicate the trait specific values indicated by the mi subscript. Finally, the observed heritabilities of FA ($h^2_{i,mi}$) are modeled as a sample from the distributions of the model parameters (*see* text for distributional details).

ject to other sources of random variation (*see* above). Therefore, traditional tests of significance may be of limited interest or at least underestimate variability in the parameter of interest. In a Bayesian analysis, parameters are viewed as random variables and a priori information (i.e. the prior distribution) can improve the obtained estimates (Gelman *et al*. 1995). Such prior distribution can be obtained from the posterior distribution of a hierarchical meta-analysis like the one presented here.

In this study, I used 66 estimates of heritability of FA from 12 studies to evaluate between-species (or between-populations) and between-trait (i.e. within-population) heterogeneity. Because this is the first Bayesian study that attempts to model the heritability of FA, I used weak prior distributions that reflect the lack of a priori information (Gelman *et al*. 1995). The results of this approach are a set of posterior distributions of the different parameters of interest that can be used as a prior in new studies of the heritability of FA. If one would be willing to make the strong assumption that the different populations and traits involved in this analysis represent an unbiased sample from all possible populations and traits and that all heritability estimates are unconfounded (which is not the case, *see* below), the posterior distribution of the heritability of FA represents the distribution from which new heritability estimates are sampled. The main target of this paper is to illustrate the potential usefulness of a Bayesian approach to combine data from different sources in modeling particular evolutionary scenarios. At present there is insufficient data to put high confidence on the obtained posteriors, but as novel information becomes available in the literature this approach will allow to increase our understanding of the genetic architecture of FA and DI, and will lead to a more reliable estimation of genetic parameters.

2. Materials and methods

2.1. Hierarchical model and analysis

The statistical model used to describe heterogeneity in the heritability of FA contains four levels and is represented schematically in Fig. 1. At the top level (i.e. level 1), the so-called hyperparameters α and β of a beta-distribution determine the location and shape of the heritability of FA at the species (population) level. I hereby assume that the unobserved, average species- (population) level heritabilities of FA, indicated by θ (i.e. level 2), can be considered as a sample from a beta-distribution. At this point, I assume that between-species and between-population heterogeneity is similar and can be modeled by one beta distribution. This may be an oversimplification since species- and population-level heterogeneity may differ, but due to a lack of sufficient data it was impossible to add an additional fifth level to the hierarchical model. The beta-distribution is a natural choice to model heritabilities as it is bounded between 0

and 1 and it can take many different shapes (Gelman *et al*. 1995). Mean and standard deviation of this distribution can be approximated as $\alpha/(\alpha + \beta)$ (further called μ) and $1/(\alpha+\beta)^{0.5}$ (further called σ_{pop}), respectively (Gelman *et al*. 1995). I used a normal distribution with mean equal to 1 000 and standard deviation equal to 1 000 000 as hyperprior distributions for α and β, expressing the lack of prior knowledge on these hyperparameters. Because α and β should be positive, I took zero as lower bound for the priors. In this way, the prior distribution plays a minimal role in the posterior distribution. This choice of prior does imply that I consider very large values of α and β less likely (Gelman *et al*. 1995). Varying mean and standard deviation gave similar results.

At the next level, the species- (population) specific, unobserved single trait heritabilities of FA, which are denoted as ρ, are considered to be a sample from a normal distribution with mean θ [i.e. average species- (population) specific heritability] and standard deviation σ_{trait} (i.e. level 3). Obviously, because heritabilities cannot be smaller than zero I limited the lower bound of these distributions at zero. As prior distribution of σ_{trait} I used an inverse gamma distribution with parameters equal to 10^{-4}, again expressing our lack of a priori knowledge (*see* Gelman *et al*. 1995 for details). At the final level (i.e. level 4), the observed heritabilities (h^2_{FA}) are represented as a sample from a normal distribution with mean ρ and standard deviation equal to the observed estimation accuracy (i.e. $\sigma_{sampling}$: standard error of the heritability estimate). The lower bound of this distribution was not limited to zero because negative heritability estimates are generally assumed to be the result of sampling variation (Lynch & Walsh 1998). The upper bound was limited to 0.637, the theoretically maximal value of the heritability of FA (Whitlock 1996, 1998). The normal distribution is symmetric, whereas the distribution of heritabilities may deviate from this pattern. However, other candidate distributions, like the log-normal, gamma and beta distribution, cannot generate negative heritabilities. Therefore, the normal distribution had to be applied, with the main advantage that parameters are easy to interpret.

The posterior distributions of the parameters of interest [i.e. α, β (and thus μ and σ_{pop}), θ, ρ and σ_{trait}] were obtained by a Markov chain simulation technique known as Gibbs sampling or alternating conditional sampling (*see* Gelman *et al*. 1995 for a good introduction). The basic idea of this algorithm (and of other Markov chain simulations) is to simulate a random walk in the parameter space. The joint posterior distribution is obtained when the simulation converges to a stationary distribution. The analysis was carried out in the package WINBUGS (D. Spiegelhalter, A. Thomas & N. Best, unpubl.). I ran 20 independent Markov chains with different and overdispersed initial values (i.e. away from their estimated values after convergence). After a 'burn in' period of 2 000 iterations during which the chains become independent and uncorrelated from their initial values, I ran 10 000 iterations for each chain. Only data from the latter iterations were analyzed such that the posterior distributions will be based on a total of 200 000 iterations from 20 independent Markov chains. This high number of simulations was required because of the high degree of autocorrelation and low rate of convergence within the chains, especially for the distribution of α and β and thus of μ and σ_{pop}. Visual inspection of the running quantiles and of Gelman and Rubin statistics (Gelman & Rubin 1992) showed that these setting were satisfactory. For ρ and σ_{trait} the Gelman and Rubin statistics converged to 1 after 2 500 iterations, whereas for μ and σ_{pop} (and also α and β) convergence occurred after 5 000 iterations. It can therefore be assumed that the simulated distributions based on the 20 Markov chains reflect a close approximation of the exact distributions.

Posterior distributions contain all the current information about the parameters of interest. These distributions are displayed graphically and mean, standard deviation, median and 95% confidence intervals are reported (*see* also Gelman *et al*. 1995). Distributions were constructed graphically from 2.5, 5, 10, 25, 50, 75, 90, 95, and 97.5% quantiles and spline smoothing in the graphical package SIGMAPLOT (Version 4.0).

2.2. Selection of studies

A total of 66 heritability estimates of 16 populations derived from 12 studies obtained after literature search in Biosys and Current Contents,

and papers cited in Møller and Thornhill (1997) and Gangestad and Thornhill (1999) were used in the analysis (Table 1). I only included studies that showed a relatively small degree of measurement error relative to FA and that found no indications of antisymmetry or directional asymmetry (unless corrected for). In addition, studies criticized earlier were excluded (*see* Leamy 1997, Markow & Clarke 1997, Palmer & Strobeck 1997, Whitlock & Fowler 1997 for details). Furthermore, only studies that provided standard errors of the heritability estimates could be included in the analyses. These standard errors were either reported directly, or were approximated from 95% confidence intervals (CI) by dividing the length of the CI by 3.92 (i.e. 2×1.96). For the Scheiner *et al*. (1991) study I included data from one treatment only (i.e. rearing at 19°) because the flies of the other treatment represented the same population. Heritability estimates from males and females of *Sepsis cynipsea* were treated as separate populations because Blanckenhorn *et al*. (1998) found indications that heritabilities may differ between both sexes. Repeating the analyses leaving out either males or females gave very similar results.

3. Results and discussion

Descriptive statistics and a graphical presentation of the posterior densities of the six parameters of interest are given in Table 2 and Fig. 2. The posterior distribution of single trait heritabilities of FA indicated that most estimates are expected to fall between 0.009 and 0.104 with an overall mean of 0.043 (Table 2, Fig. 2). This range closely corresponds with that predicted by Leamy (1997) and Whitlock and Fowler (1997). In addition, several studies that were not included in this analysis (because they did not report accuracies of the heritability estimates) appear to follow this range (e.g. Corruccini & Potter 1981, Parker & Leamy 1991, Windig 1998, J. J. Windig unpubl.).

Between-species (population) heterogeneity (SD) is likely to range between 0.016 and 0.046 with a mean of 0.025 whereas between-trait (within-population) heterogeneity was much smaller (mean = 1.18×10^{-4}; 95% CI = 5.0×10^{-6}–6.6×10^{-4}) (Table 2, Fig. 2). This relatively low amount of between-trait variation in the heritability of FA suggests it is likely to be mainly the result of sampling variation alone. In addition, it suggests that the genetic background of FA and DI affects the different traits in a comparable way. However, if studies would focus on measuring a wide variety of traits, which is rarely done, a higher degree of between trait heterogeneity might be discovered. The studies included here form a mix of analyses based on parent offspring regressions and sib rearings. As a result, not all (if not only few) heritability estimates are fully unconfounded estimates. This source of variation may have contributed to the between-study heterogeneity. However, adding an additional level to the hierarchy was not performed because of the limited sample sizes.

A second source of between-species heterogeneity may be variation in the accuracy of FA as estimate of DI. Individual single-trait asymmetry attempts to estimate a variance (i.e., DI) with two datapoints. As a consequence FA is only a crude estimator of DI. Recent studies have shown that there is substantial between-species heterogeneity in the accuracy of FA as estimator of DI (Van Dongen & Lens 2000), and this heterogeneity may contribute to between-species heterogeneity in estimates of the heritability of FA (Whitlock 1996). Ideally, meta-analyses should model the heritability of DI, yet at present there is insufficient data available in the literature (Van Dongen & Lens 2000).

In a recent theoretical approach of the genetic background of FA, Klingenberg and Nijhout (1999) showed that small positive heritabilities of FA could be obtained without any genetically determined mechanism that stabilizes trait development. Their results are based on a threshold diffusion process with non-linear growth. Slight random noise added to the model-parameters at the start of development resulted in low heritabilities of FA whereas noise is independent of the genotype. Thus, if there is indeed no underlying genetically determined developmental stability mechanism that leads to different degrees of individual FA, the results presented here would indicate that the degree of non-linear development and/or noise mainly differs between populations, but not to the same extent between traits within a population. To what extent developmental instability has in itself a (weak) genetic basis or that

Table 1. Heritability estimates and their standard errors for the different populations and traits included in this analysis.

Heritability (SE)	Species (population)	Reference	Remarks
Wing length: 0.005 (0.056); bristle number: 0.039 (0.019)	*Drosophila melanogaster*	Scheiner *et al.* (1991)	reared at 19 °C
Wing measure B: 0.02 (0.21)	*Gryllodes sigillatus*	Eggert & Sakaluk (1994)	
Cotyledon width 3: 0.40 (0.19); petal length: 0.11 (0.14); petal width: 0.07 (0.14)	*Brassica campestris*	Evans & Marshall (1996)	RCBP population
Cotyledon width 3: –0.07 (0.15); petal length: 0.18 (0.18); petal width: –0.10 (0.14)	*Brassica campestris*	Evans & Marshall (1996)	wild population
Petal length: 0.18 (0.07)	*Epibolium angustifolium*	Møller (1996)	
a–b ridge count: 0.14 (0.33)	*Homo sapiens*	Boggle & Reed (1997)	
Mandf: 0.10 (0.066); maxfi: 0.09 (0.058); maxfii: 0.02 (0.058); fpma: –0.08 (0.062); fpmp: 0.04 (0.060); forod: 0.02 (0.094); foropty: 0.05 (0.059); persut: 0.02 (0.073)	*Mus musculus*	Leamy (1997)	midparent estimates
Forewing length: –0.24 (0.22); forewing width: –0.26 (0.18); trichiae: 0.06 (0.30); setae 1: –0.02 (0.20); setae 2: –0.40 (0.24); setae 3: –0.12 (0.28)	*Trichogramma carverae*	Bennett & Hoffmann (1998)	
Wing length: –0.01 (0.068); wing width: –0.05 (0.048); hind tibia length: 0.15 (0.083); fore tibia length: 0.08 (0.068); fore femur length: 0.16 (0.083); fore femur width: 0.05 (0.063)	*Sepsis cynipsea*	Blanckenhorn *et al.* (1998)	females
Wing length: –0.03 (0.055); wing width: 0.08 (0.063); hind tibia length: –0.07 (0.038); fore tibia length: 0.02 (0.058); fore femur length: 0.06 (0.065); fore femur width: 0.07 (0.065); seta length: 0.00 (0.053)	*Sepsis cynipsea*	Blanckenhorn *et al.* (1998)	males
Sternopleural bristle: –0.076 (0.21); orbital bristle: 0.048 (0.18); cross vein: –0.332 (0.17); wing width: –0.224 (0.35); wing length: –0.398 (0.27)	*Drosophila melanogaster*	Woods *et al.* (1998)	Cairns population
Sternopleural bristle: 0.056 (0.13); orbital bristle: –0.014 (0.14); cross vein: 0.032 (0.12); wing width: –0.060 (0.13)	*Drosophila melanogaster*	Woods *et al.* (1998)	Gold coast population
Sternopleural bristle: 0.054 (0.09); orbital bristle: –0.112 (0.14); cross vein: 0.030 (0.13); wing width: 0.078 (0.11); wing length: –0.056 (0.14)	*Drosophila melanogaster*	Woods *et al.* (1998)	Cherry hill population
m1: –0.08 (0.051); m2: 0.07 (0.052); m3: –0.07 (0.049); m4: 0.06 (0.049); m5: –0.06 (0.054); m6: 0.06 (0.050); m7: 0.04 (0.043); m8: 0.09 (0.056); m9: 0.01 (0.051); m10: –0.02 (0.052)	*Mus musculus*	Leamy (1999)	midparent estimates
tibia 1: 0.01 (0.02); tibia 2: 0.04 (0.02); tibia 3: 0.03 (0.02)	*Operophtera brumata*	Van Dongen *et al.* (1999)	
front tibia: –0.036 (0.01)	*Plodia interpunctella*	S. van Dongen (unpubl.)	

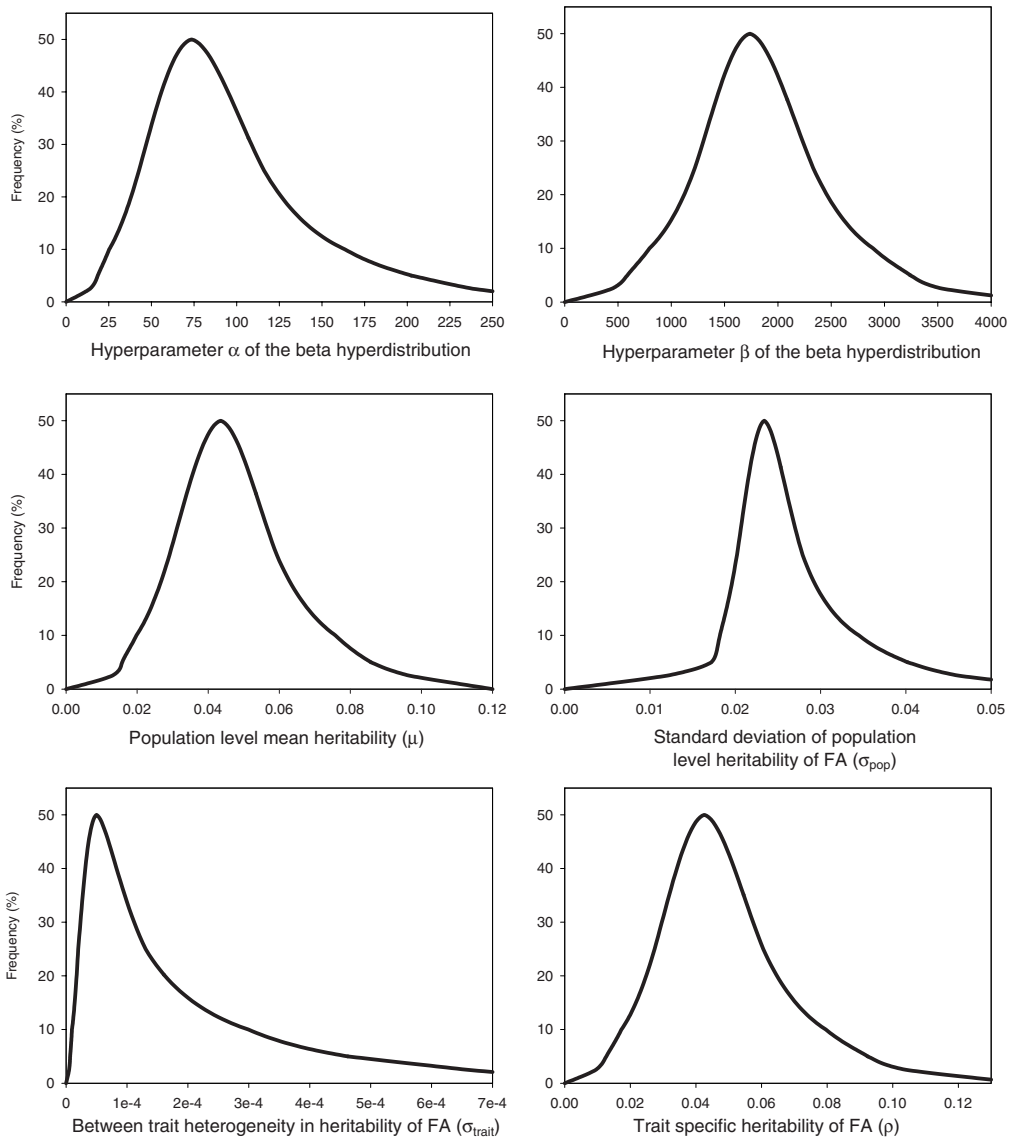

Fig. 2. Posterior distributions of the six parameters of interest that model heterogeneity in the heritability of FA (*see* text and Fig. 1 for details). Distributions are based on a total of 200 000 iterations from 20 independent Markov chains simulated in WINBUGS.

Table 2. Mean, standard deviation, median and 95 % confidence interval of the six parameters of interest based on the posterior distributions of the hierarchical Bayesian model (*see* text and Fig. 1 for details).

Parameter	mean (SD)	median	95% CI
α	86.8 (59.2)	73.6	14.1–238.4
β	1 807 (805)	1737	445–3541
Mean species level heritability (μ)	0.046 (0.022)	0.043	0.013–0.097
Between species heterogeneity (σ_{pop})	0.025 (0.008)	0.023	0.016–0.046
Between trait heterogeneity (σ_{trait})	1.2×10^{-4} (1.9×10^{-4})	5.0×10^{-5}	5.0×10^{-6}–6.6×10^{-4}
Trait heritability of FA (ρ)	0.046 (0.025)	0.043	0.009–0.104

the heritability of FA is a by-product of non-linear development should become a topic of further research.

In conclusion, this study shows that Bayesian statistics offer an interesting way to summarize available data on heritabilities. In this particular case, it confirms earlier findings that the heritability of FA is low and roughly ranges between 0 and 0.1. Furthermore, hierarchical modeling between-population and trait heterogeneity indicates that levels of FA of different traits are influenced by the same genetical factors, whereas they may differ to a larger extent between populations. However, several factors may have contributed to this heterogeneity and it is at present difficult to analyze the contribution of each to the variation in the heritability of FA. The obtained posterior distributions can be applied as priors in future studies estimating the heritability of FA. This would lead to improved estimates. In particular, since heritabilities are difficult to estimate with high accuracy even when sample sizes are large, standard errors are often very large. This may cause some estimates to deviate substantially from their underlying parameter-value (i.e. parameter ρ in Fig. 1) unless sample sizes are taken appropriately large. Making use of the available data, captured within the posterior distributions and using these as priors for future Bayesian analyses, the estimation of heritabilities can be made more accurate in the sense that spuriously high or low heritabilities with low sampling accuracy will become shifted towards these priors. The higher the accuracy of the estimate the weaker relative the effect of the prior knowledge will become. By continuously updating the prior distribution when new (unconfounded) estimates become available, and possible including other sources of variation in the heritabilities (species vs. population effects, confounding factors such as non-additive genetic variance, hypothetical repeatability), can be expected to lead to a better understanding of the factors that determine the genetic architecture of developmental instability which is estimated by FA.

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