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# Detecting directional epistasis and dominance from cross-line analyses in alpine populations of *Arabidopsis thaliana*

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1 **Detecting directional epistasis and dominance from cross-line analyses in Alpine**  
2 **populations of *Arabidopsis thaliana***

3

4 **Running title:** Directionality of non-additive genetic effects

5

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7

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17

18 **Data availability:** Data and code are available at <https://github.com/lerouzic/Epicross>

19 **Authors contributions:** J.C. initiated the project. M.R and A.W. collected the data. A.L.R.  
20 developed the statistical framework and J.C. and A.L.R. analyzed the data. All authors wrote  
21 the first draft and edited the manuscript.

22 **Conflict of interest:** The authors have no conflict of interest to declare.

23 **Abstract:** The contribution of non-additive genetic effects in general, and to the evolutionary  
24 potential of populations in particular, is a topic of long-standing theoretical and empirical  
25 interest, which nevertheless remains controversial. As a consequence, the empirical study of  
26 these effects in natural populations remains scarce, which is problematic because non-additive  
27 effects are expected to modify both the adaptive potential of populations and the way we should  
28 measure it. In this study, we explored the contribution of dominance and epistasis in natural  
29 Alpine populations of *Arabidopsis thaliana*, for two fitness-related traits, the dry weight and  
30 the number of siliques. We first found that, on average, crosses between inbred lines of *A.*  
31 *thaliana* led to heterosis for the dry weight, but outbreeding depression for the number of  
32 siliques. We found that heterosis for the dry weight was due to positive directional dominance.  
33 For the number of siliques, however, we found that outbreeding depression was due to the  
34 breakdown of positive directional epistasis. The implication of these results for the adaptive  
35 potential of the studied populations, as well as the use of line-cross analyses to detect directional  
36 non-additive genetic effects, are discussed.

37

38 **Keywords:** Non-additive genetic effects, dominance, epistasis, quantitative genetics, self-  
39 fertilization, *Arabidopsis*.

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## 46 INTRODUCTION

47

48 The contribution of non-additive genetic effects to the evolutionary potential of  
49 populations is a topic of long-standing theoretical and empirical interest, which nevertheless  
50 remains controversial (see for example Crow, 2010 and Hansen, 2013 for a debate around  
51 epistasis). Non-additive genetic effects are generally describing the dominant relationship of  
52 alleles at a given locus, and the epistatic interactions of alleles at different loci, even if other  
53 forms of non-additive effects exist (Banta & Richards, 2018). Nevertheless, one consensus  
54 derived from theoretical studies is that non-additive genetic effects only influence populations'  
55 adaptive potential if individual epistatic or dominant effects do not tend to cancel each other,  
56 *i.e.*, if a general pattern emerges (Kelly, 1999; Carter *et al.*, 2005).

57 Among the different non-additive genetic effects, epistasis has retained much of the  
58 attention, as it has the potential of modifying the short- and long-term adaptative potential of a  
59 species (Cheverud & Routman, 1995; Carter *et al.*, 2005; Hansen, 2015). In the short-term,  
60 directional positive (respectively negative) epistasis tend to increase (respectively decrease) the  
61 amount of additive variance of a quantitative trait under directional selection, and, as a result,  
62 the adaptive potential of a population (Carter *et al.*, 2005). In the long-term, when epistasis is  
63 positive on average, the evolution of a phenotypic trait is easier in the direction of high values,  
64 because the additive variance tends to increase with the phenotypic value (Le Rouzic, 2014).  
65 On the opposite, negative epistasis favours evolution toward low phenotypic values. Despite its  
66 potential major role, estimates of directional epistasis are currently rare in the literature (Le  
67 Rouzic, 2014). Pavlicev *et al.* (2010) showed a negative average directionality of epistasis for  
68 body-composition traits in *Mus musculus*, while in several plant species, epistasis tend to be  
69 positive, on average, for different floral and fitness related traits (Johansen-Morris & Latta,  
70 2006; Monnahan & Kelly, 2015; Oakley *et al.*, 2015; Clo *et al.*, 2021). Theoretical work has

71 repeatedly pointed out that epistasis on fitness (or log-fitness) should drive many diversity-  
72 generating mechanisms, including the evolution of sex, recombination, and mutation rates  
73 (Phillips *et al.*, 2000), but empirical results remain equivocal (Maisnier-Patin *et al.*, 2005;  
74 Kouyos *et al.*, 2007; Bakerlee *et al.*, 2022).

75 On its side, the directionality of dominance received less attention, because its  
76 consequence on the evolutionary potential of a species is less general (Walsh & Lynch, 2018).  
77 Directional dominance can modify the way we quantify the adaptive potential of a trait in  
78 presence of inbreeding (Kelly, 1999), such that non-additive effects can contribute to the  
79 covariance between parents and offspring, which does not occur under random mating  
80 (Falconer, 1996; Lynch & Walsh, 1998). In such a case, the adaptive potential of inbred  
81 populations is not only described by the additive variance anymore (Cockerham & Weir, 1984;  
82 Wright & Cockerham, 1985), and new dominance variances contribute to the evolvability of a  
83 trait, only if dominance is directional on average (Clo & Opedal, 2021). Directional (negative)  
84 dominance is routinely observed in fitness traits, as shown by the ubiquity of inbreeding  
85 depression (Charlesworth & Willis, 2009), but less is known about the directionality of  
86 dominance for morphological traits, which can be either positive or negative, pending on studies  
87 and traits measured (Shaw *et al.*, 1998; Kelly & Arathi, 2003; Oakley *et al.*, 2015; Clo *et al.*,  
88 2021).

89 It appears that the directionality of non-additive genetics effect remains poorly studied,  
90 despite their potential role in the adaptive potential of populations, and that inbreeding species  
91 can be key actors to start filling the gap, as both directional dominance and epistasis are  
92 expected to modify the heritable variance of populations. Due to its major role as a model  
93 species in evolutionary biology and its mating system, *Arabidopsis thaliana* appears as a natural  
94 choice to study the directionality of non-additive gene effects in plants. *A. thaliana* (L.) Heyhn.  
95 (Brassicaceae) is native to Eurasia and North Africa but is nowadays widely distributed

96 throughout the Northern hemisphere (Hoffmann, 2002). This species occurs in many mountain  
97 ranges, including the Alps, and has been reported along a wide altitudinal range, from sea level  
98 up to 2000 m in the central Alps (Hoffmann, 2002). Unlike close relatives, *A. thaliana* is a  
99 predominately self-fertilizing, annual species. Average outcrossing rates in natural populations  
100 have been reported to vary between 0.3% and 2.5% (Abbott & Gomes, 1989; Bergelson *et al.*,  
101 1998; Picó *et al.*, 2008).

102 In this study, we explored the directionality of dominance and epistasis in natural Alpine  
103 populations of *A. thaliana*, for two fitness related traits, the dry weight and the number of  
104 siliques. We first found that, on average, crosses between inbred lines of *A. thaliana* led to  
105 heterosis for the dry weight, but outbreeding depression for the number of siliques. We found  
106 that heterosis for the dry weight was due to positive directional dominance, likely due to the  
107 masking of recessive deleterious mutations segregating in the different inbred lines. For the  
108 number of siliques however, we found that outbreeding depression was likely due to the  
109 breakdown of positive directional epistasis.

110

## 111 MATERIAL AND METHODS

112

### 113 Study populations

114

115 We studied six natural alpine populations located along an altitudinal gradient in the Alps in  
116 the Saas Valley (Valais, Switzerland). Focal populations (Table S1) were selected from those  
117 studied by Luo *et al.* (2015). Three populations are from low altitude (*i.e.* altitudes ranging from  
118 850 to 1000m) and three from close to the high-elevational range margin of the species in the  
119 Alps (*i.e.* altitudes ranging from 1792 to 2012m). Distances among populations ranged from

120 0.8 to 25.8 km, with average distances of 6.3 km among low altitude and 1.9 km among high  
121 altitude populations. To characterize population genetic structure, all populations were revisited  
122 in 2013 and 2014 and 338 individuals were sampled. For our crossing experiment we used  
123 offspring of plants collected in 2007 that were propagated in the greenhouse for three  
124 generations by single seed descent to standardize maternal effects.

125

### 126 **Population genetic structure**

127

128 We sampled on average 28 *A. thaliana* individuals per population in 2013 and 2014 (Table S1).  
129 Individuals were genotyped using twenty-two of the twenty-four microsatellite markers  
130 previously genotyped by Luo *et al.* (2015) (Table S2), using the same protocol. Genotypes were  
131 called with Geneious© version R6.1.6 (Biomatters Ltd).

132

### 133 **Experimental design and measured traits**

134

135 Seeds of plants originally collected in 2007 and propagated for three generations by single seed  
136 descent in a greenhouse were used as parental lines in the crossing experiment. From each of  
137 the six study populations we randomly selected four parental lines with different genotypes  
138 based on results reported in Luo *et al.* (2015). All parental lines were submitted to spontaneous  
139 self-fertilization and three cross types: (i) outcrossing with pollen from another parental line  
140 from the same local population, (ii) outcrossing with a parental line from another population of  
141 the same altitude, and (iii) outcrossing with a parental line from another population of the other  
142 altitude. For each parental line, self-fertilization and the three cross types were realized on four  
143 different plants. Crosses were made using the pollen of plants exclusively grown for pollen  
144 production. Parental lines were randomly matched without replacement such that all four

145 parental lines of each population were included as both seed and pollen parents in all crosses  
146 types (Table S3). The F2 generation was produced by spontaneous self-fertilization of one  
147 individual from each F1 family (for an overview of the crossing design see Table S3).

148 Performance and phenotypic variation in all F1 and F2 families was assessed in a single large  
149 greenhouse experiment conducted in spring 2014. Seeds were sown on March 4th 2014 and  
150 stratified at 4 °C in the dark for six days. Plants were then grown in a greenhouse at ETH Zurich  
151 research station Lindau-Eschikon under long-day conditions (*i.e.* 10 kLux light for 16 h, dark  
152 for 8 h; 22 °C/18 °C day/night temperatures). For each parental line we grew 24 F1 and 48 F2  
153 offspring. The F1 included six offspring derived from selfing and six offspring derived from  
154 each of the three cross types. The F2 generation encompassed six selfed offspring and 14  
155 offspring from each of the three cross types. In total, the experiment encompassed 1728 plants  
156 in total (for details see Table S3).

157 Plants were grown individually in pots randomly arranged in two greenhouse compartments.  
158 Within each greenhouse compartment, pots were randomly arranged in 24-pot-trays. To avoid  
159 position effects, trays were placed on tables next to each other and surrounded by “border  
160 plants” (*i.e.* plants derived by self-pollination from the study populations, sown and grown  
161 under the same conditions as the experimental plants). Trays with experimental plants were  
162 randomized twice a week until maturation of siliques. All plants were harvested on July 1st,  
163 2014, approximately four months after germination. Plants were first dried for 48h at 45°C. We  
164 then measured the dry biomass and estimated the number of siliques per plant. To estimate the  
165 number of siliques, we first separated the different branches and isolated the reproductive  
166 sections of all branches (*i.e.* the parts of the branches carrying fruits); second, we weighted the  
167 reproductive ('reproductive weight') sections of all branches of each individual together to the  
168 nearest 0.0001g using a Mettler AE 240 analytical balance. Third, we assessed the number of  
169 siliques along three randomly selected and weighted reproductive sections and estimate the



170 number of siliques per gram ('silique density'); fourth, we estimated the total number of siliques  
171 produced per plant ('silique number') as the product of the 'silique density' and the 'reproductive  
172 weight'. We performed the following statistical analyses on the 'silique number', which was  
173 used as a proxy of individual fitness.

174

## 175 **Genetic model**

176

177 Traditional line cross models consider only two parental lines, and generally define genetic  
178 effects from the F2 population, which generally simplifies the mathematical expressions by  
179 reducing the number of parameters for the crossed populations (F1, F2, and backcrosses, Lynch  
180 & Walsh, 1998). As we aim at analyzing several line crosses at once, we reparametrized this  
181 model by taking the grand mean of the parental populations  $\mu$  as a reference. As a result, the  
182 setting resembles a diallel model (Sprague & Tatum, 1942; Falconer & Mackay, 1996), in  
183 which the general combining abilities are assimilated to additive effects, and specific combining  
184 abilities are dissociated into dominance and epistatic terms. The average phenotypic means of  
185 populations  $P_i$  and  $P_j$ , as well as their intercrosses  $F_{1,ij}$  and  $F_{2,ij}$  can be expressed as:

186

$$187 \quad P_i = \mu + A_i$$

$$188 \quad P_j = \mu + A_j$$

$$189 \quad F_{1,ij} = \mu + \frac{1}{2} A_i + \frac{1}{2} A_j + 2D_{ij} - AA_{ij}$$

$$190 \quad F_{2,ij} = \mu + \frac{1}{2} A_i + \frac{1}{2} A_j + D_{ij} - AA_{ij}$$

191

192 This setting defines one additive effect A per parental populations, and as many dominance (D)  
193 and additive-by-additive (AA) epistasis parameters as independent crosses among populations.  
194 In absence of backcrosses, additive-by-dominance epistatic effects cannot be identified and are  
195 merged with additive effects. Dominance-by-dominance interactions, as well as higher-order  
196 epistatic terms, had to be ignored.

197

198 While diallel models are designed to estimate genetic variance components (and are thus  
199 derived as random-effect statistical models), line-cross models aim to measure individual  
200 deviations from additivity, and were thus analyzed with a fixed-effect linear model:

201

$$202 \quad z_k = \mu + \frac{1}{2} A_{P(k)} + \frac{1}{2} A_{Q(k)} + d_k D_{P(k)Q(k)} + aa_k AA_{P(k)Q(k)} + e_k$$

203

204 for individual k of phenotype  $z_k$ , of parents from population P(k) and Q(k), with  $d_k = aa_k = 0$  if  
205  $P(k) = Q(k)$ ,  $aa_k = -1$  if  $P(k) \neq Q(k)$  (k is from an intercross F<sub>1</sub> or F<sub>2</sub>), and  $d_k = 2$  (or =1) if k  
206 results from an F<sub>1</sub> (or an F<sub>2</sub>) intercross.  $e_k$  is a Gaussian-distributed residual of variance  $V_e$ .

207

208 Four models of various complexity were fitted to each dataset: Additive (only the additive terms  
209  $A_i$  were considered), Dominance ( $A_i$  and  $D_{ij}$ ), Epistasis ( $A_i$  and  $AA_{ij}$ ), and Full model ( $A_i$ ,  $D_{ij}$ ,  
210 and  $AA_{ij}$ ). The four models were compared by a model selection procedure based on the Akaike  
211 Information Criterion (Anderson & Burnham, 2004); AIC differences larger than 2 units were  
212 considered as substantial differences between models. Models were fit independently on  
213 Weight and Silique number; and both genetic differentiation levels (Lineage and Population)  
214 were considered.

215

## 216 **RESULTS & DISCUSSION**

217

218           We found that performing the analyses at the scale of the genetic lineages or at the scale  
219 of the populations gave similar results, which echoes with recent results arguing that the notion  
220 of population is hard to define in predominantly selfing species (Rhode & Cruzan, 2005; Dolgin  
221 *et al.*, 2007; Clo *et al.*, 2021, but see Gimond *et al.*, 2013). We decided to presents the results  
222 for the genetic lineages in the main text, the results the populations' scale are available in  
223 supplementary materials (Table S4, Figure S1).

224

### 225 *Consequences of hybridization on dry weight and the production of siliques*

226

227           Our first question was related to the consequences of hybridization between parental  
228 lineages as different effects depending on the trait under study. The raw values of parental lines  
229 and within-population crosses are available as supplementary materials (Figure S2). We found  
230 that, on average,  $F_1$  hybrids showed a heterosis pattern for the dry weight (Figure 1), with an  
231 increase of 9.6% (0.454g in  $F_1$  hybrids), compared to the mean parental value. of 0.414g. This  
232 is in line with what is found in other predominantly selfing species (Rhode & Cruzan, 2005;  
233 Dolgin *et al.*, 2007; Volis *et al.*, 2011; Gimond *et al.*, 2013; Oakley *et al.*, 2015; Clo *et al.*,  
234 2021). In contrast,  $F_2$  hybrids were close to the parents (0.403g, -2%).

235           On the opposite,  $F_1$  and  $F_2$  hybrids showed an outbreeding depression pattern for the  
236 number of siliques (Figure 1), with respectively a decrease of 5.5% and 11.3% in  $F_1$  and  $F_2$   
237 hybrids, compared to the mean parental value. This is slightly lower than other values found in

238 other predominantly selfing species (Rhode & Cruzan, 2005; Dolgin *et al.*, 2007; Volis *et al.*,  
239 2011; Gimond *et al.*, 2013; Oakley *et al.*, 2015; Clo *et al.*, 2021).

240 This opposite patterns for dry weight and fruits number could be considered as a  
241 surprising result since both traits are often considered as fitness proxies, and are generally  
242 positively correlated (see Younginger *et al.*, 2017 for a review). However, such an observation  
243 is not unheard. Studies in natural and laboratory accessions of the highly selfing species  
244 *Arabidopsis thaliana* also found a negative relationship between dry mass and a fitness proxy  
245 (pollen viability in Nasrallah *et al.*, 2000; seed production in Barth *et al.*, 2003; fruit production  
246 Vasseur *et al.*, 2019). In the sister species *A. lyrata*, Li *et al.* (2019) also found that selfing  
247 populations exhibit an increase in above- and below-ground biomass, and a slight decrease in  
248 fitness (measured as the probability of bolting) in outcrossed progeny of selfing populations.  
249 Finally, Clo *et al.* (2021) found that in the predominantly selfing species *Medicago truncatula*,  
250 hybridization between inbred lines lead to heterosis for dry mass but outbreeding depression  
251 for seed production.

252

### 253 **Non-additive effects in natural populations of plants**

254

255 We found that non-additive effects contribute to the genetic architecture of both traits.  
256 For the dry mass, we found that the best model explaining the data was the one including  
257 additive and dominant genetic effects (Table 1), and the observed pattern of heterosis was due  
258 to directional positive dominant effect (Figure 2). Oakley *et al.* (2015) found similar results in  
259 crosses between south European and Scandinavian lineages of *A. thaliana*. The directional  
260 positive dominance likely reflects the positive effects of masking deleterious mutations fixed  
261 at different loci in the different selfing lineages (Charlesworth & Willis, 2009).

262 For the number of siliques, we found that the best model explaining the data was the  
263 one including additive and additive-by-additive epistatic genetic effects (Table 1), and the  
264 observed pattern of outbreeding depression was due to directional positive additive-by-additive  
265 epistatic interactions (Figure 2). The outbreeding depression can be explained by the breakdown  
266 of positive additive-by-additive epistatic interactions found in the parental selfing lineages  
267 during the hybridization events, as found in other species (Rhode & Cruzan, 2005; Johansen-  
268 Morris & Latta, 2006). The finding of directional positive epistasis is in line with what was  
269 found in other plant species (Johansen-Morris & Latta, 2006; Monnahan & Kelly, 2015; Oakley  
270 *et al.*, 2015; Clo *et al.*, 2021).

271

## 272 **Implications for the adaptive potential of Alpine populations of *A. thaliana***

273

274 The distinct genetic architecture among the two fitness traits studied here implies that  
275 the ways we can infer the adaptive potential of each trait are very different. For the dry mass,  
276 we found that dominance contribute to the genetic architecture, and is directional on average.  
277 When directional dominance occurs, the decomposition of the heritable variance is more  
278 complicated (Kelly, 1999). In such a case, new dominance components of the genetic variance  
279 are necessary for describing the adaptive potential of selfing species (Wright & Cockerham,  
280 1985), these new terms have been shown to contribute theoretically and empirically to the  
281 evolvability of predominantly selfing species (Shaw *et al.*, 1998; Clo *et al.*, 2019; Clo & Opedal,  
282 2021). Estimating all these components of the genetic variance are however necessary to predict  
283 the short-term adaptive potential of populations (Clo & Opedal, 2021). It is however important  
284 to note that the contribution of epistasis to this trait cannot totally be ruled out (Table S4).

285           For the number of siliques, we found directional positive additive-by-additive epistasis.  
286   In the short-term, directional positive epistasis tend to increase the amount of additive variance  
287   of a quantitative trait, and, as a result, the adaptive potential of a population (Carter *et al.*, 2005;  
288   Monnahan & Kelly, 2015). In the long-term, when epistasis is positive on average, the evolution  
289   of a phenotypic trait is easier in the direction of high values, because the additive variance tends  
290   to increase with the phenotypic value (Le Rouzic, 2014).

291           In addition, and for both traits, selfing populations are expected to harbor a lot of cryptic  
292   diversity through genetic associations and linkage disequilibrium (Rieseberg *et al.*, 1999, 2003;  
293   Lande & Porcher, 2015; Abu Awad & Roze, 2018), and that this diversity can fuel the mid-  
294   term evolvability of selfing populations by rare outcrossing events (Clo *et al.*, 2020). The  
295   potential contribution of linkage disequilibrium to evolvability can be measured through the  
296   patterns of transgressive segregation in the recombinant generations of crosses ( $F_2$ ,  $F_3$  ...),  
297   knowing that a fraction of the fraction is environmental, which can be easily measured by the  
298   variance within inbred lines, for example.

299

## 300   **Limits of the method**

301

302           Our line cross analysis makes it possible to test for the presence of directional  
303   dominance and epistasis, it suffers from technical limitations, and potential biases. First, it  
304   allows us to test for directional epistasis, which is primordial for understanding the capacity of  
305   populations to respond to selection, but do not allow to dissection the different forms of epistasis  
306   (additive-by-additive, additive-by-dominant, and dominant-by-dominant). For inferring all  
307   these parameters from cross-line analyses, ones need more generations of crosses than just the  
308    $F_1$  and  $F_2$  individuals (see (Lynch & Walsh, 1998), including reciprocal back-crosses for

309 example (see Oakley *et al.*, 2015 for a case study). Another major limitation is that our method  
310 does not allow to differentiate complex patterns of dominance and epistasis. Clo *et al.* (2021),  
311 using a similar crossing scheme in the predominantly selfing species *Medicago truncatula*,  
312 theoretically showed that it is impossible to distinguish epistasis components involving  
313 dominance (such as dominance-by-additive and dominance-by-dominance) from non-epistatic  
314 dominance using cross-line analysis. This means that the directional positive dominance we  
315 detected for the dry weight could be a mixture of directional negative dominance and epistasis,  
316 or just complex epistasis (beyond additive-by-additive interaction effects).

317

## 318 CONCLUSIONS

319

320 Our study highlights the need to study the contribution of non-additive genetic effects  
321 to the genetic architecture of fitness-related traits. Here, we found that both dominance and  
322 epistasis contribute to the genetic architecture of dry weight and silique production, leading to  
323 heterosis for the dry mass and outbreeding depression for the number of siliques in  $F_1$  and  $F_2$   
324 hybrids, and suggesting that the adaptive potential of our Alpine populations of *A. thaliana*  
325 cannot be described only by the additive genetic variance. The next step could be to determine  
326 the contribution of non-additive genetic variance to the evolvability of the fitness traits of our  
327 populations.

328

329 **Data availability:** The data and code used to perform the analyses are available at  
330 <https://github.com/lerouziC/Epicross>.

331

332 **BIBLIOGRAPHY**

- 333 Abbott, R.J. & Gomes, M.F. 1989. Population genetic structure and outcrossing rate of  
334 *Arabidopsis thaliana* (L.) Heynh. *Heredity* **62**: 411–418. Nature Publishing Group.
- 335 Abu Awad, D. & Roze, D. 2018. Effects of partial selfing on the equilibrium genetic variance,  
336 mutation load, and inbreeding depression under stabilizing selection. *Evolution* **72**:  
337 751–769. Wiley Online Library.
- 338 Anderson, D. & Burnham, K. 2004. Model selection and multi-model inference. *Second. NY:*  
339 *Springer-Verlag* **63**: 10.
- 340 Bakerlee, C.W., Nguyen Ba, A.N., Shulgina, Y., Rojas Echenique, J.I. & Desai, M.M. 2022.  
341 Idiosyncratic epistasis leads to global fitness–correlated trends. *Science* **376**: 630–635.  
342 American Association for the Advancement of Science.
- 343 Banta, J.A. & Richards, C.L. 2018. Quantitative epigenetics and evolution. *Heredity* **121**:  
344 210–224. Nature Publishing Group.
- 345 Barth, S., Busimi, A.K., Utz, H.F. & Melchinger, A.E. 2003. Heterosis for biomass yield and  
346 related traits in five hybrids of *Arabidopsis thaliana* L. Heynh. *Heredity* **91**: 36–42.  
347 Nature Publishing Group.
- 348 Bergelson, J., Stahl, E., Dudek, S. & Kreitman, M. 1998. Genetic variation within and among  
349 populations of *Arabidopsis thaliana*. *Genetics* **148**: 1311–1323. Oxford University  
350 Press.
- 351 Carter, A.J., Hermisson, J. & Hansen, T.F. 2005. The role of epistatic gene interactions in the  
352 response to selection and the evolution of evolvability. *Theoretical population biology*  
353 **68**: 179–196. Elsevier.
- 354 Charlesworth, D. & Willis, J.H. 2009. The genetics of inbreeding depression. *Nature reviews*  
355 *genetics* **10**: 783–796. Nature Publishing Group.
- 356 Cheverud, J.M. & Routman, E.J. 1995. Epistasis and its contribution to genetic variance  
357 components. *Genetics* **139**: 1455–1461. Genetics Soc America.
- 358 Clo, J., Gay, L. & Ronfort, J. 2019. How does selfing affect the genetic variance of  
359 quantitative traits? An updated meta-analysis on empirical results in angiosperm  
360 species. *Evolution* **73**: 1578–1590. John Wiley & Sons, Ltd.
- 361 Clo, J. & Opedal, Ø.H. 2021. Genetics of quantitative traits with dominance under stabilizing  
362 and directional selection in partially selfing species. *Evolution* **75**: 1920–1935. John  
363 Wiley & Sons, Ltd.
- 364 Clo, J., Ronfort, J. & Abu Awad, D. 2020. Hidden genetic variance contributes to increase the  
365 short-term adaptive potential of selfing populations. *Journal of Evolutionary Biology*  
366 **33**: 1203–1215. John Wiley & Sons, Ltd.



- 367 Clo, J., Ronfort, J. & Gay, L. 2021. Fitness consequences of hybridization in a predominantly  
368 selfing species: insights into the role of dominance and epistatic incompatibilities.  
369 *Heredity* **127**: 393–400.
- 370 Cockerham, C.C. & Weir, B.S. 1984. Covariances of relatives stemming from a population  
371 undergoing mixed self and random mating. *Biometrics* 157–164. JSTOR.
- 372 Crow, J.F. 2010. On epistasis: why it is unimportant in polygenic directional selection.  
373 *Philosophical Transactions of the Royal Society B: Biological Sciences* **365**: 1241–  
374 1244. The Royal Society.
- 375 Dolgin, E.S., Charlesworth, B., Baird, S.E. & Cutter, A.D. 2007. Inbreeding and outbreeding  
376 depression in *Caenorhabditis* nematodes. *Evolution: International Journal of Organic*  
377 *Evolution* **61**: 1339–1352. Wiley Online Library.
- 378 Falconer, D.S. 1996. *Introduction to quantitative genetics*. Pearson Education India.
- 379 Falconer, D.S. & Mackay, T.F.C. 1996. *Introduction to quantitative genetics*. Essex. UK:  
380 *Longman Group*.
- 381 Gimond, C., Jovelin, R., Han, S., Ferrari, C., Cutter, A.D. & Braendle, C. 2013. Outbreeding  
382 depression with low genetic variation in selfing *Caenorhabditis* nematodes. *Evolution*  
383 **67**: 3087–3101. Wiley Online Library.
- 384 Hansen, T.F. 2015. Measuring gene interactions. *Epistasis* 115–143. Springer.
- 385 Hansen, T.F. 2013. Why epistasis is important for selection and adaptation. *Evolution* **67**:  
386 3501–3511. Wiley Online Library.
- 387 Hoffmann, M.H. 2002. Biogeography of *Arabidopsis thaliana* (L.) heynh.(Brassicaceae).  
388 *Journal of Biogeography* **29**: 125–134. Wiley Online Library.
- 389 Johansen-Morris, A.D. & Latta, R.G. 2006. Fitness consequences of hybridization between  
390 ecotypes of *Avena barbata*: hybrid breakdown, hybrid vigor, and transgressive  
391 segregation. *Evolution* **60**: 1585–1595. Wiley Online Library.
- 392 Kelly, J.K. 1999. Response to selection in partially self-fertilizing populations. I. Selection on  
393 a single trait. *Evolution* **53**: 336–349. Wiley Online Library.
- 394 Kelly, J.K. & Arathi, H.S. 2003. Inbreeding and the genetic variance in floral traits of  
395 *Mimulus guttatus*. *Heredity* **90**: 77–83. Nature Publishing Group.
- 396 Kouyos, R.D., Silander, O.K. & Bonhoeffer, S. 2007. Epistasis between deleterious mutations  
397 and the evolution of recombination. *Trends in ecology & evolution* **22**: 308–315.  
398 Elsevier.
- 399 Lande, R. & Porcher, E. 2015. Maintenance of quantitative genetic variance under partial self-  
400 fertilization, with implications for evolution of selfing. *Genetics* **200**: 891–906. Oxford  
401 University Press.
- 402 Le Rouzic, A. 2014. Estimating directional epistasis. *Frontiers in Genetics* **5**: 198.

- 403 Li, Y., van Kleunen, M. & Stift, M. 2019. Sibling competition does not magnify inbreeding  
404 depression in North American *Arabidopsis lyrata*. *Heredity* **123**: 723–732. Nature  
405 Publishing Group.
- 406 Luo, Y., Widmer, A. & Karrenberg, S. 2015. The roles of genetic drift and natural selection in  
407 quantitative trait divergence along an altitudinal gradient in *Arabidopsis thaliana*.  
408 *Heredity* **114**: 220–228. Nature Publishing Group.
- 409 Lynch, M. & Walsh, B. 1998. *Genetics and analysis of quantitative traits*. Sinauer  
410 Sunderland, MA.
- 411 Maisnier-Patin, S., Roth, J.R., Fredriksson, Å., Nyström, T., Berg, O.G. & Andersson, D.I.  
412 2005. Genomic buffering mitigates the effects of deleterious mutations in bacteria.  
413 *Nature genetics* **37**: 1376–1379. Nature Publishing Group US New York.
- 414 Monnahan, P.J. & Kelly, J.K. 2015. Epistasis is a major determinant of the additive genetic  
415 variance in *Mimulus guttatus*. *PLoS Genet* **11**: e1005201. Public Library of Science.
- 416 Nasrallah, M.E., Yogeewaran, K., Snyder, S. & Nasrallah, J.B. 2000. *Arabidopsis* species  
417 hybrids in the study of species differences and evolution of amphiploidy in plants.  
418 *Plant Physiology* **124**: 1605–1614. American Society of Plant Biologists.
- 419 Oakley, C.G., Aagren, J. & Schemske, D.W. 2015. Heterosis and outbreeding depression in  
420 crosses between natural populations of *Arabidopsis thaliana*. *Heredity* **115**: 73–82.  
421 Nature Publishing Group.
- 422 Pavlicev, M., Le Rouzic, A., Cheverud, J.M., Wagner, G.P. & Hansen, T.F. 2010.  
423 Directionality of epistasis in a murine intercross population. *Genetics* **185**: 1489–1505.  
424 Oxford University Press.
- 425 Phillips, P.C., Otto, S.P., Whitlock, M.C., Wolf, J.D., Brodie, E.D.I. & Wade, M.J. 2000.  
426 Beyond the average: the evolutionary importance of gene interactions and variability  
427 of epistatic effects. *Epistasis and the evolutionary process* 20–38. Oxford University  
428 Press New York.
- 429 Picó, F.X., Méndez-Vigo, B., Martínez-Zapater, J.M. & Alonso-Blanco, C. 2008. Natural  
430 genetic variation of *Arabidopsis thaliana* is geographically structured in the Iberian  
431 peninsula. *Genetics* **180**: 1009–1021. Oxford University Press.
- 432 Rhode, J.M. & Cruzan, M.B. 2005. Contributions of heterosis and epistasis to hybrid fitness.  
433 *The American Naturalist* **166**: E124–E139. The University of Chicago Press.
- 434 Rieseberg, L.H., Archer, M.A. & Wayne, R.K. 1999. Transgressive segregation, adaptation  
435 and speciation. *Heredity* **83**: 363–372. Nature Publishing Group.
- 436 Rieseberg, L.H., Widmer, A., Arntz, A.M. & Burke, B. 2003. The genetic architecture  
437 necessary for transgressive segregation is common in both natural and domesticated  
438 populations. *Philosophical Transactions of the Royal Society of London. Series B:*  
439 *Biological Sciences* **358**: 1141–1147. The Royal Society.

- 440 Shaw, R.G., Byers, D.L. & Shaw, F.H. 1998. Genetic components of variation in *Nemophila*  
441 *menziesii* undergoing inbreeding: morphology and flowering time. *Genetics* **150**:  
442 1649–1661. Oxford University Press.
- 443 Sprague, G.F. & Tatum, L.A. 1942. General vs. specific combining ability in single crosses of  
444 corn. *Journal of the American Society of Agronomy*.
- 445 Vasseur, F., Fouqueau, L., De Vienne, D., Nidelet, T., Violle, C. & Weigel, D. 2019.  
446 Nonlinear phenotypic variation uncovers the emergence of heterosis in *Arabidopsis*  
447 *thaliana*. *PLoS biology* **17**: e3000214. Public Library of Science San Francisco, CA  
448 USA.
- 449 Volis, S., Shulgina, I., Zaretsky, M. & Koren, O. 2011. Epistasis in natural populations of a  
450 predominantly selfing plant. *Heredity* **106**: 300–309. Nature Publishing Group.
- 451 Walsh, B. & Lynch, M. 2018. *Evolution and selection of quantitative traits*. Oxford  
452 University Press.
- 453 Wright, A.J. & Cockerham, C.C. 1985. Selection with partial selfing. I. Mass selection.  
454 *Genetics* **109**: 585–597. Genetics Soc America.
- 455 Younginger, B.S., Sirová, D., Cruzan, M.B. & Ballhorn, D.J. 2017. Is biomass a reliable  
456 estimate of plant fitness? *Applications in Plant Sciences* **5**: 1600094. John Wiley &  
457 Sons, Ltd.
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468 **Table 1.** Summary of the statistical models fitted to data, when analyses are performed at the  
469 scale of genetic lines, for the dry weight and the number of siliques. In the table, “a” stands for  
470 additive, “d” for dominance, and “aa” for additive-by-additive epistasis.

Trait	Model	Log(likelihood)	d.f.	$\Delta$ AIC
Dry weight	a	535.20	28	60.84
	a.d	630.62	93	0.00
	a.aa	625.43	91	6.38
	a.d.aa	683.88	151	9.48
Number of siliques	a	-10729.13	28	98.10
	a.d	-10624.23	93	18.31
	a.aa	-10617.08	91	0.00
	a.d.aa	-10574.11	151	34.06

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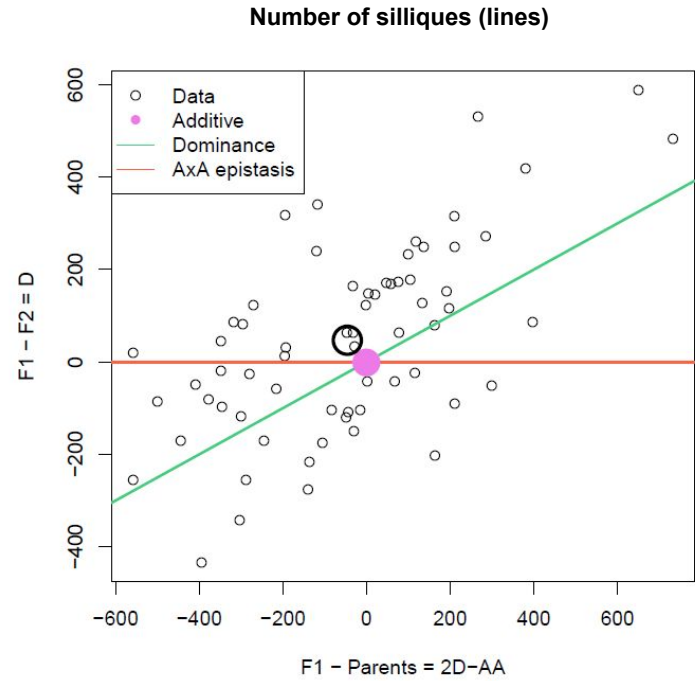
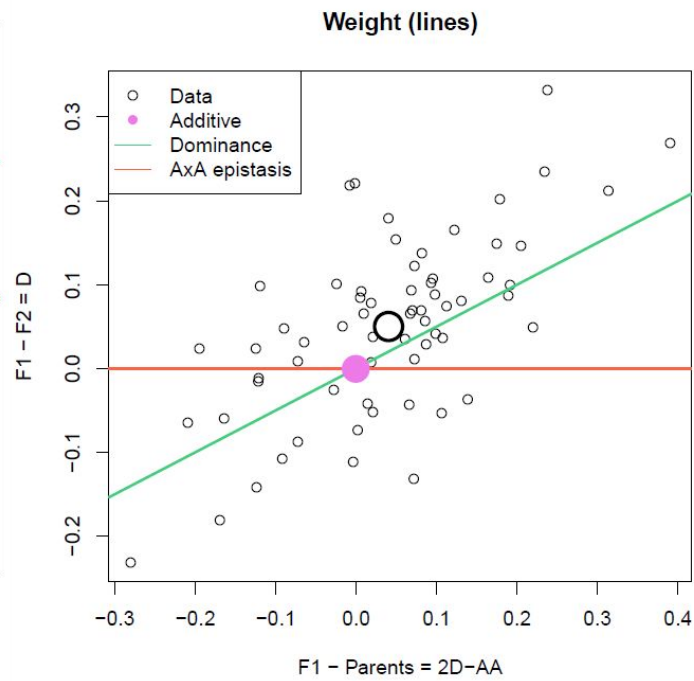
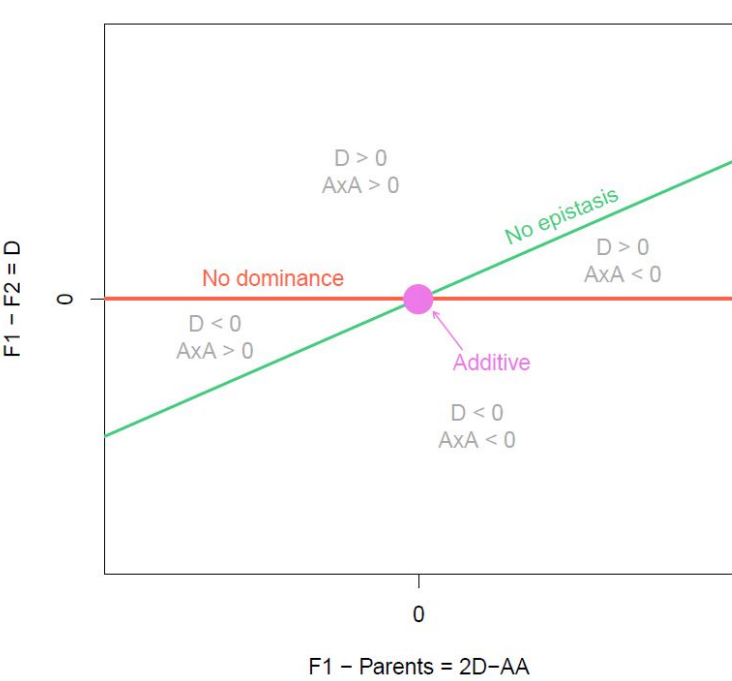
480 **Figure captions:**

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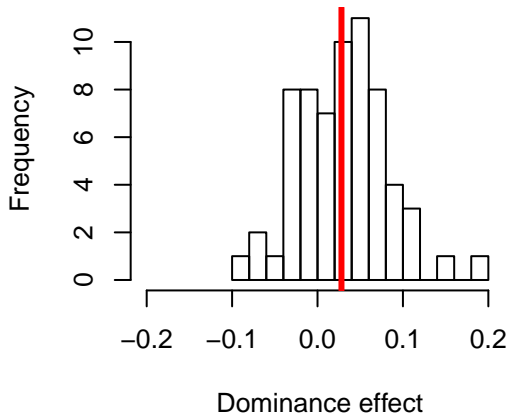
482 **Figure 1.** Graphical representation of the parental,  $F_1$  and  $F_2$  values, when analyses are  
483 performed at the scale of the genetic lineages. **Left panel.** Empty representation indicating the  
484 directionality of dominance and epistasis as a function of the position of the datapoints. **Middle**  
485 **panel.** Distribution of data for the dry weight. **Right panel.** Distribution of data for the number  
486 of siliques. The Data circle represent the barycenter of the datapoints.

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488 **Figure 2.** Distribution of the dominance and epistatic genetic effects when analyses are  
489 performed at the scale of the genetic lineages, for the dry weight and the number of siliques.  
490 The red lines are indicating mean values.



### Weight



### Number of siliques

