Heterosis indices: What do they really measure?

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Highlight

Unlike dominance indices, heterosis indices, with one exception, do not properly measure the level of deviation from additivity, thus making them unsuitable for comparative analyses.

Abstract

Heterosis (hybrid vigour) is a universal phenomenon of crucial agro-economic and evolutionary importance. We show that the most common heterosis indices do not properly measure deviation from additivity because they include both a component accounting for "real" heterosis and a term that is not related to heterosis since it is derived solely from parental values. Therefore, these indices are inadequate when the aim of the study is to compare heterosis levels between different traits, environments, genetic backgrounds or developmental stages, as these factors may affect not only heterosis but also parental values. The only relevant index for such comparisons is the so-called "potence ratio". These observations argue for the careful choice of heterosis indices depending on the purpose of the work.

Key words: Flowering, growth rate, heterosis index, hybrid vigour, maize, non-additivity, yield.

Introduction

Non-linear processes are extremely common in biology. In particular, genotype-phenotype or phenotype-phenotype relationships frequently display concave behaviours, resulting in the dominance of "high" over "low" alleles (Wright, 1934) and in positive heterosis for a wide range of polygenic traits (Fiévet *et al.*, 2018; Vasseur *et al.*, 2019). Properly quantifying the degree of non-additivity is an essential prerequisite for interpreting and

comparing genetic studies and for making predictions in plant and animal breeding. However, most of the classical heterosis indices do not meet this requirement.

First, let us recap how the degree of dominance is measured. There are two classical dominance indices:

(i) Wright (1934) defined:

$$D_{\mathrm{W}} = \frac{z_2 - z_{12}}{z_2 - z_1}$$

where z_1, z_2 and z_{12} are respectively the phenotypic values of genotypes A_1A_1, A_2A_2 and A_1A_2, with $z_2 > z_1$. D_{W} varies from 0, when A_2 is fully dominant over A_1, to 1, when A_2 is fully recessive with respect to A_1. $D_{\mathrm{W}} = 0.5$ corresponds to semi-dominance or additivity ($z_{12} = \frac{z_1+z_2}{2}$) (Table 1). Note that D_{W} is strictly equivalent to the dominance coefficient h used in evolutionary genetics (Crow & Kimura, 1970).

(ii) Falconer (1960) proposed the following index:

$$D_{\mathrm{F}} = \frac{z_{12} - \bar{z}}{\frac{z_2 - z_1}{2}}$$

where $\bar{z} = \frac{z_1+z_2}{2}$. D_{F} varies in the opposite direction to D_{W}: its value is 1 if $z_{12} = z_2$ (complete dominance of A_2 over A_1), -1 if $z_{12} = z_1$ (A_2 is fully recessive with respect to A_1) and 0 if there is additivity. In the case of overdominance, $D_{\mathrm{W}} < 0$ and $D_{\mathrm{F}} > 1$, and in the case of underdominance, $D_{\mathrm{W}} > 1$ and $D_{\mathrm{F}} < -1$ (Table 1).

The D_{W} and D_{F} indices are linearly related:

$$D_{\mathrm{F}} = 1 - 2D_{\mathrm{W}}$$

Thus, dominance can be quantified with either index, both of them giving the position of the heterozygote relative to the parental homozygotes. The

two indices merely vary in opposite directions, with D_{W} decreasing when dominance increases.

For polygenic traits, either index could be used to quantify non-additivity, *i.e.* real heterosis, without any ambiguity. Actually, one finds five heterosis indices in the literature (see their characteristic values in Table 1).

The two most popular indices are the best-parent (BP) and mid-parent (MP) heterosis indices (*e.g.* Gowen, 1952; Frankel, 1983):

$$H_{\mathrm{BP}} = \frac{z_{12} - z_2}{z_2}$$

$$H_{\mathrm{MP}} = \frac{z_{12} - \bar{z}}{\bar{z}}$$

where z_2, z_{12} and $\bar{z}$ are respectively the phenotypic values of the parent 2 (with $z_2 > z_1$), of the parent 1 $\times$ parent 2 hybrid and of the parental mean.

In some instances, the authors do not normalize the difference between the hybrid and the best- or mid-parent value:

$$H_{\mathrm{bp}} = z_{12} - z_2$$

$$H_{\mathrm{mp}} = z_{12} - \bar{z}$$

Finally, the so-called "potence ratio" (Mather, 1949) has the same expression as Falconer's dominance index:

$$H_{\mathrm{PR}} = \frac{z_{12} - \bar{z}}{\frac{z_2 - z_1}{2}}.$$

A value of 0 indicates additivity, 1 indicates $z_{12} = z_2$ (hybrid value = best-parent value), -1 indicates $z_{12} = z_1$ (hybrid value = worst-parent value) and > 1 (resp. < -1) indicates best-parent (resp. worst-parent) heterosis (Table 1). H_{PR} includes the values of the three genotypes, whereas the other indices lack one of the parental values (H_{BP} and H_{bp}) or both (H_{MP}

and H_{mp}). From a genetic point of view, H_{PR} is explicitly expressed in terms of the five genetic effects contributing to heterosis (Supplementary Table S1). Thus, the potence ratio, which is still by far the least used heterosis index, is the only one that informs us of the exact position of the hybrid value relative to the parental values. Wright's dominance index has the same property, but its inverse direction of variation, which makes comparisons less easy, probably explains why it is not used in this context.

Relationship between the potence ratio and the other heterosis indices

It is easy to show that the relationship between H_{PR}, hereafter noted h_{P} for simplicity, and the other indices is (with $z_2 > z_1$):

$$H_{\mathrm{MP}} = h_{\mathrm{P}} \left(\frac{z_2 - z_1}{z_1 + z_2} \right) = h_{\mathrm{P}} z_{\mathrm{m}} \tag{1}$$

$$H_{\mathrm{BP}} = \left(\frac{-1 + h_{\mathrm{P}}}{2} \right) \left(\frac{z_2 - z_1}{z_2} \right) = \left(\frac{-1 + h_{\mathrm{P}}}{2} \right) z_{\mathrm{b}} \tag{2}$$

$$H_{\mathrm{mp}} = h_{\mathrm{P}} \left(\frac{z_2 - z_1}{2} \right) = h_{\mathrm{P}} \bar{z} z_{\mathrm{m}} \tag{3}$$

$$H_{\mathrm{bp}} = \left(\frac{-1 + h_{\mathrm{P}}}{2} \right) (z_2 - z_1) = \left(\frac{-1 + h_{\mathrm{P}}}{2} \right) z_2 z_{\mathrm{b}} \tag{4}$$

where $z_{\mathrm{m}} = \frac{z_2 - z_1}{z_1 + z_2}$ is the variation coefficient (σ/μ) of the trait in the parents and $z_{\mathrm{b}} = \frac{z_2 - z_1}{z_2}$ is the difference between the parents normalized by the best-parent value (or $z_{\mathrm{b}} = 2\sigma/z_2$).

For a given h_{P} value, the indices H_{MP} and H_{BP} are linearly related to z_{m} and z_{b}, respectively, *i.e.* they depend on the scale of the parental values. More specifically, the relationship between H_{MP} and z_{m} is negative when $h_{\mathrm{P}} < 0$ and positive when $h_{\mathrm{P}} > 0$, while the relationship between H_{BP} and z_{b} is negative when $h_{\mathrm{P}} < 1$ and positive when $h_{\mathrm{P}} > 1$. As z_{m} and

z_b are positive, we see from equation 1 that for $h_\mathrm{P} \neq 0$, we have

$$0 < H_\mathrm{MP} < h_\mathrm{P} \quad \text{if } h_\mathrm{P} > 0 \ \text{ (positive mid-parent heterosis)}$$

and

$$h_\mathrm{P} < H_\mathrm{MP} < 0 \quad \text{if } h_\mathrm{P} < 0 \ \text{ (negative mid-parent heterosis)}$$

Regarding H_BP, we see from equation 2 that for $h_\mathrm{P} \neq 1$, we have

$$0 < H_\mathrm{BP} < \left(\frac{-1 + h_\mathrm{P}}{2}\right) \quad \text{if } h_\mathrm{P} > 1 \ \text{ (positive best-parent heterosis)}$$

and

$$\left(\frac{-1 + h_\mathrm{P}}{2}\right) < H_\mathrm{BP} < 0 \quad \text{if } h_\mathrm{P} < 1 \ \text{ (negative best-parent heterosis)}$$

If $h_\mathrm{P} = 0$ (resp. $h_\mathrm{P} = 1$), H_MP (resp. H_BP) $= 0$.

Numerical applications performed with nine h_P values, from $h_\mathrm{P} = -2$ to $h_\mathrm{P} = 2$, show that the same H_MP or H_BP value can be observed for very different h_P values (Supplementary Figure S1). For instance, $H_\mathrm{MP} \approx 0.4$ can correspond to both mid-parent heterosis ($h_\mathrm{P} = 0.5$, $z_\mathrm{m} \approx 0.8$) and best-parent heterosis ($h_\mathrm{P} = 2$, $z_\mathrm{m} \approx 0.21$).

We illustrate this using experimental data from maize. We measured six traits (flowering time, plant height, ear height, grain yield, thousand-kernel weight and kernel moisture) in four crosses (B73×F252, F2×EP1, F252×EP1, F2×F252) grown in three different environments in France (Saint-Martin-de-Hinx in 2014, Jargeau in 2015 and Rhodon in 2015). We computed h_P, H_MP and H_BP for the 72 trait-cross-environment combinations. Fig. 1A,B shows that the relationship between h_P and the other two indices is very loose, if any. A given h_P value can correspond to a wide range

of H_{MP} or H_{BP} values, and vice versa. We performed the same analyses using the data published by Shang *et al.* (2016), who measured five traits in two crosses of cotton grown in three environments. The same loose relationship between h_{P} and either heterosis index was observed (Fig. 1C,D). This means that the trait variation coefficients or the normalized difference between the parents, which are not related to heterosis since they do not include values from the hybrids, markedly affect H_{MP} and H_{BP}.

Regarding the H_{mp} and H_{bp} indices, which are not dimensionless, they only provide the direction of heterosis. For a given h_{P} value, H_{mp} can vary from $-\infty$ to 0 when $h_{\mathrm{P}} < 0$ and from 0 to $+\infty$ when $h_{\mathrm{P}} > 0$, and H_{bp} can vary from $-\infty$ to 0 when $h_{\mathrm{P}} < 1$ and from 0 to $+\infty$ when $h_{\mathrm{P}} > 1$ (equations 3 and 4).

Let us examine the possible interpretation errors that may result from the use of the most common heterosis indices.

The pitfalls of the most commonly used heterosis indices

The non-univocal relationship between h_{P} and the most commonly used heterosis indices has two consequences. (i) Comparing index values for a given trait in different crosses and/or environments and/or developmental stages leads to erroneous conclusions whenever these factors have an effect on the scale of the trait and/or on the difference between the parental values (*i.e.* on z_{m} or z_{b}). Possible differences in actual heterosis levels between these conditions cannot be detected. (ii) This problem is even more pronounced when studying different traits because each trait has its own scale of variation, making H_{MP} and H_{BP} (and to a greater extent H_{mp} and H_{bp}) useless for comparing the real levels of heterosis of these traits.

These pitfalls can easily be illustrated from our maize dataset. Fig. 2A

shows that classifying a set of traits according to their degree of heterosis can give markedly different results depending on whether one uses the h_{P} index or one of the two indices H_{MP} and H_{BP}. For instance, in the F252×EP1 cross, flowering time displays moderate heterosis according to H_{MP} and H_{BP} even though this trait actually has the highest h_{P} value. Conversely, plant height is the second most heterotic trait according to H_{MP} and H_{BP}, but not according to h_{P}. Similarly, comparing heterosis of a given trait in different hybrids results in index-specific rankings: heterosis of ear height measured with h_{P} is highest in the B73×F252 hybrid, whereas according to H_{MP} and H_{BP} the highest values are found in the F252×EP1 hybrid (Fig. 2B). Finally, the effect of the environment on heterosis reveals the same discrepancies between h_{P} on the one hand and H_{MP} or H_{BP} on the other hand (Fig. 2C).

It is also informative to compare the variation of heterosis indices for a trait measured during development or growth. We fitted the percentage of flowering individuals over time in the W117×F192 and W117×F252 hybrids and their parents, using the Hill function:

$$y = \frac{ax^n}{b + x^n}$$

where n is the Hill coefficient. We then computed the variation of heterosis for the percentage of flowering individuals estimated from the fitted curves (Fig. 3). Again, h_{P} tells a different story compared to H_{MP} and H_{BP}. Both H_{MP} and H_{BP} decrease as flowering progresses because the variation coefficient also decreases. This masks the evolution of real heterosis, which actually increases.

Similar results were observed in a simulation describing the increase in population size of a unicellular organism, which exhibits logistic growth.

We used:

$$y = \frac{K}{1 + a\,\mathrm{e}^{-r\theta}}$$

where y is the size of the population, K the carrying capacity, a a constant, r the growth rate and θ the time. We assumed that the parents differed only in their growth rate r and that there is additivity for this parameter. Results show that the variations over time of H_{MP} and H_{BP} index values for population size are clearly not congruent with that of h_{P} (Supplementary Figure S2).

Discussion

If H_{MP} and H_{BP} (and their non-normalized forms H_{mp} and H_{bp}) do not provide reliable information on non-additivity, why are they so commonly used? There are probably both historical and technical reasons: (i) The first scientists who quantified heterosis were plant breeders (Shull, 1908; East, 1936). From an economic perspective, the goal was, and still is, to develop hybrids that are "better" than the best- or mid-parent values for the desired agronomic traits, and not to know where the hybrid value is relative to the parental values. Heterosis indices have been defined accordingly and the habit has remained; (ii) The indices giving the right non-additivity values, h_{P} ($= H_{\mathrm{PR}}$) for heterosis and D_{W} or D_{F} for dominance, can take on high to very high values when the parents are close, due to the small differences $z_2 - z_1$ in the denominator of the fractions. This can produce extreme values that are not easy to represent and manipulate for statistical treatments. Nevertheless, such values are biological realities that convey precisely the inheritance of the traits under study, something that H_{MP}, H_{BP}, H_{mp} and H_{bp} do not. In addition, from a practical point of view, a single index is sufficient to know the position of the hybrid relative to the mid- or best-parent, whereas in a number of studies the authors compute

and comment both H_{MP} and H_{BP} (or H_{mp} and H_{bp}). More importantly, to compare the amplitude of heterosis between traits, developmental stages, crosses or environmental conditions, there is no other choice but to use the only heterosis index – H_{PR} – that is not affected by the scale of the parental values and that accounts for the position of the hybrid in the parental range.

Supplementary data

Table S1. Heterosis indices expressed as functions of genetic effects.

Fig. S1. Influence of the scale of the parental values on H_{MP} and H_{BP} for different values of the potence ratio h_{P}.

Fig. S2. Heterosis for population size (simulations).

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Author contributions

Conceptualization: DdV. Maize experiments: JBF. Data analyses and numerical applications: DdV and JBF. DdV and JBF wrote the manuscript.

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Table 1. Dominance and heterosis indices. D_{W}: Wright's dominance index. D_{F}: Falconer's dominance index. H_{mp}, H_{MP}, H_{PR}, H_{bp} and H_{BP}: heterosis indices. Subscripts: mp or MP, mid-parent; PR, potence ratio; bp or BP, best-parent. In the equations of the text, H_{PR} is also noted h_{P} for simplicity. z_1 (resp. z_2): the phenotypic value of parental homozygote 1 or of parent 1 (resp. 2). z_{12}: the heterozygote or hybrid value. $\bar{z}$: the mean parental value. By convention, $z_2 > z_1$.

Reference	Index	Index scales with their characteristic values
High homozygote	$D_{\mathrm{W}} = \dfrac{z_2 - z_{12}}{z_2 - z_1}$	$z_{12} = z_1$ $z_{12} = \bar{z}$ $z_{12} = z_2$ $+\infty$ 1 0.5 0 $-\infty$ Underdominance Recessivity Additivity Dominance Overdominance
Mean homozygote	$D_{\mathrm{F}} = \dfrac{z_{12} - \bar{z}}{(z_2 - z_1)/2}$	$z_{12} = z_1$ $z_{12} = \bar{z}$ $z_{12} = z_2$ $-\infty$ -1 0 $+1$ $+\infty$ Underdominance Recessivity Additivity Dominance Overdominance
Mid-parent	$H_{\mathrm{mp}} = z_{12} - \bar{z}$	$z_{12} = \bar{z}$ $-\infty$ 0 $+\infty$ Negative heterosis Additivity Mid- or best-parent heterosis
	$H_{\mathrm{MP}} = \dfrac{z_{12} - \bar{z}}{\bar{z}}$	$z_{12} = \bar{z}$ $-\infty$ 0 $+\infty$ Negative heterosis Additivity Mid- or best-parent heterosis
	$H_{\mathrm{PR}} = \dfrac{z_{12} - \bar{z}}{(z_2 - z_1)/2}$	$z_{12} = z_1$ $z_{12} = \bar{z}$ $z_{12} = z_2$ $-\infty$ -1 0 $+1$ $+\infty$ Worst-parent heterosis Negative mid-parent heterosis Additivity Positive mid-parent heterosis Best-parent heterosis
Best-parent	$H_{\mathrm{bp}} = z_{12} - z_2$	$z_{12} = z_2$ $-\infty$ 0 $+\infty$ Non-additivity or additivity Best-parent heterosis
	$H_{\mathrm{BP}} = \dfrac{z_{12} - z_2}{z_2}$	$z_{12} = z_2$ $-\infty$ 0 $+\infty$ Non-additivity or additivity Best-parent heterosis

Figure legends

Figure 1 Relationship between the potence ratio h_{P} and the two heterosis indices H_{MP} and H_{BP}. (A) & (B) Six traits were measured in maize (FLO: flowering time [days between 50 % flowering and August, 12th], PH: plant height, EH: ear height, GY: grain yield, TKW: thousand-kernel weight, KM: kernel moisture) in four crosses (H1: B73×F252, H2: F2×EP1, H3: F252×EP1, H4: F2×F252) grown in three environments in France (E1: Saint-Martin-de-Hinx, E2: Jargeau, E3: Rhodon). (A) Relationship between h_{P} and H_{MP}. (B) Relationship between h_{P} and H_{BP}. (For clarity, four of the 72 trait-cross-environment combinations are not represented because they have high h_{P} values.) (C) & (D) Five traits were measured in cotton (SY: seed yield, LY: lint yield, BNP: bolls per plant, BW: boll weight, LP: lint percent) in two crosses (H1: X1135×GX100-2 and H2: GX1135×VGX100-2) grown in three environments in China (E1: Handan, E2: Cangzhou, E3: Xiangyang) (Data from Shang *et al.*, 2016). (C) Relationship between h_{P} and H_{MP}. (D) Relationship between h_{P} and H_{BP}.

Figure 2 Heterosis values calculated using different indices. (A) Heterosis indices for six traits measured in the F252×EP1 cross grown in Saint-Martin-de-Hinx (France) in 2014. (B) Heterosis indices for ear height in four crosses grown in Saint-Martin-de-Hinx (France) in 2014. (C) Heterosis indices for plant height in the F2×F252 cross grown in the three environments. The six traits and the three environments are the same as in Fig. 1A. The scales of the heterosis indices are normalized by the maximum value in each dataset (figures at the top right of the vertical lines).

Figure 3 Heterosis for flowering in two maize hybrids. (A) Percentage of flowering over time (number of days since January, 1st) for parents W117 and F192 and their hybrid, adjusted with a Hill function. (B) Percentage of flowering over time for parents W117 and F252 and their hybrid. (C) Variations in the heterosis index values for the W117×F192 cross. (D) Variations in the heterosis index values for the W117×F252 cross.

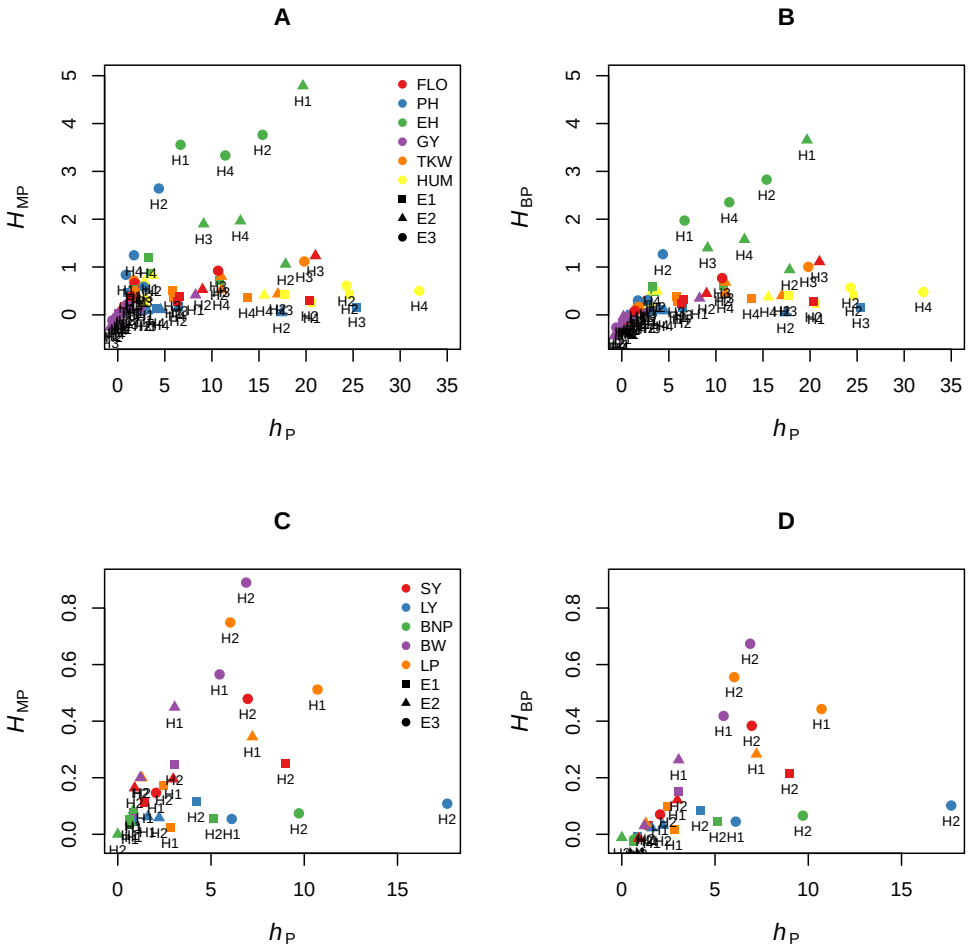

Figure 1. Relationship between the potence ratio h_P and the two heterosis indices H_{MP} and H_{BP}. (A) & (B) Six traits were measured in maize (FLO: flowering time [days between 50 % flowering and August, 12th], PH: plant height, EH: ear height, GY: grain yield, TKW: thousand-kernel weight, KM: kernel moisture) in four crosses (H1: B73×F252, H2: F2×EP1, H3: F252×EP1, H4: F2×F252) grown in three environments in France (E1: Saint-Martin-de-Hinx, E2: Jargeau, E3: Rhodon). (A) Relationship between h_P and H_{MP}. (B) Relationship between h_P and H_{BP}. (For clarity, four of the 72 trait-cross-environment combinations are not represented because they have high h_P values.) (C) & (D) Five traits were measured in cotton (SY: seed yield, LY: lint yield, BNP: bolls per plant, BW: boll weight, LP: lint percent) in two crosses (H1: X1135×GX100-2 and H2: GX1135×VGX100-2) grown in three environments in China (E1: Handan, E2: Cangzhou, E3: Xiangyang) (Data from Shang *et al.*, 2016). (C) Relationship between h_P and H_{MP}. (D) Relationship between h_P and H_{BP}.

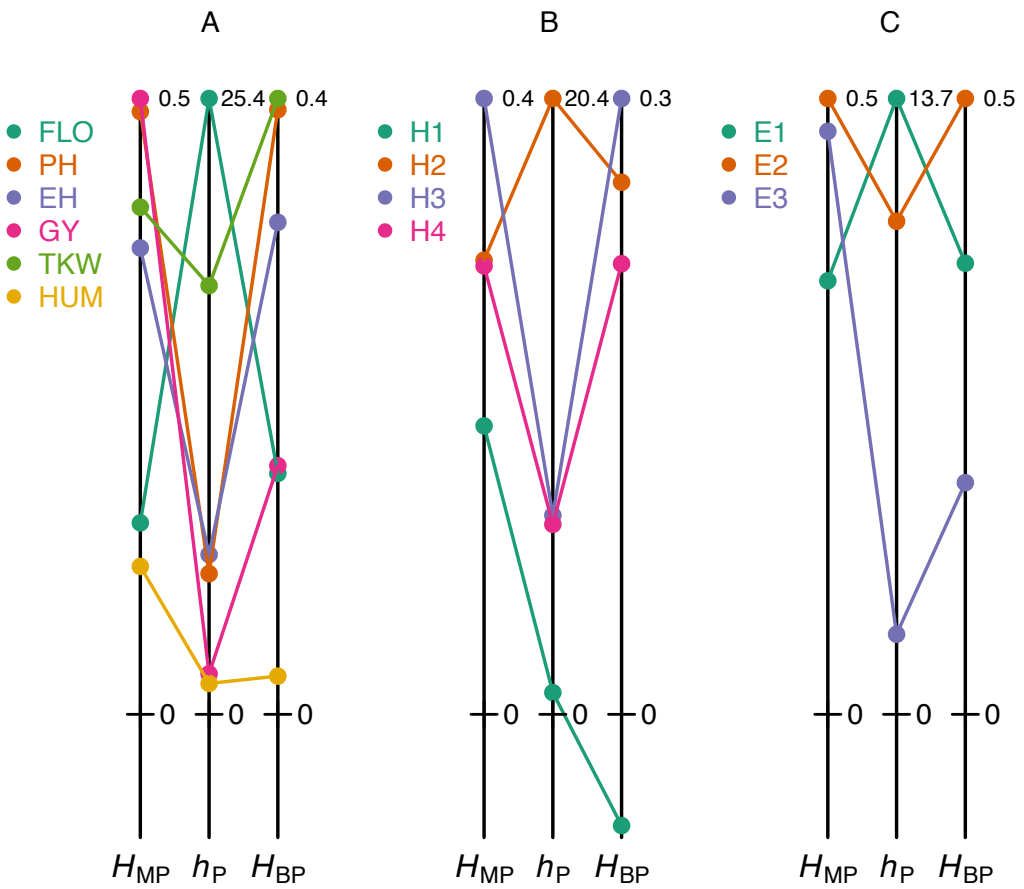

Figure 2. Heterosis values calculated using different indices. (A) Heterosis indices for six traits measured in the F252×EP1 cross grown in Saint-Martin-de-Hinx (France) in 2014. (B) Heterosis indices for ear height in four crosses grown in Saint-Martin-de-Hinx (France) in 2014. (C) Heterosis indices for plant height in the F2×F252 cross grown in the three environments. The six traits and the three environments are the same as in Fig. 1A. The scales of the heterosis indices are normalized by the maximum value in each dataset (figures at the top right of the vertical lines).

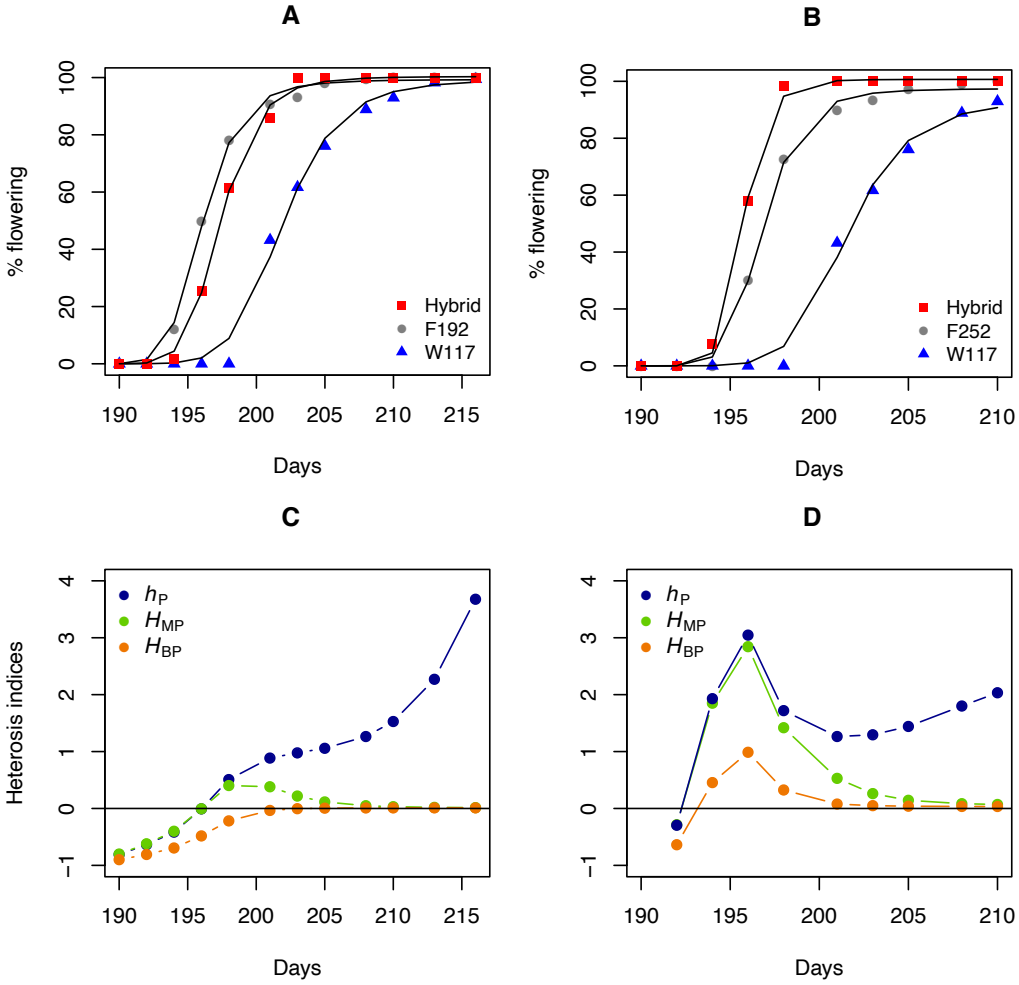

Figure 3. Heterosis for flowering in two maize hybrids. (A) Percentage of flowering over time (number of days since January, 1st) for parents W117 and F192 and their hybrid, adjusted with a Hill function. (B) Percentage of flowering over time for parents W117 and F252 and their hybrid. (C) Variations in the heterosis index values for the W117×F192 cross. (D) Variations in the heterosis index values for the W117×F252 cross.

Supplementary data

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Table S1 Heterosis indices expressed as functions of genetic effects. Subscripts: same as in Table 1. μ, mean of the multilocus homozygous genotypes; $\sum a$, sum of the additive effects; $\sum d$, sum of the dominance effects; $\sum e_{\text{dom}}$, sum of the dominance-by-dominance epistatic effects; $\sum e_{\text{add}}$, sum of the additive-by-additive epistatic effects; $\sum e_{\text{add even}}$, sum of the additive-by-additive epistatic effects involving an even number of genes; $\sum e_{\text{add odd}}$, sum of the additive-by-additive epistatic effects involving an odd number of genes (from Fiévet *et al.*, 2010).

Reference	Index	Index as function of genetic effects
Mid-parent	$H_{\text{mp}} = z_{12} - \overline{z}$	$\sum d + \sum e_{\text{dom}} - \sum e_{\text{add even}}$
	$H_{\text{MP}} = \dfrac{z_{12} - \overline{z}}{\overline{z}}$	$\dfrac{\sum d + \sum e_{\text{dom}} - \sum e_{\text{add even}}}{\mu + \sum e_{\text{add even}}}$
	$H_{\text{PR}} = \dfrac{z_{12} - \overline{z}}{(z_2 - z_1)/2}$	$\dfrac{\sum d + \sum e_{\text{dom}} - \sum e_{\text{add even}}}{\sum a + \sum e_{\text{add odd}}}$
Best-parent	$H_{\text{bp}} = z_{12} - z_2$	$\sum d + \sum e_{\text{dom}} - \sum a - \sum e_{\text{add}}$
	$H_{\text{BP}} = \dfrac{z_{12} - z_2}{z_2}$	$\dfrac{\sum d + \sum e_{\text{dom}} - \sum a - \sum e_{\text{add}}}{\mu + \sum a + \sum e_{\text{add}}}$

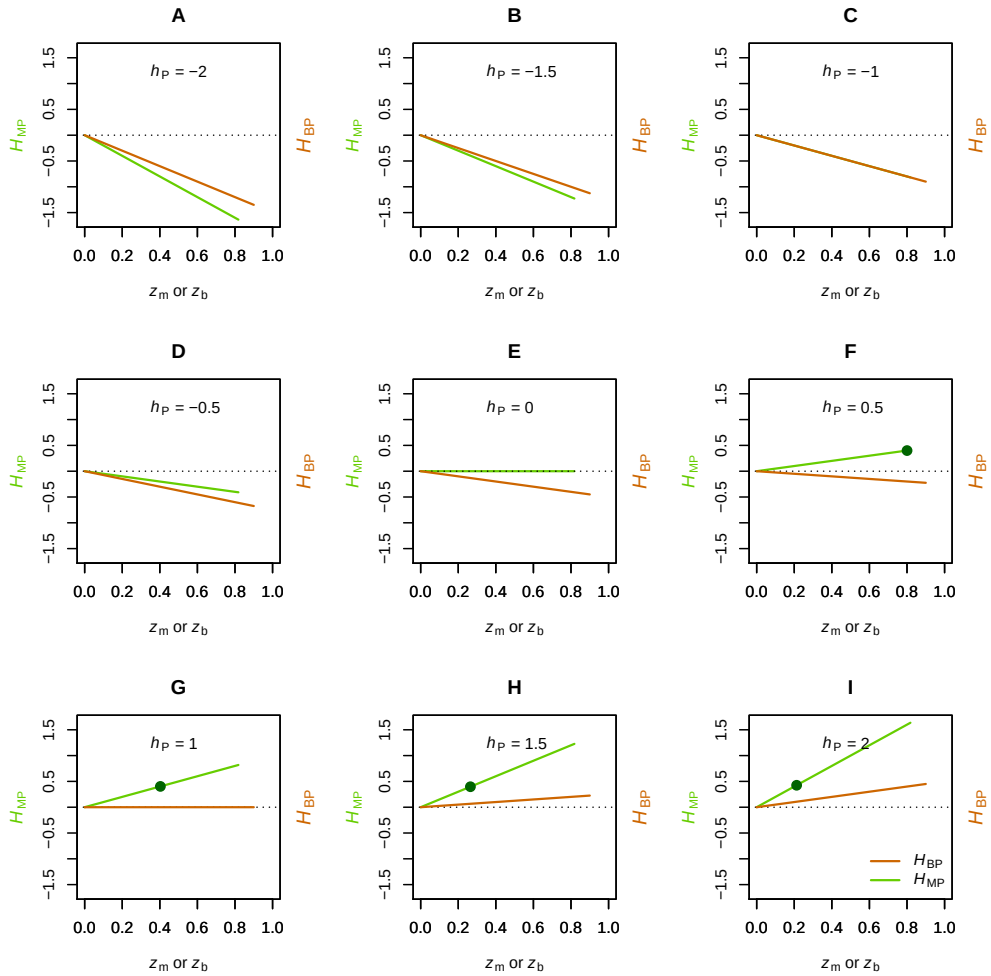

Fig. S1 Influence of the scale of the parental values on H_{MP} and H_{BP} for different values of the potence ratio h_{P}. (A) to (I) h_{P} values from -2 to 2. $z_{\mathrm{m}} = \frac{z_2 - z_1}{z_1 + z_2}$ and $z_{\mathrm{b}} = \frac{z_2 - x_1}{z_2}$, with $z_1 = 1$ and z_2 varying from 1 to 10 (see equations 1 and 2 in the text). Green line: relationship between z_m and H_{MP}. Orange line: relationship between z_{b} and H_{BP}. Dotted line: H_{MP} or $H_{\mathrm{BP}} = 0$. The dark green points show that a given H_{MP} value (≈ 0.4) can be observed for very different h_{P} values, and the same is true for H_{BP}.

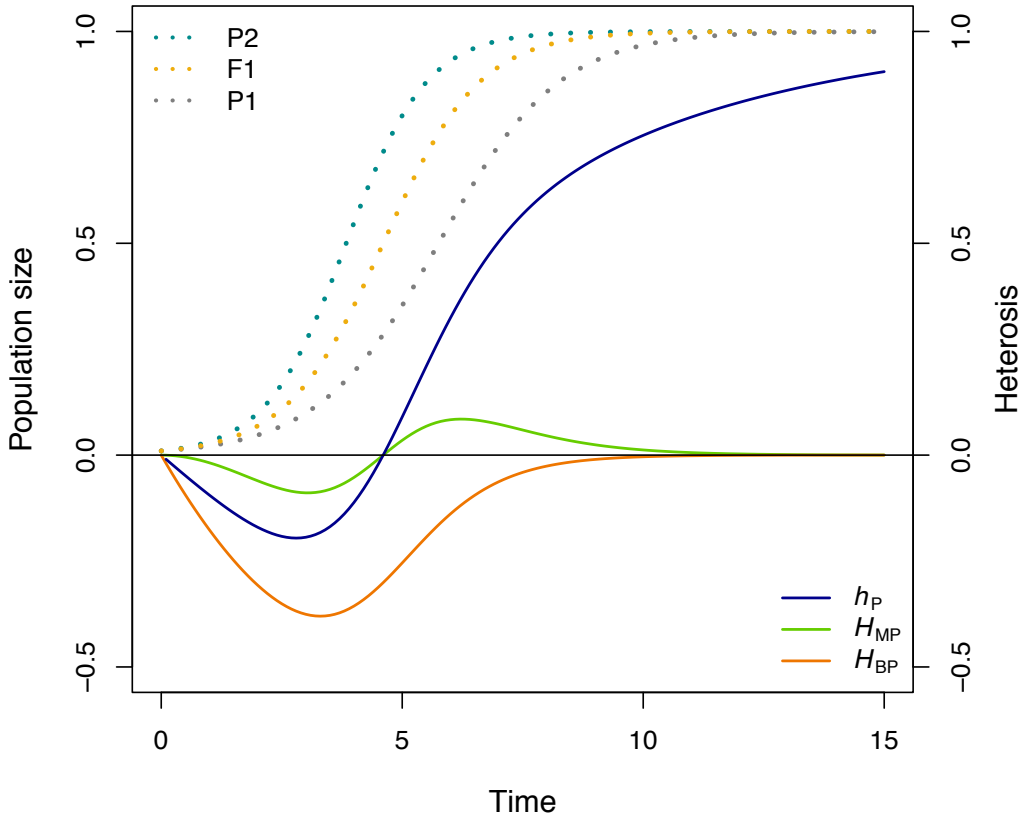

Fig. S2 Heterosis for population size (simulations). Population sizes (dotted curves) follow over time a logistic function with $K = 1$ and $a = 100$ (see text). Parents P1 and P2 and hybrid F1 have respectively growth rates $r = 0.8$, $r = 1.2$ and $r = 1$ (*i.e.* this parameter is considered to be additive). Solid curves: profiles of heterosis indices (right scale).