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Hybrid vigor: The best of both parents, or a genomic clash?

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Abstract

During evolution, mutations produce new lineages that gradually diverge in sequence and regulatory properties. Related strains or species can hybridize to produce viable offspring. Hybrids often outperform their parents, producing more biomass or growing more rapidly. This superior performance, termed heterosis, contrasts the more expected clash between the genomes, and has puzzled geneticists and evolutionary biologists for many years. In this review, we describe two classes of models explaining heterosis: the prevailing view attributes heterosis to rapid repair or enhancement of growth promoting pathways. An alternative view attributes heterosis to the impairment of growth-limiting pathways. The two classes are not mutually exclusive and can result from similar types of genetic interactions. We discuss the possible implications of heterosis on tradeoffs in species evolution.

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Introduction: hybrids and hybrid vigor

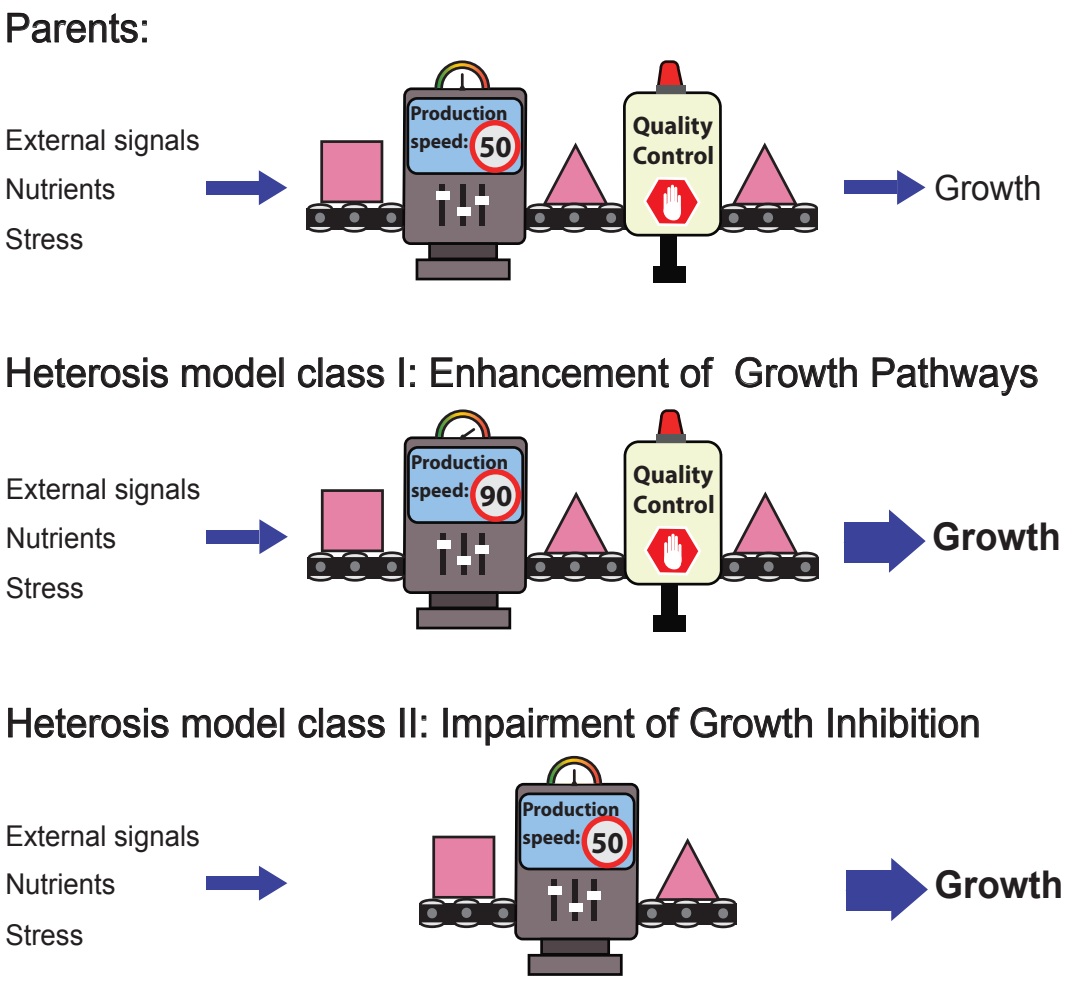
Biological processes maintain a robust function in a wide range of environmental conditions and genetic polymorphism. Perhaps the most striking manifestations of this robustness are cases of inter-species hybridization, where mating of two distinct species generates viable offspring. Thus, despite large-scale differences in the genetic makeup and regulatory properties of the two parents, basic cellular and organismal properties are maintained upon mixing the two genomes. What is the mechanistic basis of hybrid robustness? How is it manifested at the molecular and cellular level? And how can the study of hybrids teach us about genome organization and evolution?

Hybrids are produced upon mating parents from evolutionary related strains or species. Naively, one may expect that the hybrid will present an intermediate physiology, e.g. producing biomass similar to its parents' median. In many cases, however, the hybrid physiology differs greatly from that of its parents [1–3]. New quantitative properties that emerge in hybrids are classified into two categories: properties that indicate *hybrid incompatibility* and properties that indicate *hybrid vigor*. Hybrid incompatibility refers to the expected cases in which the hybrid appears inferior to its parents, likely due to clashes between the two genomes. More surprising, perhaps, are cases of *hybrid vigor*, where the hybrid phenotype appears superior to that of its parents, producing, for example, more biomass, growing more rapidly, or showing increased stress survival [3–6].

Hybrid vigor, also termed heterosis, is ubiquitous in nature, and is observed in all eukaryotic kingdoms including plants, animals and fungi [2,4,7]. It has been exploited for thousands of years in plant and animal breeding in order to increase yield [3,8–11], and in fungi for improving alcoholic drinks, or, more recently, biofuel [4,12–14]. Perhaps the most profound example is maize crops, where hybrids have been used commercially in agriculture for nearly a century in order to increase yield, resulting in hybrid maize currently making up most of the corn yield worldwide [9,15]. Hybridization is also commonly used in order to increase yield in other crops such as rice, sorghum, and sunflower [9]. Heterosis has fascinated scientists since the early days of Darwin [1] and had been extensively researched ever since. Still, its mechanistic basis remains elusive [2]. How could the mixing of two distinct genomes, both of which underwent evolutionary optimization, result in an apparent superior performance? What makes heterosis ubiquitous and what does it tell us about possible constraints and limitations of species evolution?

In this review, we discuss two classes of mechanisms that can explain heterosis (Figure 1). First, the prevailing model attributes hybrid vigor to an effective repair, or enhancement of growth promoting pathways. Such enhancement can be due to compensation of deleterious mutations through heterozygote

Figure 1



Basis of hybrid vigor. We propose to divide the heterosis models in two classes; I. Hybrid growth is stimulated through enhancement or repair of growth promoting pathways. II. Hybrid growth is stimulated through the impairment of growth limiting pathways.

complementation, or to the emergence of new favorable interactions between distinct alleles coming from the two parental genomes [3]. The hybrid is therefore viewed as "better" than its parental strains, and heterosis is considered as the opposite of inbreeding depression, perhaps speeding up evolution. Second, an alternative class of models attributes heterosis to incompatible interactions that impair processes whose role is to limit growth [16]. Within this view, hybrid vigor is an evolutionary non-preferred outcome which is prevented in the parental background through specialized pathways that function as safeguard mechanisms in order to maintain the organism's integrity, for example preventing plant growth in drought conditions, or arresting cell cycle in case of DNA damage. Thus, in this view, what appears as a superior performance is not due to the improvement of growth-promoting pathways but rather to impairment of growth-limiting processes.

Heterosis: enhancement of growth-promoting pathways?

In the prevailing view, heterosis results from effective enhancement, or repair, of growth-promoting pathways [2,3]. Classically, this improvement is explained by repair through the "dominance model" which describes repair of recessive deleterious mutations found in one of the parents, and is viewed as the opposite of inbreeding depression: During inbreeding the inbred strain accumulates recessive deleterious mutations. Such recessive mutations, accumulating differentially in each parent, can then be complemented by dominant alleles coming from the other parents [3,17–20]. This classic model was suggested in the beginning of the 20th century [17,21,22]. Since then, evidence of heterotic loci that adhere to this model were obtained [23,24]. A recent genome-wide study in *Arabidopsis thaliana*, for example, attributed a large part of heterotic loci to dominant effects, directly showing the dominant contribution of a

transcription factor, *AGAMOUS-LIKE 50* (*AGL50*), to heterosis [25].

Effective enhancement of growth promoting pathways can also be achieved through novel heterozygote interactions that emerge in the hybrid, as suggested by the "overdominance", or epistasis models [2,26]. Here, distinct alleles coming from the two strains or species interact to produce a favorable outcome, for example by forming multi-alleles protein complexes with distinct activities. Modified expression levels resulting from divergent regulation in the two strains may further lead to optimal expression pattern and improved performance, as was shown in the case of tomato where a single heterozygous combination in the *SINGLE FLOWER TRUSS* (*SFT*) led to an intermediate, optimal expression level [27] that increased yield by 60% compared to both homozygote parents [28]. Such contribution of dosage effects to heterosis may be more general, as suggested by recent studies [16,29–33].

While the dominance and overdominance models are intuitively appealing, they fail to account for recent experiments, as discussed in Ref. [2]. In short, if heterosis results from the effective repair of growth promoting pathways, it should be most effective when hybridizing strains of sub-optimal performance, and should gradually disappear following breeding that purges deleterious mutations. Contrasting this expectation, long-term improvement of inbred maize parents had limited effect on the heterosis level of their hybrid [9]. Second, heterotic effects in this model, and in particular heterozygote complementation, should lose their effectiveness when hybridizing polyploids, since in dominance–recessive interactions the presence of just one dominant allele is enough for the dominant phenotype. Contrasting this expectation, when comparing two triploid maize hybrids, which differed by the number of genomes coming from each parent, the levels of heterosis did depend on the number of genomes received from each parent [30,33,34].

Large-scale regulatory rewiring in hybrids

The prevailing view therefore attributes heterosis to effective enhancement, or repair of growth promoting pathways through the action of specific alleles that differ between the parents, motivating searches for specific genes and pathways providing the expected compensatory effects. A complementary approach for understanding the consequences of hybridization is to examine more broadly how the mixing of the two genomes impacts regulatory programs. Recent studies have shown that cellular regulatory architecture, such as the transcription program, diverges readily between strains and even more so between related species [35–38]. Since this is the case, what is the effect of mixing the two programs within the hybrid background?

Genome-wide comparisons of transcription programs of a hybrid with that of its parents were performed in multiple models including yeast, *Drosophila* and plants [36,38–41]. In all cases, the hybrid's transcription program was distinct from that of its parents. Our studies of the yeast hybrid, for example, identified a large number of genes whose expression differed between the hybrid and its parents. Most of these genes showed an expression that was intermediate between the two parents, yet ~8% of the genes, mostly associated with respiratory functions, were distinctively induced in the hybrid. Similarly, Arabidopsis hybrids showed a specific down-regulation of defense response pathways and altered abiotic response pathways [39].

A unique expression signature of the hybrids may suggest a broader rewiring not only of gene expression but also of other regulatory properties. Indeed, rewiring was observed also in nucleosome positioning, translation efficiency, protein abundances, methylation, non-coding RNA, and replication program [35,38,42–49]. To examine for rewiring at the phenotypic level, we recently asked whether, at the genomic scale, gene dosage effects differ between hybrids and their parents. This was tested by mapping the profile of dosage-sensitivity in yeast hybrid and in its parent across different conditions [16]. The analysis revealed a distinct pattern of dosage sensitivity in the hybrid, further supporting the view that hybrids undergo a large-scale regulatory rewiring affecting not only their gene expression but also the roles different genes and processes play in defining is physiology and growth.

Heterosis: impairment of growth-inhibiting pathways?

The large-scale regulatory rewiring observed in hybrids is intuitively more consistent with incompatibilities and dysregulation due to genome clashes than with improved performance. Indeed, naively, introducing large-scale changes in an apparently evolved genome is expected to reduce, rather than enhance, evolved functions. However, large-scale rewiring is observed also in hybrids that show strong vigor [16]. How can heterosis be reconciled with large-scale rewiring? One possibility is that the beneficial outcomes of the emerging dominant or overdominant interactions exceed the possible deleterious consequences of the regulatory incompatibility leading to rewiring. Alternatively, heterosis may be inherently linked to rewiring, perhaps even a consequence of this perturbed regulation.

Following this second line of thought, we recently proposed that heterosis should not be viewed as a phenomena opposite to hybrid incompatibly, but as a form of incompatibility, namely a deviation from the evolutionary optimal performance [16]. Within this view, safeguard mechanisms have evolved in species to

specifically prevent extensive vigor in order to maintain the organism's integrity, e.g. limiting excessive production of biomass or too rapid growth under stress conditions. Impairment of these specialized mechanisms in the hybrid, due to incompatible interactions between the two parental genomes, would then produce the apparent vigor phenotype.

In support of this class of models, in our recent study of budding yeast hybrid, we found multiple signs of impaired regulation of growth-related pathways [16]. This includes loss of programmed cell-cycle delays, weakened repression of respiratory metabolism and altered slowdown of growth during stress. This model is further consistent with existing literature in other organisms describing dysregulation of safeguard mechanisms in hybrids [39,40,50]. For example, when hybridizing related wheat species, transposons are induced leading to increased DNA damage [51]. Moreover, reduction in regulation of transposable elements and RNA expression was proposed as a general model for heterosis [43]. In Arabidopsis hybrids, dysregulation was observed in response to drought and disease [39,50]. This model may further explain why, while hybridization is frequent in nature, stabilization of the hybrid state is rare.

Heterosis and tradeoff in evolution

The view of heterosis as an impairment of growth-limiting mechanisms is tightly linked to the notion of tradeoffs in evolution. It assumes that the wild-type phenotype is optimized not only for growth but also for multiple survival-related properties including size homeostasis, defense, stress response or genome integrity, all of which limit growth. This notion of tradeoff between survival and growth is supported by long term experiences in agriculture: During the process of crop and animal breeding, starting with domestication, humans have constantly selected plants and animals for productivity in a way that increased growth, but at a cost of reduced fitness of the species in nature [52,53].

If heterosis indeed results from impairment of growth-limiting pathways, it implies that these protecting mechanisms are more sensitive to hybridization compared to the growth promoting pathways themselves. Indeed, safeguard mechanisms, by their very nature, should be highly tuned to environmental conditions or other adaptation requirements that may differ between species. These mechanisms are therefore likely to be late evolving and therefore differ more greatly between the two parents, compared to the core growth promoting mechanisms, such as metabolic or cell-cycle processes, which they regulate.

Conclusions

Hybridization plays an important role in the emergence of new species. First, new phenotypes that emerge in the hybrid, and in particular its apparent vigor, can help in colonizing unoccupied ecological niches [54–56]. At the same time hybrid incompatibilities can secure reproductive isolation [56–60]. These two properties, vigor and incompatibility, are often considered as two separate, and possibly opposing phenotypes: vigor, being considered as a superior performance, is classically attributed to the effective repair, or enhancement of growth promoting pathways, whereas hybrid incompatibility is attributed to the expected impairment resulting from the clashes between the two distinct genomes.

An alternative view explains hybrid vigor and hybrid incompatibility as being essentially two sides of the same coin: both resulting from impairment of evolved cellular pathways. According to this view, hybrid vigor results from incompatible heterozygote interactions that impair growth-limiting protective mechanisms. This model class shares analogy with the increased growth rate of cancer cells, resulting from dysregulation of growth suppressors [61] through mutations, ionizing radiation or toxic compounds [62–64].

The two classes of models we presented are not mutually exclusive. Further, they both can result from similar type of genetic interactions including overdominance, dosage effects, and epistasis. Still, several reasons lead us to favor the view of heterosis as an impairment of growth-limiting mechanisms. First, it is easier to impair an evolved biological process than to repair it. Second, repair is typically highly specific, target particular genes and pathways, while the apace of alterations leading to impairment is broader, likely including rewiring of general regulatory properties. Third, growth limiting pathways appear less conserved and more specialized, compared to the basic growth promoting pathways. Accordingly, incompatibilities are more likely to impair these pathways as compared to the basic cellular growth pathways.

Further studies are required to establish the relative roles of repair and impairment in heterosis, to pinpoint the mechanistic basis for this counterintuitive, yet abundant property, and to understand its implications for species evolution and for agriculture. These studies are likely to greatly benefit from the emergent of model hybrids such as budding yeast that enable comprehensive genetic and physiological analysis.

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