

Back to the future: implications of genetic complexity for the structure of hybrid breeding programs

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Abstract

Commercial hybrid breeding operations can be described as decentralized networks of smaller, more or less isolated breeding programs. There is further a tendency for the disproportionate use of successful inbred lines for generating the next generation of recombinants, which has led to a series of significant bottlenecks, particularly in the history of the North American and European maize germplasm. Both the decentralization and the disproportionate contribution of inbred lines reduce effective population size and constrain the accessible genetic space. Under these conditions, long-term response to selection is not expected to be optimal under the classical infinitesimal model of quantitative genetics. In this study, we therefore aim to propose a rationale for the success of large breeding operations in the context of genetic complexity arising from the structure and properties of interactive genetic networks. For this, we use simulations based on the NK model of genetic architecture. We indeed found that constraining genetic space through program decentralization and disproportionate contribution of parental inbred lines, is required to expose additive genetic variation and thus facilitate heritable genetic gains under high levels of genetic complexity. These results introduce new insights into why the historically grown structure of hybrid breeding programs was successful in improving the yield potential of hybrid crops over the last century. We also hope that a renewed appreciation for “why things worked” in the past can guide the adoption of novel technologies and the design of future breeding strategies for navigating biological complexity.

Keywords: genetic complexity; hybrid breeding; breeding strategies; long-term genetic gain; historical properties

Introduction

Pioneered by Shull (1908), hybrid breeding is credited as one of the most significant factors for the tremendous productivity increases of major field (Duvick 1999) and horticultural (Silva Dias 2010) crops that enabled food production to keep pace with population growth. Hybrid breeding programs originally were centered around maximum exploitation of heterosis, a phenomenon that remains largely unexplained even after a century of research (East 1936; Lippman and Zamir 2007). This later evolved into the modern concept of hybrid breeding, characterized by its distinctive structuring of germplasm into heterotic groups and patterns (Melchinger and Gumber 1998). Beyond heterotic groups, the structure of commercial hybrid breeding, particularly in major crops like maize, is characterized by the largely isolated and unique sub-heterotic patterns of the major companies (Mikel 2006; Troyer 2009; White et al. 2020) as well as a high degree of decentralization into smaller, more or less disconnected sub-programs within those (Smith et al. 2006; Cooper et al. 2014). Plant breeders further have a tendency for relying on only a small set of elite inbred lines for producing the next generation of recombinants (Rasmusson and Phillips 1997), leading to a series of significant bottleneck events in the history of, for example, the North

American maize germplasm (White et al. 2020). These characteristics drastically reduced the effective population size within breeding programs and are not predicted to be promising strategies under the additive, infinitesimal model of quantitative genetics (Gaynor et al. 2017). Nevertheless, the consistent long-term genetic gain has been demonstrated (Duvick et al. 2004).

To better describe and quantify the observed genetic variation among hybrids, the concept of general and specific combining ability was developed early on (Sprague and Tatum 1942). The former, commonly abbreviated as GCA, is a property of the additive effects of contributing genes and describes the average performance of all hybrids derived from an inbred. The latter, commonly abbreviated as SCA, is a nonadditive residual term that describes the deviation of the performance of a particular hybrid from the expectation based on the parental GCA values.

Running efficient hybrid breeding programs requires a preponderance of additive genetic variation to maximize response to selection in the next generation of inbred lines (Falconer and Mackay 1996) as well as the predictability of hybrid performance from the GCA of inbred lines (Reif et al. 2007). A preponderance of GCA variation also allows identification of inbreds that can serve as parents of several high-performing hybrids. This greatly simplifies production of commercial seed, which is a major challenge

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for many crops (Technow 2019). Therefore, hybrid breeding programs have traditionally relied on maximizing and exploiting GCA variation (Falconer and Mackay 1996; Melchinger 1999; Hallauer et al. 2010).

The historically grown paradigms around hybrid breeding designs and strategies are now being challenged by innovative concepts (e.g., Gaynor et al. 2017; Wallace et al. 2018; Hickey et al. 2019; Voss-Fels et al. 2019; Seye et al. 2020) devised in the wake of technological advances such as whole-genome prediction (Meuwissen et al. 2001), high-throughput phenotyping (Araus and Cairns 2014) and genotyping (Poland and Rife 2012), as well as gene editing (Jaganathan et al. 2018). While some of these concepts, in particular those aiming to “design” superior genotypes using gene editing or targeted recombination technology (Wallace et al. 2018; Brandariz and Bernardo 2019), as opposed to generating and evaluating natural variation in the genetic and environmental context in which it occurs, are highly speculative and might not live up to expectations (Bernardo 2016), it is clear that the next decades will change plant breeding. However, before implementing drastic changes to breeding programs we require a theoretical and simulation framework to explore and understand the structures and strategies that have contributed to the success of long-term genetic gain and germplasm improvement. From this historical basis, we can evaluate novel proposals and draw lessons for design of future breeding strategies.

Empirical reports show a preponderance of additive variation in many wild, domesticated, and laboratory species (Falconer and Mackay 1996; Lynch and Walsh 1998; Hill et al. 2008). This agrees well with published studies showing a preponderance of additive GCA over nonadditive SCA variation in hybrid breeding programs (Technow et al. 2014a; Larièpe et al. 2017). At the same time, however, advances in plant physiology and molecular and systems biology have stimulated a renewed appreciation of the intricate interactions at the molecular, metabolic, and physiological level that underlie complex traits (Carlborg and Haley 2004; Hammer et al. 2006; Phillips 2008; Saha et al. 2011; Wilkins et al. 2016; Jiang et al. 2017). Of particular relevance for hybrid breeding are recent studies indicating that heterosis is an emergent property of complex metabolic networks (Fiévet et al. 2010; Goff 2011; Fiévet et al. 2018; Vacher and Small 2019; Vasseur et al. 2019).

The paradox between the complexity of the underlying biology and the simplicity of the expressed variation can of course be resolved by distinguishing between biological and statistical effects and realizing that the former cannot be inferred from the latter (Wade 2002; Mackay 2014; Huang and Mackay 2016). Statistical effects of genes, as well as their aggregates such as GCA and SCA and their variances depend on the genetic background of the population in which they are evaluated, particularly on allele frequencies and linkage disequilibrium (LD) patterns (Falconer and Mackay 1996). For example, it was shown that, regardless of the underlying genetic architecture, genetic variances in random mating populations are expected to be predominantly additive when genes are at extreme frequencies and LD is high (Hill et al. 2008).

Thus, ratios of additive to nonadditive variation are not intrinsic properties of biological systems but at least partly a function of allele frequencies and LD patterns and thus dependent on breeding strategies (for sake of brevity, the reader is referred to the discussion section “Emergence of additive genetic variance” for a more in depth treatment of this topic). Because of the importance of additive variation for efficient operation of breeding programs, a framework to evaluate and study breeding strategies

should allow for the possibility of additivity arising from high degrees of biological complexity at the genetic level.

In this study, we will use simulations based on the NK model of genetic complexity (Kauffman 1993) to explore two distinctive, historically grown characteristics of hybrid breeding: first its decentralization into smaller, more or less independent sub-programs, and second the disproportional use of superior inbred lines for producing the next generation of recombinants. Our goal thereby is not to make specific recommendations for optimal structuring of programs, but rather to gain an appreciation for the properties of these structures in the context of different degrees of genetic complexity.

Materials and methods

Model of genetic complexity

The NK model, introduced by Kauffman (1993) will form the basis of the simulations. The NK model allows generation of a tunable series of models of trait genetic architecture with increasing dimensionality and complexity by varying the number of genes N (dimensionality) and the degree of interaction among them (K , complexity). The NK framework is an application of graph theory to network interactions (Csaszar 2018). The motivation for considering the genetic architecture of traits as graphs through the NK framework is based on decades of research deciphering the networks related to plant growth, development, and adaptation and ultimately the generation of yield and other output traits in globally important crops such as maize (e.g., Studer et al. 2017), rice (e.g., Wilkins et al. 2016), sorghum (e.g., Li et al. 2018), soybean (e.g., Fang et al. 2017), and wheat (e.g., Harrington et al. 2020). The following section will illustrate this motivation using our first-hand experience with maize as an example.

Following the availability of the complete maize genome sequence and haplotype maps, we have studied the genome to phenotype genetic architecture of many traits in historical and elite maize populations that are relevant to commercial maize breeding. One of the first examples of these was the genetic control of variation for flowering time which in maize relates to the transition of the shoot apical meristem from vegetative to reproductive floral (tassel) development (Dong et al. 2012).

This research generated many insights into the gene regulatory network underlying control of flowering time in maize. Dong et al. (2012) discuss examples of genes that were studied and tested for their combined influence on flowering time. An important investigation was also the detailed consideration of the gene ZMM28, a maize MADS-box transcription factor, found to have an important role in genetic variation for grain yield separate from its effect on flowering time (Wu et al. 2019). The discovery of the genes involved in the relationship of ZMM28 and grain yield was enabled by considering the genetic architecture of traits in terms of the gene networks underlying them.

Another experimental example of a gene network studied by a combination of mapping, transgenic, and editing approaches was based on the ARGOS gene family (Guo et al. 2014; Shi et al. 2015, 2017). The network of genes operating around the ARGOS genes are involved in regulating genetic variation for the ethylene responses of maize hybrids. These responses have important influences on genetic variation for yield that are independent of flowering time. The network of genes discovered in these studies further motivated our consideration of gene network models using the NK framework. Many other examples are described by Simmons et al. (2021).

The genetic landscape metaphor was introduced and developed by Wright (1932) to aid in conceptualizing genetic complexity in high dimensions (Svensson and Calsbeek 2013). As a metaphor it should not be taken literally but can help to gain an intuition for the complexity and ruggedness associated with increasing values of K (Kauffman 1993) as well as making the rather abstract concepts discussed henceforth more tangible. At $K=1$ (genes acting strictly additive without any inter- or intra-gene interactions), the genetic landscape can be imagined as that of Mount Fuji, i.e., a single, clearly distinguished peak with a steady and monotonous incline to the top (Figure 1). At intermediate K levels, the landscape is characterized by multiple peaks clustered together in a certain region of genetic space. This might be visualized as akin to the European Alps, i.e., a mountainous region within an otherwise flat landscape. Finally, at high value of K , the landscape resembles a sea of dunes, i.e., a range of peaks of similar height and shape distributed more or less evenly in space.

Implementation of the NK model

We implemented the NK model according to the generalized approach described by Altenberg (1994), but adapted the model to accommodate diploid genomes. Here, the complex trait is described as a normalized sum of a set of “fitness components.” The normalization was done by dividing by N out of convention (Csaszar 2018). Because N was held constant throughout this study, normalization was by a constant and thus did not affect results (e.g., the relative ranking of individuals). The value of each fitness component is computed as a function of K interacting genes drawn at random from all N genes. Following Altenberg (1994), the specific fitness values were calculated with *random functions* derived from the *ran4* pseudo-random number generator (Press et al. 1992) and are distributed uniformly between 0 and 1. For this study, the number of fitness components and the number of genes were both set to $N=500$. This number was chosen as a compromise between research showing that e.g., upwards of 1500 genes and upwards of 1800 metabolites are involved in the biomass metabolism of a complex organism such as maize (Saha et al. 2011) and computational tractability. Genes were biallelic and the simulated organism diploid. The complexity parameter K was varied from 1 to 15 in steps of 1 (i.e., creating genetic landscapes ranging in complexity from Mount Fuji to The Dunes; Figure 1). Following Altenberg (1994), we allowed for some

variation in the number of genes interacting in each component. This was achieved by using K as the rate parameter in a Poisson distribution from which the number of interacting genes was drawn independently for each fitness component. The sampled values were then truncated to fall within a range of 1 and 15. The exception to this was at $K=1$, where all components were controlled strictly by a single gene. For $K>1$, genes were assigned at random to the fitness components, with the number of genes assigned to each component depends on the value drawn from the Poisson distribution, as described. Thus, genes typically influenced multiple fitness components (i.e., act pleiotropically). For $K=1$, each of the 500 genes was assigned to exactly one fitness component, and the values of heterozygous allele configurations were constrained to be midway between the homozygous configurations. Thus, $K=1$ represents a genetic architecture in which genes act strictly additive and without any inter-gene interactions. Using order statistics, the expected value of the maximum of two samples from a Uniform distribution between 0 and 1 is $2/3$. Thus, the expected maximum attainable fitness at $K=1$ is $2/3$.

Quantification of complexity

The complexity of the generated NK models was quantified following the “one-mutant neighbor” hill-climbing algorithm described by Kauffman (1993), but adapted to diploid organisms. A randomly generated genotype was used as the starting value. From there, all possible genotypes were generated that differ from the initial genotype by one allele at one of the 500 loci. Thus, a homozygous locus was changed to the heterozygous state while a heterozygous locus was changed to both alternate homozygotes. Then, the fitness values of all one-allele neighbors were evaluated according to the defined NK model, and an improved genotype was chosen at random from all fitter one-allele neighbors. This process was repeated until no fitter one-mutant neighbor could be found, meaning that the search reached a local or global optimum. For each level of K , 100 NK models were generated independently and a minimum of 65 searches, each starting at a random initial genotype, were conducted for each. The statistics recorded were the average number of steps until a local optimum was reached, the average Hamming genotypic distance, i.e., the proportion of different genome positions (Pinheiro et al. 2005), among optima and the correlation between the fitness values of the optima and the Hamming distance to the highest optimum identified (Kauffman 1993).

The average Hamming distance between the local peaks increased from just below 0.5 at $K=2$ to $2/3$ at around K of 6 or 7 and remained constant at this value from there on (Figure 2A). Note that with three different genotypes at each locus, $2/3$ is the expected value of the Hamming distance between randomly generated genotypes. Similarly, the correlation between the fitness values of the local peaks and their Hamming distance to the highest identified peak increased from -0.25 at $K=2$ to zero at $K=9$ (Figure 2B). Here, a negative correlation means that local peaks with higher fitness tend to be found near each other and clustered around the highest peak. Furthermore, a zero correlation indicates that there is no clustering of the peaks and proximity to the highest peak. Therefore, local peaks are randomly distributed throughout the genetic landscape. Thus, somewhere between $K=6$ and $K=9$, the landscape shifts from one in which local peaks tend to cluster together, to one where local peaks of arbitrary height can exist anywhere in genetic space. The average number of steps until a local peak was reached decreased with K from 500 at $K=1$ to just 167 at $K=15$ (Figure 2C). Note that 500 is the expectation at $K=1$ when starting from randomly generated

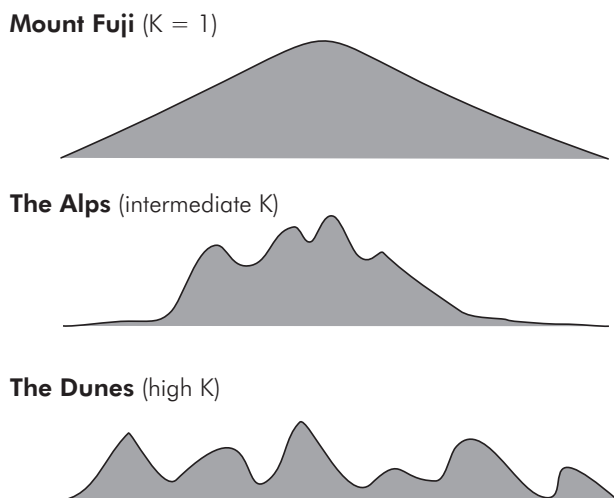


Figure 1 Schematic visualization of genetic landscapes corresponding to different values of complexity parameter K .

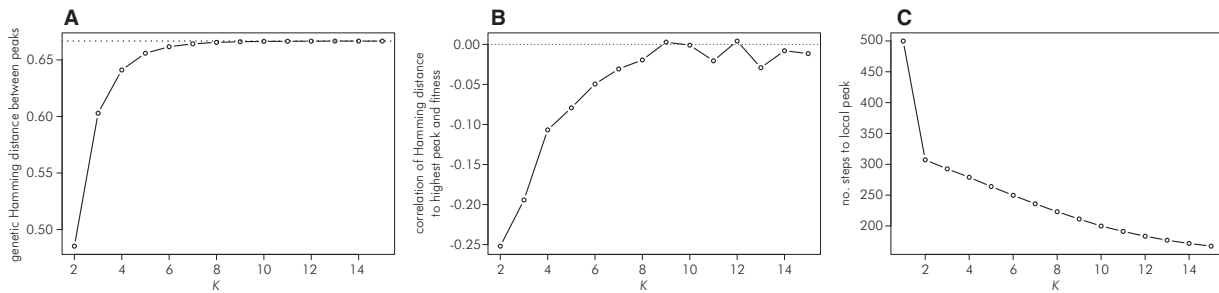


Figure 2 Relationship between the NK model complexity parameter K and (A) the average genetic Hamming distance between local peaks, (B) the average correlation between the fitness values of local peaks and their genetic Hamming distance to the highest peak and (C) the average number of steps to a local peak. Panels (A) and (B) omit results for $K = 1$, for which only a single peak exists. The dotted lines in these panels indicate values of $2/3$ and 0.0 , respectively.

genotypes, because $1/3$ of the 500 loci are already at their highest possible value, $1/3$ are one step removed (the heterozygous genotypes) and $1/3$ are two steps removed (the lower homozygotes). Thus, the complexity and ruggedness of the genetic landscapes increase further after they become uncorrelated around K of 6 to 9.

Genome definition

The simulated genome comprised 10 diploid chromosomes of 1 Morgan length each. Each of the chromosomes received a random subset of 50 of the 500 genes, which were distributed evenly across the chromosome. Recombination was simulated according to the Haldane mapping function with the R package “hybrid” (Technow 2013), in the version available from the supplement of Technow and Gerke (2017).

Simulation of the hybrid breeding process

The simulation process is visualized in Figure 3. The specific process depicted in this figure as well as the following explanations correspond to the distributed program structure of which more details will be given below. This structure is the most general of the ones considered and allows us to cover all features of the simulated process. The other structures considered, which are described in a later section as well, are special cases of this. The starting point of the simulation was a base population of inbred lines of size 1000 (Figure 3A). This population was simulated stochastically as described by Montana (2005) to result in an expected LD between two loci t Morgan apart equal to $r^2 = 0.5 \cdot 2^{-t/0.1}$ and with minor allele frequencies distributed uniformly between 0.35 and 0.50. The lines from the base population were then separated at random into two heterotic groups (arbitrarily labeled “1” and “2”) and further into sub-populations within those. The size of those sub-populations depended on the scenario. One sub-population from one heterotic group was then paired with one sub-population from the other group to form sub-heterotic patterns. These population pairs will henceforth be referred to as “breeding programs.” Hybrids were produced strictly across heterotic groups, by crossing lines from one sub-population of a program with lines from the other. Breeding crosses, i.e., crosses to generate a new generation of recombinant lines were done within and among sub-populations, depending on the scenario but strictly within heterotic groups (Figure 3B). The simulation of the breeding process described above is an approximation of the structure and evolution of long-term hybrid breeding akin to what we have observed in practice; i.e., starting from an initial germplasm base, separation into distinct heterotic

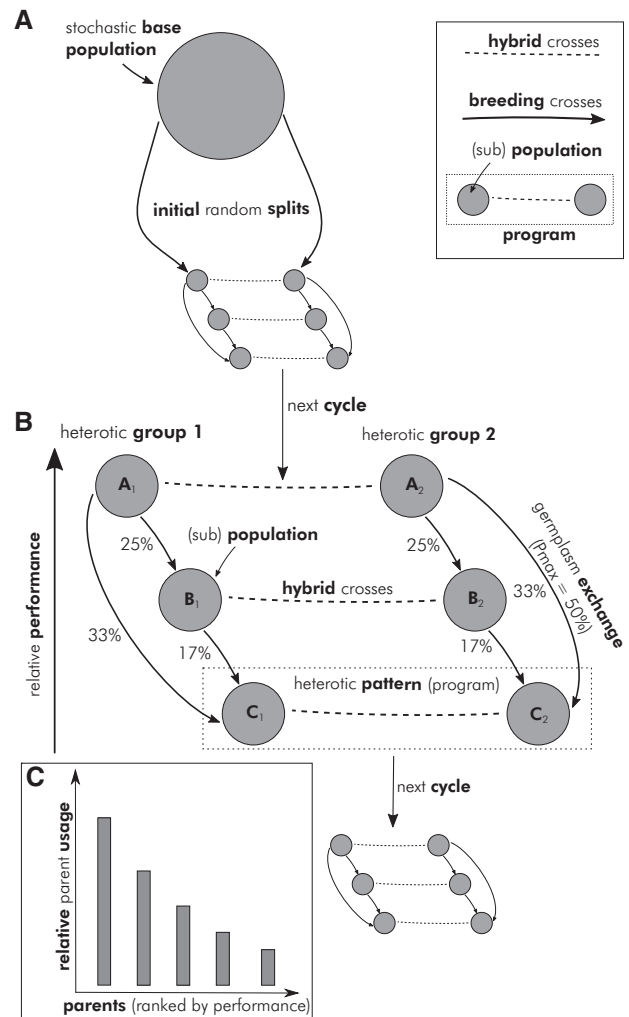


Figure 3 Schematic visualization of the simulated hybrid breeding process, exemplified for the distributed program structure. (A) Creation of initial population and random splits into heterotic groups and populations; (B) detailed view of the processes happening within each cycle; (C) relationship between the performance of parents and the proportion in which they were used in breeding crosses. The performance ranking of the programs reflects the average performance of the experimental hybrids they produced and is subject to change from cycle to cycle. The percentage values next to the arrows connecting programs indicate the percent of breeding crosses of a program that are conducted with lines from the respective higher ranked program. The total percent of such crosses for the lowest ranked program C is given by P_{max} . The higher the rank of a program, the lower the percentage of lines from other programs used in its breeding crosses, with the highest ranked program A not using any.

groups and future separation into sub-populations (Duvick et al. 2004; Mikel and Dudley 2006).

Evaluation of genetic performance

The GCA of the lines was evaluated with an incomplete mating design (Melchinger et al. 1987; Seye et al. 2020) by performing 10 crosses per line with random partners from the opposite sub-population of the same program. The performance of the resulting hybrids, as determined according to the defined NK model, was then averaged. Finally, a normally distributed noise variable with zero mean and variance equal to one-half of the variance of the GCA values of that sub-population was added to those averages to represent residual experimental and environmental noise variation. The so obtained “observed” GCA values thus had a heritability, on a progeny mean basis, of 2/3, a value easily achievable in multi-environment, multi-testcross field trials (Schopp et al. 2015). Those GCA observations were then used to predict the performance of all possible inter-group hybrids of that program. The top hybrids, how many exactly depended on the scenario, were then selected and their true performance determined according to the NK model. The average of this select group of hybrids, which represents a set of advanced experimental hybrids, was used to quantify the overall performance of the program in the current cycle. The selected hybrids from all programs were then ranked according to their true performance and the value of the top-ranked hybrid was defined as the peak performance of the whole breeding operation in the current cycle and used as a metric of genetic gain. This metric reflects that commercial breeding programs release only a handful of hybrid products each cycle.

Selection of breeding parents

Breeding crosses among inbred lines for initiating the next recombination cycle were chosen by assigning each inbred line a usage probability, which was a product between an individual and population level relative contribution value. To determine the former, the lines within each sub-population were ranked according to their observed GCA values (Figure 3C). Only the top lines, how many depended on the scenario, were selected as potential parents, the remainder given an individual contribution value of zero. The relative contributions of the selected lines from a given sub-population were drawn from a Dirichlet distribution. The concentration parameters of this distribution were used to modulate the relationship between selection rank and relative contribution. Further details about this will be given later when describing the setting for the “parental contribution theme.”

The population-level contribution values describe the overall contribution of lines from one sub-population to the breeding crosses of another. They are thus defined anew for each target population and hence the contribution value of population “A” to the crosses for population “B” might be different than that to the crosses of population “C.” The process will be explained using the example visualized in Figure 3B. Here, there are three programs (labeled “A,” “B,” and “C,” with subscript 1 or 2 indicating the heterotic group).

In each cycle, the programs are ranked from highest to lowest performing according to the average performance of the selected set of experimental hybrids, as described above. This means that the relative performance ranking of the programs was subject to change from cycle to cycle. Germplasm, in the form of lines used as crossing partners, is exchanged only from higher to lower performing programs. Specifically, the number of crosses with lines from other programs increased from zero for the best performing

program (A) to a proportion of Pmax for the lowest performing program (C), with intermediate programs staggered equidistantly between. In the example, Pmax = 50%. Thus, program A will perform no crosses with lines from other programs, program B will use lines from other programs in 25% of its new crosses and program C in 50% of its crosses. How much of that overall proportion was derived from each of the other programs was proportional to the relative performance differences. In the example, the difference between program C and program A is twice as large as that between C and B, thus, lines from program A were used in twice as many crosses than lines from program B (33% from A and 17% from B for a total of 50%).

This process thus reflects that highly successful programs tend to exploit their own genetics while less successful programs have more of an incentive to explore superior genetics from other programs. The Pmax values considered in this study were 25, 50, and 75%.

The relative individual contributions were then multiplied with the relative population contributions to arrive at a final relative contribution value for each line to the crosses of a given population. The actual breeding crosses were then determined by sampling the lines with probabilities proportional to their contribution values. This was done with replacement, meaning that the same cross could have been made multiple times, but excluding crosses that would result in selfings. One recombinant line was derived from each crossing (e.g., two full-sib progenies would have been created if a crossing was made twice). This was done through seven generations of single-seed descent selfing, after which the lines were assumed to be fully homozygous and any residual heterozygosity was ignored. This new generation of recombinants fully replaced the previous generations, i.e., a line was considered as a crossing partner in only one generation. The so obtained new recombinants then form the next breeding cycle. The simulations were conducted for 30 cycles in total and repeated independently at least 500 times for each scenario studied. All computations were conducted in the R environment for statistical computing (R Core Team 2018).

Recorded metrics

In addition to the already described true performance of the best-identified hybrid, which was used as a measure of *peak performance* in a given cycle, several other measures were recorded to describe and understand the dynamics of the system.

The *proportion of GCA to total genetic variance (%GCA)* describes the amount of exploitable additive genetic variation currently available. It was estimated using the hybrids generated for evaluating the GCA of the inbred lines. For this, the following mixed model was fitted: $h_{ij} = \mu + g_i + g_j + e_{ij}$, where h_{ij} was the true performance of the hybrid between line i from heterotic group 1 and line j from group 2, μ the overall mean, g_i and g_j were the GCA effects of lines i and j from the two heterotic groups and e_{ij} a residual term. Because the true genetic performances of the hybrids were used, e_{ij} approximates the SCA component. The model was fitted using the R package “lme4” (Bates et al. 2015) and %GCA then calculated as $(V_{g_i} + V_{g_j}) / (V_{g_i} + V_{g_j} + V_{e_{ij}})$, where V_{g_i} , etc. were the estimated variance components. In scenarios with multiple programs, %GCA was estimated separately for each and then averaged to arrive at a single estimate for each cycle.

The *modified Rogers’ distances* (Reif et al. 2005) between the heterotic groups within each program were used as measures of heterotic group divergence. The distances were calculated for all

programs and averaged to arrive at representative value for that cycle.

To describe the distribution of allele frequencies within each sub-population and hence the amount of available allelic diversity we calculated the proportion of loci with a minor allele frequency of less than 5%. This probability measures the thickness of the extreme tail of the allele frequency distribution and thus reflects the degree to which it follows a “U-shape” (Hill et al. 2008). This metric was evaluated for all sub-populations in each cycle and then averaged.

As a more high-level diversity metric, we considered the effective population size (N_e) of each sub-population. N_e was calculated according to the method described by Corbin et al. (2012) for estimating constant effective population size. The so obtained values were averaged across sub-populations.

Hybrid breeding “themes”

The term “theme” will be used to refer to a particular component of a holistic hybrid breeding strategy. The themes considered were the program structure and the relative parental contribution of successful inbred lines to the next generation. All previously described parameters, such as parameters related to the NK model and genetic architecture, parameters related to testcross evaluation, and so on, were kept constant across the themes investigated.

In the program structure theme, we explored consequences of separating hybrid breeding programs into smaller, more or less isolated, units. In addition to the previously described distributed structure, we considered two other, more extreme program structures for “searching” (Podlich and Cooper 1999) genetic space, which can be viewed as special cases of the distributed structure (Figure 4): one comprised a single, large program (centralized structure), the other structure comprised multiple smaller, but fully isolated programs (isolated structure).

The centralized structure was characterized by a single program consisting of one sub-population per heterotic group. The size of each was 500, for a total of 1000 lines generated in each cycle. The number of lines selected to contribute to the next generation was 125 per sub-population. The relative individual contributions of these lines decreased proportionally with their performance ranks. The number of selected experimental hybrids was 125. The isolated program structure comprised five programs, each with one sub-population per heterotic group. The sub-population size was 100 of which 25 were selected. Also here, the relative individual contributions of the lines were

proportional to their performance ranks. The number of experimental hybrids selected per program was 25.

For the distributed structure, we considered three levels of Pmax: 25, 50, and 75%. The number of programs as well as lines and hybrids created and selected for each followed those of the isolated structure. Note, thus, that the total number of lines and hybrids were the same across all structures as was the selection intensity.

In the parental contribution theme, we explored the consequences of different degrees of imbalance in the relative contributions of the selected inbred lines to the next generation. Throughout, the program structure corresponded to the distributed structure with Pmax = 50%. Only the relative usage of inbred lines was varied. As described above, the observed relative contributions were drawn from a Dirichlet distribution with concentration parameter chosen in a way to result in a certain average relationship between relative contribution and performance rank. Three contribution scenarios were considered (Figure 5). In the balanced contribution scenario, all selected inbreds contributed equally on average, in the proportional scenario, the relative contribution declined proportionally with the performance rank of the lines. In the disproportional scenario, contributions halved with every 5 ranks, meaning that the highest performing line will contribute twice as much to the next generation as the 5th ranked line. The increasing imbalance in contributions can be quantified as $1/\mathbf{b}'\mathbf{b}$ (with \mathbf{b} being the vector of relative contributions), which is an estimate of the effective number of contributing lines (Boichard et al. 1997). For the balanced scenario, this was 25 and thus equal to the actual number of selected lines within each sub-population. It decreased to 19.1 and 13.6 for the proportional and disproportional scenarios, respectively.

Data availability

The authors affirm that all data necessary for confirming the conclusions of this article are represented fully within the article and its figures and supplemental material. The R and C code for the simulations is provided as supplementary material. The supplementary material is available at figshare: <https://doi.org/10.25387/g3.14036627>.

Results

Program structure theme

Which structure achieved the highest peak performance depended on the value of the complexity parameter K , with the centralized structure being superior at low $K < 5$, the distributed structure at intermediate K and the isolated structure at high values of K above 8 (Figure 6A). The differences between the

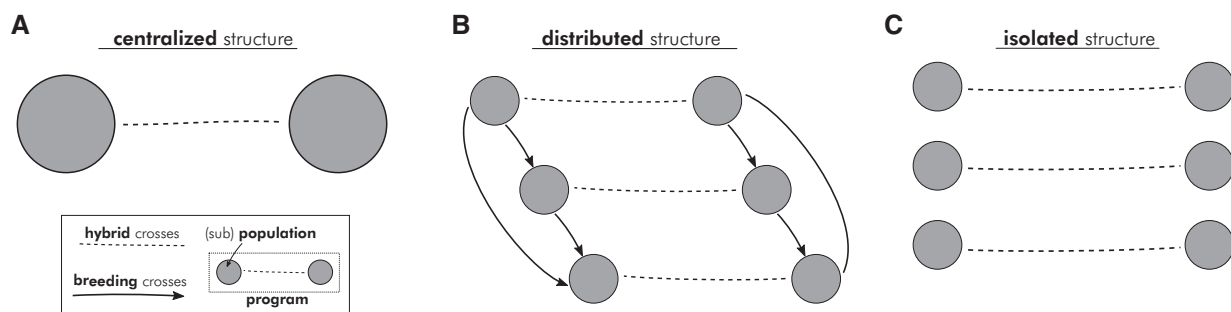


Figure 4 Schematic visualization of the three basic structures explored in the program structure theme: (A) centralized: a single program with one large population in each heterotic group; (B) distributed: multiple programs with smaller populations in each heterotic group that exchange germplasm; (C) isolated: multiple programs with smaller populations in each heterotic group that do not exchange germplasm.

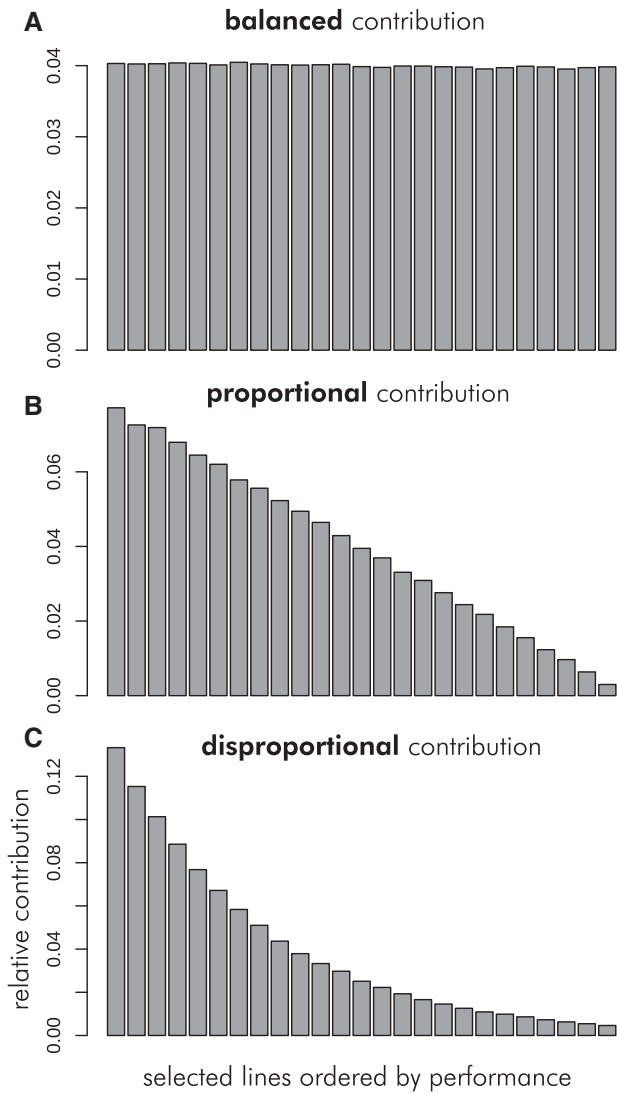


Figure 5 Scenarios for distribution of relative individual contributions of selected inbred lines considered in the parental contribution theme. (A) Balanced: selected parents contribute evenly to the next generation; (B) proportional: contribution of selected parents to next generation is proportional to their performance rank; and (C) disproportional: higher ranked parents contribute disproportionately more than lower ranked parents.

structures tended to increase with increasing K . The centralized and distributed structures came very close to reaching the theoretical maximum peak performance under purely additive gene action ($K=1$), but the isolated structure remained considerably below that. Within the distributed structure, the highest P_{max} value of 75% was superior at K -values below eight and the lowest P_{max} of 25% at high K (Figure 6B). The case of $P_{max} = 50\%$ had peak performance in between the two extremes, but more similar to $P_{max} = 75\%$. All P_{max} scenarios achieved virtually identical peak performance at $K=1$.

For brevity, trajectories across cycles are shown only for K -values of 1, 6, and 15, representing the additive, multi-peaked but clustered, and fully uncorrelated landscapes, respectively (Figure 7, A–L). Results for all values of K are available as supplemental information (Supplementary Figure S1). At $K=1$, the centralized program structure had the highest peak performance in all cycles, closely followed by the three versions of the distributed structure (Figure 7, A–C).

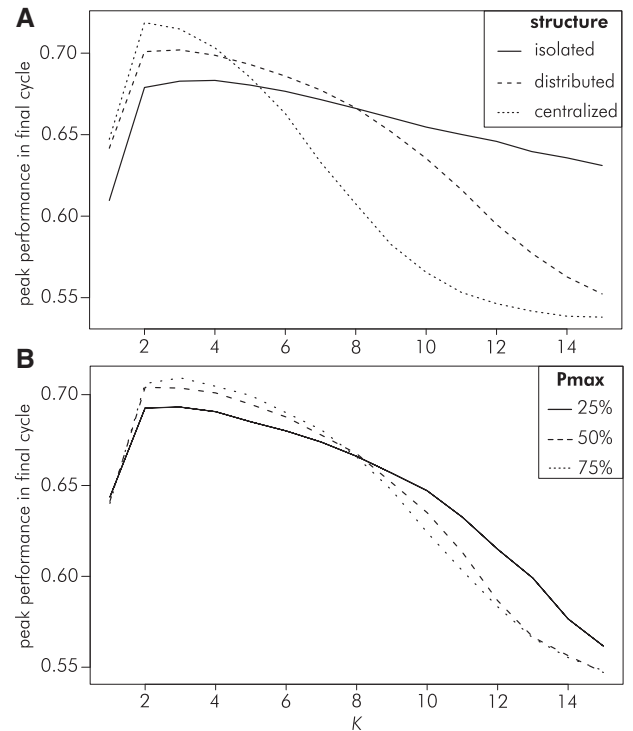


Figure 6 Relationship between the NK model complexity parameter K (average number of interacting genes) and peak genetic performance in the last cycle for the strategies explored in the program structure theme: (A) comparing the isolated, distributed, and centralized structures; (B) the different values of P_{max} within the distributed structure. The curve of the distributed structure in (A) is an average across the three P_{max} scenarios within it. P_{max} gives the maximum percent of breeding crosses conducted with lines from other programs.

The peak performance of the isolated structure was considerably lower than that of the other strategies as it increased at a lower rate and seemed to reach a plateau at around cycle 20. At $K=6$, the isolated structure achieved the highest peak performances in the earlier cycles but was overtaken by the distributed structures later. Those had very similar peak performances until the last few cycles when the version with P_{max} of 25% fell behind. The centralized structure had the lowest peak performances throughout, with the differences to the other structures being particularly large between the intermediate cycles 15–20. Finally, at $K=15$, only the isolated structure had a sizable increase in peak performance cycle over cycle. The distributed structures showed an increase only in the last few cycles and the centralized structure did not increase peak performance at all.

As expected %GCA was equal to one for all scenarios at $K=1$ (Figure 7, D–F). At $K=6$, %GCA started at just below 10% and increased from there with each cycle. The rate of increase was greatest for the isolated structure which reached a %GCA of almost 100 in the final cycles. The centralized structure had the slowest increase and was still below 50% in the final cycle. The distributed structures were intermediate between these two extremes. The increase was steepest for $P_{max} = 25\%$ case, which translated to it having a markedly higher %GCA than the $P_{max} = 50\%$ case and $P_{max} = 75\%$ case during intermediate cycles 15–20. However, all three converged to a similar value of around 80% in the final cycle.

At $K=15$, %GCA started at zero and only the isolated structure saw a marked increase in early cycles. The distributed program structure saw an increase in %GCA noticeably above zero only in

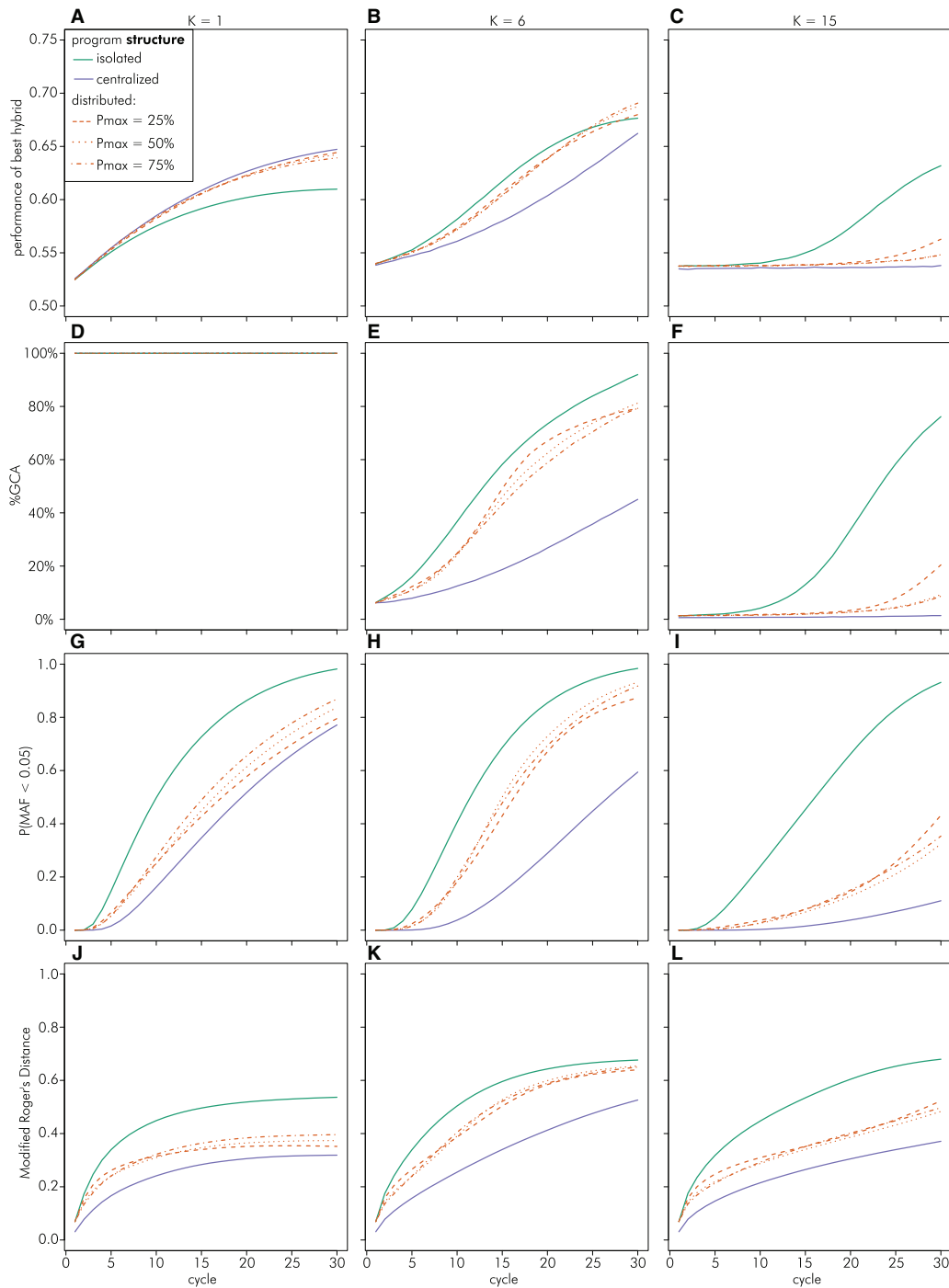


Figure 7 Evolution of metrics over cycles in the program structure theme for scenarios with K of 1 (A, D, G, and J), 6 (B, E, H, and K), and 15 (C, F, I, and L).

the final cycles and the centralized structure remained at zero throughout.

The percent of loci with $MAF < 0.05$ increased over cycles for all program structures and complexity levels (Figure 7, G–I). In all cases, the increase over cycles was strongest for the isolated structure, where it reached close to 100% in the final cycles and weakest in the centralized structure. The curves for the three P_{max} levels of the distributed structure were similar to each other and intermediate compared to the two other structures. The differences between the structures increased with K because the increase in the proportion of loci at extreme frequencies slowed for the distributed and centralized structures with

increasing K . At the highest levels of complexity, only between 30 and 40% of loci showed a $MAF < 0.05$ in the different distributed structures and less than 20% in the centralized structure.

The modified Rogers Distance between heterotic groups increased over cycles for all structures (Figure 7, J–L). For all levels of complexity, this distance was highest for the isolated structure and lowest for the centralized structure, with the three versions of the distributed structure having similar values that were intermediate to the two extremes (Figure 8).

The N_e differences among the structures remained largely constant across cycles and levels of K . For the sake of brevity results will only be reported for cycle 15 and $K = 7$. The estimated

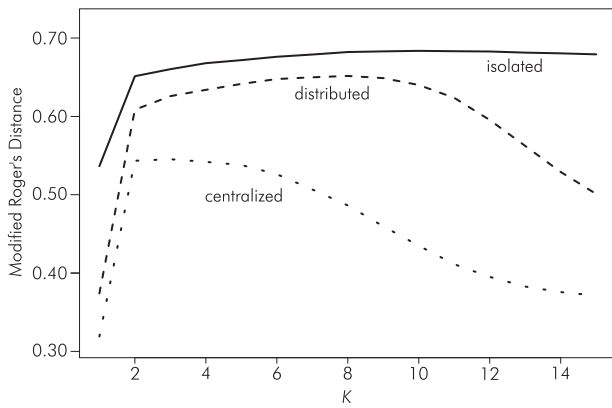


Figure 8 Modified Rogers Distance between heterotic groups as a function of K , averaged across programs, in the program structure theme. The curve of the distributed structure represents the average across the three P_{max} levels.

N_e for each-sub-population for the isolated structure was 20.0, for the three versions of the distributed structure it was 23.7 ($P_{max} = 25\%$), 31.3 ($P_{max} = 50\%$), and 35.4 ($P_{max} = 75\%$), respectively, and for the centralized structure 98.3.

Parental contribution theme

Which parental contribution scenario achieved the highest peak performance depended on the complexity level K (Figure 9). At the additive case of $K=1$, all contribution scenarios achieved very similar peak performances close to the theoretical maximum of $2/3$. Until $K=8$, the highest peak performances were reached with proportional contribution of the selected inbred lines. For $K>8$, disproportional contribution of inbred lines resulted in the highest peak performances. Balanced contribution generally resulted in the lowest peak performance, except for $K<4$, where it was slightly ahead of the disproportional contribution option. The differences between the contribution scenarios tended to increase with K .

For brevity sake, we also here show the trajectories across cycles only for K of 1, 6, and 15 (Figure 10, A–L). Results for all values of K are provided in Supplementary Figure S2. The cycle over

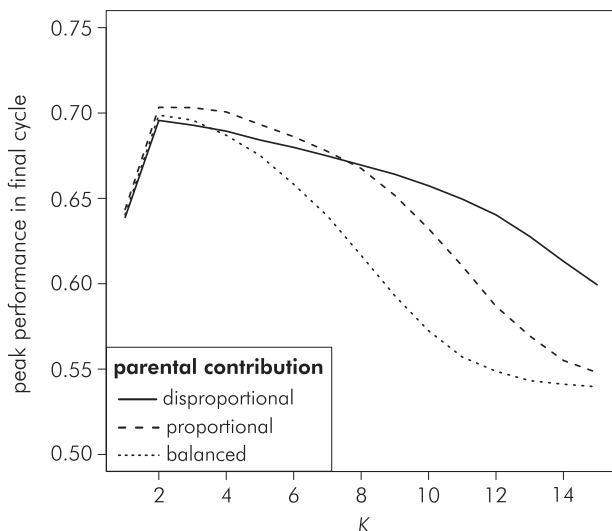


Figure 9 Relationship between the NK model complexity parameter K and peak genetic performance in the last cycle for the scenarios explored in the parental contribution theme.

cycle increase in peak performance was initially higher the more disproportional the contribution of the inbreds lines (Figure 10, A–C). However, except for the highest level of complexity, this did not result in the highest maximum performance for this scenario, because the increase started to level off in the last 5 to 10 cycles. Scenarios with proportional and balanced contribution, therefore, had the highest peak performance at $K=1$, though the differences were small. At the intermediate level of $K=6$, the disproportional contribution scenario was overtaken by the proportional contribution scenario in the last cycles. The differences between these two were small, however. Finally, at $K=15$, only the disproportional contribution scenario achieved a sizable increase in peak performance.

At $K=1$, %GCA stayed constant at one for all scenarios, as expected. At $K=6$, %GCA increased most strongly for disproportional contribution, followed by proportional and balanced contribution (Figure 10, D–F). Reaching above 90% for the former, and above 80 and 50% for the latter two, respectively. At $K=15$, %GCA remained near zero for the balanced and proportional contribution scenarios throughout. For the disproportional contribution scenario, it remained at zero as well until cycle ten and increased from there to almost 60%.

For all strategies and values of K , the percent of loci with a $MAF < 0.05$ increased from its initial value of zero (Figure 10, G–I). The increase over cycles was strongest for disproportional parental contribution, for which it reached close to 100% at K of 1 and 6. The proportional contribution scenario had the second strongest increase and the balanced scenario the weakest. As was the case in the program structure theme, the differences between the scenarios tended to increase with K . At the highest level of $K=15$, the proportional and balanced scenarios stayed below 40%, whereas the disproportional contribution scenarios reached close to 80%.

The modified Rogers distance between heterotic groups increased over cycles in all scenarios (Figure 10, J–L). Throughout it was highest for disproportional contribution, followed by proportional and balanced contribution. Overall, the distance was greatest for the intermediate complexity level of $K=6$.

N_e , again reported only for cycle 15 at $K=7$, was 23.2, 31.3, and 44.6, for the disproportional, proportional, and balanced parental contribution scenarios, respectively.

Discussion

The objective of this study was to explore properties of historically grown commercial hybrid breeding programs, particularly in maize, and aid the understanding of why they successfully generated significant amounts of genetic gain in the past and thereby impacted global food security. The infinitesimal framework (Barton et al. 2017), in which traits are described as the sum of a large number of genes all having additive, context-independent effects of similar magnitude, is our starting point. However, we seek extensions to account for the empirical observations that (a) there are results observed from operating a long-term breeding effort that is not consistent with or not easily explained within the infinitesimal model framework (Rasmusson and Phillips 1997) and (b) reflect the reality of a highly complex trait biology (Hammer et al. 2006). Therefore, we are motivated to consider the influence of complexity of trait genetic architecture on breeding strategies from the perspective of a long-term commercial breeding program (Duvick et al. 2004; Cooper et al. 2014).

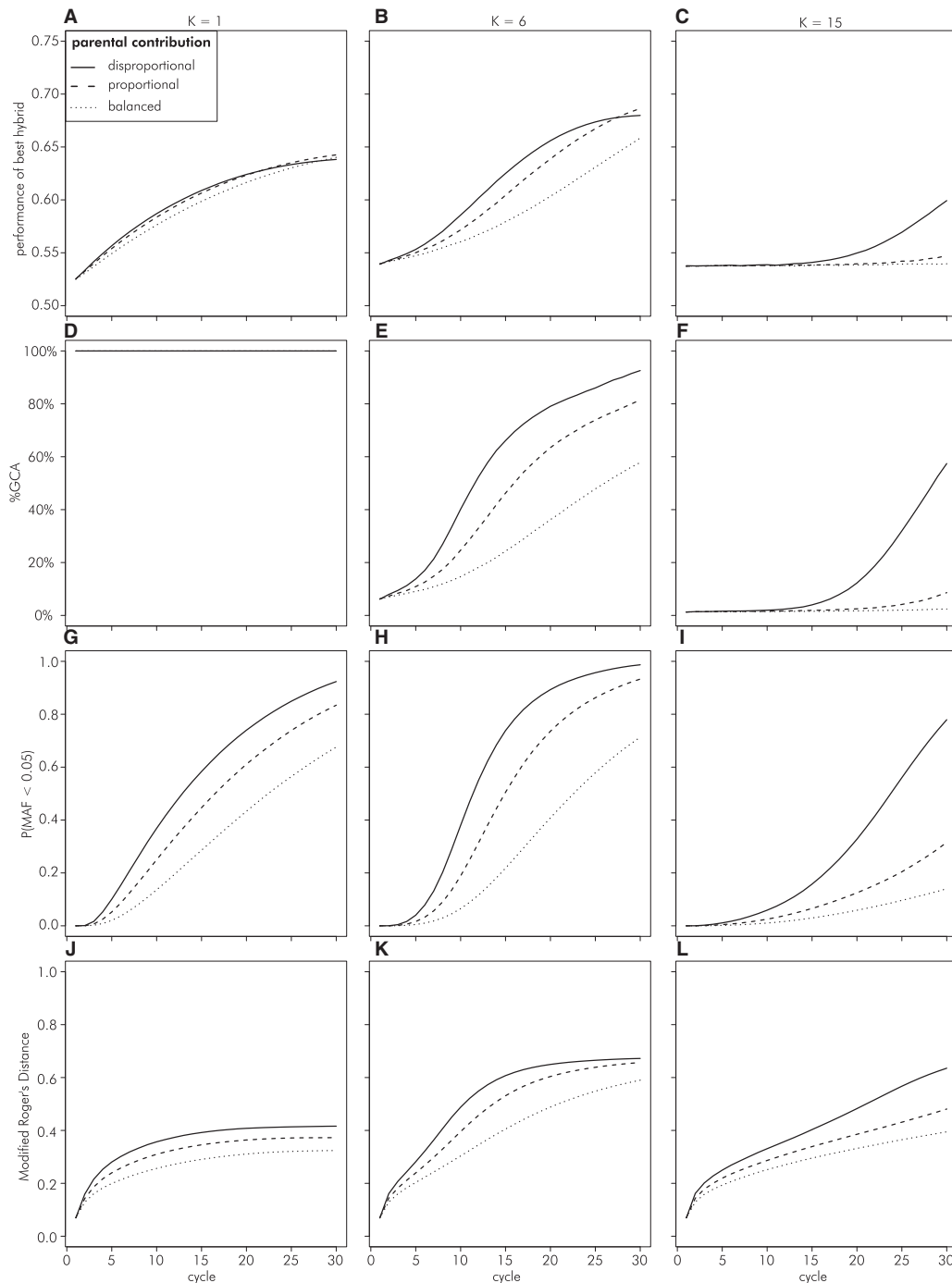


Figure 10 Evolution of metrics over cycles in the parental contribution theme for scenarios with K of 1 (A, D, G, and J), 6 (B, E, H, and K), and 15 (C, F, I, and L).

Emergence of additive genetic variance

As a representation of genetic complexity, we chose the NK model framework developed by [Kauffman \(1993\)](#), which allows exploration of the full continuum from complete additivity to deep and almost intractable genetic complexity. For reference, the NK models used in this study, corresponding to the Mount Fuji landscape at $K=1$ ([Figure 1](#)) and to the “Alps” landscape from $K=2$ to K of 7 or 8. After this, the genetic models transitioned from the multi-peaked but correlated “Alps” landscape to the uncorrelated landscape represented by the “Dunes” metaphor ([Figures 1](#) and [2](#)). In complex genetic landscapes, additive genetic

variance, the sine qua non of genetic gain, is not a constant factor of trait biology (i.e., deducible from the molecular properties of genes) but rather emerging from the interplay of biology and natural or artificial properties of population structure ([Wade 2002](#); [Cooper et al. 2005](#)). Statistical additivity is thus conditional on the sample of allele contrasts that can be observed in a breeding population and the properties of the underlying trait biology (as represented by the NK network here). In particular, additive genetic variance emerges in response to a constraining of the dimensionality of genetic space, or, in other words, by limiting genetic diversity. In practice, such constraints in dimensionality are achieved

through fixation or near fixation of genes (Wade 2002; Hill *et al.* 2008). This process is illustrated in Figure 11 for a simple digenic epistatic network (Holland 2001) that corresponds to a NK model with $N=K=2$ and two distinct fitness peaks. Thus, as genetic complexity increases, the breeder needs practical ways to reduce this complexity to a manageable level that allows genetic progress. This study explored two practical approaches that have been adopted within commercial hybrid breeding, particularly in maize. With the availability of genomics and novel thinking about genetic complexity, we can now study the genetic implications of these practical approaches, many of which were devised and adopted prior to the availability of a theoretical and empirical framework to study their effects.

Two processes, in particular, accelerate such constraint: namely the creation of population bottlenecks and the subdivision of larger populations into more or less independent “demes” (Katz and Young 1975; Goodnight 1995). Equivalent processes in the context of plant breeding programs are the degree of connectivity between breeding programs and the relative contribution of superior inbred line parents in breeding crosses for producing the next generation, both “themes” were explored in this study.

Program structure theme

Classical quantitative genetics infinitesimal theory was used to design and optimize commercial hybrid breeding programs, in combination with empirical experience of what worked and what did not (Hallauer *et al.* 2010). Yet, even though the infinitesimal

model implies optimality of a single, homogenous population, there were discussions about the relative merits of large centralized vs decentralized breeding programs early on (Baker and Curnow 1969). Later on, Podlich and Cooper (1999) explored this problem on the basis of Sewall Wright’s shifting balance theory, (Wright 1931, 1977; Wade and Goodnight 1998). The shifting balance theory describes an evolutionary process in which genetic drift resulting from population subdivision enables random movements across genetic space (*i.e.*, against selection gradients) and also converts epistatic to additive genetic variation through constraining genetic space as described above. This then enables local adaptation in complex genetic landscapes which is followed by differential migration from higher to lower performing subpopulations and thus “spreading” of superior gene complexes across the whole *meta population*.

While this theory remains controversial as a model of natural evolution (Coyne *et al.* 1997), there are remarkable similarities between meta populations in the context of the shifting balance theory and the population structure of large commercial breeding operations. The latter also do not operate as a centralized unit but rather as a decentralized network of smaller programs with the most successful germplasm being shared across (Cooper *et al.* 2014). The same seems to be the case at the industry level, with the major commercial breeding operations being based on unique and distinct germplasm backgrounds, with only occasional exchange of elite material, *e.g.*, through ex-PVP lines (Mikel 2006; White *et al.* 2020). As a result of this decentralization, plant

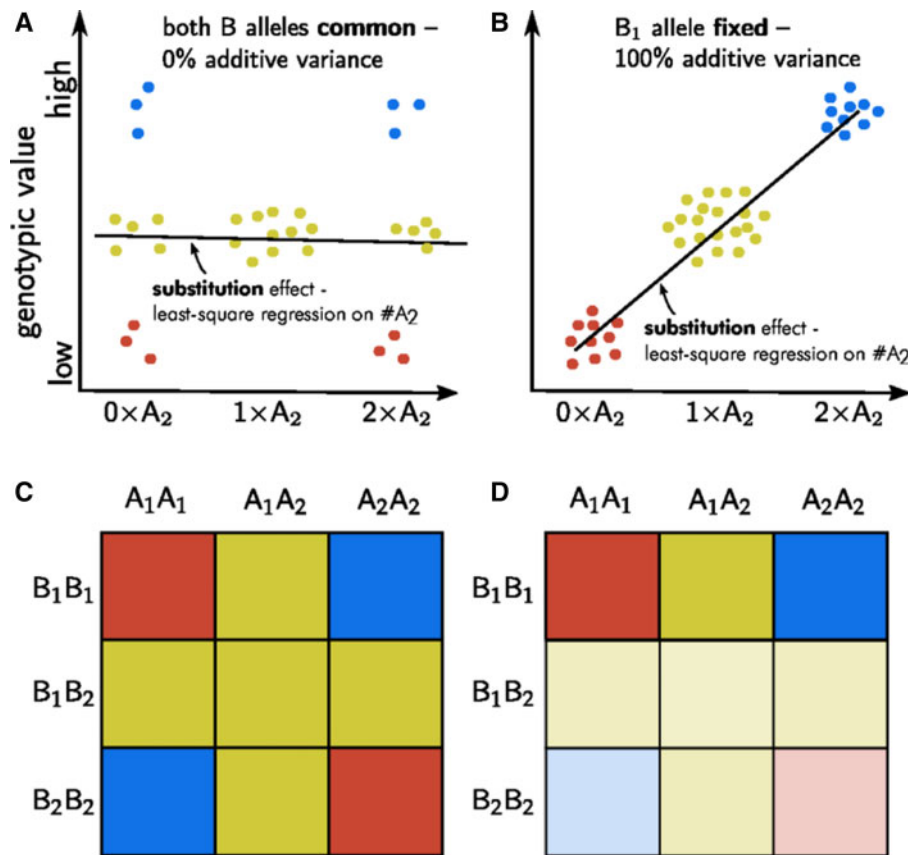


Figure 11 Illustration of a two-locus epistatic network corresponding to a NK model with $N=K=2$ and two fitness peaks (panels C and D). Neither the A nor the B locus exhibit any additive variation when all alleles have allele frequency of 0.5 (panels A and C). When the B locus becomes fixed for the B_1 allele while the allele frequencies at the A locus remain at 0.5, however, the network is reduced to an additive system in which the substitution effect of the A locus explains 100% of the variation (B and D). Note that the substitution effect of the A locus would be reversed in sign when the B_2 allele became fixed instead. Colors blue, yellow, and red represent high, intermediate, and low-phenotypic values, respectively.

breeding programs are also characterized by having low effective population sizes (Cowling 2013), which makes them more susceptible to genetic drift.

Here, we expanded on the work of Baker and Curnow (1969) and Podlich and Cooper (1999) by exploring breeding program structures with different levels of decentralization (Figure 4), ranging from a large centralized program with high N_e to an isolated set of smaller programs with low N_e , with a series of scenarios with decentralized but connected programs with N_e values in between these two extremes. We indeed found that strategies resulting in low within program N_e through increased decentralization and isolation became increasingly superior in terms of peak hybrid performance, as genetic complexity K increased, while a centralized program structure with high N_e was superior in less complex landscapes. These results thus confirm the findings of Podlich and Cooper (1999) that a distributed, decentralized program structure is superior in complex genetic landscapes. Increasing isolation and decentralization and the associated N_e reduction led to quicker increases over cycles and higher overall values of %GCA (Figure 7). At the highest levels of complexity, only complete isolation generated amounts of GCA variation sufficient for making genetic improvements cycle over cycle. The better ability to expose additivity in the form of GCA variation of the more isolated and decentralized structures was expected as per the discussion at the beginning of this section outlining the relationship between amounts of additive variation and constraint of genetic space. This explains the clear advantages in terms of genetic peak performance of the isolated program structure at the highest levels of K .

The corollary of the constraint of genetic space of course is a more rapid decline in genetic diversity and susceptibility to genetic drift, which ultimately limits the selection potential of the programs. Indeed, for values of K below eight, which marked the switch from an uncorrelated to multi-peaked but correlated genetic landscape (Figure 2), decentralized programs with increasing rates of germplasm exchange became superior. Accordingly, having a large centralized program became optimal at lower values of K . Here, the genetic landscape was simple enough to not require severe constraint of genetic space to expose sufficient amounts of GCA variation. The genetic drift experienced by small, isolated programs then unnecessarily led to the fixation of unfavorable alleles. This was most apparent at $K=1$ where all variation is additive and a decentralized structure is not expected to have any advantage (Rathie and Nicholas 1980). Here, the isolated structure experienced a fixation of almost all loci from cycle 20 onward and a stalling of genetic gain significantly below the theoretically achievable maximum (Figure 7).

An alternative hypothesis for the advantage of decentralized commercial breeding program structures can be made assuming that the selected genetic combinations associated with locally additive landscape peaks discovered by individual breeding programs are transferable to a globally additive landscape peak. Testing this alternative hypothesis would require investigation of the global structure of NK adaptation landscapes and their features that persist following evolution, domestication, and breeding in an agricultural context. This is an open area for further investigation applying the NK framework in combination with the growing body of empirical evidence generated from extensive pangenome to panphenome studies for the traits contributing to crop adaptation and performance for historical genotype-environment trajectories. We expand on the importance of genotype

by environment interactions below and consider extensions of the NK framework.

The establishment of genetically divergent heterotic groups has always been a central tenant of hybrid breeding (Melchinger and Gumber 1998). Originally, optimal exploitation of heterosis was the main driver of their establishment (East 1936). Later, however, maximization of GCA vs SCA variation was identified as an important secondary feature of heterotic groups (Melchinger and Gumber 1998). While this is well established for dominant gene action (Reif et al. 2007; Fischer et al. 2009), there are also indications for the conservation of favorable epistatic patterns that are disrupted when lines from different heterotic groups are recombined (Bernardo 2001). Often, heterotic groups are established from populations that evolved in isolation for a long time. One of the best examples for this is the Dent by Flint heterotic pattern in maize which is prevalent in Central Europe and is comprised of populations that evolved in separation for centuries (Rebourg et al. 2003). Heterotic groups are thus a different and additional form of constraint of genetic space through historically grown genetic isolation. In our simulations, the different heterotic groups were originated from the same base population, yet we still observed a significant degree of genetic differentiation evolve over cycles (Figure 7), as expected in recurrent, reciprocal selection regimes (Labate et al. 1999; Longin et al. 2013). A portion of this differentiation can be attributed to genetic drift (Gerke et al. 2015), as evidenced by the nonzero genetic distance at $K=1$, where all effects are additive and increasing genetic differentiation between heterotic groups would have no effect on the proportion of GCA variance. However, the genetic differentiation was considerably higher for $K>1$ (Figure 8), indicating that there indeed was a selection advantage to increased heterotic group divergence in complex genetic landscapes.

This was particularly clear for the isolated program structure, where heterotic patterns could form uninterrupted within programs. For the centralized and decentralized structures, the differentiation was maximal at lower values of K , because %GCA, and hence the effectiveness of recurrent, reciprocal selection, declined afterward.

Parental contribution theme

The history of North American and European maize germplasm can be described as a succession of key inbreds that were heavily used in breeding crosses and had a distinct and lasting impact on germplasm (Mikel and Dudley 2006; Technow et al. 2014b; White et al. 2020). Those inbreds owe their success either to the outstanding general combining ability relative to their peers at the time, such as was the case for the important North American line B73 (Mikel and Dudley 2006) or their unique adaptation to specific climatic conditions, such as the European Flint lines F2 and F7 (Messmer et al. 1992; Böhm et al. 2014). The highly disproportionate importance of successful inbreds led to a significant reduction in genetic diversity (Rasmusson and Phillips 1997; White et al. 2020), particularly relative to the source populations from which they were derived (Böhm et al. 2017). However, this constraint also might be responsible for the emergence of additive genetic variation from complex gene action through the so-called founder or bottleneck effect (Goodnight 1988; Cheverud and Routman 1996; Naciri-Graven and Goudet 2003; van Heerwaarden et al. 2008). We indeed observed that %GCA increased faster over cycles and reached higher values overall the more uneven the contribution of selected parents to breeding crosses (Figure 10), with the exception of $K=1$, where all variance is additive by definition. At the highest degrees of landscape

complexity only disproportionate contribution of parental inbred lines, resulting in very low N_e , succeeded in generating amounts of %GCA sufficient for genetic improvements. Like in the program structure theme, the higher values of %GCA of the disproportional contribution scenario translated into superior peak performances only at the values $K > 8$, i.e., after the landscape transitioned from multi-peaked but correlated to uncorrelated. Before that, balanced and particularly proportional contribution, both having higher N_e , achieved superior peak performances.

Maintenance of diversity

In our simulations, the constraint of genetic space and reduction of N_e through decentralization and isolation or disproportionate contribution of inbred lines, while necessary for exposing additive genetic variation, led to a rapid fixation of alleles and a slowing of genetic gain in later cycles. This was partly a consequence of genetic drift caused by the low N_e (Cowling 2013). However, the reduction of N_e was also caused in part by the effects of selection, particularly once the majority of the genetic variation was additive. This has not generally happened in commercial breeding programs, where genetic gain continues apace (Rasmusson and Phillips 1997; Duvick et al. 2004; Fischer et al. 2008; Pfeiffer et al. 2019). Several factors that maintain diversity in practical programs were not included in the simulation model. For example, the simulation implicitly assumed that the environment and management conditions remained constant across all cycles, whereas both change more or less rapidly in reality. Changing selection environments imply changing selection targets and trajectories (Hammer et al. 2009; Messina et al. 2011), which reduce the pressure on particular alleles or allele complexes and thus slow or prevent fixation. Long-term selection experiments have shown that selection response can be maintained even in isolated and narrow populations (Dudley and Lambert 2010; Durand et al. 2010, 2015). Several hypotheses were proposed for these surprising results, including epistasis (Carlborg et al. 2006), *de novo* genetic mutations, particularly when magnified through effects on epistatic complexes (Rasmusson and Phillips 1997; Durand et al. 2010), creation of heritable epigenetic variation (Hauben et al. 2009), activity of transposable elements (Dubin et al. 2018), as well as the presence of “cryptic genetic variation” through phenomena such as canalization (Gibson and Dworkin 2004). Of these, only epistasis was present in our simulations. While highly speculative, these biological phenomena might explain the presence of abundant genetic variation and continued genetic gain in largely isolated and genetically narrow commercial plant breeding programs.

Genetic gain, however, is not just a function of additive genetic variance but also of the intensity and accuracy of selection (Falconer and Mackay 1996). Increases in the latter two, can partially or fully compensate for decreases in additive genetic variance. In the present study, resources and thus selection intensity and accuracy were kept constant across cycles. This is in contrast to what happened in commercial plant breeding operations, where investments have increased considerably over the last few decades (Duvick and Cassman 1999; Kusmec et al. 2021). Thus, in addition to *de novo* creation of genetic variation and changing environments, the compensating effect of increased investments can partially explain why no significant decrease in the rate of genetic gain was observed in commercial plant breeding operations.

Applications of the NK model for plant breeding

The NK model of biological complexity, developed by the theoretical biologist Stuart Kauffman, continues to be in wide use for studying problems in theoretical biology and evolutionary genetics (e.g., Hayashi et al. 2006; Aita et al. 2007; Rowe et al. 2010; Franke et al. 2011; Østman et al. 2012; Schmiegelt and Krug 2014; Nahum et al. 2015; Weinreich et al. 2018). Recent empirical extensions to the infinitesimal model of quantitative genetics also seem to validate key tenets of the NK model. One example of this is the “omnigenic” model (Boyle et al. 2017a, 2017b), which, based on insights from genome-wide association studies and systems genetics, postulates that complex traits are influenced by virtually all genes in a genome through highly interactive regulatory networks. The NK model has also been proposed as an abstraction for explicit gene to phenotype models, such as crop growth models (Messina et al. 2011; Makumburage et al. 2013; Cooper et al. 2021). Outside of biology, the NK model has been recognized as a generic model for complex systems and found applications in disparate fields such as business administration (Csaszar 2018), organizational learning theory (Lazer and Friedman 2007), infrastructure design (Grove and Baumann 2012), and physics (Qu et al. 2002). Following the example of Podlich and Cooper (1999), we here used the NK model to represent genetic complexity navigated by commercial hybrid breeding operations to study the effect of the degree of isolation between programs as well as the degree of imbalance in parental contribution, both key aspects of breeding strategies. We propose that this model can serve as an ideal starting point to study other aspects of hybrid breeding strategies. For example, Cooper and Podlich (2002) proposed an extension to the NK model that adds an environmental dimension and thus allows modeling concepts related to genotype by environment interaction (Cooper and DeLacy 1994), yield stability (Piepho 1998; Tollenaar and Lee 2002), product placement (Messina et al. 2018), and the target population of environments (Comstock 1977). These so-called $E(NK)$ models represent different environments or management practices through a series of more or less similar genetic landscapes. This of course adds considerable complexity to the already complex static landscapes studied here and poses interesting dilemmas. For example, rapidly exposing additive variation, e.g., through isolation, might be even more important than in static landscapes because local optima have to be exploited quickly before they disappear once the environment shifts, for example, through changes in management such as the historical increases in plant population for commercial maize production (Hammer et al. 2009). However, retaining allelic diversity, which hampers the exposing of additivity, is required to enable renewed adaptation to the changed environmental conditions. We here showed that a decentralized program structure can be superior over a centralized structure even if only a single environment type is targeted. We hypothesize that the benefit of decentralization increases even further when multiple distinct environment types have to be targeted simultaneously and require local adaptation (Smith et al. 2006). The $E(NK)$ framework is well suited to investigate the implications of a simultaneous presence of genetic and environmental complexity on breeding program structure design.

We noted that genetically distinct heterotic groups are an additional means by which genetic space is constrained. A simulation framework based on the NK model could be used to compare the efficacy of different strategies of identifying and maintaining heterotic patterns, particularly for crops which are still in the

early stages of heterotic group formation (Melchinger and Gumber 1998).

A high degree of genetic complexity also implies a high degree of context dependency of genetic effects. Observe, for example, that the additive substitution effect of the “A” locus in Figure 11 changes sign when the B_1 allele instead of the B_2 allele becomes rare. This has consequences on the persistence of accuracy of estimated QTL effects and genomic prediction models and can be addressed through iteratively updating training populations for genetic model parameterization (Podlich *et al.* 2004; Wolc *et al.* 2016; Forneris *et al.* 2017). The NK model framework can help address questions about the frequency with which this has to happen and whether data from previous generations can be used. Recently, approaches were proposed that attempt to capture those context dependencies through biological models representing the interdependencies underlying the traits of interest (Technow *et al.* 2015). Such models are only approximations of the true biological complexity. However, Cooper *et al.* (2005), using the NK framework, have shown that even incomplete knowledge of biological networks can improve predictability of genetic effects and genetic gain. The context dependency of genetic effects, *i.e.*, the effects being neither universally positive or negative (Wade 2002), also has implications on innovative proposals for using CRISPR-Cas9 gene editing (Jaganathan *et al.* 2018; Gao *et al.* 2020) to either target recombination to create superior hypothetical linkage groups (Brandariz and Bernardo 2019) or even the large scale “editing away” of deleterious mutations (Wallace *et al.* 2018). Finally, this framework might help devise strategies for the efficient introduction of exotic or ancient germplasm (Yu *et al.* 2016; Böhm *et al.* 2017), which evolved not just in a very different environment, but also a different genetic context from the current elite breeding germplasm.

Back to the future

The structure of commercial plant breeding programs, particularly in major crops like maize, is characterized by a large degree of decentralization with exchange of successful germplasm within companies (Cooper *et al.* 2014), while isolation is the norm among companies (Mikel and Dudley 2006). Plant breeders further have a tendency for relying on only a small set of elite inbred lines for producing the next generation (Rasmusson and Phillips 1997), leading to a series of significant bottleneck events (White *et al.* 2020). All of these features lead to a drastically reduced effective population size and are not predicted to be promising strategies under the additive, infinitesimal model of quantitative genetics. Yet commercial hybrid breeding has delivered incredible amounts of genetic gain over the last century, and has thus contributed to food security and resource conservation (Duvick 1999). Here, we postulated that the described structure of plant breeding programs, with its constraint of genetic space, is, in fact, necessary for enabling the exploration and exploitation of genetic variation in complex genetic landscapes and that the success of a breeding program is not only determined by its germplasm *per se*, but by the structures that allow it to evolve. The breeding program structure described here grew historically (Crabb 1947) and we do not claim that it was set up with this intention. However, by doing “what worked,” breeders in preceding generations might have nonetheless been able to take advantage of the process described and postulated in this study. Understanding why these historic structures “worked” will be critical for designing breeding programs that can tackle the challenges of the century ahead.

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Conflicts of interest

None declared.

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