

Predictive breeding for maize: Making use of molecular phenotypes, machine learning, and physiological crop models

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Abstract

Maize (*Zea mays* L.) has been a focus of scientific research and breeding for over a century. It is also one of the most economically important crops in the world, with a value of approximately US\$50 billion per year in the United States alone. Additionally, maize has long been the model species of choice for the study and exploitation of hybrid vigor, and it continues to be one of the world's most efficient converters of photosynthetic energy into starch. This review discusses the history and future of maize predictive breeding in the context of both genotype centric methods, and those focusing on genotype $\times$ environment $\times$ management interactions. Current prediction challenges are highlighted, as well as important advances in technology, methods, datasets, interdisciplinary collaborations, and scientific culture that will enable accelerated progress in predictive maize (and other crop species) breeding for years to come.

1 | INTRODUCTION

Maize or corn (*Zea mays* L.) has been subject to human selection and improvement for over 10,000 yr. It has also been a key organism for scientific study since at least the time of Charles Darwin (Darwin, 1876). Throughout this effort, predicting the performance of a given maize plant based on the phenotypes of its parents has been important. Early farmers, for example, saved seeds from their best plants under the expectation that those seeds would result in better plants in the next generation. Darwin, on the other hand, was intrigued by crosses of maize, and indeed between many other animal and plant species, which often resulted in hybrids that were more vigorous than self-pollinated plants (Darwin, 1868), contrary

to what would have been predicted at the time. Improvements in our ability to predict the outcomes of maize breeding (and breeding of other crops) have increased steadily over the past century and a half but have also transitioned through distinct stages marked by technical, statistical, and methodological advancements (Ramstein, Jensen, & Buckler, 2018). In this review, we discuss the history of predictive breeding in maize, recently developed prediction strategies and methods, as well as promising advances and future directions. This discussion is divided broadly into genomic prediction methods and advancements, and current and future opportunities to enhance the prediction of phenotypes based on genomic, environmental, and management data.

2 | A BRIEF HISTORY OF MAIZE GENETICS AND PREDICTIVE BREEDING

Numerous morphological, genetic, and archaeological studies indicate that modern maize originated from the ancestors of today's teosinte [*Zea mays* L., *Zea diploperennis* H.H. Iltis,

Abbreviations: G $\times$ E, genotype $\times$ environment; G $\times$ E $\times$ M, genotype $\times$ environment $\times$ management; GBLUP, genomic best linear unbiased prediction; GFBLLUP, genomic feature best linear unbiased prediction; GWAS, genome-wide association study; IBD, identity-by-descent; LD, linkage disequilibrium; MAS, marker-assisted selection; PHG, Practical Haplotype Graph; QTL, quantitative trait locus/loci; SNP, single nucleotide polymorphism; WCP, whole-crop physiological.

Zea perennis (Hitchc.) Reeves & Mangelsd., and *Zea luxurians* (Durieu & Asch.) R.M. Bird] (Beadle, 1939; Doebley, 2004; Hufford et al., 2013; Jaenicke-Després et al., 2003; Matsuo et al., 2002; Piperno & Flannery, 2001). Some of the earliest selections and improvements to these ancient teosintes came in the form of domestication traits, which were controlled by a few genes with large effects and could be easily selected phenotypically. The *teosinte branched 1* locus is a well-known example where the modern maize allele represses lateral branching, contributing to the compact single-stalk architecture of maize plants (Doebley, Stec, & Gustus, 1995). Other alleles, such as *teosinte glume architecture 1*, have dramatically changed ear morphology by exposing the kernels (Dorweiler, Stec, Kermicle, & Doebley, 1993). Still, other domestication-related genes control important traits like seed shattering, spikelet pairing, and ear rank (Stitzer & Ross-Ibarra, 2018).

A second distinct advancement in maize breeding and prediction was the introduction of Mendelian genetics and statistically informed formal breeding strategies. These included the formalization of genetic theory, and the advent of tools like the concept of genetic gain, the breeder's equation, linear mixed modeling, and the use of pedigrees as a tool for selection (Henderson, Kempthorne, Searle, & von Krosigk, 1959; Lush, 1937; Ramstein et al., 2018). Each of these advancements gave breeders a greater ability to predict the outcome of a given cross and more efficiently allocate resources to make genetic gain more likely. Of unique importance in maize improvement was the development of heterotic groups and hybrid vigor (Duvick, 2001; Jones, 1917). Although the exact mechanisms of hybrid vigor were not understood at the time (and remain the subject of much debate today), the results of its application in maize breeding were monumental (Duvick, 2001; Lippman & Zamir, 2007; Mezouk & Ross-Ibarra, 2014; Washburn & Birchler, 2014). Concurrent with these genetic advances was a revolution in agronomy and mechanized agriculture in the early to mid-1900s. This included the broad use of fertilizers and the introduction of modern fossil-fuel-powered farm equipment (Erisman, Sutton, Galloway, Klimont, & Winiwarter, 2008; Ertel, 2001). Norman Borlaug, who would later transform agriculture in his own way, described the changes that hybrid corn, fertilizer, and mechanization made to his 1930s teenage life as follows: "The two-month horror of harvesting, harvesting, husking, and heaving hundreds of thousands of corn ears was no more... With a tractor shouldering the brutal burdens corn picking seemed almost a lark... Suddenly [young farm boys] could shape our own fate... We could get an education; maybe even a profession" (Vietmeyer, 2011).

As significant as the innovations of the early to mid-1900s had been, predictive breeding was still limited by a lack of understanding the genetic architecture of complex traits, and the ability to do large-scale genotyping. In the 1970s and

the following decades, these phenotyping and genotyping tools came into existence and enabled statistical association studies between molecular marker genotypes and trait phenotypes. Genetic mapping, genome-wide association study (GWAS), and marker-assisted selection (MAS) became feasible and enabled maize breeders to better understand the genetic underpinnings of traits and to select for them more efficiently. Marker-assisted selection allowed breeders to select traits early in the breeding cycle, and the creation of detailed genetic maps allowed scientists to better localize and understand the genetic architecture of traits (Davis et al., 1999; Helentjaris, Slocum, Wright, Schaefer, & Nienhuis, 1986; Tanksley, Medina-Filho, & Rick, 1982). However, for traits like yield, which are controlled by many genes or quantitative trait loci (QTL) with small effects, GWAS still faced the combined challenges of multiple testing correction (resulting in more stringent significance cutoffs as the number of loci tested increases) and decreased detection power due to the genetic complexity of traits and the small effect sizes of individual QTL.

3 | GENOMIC PREDICTION

3.1 | The origin and implementation of genomic prediction

In the late 1990s to early 2000s, decreasing sequencing costs and the availability of informative markers led to a major shift in the scale of quantitative genetics. Where previous experiments were largely focused on small numbers of qualitative traits, the study of complex, polygenic traits became increasingly possible. Scientists had hypothesized that MAS alone could be used to predict the phenotype of an individual (Haley & Visscher, 1998). Shortly thereafter, thousands of markers were fitted simultaneously to estimate the genetic value of individuals to predict their phenotypes (Meuwissen, Hayes, & Goddard, 2001). This strategy of predicting genome-wide effects to gain accurate breeding values for individuals allowed for the acceleration of genetic gain per breeding cycle in previously difficult or inaccessible traits with low heritability, complex genetic architectures, and/or difficult to measure phenotypes (Heffner, Sorrells, & Jannink, 2009). This methodology is commonly known today as genomic prediction or genomic selection. Many statistical variations on genomic prediction models exist, the most common being genomic best linear unbiased prediction (GBLUP), ridge regression, or Bayesian methods (Gianola, de los Campos, Hill, Manfredi, & Fernando, 2009; Wang et al., 2018a; Whittaker, Thompson, & Denham, 2000). The details of these methods and their relative utilities for different applications have been discussed broadly by other authors (see citations above).

TABLE 1 Reduced genome representation approaches commonly used for maize genotyping and genomic selection. Table modified from Rasheed et al. (2017)

Approach	No. of target sites	Technology	Reference
Array	3000–50,000	Illumina BeadChip	Ganal et al. (2011), Rousselle et al. (2015)
Array	50,000–600,000	Affymetrix Axiom	Unterseer et al. (2014), Xu et al. (2017a)
Exome capture	Variable	Roche SeqCap EZ Design	https://sequencing.roche.com/en-us/products-solutions/by-category/target-enrichment/shareddesigns.html
GBS	50–300,000	Genotype-by-sequencing	Elshire, Glaubitz, Sun, Poland, and Kawamoto (2011)
DArT-seq	50,000	Diversity Arrays Technology (DArT) sequencing	https://www.diversityarrays.com/
rAmpSeq	1–2000	Repeat amplification sequencing	Buckler et al. (2016)
rhAmpSeq	5000	RNaseH2amplificationsequencing	https://www.idtdna.com/pages/products/next-generation-sequencing/amplicon-sequencing/custom-rhampseq-panels

In typical genomic prediction experiments, two forms of information on the breeding population are often collected: (i) high density, genome wide markers, and (ii) phenotypic data on the traits of interest. In the absence of genomic marker data, population pedigree data can also be used. A training population, containing both genotypic and phenotypic data from the desired breeding population, is used to create a model of genotypic effects and to estimate the breeding values for individuals (Jannink, Lorenz, & Iwata, 2010). Models generated using the training population are then used to predict estimated breeding values for new individuals for which phenotypes are desired but only genotypic information exists (Meuwissen et al., 2001; Poland, Endelman, Dawson, Rutkoski, & Wu, 2012). Prediction accuracy relies heavily on the relationship between the training population and the individuals being predicted, as well as the number of lines in the training population (Crosa et al., 2017). The power of a given trained model is also highly dependent on trait heritability, population size, population structure, and marker density (Liu et al., 2018).

3.2 | Genotyping strategies for genomic prediction

The number of genetic markers required to make accurate genomic predictions depends on the structure and complexity of the population and trait(s) of interest. In some cases, as few as 300 single nucleotide polymorphisms (SNPs) in maize are sufficient to make predictions on traits with low complexity, but the use of tens of thousands or more SNP variants is more common (Zhang et al., 2017). In any case, genomic prediction experiments typically make use of sparse sequence data (e.g., genotyping-by-sequencing [GBS], chip-array, etc.), which, thanks to the usually extended linkage disequilibrium (LD) patterns in breeding populations, is sufficient to identify extended haplotypes that might include causal loci (Xu, Li, Yang, & Xu, 2017b). This association, however beneficial for prediction across related populations, can also hinder the

implementation of genomic prediction in other cases. For example, the ability to perform prediction over more distant populations will be diminished, as LD patterns might not be shared, and the actual causal alleles might not be associated with any genotyped markers. Increasing marker density in these cases can increase prediction accuracy (Liu et al., 2018). Saturation of markers increases the probability that a marker will be in LD with a causal variant, but adding more markers to the same LD block does not provide additional useful information and increases the complexity of the model.

The development of accurate, affordable, and reproducible genotyping platforms has been a main driver in the adoption of genomic prediction approaches. In most cases, to keep costs manageable for a breeding program, genotyping involves analyzing a reduced representation of the genome (Table 1). The choice of genotyping technology is dependent on the genetic architecture of the trait(s) of interest, and the underlying population structure of the target population: simple traits and populations with extended LD patterns require fewer markers, whereas traits with complex genetic architecture and populations with low LD structure require larger numbers of markers for successful prediction.

To achieve the desired level of affordability, genotyping technologies have been developed to achieve maximal multiplexing—that is, the inclusion of as many samples per single experiment (DNA sequencing run) as possible. This push towards higher throughput multiplexing strategies has driven the development of new DNA sequencing chemistries and reduced representation approaches. A side effect of this multiplexing, however, is that some samples might be under-represented or missing in the genotyping libraries. To alleviate this problem, several bioinformatics approaches have been developed that allow for the imputation of missing genotypes.

Imputation approaches can exploit known pedigree relationships (Swarts et al., 2014), the diversity found in identity-by-descent (IBD) regions (Browning, Zhou, & Browning, 2018), or the relative measure of LD (Money, Gardner, Migicovsky, Schwaninger, & Zhong, 2015) in the

population. For imputation, maize represents a particular challenge (Bukowski et al., 2018), specifically when looking at diverse landrace material (Romero Navarro et al., 2017; Swarts et al., 2014), where regions of IBD might be hard to identify, LD decays particularly rapidly and heterozygosity is high. To improve on this, some current and future genotyping and imputation efforts look to leverage the known haplotypic diversity of a species by capturing the entire gene set in a representative pangenome (Golicz, Batley, & Edwards, 2016; Tettelin et al., 2005). Such a representation would also eliminate the inherent bias of mapping all genotypes to a reference genome that is more closely related to some genotypes than to others. Current efforts by the maize community are generating high-quality genome assemblies for many diverse maize lines (Hufford, 2019), as well as developing a genome graph approach for representing all known maize haplotypes (Bradbury et al., 2018). This particular graph approach, named the Practical Haplotype Graph (PHG), defines a set of evolutionarily conserved regions, to which assemblies from diverse maize accessions can be anchored. This collection of haplotypes is a representation of the maize pangenome and can be used with sparse and inexpensive genotyping data to construct high-quality imputations across populations for genomic prediction. Although this effort is ongoing in maize, human geneticists have reported improvements in read mapping sensitivity and structural variant calling based on graph representations of the human pangenome (Rakocevic, Semenyuk, Lee, Spencer, & Browning, 2019). Hopefully, the PHG and other novel genotyping and imputation approaches will reduce the costs of genotyping even further, allowing for increased use and accuracy in genomic prediction.

In recent years, genomic prediction has become commonplace in state-of-the-art maize breeding programs (see examples in Cerrudo et al., 2018; Crossa et al., 2014, 2017; Eathington, Crosbie, Edwards, Reiter, & Bull, 2007; Gaffney et al., 2015; Heslot, Jannink, & Sorrells, 2015; Ramstein et al., 2018; Shikha et al., 2017), but its use remains limited in smaller scale breeding, particularly in developing countries. This is due to many factors, including genotyping costs, education about when and how to apply genomic prediction, lack of computational expertise, and logistical challenges related to genotyping, analyzing, and making decisions within the short timeframe required for breeding. Ongoing work to disseminate genomic prediction to more breeding programs around the world, both in maize and other crops, will likely be critical to yield improvements and increased food availability (Bevan et al., 2017; Rasheed et al., 2017).

Although current genomic prediction methods have revolutionized maize breeding, they still have significant weaknesses (as discussed above), and they often fail to capture important amounts of heritable variation (Manolio et al., 2009; Xiao, Liu, Wu, Warburton, & Yan, 2017). Genomic prediction also commonly fails to make accurate predictions

across environments, and to disentangle genotype $\times$ environment ($G \times E$) interactions, which are often critical to predicting yield and other economically important traits (Boer et al., 2007; Cooper, Technow, Messina, Gho, & Totir, 2016; Technow, Messina, Totir, & Cooper, 2015; Zhao & Xu, 2012).

3.3 | Improving genomic prediction through the use of molecular phenotypes

Recent developments in genomic prediction have begun to analyze molecular phenotypes such as RNA, proteins, or metabolites, produced within an individual. These molecular phenotypes can be quantitatively measured and are associated with multiple, distinct layers of biological information. Importantly, they also represent intermediate states between the effects of genomic variants and the final, complex, whole-plant phenotype traits commonly measured in breeding programs (i.e., yield, biomass, plant height, etc.). Recent developments allow for assaying many molecular phenotypes in a high-throughput manner, using tens to hundreds of samples measured for tens to hundreds of thousands of individual observations from a single experiment (Kremling et al., 2018; Seifert et al., 2018; Yobi & Angelovici, 2018). It is the combination of these two characteristics—(i) representing a more direct effect of the genotype and a less complex trait than a whole-plant phenotype, and (ii) being high-throughput—that makes molecular phenotypes in genomic prediction valuable. These characteristics also lower the burden of multiple testing in the context of QTL mapping and GWAS studies by analyzing, for example, tens of thousands of expression levels, instead of hundreds of thousands to millions of SNPs. Indeed, recent approaches combining genetic markers, with transcriptome or metabolome data for association studies, have been shown to increase the power to detect causal genes (Kremling, Diepenbrock, Gore, Buckler, & Bandillo, 2019; Mancuso et al., 2017), and to better predict hybrid performance (de Abreu e Lima et al., 2017).

The effective implementation of molecular phenotypes in genomic prediction is contingent on several important factors and assumptions. First, since molecular phenotype expression can vary dramatically across tissue types and time points, both need to be relevant to the trait being predicted. Second, molecular phenotypes cannot always be assumed to be causative of the predicted phenotype, vs. the predicted phenotype causing the molecular trait. Although that assumption is tempting due to molecular phenotypes being biochemically closer to a whole-plant trait than a SNP, molecular phenotypes can only be considered as associative unless tested under a Mendelian randomization approach (Davey Smith & Ebrahim, 2003), because pleiotropic effects are possible and difficult to disprove.

3.4 | The role of transcriptomic and metabolomic molecular phenotypes in genomic prediction

Using transcriptomic data (RNA abundance) within genomic prediction has the ability to bridge the dynamic activity of gene expression to the static profiles of molecular markers. Doing so can potentially differentiate closely related individuals who share highly similar genotypes and capture epistatic interactions between lines (Westhues et al., 2017; Zenke-Philippi et al., 2017). In practice, however, the use of transcriptomic data alone or in combination with genotypic data has seen mixed and often trait-dependent results. In some cases, transcriptomic data alone outperformed genotypic data for highly complex traits like dry matter yield, whereas in other cases, no differences, or even reductions in prediction accuracy, were found between the genotypic and transcriptomic models (Westhues et al., 2017). The combination of both genomic and transcriptomic data as predictors in genomic prediction models also show trait-specific responses compared with standard genotypic models (Guo, Magwire, Basten, Xu, & Wang, 2016). In one study, models using both transcriptomic and genotypic data as predictors outperformed genetic markers for traits like dry matter yield and protein content while performing more poorly than, or equivalent to, genetic markers for predicting sugars, fat, and fiber content (Westhues et al., 2017). Similarly, in combined genomic and transcriptomic models, numerous traits related to plant architecture and flowering time saw small improvements in predictive abilities, whereas some traits related to yield such as kernel weight and cob diameter saw decreases in prediction accuracy (Guo et al., 2016). The combination of small RNAs, messenger RNAs, genotype, and pedigree information into a single model also shows accuracy increases for some traits; however, most combination models show little to no increase in their predictive ability compared with solely genotypic data (Schrage et al., 2018). The inability of the transcriptome to show meaningful changes over standard genomic prediction models may be hindered by the availability of adequate genomic and transcriptomic data (Zenke-Philippi et al., 2016, 2017). In addition, which tissues and developmental time points are most important for predicting a given trait is not immediately obvious, and resource limitations seldom allow for the scale of data needed to test multiple tissues and time points in a breeding program. Methods for imputing missing transcript profiles from genotype data have been developed (Gamazon et al., 2015). These methods have been shown to moderately improve prediction accuracy (Westhues, Heuer, Thaller, Fernando, & Melchinger, 2019), but further improvements in this area are possible by novel machine learning techniques on sequence data (Washburn et al., 2019). Reductions in the costs of RNA sequencing, along with improved sampling strategies for large populations, should allow more

thorough testing of the ability of transcriptomic data to improve genomic prediction models (Kremling et al., 2018).

Incorporating information on the metabolome during the early stages of a plant's life cycle is another method to possibly improve genomic prediction. Although metabolites have high turnover rates, they also have extensive diversity and have been shown to be associated with numerous quantitative traits in plants (Carreno-Quintero et al., 2012; Hill et al., 2015). In rice (*Oryza sativa* L.), metabolic-based predictions nearly doubled predictive ability compared with genomic markers (Xu, Xu, Gong, & Zhang, 2016). In maize, metabolic profiles have been shown to improve predictive ability over genomic data for grain yield and grain weight, but for numerous other traits, metabolic information alone decreases predictive abilities when compared with genomic markers (Guo et al., 2016; Riedelsheimer et al., 2012; Schrage et al., 2018; Westhues et al., 2017). Within maize, combining genotypic and metabolic prediction seems to be a much more powerful approach than metabolites by themselves (Guo et al., 2016; Westhues et al., 2017). The abundance of a given metabolite may be controlled by complex biochemical pathways and interactions between multiple proteins, genes, and modules of regulatory machinery. The incorporation of metabolites may be capturing networks of activity that are not captured by genomic and/or transcriptomic data. When used all together, metabolites, genetic markers, and transcriptomic data have higher predictive abilities than standard genomic prediction for numerous traits (Guo et al., 2016; Westhues et al., 2017). This increase might be attributed to the complementary novel information content overlap between genomic, metabolic, and transcriptomic data. The information content overlap between genomic and metabolomic data is likely much lower than the overlap between genomic and transcriptomic data, therefore allowing combined genomic, metabolomic, and transcriptomic models to outperform most single or paired predictor models.

The addition of metabolite information can provide insight into how different metabolites influence a single moment of a plant's life cycle. Sampling these moments, similar to sampling the transcriptome, can be very expensive for breeding programs when compared with genomic marker and pedigree information. Additionally, the time points and/or tissues one should sample to most effectively increase prediction accuracy are not always obvious. More efficient methods for sampling plants across the life cycle and for processing, identifying, and quantifying metabolites inexpensively could have profound effects on the application of both metabolite and transcriptomic data in predictive breeding. For example, physiological and developmental information has been used to determine the developmental time points most relevant to grain yield (Li, Guo, Mu, Li, & Yu, 2018b; Millet et al., 2019). These and similar analyses could be used to prioritize sample collection. Whole-crop physiological (WCP)

models (discussed in more detail below) could also be used in this way or perhaps adapted to produce rank ordering of the most important samples to collect for prediction of a given trait. Additionally, methods for predicting or imputing metabolism related traits from limited data should be explored. For both metabolomic and transcriptomic data, the expense and labor involved in generating the data often outweighs the potential gains. However, if sampling and imputation approaches can be made inexpensive enough, then including one or both of these data types in predictive models could become commonplace.

3.5 | Functionality of genomic-derived features and microbiomes in genomic prediction

Variants on genomic prediction models that use publicly available gene ontology information have been explored for their ability to assess the biological importance of genetic marker effects to improve prediction accuracy. In GBLUP models, genetic marker effects are not differentiated based on the genomic features they reside within. An alternative version of GBLUP models called genomic feature best linear unbiased prediction (GFBLLUP), incorporates gene ontology metadata on each marker as a covariate in a standard GBLUP model (Edwards, Sørensen, Sarup, Mackay, & Sørensen, 2016). This method has shown promising results between inbred lines of *Drosophila* and between cattle breeds (Fang et al., 2017). These additional gene ontology terms serving as predictors may be picking up on unique layers of trait functionality potentially associated with gene regulatory networks or transcriptional modules. These methods, however, are still limited by the availability of accurate genomic annotations in regions of the genome affecting the trait in interest (Edwards et al., 2016; Fang et al., 2017). Gene ontology information within GFBLLUP models has the ability to increase the predictive ability compared with GBLUP and can provide some biological insight into the genetic architecture of the trait under selection in addition to trait prediction (Edwards et al., 2016).

While not a molecular phenotype of an individual, the microbiomes of mammals have been used to predict complex host phenotypes. The human microbiota has been shown to affect gut metabolic pathways (Li et al., 2008) and brain behavior in individuals with anxiety (Foster & McVey Neufeld, 2013), whereas in plants, the microbiome within the rhizosphere and leaves of maize inbreds is heritable and genotype specific (Peiffer et al., 2013; Wallace, Kremling, Kovar, & Buckler, 2018; Walters et al., 2018) and plays multiple roles in immune health, nutrient uptake, and stress responses (Berendsen, Pieterse, & Bakker, 2012). Due to the impact of microbiomes on host phenotypic variation, the use of this alternative, genetic information in genomic prediction may be insightful. A study using metagenomic profiles to predict the

body mass index and inflammatory bowel disease in humans, as well as methane production in cattle, found that genetic information from these microbiomes, without any host genotypic markers, was able to predict the traits equivalently, if not slightly better than standard genomic prediction models (Ross, Moate, Marett, Cocks, & Hayes, 2013). These microbial communities capture an additional layer of genetic information that is not found within host genomes and could assist in breeding for traits whose phenotypes are strongly influenced by these communities (Ross et al., 2013).

3.6 | Machine learning methods in genomic prediction

Machine learning, as considered here, includes statistical methods and algorithms in which the system “learns” a function for predicting outputs from inputs based on the data itself, rather than the researcher providing the function. Machine learning methods for genomic prediction have been explored as both a complement to, and a replacement for, traditional GBLUP. Many types of machine learning methods can potentially be applied to genomic prediction, but deep neural networks show particular promise and are the focus of the methods here discussed. Any mathematical function can, in theory, be approximated by the right neural network. However, training a network to accurately approximate the relationship between genotypes and phenotypes (or anything else) requires showing it numerous datasets in which that relationship exists, and designing, training, and testing a network that can correctly identify that relationship. Additionally, like many statistical techniques, neural networks cannot inherently differentiate between correlation and causation (Marcus, 2018).

One example of the application of machine learning to genomic prediction is DeepGS, a deep learning based R package developed as a reduced marker assumption nonlinear genomic prediction model (Ma et al., 2018). DeepGS uses a multilayered convolutional neural network to learn the association between genotypes and phenotypes in training populations and then predicts breeding values within the test population. In tests on an Iranian bread wheat landrace population, DeepGS was comparable with ridge regression best linear unbiased prediction (RR-BLUP) and GBLUP in predicting grain length (Ma et al., 2018). Machine learning models have also been applied to understanding $G \times E$ interactions and their impacts on predictive ability. In both single- and multi-trait models in maize and wheat (*Triticum aestivum* L.), deep learning models performed better than standard GBLUP when $G \times E$ effects were removed (Montesinos-López, Montesinos-López, Crossa, Gianola, & Hernández-Suárez, 2018). However, when $G \times E$ effects were included, GBLUP performed better than deep learning methods. In general, current machine learning methods are not able to

outperform standard genomic prediction. It remains to be seen if fine tuning of these methods, either by carefully incorporating molecular phenotypes, and/or using better dimension reduction methods to identify subsets of highly informative data, may allow them to outperform standard genomic prediction.

3.7 | Future directions of genomic prediction in maize breeding

Much of predictive breeding suffers from high dimensionality where there is more information on genetic markers than there are observations ($n < p$) within the population (Crossa et al., 2017; Ramstein et al., 2018). This issue has been addressed in genomic prediction using numerous forms of dimensionality reduction. Some examples include selecting SNPs that are more functionally relevant according to machine learning (Li, Zhang, Wang, George, & Reverter, 2018a; Ma et al., 2018), and focusing on SNPs with high conservation as inferred by Genomic Evolutionary Rate Profiling (GERP) scores (Rodgers-Melnick et al., 2015; Yang et al., 2017). The use of open chromatin regions has also been suggested to reduce the complexity of the maize genome to the small, functionally accessible regions that account for most phenotypic variation (Rodgers-Melnick, Vera, Bass, & Buckler, 2016). This reduction in the genomic space containing the most informative loci can address the problem of high dimensionality. Ramstein et al. (2018) recently reviewed the $n < p$ dimensionality problem in great detail. They suggest that overcoming high dimensionality may be a critical step towards a new era in quantitative genetics. In particular, they concluded that key improvements of genomic prediction might come from high-throughput phenotyping (increasing n), the use of molecular phenotypes and/or component traits (potentially simplifying the genetic architecture), machine learning methodologies, and replacing genomic markers with high-quality haplotype data (e.g., using methods similar to the abovementioned PHG).

4 | PREDICTING ACROSS GENOTYPE, ENVIRONMENT, AND MANAGEMENT

Numerous approaches for predicting phenotypes from a combination of genotype, environmental, and management (sometimes included in environment) have been developed over the years (Burgueño, Crossa, Cornelius, & Yang, 2008, 2011; Fisher & Mackenzie, 1923; Malosetti, Ribaut, & van Eeuwijk, 2013; Thomas, 2010; van Eeuwijk, Denis, & Kang, 1996). Several recent approaches to the problem include: (i) using environmental covariance structures within a genomic

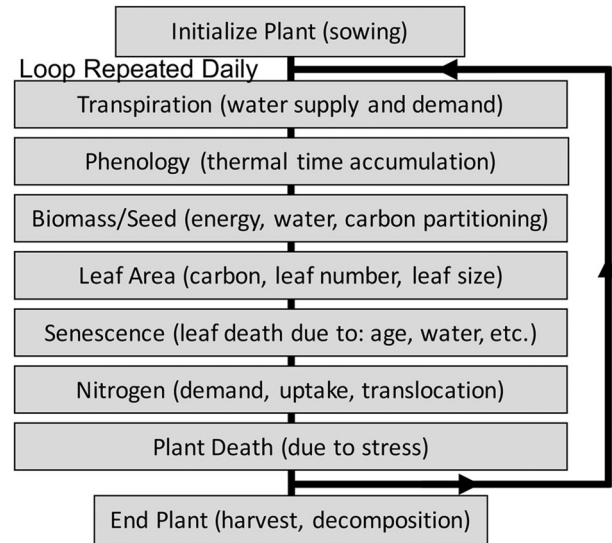


FIGURE 1 Diagram representation of a crop model (Soufizadeh et al., 2018)

prediction model (Jarquín et al., 2014), (ii) incorporating environments into genomic models through environmental indices (Li et al., 2018b), and (iii) incorporating whole crop physiological growth models into genomic prediction (Cooper et al., 2016; Technow et al., 2015). Each of these and other approaches have strengths and weaknesses that could be the subject of an entire review. Here, we will focus on the use of WCP models to improve genomic prediction. In so doing, we also discuss the importance of weather, soil, and field management data, and the inherent challenges in working across disparate disciplines such as soil science, agronomy, physiology, and breeding. Understanding these challenges will likely be crucial to any attempt at uniting genotype, environment, and management into a single useful predictive framework.

4.1 | Introduction to crop physiological models

Whole-crop physiological models rely on plant physiological measurements and calculations, as well as environmental variables to predict field level phenotypes over time (Hammer, Kropff, Sinclair, & Porter, 2002, 2016; Messina, Hammer, Dong, Podlich, & Cooper, 2009; Soufizadeh et al., 2018; Wang et al., 2002). Each day, the model cycles through a variety of modules, each determining aspects of the plant's development for the day based on the weather data provided, calculations of available water and nutrients in the soil, the plants leaf area and radiation use efficiency, and other factors. These calculations feed together into predictions about the plant's developmental stage, how much stress the plant is experiencing, and how much biomass the plant will gain on a given day (Figure 1). Whole-crop physiological models are typically constructed at a species level (i.e., a different model

for maize, sorghum [*Sorghum bicolor* (L.) Moench], wheat, etc.), but they also have built-in cultivar parameters which allow tuning to fit different genotypes (or cultivars) within a species. This tuning to a new cultivar is often referred to as model calibration and requires measuring physiological variables (phenotypes) on a new cultivar in as many environments as possible. Some of these phenotypes can be entered into the model directly, whereas others are compared with the models predictions and used as feedback in an iterative tuning process. Once calibrated, models can accurately predict cultivar specific phenotypes across widely varying locations (even future climates) given soil and weather data from those locations (Hammer et al., 2014, 2016).

Whole-crop physiological models have been applied to crop risk assessment, management decision making, and even plant breeding decisions for several decades (Hammer et al., 2014, 2016; Messina et al., 2009; Technow et al., 2015; Wallach, Makowski, & Jones, 2018). However, the models incorporate little to no genetic data, and calibrating them for new genotypes is costly, time consuming, and usually (though not necessarily) requires multiple seasons. Additionally, the estimation of model parameters can suffer from issues such as expressivity, equifinality, and instability (Lamsal, Welch, White, Thorp, & Bello, 2018). These challenges make it difficult to apply WCP models directly to novel breeding materials or even elite cultivars and make it nearly impossible to calibrate models for the large numbers of genotypes inherent in breeding programs. For these reasons, the impact of WCP models on predictive breeding in maize (and other crops) has been limited.

4.2 | Integrating physiological models with genomic prediction

The integration of quantitative genetic models with WCP models has long been proposed as a solution to the challenge of genotype $\times$ environment $\times$ management ($G \times E \times M$) prediction (Baldazzi et al., 2016; Chapman, Cooper, Podlich, & Hammer, 2003; Cooper & Hammer, 1996; Cooper & Podlich, 2002; Cooper et al., 2014, 2016; Hammer et al., 2006, 2016; Hoogenboom et al., 1997; Messina, Jones, Boote, & Vallejos, 2006; Parent & Tardieu, 2014; Reymond, Muller, Leonardi, Charcosset, & Tardieu, 2003; Technow et al., 2015; Wang et al., 2003; White & Hoogenboom, 1996; Yin, Struik, van Eeuwijk, Stam, & Tang, 2005). Various strategies for how this might be accomplished have been proposed, but in general, none of the strategies have been fully explored, implemented, and tested. One exception is a recent attempt made by scientists at DuPont Pioneer (now Corteva). In this case, approximate Bayesian computation and Bayesian hierarchical models were used to unite a standard genomic prediction model with a very simplified WCP model (Cooper et al., 2016; Messina

et al., 2018; Technow et al., 2015). These methods outperformed the standard genomic prediction model in the context of training in one environment and predicting in another while showing similar results to the standard model for within environment predictions.

In general, the development of integrated quantitative genetics and WCP models faces several significant community-level challenges. Some of these challenges are cultural or historical (the two types of models were developed by different communities and for different purposes over decades), whereas others are more specific to the challenging nature of the problem itself (i.e., need for large datasets, computational resources, etc.). Necessary in solving each of the challenges is a critical mass of investigators from multiple disciplines working together.

4.3 | Major challenges

4.3.1 | Culture

A surprising, yet significant, challenge to the development of integrated WCP and quantitative genetic methods is the educational, linguistic, and practical divides between geneticists/breeders (those whose education is genetics centric) and agronomists/physiologists/soil scientists (those whose education is more physiology or chemistry centric). Although both groups of scientists work with plant-based agriculture, the terminologies they use and their approaches to the same problems are very different. Additionally, the way these subdisciplines of plant science set up and execute experiments and the desired outcomes are not always compatible. Not surprisingly, genetics and breeding experiments often maximize the number of distinct genotypes being studied. This is particularly true in quantitative and population genetics where large numbers of genotypes are required to meet the statistical requirements in the desired analysis. Genetic experiments are also often designed with the goal of minimizing environmental variation or simply controlling for it statistically. Agronomy, physiology, and soil science projects often take the opposite approach in that genetic variation is minimized. These experiments may involve a single genotype examined under multiple sets of conditions. In some cases, many environments may be critical to these experimental designs, whereas a single well-controlled environment is preferred in others. The disparate goals between the subdisciplines make the generation of cross-discipline datasets challenging (see the section on data collection below), but they also hamper collaboration and discussion across the disciplines.

The quantitative genetics and plant breeding viewpoint, for example, often focuses on end points and static relationships (e.g., the relationship between plant yield and a given cultivar's genetic marker data). Whole-crop physiological model

practitioners, on the other hand, tend to view the world in terms of time-dependent relationships and processes that vary with the plant's developmental stage. These differences in viewpoint are not particularly surprising when one considers that a given plant's genetics are in fact stable across the entire growing season, whereas the physiological and developmental processes the plant is undergoing change with time.

Some simple yet pervasive examples of differing viewpoints can be illustrated by the different semantics of common agricultural research words and phrases. In physiological modeling, the word environment is thought of and measured in complex, time-dependent variables, which can be extremely granular and specific (e.g., temperature variations across hours, days, weeks, at a specific location). In quantitative genetics, on the other hand, environments are generally represented and thought of in a reduced or summative form. Environments may be represented as indices, for example, or more often they are simply thought of as distinct experiments or replicates in a statistical framework and characterized by plant performance differences (e.g., the yield of cultivar x is more variable across environments than is the yield of cultivar z). These differences in viewpoints and terminologies extend further into the meaning behind ideas like $G \times E \times M$ interactions. Breeders and geneticists take a plant-centric viewpoint of $G \times E$ and rarely use (or think in terms of) the $G \times E \times M$ terminology. From the plant's point of view, all influences external to it are environmental. Agronomists, physiologists, and soil scientists, on the other hand, often take the farmer's perspective and think in terms of $G \times E \times M$. Here, environment includes only factors that are out of the farmer's control, and management includes factors that can be influenced through agronomic intervention.

4.3.2 | Data collection

As mentioned above, the goals, design, implementation, and analysis of experiments varies widely across genetics, breeding, agronomy, physiology, and soil science. This presents a major challenge to the integration of quantitative genetics with WCP models because currently available datasets only include subsets of the types of data needed. For example, there are many high-quality datasets available on the effects of variations in soil type and chemistry on plant phenotypes, but these datasets are mostly limited to a few genotypes. Conversely, multiple large-scale datasets are available for maize association and diversity panels with thousands of genotypes included across multiple environments, but the matching soil data and many physiologically important variables are not available. Even when attempts are made to collect extra data (i.e., more genotypes in a soil experiment, or soil data in a genetics experiment), the financial costs and/or the expertise to collect the proper data are too prohibitive. Table 2 lists

the types of data that might be considered minimal for running both genomic prediction and WCP models given current separate implementations (based primarily on data used by the Agricultural Production Systems sIMulator, or APSIM) (Archontoulis, Miguez, & Moore, 2012; Cresswell, Hume, Wang, Nordblom, & Finlayson, 2009; Dalgliesh & Foale, 2005; Littleboy, Freebairn, Silburn, Woodruff, & Hammer, 1999). Of course, the relative importance of each of these variables within the context of a combined model, and if any of them can be imputed without significant loss of fidelity, need to be tested experimentally.

On the other hand, one phenotyping concept used in both quantitative genetics and physiological modeling is the idea of breaking complex phenotypes (like yield or biomass) into component traits (like stress tolerance, seed number, and weight, etc.). Complex traits are likely controlled by many genes and tied to multiple physiological processes. Breaking them down into simpler, better understood traits should allow more accurate and intuitive modeling and more straightforward genetics. Component traits like flowering time are relatively simple to measure, but still time consuming on a large scale. Others, like radiation use efficiency, require specialized equipment and/or highly controlled conditions for accurate measurements. Recent advances in high-throughput phenotyping allow many traits to be measured quickly and accurately using unmanned aerial vehicles, field robots, or sensors mounted on farm vehicles and driven through the field (Andrade-Sanchez, Gore, Heun, Thorp, & Elizabete Carmo-Silva, 2014; Crain, Mondal, Rutkoski, Singh, & Poland, 2018; DeChant et al., 2017; Shi et al., 2016; Wang, Singh, Marla, Morris, & Poland, 2018b). These high-throughput phenotyping systems may even be able to estimate some of the more difficult physiological traits using machine learning algorithms, carefully designed training experiments, and/or correlated traits (Ramstein et al., 2018; Rosati, Metcalf, & Lampinen, 2004; Twohey, 3rd, & Studer, 2018; Zhang et al., 2015). Such advances could enable WCP model calibration and validation at population scales.

4.3.3 | Modeling and computation

Whole-crop physiological and quantitative genetics models are built on statistical frameworks and philosophies distinct from each other. Whole-crop physiological models rely heavily on physiological calculations made from both small- and large-scale experiments and approximations calculated through differential equations. They calculate daily intermediate values that result in the final trait values (yield, biomass, height, etc.). Cultivar tuning is often performed manually and based on limited amounts of training and testing data. Genomic prediction models, on the other hand, rely almost entirely on maximum likelihood or Bayesian

TABLE 2 Minimal phenotypes, weather, soil, and management data required for running a typical crop growth model. Based on the requirements of the Agricultural Production Systems sIMulator (APSIM)

Measurement	Description or formula
Plant phenotypes	
Planting date	Date seeds were planted
Flowering/anthesis date	Date when 50% of plants have 50% of their anthers exposed
Harvest date	Date when grain was harvested
Grain yield	Weight of grain, and grain moisture content at harvest
Grain no. per ear	Average number of kernels per ear of corn
Grain weight	Average weight of a single kernel
Total leaf number	Total number of leaves produced through plant's life cycle
Largest leaf area	The area of the largest leaf (generally the ear leaf)
Biomass (at least for checks)	Aboveground total plant biomass (excluding grain)
Soil/water/residue properties (by soil layer) ^a	
Bulk density (BD)	How dense or porous the soil is. $BD = \text{dry soil weight} / \text{soil volume}$
Gravimetric water content (GWC)	Percentage water in soil. $GWC = [(\text{wet weight} - \text{dry weight}) / \text{dry weight} - \text{container weight}] \times 100$
Drained upper limit (DUL)	Water held by soil after drainage. $DUL = GWC \times BD$
Saturated water content (SAT)	Maximum water soil can hold. $SAT = [1 - (BD/2.65)] - e$, $e = 0.03$ (clay soil) to 0.07 (sandy soil)
Lower limit 15 (LL15)	Soil water content at 15 bar (1.5 MPa) vacuum pressure
Air dry (AD)	$AD = LL15 \times A$, $A = 0.5$ to 1 depending on soil depth. See Cresswell et al. (2009)
Soil texture	Relative proportion of sand, silt, and clay within the soil.
U	Water evaporation potential from bare soil. See Littleboy et al. (1999)
Conna	Soil water evaporation over time. See Littleboy et al. (1999)
Soil pH	pH of the soil
Soil and root C/N ratios	Ratio of C to N separately for soil and roots
Soil organic carbon (OC)	Organic C in soil separated into labile and inert pools
Initial water	Water in the soil profile at beginning of simulation
Initial N	N in the soil profile at beginning of simulation
Surface residue amount	Residual surface organic matter present at beginning of simulation
Surface residue C/N ratio	Ratio of C to N in surface residue
Agronomic/management details	
Irrigation (dates and quantities)	Amount of water applied to the field through irrigation
Fertilizer (dates, types, quantities)	Amount of fertilizer applied to the field
Tillage (date, type, depth)	Tillage and/or cultivation applied to the field
Row and plant spacing	Spacing between rows of plants and plants in a row
Planting depth	Depth to which seeds were planted in the soil
Harvesting equipment and scheme	Equipment used for harvesting and how harvest was carried out
Field layout (row and column)	Layout of the field. How were different cultivars or species spread across the field spatially?
Weather recording (daily measurements)	
Radiation	Average incident shortwave radiation over the day
Max. temperature	Daily maximum temperature
Min. temperature	Daily minimum temperature
Precipitation	Total precipitation over the day
Vapor pressure	Average water vapor partial pressure over the day
Daylength	Time from dawn until dusk

^asoil descriptions and calculations summarized from Archontoulis et al. (2012) and Dalgliesh and Foale, (2005).

regression frameworks, without intermediate phenotypes, and are entirely focused on predicting final trait values. When compared with WCP methods, genomic prediction models are usually relatively simple with very few inputs and outputs (single phenotype, genomic, and/or pedigree relationships). Publication standards are also different between the model types, with genomic prediction models undergoing extensive leave-one-out or k -folds testing (the product is a model that will be recalibrated for use on different populations), and WCP models generally being tested and calibrated across many environments (the product is a calibrated model). An important point here, which relates to the earlier discussion on cultural differences, is that breeders and geneticists are trained with a statistical viewpoint that does not allow for the use of testing data to improve the model in any way. Using the same data (or insights gained from it) to both improve and test the model is considered scientifically unacceptable. This viewpoint is critical because the statistical models used in breeding and genetics (i.e., genomic prediction) are generally nonmechanistic by definition and can therefore not be validated biologically. Whole-crop physiological models, on the other hand, are calibrated with the perspective that fundamental biological, chemical, or physiological mechanisms are represented within the model, and that the model should be validated, at least in part, by its mechanisms and results fitting within the realm of well-researched scientific understanding. Combined models will likely need to be validated in multiple ways including both biological sensibility and k -folds or leave-one-out testing methods that test in both genotypes and environments never previously seen by the model.

Both WCP and genomic prediction models require substantial computational resources and many iterations (e.g., iterative optimization algorithms for maximum-likelihood-based models such as GBLUP, or Markov chain Monte Carlo sampling for Bayesian regression models). Both can be run on a standard desktop computer for very simple datasets, but running larger datasets becomes too resource intensive and requires the use of high-performance computing clusters. Parallelization is possible for many use cases of both methods, and in some cases, data structure analyses have been used to efficiently organize computational runs and better utilize available resources (Lamsal et al., 2017). Any combination of WCP and genomic prediction models into a common framework will most certainly require high-performance computing, as well as careful software engineering to reduce the resources needed for computation. Even then, being able to gather all of the needed data and run the models fast enough for use in a breeding program may be challenging. As discussed above, the Messina et al. (2018) implementation of genomic prediction combined with WCP was able to run within a reasonable timeframe due to the use of a simplified WCP model. The effects of these

or any simplifications on model accuracy remain unknown at this point, but future research into the value (in terms of speed and accuracy) of simplifying WCP and genomic prediction models in a combined framework will be critical to designing the most cost-effective and useful modeling schemes. The application of machine learning, ensemble models (combination of multiple models together), and other statistical methods that are flexible to data input types and designed for modeling nonlinear properties should also be useful for incorporating $G \times E \times M$ into predictive models. These approaches are beginning to be applied to the field, but their full potential remains relatively unexplored (Montesinos-López et al., 2018).

5 | CONCLUSIONS

Maize breeding began many centuries ago with early farmers saving seeds from their best plants for use in the next generation. Today, large and highly efficient maize breeding programs carry on that tradition, but with numerous molecular, statistical, computational, and technological tools. Genomic prediction, in particular, has become a critical tool for large-scale maize breeding programs around the world and has the potential to revolutionize smaller-scale public, private, government, and nongovernment breeding efforts in maize and other species. Current challenges and opportunities in predictive breeding include: (i) better measurement and incorporation of high-throughput phenotypes, molecular phenotypes, and environmental data into predictive models, (ii) reducing the costs and increasing the availability of genotyping, phenotyping, and predictive modeling, (iii) finding new and better ways to overcome the $n \ll p$ dimensionality problem (the first and second points should help with this), and (iv) increasing collaboration and communication across disciplines. Machine learning methods show promise for overcoming some of these issues by allowing predictive models that are more flexible to data formats and can better capture nonlinear relationships. The use of crop growth models together with genomic data also shows great promise for cross-environment prediction. High-accuracy models that can predict and explain the performance of new genotypes in new environments would allow unprecedented gains in maize breeding efficiency, and the development of new maize cultivars that can survive and thrive in current and future climates.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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