



Predicting phenotypes from genetic, environment, management, and historical data using CNNs

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Abstract

Key Message Convolutional Neural Networks (CNNs) can perform similarly or better than standard genomic prediction methods when sufficient genetic, environmental, and management data are provided.

Abstract Predicting phenotypes from genetic (G), environmental (E), and management (M) conditions is a long-standing challenge with implications to agriculture, medicine, and conservation. Most methods reduce the factors in a dataset (feature engineering) in a subjective and potentially oversimplified manner. Deep neural networks such as Multilayer Perceptrons (MPL) and Convolutional Neural Networks (CNN) can overcome this by allowing the data itself to determine which factors are most important. CNN models were developed for predicting agronomic yield from a combination of replicated trials and historical yield survey data. The results were more accurate than standard methods when tested on held-out G, E, and M data ($r=0.50$ vs. $r=0.43$), and performed slightly worse than standard methods when only G was held out ($r=0.74$ vs. $r=0.80$). Pre-training on historical data increased accuracy compared to trial data alone. Saliency map analysis indicated the CNN has “learned” to prioritize many factors of known agricultural importance.

Introduction

Prediction of phenotypes from a combination of environmental (E), genetic (G), and human-imposed (often referred to as management, M) conditions has been a long-standing

challenge in biology and related fields (Messina et al. 2009, 2018; Technow et al. 2015; Cooper et al. 2016, 2021; Varshney et al. 2017; Washburn et al. 2020; Jarquin et al. 2021; Li et al. 2021). Most traditional approaches have focused on simplifying the problem by holding one or more factors constant (genetics, environment, management, or some subset within these) or accounting for some of the factors statistically as nuisance parameters. Methods have also generally been tailored to specific use cases and developed within a single siloed sub-discipline (Meuwissen et al. 2001; Jones et al. 2003; Holworth et al. 2014, 2018; Crossa et al. 2017; Boote 2019). The methods used for prediction have also varied significantly, from fine-tuned mechanistic models designed to closely replicate physical and biological processes, to abstract statistical models with the goal of predicting phenotypes using the simplest mathematical function that results in the highest accuracy.

Mechanistic models such as crop growth models (CGM) rely on physiological equations validated through detailed experimentation and can make predictions with high accuracy when provided with high-quality data (Holworth et al. 2018; Soufizadeh et al. 2018; Hammer et al. 2020). However, the types of data and quality needed are prohibitively expensive and impractical for any more than a few cultivars

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(G) at a time. Geneticists and breeders have successfully used statistical models, primarily Best Linear Unbiased Prediction (BLUP) and genomic BLUP (GBLUP), for decades (Henderson 1975; Meuwissen et al. 2001; Gaffney et al. 2015). These methods have focused on prediction within the G space (sometimes called genomic prediction (GP)), but can be extended to incorporate information from E and/or M (Jarquín et al. 2014; Li et al. 2021). The downside to these methods is that they are not mechanistic in nature and require extensive feature engineering and data complexity reduction in order to avoid overfitting, limiting their interpretation, and perhaps accuracy. Conversely, GP methods are fairly robust to lower quality multi-environment trial data. Methods that incorporate both mechanistic and statistical components have recently been developed (Technow et al. 2015; Messina et al. 2018; Millet et al. 2019), and shown promise, but they still require data that are not easily collected by most research or breeding programs, and many aspects of the models have not been publicly released.

While current methods have had significant impacts on phenotype prediction and continue to yield important results in breeding and agronomy, they are each limited in the context of prediction across G, E, and M by one or more of the following: (1) a reliance on subjective feature engineering and factor reduction, (2) a need for expensive or low through-put data, and (3) the inability to utilize historical datasets not designed specifically for that method.

Machine learning approaches such as Convolutional Neural Networks (CNN), Multilayer Perceptrons (MLP), and others have the potential to overcome many of these current limitations. CNNs are neural networks that have at least one convolutional layer. They typically also contain fully connected layers like those found in an MLP. Thanks to convolutional layers, CNNs can handle 1D, 2D or 3D input signals, whereas MLPs require flattened 1D inputs. Convolutional layers can automatically extract features, capture local and global features, utilize patterns related to the 2D or 3D positions of features, and they can do it with fewer parameters than MLPs (Botalb et al. 2018). This makes them more robust to overfitting. In theory, CNN models can estimate any continuous function regardless of its complexity, as long as enough examples are provided for training and the network is large enough (Zeng et al. 2016; Zhou 2020). This allows them to derive efficient representations of input data automatically, with limited feature engineering. CNNs are also extremely flexible to different input data types, and with large enough datasets (which is not always possible) and proper design they can perform robustly on low-quality data (Yim and Sohn 2017; Qin et al. 2019). Additionally, while CNNs are often referred to as a “black box,” there are now well-demonstrated methods for dissecting and interpreting the processes within a given CNN model, and the features the model determines to be most important to prediction

(Simonyan et al. 2013; Samek et al. 2019). Many of these interpretation tools, and even the machine learning methods themselves, are still in their infancy so it is likely they will continue to improve rapidly over the coming years.

Several authors have applied CNN, MLP, and other machine learning models to plant phenotype prediction, but the quantity of data available in these studies was typically small when compared to the hundreds of thousands or even millions of data points used in more traditional CNN applications (e.g., image classification) (Montesinos-López et al. 2018, 2019; Pérez-Enciso and Zingaretti 2019; Zingaretti et al. 2020; Abdollahi-Arpanahi et al. 2020). Perhaps for this reason, phenotype prediction with CNNs has continued to rely on extensive feature engineering and factor reduction, and primarily used very shallow neural networks. A few attempts at using larger datasets with less feature engineering have been made, but these have not included a G component (Khaki et al. 2019; Shahhosseini et al. 2021).

In this study, CNN models for predicting grain yield were developed following a philosophy of maximum feature inclusion and limited feature engineering. Additionally, every attempt was made to include as many samples as possible in the dataset, to the extent of including historical samples with only partial data available, through transfer learning (using a pre-trained model as a starting point for model fitting). Extensive public maize field study data from The Genomes To Fields (G2F) Initiative, along with historical data from the United States Department of Agriculture–National Agricultural Statistics Service (USDA-NASS) and other governmental databases made using a very large dataset (> 100,000 samples) possible (AlKhalifah et al. 2018; McFarland et al. 2020). On the other hand, all phenotypes, weather, soil, and management data came from publicly available sources and are the common types of data that a typical farmer, plant breeder, or agronomist could access or collect inexpensively today. While these models were developed in an agricultural system, the basic philosophy and results should be widely applicable across biology and other areas.

Materials and methods

Data mining and cleaning

Phenotypic, genetic, and field location and management data were obtained from The Genomes to Fields (G2F) initiative Genotype by Environment experiments from 2014 to 2017 (Gage et al. 2017; AlKhalifah et al. 2018; Falcon et al. 2020; McFarland et al. 2020). The phenotypic data were filtered to remove samples with yield values of zero and to ensure that only samples with both genotypic and phenotypic data were included. The genotype data for each cultivar were obtained directly from Anne Rogers based on the filtering process

described in (Rogers et al. 2021). Principal components (PC) analysis was performed on the genotype data using TASSEL (Bradbury et al. 2007), and the first 30 principal components were used in the CNN. Other than using PCs to represent the genotypic data, and a limited amount of quality filtering as described above and below, very little feature engineering was performed on the data. This was a purposeful choice in order to allow the model itself to determine which features were of greatest importance. Methods to account for and visualize spatial field effects were also used to examine and filter the data, but these attempts appeared to have little impact on the results and so were not used in the final datasets and models.

Historical county level data were downloaded from the United States Department of Agriculture, National Agricultural Statistics Service for all of the continental United States from 1970 to 2018. Weather data from each of these US counties as well as from each of the G2F field sites were downloaded for the same time period from the DAYMET website (<https://daymet.ornl.gov/>) using custom scripts (see bitbucket repository, https://bitbucket.org/bucklerlab/maize_yield_pred) (Thornton et al. 2016).

The soil data used were pulled from the SSURGO Database as county-specific folders containing many correlated tables. Soil attributes available for any given county were highly variable, so attributes with low representation were filtered from the set. Soil attributes were averaged across depths into three depth ranges.

Training, validation, and test set development

Training, validation, and test sets were developed to examine four scenarios to represent those faced in agricultural prediction: the “strict G and E”, “practical G and E”, “G” and “E” holdout scenarios. For the strict G and E scenario (the scenario used for model structural optimization described below), all historical data from any year and any US County within the G2F dataset were withheld from the training sets (Supplementary Fig. S1). The G2F data were divided into 50 training, validation (for model structural and other optimizations), and test sets including the historical test set for cross-validation. Some field locations with less data were combined into a single fold, but most locations were left as separate folds. Each of the 49 G2F folds contained a training, validation, and test set. Cultivars in test sets were downsampled to ensure that each fold had the same number of cultivars represented and the same number of total samples in the test set. Training sets were then formed from all locations that were not present in the test set and cultivars that were related to test set cultivars were excluded (based on k-means clusters on the genotypic data). In this testing scenario (strict G and E), different G2F years in the same location as a test set location were excluded from the

training set. The validation set was derived from the training set by randomly sampling 5% of the training set and excluding those samples from the training set. Each of the other scenarios was designed in a similar manner except that sampling conditions about G and/or E were relaxed as detailed below.

For the practical G and E holdout scenario, the historical pre-training set was relaxed to include locations sampled in the G2F data during years previous to the G2F data. The same was true for the G2F data splitting, with a given training set being able to contain locations in the test set as long as they were not from the same year. Downsampling of cultivars to enforce strict testing set balance was also relaxed in this scenario to increase the number of samples in the sets.

The E holdout scenario was designed in a similar way to the two G and E holdout scenarios except that cultivars were not considered. Environments were defined similarly to the practical holdout set with the training sets being able to include the same field location as long as it was not in the same year. Downsampling and combining of some locations was also carried out in order to create more balanced test sets.

The G holdout scenario was similarly designed to the two G and E holdout scenarios except that environments were not held out. Downsampling of genotypes was again employed with the goal of creating balanced test sets. Because of the complications of doing this while also controlling for genetic relatedness of individuals, the final G holdout test sets were based on randomly chosen cultivars and the final training sets were constrained to exclude those cultivars.

Consistent with machine learning best practices, models were developed, optimized/selected, and tested using training, validation, and test sets, respectively. The purpose of the training set is to train the model, the purpose of the validation set is to choose the best model structure, hyper-parameters, and random initialization parameters. Because MLP and CNN models are non-deterministic and rely heavily upon randomly initialized values there can be substantial variation between runs on the same training set. For this reason, it is common to run multiple replicates and average the results in order to smooth out the variation (ensemble learning on initializations). Occasionally, the randomly initialized values will result in a replicate of the model not converging well or at all. These replicates can be detected and removed using the validation set (similar to using the validation set to tune hyper-parameters or determine model structure) in order to arrive at a better model for applied prediction and/or testing using a held-out testing set (never seen by the model in any previous step). All models presented here were run in sixteen replicates. The validation sets were then used to remove the six replicates with the worst scores (See Supplementary Table S1 for results from all sixteen replicates). This resulted in ten replicates which were used to evaluate

the model's performance on the held-out test sets. This performance was averaged to provide the final predicted value for each sample. Summary statistics were then calculated on a per fold basis and averaged to find the mean performance across all folds.

CNN and MLP models

CNNs were created with 1D convolutional, dense, and dropout layers. Final models have three-streams, and these streams are concatenated to predict yield (Supplementary Fig. S2). The first two streams (Weather and soil plus some field management available historically) were used for both historical and G2F data, while the third stream (Genetics, fertility, and field management not available historically) was included only after pre-training. Since weather data were represented with a 1D time series, 1D convolutional layers were used to extract weather-related features automatically in the weather stream. A 1D convolutional layer performs convolutions over a single axis, in this case the date, while a 2D convolutional layer would perform convolutions over both axes (date and weather factor). There is no obvious use for convolutions over weather factors so a 1D layer was deemed appropriate. The use of 2D convolutional layers was also attempted but appeared to have no benefits toward model accuracy. Because other streams were not a time series, they did not have convolutional layers and started with dense layers directly. As is the case with most CNN models, our model is actually a combination of fully connected and CNN layers. We used a linear activation function in the last layer and Rectified Linear Unit (ReLU) in the rest. Mean squared error was used as the loss function. The choice of ReLU activation functions as opposed to sigmoid or hyperbolic tangent (\tanh) was based on its popularity in the field and evidence of its ability to converge more quickly than \tanh activation functions (Bishop 2006; Xavier Glorot et al. 2011; LeCun et al. 2015). Experiments were done to test the replacement of ReLU functions in our model with \tanh functions and no benefits were found. The use of a linear function in the last layer of the model is consistent with common practice for regression problems and has been previously suggested for genomic prediction (Bishop 2006; Pérez-Enciso and Zingaretti 2019). Using a \tanh function in the last layer, and data transformation, was also attempted, but accuracy was very poor.

CNN and MLP models have hyper-parameters that need to be selected and optimized for model accuracy. There are millions of possible hyper-parameter combinations, and thus an efficient method is needed to select the best hyper-parameter combination. We optimized the number of convolutional layers (1–3) dense layers (2–6 in weather stream, 2–5 in genetics stream), filter size (4, 8, 16, 32, 64, 128), number of kernels (1, 3, 5, 8, 16, 32), pool size (3, 5, 8, 16, 32), strides (1, 3,

5, 8), batch size (16, 32, 64, 128), tail layer number (1–5), tail layer size (4, 8, 16, 32, 64, 128), and Adam optimizer (used to train the model) parameters (learning rates: 0.1, 0.01, 0.001, 0.0001; beta1 and beta 2: 0.9–0.9999) using the hyperopt package (Bergstra et al. 2013) based on validation set accuracy. Hyperopt finds the best value of a scalar-valued, possibly stochastic function over a set of possible arguments to the function. The FMin function with the Tree of Parzen Estimators (TPE) algorithm in hyperopt was used. The function takes a large parameter or hyper-parameter space like the one above and uses a sequential optimization approach (SOM) and the previous hyper-parameter candidate set to maximize the expectation of improvement on performance.

Layer-by-layer details of the final optimized model and hyper-parameters can be found in Supplementary Table S2 and in the public code repository. The CNN models were built and run using the tensorflow.keras module version 2.1.0 in python 3.6.9 (Chollet 2015; Abadi et al. 2016a, b). The final model specifications can be found in the bitbucket repository. For comparison, a full multilayer perceptron (MLP) model was also created by replacing the convolutional layers in the CNN model with dense layers.

Saliency maps

Saliency maps (Shrikumar et al. 2017; Zintgraf et al. 2017) were computed from the saved models from each CNN run using the tf-keras-vis module in python (<https://github.com/keisen/tf-keras-vis>). All reported scores are based on training sets and were averaged across replicates and splits to obtain the final values shown in the figures.

BLUP models

Genotypic values of hybrids were predicted by best unbiased linear prediction (BLUP) methods, under the following $G \times E$ BLUP model (Jarquín et al. 2014):

$$\mathbf{y} = 1\mu + \mathbf{g} + \mathbf{e} + \mathbf{i} + \varepsilon;$$

$$\mathbf{g} \sim N(\mathbf{0}, \mathbf{G}\sigma_G^2), \quad \mathbf{G} = \frac{\mathbf{X}\mathbf{X}^T}{\text{tr}(\mathbf{X}\mathbf{X}^T)/n};$$

$$\mathbf{e} \sim N(\mathbf{0}, \mathbf{S}\sigma_S^2 + \mathbf{W}\sigma_W^2), \quad \mathbf{S} = \frac{\mathbf{Z}_S\mathbf{Z}_S^T}{\text{tr}(\mathbf{Z}_S\mathbf{Z}_S^T)/n}, \quad \mathbf{W} = \frac{\mathbf{Z}_W\mathbf{Z}_W^T}{\text{tr}(\mathbf{Z}_W\mathbf{Z}_W^T)/n};$$

$$\mathbf{i} \sim N(0, [\mathbf{G} \circ \mathbf{S}]\sigma_{GS}^2 + [\mathbf{G} \circ \mathbf{W}]\sigma_{GW}^2);$$

$$\varepsilon \sim N(0, I\sigma_\varepsilon^2);$$

where \mathbf{y} was the vector of hybrid phenotypes; $\mathbf{1}\mu$ is the grand mean of \mathbf{y} . The vector \mathbf{g} consisted of main genomic effects; \mathbf{G} was the genomic relationship matrix calculated from \mathbf{X} , the (non-centered) matrix of allele counts at imputed SNPs; tr is the trace operator (sum of a matrix's diagonal elements); and n is the sample size. The vector \mathbf{e} consisted of main environmental effects; \mathbf{S} and \mathbf{W} were the environmental relationship matrices calculated from \mathbf{Z}_S , the matrix of soil covariates (geographical location, management, soil properties), and \mathbf{Z}_W , the matrix of weather covariates (day of year, day length, maximum and minimum temperatures, precipitation, radiation, vapor pressure, CTT). Soil and weather covariates were adjusted by their mean and scaled by their standard deviation. Weather covariates were included as averages over adjacent windows of width 3 (e.g., average temperature between day 1 and day 3). The vector \mathbf{i} consisted of genome-by-environment interactions, as captured by $\mathbf{G} \circ \mathbf{S}$ and $\mathbf{G} \circ \mathbf{W}$, where \circ denotes the Hadamard (elementwise) products. The vector $\boldsymbol{\varepsilon}$ consisted of independent and identically distributed errors.

In the $D \times E$ BLUP model, the $G \times E$ BLUP was extended to account for dominance effects, as follows:

$$\mathbf{y} = \mathbf{1}\mu + \mathbf{g} + \mathbf{g}_D + \mathbf{e} + \mathbf{i} + \mathbf{i}_D + \boldsymbol{\varepsilon};$$

$$g_D \sim N(0, D\sigma_D^2), \quad \mathbf{D} = \frac{\mathbf{H}\mathbf{H}^T}{\text{tr}(\mathbf{H}\mathbf{H}^T)/n};$$

$$\mathbf{i}_D \sim N(0, [\mathbf{D} \circ \mathbf{S}]\sigma_{DS}^2 + [\mathbf{D} \circ \mathbf{W}]\sigma_{DW}^2);$$

where \mathbf{D} was the dominance relationship matrix calculated from \mathbf{H} , the (non-centered) matrix of heterozygosity at imputed SNPs (0 if homozygous genotype, 1 otherwise).

In GE BLUP and DE BLUP models, interaction effects (\mathbf{i} and \mathbf{i}_D) were omitted.

The BLUP models (GE/ $G \times E$ /DE/ $D \times E$ BLUP models) were fitted by restricted maximum likelihood (REML) using the R package `qgg` (Rohde et al. 2020).

Automated CGMs

Several approaches were developed and tested for calibrating APSIM version 7.10 crop growth models to new cultivars in an automated fashion based on limited phenotypic data (Holzworth et al. 2014, 2018). Calibration and testing of these approaches was carried out using the same training and test sets described above. The simplest automated method involved running APSIM on all available default maize cultivars within each of the training set environments. The best performing set of cultivar parameters for each actual cultivar in the dataset was then chosen based on the calculated error between observed and predicted yield values. In the

scenarios in which G (cultivar) was held out, the genetic similarity matrix was used to assign the cultivar parameters of the most genetically similar training cultivar to the test cultivar. A second method was also used in which the default maize APSIM cultivars were again used as a starting point, but in this case, the parameter for growing degree days to flowering was adjusted to fit the known flowering dates of cultivars in the training set. Otherwise, the two methods were identical. A third method was also developed in which standard cultivar specific APSIM parameters were optimized to cultivars in the training set in an iterative fashion. This method was more computationally intensive and did not appear to work any better than the other two, so it was abandoned and not tested extensively.

Results

All models were trained and tested under three basic holdout scenarios and some special cases. For most analyses, E and M were held out jointly due to the limited amount of M data, and the extra computational time that would be required. However, the approach could be applied to separate E and M with little modification. In each scenario, a subset of G , E , and M , or combinations of the three, were withheld from the model and used as the test set (see Materials and Methods section for more details on training, validation, and test splits). Model performance was evaluated using a variety of metrics (Supplementary Table S3), but Pearson r values were used here to discuss the results, in keeping with the GP literature. In general, the trends seen in the Pearson r values were similar to those seen for other metrics such as root mean squared error (RMSE). Situations where this was not the case were noted. All results were based on test sets that included only data from the G2F experiments. The G2F data included over 38,000 data points and the historical data consisted of over 78,000 data points (Supplementary Table S4). The MLP and CNN models performed similarly in all cases, but the MLP model had about 35% more parameters than the CNN model.

The CNN model extrapolates to unknown G , E , and M similarly or better than other methods

Two scenarios were used to evaluate model performance while holding out G , E , and M . The scenarios used k -means clustering to hold out related cultivars. The first scenario, which we named the “strict GEM holdout,” excluded all field locations in a given test set from the training set, including all data from that location in any other years. Although this scenario is not typical in agriculture, it does occur when new land is being used, or when records from the land do not exist. This scenario is also important for studying agriculture

under climate change, as it tests the models' ability to extrapolate to unknown environments and unknown cultivars, and represents a complete G, E, and M holdout. Under this scenario, all models performed poorly with average Pearson r values ranging from 0.06 and 0.23 (Fig. 1a). The GBLUP, CNN without historical data, AUTO CGM, GE BLUP and GxE BLUP methods were the poorest performers based on both Pearson r and RMSE (Supplementary Table S3). The pre-trained CNN, which leveraged the historical survey data, the MLP, and the DE and DxE BLUP models performed the best (though still poorly), with average Pearson r value of from 0.20 to 0.23. The RMSE of the pre-trained MLP model was slightly better than that of the CNN model in this case and represents a 14% decrease from that of the worst performing model (Table 1). The high standard deviation of all of the models in this scenario makes it impossible

to conclude with confidence that one model is better than another, but the CNN, MLP, and DxE BLUP models perform the best on average.

The second G, E, and M) holdout scenario is here called the "practical GEM holdout" as it is meant to replicate the types of situations farmers, breeders, and researchers most commonly encounter. In this case, the training set was constructed in a similar way to the strict GEM scenario, except it included locations that were in the test set as long as the location data came from a different year than that being tested. The models performed with Pearson r values ranging from 0.08 to 0.50 (Fig. 1b). The GBLUP and AUTO CGM models performed most poorly while the CNN with historical data performed the best ($r \sim 0.50$). The CNN with and without historical data performed more similarly based on RMSE values (Supplementary Table S3). The RMSE of

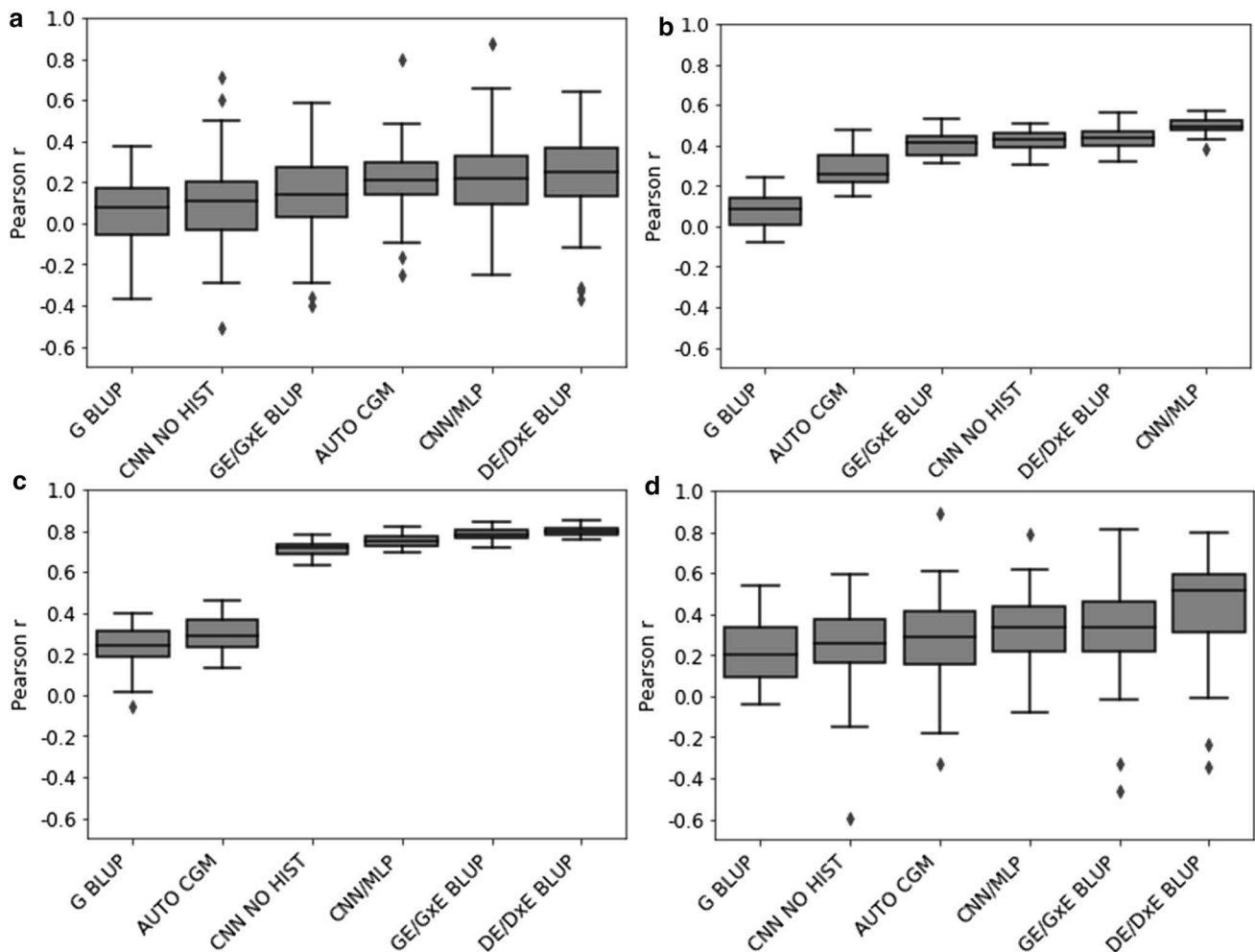


Fig. 1 Pearson r values for different tested models in four scenarios. **a** Strict genetic, environmental, and management holdout scenario with no previous year data given for held-out environments and strictly balanced test sets. **b** Practical genetic, environmental, and management holdout scenario with previous years data given. **c** Genetic hold-

out scenario. **d** Environmental and management holdout scenario. Box plot elements: center line, mean; box limits, upper and lower quartiles; whiskers, maximum and minimum with outliers excluded; points, outliers

Table 1 Percentage increase or decrease in Pearson r and RMSE values between different methods and in different scenarios

Scenario	Comparison	Method 1	Method 2	Pearson r increase	Pearson r % increase	RMSE % decrease
E holdout	With vs. Without Historical	CNN NO HIST	CNN	0.07	30.2	6.1
E holdout	Worst vs. Best	AUTO CGM	CNN/MLP	0.03	9.5	26.6
E holdout	Best BLUP vs Best CNN	DE/DxE BLUP	CNN/MLP	N/A	N/A	7.9
E holdout	A vs A + D BLUP	GE/GxE BLUP	DE/DxE BLUP	0.12	36.8	2.4
G holdout	With vs. Without Historical	CNN NO HIST	CNN	0.03	4.4	4.6
G holdout	Worst vs. Best	AUTO CGM	DE/DxE BLUP	0.50	171.7	49.1
G holdout	Best BLUP vs Best CNN	DE/DxE BLUP	CNN/MLP	N/A	N/A	N/A
G holdout	A vs A + D BLUP	GE/GxE BLUP	DE/DxE BLUP	0.01	1.9	3.0
GEM Practical	With vs. Without Historical	CNN NO HIST	CNN	0.07	17.1	2.4
GEM Practical	Worst vs. Best	AUTO CGM	CNN/MLP	0.21	74.0	24.4
GEM Practical	Best BLUP vs Best CNN	DE/DxE BLUP	CNN/MLP	0.07	16.4	4.1
GEM Practical	A vs A + D BLUP	GE/GxE BLUP	DE/DxE BLUP	0.02	5.3	3.1
GEM strict	With vs. Without Historical	CNN NO HIST	CNN	0.11	119.1	1.2
GEM strict	Worst vs. Best	AUTO CGM	CNN/MLP	0.02	11.8	14.4
GEM strict	Best BLUP vs Best CNN	DE/DxE BLUP	CNN/MLP	N/A	N/A	1.7
GEM hard	A vs A + D BLUP	GE/GxE BLUP	DE/DxE BLUP	0.10	70.7	6.0

For each scenario, a comparison is shown between a reference model (CNN without historical data, worst performing model, best performing BLUP model, best performing additive BLUP model) and a Test model (CNN with historical data, best performing model, best performing CNN model, best performing additive plus dominance model). E holdout is a training scenario in which a subset of both environment and management data are held out for testing. G holdout is a scenario where genetic data are held out for testing. The GEM scenarios holdout genetic, environmental, and management data in a “strict” or “practical” way, with environment and management data from other years in the same location being held out or not, respectively

the best performing model represents a 24% decrease from that of the worst performing.

When the models were trained under a “G holdout scenario” (training on all environmental and management data but with a portion of the cultivars withheld as a testing set), they performed with average Pearson r values across folds ranging from 0.24 to 0.80 (Fig. 1c). The standard GBLUP and AUTO CGM models performed far worse than the other models in the G holdout scenario. When trained only on the G2F data set and corresponding environmental variables, the CNN model performed with an average r value of 0.68 but was boosted to a value of 0.74 when the model was pre-trained on historical data. The best performing model in the G holdout scenario was the DxE BLUP model (Jarquín et al. 2014) with an r value of 0.80. The RMSE of the best performing model represents a 49% decrease from that of the worst performing (Table 1).

Model performance under the “E holdout scenario” (trained using all cultivars but withholding environmental and management data) resulted in average Pearson r values between 0.21 and 0.44 (Fig. 1b); however, the highest r values did not seem to track well with the RMSE values in this case. The worst performers were the G BLUP, CNN without historical data, and AUTO CGM. The CNN/MLP models with historical data training, GE BLUP, and DE BLUP models both performed the best, but all models had high standard

deviations. While the DE/DxE BLUP models had the highest r values, the CNN and MLP models actually had the best RMSE values (Supplementary Table S3). The RMSE of the best performing model represents a 27% decrease from that of the worst performing.

The BLUP models based on both additivity and dominance performed better than the additive only models in every case (Table 1, Supplementary Table S3). Previous work on a subset of this dataset showed that the inclusion of dominance improved accuracy by 7–10 percentage points under a scenario similar to our G holdout scenario (Rogers et al. 2021). In our case, the inclusion of dominance resulted in an improvement of 2 percentage points for the G holdout, 12 for the E holdout, 10 for the strict GEM holdout and 2 for the practical GEM holdout. The percent decrease in RMSE from the best additive to the best additive and dominance model for each of the scenarios ranged from 2 to 6% (Table 1). Based on RMSE, the greatest advantage for the model that included dominance occurred in the strictest GEM scenario.

Pre-training with historical data increased model accuracy

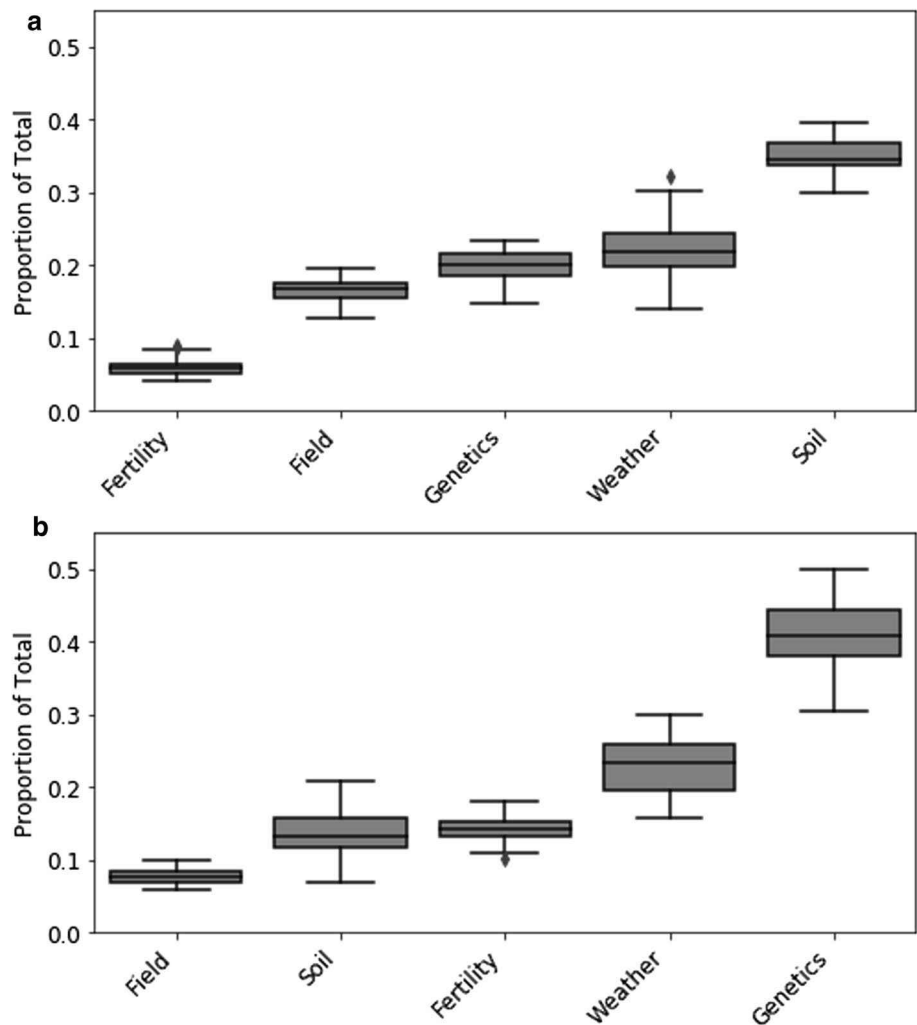
Historical maize yield and weather data by US County are available going back decades, as well as low-resolution

soil and weather data across most of the continental US (see Materials and Methods). Pre-training the CNN model based on these data and then fine-tuning the model using the modern G2F dataset (see [Materials and methods](#)) resulted in increases in accuracy for all of the scenarios (Table 1). For the G holdout scenario and the E holdout scenario, historical pre-training resulted in 5% and 6% reductions in RMSE, respectively, in comparison with the same scenario without pre-training. For the two G and E holdout scenarios, changes in RMSE were minimal. The CNN model was also run using the historical data as the only training, but still testing on the G2F data as above. In this case, the model performed much worse than it did when trained on both the historical and G2F data, or on the G2F data alone (Supplementary Table S3). Together, these results indicate that pre-training with historical data improved prediction accuracy but was not itself sufficient for predicting yield in G2F trial data.

What factors are most important in the CNN model?

Saliency maps were used to investigate the importance of each input factor in the model. In general, the holdout scenario had little impact on the relative importance scores for each model factor, but the use of historical pre-training had a major impact on the scores (Supplementary Fig. S3). Precipitation, vapor pressure, and planting density were among the most important factors in the model independent of whether or not historical pre-training was used (Supplementary Fig. S4). When summarized into overall categories (weather, soil, field, fertility, and genetics), the most important factors with historical pre-training were: soil (35% of total importance score), weather (22%), genetics (20%), field (15%), and fertility (8%) (Fig. 2a). Conversely, when historical data were not included in the model the genetic data was the most important (40%) followed by weather (23%), fertility (19%), soil (14%), and field data (3%) (Fig. 2b). These differences are likely a direct result of not having genetics and fertility data in the historical set.

Fig. 2 Saliency map score summaries displayed as a proportion of the total of all scores for each of the five main data type categories included in the models. **a** With the use of historical data in model training. **b** Without the use of historical data in model training. Box plot elements: center line, mean; box limits, upper and lower quartiles; whiskers, maximum and minimum with outliers excluded; points, outliers. All values based on the practical GEM scenario



Weather-related factors were examined in more detail both across and within the growing season. The importance of weather-related factors did not change substantially across different training set scenarios, but it did change for some factors depending on the inclusion of historical data (Supplementary Fig. S5). The most important weather-related factor in the model was precipitation, accounting for an average of 37–42% of the total saliency map weather score in the practical G and E holdout scenario (Fig. 3). The ranking of other weather factors changed somewhat depending on the use of historical pre-training (Fig. 3). Combining maximum and minimum temperature together into a single factor resulted in temperature being the second most important factor regardless of historical pre-training (20–26% on average). Vapor pressure is also one of the most important factors accounting for 11–18% of the score. Overall, factors related to humidity and temperature captured most of the signal about environments, as opposed to radiation and daylength.

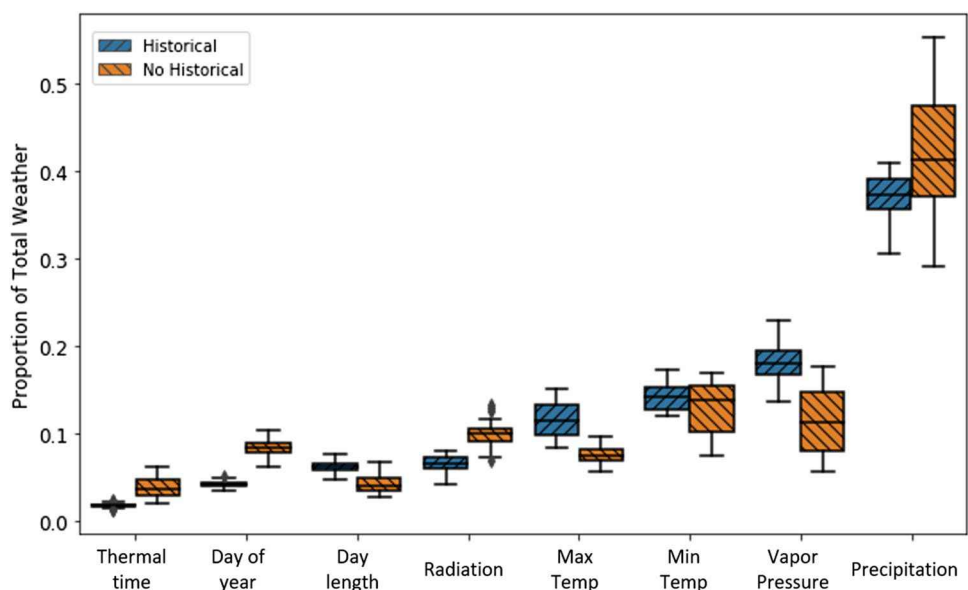
The weather-related saliency scores on a daily basis are reasonably similar across all training scenarios except for the G and E holdout scenarios where historical pre-trained CNN models show some days in which the vapor pressure exceeds the saliency score for precipitation (Supplementary Figs. S6–S7). As a general trend, precipitation had higher scores than other factors across the entire season regardless of pre-training (Fig. 4). However, the importance of other weather-related factors increased with pre-training. Precipitation typically had its highest daily scores soon after planting, peaking around 5–15 post-planting, and then having two smaller and flatter peaks around 50 and 110 days after planting. The other factors had similar trends to precipitation with the exception of vapor pressure and minimum temperature, both of which had their second peak shifted earlier at around

30–35 days post-planting when pre-trained on historical data (Fig. 4a). In the case of both the G alone and E alone holdout sets with historical pre-training, this shift was also seen for maximum temperature (Supplementary Figs. S6–S7). Therefore, pre-training affected the relative importance of weather-related factors, as well as time periods during the growing season.

Soil and fertility-related factors with highest importance scores included soil electrical conductivity, calcium carbonate, saturated hydraulic conductivity (Ksat), gypsum content, and others (Supplementary Fig. S8). Soil fertility and field management factors with the highest importance scores included planting density, irrigation, and percent sodium (Na) (Supplementary Figs. S9–S10). Standard fertilizer components such as nitrogen (N), phosphorus (P), and potassium (K) also had substantial contributions when trained without historical data. In general, soil and management factors related to water use and plant density show the highest importance values, followed by NPK, and micronutrients.

To further dissect the importance of different factors, the models were run while excluding categories of factors (Supplementary Fig. S11). Due to computational constraints, not all combinations of factors were tested, and updated models were not re-optimized. The exclusion of any single category (Soil, Fertility, Field/Management, Weather, or Genetics) from the model, under any of the training scenarios, generally resulted in a decrease in accuracy, but these decreases were typically small, and the removal of historical pre-training from the model usually resulted in larger reductions than the exclusion of any single category of factors (Supplementary Fig. S11). However, training the model with only one factor included at a time generally resulted in poor model accuracies. Therefore, there is complementarity

Fig. 3 Saliency map score summaries displayed as a proportion of the total of all weather-related scores for each of the eight weather categories used in the models. Box plot elements: center line, mean; box limits, upper and lower quartiles; whiskers, maximum and minimum with outliers excluded; points, outliers. All values based on the practical GEM scenario



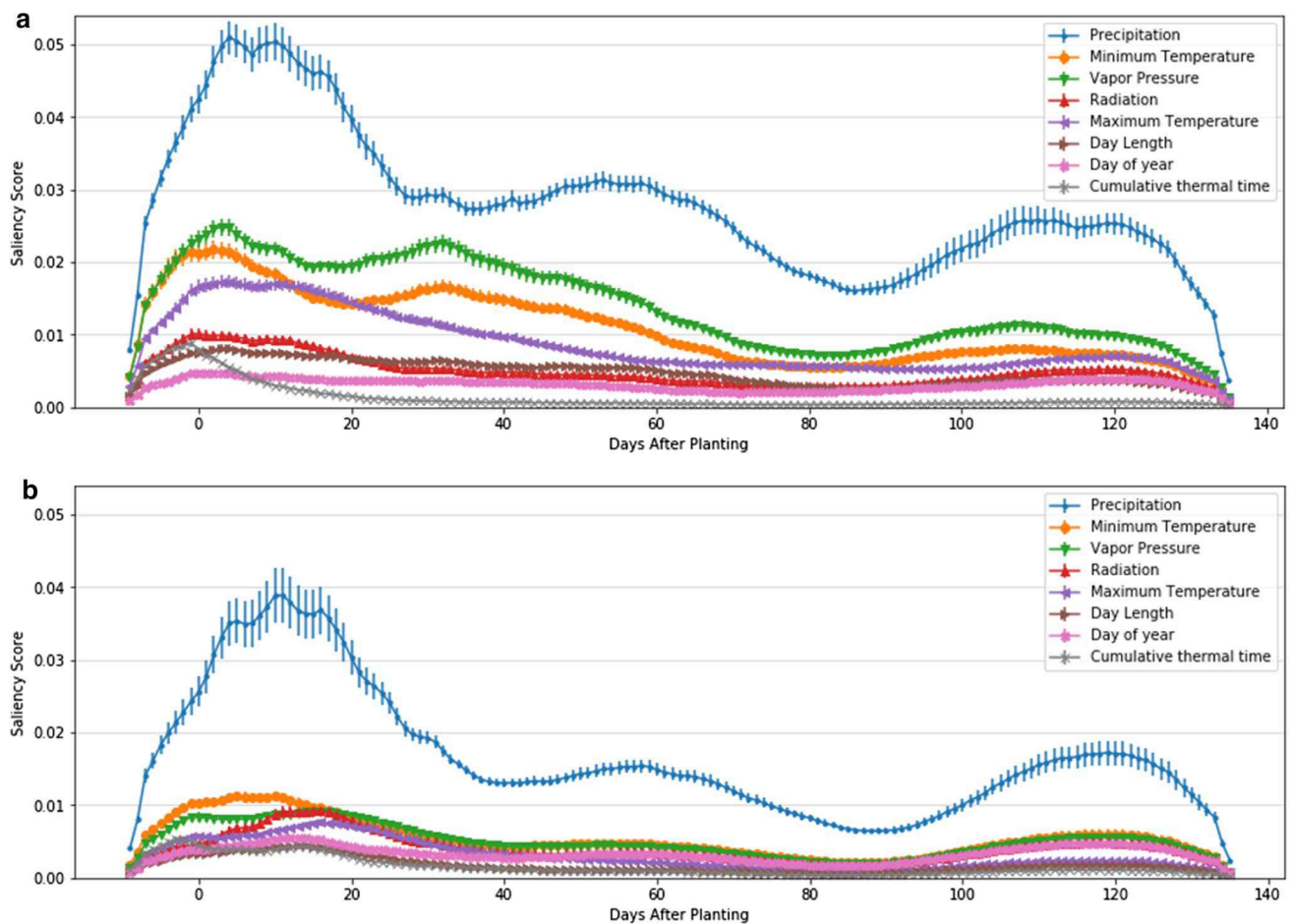


Fig. 4 Daily Saliency map weather scores. Values are the average across all splits from the practical G and E holdout set with (a) and without (b) historical pre-training. Error bars are the standard error across splits

among categories of factors, even though their contribution to accuracy is not entirely distinct.

Discussion

Assumptions, sources of error, and complexity of the data and models

The results presented above should be considered in the context of the datasets used for analysis. The final Genomes to Fields (G2F) dataset here used was a combination of phenotype, environmental, and management data taken by hundreds of different individuals across more than 90 distinct location-by-year environments spanning much of the continental US (see [Materials and methods](#)). Each site and year was different in terms of the environmental, social, and technical conditions that influenced the planting, agronomic practices, data collection, and many other variables. Extensive measures were taken to reduce these errors and to

account for them statistically, but there is no doubt that many factors remain unaccounted for even in the most complex models here developed. Because of a desire to include as many data points as possible in the models, very little data were removed through filtering.

It is also important to consider several decisions made during the construction of the CNN model that are likely to impact the results in different scenarios. The structure of the CNN model was optimized using validation data within the most challenging “strict G and E” holdout scenario (see [Materials and methods](#)). The model structure was not optimized for any of the other scenarios, but simply trained on data from each of those scenarios. For that reason, the results presented above are likely underestimates of how well a CNN model could perform in those scenarios if the structure were optimized for them. Considerable effort was spent to develop training and test sets that would not bias the model or allow it to predict well based on extraneous factors. The strict G and E holdout scenario in particular was designed as a stringent scenario to minimize opportunities for a model to

“memorize” details of the training set and still do well on the test set. While we cannot completely rule out the possibility that the model is gaining accuracy from extraneous factors, the saliency maps and results from excluding different factors indicate this is unlikely.

The large number of features and limited use of feature engineering in the model allow the exploration of many potential contributors to model performance, but they also introduce potential collinearities into the model. This is not a concern for the model’s prediction accuracy because regularization and testing sets were used. However, the saliency map results indicating the importance of different factors should be interpreted in the context of these potential collinearities. The use of principal components to represent the genetic data in the model removes any potential for collinearity in the model’s genetic components. The majority of input features for the model do not show strong correlations (Supplementary Fig. S12, Supplementary Table S5). Features that do show strong correlations between each other are primarily those with obvious mathematical connections in how they are calculated. For example, one might expect percent soil silt and percent soil sand to be correlated with each other because their calculation relies on the same denominator. Other features with strong correlations also have obvious biological or physical links such as: temperature and vapor pressures, temperature, and latitude. A close examination of correlated features indicated that collinearities in the data are likely few and saliency maps should be interpretable in the context of the statistical correlations and the known physical and biological relationships between the factors.

Value and trade-offs of using sparse historical data

The use of sparse, low-resolution historical data from commercial corn production over the past several decades, as well as additional low-resolution soil and weather data from national repositories, generally resulted in model accuracy increases and RMSE decreases (Table 1). The decreases in RMSE values were most pronounced in the E holdout scenario (6%) followed by the G holdout (5%), practical G and E (2%), and G and E (1%) scenarios. It is interesting that the historical data were most helpful in the E holdout and G holdout scenarios. The explanation for this may be at least partially attributed to the fact that these scenarios have more training data to begin with (they only hold out G or E). The historical data were also held out to a lower extent in these scenarios, so the models were trained on much larger datasets than they could be without historical data. Historical data pre-training also appeared anecdotally to increase model stability across training epochs.

The saliency map results indicate that models trained without the historical data make less use of weather and soil data than those trained with historical data. One might

reasonably conclude that the approximately 90 examples of weather and soil data corresponding to the G2F trials are simply not enough examples for the model to learn how these factors are correlated with yield. This potential lack of information about environments might be all the more limiting since empirical models like CNNs rely completely on the data they are given, as opposed to mechanistic models which use known relationships between factors and plant growth. In that case, an argument can be made that a model pre-trained on thousands of historical examples of the relationship between weather, soil, and yield is likely to be more transferable to new datasets. On the other hand, the lack of genetic, field/management, and high-resolution soil and fertility data in the historical set introduces a potential bias to the model because it has more opportunities to learn about weather and soil features, and therefore may overstate their importance. With the current dataset, we cannot test this hypothesis since we do not know how the model would perform, and what factors would be most important, in the hypothetical case where we had high-resolution genetic, fertility, and other data for each historical data point.

Importance of different factors

Arguments surrounding the relative importance of genetics, environment, and management have occurred for many decades. One would be hard pressed to conclude from the literature, or the results of this project, that any one factor is the most important or should be studied at the exclusion of the others. Additionally, management factors were largely underrepresented in the G2F dataset. That said, regardless of the training scenario, several factors consistently ranked highest in their importance scores. One clear conclusion, which is supported by both the literature and the current state of knowledge in maize production, is that planting density is a critical factor in determining maize yield (Duvick 2005). Planting density was correlated with year in the dataset (0.64, Supplementary Table S5). Year has low saliency scores in all analyses, and given both the correlations and current understanding of maize, it is likely that planting density is in fact very important in this dataset. Precipitation also showed an outsized importance score when compared to most other factors in the model and has relatively low correlations within the dataset. The importance of precipitation in plant agriculture is well known and obvious, and it has long been regarded, along with soil properties that change water availability to the plant, as one of the most critical factors in crop growth models (Barnett and Thompson 1982; Riha et al. 1996; Togliatti 2017). Our findings further validate and reinforce the idea that both soil properties and weather parameters related to water are of critical importance in predicting and/or understanding plant growth across environments. Fertilizer-related values (particularly NPK) were

not as important as we had expected, but this is likely due to the fact these values do not exist in the historical data, and even the G2F experiments were mostly performed with relatively low amounts of fertilizer compared to commercial production. There are a number of correlations between applied fertilizers and fertility-related measurements taken in the field (Supplementary Table S5). These correlations are expected, and it is possible that the importance of some of these fertility-related factors is being underestimated in the saliency scores due to collinearity or the distribution of importance across multiple factors making each one relatively small.

Weather factors associated with temperature have also long been considered of significant importance in predicting plant growth and development (Togliatti 2017; Tollenaar et al. 2017). In this study of the G2F data set, daily minimum and maximum temperature were both of high importance to the CNN model. Cumulative thermal time, calculated from the maximum and minimum temperature, is considered a critical phenological component in crop modeling, and was calculated and included as a factor in the models trained here. Thermal time had the lowest importance score of any weather factor in the CNN model. This is likely due to the strong relationship and statistical correlation between temperature and thermal time, and the ability of CNNs to produce their own functions of temperature (and other raw input data) for more accurate predictions. It appears the CNN model was able to gain more value from the two temperature factors alone than from their reduced representation as thermal time. Atmospheric vapor pressure was also an important factor (11–18%). Vapor pressure is related to effects of both water availability and temperature, and is known to play an important role in the plants' ability to transpire, draw in nutrients, and carry out photosynthesis (Rawson et al. 1977; Lobell et al. 2013; Yuan et al. 2019). Temperature and vapor pressure were highly correlated in the data set (Supplementary Table S5). Given these correlations and the physical/chemical relatedness of these factors, it is difficult to assign greater importance to one versus the other. Radiation, day length, and day of year all had relatively low importance scores, but not low enough to be assumed insignificant. These factors also generally (and based on correlations in our data) have close relationships with temperature, which may have reduced their utility in the model.

Some of the most important soil factors included soil electrical conductivity (EC), gypsum content, calcium carbonate, saturated hydraulic conductivity (Ksat), and cation exchange capacity. These features had moderate correlations to each other and to some other soil and weather factors (Supplementary Table S5), but there are no obvious patterns indicating the saliency scores for these features are untrustworthy. EC is a proxy measurement associated with water-soluble salt concentrations in the soil. The concentration of

salts in the soil can make it more or less difficult for the plant to absorb water because it changes the osmotic pressure. Gypsum content in the soil has been shown to be important to plant growth in many ways: it is a source of both calcium and sulfur, it aids in soil water absorption, it can improve root length density, it can improve the physical structure of soils, and the benefits of gypsum amendments can be very long lasting (Shamshuddin et al. 1991; Wallace 1994; Toma et al. 1999; Chaganti et al. 2019; Macana et al. 2020). Gypsum had a high percentage of missing data across the locations. Moreover, its missingness may not be random (and may carry some information). It is possible that the model inflated gypsum's importance for predictions, particularly in the pre-trained CNN models. This possibility was examined by running models without gypsum, without other soil parameters with high missing data, and without soil at all (Supplementary Fig S8). Removal of these factors did reduce model accuracies in some cases, but not in such a substantial way as to suggest that the CNN model was overfit based on the presence or absence of data for these factors. Still, a conclusion that gypsum is more important than other soil factors in the model is probably not warranted based on this and previous studies. Ksat is a physical property related to how quickly water is transmitted through soil pores and has long been recognized as an important factor in soil–plant water relations and crop growth modeling (Kunze et al. 1968; Castellini et al. 2021). Cation exchange capacity is a measure of the soil's ability to hold cations. It is related to the soil's ability to hold fertilizers as opposed to leaching them into the groundwater and therefore has potential impacts on plant growth, sustainability, and pollution (Kaiser et al. 2008). It is important to note that these factors were obtained from the SSURGO database and are therefore static factors that are the same across all years for a single location. In reality, many of these factors have the potential to vary substantially over time at any single field location. Because the factors were input as static across years, they also have the potential to artificially inflate our results in model scenarios where all years at the same location are held out. We do not see evidence of this occurring in our results, but it is a potential drawback of using static soil parameters as was done here.

While CGMs provide the means to integrate the effects on yield of these static variables in a more dynamic and biologically meaningful manner, the sensitivity of responses to water limitation likely requires quality in soil and crop data beyond that available in the G2F and historical data sets, in order to support robust CGM prediction. Messina et al., (Messina et al. 2019) showed the extreme sensitivity of maize yield to small differences in water stress level at flowering. Cooper et al., (Cooper et al. 2016) demonstrated the need to incorporate variation for soil depth (water-holding capacity) within experimental fields as an uncertainty

factor in fitting procedures to capture the added value possible in fitting GP models using advanced Bayesian computation methods to link CGM-GP. The trade-off between data quantity and data quality remains an issue of interest as limited additional effort to capture meaningful data (e.g., soil water-holding capacity estimates) may enable much more effective use of CGM and also CNN. Advanced methodologies provide a path for integrating physiological understanding of variation in elite germplasm into a breeding program without the cost and complexity associated with measuring all of the relevant traits on all of the entries within all of the environments sampled (Cooper et al. 2016; Messina et al. 2018, 2019).

Genetic factors also played a strong role in prediction accuracy. However, because these models were not designed with the genetic resolution necessary to pinpoint specific genetic factors, conclusions on which genetic factors were most important are not straightforward. Here, genotypic data was incorporated into the CNN as principal components, to capture broad patterns in genetic variability. Further developments are needed to use complex neural network architectures for genetic inference (Demetci et al. 2020; Zhao et al. 2021).

Conclusions and future directions

The CNN model approach with daily weather inputs and historical data was found to be capable of predicting maize yield at similar or higher accuracies than the standard BLUP approaches commonly used in genetics and breeding. This indicates the model is able to gain predictive value from the additional features and complexity it can take as input, and suggests further study and development of CNN models in phenotype prediction is warranted. Automated mechanics models, like the CGMs here developed and tested, appear unable to perform well given the low overall quality, and the types of data used in this study. Higher-quality data, more data of the specific types commonly used in CGMs, and/or better automation/integration methods will be needed in order to use CGM's effectively across many cultivars in the scenarios presented here. Additional and low-cost attention to improve data quality may well favor use of CGMs in the long run. Historical survey data, despite being of low-resolution and quality, contains valuable information that can be utilized by models to improve accuracy through pre-training and transfer learning. Data types that are typically underrepresented in field experiments (such as soil data, and weather across time) may be key to developing models that more realistically represent the importance of these factors.

Although CNN models are often described as being difficult to interpret, the results here demonstrate that our model reconstructed the importance of various agronomic

factors in a way that is consistent with the literature. This indicates that given sufficient data of the right kinds, CNN and other deep learning models may have some utility in the development of mechanistic hypotheses for further testing and validation. Despite the available tools for interpretation (and the many new tools that will likely come), deep learning methods are fundamentally based on empirical data, and will likely never reach the level of interpretation possible in CGMs. Additionally, deep learning models do not provide some types of interpretive data (for example heritability, additivity, and dominance scores) commonly generated by standard statistical approaches. Moreover, their assumptions, results, and potential pitfalls deserve greater attention, before they can be widely adopted by the community.

Future development and testing of machine and deep learning approaches in phenotype prediction would benefit from larger, more balanced agricultural datasets, and/or methods for better validating these models using the datasets currently available. The questions of how best to incorporate data into the models, what model architectures to use, and what data types are most important need significantly more exploration. Additionally, the possibility of incorporating known physiological, chemical, or other mechanisms into machine and deep learning models should be explored.

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Authors' contribution statement JW, EC, GR, GH, MC, and EB conceived the project. JW, EC, and GR implemented the CNN and BLUP methods. JW, TR, and RO developed the data mining tools. JW and GM developed and performed the APISM methods. All authors contributed to the writing and revision of the manuscript text.

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Code availability All code is available at (https://bitbucket.org/bucklerlab/maize_yield_pred/).

Availability of data and material (data transparency) All data are publicly available at: <https://www.genomes2fields.org/resources/>, <https://daymet.ornl.gov/>, or <https://websoilsurvey.sc.egov.usda.gov/App/WebSoilSurvey.aspx>.

Declarations

Conflict of interest The authors declare no competing financial interests.

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