A quantitative theory for genomic offset statistics

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Abstract

Genomic offset statistics assess the maladaptation of populations to rapid habitat alteration based on association of genotypes with environmental variation. Despite substantial evidence for empirical validity, genomic offset statistics have well-identified limitations, and lack a theory that would facilitate interpretations of predicted values. Here, we clarified the theoretical relationships between genomic offset statistics and adaptive traits, and proposed a new measure to predict fitness after rapid change in local environment. The predictions of our theory were verified in computer simulations and in empirical data on African pearl millet (*Cenchrus americanus*) obtained from a common garden experiment. Our results proposed a unified perspective on genomic offset statistics, and outlined their importance for conservation management in the face of environmental change.

Significance/Author's summary

Maladaptation to altered habitat resulting from global warming is likely to cause shifts in adaptive traits of natural populations. Adaptive shifts are best evaluated from experiments in which organisms are placed into an environment that differs from the one in which the traits evolved. Those experiments are costly and time-consuming, and adaptive traits are not always easily measureable. Genomic offset statistics use environmental and genomic data to predict shifts in adaptive traits without direct observations of those traits. Similar to the theory of genetic load, we developed a mathematical model to predict fitness in local populations after rapid change in their environmental conditions when adaptive traits are unobserved. Our theory not only introduces a new measure of genomic offset, the genetic gap, but also unifies previously proposed measures into a common statistical framework. Validations from simulated and empirical data sets provided support for the theory, that paves the way for further improvements of population genomic measures of maladaptation.

Introduction

Maladaptation across environmental changes. Assessing adaptive shifts resulting from traits that evolved in one environment being placed in an altered environment is a long-standing question in ecology and evolution, originally termed as evolutionary traps or mismatches (Schlaepfer *et al.*, 2002; Cook and Saccheri, 2013). With the increasing availability of genomic data, a recent objective is to determine whether those shifts could be predicted from environmental effects on the genetic loci that control adaptive traits, bypassing any direct phenotypic measurements (Capblancq *et al.*, 2020; Waldvogel *et al.*, 2020). This question is crucial to understand whether sudden changes in the species ecological niche, *i.e.*, the sum of the habitat conditions that allow individuals to survive and reproduce, can be sustained by natural populations (Grinnell, 1917; Hutchinson, 1957; Sork *et al.*, 2010; Jay *et al.*, 2012; Aitken and Whitlock, 2013; Schoville *et al.*, 2012; Foden *et al.*, 2019). To this aim, several approaches have incorporated genomic information on local adaptation into predictive measures of population maladaptation across ecological changes, called genomic offset or genomic vulnerability statistics (Fitzpatrick and Keller, 2015; Capblancq *et al.*, 2020; Waldvogel *et al.*, 2020).

Genomic offset statistics and their limitations. Genomic offset statistics first estimate a statistical relationship between environmental gradients and allelic frequencies using genotype-environment association (GEA) models (Forester *et al.*, 2018). The inferred relationship is then used to evaluate differences in predicted allelic frequencies at pairs of points in the ecological niche (Fitzpatrick and Keller, 2015; Rellstab *et al.*, 2016; Gougherty *et al.*, 2021). Recent efforts combining trait

measurements in common garden experiments or natural population censuses with landscape genomic data have shown that demographic and phenotypic changes due to abrupt environmental shift correlate with genomic offset predictions (Bay *et al.*, 2018; Ruegg *et al.*, 2018; Rhoné *et al.*, 2020; Ingvarsson and Bernhardsson, 2020; Fitzpatrick *et al.*, 2021; Chen *et al.*, 2022; Sang *et al.*, 2022). Despite substantial evidence for empirical validity (Hoffmann *et al.*, 2021), the proposed measures of genomic offset have, however, well-identified limitations, including biased predictions due to gene flow, population structure or genomic load, and difficulties to account for polygenic effects or correlated predictors (Rellstab *et al.*, 2021; Aguirre-Liguori *et al.*, 2021). More importantly, genomic offset statistics lack a theory that would clarify how those statistics are related to each other, and facilitate biological interpretations of inferred values. Thus, there is a need to link genomic offset statistics to adaptive trait values and to the geometry of the ecological niche in a way that unifies existing approaches and addresses their limitations.

Results

Geometry of the ecological niche. We developed a geometric approach to the concept of genomic offset (GO) by defining a dot product of ecological predictors built on effect sizes of those predictors on allelic frequencies. Effect sizes, $(\mathbf{b}_\ell) = (b_{\ell j})$, were obtained from a GEA model of centered allelic frequencies on scaled predictors, where ℓ stands for a locus, j for a predictor. Those effects were corrected for the confounding effects of population structure and missing predictors (Online Methods:"GEA studies"). Given predictors, recorded in vector $\mathbf{x}$, and their altered versions, recorded in $\mathbf{x}^\star$, we defined the geometric *genetic gap* as squared distance between the two vectors

$$G^2(\mathbf{x}, \mathbf{x}^\star) = (\mathbf{x} - \mathbf{x}^\star)\mathbf{C}_\mathbf{b}(\mathbf{x} - \mathbf{x}^\star)^T \,, \tag{1}$$

where $\mathbf{C}_\mathbf{b} = \mathbb{E}[\mathbf{b}^T\mathbf{b}]$ is the covariance matrix of environmental effect sizes. The mathematical notation $\mathbb{E}[.]$ stands for the average over the L genomic loci detected in the GEA analysis, ideally the number of loci controlling adaptive traits (Online Methods: "Distance in ecological space", Figure S1). We showed that the genetic gap corresponds to the average value of the squared difference between predicted allelic frequencies, $G^2(\mathbf{x}, \mathbf{x}^\star) = \mathbb{E}[(f(\mathbf{x}) - f(\mathbf{x}^\star))^2]$, where $f(\mathbf{x})$ and $f(\mathbf{x}^\star)$, are obtained from the GEA model (Online Methods: "Distance in genetic space"). Thus, the geometric genetic gap has a dual interpretation as a squared distance in the genetic space.

A quantitative theory for the genetic gap. We developped a quantitative theory for the genetic gap and for other GO statistics under the hypothesis of local stabilizing selection (Kimura, 1965; Lande, 1975). Here we summarize our main result, for which details are presented in Online Methods: "Quantitative theory" (Figure 1). Assuming a selection coefficient s/L at each locus, we considered a Gaussian gradient of fitness for each local environment. We denoted by $\omega(\mathbf{x}, \mathbf{x}^\star)$ the fitness value of a trait, $z(\mathbf{x})$, optimal in environment $\mathbf{x}$ being placed in the altered environment $\mathbf{x}^\star$. Under those assumptions, we found that the genetic gap was linked to the logarithm of fitness in the altered environment as follows

$$G^2(\mathbf{x}, \mathbf{x}^\star) \approx -2\log(\omega(\mathbf{x}, \mathbf{x}^\star))/s \,. \tag{2}$$

The result was obtained mathematically from an infinitesimal model of polygenic quantitative characters under local selection, assuming weak non-inherited variance

of fitness traits (adding a constant term to the equation) (Barton *et al.*, 2017). We recovered the same result by using a genetic load approach, in which fitness was calculated according to a multiplicative epistasis hypothesis (Gillespie, 2004). In addition, the result remained valid when environmental predictors were indirectly related to the factors that influence the traits under selection, for example when those predictors are built on linear combinations of causal predictors for selection. In conclusion, the genetic gap was robust to correlation in causal effects, and equation (2) extended to known and unknown linear combinations of those effects.

Validation of the theory. To illustrate the above theory, we analyzed simulated data in which adaptive traits were matched to ecological gradients by local Gaussian stabilizing selection (Figure 2A, Online Methods: "Extended simulation studies") (Haller and Messer, 2019). Two environmental predictors playing the role of temperature and precipitation in the studied range were considered, as well as two additional predictors correlated to the first ones (Figure 2B). The median values of temperature and precipitation determined four broad types of environments from *dry/warm* to *wet/cold* conditions. The genetic groups matched the environmental classes, generating high levels of correlation between environmental predictors and population structure in the GEA analysis (Figure S2). As predicted by equation (2), the values of the genetic gap computed according to equation (1) varied linearly with the logarithm of fitness after alteration of local conditions ($r^2 \approx 78\%, P < 0.001$, Figure 2C-D). The predictive power of the genetic gap was much higher than the predictive power of squared Euclidean environmental distance between predictors and their altered values ($r^2 \approx 45\%$, $J = 11.3$, $P < 0.001$). Although it was calculated on non-causal

predictors, the genetic gap adjusted almost perfectly to the quadratic function that determines the intensity of local Gaussian stabilizing selection ($r^2 = 97\%$, $P < 0.001$, Figure S3). The first two eigenvalues of the covariance matrix of environmental effect sizes were much larger than the last ones (Figure 2C). We found that the loadings on the first axes gave more weight to predictors associated with natural selection, while the loadings on the last axes weighted predictors that did not play a role in the simulated evolutionary process. Uninformative predictors were given only low weights in the calculation of the GO statistic. Those results provided evidence that the largest eigenvalues that characterize the genetic gap contain useful information about local adaptation.

Unifying genomic offset statistics. Beyond defining a new measure, our quantitative theory provided a unified framework for GO statistics based on redundancy analysis (RDA, Capblancq and Forester (2021)), the risk of nonadaptedness (Rona, Rellstab *et al.* (2016)), and gradient forests (GF, Fitzpatrick and Keller (2015)) (Online Methods:"Relationships to other GO statistics"). The theory predicted that differences in the ability of GO statistics to estimate the logarithm of fitness is linked to the shape of the selection gradient. When RDA is performed on both environmental and latent predictors, the RDA GO is theoretically equivalent to the genetic gap, and predicts fitness under a local Gaussian selection gradient. In contrast, the definition of Rona assumes that the selection gradient is not Gaussian, but that it is built upon an exponential (Laplace) curve. Like most machine learning techniques, GF is a nonparametric approach. In GF, no selection gradient is modelled a priori, and estimating the selection gradient from the observed data may therefore require

more information than linear approaches based on low-dimensional parameters. The GF GO nevertheless follows a construction similar to the RDA GO and to the genetic gap.

Extended simulation study. Expanding our case analysis, additional simulation scenarios were considered with traits under local stabilizing selection having distinct levels of polygenicity (Online Methods: "Extended simulation study"). Some cases were complicated by a strong correlation of environmental predictors with population structure. To overcome this complication, correction based on latent factors were included in all GO calculations (Online Methods: "GO computations"). As predicted by the theory, the values of the squared correlation between the GO statistic and the logarithm of fitness were very close to each other in all investigated cases (Figure 3, Figure S4). As expected, methods that did not use correction (undercorrection) or include population structure covariates (overcorrection) worked less well than methods with latent factor correction (Figure S5 and Figure S6). Once corrected, the GO statistics ranked similarly in all simulation scenarios. The ability of the genetic gap to predict the logarithm of fitness was equal to that of corrected RDA GO. It was slightly superior to that of Rona and to that of the GF GO. All GO statistics were highly correlated with the genetic gap (Figure S7). The genetic gap also exhibited high correlation with the quadratic distance between causal predictors explaining the traits under local stabilizing selection in the simulation model (Figure S8). This result supported the evidence of near-optimal fitness prediction by the GO statistics in all simulated evolutionary scenarios. When all genomic loci in the genotype matrix were included in the GO calculations, the predictions stayed close to those based on

subsets of loci identified in the GEA analysis, GF GO reaching then performances similar to the other GO statistics (Figure S9).

Evaluating the bias of linear allelic frequency predictions. An approximation made by the genetic gap and other GO statistics is that allelic frequencies are predicted by unconstrained linear functions of environmental predictors. To evaluate the impact of this approximation, we compared linear predictions to those of a logistic regression model, which are constrained between zero and one. For small environmental change, the effect sizes in the linear GEA model could be approximated by the effect sizes in the logistic regression multiplied by the heterozygosity at each locus (Online Methods: "Bias of linear predictors"). The genetic gap was then accurately approximated by the squared distance between constrained genetic predictors, $\mathbb{E}[(f_c(\mathbf{x}) - f_c(\mathbf{x}^\star))^2]$ (Figure S10). Using a nonlinear machine learning model (Online Methods: "Variational autoencoder GO"), we found again that the squared genetic distance between constrained genetic predictors strongly correlated with the genetic gap, supporting the approximation of fitness in altered environment using linear models (Figure S11).

Pearl millet common garden experiment. We hypothesized that GO statistics could predict the logarithm of fitness in pearl millet, a nutritious staple cereal cultivated in arid soils in sub-Saharan Africa (Rhoné *et al.*, 2020). Pearl millet is grown in a wide range of latitudes and climates with wide variety of ecotypes (landraces). The genetic gap and other measures of GO were estimated from 138,948 single-nucleotide polymorphisms for 170 Sahelian landraces in a two-year common garden experiment conducted in Sadoré (Niger, Figure 4, Online Methods: "Pearl millet experiment").

For each landrace grown in the common garden, the total weight of seeds was measured as a proxy of landrace fitness, which was explained by a Gaussian selection gradient (Figure S12). Including latent factor correction, GO statistics were computed using the climate condition at the location of origin of the landrace and the climate at the experimental site. All GO statistics displayed a consistent relationship with the logarithm of seed weight (Figure 5). Using loci identified in the GEA study and correction for confounding factors improved the performance of GO statistics substantially (Figure S13 and Table S1). The best predictions of fitness in the common garden were obtained with the genetic gap and with the corrected version of Rona ($r^2 = 61\%$, $P < 0.001$, Figure 5). The eigenvalues and eigenvectors of the covariance matrix of environmental effect sizes suggested that climatic conditions could be summarized in three axes. Temperature predictors were given higher importance in driving fitness variation than precipitation and solar radiation predictors (Figure S14).

Discussion

Quantitative theory. The geometric theory presented in our study provided a unified framework that not only explains why and when a GO statistic differs from the standard Euclidean environmental distance, but also allowed for a better understanding of previous measures of genomic offset. Based on models of local selection gradients, a theoretical analysis of GO statistics relying on Fisher's infinitesimal trait model was developed. In this framework, the genetic gap grows linearly with the logarithm of fitness in the altered environment. The genetic gap also corresponds to a classical population genetic quantity, the average value of Nei's D_{ST} ($= F_{\mathrm{ST}} \times H_{\mathrm{T}}$),

which evaluates the genetic diversity between the populations for which the predictions are made (Nei, 1973; François and Gain, 2021). Although of much lower computational complexity, the genetic gap was proved to be equivalent to a GO based on RDA, which justifies the use of RDA approaches under local Gaussian selection.

Improving GO statistics. According to Rellstab *et al.* (2021), current GO statistics provide biased predictions due to the correlation between population structure at selectively neutral loci and environmental predictors. Built on unbiased effect sizes, the genetic gap addressed this problem by including latent factors as covariates in the prediction model. Latent factor corrections were then incorporated into all considered GO statistics and increased their predictive performance. The genetic gap, which is based on a unique model for GEA estimation and for GO prediction, reached higher predictive performance than the other GO approaches. Next, the genetic gap addressed the problem of correlated predictors by modeling the covariance of their effect sizes. The importance of predictors could be assessed by examining the eigenvalues and eigenvectors of the environmental effect size covariance matrix. The eigenvalues provide a natural ranking of the importance of each axis, similar to the cumulative importance curves in GF. When a statistical analysis includes redundant predictors, reproducing information already present in a reduced set of predictors, the genetic gap gave lower weight to those redundant predictors, and differed substantially from the Euclidean environmental distance. Moreover, the genetic gap was robust to the correlation of causal effects that is unavoidable in the choice of environmental predictors.

Limitations. Our simulation models and our theoretical developments relied upon a model of genotype × environment interaction for fitness related to antagonistic pleiotropy, whereby native alleles are best adapted to local conditions (Kawecki, 2004; Anderson *et al.*, 2011). While antagonistic pleiotropy is an important mechanism for local adaptation, there are other types of interactions for fitness. If local adaptation is caused by conditional neutrality at many loci, where alleles show difference in fitness in one environment, but not in a contrasting environment, the predictive performances of GO statistics remain to be explored. In addition, GO statistics (except GF) are based on linear models for the relationship between genotype and environment. Linear models generate GO statistics that are invariant under translation in the niche, making predictions relevant at the center of the species distribution, but perhaps less relevant at margins of the range. While translational invariance could be corrected for by defining the offset as the average of squared differences between allelic frequencies in nonlinear models, we found that the results were very close to the linear models. An explanation may be that nonlinear machine learning models offer more flexible GO statistics than linear models, but that linear models achieve a better bias-variance trade-off than machine learning models, likely because less data are needed for their application. Other conceptual limitations include gene flow and constraints on adaptive plasticity that might mitigate the effect of environmental change on fitness (Aguirre-Liguori *et al.*, 2021; Kawecki, 2004). As they do not use any observed information on fitness traits, GO statistics provide measures based on the indirect effects of environment mediated by genomic loci under selection (Baron and Kenny, 1986). Since the direct non-genetic effects cannot be estimated, GO statistics are more accurate when those non-genetic effects do not covary with environmental

predictors, or when the unobserved fitness traits have high heritability.

Pearl millet experiment. To compare predictions of local adaptation with empirical data, GO statistics were estimated in a common garden experiment on pearl millet landraces in sub-Saharan Africa. Using GF, the original study reported a squared correlation of $r^2 \approx 9.5 - 17\%$ for seed weight, indicating that higher genomic vulnerability was associated with lower fitness under the climatic conditions at the experimental site (Rhoné *et al.*, 2020). In our reanalysis, signals of local adaptation were consistent across all GO statistics, and improved fitness prediction substantially, up to a value of squared correlation equal to $r^2 \approx 61\%$. The results strengthened the conclusions of (Rhoné *et al.*, 2020), and supported the use of GO statistics in predictions of fitness values across the sub-Saharan area.

Conclusions. Considering a duality between genetic space and environmental space, we developed a theoretical framework that linked GO statistics to a non-Euclidean geometry of the ecological niche. As a result of the quantitative theory, interpretation in terms of fitness in the altered environment was proposed, unifying several existing approaches, and addressing some of their limitations. Based on extensive numerical simulations and on data collected in a common garden experiment, our study indicated that GO statistics are important tools for conservation management in the face of climate change.

Methods

Methods are detailed in Online Methods. Environmental effect sizes were estimated by using LFMMs in the computer package LEA v3.9 (Caye *et al.*, 2019; Gain and François, 2021). The number of latent factors was estimated from the screeplot of principal component analysis of the genotype matrix. RDA was performed by using principal components of fitted values of the GEA regression model. Rona was computed as the average value of the absolute distance between predicted allelic frequencies across genomic loci (Rellstab *et al.*, 2016). GF computations were performed using the `R` package `gradientForest` version 0.1. For consistency, we reported squared values of GO statistics in RDA and GF. To correct statistics for the confounding effect of population structure, all analyzes were performed conditional on the factors estimated in the LFMM analysis.

Spatially-explicit individual-based simulations were performed using SLiM 3.7 (Haller and Messer, 2019). Each individual genome contained neutral mutations and quantitative trait loci (QTLs) under local stabilizing selection from a two-dimensional environment. The probability of survival of an individual genome in the next generation was computed as the product of density regulation and fitness. We designed four classes of scenarios, including weakly or highly polygenic QTLs, and weak or high correlation of environment with population structure. In scenarios with high polygenicity, traits controlled by 120 mutations with additive effects were matched to each environmental variable by local stabilizing selection. In weakly polygenic scenarios, the traits were controlled by 10 mutations. Scenarios with high confounding effects were initiated in a demographic range expansion process, creating correlation between environment and allelic frequencies at the genome level. For each scenario,

thirty replicates were run with distinct seed values of the random generator. At the end of a simulation, the genomic position of QTLs, individual geographic coordinates, environmental variables and individual fitness values before and after instantaneous environmental change were recorded. The J-test was used to test differences between predictive performances of the genetic gap and other GO statistics (Davidson and MacKinnon, 1981).

Methods regarding the common garden experiment on Pearl millet landraces conducted in Sadoré (13° 14' 0" N, 2° 17' 0" E, Niger, Africa) were described by Rhoné *et al.* (2020). For each of 170 landraces grown in the common garden, the mean total weight of seeds was measured as a proxy of landrace fitness. Using 100 plants per landrace in a pool-sequencing design, allelic frequencies were inferred at 138,948 single-nucleotide polymorphisms. Climate data were used to compute 157 metrics in three categories, precipitation, temperature (mean, maximum and minimum near surface air temperature), and surface downwelling shortwave radiation, that were reduced by principal component analysis. GO statistics were computed using the climate condition ($\mathbf{x}$) at the location of origin of the landrace and the climate conditions ($\mathbf{x}^\star$) at the experimental site.

Data Availability. The pearl millet data have already been published, and have permissions appropriate for fully public release.

Code Availability. The codes necessary to reproduce the simulations and data analyses of this study are available at `https://github.com/bcm-uga/geneticgap`

under GNU General Public License v3.0 The genetic gap is implemented in the `R` package LEA (version number > 3.9.5) available from the public repository `bioconductor` and `https://github.com/bcm-uga/LEA` (latest version).

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Author contributions

B.R., P.C., Y.V., I.S., F.F. contributed analyzes and helped drafting the manuscript. C.G., F.J. and O.F. conceived the study, developed the method, carried out analyzes, and wrote the manuscript.

Competing Interests

The authors declare no competing interests.

Additional information

Supporting methods and materials, supplementary figures and tables, are available online.

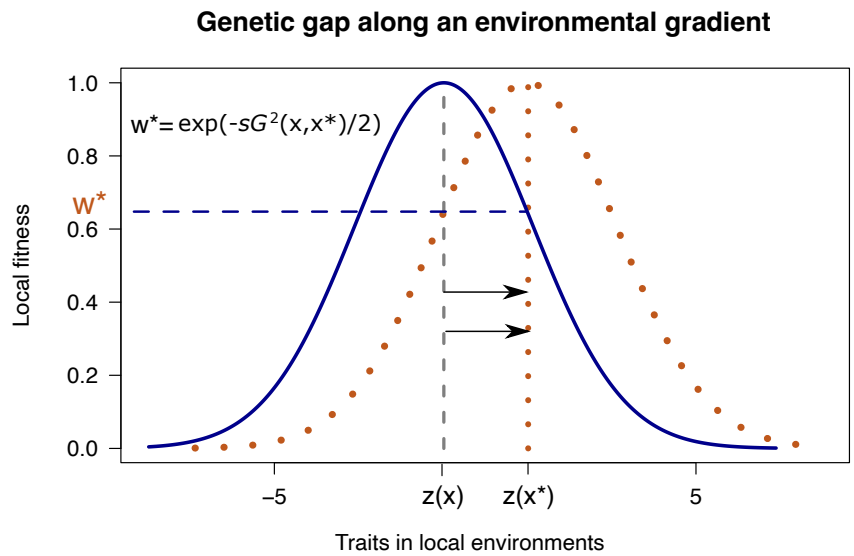

Figure 1. Genetic gap under local Gaussian stabilizing selection. The two points, $z(\mathbf{x})$ and $z(\mathbf{x}^\star)$, represent locally optimal values of an adaptive trait in respective environments $\mathbf{x}$ and $\mathbf{x}^\star$. The curves display the fitness values for the trait in each environment. An organism with trait $z(\mathbf{x})$, optimal in environment $\mathbf{x}$, being placed in altered environment $\mathbf{x}^\star$, has a fitness value equal to $\omega^\star = \exp(-sG^2(\mathbf{x}, \mathbf{x}^\star)/2)$, where $G^2(\mathbf{x}, \mathbf{x}^\star)$ is the genetic gap and s is the selection intensity (horizontal dashed line).

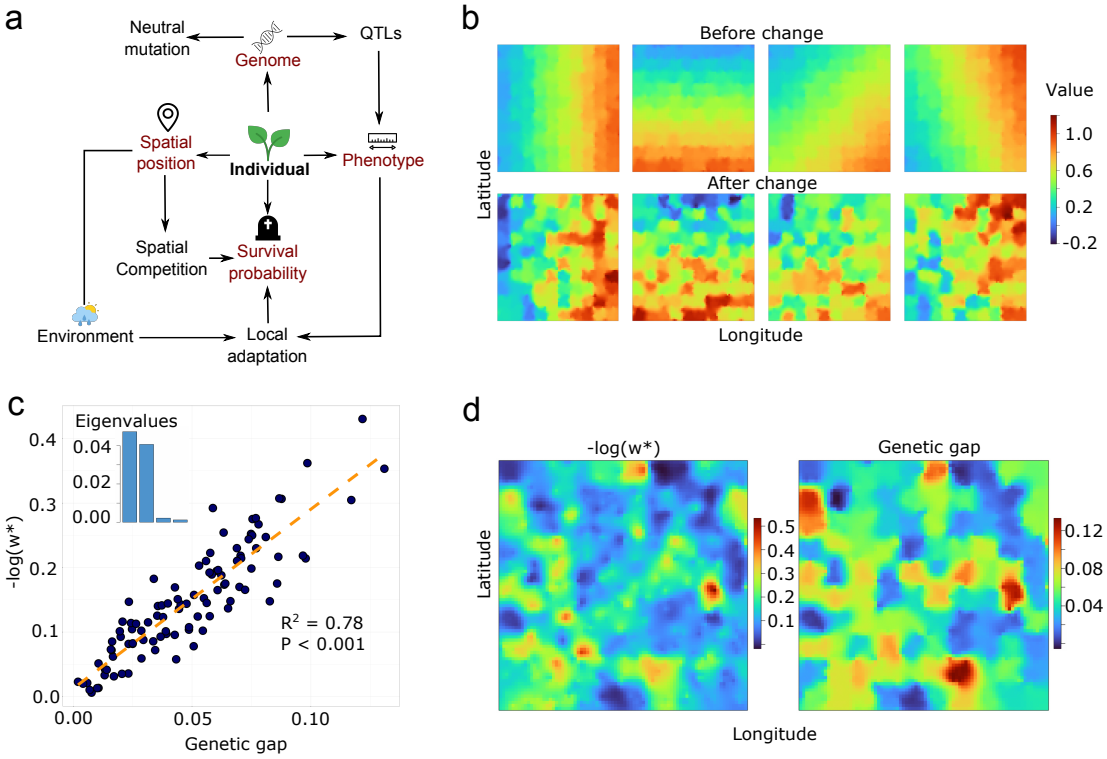

Figure 2. Simulation of fitness traits and genetic gap. **a**) Spatial individual-based forward simulations: Adaptive traits were matched to ecological gradients by local Gaussian stabilizing selection. **b**) Geographic maps of four environmental predictors before and after change. **c**) Logarithm of altered fitness values as a function of genetic gap. The eigenvalues of the covariance matrix are displayed in the top left corner. **d**) Geographic maps of the logarithm of altered fitness values (left) and genetic gap (right).

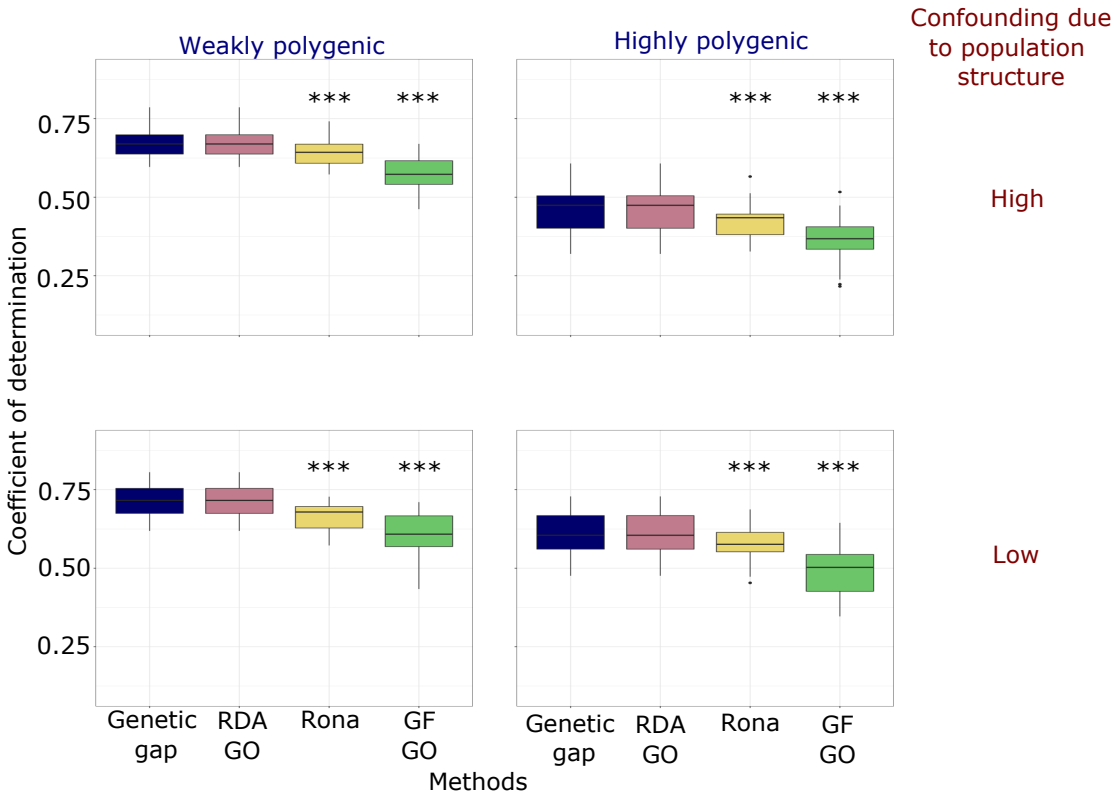

Figure 3. Predictive performances of GO statistics. Proportion of variance of fitness in the altered environment explained by GO statistics (coefficient of determination). Four scenarios with distinct levels of polygenicity in adaptive traits and correlation of environmental predictors with population structure were implemented. The stars correspond to pairwise comparisons between the genetic gap and the other GO statistics (paired t-tests, ***: $P < 0.001$). Boxplots display the median, the first quartile, the third quartile, and the whiskers of distributions. The upper whisker extends from the hinge to the largest value no further than 1.5 inter-quartile range (IQR) from the hinge. The lower whisker extends from the hinge to the smallest value at most 1.5 IQR of the hinge. Extreme values are represented by dots.

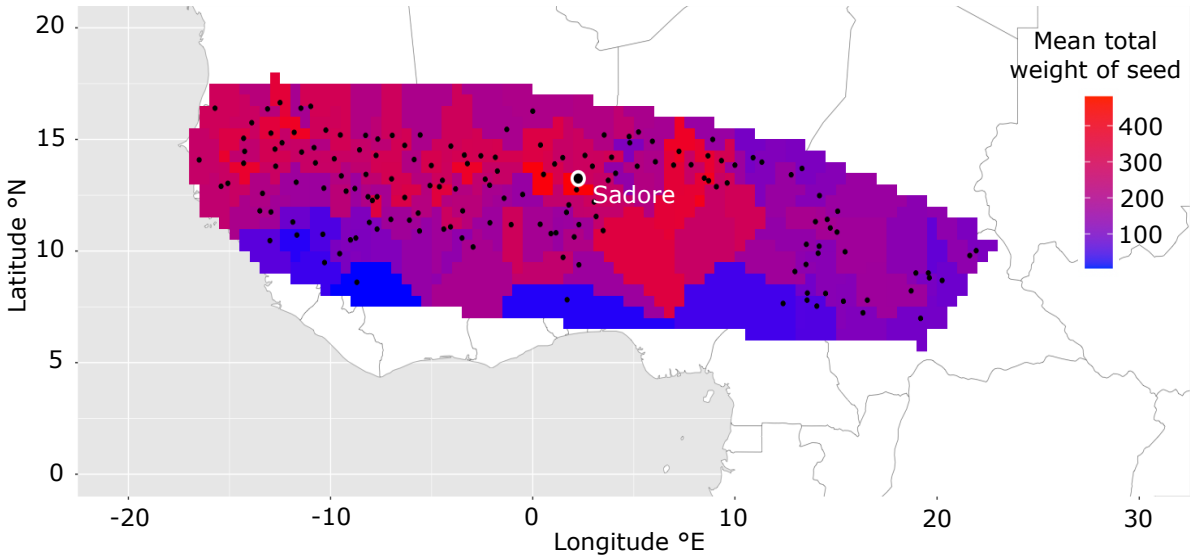

Figure 4. Sampling locations and fitness gradient for pearl millet landraces. For the common garden experiment located in Sadoré (Niger), the color represents the fitness value measured as the mean total seed weight for each pearl millet landrace. Locations of landrace origin are represented as dots. Fitness values at unsampled locations were interpolated from the nearest sampled location using the inverse distance weighting method.

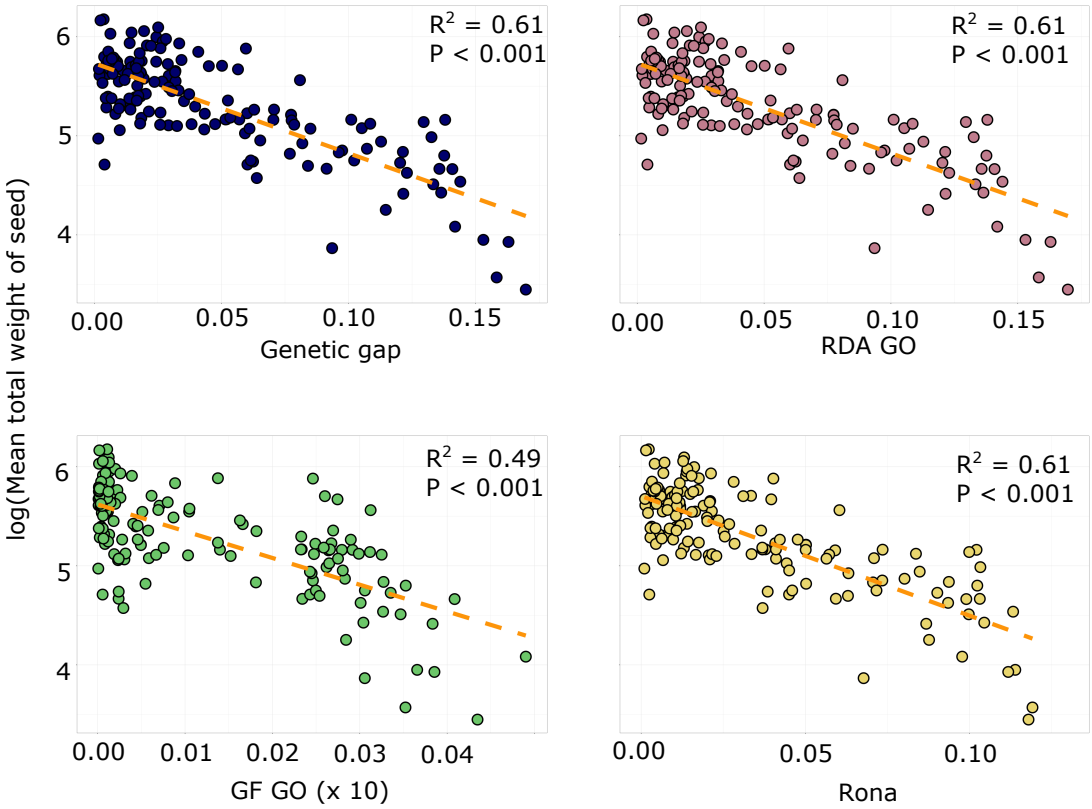

Figure 5. Logarithm of fitness in the common garden as a function of the GO statistic. Latent factor corrections were included in the calculation of all GO statistics (ten factors). Fitness was evaluated as the mean total weight of seed for 170 pearl millet landraces. GO values for GF were multiplied by a factor of ten.