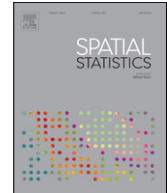




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# Detecting correlation between allele frequencies and environmental variables as a signature of selection. A fast computational approach for genome-wide studies

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## ABSTRACT

Genomic regions (or loci) displaying outstanding correlation with some environmental variables are likely to be under selection and this is the rationale of recent methods of identifying selected loci and retrieving functional information about them. To be efficient, such methods need to be able to disentangle the potential effect of environmental variables from the confounding effect of population history. For the routine analysis of genome-wide datasets, one also needs fast inference and model selection algorithms. We propose a method based on an explicit spatial model which is an instance of spatial generalized linear mixed model (SGLMM). For inference, we make use of the INLA–SPDE theoretical and computational framework developed by Rue et al. (2009) and Lindgren et al. (2011). The method we propose allows one to quantify the correlation between genotypes and environmental variables. It works for the most common types of genetic markers, obtained either at the individual or at the population level. Analyzing the simulated data produced under a geostatistical model then under an explicit model of selection, we show that the method is efficient. We also re-analyze a dataset relative to nineteen pine weevils (*Hylobius abietis*) populations across Europe. The method proposed appears also

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as a statistically sound alternative to the Mantel tests for testing the association between the genetic and environmental variables.

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## 1. Background

### 1.1. Detecting signature of natural selection

Natural (or Darwinian) selection is the gradual process by which biological traits (phenotypes) become either more or less common in a population as a consequence of reproduction success of the individuals that bear them. Over time, this process can result in populations that specialize for particular ecological niches and may eventually lead to the emergence of new species. The study of selection is an important aspect of evolutionary biology as it provides insight about speciation but also about the genetic response of possibly lesser magnitude to environmental variation. An important goal of such analyses consists in identifying genes or genomic regions that have been the target of selection (Nielsen, 2005; Hansen et al., 2012). Identifying such genes may provide important information about their function which may eventually help improving crops (Yamasaki et al., 2005) and livestock (Flori et al., 2009). Recent genotyping techniques make it possible to obtain DNA sequences at a high number of genomic locations in a growing number of both model and non-model species (Davey et al., 2011). This opens the door to methods of identifying regions under selection, even for the organisms whose genome is poorly documented (non-model organisms), but the large size of such datasets ( $10^4$ – $10^6$  variables) makes the task a formidable statistical challenge.

### 1.2. Recent methods of detecting selection

So far, identifying genomic regions targeted by selection has relied extensively on the analysis of genetic data alone, based on the idea that, if local selection occurs at a given chromosome region (or locus), differentiation (genetic difference between population) will increase at this locus compared with what is theoretically expected at neutral loci (Nielsen, 2005). To further identify the environmental characteristics associated with the observed genetic variation, a recent family of methods attempts to identify loci displaying outstanding correlation with some environmental variables. This more direct approach has the potential advantage to provide functional information about those conspicuous loci. The data required for the latter type of analyses typically consist of the genotypes of a set of individuals at various genomic loci and measurements of various environmental variables at the same sampling sites. The method amounts to quantifying the statistical dependence between allele counts and environmental variables.

The most natural method to model the dependence of count data on a quantitative or qualitative variable is the logistic regression, as implemented in this context by Joost et al. (2007). However, plain logistic regression assumes that the allele counts among different populations or individuals are independent conditionally on the environmental variable. Doing so, the logistic regression fails to capture the residual genetic dependence of neighboring individuals or populations due to their common ancestry and recent common evolutionary history. Another method to test the dependence between genetic and environmental variables is the Mantel test and its variant the partial Mantel test. These tests attempt to assess the significance of a correlation coefficient by re-sampling with permutations. They have long been popular methods in ecology and evolution. However, a recent study (Guillot and Rousset, 2013) shows that they are not appropriate if the data are spatially correlated. The method proposed by Coop et al. (2010) attempts to model the genetic structure by including a random term in the logistic regression in a fashion similar to a Generalized Linear Mixed Model. They propose to do inference with MCMC. A recent study by De Mita et al. (2013) shows that under biologically realistic conditions, accounting for structure in the data as in Coop et al. (2010) improves the accuracy of inferences. The goal of the present paper is to extend the latter approach by rooting it in a spatially explicit model and implementing inference with an MCMC-free inference approach.

The method proposed is described in the next section. Next we illustrate the method accuracy by analyzing the simulated data produced first under a purely geostatistical model then under a biological model that simulates selection explicitly. We conclude by discussing our results and outlining possible extensions.

## 2. Method proposed

### 2.1. Data considered

We consider a set of individuals observed at various geographical locations. Each individual is genotyped at  $L$  genetic loci. Besides, we consider that these loci are bi-allelic, i.e. the sequence observed at a particular locus can be only of two types (denoted arbitrarily  $A/a$  in the sequel). We consider haploid or diploid organisms, i.e. organisms that carry either one or two copies of each chromosome. A genotype is therefore a vector with  $L$  entries in  $\{0, 1\}$  or  $\{0, 1, 2\}$  respectively. As it is frequent to sample more than one individual at each location, we denote by  $n_{il}$  the haploid sample size of population  $i$  for locus  $l$ , that is the number of individuals at site  $i$  genotyped at locus  $l$  times the number of chromosome copies carried by the organism under study.

### 2.2. The pine weevil dataset

To illustrate the method proposed here, we will re-analyze a dataset relative to pine weevils initially produced by Conord et al. (2006). Anticipating on the results section and for the sake of fleshing out the presentation of the method in the next section, we briefly outline the main features of this dataset. It consists of 367 pine weevil individuals (*Hylobius abietis*) sampled in 19 geographical locations across Europe (Fig. 1). Each individual has been genotyped at 83 genetic markers (see below for details).

This dataset has been analyzed by Joost et al. (2007) who looked for signatures of selection by comparing the spatial genetic variation to ten environmental variables. We focus here on a subset consisting of four environmental variables: average diurnal temperature range, number of days with ground frost, average monthly precipitation and average wind speed.

### 2.3. Model

#### 2.3.1. Likelihood

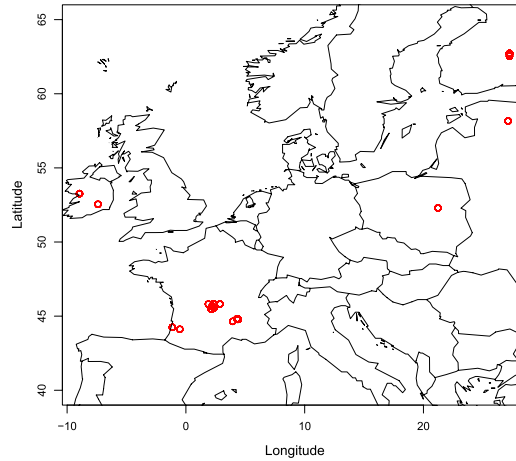
We denote by  $(s_i)_{i=1,\dots,L}$  a collection of geographical coordinates,  $(y_i)_{i=1,\dots,L}$  some measurements of an environmental variable obtained at these sites and  $(z_{il})_{\substack{i=1,\dots,L \\ l=1,\dots,L}}$  the number of alleles of type  $A$  at locus  $l$  observed in a population sampled at site  $i$ . We also denote by  $f_{il}$  the local frequency of allele  $A$  at geographical location  $s_i$  for locus  $l$ . We make the assumption that there is no within-population statistical structure and that for organisms harboring more than one copy of each chromosome, the various alleles carried at a locus by an individual are independent and that the allele counts are sampled from a binomial distribution:

$$z_{il} \sim \text{Binom}(n_{il}, f_{il}) \quad (1)$$

where  $n_{il}$  denotes the number of alleles sampled (or haploid sample size) at site  $i$ .

The above assumes that the data at hand provide exact information about the alleles carried by each individual. This is not the case for certain genetic markers such as the amplified fragment length polymorphism markers (AFLP). With this type of markers, one can only know whether an individual carries allele  $A$  or not but the number of copies carried by each individual is not known. For diploid organisms, this leads to a genotype ambiguity: the record of allele  $A$  may correspond to genotypes  $(a, A)$  or  $(A, A)$ . We therefore consider an alternative likelihood for the case above where  $z_{il}$  denotes the number of individuals at sampling site  $i$  for which allele  $A$  has been observed. Still denoting by  $f_{il}$  the frequency of a reference allele  $A$  at locus  $l$  at geographical site  $i$  but we have now

$$z_{il} \sim \text{Binom}(n_{il}, f'_{il}) \quad \text{with } f'_{il} = 2f_{il}(1 - f_{il}) + f_{il}^2. \quad (2)$$



**Fig. 1.** Geographical locations of the nineteen pine weevil populations sampled in Europe.

### 2.3.2. Latent Gaussian structure

We model the dependency between an environmental variable  $y$  and the allele frequency at locus  $l$  by assuming that

$$f_{il} = \frac{1}{1 + \exp -(x_{il} + a_l y_i + b_l)} \quad (3)$$

where  $x_{il}$  is an unobserved spatially random effect that accounts for the spatial auto-correlation due to population history and  $(a_l, b_l)$  are parameters that quantify the locus-specific effect of the environment variable  $y_i$ . The environment variable is observed and is treated as a spatially variable explanatory variable (fixed effect).

The variables  $\mathbf{x}_l = (x_{1l}, \dots, x_{nl})$  are unobserved random effects and are assumed to be independent replicates from the same Gaussian random field. Doing so, we assume the absence of linkage disequilibrium (i.e. absence of statistical dependence across loci). By assuming a common distribution for all vectors  $\mathbf{x}_l$ , we inject the key information in the model that there is a characteristic spatial scale that is common to all loci and reflects the species- and area-specific population structure of the data under study.

As commonly done in spatial statistics (Chilès and Delfiner, 1999), we make the assumption that  $x$  is 0-mean isotropic and stationary. Further, we assume that the stationary covariance  $C(s, s') = C(h)$  belongs to the Matérn family i.e.

$$C(h) = \frac{\sigma^2}{2^{\nu-1} \Gamma(\nu)} (\kappa h)^{\nu} K_{\nu}(\kappa h) \quad (4)$$

where  $K_{\nu}$  is the modified Bessel function of the second kind and order  $\nu > 0$ ,  $\kappa > 0$  is a scaling parameter and  $\sigma^2$  is the marginal variance.

### 2.4. Parameter inference

A key feature of the model above is that it can be handled within the theoretical and computational framework developed by Rue et al. (2009) and Lindgren et al. (2011). The former develops a framework for Bayesian inference in a broad class of models enjoying a latent Gaussian structure. The latter, bridges a gap between the Markov random fields and Gaussian random fields theory making it possible to combine the flexibility of Gaussian random fields for modeling and the computational efficiency of Markov random fields for inference. The approach of Lindgren et al. (2011) is based on the observation that a Gaussian random field  $x(s)$  with a Matérn covariance function is the solution of the stochastic

partial differential equation

$$(\kappa^2 - \Delta)^{\nu/2}(\tau x(s)) = \mathcal{W}(s) \quad (5)$$

where  $\Delta$  is the Laplacian,  $\kappa$  is the scale parameter,  $\nu$  controls the smoothness and  $\tau$  controls the variance. In approximating  $x(s)$  by

$$x(s) = \sum_k \psi_k(s) w_k \quad (6)$$

where the  $\psi_k(\cdot)$  are basis functions with compact support, one can choose the weights  $w_k$  so that the distribution of the function  $x(s)$  approximates the distribution of the solution of Eq. (5).

The method of Rue et al. (2009) is based on Laplace approximations of the various conditional densities involved in the inference of the hyper-parameters and latent variables. It makes use of the Markov structure of the latent variables in the computation. In contrast with MCMC, the INLA method does not compute estimates of the joint posterior distributions of hyper-parameters and latent variables but it only estimates the marginal posterior densities.

Casting the present problem in the framework of INLA-SPDE opens the door to accurate and fast computations using the R package `inla`. For parameter inference, the data relative to all loci are combined into a matrix  $Z = (\mathbf{z}_l)_{l=1,\dots,L}$  to compute the marginal posterior distribution  $\pi(\kappa|Z)$  and  $\pi(\sigma^2|Z)$ . For computational reasons (Lindgren et al., 2011), the smoothness parameter  $\nu$  is taken equal to one. A log-Gamma prior is assumed for  $\kappa$  and a Normal prior is assumed for the fixed effect ( $a_l$  and  $b_l$ ). From these marginal posterior distributions, we derive estimates of  $\kappa$  and  $\sigma$  as posterior means. In the presence of a large number of loci, implementing the above on the full dataset may become unpractical due to memory load issues. In this case we recommend to infer the parameters of the spatial covariance on a random subset of loci.

## 2.5. Model selection

For each locus, we are concerned with selecting among two competing models: a model in which the environment has an effect, i.e. where  $f_{il} = 1/[1 + \exp(-(x_{il} + a_l y_i + b_l))]$  and a reduced model in which the environmental variable has no effect, namely  $a_l = 0$  in the previous equation. For the vector  $\mathbf{z}_l = (z_{1l}, \dots, z_{il})$  of data at locus  $l$ , we denote  $\pi(\mathbf{z}_l|m) = \int \pi(\mathbf{z}_l|\theta, m) \pi(\theta|m) d\theta$  the evidence or integrated likelihood of data under model  $m$ . Assessing the strength of association with environmental variables of selection can be done by computing the Bayes factor

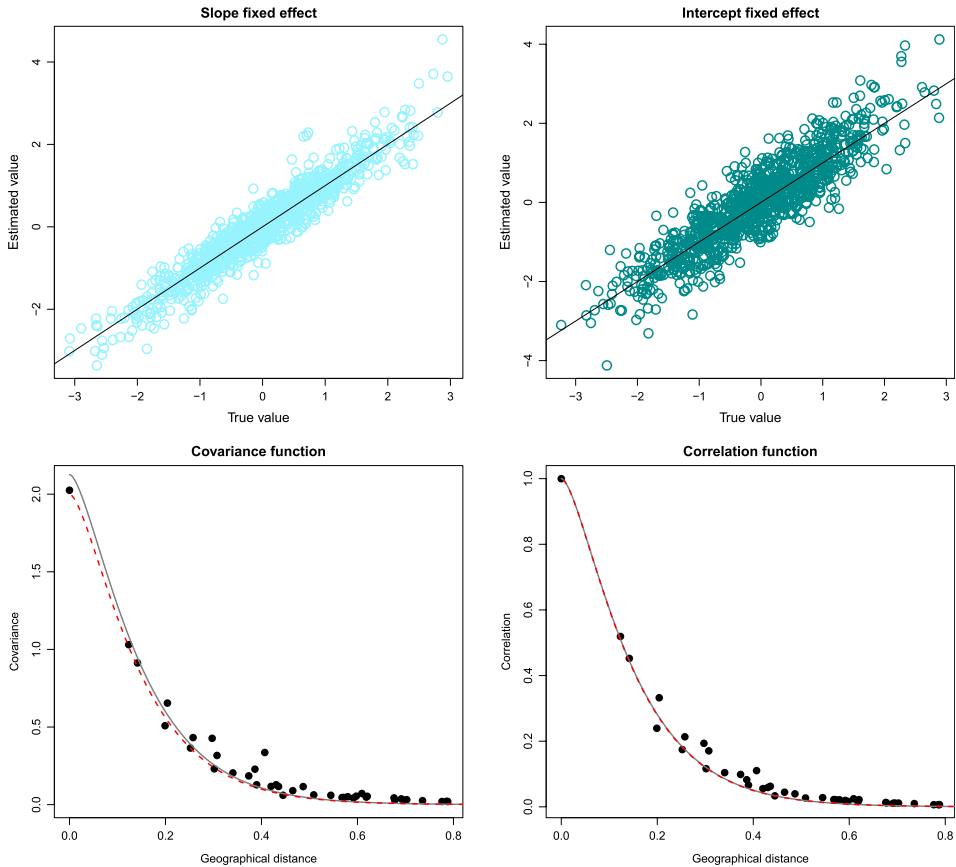
$$BF_l = \pi(\mathbf{z}_l|m_1)/\pi(\mathbf{z}_l|m_0). \quad (7)$$

We compute Bayes factors  $BF_l$  and estimate  $a_l$  and  $b_l$  locus-by-locus. In this second step of computations, the variance and scale parameters are fixed to the values inferred from the global dataset  $Z$  as explained in the previous section. The Bayes factors can be used to flag loci displaying outstanding dependence with the environmental variables and rank loci by decreasing evidence of genetic selection.

## 3. Analysis of simulated and real data

### 3.1. Simulations from a geostatistical model

We analyze here the data simulated under the exact model described above. We consider first a dataset of 1000 bi-allelic dominant markers (Eq. (2)) for 500 individuals observed at 25 geographical sites uniformly sampled in the unit square (20 individuals per site), which are typical sample sizes encountered in molecular ecology studies. For the fixed effects (Eq. (3)), we draw  $a_l$ ,  $b_l$  and  $(y_i)_{i=1,\dots,l}$  independently from a  $N(0, 1)$  distribution. The random effect  $\mathbf{x}_l$  is a Gaussian random field with a Matérn covariance function with parameters  $\sigma^2 = 2$ ,  $\nu = 1$  and  $\kappa = 0.1$ . The results of inference reported Fig. 2 show an excellent accuracy in the inference of the underlying covariance function and also a good accuracy in the estimation of the fixed effect (parameters  $a_l$  and  $b_l$ ). In the inference with INLA, we use everywhere the default prior distributions. In other simulation experiments under



**Fig. 2.** Results of inference on data from geostatistical simulations. 25 geographical sites, 20 individuals per sites, 1000 AFLP markers. Top row: slope  $a_l$  and intercept  $b_l$  of fixed effect (Eq. (3)). Bottom row: the dashed red lines depict the true Matérn functions and the continuous gray line depicts the estimated Matérn functions and the black dots the numerical result for the GMRF approximation underlying the INLA-SPDE method.

the same geostatistical model with other combinations of parameters, we observed sometimes that the estimation of the variance parameter could be inaccurate. For example, with a range parameter  $\kappa = 0.1$  However, this does not seem to affect the accuracy in the estimation of the other parameters. In particular, the slope  $a_l$  in the fixed effect which quantifies the effect of the environmental variable is consistently accurately estimated.

### 3.2. Simulations from a landscape genetic model

Individual-based simulations are produced here using the computer program SimAdapt (Rebaudo et al., 2013). The genome of each individual consists in 120 genetically-independent bi-allelic co-dominant markers: 100 neutral loci and 20 loci under habitat-specific selection. Alleles at non-neutral loci are specific to one of the two habitats 1 or 2. Homozygotes ( $A, A$ ) in habitat 1 have a fitness of 1, while homozygotes ( $a, a$ ) have a fitness of  $1 - s$  (and vice versa in habitat 2). The fitness of heterozygotes is  $1 - s/2$  in both habitats. Locus-specific fitnesses combine multiplicatively across loci to give the fitness of individuals. Among the selected loci, ten are subject to selection in one habitat, the ten others in the other habitat. Individuals are considered as hermaphrodites, and mate randomly in their patch, the mating probability being proportional to their fitness. Additional details on the model are provided in Rebaudo et al. (2013).

The landscape is a  $30 \times 10$  grid of 300 cells, which can represent habitats 1 or 2. Each cell has a carrying capacity of 100 individuals, populations grow logistically with a rate of 0.5. The landscape is designed so that habitats are distributed across a linear East–West gradient of habitat frequencies (see habitat and sampling locations Figs. 3 and 4 top-left panel), the frequency of habitat 1 being 1 at the eastern edge, and 0 at the western edge. The selection coefficient is set to  $s = 0.1$  (each maladapted locus decreases the fitness by 10%). The probability of dispersal is set to  $d = 0.1$  and  $d = 0.01$  per individual and per generation, a dispersal event consisting in moving an individual by one cell (vertically or horizontally). Simulations start with a single cell at the carrying capacity (100 individuals) close to the western edge of the grid, and mimics the invasion of the landscape for 30 generations (enough to reach all cells in the landscape). At generation 30, 25 individuals (less if the patch is not populated enough) are sampled in each of 200 cells randomly located in the grid, and genotypes at both neutral and selected loci. Here there is a loose connection between the parametrization of our inference model and that of the simulation model, in particular there is no explicit covariance function that describes the spatial genetic structure. In the inference with INLA, we use everywhere the default prior distributions. What we check here is the ability of the method to detect loci that are genuinely under selection and its false positive rate. The results are summarized in Figs. 3 and 4 and show good performance with respect to these two tasks.

### 3.3. Analysis of a pine weevil dataset in Europe

We re-analyze this dataset with the SGLMM described above and also with a plain logistic regression. The latter analysis differs from that of Joost et al. (2007) in the model selection strategy. Joost et al. (2007) used a somehow *ad hoc* combination of two tests based respectively on the likelihood ratio and the Wald statistic. We use here Bayes factors both for the logistic regression and the SGLMM. The results for four arbitrarily chosen environmental variables out of the ten variables of the initial dataset are summarized in Fig. 5. With a cut-off set at  $BF > 3$ , under a SGLMM (resp. logistic regression), 3 loci (resp. 11 loci) are significantly associated with the diurnal temperature range. The number of significant loci are 0 (5), 0 (10) and 0 (4) for the number of days with ground frost, monthly precipitation and wind speed. In the four environmental variables considered here, only one of them is considered as significantly correlated to the genetic data under the SGLMM. This is consistent with the fact that the data have been collected at highly scattered locations which makes the SGLMM better suited to “correct” the sample size for spatial auto-correlation. We note however that, there is a strong agreement between the loci detected as most significantly associated with the environment in our analysis under the SGLMM and the previous analysis of Joost et al. (2007).

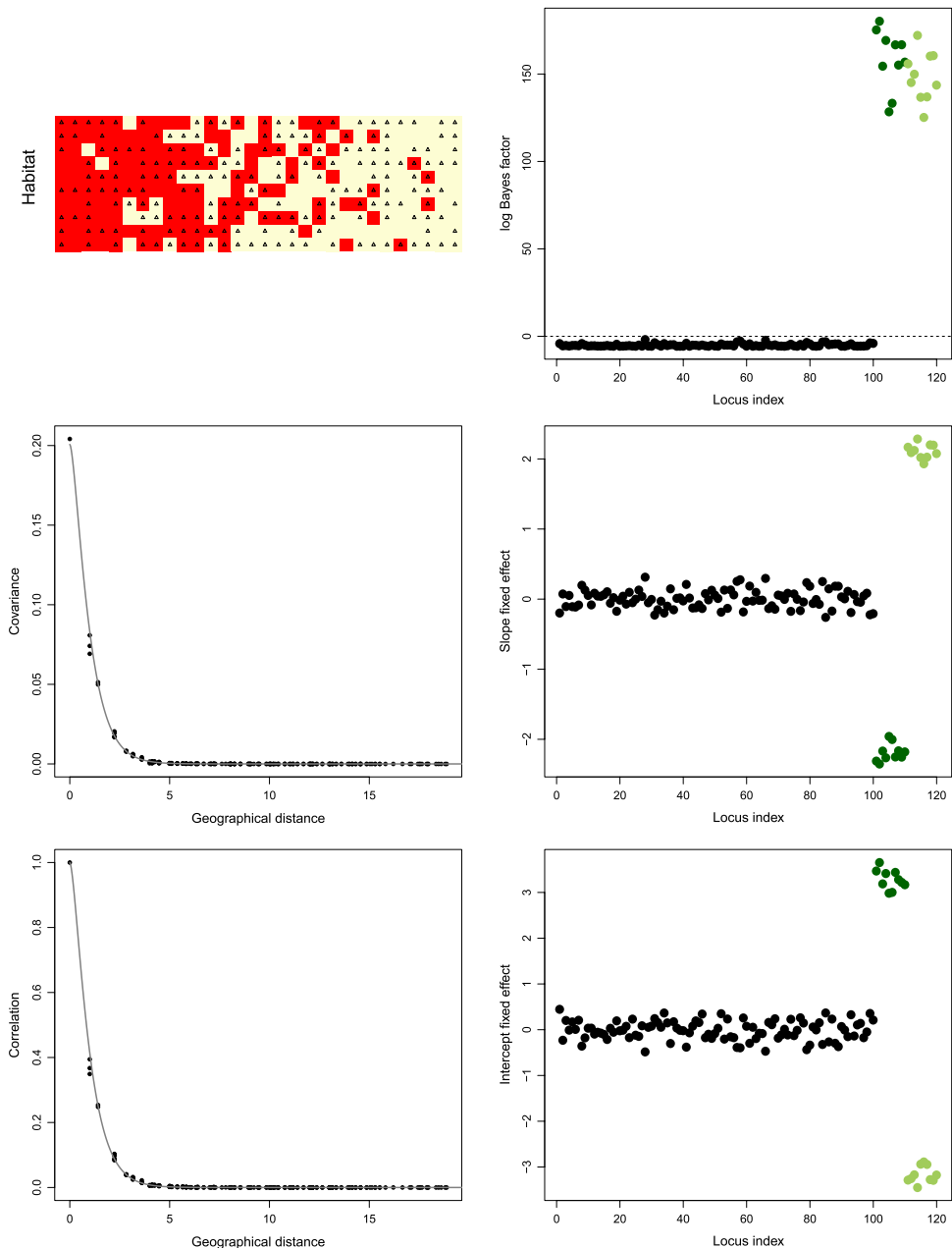
## 4. Conclusion

The approach we propose extends the existing methods in several ways: we introduce a method that (i) is spatially explicit, (ii) handles spatial coordinates either on  $\mathbb{R}^2$  (plan) or  $\mathbb{S}^2$  (sphere), (iii) works for both co-dominant and dominant markers, (iv) is equally well suited for individual data or allele counts aggregated at the population level, (v) does not require any calibration step on a subset of neutral loci, (vi) can handle quantitative as well as categorical environmental variables, (vii) returns Bayesian measures of model fit, and (viii) does not rely on MCMC computation.

One limit common to the approach proposed here and that of Coop et al. (2010) is that the loci are assumed to be conditionally independent (no residual linkage disequilibrium not accounted for by  $x$  and  $y$ ). This assumption will be clearly violated for dense SNPs datasets. This aspect requires more work for a rigorous and efficient control of false discovery. However, we note that Bonferroni-type correction offers a solution to protect oneself against false positives. Moreover, potential linkage disequilibrium not accounted for has no effect on the ranking of the loci in terms of evidence of selection. The approach proposed can be therefore readily used to identify the conspicuous loci that are likely to be the target of selection.

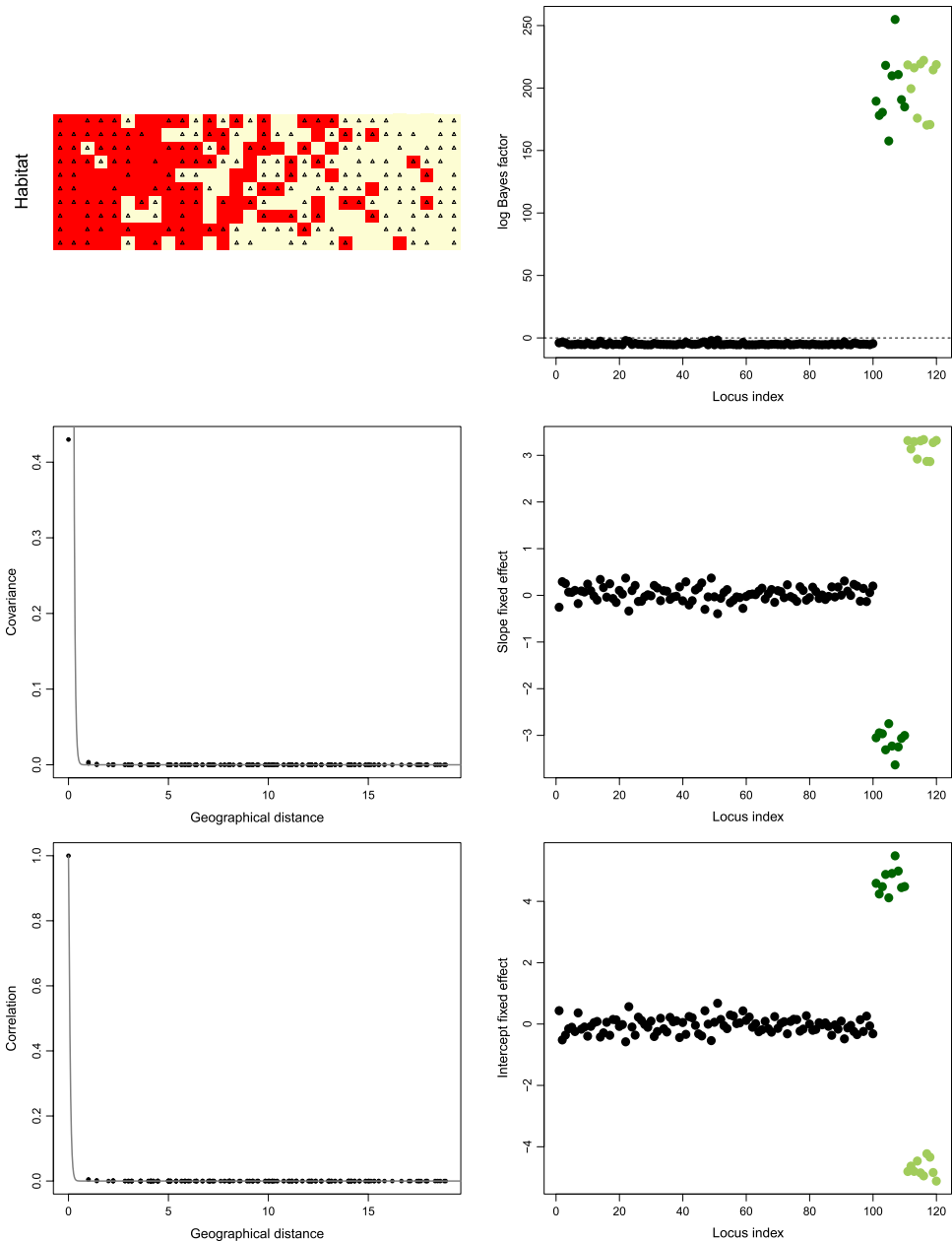
The model we described embeds the main features of the models of Coop et al. (2010) and the magnitude of the improvement in terms of inference accuracy brought by the use of an explicit spatial



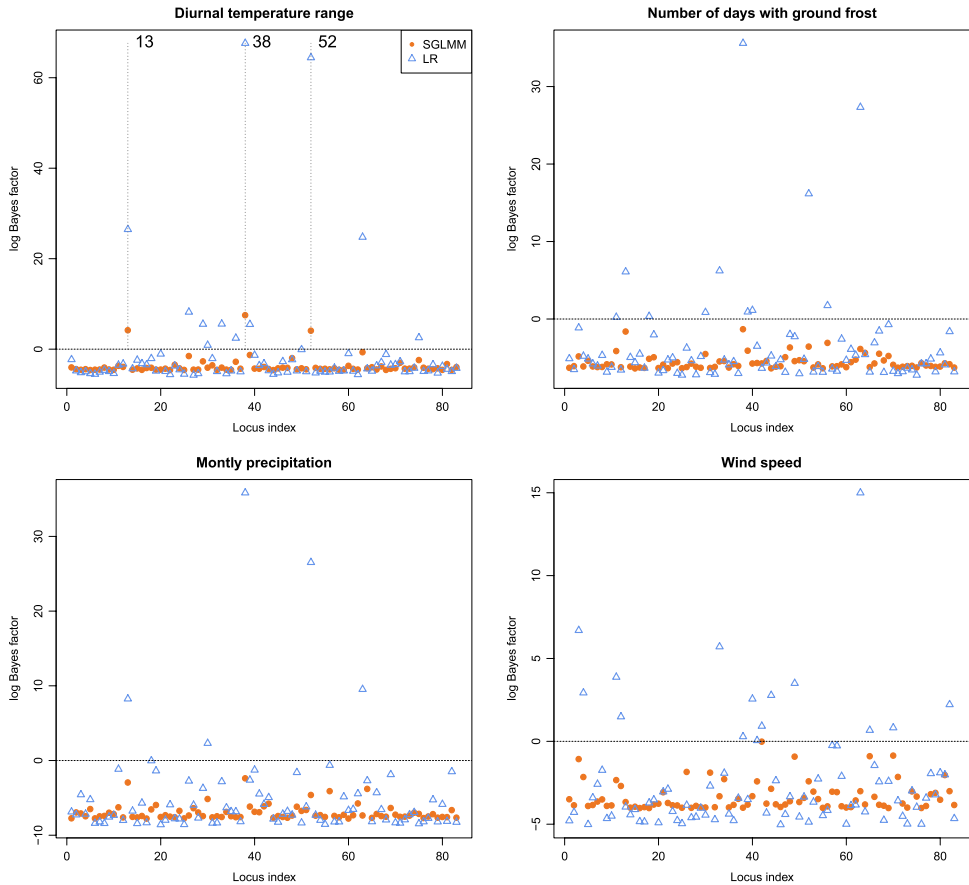


**Fig. 3.** Results for data simulated from a landscape genetics model (dispersal probability = 0.1 per individual and per generation). Top left: habitat (environmental variable) coded as two colors and sampling sites (triangles); Middle left and bottom left: the continuous gray line depicts the estimated Matérn functions and the black dots the numerical result for the GMRF approximation underlying the INLA-SPDE method. Right from top to bottom: Bayes factors and parameters  $a_l$  and  $b_l$  for the 120 loci. Dark and light green correspond to the positively and negatively selected loci respectively. The loci genuinely under selection are indexed 101–120.





**Fig. 4.** Results for data simulated from a landscape genetics model (dispersal probability = 0.01 per individual and per generation). Top left: habitat (environmental variable) coded as two colors and sampling sites (triangles); Middle left and bottom left: the continuous gray line depicts the estimated Matérn functions and the black dots the numerical result for the GMRF approximation underlying the INLA-SPDE method. Right from top to bottom: Bayes factors and parameters  $a_l$  and  $b_l$  for the 120 loci. Dark and light green correspond to the positively and negatively selected loci respectively. The loci genuinely under selection are indexed 101–120.



**Fig. 5.** Results of inference on the pine weevil data analyzed with a logistic regression (LR) and our Spatial Generalized Linear Mixed Model (SGLMM). Loci with a Bayes factor in favor of a SGLMM including an effect of the environment variable are flagged with a vertical dot line.

model depends on how much this model complies with the data at hand. We expect our model to be best suited for datasets at a scale that is large enough to observe genetic variation and spatial autocorrelation but small enough for the stationary model to make sense. The latter condition suggests that datasets collected at the continental scale may be the best targets for our approach.

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