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COMPUTER PROGRAM NOTE

2BAD: an application to estimate the parental contributions during two independent admixture events

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Abstract

Several approaches have been developed to calculate the relative contributions of parental populations in single admixture event scenarios, including Bayesian methods. In many breeds and populations, it may be more realistic to consider multiple admixture events. However, no approach has been developed to date to estimate admixture in such cases. This report describes a program application, 2BAD (for 2-event Bayesian Admixture), which allows the consideration of up to two independent admixture events involving two or three parental populations and a single admixed population, depending on the number of populations sampled. For each of these models, it is possible to estimate several parameters (admixture, effective sizes, etc.) using an approximate Bayesian computation approach. In addition, the program allows comparing pairs of admixture models, determining which is the most likely given data. The application was tested through simulations and was found to provide good estimates for the contribution of the populations at the two admixture events. We were also able to determine whether an admixture model was more likely than a simple split model.

Keywords: approximate Bayesian computation, multiple admixture

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Genetic data from present-day populations are increasingly being used to reconstruct the demographic history of populations. This history can be complex, involving population expansions, bottlenecks and admixture events. Genetic data have proven useful to infer parameters values for simple (Beaumont *et al.* 2002) or more complex (Fagundes *et al.* 2007) demographic models, including admixture models (Chikhi *et al.* 2001; Choisy *et al.* 2004; Excoffier *et al.* 2005; Sousa *et al.* 2009). Admixture occurs when two or more differentiated populations are brought into contact for a brief episode creating hybrid or admixed populations. For instance, admixture events occurred during the colonization of already occupied areas and during and after the domestication of animals and plants (e.g. the formation of new breeds through crossing; Blott *et al.* 1998). Several methods have been proposed to estimate admixture proportions based on genetic data, but only some of them try to explicitly model the demographic history of the populations sampled (e.g. Chikhi *et al.* 2001; Wang 2003). In general, these models assume that admixture took place during one unique event and that gene flow was negligible after that event; an assumption, which is particularly unrealistic for breed dynamics in some domestic species.

Here, we analyse several models, in which up to two independent admixture events may take place at different times, and we develop a method that estimates demographic parameters (the time since the admixture event, the relative contributions of the parental populations, etc.) taking into account the sampling procedure, genetic drift and mutations for microsatellite loci data. Fig. 1 shows the demographic models considered. It is assumed that an ancestral population of size N_A splits t_{split} generations ago into two or three parental populations (P_1, P_2, P_3), with effective sizes N_1, N_2, N_3. The first admixture event occurred t_{adm1} generations ago and the second admixture event occurred t_{adm2} generations ago. In the first model (Fig. 1A), admixture first occurs between P_1 and P_2 giving rise to the hybrid population (H), with

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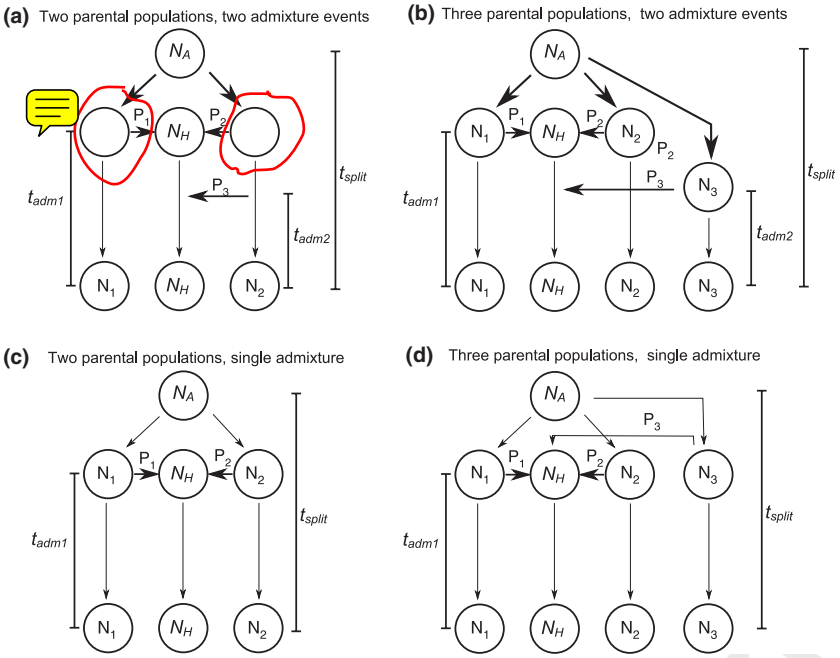

Fig. 1 The four admixture models considered.

effective size N_H. Then the second admixture event takes place, involving only P_2. In the second model (Fig. 1b), the only difference is that the second admixture event involves a third population, P_3. The last two models (Fig. 1c and d) assume a single admixture event. They can thus be seen as special cases of the previous models by fixing $t_{adm1} = t_{adm2}$. The model assumes that all loci have the same mutation rate and that the markers evolve according to the stepwise-mutation model (SMM).

The flexibility of the 2BAD program should allow its application for many biological situations, where two or three populations are thought to have potentially contributed to the genetic pool of potential admixed populations, and where the dating of these events is not clearly identified. Admixture events involving more than two parental populations are common in humans (e.g. Latin American Mestizos, Wang *et al.* 2008) and breeds (Bray *et al.* 2009). They are less documented in natural populations, but the situation could be common in freshwater fish species, when restocking is carried out from more than one source population (Kelly *et al.* 2006), and in plants that were put into contact from more than two refugia. Also, the fact that 2BAD allows testing alternative models should prove important to identify such cases where there is uncertainty on the number of admixture events and on their timing.

Recently, approximate Bayesian computation (ABC) methods (Beaumont *et al.* 2002) have become popular as an alternative to full-likelihood methods because of their flexibility and ability to be applied to complex demographic models at a relative low computational cost (e.g. Excoffier *et al.* 2005; Fagundes *et al.* 2007). ABC algorithms are based on a rejection scheme to obtain an approximate sample from the joint posterior distribution. Briefly, this involves five steps: (i) definition of a demographic model, including the prior distributions of the parameters of the model; (ii) simulation of datasets with different parameter values drawn from the prior distributions; (iii) computation of a set of summary statistics (e.g. number of alleles, expected heterozygosity, etc.) for each dataset; (iv) comparison of the observed and simulated summary statistics using a distance metric (e.g. Euclidean distance, but see Sousa *et al.* 2009 for the use of different distances); and (v) rejection of the parameters that generate datasets that are distant from the observed data.

In this study, we show that it is possible to apply an ABC approach to the admixture models described above and estimate the different parameters using reasonably large microsatellite data sets, similar to those commonly used for livestock breeds and increasingly available in endangered species. The method was implemented in a user-friendly program named 2BAD. The user provides an input file with the allele frequencies for each locus for one admixed and two or three parental populations. The user can then either estimate the parameters within one of the appropriate models, or compare two demographic models (e.g. one admixture vs. a split model, or one admixture event vs. two admixture models) using Beaumont (2008) approach. In both cases, the user selects and defines the prior distribution for each parameter (mutation rate, effective sizes, time of admixture and contribution of parental populations). Depending on the parameter, the user can select uniform, gamma, lognormal or beta prior distributions. For each parameter set,

genetic data are simulated using the coalescent with the ms program of Hudson (2002). In practice, the program uses MATLAB and C code to build the interface, run ms and perform the ABC inference step. For each locus, a set of predefined summary statistics are computed, namely: (i) expected heterozygosity for each population and over all populations; (ii) number of alleles in each population and overall populations: (iii) number of private alleles in each population; (iv) number of gaps in the allelic distribution in each population; (v) pairwise F_{ST} and overall F_{ST}. For each of these statistics, we considered the mean across loci and standardized them according to the mean and standard deviation computed using a set of 10 000 simulations. The distance between the standardized summary statistics for the simulated data and the observed data is computed with a Euclidean distance. The parameter sets that generated the simulated data with the smallest distances are then accepted. The user specifies the tolerance level defined as the proportion of simulations to be kept. The program outputs the point estimates of the different parameters and a histogram to represent the posterior distribution. Several text files are produced saving the point estimates and 95% credible intervals for each parameter, the accepted parameter values, the accepted summary statistics and the corresponding distances.

The performance of the ABC methodology was assessed using a simulation study. Datasets simulated with known parameter values were analysed as pseudo-observed datasets, and the estimates obtained using 2BAD were then compared with the known parameter values. We simulated data under an admixture model with three parental populations and two admixture events (Fig. 1B). To assess the effect of genetic drift on the quality of the estimates, we simulated data assuming a scenario with limited drift and another one with strong drift. The low and strong drift scenarios correspond to effective sizes sampled from U[1000, 15000] and U[100, 1000] respectively and to t_{split} values sampled from U[1000, 15000] and U[100, 1000] respectively. For the other parameters, we used the same priors: t_{adm1} and t_{adm2} were sampled from U[0, 100] in generations, the mutation rates (per locus per generation) from U[10^{-5}, 10^{-3}] and p_1 and p_3 from U[0,1]. For each of these two scenarios, five hundred independent datasets of twenty independent microsatellite loci each were simulated and analysed with 2BAD. The tolerance value was set as 1% (1000 accepted simulations out of 10^6). The effect of the number of simulations was assessed by repeating the analysis with 10^6 and 10^7 simulations.

The results show that 2BAD returned point estimates close to the true parameter values for all parameters (Fig. 2). As expected, the estimates obtained under the strong drift have higher error (seen in Fig. 2). It is noteworthy that the method was able to accurately estimate p_1 and p_3, showing, for the first time that ABC methods are able to quantify the contribution of parental popula-

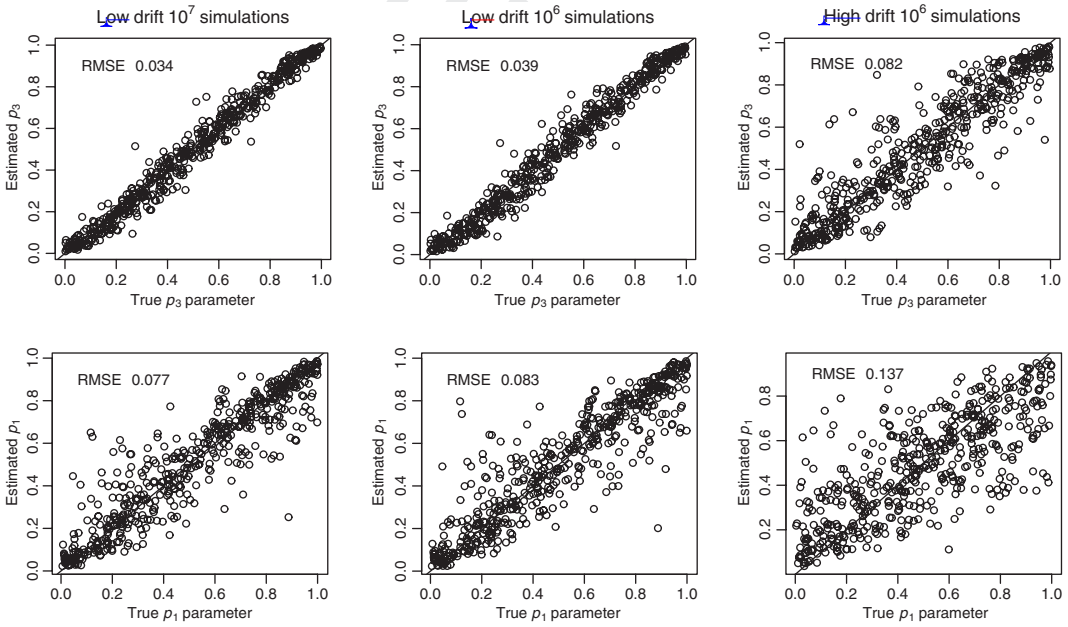

Fig. 2 True vs. point estimates of the admixture parameters. In this figure, the *x* axis represents the true value for p_1 and p_3, whereas the y axis represents the corresponding point estimates obtained using 2BAD. The different panels represent different amounts of drift and different numbers of simulations. The Root Mean Square Error is shown in each panel as a measure of precision.

tions under two admixture events. No major differences were found between the estimates obtained with 10^6 and 10^7 simulations, suggesting that one million simulations should be sufficient to obtain good estimates. While this is in agreement with our results on a simpler admixture model (Sousa *et al*. 2009), larger simulations may provide better estimates. Overall, our results show that good estimates are obtained. We also found that the method is robust to some extent to bottlenecks taking place after the admixture event, as may have been the case in some rare breeds (e.g. Bray *et al*. 2009, Sousa *et al*., in preparation).

To conclude, we have developed an easy-to-use program, which implements a method allowing population genetics inference for an admixture model involving up to two independent admixture events and an easy-to-use procedure for model choice. It is important to add as a final note that the models implemented in 2BAD do not take into account events such as bottlenecks, expansions and migration, which might all affect estimates provided by 2BAD. Testing the robustness of 2BAD to all these factors would be beyond the scope of this study. However, we are currently performing a simulation study to assess the effect of bottlenecks and the performance of the model choice procedure (Sousa *et al*., in prep). Our preliminary results suggest that recent bottlenecks do not lead to biased estimates. They also show that it is possible to separate a pure population split model from an admixture model. Finally, we found that it is also possible to determine whether a single admixture event is more likely than a model with two admixture events.

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Supporting Information

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Table S1 Relative Root Mean Square Error (RRMSE) for the different parameters estimated for the three parental, two admixture events model.

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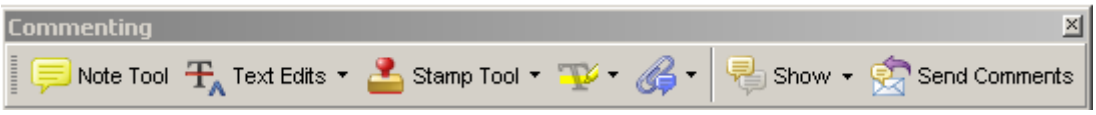

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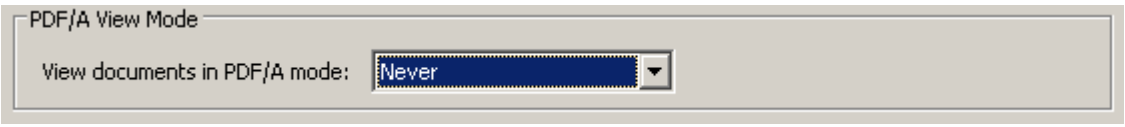

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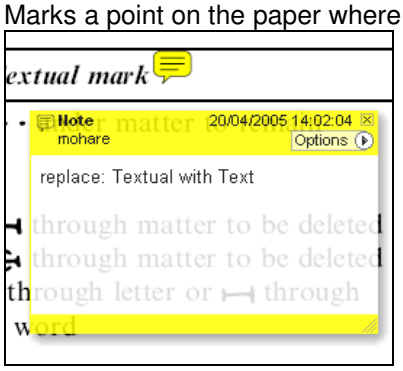

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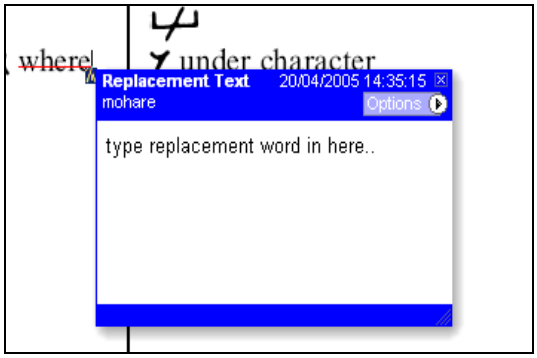

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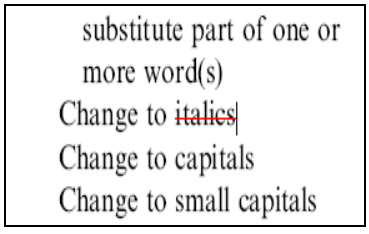

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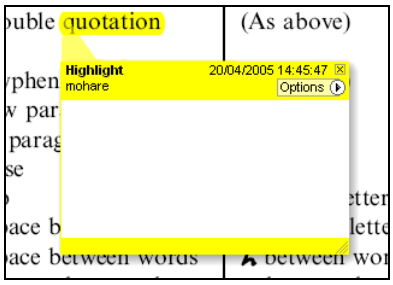

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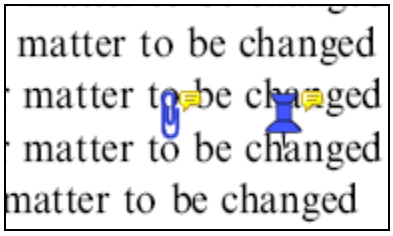

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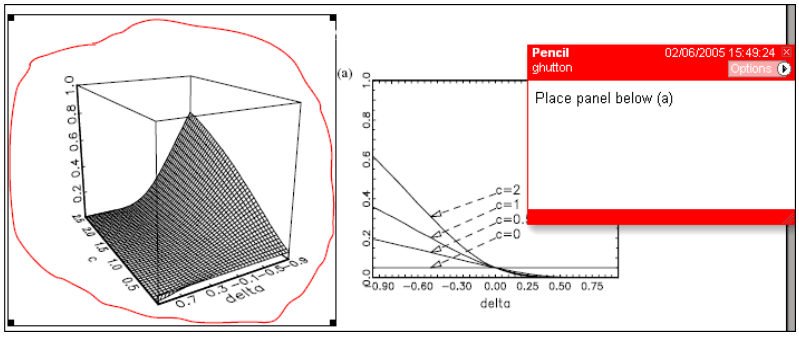

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