Digest: Demographic inferences accounting for selection at linked sites

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DIGESTS

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Complex demography and selection at linked sites can generate spurious signatures of divergent selection. Unfortunately, many attempts at demographic inference consider overly simple models and neglect the effect of selection at linked sites. In this issue, Rougemont and Bernatchez (2018) applied an approximate Bayesian computation (ABC) framework that accounts for indirect selection to reveal a complex history of secondary contacts in Atlantic salmon (*Salmo salar*) that might explain a high rate of latitudinal clines in this species.

Identifying signatures of selection within genomes is a long-standing objective in evolutionary biology. This quest is complicated by factors such as species' demographic history, which has long been recognized for its potential to produce footprints that mimic selection. Secondary contacts, for instance, can generate clines in allele frequencies correlated with spatial variation in ecological factors that may be interpreted incorrectly as representing local adaptation to an environmental gradient (Fig. 1). More recently, selection at linked sites has received particular attention as another confounding mechanism that generates genomic regions of increased divergence between populations as expected in the presence of divergent selection (Fig. 1B). Furthermore, selection at linked sites seems to affect a sufficiently large fraction of the genome of many species and challenges the basic assumption that most loci evolve neutrally. Despite those issues, few studies have attempted to include the effects of selection at linked sites in demographic divergence models (Roux et al. 2016; Rougeux et al. 2017).

In this issue, Rougemont and Bernatchez (2018) present an inference of the demographic history of Atlantic salmon (*Salmo salar*) populations using a dataset of 5034 SNPs genotyped in 77 populations covering the whole species' range. They first reassessed the population structure and confirmed the existence of genetic subdivision among regions. They then used an approximate Bayesian computation (ABC) method to compare demographic scenarios with various histories of gene flow, including divergence with migration, ancient migration, and secondary contact.

ABC avoids the explicit computation of likelihood, allowing users to choose the most appropriate summary statistics to be combined for model selection. This approach allows users to evaluate more complex and flexible models compared to other inference methods. Furthermore, ABC can be coupled with machine learning, which is well adapted to high-dimensional data. Although selection was not explicitly simulated in this study, the implemented models build on the theoretical predictions that selection against introgression locally reduces the effective migration rate between populations (Barton and Bengtsson 1986), whereas selection at linked sites enhances the effect of drift by locally reducing the effective population size (Charlesworth et al. 1993). Even if selection at linked sites can be either positive (through selective sweeps) or negative (through background selection), these two mechanisms both reduce neutral nucleotide diversity over time.

Using this modeling framework, Rougemont and Bernatchez (2018) provide a new perspective on the evolutionary history of a widely studied system in which a complex demographic history
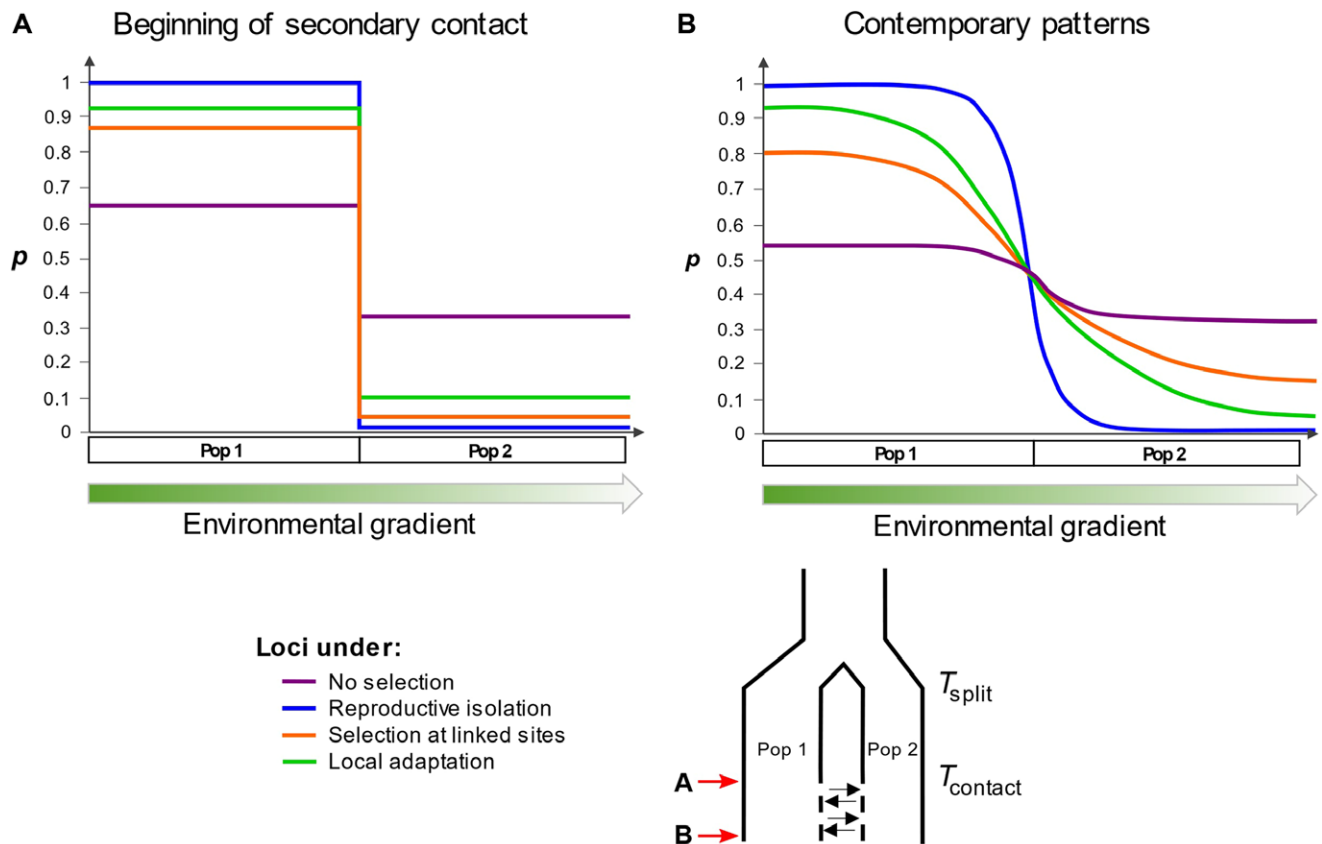
Figure 1. The fate of polymorphisms affected by different processes before and after admixture. Each color represents a different locus affected by a specific process during divergence (i.e., between T_{split} and $T_{contact}$) and secondary contact. Plots represent allele frequency clines across space, where populations 1 and 2 occupy different parts of an environmental gradient. The red arrows point to the time when cline patterns are observed. Since they are evolving under different processes, loci reach various levels of divergence and experience different levels of gene flow. **(A)** During divergence, differentiation builds up by either selection or genetic drift. Local adaptation (green) and reproductive isolation (blue) alleles rapidly increase in frequency in one population and decrease in the other. Loci under selection at linked sites (orange) diverge more rapidly than neutral ones (violet) because linked selection locally reduces the effective population size, which increases genetic drift. **(B)** During the contact, gene flow rapidly erodes the differentiation of the neutral and linked selected loci, but the cline of the second is steeper because it was more differentiated. Local adaptation loci experience reduced gene flow, and their clines are fixed by the environment. The reproductive isolation cline rapidly converged with the local adaptation cline. Clines of reproductive isolation and selection at linked sites can therefore be mistaken for local adaptation if these processes have not been taken into account when performing demographic inferences.

may confound the detection of local adaptation. A scenario of secondary contacts was favored both between and within American and European Atlantic salmon populations, providing strong evidence for a reticulated demographic history. This work emphasizes the importance of identifying a null model of demographic history for a given species that accounts for both population structure and selection at linked sites. Future studies seeking to identify signatures of divergent selection in natural populations will need to take into account variation in effective population size both in time and along the genome. Finally, this study illustrates the flexibility of ABC demographic inferences to account for dataset particularities such as the ascertainment bias in SNP chip arrays,

confirming that this approach could be widely applied to many nonmodel species.

Future studies would benefit from going a step further toward modeling the whole picture of the demographic history by considering more populations simultaneously. This goal could be achieved within an ABC framework, because population structure and phylogeography of Atlantic salmon are now well known. However, for species for which there is no a priori knowledge about population history, considering a large number of populations (meaning an exponentially large number of alternative scenarios) can quickly become intractable in terms of computational time. One way forward could be to use non-ABC methods with

minimal assumptions (e.g., Minimal-Assumption Genomic Inference of Coalescence, Weissman and Hallatschek 2017; or Approximate Blockwise Likelihood Estimation, Reddy et al. 2017). Such methods would capture the key aspects of populations' history and provide the starting point for further refinements. Those methods also have the potential to incorporate the aforementioned confounding factors such as selection at linked sites. In conclusion, an important prerequisite before starting to uncover signatures of divergent selection is to identify a relevant null model of demographic history accounting for indirect selective effects.

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