Dear Colleagues,

Please consider the attached manuscript “Space is the Place: Effects of Continuous Spatial Structure on Analysis of Population Genetic Data” for publication in *Genetics*. In this study we describe a new method of simulating populations evolving in continuous space and use it to describe how limited dispersal impacts summary statistics, demographic inference, and GWAS. Modeling populations in continuous space has been a goal of population genetics since Wright’s and Malecot’s studies of isolation by distance in the 1940’s (many published in *Genetics*). The major challenge in modeling populations in space is that the Wright-Malecot models lead to unrealistic geographic clumping. Here we implement a forward-time simulation that incorporates density-dependent probabilities of survival to maintain relatively even population density over the landscape, and returns chromosome-scale alignments of roughly ten thousand individuals. We run our model under varying levels of dispersal and use the output to test how limited dispersal and clustered sampling designs impact three common classes of genetic analyses: summary statistics, demographic inference, and GWAS.

Our results show that levels of dispersal estimated in many empirical populations cause systematic variation in most common summary statistics, including measures of nucleotide diversity and the site frequency spectrum. We find that inference of *Ne* trajectories over time; however, is relatively robust to the levels of dispersal estimated even for low-density human populations (in contrast to several recent studies noting that discrete population structure can lead to incorrect demographic inferences). Last, we simulate spatially varying environments and show that linear-regression GWAS infers thousands of spurious associations with purely environmentally-determined phenotypes, even when principal components loadings are included as covariates in the analysis. Our study is intended both to advance the theory of evolution in continuous space by thoroughly describing a new simulation framework, and to help empirical researchers set expectations when studying populations that are structured clinally over space. In addition, our analysis of association tests contributes to a major ongoing discussion in the literature over the interpretation of GWAS results from structured populations. We think our study will be of interest to many readers of *GENETICS*, which has a long history of publishing on the population genetics of continuous space.

Best regards,

C J Battey

Peter Ralph

Andy Kern