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Submission Cover Letter  
*PLoS Genetics*

To the Editor(s),

Please find enclosed our manuscript, entitled "A Spatial Framework for Understanding Population Structure and Admixture," for consideration for publication in *PLoS Genetics*.

In the paper, we present a novel statistical method (SpaceMix) for inferring and visualizing patterns of population structure in a spatial framework. Using a model of isolation by distance for a set of genotyped/sequenced samples, we construct a "geogenetic" map to visualize how samples perceive the geographic distances between them. The method accommodates admixture (anomalously long distance gene flow) by inferring, for each population, an arrow, from its source of admixture to itself, on the inferred map. The output of this method provides an intuitive and information-dense map of patterns of population structure. We demonstrate its utility with applications to Greenish Warbler and human datasets.

This work is motivated by a variety of methods for inferring population structure, such as TreeMix (Pickrell and Pritchard 2012), MixMapper (Lipson *et al.* 2013), PCA (Cavalli-Sforza *et al.* 1994; Patterson *et al.* 2006), and SPA (Yang *et al.* 2012); however, SpaceMix holds a number of advantages over these approaches. Tree-based methods, such as TreeMix, MixMapper, and others, have provided a variety of insights into patterns of population admixture. However, because gene flow is frequently pervasive, patterns of relatedness between samples may often be poorly represented by the hierarchically bifurcating tree structure assumed by these methods. PCA-based approaches, which assume no explicit model of population-level processes, are more flexible. However, their results can be strongly affected by size and design of sampling, and the linearity and orthogonality requirements of the PC axes can make interpreting results difficult. SpaceMix can capture and describe complex, non-hierarchical patterns of structure and admixture, yet also admits of simple and intuitive interpretation. We believe this method will have broad utility and that it represents a significant contribution to the field.

Olivier Francois (olivier.francois@imag.fr), John Novembre (jnovembre@uchicago.edu), Joe Pickrell (jkpickrell@nygenome.org), David Reich (reich@genetics.med.harvard.edu), and Monty Slatkin (slatkin@berkeley.edu) would be suitable reviewers. Any of these reviewers would also be a suitable external editor (as Coop is an associate editor).

Sincerely,  
Gideon Bradburd,  
Peter Ralph, and  
Graham Coop