

## Spotlight

Time to Go Bigger:  
Emerging Patterns in  
MacrogeneticsSimon Blanchet,<sup>1,\*</sup>  
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**The increasing availability of large-scale and high-resolution data sets in population genetics is moving the field toward a novel research agenda. Here, we show how this shift toward macrogenetics should generate new perspectives and theories allowing the description, understanding, and prediction of patterns of genetic diversity at broad spatial, temporal, and taxonomic scales.**

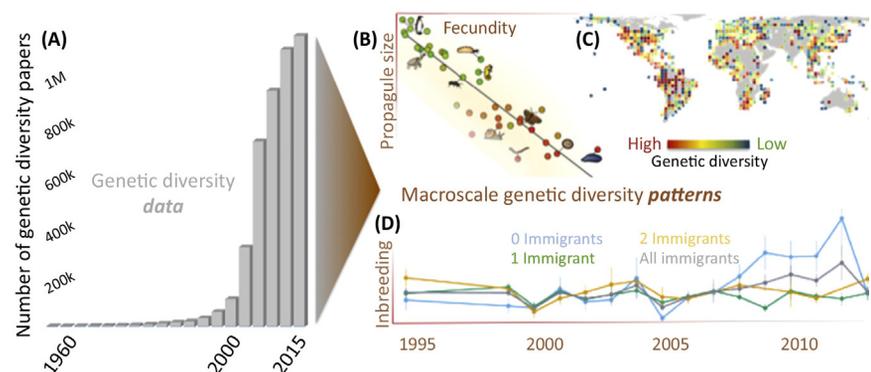
Population genetics aims to explore within-species genetic diversity over space, taxa, and time, and to identify the underlying evolutionary forces. During the early 1920s, technical limitations impeded the founding fathers of population genetics (Sewall Wright, John Haldane, and Ronald Fischer) from quantifying their central focus (i.e., genetic diversity). Therefore, the early foundations of the discipline were purely theoretical and poorly substantiated by natural observations. It was only some decades later, with the development of molecular analysis techniques, that population genetics entered a new era allowing the empirical testing of founding theories, and leading to the emergence of new theories (e.g., the neutral theory of molecular evolution [1]). More recently, high-throughput sequencing reinforced this empirical era with unprecedented abilities to gather improved genetic information over large numbers of markers, individuals, species, and locations at relatively low costs.

These two major steps in population genetics are now making many detailed data sets available to scientists (Figure 1A), allowing a shift from local-scale studies (i.e., a single species in a single environment at a given period) to fascinating perspectives on the large-scale spatial, temporal, and taxonomic distribution of genetic diversity in nature (e.g., [2]). Describing and understanding general and repeatable patterns of genetic diversity (i.e., 'laws' *sensu* [3]) should provide invaluable ecological and evolutionary opportunities to fuel the development of new theories, and to set sustainable management strategies. Here, we argue that the time is ripe to move to a 'macrogenetics' view of population genetics, echoing the recent shift of ecology to 'macroecology' and allowing the pursuit of new ambitions in population genetics.

Three recently published papers [4–6] perfectly illustrate the scientific benefits of considering macroscale genetic data sets by considering numerous taxa, large spatial extents, or long time series. First, Romiguier *et al.* [4] used transcriptome sequencing to identify taxonomic patterns of genomic diversity in 76 animal species (covering eight different phyla)

and to reveal the species traits underpinning genomic diversity. Why some species exhibit a high genetic diversity whereas others are genetically impoverished constitutes one of the oldest riddles of population genetics. Theory predicts that long-lived species with high parental investment, contrary to species with short lifespans and high fecundity, often have low population sizes, characterized by impoverished genetic diversity. The authors confirmed this theory by demonstrating that animal species investing in propagule quality (i.e., K-like strategists) have lower genomic diversity than species investing in propagule quantity (i.e., r-like strategists). More specifically, they found striking correlations between genomic diversity, fecundity, and propagule size (Figure 1B). By identifying traits underlying genomic diversity across a broad range of taxa, this study not only resolved an age-old conundrum in population genetics, but also has the potential to inform species conservation in terms of trait-mediated extinction risks.

Second, Miraldo *et al.* [5] harnessed the potential of archived genetic databases to reveal spatial patterns of genetic diversity and to explore how humans impact these patterns. The authors relied on



## Trends in Genetics

**Figure 1. Genetic Data Accumulation Is Leading to Macrogenetics.** The development of next-generation sequencing techniques [(A) during the 2000s] and the accumulation of data are generating new scientific opportunities on the large-scale and universal taxonomic (B), spatial (C), and temporal (D) patterns of genetic diversity. (B) The genetic diversity of species varies along the propagule size–fecundity continuum [4]. (C) The genetic diversity of mammals and amphibians increases towards the tropics [5]. (D) Changes over time in the inbreeding coefficient of nestlings from a bird population depend on the number of immigrant parents for each nestling [6]. Reproduced, with permission, from [2] (B), [5] (C), and [6] (D)

approximately 86 000 available georeferenced mitochondrial sequences from more than 4500 amphibian and mammal species worldwide, to provide the first global map of genetic diversity. This global mapping revealed clear latitudinal gradients (as observed traditionally for species diversity), with genetic diversity decreasing from the tropics to the poles (Figure 1C). In addition, the authors identified significant anthropogenic impacts on the genetic diversity of amphibians, pinpointing urgent biodiversity conservation challenges at the global scale. As a result of its unprecedented spatial scale, this work identified hotspots of genetic diversity across the planet, and paves the way for novel avenues into both theoretical and applied evolution research.

Third, Chen *et al.* [6] performed a 20-year field survey of the endangered Florida scrub jay (*Aphelocoma coerulescens*) to describe temporal patterns of genomic diversity in a focal population. Through detailed temporal screening of changes in genome-wide diversity, the authors identified a rapid decline in the number of individuals immigrating from peripheral populations to the focal population, likely due to increased anthropogenic fragmentation of the surrounding landscape. They further demonstrated that immigrants had a vital role in maintaining low levels of inbreeding in the focal population (Figure 1D). Inbreeding negatively influences traits related to the fitness of plants and animals, leading to inbreeding depression [7]. Accordingly, the authors showed that the reduction in the number of immigrants over time due to human activities was associated with strong inbreeding depression on several fitness-related traits, including reduced hatching success and survival rates. This study demonstrates the strength of long-term genetic surveys to illuminate harmful effects of habitat fragmentation on the well-being of wild populations, and to uncover 'early signals' of population decline that can be efficiently used to preclude population extinctions.

Ongoing data generation and accumulation clearly is initiating a major shift towards unraveling broad-scale patterns of genetic diversity and their underlying processes, and, hence, to resolving open and integrative questions in evolutionary biology. This shift to a macrogenetics view of population genetics goes beyond comparative population genetics by embracing all scales of variation (i.e., taxonomic, spatial, and temporal scales), which is a necessary step to better appraise how underlying processes interact across scales. To further exemplify this perspective, we highlight how this shift toward macrogenetics will improve long-term species conservation, provided that massive data generation is accompanied by parallel computational developments to reduce both data and systematic errors that may drastically slow down the achievements of these fascinating goals. First, understanding the role of genetic diversity in structuring ecological communities has been the focus of many studies, yet we still do not know the large-scale impacts of genetic diversity on the assemblages of species to recommend management of high genetic diversity as a means of preserving ecosystem functioning [8]. Second, a more holistic perspective on population genetic patterns associated with the interactions of species (e.g., host–parasite or plant–pollinator dynamics) could highlight the crucial role of 'genetic synchronism' in rendering specialized ecological networks of interacting species more vulnerable to environmental change [9]. Third, it is widely accepted that both nonadaptive and adaptive (i.e., driven by natural selection) components of genetic diversity govern the ecoevolutionary dynamics underlying the long-term survival of species. However, we still question whether these distinct, yet not mutually exclusive, components follow similar temporal and spatial patterns and to what extent they contribute to the ability of species to cope with environmental changes [10]. We argue that the opportunities provided by

recent sequencing approaches and decades of genetic diversity data accumulation should be exhaustively exploited to boost our understanding of the broad-scale processes driving macrogenetic diversity in light of the sustainable conservation of ecosystems and their services.

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<http://dx.doi.org/10.1016/j.tig.2017.06.007>

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## Spotlight

# CRISPRing the Regulatory Genome, the Challenge Ahead

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**CRISPR saturation mutagenesis has the potential to dissect the functional landscape of**