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Review and synthesis

The value of space-for-time substitution for studying fine-scale microevolutionary processes

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When the drivers of biological turnover in space are the same as those that drive turnover through time, space can be substituted for time to model how patterns of variation are predicted to change into the future. These space-for-time substitutions are widely used in ecological modeling but have only recently been applied to the study of microevolutionary processes, particularly over relatively fine spatial and temporal scales. Here, we review recent examples that have employed space-for-time substitution to study genetic patterns on stationary and non-stationary landscapes and examine whether space can reliably substitute for time in studies of population divergence, genetic structure, and adaptive evolution. Although there are only a relatively few examples, several recent studies were excellently crafted to provide valuable insights into the conditions governing the validity of space-for-time substitutions applied to population genetic data. We found that, although caution should be taken, space-for-time substitutions appear valid for studying microevolutionary processes on both stationary and non-stationary landscapes. Further studies can help to evaluate the conditions under which space-for-time substitutions are reliable. When these methods are reliable, they will play an important role in modeling genetic responses to environmental change, population viability on non-stationary landscapes, and patterns of divergence and adaptation.

Introduction

Space-for-time substitution – in which contemporary spatial patterns of biodiversity are used to model temporal processes and project changes through time, either into the future or into the past – are widely used in ecological modeling (Pickett 1989, Algar et al. 2009, Blois et al. 2013). Space-for-time substitution models can basically take two forms, both of which rely on the assumption that the factors driving spatial turnover in an ecological process are also those driving temporal turnover. In the first, sites of different ages (e.g. volcanic islands), or experiencing a phenomenon of interest for different lengths of time (e.g. habitat fragmentation), are compared to infer how temporal processes have driven patterns currently observed in different parts of

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space (Pickett 1989, Johnson and Miyanishi 2008). In the second, sites are assumed to be of the same age, and patterns of turnover in space, potentially along ecological gradients (e.g. temperature or precipitation), are used to predict turnover through time (Fitzpatrick and Keller 2015). Hereafter, we refer to these approaches as 'different aged sites' and 'spatiotemporal turnover', respectively. In principal, any level of biological organization could be modeled with these methods, from community composition to genetic variation.

Many disciplines have developed methods that use space-for-time substitution as an alternative to long-term, longitudinal studies. For instance, ecological chronosequences are used to study long-term nutrient cycling and plant succession (Johnson and Miyanishi 2008, Buma et al. 2017), spatial climate modeling is used to predict the effects of climate change on biodiversity (Blois et al. 2013, Fitzpatrick and Keller 2015), niche modeling can be used to project species range shifts under future climate scenarios (Kharouba et al. 2009, Dobrowski et al. 2011), and geomorphic mapping has been used to model erosion and topographic responses to geological deformation (Brooks 1987, Hilley and Arrowsmith 2008). In ecology and evolution, methods employing space-for-time substitution are frequently used to infer the processes driving community composition and species richness (Rosenzweig 1995, Johnson and Miyanishi 2008, Walker et al. 2010, Blois et al. 2013), cycles of ecological succession (Johnson and Miyanishi 2008, Walker et al. 2010), biodiversity loss (França et al. 2016), changes in behavior and phenology (Buyantuyev et al. 2012, Charmantier and Gienapp 2014), responses to disturbance events (DeLuca et al. 2002, Wardle et al. 2004), range shifts (Eskildsen et al. 2013), and the transferability of ecological niche models over timespans of decades to millennia (Randin et al. 2006, Dobrowski et al. 2011, Heikkinen et al. 2012, Wogan 2016). The accuracy of these approaches has been debated (Pickett 1989, Johnson and Miyanishi 2008, Algar et al. 2009, Walker et al. 2010, Elmendorf et al. 2015); they appear to be robust at broad spatial and temporal scales for community level biodiversity (Algar et al. 2009, Walker et al. 2010) and reasonably accurate for predicting species turnover during broad scale (1000s of years) climate change (Blois et al. 2013), but they may underperform when the trajectory of environmental change is unstable (Johnson and Miyanishi 2008), when the rate of change is rapid (Blois et al. 2013, Elmendorf et al. 2015), or if there are unrecognized effects of past events (Pickett 1989). In any case, although space-for-time substitution has been evaluated for higher levels of biodiversity (Johnson and Miyanishi 2008, Algar et al. 2009, Dobrowski et al. 2011, Blois et al. 2013), its accuracy and applicability for studying processes acting on the finer levels of biodiversity, like microevolutionary changes in genetic diversity through time, over shorter temporal scales (10s to 100s of years) remain largely untested.

When applied to genetic diversity, space-for-time substitution models genetic turnover (typically allele frequency shifts or changes in population genetic composition) in space as an approximation of genetic turnover through time (Travis and Hester 2005, Espíndola et al. 2012, Wang and Bradburd 2014, Fitzpatrick and Keller 2015). Like studies at the species or community levels, many recent studies of spatiotemporal patterns of genetic variation have been concerned with forecasting potential changes in biodiversity under anthropogenic climate change (Kelly et al. 2013, Fitzpatrick and Keller 2015). These studies typically analyze spatial climate gradients to predict how populations will respond to climate change scenarios (Therkildsen et al. 2013, Zgurski and Hik 2014) instead of using longitudinal temporal sampling, although exceptions exist (Kovach et al. 2012, Bergland et al. 2014, Terekhanova et al. 2014). Spatial inferences are often made using landscape genetics, which relies on spatially explicit analyses of environmental variables (e.g. temperature, precipitation) and landscape features (e.g. habitat types, barriers) to identify the geographic, environmental, and microevolutionary drivers of spatiotemporal genetic variation at relatively recent time scales (Spear and Storfer 2010, van Strien et al. 2013, Richardson et al. 2016). What remains unknown is whether space-for-time substitutions are valid at the shorter time scales (decades to centuries) necessary to evaluate the effects of and predict responses to rapid anthropogenic climate change.

So far, assessments of biological responses to climate change and the development of predictive models have largely focused on the species level or above (Currie 2001, Moritz et al. 2008, Fitzpatrick et al. 2011, Lawler et al. 2013). However, studies at the population level are critical for understanding how genetic diversity, population connectivity, and adaptive potential can be maintained in the face of ongoing climate change (Holt 1990, Hampe and Petit 2005, Hoffmann and Sgrò 2011, Anderson et al. 2012, Hansen et al. 2012). This is where studies of spatiotemporal patterns of genetic variation can help to evaluate the processes driving changes in genetic diversity (Wang and Bradburd 2014). Of course, direct assessment of the effects of climate change on genetic variation may require temporal sampling (Hansen et al. 2012), and new methods have been developed to overcome many of the limitations on the use of historical DNA (Mamanova et al. 2010, Carpenter et al. 2013, Hykin et al. 2015), making temporal landscape genetic studies possible even without new longitudinal sampling programs being undertaken (Bi et al. 2013, Holmes et al. 2016). However, if space-for-time substitutions are reliable at short time scales, then we already have a strong predictive framework for better understanding the effects of climate change on microevolutionary processes.

The application of space-for-time substitution to study population genetic diversity falls under two general models: 1) populations evolving on landscapes that are stationary in time and space, and 2) populations evolving on landscapes that are non-stationary in time and space. Here, stationary does not mean that landscapes are necessarily homogenous but that there is no clear trend or trajectory to landscape changes in time or space. Hence, there is no spatial or temporal autocorrelation for environmental variables; sites that are

farther apart in space or time are not more likely to have different environmental values (e.g. temperature, precipitation, or habitat). Non-stationary landscapes, on the other hand, exhibit changes with clear trends through time or across space (Manel et al. 2010, Duforet-Frebourg and Blum 2014). Thus, they have values of some variable of interest that increase with greater distances between sites or greater intervals of time between observations within a site (Manel et al. 2010). For instance, ecotones and climate gradients are examples of non-stationarity in space, and anthropogenic climate change is an example of non-stationarity through time. In other words, the rate of accumulation of differences among individuals or populations can be independent of (stationary) or dependent on (non-stationary) their distance in space or time (Manel et al. 2010, Duforet-Frebourg and Blum 2014).

Studies of stationary landscapes typically investigate populations evolving under neutral processes, including mutation, gene flow, and genetic drift (Wright 1943, Slatkin 1987), whereas studies on non-stationary landscapes typically examine populations evolving under selective processes, including divergent selection along environmental gradients and other forms of heterogeneity in the strength or agents of natural selection through time or space (Manel et al. 2010, Duforet-Frebourg and Blum 2014, Wang and Bradburd 2014). While studies interested in identifying the environmental or climatic drivers of genetic changes focus primarily on the latter, the former provides an important foundation for setting null expectations for how genetic diversity changes through time and space. Both come with sets of assumptions that govern the cases to which they can be applied and expectations that we can test to evaluate their reliability.

In this review, we first outline the processes driving patterns of genetic variation under each scenario and their assumptions. We then examine evidence for whether the expectations for applying space-for-time substitution to analyses of genetic diversity are met. Specifically, we compare space-for-time analyses, and their general predictions, to temporal analyses (time-for-time) to determine whether (and under what conditions) analyses of spatial genetic variation can be used to model changes in genetic variation through time.

Literature search

We used the web of science core collection to seek out relevant literature for inclusion in this review. We used keyword searches for terms commonly associated with space-for-time substitution studies and spatiotemporal analysis in ecology and evolution: space-for-time, isolation by time, isolation by distance, temporal FST, known age, colonization history, invasive, urban, habitat fragmentation, altitudinal gradient, latitudinal gradient, genomic and environmental association. In addition to the Web of Science search, we further augmented the list of studies through citation backtracking. While we have attempted to include all relevant studies, our search is likely not comprehensive. Since we are not conducting a quantitative meta-analysis of population genetic space-for-time substitutions but rather a synthetic overview of an emerging topic, this strategy should be appropriate for recovering a representative and unbiased set of studies on the core topics of this review. Each keyword search returned a list of up to 3574 potential studies (Supplementary material Appendix 1); from the total search results, we curated a list of 24 space-for-time studies (Supplementary material Appendix 1 Table A1) and eight time-for-time studies (Supplementary material Appendix 1 Table A2) that fit the criteria for inclusion in this review.

Genetic variation on stationary landscapes

Studies applying space-for-time substitution to analyses of genetic variation on stationary landscapes are primarily concerned with two population genetic parameters: genetic diversity and genetic differentiation. Genetic diversity is essentially the amount of genetic variance in a population (or set of populations) and can be measured by allelic or nucleotide diversity, allelic richness (number of alleles), or heterozygosity (Wright 1943, Slatkin 1987). Genetic differentiation is the degree to which populations have diverged from one another, in space or time, and is frequently measured by F_{ST} or other metrics of population genetic structure (Slatkin 1987). Higher levels of genetic diversity generally indicate greater capacity for evolutionary responses in a population, while higher levels of genetic differentiation indicate more genetic variation distributed between populations rather than shared by them (Hoffmann and Sgrò 2011, Schoville et al. 2012). Hence, both are important measures of genetic variation that are informative for evaluating population dynamics, conservation status, and evolutionary potential. The key, then, for applying space-for-time substitution to these studies is whether the processes that drive changes in genetic diversity and differentiation are the same across space and through time.

Changes in neutral genetic variation, in time or space, are driven by mutation, gene flow, and genetic drift (Spieth 1974, Slatkin 1987). Mutation introduces variation into a population at a rate proportional to the effective population size and the mutation rate, while genetic drift removes variation at a rate inversely proportional to the population size (Kimura 1983, Slatkin 1993). The rate at which gene flow introduces new variation to a population depends upon the rate of gene flow into the population and the difference in the allele frequencies between that population and the source populations (Spieth 1974, Slatkin 1987). When populations are highly differentiated, migrants are more likely to introduce different alleles into a population; as they become more similar, the rate at which gene flow changes allele frequencies decreases. In principal, how these processes operate through time and space is roughly analogous (Duforet-Frebourg and Slatkin 2016), suggesting that space-for-time substitution

approaches could be valid for predicting how genetic diversity within populations and genetic divergence between populations change through time. Both the different aged sites and spatiotemporal turnover approaches have been used to apply space-for-time substitution to the study of genetic variation on stationary landscapes. Below we evaluate the outcomes of those studies and whether they meet the expectations set by time-for-time studies.

Stationary landscapes – different aged sites

Studies of neutral genetic variation on stationary landscapes that apply space-for-time substitution via the different aged sites approach primarily seek to understand how the genetic diversity of a population changes through time under neutral processes. Because the rate at which genetic diversity is gained or lost depends on population size, a key characteristic of these populations is how they were formed (Keyghobadi et al. 2005). Populations founded by colonization events start with small but growing population sizes, and, therefore, genetic diversity will generally increase with population age until it reaches its equilibrium (Fig. 1A). Populations formed by vicariance events, on the other hand – for instance, through fragmentation – begin with large population sizes that may decrease through time, since carrying capacity is reduced following population isolation. Genetic diversity in these populations will generally decrease until it reaches its equilibrium (Fig. 1A). In either case, if space-for-time substitution is valid, then we expect changes in genetic diversity measured within populations through time to match the relationship between genetic diversity and the age of different populations sampled in space.

We reviewed two classes of studies that fit the different-aged-sites substitution model: studies that use urban landscapes or landscapes experiencing habitat fragmentation on which the ages of fragments are known, and studies of invasive species for which the times since colonization are known (Supplementary material Appendix 1 Table A1).

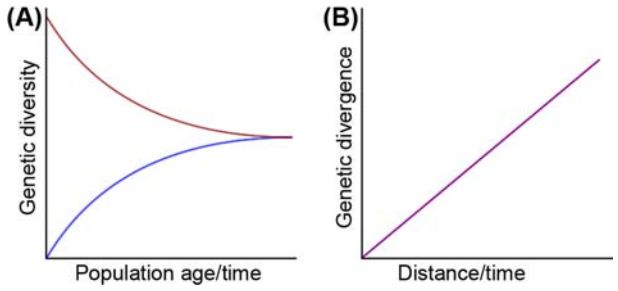

Figure 1. Graphs of the general spatiotemporal trends for (A) genetic diversity and (B) genetic divergence. Genetic diversity will either increase (blue) or decrease (red) toward its equilibrium through time or among differed aged populations, depending on whether populations are formed by colonization or vicariance, respectively. Genetic divergence will generally increase linearly with the distance between populations (IBD) or with the length of time separating different observations within a population (IBT).

Under colonization scenarios, we predict that recently founded populations will have less genetic diversity than older populations, while under fragmentation scenarios, we expect population age to be negatively correlated with genetic diversity (Dlogosch and Parker 2008). In each case, knowing the age of each site provides an opportunity to implement space-for-time substitution.

Among fragmentation studies, we found little support for the validity of space-for-time substitution. Several studies investigating fragment age and genetic diversity found no significant relationship between them. For instance, Delaney et al. (2010) found no significant association between patch age and genetic diversity in three species of lizards and one bird in Southern California, all with populations inhabiting patches fragmented by urban development, and Lourenco et al. (2017) found no significant relationship between genetic diversity and population age in urban populations of fire salamanders *Salamandra salamandra* that have been isolated in the city of Oviedo, Spain for 20 to > 1000 yr. A third study, focused on populations of great tits *Parus major* in the urban parks of Barcelona, which range in age from 18 to 305 yr, also found no correlation between patch age and genetic diversity (Björklund et al. 2010). Why these results diverge from expectations is not clear, but these studies revealed conditions that suggest the studied populations were not behaving as isolated populations with comparable features. Delaney et al. (2010) and Lourenco et al. (2017) found that patch characteristics varied substantially and that some features, like patch size, had strong effects on population size and genetic diversity. Björklund et al. (2010), meanwhile, found evidence for gene flow between urban park populations and populations in large, contiguous forests nearby. Thus, in each of these cases, numerous other factors may have obscured the effects of population age, and these studies suggest that applying space-for-time substitution to different aged sites on stationary landscapes may be difficult unless the populations are effectively isolated in comparable patches.

Among colonization studies, on the other hand, some recovered the predicted pattern of low initial genetic diversity followed by gradually increasing diversity through time. For example, Haag et al. (2005) examined genetic diversity in populations of *Daphnia* in Finland founded over a 20-yr period and found less genetic variation in recently colonized populations than in those that had been colonized earlier. Others, however, revealed exceptions to this pattern. For example, introduced populations of *Anolis* lizards derived from multiple source populations showed no clear pattern of genetic diversity (Kolbe et al. 2004), suggesting that space-for-time substitution with populations of different ages may only be applicable for cases with single founding events. This finding is similar to results from ecological studies that found that unrecognized effects from past events may inhibit the application of space-for-time substitution (Pickett 1989). More examples of space-for-time colonization studies are needed to better understand the full range of scenarios to which these methods can be applied.

Stationary landscapes – spatiotemporal turnover

Studies of neutral genetic variation on stationary landscapes that apply space-for-time substitution via the spatiotemporal turnover approach generally try to model how a population will diverge genetically through time from its previous states as a function of how populations diverge from one another through space. Spatial population divergence on a stationary landscape frequently follows a pattern of isolation by distance (IBD), in which genetic divergence is correlated with the geographic distances between populations (Wright 1943). This arises in continuously distributed populations when the geographic range of a species is greater than the dispersal distance of individuals (Slatkin 1987). Essentially, populations that are farther apart typically experience lower rates of gene flow, and therefore less of its homogenizing effects, and generally have deeper divergence times, meaning they have had more time to drift apart (Wright 1943, Slatkin 1987). Hence, populations that are farther apart in space tend to accumulate more genetic differences.

The same processes drive the accumulation of genetic differences between the states of a population through time as well – drift and gene flow change allele frequencies in each generation, and mutation can introduce new variants (Kimura 1983). This can, theoretically, lead to a pattern of 'isolation by time' (IBT), in which genetic divergence between population states increases with the time between them (Fig. 1B). The term 'isolation by time' can also refer to increased genetic differentiation between groups that have reduced overlap in reproductive periods (Hendry and Day 2005). Here, we consider IBT as only isolation through time between population states rather than 'isolation by reproductive timing.' IBT, by this definition, arises due to the stochastic sorting of alleles within a population during coalescent processes and is directly tied to the effects of genetic drift (Skoglund et al. 2014, Duforet-Frebourg and Slatkin 2016). Thus, under neutral processes on a stationary landscape, populations can diverge through both space and time, potentially leading to 'isolation by distance and time' (IBDT; Duforet-Frebourg and Slatkin 2016). In this scenario, genetic covariance between populations decreases as a function of geographic distance and separation through time (Skoglund et al. 2014, Duforet-Frebourg and Slatkin 2016). Just as IBD can be used as the null model for spatial structure, IBT can be used as the null model for temporal structure. If space-for-time substitution is valid for modeling spatiotemporal genetic turnover, then IBD should be proportional to IBT, and the relationship between genetic divergence and time should be linear, matching the linear relationship between genetic divergence and geographic distance.

There are far fewer empirical studies that test IBT than IBD, since its study requires longitudinal sampling of a population over time and technologies that allow the sequencing of ancient or historical DNA samples have only recently become available. Even when the appropriate data are available (e.g. longitudinal sampling of multiple populations), studies often do not consider the effects of both space and time on population differentiation. Many studies with time series data which could consider temporal isolation instead assess spatial differentiation within each time period and then report populations as more or less spatially differentiated between time periods, while other studies assess temporal differentiation but not spatial differentiation.

Nevertheless, we found some studies that calculated both spatial and temporal patterns of genetic differentiation and provide valuable insights into the dynamics of population divergence through time and space. For example, Peery et al. (2010) evaluated historic (1888–1940) and modern (1997–2007) samples of marbled murrelets *Brachyramphus marmoratus* and characterized both spatial F_{ST} and temporal F_{ST} for historic and modern samples. They found increased levels of differentiation in central Californian populations through time (IBT) and suggest that small population size and, therefore, genetic drift drove the differentiation, consistent with expectations. Martin et al. (2014) examined spatial and temporal patterns of genetic differentiation of invasive ragweed *Ambrosia artemsifolia* in the US and found significant genetic structure through time but with a greater degree of IBT in Western populations ($F_{ST} = 0.018$) than Northeastern populations ($F_{ST} = 0.002$). Wang and Shaffer (2017) examined temporal and spatial F_{ST} in California tiger salamanders *Ambystoma californiense* over a 6-yr period (1995–2001) by resampling a set of breeding pond populations on a protected landscape. They found that temporal F_{ST} ranged from 0.002 to 0.044 in six ponds sampled between years, while spatial F_{ST} ranged from 0.071 to 0.153 among those same ponds, even over fairly short distances (< 1 km). The pairwise estimates of spatial F_{ST} were highly consistent for both years of sampling. Finally, Ugelvig et al. (2011) assessed population structure using museum samples collected at nine different time points over a 77-yr period for the large blue butterfly *Maculinea arion* from the Island of Mon, Denmark. They calculated pairwise temporal F_{ST} statistics and recovered a pattern of IBT, increasing genetic differentiation with increasing number of years between samples. They also performed spatial F_{ST} analyses at a wider geographic scale, which fit a general pattern of IBD.

Stationary landscapes – conclusions

The results of studies on different aged sites present mixed news for the validity of space-for-time substitutions. Several studies of different aged sites on stationary landscapes (Delaney et al. 2010, Lourenco et al. 2017) found patterns inconsistent with expectations for how genetic diversity should change through time within a population (Fig. 1A), but other studies (Haag et al. 2005) recovered a pattern consistent with asymptotically increasing or decreasing genetic diversity, depending on how the populations were formed. For all of the cases in which no relationship between genetic diversity and population age was detected there were several

potentially confounding factors involved. For instance, multiple colonizations, admixture with other populations, and differences in patch size or environmental quality could all be drivers of differences in genetic diversity between populations that would obscure the role of population age (Kolbe et al. 2004, Delaney et al. 2010, Lourenco et al. 2017). More studies are needed to better understand whether these are general trends that would apply to most systems or whether they are factors that can be controlled for with sampling design. At the very least, these studies highlight the many potential forces that can act on genetic diversity and reveal important caveats regarding the use of space-for-time substitution. In particular, making sure that populations of different ages are comparable in terms of demographics and that they occupy patches of similar size and quality are clearly important for applying space-for-time substitution. Whether space-for-time substitution can be applied to systems that do not meet these requirements remains to be seen, and future studies that explicitly consider population age and its relationship to genetic diversity, simultaneously with other factors, will be important for better understanding this question.

Studies of spatiotemporal turnover on stationary landscapes provide more encouraging results. Several carefully designed studies (Peery et al. 2010, Ugelvig et al. 2011, Martin et al. 2014) detected patterns of IBT that were roughly linear, as expected. Moreover, these studies also suggest that rates of genetic differentiation through time and space are comparable over relatively fine spatial and temporal scales, which is particularly important for studies of microevolutionary processes acting at finer scales and over smaller spatiotemporal domains. Additional studies that explicitly compare IBT and IBD would help to quantify the relationship between genetic differentiation through time and genetic differentiation through space. These studies could help to identify the conversion between units of time and units of space with respect to their effects on genetic differentiation, which will be critical for modeling genetic turnover using space-for-time substitution.

Genetic variation on non-stationary landscapes

Predicting how species will respond to non-stationary environmental change is a major goal of evolutionary modeling (Hansen et al. 2012, Duforet-Frebourg and Slatkin 2016). Scenarios that are non-stationary through time include global climate change, landscape alteration that affects population dynamics or demographics, and the introduction of novel selective regimes, like pests or pathogens. Understanding genetic responses to these scenarios has clear benefits for conservation and management, but projecting evolutionary outcomes is inherently difficult (Holt 1990, Hoffmann and Sgrò 2011, Hansen et al. 2012). To overcome this challenge, a number of studies have now employed space-for-time substitution methods to model potential outcomes based on microevolutionary responses in populations experiencing different selection regimes across different parts of space (Franks and Hoffmann 2012, Merila and Hendry 2014).

In these scenarios, the neutral processes of mutation, drift, and gene flow are still acting, but changes in adaptive genetic variation are driven primarily by natural selection. Unlike stationary landscape scenarios, in which population sizes are also expected to be stationary, selective forces can potentially cause non-stationary changes in population demographics that could affect how populations experience mutation and drift (Haig 1998, Epps and Keyghobadi 2015, Kozma et al. 2016). For example, some studies have evaluated the loss of genetic variation over time on non-stationary landscapes to demonstrate IBT. Ortego et al. (2011) found strong evidence for IBT in a single isolated population of mountain goats experiencing a population increase over a 14-yr period, as did Demandt (2010) when evaluating isolated populations of fish with shifting demographics sampled 23 yr apart. Non-stationary landscapes can also influence patterns of gene flow through selection against migrants from divergent environments or biased dispersal, both of which limit gene flow between parts of space with different environmental characteristics (Wang and Bradburd 2014). The dynamics between these different processes can become considerably more complicated than on stationary landscapes, but, as is critical for the validity of space-for-time substitutions, the processes that drive adaptive genetic variation in time and space are ostensibly the same. Again, studies have used both the different aged sites and spatiotemporal turnover approaches to apply space-for-time substitution to the study of genetic variation on non-stationary landscapes. Below, we evaluate the outcomes of those studies, both for neutral and adaptive genetic variation, and whether they match the findings from time-for-time studies.

Non-stationary landscapes – different aged sites

Perhaps the best way to predict how species will respond to novel selection regimes is to evaluate how they have responded to them before. When this is possible, studies employing space-for time substitution with different aged sites evaluate contemporary patterns of genetic variation among populations that were exposed to new agents of selection at different times in the past. This is a potentially powerful approach for forecasting evolutionary outcomes if space-for-time substitution is accurate and reliable. If it is, then we expect that differences in population size, demographics, and fitness among populations experiencing a selection regime for different lengths of time will match the changes in these variables observed within populations through time. We also expect that the time for signatures of selection to arise will be consistent between space-for-time and time-for-time studies as will the order in which mutations arise, for adaptations involving multiple loci.

To our knowledge, this approach, while seemingly powerful, has only rarely been used in empirical systems. For instance, Terekhanova et al. (2014) examined freshwater

populations of sticklebacks of known ages (< 1 yr to > 700 yr) using the strong genomic foundation available for sticklebacks to estimate the rate of adaptation and strength of selection at loci that are highly divergent between marine and freshwater populations. They demonstrated that the same genomic regions that are highly divergent between marine and freshwater populations are responsible for the rapid evolution of freshwater ecotypes in each population. They also found that the frequency of adaptive SNPs was positively correlated with population age, suggesting a trajectory of ongoing adaptation through time and meeting the expectations of space-for-time substitution. Bi et al. (2013) used historical museum specimens to assess temporal isolation in chipmunks over a 90-yr period, using exome sequencing to examine changes in genetic diversity following a climate-related range retraction. They found increased genetic subdivision following range retraction but no significant changes in genetic diversity at either neutral or non-neutral loci. Another study examined genomic response of Tasmanian devils *Sarcophilus harrisii* to a disease (devil facial tumor disease) that causes almost 100% mortality within six months of tumor appearance. Exposure often happens with mating, and there is some inter-individual variation in the incubation period after exposure, which allows some Tasmanian Devils to successfully wean litters before succumbing to the transmissible cancer (McCallum et al. 2009, Brüniche-Olsen et al. 2016). Using populations that were exposed to the disease at different times spanning a 14-yr period, Brüniche-Olsen et al. (2016) used both spatial and temporal analyses to look for RAD loci under selection to see if there was a common genomic response either across populations or within a single population over time. They did not find any consistencies in the loci identified as being under selection among the exposed populations, nor was there any commonality with the loci identified as being under selection from the temporal analysis, suggesting that population responses to this agent of selection were too idiosyncratic to be suitable for space-for-time substitution.

Non-stationary landscapes – spatiotemporal turnover

Another method for using space-for-time substitution to predict evolutionary responses to environmental change is to model genetic variation across environmental gradients in space using spatiotemporal turnover approaches. Some have argued that this represents an optimal approach for forecasting the genetic consequences of ongoing climate change (Thomassen et al. 2010, Wang and Bradburd 2014). Longitudinal studies are costly and may take too long to yield results, especially for vulnerable species, whereas studies on spatial environmental gradients can sample populations in a single season and be completed in a much shorter timeframe. Thus, these studies would be extremely valuable if space-for-time substitution is reliable under this approach. If it is, then we expect that adaptive genetic responses along environmental gradients in space will match those observed in populations experiencing environmental change (along the same axes) through time. These responses include patterns of genetic variation that emerge on non-stationary landscapes, like isolation by environment (IBE), in which genetic divergence is correlated with the environmental differences between populations (Wang and Bradburd 2014), and isolation by adaptation (IBA), in which greater adaptive genetic divergence is associated with increasing strength of divergent selection between different populations (Nosil et al. 2008). They also include genomic patterns of adaptation – for instance, whether signatures of selection appear at the same loci or, at least, in the same genes or molecular pathways.

The dynamics on non-stationary landscapes can also become increasingly complex when selection does not follow a single trajectory and instead fluctuates in space or through time. The degree to which adaptive genetic variation is maintained within a population or a species will depend on the strength of selection and the rate at which it fluctuates, among other factors (Fig. 2). When selection varies spatially, adaptive genetic variation will typically be maintained across a species but reduced within each population (Felsenstein 1976). However, spatially varying selection (e.g. divergent selection between different environments in space) is likely to give rise to local adaptation only if the selection regime is relatively stable over time (i.e. does not also fluctuate temporally). If selection varies temporally, on the other hand, theory predicts that polymorphism will not be maintained except under very specific conditions (Fig. 2). When selection varies at similar rates across space (between populations) and time (between generations), then spatial genetic variation will typically fall closer to the fitness optimum than temporal genetic variation does (Ellner and Hairston 1994, Lande 2007, Svardal et al. 2011). This is because populations have generally had a longer time to adapt to selection that fluctuates in space but which remains consistent through time (Siepielski et al. 2009). Space-for-time substitution applied to these scenarios could lead to spatial responses over-predicting temporal responses, as has been found in the ecological literature for the same reason (Elmendorf et al. 2015). When the rate at which selection fluctuates through time is relatively rapid (within a few generations), generations may fail to 'track' changes in fitness optima because insufficient variation persists to allow for adaptive shifts (Svardal et al. 2011), for instance if the new fitness optimum is outside of the range of variation in the preceding generation. However, if the rate of fluctuation is very rapid (< 1 generation), then variation is maintained because different individuals within a generation will experience different selective regimes and fitness optima (Ellner and Hairston 1994, Siepielski et al. 2009, Svardal et al. 2011).

In all cases, specific genetic scenarios will allow genetic variation to be maintained. For instance, heterozygote advantage is essentially selection for genetic diversity and will maintain variation, including in species with non-overlapping generations (Barton and Turelli 1989) and in many scenarios for species with overlapping generations (Ellner and Hairston 1994, Hedrick 2005). Likewise, balancing selection will also promote adaptive genetic diversity, because selection operates on multiple fitness optima

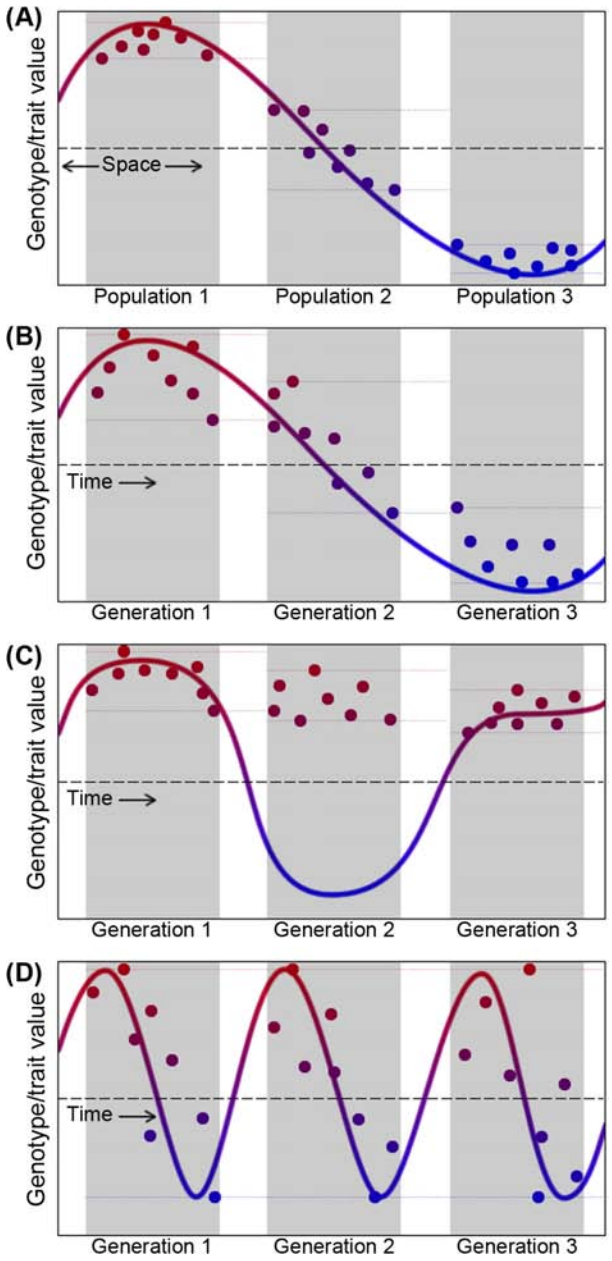

Figure 2. Distributions of adaptive genetic variation in populations across space (A) or in generations through time (B–D) experiencing fluctuating selection. Curves indicate the fitness optimum for an adaptive genotype or quantitative trait (y-axis) at points in space or time (x-axis). Circles represent hypothetical genotypes for each population or generation, and the heavy dashed lines (black) indicate the median genotype/quantitative trait values. The thin dotted lines (colored) indicate the upper and lower bounds for each population or generation. When selection fluctuates at similar rates across space (between populations) and time (between generations), the genotypes in different populations in space will typically fall closer to their fitness optima (A) than do the genotypes in different generations through time (B). This is because populations have generally had a longer time to adapt to selection that fluctuates in space (but remains consistent through time). When the rate at which selection fluctuates through time is relatively rapid (within a few generations), generations may fail to 'track' changes in fitness optima (C) because insufficient variation persists from previous generations to allow for adaptive shifts (i.e. the new fitness optimum is outside of the range of variation in the preceding generation). However, if the rate of fluctuation is very rapid (< 1 generation), then variation is maintained because different individuals within a generation will experience different selective regimes and fitness optima (D).

(Bergland et al. 2014). Explicit studies of microevolutionary dynamics under these scenarios of fluctuating selection in time or space are needed to know when and how space-for-time substitution can be applied – ecological studies have revealed that space and time may not be transferrable when environmental change is rapid or unstable (Johnson and Miyanishi 2008, Blois et al. 2013, Elmendorf et al. 2015), and these findings could apply to changes in environmentally-mediated natural selection as well.

Clinal variation studies tend to focus on altitudinal or latitudinal environmental clines across which genotypes and phenotypes vary since they represent ideal systems in which to study spatially varying selection (Flatt 2016). Altitudinal gradients in montane systems have proven valuable proxies for studying physiological adaptation to climate and responses to rapidly changing temperatures (Moritz et al. 2008, Tingley et al. 2009). Recent studies on amphibians (Bonin et al. 2006, Guo et al. 2016) and mammals (Bi et al. 2013, Henry and Russello 2013) using genome wide markers and genome scans have been conducted along altitudinal gradients and have identified outlier loci that may be relevant in adaptation to climate change. Other studies have used parallel latitudinal clines between sister species to identify shared genes undergoing selection that are related to adaptation along the cline (Machado et al. 2015), demonstrating that there is increased inferential power that comes from examining genomic response in closely related co-distributed clinal species. There are also numerous environmental association studies that use spatial variation across a range to identify loci related to specific environmental or climatic gradients (Hancock et al. 2011, Lv et al. 2014, Hornoy et al. 2015, Pluess et al. 2016), including some that have performed breeding experiments to identify adaptive genetic differences between populations (D'Croz and Maté 2004, Kelly et al. 2013). These studies have clearly demonstrated the power of genomic data and spatial analysis methods to detect signatures of selection linking specific genes to particular environmental variables; the question that remains is whether the genes underlying adaptation to environmental variation in space are the same as those that provide adaptive responses to changing environmental conditions through time.

Time-for-time studies often focus on whether patterns of genetic response to environmental selection are generalizable or repeatable across different populations. If space-for- time substitutions are valid, we might expect to see selective

signatures on the same loci or molecular pathways across time and space. For example, using a time-series of *Drosophila melanogaster* generations spanning three years, Bergland et al. (2014) investigated genetic response to temporally fluctuating selection imposed by seasonality in a temperate North American orchard. They found that spatial genetic variation is a good predictor of temporal genetic variation, showing that high latitude populations are more similar to spring populations, while low latitude populations are more similar to fall populations. Using 13- to 46-yr time-series datasets for chromosomal inversion frequencies and climate for 26 populations of *Drosophila subobscura* from three continents, Balanyá et al. (2006) found that 22 of the populations experienced climate warming during the time period and that 21 of those populations exhibited increases in genotypes characteristic of warmer, low latitude populations. Therkildsen et al. (2013) used spatial and temporal outlier analyses to look for signatures of environment-related selection in modern and historical (55 to 80 yr bp) populations of Atlantic cod *Gadus morhua*. While spatial analyses revealed 47 outlier loci, temporal analyses revealed fewer than ten SNPs within any single population, and only three loci were identified in common between the spatial and temporal outlier analyses. Most of the loci identified as outliers were also highly correlated with environmental variables, suggesting that divergent selection is driving adaptive response to different environments. The temporal analyses recovered more outlier loci in the contemporary populations than was present in the historical populations, suggestive of ongoing adaptation over the past several decades.

While there are relatively few studies in natural populations that have used time-for-time experimental designs to understand adaptation to changing environments, there are numerous insights that come from experimental evolution studies. For example, Huang et al. (2014) set up an elegant experiment with *Drosophila* to test if homogenous or heterogeneous environments maintain greater genetic diversity within a population, and further to test if spatially variable versus temporally variable environments maintain greater genetic diversity within a population. They broke down their results to look at the patterns arising from just the loci under selection and any linked sites versus neutral genetic variation (unlinked). When evaluating loci under selection they found that heterogeneous environments do indeed maintain greater genetic diversity than homogeneous environments, and spatially variable environments held more diversity than temporally variable environments.

Non-stationary landscapes – conclusions

There have been few studies that explicitly compare genetic patterns in time and space on non-stationary landscapes; so, much remains unknown. Nevertheless, the few studies that do exist provide some very exciting results. Especially because many studies employing space-for-time substitution have the goal of projecting evolutionary responses to climate change, the finding that patterns of genetic turnover across environmental gradients sometimes mirrors genetic turnover through time under a changing environment suggests there may be tremendous potential for space-for-time substitution applied to studies of variation across the genome. Perhaps even more surprising is that not only does the overall pattern of variation across the genome in space match the pattern through time but that studies of adaptive genetic variation have found evidence of selection and adaptive responses in the same genes in both time and space (Therkildsen et al. 2013, Bergland et al. 2014). More studies are still needed to understand whether this is a general trend and whether certain traits or particular forces of selection are more likely to be amenable to space-for-time substitution than others.

Carefully designed studies that simultaneously consider patterns of IBD, IBE, and IBT for neutral and adaptive loci should be well positioned to answer these questions (Fig. 3). Ideally, these studies will be designed to sample across multiple generations, either using forward in time sampling or historical sampling based on existing specimen collections (Bi et al. 2013, Holmes et al. 2016), and across a diversity of environments separated by a wide range of geographic distances (Fig. 3). These studies do not have to sample all of the same populations through time, but at least some of the populations should be sampled at multiple time points to enable direct comparisons of genetic changes through time. If some of the longitudinally sampled localities also exhibit environmental changes through time, then comparisons of non-stationary landscape changes in time and space can also be performed. These analyses will be especially valuable for better understanding microevolutionary responses to environmental change, but any study designs in which IBD, IBT, and IBE can be disentangled (Fig. 3) will contribute to our understanding of the spatiotemporal processes influencing patterns of genetic variation.

Conclusions

The studies needed to fully evaluate the reliability of space-for-time substitution for modeling microevolutionary processes are still few in number, leaving much still to be uncovered. However, the initial evidence suggests that there are indeed opportunities to substitute space-for-time to study changes in genetic variation on both stationary and non-stationary landscapes. At the same time, current studies have also revealed a number of caveats that suggest space-for-time substitutions should be applied with caution until the range of conditions over which they are reliable is better understood. Future studies should seek to make explicit comparisons between spatial and temporal patterns of genetic variation to outline the scenarios under which space-for-time substitution is valid and to provide more information on the major drivers of genetic turnover in space and time. New studies that quantify patterns of genetic variation in both space and time can also help to identify

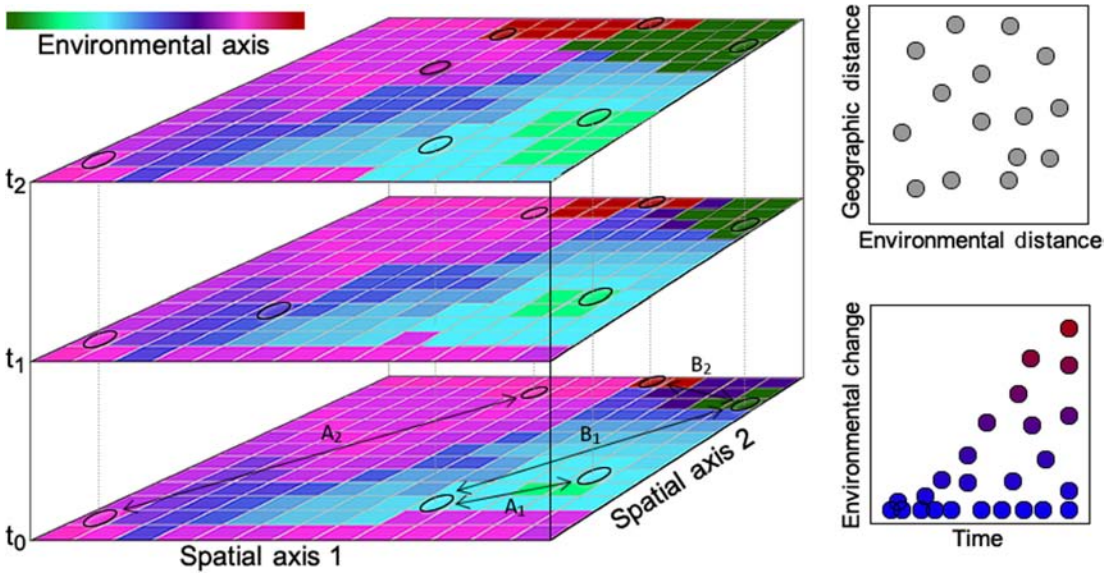

Figure 3. Considerations for sample design in studies aimed at quantifying patterns of IBD, IBE, and IBT for neutral and adaptive loci. Ideally, studies should sample across multiple generations and across a diversity of environments separated by a wide range of geographic distances (left). These studies do not have to sample all of the same populations through time, but at least some of the populations should be sampled at multiple time points to enable direct comparisons of genetic changes through time. If some of the longitudinally sampled localities exhibit environmental changes through time while others do not (lower-right), then examinations of IBT vs IBE can be performed. To disentangle, IBD and IBE (and to distinguish both from IBT), good sampling design should ensure that geographic and environmental distances are not significantly correlated (upper-right) by sampling similar environments that are both geographically near (A_1, left) and distant (A_2, left) and divergent environments at different geographic distances (B_1 and B_2, left) as well.

the relationships between the spatial and temporal factors that generate spatiotemporal genetic patterns. For instance, Bergland et al. (2014) were able to make a quantitative space-for-time conversion suggesting that 1 to 3 yr of time between samples (temporal distance) is approximately equivalent to 5–10° latitude (spatial distance), for their study system. A more generalized conversion such as this, compiled across systems, geographies, and taxonomies would be a useful metric when used in combination with projected anthropogenic climate change and climate velocities (Loarie et al. 2009, Ackerly et al. 2010, Hamann et al. 2015). Even if a generalized conversion is not possible, or if one cannot apply to more than a few closely related taxa, these comparisons will still contribute to furthering our understanding of the rate and trajectory of changes in the genome through time and space.

In fact, studies that examine both spatial and temporal patterns of genetic variation will be positioned to contribute to many different areas of ecology and evolution. Understanding the factors and forces that drive genetic turnover in space and time can help to uncover the mechanisms underlying divergent selection, local adaptation, and population viability on changing landscapes. The efforts to describe these microevolutionary processes would be aided significantly by reliable space-for-time substitution methods. Although relatively few studies have done so thus far, those that exist present some compelling evidence that space-for-time substitution methods are valid for studying genetic turnover and that further investigating their reliability is a worthwhile pursuit.

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Supplementary material (Appendix ECOG-03235 at <www.ecography.org/appendix/ecog-03235>). Appendix 1.