ANNUAL REVIEWS

Annual Review of Ecology, Evolution, and Systematics

(Non)Parallel Evolution

Daniel I. Bolnick,[1,2] Rowan D.H. Barrett,[3] Krista B. Oke,[3,4] Diana J. Rennison,[5] and Yoel E. Stuart[1]

[1]Department of Integrative Biology, University of Texas at Austin, Austin, Texas 78712, USA; email: yestuart@utexas.edu

[2]Current affiliation: Department of Ecology and Evolution, University of Connecticut, Storrs, Connecticut 06268, USA; email: daniel.bolnick@uconn.edu

[3]Redpath Museum, McGill University, Montreal, Quebec H3A 2K6, Canada; email: rowan.barrett@mcgill.ca

[4]Department of Ecology and Evolutionary Biology, University of California, Santa Cruz, California 95060, USA; email: kristaoke@gmail.com

[5]Institute of Ecology and Evolution, University of Bern, 3012 Bern, Switzerland; email: diana.rennison@iee.unibe.ch

Annu. Rev. Ecol. Evol. Syst. 2018. 49:303–30

First published as a Review in Advance on August 15, 2018

The *Annual Review of Ecology, Evolution, and Systematics* is online at ecolsys.annualreviews.org

https://doi.org/10.1146/annurev-ecolsys-110617-062240

Keywords

adaptation, convergence, divergence, many-to-one mapping, nonparallel evolution, parallel evolution

Abstract

Parallel evolution across replicate populations has provided evolutionary biologists with iconic examples of adaptation. When multiple populations colonize seemingly similar habitats, they may evolve similar genes, traits, or functions. Yet, replicated evolution in nature or in the laboratory often yields inconsistent outcomes: Some replicate populations evolve along highly similar trajectories, whereas other replicate populations evolve to different extents or in distinct directions. To understand these heterogeneous outcomes, biologists are increasingly treating parallel evolution not as a binary phenomenon but rather as a quantitative continuum ranging from parallel to nonparallel. By measuring replicate populations' positions along this (non)parallel continuum, we can test hypotheses about evolutionary and ecological factors that influence the extent of repeatable evolution. We review evidence regarding the manifestation of (non)parallel evolution in the laboratory, in natural populations, and in applied contexts such as cancer. We enumerate the many genetic, ecological, and evolutionary processes that contribute to variation in the extent of parallel evolution.

1. INTRODUCTION

Parallel evolution (see the sidebar titled Definitions) holds a special place in the annals of evolutionary biology because it provides strong evidence for adaptation. The replicated independent evolution of similar traits leads us to infer that evolution was driven by a deterministic process, usually assumed to be natural selection (Harvey & Pagel 1991). Biologists therefore use the repeated, parallel evolution of genes, phenotypes, or ecotypes to infer that (*a*) similar environments impose similar natural selection, (*b*) selection favors only a few solutions, and (*c*) the traits or genes that evolve in parallel are adaptations. These inferences offer the hope that, in some situations, evolution may even be predictable enough that we can anticipate evolution of pests or disease-causing agents or of evolutionary responses to anthropogenic environmental change (Agrawal 2017, Day 2012, de Visser & Krug 2014, Langerhans 2018). However, this optimistic goal of predicting future evolution is plausible only if parallel evolution is common and reliable.

Many textbook cases of parallel evolution have rightfully received a lot of attention (e.g., Colosimo et al. 2005, Elmer et al. 2014, Khaitovich et al. 2005, Thompson et al. 1997). But, are these cases representative of replicated evolution more generally or have we given undue attention to a few exceptionally parallel genes, traits, or species? If we objectively surveyed replicate populations in similar habitats, how common and how extensive would parallel evolution be? What fraction of replicate populations would evolve in parallel, for what number of traits and genes? Conversely, how often would replicate populations diverge genetically or phenotypically despite experiencing seemingly similar environments?

As we describe in this review, widespread evidence shows that replicate populations in similar environments sometimes evolve more similar traits (or genes) and sometimes evolve more dissimilar traits (or genes). From a multivariate standpoint, however, evolution is rarely just one or the other. Thus, we argue here that parallel evolution is best viewed as an extreme end of a quantitative continuum of (non)parallel evolution (see the sidebar titled Definitions and **Figure 1** for a visual glossary). Section 2 provides examples of this continuum of (non)parallel evolution, drawn from

DEFINITIONS

Parallel evolution: The standard definition describes the evolution of similar phenotypes or genotypes in multiple independent populations, in response to similar selection pressures, from similar initial conditions. Here, we advocate a geometric definition (**Figure 1**) that describes a very low angle (θ is not statistically different from 0°) between evolutionary trajectories of independent replicates through trait (or genotype) space.

(Non)parallel evolution: Shorthand for the distribution of outcomes across populations and traits forming a continuum from parallel to orthogonal, or even antiparallel, evolution.

Nonparallel evolution: When evolutionary vectors of two replicates are not parallel ($\theta \gg 0°$), potentially resulting in convergent or divergent evolution.

Convergent evolution: The standard definition is the evolution of similar phenotypes or genotypes in multiple independent populations, in response to similar selection pressures, from different initial conditions. A geometric definition is when the end points of two evolutionary vectors are closer together than the vectors' origins.

Divergent evolution: The evolution of increased distance between populations in phenotype or genotype space.

Antiparallel evolution: The most extreme nonparallelism, when replicate vectors point in exactly opposite directions ($\theta \sim 180°$).

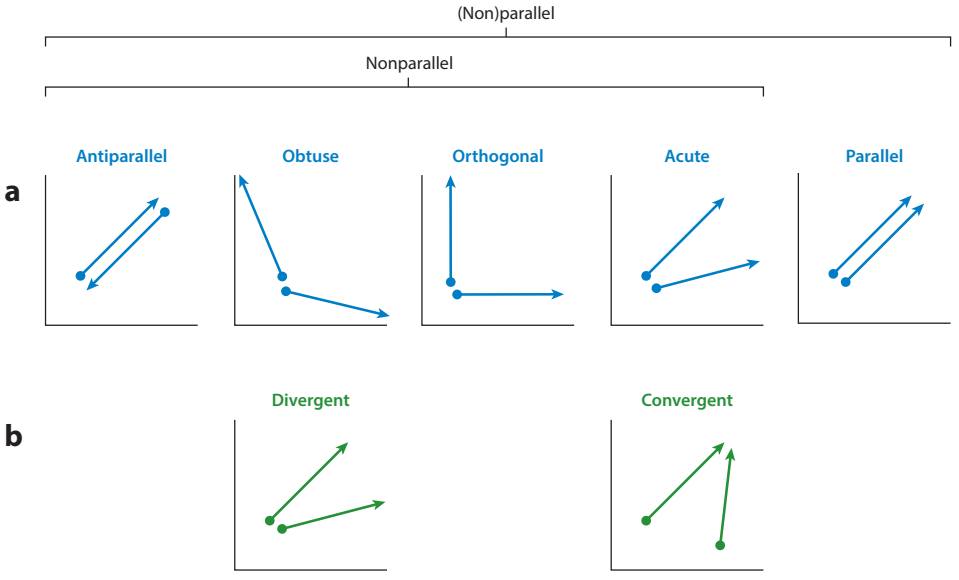


Figure 1

A visual glossary illustrating our use of terms. Each panel represents two replicate evolutionary trajectories (e.g., from ancestor to descendant) plotted as arrows in multivariate trait space. (*a*) Drawing on geometric definitions, evolution can range from parallel (*arrows pointing in the same direction*) to antiparallel (*arrows pointing in opposite directions*) and various angles in between. We use nonparallel to refer to the logical complement of parallel and (non)parallel to refer to the entire continuum. (*b*) Continuing with this geometric theme, convergent and divergent are separate concepts from (non)parallelism, having more to do with whether or not descendants are more similar to each other than their ancestors were to each other. The relationship between the (non)parallel continuum and the convergence–divergence continuum is illustrated in more detail in **Figure 3**.

settings of practical interest (e.g., disease, agriculture) to motivate study of (non)parallelism. After addressing some semantics (Section 3), we then describe approaches to quantify (non)parallel evolution (Section 4). Using these quantitative tools, we reevaluate the extent to which evolution is parallel or nonparallel (Section 5) and discuss various evolutionary processes that influence where populations fall on the (non)parallel continuum (Section 6). Throughout this essay, we seek answers to questions such as: What evolutionary forces generate variation in (non)parallelism among replicate populations? What kinds of traits are more or less parallel? Perhaps most fundamentally: When we see deviations from parallel evolution, what are we to conclude about adaptation? Biologists use parallel evolution as evidence of adaptation, but when evolution in similar environments falls toward the nonparallel end of the continuum, should we infer that maladaptation, neutral evolution, or adaptation has occurred?

2. INCOMPLETELY PARALLEL EVOLUTION

As motivation, our first goal for this review is to establish that evolution is often less parallel than we might have reasonably expected. Intuitively, we expect that initially similar populations that are exposed to similar selection pressures will evolve similar phenotypic adaptations. As we show in this section, however, in many contexts this expectation is only partly true, and the examples of nonparallel evolution described here illustrate the need for quantitative rather than binary approaches to studying parallel evolution. In presenting these cases of (non)parallel evolution, we

focus on evolution in applied contexts (e.g., cancer, pathogens, agriculture). The insights emerging from these applied examples are quite general and could also be illustrated with cases from basic research. But, we hope to bring attention to some examples that evolutionary biologists may have missed (e.g., that are not covered in reviews of parallel evolution). Also, we hope this applied focus draws interest from applied researchers who might not normally read about parallel evolution.

2.1. (Non)Parallelism in Cancer

Cancer tumors are evolving populations of cells (Burrell et al. 2013, Nowell 1976, Shpak & Lu 2016, Swanton 2014). Tumors originate when somatic mutations confer an escape from normal cell cycle regulation. Growing tumors contain multiple genetically divergent cell lines that differ in their ability to proliferate, evade the immune system, resist chemotherapy, and metastasize. This genetic variation can therefore be subject to strong selection within a tumor. Typically, each cancer patient is an independent, replicated case of one or more oncogenic mutations that initiate a tumor and the subsequent clonal selection on additional mutations. If tumor evolution is highly parallel, the same mutations in the same genes should evolve repeatedly in most or all patients. It is increasingly clear, however, that ostensibly similar tumors (i.e., same tissue and histology) often comprise fundamentally different mutations across patients.

In an experimental evolution study, Tegze et al. (2012) applied identical selection (18 months of chemotherapy) to 29 identical artificial tumors that were all derived from one breast cancer cell line. Only 18 of the 29 replicates evolved resistance. Within the subset of resistant replicates, the underlying genetic changes were nonparallel—affecting different cell functions (Tegze et al. 2012). This result highlights some key themes: First, even identical starting populations subjected to identical selection can show nonparallel evolutionary responses. Second, parallel evolution of resistance (an emergent function) occurred without parallel evolution of the underlying genes.

Such evolutionary inconsistency also occurs in real cancer patients. Takahashi et al. (2007) searched for selective sweeps (large changes in allele frequency) during metastasis of lung tumors. Most of the genes experiencing selection evolved in only one or a few patients. At most, a particular gene experienced selection in half the patients (Takahashi et al. 2007). This (non)parallel evolution is why cancer treatment increasingly relies on personalized genomics to tailor therapies to the particular causal gene(s) in an individual (Abbosh et al. 2017).

2.2. (Non)Parallel Evolution in Pathogens

Like cancer, human pathogens show (non)parallel evolution in response to therapies and host immunity. In HIV patients with low viral load during drug therapy, an interruption to therapy often results in a rapid rebound of viral load. One study of 12 chronic HIV patients undergoing viral rebound revealed that the HIV-1 *GP120* gene evolved rapidly in each patient (Martinez-Picado et al. 2002). If *GP120* evolved in parallel following therapy interruption, we could potentially develop drugs targeting the *GP120* variants that facilitate rapid viral rebound. However, for unknown reasons, different mutations contributed to this rebound in each patient, undermining attempts at developing preemptive therapies.

Human macrophages protect against pathogenic strains of *Escherichia coli*, but this bacterium sometimes evolves immune-escape variants, leading to life-threatening illness. In vitro experimental evolution of *E. coli* in macrophage culture led to recurrent evolution of bacteria with increased resistance to macrophage attack (Ramiro et al. 2016). However, the magnitude of this resistance differed among replicates, highlighting yet another major pattern of (non)parallel evolution: The magnitude of resistance evolution differed among cultures, even though all replicates evolved

resistance to some extent. This quantitative variation was attributed to the evolution at a unique gene within each replicate (i.e., nonparallel genetics), although most causal genes were part of the electron transport chain (i.e., parallel at the level of biochemical pathways). Notably, through pleiotropy, these electron transport changes made all resistant strains more sensitive to certain antibiotics (Ramiro et al. 2016). These parallel pleiotropic changes offer a therapeutic strategy for anticipating and combating evolution of *E. coli* resistance to macrophage attack.

2.3. (Non)Parallelism in Agriculture

Agricultural pests frequently evolve new mechanisms to subvert the herbicides and pesticides we use to control them. For example, quinone outside inhibitor (Q_oI) fungicides act to inhibit *cytochrome* bc_1 function in the mitochondria of fungi that damage crops. If Q_oI resistance always evolved using the same single nucleotide polymorphism (SNP), or the same gene, it would be easy to design molecular probes to monitor the spread of resistance through agricultural systems and perhaps to develop fungicides that target the resistance-causing mutation. Nonparallel evolution undermines this goal. Four pathogenic fungi have evolved Q_oI resistance, using at least four independent mutations at the same *cytochrome b* codon (Torriani et al. 2008). But, several other fungi evolved Q_oI resistance via mutations at other genes (Fernández-Ortuño et al. 2008). So, the extent of parallel change differed across biological levels of organization: Q_oI resistance has evolved in parallel at the level of phenotype, partly in parallel at the level of coding locus (shared by some but not all species), and in nonparallel at the level of particular SNPs.

Parallel evolution of domesticated species could reveal useful traits and genes for breeding strategies. The common bean was domesticated twice from wild *Phaseolus vulgaris*, once in Mexico and once in the Andes (Bitocchi et al. 2013), providing an unusual opportunity to consider (non)parallelism in the origins of a major agricultural resource (albeit with $N = 2$). Across the 27,197 genes surveyed, 1,835 and 748 exhibited signatures of selection in these respective geographic replicates, but only 59 appear to be selected in both regions (0.2% of all genes, which does not exceed null expectations) (Schmutz et al. 2014). An equivalent result was seen for two independent instances of maize domestication at high altitude (Takuno et al. 2015). With the limited evidence available to date, it appears that artificial selection for domestication has involved largely nonparallel genomic changes. It would be fascinating to extend this type of analysis to more instances of domestication (e.g., replicate origins of fish aquaculture) to locate essential domestication genes (those evolving in parallel) or to identify nonparallel changes that might be combined for further improvements.

The cases described above illustrate several recurring themes in (non)parallel evolution. Most notably, when similar populations are exposed to similar selection pressures, only a subset of the replicates will evolve similar responses. The magnitude and direction of evolution can differ among replicates, among traits, and across biological levels of organization (gene, pathway, trait, function). The same themes frequently apply to wild populations (e.g., Langerhans 2018, Rosenblum & Harmon 2011, Stuart et al. 2017). This multilevel continuum of (non)parallel evolution offers opportunities to learn more about evolutionary processes, as we describe below. To do so, however, we first need clear terminology and the quantitative tools for measuring where traits and populations fall along the (non)parallel continuum.

3. AN ASIDE ON TERMINOLOGY

The study of (non)parallel evolution has been the source of recurrent semantic disagreements. In the 150-year history of evolutionary biology, parallelism first described simultaneous fossil record

transitions across many continents (Darwin 1859). Later, evolutionary biologists used parallelism to describe the similarity between embryological development and paleontological transitions (Cope 1876, Cope & Kingsley 1891, Packard 1898, Wilson 1941). The standard modern use of parallelism emerged in the early 1900s (Nichols 1916, Osborn 1900, Vavilov 1922) following observations of recurrent similar mutations in *Oenothera* flowers (Gates 1912). These recurrent mutations led Dobzhansky (1933, p. 108) to suggest that "the essential similarity of the germplasm" predisposed related species to have similar mutations. However, Gates (1936) cautioned that this conclusion was premature: "In very few instances, either in plants or animals, has it been shown genetically that these parallelisms are due to the same gene in related species" (p. 513).

During this time, convergence was often conflated with parallelism (Haas & Simpson 1945), until Carl Hubbs clarified the distinction between homology and homoplasy (Hubbs 1944). G.G. Simpson (1961) provided a modern definition of parallel evolution as "the independent occurrence of similar changes in groups with a common ancestry and *because* they had a common ancestry" (p. 103). Common ancestry was crucial in Simpson's view, because it implied that initially similar populations evolved similar adaptations. This requirement that initial populations share a recent common ancestry is in contrast to convergent evolution, which entails similar evolution but from initially dissimilar (less related) taxa (Gould 2002). The boundary between "common ancestry" and "less related" is unclear, which has long blurred the distinction between parallel and convergent evolution (Arendt & Reznick 2008, Scotland 2011, Wake 1999; see the sidebar titled Definitions and **Figure 1** for our operating definition). Some have debated whether common ancestry is even an important criterion. That is, phylogenetically closely related taxa are more likely to use similar genes to produce similar phenotypes (Conte et al. 2012), whereas distantly related taxa more often use different genes when they converge phenotypically. However, examples of both distantly related species that nevertheless use the same genes to adapt to the same challenge (Rosenblum et al. 2010) and closely related populations that use different genes for the same phenotype have been found (Sturm & Duffy 2012). This decoupling of shared genetics from recent ancestry has led some biologists to argue that no clear distinction exists between parallel and convergent evolution (Arendt & Reznick 2008, Manceau et al. 2011).

Developmental biologists, meanwhile, have used the term convergent to describe the evolution of similar phenotypes but with different underlying genes or developmental pathways (Abouheif 2008, Baguñà & Garcia-Fernàndez 2003). From this point of view, ancestry is irrelevant, and the key distinction between convergent and parallel has to do with genetic mechanism. Evolution is parallel when the same gene caused the evolution of similar phenotypes in different groups (Rosenblum et al. 2014). But, again, a gray area exists between parallel and convergent: What constitutes sufficiently similar molecular explanations (Losos 2011, Wake et al. 2011)? For instance, evolution can result from repeated change at the same gene but not the same nucleotide (Storz 2016). Or, for polygenic traits, evolution may reflect repeated changes at some causal loci but divergent evolution at others (Elmer & Meyer 2011).

Given the semantic ambiguities described above, some researchers have argued we should always apply convergent when discussing phenotypes and parallel to describe genes (Rosenblum et al. 2014, Scotland 2011). Other researchers advocate dropping the term parallel entirely (Arendt & Reznick 2008). An emerging alternative view is that the terms parallel and convergent (and their antonyms, nonparallel and divergent) can be defined in terms of the geometry of evolution in trait space (**Figure 1**). Parallel evolution can then be defined as evolution of two (or more) populations in very similar directions in trait space. Nonparallel evolution is when populations evolve in different directions in trait space, which can encompass anything from weakly similar and orthogonal directions to opposite directions (antiparallel). Finally, we use (non)parallel to denote the entire continuum illustrated in **Figure 1**. In contrast, convergent evolution occurs when

derived populations are phenotypically more similar than their ancestral states were; divergence is the reverse (**Figure 1**).

4. QUANTIFYING (NON)PARALLEL EVOLUTION

The semantic challenge in defining parallel or convergent evolution is, in part, a consequence of trying to make a binary decision (e.g., "parallel or not?") to describe a quantitative, multivariate, and multiscale phenomenon. Therefore, a promising solution is to augment the binary approach with quantitative measures of (non)parallelism (Langerhans 2018, Oke et al. 2017, Speed & Arbuckle 2017, Stuart et al. 2017). Below, we summarize three widely used approaches to quantifying where replicates fall along this (non)parallel continuum. By quantifying (non)parallelism across many replicate populations, researchers can ask questions such as: How do abiotic conditions, community ecology, historical events, and genetic processes generate variation along this continuum? We focus on phenotypic traits hereafter, with the understanding that the methods we describe can also be applied to other traits, including protein structures (Rokas & Carroll 2008, Storz 2016), allele frequencies (Jones et al. 2012), gene expression (Cooper et al. 2003, Manousaki et al. 2013, Velotta et al. 2017), quantitative trait locus (QTL) effects (Conte et al. 2015), and so forth.

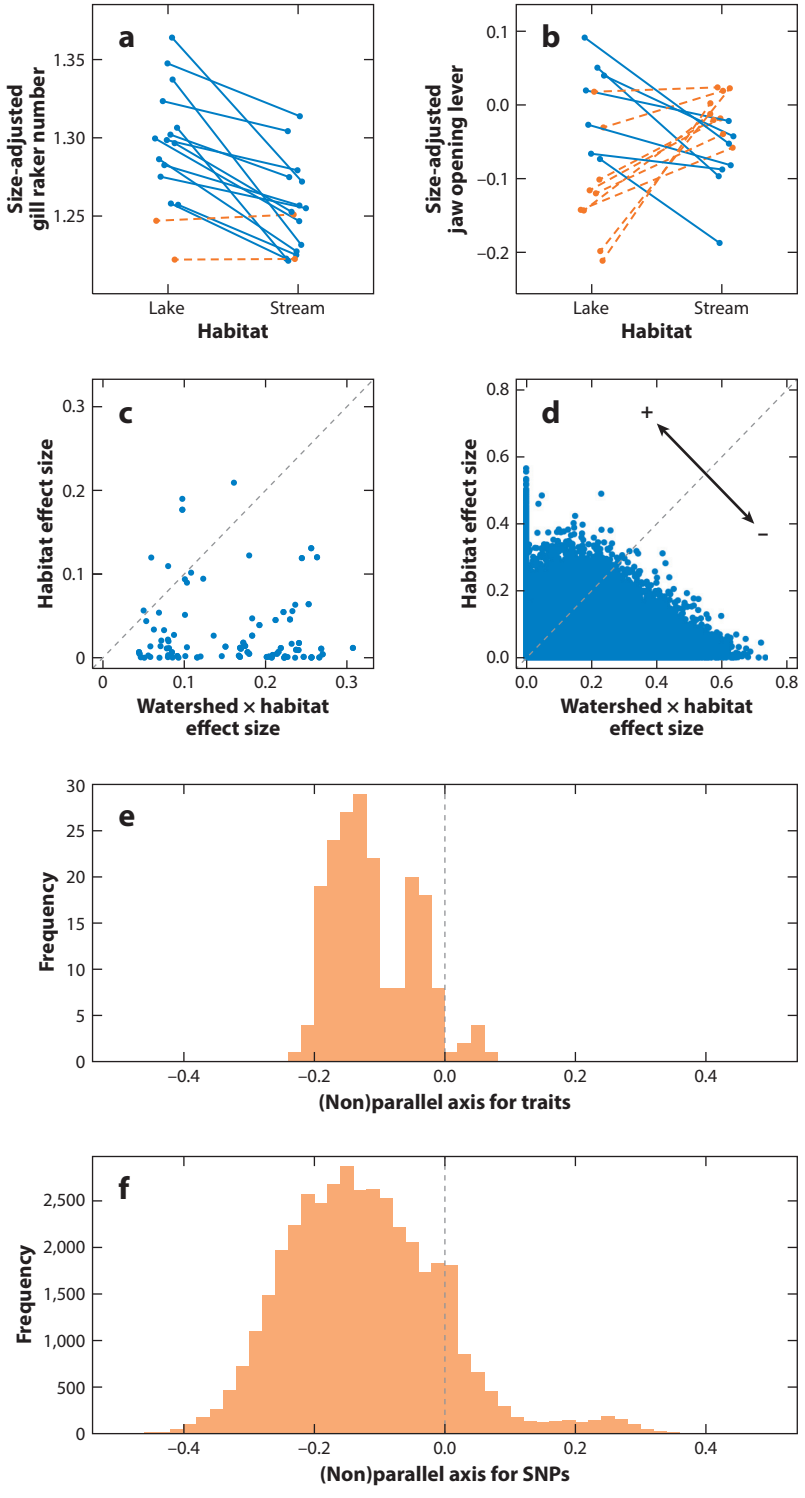
4.1. Counting

The simplest strategy when quantifying (non)parallelism is so-called vote counting—estimating the probability that a given trait evolves in parallel or not in parallel (Orr 2005). Consider a single univariate trait measured in multiple independently established populations. One can quantify the fraction of evolutionary transitions that go in a particular direction (increase or decrease). This approach was used in the cancer and pathogen evolution examples described above. When 100% of the replicate populations evolve in the same direction, the case for parallel evolution seems clear (given enough populations). It may be more typical, however, for only a subset of populations to evolve in the same direction.

When interpreting vote counts, clearly defining a null hypothesis is important. For a single quantitative trait evolving strictly neutrally, we would expect half the replicate populations to evolve in the same direction (e.g., increase) by chance. Using a sign test, one needs a minimum of 6 replicate populations to all evolve in the same direction for a given trait to reject the null hypothesis of random evolutionary change at a significance threshold of 0.05. For instance, in half of 16 replicate pair comparisons of parapatric lake and stream threespine stickleback (*Gasterosteus aculeatus*), stream fish had higher suction feeding ability than lake fish (Thompson et al. 2017). This finding was no different from the null expectation. Thus, it was unclear whether suction feeding capacity was evolving neutrally or was adaptive but selection itself was inconsistent among watersheds. In contrast, lake fish had more gill rakers than stream fish in 14 of 16 lake–stream pairs (**Figure 2*a***), which is clearly, but still incompletely, parallel (Stuart et al. 2017).

4.2. Variance Partitioning

Vote counting ignores variation in effect size. Populations might all evolve in the same direction but to different magnitudes. One approach to account for effect sizes was popularized by Langerhans & Dewitt (2004), assuming a researcher has uni- or multivariate quantitative trait data measured for multiple individuals in each of two (or more) categorically defined habitats. These habitats must be replicated across multiple locations (e.g., different islands, watersheds). One then estimates a statistical model that partitions trait variance among habitats, locations, and habitat × location interactions. The main effect of habitat measures the extent to which between-habitat evolutionary



(*Caption appears on following page*)

Figure 2 (*Figure appears on preceding page*)

An example of variation along the (non)parallel continuum in 16 lake–stream pairs of threespine stickleback (*Gasterosteus aculeatus*) (replotted using data from Stuart et al. 2017). (*a*) The gill raker number (size-standardized) shows strong parallel changes with more gill rakers in lake fish in 14 out of 16 pairs (*orange dashed lines* indicate contrary directions), resulting in a strong main effect of habitat (shared change). (*b*) Lower jaw opening KT exhibits little parallel evolution with equal numbers of cases of lake or stream fish having higher mean KT, resulting in a strong watershed × habitat interaction (unique change). To summarize this variation, Stuart et al. (2017) plotted habitat versus watershed × habitat effect sizes (partial η^2) for (*c*) all 86 morphological traits and (*d*) 74,000 SNPs from ddRADseq. Points lie mostly below the dashed line of equal effect, indicating that unique evolution is typically stronger than shared evolution. To view this variation along a single nonparallel–parallel axis, we calculated each trait or SNP's distance from the line of equal effect (positive values above the line denote more parallel evolution; negative values below the line indicate more nonparallel evolution). We plotted histograms of (*e*) traits and (*f*) SNPs on this (non)parallel axis to illustrate the point that evolution at both levels is primarily nonparallel, but a small number of traits and SNPs form a distinct peak of parallelism, likely representing targets of parallel selection. Abbreviations: ddRADseq, double digest Restriction Associated Digest sequencing; KT, kinematic transmission; SNP, single nucleotide polymorphism.

divergence is shared across replicate locations (**Figure 2**) and thus measures parallel evolution. The location effect summarizes properties unique to different replicates (e.g., different islands). The habitat × location interaction measures how the direction or magnitude of between-habitat divergence is inconsistent among replicate populations, implying nonparallel evolution. A closely related method focuses on exchangeability—a quantitative measure of the extent to which statistical classification tools correctly or incorrectly assign individuals to the correct habitat or location (Hendry et al. 2013); high exchangeability implies strongly parallel evolution across independent replicate populations.

Variance partitioning has been applied to a wide variety of measures of population divergence including karyotypes (Dunn et al. 2005), genomes (Ravinet et al. 2016), physiology (Pfenninger et al. 2015), and morphology (Langerhans & DeWitt 2004). For instance, an experimental comparison of inland versus coastal California poppies (*Eschscholzia californica*) in California and their invasive range in Chile found equally large effects of habitat and habitat × location interaction, indicating that different traits contributed to inland–coastal divergence in each region (Leger & Rice 2007).

This analytical approach is appealing because it builds on statistical tools familiar to many biologists and provides multivariate quantitative estimates of each effect: percent partial variance (Langerhans & DeWitt 2004) or r^2 (Langerhans 2018). One weakness to this approach is the ambiguity in interpreting the habitat × location interaction. A significant interaction could stem from variance in the direction of evolution, the magnitude of evolution, or both.

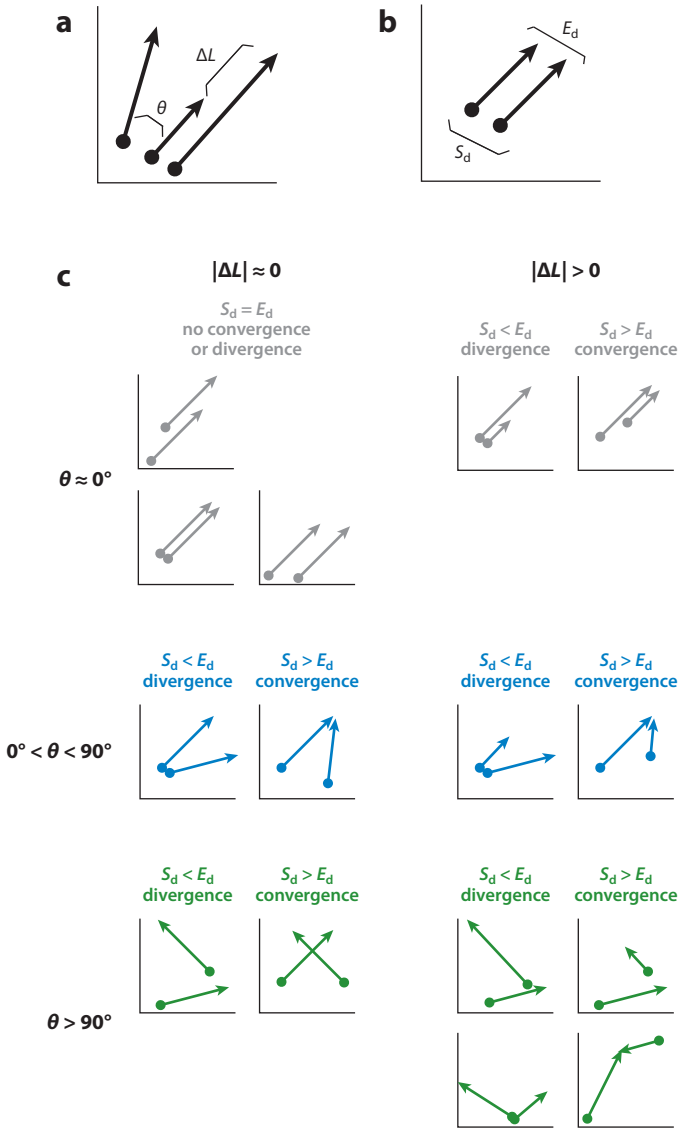
4.3. Vector Analysis

Phenotypic Change Vector Analysis (PCVA): a multivariate approach to measuring trait change or (non)parallel evolution by quantitatively comparing change vectors

Phenotypic Change Vector Analysis (abbreviated as PCVA) offers a geometric definition of parallel and nonparallel evolution (Adams & Collyer 2009, Collyer & Adams 2007, Collyer et al. 2015) in the spirit of our definitions (see the sidebar titled Definitions) and as illustrated in **Figures 1** and **3**. Unlike variance partitioning, PCVA separately measures both magnitude and direction of evolution. For instance, Stuart et al. (2017) used PCVA to show that the direction of phenotypic divergence between lake and stream stickleback depended on environmental variation, whereas the magnitude of divergence was best explained by gene flow (or the lack thereof).

PCVA requires replicate population pairs (e.g., ancestral and derived populations) that span some putative evolutionary change or habitat contrast. For each population, one calculates the

phenotypic centroid in multivariate trait space (or the centroids for breeding values, gene expression, genomic data, etc.). The vector connecting one population's centroid to the other population's centroid gives a formal measure of the direction and magnitude of divergence through trait space (**Figure 3*a***). The longer the vector, the more divergent the paired populations are, whereas the orientation of a vector in trait space describes the relative contributions of different traits to divergence between that pair of populations. To quantify (non)parallel evolution, one needs two such vectors representing replicated, independent trajectories (**Figure 3*a***) from which one calculates two metrics: the angle between the vectors, θ, and the difference in their magnitudes, ΔL (**Figure 3*a***). A definition of parallel evolution, then, is that replicate vectors point in the same direction so that the angle between them is near zero (**Figure 3**). Evolutionary change is



(*Caption appears on following page*)

Figure 3 (*Figure appears on preceding page*)

Use of Phenotypic Change Vector Analysis (PCVA) to quantify (non)parallel evolution as well as divergence or convergence. We illustrate the approach using the evolution of two quantitative traits (x- and y-axes on the small graphs). (*a*) The trajectory of evolution can be represented in morphospace as a vector connecting the centroids of two paired populations from different habitats. Each evolutionary replicate pair constitutes its own vector (here, we plot vectors for three such pairs). Any two replicate evolutionary trajectories can be compared to calculate an angle θ and a length difference ΔL. (*b*) In addition to calculating measures of (non)parallelism, we can measure the extent of convergence or divergence. We define S_d as the distance between two replicates' starting points and E_d as the distance between ending points. The two vectors diverge if the end points are farther apart than the starting points ($S_d < E_d$) and converge if $S_d > E_d$. Panel *c* presents various combinations of scenarios for (non)parallelism and convergence or divergence. Two replicate evolutionary trajectories are highly parallel when the angle between them (θ) is near 0° (*top row*), acute nonparallel when they point in roughly the same direction but with some moderate angle (e.g., $\theta <$ 90°; *middle row*), and obtuse nonparallel or even antiparallel when the replicates evolve in opposite directions ($\theta > 90°$; *bottom row*). The left and right columns of panel *c* represent cases for which vector lengths are similar ($\Delta L \approx 0$; *left column*) or different ($\Delta L > 0$; *right column*). Evolution is highly parallel in the top left box ($\theta \approx 0°$ and $\Delta L \approx 0$), and no divergence or convergence is possible. For all other scenarios, it is possible to have divergence or convergence for both parallel and nonparallel evolution.

literally parallel in the geometric sense of the word. For instance, two sister species of *Brachyrhaphis* fishes diverged in multivariate behavior; the direction of this divergence was similar across independent watersheds (low θ) (Ingley et al. 2014). The greater the angle between two vectors, the less parallel is their evolution. The point here is to avoid artificially discretizing the (non)parallel continuum. But, if we must use categorical descriptions, parallel evolution has occurred when θ is statistically indistinguishable from zero (assuming decent power), and nonparallel evolution has occurred when θ significantly exceeds 0°. Several subgroups along the continuum might also be useful (**Figure 1**): acute nonparallel when the vectors proceed in roughly the same direction with $0° < \theta < 90°$; orthogonal nonparallel when $\theta \sim 90°$; obtuse nonparallel when $90° < \theta < 180°$; and antiparallel—a standard mathematical term—when vectors point in opposing directions (θ is statistically indistinguishable from 180°).

A more stringent definition of parallel evolution could also require that the vectors have similar magnitudes (the difference in lengths is near zero). For example, in the *Brachyrhaphis* example discussed above, the magnitude of divergence was inconsistent between watersheds (large ΔL), suggesting some nonparallel evolution. An even stricter criterion could require the two vectors begin and/or end close together in morphospace [e.g., the Euclidian distances between starting points of any two vectors (S_d), and/or the distance between their ending points (E_d), have near-zero lengths; **Figure 3*b***]. These alternatives highlight a benefit of PCVA: We can simultaneously quantify parallel evolution, convergent evolution versus divergent evolution, and the magnitude of change (**Figure 3*c***). For example, with replicate ancestor–descendant pairs, evolution is divergent when descendant populations are farther apart than the ancestral populations ($S_d < E_d$), whereas convergence occurs when $S_d > E_d$. Note also that convergence or divergence can result from parallel or nonparallel evolution (**Figure 3*c***). In PCVA terminology, parallelism and convergence are neither mutually exclusive nor redundant terms. Thus, PCVA provides substantially more information than vote counting or variance partitioning approaches.

PCVA is best applied to ancestor–descendant pairs, because the resulting vector represents an evolutionary trajectory through time. This is possible when the ancestor is still extant (largely unchanged) or when fossil data, ancient DNA, or phylogenetic reconstructions can be used to infer ancestral states. Unfortunately, such data are rare. Therefore, many researchers apply PCVA in other contexts such as comparing replicate, extant population pairs in different habitats. The vector then represents evolutionary divergence between sister populations, rather than a trajectory through time. We can compare replicate contemporary population pairs to estimate the extent

to which between-habitat divergence proceeds in similar directions. PCVA can also be extended to describe more continuous evolutionary trajectories through time or along a cline (Phenotypic Trajectory Analysis) (Adams & Collyer 2009, Lohman et al. 2017). Because summary statistics from PCVA can be collected for any kind of multivariate data, it is possible to compare the extent of (non)parallel evolution across biological levels (Stuart et al. 2017).

Phenotypic Trajectory Analysis: entails a series of head-to-tail PCVA vectors forming an evolutionary trajectory through trait space

PCVA has drawbacks. First, interpreting angle and length differences between multivariate vectors and translating those differences back to real traits are not always intuitive to biologists whose mathematical training often emphasizes statistical tests rather than geometry. A given angle between two vectors can be achieved many different ways through divergence in different combinations of traits across different replicate pairs. Interpretation is especially challenging for high-dimensional data because the mathematical measures of (non)parallel evolution might be hard to represent effectively with 2- or 3-dimensional graphics. Note also that PCVA vector angles are only really useful when the vectors are long enough to be biologically meaningful.

A second unresolved challenge entails development and testing of biologically useful null hypotheses. The initial implementations of PCVA provided a permutation-based test for whether two vectors had a nonzero angle (Collyer & Adams 2007). One problem is that the randomization procedure has very low power. Another problem is that this permutation test treats perfect parallel change as the null hypothesis, whereas for many researchers parallel change is the alternative hypothesis they seek to demonstrate. Should the null instead be that the vectors are orthogonal? Or, should we test whether vectors are randomly oriented in multivariate trait space? New techniques that use Bayesian methods to estimate the posterior probability distribution of θ or that compare support for alternative models of θ are needed. Another advance could use populations' G matrices to define the null orientation for evolutionary vectors.

Finally, perhaps the biggest problem with PCVA is that angle and length metrics may be sensitive to one's choice of trait space. Sampling more traits may change vector orientations and the angles between them (Carscadden et al. 2017). The implication is that researchers' decisions about what and how many traits to measure might substantially alter PCVA interpretation.

5. HOW (NON)PARALLEL IS EVOLUTION?

Disagreements over the prevalence of parallel evolution are as old as the discipline itself. Darwin was keenly aware of nonparallel evolution: "There is hardly a climate or condition in the Old World which cannot be paralleled in the New. . . Notwithstanding this general parallelism in the conditions of the Old and New Worlds, how widely different are their living productions!" (see chapter 12 in Darwin 1859, p. 394). Similarly, Calman (1935) argued that parallel evolution was the exception rather than the rule, with divergent evolution far more common. Yet other researchers felt that parallel evolution was widespread (Muller 1939, Rensch 1939).

This long-standing debate is likely to see substantial progress as the analytical tools described above are widely adopted to quantify (non)parallel evolution, replacing the practice of counting examples. For examples of this quantitative approach, see studies by Conte et al. (2012, 2015); Eroukhmanoff et al. (2009); Evans et al. (2013); Fitzpatrick et al. (2014); Kaeuffer et al. (2012); Langerhans & Makowicz (2009); Laporte et al. (2015); Manousaki et al. (2013); McGee et al. (2016); Oke et al. (2017); Perreault-Payette et al. (2017); Perrier et al. (2013); Pfenninger et al. (2015); Pujolar et al. (2017); Ravinet et al. (2016); Rosenblum & Harmon (2011); Siwertsson et al. (2013); and Stuart et al. (2017). Below, we describe examples of how these and other studies have provided valuable insights into how strong, and how variable, (non)parallel evolution can be in natural populations. In Section 6, we describe the biological processes underlying (and revealed by) this (non)parallel continuum.

5.1. Evolution in Replicate Populations Is Often Nonparallel

Studies of parallel evolution often note inconsistencies or variation among replicate population pairs without directly explaining them (e.g., Brinsmead & Fox 2002, Gíslason et al. 1999, Hoekstra & Nachman 2003). Recently, these inconsistencies have become an area of research in their own right to describe the extent of (non)parallel evolution and explain heterogeneity along this continuum. Langerhans (2018) used variance partitioning to analyze replicated populations of Bahamian mosquitofish in high- versus low-predation environments. He found that half of the overall among-population phenotypic variation (of 90 traits) was driven by something other than shared selection arising from predation regime. In a meta-analysis of parallel evolution in many species of fishes, Oke et al. (2017) found large variation within and among species in the extent of parallel evolution among replicated conspecific populations. Here, variance partitioning found that fish ecotype (presumably evolved in parallel in shared environments) accounted for less than 10% of the partial variance of morphology in some systems but accounted for more than 90% in other studies. The nonparallel cases tended to be more common. Oke et al. (2017) reached the same result using PCVA, and these results were applicable to 14 fish systems with paired populations replicated across habitat boundaries (e.g., benthic–limnetic stickleback, lake–stream stickleback, dwarf–normal whitefish). Of these 14, only 4 had a consistent trend toward parallel divergence across a boundary ($\theta < 90°$ for all pairwise vector comparisons).

Perhaps the clearest evidence for (non)parallel evolution comes from laboratory experimental evolution studies (see sidebar titled Experimental Study of Parallel Evolution). Researchers have subjected replicate laboratory populations (e.g., of bacteria, *Drosophila*, etc.) to identical artificial selection and then evaluated the repeatability of subsequent evolution (Cooper et al. 2003, Ferea et al. 1999, Fong et al. 2005, Roberge 2006). However, most of these studies used vote counting as their measure of parallel evolution. For example, Ferea et al. (1999) raised three replicate yeast cultures, selected to live in glucose-limited media, and identified several hundred genes that evolved the same expression changes in all three populations. A similar experiment with *E. coli* found 59 genes (out of the entire genome) that evolved strongly and in the same direction in 2 replicate populations (Cooper et al. 2003). Both studies support parallel evolution, but their reliance on vote counting from a few replicates makes it more likely that parallel changes are coincidental.

EXPERIMENTAL STUDY OF PARALLEL EVOLUTION

Many convincing studies of (non)parallelism come from selection experiments in laboratory populations (Bailey et al. 2015, Graves et al. 2017, Lenski 2017, Meyer et al. 2010). By limiting variation in as many explanatory factors as possible, the design of these experiments permits careful tests of a limited number of mechanisms at a time. A meta-analysis of evolve-and-resequence experiments with bacteria and yeast revealed a positive relationship between population size and the probability of parallel change (Bailey et al. 2017). Mutation rate heterogeneity strongly influenced the extent of parallel genetic change during selection in shared environments. Deviations from parallel evolution were therefore partly nonadaptive. An important lesson from these studies is that the likelihood of observing parallel evolution is often dependent on the level of the biological hierarchy that is investigated. Because of many-to-one mapping (see Section 6.5), repeatability is typically highest for fitness itself, lower for phenotypes, lower still at the level of the genes, and lowest at the level of individual mutations (Tenaillon et al. 2016). Growing experimental evidence also shows that frequency-dependent ecological interactions can contribute to (non)parallel evolutionary dynamics (Douglas et al. 2016, Herron & Doebeli 2013, Josephides & Swain 2017).

5.2. Evolution Across Traits Is Often (Non)Parallel

Within a given study system, it is often the case that some traits will show parallel change, whereas others show nonparallel change or even no evolution at all (Oke et al. 2017). For example, in lake–stream pairs of stickleback, a study of 86 phenotypic traits found that the effect of crossing the lake–stream habitat boundary explained 0% of variation in some traits but more than 20% of variation in others (Stuart et al. 2017). Similarly, the 90 traits measured in high- and low-predation Bahamian mosquitofish varied from highly parallel to nonparallel changes that did not match the predator regimes (Langerhans 2018). Neither study found any evidence that certain categories of traits (e.g., trophic, locomotion, defense) were more strongly parallel than others.

5.3. Evolution Across Biological Scales Is Often (Non)Parallel: Genotype Versus Phenotype

To what extent does (non)parallelism at one biological scale necessarily correlate with (non)parallelism at other biological scales? We may be able to predict this in some cases. For example, because parallel phenotypic evolution is mostly attributed to selection, we would not expect parallel evolution for neutral genetic markers. This expectation was corroborated by the study of lake–stream stickleback mentioned above (**Figure 2**). Focusing on putatively neutral markers [by excluding SNPs in the top 5% of lake–stream F_{ST} (Fixation Index) values], the orientation of genomic PCVA vectors was unrelated to the orientation of both phenotypic trait PCVA vectors and environmental vectors (Stuart et al. 2017). That is, the combination of neutral SNPs that diverged did not predict the combination of traits that diverged, consistent with the putative neutrality of these SNPs. However, the magnitude of trait divergence (ΔL) was strongly and positively correlated with measures of genomic divergence [e.g., F_{ST}, or coalescent estimates of Nm (number of lake-stream migrants)]. This positive relationship is consistent with the hypothesis that gene flow between adjoining habitats constrains lake–stream divergence. When gene flow differs between replicate watersheds, it creates variance in the magnitude of trait divergence (ΔL) and thus (non)parallelism.

The same study found a different result for putatively non-neutral genetic markers (top 5% of lake–stream F_{ST} outliers). Replicate watersheds that shared more outlier SNPs were more phenotypically parallel and environmentally more similar. This result implies that more similar selection pressures drive evolution of more parallel phenotypes via lake–stream divergence at more overlapping sets of genes.

In a study that used a vote-counting approach to estimate (non)parallelism in two benthic–limnetic stickleback species pairs, Conte et al. (2015) found that 76% of 42 morphological traits diverged in the same direction in replicate instances of benthic and limnetic divergence. These parallel traits were controlled by 43 identifiable chromosomal regions (QTLs), but only 49% of these QTLs evolved in parallel in both lakes. Like the lake–stream system, evolution was less parallel at the genetic level than at the phenotypic level (Conte et al. 2015). This pattern is also found in repeated coastal ecotypes of *Senecio* that exhibit only partial reuse of QTL among replicate populations (Roda et al. 2017).

Another strategy for comparing across levels is to deliberately focus on only strongly parallel phenotypic evolution and then ask to what extent it is underlain by parallel genetic changes (e.g., Colosimo et al. 2005). Because this approach cherry-picks the most parallel phenotypes, it is not a representative measure of genetic parallelism overall but probably serves to set an upper bound for genetic parallelism. This approach has been used in studies of lodgepole pine versus interior spruce (Yeaman et al. 2016); wild versus weedy sunflower (Lai et al. 2008); dwarf versus normal whitefish ecotypes (Derome et al. 2006); and Midas cichlid ecotypes (Manousaki et al. 2013). Using F_{ST}

outliers to detect putative genomic targets of selection, these studies showed that phenotypically very parallel populations often share only a small proportion of their F_{ST} outliers (e.g., Kautt et al. 2012, Le Moan et al. 2016, Westram et al. 2014). For highly parallel traits in two pairs of benthic–limnetic stickleback, only 32% of the underlying QTLs are shared (Conte et al. 2012). Thus, even dramatically parallel phenotypes can be generated by a continuum of (non)parallelism at the genetic level.

5.4. Evolution Among Species Is Often (Non)Parallel

This review has focused on replicated evolution of multiple populations within a species. However, textbook cases of parallel evolution often come from interspecific comparisons in which replicated geographic areas (e.g., islands or lakes) promote the repeated evolution of independent sets of species, each set containing similar ecotypes that are adapted to specific habitats, suggesting that ecological conditions across geographic areas generate adaptive landscapes with similar selective optima, resulting in convergent evolution. Examples include African rift lake cichlids (Kocher et al. 1993), Hawaiian silverswords (Baldwin & Sanderson 1998), and *Tetragnatha* spiders (Gillespie 2004). Many of these replicated adaptive radiations also contain species that do not fall neatly into ecotype categories (Leal et al. 2002), however, representing cases of nonparallel evolution. Comparative phylogenetic methods could be applied to measure this (non)parallelism at a higher taxonomic scale than we considered above (Pérez-Pereira et al. 2017).

Such phylogenetic methods have been used to study (non)parallelism in *Anolis* lizards of the Greater Antilles. Anoles have repeatedly evolved island communities containing four to six morphologically distinctive habitat specialists termed ecomorphs (Langerhans et al. 2006, Losos 2009). However, of the 120 *Anolis* species in the Greater Antilles, 25 do not fall into a classic ecomorph category (Losos 2009) nor do most of the several hundred species found across the Lesser Antilles and mainland Central and South America. This vote-counting measure of (non)parallelism raises the questions of whether the ecomorphs are really phenotypic clusters arising from parallel evolution and whether unique species are due to unique selection pressures. To address these questions, Ingram, Mahler, and colleagues (Ingram & Mahler 2013, Mahler et al. 2013) developed a phylogenetic comparative method that tests whether trait distributions are best explained by genetic drift or stabilizing selection around one or more phenotypic optima. Mahler et al. (2013) modeled phenotypic evolution on the *Anolis* phylogeny, contrasting alternative hypotheses of Brownian motion alone, Brownian motion around a single optimum (an Ornstein–Uhlenbeck process), or multiple optima. The empirical data best matched a model with multiple adaptive optima corresponding to different ecomorphs that evolved independently on different islands (and in different subclades) (Mahler et al. 2013). Yet, the analysis confirmed that some unique species do not fit any broader ecomorph type. These unique species were mostly confined to the two largest Greater Antillean islands, suggesting the occasional cases of nonparallel *Anolis* evolution in the Greater Antilles require particular biogeographic or ecological settings (e.g., context-dependent evolution). Phylogenetic comparative methods like these allow us to quantify (non)parallel evolution above the population level and do not require paired populations that span some sort of habitat boundary, unlike the quantitative methods described above. However, these methods do not consider parallel evolution in the strict sense of similar trajectories of trait change, which is an area where more progress might be made.

6. WHY DOES VARIATION EXIST ALONG THE (NON)PARALLEL CONTINUUM?

From relatively early in the Modern Synthesis, researchers interpreted parallel evolution as evidence for similar natural selection (Muir 1924, Simpson 1953) because few if any other

Many-to-one mapping: when many distinct genotypes can yield the same phenotype or many distinct phenotypes can yield the same function

evolutionary forces can produce such deterministic outcomes. In contrast, many evolutionary forces can give rise to nonparallel evolution. So, observing nonparallel evolution does not clearly provide evidence for any one evolutionary process. Most biologists' first instinct may be to explain nonparallel evolution by invoking a nonadaptive process (Losos 2011, Rosenblum et al. 2014). For example, when researchers impose identical selection on identical starting populations, stochastic mutation and fixation processes yield nonparallel results (Cooper et al. 2003, Ferea et al. 1999, Fong et al. 2005, Orr 2005, Roberge 2006). In natural settings, this evolutionary stochasticity can be exaggerated by population differences in effective population size, connectivity, ancestry, plasticity, or many-to-one mapping (Alfaro et al. 2004, Kolbe et al. 2012, Leinonen et al. 2012, Nosil & Crespi 2004, Oke et al. 2017, Stayton 2008, Stuart et al. 2017, Thompson et al. 2017). Alternatively, (non)parallelism could also be adaptive if selection differs among qualitatively similar environments (Kaeuffer et al. 2012, Landry & Bernatchez 2010, Landry et al. 2007, Langerhans & DeWitt 2004, Stuart et al. 2017). In this section, we expand on these topics to address the question: Why is evolution (non)parallel where we might reasonably have expected parallel change?

6.1. Population Size

In small populations, enhanced genetic drift will reduce the extent of parallel change across replicate populations (Szendro et al. 2013). Small populations maintain lower genetic diversity, reducing the probability that the same alleles are available for selection in replicate populations (Chevin et al. 2010, Feiner et al. 2017, Gompel & Brud'homme 2009, MacPherson & Nuismer 2017). Small populations also have lower rates of mutational input to enable responses to selection (Barrett & Schluter 2008, Coyle et al. 2007). Stochastic allele frequency changes reduce the efficacy of natural selection, so drift decreases the likelihood that initially similar populations fix the same alleles in response to similar selection (Kimura 1964, Orr 2005). Note that selection also reduces effective population size (Charlesworth 2013), so strong selection can induce drift that inhibits populations' subsequent adaptive capacity.

6.2. History

The direction of evolution is contingent on populations' initial genetic conditions: available genetic diversity upon which selection can act, linkage between loci, and epistatic interactions. These conditions are likely to differ if two populations are initially genetically divergent, and populations will therefore respond in different ways even if selection is identical. Accordingly, studies in the field and laboratory have shown that more recently diverged populations are more likely to use the same alleles or loci during adaptation to a particular environment (Bollback & Huelsenbeck 2009, Conte et al. 2012).

Many phenotypes are controlled by epistatically interacting networks of genes. The phenotypic effect of any one allele is therefore contingent on the genotypic state at other loci (Cohen 1967, Costanzo et al. 2016). Even mutations at different positions within a single gene will interact epistatically (Sailer & Harms 2017). Thus, the fitness effects and evolutionary trajectory of a single mutation will differ among populations, depending on their genotypes at other loci with which the mutant allele interacts. This dependence is sometimes called a mutation order effect because the same mutations may lead to very different evolutionary results depending on the order in which they arise and (perhaps) fix (Gerstein et al. 2012). The importance of epistatic contingency has been confirmed by artificial selection experiments that yield nonparallel results (Jerison & Desai 2015, Vogwill et al. 2014).

The historical duration of evolutionary divergence is also relevant to (non)parallelism (Lucek et al. 2014). Populations that have been diverging for more time have more scope for genetic drift

to introduce stochastic differences into replicate populations' evolutionary trajectories. This is, after all, why Brownian motion models of evolution lead to greater divergence through time (Ord & Summers 2015). Yet, if evolution is mutation limited, older populations will have had more time to accumulate the similar adaptive mutations needed to converge on similar phenotypic solutions to a given environment (Orr 2005, Whitlock & Gomulkiewicz 2005).

6.3. Selection Landscape

It is intuitive that replicate populations in more similar environments should experience more similar selection and evolve more parallel traits. However, few studies have tested this inference directly. Theoretical studies of parallel evolution typically assume that selection is identical and constant across all replicate populations (Orr 2005). Laboratory studies of experimental evolution attempt to impose identical selection regimes across replicate populations experiencing the same treatment (Wichman et al. 1999). Even field studies often focus on comparisons between apparently discrete habitat categories (e.g., lake versus stream), implicitly assuming that variation within habitat categories is minimal. However, natural selection is unlikely to be exactly replicated, owing to unrecognized site-to-site environmental differences, community structure differences, or fluctuating selection through time (Siepielski et al. 2009). Thus, environmental heterogeneity among ostensibly replicate habitats might contribute to nonparallel evolution. For example, replicate lake whitefish populations in eastern Canada have repeatedly diverged into coexisting dwarf and normal ecotypes that evolved (non)parallel morphology. Dwarf–normal pairs are more phenotypically (and genetically) divergent in lakes with greater seasonal variation in oxygen (Landry et al. 2007) and larger diet differentiation (Landry & Bernatchez 2010), whereas nonparallel evolution of immunologically important *MHCIIb* genes is linked to nonparallel parasite communities (Pavey et al. 2013). Thus, lake-to-lake environmental differences influence lake-to-lake differences in how dwarf and normal ecotypes diverge. Similar environment-dependent (non)parallelism has been demonstrated in whitefish in Europe (Siwertsson et al. 2013), in lake–stream stickleback (Stuart et al. 2017), and in Trinidadian guppies (Fitzpatrick et al. 2014).

Some traits' evolution may be highly parallel because they experience highly parallel selection. Other traits may be subject to divergent natural selection between superficially similar habitat replicates. Among-trait differences in (non)parallel evolution can therefore provide a tool for inferring which traits have adaptive value in particular environments.

Finally, natural selection fluctuates over time in nature (Siepielski et al. 2009). Abiotic conditions change from year to year, and as a result, replicate populations may experience different selection in any one year. Even if populations experience similar selection, they will tend to diverge over time in a drift-like process driven by fluctuating selection (Gillespie 1994). For example, antagonistic coevolution (e.g., between predator and prey, host and parasite, or males and females) can generate fluctuating selection, as initially winning defensive strategies become targets for attack by the antagonist and lose their advantage (Ellner et al. 2011, Tellier & Brown 2007). If replicate populations' eco-evolutionary cycles are out of phase, they may be phenotypically nonparallel at any one instant in time, yet experience similar cyclical dynamics over long timescales (Auld & Brand 2017).

6.4. Gene Flow

(Non)parallelism should also depend on levels of population connectivity. Gene flow typically constrains divergence between populations (Lenormand 2002, Slatkin 1985). Therefore, gene flow between replicate populations in the same habitat type should make them more genetically

similar and hence facilitate more parallel evolution. Gene flow between different habitat types, however, tends to constrain local adaptation within each habitat. If some replicate populations in a given habitat receive large numbers of immigrants, and other replicates are isolated, migration–selection balance will act differently across replicates contributing to nonparallelism (Hendry & Taylor 2004, Moore et al. 2007, Stuart et al. 2017). Such variation in gene flow may especially effect the magnitude of change (PCVA vector lengths). For example, gene flow between lake and stream stickleback is strong in some watersheds (constraining trait divergence) and weak in others (permitting trait divergence), explaining some of the variation in the magnitude of lake–stream divergence but not the orientation of this divergence (Stuart et al. 2017).

6.5. Many-to-One Mapping

Natural selection acts on morphological traits indirectly via trait function (Arnold 1983, Lauder 1981, Wainwright 1996, Walker 2007). If a simple 1:1 relationship exists between form and function, replicated selection on function will favor the evolution of similar underlying phenotypes. However, many physiological or biomechanical functions have many-to-one mapping, in which different trait combinations can generate the same functional output. Such redundancy allows trait divergence (and nonparallel evolution) even when stabilizing selection favors a single function (Alfaro et al. 2005, Wainwright et al. 2005). Hence, many-to-one mapping enables nonparallel evolution of structural traits even when the emergent functional traits are evolving in parallel. Consistent with this theory, some studies have found that functional trait evolution is more predictable (i.e., has a higher percent variance explained by ecotype) than the underlying structural traits (Thompson et al. 2017). This observation highlights the importance of describing the extent of (non)parallel evolution at different levels of biological organization.

6.6. Genomic Architecture

Replicate populations' (non)parallel response to selection also depends on their respective genetic architectures (e.g., recombination rates, mutation rates, chromatin packing, and epigenetic modifications), which can vary among populations and across the genome (Hodgkinson & Eyre-Walker 2011, Nachman 2002). Mutational hot spots within the genome (Burch & Chao 2000, Holland et al. 1982) harbor greater genetic variation and thus present more fodder for natural selection. Because mutational hot spots are more evolvable, they increase the probability that mutations arise independently in the same hot spot genes, facilitating parallel evolution at the genetic level across independent taxa. For example, *Pitx1* resides in a fragile region of the stickleback genome and has independently mutated in multiple independent populations to confer a reduced pelvis, which selection then fixed (Chan et al. 2010, Coyle et al. 2007). Remarkably, this mutational bias confirms Gates's (1936) early explanation for parallel evolution.

Empirical work suggests that shared adaptive alleles tend to be found more often in regions of low recombination, particularly during divergence with gene flow (Roesti et al. 2013, Samuk et al. 2017). The most dramatic version of this effect entails chromosomal inversions segregating within populations. Inversions usually suppress recombination, creating linked groups of coadapted alleles at various loci. Selection acts on these loci as a group, facilitating parallel adaptation to new environments when inversions are shared among founder populations (Terekhanova et al. 2014).

Polygenic traits enable a many-to-one mapping of genotype to phenotype. So, much like the many-to-one form-to-function mapping discussed above, parallel genetic evolution is more likely when only a single gene underlies an evolving trait (Orr 2005). Nonetheless, parallel genomic evolution has been found even when there are multiple mutations in many genes that can produce

similar phenotypic changes (e.g., *FRIGIDA*, for flowering time) (Levy & Dean 1998, Shindo et al. 2005).

Mutations that improve fitness through one trait might have deleterious effects via a different trait. This negative pleiotropy reduces the likelihood that the mutation will persist in a population and eventually fix (Cooper et al. 2007, Otto 2004). If negative pleiotropy is common, replicate populations are less likely to have the same genetic variants available for adaptation and evolution will be more nonparallel. Alternatively, pleiotropy may constrain the number of plausible evolutionary trajectories, increasing the extent of parallel change. Little empirical evidence distinguishes these opposing hypotheses, though one study found that genes with higher pleiotropy exhibited less parallel evolution of gene expression (Papakostas et al. 2014).

Pleiotropy may also reduce the likelihood of parallel evolution through correlated selection. Basic quantitative genetics tells us that the direction and speed of evolution of a focal trait depend on selection that might act on other genetically correlated traits. A focal trait may be subject to parallel selection, but if correlated traits experience inconsistent selection among replicate populations, even the focal trait will not evolve in parallel (Brodie 1992, Falconer 1952, Gratten et al. 2008, Lande & Arnold 1983, Thompson et al. 2017).

In our introduction, we posed the question, When we see deviations from parallel evolution, what are we to conclude about adaptation? The material reviewed above makes it clear many answers may be true, perhaps simultaneously. Nonparallel evolution may or may not be adaptive. But, when replicate populations vary along the (non)parallel continuum, such variable evolutionary outcomes can provide an opportunity to test the effects of multiple evolutionary forces including but not limited to natural selection.

7. WHERE NEXT?

In a replicated study of bacteriophage evolution in response to artificial selection in the laboratory, only 25% to 50% of genetic substitutions in any one replicate population also evolved in at least one other replicate population (Wichman et al. 1999). This percentage is more parallel than expected by chance but certainly is less than 100%. Such inconsistent responses to selection are common in nature, as our review has made clear. Thus, Wichman and colleagues' (1999, p. 424) closing question, "Why is parallel evolution not complete?," remains germane. We now have a wide array of plausible answers to this question, but many important questions remain unanswered. In this final section, we summarize some next steps.

First, we must improve quantitative approaches for describing the continuum of (non)parallel evolution and statistically distinguishing different patterns of parallel and nonparallel change (**Figure 2**). The multivariate vector-based approach (PCVA) is a promising tool, but problems remain with statistical power, defining suitable null hypotheses, sensitivity to the number of measured traits, and reliance on pairwise comparisons. Nevertheless, PCVA has proved to be useful for making evolutionary inferences (e.g., Stuart et al. 2017), so we advocate applying this method to more research systems in the laboratory and wild. An intriguing future direction is to apply PCVA to population triplets using vectors to connect an ancestral population to two descendant populations that have diverged in different habitats. This latter option offers a more complex geometry (a triangle of vectors) that describes the temporal trajectories of between-population divergence.

Second, we need formal tools for comparing measures of (non)parallelism across levels of biological organization. One clear theme in the existing literature is that evolution may be parallel for a higher-level trait (e.g., phenotype or function) but nonparallel for lower-level traits (e.g., physiological processes, biochemistry, genes). Understanding how (non)parallel evolution correlates across levels may increase our ability to predict evolutionary change.

Third, the vast majority of studies of (non)parallelism focus on wild-caught individuals whose traits are affected by phenotypic plasticity that may exaggerate or obscure patterns of parallel evolution (Oke et al. 2015). The obvious solution is to evaluate (non)parallelism based on trait measurements taken in common-garden settings or from quantitative genetic estimates of breeding value. Of course, an important open question concerns the contribution of plasticity and genotype by environment interactions to (non)parallel trait change (Mazzarella et al. 2015).

Fourth, most studies of (non)parallelism examine extant populations, rather than ancestor–descendant pairs. The field would benefit from temporal transects that trace replicate trajectories of evolutionary change through time. Such temporal transects are possible with experimental evolution of organisms with short generation times. For wild populations, evolutionary vectors through time might be available using fossil and subfossil samples to measure phenotypes (or ancient DNA genotypes) from different points in history. For most taxa (and most traits), the fossil record is too sparse, generates small sample sizes, or is entirely absent. However, in exceptional cases for which we can measure many individuals continuously through time, we will surely find that evolution traces nonlinear paths through trait space over time, which would complicate geometric measures of parallel evolution (Adams & Collyer 2009). Such nonlinear multivariate trajectories have been observed across spatial transects (Lohman et al. 2017), but temporal trajectories that might arc through trait space have not been integrated into (non)parallel evolution studies. Plant domestication offers an exceptionally promising venue for this work because archaeological studies provide temporal transects of food plant materials (Fuller et al. 2014). Trajectories through time could also be studied using so-called resurrection studies, in which ancestral populations can be recreated from seed or egg banks (Decaestecker et al. 2007).

Fifth, we need to explain variation in the extent of (non)parallelism among evolutionary replicates. This requires investigation of the ecological, genetic, and historical mechanisms that lead to that pattern in the first place. For instance, we tend to assume that similar environments impose similar selection pressures, but we must test this explicitly by measuring selection on population pairs that are both more and less parallel. Better still, experimental manipulation of selective forces to track parallel responses to selection is an important future direction. Furthermore, a mechanistic understanding of evolutionary genetics and how traits are constructed may be necessary to effectively account for nonparallel evolution. Functional genetics studies that dissect the specific pathways by which traits are built during development will be needed to understand how genes and traits respond to (non)parallel selection. In particular, it is increasingly clear that epistasis is common and strongly influences evolution (Jerison & Desai 2015). To what extent is epistasis responsible for nonparallel genetic (or phenotypic) evolution when selection would otherwise favor parallel change?

Sixth, biomedical and agricultural practices increasingly draw on genome-wide association studies (GWAS) that pinpoint genetic variants correlated with traits. A common approach is to obtain genomic SNP data for a large number of individuals from many populations then identify SNPs correlated with an environment or trait (Coop et al. 2010, Davey et al. 2011). Genetic nonparallel evolution undermines the strength of these correlations, reducing the power of GWAS. At the extreme, GWAS would fail if each population evolved a given trait via unique genes or alleles, as in the HIV-1 *GP120* gene (Martinez-Picado et al. 2002). Because among-population GWAS currently assume parallel evolution, many opportunities to explore ways to relax this questionable assumption exist.

Last, we need to expand research on the practical consequences of variation along the (non)parallel continuum. In the introduction to this review, we summarized a variety of studies related to medicine or agriculture. To make our basic research useful, we must consider how to apply the perspectives discussed here to solve real-world challenges. The evolution of tumors,

pathogens, weeds, and pests poses major health and economic burdens. When a pest's evolution is strongly parallel, we might effectively anticipate future changes and thereby develop therapies to preemptively combat any ill effects of evolution. In contrast, nonparallel evolution will prove harder to anticipate. The (non)parallel continuum also has implications for other applied concerns. To mitigate extinction risk, conservation biologists and managers sometimes transfer organisms from healthy populations into declining populations to boost their abundance and genetic diversity (Rinkevich 2005). When replicate populations have evolved in parallel, they are preadapted to each other's habitats and so may be especially well suited to rescuing declining populations. However, nonparallel local adaptation might produce noninterchangeable populations, in which case transplants may undermine population viability (Kenkel et al. 2015, Stockwell et al. 2003). Further work is needed to study the conservation implications of (non)parallel evolution for population recovery and restocking efforts.

8. CONCLUSIONS

Evolution is often described as being parallel, convergent, or divergent. These semantic designations draw us into binary thinking about evolutionary processes and their resulting patterns. The reality is wonderfully more subtle and complex: The evolution of multiple phenotypes or genes in replicate populations is best described by a quantitative continuum from parallel to antiparallel and convergent to divergent. Some populations will be highly parallel to each other, whereas other populations will follow unique trajectories, and some phenotypes and genes are more prone to parallel evolution than others. A growing number of studies have embraced this complexity, recognizing that parallel evolution is a measurable continuum along which populations and traits and genes will vary. This quantitative view of a (non)parallel continuum opens up new opportunities to study the processes that generate heterogeneity in the extent of parallel evolution.

In the past, biologists have used parallel evolution to argue that evolution can be (sometimes) predictable. Yet, growing evidence suggests that deviations from parallel evolution can also be deterministic, so nonparallel change need not imply unpredictable evolution. Many research opportunities lie ahead for biologists seeking to develop tools to explain why evolution generates a continuum of (non)parallel results. With these tools, we hope to improve our ability to predict the future course of evolution.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

ACKNOWLEDGMENTS

We thank A.P. Hendry, S. den Haan, B. Langerhans, D. Lowry, E. Resetarits, S. Stockmaier, and the Bolnick Laboratory for discussions and constructive feedback on the manuscript. This article was made possible by National Science Federation grants DEB-1456462 (D.I.B.) and DEB-1144773 (D.I.B.), a National Sciences and Engineering Research Council of Canada Discovery Grant (R.D.H.B.), and a Canada Research Chair (R.D.H.B.).

LITERATURE CITED

Abbosh C, Birkbak NJ, Wilson GA, Jamal-Hanjani M, Constantin T, et al. 2017. Phylogenetic ctDNA analysis depicts early-stage lung cancer evolution. *Nature* 545:446–51

Abouheif E. 2008. Parallelism as the pattern and process of mesoevolution. *Evol. Dev.* 10:3–5

Adams DC, Collyer ML. 2009. A general framework for the analysis of phenotypic trajectories in evolutionary studies. *Evolution* 65:1143–54

Agrawal AA. 2017. Toward a predictive framework for convergent evolution: integrating natural history, genetic mechanisms, and consequences for the diversity of life. *Am. Nat.* 190:S1–12

Alfaro M, Bolnick DI, Wainwright PC. 2004. Evolutionary dynamics of complex biomechanical traits: an example from the 4-bar lever system of labrids. *Evolution* 58:495–503

Alfaro M, Bolnick DI, Wainwright PC. 2005. Evolutionary consequences of many-to-one mapping of jaw morphology to mechanics in labrid fishes. *Am. Nat.* 165:e140–54

Arendt J, Reznick DN. 2008. Convergence and parallelism reconsidered: What have we learned about the genetics of adaptation? *Trends Ecol. Evol.* 23:26–32

Arnold SJ. 1983. Morphology, performance, and fitness. *Am. Zool.* 23:347–61

Auld SKJR, Brand J. 2017. Environmental variation causes different (co) evolutionary routes to the same adaptive destination across parasite populations. *Evol. Lett.* 1(5):245–54

Baguñà J, Garcia-Fernàndez J. 2003. Evo-Devo: the long and winding road. *Int. J. Dev. Biol.* 47:705–13

Bailey SF, Blanquart F, Bataillon T, Kassen R. 2017. What drives parallel evolution? *BioEssays* 39:e201600176

Bailey SF, Rodrigue N, Kassen R. 2015. The effect of selection environment on the probability of parallel evolution. *Mol. Biol. Evol.* 32:1436–48

Baldwin BG, Sanderson MJ. 1998. Age and rate of diversification of the Hawaiian silversword alliance (Compositae). *PNAS* 95:9402–6

Barrett RDH, Schluter D. 2008. Adaptation from standing genetic variation. *Trends Ecol. Evol.* 23:38–44

Bitocchi E, Bellucci E, Giardini A, Rau D, Rodriguez M, et al. 2013. Molecular analysis of the parallel domestication of the common bean (*Phaseolus vulgaris*) in Mesoamerica and the Andes. *New Phytol.* 197:300–13

Bollback JP, Huelsenbeck JP. 2009. Parallel genetic evolution within and between bacteriophage species of varying degrees of divergence. *Genetics* 181:225–34

Brinsmead J, Fox MG. 2002. Morphological variation between lake- and stream-dwelling rock bass and pumpkinseed populations. *J. Fish Biol.* 61:1619–38

Brodie EDB. 1992. Correlational selection for color pattern and antipredator behavior in the garter snake *Thamnophis ordinoides*. *Evolution* 46:1284–98

Burch CL, Chao L. 2000. Evolvability of an RNA virus is determined by its mutational neighborhood. *Nature* 406:625–28

Burrell RA, McGranahan N, Bartek J, Swanton C. 2013. The causes and consequences of genetic heterogeneity in cancer evolution. *Nature* 501:338–45

Calman WT. 1935. Presidential address: the meaning of biological classification. *Proc. Linn. Soc. Lond.* 147:145–58

Carscadden KA, Cadotte MW, Gilbert B. 2017. Trait dimensionality and population choice alter estimates of phenotypic dissimilarity. *Ecol. Evol.* 7:2273–85

Chan YF, Marks ME, Jones FC, Villarreal G, Shapiro MD, et al. 2010. Adaptive evolution of pelvic reduction in sticklebacks by recurrent deletion of a *Pitx1* enhancer. *Science* 327:302–5

Charlesworth B. 2013. Why we are not dead one hundred times over. *Evolution* 67:3354–61

Chevin L-M, Lande R, Mace GM. 2010. Adaptation, plasticity, and extinction in a changing environment: towards a predictive theory. *PLOS Biol.* 8:e1000357

Cohen D. 1967. Optimizing reproduction in a randomly varying environment when a correlation may exist between the conditions at the time a choice has to be made and the subsequent outcome. *J. Theor. Biol.* 16:1–14

Collyer ML, Adams DC. 2007. Analysis of two-state multivariate phenotypic change in ecological studies. *Ecology* 88:683–92

Collyer ML, Sekora DJ, Adams DC. 2015. A method for analysis of phenotypic change for phenotypes described by high-dimensional data. *Heredity* 115:357–65

Colosimo PA, Hosemann KE, Balabhadra S, Villarreal G, Dickson A, et al. 2005. Widespread parallel evolution in sticklebacks by repeated fixation of ectodysplasin alleles. *Science* 307:1928–33

Conte GL, Arnegard ME, Best J, Chan YF, Jones FC, et al. 2015. Extent of QTL reuse during repeated phenotypic divergence of sympatric threespine stickleback. *Genetics* 201:1189–200

Conte GL, Arnegard ME, Peichel CL, Schluter D. 2012. The probability of genetic parallelism and convergence in natural populations. *Proc. R. Soc. B* 279:5039–47
Coop G, Witonsky D, Di Rienzo A, Pritchard JK. 2010. Using environmental correlations to identify loci underlying local adaptation. *Genetics* 185:1411–23
Cooper TF, Ostrowski EA, Travisano M. 2007. A negative relationship between mutation pleiotropy and fitness effect in yeast. *Evolution* 61:1495–99
Cooper TF, Rozen DE, Lenski RE. 2003. Parallel changes in gene expression after 20,000 generations of evolution in *Escherichia coli*. *PNAS* 100:1072–77
Cope ED. 1876. The progress of discovery of the laws of evolution. *Am. Nat.* 10:218–21
Cope ED, Kingsley JS. 1891. Editorial. *Am. Nat.* 25:558–60
Costanzo M, VanderSluis B, Koch EN, Baryshnikova A, Pons C, et al. 2016. A global genetic interaction network maps a wiring diagram of cellular function. *Science* 353:aaf1420
Coyle SM, Huntingford FA, Peichel CL. 2007. Parallel evolution of *Pitx1* underlies pelvic reduction in Scottish threespine stickleback (*Gasterosteus aculeatus*). *J. Hered.* 98:581–86
Darwin C. 1859. *On the Origin of Species*. Cambridge, MA: Harvard Univ. Press
Davey JW, Hohenlohe PA, Etter PD, Boone JQ, Catchen JM, Blaxter ML. 2011. Genome-wide genetic marker discovery and genotyping using next-generation sequencing. *Nat. Rev. Genet.* 12:499–510
Day T. 2012. Computability, Godel's incompleteness theorem, and an inherent limit on the predictability of evolution. *J. R. Soc. Interface* 9:624–39
de Visser JA, Krug J. 2014. Empirical fitness landscapes and the predictability of evolution. *Nat. Rev. Genet.* 15:480–90
Decaestecker E, Gaba S, Raeymaekers JAM, Stoks R, Van Kerckhoven L, et al. 2007. Host-parasite 'red queen' dynamics archived in pond sediment. *Nature* 450:870–73
Derome N, Duchesne P, Bernatchez L. 2006. Parallelism in gene transcription among sympatric lake whitefish (*Coregonus clupeaformis* Mitchill) ecotypes. *Mol. Ecol.* 15:1239–49
Dobzhansky T. 1933. Geographical variation in lady-beetles. *Am. Nat.* 67:97–126
Douglas SM, Chubiz LM, Harcombe WR, Ytreberg FM, Marx CJ. 2016. Parallel mutations result in a wide range of cooperation and community consequences in a two-species bacterial consortium. *PLOS ONE* 11:e0161837
Dunn B, Levine RP, Sherlock G. 2005. Microarray karyotyping of commercial wine yeast strains reveals shared, as well as unique, genomic signatures. *BMC Genom.* 6:53
Ellner SP, Geber MA, Hairston NG. 2011. Does rapid evolution matter? Measuring the rate of contemporary evolution and its impacts on ecological dynamics. *Ecol. Lett.* 14:603–14
Elmer KR, Fan S, Kusche H, Spreitzer ML, Kautt AF, et al. 2014. Parallel evolution of Nicaraguan crater lake cichlid fishes via non-parallel routes. *Nat. Commun.* 5:5168
Elmer KR, Meyer A. 2011. Adaptation in the age of ecological genomics: insights from parallelism and convergence *Trends Ecol. Evol.* 26:298–306
Eroukhmanoff F, Hargeby A, Arnberg NN, Hellgren O, Bensch S, Svensson EI. 2009. Parallelism and historical contingency during rapid ecotype divergence in an isopod. *J. Evol. Biol.* 22:1098–110
Evans ML, Chapman LJ, Mitrofanov I, Bernatchez L. 2013. Variable extent of parallelism in respiratory, circulatory, and neurological traits across lake whitefish species pairs. *Ecol. Evol.* 3:546–57
Falconer DS. 1952. The problem of environment and selection. *Am. Nat.* 86:293–98
Feiner N, Rago A, While GM, Uller T. 2017. Signatures of selection in embryonic transcriptomes of lizards adapting in parallel to cool climate. *Evolution* 72:67–81
Ferea TL, Botstein D, Brown PO, Rosenzweig RF. 1999. Systematic changes in gene expression patterns following adaptive evolution in yeast. *PNAS* 96:9721–26
Fernández-Ortuño D, Torés JA, de Vicente A, Pérez-García A. 2008. Field resistance to QoI fungicides in *Podosphaera fusca* is not supported by typical mutations in the mitochondrial cytochrome *b* gene. *Pest Manag. Sci.* 64:694–702
Fitzpatrick SW, Torres-Dowdall J, Reznick DN, Ghalambor CK, Funk WC. 2014. Parallelism isn't perfect: could disease and flooding drive a life-history anomaly in Trinidadian guppies? *Am. Nat.* 183:290–300
Fong SS, Joyce AR, Palsson B. 2005. Parallel adaptive evolution cultures of *Escherichia coli* lead to convergent growth phenotypes with different gene expression states. *Genome Res.* 2005:1365–72

Fuller DQ, Denham T, Arroyo-Kalin M, Lucas L, Stevens CJ, et al. 2014. Convergent evolution and parallelism in plant domestication revealed by an expanding archaeological record. *PNAS* 111:6147–52
Gates RR. 1912. Parallel mutations in *Oenothera biennis*. *Nature* 89:659–60
Gates RR. 1936. Mutations and natural selection. *Am. Nat.* 70:505–16
Gerstein AC, Lo DS, Otto SP. 2012. Parallel genetic changes and nonparallel gene-environment interactions characterize the evolution of drug resistance in yeast. *Genetics* 192:241–52
Gillespie JH. 1994. *The Causes of Molecular Evolution*. Oxford, UK: Oxford Univ. Press
Gillespie R. 2004. Community assembly through adaptive radiation in Hawaiian spiders. *Science* 303:356–59
Gíslason D, Ferguson MM, Skulason S, Snorrason SS. 1999. Rapid and coupled phenotypic and genetic divergence in Icelandic arctic char (*Salvelinus alpinus*). *Can. J. Fish. Aquat. Sci.* 56:2229–34
Gompel N, Brud'homme B. 2009. The causes of repeated genetic evolution. *Dev. Biol.* 332:36–47
Gould SJ. 2002. *The Structure of Evolutionary Theory*. Cambridge, MA: Harvard Univ. Press
Gratten J, Wilson A, McRae A, Beraldi D, Visscher P, et al. 2008. A localized negative genetic correlation constrains microevolution of coat color in wild sheep. *Science* 319:318–20
Graves JL Jr., Hertweck KL, Phillips MA, Han MV, Cabral LG, et al. 2017. Genomics of parallel experimental evolution in *Drosophila*. *Mol. Biol. Evol.* 34:831–42
Haas O, Simpson GG. 1945. Analysis of some phylogenetic terms, with attempts at redefinition. *Proc. Am. Philos. Soc.* 90:319–49
Harvey PH, Pagel MD. 1991. *The Comparative Method in Evolutionary Biology*. New York: Oxford Univ. Press
Hendry AP, Kaeuffer RE, Crispo E, Peichel CL, Bolnick DI. 2013. Evolutionary inferences from exchangeability: individual classification approaches based on the ecology, morphology, and genetics of lake-stream stickleback population pairs. *Evolution* 67:3429–41
Hendry AP, Taylor EB. 2004. How much of the variation in adaptive divergence can be explained by gene flow? An evaluation using lake-stream stickleback pairs. *Evolution* 58:2319–31
Herron MD, Doebeli M. 2013. Parallel evolutionary dynamics of adaptive diversification in *Escherichia coli*. *PLOS Biol.* 11:e10001490
Hodgkinson A, Eyre-Walker A. 2011. Variation in the mutation rate across mammalian genomes. *Nat. Rev. Genet.* 12:756–66
Hoekstra HE, Nachman MW. 2003. Different genes underlie adaptive melanism in different populations of rock pocket mice. *Mol. Ecol.* 12:1185–94
Holland J, Spindler K, Horodyski F, Grabau E, Nichol S, Van de Pol S. 1982. Rapid evolution of RNA genomes. *Science* 215:1577–85
Hubbs CL. 1944. Concepts of homology and analogy. *Am. Nat.* 78:289–307
Ingley SJ, Billmann EJ, Hancock C, Johnson JB. 2014. Repeated geographic divergence in behavior: a case study employing phenotypic trajectory analyses. *Behav. Ecol. Sociobiol.* 68:1577–87
Ingram T, Mahler DL. 2013. SURFACE: detecting convergent evolution from comparative data by fitting Ornstein-Uhlenbeck models with stepwise Akaike Information Criterion. *Methods Ecol. Evol.* 4:416–25
Jerison ER, Desai MM. 2015. Genomic investigations of evolutionary dynamics and epistasis in microbial evolution experiments. *Curr. Opin. Genet. Dev.* 35:33–39
Jones FC, Grabherr MG, Chan YF, Russell P, Mauceli E, et al. 2012. The genomic basis of adaptive evolution in threespine sticklebacks. *Nature* 484:55–61
Josephides C, Swain PS. 2017. Predicting metabolic adaptation from networks of mutational paths. *Nat. Commun.* 8:685
Kaeuffer R, Peichel CL, Bolnick DI, Hendry AP. 2012. Parallel and nonparallel aspects of ecological, phenotypic, and genetic divergence across replicate population pairs of lake and stream stickleback. *Evolution* 66:402–18
Kautt AF, Elmer KR, Meyer A. 2012. Genomic signatures of divergent selection and speciation patterns in a 'natural experiment', the young parallel radiations of Nicaraguan crater lake cichlid fishes. *Mol. Ecol.* 21:4770–86
Kenkel CD, Almanza AT, Matz MV. 2015. Fine-scale environmental specialization of reef-building corals might be limiting reef recovery in the Florida Keys. *Ecology* 96:3197–212
Khaitovich P, Hellmann I, Enard W, Nowick K, Leinweber M, et al. 2005. Parallel patterns of evolution in the genomes and transcriptomes of humans and chimpanzees. *Science* 309:1850–54

Kimura M. 1964. Diffusion models in population genetics. *J. Appl. Probab.* 1:177–232
Kocher TD, Conroy JA, McKaye KR, Stauffer JR. 1993. Similar morphologies of cichlid fish in Lakes Tanganyika and Malawi are due to convergence. *Mol. Phylogenetics Evol.* 2:158–65
Kolbe JJ, Leal M, Schoener TW, Spiller DA, Losos JB. 2012. Founder effects persist despite adaptive differentiation: a field experiment with lizards. *Science* 335:1086–89
Lai Z, Kane NC, Zou Y, Rieseberg LH. 2008. Natural variation in gene expression between wild and weedy populations of *Helianthus annuus*. *Genetics* 179:1881–90
Lande R, Arnold SJ. 1983. The measurement of selection on correlated characters. *Evolution* 37:1210–26
Landry L, Bernatchez L. 2010. Role of epibenthic resource opportunities in the parallel evolution of lake whitefish species pairs (*Coregonus* sp.). *J. Evol. Biol.* 23:2602–13
Landry L, Vincent WF, Bernatchez L. 2007. Parallel evolution of lake whitefish dwarf ecotypes in association with limnological features of their adaptive landscape. *J. Evol. Biol.* 20:971–84
Langerhans RB. 2018. Predictability and parallelism of multitrait adaptation. *J. Hered.* 109:59–70
Langerhans RB, DeWitt T. 2004. Shared and unique features of evolutionary diversification. *Am. Nat.* 164:335–49
Langerhans RB, Knouft JH, Losos JB. 2006. Shared and unique features of diversification in greater Antillean *Anolis* ecomorphs. *Evolution* 60:362–69
Langerhans RB, Makowicz AM. 2009. Shared and unique features of morphological differentiation between predator regimes in *Gambusia caymanensis*. *J. Evol. Biol*. 22:2231–42
Laporte M, Rogers SM, Dion-Cote AM, Normandeau E, Gagnaire PA, et al. 2015. RAD-QTL mapping reveals both genome-level parallelism and different genetic architecture underlying the evolution of body shape in lake whitefish (*Coregonus clupeaformis*) species pairs. *G3* 5:1481–91
Lauder GV. 1981. Form and function: structural analysis in evolutionary morphology. *Paleobiology* 7:430–42
Le Moan A, Gagnaire P-A, Bonhomme F. 2016. Parallel genetic divergence among coastal–marine ecotype pairs of European anchovy explained by differential introgression after secondary contact. *Mol. Ecol.* 25:3187–202
Leal M, Knox AK, Losos JB. 2002. Lack of convergence in aquatic *Anolis* lizards. *Evolution* 56:785–91
Leger EA, Rice KJ. 2007. Assessing the speed and predictability of local adaptation in invasive California poppies (*Eschscholzia californica*). *J. Evol. Biol.* 20:1090–103
Leinonen T, McCairns RJ, Herczeg G, Merila J. 2012. Multiple evolutionary pathways to decreased lateral plate coverage in freshwater threespine sticklebacks. *Evolution* 66:3866–75
Lenormand T. 2002. Gene flow and the limits to natural selection. *Trends Ecol. Evol.* 17:183–89
Lenski RE. 2017. Convergence and divergence in a long-term experiment with bacteria. *Am. Nat.* 190:S57–68
Levy YY, Dean C. 1998. Control of flowering time. *Curr. Opin. Plant Biol.* 1:49–54
Lohman B, Berner D, Bolnick DI. 2017. Clines arc through multivariate morphospace. *Am. Nat.* 189:354–67
Losos JB. 2009. *Lizards in an Evolutionary Tree: Ecology and Adaptive Radiation of Anoles*. Berkeley: Univ. Calif. Press
Losos JB. 2011. Convergence, adaptation, and constraint. *Evolution* 65:1827–40
Lucek K, Sivasundar A, Kristjánsson BK, Skúlason S, Seehausen O. 2014. Quick divergence but slow convergence during ecotype formation in lake and stream stickleback pairs of variable age. *J. Evol. Biol.* 27:1878–92
MacPherson A, Nuismer SL. 2017. The probability of parallel genetic evolution from standing genetic variation. *J. Evol. Biol.* 30:326–37
Mahler DL, Ingram T, Revell LJ, Losos JB. 2013. Exceptional convergence on the macroevolutionary landscape in island lizard radiations. *Science* 341:292–95
Manceau M, Domingues VS, Mallarino R, Hoekstra HE. 2011. The developmental role of Agouti in color pattern evolution. *Science* 331:1062–65
Manousaki T, Hull PM, Kusche H, Machado-Schiaffino G, Franchini P, et al. 2013. Parsing parallel evolution: ecological divergence and differential gene expression in the adaptive radiations of thick-lipped Midas cichlid fishes from Nicaragua. *Mol. Ecol.* 22:650–69
Martinez-Picado J, Frost SDW, Izquierdo N, Morales-Lopetegi K, Marfil S, et al. 2002. Viral evolution during structured treatment interruptions in chronically human immunodeficiency virus-infected individuals. *J. Virol.* 76:12344–48

Mazzarella AB, Voje KL, Hansson TH, Taugbøl A, Fischer B. 2015. Strong and parallel salinity-induced phenotypic plasticity in one generation of threespine stickleback. *J. Evol. Biol.* 28:667–77
McGee MD, Neches RY, Seehausen O. 2016. Evaluating genomic divergence and parallelism in replicate ecomorphs from young and old cichlid adaptive radiations. *Mol. Ecol.* 25:260–68
Meyer JR, Agrawal AA, Quick RT, Dobias DT, Schneider D, Lenski RE. 2010. Parallel changes in host resistance to viral infection during 45,000 generations of relaxed selection. *Evolution* 64:3024–34
Moore J-S, Gow JL, Taylor EB, Hendry AP. 2007. Quantifying the constraining influence of gene flow on adaptive divergence in the lake-stream threespine stickleback system. *Evolution* 61:2015–26
Muir F. 1924. Homoplasmy or convergent development in evolution. *Proc. Hawaii. Entomol. Soc.* 5:473–83
Muller HJ. 1939. Reversibility in evolution considered from the standpoint of genetics. *Biol. Rev. Camb. Philos. Soc.* 14:261–80
Nachman MW. 2002. Variation in recombination rate across the genome: evidence and implications. *Curr. Opin. Genet. Dev.* 12:657–63
Nichols JT. 1916. On primarily unadaptive variants. *Am. Nat.* 50:565–74
Nosil P, Crespi BJ. 2004. Does gene flow constrain adaptive divergence or vice versa? A test using ecomorphology and sexual isolation in *Timema cristinae* walking sticks. *Evolution* 58:102–12
Nowell PC. 1976. The clonal evolution of tumor cell populations. *Science* 194:23–28
Oke KB, Bukhari M, Kaueffer R, Rolshausen G, Räsänen K, et al. 2015. Plasticity enhances phenotypic parallelism: evidence from lake-stream stickleback. *J. Evol. Biol.* 29:126–43
Oke KB, Rolshausen G, LeBlond C, Hendry AP. 2017. How parallel is parallel evolution? A comparative analysis in fishes. *Am. Nat.* 190:1–16
Ord TJ, Summers TC. 2015. Repeated evolution and the impact of evolutionary history on adaptation. *BMC Evol. Biol.* 15:137
Orr HA. 2005. The probability of parallel evolution. *Evolution* 59:216–20
Osborn HF. 1900. The geological and faunal relations of Europe and America during the Tertiary period and the theory of the successive invasions of an African fauna. *Science* 11:561–74
Otto SP. 2004. Two steps forward, one step back: the pleiotropic effects of favoured alleles. *Proc. R. Soc. B* 271:705–14
Packard AS. 1898. The philosophical views of Agassiz. *Am. Nat.* 32:159–64
Papakostas S, Vøllestad LA, Bruneaux M, Aykanat T, Vanoverbeke J, et al. 2014. Gene pleiotropy constrains gene expression changes in fish adapted to different thermal conditions. *Nat. Commun.* 5:4071
Pavey SA, Sevellec M, Adam W, Normandeau E, Lamaze FC, et al. 2013. Nonparallelism in MHCIIβ diversity accompanies nonparallelism in pathogen infection of lake whitefish (*Coregonus clupeaformis*) species pairs as revealed by next-generation sequencing. *Mol. Ecol.* 22:3833–49
Pérez-Pereira N, Quesada H, Caballero A. 2017. Can parallel ecological speciation be detected with phylogenetic analyses? *Mol. Phylogenetics Evol.* 116:149–56
Perreault-Payette A, Muir AM, Goetz F, Perrier C, Normandeau E, et al. 2017. Investigating the extent of parallelism in morphological and genomic divergence among lake trout ecotypes in Lake Superior. *Mol. Ecol.* 26:1477–97
Perrier C, Bourret V, Kent MP, Bernatchez L. 2013. Parallel and nonparallel genome-wide divergence among replicate population pairs of freshwater and anadromous Atlantic salmon. *Mol. Ecol.* 22:5577–93
Pfenninger M, Patel S, Arias-Rodriguez L, Feldmeyer B, Riesch R, Plath M. 2015. Unique evolutionary trajectories in repeated adaptation to hydrogen sulphide-toxic habitats of a neotropical fish (*Poecilia mexicana*). *Mol. Ecol.* 24:5446–59
Pujolar JM, Ferchaud AL, Bekkevold D, Hansen MM. 2017. Non-parallel divergence across freshwater and marine three-spined stickleback *Gasterosteus aculeatus* populations. *J. Fish Biol.* 91:175–94
Ramiro RS, Costa H, Gordo I. 2016. Macrophage adaptation leads to parallel evolution of genetically diverse *Escherichia coli* small-colony variants with increased fitness in vivo and antibiotic collateral sensitivity. *Evol. Appl.* 9:994–1004
Ravinet M, Westram A, Johannesson K, Butlin R, Andre C, Panova M. 2016. Shared and nonshared genomic divergence in parallel ecotypes of *Littorina saxatilis* at a local scale. *Mol. Ecol.* 25:287–305
Rensch B. 1939. Typen der Artbildung. *Biol. Rev.* 14:180–222

Rinkevich B. 2005. Conservation of coral reefs through active restoration measures: recent approaches and last decade progress. *Environ. Sci. Technol.* 39:4333–42
Roberge C. 2006. Rapid parallel evolutionary changes of gene transcription profiles in farmed Atlantic salmon. *Mol. Ecol.* 15:9–20
Roda F, Walter GM, Nipper R, Ortiz-Barrientos D. 2017. Genomic clustering of adaptive loci during parallel evolution of an Australian wildflower. *Mol. Ecol.* 14:3687–99
Roesti M, Moser D, Berner D. 2013. Recombination in the threespine stickleback genome–patterns and consequences. *Mol. Ecol.* 22:3014–27
Rokas A, Carroll SB. 2008. Frequent and widespread parallel evolution of protein sequences. *Mol. Biol. Evol.* 25:1943–53
Rosenblum EB, Harmon LJ. 2011. "Same same but different": replicated ecological speciation at White Sands. *Evolution* 65:946–60
Rosenblum EB, Parent CE, Brandt EE. 2014. The molecular basis of phenotypic convergence. *Annu. Rev. Ecol. Evol. Syst.* 45:203–26
Rosenblum EB, Römpler H, Schöneberg T, Hoekstra HE. 2010. Molecular and functional basis of phenotypic convergence in white lizards at White Sands. *PNAS* 107:2113–17
Sailer ZR, Harms MJ. 2017. Molecular ensembles make evolution unpredictable. *PNAS* 114:11938–43
Samuk K, Owens GL, Delmore KE, Miller SE, Rennison DJ, Schluter D. 2017. Gene flow and selection interact to promote adaptive divergence in regions of low recombination. *Mol. Ecol.* 26:4378–90
Schmutz J, McClean PE, Mamidi S, Wu GA, Cannon SB, et al. 2014. A reference genome for common bean and genome-wide analysis of dual domestications. *Nat. Genet.* 46:707–13
Scotland RW. 2011. What is parallelism? *Evol. Dev.* 13:214–27
Shindo C, Aranzana MJ, Lister C, Baxter C, Nicholls C, et al. 2005. Role of *FRIGIDA* and *FLOWERING LOCUS C* in determining variation in flowering time of Arabidopsis. *Plant Physiol.* 138:1163–73
Shpak M, Lu J. 2016. An evolutionary genetic perspective on cancer biology. *Annu. Rev. Ecol. Evol. Syst.* 47:25–49
Siepielski AM, DiBattista JD, Carlson SM. 2009. It's about time: the temporal dynamics of phenotypic selection in the wild. *Ecol. Lett.* 12:1261–76
Simpson GG. 1953. *The Major Features of Evolution*. New York: Columbia Univ. Press
Simpson GG. 1961. *Principles of Animal Taxonomy*. New York: Columbia Univ. Press
Siwertsson A, Knudsen R, Adams CE, Praebel K, Amundsen PA. 2013. Parallel and non-parallel morphological divergence among foraging specialists in European whitefish (*Coregonus lavaretus*). *Ecol. Evol.* 3:1590–602
Slatkin M. 1985. Gene flow in natural populations. *Annu. Rev. Ecol. Syst.* 16:393–430
Speed MP, Arbuckle K. 2017. Quantification provides a conceptual basis for convergent evolution. *Biol. Rev.* 92:815–29
Stayton CT. 2008. Is convergence surprising? An examination of the frequency of convergence in simulated datasets. *J. Theor. Biol.* 252:1–14
Stockwell CA, Hendry AP, Kinnison MT. 2003. Contemporary evolution meets conservation biology. *Trends Ecol. Evol.* 18:94–101
Storz JF. 2016. Causes of molecular convergence and parallelism in protein evolution. *Nat. Rev. Genet.* 17:239–50
Stuart YE, Veen T, Weber JN, Hanson D, Lohman BK, et al. 2017. Contrasting effects of environment and genetics generate a continuum of parallel evolution. *Nat. Ecol. Evol.* 1:158
Sturm RA, Duffy DL. 2012. Human pigmentation genes under environmental selection. *Genome Biol.* 13:248
Swanton C. 2014. Cancer evolution: the final frontier of precision medicine? *Ann. Oncol.* 25:549–51
Szendro IG, Franke J, de Visser JAGM, Krug J. 2013. Predictability of evolution depends nonmonotonically on population size. *PNAS* 110:571–76
Takahashi K, Kohno T, Matsumoto S, Nakanishi Y, Arai Y, et al. 2007. Clonal and parallel evolution of primary lung cancers and their metastases revealed by molecular dissection of cancer cells. *Hum. Cancer Biol.* 13:111–20
Takuno S, Ralph P, Swarts K, Elshire RJ, Glaubitz JC, et al. 2015. Independent molecular basis of convergent highland adaptation in maize. *Genetics* 207:1297–312

Tegze B, Szállási Z, Haltrich I, Pénzváltó Z, Tóth Z, et al. 2012. Parallel evolution under chemotherapy pressure in 29 breast cancer cell lines results in dissimilar mechanisms of resistance. *PLOS ONE* 7:e30804
Tellier A, Brown JK. 2007. Polymorphism in multilocus host parasite coevolutionary interactions. *Genetics* 177:1777–90
Tenaillon O, Barrick J, Ribeck N, Deatherage DE, Blanchard JL, et al. 2016. Tempo and mode of genome evolution in a 50,000-generation experiment. *Nature* 536:165–70
Terekhanova NV, Logacheva MD, Penin AA, Neretina TV, Barmintseva AE, et al. 2014. Fast evolution from precast bricks: genomics of young freshwater populations of threespine stickleback *Gasterosteus aculeatus*. *PLOS Genet*. 10:e1004696
Thompson C, Ahmed N, Veen T, Peichel CL, Hendry AP, et al. 2017. Many-to-one form-to-function mapping weakens parallel morphological evolution. *Evolution* 71:2738–49
Thompson CE, Taylor EB, McPhail JD. 1997. Parallel evolution of lake-stream pairs of threespine sticklebacks (*Gasterosteus*) inferred from mitochondrial DNA variation. *Evolution* 51:1955–65
Torriani SFF, Brunner PC, McDonald BA, Sierotzki H. 2008. QoI resistance emerged independently at least 4 times in European populations of *Mycosphaerella graminicola*. *Pest Manag. Sci.* 65:155–62
Vavilov NI. 1922. The law of homologous series in variation. *J. Genet.* 12:47–89
Velotta JP, Wegrzyn JL, Ginzburg S, Kang L, Czesny S, et al. 2017. Transcriptomic imprints of adaptation to fresh water: parallel evolution of osmoregulatory gene expression in the Alewife. *Mol. Ecol.* 26:831–48
Vogwill T, Kohadinovic M, Furió V, MacLean RC. 2014. Testing the role of genetic background in parallel evolution using the comparative experimental evolution of antibiotic resistance. *Mol. Biol. Evol.* 31:3314–23
Wainwright PC. 1996. Ecological explanation through functional morphology: the feeding biology of sunfishes. *Ecology* 77:1336–43
Wainwright PC, Alfaro M, Bolnick DI, Hulsey CD. 2005. Many-to-one mapping of form to function: a general principle in organismal design. *Integr. Comp. Biol.* 45:256–62
Wake DB. 1999. Homoplasy, homology and the problem of 'sameness' in biology. In *Homology*, ed. GR Bock, G Cardew, pp. 24–46. New York: Wiley
Wake DB, Wake MH, Specht CD. 2011. Homoplasy: from detecting pattern to determining process and mechanism of evolution. *Science* 331:1032–35
Walker JA. 2007. A general model of functional constraints on phenotypic evolution. *Am. Nat.* 170:681–89
Westram AM, Galindo J, Rosenblad MA, Grahame JW, Panova M, Butlin RK. 2014. Do the same genes underlie parallel phenotypic divergence in different *Littorina saxatilis* populations? *Mol. Ecol.* 23:4603–16
Whitlock MC, Gomulkiewicz R. 2005. Probability of fixation in a heterogeneous environment. *Genetics* 171:1407–17
Wichman HA, Badgett MR, Scott LA, Boulianne CM, Bull JJ. 1999. Divergent trajectories of parallel evolution during viral adaptation. *Science* 285:422–24
Wilson HV. 1941. The recapitulation theory or biogenetic law in embryology. *Am. Nat.* 75:20–30
Yeaman S, Hodgins KA, Lotterhos KE, Suren H, Nadeau S, et al. 2016. Convergent local adaptation to climate in distantly related conifers. *Science* 353:1431–33

Annual Review of Ecology, Evolution, and Systematics

Volume 49, 2018

Contents

Behavioral Isolation and Incipient Speciation in Birds
J. Albert C. Uy, Darren E. Irwin, and Michael S. Webster 1

The Ecology and Evolution of Alien Plants
Mark van Kleunen, Oliver Bossdorf, and Wayne Dawson 25

Biodiversity and Functional Ecology of Mesophotic Coral Reefs
Michael P. Lesser, Marc Slattery, and Curtis D. Mobley 49

Evolutionary Conflict
David C. Queller and Joan E. Strassmann 73

Evaluating Model Performance in Evolutionary Biology
Jeremy M. Brown and Robert C. Thomson 95

Plant Secondary Metabolite Diversity and Species Interactions
André Kessler and Aino Kalske 115

Variation and Evolution of Function-Valued Traits
Richard Gomulkiewicz, Joel G. Kingsolver, Patrick A. Carter, and Nancy Heckman 139

Climate Change and Phenological Mismatch in Trophic Interactions Among Plants, Insects, and Vertebrates
Susanne S. Renner and Constantin M. Zohner 165

Bivalve Impacts in Freshwater and Marine Ecosystems
Caryn C. Vaughn and Timothy J. Hoellein 183

Uses and Misuses of Environmental DNA in Biodiversity Science and Conservation
Melania E. Cristescu and Paul D.N. Hebert 209

Frontiers in Metapopulation Biology: The Legacy of Ilkka Hanski
Otso Ovaskainen and Marjo Saastamoinen 231

Integrating Networks, Phylogenomics, and Population Genomics for the Study of Polyploidy
Paul D. Blischak, Makenzie E. Mabry, Gavin C. Conant, and J. Chris Pires 253

Ecological Response to Permafrost Thaw and Consequences for Local and Global Ecosystem Services
Edward A.G. Schuur and Michelle C. Mack 279

(Non)Parallel Evolution
Daniel I. Bolnick, Rowan D.H. Barrett, Krista B. Oke, Diana J. Rennison, and Yoel E. Stuart 303

Mechanisms of Plastic Rescue in Novel Environments
Emilie C. Snell-Rood, Megan E. Kobiela, Kristin L. Sikkink, and Alexander M. Shephard 331

Challenging Dogma Concerning Biogeographic Patterns of Antarctica and the Southern Ocean
Kenneth M. Halanych and Andrew R. Mahon 355

Dinosaur Macroevolution and Macroecology
Roger B.J. Benson 379

Life in Dry Soils: Effects of Drought on Soil Microbial Communities and Processes
Joshua P. Schimel 409

Using Genomic Data to Infer Historic Population Dynamics of Nonmodel Organisms
Annabel C. Beichman, Emilia Huerta-Sanchez, and Kirk E. Lohmueller 433

The Contemporary Evolution of Fitness
Andrew P. Hendry, Daniel J. Schoen, Matthew E. Wolak, and Jane M. Reid 457

The Deep Past Controls the Phylogenetic Structure of Present, Local Communities
Pille Gerhold, Marcos B. Carlucci, Şerban Procheş, and Andreas Prinzing 477

Development and Evolutionary Constraints in Animals
Frietson Galis, Johan A.J. Metz, and Jacques J.M. van Alphen 499

Indexes

Cumulative Index of Contributing Authors, Volumes 45–49 523

Cumulative Index of Article Titles, Volumes 45–49 527

Errata

An online log of corrections to *Annual Review of Ecology, Evolution, and Systematics* articles may be found at http://www.annualreviews.org/errata/ecolsys