per million years) but could not generate diversity trajectories with temporally symmetrical waxing and waning phases nor the switch in the magnitudes of the initial origination and extinction rates with their final rates (*10*). Instead, clades quickly reached equilibrium diversity and then slowly rode the decaying equilibrium diversity down to extinction—the decline phase was longer than the diversification phase, and the final origination and extinction rates remained at intermediate values between the high initial origination rate and the low initial extinction rate, rather than switching in value.

The only way to accommodate the observed diversity dynamics is if the intrinsic diversification rate (and thus the equilibrium diversity) deteriorated sufficiently fast. For example, when we modeled the decay in the intrinsic diversification at a rate of ~3% per million years, the clade was left with a standing diversity that increasingly lagged behind the equilibrium diversity as the clade went extinct (Fig. 3C). This resulted in the switching in the values of the initial and final per-genus origination and extinction rates and led to a sufficiently negative diversification rate during the clade's decline to produce the temporally symmetric waxing and waning phases of diversity change.

An unexpected consequence of the rapid decline in the per-genus rate of diversification is that a clade's diversity only transiently equals the equilibrium diversity. In contrast, in typical diversity-dependent models, species diversity remains at or close to the equilibrium diversity after the initial radiation, even when the equilibrium diversity decays with time, for example, as in Whittaker *et al.*'s modeling of the disappearance of islands through erosion (*18*, *19*). Under our model, the diversification phase involves a gain toward an equilibrium diversity, as in standard logistic growth. However, as diversity increases, the equilibrium diversity is decaying in response to an already deteriorating environment, and the clade reaches its peak diversity at an equilibrium value less than the initial equilibrium diversity. Then, as the clade moves into the decline phase, the decay in its intrinsic rate of diversification leads to a sufficiently rapid decrease in its equilibrium diversity that the clade's realized diversity increasingly lags behind the decaying equilibrium diversity (Fig. 3). Thus, although diversity dependence in the per-genus origination and extinction rates plays a role in determining the duration of the clade's history, the diversity dynamics is dominated by the decay in the intrinsic diversification rates, not by the diversity-dependent equilibrium processes.

The secondary role that diversity-dependent rates of origination and extinction play in the diversity dynamics of the mammalian clades in decline offers a resolution to a debate in the paleontological literature, where diversity dependence has been proposed (*13*, *20*) but where the evidence of equilibrium is scarce (*21*–*23*). In our model, the mechanism of diversity dependence is decoupled from the ultimate factors that determine the clades' fates: the deterioration of their environment. Our results suggest that diversity dependence plays a role in diversity dynamics similar to the role that friction plays in the dynamics of motion—although it must be accounted for in the dynamics of diversity change, the dominant forces of diversity change lie beyond the existence of diversity dependence.

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Exceptional Convergence on the Macroevolutionary Landscape in Island Lizard Radiations

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G. G. Simpson, one of the chief architects of evolutionary biology's modern synthesis, proposed that diversification occurs on a macroevolutionary adaptive landscape, but landscape models are seldom used to study adaptive divergence in large radiations. We show that for Caribbean *Anolis* lizards, diversification on similar Simpsonian landscapes leads to striking convergence of entire faunas on four islands. Parallel radiations unfolding at large temporal scales shed light on the process of adaptive diversification, indicating that the adaptive landscape may give rise to predictable evolutionary patterns in nature, that adaptive peaks may be stable over macroevolutionary time, and that available geographic area influences the ability of lineages to discover new adaptive peaks.

The concept of a macroevolutionary adaptive landscape—a multivariate phenotype surface on which species evolve up local adaptive peaks—has guided thinking about adaptive radiation since G. G. Simpson proposed it in 1944 (*1*–*4*). Although influential as a metaphor, Simpson's landscape has only rarely been applied to study large adaptive radiations in nature. Moreover, when applied the macroevolutionary landscape generally has been invoked to describe evolutionary dynamics within a single lineage in a particular ecological setting. In recent years, however, a number of studies have suggested that entire evolutionary radiations can exhibit phenotypic convergence when they diversify in similar environments (*5*–*10*). To the extent that such

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"replicated adaptive radiations" exist (*11*), they suggest not only that diversification over macro-evolutionary time scales may be surprisingly deterministic but also that ecological factors can give rise to highly similar adaptive landscapes in geographically distinct regions (*1*, *2*, *12*).

Laboratory investigations of microbial divergence (*13*) and computer simulation studies (*1*) both suggest that stable adaptive landscapes can generate predictable evolutionary patterns, but testing this hypothesis in naturally evolving radiations requires the comparison of adaptive landscapes over macroevolutionary time scales. Investigations of this type require a two-step process in which we first test the hypothesis that radiations are more convergent than expected by chance (*11*), and then we ask if this convergence has resulted from diversification on similar macroevolutionary landscapes.

We used this approach to study the putative replicated adaptive radiations (*2*, *14*) of *Anolis* lizards (anoles) on Caribbean islands. On each island in the Greater Antilles (Cuba, Hispaniola, Puerto Rico, and Jamaica), anoles have independently evolved a similar set of habitat specialists termed "ecomorphs" (such as "twig" or "grass-bush") (*14*, *15*). Each ecomorph is composed of morphologically and behaviorally similar species that occupy similar microhabitats. Prior studies have documented that members of the same ecomorph category from different islands cluster morphologically, providing evidence for repeated

instances of convergent evolution (*16*). However, these analyses omitted an important dimension of the anole radiations: so-called "unique" species that evolved a morphology and ecology not found on other islands (*14*, *15*). The number of unique species varies among islands, from none on Puerto Rico to 14 on Cuba, and they collectively constitute approximately 20% of Greater Antillean *Anolis* diversity. Thus, although repeated evolution of the ecomorphs has been demonstrated, whether the anole radiations themselves are convergent remains an open question.

Thus, we began by asking whether the four Greater Antillean anole faunas exhibit exceptional species-for-species matching (*2*); i.e., greater pairwise phenotypic similarity between species on different islands than expected by chance, when the full ecomorphological diversity of lineages is considered. We compiled phylogenetic and phenotypic data for 100 of 119 Greater Antillean *Anolis* species, representing the diversity of both the ecomorph and unique species. We tested for species-for-species matching among islands using a phylogenetic comparative analysis of species similarity in a four-dimensional principal components morphospace generated from 11 traits important for niche partitioning in *Anolis*, including body size, limb and tail lengths, and adhesive toepad lamella number (*14*, *17*). We measured the among-island Euclidean distance between each species and its nearest neighbor from each other

island in morphospace, and assessed whether the average among-island distance for anoles was lower than expected by chance via comparison to a phylogenetic null distribution (*18*). We simulated null morphospaces using the empirical maximum clade credibility (MCC) phylogeny from a Bayesian analysis of mitochondrial DNA and evolutionary models that account for temporal and among-trait evolutionary rate variation (*17*, *19*). We repeated the analysis across a Bayesian posterior tree sample, obtaining qualitatively identical results (*18*). These analyses provide strong evidence for exceptional species-for-species matching among island anole faunas: Most species on each island are more morphologically similar to species from other islands than expected by chance ($P = 0.003$; Fig. 1A).

Next, we investigated whether a macroevolutionary model involving convergent shifts to common peaks on a Simpsonian landscape can explain the evolution of remarkably similar faunas on these four Caribbean islands. We applied a new method (SURFACE) to infer the history of adaptive diversification in anoles using a phylogeny and phenotypic data. This method fits a model of adaptive radiation in which lineages may undergo shifts to adaptive peaks on a macroevolutionary landscape without reference to a priori hypotheses specifying which lineages correspond to particular peaks (*18*, *20*). In this model, lineages may undergo shifts to otherwise unoccupied peaks or to those shared with other lineages, which gives us the ability to explicitly model the macroevolutionary convergence of independent lineages in a common phenotype space. Starting with an Ornstein-Uhlenbeck model (*21*, *22*) in which all species are attracted to a single adaptive peak in trait space, SURFACE uses a stepwise model selection procedure based on the finite-samples Akaike information criterion (AIC_c) (*23*, *24*) to fit increasingly complex multipeak models. At each step, a new peak shift is added to the branch of the phylogeny that most improves model fit across all traits, and shifts are added until none result in further improvement. To identify convergence, the method then evaluates whether the AIC_c score is further improved by permitting these independent lineages to shift toward shared adaptive peaks rather than requiring each to occupy a unique peak. We compared the convergent landscape model to several alternatives, including three variants of the "early burst" model of adaptive radiation, which features a diversity-dependent decline in evolutionary rate but does not explicitly model adaptation or convergence on a macroevolutionary landscape (*17*, *19*).

A Simpsonian model of peak shifts on a shared macroevolutionary adaptive landscape best explains the evolution of ecomorphological traits in Greater Antillean *Anolis*. Convergence of lineages to shared adaptive peaks was the dominant mode of macroevolutionary trait change for these replicated island radiations: A landscape model with explicit convergence was strongly favored over the best non-convergent landscape model ($\Delta AIC_c = 162.6$;
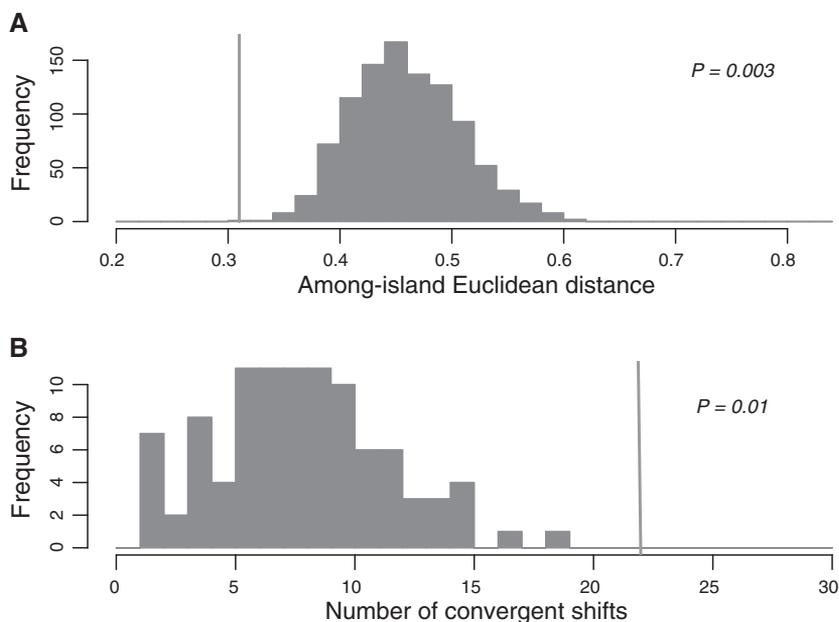

Fig. 1. Morphological similarity among Greater Antillean *Anolis* faunas is due to exceptional convergence. (**A**) Anole species are more similar to their closest matches from other islands than expected by chance. The vertical line indicates the average distance separating each Greater Antillean species from the most morphologically similar species on other islands (among-island Euclidean distance); the histogram depicts a null distribution of the same scores calculated from 999 data sets generated by evolutionary simulation. (**B**) The great inter-island similarity (low distance) results from an exceptionally large number of convergent shifts to shared peaks on a macroevolutionary adaptive landscape during anole diversification. Here, the vertical line depicts the number of convergent peak shifts detected for Greater Antillean anoles, and the histogram depicts a null distribution of convergent shifts detected from 99 simulated data sets.

fig. S2), and even more strongly favored over models without peaks (ΔAIC$_c$ ≥ 279.3; fig. S2). Peak shifts on the adaptive landscape were common as anoles diversified (29 lineage-specific shifts), with 76% of shifts involving convergence in morphospace (Figs. 1B and 2 and Table 1). The estimated landscape contained 15 adaptive peaks, with 8 occupied by more than one lineage. These convergent peaks attracted 2.8 lineages on average, and all but one hosted lineages from multiple islands. Overall, the number of convergent adaptive peak shifts was significantly greater than expected by chance (P = 0.01; Fig. 1B), and these shifts account for the exceptional similarity among island faunas (18). The number and position of peak shifts varied across 100 phylogenies, but the number of convergent shifts was similar for all trees (Table 1). Species traditionally grouped in the same ecomorph class (14–16) tended to be attracted toward the same adaptive peak (fig. S4).

Our comparison of macroevolutionary models suggests that the adaptive landscape plays an important role in shaping parallel diversification. The only model to account for the observed convergence of entire island anole faunas was a Simpsonian model (3, 5, 20–22), in which lineages experience selection toward common peaks on the adaptive landscape (fig. S1). Fitted peaks on the anole landscape correspond to trait combinations that have been shown experimentally to be adaptive for microhabitat partitioning (14) (fig. S4). Although it is possible that evolutionary constraints may play a role in shaping whole-fauna convergence, in the case of anoles the evidence points to a dominant role for selection. The Anolis radiation unfolded over tens of millions of years (14), a time scale over which constraints on the production of variation are unlikely to be maintained, especially for quantitative traits (25). Constraint seems an even less likely culprit considering that diverse radiations of Central and South American Anolis, which occur in ecologically different communities, exhibit many morphologies not seen in Caribbean forms (26), strongly suggesting that repeated Greater Antillean convergence is not due to intrinsic limits on morphological variation.

Replication of adaptive radiations is readily attainable in simple systems over short time scales (2, 13), but convincing examples at a grander macroevolutionary scale have so far been lacking. Why this is the case is not yet clear, but our results argue against the possibility that the temporal lability of adaptive landscapes precludes faunal convergence over long time scales. The Greater Antillean anole radiation is old (with a minimum age of 30 to 40 million years) (14), and most ecomorphological diversity among anoles arose long ago (17) (Fig. 2), suggesting not only that the adaptive landscape for anoles is similar across islands but also that it is relatively static in its principal features (14, 27). Stable landscapes are further indicated by the similarity of adaptive peaks discovered by anole lineages from different islands, which would be highly unlikely if adaptive landscapes were themselves highly labile (3, 27). It

remains to be seen whether this stability is a general feature of adaptive radiation, but our observations support the hypothesis that stable macroevolutionary landscapes underlie the common pattern of long-term phenotypic stasis in both fossil and comparative data sets (28, 29).

Although convergence is the most conspicuous feature of Greater Antillean anole radiations, the island faunas are far from identical. Most no-

tably, we found evidence for a number of non-convergent shifts to island-specific peaks. However, such peaks are occupied only on the larger islands of Hispaniola and Cuba, a predicted "area effect" from adaptive radiation theory (1). Larger areas provide greater opportunities for diversification (1, 30), which may permit lineages to more fully explore the macroevolutionary landscape and discover peaks not reached on smaller islands (1).
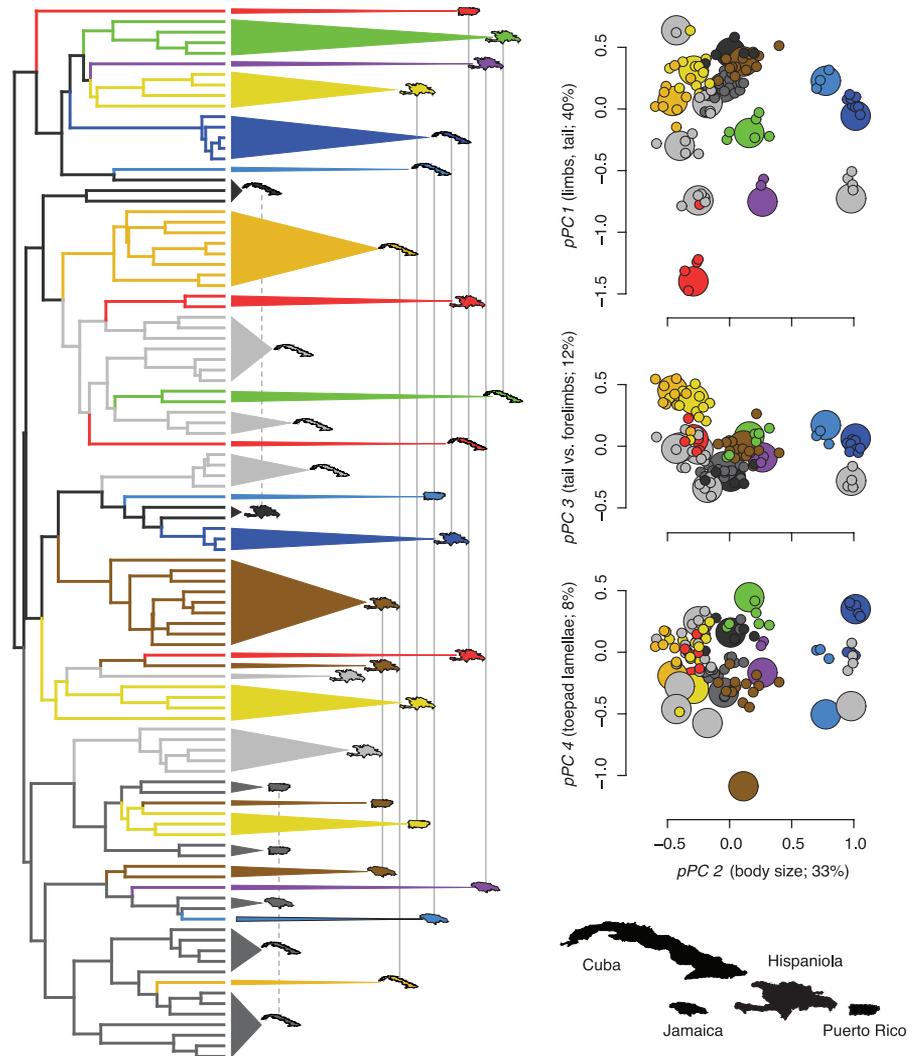

Fig. 2. Phenotypic convergence on the macroevolutionary adaptive landscape in island radiations of Greater Antillean *Anolis*. MCC phylogeny (left panel), painted to depict the estimated phylogenetic history of adaptive peak shifts. Branches and island silhouettes representing geographic location are colored according to adaptive peak. Convergent peaks are colored and are connected by solid lines; with one exception, these peaks attract lineages from multiple islands. Nonconvergent peaks are light gray (single-island radiations), or black or dark gray (radiations that spread to multiple islands; these islands are connected by dashed lines). Right panels show that anole species (small circles) cluster near their inferred adaptive peak (large circles) in morphospace, especially for pPCs 1 to 3 (primary trait correlations and variance explained are reported in the axis labels). Inferred convergent peaks broadly correspond to *Anolis* ecomorph classes, a consistent finding across phylogenies, although specific peak assignments vary from tree to tree (18) (fig. S4). In the MCC estimate plotted here, grass-bush specialists are attracted to dark or light yellow peaks. Larger and smaller twig specialists occur on purple and red peaks, respectively. Green peaks contain trunk-crown specialists, and brown peaks contain trunk-ground specialists. Dark blue peaks contain large crown-giant anoles; light blue peaks contain smaller giant anoles. A single dark gray peak contains additional trunk-ground and trunk-crown species; although similar because of inherited ancestral condition rather than convergence in this reconstruction phenotypically similar species on this peak occur on three different islands.

Table 1. SURFACE convergence parameters estimated using the MCC tree, as well as 100 trees from the Bayesian posterior probability distribution of *Anolis* phylogeny.

	MCC phylogeny	Mean (SD) for 100 sampled phylogenies
Adaptive peak shifts	29	25.7 (2.1)
Convergent adaptive peak shifts	22	20.2 (1.9)
Adaptive peaks	15	12.7 (1.4)
Convergent adaptive peaks	8	7.2 (0.97)
Convergence fraction (convergent peak shifts/total peak shifts)	0.76	0.79 (0.045)
Average number of lineages converging to each shared adaptive peak	2.8	2.8 (0.30)
Fraction of convergent peaks with lineages from multiple islands	0.88	0.94 (0.074)

Anoles have diversified into many more species on the larger islands (*14, 31*). Given the number of convergent and unique adaptive peak shifts that have occurred across the Greater Antilles in anoles, the area effect hypothesis predicts that all endemic unique peaks should occur on Cuba and Hispaniola, as observed (*18*) (fig. S3). Thus, in this system, even the apparently contingent evolution of unique ecomorphologies may be, to some extent, predictable—in this case a result of the speciation-area relationship (*30*).

Gould famously argued that evolution over long time scales is "utterly unpredictable and quite unrepeatable" (*32*, p. 14) due to historical contingency. Widespread convergence among entire faunas of Greater Antillean *Anolis* refutes Gould's claim and shows that adaptation can overcome the influence of chance events on the course of evolution. Our demonstration of deterministic convergence on a macroevolutionary adaptive landscape complements studies of diversification in species numbers in showing that many features of large-scale radiations may be surprisingly predictable. A recent analysis discovered that both island diversification rate and standing species richness in Greater Antillean anoles could be predicted from island size and time since colonization (*31*). In cichlids, whether colonizing lineages will radiate in African lakes can be predicted from the intrinsic traits of the colonist and the ecological opportunities provided by the new habitat (*33*). Together, these studies suggest that the primary aspects of evolutionary radiation—adaptation and the proliferation of species—may in some cases be largely deterministic.

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Predicting and Manipulating Cardiac Drug Inactivation by the Human Gut Bacterium *Eggerthella lenta*

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Despite numerous examples of the effects of the human gastrointestinal microbiome on drug efficacy and toxicity, there is often an incomplete understanding of the underlying mechanisms. Here, we dissect the inactivation of the cardiac drug digoxin by the gut Actinobacterium *Eggerthella lenta*. Transcriptional profiling, comparative genomics, and culture-based assays revealed a cytochrome-encoding operon up-regulated by digoxin, inhibited by arginine, absent in nonmetabolizing *E. lenta* strains, and predictive of digoxin inactivation by the human gut microbiome. Pharmacokinetic studies using gnotobiotic mice revealed that dietary protein reduces the in vivo microbial metabolism of digoxin, with significant changes to drug concentration in the serum and urine. These results emphasize the importance of viewing pharmacology from the perspective of both our human and microbial genomes.

Humans are home to large and diverse microbial communities, the most abundant of which resides in the gastrointestinal tract. Recent studies have highlighted the clinical relevance of the biotransformations catalyzed by the human gut microbiome, including alterations to the bioavailability, activity, and toxicity of therapeutic drugs (*1, 2*). Although >40 drugs are metabolized by the gut microbiome, little is known about the underlying mechanisms. This