

the frequency band where natural flowers move. One reason moths might rely on both temporal and spatial adjustments to deal with low light (10) is to limit the costs to both motion-tracking performance and spatial resolution.

The frequencies with which a moth can maneuver could provide a selective pressure on the biomechanics of flowers to avoid producing floral movements faster than those that the moth can track in low light (22). The converse interaction—flower motions selecting on the moth—could also be important, suggesting a coevolutionary relationship between pollinator and plant that extends beyond color, odor, and spatial features (23) to include motion dynamics.

The emerging use of system identification to connect open- and closed-loop experiments (6, 14, 15, 18, 24, 25) provides a useful paradigm for exploring sensorimotor strategies in many systems. Robotic models enable rapid, repeatable experiments that extract critical features of the biological system (26) and extend the physical modeling toolkit that has been useful for teasing apart pollinator-plant interactions (7, 9, 23). Here the robotic flower enabled us to test predictions about closed-loop behavior from open-loop electrophysiological results and models of neural processing (6, 15).

The dual demands of acquiring reliable sensory information and maintaining motor performance are a general challenge, especially for animals such as *Manduca*, which operate in impoverished sensory environments (4–6, 27) and on the edge of flight instability (6, 25). Matching the requirements of the motor system to constraints imposed by the dynamics of the environment can provide strategies that enable more extreme sensory performance while averting tradeoffs in motor performance.

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ACKNOWLEDGMENTS

J. Riffell kindly provided the artificial *Datura wrightii* scent. We are also grateful for valuable contributions from J. Lockey, M. Salcedo, S. Kazi, A. Molback, A. Hinterwirth, A. Mountcastle, E. Roth, and N. Cowan. Data are available on Dryad, accession no. 10.5061/dryad.jd7b9. This project was supported by the Komen Endowed Chair, an Air Force Research Laboratory grant (FA8651-13-1-0004), an Office of Naval Research Multi University Research Initiative grant (N00014-10-1-0952), an Army Research Office grant (W911NF-13-1-0435), and an Air Force Office of Scientific Research grant (FA9550-14-1-0398) to T.L.D. and by NSF fellowship DBI-1103768 to J.P.D.

SUPPLEMENTARY MATERIALS

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26 November 2014; accepted 29 April 2015
10.1126/science.aaa3042

BIOGEOGRAPHY

The dispersal of alien species redefines biogeography in the Anthropocene

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It has been argued that globalization in human-mediated dispersal of species breaks down biogeographic boundaries, yet empirical tests are still missing. We used data on native and alien ranges of terrestrial gastropods to analyze dissimilarities in species composition among 56 globally distributed regions. We found that native ranges confirm the traditional biogeographic realms, reflecting natural dispersal limitations. However, the distributions of gastropods after human transport are primarily explained by the prevailing climate and, to a smaller extent, by distance and trade relationships. Our findings show that human-mediated dispersal is causing a breakdown of biogeographic barriers, and that climate and to some extent socioeconomic relationships will define biogeography in an era of global change.

The reduced similarity in species composition between distant locations is one of the most noticeable patterns in nature (1–3). Dispersal limitation is at the heart of this pattern, either simply because of the accessibility of nearby locations or because environmental factors of ecophysiological importance tend to be spatially autocorrelated within the

range of natural dispersal (4). Notwithstanding, human trade and travel have been transgressing natural barriers to dispersal (5), and increasing numbers of species are becoming established in places far away from their native range (6, 7). Ultimately, this may cause the breakdown of the “classical” biogeographic regions (8)—mainly determined by dispersal barriers and historical factors such as continental drift or paleoclimates—and the emergence of new biogeographic arrangements determined primarily by environmental requirements and by geographic patterns in human transport pathways.

In recent centuries, and particularly during the past few decades, transport pathways have intensified in frequency and extended worldwide (5, 9). This accelerates the speed at which species colonize suitable areas across the globe and inherently contributes to the homogenization of species assemblages at a global scale (10–12). Niche theory and metacommunity theory suggest that the

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breakdown of geographic dispersal barriers will allow species to progressively occupy their potential environmental niche (2, 13, 14), although other factors, such as the biotic composition of the receiving communities, may also play a role (15). This dispersal release should give rise to coherent spatial units reflecting environmental similarities among regions, and climatic similarities in particular (16, 17). Despite a strong theoretical rationale, clear evidence of a global, climate-filtered, biogeographic regionalization originated by human activity is still lacking.

Here, we report the results of a global-scale analysis comparing the biogeographic patterns of terrestrial alien gastropods before and after dispersal by humans. In contrast to most previous studies of biotic homogenization, our analysis is

global and therefore particularly appropriate to test the climate filter hypothesis. Regional studies capture only a fraction of worldwide climatic variation and are thus more likely to miss climatic signals. We also expect that increases in distributional equilibrium with climate should be particularly apparent for terrestrial gastropods because they are frequently introduced over long distances by means of trade (18, 19).

We collected national and subnational species lists of alien terrestrial gastropods, here defined as established alien species originating from human introductions after 1500 CE. We found data for regions across all continents except Antarctica, representing most of the major climatic types and biogeographic realms of the world (fig. S1 and table S1). For each alien species, we also identified

from the literature those regions in our data set that belong to their native range (fig. S2) (20). For simplicity, native range was defined as any location in which the species occurred before 1500 CE. This eventually may have led to the inclusion of a few locations to which the species were introduced earlier; however, those introductions have likely occurred within biogeographic realms (5, 9). Our alien distribution data set contained 802 occurrence records spread across 56 countries and subnational entities (e.g., federal states, islands), for a total of 175 species. The native distribution data set represented a subset of 140 species and 45 countries and subnational entities and contained 703 occurrence records.

We quantified pairwise compositional dissimilarity of the species lists in two ways: (i)

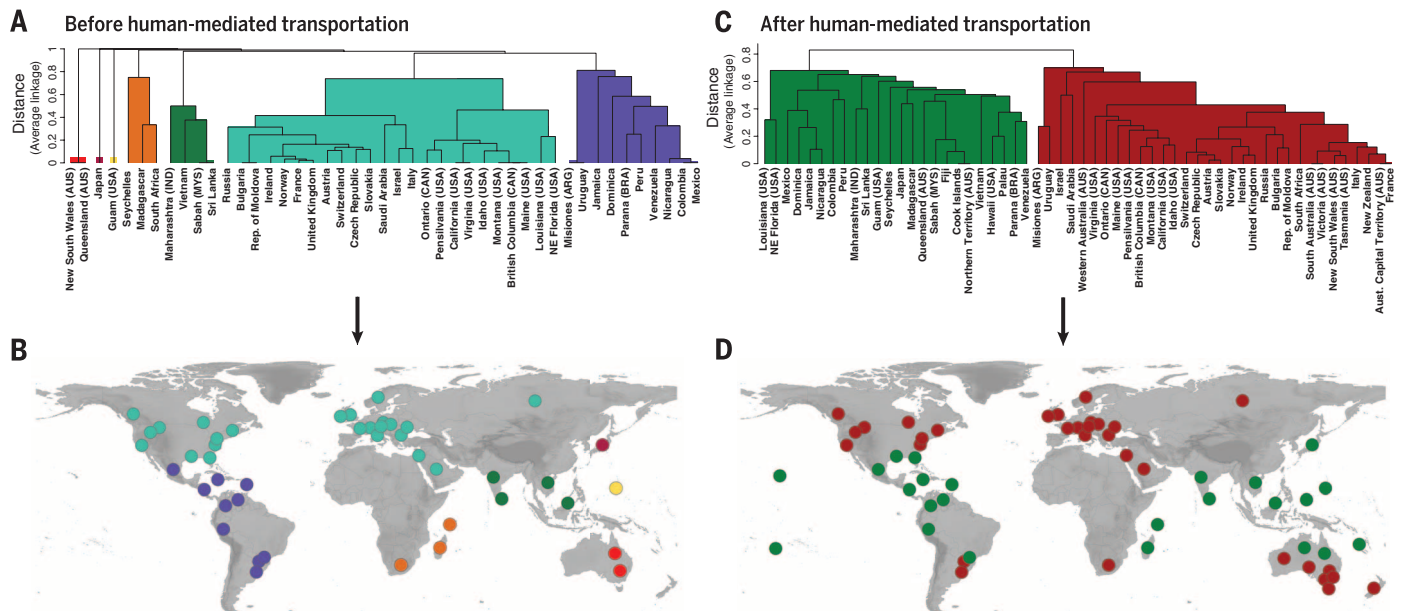
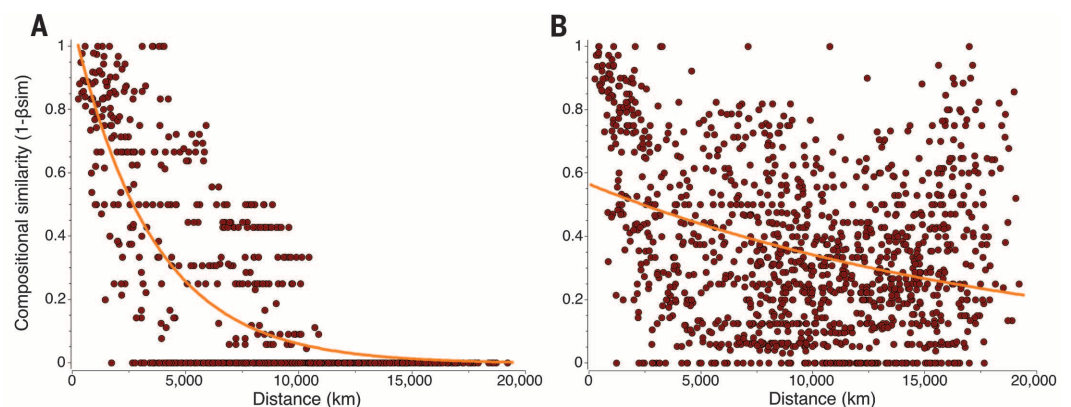


Fig. 1. Dendrogram and map of compositional similarities among lists of alien terrestrial gastropods. (A and B) Before dispersal by humans. (C and D) After dispersal by humans. Compositional dissimilarity was measured by the β_{sim} index. Clusters were built through the minimization of the average compositional dissimilarity of one location to the others [i.e., UPGMA (unweighted pair group method with arithmetic mean) grouping]. Colors indicate main clusters identified by the dendrogram and their corresponding locations in the world map.

Fig. 2. Relationship between compositional similarities of lists of alien terrestrial gastropods and geographical distances. (A) In native ranges. (B) In current ranges. Compositional similarities were measured by $1 - \beta_{sim}$. Relationship of compositional similarity for species in their native ranges was assessed on the basis of 990 unique pairs of 45 countries and subnational entities. Relationship for species in their current ranges is based on 1540 unique pairs of 56 countries and subnational entities. Model fits of exponential decay of compositional similarity with increasing distance are shown (orange). Model coefficients are provided in the text; tests of significance were obtained by comparison with distribution of coefficients generated from 1000 permutations of the matrix of compositional similarities.



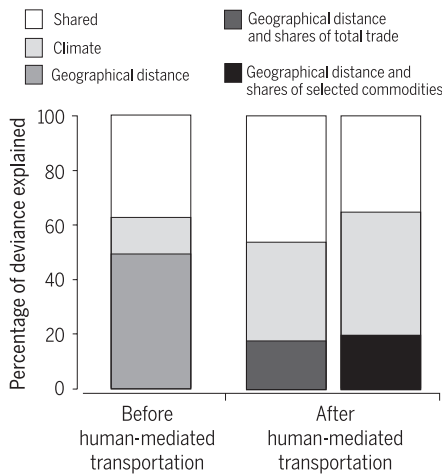


Fig. 3. Proportion of deviance explained in compositional dissimilarity of lists of alien terrestrial gastropods.

Proportions are given for species in native ranges (i.e., before dispersal by humans; left bar) and for species in current ranges (i.e., after dispersal by humans; middle and right bars) and represent deviance that is explained by (i) climate- and dispersal-related predictors combined (white), (ii) climate alone (lighter gray), (iii) geographical distance alone (representing natural dispersal; mid-gray), and (iv) geographical distance and trade shares (representing anthropogenic dispersal) combined (darker gray and black). Climate is characterized by prevailing values of four variables: annual mean temperature, temperature seasonality, annual precipitation, and precipitation seasonality.

using only the native distribution, representing the spatial arrangement before human-mediated dispersal, and (ii) using both native and alien distribution, representing their current distribution. Dissimilarity was measured by the β_{sim} index (figs. S3 and S4). This is a standard metric in biogeographic studies (3, 27) because it accounts for differences in species richness. For each of the two dissimilarity matrices, we used an agglomerative hierarchical clustering algorithm (table S3) and nonmetric multidimensional scaling to analyze compositional dissimilarities among the lists (20).

Results from both analyses show that native-only distributions reflect “classical” broad-scale biogeographic patterns, which arose over geological time scales (Fig. 1A and fig. S5). For example, faunas located in the Australian, African, Oriental, Neotropical, and Holarctic biogeographic realms become clearly differentiated (Fig. 1, A and B) (1–3). Moreover, the compositional similarity (i.e., $1 - \beta_{sim}$) distinctly decreases with increasing geographical distance, indicating that dispersal limitations largely control these patterns (Fig. 2A, exponential decay rate of compositional similarity per 1000 km = -0.29 , $P < 0.001$). Highly similar species compositions ($1 - \beta_{sim} > 0.5$) do not occur at distances greater than ~ 6500 km, and none of the represented species are shared beyond $\sim 11,000$ km.

Combining the native and alien distributions of gastropods changes the grouping patterns: Species lists from temperate regions cluster into one group, while lists from tropical and subtropical regions cluster into another group (Fig. 1, C and D, and fig. S6). For example, regions in temperate North America (e.g., Virginia, California, British Columbia) have, on average, a higher proportion of species shared with sites in other temperate but distant regions of the world, such as Europe, New Zealand, southern Australia, or South Africa, than with “nearby” (sub)tropical regions such as Florida, Louisiana, México, or Jamaica. This bipartite division of species compositions into two latitudinal biogeographic regions—a (sub)tropical belt and a region composed by temperate to arctic areas in both hemispheres (Fig. 1D) (2)—suggests a reorganization of species distributions constrained only by climate. Within each of these broad regions, compositional differences and geographical proximity remain associated (see subclusters in Fig. 1C); however, at the global scale, the arrival of aliens leads to the weakening of the distance decay of similarity (Fig. 2B, exponential decay rate of compositional similarity per 1000 km = -0.05 , $P < 0.001$) and to the occurrence of highly similar species compositions ($1 - \beta_{sim} > 0.5$) along the whole range of geographical distances (i.e., up to $\sim 19,000$ km).

To explicitly test for the role of climate in shaping biogeographic changes, we tested climate as a predictor for compositional dissimilarity before and after human-mediated dispersal. For species in native ranges (i.e., before human transportation), we compared the explanatory power of climate (as represented by prevailing values of annual means and seasonality of temperature and precipitation) (20) with that of geographical distances (which we assume to represent dispersal limitations) (4). For the analysis of combined native and alien distributions (i.e., after human dispersal), we additionally accounted for the role of anthropogenic dispersal. Because global patterns of introduction of terrestrial gastropods are primarily determined by commodity trading (18, 19), we used bilateral trade shares as proxy. We calculated this variable in two alternative ways: (i) considering all traded commodities (a general indicator of trade integration among the countries), and (ii) considering only those commodities that are known vectors of gastropods (e.g., household tiles, live plants, or fresh vegetables and fruits for consumption) (18, 20). Because bilateral trade data are not available for most subnational entities, the tests were performed using country-level data representative of the biogeographic groupings identified above (figs. S7 to S12) (20).

Monte Carlo permutation of generalized dissimilarity models (22) shows that climate and geographical distance are both significant predictors of native-range compositional dissimilarities ($P < 0.001$) (20), accounting together for about 61% of total deviance. However, the partitioning into unique and shared components of the factors (20) reveals that the unique explan-

atory power of geographical distance (representing dispersal limitation) is much greater (proportion of total explained deviance = 49.5%) than that of climate (proportion of total explained deviance = 13.3%) (Fig. 3). In contrast, for the current distribution of gastropods (i.e., including both native and alien ranges), climate rather than dispersal becomes the most important predictor. More specifically, when used jointly, both climate- and dispersal-related variables (i.e., geographical distances and trade shares) are significant predictors of current patterns of compositional dissimilarity ($P < 0.001$), accounting for about 63% of its total deviance. But the unique contribution of climate to the total explained is now about 2 to 2.3 times that of the unique contribution of dispersal (climate = 36.4% and dispersal represented by geographical distance and shares of selected commodities = 19.6%) (Fig. 3). We cannot exclude the possibility that anthropogenic dispersal pathways that covary with climate (23) may also have contributed to the formation of this pattern; however, the reduced relative influence of dispersal-related variables in explaining current distribution patterns suggests that this process, if causative, is of moderate importance.

Signs of ongoing and intensifying biodiversity change are increasingly ubiquitous (24, 25). Still, a recent global analysis of monitoring studies found no significant changes in local species richness, but instead a strong temporal species turnover (6). Human-mediated dispersal of species has already caused substantial biotic intermixing worldwide (12, 26, 27) and may contribute to this turnover. Biotic intermixing is predicted to continue or even intensify in the future (5, 28). The resulting “biogeography of the Anthropocene” defies physical boundaries and reduces compositional dissimilarities among distant regions (7). However, our results suggest that instead of a progression toward a uniform biosphere, ecophysiological limitations will cause a higher prevalence of biotic homogenization among areas sharing similar environments. Our results also suggest that homogenization will be greater among regions that have intense trade relations and that are closely located. These novel species assemblages will be dominated by relatively few but widespread alien species, which mostly consist of competitive generalists (10). This profound biogeographic reorganization will put additional pressure on native biota [e.g., (29)]. A recent international assessment has shown that the rate of alien introduction events shows no signs of abating (30). Renewed efforts are needed to slow biotic homogenization if the targets of the Convention on Biological Diversity for 2020 are to be met (30).

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ACKNOWLEDGMENTS

We thank the many researchers who provided information on the native and current distribution of the species, particularly B. Roth, D. Herbert, D. Robinson, G. Stuffle, H. Kappes, J. Ablett, J. Gerlach, K. Hayes, O. Griffiths, R. Preece, R. Forsyth, S. Martin, T.-S. Liew, and T. A. Pearce. We highly appreciate the comments and suggestions of three anonymous reviewers. All sources of species distribution data used in this study are listed in the supplementary materials. Climate and trade data are freely available in the WorldClim (www.worldclim.org) and the UN Comtrade (<http://comtrade.un.org>) online databases, respectively. Supported by a postdoctoral grant from the Portuguese Foundation for Science and Technology (FCT/MCTES) and POPH/FSE (EC) grant SFRH/BPD/84422/2012 (C.C.), the Austrian Climate and Energy Fund (project no. KR11ACOK00355, SpecAdapt) (F.E.), the German VW-Foundation (H.S.), the German Centre for Integrative Biodiversity Research (iDiv) Halle-Jena-Leipzig funded by German Research Foundation grant FZT 118 (H.M.P.), and Cátedra-REFER-Biodiversidade.

SUPPLEMENTARY MATERIALS

www.sciencemag.org/content/348/6240/1248/suppl/DC1
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10 February 2015; accepted 6 May 2015
10.1126/science.aaa8913

INNATE IMMUNITY

Cytosolic detection of the bacterial metabolite HBP activates TIFA-dependent innate immunity

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Host recognition of pathogen-associated molecular patterns (PAMPs) initiates an innate immune response that is critical for pathogen elimination and engagement of adaptive immunity. Here we show that mammalian cells can detect and respond to the bacterial-derived monosaccharide heptose-1,7-bisphosphate (HBP). A metabolic intermediate in lipopolysaccharide biosynthesis, HBP is highly conserved in Gram-negative bacteria, yet absent from eukaryotic cells. Detection of HBP within the host cytosol activated the nuclear factor κ B pathway *in vitro* and induced innate and adaptive immune responses *in vivo*. Moreover, we used a genome-wide RNA interference screen to uncover an innate immune signaling axis, mediated by phosphorylation-dependent oligomerization of the TRAF-interacting protein with forkhead-associated domain (TIFA) that is triggered by HBP. Thus, HBP is a PAMP that activates TIFA-dependent immunity to Gram-negative bacteria.

The mammalian innate immune system detects microbes by recognizing pathogen-associated molecular patterns (PAMPs) that are absent from the host yet broadly conserved among classes of microbes (1, 2). However, in many cases, the specific microbial patterns responsible for inducing protective immunity are unclear, suggesting that additional PAMPs may exist that alert the immune system to the nature of a pathogen.

The human pathogens *Neisseria meningitidis* and *Neisseria gonorrhoeae* release a heat-resistant molecule that activates the transcription factor nuclear factor κ B (NF- κ B) in human embryonic kidney (HEK) 293T and Jurkat T cells—cell types whose ability to respond to PAMPs was thought limited to detection of flagellin by Toll-like receptor 5 (TLR5) (3). We previously showed that the *Neisseria* gene *hldA* was required for this molecule’s production (3). HldA catalyzes the second step in the adenosine 5′-diphosphate (ADP)-heptose biosynthetic pathway, which supplies the precursor for heptose residues found within the inner core of lipopolysaccharide (LPS) (fig. S1A). We tentatively identified a heptose-containing metabolite downstream of HldA as the activating molecule (3), yet the specific identity of the active conformation remained unknown. Therefore, we took a genetic approach and examined the ability of culture supernatants from bacterial mutants of the ADP-heptose pathway to activate NF- κ B. Although HldA was essential, the ensuing enzymes in the pathway were not (Fig. 1A), indicating that the product of HldA, D-glycero-D-manno-heptose-1,7-bisphosphate (HBP), was both necessary and sufficient for NF- κ B

activation. Both Δ *gmhB* and Δ *hldA* *N. meningitidis* display the “deep-rough” phenotype (4), possessing a truncated, heptose-less lipooligosaccharide (LOS) (Fig. 1B), which indicates that the proinflammatory ability of HBP is independent of the incorporation of heptose into the LOS. To confirm this notion, we enzymatically synthesized and purified HBP from sedoheptulose-7-phosphate, using recombinant GmhA and HldA. The reaction product potently stimulated NF- κ B only when the substrate and both enzymes were supplied (Fig. 1C), and the activity decreased when the downstream phosphatase GmhB was added (Fig. 1D). Finally, we performed mass spectrometry to show that the proinflammatory product of the GmhA-HldA reaction was indeed HBP (fig. S1, B and C). Thus, HBP is the innate immune agonist shed by *Neisseria*.

Transcriptome analysis identified primarily NF- κ B target genes as induced by HBP in Jurkat cells (fig. S2A). The kinetics of HBP-induced transcription and NF- κ B activation was slower than stimulation with flagellin or tumor necrosis factor- α (TNF α), both of which signal extracellularly (fig. S2, B to D). Therefore, we considered whether HBP required entry into the host cytosol to signal. Indeed, using reversible digitonin permeabilization (5) to deliver HBP-containing supernatants into the cytosol of Jurkat 1G5 cells, which harbor an NF- κ B-dependent HIV long terminal repeat (LTR)-luciferase construct (6), increased luciferase activity, whereas TLR5 activation was unaffected (Fig. 1E). Moreover, an inhibitor of the guanosine triphosphatase dynamin (7) attenuated the NF- κ B response to HBP (fig. S3A), indicating that HBP can enter cells via dynamin-dependent endocytosis. HBP enhanced signaling by TLR ligands in THP-1 macrophages, yet did not induce inflammatory cell death (fig. S3, B to D). Finally, HBP induced proinflammatory cytokine production from primary human immune and nonimmune cells (fig. S4, A to C).

The ADP-heptose biosynthetic pathway is highly conserved among Gram-negative bacteria (8)

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The dispersal of alien species redefines biogeography in the Anthropocene

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Science **348**, 1248 (2015);
DOI: 10.1126/science.aaa8913

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