Published in final edited form as:

Trends Parasitol. 2017 April ; 33(4): 264–275. doi:10.1016/j.pt.2016.10.008.

Prediction and prevention of parasitic diseases using a landscape genomics framework

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Summary

Substantial heterogeneity exists in the dispersal, distribution and transmission of parasitic species. Understanding and predicting how such features are governed by the ecological variation of landscape they inhabit is the central goal of spatial epidemiology. Genetic data can further inform functional connectivity among parasite, host and vector populations in a landscape. Gene flow correlates with the spread of epidemiologically relevant phenotypes among parasite and vector populations (e.g., virulence, drug and pesticide resistance), as well as invasion and re-invasion risk where parasite transmission is absent due to current or past intervention measures. However, the formal integration of spatial and genetic data ('landscape genetics') is scarcely ever applied to parasites. Here, we discuss the specific challenges and practical prospects for the use of landscape genetics and genomics to understand the biology and control of parasitic disease and present a practical framework for doing so.

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Parasites, genes, and landscapes

Individual parasite species around the world are distributed across different ecological settings, spanning rural, peri-urban and urban areas. For widely distributed parasitic diseases, ‘patchy’ geographic distribution of cases frequently occurs, where parasite, vector and host-related factors conspire to promote intense local transmission [1]. Understanding how abiotic and biotic environment features affect the movement of parasites, their hosts and vector species, is critical for disease control.

Spatial or landscape epidemiologists aim to exploit prior knowledge about spatial heterogeneity in the environment, often to the level of communities and households, to map current parasite distributions and develop models to predict future disease incidence (e.g., [2]). In addition to using spatial information to predict the presence and abundance of parasitic agents, it is also vital to establish the extent to which environmental features impact genetic connectivity between individuals and populations. The spatial distribution of genetic diversity directs the co-evolutionary outcome of host-vector-parasite interactions when selection is spatially heterogeneous [3]. Gene flow modifies this genetic distribution and therefore not only correlates to the spread of epidemiologically relevant traits (e.g., drug resistance [4] and virulence [5]) but also regulates local adaptation, the emergence of novel phenotypes and their invasion of areas free of parasite transmission (e.g., [6]), including those subjected to past or current intervention measures. However, while models of parasitic disease spread are becoming spatially-explicit (e.g., [2]), these still rarely incorporate genetic data. Studies on host, vector and parasite population genetics also abound, but these, in turn, too seldom incorporate spatial data. We believe that a framework for the formal integration of parasite genetic connectivity with host-vector dynamics in heterogeneous space is needed to bridge these gaps.

Landscape genetics, a body of theory aimed at combining landscape ecology and population genetics, is now over 10 years old [7]. Over this period, landscape genetic approaches have primarily examined the impact of habitat fragmentation on genetic differentiation (e.g., [8]), land use and environmental change on the genetic diversity of threatened species (e.g., [9]), as well as the sustainable management and commercial exploitation of others (reviewed in [10]). The spread of parasitic disease, however, has drawn only limited attention from the field. Pioneered by work on rabies [11] and chronic wasting disease [12], research has targeted a handful of viruses (reviewed in [13]; see also [14]) and microbes (notably *Batrachochytrium dendrobatidis* [15]), helminths with direct life cycles [16,17] and their hosts. Systems involving vector-borne pathogens [18–21] or several intermediate hosts [22] have been mostly spared from investigation. We believe the application of landscape genetics to vector-borne disease agents, especially including **landscape genetic simulation modelling** [23] (see Glossary), has significant, underappreciated potential to inform targeted disease control strategies.

In this opinion piece, we highlight the need for landscape genetic and genomic tools to study parasitic disease and present a framework for how they might be implemented. In doing so, we first provide an overview of landscape genetics/genomics, the role of landscapes in driving genome-wide adaptation in parasites, and discuss the specific challenges and

practical prospects for the use of landscape genomics to understand the biology and control of parasitic disease. We often refer to Chagas disease, recently ranked as the highest parasitic disease burden in the Western hemisphere [24]. In the absence of vaccine or cure, intervention strategies against such neglected zoonoses may profit most from the landscape genomic approach.

What is landscape genetics?

A primary goal of landscape genetics is to understand how landscape features influence observed spatial genetic (neutral or selection-driven) structure [25]. Key concepts in landscape genetics involve correlating genetic data with geographic data through individual-based measurements of dissimilarity. For example, genetic distances (i.e., dissimilarity matrices) can be quantified using individual-based metrics, such as proportion of shared alleles D_{ps} [26] or Rousset's A [27]. In all but the simplest models (i.e., **isolation-by-distance** or isolation-by-barrier), geographic distance is typically replaced by **cost-distance** [28], which reflects both the geographic distance between individuals and the degree to which the intervening landscape is hypothesized to impede gene flow and underlying dispersal movements (i.e., **isolation-by-resistance** [29]). Cost-distance is calculated across a **resistance surface** wherein each cell in a Geographic Information Systems (GIS) raster map is assigned a value based on a hypothesized species-specific resistance to traversing the landscape feature the cell represents [30].

In a typical landscape genetic approach, cost-distances among individuals are calculated based on multiple, competing resistance hypotheses. These cost-distances are then evaluated (i.e., correlated) against empirical genetic distances among the same individuals, primarily using the Mantel test and its derivatives (e.g., multiple regression on distance matrices (MRDM) or partial Mantel tests within a causal modelling framework [31]). Although techniques such as distance-based redundancy analysis [32] are increasingly applied to test landscape resistance on gene flow (e.g., [33]), Mantel-based approaches are still the mainstay of landscape genetic analyses.

Landscape genomics extends landscape genetics to the exploration of genome-wide data (the two terms are applied accordingly herein), often in search of patterns of covariation between allele frequencies and environmental conditions (i.e., **genotype-by-environment associations** (GEAs) – see Box 1). As these signs of selection may point to the role of local adaptation in structuring populations, their investigation necessarily fuses into the framework that follows below.

Landscape genomics to study parasitic disease

With the exception of recent theoretical work in the context of Lyme disease [21], essentially all landscape genetic studies applied to parasitic diseases to date have considered a single level of transmission, focusing primarily on landscape resistance hypotheses that influence movement processes and thus, gene flow, of principal reservoir hosts. For complex, multi-species disease systems, we find that today's landscape genomic methods warrant a more inclusive, multi-level approach. In particular, we recognize resistance surface construction, a

precursor to several landscape genetic applications, as a convenient analytical step during which interactions among host, vector and parasite can be formally integrated for further analysis. In Box 2, we outline a multi-species landscape genomic approach to predicting disease spread in host-vector-parasite systems. Box 3 breaks down the key translational step, resistance surface construction, by example of Chagas disease. In brief, host distribution (i.e., all spaces that permit host movement) is abridged by vector distribution relative to host movement rate (parasite transmission remains viable where the two distributions do not coincide so long as movement rate allows the host to re-enter areas of overlap within the infective period). Likewise, vector distribution is abridged by host distribution relative to vector movement rate. Added together, these effective distributions determine parasite distribution. First, the values of different potential environmental influences on principal local host and vector species movement through the landscape are mapped. These landscape data become the primary sources for studying parasite spread. Host and vector conductivity-to-movement surfaces are then calibrated based on transmission competence and merged to create a parasite resistance-to-movement surface. Parasite dispersal and resultant population genetic structure over this composite surface are modelled directly using landscape genetic simulation software. Finally, simulated and empirical parasite population genetic structure are compared to evaluate hypothesized landscape effects at the multiple transmission levels that take part in the spread of parasitic disease. Crucially, this approach does not rely on any assumption of genetic co-structure between vector and parasite or host and parasite, a phenomenon rare ever observed in natural systems (reviewed by Mazé-Guilmo et al. [34]).

What makes landscape genomics such a powerful tool to study parasitic disease?

Accuracy in detection, precision in prediction

Spatially-explicit models of parasite dispersal (increasingly individual (e.g., [35]) and network-based algorithmic methods (e.g., [36])) have traditionally been fitted and validated against occupancy and abundance data. Genetic structure of the disease agents still rarely replaces these response variables despite several clear advantages for host-vector-parasite systems. Interpretation of occupancy and abundance data is complicated by imperfect detection, and many zoonoses (e.g., Chagas disease and leishmaniasis, for which surveillance is under-resourced, diagnostics are substandard and symptoms are inconsistent) are highly prone to this bias. Pairwise genetic data are robust to detection bias and offer far greater resolution to inference on parasite dispersal, chiefly because genotypes not only identify individuals but also dynamic associations of alleles, their origin and putative location of intermediate genotypes. Predicting when and where genotypes and alleles end up in the landscape based on their current spatial distribution is critical for disease control. For example, increased resistance, virulence and transmission potential often arise only when certain sets of genes come to combine (e.g., [4,37,38]), each uniquely routed by ecological features of variable resistance-to-movement and selective force. As spatially-explicit, individual-based modelling turns ‘genotype-based’, intricate demographic and evolutionary interactions (e.g., heterosis or selection for/against specific alleles and reproductive modes) become decipherable from neutral and adaptive genetic structure in space and time.

Early attempts to apply landscape genetic methodologies to infectious agents have yielded unprecedented precision in disease prediction and surveillance. For example, by coupling spatial analysis with phylogenetic methods, Biek et al. demonstrated segregated dispersal trajectories and intermittent expansions among the viral lineages of an explosive rabies outbreak in the mid-Atlantic United States [39]. Unrelated to selection on novel variants (given few, irregular changes at adaptive loci), dispersal patterns were explained by viral spread into low-elevation raccoon habitats and restrained dispersal behind the wave front. This elevation-based patterning was recently affirmed using cost-distance approaches akin to those outlined above (Box 2) [14] (see also applications on principal rabies hosts [40]).

As cost-distance methods begin to spread through virus research, cases from vector-borne disease systems remain few and far between, but all the more compelling. In West Africa, for example, Bouyer et al. built ‘friction’ maps to model least-cost paths between *Glossina palpalis* populations and the ‘main tsetse belt’ of the region [20]. Paths were then ranked by cost to identify isolated eradication targets in the fight against African trypanosomiasis. Medley et al. also used landscape genetics to study disease vectors, decomposing the invasion process of *Aedes albopictus* through the United States [19]. Here, deft study design (e.g., flower vases recognized as preexistent larvae repositories in 26 cities connected by various traffic intensities) and high-resolution (30 m) land-cover sensing provided for MRDM on range-wide data at multiple spatial scales. Results depict occasions of long-distance, human-aided *A. albopictus* expansion, followed by stepping-stone dispersal as a function local landscape. Unfortunately, however, [19] and [20] did not advance their powerful resistance models to simulation for additional validation, refinement and extrapolation (i.e., steps E and F in Box 2) (yet, see an intriguing follow-up study [41] on the scope of landscape genetic simulation modelling to evaluate pattern-process relationships such as those inferred by Medley et al [19].).

Power to explore the unorthodox and unknown

As isolation-by-resistance featured prominently in the studies above, landscape effects on non-neutral genetic structure have been largely discounted so far. Yet, dispersal outcomes are without question also shaped by context-dependent adaptive change (and vice versa – see Box 1), sometimes to profound effect (e.g., hybridization under insecticidal pressure [42]). To this end, landscape genomics’ pioneering approach to simultaneously detect divergent alleles and their ecological drivers, then to visualize and simulate both neutral and selection-driven structure in heterogeneous space, has received special attention (Box 1). There is considerable scope for the use of landscape genomic approaches to study adaptive genetic change in parasitic disease and clear advantages over traditional population genetic approaches.

Among several parasite species, reproduction is not uniform, with clonal propagation interspersed by unorthodox modes of genetic exchange. Especially for parasitic protozoa, these episodes of recombination remain incompletely defined both in mechanism (e.g., non-Mendelian sex without meiosis) and extent [43]. Traditional approaches to detect targets of selection scan for excess genetic differentiation between discrete populations (e.g., outlier analyses such as BAYESCAN [44]). However, methods to define such populations *a*

posteriori (e.g., [45]) rely on assumptions of Mendelian sexuality and are thus liable to distort results at the earliest stage of analysis when applied to parasitic species. In contrast, landscape genomics' correlative GEA methods (see Box 1 and [46]) are individual-based and make few assumptions about the underlying reproductive mode.

Host-vector-parasite systems are also inclined to subtle, step-wise adaptive change, i.e., weak selection on individual alleles [47]. In parasites, this tendency relates to high mutation rates and population sizes [4,47,48], as well as elevated gene redundancy and ploidy [43]. In hosts and vectors, the effect likely arises from prevalent polygenic, epistatic and pleiotropic control of interaction traits [49,50]. Simulations show how quickly differentiation-based methods lose power to detect adaptive change as selection intensity weakens, reaching complete impotence at levels still easily managed by correlative alternatives [51]. The latter take further leverage from study designs that prioritize environmental representation over genetic sampling intensity per site, a strategy counter to classic methods based on clustered sampling. These arguments were recently taken from simulation to reality in coastal Kenya, where Mackinnon et al. applied environmental association analysis to genotypes obtained from a hospital serving ethnic groups long segregated among ecotypes of contrasting malaria prevalence [50]. After rejecting dozens of disappointing candidates proposed by methods of the past, this search for resistance loci exposed several divergent genes that mitigate brain inflammation, a symptom of severe malaria. Moreover, the study detected subtle clines in the sickle-cell mutation β^S , signs of balancing selection seldom distinguished at such fine spatial scales.

While landscape genomics holds significant promise for improved precision and power in the study of parasitic disease, the discipline has its own list of cautionary notes and caveats. These are introduced in Box 4.

Prospects

Conservation genomics in reverse

In conservation biology, landscape genomics strives to identify 'conservation units', i.e., genetically unique subpopulations to be preserved and/or managed distinctly to sustain biodiversity of the whole [52]. In epidemiology, spatial genomics are crucial to identifying operational units that maximize the reach of surveillance and control. Apprised of such epidemiological units and their distribution, insecticidal campaigns (often too indiscriminate to be sustainable in the past [53]), for example, might aim precisely to rule out pivotal hybridization outcomes observed *in vitro* (see below) or capitalize on high landscape resistance to gene flow (see [20]), while diagnostic approaches might be differentiated based on particular genotypes expected to arrive in a region. A look at leishmaniasis further elaborates these points. Hundreds of thousands, primarily the poor, fall victim to this neglected zoonosis every year, with cases ranging from self-healing cutaneous infection to severe disfigurement and fatal visceral disease. The distinct pathologies ascribe to certain subsets of *Leishmania* species [54], yet these may also proliferate as natural hybrids of enhanced virulence, resistance and plasticity [55]. For good reason, therefore, underdeveloped molecular surveillance strategies are now remonstrated in such places as Colombia, where massive efforts to innovate this area are currently underway [56].

Elsewhere, especially in Brazil, much effort has been devoted to ecological niche modelling (ENM) to inform *Leishmania* control. While such occupancy-based correlative and algorithmic methods provide essential guidance, direction is generally less immediate. For example, ENM rates nearly all of Amazonia at current risk to leishmaniasis and projects southward vector expansion under climate change [57], but what next? Where are limited intervention resources to be allocated, and when? Might temperatures be approaching tipping points to rapid proliferation of disease? In a landscape genomic cost-distance framework that models connectivity and genotype movement in the very process of identifying resistance variables, simulation-based analysis may promptly transition to such questions. For example, after pattern-process modelling American marten (*Martes americana*) dispersal in the Rocky Mountains, Wasserman et al. proceeded right to forward-simulation of population structure in a warming climate [58]. Results not only detail gradual habitat and population fragmentation through space and time, but specify imminent warming thresholds beyond which genetic connectivity plummets to levels that threaten extinction. Translating such innovations from landscape genetic/genomic conservation studies offers to accelerate progress towards high-impact solutions against pervasive disease under global change.

Groundwork for genetic modification in disease control

In sub-Saharan Africa, the burden of neglected diseases such as leishmaniasis is far outweighed by that of malaria. As existing control strategies cannot keep pace (e.g., ca. 400,000 malaria deaths in 2015 [59]), the swift replacement of natural vector populations through transgenic, *Plasmodium*-refractory types offers much appeal. However, this approach depends on mating among transgenic and natural mosquitos in populations unlikely to be panmictic (in fact, cryptic speciation is rather notorious to *Anopheles gambiae*, principal malaria vector of the sub-Sahara [60]). Therefore, patterns and processes of genetic connectivity and reproductive isolation in the target environment must be well understood to legitimize transgenic release and predict its manifold effects [61]. Landscape genomic tools are designed precisely to forward such understanding. For example, after identifying key drivers of dispersal from cost-distance analyses applied to native vector populations (e.g., as in [19]), transgenic genotypes can be placed into landscape genomic simulation modelling of mating, selection and dispersal in the landscape. Should the transgene confer environment-dependent fitness costs (see [62]), various simulators can also integrate this information to forecast gene flow and consequent distribution of refractory types through the environment [63]. Simulations might also explore to what extent transgene fitness costs must be reduced or inheritance must be biased (transgenesis methods often exploit ‘selfish genetic elements’ [64]) for effective replacement of native vector populations. Finally, based on resultant equilibrium conditions, *Plasmodium* dispersal can be modelled among remnant (e.g., reproductively isolated) vector and human populations in the framework outlined above. Here, resistance surface construction offers to incorporate temperature-dependent vectorial capacity (e.g., changes in *Anopheles* immunity and *Plasmodium* fitness [65]) and other theoretical updates on disease spread in heterogeneous space. In times to come, these explorations will help disambiguate and enhance the potential of transgenic release strategies as well as consider how standard methods best round off novel efforts to defeat malaria and other major parasitic disease.

Concluding remarks

Here, we claim a strategic place for host-vector-parasite interactions to join spatially-explicit analyses of genetic connectivity. This integration not only allies molecular epidemiology with landscape ecology, but advances both into the realm of ‘landscape community genomics’ [66], only just envisioned to explore previously impenetrable eco-evolutionary causes and consequences of genomic structure. First inroads would be well-timed to seek out the potential of landscape genomics in forecasting land use, climate change and intervention impacts on parasite dispersal. Parallel efforts underway across various disciplines offer ample opportunity to validate and synthesize results to ‘best practices’ for sustainable disease control. Novel genome-typing strategies (e.g., restriction site-associated DNA sequencing – see [67]) that now place individual-based, multi-species genomic analyses within possibility of a single study also impel research on interactions between genotype-genotype factors (e.g., hybridization and co-evolution) and disease heterogeneity (see Outstanding Questions). However, no single study can or should take on too many questions at once. Only following clear hypotheses on a few factors of interest can landscape genomic methods such as those presented above be adequately tuned and, when necessary, replaced. Indeed, the framework presented here is just that – a framework, and discretion is advised. We hope to have placed helpful rails, not rules, into challenging new terrain for the study and prevention of parasitic disease.

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Glossary

Cost-distance

The cumulative resistance of intervening landscapes to the movement of individuals (or populations, etc.) between a pair of sites. These ‘distances’ are typically calculated by scoring landscape variables (e.g., elevation) based on (putative) resistance-to-movement, plotting resistance scores into a raster grid (see ‘resistance surface’ below) and adding up grid values along the path(s) of interest

Genotype-by-environment association (GEA)

A correlation between genetic and environmental variation and possible effect of natural selection. In landscape genomics, specialized regression models are applied to genome-wide data collected in heterogeneous landscapes to detect these GEAs as environment-related clines in allele frequencies

Isolation-by-distance (IBD)

In the IBD model, the probability that an individual disperses to any site in the landscape depends only on its distance to that location. Here, no matter the heterogeneity in the landscape, ‘cost-distances’ (see above) between sites relate directly to straight-line Euclidian distances, given that landscape features are not considered to resist movement and/or modify paths of dispersal

Isolation-by-resistance (IBR)

Unlike for 'IBD' (see above), Euclidian distances do not suffice to predict the level of dispersal between a pair of sites in the presence of IBR. Rather, the probability that an individual disperses from one site to another depends also on the resistance of the intervening landscape to the movement of that individual (see 'cost-distance', above)

Landscape genetic simulation modelling

A spatially-explicit modelling framework to simulate the actions and reactions of organisms and attendant genetic structure in heterogeneous space. Simulations are generally individual-based, such that these actions and reactions (e.g., dispersal, mating, survival) depend not only on user-defined landscape heterogeneity but also on inter-individual differences in age, sex, fitness, etc

Pattern-process modelling

A modelling scheme that evaluates whether an underlying process inferred through empirical induction can produce the patterns (e.g., population genetic structure) observed in the data, and how well (i.e., at what precision, accuracy and repeatability) it can do so

Resistance surface

A representation of the landscape, often in raster form, in which each location (e.g., raster cell) is assigned a cost or resistance value which affects movement and gene flow through the landscape

Box 1. Landscape genomics and genotype-by-environment associations of parasitic disease

Landscape genomics scans genome-wide, high-density marker datasets to elucidate GEAs [46]. As specialized regression methods (e.g., mixed models that control for demographic history and drift [68]) identify environment-related clines in allele frequencies, possible targets of selection are not exposed *per se*. Better yet perhaps, these emerge from regression as correlations to environmental predictors, i.e., coupled to possible cause. Central ecological proxies such as temperature present intuitive starting points in the search for these GEAs. Yet, depending on the system and objective, exploration may venture far beyond classic considerations. In exploring the ‘landscapes’ of parasites, for example, hosts and vectors often bear environmental variables of primary interest (and relevant values might be retrieved from auxiliary sampling – e.g., clinical observations or genetic data from the vector source). Here, the genetic bases of a certain phenotype (e.g., virulence) may stand at question, such that putative ecological pressures (e.g., host density, coinfection [69]) on this particular trait are chosen to be scanned for responsive loci. In time, as countless cases of heterogeneity enter regression and ever more GEAs unfold, landscape genomics promises to pass on a kaleidoscope of potential gene function for follow-up experimental studies to explore.

GEAs are also essential to downstream analyses within the same field, e.g., to incorporate selective forces in spatially-explicit simulations of population genetic change (e.g., CDPOP [70]). Analyses of this type may expose fundamental adaptive constraints that limit parasite range expansion and response to climate change. Apart from such implementation, GEAs also enhance interpretation of independent results. The upscaling of analysis to many thousands of markers vastly improves power to unmask intricate demographic and evolutionary structures – gradients of selection, incipient speciation, cryptic niches, etc. This enhanced resolution, however, also requires enhanced approaches to interpretation and often calls on GEAs. For example, novel spatio-genetic visualization tools (e.g., MEMGENE [71]) may expose instances where gene flow deviates from consistent patterns of isolation-by-resistance. These deviations may issue from any number of selective processes. Local adaptation is one such process and a topic of ongoing discussion in the study of parasites. While the presence of locally adapted residents may impede genetic introgression (e.g., selection against hybrids), it may just as well take opposite effect (e.g., frequency-dependent selection of rare variants) [72]. Complementary information on GEAs provides critical guidance in navigating the many possibilities and understanding how gene flow, drift and selection mosaics interact to drive parasite local adaptation (see [73]).

Box 2. Exploiting landscape genomics to predict parasite dispersal in heterogeneous landscapes

The construction of a predictive map of parasite dispersal from high-resolution landscape and genetic data is outlined in six steps (Figure I). Step A is further detailed in Box 3 by example of Chagas disease transmission in southern Ecuador.

A. Host/vector resistance surface construction

Informed by biological and ecological data, principal host and vector species are specified and the landscape variables underlying their movement are mapped. Landscape features are assigned levels according to their putative impact on host and vector movement and merged to create a landscape conductivity-to-movement surface. Surfaces generated for both host and vector are then weighted, merged and converted to a composite resistance-to-movement surface. If additional, host/vector-independent variables extrinsic to parasite survival and development are hypothesized, the resistance surface may be further updated to incorporate these requirements.

B. Landscape connectivity analysis

A landscape connectivity model (e.g., least-cost path analysis or circuit theory) is generated using programs such as PATHMATRIX [74] or CIRCUITSCAPE [75]. While least-cost models specify single optimal paths of movement between sites on a resistance surface, circuit theory considers multiple pairwise connections [29] and may enhance prediction of passive, multi-dependent dispersal systems in landscapes of continuous resistance.

C. Study site identification and phase one genetic data collection

Guided by path analysis results, phase one sampling locations are selected to encompass heterogeneous landscape resistance. Parasites are sampled (i.e., host/vectors captured, parasites isolated and DNA extracted) and DNA is sequenced.

D. Cost-distance analysis

Metrics of dissimilarity are calculated among individual genotypes (e.g., based on genome-wide single nucleotide polymorphisms) and correlated to cost-distances (computed in, e.g., PATHMATRIX [74]) separating these individuals (see main text) for preliminary validation of the resistance surface constructed in step A. GEA interactions are also explored based on various landscape features (see Box 1).

E. Data simulation and iterative resistance surface modification

Using tools like CDPOP [70], spatially-explicit changes in population genetic structure are simulated as functions of individual-based movement, reproduction, mortality and dispersal [23]. These models predict patterns of gene-flow (i.e., connectivity) between individuals based on the resistance surface constructed in step A and GEAs detected in step D. Simulated connectivity measures are then compared to empirical estimates from step D to further validate the resistance surface. Surface components (e.g., conductivity values (see Box 3, step A3)) are iteratively re-weighted until connectivity matches the observed (i.e., **pattern-process modelling**).

F. Landscape model validation

The refined landscape resistance surface underlying parasite dispersal in the phase one sampling area can now be extrapolated regionally. At a second, independent site, parasites are sampled, sequenced and genotyped. Cost-distance analysis and the goodness-of-fit between simulated and empirical connectivity at the second site determine the power of the resistance map.

Box 3: Composing a resistance map for the regional transmission of Chagas disease

Resistance surface construction, the first step in cost-distance analysis (Box 2, step A), allows multi-species parasitic disease systems to fold neatly into the landscape genomic approach. We work through this key translational step by example of *Trypanosoma cruzi* transmission in southern Ecuador (Figure I).

A1. Specification of principal host/vector species

As host/vector specification founds all further analyses, factors relating to transmission competence must be thoroughly examined, e.g., abundance, vagility, physiological and life-history traits determining susceptibility, tolerance and transmission intensity. Studies on eclectic (e.g., ‘host-fitting’ [76]) parasites such as *T. cruzi* may require that spatial study extent be reduced to scales at which limiting agents emerge. In Loja Province (ca. 100 km × 100 km), *Sciurus stramineus* is specified as principal *T. cruzi* host based on the rodent’s year-round arboreal nesting, i.e., triatomine habitat that holds against limiting vegetation phenology at the domestic-sylvatic interface [77]. This triatomine association is supported by other randomized sampling [78] and blood meal analyses that link high infection tolerance to short-lived species with high reproductive rates [79]. *Rhodnius ecuadoriensis* is specified as primary *T. cruzi* vector based on its ecology, defecation and feeding patterns [80] and wide distribution of sylvatic and synanthropic populations in southern Ecuador [78].

A2. Specification of landscape features underlying host/vector movement

Data modelling [81] and algorithmic approaches [82] specify land-cover type and elevation as two principal determinants of triatomine movement at the scale applied in Loja. Analyses of triatomine genetic structure also suggest a strong influence of human transport (i.e., roads) on dispersal at this scale [83]. These three features also regulate host movement. *S. stramineus* is native to the Andes and, despite declines from land-use change, populations are now common from 2000 m to sea-level (similar to *R. ecuadoriensis* [84]) in various forest and man-made environments [85].

A3. Composition of conductivity surfaces

Remote sensing data on elevation, land-cover and roads are rasterized and re-coded to conductivity-to-movement scores. In this case, re-coding is coarse (e.g., for both host and vector, conductivity = 1 if elevation > 2000 m), given that ecological traits of *S. stramineus* (e.g., habitat/trophic flexibility [85]) and *R. ecuadoriensis* (e.g., microhabitat selection [84]) likely buffer continuous landscape effects on movement. The product of the three scores is then taken for each cell to generate host and vector conductivity surfaces.

A4. Abridgement and weighting of conductivity surfaces

The distribution of raster cells that allow for host movement is now abridged based on vector distribution relative to host movement rate and infection time. Cells conducive to vector movement are corrected based on host distribution in the same manner: if the distance to the nearest cell where host-vector interaction is possible (i.e., where *S.*

stramineus conductivity is non-zero) exceeds maximum parasite carriage distance by the vector (equable to *R. ecuadoriensis* dispersal range (ca. 2000 m, based on [86]) when infection does not compromise lifespan and movement (e.g., [87,88])), the vector conductivity score is re-coded to zero. Once abridged, host conductivity values are scaled by a coefficient that quantifies host relative to vector competence in dispersing *T. cruzi*, weighing in factors such as vagility and transmission intensity (e.g., ca. 1:5 [35]).

A5. Conversion to a composite resistance surface

The refined conductivity surfaces for *S. stramineus* and *R. ecuadoriensis* are merged by addition, then inverted to generate the resistance surface.

Box 4: Limitations of landscape genomics to study parasitic disease

As landscape genetics is just entering its teenage years, uncertainties come and go. Lasting concerns relate primarily to statistical power (e.g., high type-1 error due to non-independence, multicollinearity and multiple testing) and empirical sampling design (e.g., how to select spatiotemporal scales). These issues affect the entire body of landscape genetics/genomics and are under extensive treatment [89,90], increasingly aided by simulation software [63]. We therefore turn to caveats of particular relevance to applications on parasitic disease.

We share concerns that high-resolution model output from simulations of gene flow is easily generated, taken for precision and misapplied [91]. Ethical arguments for immediate translation and high visibility of research on human disease (e.g., [92]) intensify this risk. Also, our framework may at times rely on limited ‘expert knowledge’ to elaborate core model input (i.e., the multi-species resistance surface). Moreover, resistance-to-movement may involve variables (e.g., soil conditions for helminths [93]) and scales (e.g., micro-geographic differentiation in *Plasmodium* [94]) for which empirical data are unavailable.

We also emphasize that landscape genomics may miss principal causes and consequences of disease spread for phenotypes of non-heritable or complex genetic basis. Consider, for example, the dispersal outcome of foremost interest to epidemiology – pathogenicity. This ‘extended parasite phenotype’ may also take a primary role in regulating disease spread [95] and founds upon complex epistatic host-parasite interactions. Not only is genetic structural variation known to underlie pathogenic differences (e.g., [96]), host tolerance (likely of low heritability itself [97]) further modifies infection outcomes. Classic models of dispersal skirt this complexity by directly implementing phenotypic data (e.g., infection intensity, clinical forms), and classic approaches to detect adaptive variation have adjusted to search beyond the single locus. Meanwhile, landscape genomics continues to define and apply genotypes as proxies for phenotypes with limited discretion. For example, environmental resistance may differ among genetic structural variants [98], but standard metrics of dissimilarity do not measure such differentiation. Indeed, defining and interpreting genetic structure is often troublesome and tempts to simplifying but spurious assumptions. Such shortcuts through our framework require caution. For example, in step A1 (Box 3), resorting to analysis of host/parasite genetic co-structure to distinguish principal host species (see [34]) is rather hazardous, as is linking GEAs to local adaptation while slighting other forms of selection (see [99]). Clearly, landscape genomic tools require discreet handling and refinement based on underlying hypotheses, as will interdisciplinary complementation remain indispensable to the study of parasitic disease.

Outstanding Questions Box

- How transferable are environmental resistance models among host, vector and parasite gene flow hypotheses?
- Can basic landscape resistance functions predict dispersal in multiple parasite taxa?
- Is hybridization among parasite and/or vector species predictable from landscape configuration and to what extent does reproductive mode influence the spread and severity of parasitic disease?
- Does host and/or vector genetic diversity mediate parasite dispersal?
- Will adaptive constraints limit parasite and/or vector range expansion and response to climate change?
- To what extent does local adaptation regulate parasite dispersal?

Trends Box

Landscape genomics introduces novel analytical tools to derive the ecological determinants of spatial genetic structure from unprecedented remote sensing and genomic resources.

Human risk to parasitic disease relates directly to the distribution and movement of host, vector and parasite genotypes in the environment.

Landscape resistance to host and vector movement constrains parasite dispersal and cumulates high ecological sensitivity to the spread of parasitic disease.

Nonetheless, landscape genomic tools are rarely engaged to model multi-dependent parasite dispersal or selection-driven genetic structure.

Intuitive adjustments to cost-distance methods, resistance surface simulation modelling and genotype-by-environment association analyses offer to unite epidemiology with landscape genomics for enhanced disease surveillance and control.

Figure I (Box 2).

Steps A – F depict the construction of a predictive map of Chagas disease transmission for Loja Province, Ecuador.

Figure I (Box 3).

Resistance surface construction for *Trypanosoma cruzi* transmission in Loja Province, Ecuador.