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Genetic diversity and disease: the past, present and future of an old idea

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Abstract

Why do infectious diseases erupt in some host populations and not others? This question has spawned independent fields of research in evolution, ecology, public health, agriculture, and conservation. In the search for environmental and genetic factors that predict variation in parasitism, one hypothesis stands out for its generality and longevity: genetically homogeneous host populations are more likely to experience severe parasitism than genetically diverse populations. In this perspective piece, I draw on overlapping ideas from evolutionary biology, agriculture, and conservation to capture the far-reaching implications of the link between genetic diversity and disease. I first summarize the development of this hypothesis and the results of experimental tests. Given the convincing support for the protective effect of genetic diversity, I then address the following questions: 1) Where has this idea been put to use, in a basic and applied sense, and how can we better use genetic diversity to limit disease spread?; 2) What new hypotheses does the established disease-diversity relationship compel us to test? I conclude that monitoring, preserving, and augmenting genetic diversity is one of our most promising evolutionarily-informed strategies for buffering wild, domesticated, and human populations against future outbreaks.

Keywords

genetic diversity; host-parasite interactions; infectious disease; monoculture effect; crop disease; host heterogeneity; varietal mixtures; genetic erosion; intraspecific variation; Red Queen

Introduction

The hypothesis that genetic diversity limits parasitism is arguably one of the most broadly influential ideas in the study of host-parasite interactions. If parasites have some degree of genetic specificity for infection, then we expect them to transmit more readily between closely-related hosts than distantly-related hosts. From this assumption, we arrive at the hypothesis that genetically diverse host populations face a lower risk from infectious disease than do genetically homogeneous populations. This idea has garnered significant empirical support, spurred influential evolutionary hypotheses, and instigated genetic diversification as a critical tool in the sustainable management of infectious diseases in crop and wildlife populations.

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Here, I draw on insights from evolutionary biology, agriculture, and conservation to provide a broad perspective on the link between genetic diversity and disease. The varied application of the diversity-disease connection necessitates a few clarifications up front: I use the term diversity to refer to intraspecific genetic diversity of hosts within population. Genetic diversity may be functional or neutral and can be quantified in many ways, like allelic or genotypic richness (see Table 1 in Hughes et al. 2008a). For the most part, I will not directly consider the effects of interspecific diversity (Halliday and Rohr 2019; Halliday et al. 2020b) or genetic heterozygosity of individuals (Spurgin and Richardson 2010). I use the term "parasite" broadly to encompass organisms historically separated as microparasites (e.g. viruses, bacteria) and macroparasites (e.g. mites, trematodes) (Lafferty and Kuris 2002). Empirical studies quantify population-level parasitism in many ways, including estimates of the fraction of hosts infected (e.g. prevalence) and the average size of a host's infection (e.g. load) (Gibson and Nguyen 2021). For my purposes, I use the term "parasitism" to broadly refer to this suite of approaches, with the recognition that metric may matter in interpretation of specific experiments. I adopt this general terminology in order to provide an inclusive treatment of the varied fields that have interrogated the relationship between parasitism and the genetic diversity of host populations.

I begin with a brief overview of the hypothesis that genetic diversity limits parasitism – how has this idea developed, and how does it work? I conclude that experiments and quantitative syntheses now provide substantial evidence that genetically diverse host populations experience less parasitism on average than genetically homogeneous populations. I then consider the implications of this protective effect of genetic diversity - what opportunities and challenges does it present, and what questions and hypotheses does it inspire? I highlight the clear significance of the disease-reducing benefit of genetic diversity today, as we face down the threat of emerging infectious diseases. The link between diversity and disease provides powerful motivation and practical guidance for rectifying the ongoing loss of genetic diversity in crop and wildlife species.

Foundations of the hypothesis

In this section, I introduce some historical events relevant to development of the hypothesis that genetic diversity limits parasitism. I then summarize the findings of theoretical and empirical tests of this hypothesis.

The idea has its origins in agriculture. In one of the early recorded observations of disease in crop mixtures, the pathologist Giovanni Tozzetti (1767) puzzled over an epidemic of stem rust in 1766 in Italy: "It is not so easy to render a reason, why Wheat growing seeded with Rye, or with Vetch, was not damaged by the rust, while a Field of Wheat alone, standing between one of rye, and one of Vetch, yielded scarcely any seed, and that the most miserable."

In the second half of the 1800s, repeated failure of the potato crop in Europe due to the oomycte *Phytopthora infestans* fueled ongoing concern about the clonal propagation of crop varieties (Gray 1875). Hunting for a solution to the potato problem, the Irish merchant James Torbitt found inspiration in Charles Darwin's writings on variation and natural selection.

He exchanged 141 letters with Darwin seeking intellectual and financial support for his scheme to propagate potatoes by seed (products of sexual reproduction) rather than by tubers (products of clonal reproduction) (DeArce 2008). To test his idea, Torbitt oversaw a large-scale field experiment in which farmers planted his variable potato seeds near infected clonal varieties. Farmers reported relatively low rates of *P. infestans* in the variable set, with several reporting no infection at all (Torbitt 1867). In spite of these promising results, Torbitt's scheme never took off. Its greatest strength – the variation among individuals – was a commercial weakness: buyers preferred the consistent phenotype of Scotch Champion, a clonal variety bred for *P. infestans* resistance that came to occupy 80–90% of Ireland's late-maturing potato acreage in the late 1800s (DeArce 2008). Torbitt's idea, however, persisted.

Subsequent catastrophic crop failures gave further weight to a connection between homogeneity and infection. In 1882, Harry Marshall Ward warned against the dangers of dense, homogeneous plantings following the emergence of coffee rust on Sri Lanka (then Ceylon), which destroyed the island's coffee industry (Ward 1882; Ainsworth 1994). The banana industry developed around the Gros Michel cultivar only to face fusarium wilt in the early 1900's, a drawn-out battle with devastating economic, environmental and social ramifications. In 1962, the industry was restructured around monocultures of Cavendish, a cultivar that was originally resistant but is now succumbing to another *Fusarium* lineage (Marquardt 2001; Ploetz 2015; Kema et al. 2020). Modern breeding practices fostered further epidemics by facilitating wide dissemination of varieties derived from a single parent lineage: 80% of acreage planted to a single lineage explained the severity of the 1940s epidemic of crown rust on oats and the 1970 Southern leaf blight on corn in the US (Browning 1972). These epidemics are not merely historical anecdotes. The latest global threat to wheat comes from the Ug99 stem rust group. Several major rust resistance genes are ineffective against Ug99, and the overrepresentation of these genes in commercial stock resulted in >85% of wheat varieties grown globally being at risk of Ug99 infection in the 2000's (CIMMYT 2005; Singh et al. 2011). These repeated disease-induced collapses of crop monocultures have led to widespread adoption of the idea that genetic homogeneity promotes disease risk, and of its corollary, that genetic diversity limits disease risk.

Why would genetic diversity limit parasitism? We first assume host genotypes vary in their susceptibility to a given parasite genotype. Parasites achieve high fitness when they encounter a susceptible host genotype, while encountering a resistant host genotype curtails transmission. Genetic diversity in host populations could then limit the success of parasites in at least three ways: 1) Increasing diversity reduces the frequency of any given host genotype, thus reducing the rate at which a parasite encounters a susceptible host genotype. 2) For a finite population size, more host genotypes means fewer individuals of the susceptible genotype(s), suppressing density-dependent transmission. 3) Both of the above mechanisms may contribute to limiting adaptation of parasites (King and Lively 2012). The agricultural literature cites additional mechanisms that may apply in specific contexts, including resistant hosts as physical barriers to parasite dispersal ("fly-paper effect" - Trenbath 1975). These mechanisms are not mutually exclusive.

Theory has evaluated these verbal arguments through epidemiological, evolutionary, and agricultural lenses. Leonard (1969)'s model provided a valuable guide for agricultural researchers. Building off ideas put forth by Borlaug (1953; 1958) and Jensen (1952), Leonard (1969) modeled the spread of stem rust in a simple mixture of two oat varieties, one susceptible and one entirely resistant. In his model, infection of the susceptible genotype declines logarithmically as its frequency in the mixture declines. All else equal, this result supports the planting of resistant monocultures rather than mixtures. Leonard, however, inferred from his findings that mixtures may have special value against diverse parasite populations. This model inspired subsequent theory (e.g. Kiyosawa and Shiyomi 1972; Kiyosawa 1976; Jeger et al. 1981) and garnered empirical support (e.g. Burdon and Chilvers 1977; Luthra and Rao 1979). With livestock populations in mind, Springbett et al. (2003) allowed for multiple genotypes with susceptibility varying quantitatively in a classic Susceptible-Infected-Recovered (SIR) model. Genetic variation had no effect on the average probability of an epidemic occurring: in other words, it did not change the probability that the expected number of secondary infections produced by an initial infection (R_0) was equal to or greater than one (see also Nath et al. 2008). It did, however, lower the proportion of individuals infected during an epidemic for a given R_0. A key feature of the models above is that host genotypes vary in susceptibility to a single parasite genotype.

Later theory allowed for multiple parasite genotypes. These models predict that genetic diversity strongly limits disease spread when parasite genotypes vary in their host specificity. Several models follow the matching-alleles assumption, a classic representation of genetic specificity in which each host genotype is susceptible to a different "matching" parasite genotype and resistant to all others. In finite populations, increasing host diversity decreases the host density required for a parasite to spread (Lively 2010a) and the size of an epidemic (Ashby and King 2015). Diversity limits disease spread even in very large populations, because it reduces the frequency of a parasite's matching host genotype ($\bar{R}_0 = B/G$ where B is the realized fecundity of the parasite and G is the number of host genotypes in the population) (Lively 2010a). Lively (2016) added reciprocal adaptation to these models, showing that when the host population becomes dominated by a single host genotype, adaptation of the parasite population to the common host escalates R_0. Mikaberidze et al. (2015) varied the degree of genetic specificity, demonstrating that the prevalence of infection in mixtures relative to monocultures declines with increasing specificity and number of host genotypes in the mixture (see also Gumpert and Geiger 1995; Ohtsuki and Sasaki 2006).

Does genetic diversity in fact limit parasitism? Until relatively recently in the history of this idea, the nature of the evidence was observational. The first direct experimental tests began in the 1950's with mixtures of different varieties of the same crop (varietal mixtures) (Rothman and Frey 1953; Leonard 1969). Crop experiments have typically compared field plots planted with monocultures and mixtures of a few varieties with known disease resistance phenotypes (e.g. resistant or susceptible). Many specifically addressed fungal diseases of wheat and barley. Their results clearly support a reduction in parasitism with diversity: of the 55 studies included in a meta-analysis by Gibson and Nguyen (2021), 48 reported a mean reduction in parasitism in mixtures relative to the means of their component

monocultures. The estimated effect of diversity is staggering: mixtures reduced estimates of parasitism by ~50% on average relative to monocultures (see also Huang et al. 2012). In the most famous example of the protective effect of genetic diversity, mixtures of japonica and indica rice varieties had 75–95% less rice blast than the means of their component monocultures (Zhu et al. 2000). This massive effect may reflect parasite specificity: japonica and indica rice differ in the rice blast lineages to which they are susceptible (Liao et al. 2016).

Enthusiasm for the diversity-disease connection spilled over to evolutionary biology (Haldane 1949) and conservation (Elton 1958; O'Brien and Evermann 1988), and experiments on non-crop systems began in the late 1980's (Jarosz and Levy 1988; Alexander 1991; Schmid 1994). These studies have tested the effect of host diversity in a wide range of host species, from plants to invertebrates to bacteria. Experimental designs vary substantially: some mix clonal or family lineages, while others manipulate mate number to increase offspring diversity. In contrast to crop studies, phenotypes of host genotypes are often unknown, so mixtures are constructed for genetic diversity alone, blind to the consequences for phenotypic diversity in disease resistance (i.e. functional diversity). It is thus all the more striking that genetic diversity still has a negative effect on parasitism in these non-crop experiments: two independent meta-analyses reported moderate reductions in parasitism (~20%) with genetic diversity (Ekroth et al. 2019; Gibson and Nguyen 2021). Altermatt and Ebert (2008) provided one of the clearest demonstrations of this effect: they established *Daphnia magna* populations with high diversity (10 genotypes) and low diversity (1 genotype). Host genotypes were randomly selected from different natural rock pools, so traits did not differ systematically between hosts in the two diversity treatments. Moreover, each host genotype was represented in only one population, so each replicate host population represented an independent test of its diversity level. They then tracked the spread of a microsporidian parasite for three years. The parasite spread more rapidly and maintained higher prevalence in low diversity populations. These studies established that the benefits of genetic diversity are not limited to the unique genetics and environments of crops. Together, this large body of experimental work leaves little doubt that, on average, genetic diversity limits parasitism in host populations.

Applying the hypothesis

Given the weight of evidence that genetic diversity limits parasitism and the long-standing acceptance of this hypothesis as "conventional wisdom" (King and Lively 2012), how are we making use of this idea in a basic and applied sense? Evolutionary biologists, agricultural researchers, and conservationists have all found inspiration in this idea, spurring the development of independent fields built on a shared foundation. In this section, I provide an overview of the opportunities and challenges presented by the diversity-disease connection in these three areas of research.

In agriculture

The link between diversity and disease initially emerged in response to the devastation wreaked by epidemics in crop fields. Therefore, the agricultural community has decades

of practical experience with the benefits and challenges of genetic diversification as a tool in disease management. The interest in diversity stems from its potential to both promote crop yield within a growing season and protect valuable resistance genes from parasite counter-adaptation ("durable resistance" - Mundt 2014; Brown 2015). Diversity also enhances resilience in the face of many other biotic and abiotic variables, like insect pests and drought (Hajjar et al. 2008; Grettenberger and Tooker 2015; Yang et al. 2019). As a result, varietal mixtures have larger, more stable yields on average, with greater gains when disease pressure is high (Kiær et al. 2009; Borg et al. 2018; Reiss and Drinkwater 2018).

Given these positive results, how, and to what extent, are diversification strategies adopted in agriculture? There are many comprehensive reviews of the strategies used to increase genetic diversity for disease protection in crops (Browning and Frey 1969; Wolfe 1985; Smithson and Lenne 1996; Mundt 2002; Finckh and Wolfe 2006; Newton et al. 2009). I provide a brief overview of the key strategies and problems. Though these concepts can be extended to other domesticated organisms (e.g. microbes - Rahn 1922; livestock - Bruford et al. 2015; fish - Ren et al. 2018; forestry - Ingvarsson and Dahlberg 2019), I focus on crop plants given the depth and breadth of research in this area.

A simple and effective diversification strategy is to plant mixtures of multiple distinct crop varieties. Historically, agriculture entailed the planting of multiple landraces, which are highly diverse lineages selected for performance in local areas. These practices persist today in many regions (Villa et al. 2007; Jarvis et al. 2008). Surveys show that small-scale farmers continue to grow more than one variety of a crop, with communities and regions collectively growing many varieties (Jarvis et al. 2008; Kiwuka et al. 2012; Mulumba et al. 2012; Katwal et al. 2015; Tiongco and Hossain 2015; Ruelle et al. 2019). Seeds may be mixed randomly or spatially, in rows or small plots (Mulumba et al. 2012). Mixtures do not appear to be assembled specifically for disease protection; many factors motivate the preservation of varietal diversity on small farms (Perales et al. 2003; Jiao et al. 2012; Dedeurwaerdere and Hannachi 2019). The Yunnan rice terrace system provides a compelling example of long-term mixture use: a 2008 survey reported that residents of Yuanyang County draw from at least 47 landraces to plant complex mosaics of rice genotypes in these ancient mountain terraces. This diversity may explain the relatively high yield and very low disease impacts in this region (Jiao et al. 2012; Liao et al. 2016; Dedeurwaerdere and Hannachi 2019). In contrast, industrial agriculture and commercial breeding has historically been dominated by the pursuit of uniformity (Newton et al. 2009; Wolfe and Ceccarelli 2020). Several large-scale programs have reduced disease by introducing varietal diversity at regional scales. Famously, the former German Democratic Republic converted the majority of barley acreage to varietal mixtures during the 1980's to control powdery mildew, and the fraction of fields with severe mildew infections declined from 50% to 10% (rev. in Finckh et al. 2000; Mundt 2002). Such programs have fostered optimism about the growth of mixtures in intensive agriculture, notably for wheat and barley, but data on the frequency of their use remains sparse (Finckh et al. 2000; Mundt 2002; Newton 2009; Wolfe and Ceccarelli 2020).

Multilines provide a more targeted alternative to varietal mixtures (Borlaug and Gibler 1953; Browning et al. 1964; Groenewegen 1977). Multilines mix genotypes that resemble one another in all but the pathogen genotypes to which they are susceptible. Transgenic

methods can produce near-isogenic lines that vary only at specific resistance loci (Brunner et al. 2012). Several multilines have been successfully deployed for control of specific diseases (Smithson and Lenne 1996). In 2009, governmental and coffee organizations in Columbia supported farmers in replanting >50% of coffee fields with a resistant multiline, driving coffee rust incidence down from >40% to 3% by 2013 (Avelino et al. 2015). The advantage of multilines is that they preserve crop uniformity while incorporating functional diversity for resistance to a focal parasite. They have proven less popular than mixtures, however (Mundt 2002): their genetic base is narrow, restricting the potential benefits of diversification, and they can be challenging to breed.

Though I focus on intraspecific diversity, the protective effect of diversification can also be achieved by increasing interspecific diversity in space or time. Intercropping – the practice of planting multiple species in spatial proximity – remains a dominant practice in many parts of the world, but it is rare in intensive agriculture where the varied traits of mixed species impede mechanization (rev. in Brooker et al. 2015). Rotation – the practice of alternating between two or more species in time – has much more adherence in intensive agriculture: USDA survey data reported that, from 1996–2010, 82–94% of US wheat, corn and soybean acreage was grown under rotations of 1–3 years (Wallander 2020). Adoption of this practice does, however, vary with location, crop species, and a crop's current value (Plourde et al. 2013; McBride et al. 2018). There are many differences between the effect of inter- and intraspecific diversity on disease. From a practical standpoint, however, both have the potential to limit parasitism (Curl 1963; Boudreau 2013; Civitello et al. 2015).

Scientific and technological advances hold enormous promise in furthering the pursuit of genetic diversification in agriculture. Landraces and crop wild relatives serve as valuable sources of genetic variation in disease resistance (Dinoor 1970; Harlan 1976; Dempewolf et al. 2017). For example, wild relatives of potatoes show extensive variation in resistance to *P. infestans* (Pérez et al. 2014; Karki et al. 2021). Genetic mapping and modification tools can readily identify and mobilize these resistance loci for use in breeding new crop varieties (Arora et al. 2019; Wolter et al. 2019). Critically, these technologies can and should be used for innovative long-term management of disease risk through dynamic diversification in space and time, rather than short-term maximization of resistance by widespread deployment of resistance loci (McDonald 2014; Stam and McDonald 2018). Ecological and evolutionary theory provide guidance for how to implement diversification in breeding and planting programs so as to minimize the spread and adaptive potential of parasites (Zhan et al. 2015; Wuest et al. 2021). This accumulation of scientific, technological, and conceptual knowledge argues that genetic diversification in agriculture is no longer limited by awareness of the problem or by breeding technology. Rather, progress depends upon the social, regulatory and economic factors that govern information exchange, planting practices, and access to diversity at the regional and farm level (Finckh 2008; Labrada 2009; Lin 2011; Louwaars 2018; Wolfe and Ceccarelli 2020; Halewood et al. 2021).

In evolutionary biology

I now move on to evolutionary biology, where the relationship between diversity and disease contributed to the development of foundational evolutionary and coevolutionary

theory. This idea is a key component of hypotheses on rare advantage and the evolution of reproductive modes. Haldane (1949) helped lay the groundwork for these hypotheses. Generalizing from the collapse of Gros Michel due to fusarium wilt and the consistent ability of rust fungi to adapt to infect initially resistant wheat varieties, Haldane argued that parasite populations rapidly adapt to infect common host genotypes in a population. Therefore, rare host genotypes have a fitness advantage in the presence of parasites, and genetically diverse host populations - with more rare genotypes - maintain lower levels of parasitism. He hypothesized that this parasite-mediated rare advantage explains the immense variation in parasite resistance maintained in host populations.

This line of reasoning has been applied to explain polyandry (multiple mating by females) in social Hymenoptera. Multiple mating appears paradoxical in eusociality: if kin selection explains the evolution of eusociality, why do some social insects engage in mating behaviors that reduce the genetic relatedness of nest mates? Polygyny (multiple queens) is similarly paradoxical (Hughes et al. 2008b). Hamilton (1987) and Sherman et al. (1988) hypothesized that behaviors that increase genetic variation are favored because they reduce the potential for parasites to severely damage a colony. Experimental tests of this hypothesis report striking reductions in parasitism when colonies are established by females mated with multiple, unrelated males (e.g. Baer and Schmid-Hempel 1999; Tarpy and Seeley 2006) (though see Schmidt et al. 2011).

Though the idea that polyandry reduces disease was developed for eusocial Hymenoptera (Soper et al. 2021), there is some evidence for related phenomena in other taxa. Soper et al. (2014) found that female snails increased their mating rate and number of distinct mating partners when exposed to native parasites. A recent meta-analysis of a taxonomically broad dataset supports the idea that parasites inflict particular damage when members of a group are related: in the presence of parasites and herbivores, mortality rates increase with relatedness of group members, even though grouping with related individuals appears to carry a fitness benefit in the absence of enemies (Bensch et al. 2021).

The idea that genetic diversity defends against parasites also features as a crucial assumption of the Red Queen Hypothesis, a major hypothesis for the maintenance of sex. This hypothesis seeks to explain why sexual reproduction is maintained when the necessary production of male offspring means that sexual females have half the per-capita birth rate of asexual females (Maynard Smith 1971; Gibson et al. 2017). The Red Queen hypothesis argues that coevolving parasites counterbalance the cost of sex, because the potential to produce genetically diverse offspring gives sexual females an advantage over asexual females in the presence of parasites. If parasites rapidly adapt to infect common clonal lineages, then a fit asexual genotype becomes a target of coevolving parasites when it reaches high frequency (e.g. Lively and Dybdahl 2000). Meanwhile, parasite spread and adaptation is stymied by the diversity of rare genotypes that constitute sexual lineages (Jaenike 1978; Hamilton 1980; Bell 1982).

There is significant empirical support for the Red Queen hypothesis (rev. in Lively and Morran 2014). In one illustrative body of work on sweet vernal grass (*Anthoxanthum odoratum*), Kelley et al. (1988) planted paired arrays of clonal progeny and sexual progeny

from the same parent plant. The fitness of sexual progeny was 1.43 times that of their paired asexual siblings. Were parasites responsible for this large fitness difference? Aphid infestation reduced survival by 23% for groups of related *A. odoratum* relative to groups of unrelated plants (Schmitt and Antonovics 1986). Moreover, groups of clonal progeny had double the prevalence of an aphid-transmitted virus relative to groups of sexual progeny, suggesting disease reduction as a mechanism for the fitness advantage of sexual progeny. Individuals also had much higher infection rates when planted with their clonal siblings than with unrelated individuals (Kelley 1994). As a whole, these experiments and many others lend weight to the idea that coevolving parasites pose a greater risk to genetically depauperate populations of hosts and impose negative-frequency dependent selection that maintains genetic variation in host populations.

What relationship do we then predict to find between genetic diversity and disease in natural populations? If parasites transmit more readily between closely-related individuals, we intuitively predict a negative correlation between markers of genetic diversity and parasitism across host populations (e.g. Whiteman et al. 2006). However, by preferentially infecting hosts of common genotypes, parasites can impose negative frequency-dependent selection, which maintains genetic variation in coevolving host populations. By this argument, we predict a positive correlation between diversity and parasitism (e.g. King et al. 2011). Thus the same process – the limited ability of parasites to spread between unrelated hosts– can generate a negative or a positive correlation between host diversity and parasitism depending on whether host populations evolve in response to parasite selection (Meagher 1999). Coevolutionary simulations by Lively (2021) demonstrate that even when genetic diversity and parasite prevalence have a strong causal relationship, the measured correlation between these two variables can vary from negative to zero to positive. Consistent with this theoretical work, Gibson and Nguyen (2021) found no mean correlation between genetic diversity and parasitism in observational studies of natural populations. They did, however, find strong negative correlations of diversity and parasitism for threatened and island host populations, where founder effects and reduced genetic variation may limit the potential for hosts to evolve in response to parasite selection. In summary, for natural populations, the absence of a correlation between genetic diversity and parasitism, or even a positive correlation, should not be taken as evidence against the significance of host diversity in limiting parasitism. This important lesson from coevolutionary theory bears upon interpretation of data for conservation purposes.

In conservation

Lastly, I review the significance of the diversity-disease connection as a driver of conservation research and policy. The relationship between genetic diversity and disease matters in conservation because it predicts that the loss of genetic diversity during population bottlenecks puts populations at heightened risk of disease epidemics. This idea gained traction in the 1980’s with epidemics in threatened vertebrate species (O’Brien and Evermann 1988), including canine distemper in black-footed ferrets (Williams et al. 1988) and feline infectious peritonitis in captive cheetahs (O’Brien et al. 1985).

The problem begins with the reductions in population size that define threatened populations. These population bottlenecks are predicted to drive particularly large declines in allelic diversity of loci involved in disease resistance. If hosts with rare alleles at resistance loci have an advantage in the presence of coevolving parasites, then negative frequency-dependent selection maintains many alleles, with few to none at high frequency in a host population (Clarke 1976; Tellier and Brown 2007). Indeed, genes linked to disease resistance typically show extremely high allelic diversity relative to the rest of the genome (Bodmer 1972; Hedrick 1998; Rose et al. 2004; Norman et al. 2017; Koenig et al. 2019). Allendorf (1986) demonstrated that an allele's probability of retention after a bottleneck declines with the size of the bottleneck, the number of other alleles at the locus, and the initial rarity of the allele. Thus individuals in declining populations are predicted to become relatively much more similar to one another at loci involved in disease resistance. Population bottlenecks can also increase the frequency of homozygous individuals, who may be more susceptible to parasites because of their limited repertoire of resistance alleles (Oliver et al. 2009; Radwan et al. 2020). Allendorf (1986), however, predicted that allelic richness at resistance loci declines much more dramatically than heterozygosity during population bottlenecks.

Experimental and observational data support the prediction that the genetic homogeneity of bottlenecked populations increases their disease risk. Marden et al. (2017) found a negative relationship between local population size of six tropical tree species and diversity of parasite resistance genes (relative and absolute abundance of nonsynonymous polymorphisms). Population size did not, however, correlate with diversity at other loci. Lower resistance gene diversity corresponded to reduced induction of defense genes in response to parasites and less variation among maternal families in susceptibility. For vertebrate populations, bottlenecked populations show reduced diversity at MHC loci, key immune genes involved in self-nonself recognition (O'Brien et al. 1985; Mikko and Andersson 1995; Eimes et al. 2011; Sutton et al. 2015) (though see: Aguilar et al. 2004; Jarvi et al. 2004). Limited MHC diversity likely contributed to the rapid spread of two transmissible facial cancers in Tasmanian Devils: devils fail to recognize and resist transmissible tumors in part because host and parasite share MHC alleles that are common in devil populations (Siddle et al. 2007; Cheng et al. 2012; Caldwell et al. 2018). Importantly, neutral genetic diversity can also strongly inform disease risk: for populations of the endangered Italian agile frog, genetic diversity at microsatellite loci declines with founder events and population isolation (Garner et al. 2004). Pearman and Garner (2005) exposed populations subsampled from this diversity gradient to an emerging virus that had not yet spread to these populations. After exposure to a low dose of virus, low diversity populations experienced 100% mortality by the experiment's midpoint, while high diversity populations persisted for the duration. These studies validate the concern that threatened populations are genetically predisposed to more severe outbreaks upon exposure to parasites.

In contrast, the ecology of threatened populations can limit their risk of initial exposure to parasites. Threatened populations may be too small and fragmented to support parasite populations (Carlsson-Granér and Thrall 2002). Altizer et al. (2007) reported fewer parasite species infecting threatened primate species relative to non-threatened primates. Gibson et al. (2010) found a lower prevalence of anther-smut disease (*Microbotryum violaceum*) on

threatened vs. non-threatened *Silene* species, and lower richness of fungal parasite species on federally endangered vs. non-endangered plant species (see also Smith et al. 2006; Heard et al. 2013; Farrell et al. 2015). Thus, there is a contrast between the genetic vulnerability of threatened populations and their ecological defense. This contrast means there may be high variability in the degree to which infectious disease actually impact threatened populations: parasite exposure may be rare, but these rare exposure events – often via spillover of parasites from neighboring species (Pedersen et al. 2007; Das et al. 2020) – can have devastating consequences in naïve, genetically homogeneous populations (Duxbury et al. 2019). This potential for extreme variability argues for prioritizing infectious disease management in conservation, even when disease does not appear to pose an immediate problem.

Given these arguments, how should the genetics of threatened populations be managed to reduce disease risk? This question raises the important and interesting challenge of how best to maintain and augment genetic diversity. Gene flow can rapidly restore genetic diversity, particularly for loci with rare advantage (Muirhead 2001; Fijarczyk et al. 2018; Phillips et al. 2018), but it can also generate outbreeding depression (Frankham et al. 2011). A quantitative synthesis addressed this problem, finding a consistent net fitness benefit of gene flow for populations thought to be genetically depauperate and/or inbred (Frankham 2015) (see also Fitzpatrick et al. 2020). Decisions about breeding and translocations also require a weighing of neutral vs. functional diversity. Some have argued that conservation programs should focus less on increasing neutral diversity and instead actively increase functional diversity, notably diversity at loci under balancing selection (Teixeira and Huber 2021). In an earlier version of this argument, Hughes (1991) proposed that vertebrate breeding programs be specifically designed to prioritize MHC diversity. This viewpoint has been sharply criticized as overly simplistic and counter to scientific evidence (Miller and Hedrick 1991; Vrijenhoek and Leberg 1991; DeWoody et al. 2021). Akin to the issues with crop multilines, prioritizing specific immune loci neglects diversity at loci unrelated to disease but nonetheless valuable for adaptation and long-term stability (Radwan et al. 2010). Moreover, in wild host-parasite systems, we have not characterized the majority of loci underlying variation in the diverse strategies hosts use to fight parasites in natural settings. Thus prioritizing one to a few resistance loci will not reflect genetic diversity at the full suite of loci involved in defense. The experimental literature provides valuable insight on this problem: parasitism declines with increased genetic diversity, even when diversity is increased without consideration of its functional consequences (Baer and Schmid-Hempel 1999; Altermatt and Ebert 2008; Kristoffersen et al. 2020). Currently, the most tractable option in conservation genetics is the maintenance and augmentation of neutral genetic diversity (DeWoody et al. 2021), and the data argue that this approach works for reducing disease risk in threatened populations (Gibson and Nguyen 2021).

Open questions on genetic diversity and disease

The rich and varied work reviewed above has built a deep conceptual foundation on the link between genetic diversity and disease. Looking towards the future, what new conceptual questions does this foundation compel us to ask? Below, I outline several outstanding problems.

When does genetic diversity fail to limit parasitism?

The mean effect of diversity on parasitism is negative, but it varies dramatically, with some experiments reporting increased parasitism with diversity (Smithson and Lenne 1996; Ekroth et al. 2019; Gibson and Nguyen 2021). What factors explain this variation? This question matters both for understanding the mechanisms underlying the relationship between diversity and disease and for applying genetic diversification as a management tool.

Meta-analyses have attempted to identify factors that explain variation in the effect of genetic diversity on disease risk in experiments with non-crop hosts. Ekroth et al. (2019) examined seven factors that differed between experiments, including aspects of experimental design, host traits, and parasite traits. They found a negative effect of diversity on microparasite infection but not macroparasite infection and in field settings but not laboratory settings. Gibson and Nguyen (2021) did not replicate these findings: the effect of genetic diversity did not vary with any of 11 factors tested. Taken together, these two meta-analyses do not consistently identify factors that explain variation in the effect of genetic diversity. I believe this reflects limitations of the available data: the analyzed studies differ in too many ways to isolate a single variable with much power, and very few studies explicitly test hypotheses for variation in the effect of diversity. It would be particularly valuable to test the hypothesis that the protective effect of host diversity grows with increasing amounts of genetic variation in both the host and parasite populations (see below). Both meta-analyses found insignificant trends consistent with this idea. Controlled experiments are needed to test these hypothesized effects in isolation, building off examples like van Houte et al. (2016) and Ganz and Ebert (2010).

For crops, variation in the performance of varietal mixtures is a key obstacle to their widespread adoption (Smithson and Lenne 1996; Cowger and Mundt 2002; Mundt 2002, 2014). The protective effect of genetic variation in crop fields is predicted to increase with the number of functionally distinct host genotypes in the mixture (Mundt et al. 1996), host specificity of the parasite population (Lively 2010a; Mikaberidze et al. 2015), scale of mixture deployment (Newton and Guy 2011), and parasite dispersal ability (Cox et al. 2004). Evidence for each of these predictions is mixed (Mundt 2002). Most syntheses on the drivers of variation have largely been qualitative, but the extent of experimental work in crop systems suggests that quantitative syntheses may have sufficient sampling to test specific hypotheses for factors that explain variation in the effect of diversity (e.g. Huang et al. 2012; Gibson and Nguyen 2021). Identification of sources of variation would enhance commercial appeal by facilitating the design of more reliable mixtures (Lopez and Mundt 2000; Mikaberidze et al. 2015; Wuest et al. 2021).

Does host diversity stabilize disease risk?

Genetic variation stabilizes population dynamics (Forsman and Wennersten 2016). For example, genetic variation reduces extinction rates and reduces variation in population sizes for experimental populations of flour beetles (Agashe 2009). Crop yield is also less variable across years for varietal mixtures relative to monocultures (Reiss and Drinkwater 2018).

Does host diversity also reduce variation in parasitism? Springbett et al. (2003) simulated epidemics in host populations with and without diversity in susceptibility and found that host diversity can reduce variation in parasitism across populations. Populations with diversity were more likely to experience small epidemics than populations without diversity, but they were less likely to have major epidemics (>10% of individuals infected). This finding supports the idea that diverse populations may not avoid infection altogether – they are likely to contain some susceptible individuals – but the presence of resistant hosts limits parasite spread. In an experimental test of this idea, Ganz and Ebert (2010) found that host diversity reduced variation in parasite prevalence across *D. magna* populations, though only at intermediate levels of parasite diversity (see also Tarpy 2003; Bensch et al. 2021).

Genetic diversity could also dampen fluctuations in the size of parasite populations through time. Dwyer et al. (2000) demonstrated theoretically that heterogeneity in susceptibility stabilizes epidemiological dynamics by reducing the fraction of hosts infected in a single epidemic. These models suggested that the degree of heterogeneity in susceptibility observed in gypsy moth populations could stabilize the dynamics of baculovirus epidemics in nature. Coevolutionary theory further predicts that genetic diversity reduces fluctuations in parasite population size through time by limiting rapid expansion as parasites adapt to common host genotypes (Lively 2010b; Gibson et al. 2018). These studies make important predictions that have rarely been directly tested. The answers could prove particularly valuable for agriculture and conservation, where managing variability in disease, to limit the risk of very large outbreaks, may reap more long-term benefits than managing mean levels of disease.

How much is enough?

King and Lively (2012) raised the idea of the diversity threshold, the level of host diversity at which parasite transmission is sufficiently impeded that R_0 falls below one. Their simulations show that, with high host specificity of parasites, increasing the number of host genotypes in a population can drive R_0 below one, even if the density of the host population is more than doubled to accommodate the new host genotypes. Mikaberidze et al. (2015) also identified diversity thresholds in their simulations of varietal mixtures, demonstrating that the number of host genotypes necessary to eliminate parasites increases with decreasing specificity and increasing transmission rates. As parasites become less specialized, they can infect multiple host genotypes, so disease eradication becomes less likely, even at very high diversity.

Practical application of diversity thresholds requires empirical estimates of the degree of genetic variation necessary to prevent initial invasion and subsequent spread of disease in natural populations. This represents a significant but worthwhile challenge: quantification of diversity thresholds has clear value for agriculture, conservation, and management of human disease vectors (e.g. Campbell et al. 2010).

Does parasite diversity increase parasitism?

Genetic diversity of parasites has received very little attention relative to host diversity. Experiments have addressed the effect of parasite diversity on features of individual

infections, like virulence and transmission (e.g. Davies et al. 2002; de Roode et al. 2005). The question posed here is at the population-level: do genetically diverse parasite populations have on average higher performance at the population level (e.g. higher prevalence) than genetically homogeneous parasite populations? If parasite genotypes vary in which host genotypes they are best able to infect, then parasite diversity should increase the establishment and spread of parasites in the host population by increasing the probability that a host genotype encounters an infective parasite genotype (sampling effect). Parasite genotypes may also facilitate one another, perhaps by compromising the immune system (complementarity) (Karvonen et al. 2012; Halliday et al. 2020a). Beyond the establishment phase, genetic diversity accelerates adaptation to the host population. On the other hand, parasite diversity could reduce parasitism in a host population if parasite genotypes interfere with one another (Lannou et al. 1995).

Ganz and Ebert (2010) addressed this question by exposing *D. magna* populations to one, two, three, or four strains of a microsporidia parasite, with total dose equal across diversity treatments. Mean parasite prevalence increased with parasite diversity, approximately doubling in going from one to four parasite genotypes. Mean prevalence increased more sharply for host monocultures than for genetically diverse host populations. This result suggests that parasite diversity increases average establishment success across a range of genetically distinct host environments, akin to the hypothesis that genetic diversity increases colonization success (Crawford and Whitney 2010; Vahsen et al. 2018). Moreover, this study supported the idea that the protective effect of host diversity varies with the diversity of the parasite population (van Baalen and Beekman 2006): diverse host populations had lower parasite prevalence than monocultures only when hosts were exposed to a diverse parasite population.

These findings argue that parasite diversity has value as a tool for increasing the mean establishment success of biological control parasites. Phage therapy uses viruses of bacteria (phages), rather than antibiotics, to fight bacterial infections in medical or agricultural settings. Phages tend to be quite specific, infecting only a subset of strains of a particular bacterial species (de Jonge et al. 2019). Hence, combining multiple phages with diverse specificities can increase the probability of controlling the bacterial infection initially and limit the evolution of resistance in the bacterial population (Chan and Abedon 2012). The same approach may prove useful in other biological control systems showing strong host specificity, like parasitoid wasps used in control of aphids (Rouchet and Vorburger 2014) and bacterial parasites used in control of plant-parasitic nematodes (Channer and Gowen 1992).

How do parasites evolve in genetically diverse host populations?

First, host diversity may slow the rate at which parasites evolve to overcome host resistance. Several recent experiments provide direct support for this hypothesis. Van Houte et al. (2016) generated bacterial genotypes that each recognized, and thus resisted, a distinct phage sequence via CRISPR-Cas immunity. Phage populations quickly evolved to overcome immunity in monocultures of single bacterial genotypes. As host diversity increased, the extinction rate of phage populations increased, indicating a failure to evolve to overcome

host immunity with increased host diversity. Host diversity may impede parasite adaptation through trade-offs in performance across genotypes (as in Sant et al. 2021) and through reduced opportunities for selection on any one host genotype (as in Chabas et al. 2018). The relative contribution of these two factors remains an open question (Bono et al. 2017; White et al. 2020).

If host diversity slows parasite adaptation, mixtures can be used as a tool to preserve valuable resistance mechanisms. In agriculture, varietal mixtures should increase the durability, or lifespan, of resistance genes (Zhan and McDonald 2013; Mundt 2014). This approach has been successfully implemented to delay evolution of resistance against *Bacillus thuringiensis* toxins in insect pest populations (Shelton et al. 2000; Tabashnik et al. 2008). Similarly, evolution to overcome vaccines may be limited by the variation in immune responses across individuals elicited by a single vaccine (Kennedy and Read 2017) or by the distribution of multiple vaccines against different targets of a single parasite (mosaic vaccination: McLeod et al. 2020). These practical applications raise the question of deployment: what distribution of diversity best limits parasite evolution – between-individual variation (i.e. mixtures of individuals with distinct resistance genes or vaccines), or within-individual variation ("pyramiding" of resistance genes in one host genotype or a single vaccine against multiple parasite genotypes)? Though theoretical treatments of this question do not agree (REX Consortium 2016; Djidjou-Demasse et al. 2017; Rimbaud et al. 2018), between-individual variation has growing experimental support as a brake on parasite evolution. Moreover, from a logistical perspective, mixtures can be constructed from existing diversity and readily changed by swapping in new components (e.g. distinct host genotypes), so they may prove to be quicker and cheaper in many cases.

A second prediction is that host diversity may select for generalist parasites. This hypothesis emerged in agriculture, when concerns surfaced that the use of varietal mixtures to limit parasitism in the short-term would come with the long-term price of "super" parasites able to overcome multiple resistance genes (Groth 1976; Marshall 1989; Lannou and Mundt 1996). Field trials demonstrated that barley mixtures favored generalist genotypes of the fungus *Blumeria graminis,* the causal agent of powdery mildew (Chin and Wolfe 1984; Huang et al. 1994, 1995). Chin and Wolfe (1984), however, argued that the reduced size of the fungal population in mixtures limited the threat posed by these generalists. Several experimental evolution studies have expanded upon this idea in phage-bacteria systems (see also Gibson et al. 2020; Ekroth et al. 2021 in nematode systems). The evolution of increased host range is predicted to peak at intermediate levels of host diversity: low diversity results in weak selection for increased host range, because parasites may frequently encounter the same host genotype, while high diversity slows the response to selection by limiting the effective population size of the parasite (Benmayor et al. 2009; Chabas et al. 2018). Consistent with this prediction, Common et al. (2020) found that generalist phages evolved readily in bacterial populations with intermediate diversity, but less so when host diversity was low and not at all when it was maximal. Sant et al. (2021) also reported the evolution of generalist phages in moderately diverse bacterial populations, where the high probability of encountering an alternate host genotype selected against specialists. Generalists had lower fitness on any individual host genotype, however, resulting in slower rates of phage adaptation in diverse bacterial populations. These experimental evolution studies differ from

prior genetic diversity-disease literature in following host and parasite populations over multiple generations (see also Altermatt and Ebert 2008). This approach has made it feasible to address an important open question: what are the relative contributions of ecological vs. evolutionary processes to the protective effect of genetic diversity (e.g. van Houte et al. 2016; Common et al. 2020)?

Conclusion

I have provided a perspective on the historical development, current state, and possible future of the hypothesis that genetic diversity in host populations limits parasitism. Though disease protection is among the most well-supported consequences of genetic diversity in populations, it is but one of the proposed benefits of diversification. Many studies speak to the broader role genetic diversity plays in supporting adaptation, growth, and stability for wild and managed populations (reviewed in Hughes et al. 2008a; Forsman and Wennersten 2016; Reiss and Drinkwater 2018).

This clear significance of genetic diversity contrasts with its low prioritization in management of wild and domesticated species. The agricultural community has long warned of “genetic erosion” or the loss of genetic diversity in crop species (Browning 1972; Harlan 1972; Commission on Genetic Resources for Food and Agriculture 2010; Van de Wouw et al. 2010a; Thormann and Engels 2015). This loss has been attributed to early bottlenecks under domestication and dissemination (Vavilov 1926; Haudry et al. 2007), the loss of diverse, local landraces (Van de Wouw et al. 2010a; Bonnin et al. 2014; Sthapit et al. 2020), and the promotion of uniformity by twentieth century plant breeding’s selection for desirable traits and dissemination of high-yielding lineages (Jordan et al. 1998). Strikingly, Gatto et al. (2021) estimated that the adoption of a few commercial varieties resulted in an 88% reduction in acreage planted with diverse landraces in Asia from 1970–2014. Hopes of reversing this loss of genetic variation rest in part on the preservation of landraces and wild crop relatives in national and international germplasm centers (Hoisington et al. 1999; Halewood et al. 2020). The long-term success of these collections requires more consistent characterization and curation of their genetic resources (Singh et al. 2019) and better representation of wild crop relatives, which are in urgent need of conservation (Khoury et al. 2020; Warschefsky and Rieseberg 2021). While historically blamed for the genetic erosion of crop species, scientific plant breeding has a critical role to play in leveraging these resources to maintain diversity in space and time by testing and disseminating old varieties and breeding new ones (Van de Wouw et al. 2010b; Swarup et al. 2021). Progress depends equally on changes to regulatory structures to prioritize access to diversity in the breeding and sharing of varieties (Louwaars 2018). Motivation for these changes is in place: there is a general consensus in the community that homogeneity leaves crops vulnerable to collapse in the face of disease and environmental change.

Relative to crop species, genetic diversity in populations of wild species has received even lower prioritization. The scope of the problem is emerging. The World Wildlife Fund’s Living Planet Index reports a 68% drop in population sizes of vertebrates since 1970, which is expected to drive major losses of genetic diversity (WWF 2020). Indeed, evaluating trends for 91 species (largely vertebrates) over the past ~100 years, Leigh et al. (2019)

estimated a mean decline in allelic richness of 6.5%, with an even larger decline of 31% for island species. Yet the Convention on Biological Diversity and similar initiatives have been criticized for a lack of commitment to conserving genetic diversity beyond crops and livestock, and a failure to articulate specific, measurable goals for the future (Laikre 2010; Willoughby et al. 2015; Hoban et al. 2020; Hoban et al. 2021b; Thomson et al. 2021). Hoban et al. (2021a) argues that the necessary knowledge, tools, and infrastructure are now in place to set quantitative goals for genetic diversity of wild species. They recommend ambitious global monitoring programs that leverage advances in collection of genetic and non-genetic data, data analysis, data sharing, and conservation policies and networks. For both wild and crop species, genetic diversity is a public good for which monitoring and maintenance is feasible and urgently needed.

I have devoted a substantial amount of this perspective piece to the diversity-disease connection in agriculture and conservation, because of the idea's historical development and its ongoing importance in resolving the major challenges facing these fields. To conclude, I'd like to emphasize that evolution is the undercurrent uniting the independent areas of research built on the hypothesis that genetic diversity limits parasitism. Indeed, the literature on the relationship of genetic diversity and disease provides a compelling example of the pervasiveness and value of evolutionary thinking across basic and applied scientific fields. Evolutionary principles have often been enlisted to justify the pursuit of homogeneity. For example, breeding of domesticated species has commonly sought to create and distribute optimal genotypes via selection for favorable traits, like parasite resistance. Yet the data on genetic diversity and disease soundly reject homogeneity. They teach the opposite lesson: for managing infectious diseases, the most powerful evolutionarily-informed approach is the relentless pursuit of diversity.

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