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Role of dispersal in resistance evolution and spread

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Abstract

Gene flow via immigration affects rate of evolution of resistance to a pest management tactic, while emigration from a resistant population can spread resistance alleles spatially. Whether resistance detected across the landscape reflects ongoing *de novo* evolution in different hotspots or spread from a single focal population can determine the most effective mitigation strategy. Pest dispersal dynamics determine the spatio-temporal scale at which mitigation tactics must be applied to contain or reverse resistance in an area. Independent evolution of resistance in different populations appears common but not universal. Conversely, spatial spread appears to be almost inevitable. However, rate and scale of spread depends largely on dispersal dynamics and interplay with factors such as fitness costs, spatially variable selection pressure and whether resistance alleles are spreading through an established population or being carried by populations colonizing new territory.

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Role of dispersal in resistance evolution and spread

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Gene flow via immigration affects rate of evolution of resistance to a pest management tactic, while emigration from a resistant population can spread resistance alleles spatially. Whether resistance detected across the landscape reflects ongoing *de novo* evolution in different hotspots or spread from a single focal population can determine the most effective mitigation strategy. Pest dispersal dynamics determine the spatio-temporal scale at which mitigation tactics must be applied to contain or reverse resistance in an area. Independent evolution of resistance in different populations appears common but not universal. Conversely, spatial spread appears to be almost inevitable. However, rate and scale of spread depends largely on dispersal dynamics and interplay with factors such as fitness costs, spatially variable selection pressure and whether resistance alleles are spreading through an established population or being carried by populations colonizing new territory.

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Introduction

Insect dispersal plays a pivotal role in both the evolution of resistance to an insecticide or other management tactic at a location, and in the rate and pattern of its spatial spread [1,2]. Dispersal by individual insects is the fundamental process by which resistance genes move across a landscape. Consider a population where resistant individuals are favored by local selection. At its simplest level, immigration of susceptible individuals decreases the frequency of resistance alleles in the receiving population and thus slows the local rate of resistance evolution. Conversely, immigration of resistant individuals increases

resistance allele frequency and thus increases the rate of resistance evolution in that population. Immigration in one population presupposes emigration from another, and the rate of emigration of individuals from a resistant source population affects the rate of resistance spread in the landscape (Figure 1). The relative roles of *de novo* resistance evolution vs. subsequent spread can be of great practical importance because it determines the most appropriate mitigation strategy to be employed. The spatial scale at which mitigation tactics must be applied within the larger landscape to contain or reverse resistance that has evolved in a local ‘hotspot’ depends on dispersal dynamics of the species. As critical as these rates of inflow and outflow are to all aspects of insect resistance management (IRM), they are poorly understood for most species. Accordingly, the complex dynamics of resistance evolution and spread are likewise difficult to characterize.

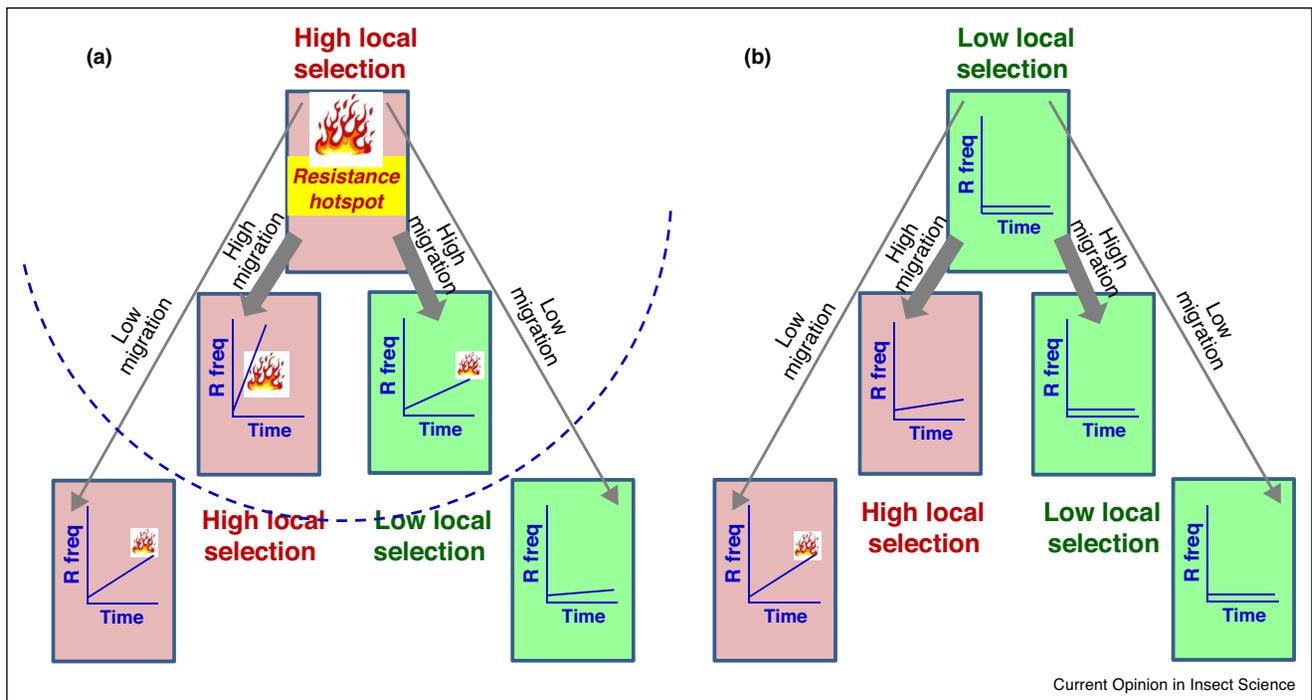
A distinction can be made between dispersal that moves resistance genes between existing populations by gene flow, and dispersal that moves resistance genes into new territory as the insect colonizes previously unoccupied habitat. The first involves a process that can be likened to an invasion of resistance alleles into parts of the larger metapopulation that originally had none. The second, colonization of new habitat by insects carrying resistance alleles conflates the spatial invasion of alleles via gene flow with the genetic consequences associated with geographic invasion by a species, such as bottlenecks. The evolutionary ecological outcomes of both processes can be quite interesting.

Spread of resistance among existing populations

Case study: *Culex pipiens* resistance allele clines

An especially well studied case of the spatial and temporal distribution of resistance alleles in established populations comes from the mosquito *Culex pipiens* in the south of France [3–6]. In this case, the dynamics of resistance were studied at a small geographical scale relative to dispersal distances. Consequently, alleles have usually been observed at migration-selection equilibrium. In this region there is an annual program of mosquito control whereby breeding sites within approximately 20 km of the Mediterranean coast are treated with insecticides every breeding season. This program relied heavily on organophosphate insecticides (OPs) until the mid 2000s, when they were replaced with *Bacillus thuringiensis*. Resistance by southern French populations of *C. pipiens* to OPs involves both mutations that render the OP target, acetyl cholinesterase, less sensitive to the insecticide, and that increase expression of detoxifying

Figure 1



Schematic conceptualization of the effects of rate of migration from (a) a hotspot of resistance, or (b) a wild-type susceptible population, into receiving populations of high or low selection for resistance on relative rates of increase in resistance allele frequency (R freq) over time (generations). The dashed arc indicates the region around the resistance hotspot within which mitigation tactics must be implemented to slow the spread of resistance alleles through the larger landscape. Determining the spatial scale at which mitigation will effectively contain spread of resistance from a hotspot depends in part on the insect's dispersal rate and distance, and on spatial variation in selection pressure across the landscape. In practice, this scale can be very difficult to determine. If it extends beyond the dimensions of a farm, implementation of coordinated mitigation tactics by growers across an area may be necessary, with all the difficulties that implies. Thus, rapid implementation of mitigation around a still-localized hotspot offers the best hope of containment (see Andow *et al.* [22*] for discussion in the case of *D. v. virgifera*).

esterases that degrade the insecticide. Both forms of resistance entail significant fitness costs in the absence of insecticide. The interplay of gene flow mediated by mosquito dispersal, selection for resistance near the coast, and fitness costs further inland produces clines in resistance allele frequencies. A joint analysis of the clines in target-site insensitivity and esterase overproduction produced an estimate of the standard deviation in parent-offspring dispersal of 6.6 km [3]. This rate of dispersal was sufficient to rapidly reestablish selection-migration equilibrium each year at both loci [4]. In the case of the *Ester* locus in southern France, the *Ester*² resistance allele increased in frequency between 1999 and 2002 but did not replace *Ester*⁴ despite a higher level of resistance, because it also imposed a higher fitness cost in the absence of insecticide [5]. After the use of OPs was discontinued in 2007, the *Ester*² allele was rapidly lost from the population. The *Ester*⁴ allele persisted but the cline in *Ester*⁴ frequency, while still significant, flattened markedly [6], presumably due to a combination of reduced selection at the coast and gene flow between the coast and inland.

Case study: spread of *Diabrotica virgifera virgifera* rotation resistance

Resistance to crop rotation in the western corn rootworm, *Diabrotica virgifera virgifera*, provided an opportunity to observe resistance spreading over a wide area as it occurred. Thus, the spatiotemporal dynamics of resistance were observed at a much larger geographical scale relative to adult dispersal distance than in the case of *C. pipiens* described above, so that alleles were not at migration-selection equilibrium during their years-long invasion of the surrounding metapopulation. The basic biology and history of adaptation to crop rotation by *D. v. virgifera* was comprehensively reviewed by Gray *et al.* [7]. Resistance to crop rotation is almost certainly based on a reduced preference for cornfields by females as oviposition sites. Thus in landscapes dominated by corn-soybean rotated crop fields, eggs (the overwintering stage) laid outside of corn have a better chance of hatching in a cornfield the following year than those that were laid in corn. In contrast to OP resistance in *C. pipiens*, the precise genetic basis of adaptation to crop rotation is not known. Recent research has focused on adaptations that allow

rotation resistant adult *D. v. virgifera* to cope with feeding on soybean foliage defended by plant protease inhibitors. Rotation resistant *D. v. virgifera* have elevated capthepsin-L protease activity, compared to wild-type beetles [8]. This difference is related to differences in the gut flora of rotation resistant and susceptible beetles [9] which, in turn, may be related to differences in the expression of antimicrobial and immune-related genes [10,11]. It is currently unknown if these differences are part of the proximate mechanism of resistance to crop rotation or, more likely, a secondary adaptation improving fitness of beetles that encounter more soybean in their environment due to their decreased fidelity to cornfields.

Adaptation to crop rotation spread steadily from the original 1987 focus in Piper County, Illinois over the subsequent two decades. By 2007 populations throughout most of Illinois and neighboring Indiana were adapted to crop rotation, as were some populations in adjacent states. Little to no general genetic differentiation was observed between rotation resistant populations and surrounding susceptible populations [12,13]. This, in combination with the observed pattern of spread suggests that resistance to crop rotation moved across the landscape as a result of gene flow among established populations. Resistance to crop rotation apparently ceased to spread about a decade ago, after most of the region in which corn-soybean rotation is extremely common was occupied. Ovipositing in non-corn environments becomes more costly as the probability that such environments will be rotated to corn the following year declines. Furthermore, the advantage of the host-selective wild type behavior increases as the presence of corn becomes a more reliable indicator that corn will be present the following year (*i.e.*, continuous planting). Simulation studies suggest that the evolution and spread of this adaptation is impeded by increasing diversity of vegetation in the landscape [14,15]. A decrease in crop diversity in favor of continuously planted corn could be enough to impede spread of rotation resistance.

In recent years, the region in which rotation resistance is a problem appears to have receded (*e.g.*, [16]). This may be related to the commercialization of rootworm-targeting transgenic corn expressing various insecticidal proteins derived from *Bacillus thuringiensis* (Bt). Growers tend to plant rootworm Bt corn even in rotated fields, either to protect against rotation resistant populations, or because elite high-yielding non-Bt hybrids are difficult to obtain [17]. This practice reduces the selective advantage to rotation resistant phenotypes in rotated fields, because mortality is as high as among susceptible phenotypes ovipositing in non-rotated Bt corn [18]. Modeling indicates that the prevalence of rotation resistance in the landscape can even decrease if growers plant Bt corn more frequently in rotated fields than continuous fields [19].

Box 1 Larval dispersal, premating adult dispersal, and efficacy of Bt refuge configurations.

The most common type of proactive IRM strategy for Bt crops involves planting a non-Bt variety – the ‘refuge’ – as a nursery of susceptible insects. Refuges are often planted as blocks or strips of the required spatial dimensions in or near the larger Bt fields. A recent trend in some crop systems is to mix the requisite percentage of non-Bt refuge seed in a bag with the Bt seed. There is ongoing concern about the effectiveness of this blended refuge strategy in slowing resistance evolution. Larval dispersal between Bt and non-Bt plants can result in a sublethal dose, promoting differential survival of heterozygotes over homozygous susceptible larvae, thus accelerating accumulation of resistance alleles in the population. Models generally affirm that larval dispersal leads to faster evolution of resistance in a blended than in a block refuge system [17,50], unless substantial (but, unfortunately, realistic) grower noncompliance is included for the latter [51]. Recent research indicates that larval movement in several lepidopteran pest species is a threat to the blended refuge strategy [52–54]. Although less extensive than lepidopteran caterpillars, dispersal rate of subterranean rootworm larvae between adjacent plants is high enough [55] to potentially compromise a blended refuge strategy, as observed in laboratory evolution experiments [56]. However, in the case of *D. v. virgifera*, a blended refuge has the possible offsetting advantage of promoting mating of refuge adults with adults emerging from Bt plants. Most *D. v. virgifera* females mate near their natal plant, which can increase assortative mating among beetles emerging within Bt and refuge blocks, thus compromising the block refuge strategy [22,57]. Improved mixing of resistant and susceptible adults is often considered an advantage of blended refuge, which can be true for other species with limited premating dispersal [58], such as *L. decemlineata* [24]. But the argument of improved mixing of adults in a blended refuge field does not apply to species where significant dispersal from the natal plant occurs before mating. For example, young European corn borer, *Ostrinia nubilalis*, females disperse long distances before mating [59], a behavior common among many Lepidoptera, especially migratory species.

Understanding the evolutionary dynamics of rotation resistance in *D. v. virgifera* is important because crop rotation is the favored tactic for mitigating the emerging problem of resistance to Bt corn [20,21]. How fast and how far Bt resistance may spread is of concern to farmers who must manage the risk of crop losses caused by a product that could start to fail. Mitigation tactics are most effective while resistance is still spatially localized [22,23]. For monophagous or oligophagous insects with low premating dispersal, like *D. v. virgifera* and the Colorado potato beetle, *Leptinotarsa decemlineata*, crop rotation can be an excellent tactic to both limit spread of a resistance allele and lower its frequency *in situ* [22,24]. Rate of premating dispersal also impacts efficacy of various types of IRM refuges (Box 1).

Spread of resistance during species invasion or range expansion

When insects disperse into new territory, their initial population sizes are often small. Species introduced into an entirely new territory can experience severe bottlenecks [25,26], as can ‘pioneer’ populations of a species that is expanding its existing range [27]. Small

populations at the front of a range expansion can result in ‘gene surfing’, whereby rare alleles and/or new mutations are catapulted to high frequency by drift at the front and are then carried forward as the front moves, generating allele frequency clines [28,29]. Even mildly deleterious alleles can surf to high frequency [30], presumably including resistance alleles with moderate fitness costs.

D. v. virgifera and *L. decemlineata*, two chrysomelid pests notorious for evolving resistance, have undergone both range expansions and introductions to new continents. For both species, the likely ancestral range was in Mexico, but significant pest populations first arose in the Plains regions of Nebraska and Kansas, followed by eastward expansion across the United States and Canada. Both species were also subsequently introduced into Europe. Resistance to cyclodienes in *D. v. virgifera* is due to a mutation in the target gamma-amino butyric acid receptor gene, which exhibits a cline of increasing frequency toward the east coast of the United States [31]. This is surprising given that cyclodienes were withdrawn from use over a decade before the species reached the east coast and may represent an example of gene surfing [31]. Unlike populations in the United States, introduced European populations of *D. v. virgifera* are uniformly resistant to cyclodienes and susceptible to organophosphates [32]. Neither class of insecticide has been used extensively to control *D. v. virgifera* in Europe, so the current pattern of insecticide resistance there is probably a consequence of the North American populations that acted as the sources for introductions in Europe and bottlenecks during the introduction process [32]. The frequencies of an organophosphate resistance allele in *L. decemlineata* show a surprising spatial distribution. The allele is fixed in ancestral Mexican populations, is at high frequency (0.95) in US populations, and is variable, but lower on average, in Europe [33]. This suggests that the species may have been preadapted to organophosphates but lost resistance alleles during bottlenecks upon introduction to Europe.

Increased resistance incidence across space: spread or independent evolution?

There is often uncertainty in the extent to which resistance evolves independently or spreads from a single source. Modeling indicates that the spatial scale over which resistance evolves depends in large part on the interplay between insect dispersal rate and the availability of refuge habitat in the landscape [60]. Multiple lines of evidence make it clear that *D. v. virgifera* resistance to various Bt toxins is evolving quickly and independently in local hotspots across a wide area [20,34,35]. Nevertheless, post-mating dispersal of *D. v. virgifera* can be extensive [36], and spatial spread from hotspots seems inevitable [22••]. Evidence suggests resistance spread from an unknown distance to fields in Iowa where damage to Cry34/35 Bt corn was detected [21]. The spatial

dimensions over which mitigation tactics must be employed to contain or eliminate a hotspot depends on a better understanding of long-range dispersal in this species, an area of active research [23•].

Codling moth, *Cydia pomonella*, dispersal seems to be mostly local, but with capacity for long-distance flights [37], causing uncertainty in whether regional variation in insecticide resistance is the result of independent evolution or spread [38]; most likely both processes are involved. Widespread resistance of *B. fusca* to Cry1Ab Bt corn developed rapidly after the crop’s introduction to South Africa, and was assumed to have evolved independently in different locations for widespread agronomic and refuge non-compliance reasons [39]. But, as explained by Peterson *et al.* [40], this is a pest with high dispersal capacity, and resistance could have spread quickly from a single location, especially given it is not a recessive trait. Population genetics analyses suggest that both phenomena are at work [41•]. Even in extreme cases, such as independent evolution of pyrethroid resistance in the Chagas’ disease vector, *Triatoma infestans*, at a micro-scale – for example, between neighboring dwellings – local spread from a focal point also seems to occur [42].

S. frugiperda is a complicated case where the relative roles of spread of Bt resistance by migration or independent evolution in hotspots remains uncertain. Cry1F resistance was detected in Puerto Rico in 2006 [43], and has since been found in Brazil [44] and parts of Florida [45]. *S. frugiperda* is a strong migrant, and the spread of Cry1F resistance from Puerto Rico to Florida by dispersing adults is possible. On the other hand, recent susceptibility surveys suggest resistance in different areas of Florida may be of independent evolutionary origin [46,47]. Resistance alleles were detected at low frequency in North Carolina, which receives annual migrants from Florida [48]. Population genetic and atmospheric trajectory analyses have effectively ruled out a Caribbean origin of the Cry1F resistance found in Brazil [49••].

Overall, theory and available data suggest that spatial and temporal distribution of resistance alleles differs depending on whether insect dispersal is spreading them among established populations or into new territory. In the former case, deterministic processes driven by selection, fitness costs and dominance appear to be central, whereas in the latter case, stochastic processes play a key role. One could argue that annual colonization of an agricultural field, or colonization by refuge insects of a Bt field cleared of conspecifics by the toxin, are cases of invasion on an accelerated temporal and micro-spatial scale. This seems analogous to the situation with *C. pipiens* mosquitoes in southern France, where resistance alleles annually come to migration-selection equilibrium at a small geographic scale relative to

individual dispersal distances. Comparing the dynamics of resistance evolution or spread in the case of classical invasion versus annual colonization of crops could be instructive for both. Large scale planting of Bt crops in concert with refuges to try and manage resistance evolution offers an exceptional opportunity to conduct such studies in a number of pest-crop systems.

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