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Abstract:

BACKGROUND: Resistance of pathogens and pests to antibiotics and pesticides worldwide is rapidly reaching critical levels. The common-pool-resource nature of this problem (i.e., whereby the susceptibility to treatment of target organisms is a shared resource) has been largely overlooked. Using herbicide-resistant weeds as a model system, we developed a discrete-time landscape-scale simulation to investigate how aggregating herbicide management strategies at different spatial scales from individual farms to larger cooperative structures affects the evolution of glyphosate resistance in common waterhemp (*Amaranthus tuberculatus*).

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RESULTS: Our findings indicate that high-efficacy herbicide management strategies practiced at the farm scale are insufficient to slow resistance evolution in *A. tuberculatus*. When best practices were aggregated at large spatial scales, resistance evolution was hindered; conversely, when poor management practices were aggregated, resistance was exacerbated. Tank mixture-based strategies were more effective than rotation-based strategies in most circumstances, while applying glyphosate alone resulted in the poorest outcomes.

CONCLUSIONS: Our findings highlight the importance of landscape-scale cooperative management for confronting common-pool-resource resistance problems in weeds and other analogous systems.

Keywords: Common-pool resources, cooperative weed management, herbicide resistance, spatial modeling, common waterhemp, *Amaranthus tuberculatus*

1. Introduction

Common-pool resources (CPRs) have long presented society with challenging environmental, social and policy dilemmas.^{1,2} Common-pool resources are those for which 1) user access is difficult to exclude or limit, and 2) the resource is finite, i.e., once a quantity of the resource has been extracted, it is no longer available to others.³⁻⁵ Antibiotic and pesticide resistance represent contemporary instances of CPR challenges,⁶⁻⁸ where susceptibility to treatment of target organisms is a shared resource. Failure to manage these resources effectively can result in existential crises, with potential consequences for society's ability to fight disease and feed itself.

However, thoughtful and sustainable management of CPRs is possible. The management of global fisheries provides well-known examples of both cases.^{2, 9, 10}

The evolution and management of herbicide-resistant weeds within agricultural landscapes is a classic example of a CPR problem: individual farmers face strong short-term incentives to apply herbicides without regard to future herbicide resistance, despite it being in the collective interest of farmers to conserve the long-term efficacy of herbicides as important weed management tools.⁴ Because weed seeds and pollen often have high dispersal capability, individual fields can face strong weed pressure from neighboring fields,¹¹⁻¹⁵ so a resistance problem on one farm can rapidly spread anywhere resistant pollen or seeds can reach. Thus, the susceptibility of weeds to herbicides is a resource shared by all operators in a locality.⁴ This means that judicious weed management by a single farm, e.g., using herbicide mixtures, rotating herbicides, or using non-herbicidal weed control tactics,¹⁶ will make little impact on the rate of herbicide resistance evolution in the broader landscape context, and will still likely suffer the consequences of herbicide resistance. This makes it unlikely that individuals will unilaterally incur the costs of such actions,^{4, 7} and thus points to the possibility of cooperative, community-based management to slow the rate of evolution and spread of herbicide resistance.⁴ While research has considered the CPR nature of resistance evolution for antibiotics and insect pests,^{8, 17-19} it has only more recently focused on CPR-based management problems for herbicide resistant weeds.^{4, 5, 16, 20-23} This has been in part because weeds were assumed to have low dispersal capability,^{17, 18, 24} and few have considered these problems in a formal, quantitative way,^{20, 21} which has hindered progress on delaying the emergence and spread of herbicide-resistant weeds.

Using an economically important agricultural weed as a model, we asked whether CPR-based management strategies could reduce the evolution and spread of herbicide resistance traits within agricultural landscapes, compared to uncoordinated farm-scale management. To answer this, we developed a simulation model to test our hypothesis that (a) effective weed management strategies which minimize selection for herbicide resistance (b) applied at spatial scales larger than individual farms could reduce the spread of herbicide resistance compared with (c) alternative management strategies with greater selection for resistance or (d) application at smaller spatial scales.

2. Methods

Our study focused on a common and economically important agronomic weed with rapidly spreading herbicide resistance traits. Common waterhemp (*Amaranthus tuberculatus* (Moq.) Sauer) is a geographically widespread, highly competitive species that represents a considerable challenge to grain production in the U.S. Midwest.^{25,26} Populations of *A. tuberculatus* have evolved resistance to at least six different herbicide modes of action (MOA), including multiple herbicide resistance to as many as 5 MOAs within a single plant, with glyphosate resistance found in at least 18 US states.²⁷ *Amaranthus tuberculatus* is a dioecious summer annual with continuous germination, high seed output, and a persistent soil seed bank.²⁸ Like other similar species, obligate outcrossing weeds such as *A. tuberculatus* are highly mobile via seeds and pollen,¹¹ allowing herbicide-resistance traits to move easily between farms.^{29,30}

We developed a discrete-time landscape-scale simulation model to quantify the CPR nature of herbicide-resistance evolution. The model had four main components: 1) a grid of 4×4 m cells

that together comprised a $\sim 114 \times 114$ km landscape ($\sim 8 \times 10^8$ cells). Cells were organized around a grid of non-crop roads spaced every 1.6 km and grouped into fields ranging from ~ 16 -258 ha (0.0625 - 1.0 mile²) which could then be organized into multi-field farms and larger management units; 2) a stochastic demographic and population genetics model based on *A. tuberculatus* vital rates that drove local, patch scale population dynamics and resistance evolution within each cell; 3) mechanisms that dispersed pollen by wind and seeds by either gravity or on combines; and 4) multiple weed management strategies with varying selection for glyphosate resistance that could be aggregated at spatial scales from individual farms to larger management units that provided landscape context.

Our principal foci were the dispersal-driven relationships between management unit size and management strategy defined by our organizing question, rather than minutia about *A. tuberculatus* demography. As such, our characterization of *A. tuberculatus* biology was simplified where possible to allow greater allocation of human and computing resources to overall landscape scale and spatial resolution. Indeed, recently published modeling work has shown the mobility of resistance traits within populations is largely a function of the weed's dispersal capacity relative to the spatial grain or resolution of the model,³¹ which we feel supports our choice in this tradeoff.

2.1 Model overview

The demographic model that underlies the simulation was based on the *A. tuberculatus* life cycle and parameterized with a combination of published and experimental data and expert knowledge (see Supplementary Materials, Table S2). Model construction and parameterization are detailed

in Supplementary Materials, and are described in brief here. Each field followed an annual corn-soybean rotation, such that the landscape was approximately 50% corn and 50% soybean in any given year. The model tracked individual *A. tuberculatus* plants in each cell in each of three genotypes: homozygous susceptible (SS), heterozygotes (SR), and homozygous resistant (RR). We made the simplifying assumption that glyphosate resistance traits followed simple Mendelian genetics, with two alleles at a single locus and incomplete dominance of the resistance allele. We know that resistance inheritance in natural populations is more complicated than this,²⁶ but to model the many known and unknown ways in which resistance is inherited in *A. tuberculatus* is not yet tractable and likely would not have improved our inference with respect to management aggregation. The soil seed bank was divided into seeds at the surface (0-5 cm depth) and deep seeds (>5 cm depth). The seed bank was mixed by tillage. Corn stubble was always tilled in the fall, and soy fields are tilled with probability 0.80. Surface seeds germinated with probability 0.13, and the seedlings were then split into three germination cohorts to approximate continuous germination with 79, 17, and 4% of seedlings assigned to cohorts 1, 2, and 3, respectively. Seedlings faced density dependent mortality calculated as a rectangular hyperbolic³² function of total conspecific density with older cohorts weighted more heavily (e.g., cohort 3 survival was a function of cohorts 1, 2, and 3). These surviving juvenile plants matured to adulthood with probability 0.90 and then were exposed to crop-, cohort-, genotype-, and treatment-specific management mortality. Survivors were divided randomly into male and female plants. Pollen and seed production were calculated using the frequencies of S and R alleles in each cell with an overdispersed normal approximation of the Poisson distribution. Pollen was dispersed with a Fourier Fast Transform (FFT). The pollen dispersal kernel was defined as a two dimensional exponential function of distance from the source plant, with a mean dispersal distance of ~454 m

and a maximum of 1.6 km. A female plant would likely source three times as much pollen from a male in the same cell as from a male in an adjacent cell, 13 times as much as from a male 20 m away, or 4975 times as much as a male 1 km away. In a large landscape with one identical male per cell, a female would likely source just 0.4% of pollen from a male in the same cell. For computational reasons, this kernel was flatter and fatter tailed than that recorded by others^{33, 34} and is discussed in the online supplement. We calculated Hardy-Weinberg probabilities for pollinated seed genotypes at each position on landscape based on the proportions of S and R pollen that lands and the S and R alleles in the unfertilized seeds. A portion of seeds produced in each cell were picked up by the combine at harvest time. This includes 80% of seeds from cohorts 1 and 2, and a fraction of cohort 3 seeds calculated as a function of management efficacy, where survivors of more efficacious management would likely be stunted and escape the combine's cutter bar. These seeds could be transported within the same field or moved to a different field within the same management unit, which could result in seed movement of 10 km or more. Seeds not picked up by the combine fell within 8 m of the parent plant.

Resistance alleles evolved through discrete, random mutation events and were transmitted with a single locus, two allele Mendelian inheritance model. Each new seed was set to have a 1×10^{-10} probability of mutating from SS to SR or for SR to RR. This mutation rate was conservatively lower than some published rates and is discussed in the Supplementary Material. The calculation was executed with a separate random binomial draw for each genotype. Following this, we added the new seeds to the dormant surface seeds in the seed bank and applied the annual mortality rate to the dormant deep seeds in the seed bank with a survival probability of 0.60 and to surface

seeds with a survival probability of 0.43. The structure of the model is illustrated in a supplementary schematic diagram online.

We ran ten replicate runs of the simulation. All model runs started with a 29 year “burn-in” period, where year 1 corresponded with 1987, nine years prior to the introduction of glyphosate-tolerant crops in 1996.³⁵ Landscapes were initialized with populations of 100% herbicide-susceptible *A. tuberculatus*, and glyphosate usage was gradually introduced on an increasing proportion of independently managed farms to mirror the rate of glyphosate-based herbicide adoption in the U.S. state of Illinois from 1996-2015.^{36,37} This was followed by a 35-year experimental period repeated at each of three spatial scales of management aggregation (Fig. S1, described below). Each management unit was assigned to one of seven herbicide treatments (Table S1) and allowed to diverge from burn-in conditions. The prevalence of *A. tuberculatus* herbicide resistance within each model landscape was assessed 10 and 35 simulation years into the experimental period (see Supplementary Materials).

Herbicide treatments were divided between two broad strategies: 1) annual rotation of herbicides, and 2) tank mixtures of herbicides, both of which are recommended for reducing the risk of herbicide resistance.¹⁶ For the rotation strategy, we investigated the efficacy of farmers using either a two- or three-year herbicide rotation, applying glyphosate-only every second or third year, respectively, with a different mode of action (MOA) applied in the intervening years. For the tank mixture strategy, we investigated the efficacy of farmers annually applying glyphosate plus one, two, three, or four additional MOA (giving two, three, four, or five MOA mixture complexities, respectively). We compared these rotation and mixture strategies with an

annual post-emergence application of glyphosate only (single MOA), which has been a common weed management strategy on many U.S. farms^{16, 35} and exerts strong selective pressure for resistance evolution. This gave seven total herbicide treatments present in each landscape, which were randomly allocated to individual management units.

We simulated the evolution and spread of glyphosate resistance across the landscape when the seven herbicide treatments were aggregated at one of three spatial scales: farm-scale (individual farms cultivating one or more fields in a corn-soybean rotation), farmer cooperative-scale (groups of ten neighboring farms applying a common herbicide treatment), and CWMA-scale (cooperative weed management areas comprised of ten neighboring cooperatives applying a common herbicide treatment). This was achieved by randomly allocating the seven treatments to individual farms, cooperatives or CWMA (see supplementary methods). Farm, cooperative, and CWMA mean sizes and standard deviations were 400 ± 260 , 3960 ± 1890 , and 38870 ± 15320 ha, respectively.

2.2 Data analysis

We used graphical analysis supported by generalized linear mixed models (GLMMs) to analyze the results of the simulation model. The principal questions we sought to answer for each response variable were (a) does the response variable differ across herbicide treatments, (b) does it vary with management unit size, and (c) does the slope of the response to management unit size vary across treatments. Response variables were analyzed in years 10 and 35 of the experimental period and included: mean resistance allele frequency per management unit, resistance allele density (R alleles m^{-2}), adult (flowering) plant density (plants m^{-2}), and

management failure time, defined as when half of fields in each treatment contained plants carrying glyphosate-resistance alleles. We experimented with several metrics of failure but chose this one because all treatments crossed this threshold within the 35-year experimental period. This wasn't used as an agronomic metric of failure such as yield loss, since individual "failed" management units could have any non-zero density of resistant weeds. Rather, it allowed comparison of rates of resistance spread across all treatments using a simple, intuitive metric. Treatment values and effect sizes were reported as marginal mean predicted values from the best supported model of a given response variable. See statistical methods in the Supplement Materials for details.

3. Results

Aggregating farms into larger weed management units reduced the frequency of resistance alleles across the landscape (Fig. 1). The mixture treatments collectively proved more effective than rotations for reducing the prevalence of resistance alleles in new seeds, at both 10 and 35 years after management aggregation began (Figs. 2, 3, S2, S3; Tables S3, S4, S5, S6). For the two-year rotation, benefits of aggregation on reducing resistance allele frequency were only apparent at 10 years, indicating relatively ephemeral treatment efficacy. Using a three-year rotation maintained the efficacy of glyphosate for at least 35 years, reducing the presence of resistance alleles from ~90% at farm-scale to ~60% at CWMA-scale, but had substantially lower efficacy than any of the mixture treatments at the cooperative and CWMA-scales, which showed reductions from ~90% at farm-scale to ~20-30% at CWMA-scale (Fig. 2). Conversely, aggregating the glyphosate-only treatment at larger spatial scales increased the proportion of resistance alleles at both 10 and 35 years (Fig. 2, Tables S3, S4). *Amaranthus tuberculatus* plant

density declined with increasing management aggregation for each mixture treatment at 35 years, but proved unresponsive to aggregation in the rotation and glyphosate-only treatments (Fig. S4, S5; Tables S7, S8; at 35 years, the mixture treatments had significantly negative slopes based on parameter estimate confidence intervals, Table S8.B).

Before the start of the experimental treatment period, after 20 years of glyphosate exposure, 11.2% of fields harbored at least some plants with resistance alleles. Within these fields, the mean and median frequencies of resistance alleles were 3.9×10^{-4} and 1.9×10^{-7} . Thus, resistance traits were initially widespread spatially, but relatively rare. All trialed herbicide treatments had similar failure times in the smaller farm scale aggregations, around 10-11 years, despite the fact that the non-glyphosate herbicides in the mixtures remained fully effective. (Fig. 4, Table S9). This was driven principally by pollen dispersal of resistance genes from glyphosate-only farms into neighboring management units. However, the glyphosate-only treatment failed more rapidly as the scale of management aggregation increased, failing after just six years at the CWMA scale. The two-year rotation showed little response to management scale, while failure time of the three-year rotation increased significantly with management scale, up to a maximum of 14 years. The mixture treatments were more robust, showing similar and significant increases in failure time across all mixture treatments (Fig. 4). Furthermore, the mixture treatments all showed strong positive, accelerating interactions with spatial scale. For example, failure time for all mixture treatments ranged between ~17-22 years, taking longest at CWMA-scale; when practiced at farm-scale, the five MOA mixture treatment took on average 11.7 years to fail, but at the CWMA-scale failed after 22.5 years (Fig. 4, Table S9.C).

4. Discussion

Our results reveal that confronting CPR resistance problems requires implementation of effective management strategies over large spatial scales. Recent studies of antibiotic and herbicide resistance evolution have observed greater efficacy of mixture strategies compared with rotation strategies for reducing resistance, because mixtures apply more heterogeneous selection pressures than rotations on a time-scale relevant to resistance evolution in their respective target organisms;^{38,39} this relates to target organism generation time, frequency of gene mutation events, and fitness costs associated with resistance.⁶ Our work adds a novel element of understanding to these findings by accounting for target organism mobility and capability to disperse between management units. Where susceptibility of target organisms to a treatment, e.g., an antibiotic or herbicide, is a resource shared by all operators in a locality, and where target organisms are highly mobile, judicious management by a single operator will make little impact on resistance evolution in the broader landscape.⁴ Thus, the individual operator will still suffer the consequences of resistance as it spreads across management units. Cooperative management between operators of individual management units has potential to confront this problem and extend the lifespan of these critical CPRs.

This study emphasizes the important context dependence of adopting a spatially aggregated management approach. In our simulation, annual use of glyphosate-only (single MOA) resulted in the worst outcomes: the largest *A. tuberculatus* populations and the greatest frequency of resistance alleles compared with all other herbicide treatments across all spatial scales of management. Implemented at farm-scale, glyphosate-only had negative spillover effects on neighboring farms through efflux of resistant pollen. Smaller management units have higher

edge to interior ratios, exposing a greater proportion of a given management unit to exogenous pollen. Aggregating glyphosate-only management beyond farm-scales exacerbated treatment failure. Thus, when treatments effective for reducing resistance evolution—i.e., that function on relevant evolutionary time-scales—are implemented by individual operators, cooperative management can synergize those benefits; when ineffective or harmful practices are adopted, cooperative management rapidly compounds the problem. The fine spatial resolution of our model implemented at large, landscape-wide spatial scales allowed us to account for both within-field, subpopulation dynamics and dispersal, as well as landscape scale dynamics that drive herbicide resistance evolution and spread.³¹

While the model presented here offers important insights on managing herbicide resistant weeds, it is critical to keep in mind the scope of its inference space. We modeled *A. tuberculatus* with a single resistance trait using a simplified model of inheritance and prohibited it from evolving single or multiple-resistance to other chemistries. Real world populations of *A. tuberculatus* have evolved resistance to multiple herbicides. Thus, our interpretation of the benefits of scaling up management units to control a single trait represents a simplification in the interest of tracking a single trait. That said, the principles demonstrated are sound: scaling up efficacious management worked in the model because the tools used remained effective against both susceptible and resistant weeds. As Palumbi⁶ explains in describing “overkill” strategies such as our mixture treatments, treatments that kill all reproductive individuals effectively halt resistance evolution.

Designing and implementing effective cooperative management structures can be extremely challenging.⁴⁰ For resistance evolution, simply defining the spatial scale of cooperation is

particularly difficult, due to the mobility of target organisms across both space and time.⁴

However, with careful planning, effective cooperative management structures to confront CPR-based resistance problems can be implemented, and with demonstrable success.^{4, 19, 41-44} For example, in work on areawide control of codling moth, interest in participation spread by word of mouth when growers saw the reduced pesticide use their neighbors achieved by adopting an experimental treatment.⁴¹ Ten key principles for developing cooperative landscape approaches to reconcile conflicting land uses were recently circumscribed,⁴⁵ and provide a promising template from which to initiate a design process.

Confronting resistance evolution is a critical global issue. In the case of herbicide resistance, growing numbers of populations of major agricultural weeds show resistance to multiple herbicide MOAs,^{25, 46} and no novel herbicide chemistries have been brought to market for over 30 years.⁴⁷ This represents a dire situation of dwindling effective herbicide resources available to tackle a growing problem. Moreover, weeds are the most important group of pests for many of the world's crops, and their control constitutes a heavy economic burden.^{6, 48} Herbicides are currently the most effective weed control tool available.⁴⁹ If rendered obsolete due to herbicide resistance, there will likely be severe consequences for global food security.⁵⁰ Additionally, without effective herbicides, farmers will resort to increased tillage intensity to control weeds, thereby degrading soil health and the environment.⁵¹

We have taken an important first step towards identifying the spatial scales at which cooperative management among farms can effectively slow the evolution and spread of herbicide resistance in highly motile weed species, thereby extending the longevity of a critical CPR. Our work

suggests that such areawide approaches are not only justified, but perhaps even necessary to ensure the success of this process. While our results are specific to herbicide resistance, the principles of resistance evolution are the same across disciplines.^{6,39} Thus, strategies designed to thwart resistance evolution in one discipline, e.g., herbicide resistance, may serve to improve management in another, e.g., antibiotic resistance.^{17,39} Mismanagement of CPRs can lead to resource collapse, with large-scale negative economic, social, and environmental outcomes.¹⁰ However, appropriate governance of CPRs can lead to broadly beneficial and sustainable outcomes, demonstrating that the “tragedy of the commons” is not always inevitable.⁹

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Figure Legends

Fig. 1. Spatial distribution of resistance allele frequencies in new *A. tuberculatus* seeds, as affected by the spatial scale of management aggregation, in one of the simulated landscapes 10 and 35 years after management aggregation. All herbicide treatments are present at equal proportions within the landscape, regardless of the scale of management aggregation. A and D show farm-scale; B and E show cooperative-scale; C and F show CWMA-scale.

Fig. 2. Mean proportion of resistance (R) alleles in new *A. tuberculatus* seeds per field across each landscape 10 and 35 years after management aggregation, using either a rotation (A and C) or mixture (B and D) herbicide strategy. Statistics were calculated prior to seed dispersal. The three management unit sizes refer to farm-, cooperative- and CWMA-scales, respectively, in ascending order. The same glyphosate-only data are plotted in the left and right columns for comparison.

Fig. 3. Mean density of resistance (R) alleles in new *A. tuberculatus* seeds across each landscape 10 and 35 years after management aggregation, using either a rotation (A and C) or mixture (B and D) herbicide strategy. The three management unit sizes refer to farm-, cooperative- and CWMA-scales, respectively, in ascending order. The same glyphosate-only data are plotted in the left and right columns for comparison.

Fig. 4. Failure time for each treatment within the rotation (A) and mixture (B) herbicide strategies. Failure was defined as when half of fields contained *A. tuberculatus* plants carrying

glyphosate-resistance alleles. The three management unit sizes refer to farm-, cooperative- and CWMA-scales, respectively, in ascending order. The same glyphosate-only data are plotted in A and B for comparison.

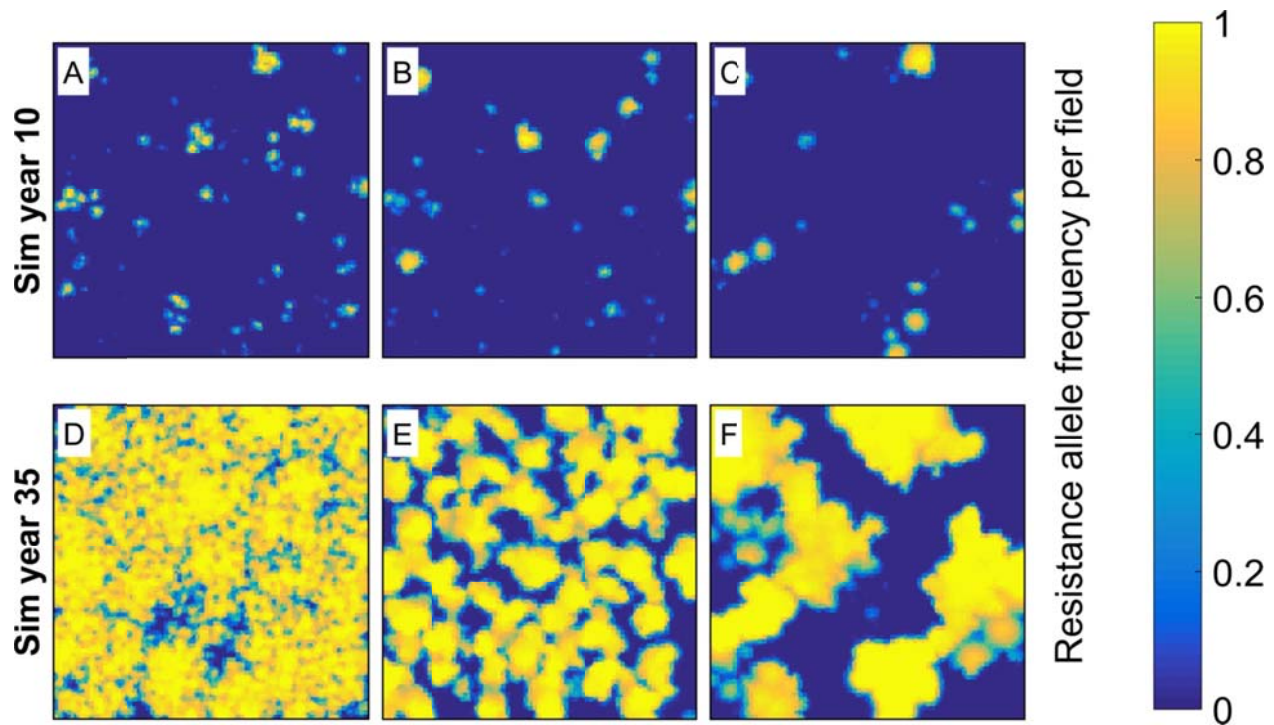


Fig. 1. Spatial distribution of resistance allele frequencies in new *A. tuberculatus* seeds, as affected by the spatial scale of management aggregation, in one of the simulated landscapes 10 and 35 years after management aggregation. All herbicide treatments are present at equal proportions within the landscape, regardless of the scale of management aggregation. A and D show farm-scale; B and E show cooperative-scale; C and F show CWMA-scale.

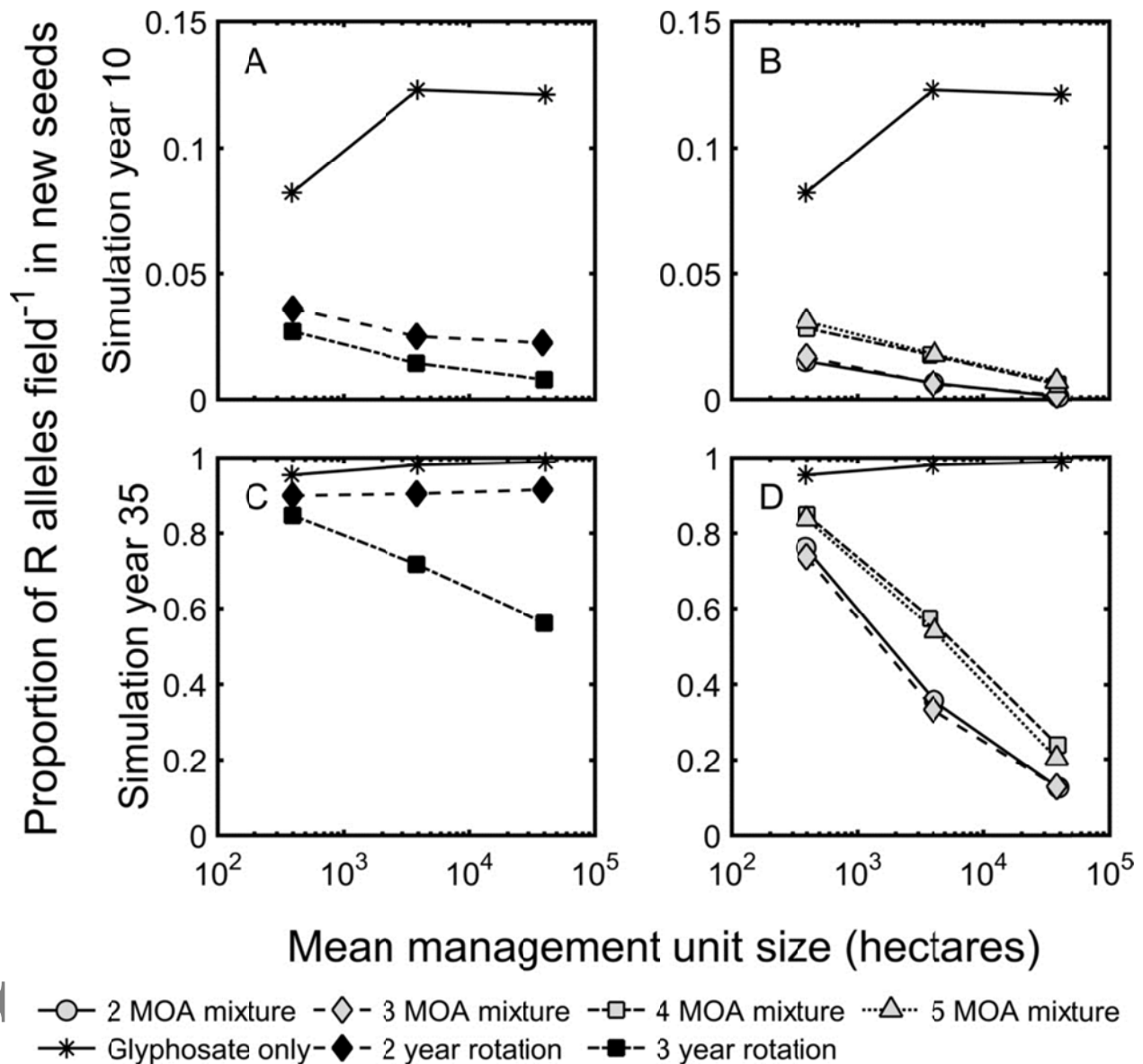


Fig. 2. Proportional abundance of resistance (R) alleles in new *A. tuberculatus* seeds across each landscape 10 and 35 years after management aggregation, using either a rotation (A and C) or mixture (B and D) herbicide strategy. The three management unit sizes refer to farm-, cooperative- and CWMA-scales, respectively, in ascending order. The same glyphosate-only data are plotted in the left and right columns for comparison.

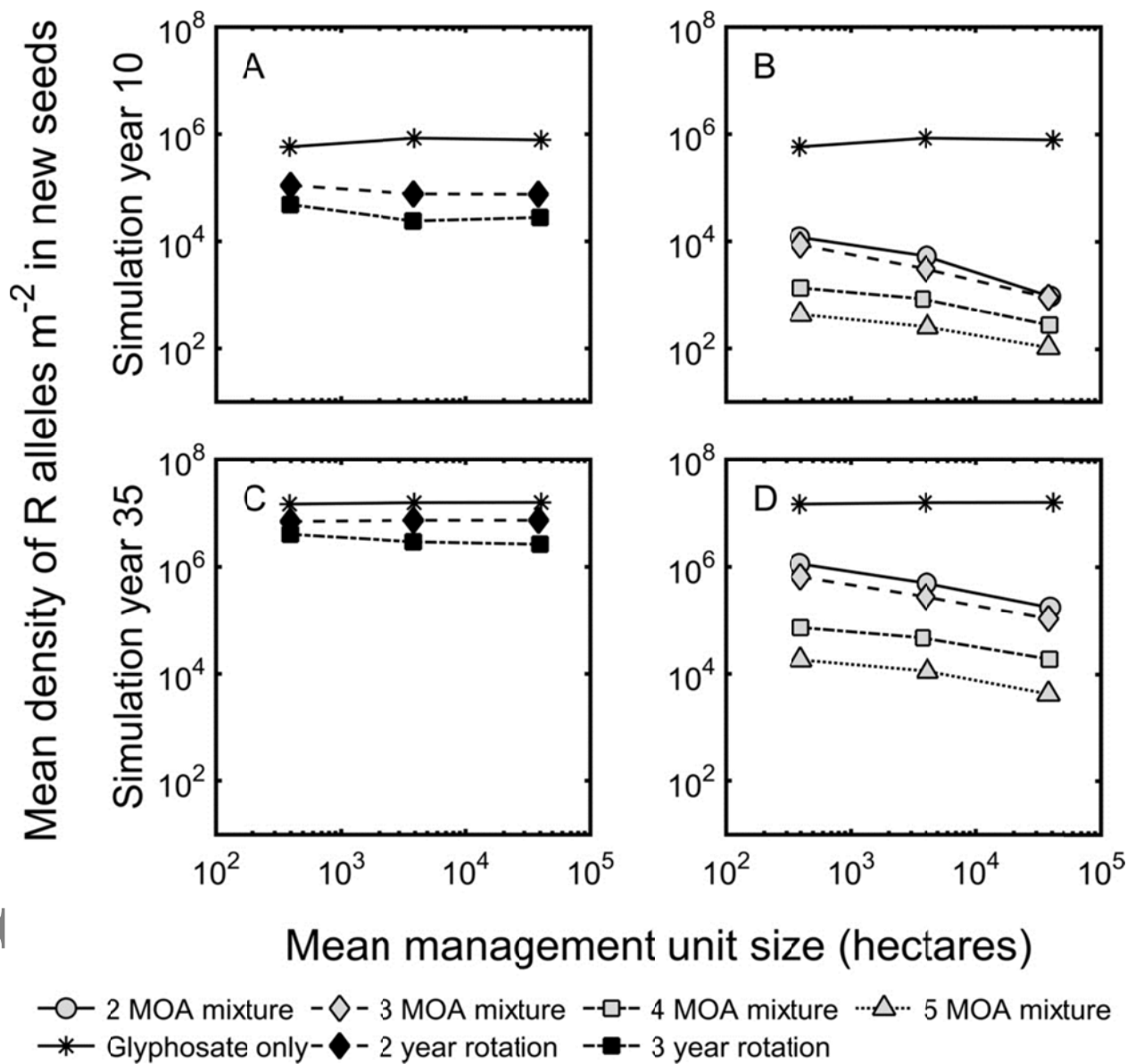


Fig. 3. Mean density of resistance (R) alleles in new *A. tuberculatus* seeds across each landscape 10 and 35 years after management aggregation, using either a rotation (A and C) or mixture (B and D) herbicide strategy. The three management unit sizes refer to farm-, cooperative- and CWMA-scales, respectively, in ascending order. The same glyphosate-only data are plotted in the left and right columns for comparison.

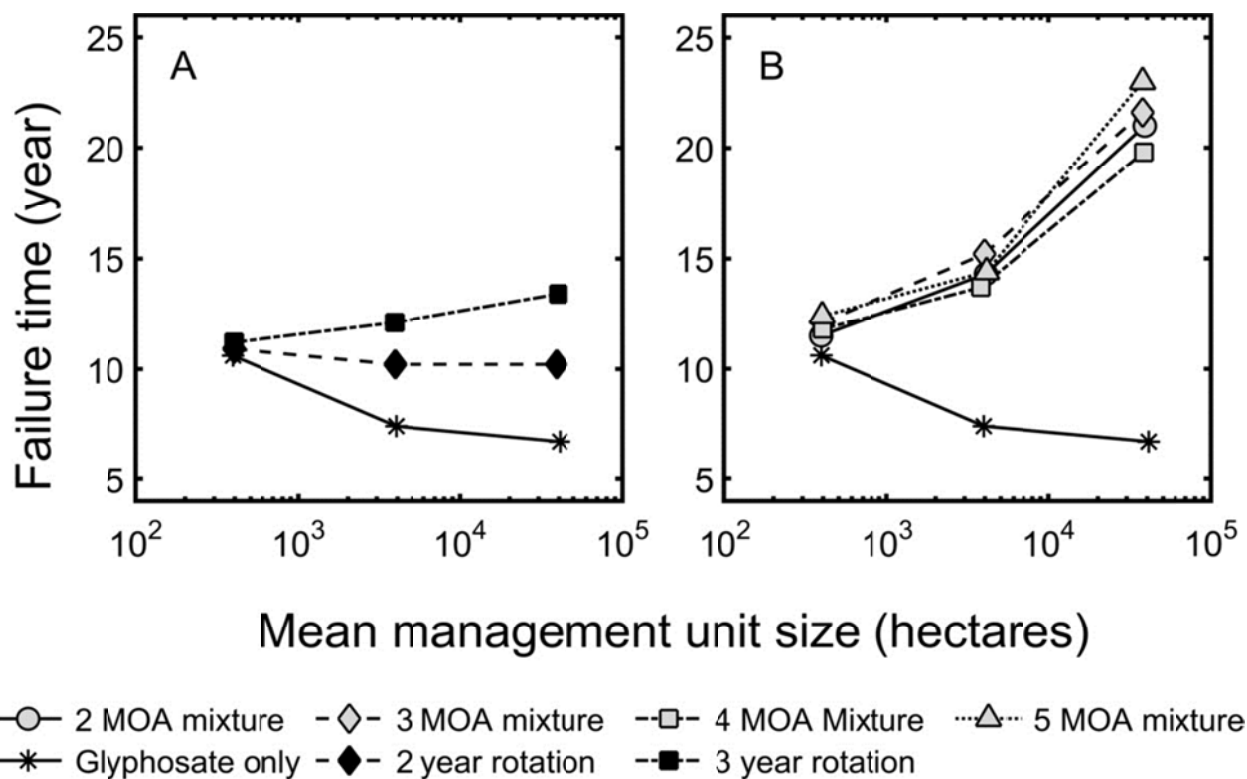


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Supplementary Materials:

Materials and Methods

Supplementary Text

Figure S1

Tables S1-S8

Model Schematic