Research Article

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A generalised individual-based algorithm for modelling the evolution of quantitative herbicide resistance in arable weed populations

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Abstract

BACKGROUND: Simulation models are useful tools for predicting and comparing the risk of herbicide resistance in weed populations under different management strategies. Most existing models assume a monogenic mechanism governing herbicide resistance evolution. However, growing evidence suggests that herbicide resistance is often inherited in a polygenic or quantitative fashion. Therefore, we constructed a generalised modelling framework to simulate the evolution of quantitative herbicide resistance in summer annual weeds.

RESULTS: Real-field management parameters based on *Amaranthus tuberculatus* (Moq.) Sauer (syn. *rudis*) control with glyphosate and mesotrione in Midwestern US maize–soybean agroecosystems demonstrated that the model can represent evolved herbicide resistance in realistic timescales. Sensitivity analyses showed that genetic and management parameters were impactful on the rate of quantitative herbicide resistance evolution, whilst biological parameters such as emergence and seed bank mortality were less important.

CONCLUSION: The simulation model provides a robust and widely applicable framework for predicting the evolution of quantitative herbicide resistance in summer annual weed populations. The sensitivity analyses identified weed characteristics that would favour herbicide resistance evolution, including high annual fecundity, large resistance phenotypic variance and pre-existing herbicide resistance. Implications for herbicide resistance management and potential use of the model are discussed.

Supporting information may be found in the online version of this article.

Keywords: quantitative resistance; individual-based models; evolution; *Amaranthus tuberculatus* Sauer; weed management; polygenic resistance

1 INTRODUCTION

The evolution of herbicide resistance in arable weed populations is a global economic and ecological problem.[1] Herbicide resistance has been recorded on most continents in many weed species and populations in a variety of crop systems.[2] Identifying management strategies that mitigate the evolution of herbicide resistance in weeds is crucial for maintaining the long-term sustainability of modern agriculture. With a number of herbicide-resistant traits available and a declining number of herbicides used in different agroecosystems, the issue of how to manage herbicide resistance is complex and difficult to address using only experimental or field-based approaches. This situation is further complicated by the evolution of multiple herbicide resistance in economically impactful weeds such as *Amaranthus tuberculatus* (Moq.) Sauer (syn. *rudis*) (waterhemp) and *A. palmeri* Wats (Palmer amaranth) in Midwestern and Southern US row crop production systems.[2]

Simulation and mathematical models can be effective tools for making predictions in complex crop systems where opportunities for experimentation are limited. Over the previous decades, a number of models have been developed to study weed population dynamics and herbicide resistance evolution.[3,4] Some early

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theoretical models represented simple systems that facilitated the identification of factors affecting herbicide resistance evolution.[5,6] Subsequent algorithms incorporated more details about the mating systems and the dynamics of weed populations.[7,8] More explicit models considered how specific management regimes impact weed population dynamics and herbicide resistance.[9,10] The majority of these models assumed that the herbicide resistance traits were conferred by a single dominant or partially dominant gene. However, it is now recognised that many herbicide resistance traits are polygenic,[11] and some models have illustrated important differences between these two assumptions.[12,13] Typically, monogenic herbicide resistance has a discrete distribution of resistance phenotypes.[11] Quantitative herbicide resistance, on the other hand, commonly results in a continuous phenotypic distribution of varying levels of resistance.[12] Examples of quantitative herbicide resistance traits include genes that code for enhanced herbicide metabolism, decreased absorption and decreased translocation.[11,14] Likewise, gene amplification has been confirmed to confer quantitative resistance to glyphosate in at least two *Amaranthus* species.[15–17] Importantly, non-target-site-based herbicide resistance mechanisms can result in cross- and multiple resistance to herbicides to which weed populations were not previously exposed, and these resistance traits are typically quantitatively inherited.[11,14]

In light of the growing evidence for quantitatively inherited herbicide resistance traits, models predicting evolution of herbicide resistance should also explicitly address this genetic mechanism. It is often uncertain how many and which genes contribute to the cumulative effects of a quantitative herbicide resistance trait.[12] However, a quantitative trait with 20 genes, each contributing a modicum of herbicide resistance, has been shown to behave approximately the same as a trait with an infinite number of genes,[18] and thus quantitative genetics can be implemented using the so-called infinitesimal model.[19]

Here, we developed a generalised modelling framework that addresses quantitative genetic assumptions for herbicide resistance evolution. The algorithm can be used to explore the impacts of different weed species traits and management scenarios on the evolution of quantitative herbicide resistance. This individual-based model (IBM) explicitly accommodates variability in weed life-history traits and herbicide resistance phenotypes. In this paper, we present the structure of the modelling framework and demonstrate the use of it with a case study of waterhemp in maize–soybean agroecosystems in the Midwestern United States: (1) we have parameterised the model to represent a worst case of confirmed resistance to glyphosate and to a *p*-hydroxyphenylpyruvate deoxygenase (HPPD)-inhibiting herbicide (mesotrione);[2,20] (2) we have conducted sensitivity analyses to evaluate how changes in various parameters related to weed biology, genetic traits and weed management affect the model predictions.

2 METHODS

2.1 Model description

The model description follows the 'Overview, Design concepts, Details' (ODD) protocol for describing IBMs.[21] The model is implemented in NetLogo 4.1[22] and is available upon request.

2.1.1 *Purpose*

A generalised modelling framework was developed for predicting the evolution of quantitative herbicide resistance in agroecosystems. The model is individual based and implements different life-history stages of summer annual weed species. Despite the flexibility of the generalised framework in representing summer annual weed species, we have here parameterised the model to simulate evolution of glyphosate resistance in waterhemp in a maize–soybean production system and mesotrione resistance in a continuous maize production system in the Midwestern United States.

2.1.2 *Entities, state variables and scales*

Waterhemp is a dioecious species with populations usually exhibiting a 1: 1 sex ratio,[23] and we assume herbicide treatment does not alter this ratio. Each individual in the model has state variables describing its sex, emergence date and herbicide resistance phenotype(s). The phenotypic value (denoted as Pz_i) defines the highest herbicide rate an individual weed *i* can survive. When more than one resistance trait is modelled, the phenotypes for each are considered to be herbicide specific, and no cross-resistance between herbicides is assumed. Independent of the herbicide resistance phenotypes, fecundity and natural mortality of the individuals are modelled as functions of their emergence dates, based on regression of field data (see Sections 2.1.7.4 and 2.1.7.5).

We simulated a 100 ha agricultural field in our simulations; however, the model is not spatially explicit. A single time step in the model corresponds to one generation for an annual weed species. Model parameters and the default values for waterhemp are listed in Table 1. The basic rationale for determining parameter values was to use (in order of priority): published data where available, unpublished data, expert knowledge and values for a related *Amaranthus* sp. used in a previous herbicide resistance model.[9] We assume that waterhemp populations will have inherent differences in sensitivity to, for example, glyphosate,[24] prior to selection. In a quantitative genetic framework, and where weed management scenarios are identical, those populations with the greatest variance in *Pz* will evolve herbicide resistance most rapidly. In the absence of robust data to define this variable, we have parameterised the model to represent a worst-case scenario based on field observations of the most rapid examples of herbicide resistance evolution under known management regimes (number of previous herbicide applications). Although absolute model predictions may be sensitive to these assumptions, comparisons between contrasting management scenarios will be robust. In addition, sensitivity analyses alleviated the lack of data for some parameters.

2.1.3 *Process overview and scheduling*

A full life cycle of the weed species is considered within each season, and the weed population is modelled for a number of generations to simulate annual changes in population size and LD_{50}. The life-history stages included in the model are the seed bank, seedlings, reproductively mature adult plants and progeny. Key processes in the model are schematically described in Fig. 1.

2.1.4 *Design concepts*

Design concepts are summarised in the supporting information.

2.1.5 *Initialisation*

The model starts with a seed bank at the beginning of a growing season. The size of the seed bank is defined by the initial seed bank density and the field size. The resistance level of the seed bank is defined by the initial LD_{50} (equivalent to the median *Pz* value)

Table 1. Model parameters, default values and references

#	Parameter	Value	Unit	Source
1	Field size[a]	100	ha	Expert knowledge
2	Initial seed bank density	500	seeds m^{-2}	Expert knowledge
3	Seed bank mortality rate[b]	70	%	Literature[35]
4	Fraction of annual seed bank emergence[c]	5	%	Literature[25,36]
5	Predation risk for new seeds[d]	50	%	Literature[9,33]
6	Viability of new seeds	90	%	Literature[37]
7	Planting date			
	Maize[e]	23 Apr		Literature[38]
	Soybean	8 May		Literature[38]
8	Weed emergence curve in maize fields[f]			
	Weibull shape a_{emg1}	6.5		Literature[25,26]
	Weibull scale b_{emg1}	85		
9	Weed emergence curve in soybean fields[f]			
	Weibull shape a_{emg2}	6.5		Expert knowledge
	Weibull scale b_{emg2}	95		
10	Weed fecundity in maize fields[g]			
	a_{f1}	−30 613		Literature[28,29]
	b_{f1}	143 866		
11	Weed fecundity in soybean fields[g]			
	a_{f2}	−56 664		Literature[30]
	b_{f2}	272 306		
12	Weed annual mortality rate in maize fields[h]			
	a_{mort1}	1.67		Literature[28,29]
	b_{mort1}	−90.78		
13	Weed annual mortality rate in soybean fields[h]			
	a_{mort2}	2.25		Literature[30]
	b_{mort2}	−193.52		
14	Pre-emergence application time[i]			
	Maize	23 Apr		Expert knowledge
	Soybean	8 May		
15	Early post-emergence application time			
	Maize	23 May		Expert knowledge
	Soybean	1 Jun		
16	Late post-emergence application time			
	Maize	15 Jun		Expert knowledge
	Soybean	30 Jun		
17	Initial LD_{50} of a pristine population[j]			
	Glyphosate	210	g a.e. ha^{-1}	Literature[24,39]
	Mesotrione	5	g AI ha^{-1}	Literature[40]

Table 1. Continued

#	Parameter	Value	Unit	Source
18	Initial proportion of resistant individuals in a pristine population[k]			
	Glyphosate[l]	5/10 000		Assumption
	Mesotrione[m]	5/1000		
19	Sigma (σ) of the log-normal distribution of *Pz*			
	Glyphosate	0.5087		
	Mesotrione	1.182		
20	Inheritance h^2			
	Glyphosate	0.3		Cockerton HM, unpublished
	Mesotrione[n]	0.6		Assumptions
21	Sex ratio[o]	1: 1		Literature[23]

[a] A discrete and finite population is modelled. For justification for the field size, see the supporting information.
[b] Represents loss of viability and other causes of mortality. Estimate based on *Amaranthus* sp.
[c] Range in the literature is 1–22%. Data are from Iowa.
[d] We here followed the conservative estimate of parameter values by Neve *et al.*,[9] and the field data were based on Gallandt *et al.*[33]
[e] Fifty-three days after the start of a season (DASS). Varies between states. Here, Iowa data were used to represent an average situation in the Midwest. Day 1 set as 1 March throughout the model.
[f] Two-parameter Weibull distribution [see equation (1)]. Parameters adjusted according to maize and soybean planting date and expert knowledge.
[g] Linear regression with logarithmic transformation of *x* variable [see equation (3)].
[h] Linear regression [see equation (2)].
[i] On the same day as crop planting.
[j] Resistance trait value *Pz* is assumed to be log-normally distributed in the population and the seed bank. See submodel description in Section 2.1.7 for more detail. LD_{50} is the median of *Pz*. It is assumed that pristine populations have never been exposed to the herbicide(s) of interest.
[k] Percentage of individuals with $Pz_i \geq$ herbicide application rate, i.e. the right-hand tail of the log-normal distribution, in the initial population. This value is determined by the log-normal distribution of *Pz* [which is defined by the initial LD_{50} (#17) and σ (#19)] and the herbicide application rate (Table 2). Also, note the difference in the proportion of resistant individuals in this quantitative genetic framework and the resistant allele frequencies in models based on single-gene assumptions.[9]
[l] Modified to represent the reported case where glyphosate resistance evolved within 8 years in the glyphosate-only scenario (see Table 2).
[m] Modified to represent the reported case where resistance to HPPD-inhibiting herbicides evolved within 7 years in the seed corn production scenario (see Table 2).
[n] Based on the assumption that mesotrione is less robust than glyphosate, so has a higher h^2 value; modified to represent the reported case where resistance to HPPD-inhibiting herbicides evolved within 7 years in the seed corn production scenario (see Table 2).
[o] Some bias may exist, but 1: 1 is a common value.

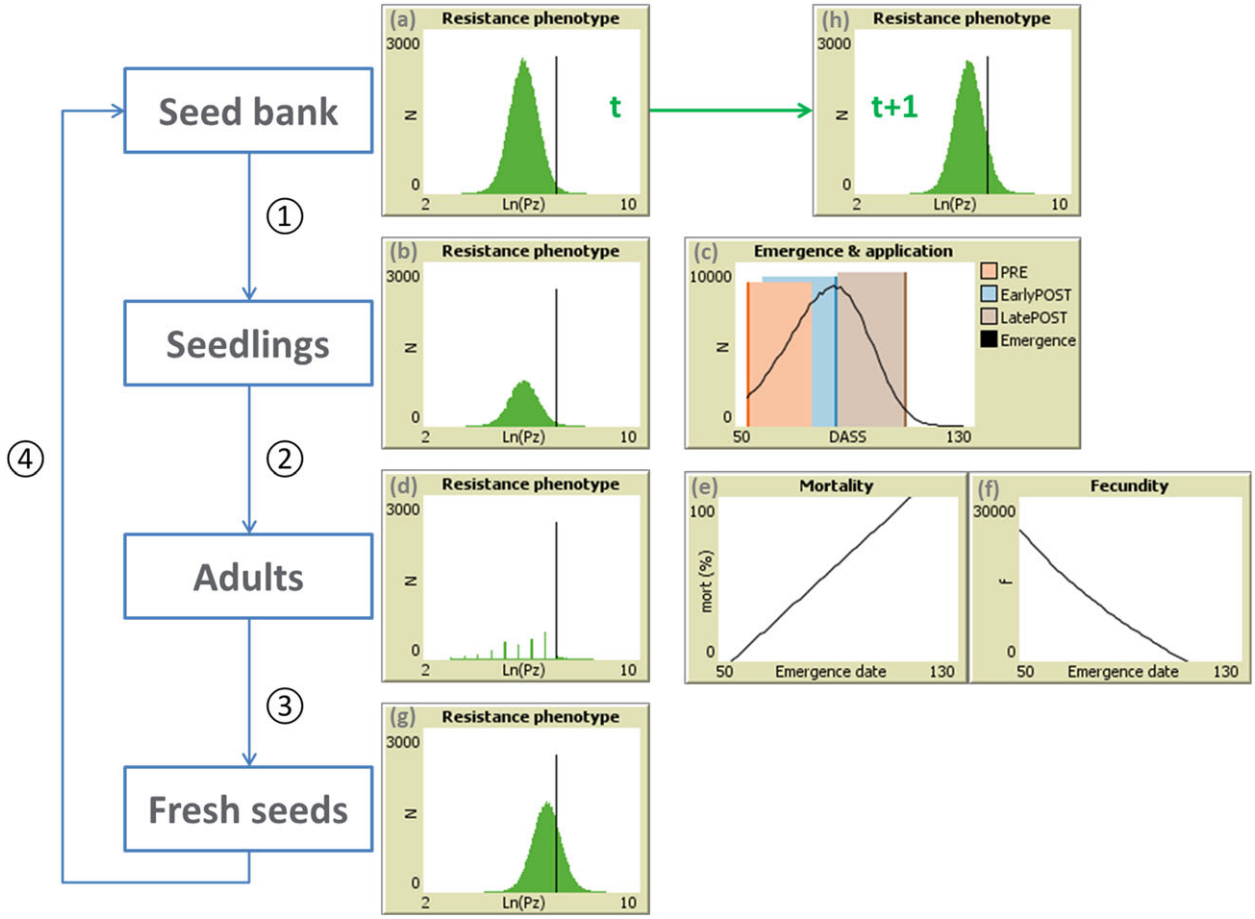


Figure 1. Conceptual design of the modelling framework for quantitative resistance evolution in annual weed species. Starting with a seed bank, a proportion of the seeds germinate and emerge as seedlings each year (①). Herbicide resistance phenotypic values (*Pz*) have the same distribution in the seedlings (b) as in the seed bank (a). Each plant is assigned a discrete emergence time determined by a distribution that describes the periodicity of emergence for the study species (c). Emergence time is in units of days after start of season (DASS). The exposure of individual weeds to different herbicides and weed management interventions is dictated by emergence timing (c) – the dark-coloured vertical lines indicate application time and the light-coloured blocks indicate the effective time window of the three optional herbicide applications. The vertical lines in (a), (b), (d) and (g) represent the herbicide application rate. Those with $Pz_i \geq$ herbicide application rate (i.e. the herbicide-resistant individuals) can survive the treatment (d). Sensitive individuals ($Pz_i <$ applied herbicide rate) either escape the treatment or die (d). Besides herbicide mortality, weeds are subject to natural mortality (e). The surviving subpopulation is a mixture of the resistant individuals and the escaping sensitive plants, with a higher proportion of resistance (d). When they reach maturity (②), they form the parental generation and produce new seeds (③, f), which are expected to have a higher level of resistance (g). Newly produced offspring (g) are subject to predation before being added to the seed bank (a). The seed bank is subject to overwinter mortality, and the remaining seeds form the new starting population for the next annual iteration of the model (④, h). The median phenotypic value *Pz* of the population (i.e. LD_{50}) (h) evolves within the weed life cycle under the selection pressure of herbicides and across generations through reproduction. The population density of the surviving individuals is a measure of the effectiveness of weed control methods (d). Subgraphs (a) to (g) correspond to the life-history stages on the left (① to ④). Note that the values in the graphs are for demonstration of concepts and do not represent explicit simulation values.

and a fixed phenotypic variance σ^2 (see Table 1, #17–19, and the submodel described in Section 2.1.7.2). Note that seeds are not modelled as individuals, but characterised by the population-level parameters mentioned above. Emerged seedlings are modelled explicitly as individuals.

For model simulations presented here, we assume that the initial waterhemp population has never been exposed to herbicides (i.e. a pristine population). This assumption permits us to predict the time required for herbicide resistance evolution to occur in fields with wild-type waterhemp populations. However, after many years of intensive use of herbicides such as glyphosate, many fields are likely to have partially resistant waterhemp populations, and therefore it is important to consider some non-pristine populations for practical model predictions (see the test of different initial LD_{50} values in supporting information Fig. S2).

2.1.6 *Input data*

All parameter values are predefined, and the model does not use any external data files.

2.1.7 *Submodels*

2.1.7.1 Emergence. A proportion of randomly selected individuals emerge from the seed bank each year (Table 1, #4). The emergence curve of the seedlings is implemented as a Weibull probability distribution function (pdf) ranging between 0 and infinity [equation (1)]:

$$y_{emg} = \frac{a_{emg}}{b_{emg}} \times \left(\frac{x}{b_{emg}}\right)^{a_{emg}-1} \times e^{-\left(\frac{x}{b_{emg}}\right)^{a_{emg}}} \quad (1)$$

where y_{emg} is the percentage of the weed population having emergence date x ($x \geq 0$), a_{emg} is the Weibull pdf shape parameter and

b_{emg} is the scale parameter. The parameters are set relative to the beginning of the season and their default values represent an average emergence pattern for waterhemp in the Midwestern United States.[25,26] Emergence dates are assigned to an individual based on a random draw from this distribution (Table 1, #8 and 9). Changing a_{emg} and b_{emg} can reflect different weed species or populations of the same species under different environmental conditions. This function is especially useful for studying weed species with a prolonged emergence pattern, such as waterhemp, which consequently leads to relative differences in herbicide exposure, fecundity and natural mortality.[25]

2.1.7.2 Genetics – infinitesimal model and herbicide resistance phenotype (Pz). In the model, Pz_i determines the maximum herbicide rate an individual can survive. Quantitative genetics were implemented based on the infinitesimal model, in which the distribution pattern of *Pz* of a weed population can be considered as a continuum that satisfies normality.[19,27] Log-normal distribution is a better representation of resistance phenotypes than normal distribution because it avoids negative *Pz* values which do not make biological sense; the skewed shape with a lighter tail also fits better with the rare occurrence of resistant individuals in a population. In addition, dose–response survival data from a pristine population in Iowa[24] were shown to follow a log-normal distribution (supporting information Fig. S7). Therefore, here we modelled *Pz* using a log-normal distribution, which is described by two parameters, μ and σ, namely the mean [$\mu = \ln(LD_{50})$] and the standard deviation of the natural logarithm of *Pz*. A proportion of the initial population have high Pz_i values and will survive the normal field application rate of the herbicide, i.e. the right-hand tail of the log-normal distribution. Infinitesimal models assume an infinitely large number of loci, each contributing an infinitesimal effect to the phenotype. Changes in the allele frequency of any given locus are expected to be very small because of minimal selection acting on a single locus; however, even with small changes in variance, the sum over a large number of loci can result in significant changes in the mean.[19] In keeping with these assumptions, we implement a constant σ, as μ evolves under selection across the simulations. Among the four aforementioned parameters, LD_{50}, σ, application rate and proportion of resistant individuals in the population, if the values of three of them can be determined (usually LD_{50} through dose–response studies, application rate predefined and proportion of resistant individuals estimated from dose–response studies or field trials), the fourth one (usually σ) can be mathematically solved. For a species other than waterhemp or a non-pristine population, glasshouse or field experiments are needed to parameterise the model, while the model structure remains unchanged regardless of the parameter values.

2.1.7.3 Herbicide applications. Emerging individuals are subject to phenotypic selection by herbicides. The efficacy of herbicides on the weed population depends on application timing, application rate and the resistance phenotype of the individuals. In reality, herbicides are never 100% efficacious – even weeds with sensitive phenotypes may survive.[12] Pre-emergence-applied herbicides control weeds emerging after the treatment, with the period and level of control depending on their residual activity. Post-emergence-applied herbicides (e.g. glyphosate) control weeds that have already emerged, but can also affect individuals yet to emerge if herbicides with residual activity (e.g. mesotrione, fomesafen) are used. In a broader sense, a treatment could also represent a non-chemical tactic, such as tillage.

For herbicides where resistance is being simulated, if a weed is exposed and its Pz_i value is equal to or higher than the application rate (i.e. a herbicide-resistant individual), it survives. If its Pz_i is smaller than the application rate (i.e. a sensitive individual), depending on the efficacy of the herbicide, it either escapes from the treatment or is killed by the treatment. For example, if a herbicide has an efficacy of 95%, 5% of the sensitive individuals will escape (a random draw from the sensitive individuals; resistant individuals are not accounted for in this step). For herbicides where resistance is not being simulated (from hereon called 'alternative' herbicides), it is assumed that all individuals are sensitive and the probability of survival depends merely on efficacy. The process described above is similar to the 'smooth selection' proposed by Gardner *et al.*[12]

2.1.7.4 Natural mortality. In addition to death caused by herbicide treatments, individual weeds are also subject to natural mortality, the rate of which varies depending on the emergence date. Later-emerging individuals are more susceptible to competition with crops and thus have higher natural mortality.[28] Field data of mortality and seed production in waterhemp that emerges at different crop stages have been reported in weed–crop interference studies (maize;[28,29] soybean[30]). Linear regressions were fitted to the field data and used in the model to represent the effects of crop competition on waterhemp mortality rate [equation (2) and Table 1]:

$$mort_i = a_{mort} \times x_i + b_{mort} \quad (2)$$

where $mort_i$ is the natural mortality rate (%) for each weed plant per season ($0 \le mort_i \le 100$), x_i is the emergence date ($x_i \ge 0$) and a_{mort} and b_{mort} are the slope and intercept, respectively, of the linear regression. For a prolific weed species such as waterhemp, an average of 1 plant m^{-2} across the whole field surviving at maturity to produce thousands of seeds is a great threat to crop production and can be considered as a failure in weed control; therefore, we used this as a density threshold in the simulations. At low weed population densities, the field carrying capacity is not explicitly considered, and so we assumed that mortality and fecundity of each waterhemp is independent of the population density and is regulated predominantly by the crop. However, there should be no obstacles to introducing an intraspecific density-dependent function in the model, when necessary, using, for example, the Beverton–Holt model.[31]

2.1.7.5 Reproduction. Weed plants that have survived the herbicide treatment and natural causes of mortality form the parent population (adult plant stage) and produce new seeds. Random mating is assumed. The number of seeds a female plant produces (i.e. fecundity) is modelled as a function of its emergence time, such that an individual emerging later in the season is less fecund. Linear regression was fitted to field waterhemp data [equation (3) and Table 1; see Section 2.1.7.4 for field data details]:

$$f_i = a_f \times ln\left(x_i\right) + b_f \quad (3)$$

where f_i is the annual seed production of an individual weed ($f_i \ge 0$), $\ln(x_i)$ is the logarithmic transformation of emergence date x_i ($x_i \ge 0$) and a_f and b_f are the slope and intercept, respectively, of the regression. Modification of fecundity to account for the genetic contribution from both sexes is described in Section 2.1.7.6. Similar to natural mortality rate, fecundity is also assumed to be independent of waterhemp population density.

2.1.7.6 Inheritance of herbicide resistance. The mean *Pz* of the parental generation (those individuals reaching reproductive maturity) is calculated as a weighted average of individuals' fecundity:

$$\text{mean } Pz_{\text{parents}} = \frac{\sum (f_i \times Pz_i)}{\sum (f_i)} \quad (4)$$

where f_i and Pz_i are the fecundity and phenotypic values of individual *i*. Fecundity f_i is the number of seeds produced by a female plant; however, to account for the genetic contribution from male parents, f_i was divided by 2, with each half assigned to males and females under the precondition that the sex ratio in the population is 1: 1 throughout the model.

Phenotypic value *Pz* has log-normal distribution, and thus its natural logarithm ln(*Pz*) has normal distribution. Note that μ is not the mean *Pz* but the mean ln(*Pz*) and the transformation can be realised via equation (5):

$$\mu = ln\,(\text{mean } Pz) - \frac{\sigma^2}{2} \quad (5)$$

Parameter μ for the new seeds (offspring) is then calculated using Breeder's equation: [27]

$$\mu_{\text{offspring}} = \mu_{\text{original}} + h^2 \times \left(\mu_{\text{parents}} - \mu_{\text{original}}\right) \quad (6)$$

where $\mu_{\text{offspring}}$ is the mean ln(*Pz*) of the newly produced seeds, μ_{original} is the mean ln(*Pz*) of the generation before selection (the same for the seed bank and the emerged plants), μ_{parents} is the mean ln(*Pz*) of the parents surviving the selection and h^2 is the heritability.

Before incorporation in the seed bank, a proportion of the new weed seeds are removed from the population to account for seed predation and those that are non-viable at production (Table 1, #5 and 6).[32,33] Independent of the new seeds, the size of the old seed bank is modified by a seed bank mortality rate, which accounts for all causes of mortality in the old seeds. Then the remaining new seeds and old seeds are incorporated as the new soil seed bank, which has the potential to emerge in the next season. The mean *Pz* value of the seed bank is updated as

$$\text{mean } Pz_{\text{incorporated seed bank}} = \frac{\text{mean } Pz_{\text{offspring}} \times N_{\text{offspring}} + \text{mean } Pz_{\text{old seed bank}} \times N_{\text{old seed bank}}}{N_{\text{offspring}} + N_{\text{old seed bank}}} \quad (7)$$

where $N_{\text{offspring}}$ is the total number of viable new seeds, $N_{\text{old seed bank}}$ is the size of the seed bank after seed bank mortality is considered but before the new seeds are incorporated and the mean *Pz* values of the offspring and the old seed bank can be calculated from μ using equation (5). At the end of each step, LD_{50} of the incorporated seed bank (= median $Pz = e^{\mu}$) represents the resulting resistance level of the population.

2.2 Simulation experiments

The model simulates 20 waterhemp generations with 100 runs. Stochasticity stemmed from variables assigned by random draw from predefined distributions (e.g. emergence date from Weibull distribution) and Bernoulli processes when probabilities (e.g. mortality rate) are implemented. The main endpoints are the weed population density (number of surviving adult plants m^{-2}) and the population LD_{50} values (i.e. median *Pz*) of each generation. A population is considered to be resistant when more than 20% of the population have Pz_i values higher than the herbicide application rate (after Neve *et al.*[9]). The average annual LD_{50} value ($n = 100$) is used to predict the first year when the population will become resistant to the herbicide in question.

2.2.1 Model verification

As a first step in the model verification, it is necessary to determine whether the model simulates realistic waterhemp population dynamics in Midwestern maize–soybean crop systems; the assumption is that, in the absence of herbicide resistance, populations would be well controlled under standard weed management scenarios. Model runs were performed with default parameters (Table 1), but without the evolution of herbicide resistance (h^2 set to zero). To determine whether the model realistically simulated the evolution of resistance to glyphosate and HPPD-inhibiting herbicides, model runs were performed with representative management parameters in the Midwestern crop systems where resistance to these herbicides existed. Glyphosate resistance in waterhemp populations was reported within 10 years of adoption of glyphosate-resistant crops in maize–soybean rotations in the Midwestern United States.[2] Although detailed field histories of management practices were not available, expert knowledge suggests that there were typically at least two annual post-emergence applications of glyphosate. Similarly, in a seed corn production field in Illinois, resistance to HPPD-inhibiting herbicides was reported after 7 years of recurrent applications.[20,34]

2.2.2 Sensitivity analyses

Sensitivity analyses were performed on the basis of the glyphosate-only management scenario (Table 2a) to assess the sensitivity of important biological, genetic and weed management parameters (Table 1). Biological (i.e. new seed viability, initial seed bank density, germination probability, seed predation, seed bank mortality rate, adult plant fecundity and natural mortality rate) and genetic parameters (i.e. heritability, initial glyphosate LD_{50} and phenotypic glyphosate resistance variance) were varied systematically by ±10%. In addition, parameter values were varied between biologically realistic upper and lower limits. The former allows a 'normalised' comparison across parameters with the same level of change, and the latter captures the realistic range of model sensitivity to those parameters. Dates of herbicide application were changed to represent applications 1 week earlier and 1 week later than the default dates.

3 RESULTS

3.1 Model verification with *A. tuberculatus*

In the absence of herbicide resistance evolution, the model simulated realistic waterhemp population densities and dynamics. Population density was controlled to levels of <1 plant m^{-2} for 20 years by two annual glyphosate applications with typical efficacies (99.9% for early POST and 95% for late POST[9]). The population density level with these efficacy values was considered to be sustainable and a realistic representation of waterhemp population dynamics (Fig. 2a), although it showed a slight increase over the years. In further simulations, in order to make it easier to identify population density increase caused purely by the evolution of

Table 2. Detailed application schemes in the Midwestern United States for model verification: (a) glyphosate-only scenario in maize–soybean systems (same application in maize and soybean except for application time, see Table 1), and (b) a typical scenario with the use of mesotrione in continuous maize planting, examining mesotrione resistance

Option	Application time	Herbicide(s)	Rate (g a.e. ha^{-1} for glyphosate and g AI ha^{-1} for others)	% Control of susceptible waterhemp	Length of initial control (weeks)[a]	Number of weeks to <60% control[b]
(a) Maize–soybean crop system with glyphosate	Early POST	Glyphosate	1120	99.7[c]	NA	NA
	Late POST	Glyphosate	1120	96[c]	NA	NA
(b) Seed corn production system with HPPD inhibitor	PRE	Simazine	1120	20	NA	NA
		S-Metolachlor	1050	80	3	4
	Early POST	Mesotrione	105	95	2	4
		Atrazine	560	85	2	3

[a] For herbicides with soil residual activity, this is the number of weeks they have full efficacy.
[b] After the initial period with full efficacy (see above), soil residual activity declines as a result of dissipation. This is the time period when efficacy drops to 60% of its full value, after which efficacy is assumed to drop to 0%. Glyphosate does not have soil residual activity.
[c] These efficacy values were fine-tuned so that, in the absence of glyphosate resistance, the application scenario would result in a strictly non-increasing weed population. See Section 3.1 and Fig. 2.

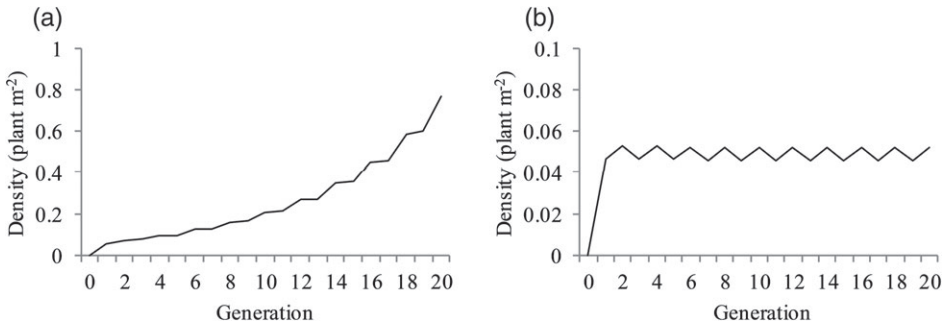


Figure 2. Simulated waterhemp population dynamics over 20 generations in the absence of herbicide resistance in a field with annual maize–soybean rotation, with (a) benchmark glyphosate efficacy (early POST = 99.9% and late POST = 95%) and (b) fine-tuned glyphosate efficacy (early POST = 99.7% and late POST = 96%). Note the different scales of the *y*-axes.

glyphosate resistance, we fine-tuned efficacy values to 99.7 and 96% to obtain a strictly non-increasing low population density as baseline (<0.1 plants m^{-2}) (Fig. 2b).

In the presence of resistance evolution, with two annual applications of glyphosate, waterhemp populations were predicted to evolve resistance in approximately 8 years in the model (Fig. 3b), which is a reasonable timescale according to field observations.[2] Similarly, the model predicted mesotrione resistance to evolve in 7 years (Fig. 3d) with the herbicide application scheme used in seed corn production, which matches what has been reported in that crop system.[20,34] Waterhemp population density exceeded the threshold of 1 plant m^{-2} in the same year the population evolved resistance to glyphosate (Fig. 3a), while in the scenario with mesotrione, population density exceeded the threshold 2 years later than the LD_{50} (Fig. 3c). The population density increased less quickly in the latter scenario because herbicides with other modes of action also played a role in controlling waterhemp, while in the former scenario the control was provided solely by glyphosate. Error bars indicated that there was little variation between model runs.

The model realistically simulated population dynamics and herbicide resistance evolution, ensuring that all subsequent sensitivity and management analyses provided comparative and credible predictions.

3.2 Sensitivity

3.2.1 Biological parameters

The default field size in the model simulations was set to 100 ha, which represents a realistic field size in the Midwestern United States. Sensitivity analysis also showed that this is a sufficient field size to capture the pattern of herbicide resistance evolution (supporting information Fig. S1). The comparison of resulting changes in waterhemp population density and LD_{50} with same-scale changes of 10% in the parameters showed that demographic parameters were generally not influential (Fig. 4). However, extreme but biologically realistic values of these parameters resulted in clear contrast to the baseline. For example, if new seeds had extremely low success, owing to either viability as low as 10% or a predation rate as high as 90%, resistance evolution would be delayed for at least 5 years (Fig. 5). On the other hand, the old seeds were less important – with a mortality rate of as high as 90%, the population still evolved herbicide resistance in the same year as the baseline. Extreme germination rates had a strong influence – the maximum rate (50%) resulted in the waterhemp population density exceeding the control threshold within 2 years, and the minimum rate (1%) delayed herbicide resistance evolution for 6 years (Fig. 5). Other full time series of the sensitivity analyses with parameters changed by ±10% and set to the possible maximum and minimum values are presented in supporting information Figs S2 to S4.

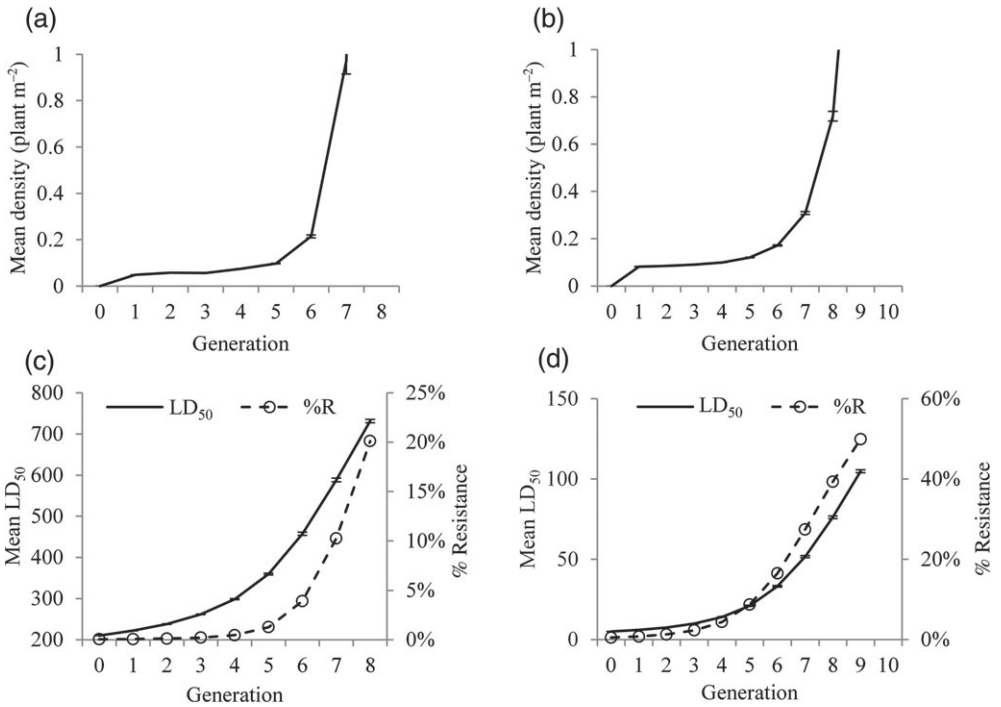


Figure 3. Simulated waterhemp population dynamics and the evolution of glyphosate and mesotrione resistance, respectively, in the glyphosate-only scenario (a) and (b) and in the typical seed corn production scenario with the use of mesotrione (c) and (d). Graphs (a) and (c) show the waterhemp population densities (plants m^{-2}) over 20 generations of model simulation. Graphs (b) and (d) show the time series of LD$_{50}$ for glyphosate (b) and mesotrione (d) (primary vertical axis), as well as the corresponding risk of resistance (secondary vertical axis). For detailed scenarios, see Table 2. Each data point represents an average of 100 model runs, with error bars showing the standard deviation.

3.2.2 *Genetic parameters*

Genetic parameters, in particular sigma (σ) of the log-normal distribution for phenotypic herbicide resistance values, were very influential (Fig. 4). For example, a 10% reduction in σ delayed resistance evolution by up to 7 years. Heritability h^2 had the lowest sensitivity among the three genetic parameters. Higher initial LD$_{50}$ values in the sensitivity analysis represented cases with pre-existing resistance to the particular herbicide mode of action (here glyphosate). An initial glyphosate LD$_{50}$ of 231 g a.e. ha^{-1} (i.e. 10% increase from the baseline 210 g a.e. ha^{-1}) represented 0.1% of glyphosate-resistant individuals in the initial waterhemp population, which is a small difference to the 0.05% in a pristine population with the baseline LD$_{50}$, and resulted in the population evolving glyphosate resistance 1 year quicker than default (Fig. 4). In real fields, pre-existing levels of glyphosate resistance may be much higher. For example, for a waterhemp population with glyphosate LD$_{50}$ of 500 g a.e. ha^{-1} (equivalent to 5.65% of glyphosate-resistant individuals in the beginning), the same scheme with two annual applications of glyphosate quickly failed and the population density exceeded the control threshold within 2 years (supporting information Fig. S2).

3.2.3 *Management parameters*

Herbicide efficacies and application rates showed high sensitivity in terms of waterhemp population density: 10% lower efficacies resulted in the waterhemp population density increasing to problematic field levels 3–5 years sooner than the standard efficacy values (supporting information Fig. S3). A 10% increase in the application rate delayed herbicide resistance evolution to a greater extent than the demographic changes in seed bank size, but had a smaller effect than a 10% reduction in phenotypic variance.

Postponing the time of PRE, or advancing the time of early POST applications, delayed herbicide resistance evolution by 1–2 years. Changes in the same management-timing-related parameters in different crop planting years (maize versus soybean) resulted in similar changes in LD$_{50}$ (Fig. 4).

4 DISCUSSION

In this study, we developed a modelling framework for predicting herbicide resistance in arable weed populations under different herbicide use schemes. The generalised algorithm is based on quantitative genetic assumptions and flexibly incorporates life cycle and population dynamics of summer annual weed species. Qualitative model verification, using waterhemp as a representative weed species in the Midwestern United States, showed that the framework is valid for representing realistic weed population dynamics and timescales for the evolution of herbicide resistance based on field observations. Sensitivity analyses indicated that the rate of herbicide resistance evolution was influenced more by changes and variations in genetic parameters and management strategies than by biological parameters.

Population models have been previously used to implement quantitative genetics for herbicide resistance evolution. Gardner *et al.*[12] implemented a continuous distribution of the quantitative resistance phenotype to explore the impact of revolving herbicide dose on the evolution of resistance, although without simulating more complex species biology or management options. Later, individual-based approaches became favoured in resistance modelling because they better addressed the complexity of weed emergence pattern, life-history processes and genetics, as well as multiple treatment timings; for example, Renton *et al.*[13] developed an IBM that accounts for up to five genes involved in herbicide

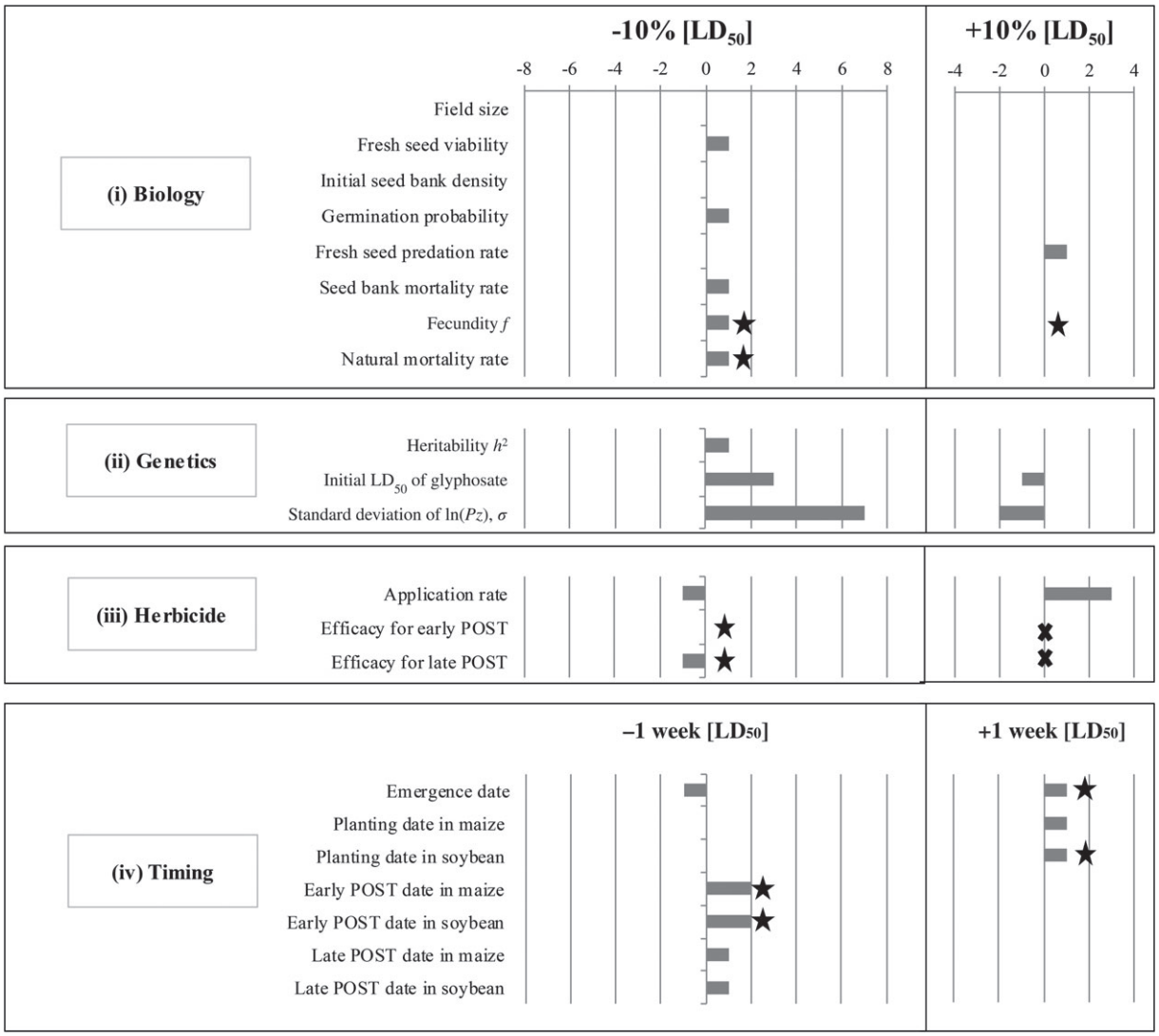
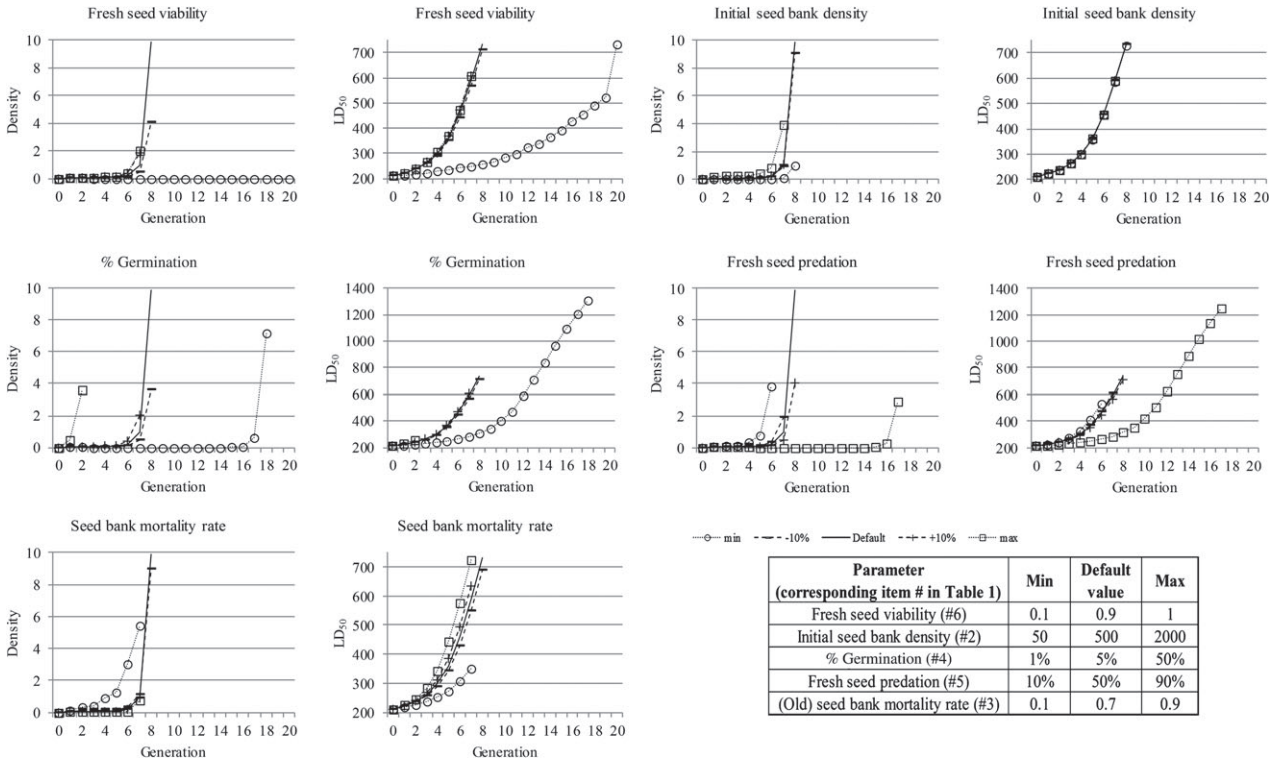


Figure 4. Sensitivity of parameters related to (i) biology, (ii) genetics, (iii) herbicide treatment and (iv) timing of emergence and herbicide application. Parameters in (i), (ii) and (iii) were changed by −10% (first column) and +10% (second column), and parameters in (iv) were changed by −1 week (first column) and +1 week (second column). The resulting changes in the first year when the population LD_{50} exceeds the resistance threshold (730 g a.e. ha^{-1} of glyphosate) are shown. The horizontal axes represent changes in time (years). Stars indicate that population density exceeded the control threshold of 1 plant m^{-2} before herbicide resistance was detected in the model; therefore, the actual time to resistance can potentially be longer. Herbicide efficacies increased by 10% exceed 100% and do not make practical sense, so the two data points in (iii) are not available (indicated by crosses). Note that only the state variables are tested for sensitivity, and the corresponding changes in other parameters may not be linear; for example, a 10% increase in σ results in an increase in the initial proportion of resistant individuals from 0.05 to 0.14%.

resistance and presented a case study to explore the impacts of reduced herbicide doses on the evolution of resistance. Our simulations support the findings of Renton *et al.* that a reduced dose could accelerate resistance evolution (supporting information Fig. S3). Fundamentally different to the oligogenic model by Renton *et al.*,[13] our framework does not rely on knowledge of the number of interacting genes underlying the phenotypic herbicide resistance trait, because the premise of quantitative genetics is that the response to selection is determined by the heritability of the trait, not the number of genes. As more evidence of quantitative herbicide resistance becomes available (e.g. for glyphosate: amplification of *EPSPS* gene copy number, vacuolar glyphosate sequestration, reduced translocation),[16,24] we think it is important to provide a modelling framework based on quantitative genetic assumptions which is also able to flexibly account for different annual weed species. As the core biology and genetic processes are captured, a model user would only need to update the parameters and management strategies for different weed species to obtain predictions for the new system in question. Additional modules can be added to the current framework to address oligogenic and quantitative mechanisms in parallel. If the genetic basis of a herbicide resistance case is not known, predictions from our model can be compared with those from oligogenic models as pilot studies to inform further molecular-level investigations.

Sensitivity analyses provide a basis for the understanding of model structure and sources of uncertainty. High sensitivity indicated the need to obtain more accurate values for these parameters in future experiments to reduce the uncertainty in model predictions. Results from the present analyses indicated that herbicide resistance evolution was most affected by genetic parameters, such as the phenotypic variance and the weed population's initial LD_{50} (Fig. 4). Similar conclusions were reached in earlier



Parameter (corresponding item # in Table 1)	Min	Default value	Max
Fresh seed viability (#6)	0.1	0.9	1
Initial seed bank density (#2)	50	500	2000
% Germination (#4)	1%	5%	50%
Fresh seed predation (#5)	10%	50%	90%
(Old) seed bank mortality rate (#3)	0.1	0.7	0.9

Figure 5. Sensitivity of the biological parameters in terms of weed population density (plants m^{-2}, left-hand panels) and LD_{50} of the population (g a.e. ha^{-1}, right-hand panels) at each generation. The min, default and max values of the parameters are listed in the inset table.

models. Renton *et al.*,[13] for example, found that phenotypic variation and initial frequency of herbicide-resistant alleles have the most impact in a polygenic model. The same was true in models with single-gene assumptions: Maxwell *et al.*[7] suggested that ecological fitness and gene flow are key factors in herbicide resistance prediction. Neve *et al.*[9] demonstrated that model output is particularly sensitive to the initial frequency of herbicide-resistant alleles. For effective weed control, both herbicide resistance risk and weed population density are important endpoints to monitor. The high sensitivity of herbicide efficacy in terms of weed density indicated that a weed control problem does not only arise from evolved herbicide resistance but may also be the result of poor or suboptimal herbicide application. Initial seed bank size had little influence on predicted rates of resistance evolution, and here the predictions from the quantitative model are quite different from those of previous single-gene models.[9] Where resistance is conferred by a single rare allele (with an initial frequency of 5×10^{-8}), the number of phenotypically resistant individuals within a weed population is proportional to population size, with small populations having no herbicide-resistant individuals and therefore no standing genetic variation on which selection can act. For quantitative traits, individuals with low levels of herbicide resistance are typically present in populations prior to selection at higher frequencies, and the rate of resistance evolution is influenced by the heritability of resistance traits, rather than by frequency of rare resistant individuals.

Despite its applicability and insights provided by the sensitivity analyses, there are a few shortcomings with the current modelling approach that can be addressed by overcoming current data limitations. There is a lack of data available for distinguishing between genetic and environmental variance of a herbicide resistance trait; therefore, we directly modelled phenotypes and assumed a fixed variance on the basis of an infinitesimal model. Employing classical quantitative genetic frameworks overcomes the requirement to know the number of genes conferring herbicide resistance traits, although these assumptions may be open to question in cases where quantitative resistance is conferred by a small number of genes (oligogenic traits). Nevertheless, in the absence of this knowledge, this framework is believed to be more robust and tractable than models based on assumptions that traits are based on a defined number of interacting alleles. Unstable inheritance of *EPSPS* gene duplication may also be an important aspect to consider once more is known on this phenomenon at the molecular level.[41] There is, to our knowledge, no precedence for quantitative genetic models that account for overlapping generations (in this instance, an age-structured seed bank with contrasting selection histories), and this presents unique challenges when attempting to reconstruct the population-level parameters for *Pz*, i.e. median and variance. We have adopted a pragmatic approach to this problem, and we believe that the approximations to calculate these values are a justifiable simplification in large weed populations (see supporting information). Regarding fecundity, individuals with a Pz_i value close to the applied dose may be partially affected and thus produce fewer seeds than individuals with a higher Pz_i. However, accounting for this phenomenon would require the addition of further parameters without good supporting data. In the current model, fecundity is dependent upon emergence time but independent of herbicide resistance phenotypes.

Model simulations presented in this study were based on parameters of typical waterhemp populations in maize and soybean agroecosystems in the Midwestern United States. However, insights provided by the sensitivity analyses were not limited to waterhemp and its specific environment. Instead, the analyses served as a basis for predicting which system and species characteristics would favour the evolution of quantitative herbicide

resistance. Results from the study suggested that different propensities to evolve resistance under the same management scenario reflected differences in *Pz*, its variance and the heritability of herbicide resistance among species. Coarse estimates of risk can be obtained by combining a set of parameter values that best describe the system in question. For example, weed populations that have large variance in herbicide resistance phenotypes (i.e. a wide sigmoid dose–response curve) and whose post-emergence treatment is applied later than recommended are more likely to evolve herbicide resistance. Within the same weed species and agroecosystem, the model can be used to test the validity and efficiency of a proposed weed management strategy, or compare across several similar management strategies and identify an effective solution. The model is also capable of simultaneously evaluating evolution of resistance to multiple herbicide modes of action. Therefore, in addition to the sensitivity analysis on initial glyphosate LD_{50} presented in this paper, the model can be further used to explore the impact of pre-existing or evolved resistance to glyphosate on the risk of resistance to other herbicide modes of action; for example, when both glyphosate and mesotrione are used, different initial LD_{50} values of glyphosate can be tested to see how the rate of mesotrione resistance is affected.

In conclusion, the modelling framework serves as an applicable tool to study the evolution of quantitative herbicide resistance in annual weeds. The model simulations provided useful insights into weed management strategies for resistance mitigation. Given that no novel herbicide modes of action have been discovered over the past 30 years, it is important to ensure a sustainable use of the herbicides that are still available.

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SUPPORTING INFORMATION

Supporting information may be found in the online version of this article.

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